PAEDIATRIC PATIENT CENTRIC DEVELOPMENT OF NOVEL PROCESSES FOR THE FORMULATION OF ORALLY DISINTEGRATING TABLETS

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Thesis Summary

Following the European regulation for paediatric formulations, the demand for the production of paediatric dosage forms has escalated. Managing the clinical needs of children is challenging, especially as this must often be accomplished using adult medicine formulations. For this reason, further paediatric dosage forms need to be developed to address their clinical needs. There are various formulations which can be administered via the oral route including tablets, capsules, liquids and chewable tablets. It is essential to mention orally disintegrating tablets (ODTs) which have been a popular area of research for scientists in the last decade.

The overarching aim of this thesis was to develop novel oral dosage forms for children and young adults aged 6 to 18 years. The principal theme of this thesis is sub divided into two main areas of research: the first area evaluated dosage form preferences in children and young adults and assessed the key pragmatic dosage form characteristics that would enable formulation of patient centred ODTs; the second area focused on a wide range of laboratory-based investigations for development of low dose blends and pre-blends of ODT formulations using various blending techniques.

The results of clinical investigations revealed that ODTs are a preferred dosage form among children because they combine the advantages of both solid and liquid dosage forms, without incorporating their disadvantages such as difficulty in swallowing and lack of stability respectively. Healthcare professionals indicated that taste and disintegration time were the most important factors to provide both suitable dose units and acceptable medicines for paediatric patients.

Results from powder blending indicated that the dry particle coater provided a robust platform for obtaining content uniformities at 1% and 0.5%w/w API using non-sieved carriers. Micro crystalline cellulose as a carrier showed superior flow properties and better drug content uniformity for both geometric and ordered blending techniques. Furthermore, the co-processed excipients containing 86.5% w/w of milled-mannitol, 12% w/w pregelatinised starch and 1.5% w/w silica using Aston Particle Technology (APT's) new coating technique can be utilised as a potential multifunctional directly compressible ODT pre-blend. An investigation into the role of moisture content on micro/macro properties of ODTs illustrated that moisture considerably affects the consolidation characteristics of blended powders; and the extent of consolidation and the bonding of particles depend, not exclusively on moisture content, but also on the powder processing conditions.

In conclusion this work supports the World Health Organisation (WHO)'s claim for a paradigm shift from liquid towards ODT dosage forms for drug administration to young children older than 6 years. Data from this study will equip formulators to prioritise development of key physical/performance attributes within the delivery system.

Key words: *Paediatric formulations, clinical needs, oral route, blending techniques, moisture content.*

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Dedication

I dedicate this work to all my family and many friends, a special feeling of appreciation to my loving mother Bakhetah Alyami, my eldest brother Jaber Alyami and my wife Wadha Alarjani who encouraged me throughout my studying journey and for being patient. They have prayed for me, supported and strengthened me, I couldn't achieved this without their inspirations. I also dedicate this thesis to my wonderful daughter Sarah and my son Saleh, for not failing to put a big smile on my face every time, both of you have been my cheerfulness. Special dedication goes to my uncle Hamad Alyami, my friends Fahad Alyami, Ali Al Rashid, Mohammed Alyami and Abdullah Basulayyim who stood by my side during my PhD studies. The memory of my father Saleh Alyami who implanted in me the hard work, confidence, forgiveness and modesty.

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List of Abbreviations

AFM	Atomic force microscopy
ANOVA	Analysis of variance
API	Active Pharmaceutical ingredient
APT	Aston Particle Technologies
BCH	Birmingham Children's Hospital
BOS	Bristol Online Survey
BP	British Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CLSM	Confocal laser scanning microscopy
EMA	European Medicines Agency
EP	European Pharmacopeia
Eq	Equation
FDA	Food and Drug Administration
FG	Focus group
g	gram
GCP	Good Clinical Practice
HCPs	Healthcare Professionals
IBU	Ibuprofen
ICH	International Counsel of Harmonisation
LOD	limit of detection
LOQ	limit of quantification
MCC	Microcrystalline cellulose
mg	milligram
mg/mL	milligram per millilitre
MgSt	magnesium stearate
min	minute
mm	millimetre
nm	nanometre
%	percentage
ODTs	Orally Disintegrating Tablets
PSD	Particle Size Distribution
PSP	Paediatric Study Plan
RES	Research Ethics Committee
rpm	round per minute
SI	Semi-structured interview
SEM	Scanning electron microscopy
TGA	Thermogravimetric analysis
USP	United States Pharmacopoeia
VMD	Volume median diameter
WHO	World Health Organization
W/W	weight per weight

Publications List

Peer reviewed articles:

1. Ali Al-Khattawi, **Hamad Alyami**, Bill Townsend, Xianghong Ma and Afzal R Mohammed (2014) Evidence-Based Nanoscopic and Molecular Framework for Excipient Functionality in Compressed Orally Disintegrating Tablets. PLOS ONE, 9(7):e101369.

2. Ali Al-Khattawi, **Hamad Alyami**, Afzal R Mohammed (2013) A Systematic Investigation of D-Mannitol Functionality in the Development of Age Appropriate Formulations CRS newsletter, (April).

3. **Hamad Alyami**, Eman Dahmash, Fahad Alyami, Dania Dahmash, Chi Huynh, David Terry and Afzal R Mohammed (2016). Dosage form preference consultation study in children and young adults: paving the way for patient-centred and patient-informed dosage form development. European Journal of Hospital Pharmacy: ejhpharm-2016-001023.

4. **Hamad Alyami**, Jasdip Koner, Eman Dahmash, James Bowen, David Terry and Afzal R Mohammed (2016). Microparticle surface layering through dry coating: impact of moisture content and process parameters on the properties of orally disintegrating tablets. Journal of Pharmacy and Pharmacology DOI: 10.1111/jphp.12623.

5. **Hamad Alyami**, Jasdip Koner, Chi Huynh, David Terry and Afzal R Mohammed (2016). Current Opinions and Recommendations of Healthcare Professionals Regarding the Importance and their Preferences Concerning Paediatric Dosage Forms. PLOS One. Accepted.

6. **Hamad Alyami**, Eman Dahmash, James Bowen, David Terry and Afzal R Mohammed (2016). An investigation into the effects of excipient particle size, blending techniques and mixing parameters on the homogeneity and content uniformity of a blend containing low-dose API. PLOS One. Accepted.

Conference Proceedings:

1. **Hamad Alyami**, Eman Dahmash, Fahad Alyami and Afzal R Mohammed. Multi-centre consultation study on acceptability of orally disintegrating tablets (ODTs) in paediatric and young people. UKICRS Cork, April 2014

2. **Hamad Alyami**, David Terry, Eman Dahmash and Afzal R Mohammed. International acceptability study of orally disintegrating tablets (ODTs) in children and young adults. EuPFI Athena, September 2014

3. **Hamad Alyami,** David Terry and Afzal R Mohammed. Study the effect of moisture content and dry particle coating on powder and tablets performance. CRS Edinburgh, July 2015

4. **Hamad Alyami**, David Terry and Afzal R Mohammed. Formulation and process development of paediatric ODTs: A systematic investigation into the role of moisture content on micro/macro properties of pharmaceutical excipients. UKICRS Cardiff, April 2016

5. **Hamad Alyami**, David Terry and Afzal R Mohammed. Effect of composite particles and moisture level on powder flow and tablets performance. UK PharmSci, Glasgow ,September 2016

Oral Presentations:

Formulation and process development of the main core for a small drug dose of oral disintegrating tablets (ODTs): A systematic investigation into the role of Starch and pregelatinisd starch using various blending techniques. UK PharmSci, Hertfordshire, September 2014

Chapter 1

Introduction

1.1. Introduction

Paediatric medication development has advanced extensively worldwide due to legislative encouragements and requirements directed towards the development of studies of drugs for use in the paediatric population (FDA, 1994). European Medicines Agency (EMA) has reviewed its legislative requirements to drive innovations in paediatric formulations (European Commission, 2013). An approved paediatric investigation plan is required for all new drugs and all line extensions that are submitted for EMA approval after January 2009. Such plans should cover all paediatric age groups. Furthermore, the EMA has issued guidelines on pharmaceutical development of medicines for paediatric use including route of administration, dosing frequency, excipients, patient acceptability, container closure systems and devices and user information (CHMP, 2006, Gauthier and Cardot, 2011). The FDA has issued in 2012, a law requiring the implementation of the Paediatric Research Equity Act and Best Pharmaceuticals for Children Act (Christensen, 2012). Similar to the EMA requirements, a paediatric study plan (PSP) is required for submission and approval by the FDA (FDA, 2013). There are various routes of drug administration as depicted in (Figure 1.1). Oral route of administration is inevitably the most popular route of delivery due to ease of ingestion, availability of a wide variety of dosage forms and most significantly enhanced compliance and adherence. Different drug formulations can be administered orally, including solid and liquid dosage forms (Fasano, 1998, Sastry *et al.*, 2000).

Figure 1.1: Various routes of administration in the UK market adapted from (Aulton and Taylor, 2013).

The provision of safe, as well as effective, pharmacotherapy in paediatrics necessitates the availability of medicines alongside information for proper utilisation, which is compliant with the patient's age, physiology and body surface area (Mulberg *et al.*, 2013). Therefore, dosage forms formulated specifically for children, are often required. Till date, the utilization of unlicensed (medicine with no marketing authorisation) as well as off-label medicines in paediatrics is extensive (Mason *et al.*, 2012). The disadvantages of this being that there are limited studies on their effects on the paediatric population; age-appropriate formulations are usually not presented, and available formulations are not licensed for paediatric use (Choonara and Conroy, 2002) .The paediatric population is heterogeneous; ranging from new-borns to young people, with large physical as well developmental differences, regarding pharmacokinetics and pharmacodynamics. Organ development, metabolic competence and skin maturation are some factors that may vary based on age,

particularly in early infancy. The paediatric age groups recognized by ICH are shown in Table 1.1 (EMA, 2006).

Table 1.1: Classification of Paediatrics based on age groups.

• Preterm newborn infants;
• Term newborn infants (0–28 days);
• Infants and toddlers (28 days–23 months);
• Children (2–11 years)
• Adolescents (12 to 16 or 18 years (dependent on region).

1.2. Paediatric Dosage Forms

Paediatric dosage forms should be versatile so that drugs can be administered to neonates, children, and adolescents. The common paediatric dosage forms include solid dosage forms (such as tablets); powders, solutions, and syrups (Viner and Barker, 2005). Solid dosage forms are drugs, which have been compounded to give a definite shape and a standard dose, as is the case with tablets. Powders are a type of solid dosage form, which have been ground and are finely divided. They are usually administered topically on the skin, sprinkled on food or mixed with liquid diet. On the other hand, solutions are dosage forms which are made up of an aqueous base (majority) and other pharmaceutical ingredients which give the solution its therapeutic effect. Syrups form sugary and have a thicker consistency than solutions, a factor which makes them more viscous (Ansel *et al.*, 1995).

1.2.1. Age Development and Dosage Forms of Choice

Dealing with children is quite challenging, particularly when it comes to diseases and their remedies. For neonates, the challenge is even more pronounced because diagnosis alone poses a difficult step. After diagnosis, other challenges include the

appropriate choice of formulation and route of administration. Children are remarkably sensitive to the effects of drugs; not just on the internal effects that the drugs have but also on the outward appearance and the taste. A child may refuse to take a drug because the colour is not appealing or because it smells 'weird'. Even after succeeding in making the child swallow the drug in the first instance, this result may not be repeated for subsequent doses. This is because children have a unique fine memory to conditions, circumstances, and experiences of their past (Sahler *et al.*, 2000). To say the least, it will pose a massive challenge trying to convince them to take the drug again. For this reason, paediatric dosage forms need to be tailored to address the fears and the expectations of the target users. This requests for a higher level of interest during manufacturing and even prescribing, since children require lower dose amounts to achieve the same effects as seen in adults. In addition, various factors need to be taken into consideration, notably taste masking. For drugs that come in the form of powders, the dosage form can be changed by tableting the powders and converting them into solid dosage forms. Powders can also be granulated to make it easier to determine the dose since this becomes a major issue, especially with regard to children (van Riet-Nales *et al.*, 2013).

Table 1.2 shows a matrix developed by the EMA from responses to questionnaires sent out to 40 participants (including parents, pharmaceutical scientists and clinical paediatricians) in different European countries to develop a relationship between age development, dosage form and route of administration (Cram *et al.*, 2009). Moving from the left to the right, the emphasis in the columns changes from the applicability to preference.

Table 1.2: EMA matrix relating oral dosage forms/ route of administration to dosage form and age; adapted from references (EMA, 2006, Breitkreutz and Boos, 2007).

Oral dosage forms	Preterm new-born infants	Term new-born infants (0d-28d)	Infants and Toddlers (1m-2y)	Children (pre-school) (2-5y)	Children (school) (6-11y)	Adolescents (12-16/18y)
Solutions/ drops	2	4	5	5	4	4
Emulsion/Suspension	2	3	4	5	4	4
Effervescent dosage form	2	4	5	5	4	4
Powders/ Multiparticulates	1	2	2	4	4	5
Tablets	1	1	1	3	4	5
Capsules	1	1	1	2	4	5
Orodispersible dosage form	1	2	3	4	5	5
Chewable tablets	1	1	1	3	5	5

Key*:*
Younger ages (preterm-pre-school): 1- not applicable, 2 - applicable with problems, 3 - probably applicable but not preferred, 4 - good applicability, 5 - best and preferred applicability.

Older ages (school-adolescents): 1 -not accepted, 2 - accepted under reserve, 3 - acceptable, 4 -preferred acceptability, 5 - dosage form of choice.

1.2.2. Definition of Acceptability

The acceptability of a drug is its ability to meet the patient's requirements and needs. Acceptability also entails the quality of the drug to realize the objectives set out by the physician. It involves a number of aspects including the dosage amount and proper diagnosis. Of the two, proper diagnosis is of immense importance before embarking on managing an ailment, a condition, or a disorder. Proper diagnosis not only gives the physician the knowledge of the condition in question, but also provides a head start on the best way of managing it. Managing in this case, refers to administration of the right

medicine. As mentioned earlier, the administration is determined by a number of factors. This calls for a choice on the route of administration to be used. The route of administration should be in line with the pharmacokinetic properties of the drug. For example, drugs that are absorbed in the stomach are administered orally. Care has to be taken regarding some drugs taken orally, as they may undergo breakdown while in the stomach. Such drugs (proton pump inhibitors, omeprazole) are usually enteric-coated to minimize, if not effectively curb, their breakdown as they pass through the gastrointestinal tract (Standing and Tuleu, 2005). Enteric coating provides a layer that inhibits the action of acids enzymes present in gastric juice and other stomach secretions, which contribute to the breakdown of the acid sensitive's active pharmaceutical ingredients (APIs) in the formulation. If such drugs are not enteric-coated, there is a high likelihood that they will undergo breakdown while still in the stomach, and the APIs may fail to reach their intended area of absorption, which could be the ileum or even the large intestine (van Riet-Nales *et al.*, 2013).

1.2.3. Important Factors in the Overall Acceptability of an Oral Paediatric Medicine

For oral paediatric medicines to be acceptable and therefore effective, there are a number of factors that need to be considered. One of these is elegance. Elegance refers to the outward appearance of the dosage form and its ability to appeal to the eye. Among children, this factor becomes crucial because of the sensitivity of children to seemingly unimportant matters (EMA, 2006). A child may refuse to take a medicine just because it does not look appealing. A factor related to acceptability and which is closely related to elegance, is palatability. Children will rarely take drugs that are bitter tasting (Hoppu, 2008). For this reason, most drugs which have a bitter taste are coated with a sweet tasting substance. If the bad taste is not masked, such drugs may

predispose the child to vomiting. If the smell of the drug is putrid, it may also negatively influence the acceptability of the drug. The ability of children to differentiate drugs by their smell is testimony of their attention to detail. In the same way, a dosage form needs to be convenient for it to be acceptable among children. The term convenience refers to the method by which it is administered, for instance, as a tablet, a syrup or as a powder. Among children of school age, tablets are more popular compared to powders because they can easily be administered (Nunn and Williams, 2005). Dosage is also accurate and can be easily determined since most tablets are already portioned in specific doses. Syrups are also more popular compared to solutions, which in turn are preferred over powders (Maheshwari *et al.*, 2013). Excipients added in solutions to increase their volume should be neutral and need not have an effect on the ultimate intended therapeutic effect of the drug. Lastly, the stability of a drug is of great importance with regard to its acceptability. Stability is the ability of a drug to maintain its original form in terms of physical appearance, its therapeutic effects, and its chemical composition (Allen and Ansel, 2013). A medicine whose chemical structure varies after a period, or changes taste, is likely to have low acceptability compared to the one whose properties do not vary. In addition, the drug may not produce the intended outcome, especially if both chemical and therapeutic variations occur (Overgaard *et al.*, 2001).

1.2.4. A WHO Consultation on Paediatrics and Guidelines

The World Health Organization (WHO) is the international body that controls products and services with regard to human health. As such, it has laid down guidelines and procedures for production of paediatric dosage forms. WHO recognizes the need to develop drugs and formulations that specifically target children. It admits that even though the search for the appropriate dosage formulation with regard to the age, physical and physiological conditions of children has been challenging, it is not a lost

war (Hill, 2011). However, WHO warns against administering unlicensed drugs to the paediatric population, as this is likely to culminate in grave consequences. WHO recommends that dosage formulations should be prepared to cover as wide an age bracket as possible. This is because the age bracket of children is vaguely defined and stretches from preterm infants to term infants, to toddlers and even adolescents. It also recommends that manufacturers uphold good manufacturing practices with regard to obtaining and processing raw materials, up to preparation of the final pharmaceutical product. WHO stipulates that the dosage administered should be in line with the age and specific needs of the child. More importantly, the dosage, whether in volume or size, needs to be accurate. An overdose or an under dose may result in toxicity or sub therapeutic effect respectively. In addition, paediatric formulations should be made in ready-to-use preparations, as much as possible. This will minimize, if not eradicate, the need to modify the preparation by parents or health care professionals.

According to WHO, the dosage form should be acceptable and palatable. Furthermore, the drug formulation should be palatable without the need to mask the taste or sugar coating. Palatability will make it easier for children to accept and swallow the drug. Acceptability of the dosage formulation stretches beyond its use among children and extends to parents/caregivers and physicians – the dosage formulation should be acceptable among parents to increase its chances of being purchased. At the same time, acceptability or palatability should not be enhanced by mixing the drug formulation with food or drinks. This is because food and drink may affect the absorption of the drug or may interact with it, resulting in physical or chemical alterations. If there is no alternative, then the food or drink should be in a small amount such that it will not have an impact on the effects of the drug (Kozarewicz, 2014). Manufacturers also need to indicate whether it is possible to administer a given drug with food or beverages, and also incorporate any exceptions. When administering drugs to children, it should be ensured that minimum dosing is adhered to. The

frequency with which a drug is administered should be made minimal because frequent dosing, especially more than twice a day, may have a negative impact on patient compliance (Greenberg, 1983).

WHO recommends that manufacturers should aim at production of quality dosage formulations, with the needs of the target population in mind. For instance, the dosage formulation should be affordable to most people and the production process should be simple. The drug should be able to reach the target population easily by implementing viable transport and supply strategies. In addition, instructions for proper storage of the drug should be made available. For drugs that need to be dissolved in water before being swallowed or those that need water when swallowing, procedures for obtaining standard clean water should be outlined. This is because clean water may not be locally available in some locations (Hill, 2011). Furthermore, the need to produce dosage formulations that are effective among the paediatric population has brought up the need to conduct further research in the field of excipient's toxicity. As a result, newer methods, which are still under trial, are being investigated to study the effect of commonly used excipients in dosage form development, and their impact on the paediatric patient population (Walsh and Mills, 2013). The excipients used in making paediatric formulations have witnessed an increasing interest, with the belief that the right excipient will be the answer to most of the questions that still remain unanswered. To begin with, the excipients to be employed need to have a high safety profile to prevent any side effects. They also have to be tolerable because this influences the acceptability of the paediatric formulation. Current research projects of excipients used in paediatric formulations incorporate all stakeholders, including the target age group (children), medical practitioners, and even parents/ care-givers (Fabiano *et al.*, 2011).

1.2.5. Standard features of dosage forms for paediatrics

The goal is to find one formulation suitable for every age group. The primary focus should be the safety of the formulation and ideally cover as broad an age range as achievable. The guiding standards for choosing paediatric dosage forms should be based on the risk/benefit ratio accounting for the precise needs of this susceptible population. Desirable characteristics of quality paediatric drugs common to different kinds of dosage forms are outlined in (Table 1.3).

Table 1.3: Standard features for dosage forms of paediatrics are outlined by WHO (2010).

Convenient, reliable administration	The administered dose should contain an amount of API adjusted to the age and needs of paediatrics. More than one dosage form of API or strength of a dosage form is required to cover different age groups. The intended dose volume or size should be appropriate. Paediatric medicines should be ready to administer. Manipulation of dose should be minimal.
Acceptability and palatability	Acceptability is the overall acceptance of the dosage form regardless of the route of administration. Acceptability depends on suitability for the particular age group, dosing device for a liquid medicine, palatability of an oral medicine, dose volume or size to be administered, appropriate packaging, clear and accurate labelling information and directions for use.

	Palatability is the overall acceptance of the taste, flavour, smell, dose volume or size and texture of a medicine to be administered in the mouth. Compliance can be highly dependent on palatability. API palatability may influence the choice of dosage form and its design, which may include taste-masking ingredients. The dosage form should, however, not become too attractive to the child (e.g. a sugar-coated tablet that is candy-like) in order not to increase risk of accidental poisoning.
Minimum dosing frequency	Minimal dosing frequency should be attempted. Instructions on the dosing frequency are based on the pharmacokinetic as well as pharmacodynamics properties of the API, but may also be influenced by the design of the dosage form. Frequent dosing may conflict with the lifestyle of older children.
End-user needs	It is important that dosage forms are convenient to produce, as well as affordable. It is also important to bear in mind supply chain considerations such as ease of transportation and storage requirements. Storage in a refrigerator by the user is not always possible. Depending on age and clinical condition of the child, there are restrictions to the applicable dose volume or size. Generally, in developing

	the product, minimum dose volume and size should be attempted. Lack of access to clean water is an important issue to take into consideration in the development of medicines to be dissolved, diluted or dispersed prior to administration, as it may compromise the quality. It may be necessary to educate patients on how to obtain water of suitable quality, e.g. boiling or filtering instructions. Provision of the liquid vehicle as a part of the package may be an option to be considered, or the dose may be dispersed or dissolved in suitable food or beverage prior to administration. Instructions on such use should always be labelled.

Dosage form development for the paediatric population should ensure global application including addressing limitations such as lack of appropriate storage conditions, cost of production and the lack of access to clean water encountered in developing countries. A flexible dosage form platform should also be used to ensure delivery of a wide range of APIs.

1.3. ODTs and Why ODTs for Paediatrics

It is essential to mention orally disintegrating tablets (ODTs) which have been a popular area of research for scientists in the last decade as new 'drug delivery systems' have found to be well accepted by many patients, specifically paediatric as well as geriatric patients (Parkash *et al.*, 2011). Orally disintegrating tablets (ODTs) are drug

formulations, which quickly disintegrate in the mouth and can be absorbed within the buccal cavity. The European Pharmacopoeia places the disintegration time at less than three minutes (Pharmacopoeia, 1998). The different terminologies for ODTs include rapidly disintegrating tablets, orodispersibles, fast dissolving and fast melting tablets. They are also designated as fast melting, fast dispersing, rapid dissolve, rapid melt and/or quick disintegrating tablets. The European Pharmacopeia (EP) approved the term “orodispersible tablet” for those that disintegrate within three minutes or less in the mouth before swallowing. Such tablets disperse into smaller granules, melting from a hard solid to a gel-like structure in the mouth, permitting patients to swallow with ease. The disintegration time (DT) for effective ODTs differs from a few seconds to about a minute.

ODTs are widely viewed, from dosage administration point of view, as intermediates between solid dosage forms and liquid dosage forms. However, they lack the instability that is associated with the liquids and the difficulty in swallowing that is common with regards the solid dosage forms. Swallowing is a major issue for toddlers and children under the age of six. As such, ODTs overcome this disadvantage because they do not need to be swallowed, but rather disintegrate upon introduction into the oral cavity (Thomson *et al.*, 2009). ODTs are also safer than solid dosage forms because they do not have the risk of choking. In addition, they are stable and rarely undergo deterioration, be it physical, microbial or even chemical breakdown. Lastly, the importance of dosage and dose accuracy has been mentioned before. ODTs have the advantage of having dose uniformity because most, if not all come in predetermined doses. Figure 1.2 shows the popularity of ODTs in comparison to other dosage forms such as tablets and liquids. Even though a good segment of the world’s population still prefer tablets and liquids as dosage forms, more people are realizing the benefits of ODTs (Brown, 2003).

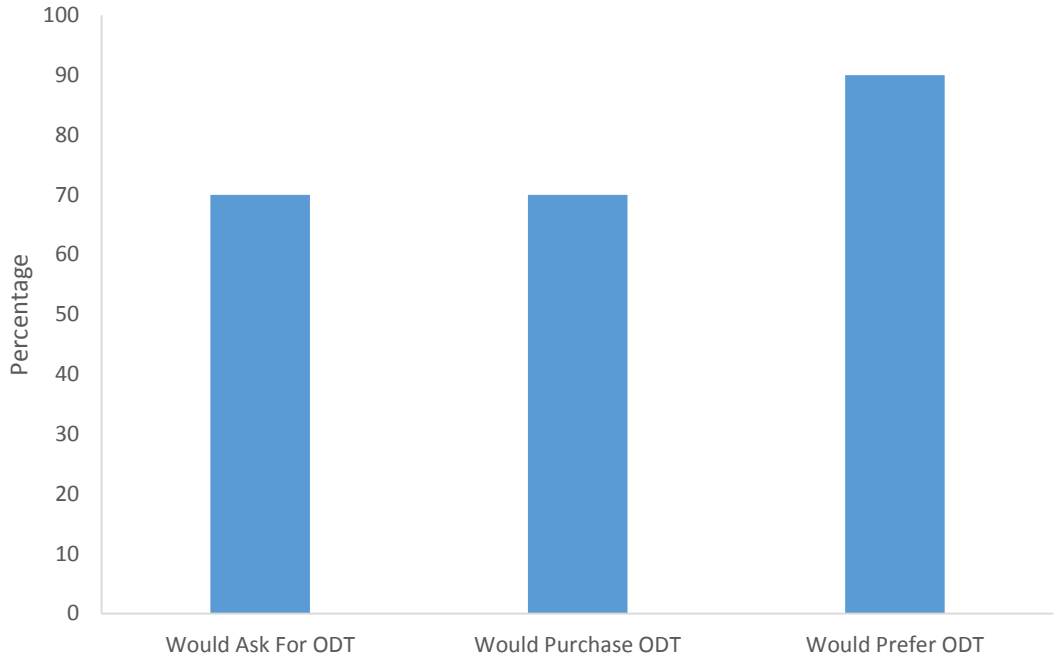


Figure 1.2: Consumer Preferences of ODT to regular tablets or liquids adapted from (Brown, 2003).

Since their inception into the market, the demand and preference for ODTs has been steadily rising. Consequently, the market base for this dosage formulation is also expanding. Analysts project a further increase in the number of consumers who prefer and therefore use ODTs at the expense of other dosage forms, in line with the increase in oral dosage form use in the past seven years (Figure 1.3). Statistics show that half of the population of the patient have a preference for ODTs compared to other dosage forms (Deepak, 2004). Furthermore most patients would request their healthcare professionals for ODTs (70%), buy ODTs (70%), or choose ODTs to standard tablets or liquids (>80%) as shown in (Figure 1.2) (Brown, 2003). (Sastry *et al.*, 2000) carried out a study on dysphagia and stated that "dysphagia is common in about 35% of the population, as well as an additional 30–40% of elderly institutionalized patient's and18–22% of all persons in long-term care facilities." Another study revealed that approximately 50% of the general public experience dysphagia (Seager, 1998). In many developing countries there is lack of supply of pure water and many children die

due to drinking of contaminated water. Moreover, pure water might not be available while patients are outside, away from their home or any shops. In these unavoidable circumstances, the advantages of ODTs are immense and they present a most convenient form of taking a drug. Among all the dosage forms available such as oral tablets, rectal, parental, and nasal or inhalation products, ODTs are undoubtedly the most preferred of dosage form by children (Alyami *et al.*, 2016). Many parents prefer ODTs for their children as the tablets give a good mouth feel when they disperse or dissolve immediately into small particles by means of dissolution in the saliva. According to WHO (Organization, 2010), orally disintegrating dosage forms can be divided into orodispersible tablets, oral lyophilisates, and thin flat films (wafers) as seen in (Figure 1.4).

Figure 1.3: Oral Drug delivery Market Forecast (2009-2016) adapted (Konar and Mukhopadhyay, 2014).

Orodispersible as well as orosoluble dosage forms have a wide range of applications. They provide the necessary benefits of liquid formulations, making it possible for children who cannot consume a complete tablet, to take an ODT. In some situations, particularly for younger children, the ODT may need to be dissolved in a little volume

of liquid prior to administration. Taste masking may be facilitated by the utilization of water-soluble sweeteners in addition to the inclusion of flavours (Fu *et al.*, 2004).

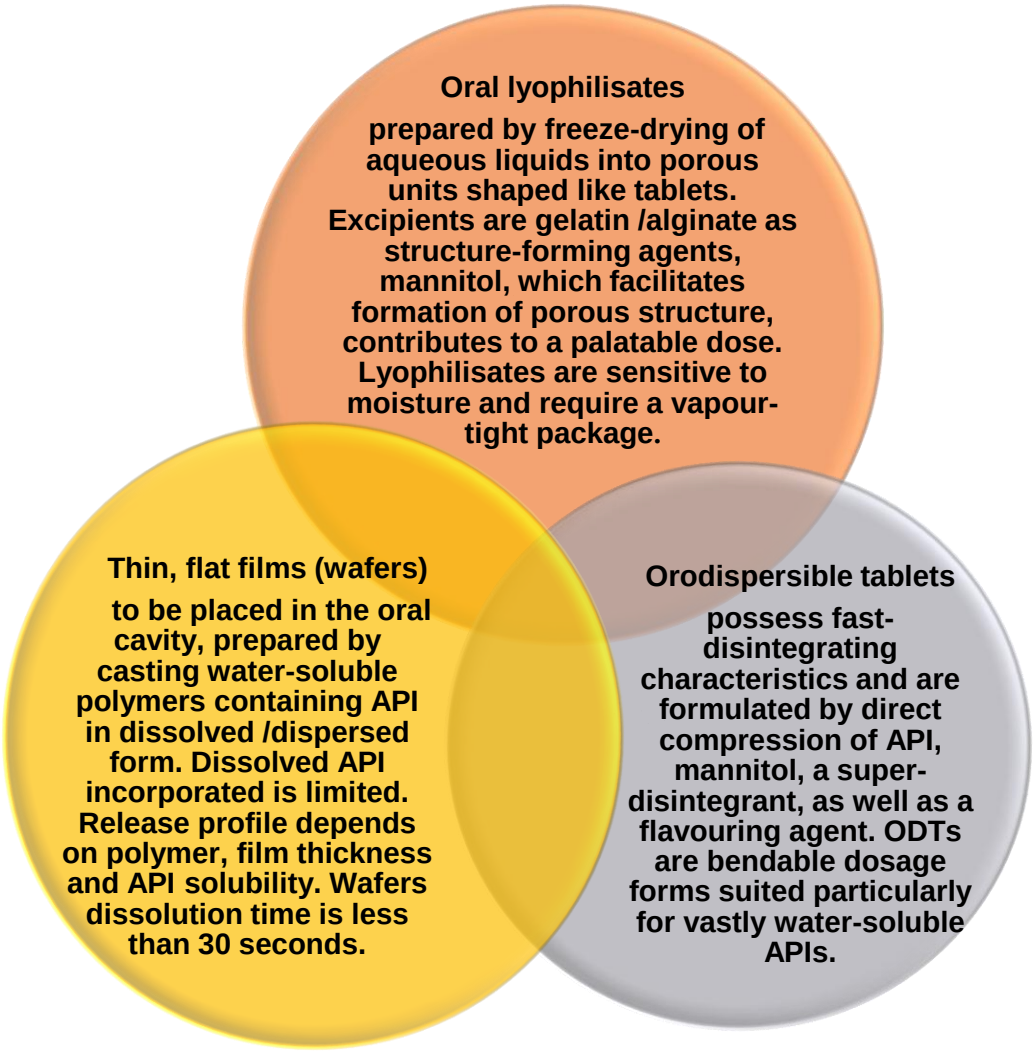


Figure 1.4: Three forms of orally disintegrating dosage forms adapted from (Organization, 2010).

1.3.1. Current status of ODT formulation and future developments

Advancements in the area of ODT formulation are aimed equally at escalating the performance of the dosage form by lessening the disintegration time, and by increasing the compliance of patients via masking the unpleasant taste of the API. These successes require stable improvement of formulation variables, together with

technologies concerned in the manufacture of dosage forms. The inclusion of super-disintegrants to produce efficient ODTs is not new. Conversely, with the development design of innovative techniques, it has become promising to formulate ODTs with less content of super disintegrants and with improved mouth feel (Pahwa and Gupta, 2011). Additionally, the use of dosage forms such as fast dissolving films, chewing gums and micro particles, is anticipated to offer an extremely satisfactory means of delivering drugs too, particularly among paediatric and geriatric patients. The application of techniques such as freeze drying and direct compression is appropriate for formulating dosage forms of vitamins, enzymes and thermo-labile drugs, subsequently these methods do not generate heat. Likewise, significant research towards constructing modified microcrystalline cellulose (MCC) or starch to obtain appropriate forms for direct compression has extensively decreased the product development time for optimizing ODT formulations. Rational excipient use along with technology can ensure the formulation of a satisfactory and efficient ODT, more easily than in the past (Goel *et al.*, 2008).

As ODTs are an excellent dosage form for elderly patients suffering from dysphagia and also diabetes, so, an approach was taken by (Mohapatra *et al.*, 2014) to formulate metformin hydrochloride which is an anti-hyperglycaemic drug as ODTs (Parkash *et al.*, 2011). In their research, key areas of emphasis for ODTs included fast disintegration, taste of active ingredients, drug properties, tablet strength and porosity as well as moisture sensitivity. For production of ODTs, many aspects need to be taken into account such as relevance of powder mixing, mixing powders using dry mixing and granulation, sampling of powder mixtures, simple manufacturing processes and a systematic selection of excipients. Direct compression is an easy, cheap and convenient method to manufacture ODTs. This method requires only two stages in the manufacturing process that is, blending and mixing of APIs and excipients, followed by compression. Efficient mixing is a very essential and an important step, in order to

generate ODTs with high efficacy and fast disintegration in the mouth within few seconds.

1.3.2. Formulation of ODTs

Desirable characteristics of ODTs include their disintegration in the oral cavity without water, and the conversion of this disintegrated tablet into a soft paste or liquid suspension, which gives an excellent mouth feel in addition to ease of swallowing. The popularity of ODTs has given rise to various ODT manufacturing technologies, which are based on lyophilisation (freeze drying), moulding, sublimation and compaction, together with advances to increase the ODT's characteristics—for example, spray drying, moisture treatment and sintering, in addition to use of sugar-based disintegrants (Douroumis, 2007, AlHusban *et al.*, 2010). Experimental measurements of disintegration times and clinical studies are also carried out to formulate and develop an efficient ODT.

Furthermore, during ODT development, the features of the drug such as, solubility, crystal morphology, size of particle, hygroscopicity, compressibility as well as bulk density of a drug can significantly affect the tablet's characteristics, such as tablet strength and disintegration time. It is also necessary to optimise tablet porosity to ensure quick water absorption, for which elevated wettability of excipients as well as high porous tablet network structures are necessary. Tablet strength is directly connected with compression pressure, as porosity is inversely associated with compression pressure. It is very important to strike a balance between porosity (with the intention of fast water absorption) and enhanced mechanical strength. Low sensitivity to humidity is also a necessary condition for excipients used in ODTs. This requirement is challenging, as water-soluble excipients are often utilized in the formulation of ODTs.

1.3.3. Methods to formulate ODTs

Different formulation processes have been used to develop fast-dissolving tablets. These processes are summarized in (Table 1.4).

Table 1.4: Processes employed in the manufacture of ODTs (Bandari *et al.*, 2014).

Procedures	Description
Freeze drying	In the process of freeze drying (lyophilisation), the solvent is separated from a frozen drug solution or a suspension comprising structure-forming excipients. Tablets generated are especially light as well as having highly porous structures to permit rapid dissolution/ disintegration. When the dosage form is taken, the freeze-dried unit dissolves immediately to free the incorporated drug. The freeze-drying procedure might result in glassy amorphous structure of excipients as well as of the drug substance, which leads to improved dissolution rates. Disadvantages are that the process is expensive, and at higher temperatures and humidity, the stability of ODTs is poor.
Moulding	The core material of moulded tablets is usually water-soluble polymers. The powder mixture is moistened with a solvent (generally ethanol or water), then moulded into tablets under pressures less than those utilized in conventional tablet compression. This is recognized as compression moulding. The solvent can be separated by air drying. As moulded tablets are often compressed at a lesser pressure than other compressed tablets, a superior porous structure is formed to improve the dissolution. To obtain a better dissolution rate, the powder blend typically must be passed through a fine screen.

Compaction	Granulation methods include wet granulation, dry granulation, melts granulation, spray drying. Direct compression disintegrants and inorganic excipients used in ODTs. Compaction and ensuing treatments: sublimation, humidity treatment, sintering. Among these, direct compression is featured extensively as the objective of this project is to utilize the technique of direct compression to develop and produce ODTs.

However, the easiest and most convenient way to manufacture ODTs is using direct compression.

1.3.4. Direct compression technique

Direct compression is the cheapest and simplest procedure for manufacturing tablets, as conventional machineries and common excipients can be used by pharmaceutical companies. Direct compression is the common technique for the production of tablets, including tablets containing thermo-labile and moisture-sensitive drugs. This procedure can easily be used to produce ODTs by selecting a potential combination of ingredients that will allow fast disintegration combined with good physical resistance. Generally, sugar-based ingredients are used commonly as bulking agents for various reasons, such as extensive aqueous solubility, sweetness, pleasant mouth feeling and effective taste masking (Chang *et al.*, 2000). A flow chart outlining the steps of direct compression is shown in (Figure 1.5).

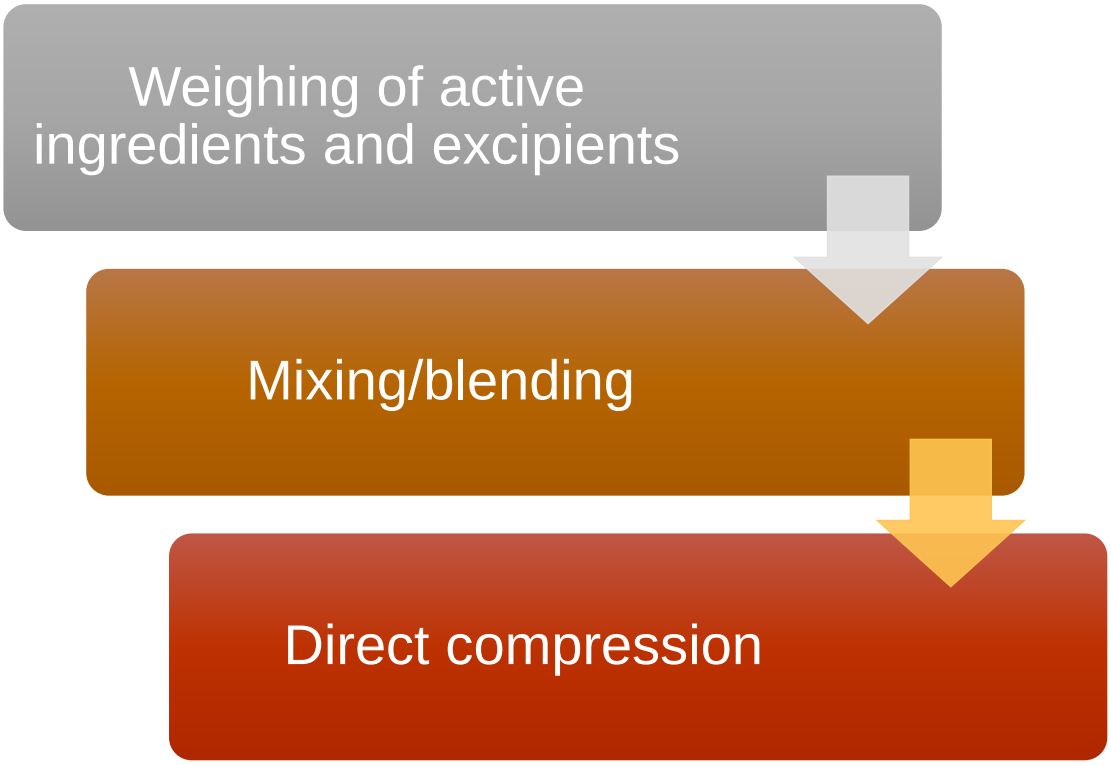


Figure 1.5: Stages involved in the production of ODTs using direct compression.

1.3.5. Compression and preparation of orally disintegrating particulates (ODPs)

Multiparticulate dosage forms consisting of pellets and granules are gaining increasing attention as an optional oral drug delivery system known as particulate unit dosage forms and ranging in size from about 0.05–2.0 mm (Dey *et al.*, 2008). Pellets can be generated by utilizing diverse methods in accordance to the appliance as well as manufacturer's choice (Chamsai and Sriamornsak, 2013). The most extensively used techniques for pelletization include extrusion/spheronization, solution or suspension layering and powder layering. Of the procedures used, extrusion/spheronization is the most preferred (Ghebre-Sellassie, 1989). Multiparticulates as a tool provide the flexibility to expand dosage form and administration options for paediatric populations (Figure 1.6).

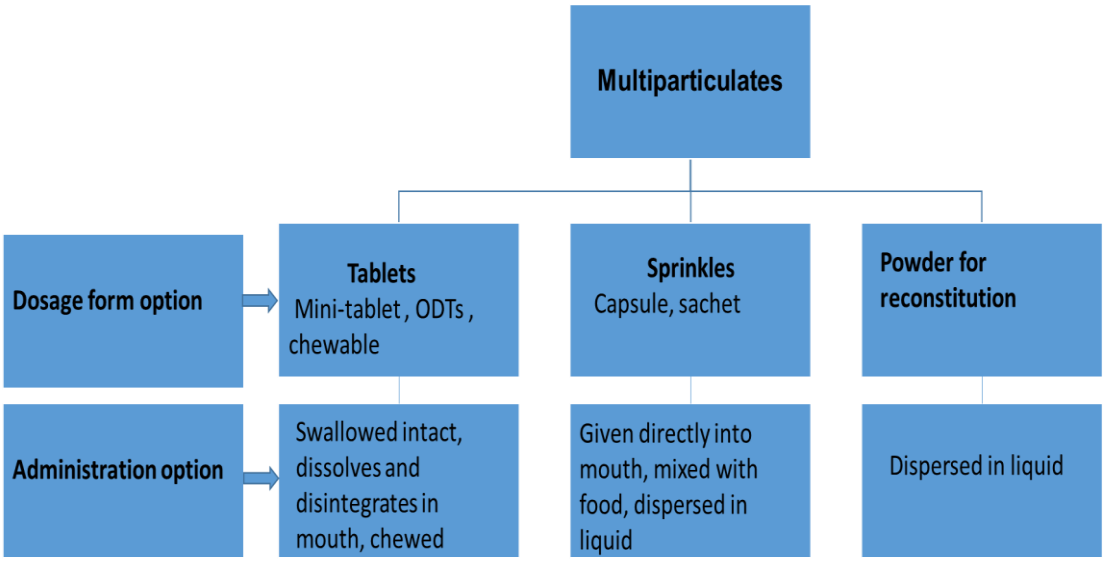


Figure 1.6: Versatility of multiparticulates with reference to formulation and method of administration, adapted (Stoltenberg *et al.*, 2010).

1.3.6. Excipients Used in Direct Compression

In the direct compression method, different excipients are used for different purposes.

Some of the commonly used excipients are listed in (Table 1.5).

Table 1.5: List of excipients used in direct compression (Gupta *et al.*, 2012).

Function of excipients	Commonly used examples
Diluents	Lactose monohydrate, anhydrous lactose, microcrystalline cellulose, partly pregelatinised starch, mannitol, dibasic calcium phosphate (anhydrous & dihydrate)
Disintegrant	Croscarmellose sodium, sodium starch glycolate, crospovidone, partly pregelatinised starch, low substituted hydroxypropyl cellulose

Lubricant	Magnesium stearate, calcium stearate, sodium stearyl fumarate, stearic acid
Stabiliser	Buffers such as sodium carbonate and citric acid. Antioxidants such as butylated hydroxyanisole and butylated hydroxytoluene
Surfactants	Sodium lauryl sulphate, polysorbates

1.3.7. Inorganic Excipients Used in ODTs

Tablet disintegration is directly proportional to the quantity of the disintegrant and insoluble excipients. Disintegration is furthermore dependent on the relative weight ratio amongst the water insoluble and soluble excipients, when water-soluble ingredients are utilized (Hirani *et al.*, 2009). Research by Dobetti (2003) produced a formulation using insoluble inorganic excipients as the key ingredients of ODTs. It was obvious from their formulations that sufficient compression could be exerted to generate tablets with hard tensile strength in addition to low friability. Rate of disintegration was not significantly influenced by elevated compression force. In the formulation, the main excipients used were:

- Water insoluble components consisting of insoluble excipients, water-insoluble drugs (coated or uncoated) and water- insoluble lubricant together with a glidant. The excipients consisted of insoluble inorganic salts (such as di- or tri-calcium phosphate) or organic fillers (such as microcrystalline cellulose).
- Significantly soluble excipients consisted of compressible sugars, flavouring agents, sweeteners, binders as well as surfactants.

- Disintegrants consisted of maize or modified starch, cross-linked PVP (polyvinylpyrrolidone) or sodium carboxy-methylcellulose.

Disintegration time was enhanced as the amount of insoluble components was lessened. If the API was a low dose drug, disintegration time could be elevated by including insoluble fillers (such as microcrystalline cellulose and silicon dioxide) or by increasing quantity of insoluble inorganic excipients (such as dibasic calcium phosphate) (Fu *et al.*, 2004).

1.4. Significance of powder mixing

Mixing of dry powders is an important area of research because of its wide application in the food, as well as the pharmaceutical industry. This is because unproductive (non-uniform) mixing procedures can lead to a non-homogenous mixture which gives rise to variation in API content within a single dosage form (Bridgwater, 1976). In pharmaceutical operations, mixing is an important procedure and it is essential to understand the different types of mixing processes and their advantages and disadvantages.

In order to avoid variation in flowability of the powder mixture, segregation needs to be monitored by controlling particle size of the API as well as excipients. It is also essential to use the correct mixing apparatus and mixing technique. Pilot studies can be carried out to investigate whether agglomeration is taking place due to fine particles, volume of low meting point solid content and moisture content leading, to softening of particles (Portillo, 2008). Table 1.6 summarizes the parameters which need to be considered for efficient mixing, these include physical properties of powder, and type of mixing.

Table 1.6: Factors to consider efficient powder mixing adapted (Jallo *et al.*, 2012).

Physical properties of powder
Components parameters pertinent to particle size
Shape and size distribution
Density, hardness and cohesivity
Nature of the powder
Particle charge
Factors of mixing equipment
Speed, processing time and load
Type of mixing equipment
Tumbling mixers
Agitator mixers
V-blenders
Double-cone mixers

1.4.1. Types of powder mixing

Mixing identifies a procedure where two or more components, which are either separated or are in a randomly oriented direction with each other, are treated in a way that the particles come close to one another at equal proportion (Çelik, 2016). Depending on the flow characteristics of powders, solids are divided into cohesive and non-cohesive materials. Due to the operation of the cohesive forces between the surfaces of the particles, powders which exhibit high degree of attraction either due to small particle size or shape present significant barriers in powder blending leading to the formation of aggregates.

Table 1.7 lists the different types of powder mixing including ordered mixing, geometric mixing, shear mixing, dry mixing, convective mixing and macro mixing.

Table 1.7: Different types of mixing process and their description adapted from (Bhatt and Agrawal, 2008, Deveswaran *et al.*, 2009).

Mixing process	Description
Convective or macro mixing	Mixing technique in which groups of particles are transferred from one region of a powder bed into another part.
Shear mixing	Shear forces are generated in the materials by utilizing an agitator arm or a gust of air.
Diffusive or micro mixing	The material is subjected to gravitational forces that cause the upper layers to slide, and diffusion of each particle occurs above newly developed surfaces.
Geometric mixing	With this method, a homogenous mixture is achieved. The smallest amount of active ingredient is mixed methodically with an equivalent amount of the other component. In other words, it is a method in which two components of unequal quantities are mixed where the procedure is started with the smallest quantity.
Ordered mixing	When one of the components that is added is a fine, micronized powder, the combination with the larger components (larger particle size) results in adsorption of the micronized particles to the surface of the active sites where they are

	attached due to weak forces (Van der Waals forces). Ordered mixing is generated via mechanical adhesion, such that the ordered entity will be the smallest model of the mix and will be as close in composition to other ordered entities in the mix.

1.4.2. Sampling of powder mixtures

Information on the particle size distribution (PSD) of powder blends is a prerequisite for most industrialised processes, including the manufacture of pharmaceutical and biopharmaceutical products. Results of particle size investigations are most appropriate when samples taken are representative; more so when suitable dispersion methods are utilized. The common variation in particle sizing measurements can be traced to incorrect sampling or sample preparation. When determining PSD of powdered solids, results will be of minimal value, unless and until the analytical sample represents the bulk from which the sample was taken. There are challenges associated with sampling of pharmaceutical mixtures. Accurate characterization of granular mixtures is sometimes not possible due to the complexity of the system and the lack of standard sampling techniques which represent the bulk of the total powder under investigation (Muzzio *et al.*, 2003). For most pharmaceuticals, particularly powders, various factors should be considered when planning a sampling method. These factors consist of: the characteristic of the collection powder from where the sample is taken, sampling cost as well as associated assays, expediency and degree of precision. The following factors need to be taken into consideration when developing, or adapting a sampling process:

- Powder quantity from which samples are to be acquired
- Sample amount required
- Characteristics of powder consisting of flow behaviour, shape of particle, tendency to separate and surface chemistry
- Mechanical strength such as friability

Sampling can be dynamic and static. A summary of sampling techniques and their advantages as well as disadvantages are shown in the (Table 1.8).

Table 1.8: Summary of devices used in sampling and their advantages and limitations (Allen, 2003).

Device	Advantages	Disadvantages
Cone and Quartering	Good for powders with poor flow characteristics	Operator-dependent
Scoop Sampling	Reliable for homogenous and non-flowing powders	Particle segregation in non-flowing powders
Table Sampling	Able to separate large quantity of material	Very dependent on initial feed
Chute Splitting	Can reduce powder sample	Operator bias by 50% in one pass
Spin Riffling	Reliable for free flowing powder samples	Not efficient at handling large samples of powder

As it is not possible to test the complete powder mixture, it is necessary to take sufficient quantities and numbers of samples randomly, to make sure that it represents the whole powder bulk. This can be carried out by utilizing a powder thief (Muzzio et al., 2003). A powder thief is an apparatus particularly designed for taking out definite sample amounts from a powder batch. A powder thief has more than one cavity engraved in a hollow cylinder which can be opened as well as closed in a controlled fashion by an external rotation or else pulled down sleeve (Muzzio *et al.*, 1997) . The

powder thief is placed into the powder with closed cavities. When insertion is done, cavities are opened and powder runs into the cavities, which can be closed so that powder thief is taken out from the powder bed. For arbitrary sampling utilizing a powder thief, the idea is that all particles in the powder mixtures should have an equivalent possibility of being selected for homogeneity testing.

1.5. Functionalised particles using dry powder coating

Dry coating is a pioneering technique in which fine particles are mechanically coated onto the surface of larger carrier particles to impart useful properties to the final product, which are engineered particles. In dry particle coating, “guest” particles are brought in contact with “host” particles by means of mechanical forces (Figure 1.7). Due to the high number of clashes between the particles, guest particles are coated on the surface of host particles as the Van der Waal’s forces are principal in creating a strong adhesive bond between the host and guest particles, which results in the formation of value added and engineered composites. Therefore, dry particle coating is used to deposit a very small amount of functionalised particles with high degree of precision onto drug or excipient particles in order to improve their flow and other properties (Honda *et al.*, 1994).

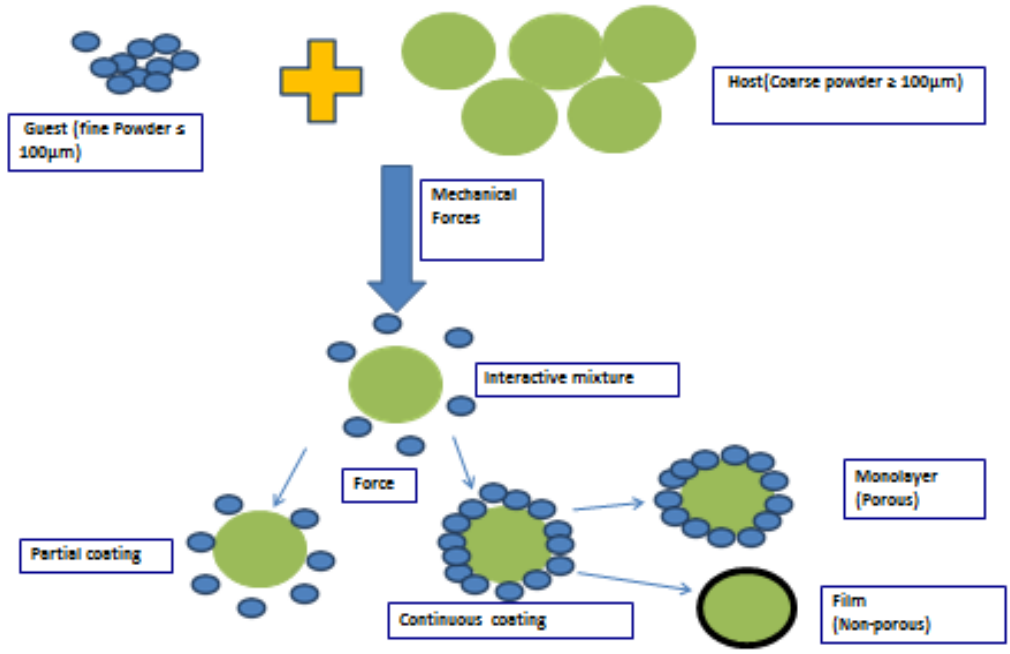


Figure 1.7: Schematic overview of coating process technique, the inner part is the coarse carrier particle (host) and the outer is particles of the cohesive fine particles (guest) adapted (Alonso *et al.*, 1990).

1.6. Role of Moisture Content

The levels of moisture associated with solids may significantly affect the physical, chemical and mechanical properties of APIs and excipients. Moisture content is an important factor during the development of an ideal composition for solid dosage forms as well as during the upscaling process (Stubberud *et al.*, 1995). Properties such as flow, compaction, disintegration, hardness and porosity are highly sensitive to the amount of moisture present. The amount of water present, where it is located and how it is distributed within the powder/dosage form, are all crucial factors that should be addressed to allow users to control the performance of the powder during processing (Faqih *et al.*, 2007). In addition, water interacts with pharmaceutical solids at essentially all stages of manufacture. Therefore, water–powder interaction is a key factor in the formulation process, and performance of the final solid dosage form.

The amount of water associated with a solid at a particular relative humidity (RH) and temperature is based on its chemical affinity for the solid, the number of available sites for interaction, surface area and nature of the material (Dawoodbhai and Rhodes, 1989). For example, nonporous talc has low equilibrium moisture content (EMC); on the contrary, organic sugars, polymers consisting of hydrogen bonding and crystalline hydrates, have high EMCs. In a dry atmosphere, the water will be comparatively tightly bound as a non-freely movable layer, which sometimes is represented as a monolayer of adsorbed moisture (York, 1981), whereas, at higher RH (>80%), multilayer adsorption occurs and the water becomes more moveable and may be present as condensed water (Nokhodchi, 2005).

On this issue, (Nokhodchi *et al.*, 1996) and his team studied the increase in polymer chain mobility associated with the presence of internally absorbed water, known as the plasticizing effect. This occurrence should adversely affect powder flowability due to the increase in particle cohesive and adhesive forces; but on the other hand, should have a positive effect on particles consolidation under compression. For externally adsorbed water, the effect on the technological parameters is evidently influenced by its amount. Thus, lower percentages of water adsorbed on the particles can have a very positive effect on powder flowability and compression, due to its lubricating effect which improves the particles slippage by removal of micro irregularities on the particle surface, and electrostatic charge. Nonetheless, if the adsorbed water content increases, the formation of agglomerates due to the presence of liquid bridges could clearly worsen flow properties of the solid. As for compression, this increased cohesion could promote the formation of interparticulate bonds under pressure, as a result, if the presence of water absorbed is excessively high, the hydrodynamic effect must significantly limit the compressibility of particles (Bravo-Osuna *et al.*, 2007).

1.7. Research aims and objectives

The overarching aim of this thesis is to design the development of novel oral dosage forms for the paediatric patient population. The content in this thesis will cover the following main paediatric challenges/gaps in the knowledge:-

1- To identify children's experience of taking medicines and the child's preferences/opinions for oral dosage forms, in particular ODTs (Chapter 2).

2- To investigate healthcare professionals perceptions or opinions regarding the use of different dosage forms for paediatric use (Chapter 3).

3- To develop pre-blend for potent model low dose drug using various blending techniques (Chapter 4).

4- To optimise and characterise ODT pre-blend of excipients for direct compression (Chapter 5).

5- To study the role of moisture content on micro/macro properties of paediatric pharmaceutical excipients (Chapter 6).

Further details of the aims and objectives of each chapter are discussed at the beginning of each chapter.

Chapter 2

Dosage form preference consultation study in children and young adults: Paving the way for patient-centred and patient-informed dosage form development

Publications relating to chapter 2

Hamad Alyami, Eman Dahmash, Fahad Alyami, Dania Dahmash, Chi Huynh, David Terry and Afzal R Mohammed (2016). Dosage form preference consultation study in children and young adults: paving the way for patient-centred and patient-informed dosage form development. European Journal of Hospital Pharmacy: ejhpharm-2016-001023.

2.1. Introduction

Paediatric drug administration has gained significant attention over the last 5-7 years. Pharmacists and other healthcare professionals in the pharmaceutical industry face a myriad of challenges regarding the appropriate choice of the dosage forms for drug administration to this important target population (Gauthier and Cardot, 2011). For this reason, the common trend has been the manipulation of adult dosage forms into a form that can be administered easily to children and young people. However, existing knowledge in this field is limited, making it difficult to identify viable solutions. The European Regulation on medicinal products (Committee for Medicinal Products for Human Use, 2006) stipulates that all formulations produced for young people should include safety measures such as assessment of excipient toxicity, appropriate delivery system capable of offering dose flexibility and should generally be acceptable to the target population.

The term paediatric dosage forms need to suffice for a wide age range including neonates to adolescents (0-16 years). The common oral paediatric dosage forms in use are: solid dosage forms (such as tablets), powders, solutions, and syrups (Viner and Barker, 2005). For oral paediatric medicines to be acceptable to young patients, there are a number of factors that need to be considered, especially elegance and palatability. Elegance refers to the outward appearance of the dosage form and its appeal to the end user. This may be particularly important for children and their adherence to medication regimens (Committee for Medicinal Products for Human Use, 2006) .Palatability is closely related to elegance and is a factor related to acceptability. Children will rarely take drugs that are bitter in taste (Hoppu, 2008) .Therefore, any active ingredients with a bitter taste are often coated with a sweet tasting substance. If the unacceptable taste is not masked, such drugs may predispose the child to reject

the medicine. If the smell of the drug is unpleasant, it may also negatively influence the acceptability of the drug. The term convenience refers to the method by which it is administered, for instance, as a tablet, syrup or as a powder. Oral liquid drug preparations, including solutions, syrups, emulsion and suspension, are considered as the most suitable oral formulation for children, since they are developed for younger new-borns unable to swallow tablets and accommodate palatability and dose adjustment changes required by children (Nahata, 1999, Salunke *et al.*, 2011).

Nonetheless, liquid formulations present several drawbacks, such as low stability, difficulties in taste masking, inappropriate excipients for children (e.g. propylene glycol, benzyl alcohol,) and low transportability (Committee for Medicinal Products for Human Use, 2006, Hoppu *et al.*, 2012). WHO recognises the need to develop drugs and formulations that specifically target children. According to WHO, the dosage form should be both acceptable and palatable (Kristensen, 2012). Furthermore, whenever possible the drug formulation should be palatable without the need to further mask the taste. Dosage form acceptability, which encapsulates a multitude of factors including preference, palatability, presentation and ease of use, has a significant influence on paediatric patient compliance (Committee for Medicinal Products for Human Use, 2006). Orally disintegrating tablets (ODTs) may increase bioavailability and faster onset of action in adults and children, since dispersion in saliva in oral cavity causes pregastric absorption from some water-soluble actives. Taste and flavour together primarily determine the acceptability of ODTs (Virley and Yarwood, 1990). Any pregastric absorption avoids first-pass metabolism and can be of a great advantage in drugs that undergo extensive hepatic metabolism. The study described in this chapter was designed with two key objectives: (1) to evaluate dosage form preferences for a wide range of formulations (liquids, injections, suppositories, solid dosage forms, and patches) among children and young adults who have a history of taking medicines. The study was conducted in three regions (the UK, Saudi Arabia and Jordan) at five

different centres. These were Birmingham Children's Hospital (the UK), Nottingham Children's Hospital (the UK), Najran Maternity and Children Hospital (Saudi Arabia), General Thar Hospital (Saudi Arabia) and Speciality Hospital (Jordan). Countries were chosen based on diverse geographical regions and ethnic mix, ease of access to suitable subjects, lack of published data regarding children preferences of dosage forms. In addition; (2) the study would provide pragmatic and translatable outcomes to support formulating stable and acceptable dosage forms. It is recognised that commonly prescribed liquid formulations used in hot and humid Middle Eastern countries can present significant stability issues (Spomer *et al.*, 2012). A suitable method to collect and understand a stance to a hypothesis is a Questionnaire (Powell and Renner, 2013).

2.2. Materials and Methods

2.2.1. Materials

Microcrystalline cellulose (Avicel PH-102 NF) was purchased from FMC BioPolymer (Philadelphia, USA). D-mannitol and magnesium stearate were obtained from Sigma-Aldrich Company (Pool, UK). Paracetamol 500mg tablets were purchased from a local pharmacy.

2.2.2. Methods

2.2.2.1. Study Design

Multi-national, 5 sites, participant-supported questionnaire of children aged (6 to 18 years) following a demonstration of orally disintegrating tablets. The questionnaire was conducted in both English and Arabic languages.

2.2.2.2. Preparation of direct compression ODTs placebos based on 40% of microcrystalline cellulose (MCC)

Placebo orally disintegrating tablet (ODTs) with various sizes (200, 350 and 500mg) were prepared using the direct compression method. Based on a previous study carried out in our laboratory, powder blend made of 40% w/w microcrystalline, 59% w/w mannitol, and 1%w/w of magnesium stearate was compressed at 2 tonnes using a Specac auto tablet press (Slough, UK). ODTs were assessed for *in vitro* disintegration time using USP <701> method (USP-29, 2009) via ERWEKA 2T3 (ERWEKA GmbH). The prepared tablets were evaluated for disintegration characteristics. All the measurements were conducted three times and presented as (mean ± standard deviation).

2.2.2.3. *In vitro* disintegration study of the tablets

Disintegration time is the time necessary for ODTs to disintegrate completely without solid residue. *In vitro* disintegration time for ODTs was assessed with the help of US pharmacopoeia monograph (<701> disintegration). In this study, Erweka ZT3, Appartebau, GMBH was used as disintegration apparatus as well as distilled water as disintegration medium which was maintained at a temperature of 37^0C by thermostat. Time necessary for entire tablet disintegration was calculated using a stopwatch. The plastic disk as well as basket rack assembly were washed and dried properly after every measurement. All the measurements were conducted three times and presented as (mean ± standard deviation) (Table 2.1).

Table 2.1: The disintegration time of ODTs placebo at different sizes (n=3).

Size (mg)	Disintegration time (Seconds)
200	12± 0.541
350	17± 0.783
500	21± 0.642

2.2.2.4. The Questionnaire

The questionnaire was developed by an iterative process between the study team and paediatric based healthcare professionals. The final questionnaire consisted of four sections. These were: demographic and educational data including gender, age, and education; participant experience of taking medicines and their preferences for various oral dosage forms (liquids, tablets, capsules and ODTs); preference for colour, shape, size, thickness, taste, flavour and disintegration time of tablets; participant feedback about the questionnaire.

2.2.2.5. Ethical approval

The study was conducted at five centres; in England (2 hospitals), Saudi Arabia (2 hospitals) and Jordan (1 hospital). Birmingham Children's Hospital Research and

Development provided the necessary research governance approval. The Pharmacy Academic Practice Unit at the Birmingham Children's Hospital oversaw the study. Consultation centres in Saudi Arabia and Jordan received a copy of the approved letter for the study.

2.2.2.6. Exclusion criteria and some challenges

Exclusion criteria included:

- Under 6 years of age
- Over 18 years of age
- Perceived difficulty in age appropriate communication (e.g. the capacity to understand and responding to the questionnaire questions)
- No history of taking any medication (i.e. not for a chronic disease)

2.2.2.7. Statistical analysis

Participant responses were entered into MS Excel 2007 for analysis. The chi - square test was used to examine the independence in the data that was collected. The level of significance was chosen to be 0.05. Two-way analysis of variance (ANOVA) was used to compare data per age groups and per gender. Statistical analysis was performed using Graph Pad Prism software.

2.3. Results and discussion

2.3.1. Results obtained from agenda design

A total of 104 questionnaires (study cohort n=120, response rate 87%) were completed to determine the preference for pharmaceutical dosage forms in the study population. A presentation concerning the different dosage forms was delivered to the participants in an open-forum style, prior to completion of the questionnaire. This allowed for both proactive and interactive contribution from the participants. The participants were allowed to ask questions concerning dosage formulations. The questionnaire was shown in (appendix 1). The agenda of the study was to determine the opinion of children on different aspects of paediatric medication. Seven different events were allocated for the time stipulated with each event accorded time, according to its relevance and importance. After obtaining the feedback, the participants were engaged in an interactive platform in which they were given the chance to voice their opinion on areas that could be improved with regard to orally disintegrating tablets and the study itself. This session lasted for ten minutes. The last event of the day was to thank the participants and to appreciate their input (Appendix 2).

The slide presentation for orally disintegrating tablets was presented to the participants to describe what ODTs are and their use. It was meant to bring out clearly the topic of study so that participants do not confuse or mix up the topic of study and other dosage formulations. The presentation was prepared prior to the event. This allowed for both proactive and interactive contribution by the participants. Every so often, the slides were paused and questions posed to find out if the participants were following the proceedings. In addition, the participants were allowed to ask questions and for clarifications in areas that they felt were vague or simply needed more information. They were also allowed to give their opinion about each slide and to contribute by

giving any additional information that they thought was not relevant to the presentation but was included. Generally, the event was made more of an open forum than an interview process. The opportunity presented to the participants to ask questions was a commendable idea. Most of the participants had little information on the details of composition of drugs and disintegration time. Therefore, the chance to ask questions came with numerous benefits with regard to the study. Questions regarding the composition of medicines were the most common. With every answer provided, it appeared as if a new question would pop up from the answer. For example, when explaining that orally disintegrating tablets are made of a combination of excipients and active pharmaceutical ingredients, a new question arose on taste. For instance, why some drugs tasted sweet, whereas others were bitter. The question of disintegration time of orally disintegrating tablets also arose. The difference in flavour and taste of tablets was also questioned. To improve their understanding of how drugs are produced and how their effects on the target population are measured, the participants were given a practical demonstration of the difference between immediate release tablets and ODT placebo. They were made to understand that placebos provided the basis of understanding the medication needs of the target population and that they were important as control measures in drug design and manufacture. They were also informed of the importance of placebo in the research for new drugs and better treatment methods. The interactive and proactive forum led to the desire of the participants to want to witness the actual processes involved in drug making and drug testing. The UK participants requested to be permitted to visit the laboratories to get a first person account of what drug manufacture involved. Drug design and manufacture goes beyond the basic principles of producing drugs with the best therapeutic profile. It also involves the manufacture of drugs whose taste is acceptable to the target age group, in this case the paediatric population. Drugs, which are not palatable, have lower acceptability. For this reason, the taste may be masked or the drug flavoured to

'conceal' the bad taste. Flavouring involves adding substances that give the drug a characteristic taste and smell, different from that of the actual drug (EMA, 2006). Taste addiction is a situation in which the patient develops a liking for the taste of the drug and feels an urge to take the drug often. Whereas this is beneficial because it gives a solution to the question of acceptability, it may result in grave consequences such as abuse of the drug. Care should be taken to avert this. The flavouring is important because it tailors the taste and smell of the drug to the convenience of the target age group. Previous results obtained from research studies on the popular flavours aid in developing drugs with specific flavours and which suit the needs of the target age group (Noble, 1996, Levitan *et al.*, 2008)

2.3.2. Questionnaire results

2.3.2.1. Demographic and educational background of participants

The current study explores the preference of children not only for the route of administration of medicines but also investigates the preferred oral dosage form. This study for the first time also incorporates elements of pharmaceutical development attributes that should be taken on board when developing medicines for children. Table 2.2 summarises the demographic characteristics of participants. It gives the breakdown of their gender, age and educational level.

Table 2.2: Demographic characteristics of participants.

Characteristics		UK N=29 (%)	Saudi Arabia N=41 (%)	Jordan N=34 (%)	Total N=104 (%)	P value
Gender	Male	8 (27.6%)	26(63.4%)	18(52.9%)	52(50%)	>0.05**
	Female	21(72.4%)	15(36.6%)	16(47.0%)	52(50%)	
Age in years	6-8	0 (0%)	7(17.0%)	10(29.4%)	17(16.3%)	p>0.05 for age group p=0.001 for regions)*
	9-11	4 (13.8%)	14(34.2%)	14(41.2%)	32(30.8%)	
	12-14	8 (27.6%)	12(29.3%)	10(29.4%)	30(28.8%)	
	15-18	17(58.6%)	8(19.5%)	0 (0%)	25(24%)	
Educational level	School	20(69%)	40(97.6%)	34(100%)	94(90.4%)	0.0001**
	Higher education	9 (31%)	0 (0%)	0 (0%)	9 (8.7%)	
	Working	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
	Other	0 (0%)	1(2.4%)	0 (0%)	1(0.9%)	
*Two way- ANOVA **Chi-Square						

Figure 2.1 shows the gender distribution according to age group. Data analysis showed that there was no significant difference between the number of male and female participants (P> 0.05).

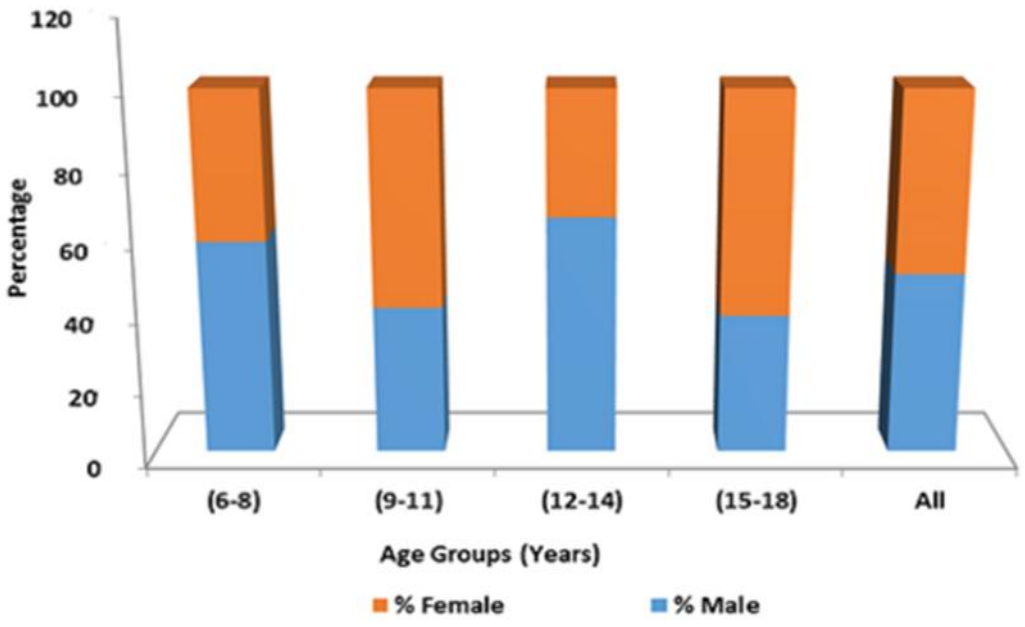


Figure 2.1: Gender distribution according to age groups for all regions.

In Figure 2.2 the educational level of the participants across the three regions is shown. Jordan had the highest percentage of participants who had basic education (100%). This was followed by Saudi Arabia and the United Kingdom which had 97 percent and 68 % respectively. Data analysis shows that the difference is significant as the p-value is <0.05.

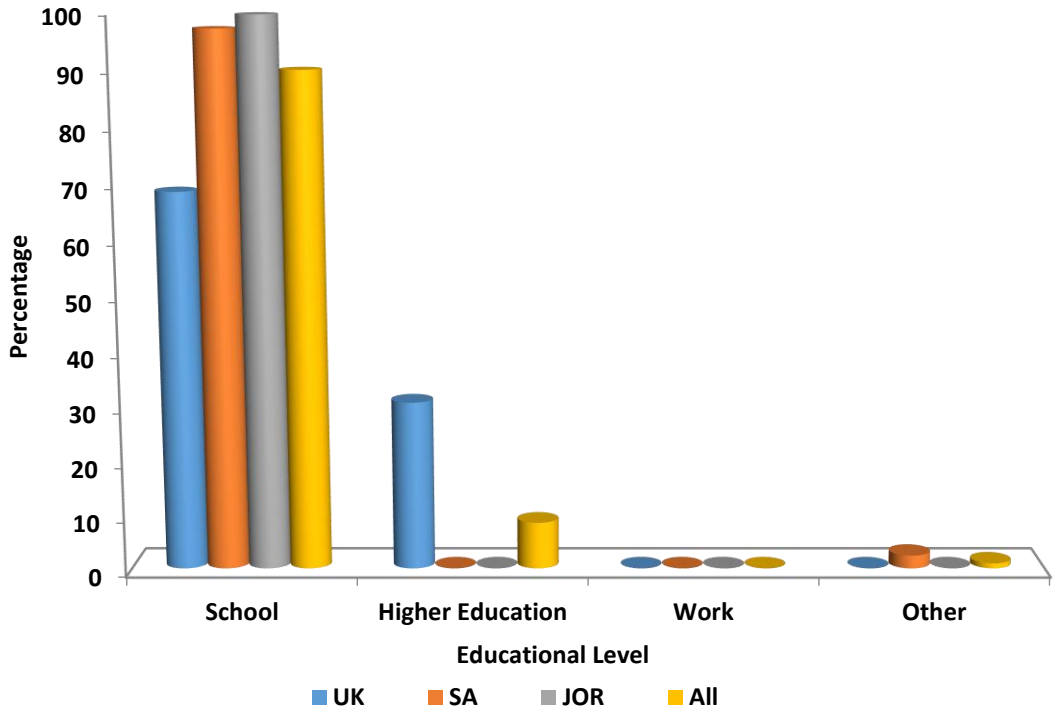


Figure 2.2: Distribution of participants according to their educational level per region.

2.3.2.2. Experience of taking medicines and preferred dosage forms

This section involves the analysis of the responses of the participants on their frequency of taking medicines. Females had the highest frequency of taking daily medicines (28.6%). On a weekly and monthly basis, the male participants recorded a higher frequency of taking medicine than females (27% and 31% respectively) (Figure 2.3).

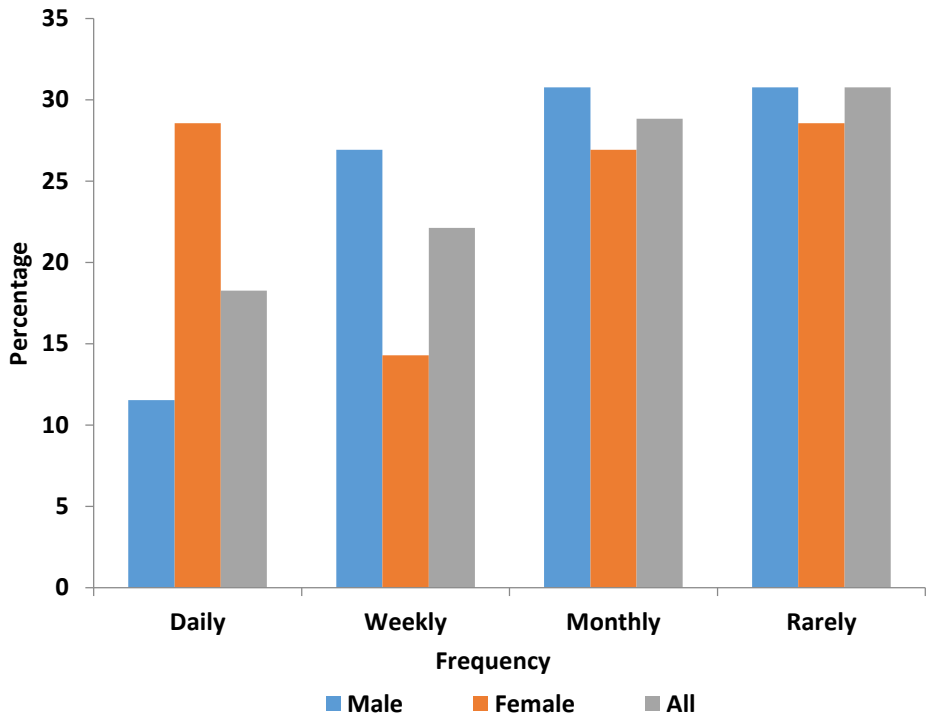


Figure 2.3: Distribution of the frequency in taking medicines for all regions according to gender.

Figure 2.4 demonstrates that oral route and in particular tablets were more popular across both genders compared to liquids, capsules, powders and other dosage forms. Furthermore, male participants (54%) registered their preference for tablets as compared to the female participants. In order to explore further their preference for oral route, the participants were asked for their preferred oral dosage forms. Alhaddad et al (2014) used a cross- sectional study design and validated questionnaires were distributed to the people who were above the age of 18 years through face to face interviews. They found tablets (69.6%) and capsules (37.6%) represented the highest preferred dosage forms. Therefore, it was concluded that prescribers should prescribe to patients their preferred dosage forms to improve medication adherence, and hence improve outcomes (Alhaddad,et al.,2014). Interestingly, in our study there was no significant difference among gender $p>0.05$(Chi square test) in their preferences. However, using two way ANOVA there was a significant difference for dosage forms where suppositories and injections were the least preferred dosage forms ($p<0.05$).

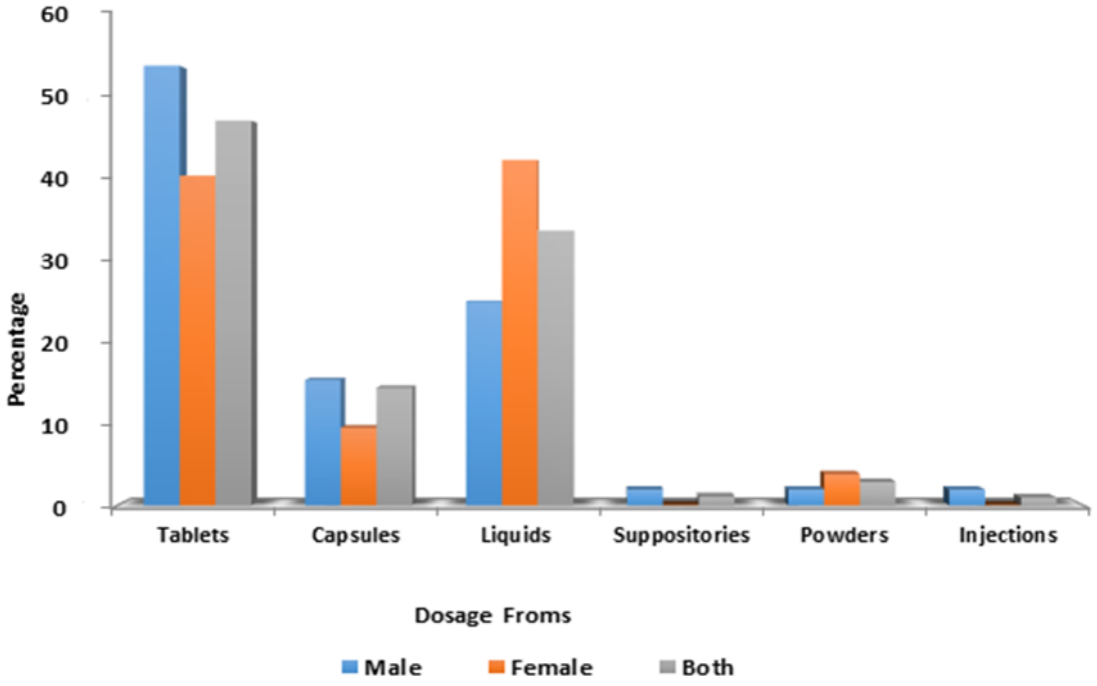


Figure 2.4: Distribution of the patients' preferences of dosage forms according to gender for all regions.

In our study, results show that ODTs were the most popular oral dosage forms (58%) followed by liquids (20%), tablets (12%) and capsules (11%) (Figure 2.5). Regional analysis of the data for preferred oral dosage forms indicated that ODTs was the most preferred by the majority of respondents (66%, 65%, and 38%) for Saudi Arabia, Jordan and UK respectively (Figure 2.6).

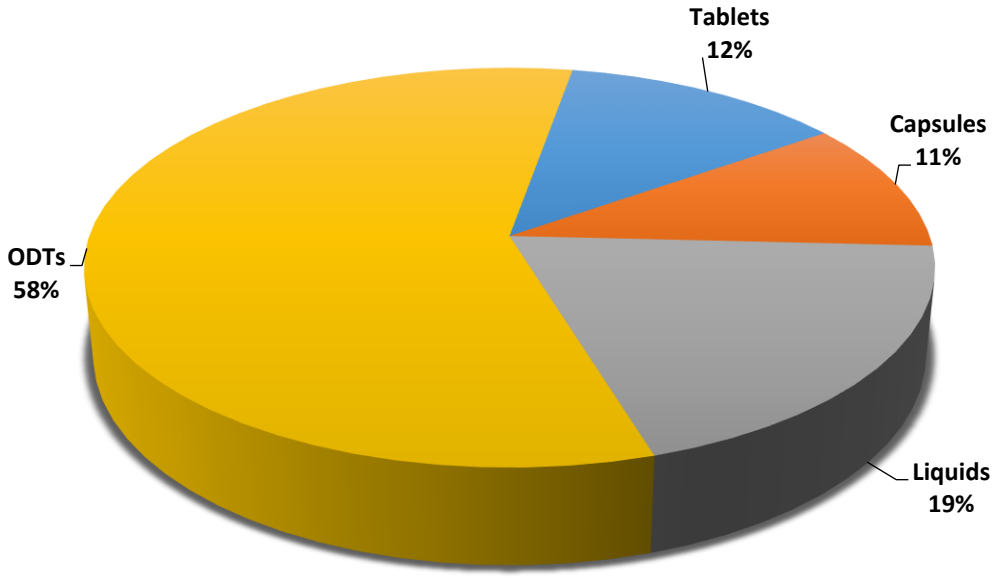


Figure 2.5: Distribution of the preferred oral dosage forms among paediatrics in all regions.

The popularity of ODTs in the pediatric population is possibly due to a number of factors including ease of administration, stability and convenience of storage (as opposed to liquids). However, a study by Ibrahim (2010) showed that the capsules were the most prefered oral solid dosage forms when compared to tablets, caplets and soft gel. Their results also showed that ethinicity and age group directly influenced the participant preferences for oral dosage forms. For example, capsules were prefered by both Malays and Chinese (Ibrahim *et al.*, 2010).

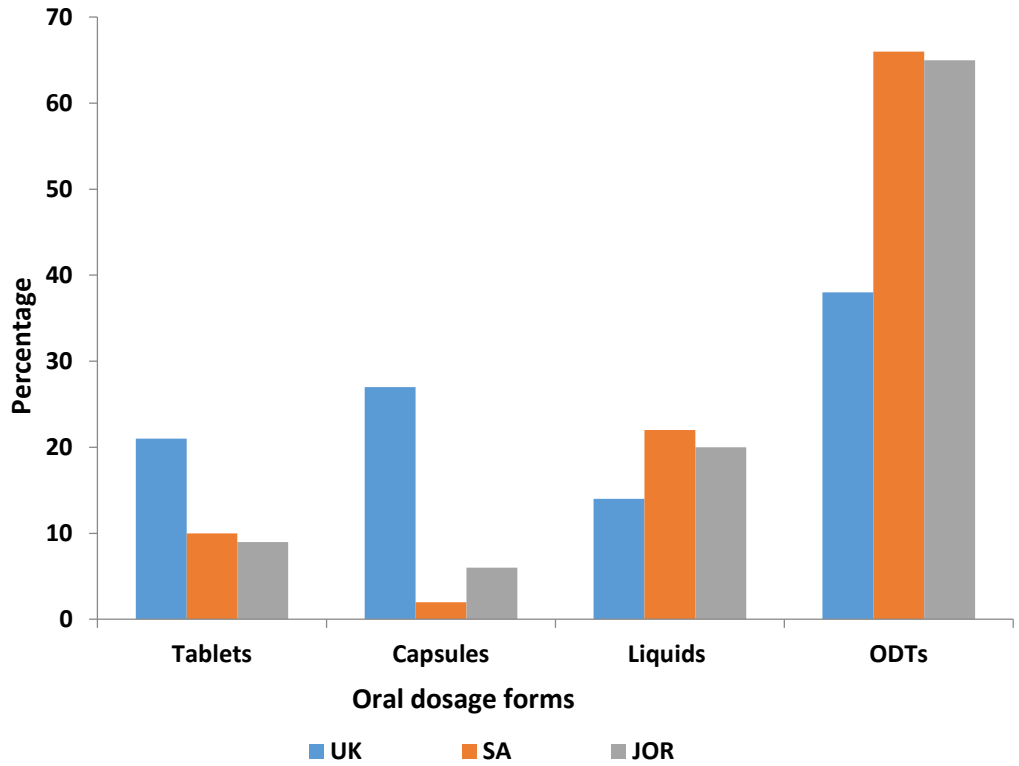


Figure 2.6: Distribution of paediatrics who preferred oral dosage form according to regions.

Analysis of distribution of responses for ODTs as preferred oral dosage form according to age group and gender in all regions showed a highest percentage of the children were male between 12-14 years of age who preferred ODTs (44.83%) followed by females between age group of 11-13 years (38.7%). However, there was no significant difference according to age group and gender ($p>0.05$) (Figure 2.7). The superiority of ODTs as a preferred alternative to capsules and conventional tablets is possibly due to better patient compliance as it does not require water for administration and the tablet disintegrates and dissolves in the oral cavity within seconds (Hirani *et al.*, 2009). According to Virley and Yarwood (1990) ODTs may increase bioavailability and result in faster onset of action, therefore, dispersion in saliva in oral cavity causes pregastric absorption from some formulations. Buccal, pharyngeal and gastric regions are all areas of absorption for many drugs. Any pregastric absorption avoids first pass metabolism and can be a great advantage in drugs that undergo hepatic metabolism. Capsule was the second preferred form by the British respondents; possible

explanation for this capsule preference includes the effect of its design, which comprises of two different parts, making this dosage form easily distinguishable from the other formulations (Reisenwitz and Wimbish Jr, 1996). Another possible explanation for the preference of capsules could be attributed to the previous experience of the participants in taking capsules over liquid or tablet dosage forms.

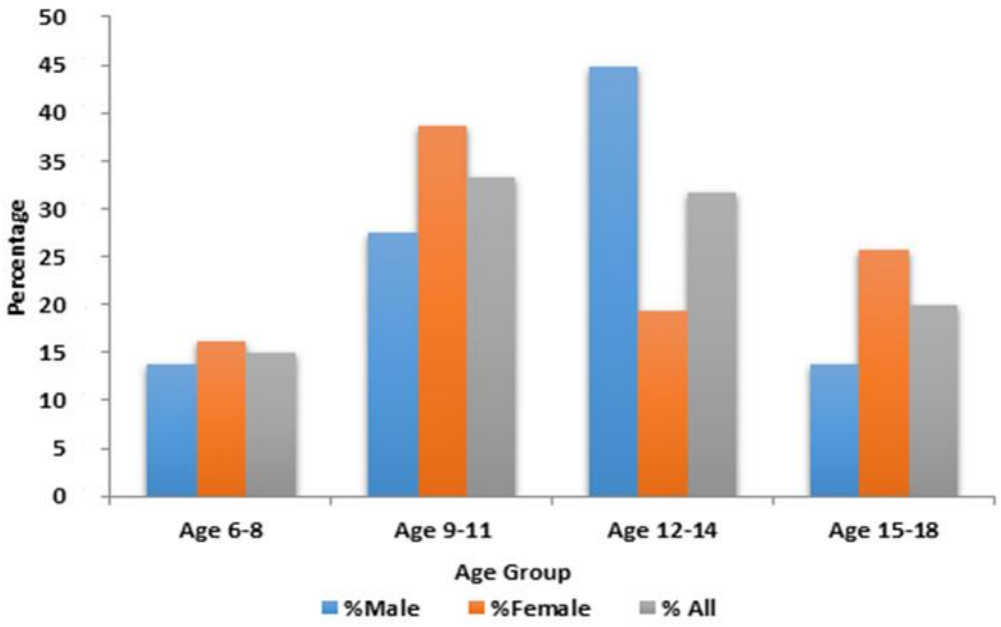


Figure 2.7: Distribution of paediatrics who preferred ODTs as oral dosage form according to age group and gender in all regions.

2.3.2.3. Physical characteristics results for orally disintegrating tablets (ODTs)

As the first part of the study concluded that the orally disintegrating tablets were the preferred dosage forms, the next set of investigations were centred around evaluating the preference of different attributes of ODT such as colour, taste, shape, flavour and disintegration time.

2.3.2.3.1. Colour Preferences

The colour of the medicine is of immense importance to most patients and is a great determinant of the popularity and acceptability of the medicine (EMA, 2006). Figure 2.8 showed that pink was the preferred colour for ODTs by more than a quarter of the respondents (30.8%) followed by white (26.0%), blue (14.4%), yellow (11.5%), orange (7.7%) and finally purple (7.7%). Similarly, (Ibrahim *et al.*, 2010) stated that orange and purple were the least preferred while white was the most preferred colour.

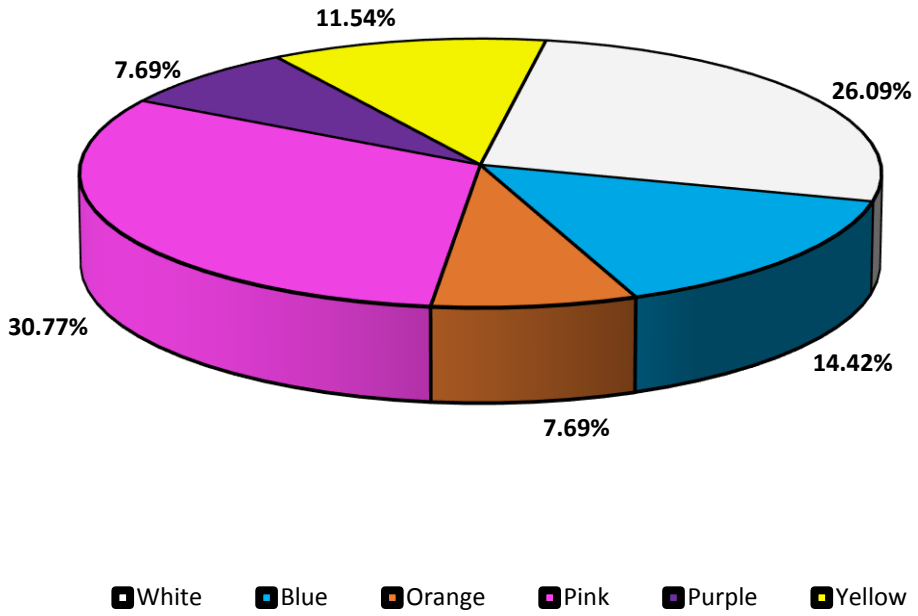


Figure 2.8: Distribution of preferred ODTs colour for all regions.

Our study exposed an interesting result in which genders and age group have their different colour preferences for ODTs. For example, 27 out of 32 female participants preferred pink colour ODTs while male participants tend to prefer white. In European and Middle East cultures, white colour represents purity and virtue while pink shows femininity and girlishness (Ibrahim *et al.*, 2010). Surprisingly, neither blue nor yellow coloured ODTs were preferred by female gender (Figure 2.9). An extremely significant difference was detected by Chi- square test in colour preferences ($p<0.05$).

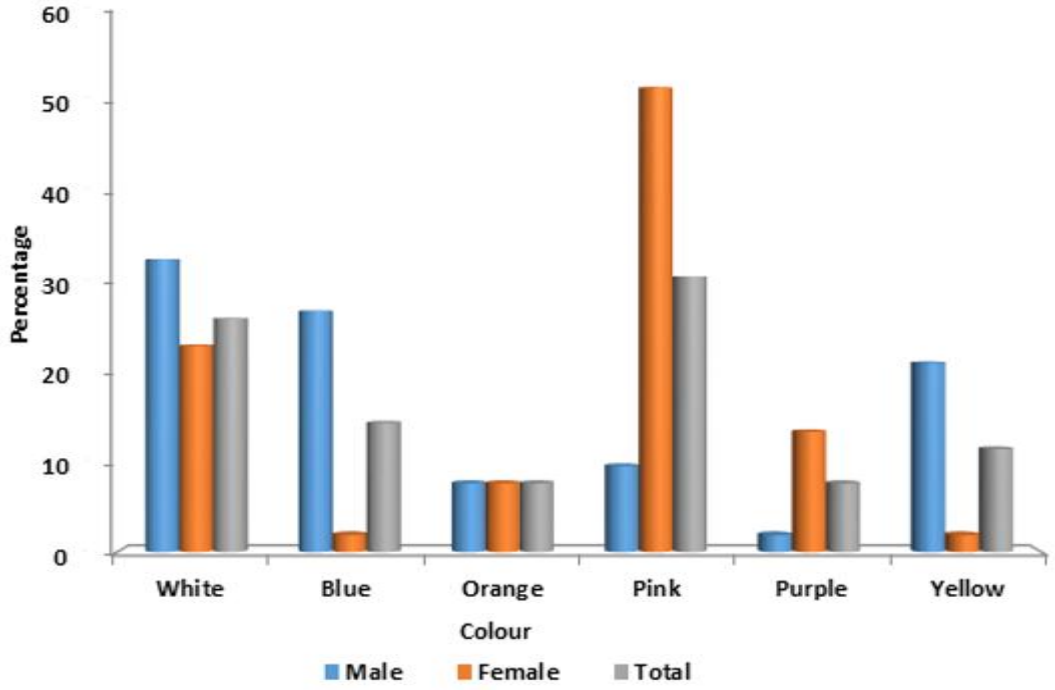


Figure 2.9: Distribution of preferred colour according to gender in all regions.

Similarly, Figure 2.10 showed that there was a significant level of distribution of the preferred colour by age group and gender ($p<0.05$). The majority of female (6-8 years) respondents (85.71 %) preferred pink colour of ODTs while the highest percentage (38.89 %) for white colour was recorded for male participants (12-14 years).

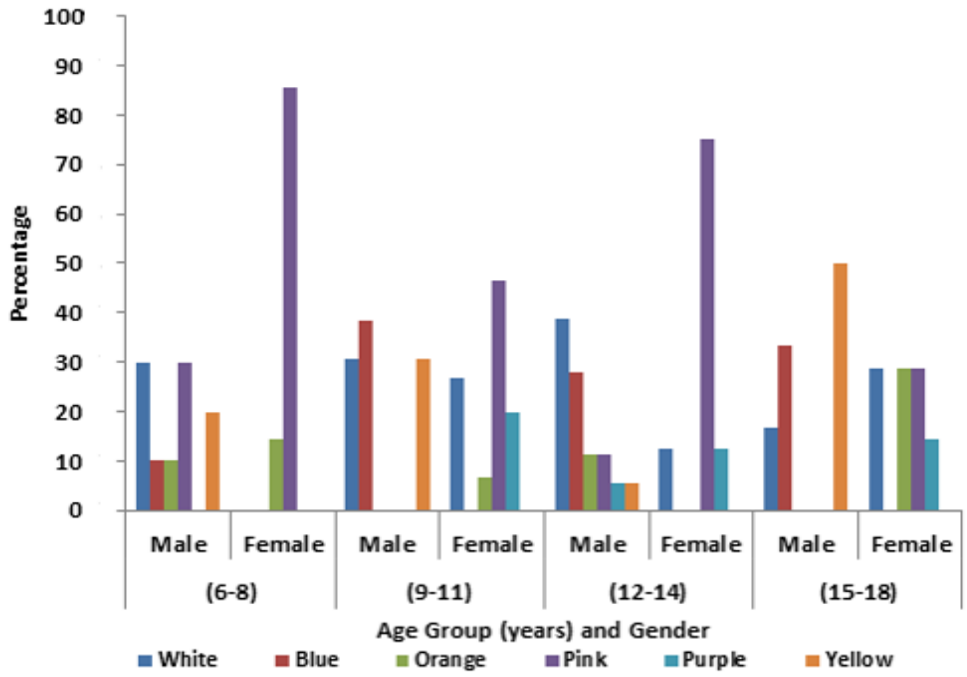


Figure 2.10: Distribution of the preferred colour by age group and gender.

With respect to the preferences of colour regionally, although pink colour was the most preferred colour, Figure 2.11 shows that Saudi participants preferred white colour (32%) than pink (17%), as it was obvious that more than half of the participants were male (63%). Similarly, investigations by (Ibrahim *et al.*, 2010) for the preferences of colour, shape and taste of oral solid dosage forms among 350 participants in Malaysia

found that white was the most preferred colour by more than half of the respondents (55%) followed by blue (20%).

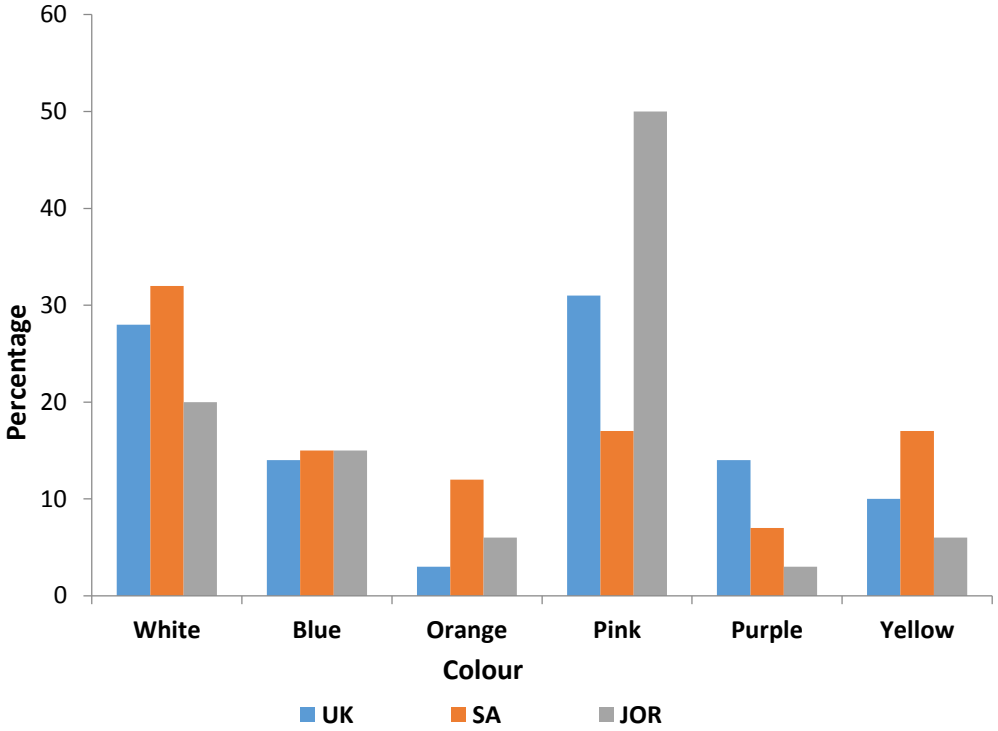


Figure 2.11: Distribution of paediatrics who preferred colour according to regions.

2.3.2.3.2. Shape Preferences

Figure 2.12 shows the user preferences based on the shape of the tablet. Majority of the participants preferred ODTs that are round in shape. This accounted for 35.6 % of the responses while the heart shape was second with a preference of 22.12%. Least preferred shapes were square (94.67 %) and diamond (1.92%).

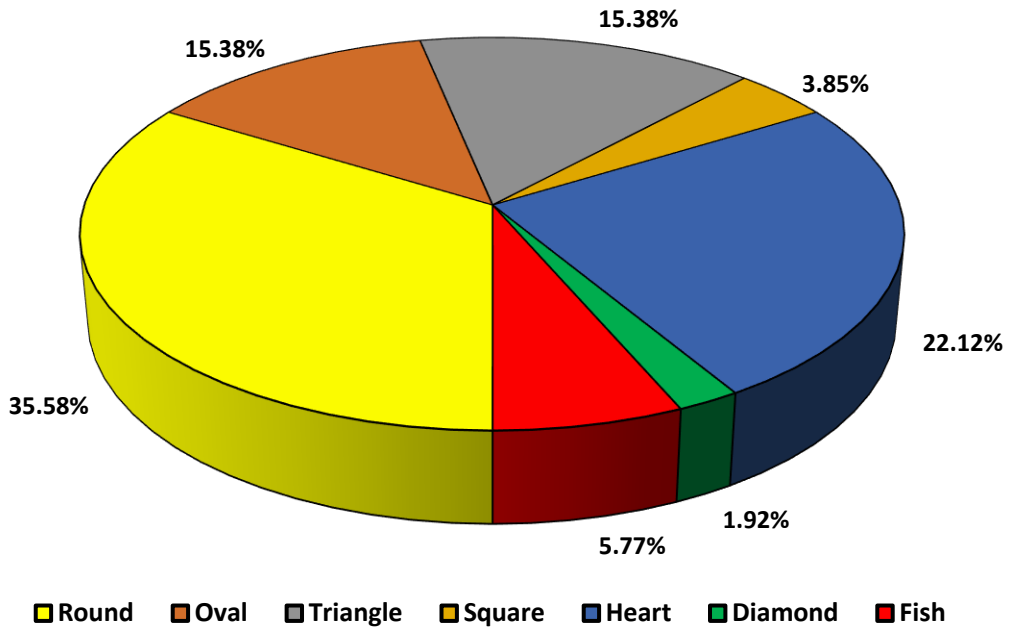


Figure 2.12: Distribution of preference of ODTs shape for all regions.

With respect to the regional distribution of participants, the results showed that British and Jordanian participants did not prefer square shaped tablets (Figure 2.13).

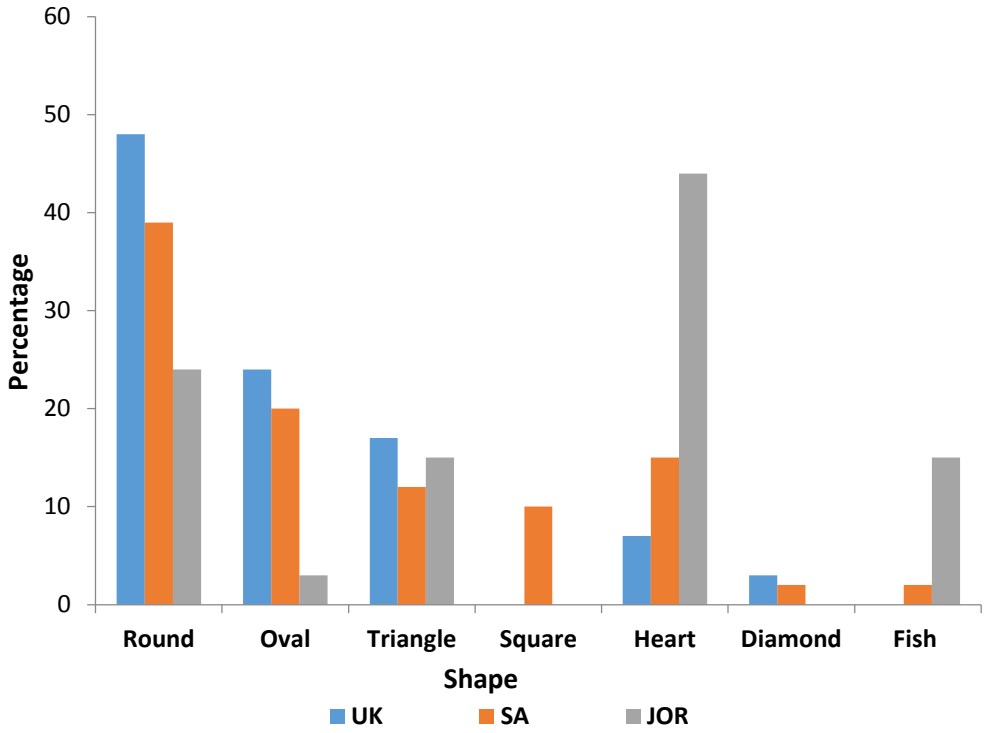


Figure 2.13: Distribution of Paediatrics who preferred shape According to regions.

Figure 2.14 showed that more female (36%) respondents preferred heart shape, whereas around 44 % of male preferred round shaped ODTs. Statistical analysis test displayed no significant difference ($p>0.05$) for distribution of participants according to their gender for shape preferences across all the regions.

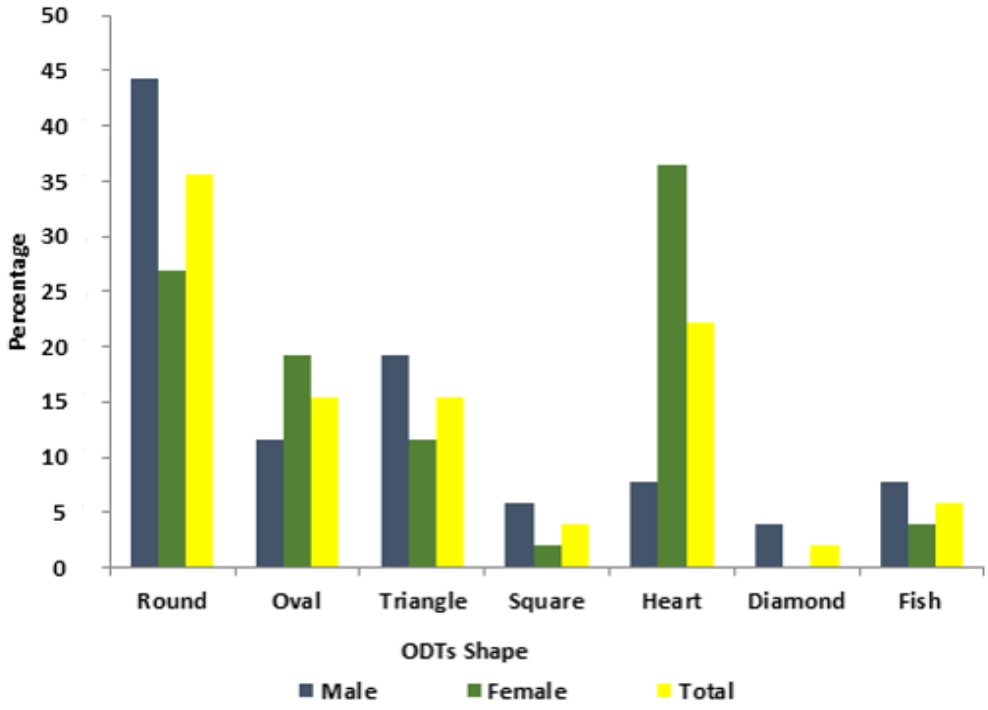


Figure 2.14: Distribution of participants according to their gender preferred shape in all regions.

2.3.2.3.3. Size and thickness Preferences

The size and thickness of a dosage form is vital in its acceptability (Breitkreutz, 2008). Small sized (0.15 cm^3 ±0.002) ODTs were most preferred (64.42%) compared to the medium 33.65% (0.27 cm^3±0.006) or large 1.92% (0.33 cm^3±0.006) ODTs (Figure 2.15).In this study, participants felt that small ODTs are easier or comfortable to swallow than big ones. Similarly, Overgaard et al (2001) investigated 18 years old patient's acceptance of tablets and capsules based on size, shape and colour. The results from the study showed that the difficulty in swallowing increased with the increase in tablet size. Correspondingly, size of dosage forms may affect the transit of the product through the pharynx and oesophagus and may directly affect a patient's ability to swallow a particular drug product. Larger tablets and capsules have been reported to extend oesophageal transit time. This can give rise to disintegration of the product in the oesophagus, resulting in pain and localized esophagitis (Channer and Virjee, 1986).

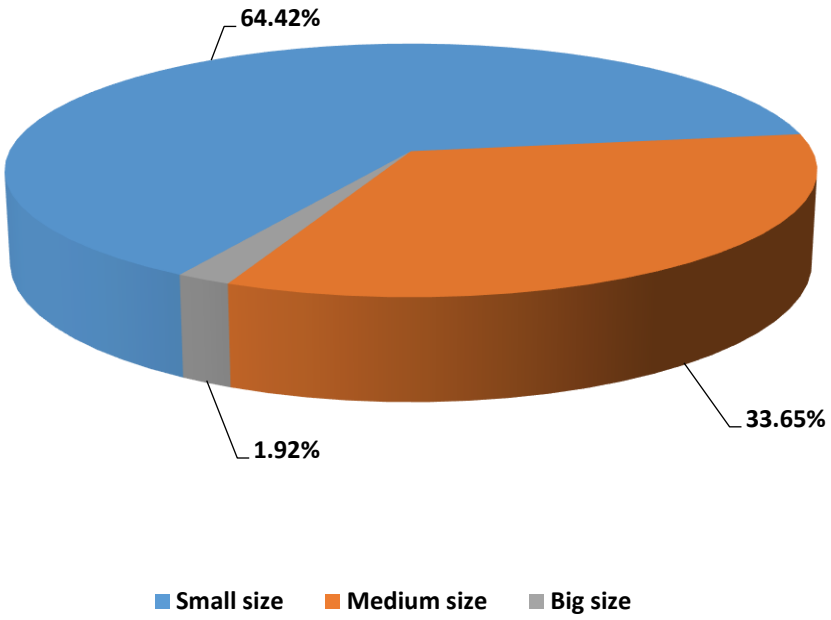


Figure 2.15: Distribution of preferred ODTs size for all regions.

Our results demonstrate that the preference for small sized ODTs cuts across all age groups ($p>0.05$) and gender for all study regions (Figure 2.16).

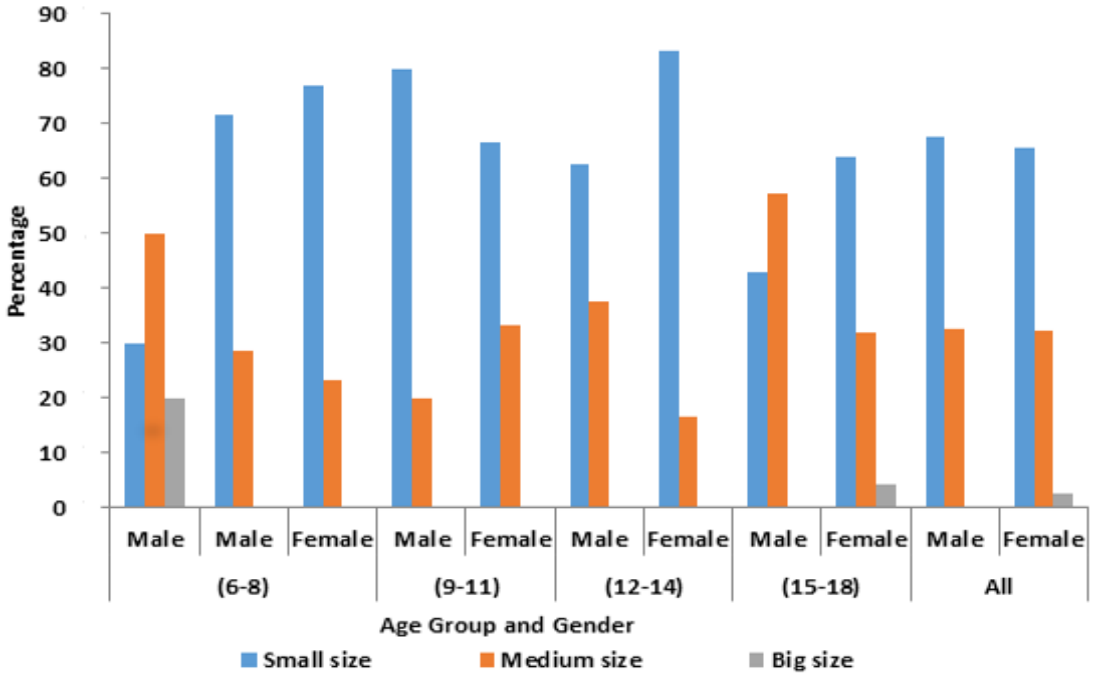


Figure 2.16: Distribution of preferred ODTs size according to age group and gender for all regions.

Figure 2.17 showed that analysis of thickness of ODTs also, highlights the preference of the participants for thin formulations at the expense of thick ODTs. The majority of respondents (66.35%) preferred thinner ODTs (1.14mm ± 0.002); however, 33.65% of the participants preferred thicker ODTs (2.47mm ± 0.03).

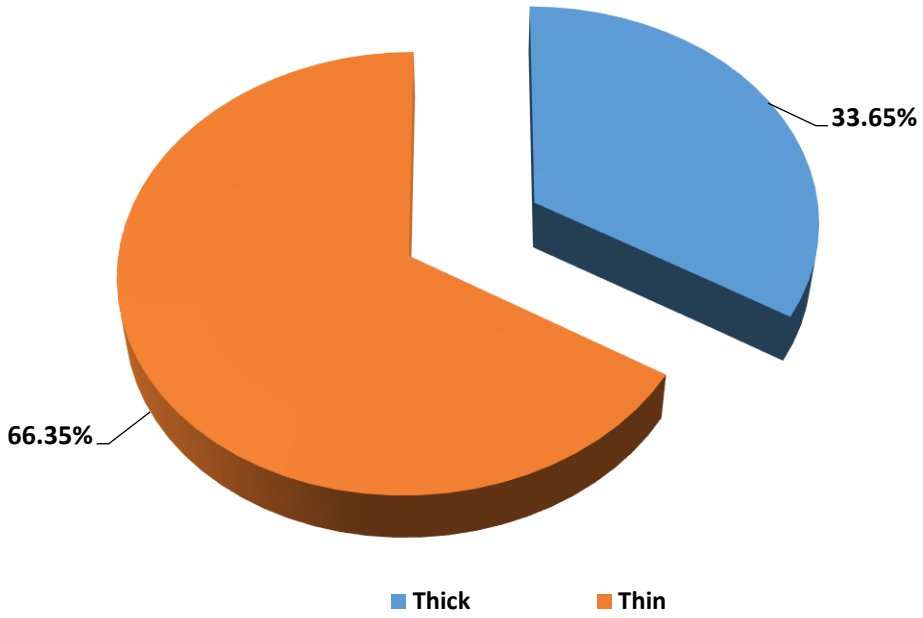


Figure 2.17: Distribution of preferred ODTs thickness for all regions.

2.3.2.3.4. Taste and flavour Preferences

The taste of a drug is the result of a perception initiated by afferent sensors in the tongue; and may be sweet, neutral, bitter or salty. Flavour is usually a result of the addition of excipients. In this present study the majority of the participants (76.9%) preferred sweet taste (Figure 2.18).

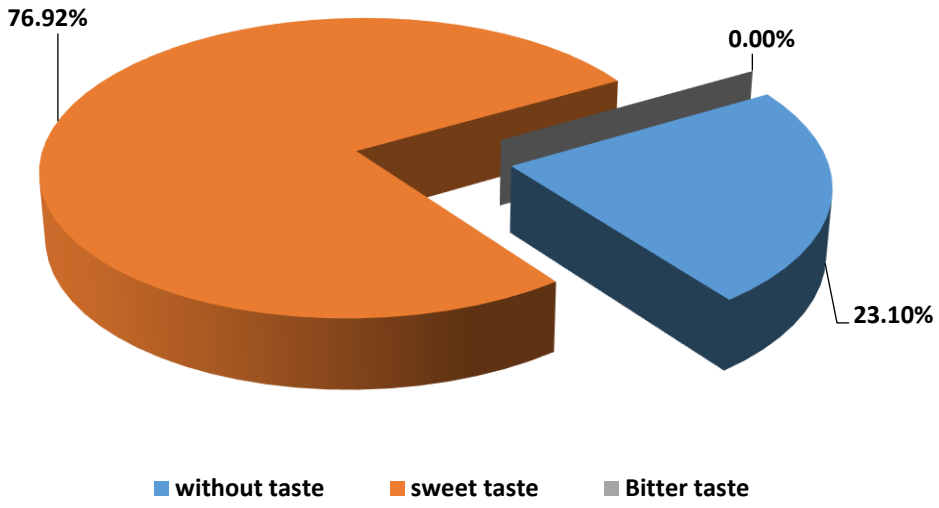


Figure 2.18: Distribution of preferred ODTs taste for all regions.

Sweet taste preference in our study for paediatric population is contrasted in another published study that evaluated the most preferred oral solid dosage forms (OSDF) in adult participants. More than half (55.0%) of participants preferred their OSDF to be without taste while 40.7% preferred sweet taste (Ibrahim *et al.*, 2010). According to other studies, the preference for sweet taste remains high throughout childhood and then switches to neutral during late adolescence (Desor and Beauchamp, 1987, Mennella *et al.*, 2005). Furthermore, Pepino *et al.* reported that not only do children prefer sweet taste, but sweet tasting solutions in the oral cavity supposedly decrease pain in both infants and children, probably via the involvement of the endogenous opioid system. Therefore, it is not surprising that many oral formulations for children are sweetened (Pepino and Mennella, 2005).

With regard to flavour, strawberry was the most preferred (30.8%) while orange was the least preferred (5.8%) as shown below in (Figure 2.19).

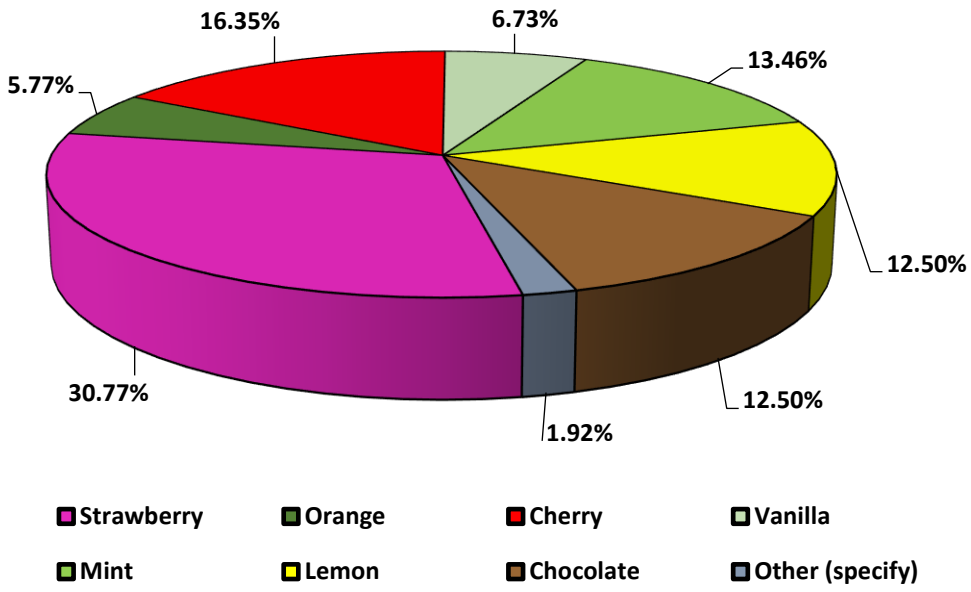


Figure 2.19: Distribution of preferred ODTs flavours for all regions.

Strawberry preference in our study group was confirmed by other studies. For example, a study was carried out in 48 healthy schoolchildren in Tanzania and results showed that cherry flavour appeared favourable to ensure a high acceptability of anti-malarial dispersible tablets in small infants and children (Abdulla *et al.*, 2010). A possible explanation could be that strawberry is found as a common flavouring in various food additives and is effective even at low concentration (Sharma and Lewis, 2010). According to the EMA, (Committee for Medicinal Products for Human Use, 2006) cherry and strawberry flavours were most preferred in medication for pain and infectious diseases within the European paediatric population; whereas lemon, peppermint and orange were recommended for indigestion remedies.

When considering flavour preference by gender, it was found that strawberry was the most preferred flavour by female participants (47.1%). On the other hand, 22.6% of male participants preferred lemon followed by mint (17%), then chocolate and strawberry with 15.1% each (Figure 2.20).

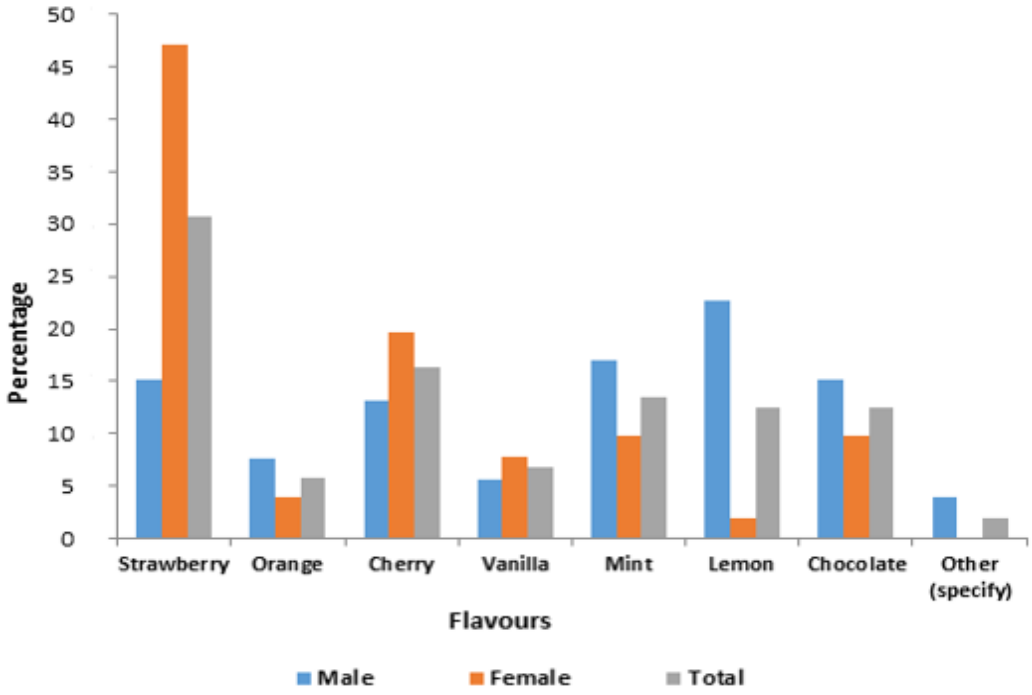


Figure 2.20: Distribution of preferred ODTs flavours for all regions by gender.

Although, overall strawberry was the most preferred flavour, significant differences were found among participant preferences according to the geographical regions. Lemon was the second most preferred flavour in Saudi children (24%) while it was the least with British (3%) participants (Figure 2.21).

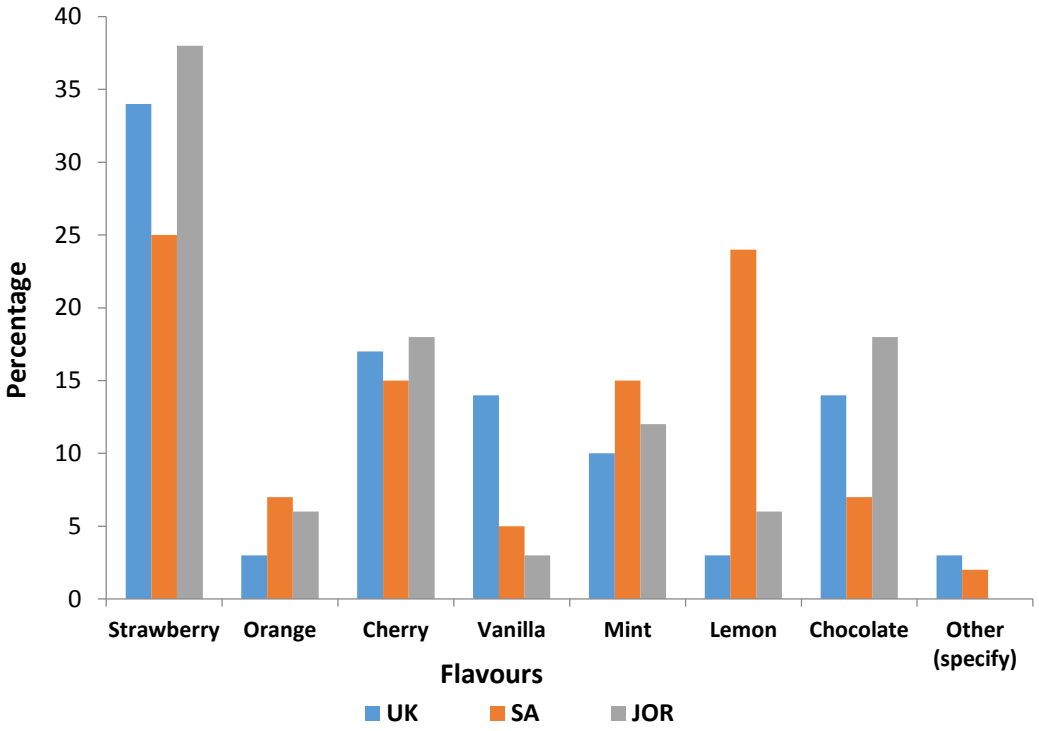


Figure 2.21: Distribution of preferred ODTs flavours for all ages by region.

2.3.2.3.5. Disintegration time preferences for ODTs

In accordance with the official European Pharmacopoeia Monograph the maximum permissible disintegration time for orally disintegrating tablets is three minutes. The results showed (Figure 2.22) that that the majority of the participants (87.5%) preferred very rapidly (<30sec) disintegrating ODTs followed by rapidly (10.58%) and the least preference was for ODTs that would disintegrate between 1.5 and 3 minutes (1.92%) respectively. Most participants believed that some tablets have bad taste and that rapid disintegration would ensure unpleasant taste can be reduced by quickly swallowing the contents of the tablet. Also some participants stated that this is indicative of quick onset of action.

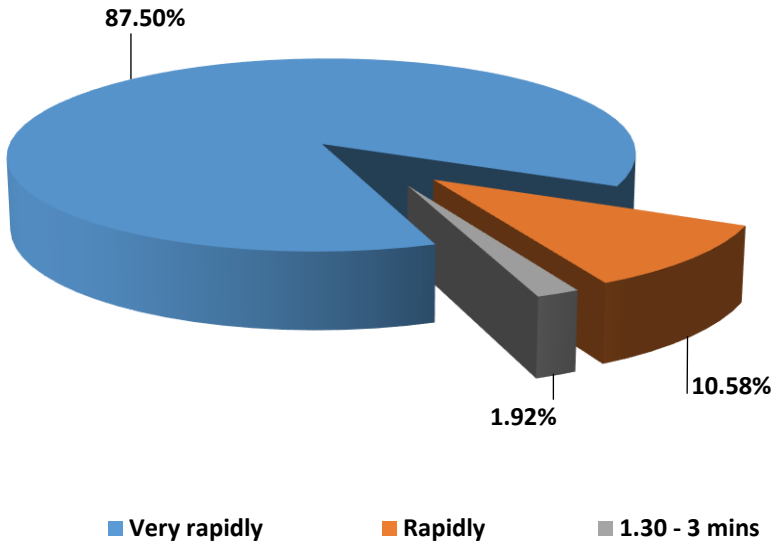


Figure 2.22: Distribution of preferred disintegration time for all regions and all age group.

2.3.2.3.6. Results obtained from the importance of physical characteristics for ODTs

The results obtained for the analysis of the physical characteristics of ODTs showed that 25.0% rated the duration for tablet disintegration in the mouth as the most important characteristic, followed by the taste (24.1%), size (15.7%), and flavour (13.8%) respectively as shown in (Figure 2.23). Similarly, results were found by (Ibrahim *et al.*, 2010) with respect to the importance of the physical characteristics of oral solid dosage forms, with slightly more than half (52%) of the respondents ranking the size as the most important followed by taste (40%), shape (13.6%), and colour (13.4%) respectively.

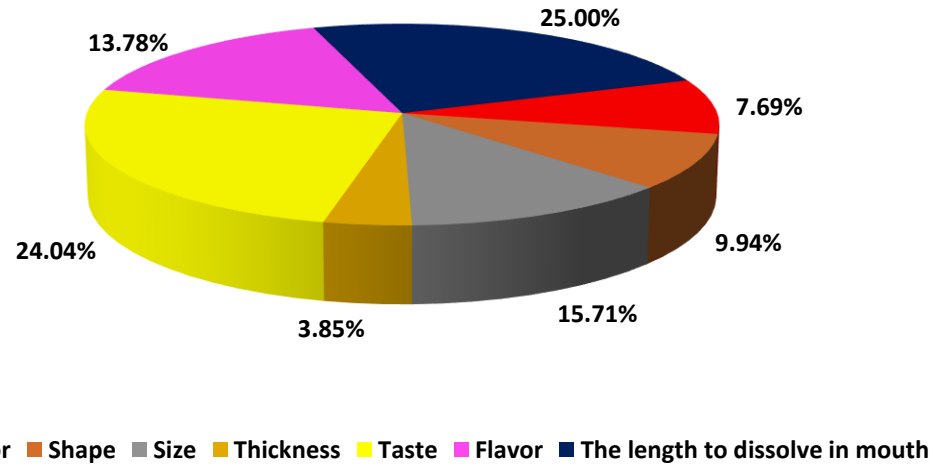


Figure 2.23: Distribution of the most important characters of ODTs for all regions.

2.3.2.4. Participants' feedback about the study

Towards the end of the study, the participants were given the opportunity to give their opinions and feedback on how the study was conducted. The participants indicated that despite the fact that it was a good questionnaire, there were areas that could be improved on. They pointed out that most of them had difficulty making out the difference between taste and flavour. Therefore, they suggested that the difference between taste and flavour be written on the questionnaire so that the interviewees remain informed when making choices. With regard to drug manufacture and design, the participants pronounced that the manufacturers should ensure that the taste is not terrible. For question three in the questionnaire where the participants were asked to indicate their level of education, some of the participants had an issue with the choices. In particular, they pointed out that choice two was vague. Therefore, they suggested that the term higher education should be specified whether it meant high school, college or university level. In contrast, another significant segment of the participants

thought that it was a very good questionnaire. The participants also thought that the experiment was good and eye opening. The hands-on experience and the practicality also earned some credit.

Overall, in all the regions the participants stated that ODTs are a good idea. Findings from this study propose that the formulation of ODTs and their physical characteristics are of high importance in encouraging paediatric patients to continue using a particular medicine.

2.4. Conclusion

The general outcome was that solid dosage forms are the preferred dosage forms and orally disintegrating tablets are a preferred dosage form for children and young adults. The benefits that accrue to ODTs include safety, higher compliance, dose accuracy, stability and ease of swallowing. Within the paediatric population, orally disintegrating tablets are more convenient because they combine the advantages of both solid and liquid dosage forms but without incorporating their disadvantages such as difficulty in swallowing and lack of stability. From the results in the current study, it can be concluded that the most preferred colours were pink and white, the most preferred size is the small sized tablets and the most preferred shape was round . Similarly, physical characteristics in order of priority with regard to the acceptability of ODTs included disintegration time, taste, size and flavour. This study has identified the favoured medication characteristics as expressed by the participants. However, it has not been tested whether these desirable characteristics are deliverable due to the physical properties of the active ingredients. Similarly the potential benefits in terms of patient adherence are implied only, and have not been tested in this present study.

Chapter 3

Current Opinions and Recommendations of Healthcare Professionals Regarding the Importance and their Preferences Concerning Paediatric Dosage Forms

Publications relating to chapter 3

Hamad Alyami, Jasdip Koner, Chi Huynh, David Terry and Afzal R Mohammed (2016). Current Opinions and Recommendations of Healthcare Professionals Regarding the Importance and their Preferences Concerning Paediatric Dosage Forms. PLOS One. Accepted.

3.1. Introduction

The European Medicines Agency (EMA) recognised that there have been limited data concerning paediatric population acceptance of oral dosage forms in relation to age and developmental status along with the inadequate availability of licensed medicines appropriate for administration to children (EMEA, 2006). In addition, there is anecdotal evidence that there are increasing concerns amongst healthcare professionals about paediatric patients failing to take their prescribed medication (Michaud *et al.*, 2004). Many medicines are formulated to enable usage in adults, and these may not be suitable for use by children. There may be difficulties in swallowing solid dosage forms (e.g. tablets) and there may be issues concerning the availability of the dose strength based on current dosage forms available. Many children will require doses smaller than adults prompting use of liquids or splitting the dose of solid tablets by cutting them into halves and quarters. If suitable dosage forms are not available then patient compliance with prescribed medication may be reduced with potential adverse clinical consequences (Bauman and Drotar, 2000).

Reasons that may affect a child's success in swallowing solid dosage forms include developmental stage depending on their age (0 to 18 years), anxiety, fear, intolerance to unpleasant flavours and not being able to appreciate the risks associated with noncompliance (Patel *et al.*, 2015).

Treatment failure may result leading to poor clinical control and unnecessary expense as a result of unused medication waste. In primary care around £300 million worth of medicines are wasted every year of which £150 million is preventable (Barr, 2014). Formulation work so far has revealed that liquids seem to be more customary with the paediatric population (infant age between 1 month to 2 years and pre-school age between 2 to 5 years), whereas oral disintegrating tablets (ODT) may be preferred by

those who are older (5 to11 years), and in the adolescent age (12 to16/18 years), tablets and capsules may be more appropriate and convenient (Nunn and Williams, 2005). An ODT is an easy to use dosage form which disintegrates in the mouth upon contact with saliva. ODTs can be taken without the need to swallow tablets whole and does not require water.

There is evidence to suggest that ODTs are a potential ideal formulation for children since they avoid concerns children may have regarding swallowing tablets (Sumiya *et al.*, 2000, Varia *et al.*, 2006).

Our previous study, which was conducted in three countries including the UK, found that approximately 58% of the participants (children age 6-18 years) preferred taking ODTs compared to conventional tablets, liquids and capsules (see chapter 2).

Few studies have been carried out aimed at identifying healthcare professional perceptions or opinions regarding the use of different dosage forms for paediatric use. However, previous research conducted in similar fields has explored healthcare professional's perceptions on HIV treatment adherence in children with an investigation in to unlicensed/off label medicines use (Mukattash *et al.*, 2011) and those exploring paediatric nurses knowledge and practice of mixing medicines with foodstuffs (Akram and Mullen, 2012). Most research in this field is targeted at reducing prescribing and dispensing errors for children. However, to ensure medication adherence in children is supported, when making a decision on medication formulation choice for a child, clinicians should take into consideration the acceptability of the item to paediatric patients. To the best of our knowledge there are no published studies regarding the opinions of healthcare providers concerning paediatric dosage regimens including ODTs. Furthermore, limited data is available concerning the effect of ODT properties (i.e. taste, texture, flavour, colour, shape, size and disintegration time) of individual medicines on child acceptance. It was therefore necessary to conduct a

study, exploring the opinions of healthcare professionals regarding paediatric dosage forms.

The primary aim of the present work is to evaluate healthcare professional's perceptions of the paediatric dosage forms to support patient choice and ultimately patient adherence to prescribed medication regimens.

The main objective of the focus group and semi-structured interviews (phase 1 and 2 respectively) was to design a validated online survey (phase 3) delivered to pharmacists, nurses and medical practitioners to evaluate their views and perceptions with regards to paediatric dosage forms. This study will provide the opinion of healthcare professionals in what dosage forms they believe are preferred by children and to also identify healthcare professional's personal opinions concerning the safety and cost effectiveness of formulation types. The secondary aim of this study was to compare the findings of this present study concerning healthcare professionals with the findings from our previous study concerning children in respect to dosage forms (Alyami *et al.*, 2016).

3.2. Methodology and Ethical considerations

Healthcare professionals at BCH were invited via email to participate in the study and provided with an information sheet explaining the purpose of the study focus group followed by semi-structured interviews.

Prior to commencing the study, Hamad Alyami (HA) obtained an honorary contract at BCH (appendix 3), a variety of focus group and semi-structured interviews were performed between June and July 2016 by the researcher (HA). This preliminary scoping work was used to develop the experimental design (online survey).

Focus groups gather a plethora of information in a short period of time and explore attitudes, perceptions and approaches. Once piloting a focus group between six and eight participants is optimal, the group should have enough participants to get a wide perspective without being too large, and thus disordered or disjointed (Eriksson and Kovalainen, 2015).

3.2.1. Overall methodological design of the study

The study consisted of dual site, cross-sectional, mixed methods study of hospital based paediatric doctors, pharmacists and nurses, using an anonymised electronic survey (Bristol Online Survey software – BOS); informed by a literature search, focus groups and semi-structured interviews.

This study was carried out at two paediatric hospitals:

- Birmingham Children's Hospital BCH (Phases 1,2 and 3)
- Alder Hey Children's Hospital, Liverpool (Phase 3 only)

Informed by a literature search, this study included a three-phase consensus-building process comprising of

- Phase (1) focus groups with pharmacists and nurses (separately);

- Phase (2) semi-structure face-to-face interviews with each of the three main groups of professionals, consent forms were given to focus group phase (1) and semi-structure interviews phase (2) and
- Phase (3) electronic survey of paediatric hospital healthcare professionals.

Qualitative verbatim transcripts from phases 1 and 2 were subjected to framework analysis (Gale *et al.*, 2013). Themes from phase 1 underpinned the basis for phase 2 interviewees. Themes from phases 1 and 2 generated issues for inclusion within phase 3.

The final electronic questionnaire (phase 3) was assembled and managed using bespoke software (Bristol Online Survey ™). Results were transferred to SPSS version 22 and NVivo version 10 software for analysis to facilitate descriptive statistical analysis and framework analysis respectively.

Figure 3.1 presents a flow diagram of the three phases that were carried out. The questionnaire was comprised of both closed and open questions to identify participants' perceptions and opinions about dosage forms for children.

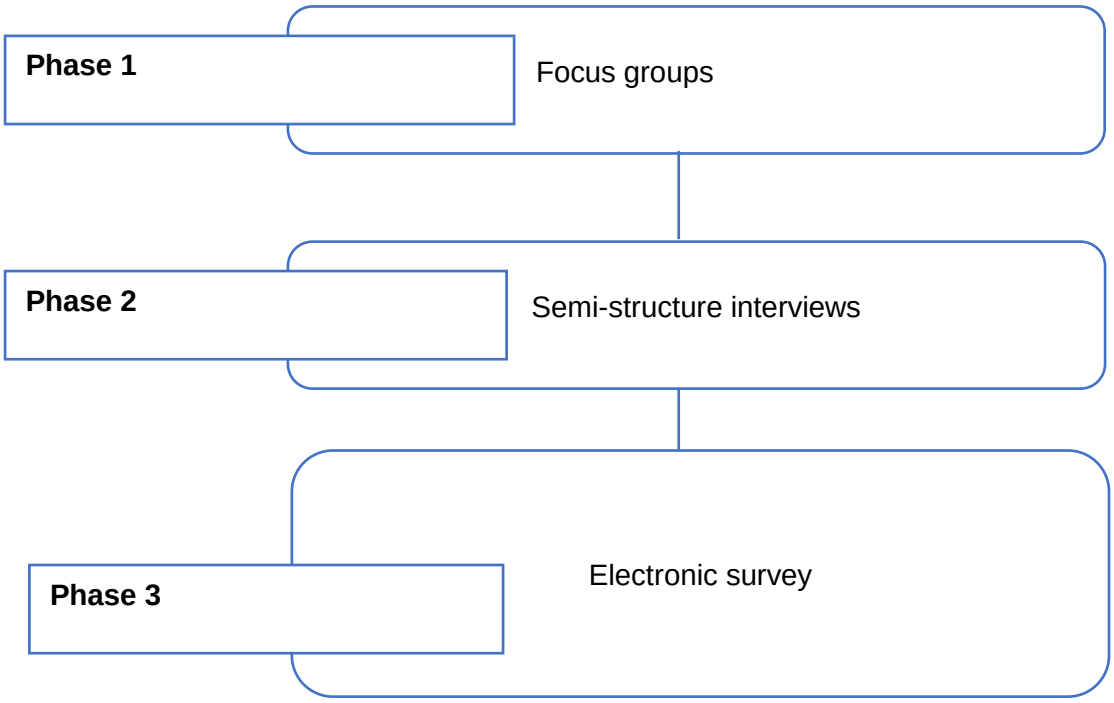


Figure 3. 1: Flow chart of research methodology

3.2.2. Recruitment and consent

3.2.2.1. Phase 1 – Focus group

Two focus groups were undertaken within this study. One focus group consisted of 4 nurses and one of 7 pharmacists. These focus groups were designed to support the development of the healthcare professionals' questionnaire. All focus groups were conducted at the primary study site (BCH). Email invitations to attend the focus groups were arranged via the research leads of the two professions at BCH. All potential participants received a Participant Information Sheet (appendix 4) and those recruited to the study completed and signed the relevant consent form (appendix 5). Private rooms were pre-booked within BCH in locations accessible for staff, to create a suitable and convenient environment for discussion. The focus groups were facilitated by HA (Hamad Alyami) and assisted by CH (Chi Huynh) (research pharmacist/lecturer in clinical pharmacy). The groups were digitally audio-recorded using an Olympus digital audio-recording device. A question guide (appendix 6) was developed including questions to be discussed by the facilitator to ensure coverage of pre-determined themes identified by the project support team.

3.2.2.2. Phase 2 – Semi-Structured Interviews

Participants from the three professional groups were recruited to undertake semi-structured interviews. They were recruited by recommendation from the professional research leads or via their involvement in the Academic Practice Unit at BCH. A minimum of three participants from each of the three professional groups were recruited to the study. All potential participants received a Participant Information Sheet and those recruited to the study completed and signed the relevant consent form.

3.2.2.3. Analysis of the focus groups and semi-structured interviews data

The data collected from Phase 1 and Phase 2 were analysed using framework analysis by (Ritchie and Spencer, 2002, Smith, 2015) with the following stages, 1) Data entry

and processing; 2) Familiarisation of the focus group and interview data collection and identifying an initial framework based on the question guide (for initial framework see appendix 6); 3) Coding – all focus groups and interviews were coded and indexed using NVIVO 10; 4) Generation of themes (charting) results were charted according to the themes; 5) Finalised framework (mapping and interpretation).

HA transcribed each focus group and semi-structured interview as soon as was possible after facilitating the group and interview. Verbatim transcripts were produced in Microsoft Office Word 2013 from the digital audio-recordings, hence, the focus groups and semi-structured interviews provided 31,895 words of text. Participants were anonymously assigned a coded identifier within the text (e.g. speaker 1, speaker 2 etc.) to ensure the extent to which views were shared could not be identified. The verbatim text was copied in to a qualitative data analysis and coding software (QSR NVivo 10) and framework content analysis was developed to analyse the verbatim files. Qualitative research software (NVivo 10) was used to arrange information and combine analysis with linking (Gibbs, 2002). A framework analysis approach was used to qualitatively analyse the data (Brooks *et al.*, 2015). The data was coded using coding framework based on the question guide for the focus group, interviews and objectives of this study (see Table 3.1) .The initial 10 minutes (20%) of the transcript recording, was coded independently by two investigators, HA and CH, using the initial framework with NVivo Version 10 to assist with indexing the codes. The similarity and differences between the two coders was discussed and a final framework developed. The coding framework was used to code the rest of the transcript. The interpretation of the results from the coding of the focus group and semi-structured interviews were conducted by HA and was based on the objectives of the focus group and interviews.

Table 3.1: Compiled sample of framework coding for focus groups and semi-structured interviews.

Main code	Sub codes (Nvivo nodes)
1. Most common paediatric dosage forms	1.1 Liquids 1.2 Tablets 1.3 Suspensions 1.4 ODTs
2. Your preferences for paediatric oral dosage forms	2.1 Tablets 2.2 Solutions 2.3 Capsules 2.4 ODTs 2.5 Mini- tablets 2.6 Depends on age, patient
3. ODTs as an alternative dosage forms	3.1 Yes, for young children 3.2 Yes, it is good alternative 3.3 Children and parents need education regarding ODTs 3.4 Sometimes not always 3.5 Should taste good (sweet) 3.6 Not suitable for less than 6 yrs
4. Enhancement of compliance and adherence regarding taking ODTs	4.1 Absolutely, if it tastes good 4.2 I think so 4.3 Taste is going to be important 4.4 Depends on age/ patient 4.5 lot of lansoprazole ODTs, it helps
5. ODTs cost effectiveness	5.1 Definitely much cheaper than liquids 5.2 Much more expensive 5.3 No idea
6. Any feedback from the patients or their parents regarding any issues of ODTs	6.1 Taste not good, talk about taste 6.2 Too big in size 6.3 Ease of being able to swallow

	6.4 Not really
7. Physical characteristics of ODTs	7.1 Taste 7.2 Flavour 7.3 Size 7.4 Colour 7.5 Shape 7.6 Disintegration time
8. Taste	8.1 Sweet 8.2 Neutral 8.3 Not bitter taste 8.4 Very important
9. Flavour	9.1 Strawberry most preferred 9.2 Lemon 9.3 Orange 9.4 Fruity 9.5 Banana
10. Size	10.1 Small 10.2 Not big size 10.3 Size isn't that important, if it disperses in mouth
11. Colour	11.1 Not important as taste 11.2 Keep it white 11.3 May be pink
12. Shape	12.1 Round 12.2 Not square 12.3 Not that important
13. Disintegration time	13.1 Very fast 13.2 Not too long
14. Any comments or any recommendations	14.1 No, thanks 14.2 I like the idea 14.3 I think it's a novel idea for children 14.4 The most important things will be flavour and the length of time

	14.5 Talk to the nursing staff as well 14.6 Taste is the important thing 14.7 I think it will help a lot of kids get away from the liquids 14.8 More education regarding ODTs for patient and their parents will be useful

3.2.2.4. Phase 3 – Electronic survey

An electronic survey tool was chosen as the instrument for this study. Healthcare professionals working at the time of the study for BCH and Alder Hey Children's Hospitals were invited to complete an online survey. Managing of this survey by the use of purpose designed electronic survey software was therefore considered to be both deliverable and efficient due to suitability of having automated data collection, which saves researcher time, effort and offers cost savings advantages (Wright, 2005). The questionnaire development was supported by the HCPs focus groups and the semi-structured interviews.

The themes and concerns identified in the phase 1 and 2 were considered for inclusion in the survey, including for example factors influencing choice of formulations for paediatric patients. A draft survey was created on 11th August 2016 using Bristol Online Survey software (BOS).

The draft questionnaire was piloted with academic supervisors AM and DT (Afzal Mohammed and David Terry) and research pharmacist (CH) at BCH. A number of comments were received leading to changes in the survey instrument. For example,

- 'Why is gender relevant? You need to justify it or remove it'
- Question 2- change word physician to 'junior medical staff' and add 'medical staff to consultant'
- Question 4- add 'part years'

- Question 7,15 and 16- add ‘other’ option and please specify
- Question 8 to 10 add ‘don’t know’ options

The resulting second draft was sent to a small number of HCPs for comments ED and JK (Eman Dahmash and Jasdip Koner). Further changes included:

- Questions 13 - just put ‘which flavour of ODT’
- Questions 19 – comma after paediatric patients
- Question 21 - question re-worded

Email addresses of HCPs were obtained from the site leads at BCH and Alder Hey Children’s Hospital (CH and chief pharmacist) respectively and they managed this process by reference to staffing lists and responses. The invitation to participate was sent from Bristol online survey to the NHS Trust email addresses of the study cohort with a link to the survey. First emails were sent out on 1st September 2016, reminder emails sent to all respondents 3 and 6 weeks after the initial email was sent. Each site was required to return completed surveys from a minimum of five professionals in each group.

Participants were advised that all data were held confidentiality and anonymity was assured.

Responses were exported from Bristol survey into MS Excel 2013 and IBM SPSS version 22 for analysis and production of descriptive statistics.

3.2.3. Inclusion and exclusion criteria

Inclusion criteria:

- Healthcare professionals (HCPs) (doctor, nurse, and pharmacist) at Birmingham Children's Hospital (BCH).
- Healthcare professionals (doctor, nurse, and pharmacist) at Alder Hey Children's Hospital, Liverpool.

Exclusion criteria:

- General public.
- Refusal of consent; Unable to give consent; Withdrawal of consent.

3.2.4. Ethical considerations

An application was submitted online to School of Life & Health Sciences Ethics Committee at Aston University and to the Research & Development Departments of Birmingham Children's Hospital (BCH) and Alder Hey Children's Hospital. No study activity commenced until all approvals were granted. Participants were recruited following informed consent. The process for obtaining applicant informed consent was in accordance with the Research Ethics Committee (REC) guidance and Good Clinical Practice (GCP). Participant information sheets and information governance certificate were provided. Ethical approval was obtained from School of Life & Health Sciences Ethics Committee at Aston University (see appendix 7). Although, Research and Development approvals were obtained from BCH and Alder Hey Children's Hospital, the study was confirmed as service evaluation by the head of Research and Development of Birmingham Children's Hospital (BCH) and Alder Hey Children's Hospital (see appendix 8).

Responses to the invitation to complete the survey was managed within NHS secure systems (including NHS protected servers and NHS email systems). Data was accessed by the study team only who all hold contracts with the study sites and

possess up to date NHS Information Governance certificates. All responses were fully anonymised prior to analysis and all reports accommodated confidentiality requirements. Audio files from the focus groups/semi-structured interviews were held on-site at BCH, within the secure area of the Academic Practice Unit. Once transcripts were approved, original recordings were destroyed. Additionally, paper records (from the semi-structured interviews) were also kept within the secure area of the Academic Practice Unit at BCH, and were destroyed upon transcription of the interviews.

3.3. Results and discussion

The presentation of the findings is divided into three phases. The first phase reports the focus groups of healthcare professionals. The second phase addresses the semi-structured interviews and the third phase (main phase) presents the online survey for healthcare professionals concerning paediatric dosage forms. The healthcare professionals that were selected to participate in this study were medical practitioners, pharmacists and nurses. The rational for selection of HCPs was to show the relationship leading from the prescribing (doctor) through to dispensing medicine (pharmacist) and lastly administration by a nurse.

3.3.1. Phase 1- Focus group

The focus groups were used to scope the research and inform design of the online survey with healthcare professionals (phase 3) and aimed at seeking opinions of participants with a different range of backgrounds. One limitation of this method was that participants had to obligate their time to take part. Although, it was planned to conduct a focus group for doctors, it was not feasible due to the clinical demands of the service. However, the information gathered from the BCH focus groups provided an understanding in to the opinions of pharmacists and nurses concerning paediatric dosage forms, whilst the sample size for doctors was proposed to be increased within the semi-structured interviews (phase 2). Table 3.2 shows the number of participants, dates conducted and location of the focus groups .The pharmacist and nurse groups were conducted at lunchtime, it was intended that each session would last between 30 and 50 minutes. The exact timings of digital audio-recordings are shown in (Table 3.2) below and discussion flowed well between the group members.

Table 3.2: Details of the two focus groups for healthcare professionals.

Focus group	Date conducted	Number of participants	Location	Time duration of group (minutes)
Pharmacists	7th July 2016	7	BCH	43
Nurses	14th July 2016	4	BCH	32

Pharmacist 5 mentioned that the most preferred dosage forms for paediatric population age (6-18 years) depends upon the patients and what they would prefer so "if they were unable to swallow tablets, liquid is obvious default, but if we can't get a liquid then we look for alternatives, so do we have to crush a tablet or any ODTs available "

In addition, pharmacist 2 reported that texture and taste of ODTs was important for children so the ideal taste would be sweet with either citrus or strawberry flavours.

Across the focus groups, the large sizes of tablets were related to swallowing difficulties in paediatric patients especially those less than 6 years of age.

Several studies exploring children suffering from HIV support these findings and stated the negative attitudes of children regarding the size of antiretroviral tablets (Roberts, 2005, Patel *et al.*, 2015, Ricci *et al.*, 2016).

3.3.2. Phase 2- Semi-structured Interviews

A total of 12 healthcare professionals were interviewed at BCH during the study period, the HCPs recruited for this phase of the study were predominantly medical staff (2 consultants and 4 junior doctors) (Table 3.3). All participants answered the questions regarding the paediatric dosage forms followed by physical properties of ODTs. Phase 2 findings suggested that the main issues with the properties of ODT formulations are those associated with taste, size and disintegration time. However, colour and shape of ODTs were highlighted the least important by 85% of respondents.

"I think bitter taste they will spill it out, so I think sweet or neutral would be better from taste point of view." (Pharmacist 1)

"Size, yes, it should be as small as possible really, just so that they can actually get it into their mouths and so they don't feel uncomfortable with it in their mouth, so they're not going to choke or anything. So if it's a small tablet and it dissolves that would be great." (Doctor 4)

"Shape probably not that important." (Doctor 1)

"I don't think colour really matters. I suppose white is a kind of neutral but I don't think it's really an issue." (Pharmacist 3)

"Shape and colour, I don't think it doesn't really matter" (Nurse 2)

Table 3.3: Details of the semi- structured interviews for healthcare professionals.

Semi-structured interviews	Date conducted	Number of participants	Location
Pharmacists	18th -25th July 2016	3	BCH
Nurses	18th -25th July 2016	3	BCH
Doctors	18th -25th July 2016	6	BCH

Additional informal recommendations from healthcare professionals within phase 2 on how to improve ODTs formulations were reported in (Table 3.4)

Overall, in phase 1 and 2, the majority of respondents (90%) recommended that taste and disintegration time were the most important physical properties respectively in order to develop and design ODTs formulations. Similarly, various studies stated that taste was an important factor in influencing medication adherence and acceptability in paediatric population (Matsui, 2007, Squires *et al.*, 2013).

Table 3.4: Recommendations and improvements to ODTs formulations as reported by focus groups and semi-structured interviews healthcare professionals.

HCPs recommendations to ODTs formulations	**Reports of healthcare professionals**
Enhancing the taste of ODT formulations using sweet to neutral sweeteners	Pharmacist FG Doctor 1, 3, 4 and 5 SI Pharmacists SI Nurse 1 and 3 SI
Using strawberry (most preferred), orange or banana flavours.	Nurse FG Pharmacist 1,2 and 3 SI
Using small size of ODTs	All participants for FG and SI
Improving disintegration time (Dissolving very quickly)	All participants for FG and SI
Designing shape to be round with white colour	Pharmacist FG Doctor 2 SI
Educating children and may be their parents concerning ODTs formulations	Doctor 4 and 5 SI Nurse 3 SI

FG: Focus group; SI: Semi-structured interview

3.3.3. Phase 3- Online survey

A total of 41 online surveys (study cohort n=110, response rate 37.3%) were completed. The final online survey consisted of four sections. These were: demographic data including details of different healthcare professionals and participant years' experience of working with paediatric patient; healthcare professionals views and their preferences for various oral dosage forms (liquids, tablets, capsules and ODTs); HCPs recommendations concerning colour, shape, size, thickness, taste, flavour and disintegration time of tablets; participant feedback about the survey and further recommendations.

3.3.3.1. Demographic results of 41 healthcare professionals

The first section of results displayed the names of the Children Hospitals that took part and the number of respondents from each Hospital. Participants were from multidisciplinary professions. It gives the breakdown of their professions and years' experience working in paediatrics. Pharmacist were the highest percentage of participants in this phase (46%) followed by nurse (29%) and medical practitioners (24%) respectively. Approximately more than half (54%) of the respondents reported their experience ranged from 1 to 5 years. The results showed a significant difference among the different healthcare professionals years of experience ($p<0.05$) (Table 3.5). The survey instrument is shown in (appendix 9).

Table 3.5: Details of healthcare professional's respondents at ACH and BCH, including number and percentage of each profession and years of experience.

Characteristics		ACH N=21 (%)	BCH N=20 (%)	Total N=41 (%)	P value
Professions	Consultant (Medical staff)	0 (0%)	0(0%)	0(0%)	<0.05
	Junior medical staff	7(33.3%)	3(15%)	10(24.4%)	
	Nurse	3 (14.3%)	9(45%)	12(29.3%)	
	Pharmacist	11 (52.4%)	8(40%)	19(46.3%)	
Years of experience	1-5	10 (47.6%)	12(60%)	22(53.7%)	<0.05
	6-10	7 (33.33%)	4(20%)	11(26.8%)	
	11-15	2 (9.5%)	0(0%)	2(4.9%)	
	16-20	0(0%)	3(15%)	3(7.3%)	
	>20	2(9.5%)	1(5%)	3(7.3%)	

ACH: Alder Hey Children's Hospital, Liverpool and BCH: Birmingham Children's Hospital

3.3.3.2. Healthcare professionals views regrading paediatric dosage forms

This section involves the analysis of the responses of the participants according to types of dosage forms that have been prescribed, supplied or given to paediatric patients. Figure 3.2 illustrated that liquids dosage forms were more popular (58%) compared to tablets (33%), ODTs (8%), capsules (1%) and other dosage forms. There was a significant difference among distribution of different dosage forms to children ($p<0.05$). In this study liquids were the most prescribed dosage forms among dual sites, possibly due to availability as well as shortages for other dosage forms. This was supported by evidence from (Adams *et al.*, 2013) who indicated that when healthcare professionals were asked to rank the factors that impact their selection of paediatric medicines, availability was the most important factor when prescribing oral medications to children.

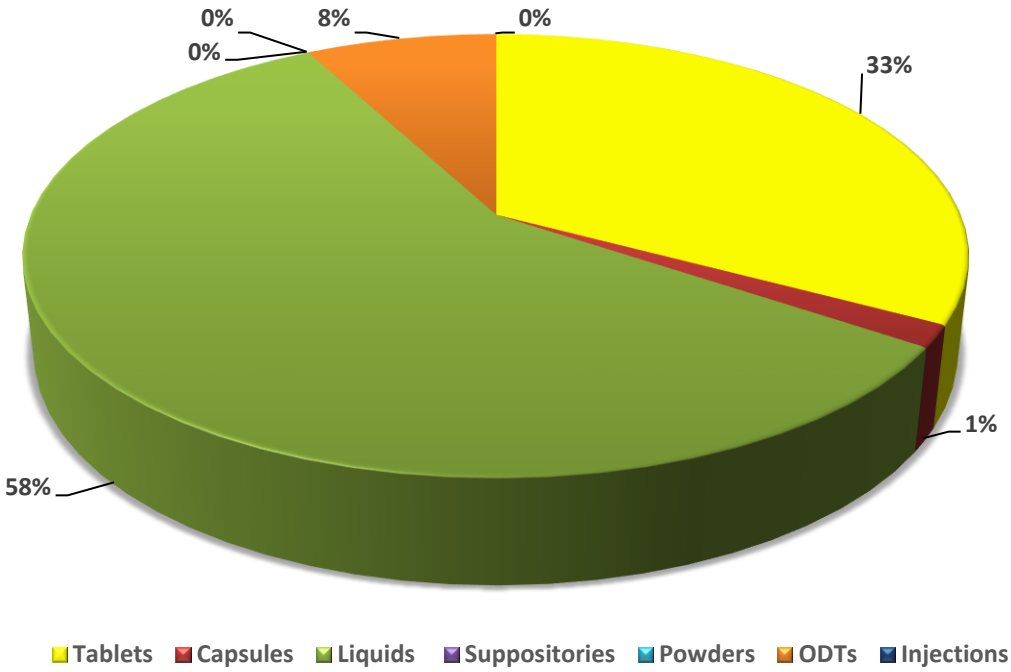


Figure 3. 2: Distribution of the types of dosage forms which are prescribed, supplied or given by healthcare professionals to paediatric patients indicating a massive preference for liquid oral dosage forms, then followed by tablets.

In our study, when respondents were asked to rank the most preferred oral dosage forms, results showed that liquids were the most popular oral dosage form (52%) followed by ODTs (30%), tablets (18%) with no preference for capsules (0%) (Figure 3.3). The rational for healthcare professionals on preference of liquids in the pediatric population was possibly due to a number of factors (Figure 3.4), including child age weight, parents, cost effectivness and medicine manipulation. Furthermore, there is a regularly thought bias amongst healthcare professionals that liquids are preferred by younger children (Bryson, 2014).

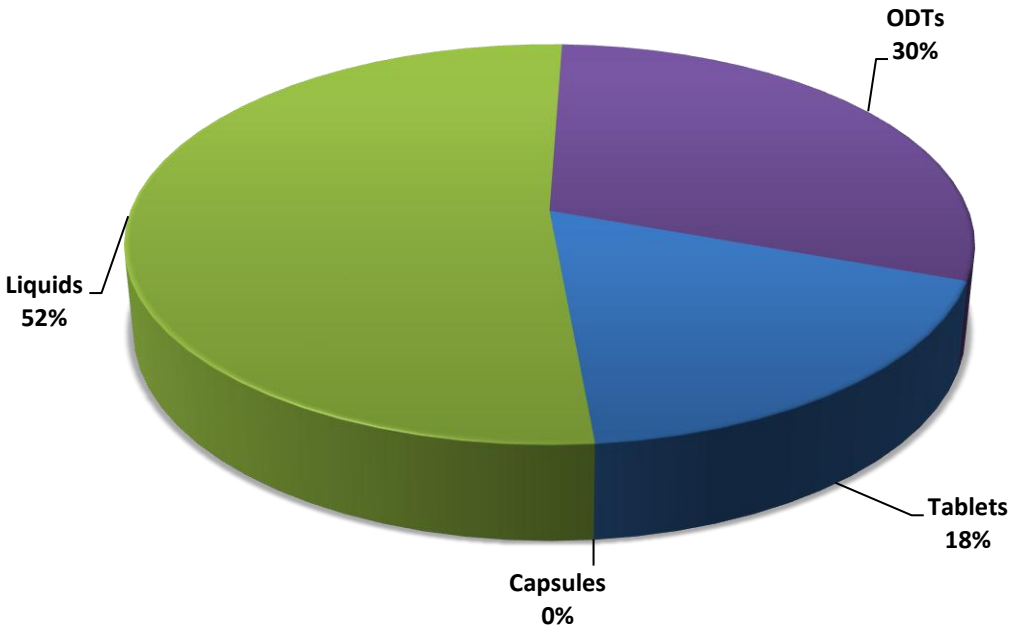


Figure 3.3: Distribution of the preferred oral dosage forms among healthcare professionals, indicating a preference for liquid dosage forms, which is then followed by ODTs and traditional tablets.

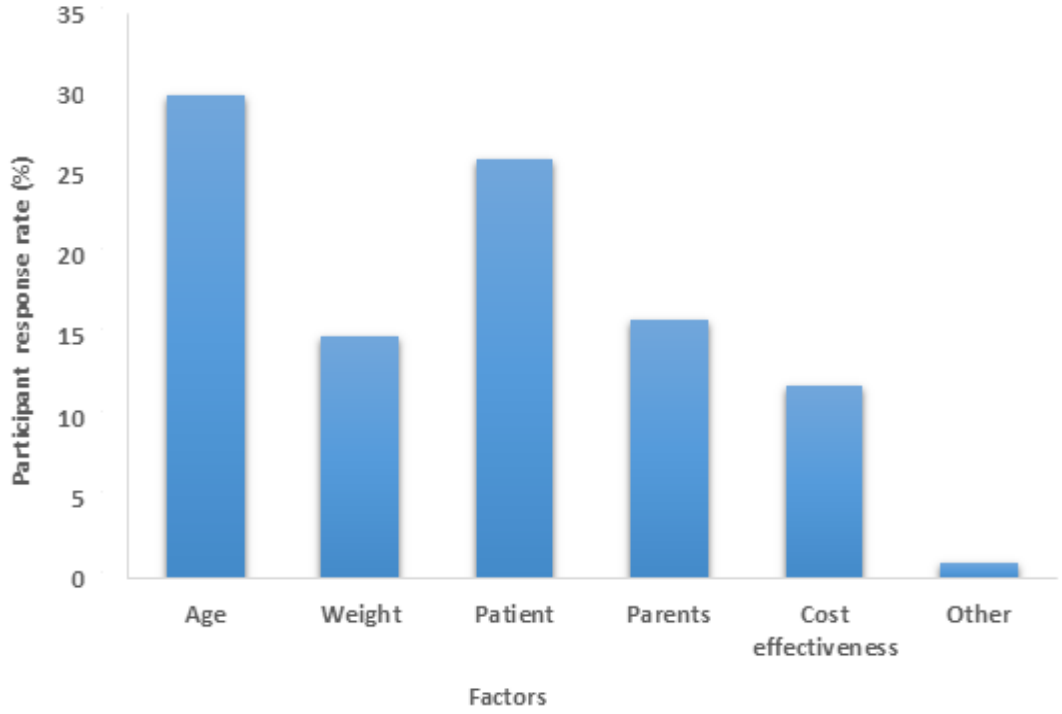


Figure 3.4: Distribution of factors which influence choice of formulations for paediatric patients indicating that patient age is the most influential factor that dictates the preference of dosage form.

3.3.3.3. ODTs formulations

3.3.3.3.1. Healthcare experience regarding ODTs

It is essential to mention that ODT have become a popular area of research for scientists in the last decade as a new 'drug delivery system', with benefits including ODTs being a more acceptable dosage form specifically for paediatric patients due to ease of use and administration (Parkash *et al.*, 2011). Orally disintegrating dosage forms have great promise for paediatric patients as they are easy to administer and don't require water, with a reduction in choking risk due to the rapid disintegration (EMEA, 2006). Furthermore, previous studies and surveys stated that ODTs are well received by paediatric patients and healthcare professionals (MacGregor *et al.*, 2003, Carnaby-Mann and Crary, 2005). The results in this study (Table 3.6) showed that a total of 32 (78%) healthcare professionals prescribed/dispensed or administered ODT

formulations to children whereas 22% of participants did not prescribe ODTs. Additionally, respondents were asked regarding the number of ODT dosage forms that had been given to patients; approximately half of the respondents (53.7%) followed by only (2.44%) indicated that between 1 to 5 and more than 10 formulations were given over the last 12 months respectively.

Table 3.6: Details of respondents regarding ODTs prescribing/ dispensing or administering and total number of prescribed ODTs over last 12 months**.**

Have you ever prescribed (doctor)/dispensed and supplied (Pharmacist)/ given or administered (nurse) ODTs to paediatric patients?	In the last 12 months, do you know how many ODTs formulations have you prescribed, dispensed or administered?					Totals
	None	1-5 Formulations	6-10 Formulations	More than 10 Formulations	I don't know	
Yes	0.00%	22(53.66%)	5(12.20%)	1(2.44%)	4(9.76%)	32(78.05%)
No	8(19.51%)	0(0.00%)	0(0.00%)	0(0.00%)	1(2.44%)	9(21.95%)
Not applicable	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)
I don't know	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)
Totals	8(19.51%)	22(53.66%)	5(12.20%)	1(2.44%)	5(12.20%)	41(100.00%)

Interestingly, when healthcare professionals were asked concerning what extent they agree or disagree that liquid formulations could be substituted with ODTs in paediatric patients, approximately (63%) of respondents agreed that a suitable alternative to liquids was the ODT dosage form as shown in (Figure 3.5). Similarly, Lajoinie *et al.*(2014) identified that approximately 80% of prescribed liquid formulations could be substituted with a solid dosage forms in children.

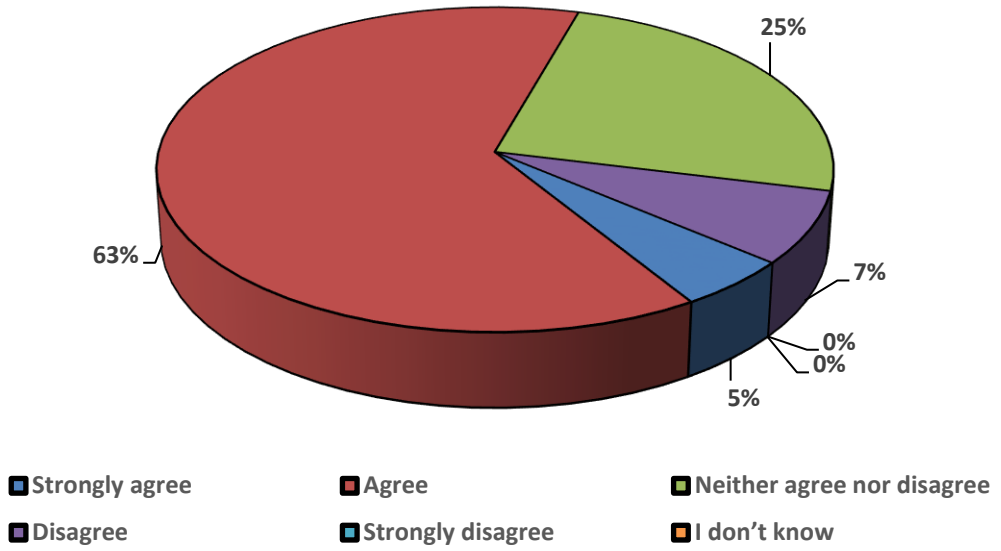


Figure 3.5: Distribution of total respondents' opinions regarding liquid formulations substitution with ODTs in paediatric patients, indicating that the participants would strongly agree that liquid dosage forms could potentially be replaced with ODTs.

Considering ODTs could be an alterative to liquid formulations, healthcare professionals were asked to give their opinions regarding multiple factors such as safety,efficacy, cost effictviness and compliance. Pharmacists indicated more benefits regarding safety and suggested that "liquid medications may be more likely to have unsuitable excipients for children particularly if they have been formulated for the adult population". Furthermore, regarding dosing error, liquid formulations require calculation and measurement of the dose volume, whereas ODT's are used because they are available in the appropriate dose and don't need further manipulation. They also mentioned that possible risk of accidental overdose for the patient was higher with liquids, for instance, if a young sibling accessed a liquid medicine they may be more likely to consume more than if they accessed ODTs. On the contrary, one pharmacist stated that "a lot of solid forms come in very poor dosing variances so the tendency is to dissolve in liquid and give a proportion, but an accurate dose cannot be guaranteed.

Lastly, there was a number of issues with children who have feeding tubes and the tablets blocking them (EMA, 2006). When asked regarding efficacy, the majority of participants indicated that they had no idea as there were too few ODT formulations available compared to liquids, however, medical staff hypothesised that as ODTs melt or dissolve in the mouth then it would go to the blood system quicker than a liquid and therefore potentially was more efficacious and faster acting. The vast majority of respondents mentioned that, in general, oral solid forms are much less costly than liquid formulations, since they are easier to develop, manufacture, transport, store and distribute. These findings were in line with previous results by Lajoinie *et al.*(2014) who stated that solid dosage forms were more convenient and less costly compared with liquid medications for paediatric patients. With regard to compliance and adherence, respondents recommended that ODT formulations may increase compliance but it depended on the taste "if it tastes nice, sweet taste, my concern about taste, mostly sweet if you compare it with something that children know, like Calpol". Similarly, a study concluded that tablets for children may be considered as a viable alternative to improve adherence and therefore overall acceptability (Ansah *et al.*, 2001). Furthermore, research by (Bagenda *et al.*, 2011) confirmed that adherence to tablet formulations was significantly superior to liquid formulations.

3.3.3.3.2. Physical characteristics of ODTs

Acceptability and adherence of medication in paediatric patients is potentially affected by physical characteristics (i.e. taste, flavour, size, shape and colour) of dosage forms (Cheng and Ratnapalan, 2007, Squires *et al.*, 2013). Consequently, the next set of investigations were focused on assessing the healthcare professionals views and their preferences on different attributes of ODTs such as colour, taste, shape, flavour and disintegration time. We asked healthcare professionals how medicines for children should taste. Their responses–overall and stratified by healthcare profession types are shown in (Figure 3.6). The majority of participants (65%) preferred sweet tasting

medicines for children followed by neutral/no taste and bitter taste (33% and 2% respectively). There was a statistically significant difference ($p<0.05$) between acceptable taste by healthcare care professionals. This is in line with findings from Adams *et al.* (2013) who stated that the majority of participants preferred sweet tasting medicines for paediatric populations.

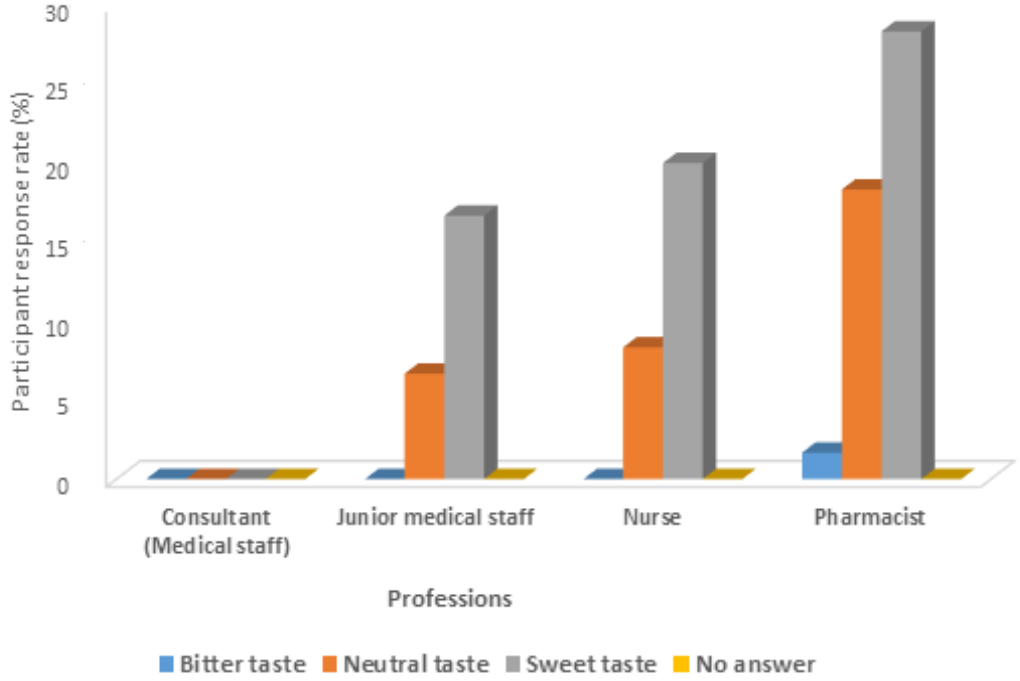


Figure 3. 6: Distribution of preferred ODTs tastes stratified by different professions indicating that sweet taste is preferred by all three sets of healthcare professionals, with neutral taste also being popular.

The addition of flavours into formulations not only masks the taste of active ingredients but also improves medication adherence, for instance flavouring medicine increases patient adherence to over 90%, from an average of 50% (Bryson, 2014). In the present study nearly the half of the participants (49%) preferred strawberry followed by orange and banana (19% and 18% respectively) while no preferences (0%) was recorded for mint and lemon (Figure 3.7). Overall strawberry was the most preferred flavour, significant differences were found among respondent preferences ($p<0.05$). Similarly, in our previous study which was carried out with the paediatric population confirmed that the vast majority of participants preferred sweet taste along with strawberry flavour (Alyami *et al.*, 2016).

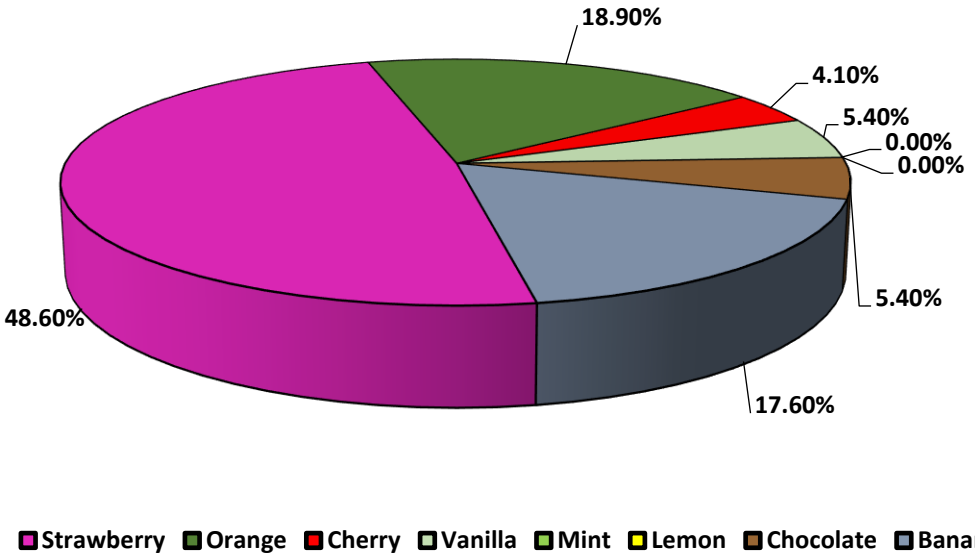


Figure 3.7: Distribution of preferred ODTs flavours by all respondents, with strawberry flavour being the most popular, followed by orange and banana.

Due to consideration of size and shape of dosage forms, size and shape may affect the transit of the product through the pharynx and oesophagus and may directly affect a patient's capability to swallow a particular drug product (Ranmal *et al.*, 2016). The current study reported that vast majority (90%) of respondents' preferred small size (5

to 7 mm) compared to the medium 10 % (8 to 12 mm) or big with 0% preference 0% (≥13mm), as shown in (Figure 3.8). The size of ODTs was potentially highlighted across all groups of healthcare professionals with small size highly recommended. Several studies support this findings and have stated the negative attitudes of children concerning big sizes of tablets (Reddington *et al.*, 2000, Roberts, 2005, Paranthaman *et al.*, 2009).

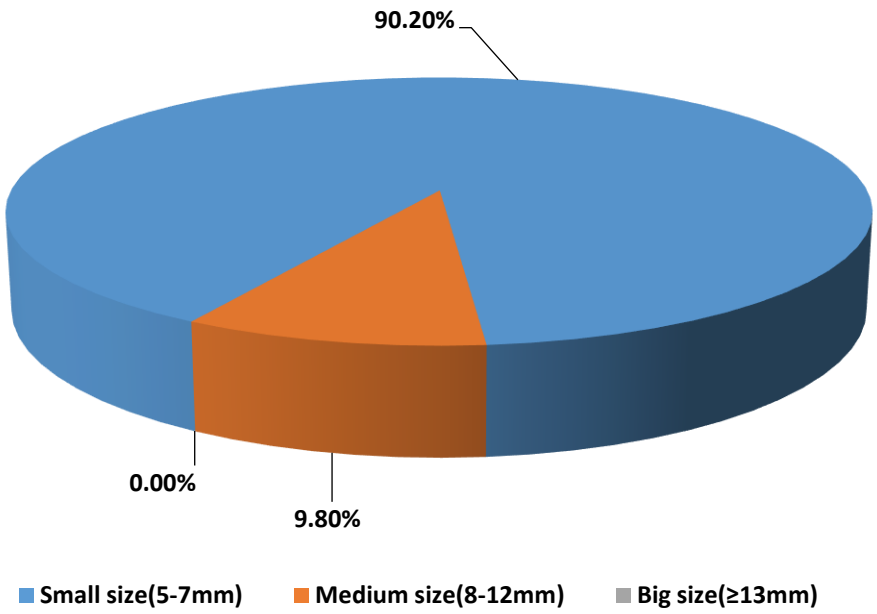


Figure 3.8: Distribution of preferred ODTs sizes by all respondents clearly showing that a small dosage form would be preferable.

Figure 3.9 shows the respondents preferences based on the shape of the ODT formulations. The majority of the participants preferred ODTs that are round in shape. This accounted for 83 % of the responses while the oval shape was second with a preference of 10%, approximately 5% reported that they had no preference for shape with the least preferred shapes being triangle and square at 2.4% and 0% respectively.

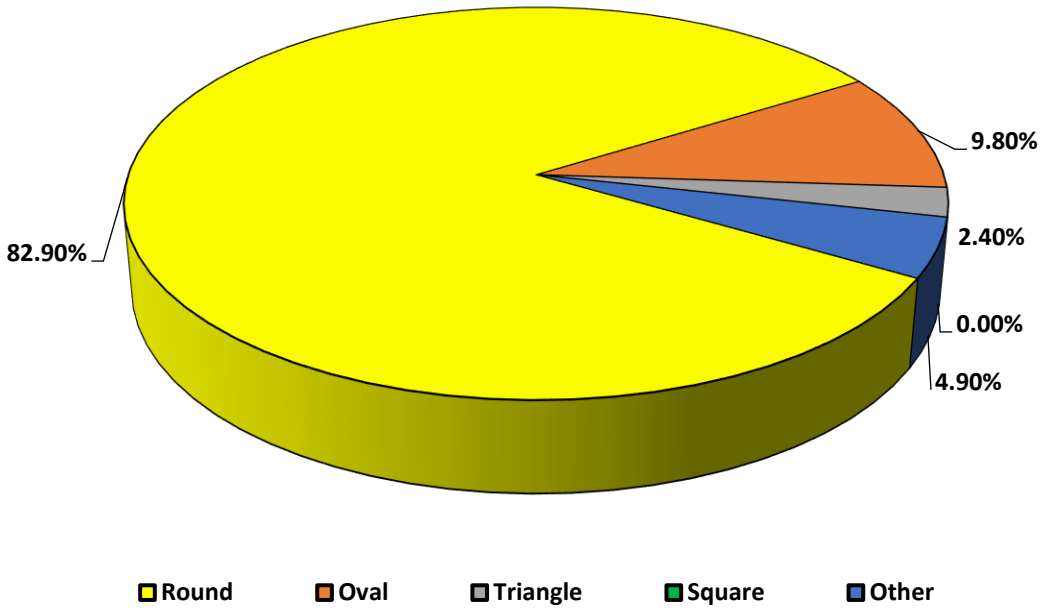


Figure 3.9: Distribution of preferred ODTs shapes by all respondents indicating that a round shape is massively preferred compared to any other tablet shapes.

With respect to colour preferences, (Figure 3.10) demonstrated that white was the most preferred colour for ODTs by more than 70% of the respondents followed by pink (17%), yellow (5%) and finally blue (2%). A significant difference was identified by Chi-square test for colour preferences $p<0.05$. It was worth mentioning that the selection of an appropriate colouring agent may positively impact child acceptance and also enhance medication adherence (Levitan *et al.*, 2008). The results in (Figure 3.11) showed that the healthcare professionals opinions regarding length of time for ODT formulations to be dissolved in the mouth, with the vast majority of the participants (95%) preferring very rapidly (<30sec) disintegrating ODTs followed by rapidly disintegrating ODTs (between 30 to 90 sec) at about 5%.

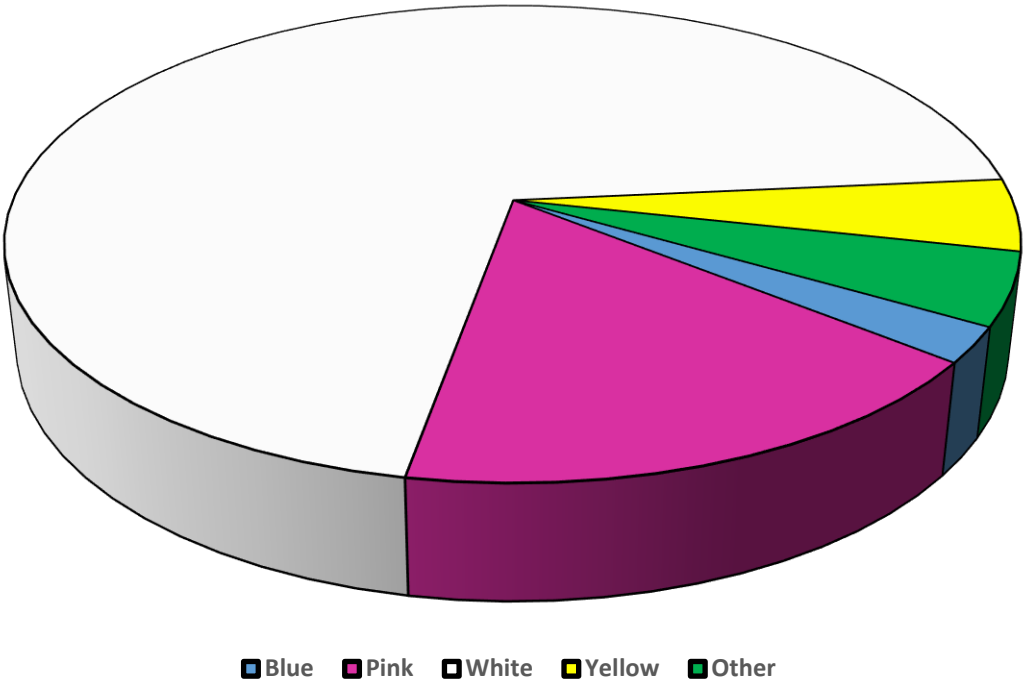


Figure 3.10: Distribution of preferred ODTs colours by all respondents showing that a white tablet is the most preferred colour amongst the healthcare professionals for paediatric administration.

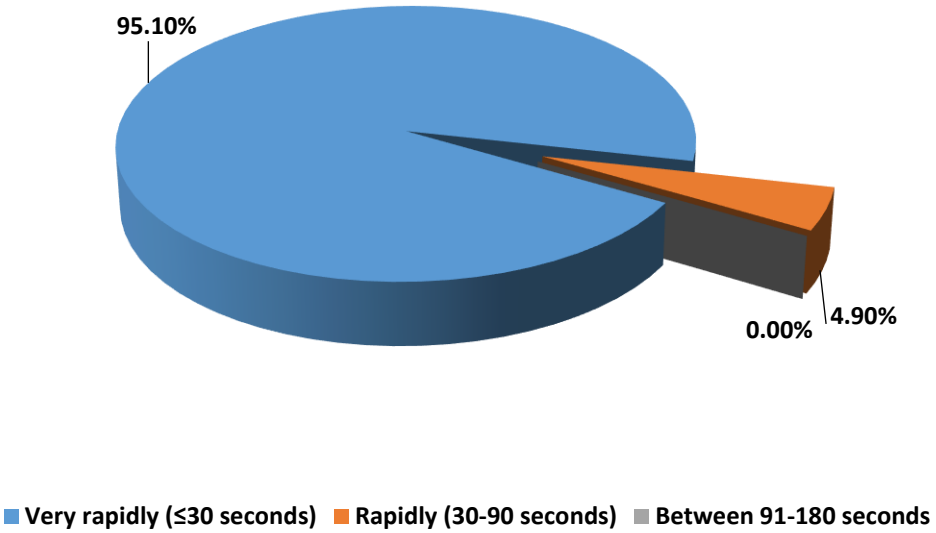


Figure 3.11: Distribution of preferred ODTs disintegration times by all respondents showing that a rapidly disintegrating tablet would be seen as the ideal ODT by the healthcare professionals.

Respondents were also asked what the most important physical characteristics of ODTs were and the results showed that taste was the most important property (approximately 30%), followed by disintegration time, flavour and size (29%, 22% and 19% respectively) whereas, colour and shape were the least important characteristics (Figure 3.12). A significant difference was found between those characters ($p<0.05$). The results indicated that the most important factor was taste with the findings aligning with the published literature (Matsui, 2007, Hasamnis *et al.*, 2011, Squires *et al.*, 2013).

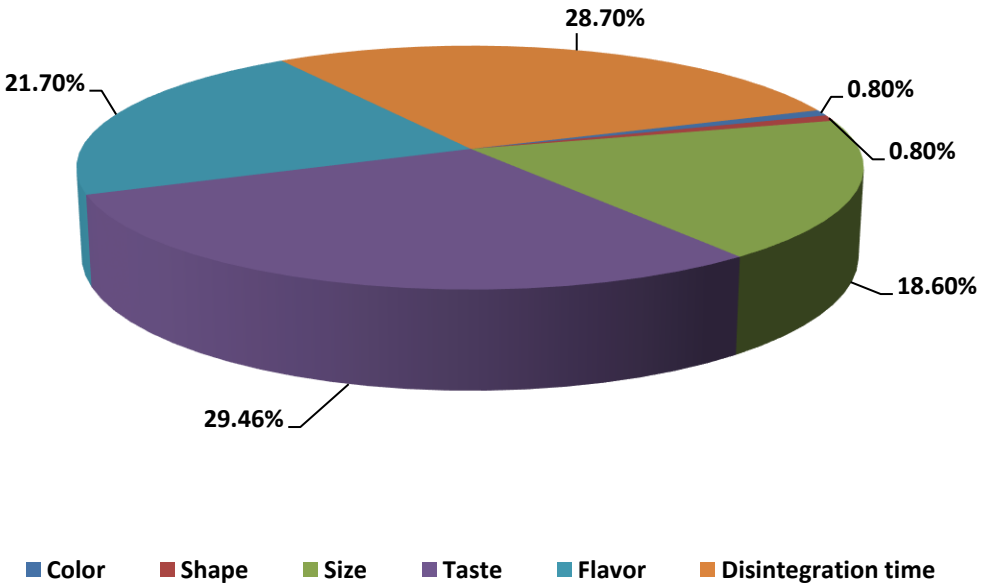


Figure 3.12: Percentages distribution of the most important characteristics of ODTs. Taste, disintegration time and flavour appeared as the most important factors by the healthcare professionals when considering ODTs.

3.3.3.4. Further recommendations, feedback and limitations

In the last section of the study, the healthcare professionals were asked to give their opinions, recommendations and feedback on how the study was conducted. The vast majority of respondents designated that regardless of the fact that it was a good idea, there were areas that could be improved. For instance, they pointed out that most questions should be asked to paediatric patients, however this has been covered in the previous chapter of this thesis. In addition, pharmacists also indicated that there

were very few ODT formulations available to enable them to make an informed answer to most of survey questions. With regard to drug manufacture and design, a few participants recommended that film formulations may be another form of oral dispersible formulations that could offer further advantages. Participants also suggested that taste was the most important property reported for ODT administration, hence, the manufacturers should ensure that the taste is neutral to sweet, but not bitter. The recruitment process in focus groups (phase 1) was carried out through pharmacists and nurses but not the medical practitioner group. This may have led to under representation of doctors' perspectives and input. Certainly some healthcare professionals participating in focus group from the same institution were known to each other, this might have been seen as a potential limitation as respondents may have been more disposed to speak in a 'socially accepted' style (i.e. less fairly) (Rabiee, 2004). The study was conducted at two sites in the UK, thus it cannot be generalised and viewed as a nationwide perspective, and further exploration in another countries is required.

3.4. Conclusion

In summary, this study identified a plethora of recommendations and opinions for paediatric dosage forms, particularly how ODTs are perceived by healthcare professionals. Secondly, the study identified that HCP perceived suitable organoleptic properties of ODTs (e.g. dissolving time) which influenced acceptability in paediatric patients. As a result this pragmatic study filled the research gap that existed through exploring such healthcare professional's views and recommendations of the acceptability and physical characteristic properties of ODT using a mixed methods approach (focus group, semi-structured- interviews and online survey). The overall results from dual sites demonstrated that liquid dosage forms are the most prescribed/administered dosage form followed by ODTs. Factors found to significantly influence choice of formulations for paediatric patients were age, weight, parent/care giver and cost effectiveness of dosage forms. Although, the majority of respondents agreed that liquid formulations could be substituted with ODTs in paediatric patients, the number of available ODTs in the market were insufficient to be prescribed or administered. From the physical characteristics results in this study, it can be concluded that taste, disintegration time and flavours were the most important properties related to ODT administration supporting the results reported from the previous study (Alyami *et al.*, 2016). Additionally, the other important characteristics of solid dosage forms were white colour, small size, round shape, strawberry flavour and rapid disintegration time. Further studies exploring the opinions of parents concerning paediatric dosage forms would complement this research. This study also suggests that there is a need for further research to develop a wider range of ODTs for use in the paediatric population.

Chapter 4

An investigation into the effects of excipient particle size, blending techniques and mixing parameters on the homogeneity and content uniformity of a blend containing low-dose API

Publications relating to chapter 4

Hamad Alyami, Eman Dahmash, James Bowen, David Terry and Afzal R Mohammed (2016). An investigation into the effects of excipient particle size, blending techniques and mixing parameters on the homogeneity and content uniformity of a blend containing low-dose API. PLOS One. Accepted.

4.1. Introduction

Oral drug delivery is the favoured route of drug administration, due to the convenience of administration, being non-invasive and therefore more likely to promote patients compliance with their treatments (Siddiqui *et al.*, 2011). Efficient and reproducible blending process is critical to manufacturing of oral drug delivery systems, as the quality of the final product is driven by the quality of the blend (Harnby, 2000). Hence, production of non-homogenous blends results in discrepancy in the content of the active pharmaceutical ingredient (API) and product failure (Dahmash and Mohammed, 2015).

Blending is a process where two ingredients or more are processed in order to achieve a homogenous product (Harnby, 2000, Maynard, 2007). To achieve that, three main mechanisms of powders blending are involved; convection, diffusion, and shear. Convective blending encompasses gross movement of particles within the blend, whereas, diffusion is a slow blending process where individual particles are distributed upon blending into newly formed interface. Lastly, the shear mechanism of blending comprises of blending of material while passing along forced slip planes which could aid in breaking agglomerates and hence enable blending (Kaye, 1997, Maynard, 2007, Deveswaran *et al.*, 2009). Depending on the flow characteristics of powders, solids are broadly divided into cohesive materials and non-cohesive materials. Blending of cohesive materials is more complex because of the possibility of developing aggregates and lumps (Harnby, 2000, Maynard, 2007).

Normally, a high drug loading capability is ideal in such formulations; the overall weight of tablets is relatively low to allow for rapid disintegration and dissolution (Parkash *et al.*, 2011). However, for high potency or low load drugs like vitamins that exist at lower loading in formulations, this is a major issue. The problem with manufacturing using

such drugs is obtaining a uniform distribution of drug throughout the formulation (Zheng, 2009). Uniformity of API is important as it will impact drug dissolution, absorption, bioavailability and onset of clinical effect (Hirani *et al.*, 2009).

Developing formulation for low load drugs where small amount of the API is blended with a large amount of excipients/carriers is challenging. Blend homogeneity is dependent on multiple factors including: particle size, size distribution and density of the individual components, blending process or blending equipment and presence of agglomerates within the blend (Kaye, 1997, Portillo *et al.*, 2008). Understanding of powder properties particularly particle size, shape, size distribution particle surface roughness will enable the selection of appropriate excipients and blending process (Flament *et al.*, 2004, Jallo *et al.*, 2012, Dahmash and Mohammed, 2015).

Various blending techniques to obtain homogenous blends for low API load are reported. Apart from the multistep techniques like granulation and spray drying, geometric dilution is a commonly used technique when low load API formulation is developed. It implies gradual addition of equal portions of the diluent/ excipient to the API upon blending. The process increases the chances of equal distribution of the API particles within the blend. Ordered mixing or interactive mixing is another promising technique where fine API particles are adsorbed to the surface of coarse carrier/excipient particles as depicted in (Figure 4.1) (Kukkar *et al.*, 2008, Saharan *et al.*, 2008, Dahmash and Mohammed, 2015).

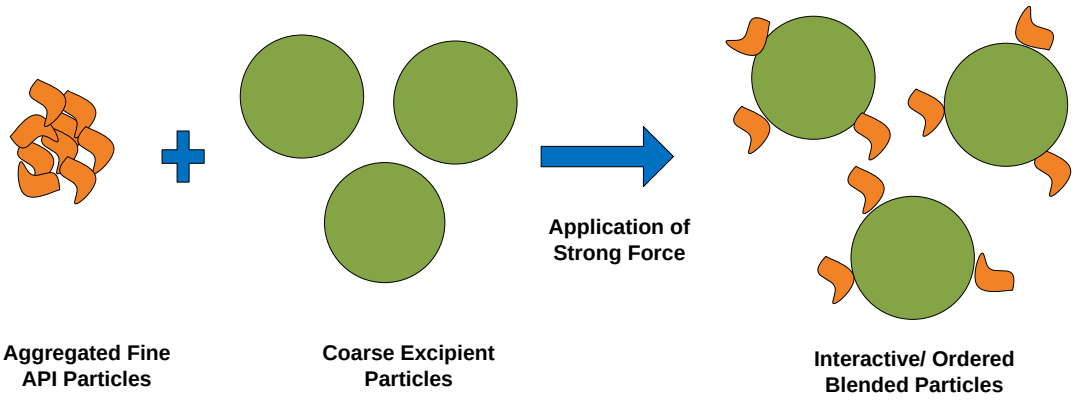


Figure 4.1: Schematic diagram showing the process of interactive/ordered blending. Fine aggregated API particles blended with coarse carrier/ excipient particles upon the application of strong mechanical force the fine API particles are de-aggregated and get attracted to the surface of the excipient particles producing interactive/ ordered blended particles.

Obtaining optimal concentrations of excipients at the correct particle size and thereby enhancing flow is critical in improving manufacturability (Pingali *et al.*, 2011). Particle size also has an impact on uniformity of content, with smaller particles allowing for more uniform mixes to be achieved (Muselík *et al.*, 2014). This produces a trade-off and the need for a balance to be found in order to produce powder blends with ideal characteristics for tableting whilst maintaining uniformity of content.

The work in this chapter aims to evaluate the impact of particle size and dilution potential of three model carriers to develop a uniform blend comprising of small dose model drug, ergocalciferol using various blending techniques. The objectives of the study are:

- To evaluate the impact of different particle size (non-cohesive, cohesive and non-sieved) for three model carriers – starch, pregelatinised starch and micro crystalline cellulose (MCC) on blend homogeneity.
- To study the flowability of cohesive, non-cohesive and non-sieved carriers using the angle of repose method.

- Evaluation of morphological properties, surface topography and particle roughness using surface interferometry and scanning electron microscopy (SEM).
- To study the effect of increasing carrier ratio from1:5 to 1:50 on drug content uniformity (geometric dilution).
- To investigate the effect of increasing mixing time from 0 to 32 minutes on drug content uniformity (ordered mixing, interactive mixing).
- To explore the influence of mixing order of different pharmaceutical excipients namely D-mannitol, Microcrystalline cellulose, crospovidone and Magnesium stearate during mixing on blend flow and tablets properties.

4.2. Materials and Methods

4.2.1. Materials

Starch and pregelatinised starch (starch 1500®) were obtained from Colorcon (Dartford Kent, UK). Ergocalciferol (Vitamin D2) was purchased from Discovery Fine Chemicals (Dorset, UK), whereas two grades of microcrystalline cellulose MCC Avicel type (PH-200) and (PH-102) were donated by FMC BioPolymer Europe (Brussels, Belgium). D-mannitol, ethanol and magnesium stearate were purchased from Sigma-Aldrich (Pool, UK), while Crospovidone (CrosPVP, Polyplasdone® XL-10) was obtained from Ashland (Wilmington, USA).

4.2.2. Methods

4.2.2.1. Micronisation of Vitamin D2

Vitamin D2 was micronised by manual grinding using mortar and pestle for 30 minutes followed by sieving through different sieves for 12 minutes. 4 sieves (with 20cm diameter) were selected and weighed with the following mesh size range; 125 µm, 106 µm, 75 µm, 53 µm arranged as a nest according to size with coarsest on top using the vibratory sieve shaker Analysette- Spartan (Fritsch- GmbH) with deep amplitude (2.5mm). Then the fraction of particle size< 53 µm was manually passed through sieve with mesh size of 20 µm (particles with size ≤20µm were used for the study) in order to optimise distribution within powders and ensure better uniformity of content in the batches (Zhang and Johnson, 1997).

4.2.2.2. Sieving process

The original powders of the carriers (starch, pregelatinised starch and MCC) were sieved through different sieves. 8 sieves (with 20 cm diameter) were selected and weighed with the following mesh size range; 710 µm, 500 µm, 355 µm, 250 µm, 125

µm, 106 µm, 75 µm, 53 µm arranged as a nest according to size with coarsest on top. Sieving was carried out for 12 minutes using the vibratory sieve shaker Analysette-Spartan (Fritsch- GmbH) at deep amplitude (2.5mm) in order to achieve separation of non-cohesive and cohesive parts of the powder. Approximately 40g of each powder was collected and labelled for use in the study. The particle size ranging between 125-180 µm was chosen as a non-cohesive fraction whereas particles with size with less than 53 µm were considered cohesive powders. Individual sieves were weighed to estimate the powder content. The process was repeated for additional 5 minutes to ensure weight difference did not exceed 5%.

4.2.2.3. Analytical technique

The amount of ergocalciferol dissolved in the solution samples was quantified using UV spectrophotometry (Jenway 6305 from Bibby Scientific Ltd. Staffordshire, UK) set at wavelength of 265 nm. Method validation was done based on the International conference on Harmonization (ICH) guidelines for validation of analytical procedures (ICH, 2005). Calibration curve was prepared from dilution of stock solution of ergocalciferol (10 µg/ml), using ethanol as solvent. The absorbance of the dilutions of stock solutions were determined by UV spectrophotometer, at wavelength of 265 nm (USP, 2003). Six point calibration curve was obtained in a concentration range from 0-3.6 µg/ml for ergocalciferol. Calibration curve was validated against specificity, linearity, accuracy, precision, limit of detection (LOD) and limit of quantification (LOQ).

4.2.2.4. Powder characterisation

4.2.2.4.1. Powder flowability (angle of repose method)

Powder flowability was evaluated using angle of repose method (USP-29, 2009). 5g of powders were poured through a funnel onto a flat surface. The funnel was positioned 10 cm from the horizontal surface, and the powders were allowed to flow freely until the formation of a symmetrical cone. Both the base (b) and height (h) of the formed

cone were measured and recorded. Equation 4.1 was used to calculate the angle of repose ($\boldsymbol{\theta}$). Values were expressed as mean ± standard deviation (n=3).

$$\boldsymbol{\theta = \tan^{-1}(h/0.5b)} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \boldsymbol{Eq\ (4.1)}$$

Results of the angle of repose correlate to flowability. Angle less than 30° indicates excellent flowability, between 31-35° is for good flowability, whereas angles above 45° is an indication of poor flowable powder (USP-29, 2009).

4.2.2.4.2. Particle size analysis (laser diffractometer)

Powder particle size analysis was performed using laser diffractometer, Sympatec HELOS/ RODOS T4.1 (Clausthal-Zellerfeld, Germany). An R3 lens with a working range in between 0 and 178 µm was used for this study. The instrument permits the powder to circulate continuously through the system during the measurements through the sample dispersing system RODOS (dry disperser). Powder sample (0.5 g) was spread over the feeding tray of the VIBRI that transfers the sample into the dispenser (RODOS). Plots of particle size distribution wereobtained covering the range from 0.5-175 µm. Parameters such as the volume mean diameter (VMD), X10, X50 (median, 50% volume percentile) and X90 were obtained. The span of distribution was calculated using equation 4.2. All the measurements were conducted in triplicate.

$$Span\ of\ distribution = \frac{(\times_{90} - \times_{10})}{\times_{50}} \quad \ldots\ldots\ldots Eq\ (4.2)$$

It should be noted that laser diffraction method produces high velocity for the powder which is aided by compressed air set at 3 bars that affects dispersion of the sample and hence, it is expected that the agglomerates originating from fine powder are dispersed into their primary particles and perfectly distributed (Jallo *et al.*, 2012).

4.2.2.4.3. Scanning Electron Microscopy (SEM)

SEM was used to study the morphological structure of particles. Samples were distributed by sprinkling on a double adhesive carbon tape placed over an aluminium

stub. Then samples were coated twice with gold in a sputter coater Polaron SC500 (Polaron Equipment, Watford, UK) at 20 mA for three 4 minutes and then examined by the SEM before imaging to enable sample conductivity. The sample imaging was performed on a field emission scanning electron microscope (Cambridge Stereo Scan (S90) Electron Microscope, Cambridge Instrument, Crawley,UK). Different magnifications were taken to identify various characteristics and surface features of the powders.

4.2.2.4.4. Surface topography using Interferometer

Interferometric measurements of particle surface topography were performed using a MicroXAM2 interferometer (Omniscan, UK), operating using a white light source. Samples were imaged using a 50X objective lens. Scanning Probe Image Processor software (Image Metrology, Denmark) was used for the analysis of acquired images. Multiple images were stacked together to produce extended fields of average roughness in 3-D (Sa), root-mean-square roughness in 3-D (Sq), maximum height of the surface (Sy). The software enabled the calculation of adhesion energy and flowability parameters.

4.2.2.5. Blending techniques

Initial investigations focussed on developing formulations at four different weight ratios; 1:5, 1:10, 1:20, 1:50. Each of these would contain 10mg of API and 50, 100, 200 and 500mg of the carrier respectively, weighed out using precise analytical balance then blended according to the designed blending technique.

4.2.2.5.1. Geometric blending technique

The first blending technique was based on geometric blending. A stepwise geometric addition of excipient to the API was carried out to investigate the impact on content uniformity. The blending time was set either at one or five minutes and was achieved by shaking of the sample containing tube by hand. In this instance, each created batch

was made of 600mg that was mixed in a 30ml screw cap tube. Therefore the mass of API included and excipient added in order to maintain geometric addition was altered to maintain the desired ratio at this increased batch size. Three batches were prepared for each ratio and the process was repeated for each of the three carrier powders. All samples were prepared and 5mg of the blend was used for analysis of content uniformity using UV spectroscopy.

4.2.2.5.2. Manual blending technique

600mg batch size at 1:50 ratio was carried forward for evaluating the impact of manual blending on content uniformity. This consisted of addition of the total quantity of carrier in one step into the sample tube after the required amount of API had been added. 5mg was taken from the blended powder over different time points (0, 2, 4, 8, 16, 32 minutes) for content analysis. The process was repeated for each of the three carrier powders.

4.2.2.5.3. Ordered mixing using dry powder coater

The ‘dry powder hybrid mixer prototype’ was assembled by the research group at Aston University. The machine is designed to supply sufficient mechanical force essential to break the agglomerates that are created by the cohesive powder and promote ordered and structured blending of powder mixtures. The machine comprises of a high speed rotating motor which has a speed ranging between 300-2000 rpm which is linked to a rotating container by means of a smooth inner surface in which the powder (API as well as carrier/excipient) is enclosed. To assist collision external air supply is provided via nitrogen gas which is linked to the mixing container providing pressures from 20-40 psi. The aim was to attain a homogenous mixing at 300 rpm, the total powder used was 3 g. 2% w/w API was examined for each type of carrier.

A final investigation was performed using ordered addition of non-sieved carrier which comprised of six batches made up to 3 g, containing 1% w/w API and 0.5% API.

Blending was done by the same dry powder coater at 300rpm for a total 32 minutes. 5mg samples were taken from the blended powder over a range of time points (0, 2, 4, 8, 16 and 32 minutes) to assess blend homogeneity.

4.2.2.6. Drug content uniformity using UV analysis

5 mg of the blended powders of ergocalciferol and carriers at 1:5, 1:10, 1:20, and 1:50 were dissolved in 50, 25, 10, 5ml respectively of ethanol. The solution was filtered through a 0.45 µm nylon filter (CHROMACOL LTD, Herts., UK). Ergocalciferol content uniformity was assayed using spectrophotometer using UV analysis. Spectrophotometer at wavelength 265 nm was used (USP and Volume, 2003, USP-29, 2009). Values are expressed as mean ± standard deviation (n=9).

4.2.2.7. Tablet Preparation and Characterization

Mannitol, MCC, magnesium stearate and crospovidone powders were mixed in different order and compacted into 500 mg tablets under compression force at 10 KN. The tablet press utilized for preparing the tablets was a bench-top semi-automatic hydraulic press from Specacltd. (Slough, UK) which was equipped with flat faced dies 13 mm in diameter. The tablets were characterized for porosity, hardness, disintegration time and friability. All tests were carried out in triplicates (n=3).

4.2.2.7.1. Porosity and true density of tablets

A MultiPycnometer® (Quantachrome Instruments, Syosset, USA) was used to determine the true density and porosity of the components in the tablet form using helium as the displacement gas set at pressure of 2 bars. Powder sample was placed into a tarred sample cell and accurately weighed. The sample true density was calculated from the pressure values obtained initially from filling the sample cell with helium gas and the pressure of discharged gas from a second empty cell. Calculation

of porosity was done using multiPycnometer software. The Samples were repeated in triplicate.

Tablet porosity was calculated by the following equation:

Porosity = 1-(bulk density/true density)

4.2.2.7.2. Hardness

The tablet hardness tester from Schleuniger (Thun, Switzerland) was used to measure the hardness of three tablets of each formulation. Hardness is the force required to break up the tablet into pieces. All measurements were carried out in triplicate and the values reported as mean ± standard deviation.

4.2.2.7.3. Disintegration Time

The disintegration time was obtained according to the official USP monograph 701 for tablet disintegration testing. Disintegration test apparatus used was ZT3 from Erweka (Heusenstamm, Germany). A tablet was placed in the disintegration basket (without using a disk) which was raised and lowered at a constant frequency of 30 cycles/min in the disintegration medium. Distilled water (800 ml) maintained at 37°C was used as the medium of disintegration while disintegration time was recorded for one tablet at a time to improve accuracy of recording. Time of disintegration was recorded when all the disintegrated fractions of tablet passed through the mesh of disintegration basket. Measurements were carried out in triplicate and values were reported as mean ± standard deviation.

4.2.2.7.4. Friability

The ability of the tablets to withstand mechanical stress, known as friability was measured using Roche friabilatorfrom J. Engelsmann AG (Ludwigshafen, Germany). Six tablets were utilised at 25 rpm for 100 revolutions. Tablets were sensibly de-dusted before and after the test, and friability expressed as the percentage loss in weight. The

percentages of loss in tablets (% Friability) weights were calculated using the following equation.

% Friability = (initial weight- final weight) / initial weight x 100

4.2.2.8. Statistical Analysis

Statistical analysis were done using Graph Pad Prism software (Version 3.01, CA, USA). One way analysis of variance (ANOVA) and pair-wise multiple comparisons method (Tukey's test) were used to compare data groups by using mean values and standard deviation (SD). The significant difference was determined using the probability value of 95% ($P < 0.05$).

4.3. Results and Discussion

4.3.1. Analytical technique

Absorption spectrum of ergocalciferol showed maximum absorbance at 261nm (appendix 10.a). According to specification from the manufacturer, ergocalciferol absorbs UV at 265nm, and the result obtained in this study is similar to the specification supplied by the manufacturer. It was also found out that analysis by UV spectrometry, MCC starch and pre gelatinised starch had no interference (See appendix 10).

The response of the drug was linear in the concentration range investigated and the linear regression equation was $y = 0.0443x$ with correlation coefficient $R^2 = 0.999$ (appendix 11).

The accuracy of the method is the closeness of the measured value to the true value for the sample (Zhang and Johnson, 1997). Accuracy of the method was studied by recovery experiments. The recovery was performed by preparing three different concentrations of 2, 5 and 10 µg/ml of ergocalciferol standard solution. Three samples

were prepared for each recovery level. The solutions were then analysed, and the percentage recoveries were calculated from the calibration curve (Table 4.1).

Table 4.1: Evaluation data for accuracy study of ergocalciferol.

Sample	Theoretical amount(µg/ml)	Actual amount(µg/ml)	% recovery
1	2	2.023±0.04	101.1±2.01
2	5	4.933±0.05	98.667±1.01
3	10	9.918±0.38	99.177±3.802

In addition, precision of the analytical method was ascertained by carrying out the analysis for two different concentrations (2 and 10 µg/ml) for ergocalciferol and the analysis was repeated six times. Assay of method precision including intra-day and inter-day precision were evaluated and samples were kept in the refrigerator. The % assay, mean assay, standard deviation and % relative standard deviation (RSD) were calculated (Table 4.2 and 4.3).

Table 4.2: Precision study for 2 µg/ml ergocalciferol.

Sample	% Assay Intra-day	% Assay Inter-day
1	98.93	98.21
2	102	99.24
3	101.10	99.30
4	103	96.24
	101.3	95.54
5	100.78	99.64
6	101.17	98.03
Mean	98.93	98.21
SD	1.271	1.59
%RSD	1.25	1.62

The developed process was precise as the %RSD values for the repeatability and intermediate precision studies were <1.26% and <1.62%, respectively (Table 4.2) for

2 µg/ml ergocalciferol. The percentage recovery for three samples was found to be near to 100% which shows that the procedure was accurate and hence validated.

Table 4.3: Precision study for 10 µg/ml ergocalciferol.

Sample	% Assay Intra-day	% Assay Inter-day
1	101.10	97.68
2	101.50	97.46
3	100.70	95.15
4	99.50	96.46
5	101.25	94.21
6	100.97	99.64
Mean	100.83	96.77
SD	0.71	1.77
%RSD	0.70	1.82

The Limit of detection (LOD) and limit of quantification (LOQ) of ergocalciferol were determined by using standard deviation of the response and slope approach as defined in International Conference on Harmonization (ICH) guidelines. LOD and LOQ values were calculated (Table 4.4) using below equations

$$LOD=3.3\delta /S$$

$$LOQ=10\ \delta /S$$

Where, δ= standard deviation of residuals from the curve; S=slope of the curve

Table 4.4: Regression and validation parameters of ergocalciferol.

	Parameter	Results
1	Slope	0.0443
2	Intercept	0.000
3	Standard regression equation	y=0.0443x
4	Correlation Coefficient (R2)	0.999
5	Residual standard deviation	0.0021
6	LOD (µg/ml)	0.16
7	LQD (µg/ml)	0.48

The limit of detection (LOD) for lowest amount of analyte which can be detected and is analysed by means of a statistical approach that is based on determining replicate blank (negative) samples or by means of an empirical approach, comprising of measuring gradually more dilute analyte concentrations. The limit of quantitation (LOQ) is the concentration at which quantitative data can be recorded with an elevated degree of confidence (Armbruster *et al.*, 1994). Our method showed that the LOD was 0.16µg/ml and LOQ was 0.48µg/ml (Behera *et al.*, 2012).

4.3.2. Powder characterisation

In-depth analysis of powder properties enables understanding or even predicting their performance upon blending with API. The primary aim of this study was to investigate the impact of particle characteristics on blending small quantities of candidate API. The classification of the powders into cohesive and non-cohesive was done to identify the impact of particle size during the process of blending on dose uniformity. The study commenced with the evaluation of particle size measurements and was followed up with powder flow, scanning electron microscopy and interferometry studies.

Understanding powder flow is a critical attribute during pharmaceutical manufacturing processes like, mixing, packaging, transportation, tabletting and capsule filling.

Therefore, it becomes vital to determine the flow properties of powders prior to commencing the manufacturing process.

There are two classes of material properties that need to be considered in blending powders. The first is the cohesive materials that tend to aggregate leading to flowability issues while the second class is the non-cohesive free flowing materials that could demonstrate excellent flowability but can lead to occasional segregation (Ottino and Khakhar, 2000, Aulton, 2002, Builders *et al.*, 2010, Bridgwater, 2012).

Particle size analysis results as depicted in (Table 4.5) showed that the average particle size of starch is around 11.9±0.51 µm which is expected from a cohesive fine powder. Optimising drying conditions to produce gelatinisation of starch can cause the particles to adhere together to form aggregates (Newman *et al.*, 1996) and hence the average particle size of pregelatinised starch exhibited an increase of VMD to 79.75±1.49 µm. With regard to MCC, using the laser diffraction particle size analyser results produced an incomplete distribution curve as the powder contains particles with size exceeding 175 µm. Similar results were obtained for ergocalciferol (VMD: 73.66±5.18 µm). According to a publication by Zhang et al (1997) which analysed if drug particle size or mixing impacts on poor content uniformity, it was noted that decreasing particle size enhances content uniformity provided drug aggregation is controlled .Therefore, ergocalciferol was micronised to enhance content uniformity in this study.

Table 4.5: Flow properties of starch, pregelatinised starch (P.starch), MCC and ergocalciferol (Erg.) showing the particle size analysis parameters (X10, X50, X90, Span and volume mean diameter (VMD)), angle of repose (°) and the corresponding flow property.

Product	X10	X50	X90	Span	VMD (µm)	θ (°)	Flow property
Starch	7.72±0.62	11.75±0.43	16.65±0.33	0.761±0.05	11.9±0.51	42.46±2.5	Passable
P. Starch	27.72±2.46	77.24±2.52	134.27±3.39	1.38±2.48	79.75±1.49	34.90±2.2	Good
MCC	18.65±0.29	62.75±2.07	141.26±0.66	1.96±0.05	73.05±0.89	28.0±1.44	Excellent
Erg.	9.22±1.31	67.52±13.15	142.10±3.76	2.07±0.33	73.66±5.18	34.98±1.98	Good

The results of flowability based on angle of repose showed that (apart from starch) flowability was good to excellent for the non-sieved materials. Owing to its small particle size, starch demonstrated low flowability profile which was further evident from the SEM images that showed individual particles as well as cluster of granules. Starch particles were small in size and had typical angular, spherical shape or rounded shape with smooth surface (Figure 4.2 a). Pregelatinised starch SEM images (Figure 4.2 b) showed larger clusters of particles and hence have enhanced flowability when compared to starch. The excellent flowability of MCC could also be attributed to the granular particle shape and larger particle size (Figure 4.2 c). The general shape for ergocalciferol can be described as longitudinal and irregularly shaped with some roughness on the surface (Figure 4.2 d) but as the particle size was large, flowability was good.

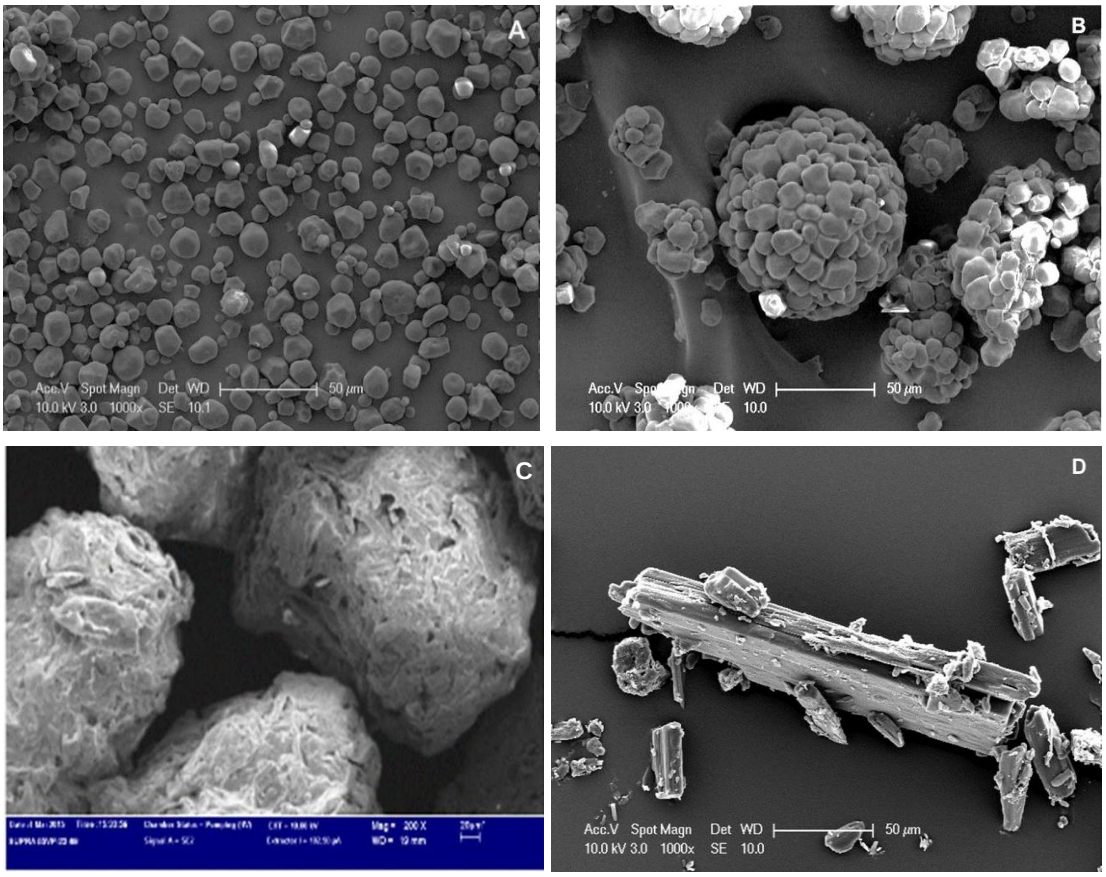


Figure 4.2: Scanning electron microscopy micrographs at 1000 times magnification of (a) starch (b) pregelatinised starch (c) MCC and (d) ergocalciferol.

As the aim of the work was to further investigate powder behaviour upon mixing and the performance of blend, the three excipients (pregelatinised starch, starch and MCC) were sieved and the cohesive part of the powder (particle size less than 53 µm) as well as non-cohesive part where the size of the particles was between 125-180 µm were collected and further investigated except for starch where only non-sieved and cohesive portions were used as the particle size of starch was low. Flow properties of non-cohesive pregelatinised starch was found to be excellent as depicted in Table 4.6. Similarly as expected, cohesive fractions of both starch and pregelatinised starch materials showed poor flowability due to their smaller particle size. The non-sieved and non-cohesive MCC fell into the excellent flow properties category whereas the cohesive MCC portion had fair flow. The results obtained were statistically significant ($p<0.05$) as larger particles have better flow properties whereas smaller particles due to increased Van der Waals interactions exhibit poor flowability (Zhang and Johnson, 1997). The non-cohesive MCC and non-sieved had similar flow properties as the particles around 200µm generally have excellent flow properties (Liu *et al.*, 2008).

Table 4.6: Flow properties of cohesive starch, cohesive and non-cohesive pregelatinised starch and cohesive and non-cohesive MCC showing the particle size range (obtained upon sieving), angle of repose (°) and the corresponding flow property.

Carrier (particle size)	Particle size range (µm)	Angle of repose (°)	Flow property
Cohesive starch	<53	49.30 ± 0.59	Poor
Non-cohesive pregelatinised starch	125-180	30.14 ± 2.3	Excellent
Cohesive pregelatinised starch	<53	48.44 ± 4.2	Poor
Non-cohesive MCC	125-180	25.0 ± 0.86	Excellent
Cohesive MCC	< 53	39.46 ±1.29	Fair

An attempt to further understand the material enhanced functionality and performance upon processing with various APIs was studied using interferometry. The technique provides an in-depth analysis of the surface properties and topography parameters as summarised in (Table 4.7). The first parameter is the average surface roughness (Sa) and the results showed high surface roughness for MCC followed by pregelatinised

starch and then starch. Sieving to obtain the fine fraction of material resulted in a significant increase in surface roughness for pregelatinised starch (ANOVA, $p<0.05$) whereas the starch showed slight reduction in roughness. The increase in roughness upon sieving could be attributed to the increase in surface area with lower particle size as the average size of pregelatinised starch dropped from 40 to 25µm. The change in particle size upon sieving for starch was minimal and the particles were <10 µm.

Table 4.7: Surface topography parameters and flow properties of the main excipients showing average roughness (Sa), mean square value of average roughness (Sq), maximum roughness height (Sy) particle radius (R), adhesion energy (AE), angle of repose ($\boldsymbol{\theta}$) and flow property (FP) (mean ± SD, n=5).

Material	Sa (nm)	Sq (nm)	Sy (nm)	R (μm)	AE (aJ)	($\boldsymbol{\theta}$)	FP
Cohesive MCC	875±60	1230±115	9604±105	26.5	28.5	39.46±1.29	Fair
Non-sieved starch	126±38	168±60	1700±103	6.0	114.5	42.46±2.5	Passable
Cohesive starch	81±34	109±46	703±156	3.5	108.5	49.3±0.59	Poor
Non-sieved pregelatinised starch	174±53	233±80	2934±160	40.0	251.5	34.9±2.2	Good
Cohesive pregelatinised starch	264±109	390±212	5216±173	25.0	153.6	48.44±4.2	Poor

In this study the high surface roughness of MCC was anticipated to enhance content uniformity compared to starch and pregelatinised starch. It was expected that fine API particles will be easily lodged into and between the rough surface apertures of MCC and hence enhance uniformity. It was reported that the higher the degree of roughness results in better content uniformity of the blend (Leach *et al.*, 2008). Therefore, based on particle size and surface roughness, MCC showed best uniformity followed by pregelatinised starch and starch. Further the poor content uniformity of starch could also be attributed to the small particle size (3.5-6μm) and cohesive nature of starch that showed high cohesive energy (~110aJ). The second parameter from table3 is the *Sq.* It is the root mean square value of the surface roughness within the sample area. It is considered as a more statistically significant parameter than *Sa* (Leach *et al.*, 2008). Similar to the results obtained from Sa values, MCC particles showed higher Sq values than that of pregelatinised starch or starch.

The third parameter Sy is the maximum height of surface. It is the sum of the height of the largest peak height value and the largest valley depth within the sample. Examining both the *Sq* value and the *Sy* value, an indication of whether the apparent roughness is due to isolated features or the overall surface roughness can be derived (Leach *et al.*, 2008).

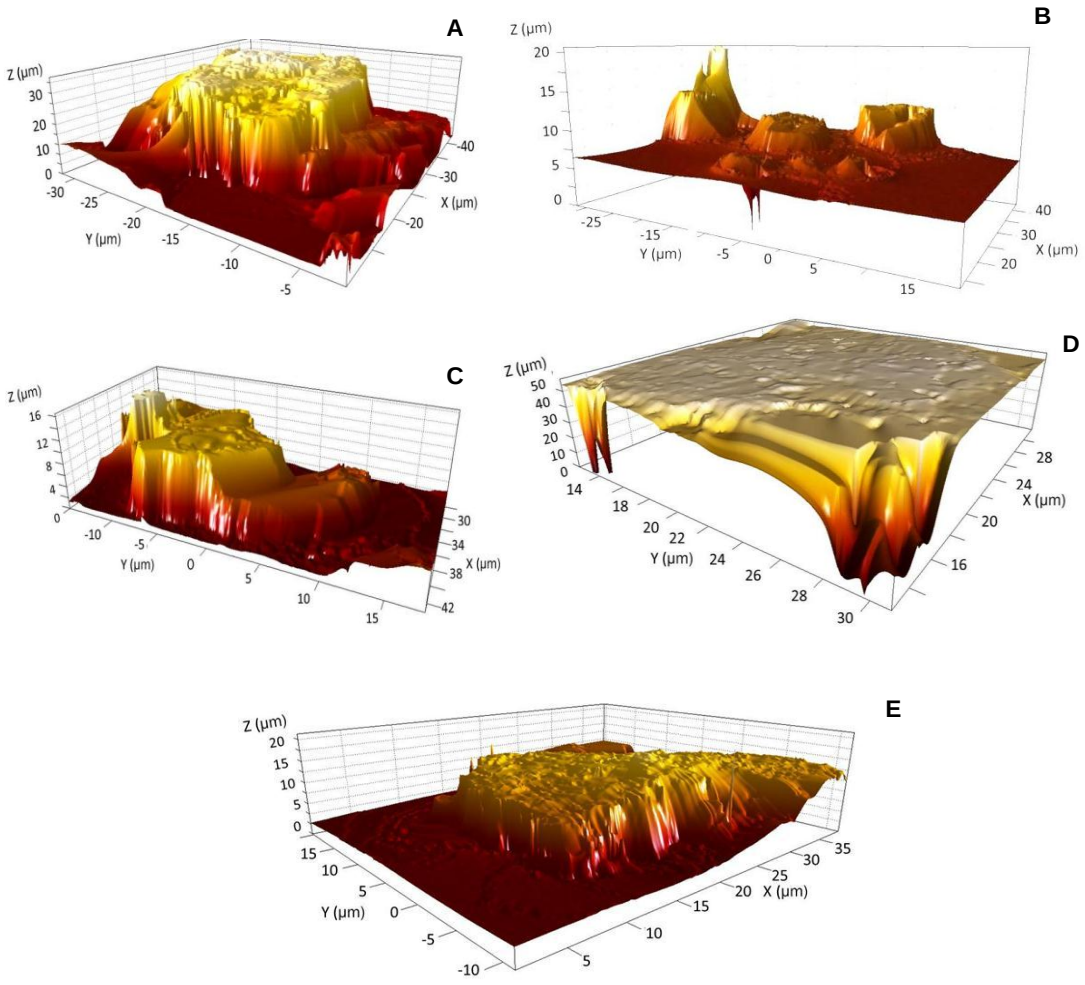


Figure 4.3: Interferometer topographical images of (a) cohesive MCC, (b) non-sieved starch, (c) cohesive starch, (d) non-sieved pregelatinised starch and e) cohesive pregelatinised starch.

Results for all the samples indicated that the Sy value were different compared to that of Sq value which indicates that the topography is irregular as evident from the 3D images in (Figure 4.3). On the other hand, the change in Sy value for MCC particles was of a greater magnitude and provides a stronger evidence of the degree of roughness compared to the other excipients. Surface energy parameters as depicted in (Table 4.7) showed the change in adhesion energy for different materials. The lowest was noted for cohesive MCC with particle size of around 26µm and adhesion energy of 28.5aJ. Such low energy for MCC possibly explains fair flowability despite the small particle size (39.46±1.29). It was reported that particles of less than 50µm are highly

cohesive (Dahmash and Mohammed, 2015). This also could be further correlated to surface roughness (Sa) where high roughness values will result in less surface contact between particles and hence less cohesiveness, better flowability to produce homogeneous blend (Leach *et al.*, 2008). The cohesive energy for pregelatinised starch and starch were related to the change in surface roughness of material and hence could justify that higher roughness is related to lower cohesive energy however, that could not clearly relate to flowability as the particle size of pregelatinised starch and starch were very low.

4.3.3. Investigation of various blending techniques and their impact on drug content uniformity

Ergocalciferol is a suitable model as the maximum dose is generally around 750-800 micrograms per tablet. The different ratios of drug to carrier were selected to simulate dilution of drug during tablet development when mixed with different excipients. Starch, pregelatinised starch and MCC are routinely used in tablet manufacturing and represent a pragmatic choice to investigate the above hypothesis.

Having investigated material properties for the model drug as well as the different particle fractions for the three carriers, the next objective was to study the impact of different blending techniques primarily on the content uniformity of the drug. Geometric blending including the impact of total powder content as well as duration of blending was investigated. In addition ordered mixing using two different approaches including manual blending and high speed blending were investigated.

4.3.3.1. Geometric mixing technique

Geometric blending is a standard technique to mix small amounts of drug and according to British Pharmacopeia (BP, 2012), drug content for ergocalciferol should range between 90 to 120% of the claimed label. Four formulations were prepared for

geometric blends (drug: carrier ratios: 1:2, 1:10, 1:20 and 1:50). All mixtures were prepared with a total batch size of 600mg.

4.3.3.1.1. One minute geometric mixing

The first set of studies focussed on the impact of particle size characteristics of pre gelatinised starch on content uniformity. The results presented in (Figure 4.4) showed that blending for one minute using different particle size fractions of pregelatinised starch in various ratios resulted in poor drug recovery. Although the deviation increased with the increase in dilution, all the different batches that were tested failed the content uniformity test. Similar trends were observed for non-sieved as well as cohesive blends. Despite the failure to meet the required pharmacopeia standards for drug recovery, the results showed some interesting trends. It would be expected that cohesive powders would potentially result in non-uniformity due to particle aggregation whereas non-sieved powders would generate a more uniform drug mix. From the current study, it can be clearly seen that the recovery was the least from non-cohesive blends followed by non-sieved and cohesive powders. Although the cohesive blends provide greater surface area for particle interaction, the short blending duration (1 minute in this case) ensures that particle aggregation is controlled thereby resulting in a slightly better distribution and recovery of the drug. On the other hand, despite the good flow properties of the other two mixtures, uneven particle distribution possibly resulted in segregation and low drug recovery. One-way Analysis of Variance (ANOVA) for the data set demonstrates that p value was <0.05.

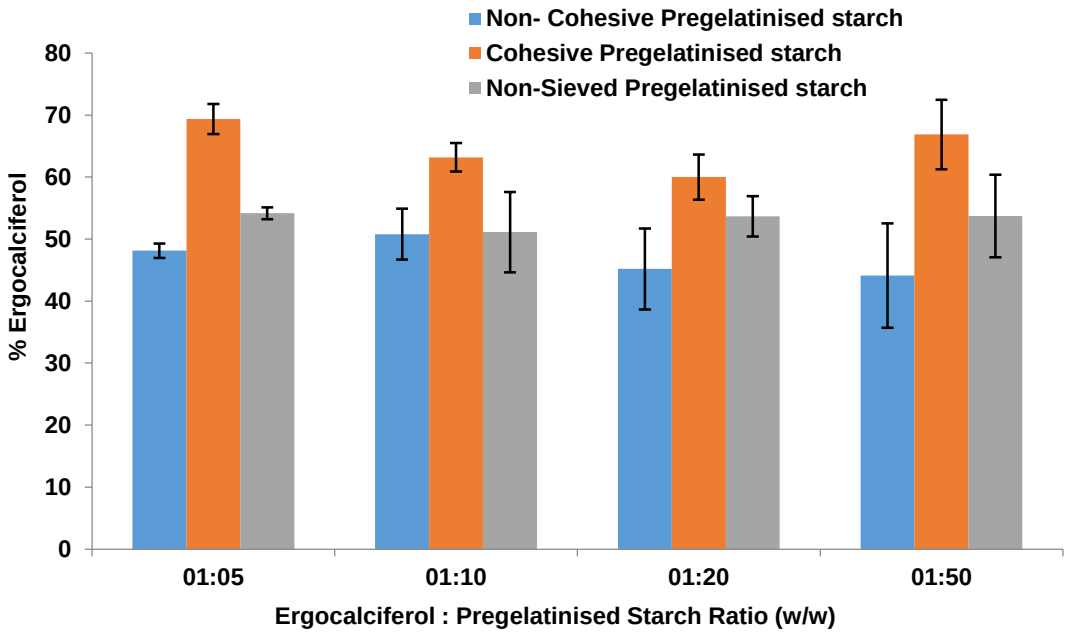


Figure 4.4: Influence of drug: carrier ratio and carrier particle size on content uniformity of ergocalciferol. Blends are made of ergocalciferol and pregelatinised starch (non-sieved, cohesive and non-cohesive) mixed at various ratios (1:5, 1:10, 1:20 and 1:50) using geometric mixing for 1minute (mean± SD, n=9).

Studies investigating dilution and blending using starch showed similar results as shown in (Figure 4.5). The different grades of starch (with different particle sizes) in the various ratios tested resulted in low drug recovery. All the batches that were tested failed the regulatory requirement. The results showed that the percentage drug recovery decreased with an increase in dilution of the drug with the carrier. The cohesive blend of starch resulted in lower drug uniformity with the increase in dilution compared to non-sieved this could be attributed to the high cohesive nature of the starch.

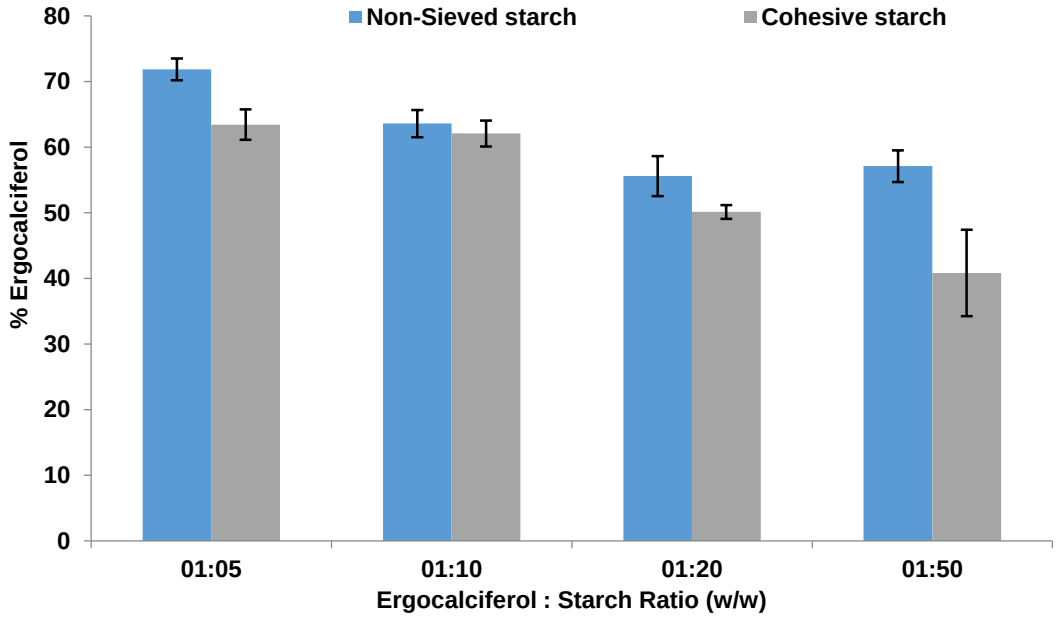
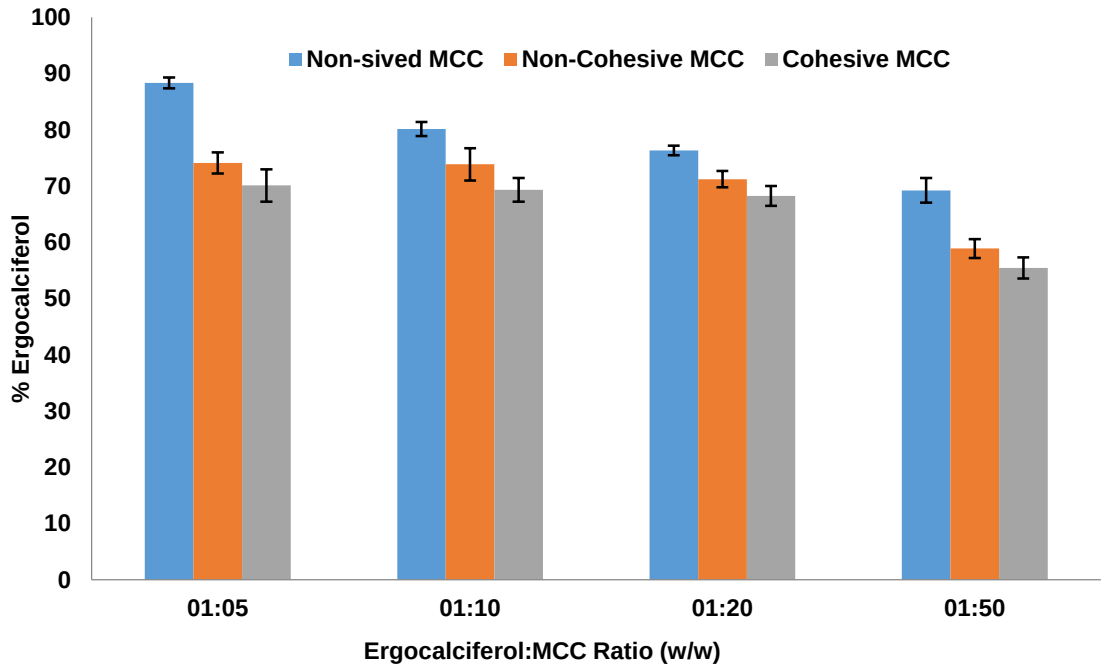


Figure 4.5: Influence of drug: carrier ratio and carrier particle size on content uniformity of ergocalciferol. Blends are made of ergocalciferol and starch (non-sieved and cohesive) mixed at various ratios (1:5, 1:10, 1:20 and 1:50) using geometric mixing for 1minute (mean± SD, n=9).

There was a significant difference between the different ratios for MCC ($p<0.05$, two way-ANOVA) (Figure 4.6). Further, the non-sieved grade was superior to the other grades in term of content uniformity. Overall, geometric mixing for one minute for all carriers including pregelatinised starch, starch as well as MCC did not meet the required uniformity range. Nevertheless, non-cohesive pregelatinised starch together with ergocalciferol in various ratios was shown to be produce statistically insignificant drug uniformity.



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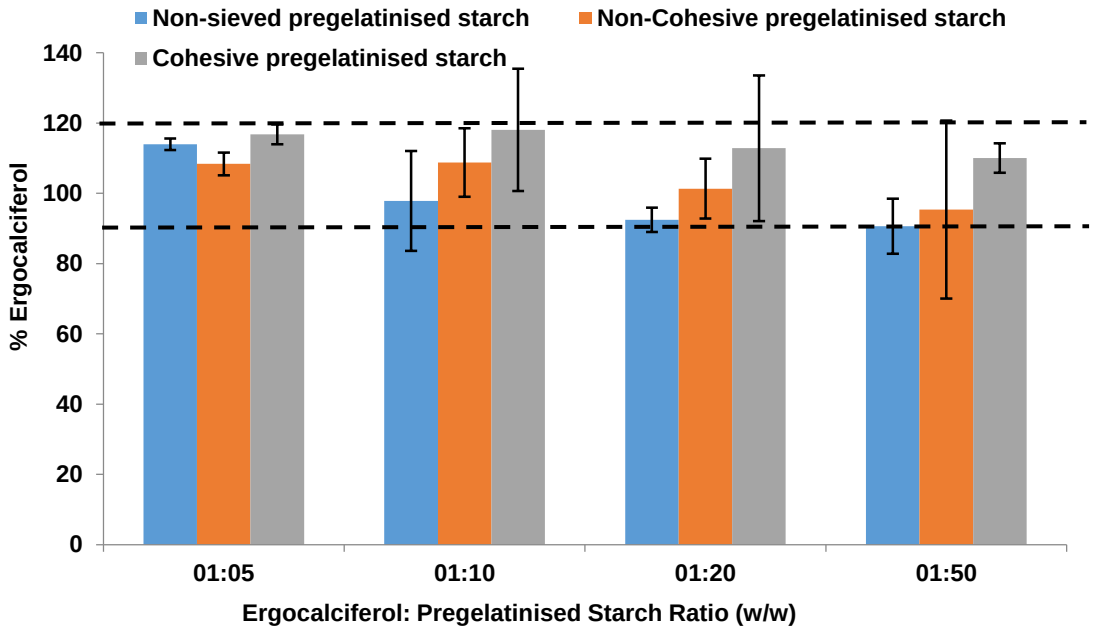
4.3.3.2. Effect of increasing blending time on drug content uniformity

Based on the results achieved from the earlier experiment, the time of mixing was elevated up to five minutes from one minute. The rationale was to determine if longer blending time would promote uniform distribution and aid diffusion of the API particles within the carrier particles. The longer the time for mixing, greater is the time of contact between all the particles and this may induce better homogeneity due to more chances of collision and particle distribution (Muselík *et al.*, 2014).



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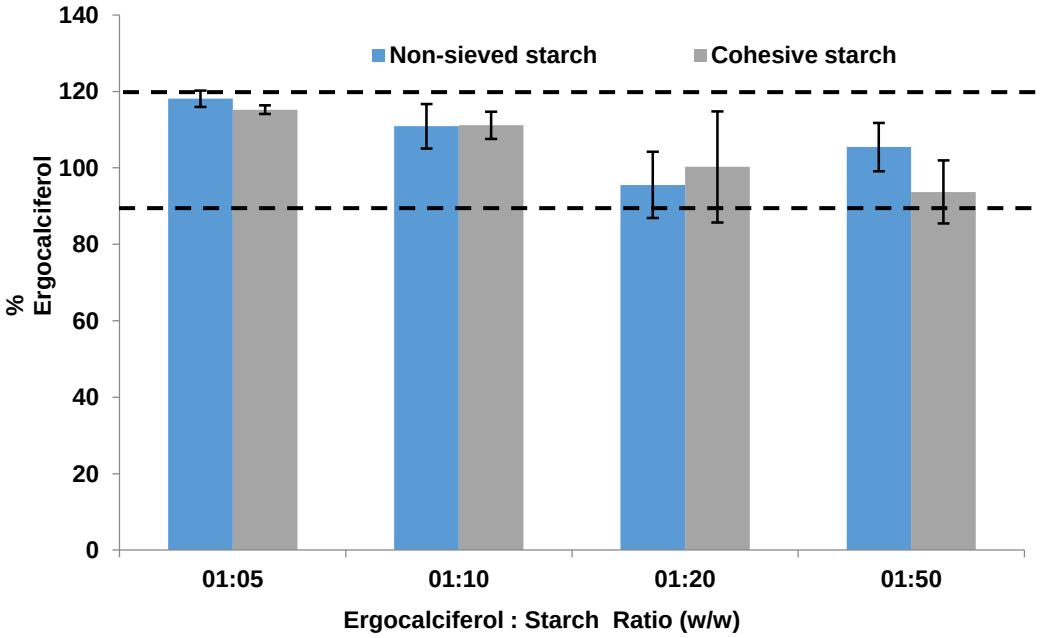
The results obtained in (Figure 4.7) showed that drug recovery was complete and all the ratios tested showed that prolonged blending time resulted in complete drug recovery. The results showed no significant difference (one-way ANOVA, $p>0.05$) between the different ratios of pregelatinised starch. Similar trends were obtained when pregelatinsed starch was replaced with starch (Figure 4.8). It can be hypothesised that the increase in blending time promotes better distribution of the drug irrespective of the particle characteristics and the type of the carrier. The process of powder blending is influenced by different forces including diffusional, shear and convective forces. In the method employed for geometric blending, it can assumed that the impact of shear forces would be minimal as the powder particles are not subjected to higher magnitude forces as that would be obtained in fluidised bed or high speed blenders. It is likely that the resultant uniform mix of the powder blend for both the carriers with different particle size fractions could be due to the combination of diffusion and convective blending. In the case of non-sieved and free flowing powder blends,

convective mixing ensures the transport of powder bed from one location to the other. This allows for the movement of large particles from one area of the mixing vessel to the other generating a random blend. The results from the investigation above where the duration of blending was one minute possibly initiated the transfer of the bulk powder without the generation of a consistent random mix (Muselík *et al.*, 2014). Following the increase of the duration of blending, it is likely that the movement of powder beds through convection increases the distribution of the particles of the drug between the carrier particles resulting in the generation of a random mix. The longer duration of blending also ensures that diffusional mixing promotes movement of particles at the micro-level thereby enhancing content uniformity. The longer duration of powder blending results in prevention of de-mixing which can take place before an ultimate random state is obtained. Cohesive blends on the other hand present a different set of challenges. Although the increase in blending time resulted in a uniform mix for both the carriers containing cohesive powders, the outcomes can be explained based on the processes that occur during dry cohesive blending.



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Previous research has shown that cohesive blends segregate due to multiple factors including particle shape, size and the intensity of cohesion (Tang and Puri, 2004). The process of blending for cohesive powders relies on not only the properties of the cohesive particles but also on the adhesive interactions in a binary mixture. Simulation studies for dry blending of cohesive mixtures by (Chaudhuri *et al.*, 2006) confirmed that the extent and intensity of the cohesive forces between similar particle sizes controls the degree of segregation which ultimately impacts on the homogeneity of the powder blend. The studies showed that the presence of low intensity cohesive forces promotes mixing possibly due to the larger surface area available for the particles within the binary mixture to achieve a random state of distribution. In our study, it can be concluded that the intensity of the cohesive forces between the particles for both carriers is relatively weak thereby ensuring that aggregation between similar particles is reduced and therefore promotes a more uniform distribution of the particles of the drug (i.e. mixing drug-carrier). Interestingly, the non-sieved MCC formulation displayed ideal uniformity whereas the non-cohesive and cohesive formulations became slightly less uniform as shown in (Figure 4.9). The difference between these formulations was significant ($p<0.05$), indicating that the increasing mixing time still showed benefit for obtaining uniformity with the largest particle size.

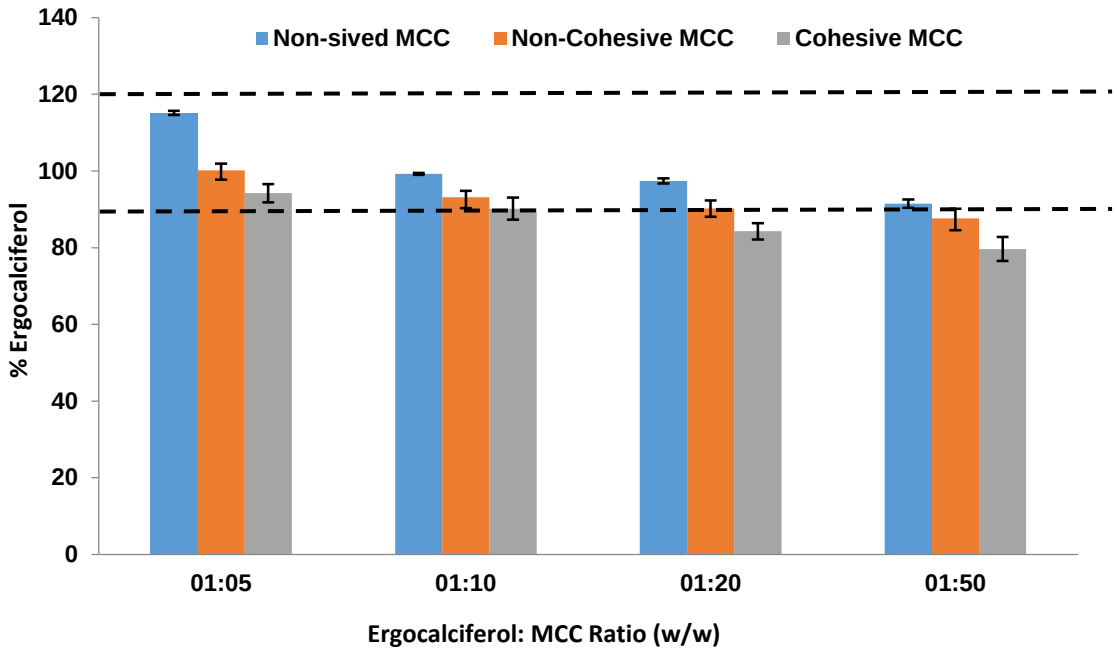

Figure 4.9: Influence of drug: carrier ratio and carrier particle size on content uniformity of ergocalciferol. Blends are made of ergocalciferol and MCC (non-sieved, cohesive and non-cohesive) mixed at various ratios (1:5, 1:10, 1:20 and 1:50) using geometric mixing for 5 minute (mean± SD, n=9).

Although the results for the 5 minute mixing were promising, the true focus for this part of the investigation was the API dilution ratio (1:50 formulations) for which 8 batches were created for each carrier type. Therefore, it becomes evident that geometric addition with 5 minute mixing serves to improve uniformity for highly dilute blends (1:50) compared to 1 minute mixing. A similar need for increasing blending time for dilute blends was found by (Kornchankul *et al.*, 2002) for the drug Buspirone between two blends of differing concentrations.

4.3.3.2. Ordered blending technique

Following investigations of geometric blending, ordered mixing using bulk powder quantities was investigated to study the impact on drug content uniformity. Ordered bulk mixing represents a more convenient method from an industrial perspective due to the availability of a wide range of equipment and relatively shorter processing time.

4.3.3.2.1. Ordered blending using manual blending

The objective of this study was to determine the time dependent effect on content uniformity during bulk mixing using a manual blending technique. The 1:50 ratio was chosen for this technique as it represents the maximum dilution potential for the drug that was used in our previous studies. This technique was carried out to find the relationship between percentage drug recoveries with respect to time. Blending was performed until a constant relative standard deviation for drug content was obtained. Similar to the above investigations, the three different particle size ranges for the three carriers were investigated.

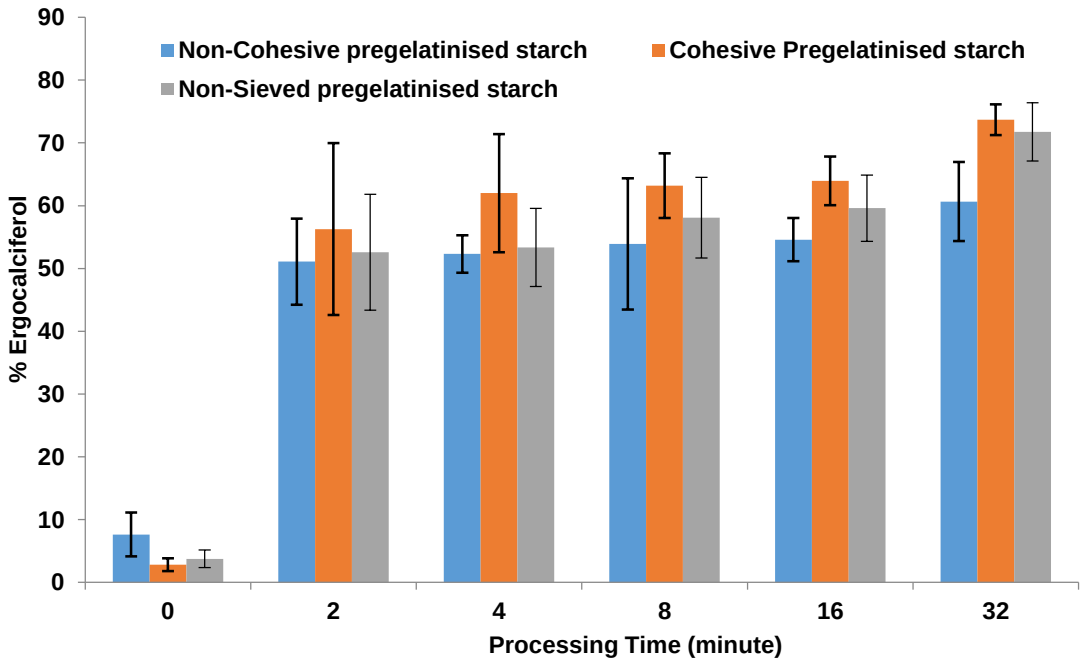

Figure 4.10: Influence of processing time and carrier particle size on content uniformity of ergocalciferol. Blends are made of ergocalciferol and pregelatinised starch (non-sieved, cohesive and non-cohesive) mixed at drug: carrier ratio of 1:50 using vigorous hand blending technique (mean± SD, n=9).

The results in (Figure 4.10) demonstrate that content uniformity increased with blending time with all forms of pregelatinised starch and the highest percentage drug content uniformity was achieved after 32 minutes in all three forms of pregelatinised starch. Cohesive pregelatinised starch showed the highest percentage of drug

recovery at various time points when compared to the non-cohesive blends. For example, after half an hour of physical mixing, cohesive powder of pregelatinised starch showed highest content uniformity of about 75% while non cohesive was lowest around 55% (ANOVA, $p<0.05$). Interestingly these results are similar to that obtained using geometric blending where the cohesive blends of pregelatnised starch outperformed the non-cohesive mixtures despite all the three grades not achieving the pharmacopeia standards.

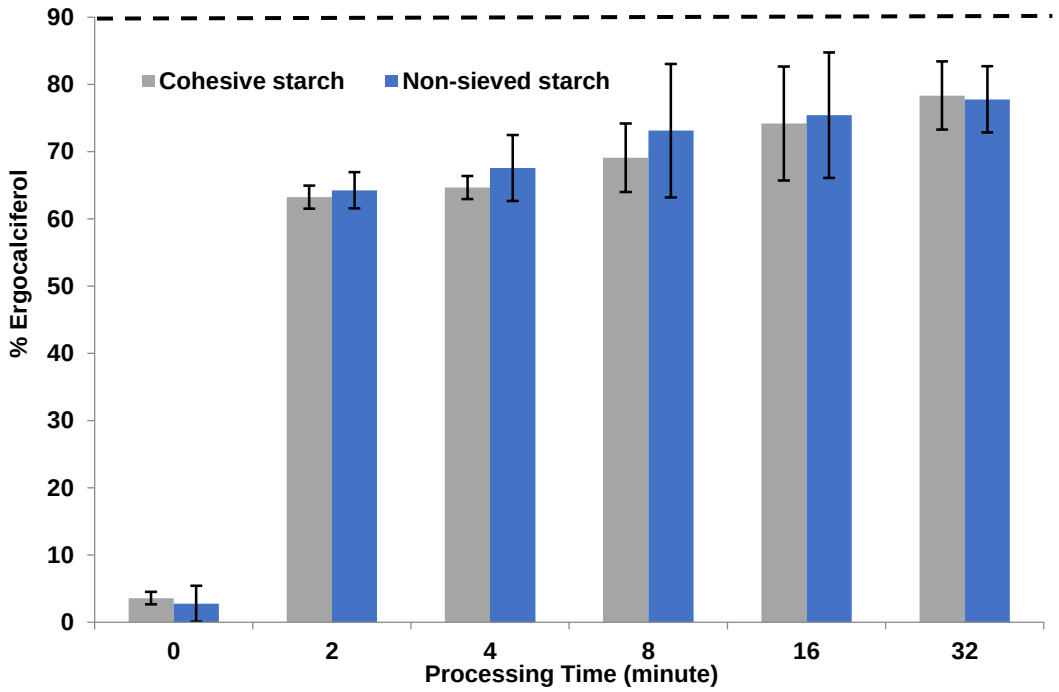

Figure 4.11: Influence of processing time and carrier particle size on content uniformity of ergocalciferol. Blends are made of ergocalciferol and starch (non-sieved and cohesive) mixed at drug: carrier ratio of 1:50 using vigorous hand blending technique (mean± SD, n=9).

In the case of starch with ergocalciferol as shown in (Figure 4.11) it was observed that the increase in percentage of drug recovery was exhibited by non-sieved starch (one way ANOVA, $p>0.05$). The non-sieved MCC reached the lowest acceptable level of uniformity at 32 minutes of mixing as shown in (Figure 4.12). However, smaller particles allowed for faster achievement of uniformity within a powder blend (Rohrs *et al.*, 2006). It is evident from the graph that the relative standard deviation for all the samples as shown in (Figure 4.13) followed a similar pattern. The results showed that

the standard deviation began to plateau just after five minutes and there was no difference until the conclusion of the study.

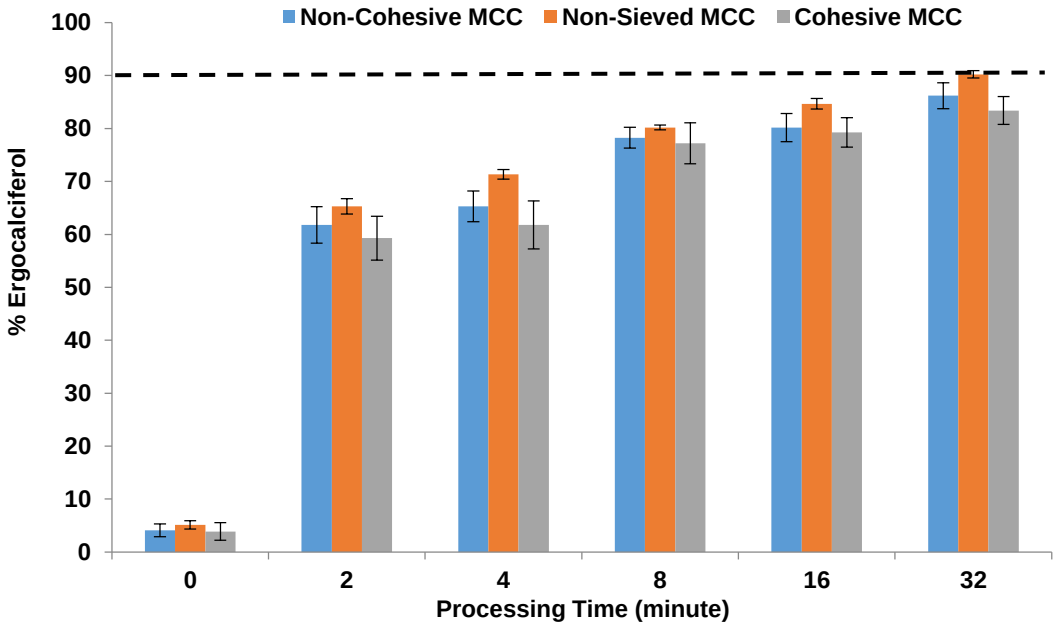

Figure 4.12: Influence of processing time and carrier particle size on content uniformity of ergocalciferol. Blends are made of ergocalciferol and MCC (non-sieved, cohesive and non-cohesive) mixed at drug: carrier ratio of 1:50 using vigorous hand blending technique (mean± SD, n=9).

Using this type of mixing, all batches for the three carriers (except non-sieved MCC) did not achieve the requirements of BP for drug content uniformity of ergocalciferol (90-120%). Figure 4.13 shows relative standard deviation (RSD) for ergocalciferol based on 1:50 pregelatinised starch, starch and MCC after physical mixing over different time points. It was observed that RSD for ergocalciferol was the lowest for non-sieved MCC which showed an initial value of 15% at 0 minute which decreased to approximately 1% after 32 minutes. Hence, non-sieved MCC had the lowest standard deviation compared to all carrier formulations. The graph demonstrates that the drug distribution for the different types of blends requires longer duration to obtain more homogenous blend. The higher deviation at the start indicates that the drug is concentrated in various pockets comprising of “drug-concentrated” areas which need to be relocated within the bulk of the diluent. Continuous blending ensures that

convective mixing predominates and the drug has the opportunity to distribute itself between the carrier particles. The standard deviation begins to plateau after about five minutes which possibly suggests that the drug rich domains have been redistributed randomly within the bulk of the carrier. It is possible that after the first five minutes, the diffusional mixing predominates and therefore micro mixing of the drug between the particles is the key factor. Despite the expected cohesive forces between the smaller particles fractions which can promote aggregation, it is possible that weak/lower intensity forces operate which ensure that diffusional micro mixing predominates over the cohesive interactions.

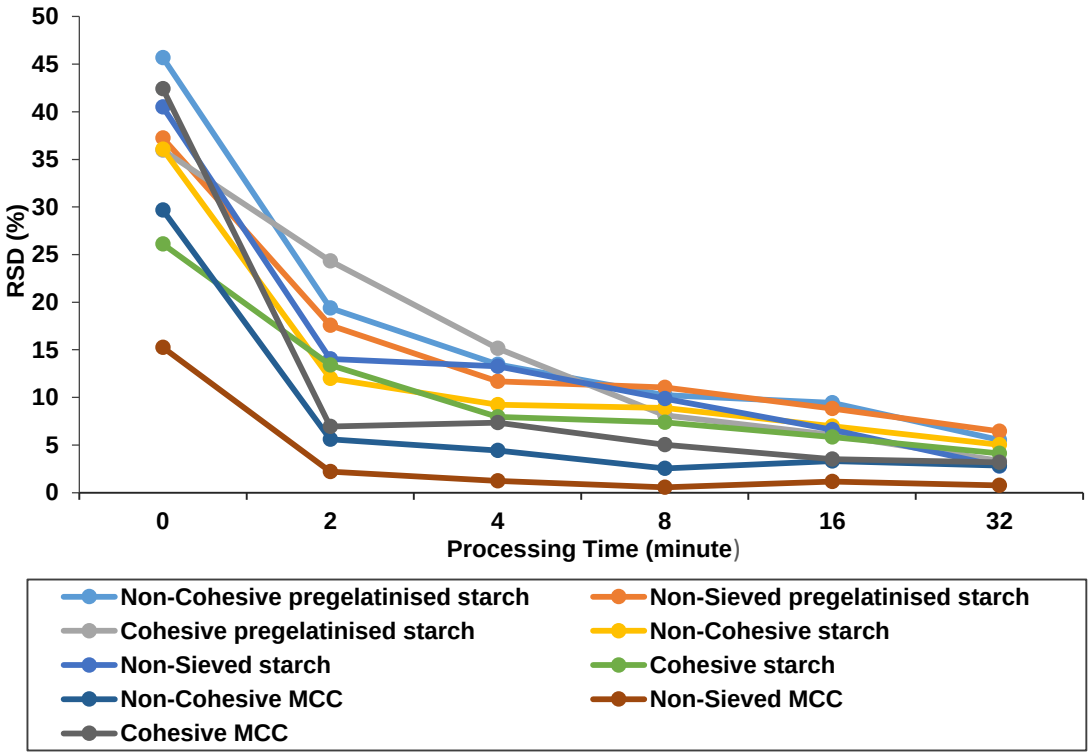

Figure 4.13: Influence of processing time, carrier type and carrier particle size on blend homogeneity as expressed in RSD. Blends are made of ergocalciferol and carrier mixed at drug: carrier ratio of 1:50 using vigorous hand blending technique (n=3).

The likely variation when mixing by hand poses problems as it cannot be standardised enough to eliminate any experimental error, particularly with rate and force of mixing applied to the mixing vessel. Furthermore, hand mixing is not a viable mixing process for scaling-up and therefore machine mixing was investigated.

4.3.3.2.2. Ordered mixing using dry powder mixing device

The last method of blending included investigation of a dry powder blender/coater as a technique to generate homogenous powder blends. Hersey (1975) and Ishizaka (1989) ((Hersey, 1975, Ishizaka *et al.*, 1989) described “ordered mixing” as cohesive powder mixing process where fine particles are dispersed/attached to the surface of coarse particles to generate an ˝interactive mixture˝.

The blending device used in this study was built at Aston University. The device consists of a rotating chamber fitted on to a central fixed shaft. The fixed shaft is perforated allowing for fluidisation of powder. In the current study the speed of the device was fixed at 300rpm with no air injection. The speed was chosen after optimisation studies in another project within our group showed that higher speeds lead to the formation of dry coated particles whereas lower speed promotes homogenous blending and formation of interactive/ordered blend. The total amount of powder blends was 3 g. Three samples were taken out for each batch: first sample was 5 mg taken from the right side, second sample from the middle and the third sample from left side. In interactive mixing using dry powder mixing device, the mixing process of the mixture depends on two forces. The adhesion forces of the API to the carrier particles and the cohesion forces between the drug particles. Proper mixing will be achieved and no agglomerates will be left only if the adhesion force between materials is greater than the cohesive forces between similar particles (Lohrmann *et al.*, 2007). Based on the results obtained from ordered mixing using manual blending, the dry powder mixing device at speed 300 rpm was investigated in order to promote uniform distribution of the drug between the carrier particles.

The results obtained in (Figure 4.14, 4.15 and 4.16) showed that drug recovery was achieved after 4, 32 and 2 minutes of mixing for all blends of pregelatinised starch, starch and MCC respectively. The possible reason behind the enhancement of drug uniformity is a result of sufficient mixing process that included different forces such as

convective, shear and diffusional forces. Two-way analysis of variance (ANOVA) test and Tukey's test demonstrated a statistically significant difference between batches and between each batch with different times ($p<0.05$). It can be hypothesised that the impact of shear forces was achieved after 16 minutes of mixing, so that the deviation sharply decreased with all forms of carriers at 32 minutes of mixing.

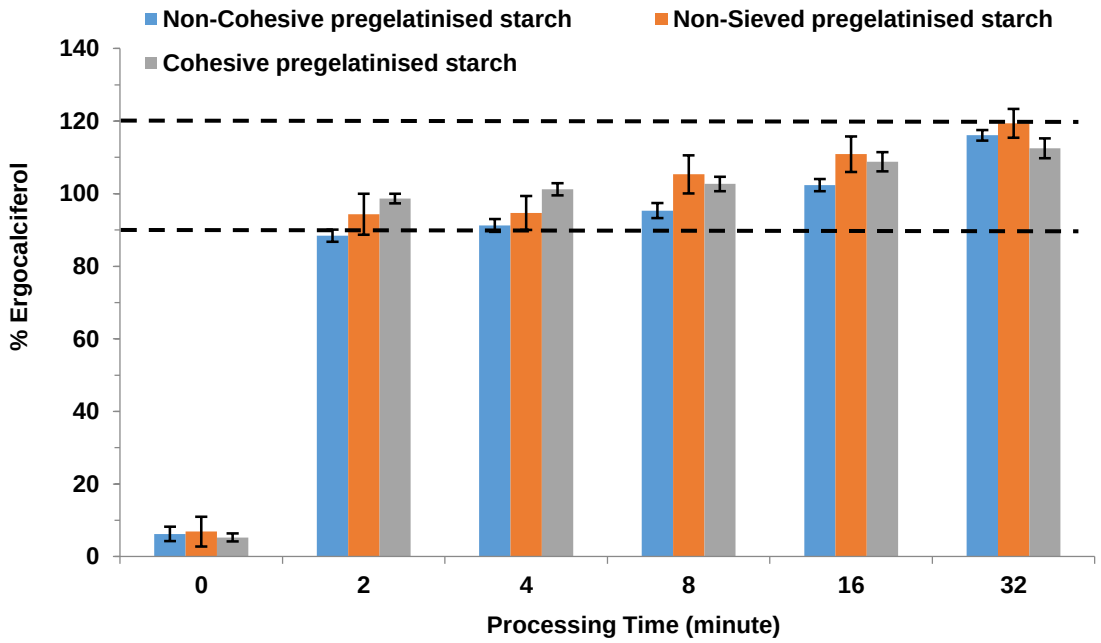

Figure 4.14: Influence of processing time and carrier particle size on content uniformity of ergocalciferol. Blends are made of ergocalciferol and pregelatinised starch (non-sieved, cohesive and non-cohesive) mixed at drug: carrier ratio of 1:50 using interactive blending technique (mean± SD, n=9).

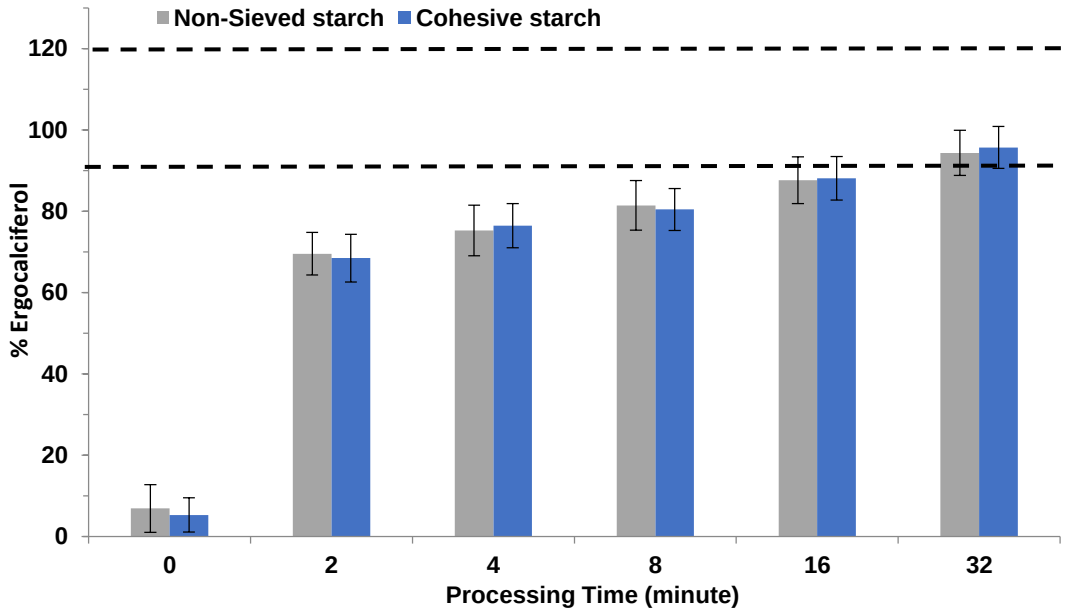

Figure 4.15: Influence of processing time and carrier particle size on content uniformity of ergocalciferol. Blends are made of ergocalciferol and starch (non-sieved and cohesive) mixed at drug: carrier ratio of 1:50 using interactive blending technique (mean± SD, n=9).

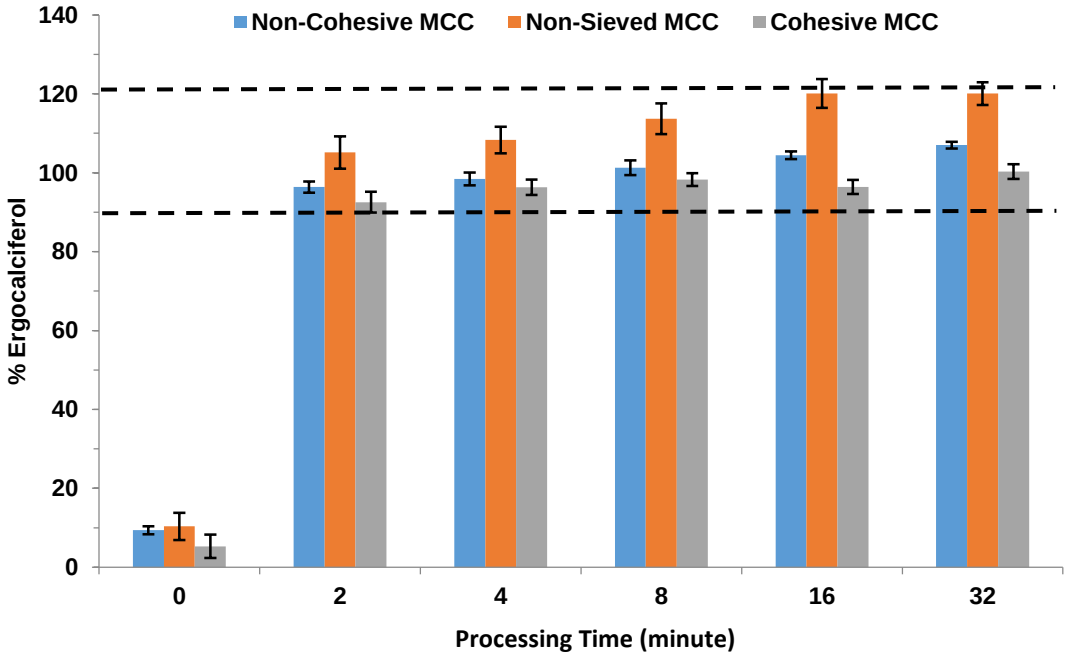

Figure 4.16: Influence of processing time and carrier particle size on content uniformity of ergocalciferol. Blends are made of ergocalciferol and MCC (non-sieved, cohesive and non-cohesive) mixed at drug: carrier ratio of 1:50 using interactive blending technique (mean± SD, n=9).

From (Figure 4.17), it was seen that the RSD for ergocalciferol was the highest for non-sieved and cohesive starch which showed an initial RSD of 85% and 80% at 0 minute and decreased to approximately 5% in 32 minutes.

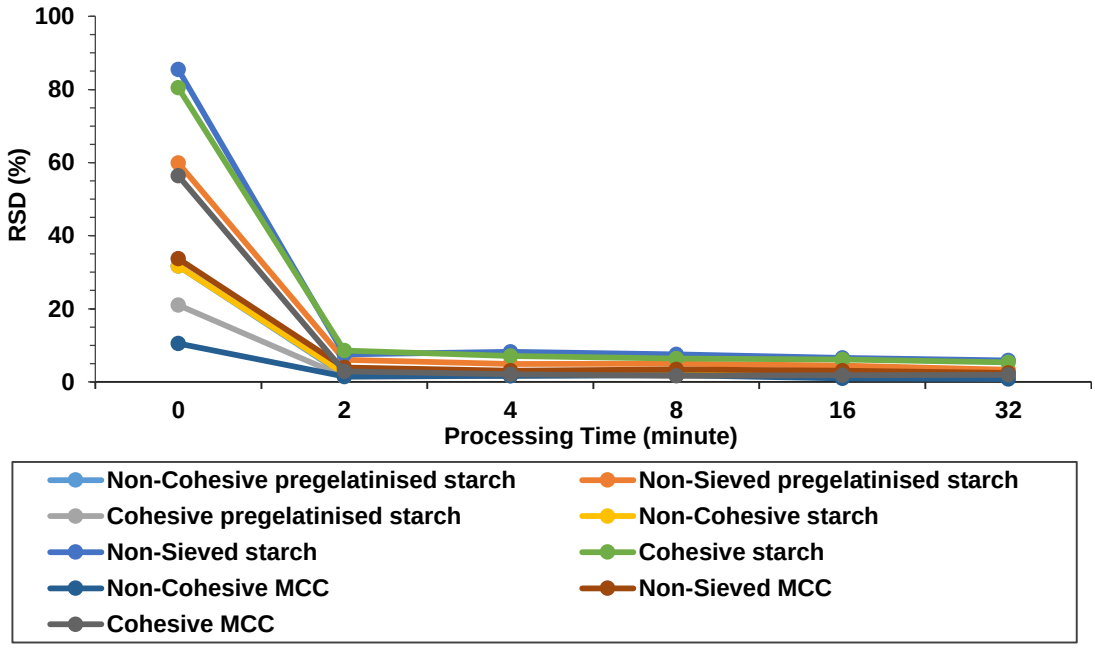

Figure 4.17: Influence of processing time, carrier type and carrier particle size on blend homogeneity as expressed in RSD. Blends are made of ergocalciferol and carrier mixed at drug: carrier ratio of 1:50 using interactive blending technique (n=3).

4.3.3.2.3. Mixing of 0.5% and 1 % of API: non-sieved carrier using dry powder blending device

The blending process was then carried forward to investigate two further diluted batches of API (Figure 4.18 and 4.19). These blends were closer to low dose levels seen in manufactured formulations (Zheng, 2009). Although the 1% formulation was at an acceptable uniformity only for MCC after 8 minutes of mixing (99%), pregelatinised starch and starch formulations achieved uniformity after 16 and the full 32 minute mixing period respectively. Therefore, it is clear from (Figure 4.18) that less time was required to get good content uniformity (8 minutes) with MCC compared to pregelatinised starch and starch that required longer mixing durations with less

homogeneous blend. On the other hand, more time was required for starch as significantly more blend was present in the non-mixing zone which was observed after mixing was ceased. Thus, Any API held in this zone would have a greater impact on sample uniformities obtained, and this problem is well documented with low dose blends (Zheng, 2009). Furthermore, a smaller API concentration would be more likely to experience segregation of API due to the comparatively reduced interactions with the larger MCC particles, as well as the tendency for API to form agglomerates in blends at concentrations below 3% (Muzzio *et al.*, 2002, Alchikh-Sulaiman *et al.*, 2016).

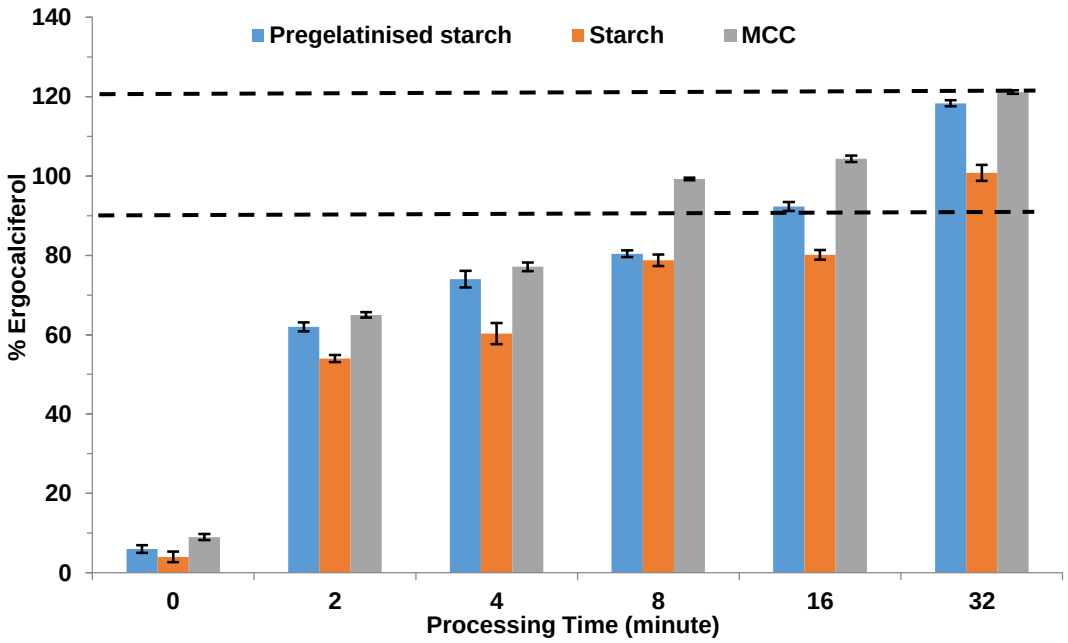

Figure 4.18: Influence of processing time and carrier type on content uniformity of ergocalciferol. Blends are made of 1% ergocalciferol and non-sieved carrier (pregelatinised starch, starch and MCC) mixed using interactive blending technique using the novel dry powder coater at 300rpm (mean± SD, n=9).

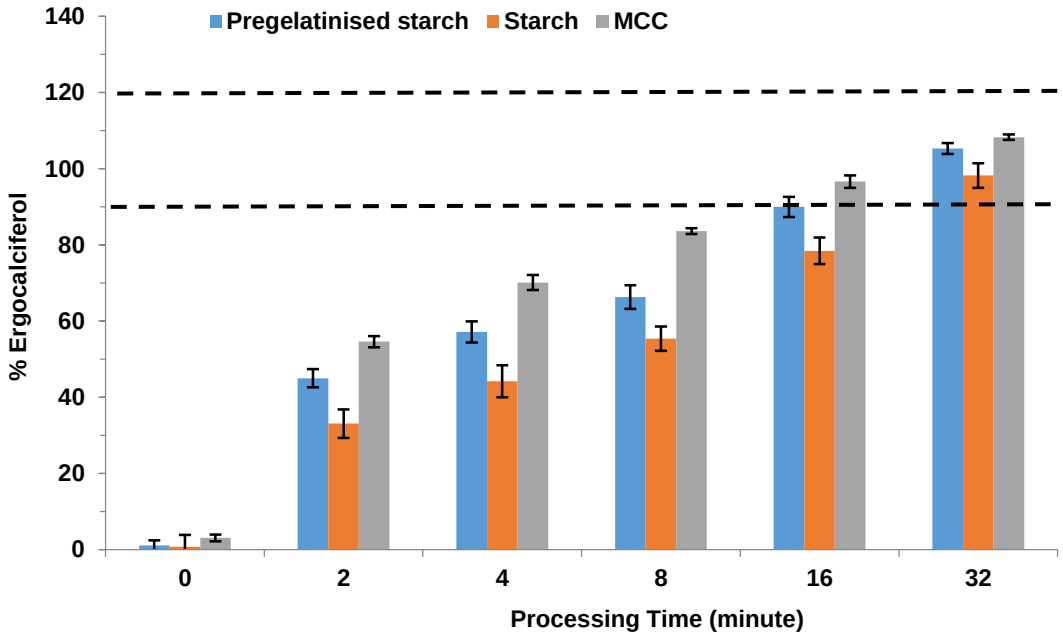

Figure 4.19: Influence of processing time and carrier type on content uniformity of ergocalciferol. Blends are made of 0.5% ergocalciferol and non-sieved carrier (pregelatinised starch, starch and MCC) mixed using interactive blending technique using the novel dry powder coater at 300rpm (mean± SD, n=9).

However, in this study, it is expected that homogeneity with MCC and pregelatinised starch was achieved earlier due to the formation of ordered mixing between fine API particles and the surface of the excipient. These two excipient surfaces showed high degree of roughness that will promote the interactive blend formation. The energy produced within the device throughout the processing time will enable the break of API agglomerates and aid collision between particles through both convective and diffusional currents resulting in interactive blends.

4.3.4. Effect of different order of mixing on powder flow

The secondary aim of this study was to provide a systematic investigation of the effect of mixing order of excipients mannitol, MCC, crospovidone and magnesium stearate on powder flow and tablet characterisation in the formulation of compressed ODTs. These excipients were selected based on their role as binder, filler, or dual functional

binder/disintegrant systems. The formulation and the processing parameters are listed in (Table 4.8).

Table 4.8: Formulation content, order of blending mannitol, MCC, crospovidone (Cros) and magnesium stearate(Mg. Stearate) and processing parameters for pharmaceutical excipients using dry mixing device.

Formulation	Mannitol (64.5%)	MCC 30%	Cros (5%)	Mg. stearate (0.5 %)	Mixing technique	Duration per blend (min)	Speed (rpm)	Batch size (gm)
F1	**1**	**2**	**3**	**4**	**Interactive**	**5**	**300**	**20**
F2	**1**	**3**	**2**	**4**	**Interactive**	**5**	**300**	**20**
F3	3	1	2	4	**Interactive**	**5**	**300**	**20**

Prior to studying the compaction properties of quaternary mixtures, powder characterisation of the individual powders and mixtures were investigated to understand the compaction mechanism of materials and determine the impact of order of each excipient in quaternary blends (Table 4.9).

Table 4.9: Flow properties of starch, magnesium stearate (Mg.stearate), Mannitol, crospovidone, F1,F2 and F3 showing the particle size analysis parameters (X10, X50, X90, Span and volume mean diameter (VMD)), angle of repose (°) and the corresponding flow property. (F1: mannitol and MCC mixed at first stage, crospovidone was added at stage 2, F2: mannitol and crospovidone mixed at first stage, MCC was added at stage 2 and F3: MCC and crospovidone mixed at first stage, mannitol was added at stage 2. Magnesium stearate added at the end and mixed for 2 minutes.

Product	X10	X50	X90	VMD (µm)	Span	θ (°)	Flow property
Mg stearate	1.35±0.01	5.49±0.07	25.16±1.21	10.4±1.39	4.33±0.19	47.38±2.75	Poor
Mannitol	4.51±0.174	28.06±0.61	75.02±6.85	34.99±2.37	2.52±0.18	46.56±4.92	Poor
Crospovidone	8.66±0.14	22.74±0.49	55.66±5.01	29.37±2.73	2.09±0.19	31.22±4.25	Good
F1	8.71±0.09	36.32±0.36	108.31±2.55	47.7±0.74	2.74±0.05	42.8±4.56	Passable
F2	8.51±0.09	36.27±0.59	110.91±2.26	47.98±1.00	2.82±0.02	43.74±1.36	Passable

F3	8.64±0.14	36.08±0.51	105.87±1.27	47.06±0.54	2.71±0.01	36.67±1.11	Fair

Mannitol showed a high angle of repose 46.56±4.92 whereas crospovidone demonstrated a slightly lower value of 31.22±4.25. Based on the classification (Table 4.9), mannitol has poor flowability and crospovidone has good flowability. The flowability for all formulations, prepared at various order of blending was passable (F1 and F2) and fair (F3), however no significant difference (P>0.05) was observed for the measured angle of repose for all the different mixtures studied. An enhanced flow was showed in powders F3 and, where the largest amount of agglomeration was formed. It was hypothesised that the larger agglomerated particles lost the needle shaped feature of mannitol and had reduced cohesive forces and levels of segregation which resulted in slightly improved powder flow (Koner *et al.*, 2015).

Kaerger, et al. examined the influence of particle size and shape on the flowability and compactibility of paracetamol and MCC mixture. It was identified that blend prepared from small particles exhibited increased angle of repose and densification of the blends; these findings support the observations of this study (Kaerger *et al.*, 2004). Mean volume distribution (VMD) for mannitol was 34.99 µm and median (X50) was 28.06µm. Mannitol shows a particle size distribution pattern with a span of distribution of 2.52 and 90% of mannitol particles were below 75.02µm indicating that the largest proportion of the powder mix is made of fine powder.

4.3.5. Effect of different order of mixing on tablet properties

In this section tablet properties containing the different order of mixing of excipients were investigated. Nearly all ODT products contain mannitol as formulation diluent as it has low hygroscopicity profile as well as the sweetness and creamy mouth feel. However, the main disadvantage of powdered mannitol is the poor compaction

property usually resulting in low tablet hardness and subsequent unacceptable friability levels (Al-Khattawi *et al.*, 2012).

4.3.5.1. Mechanical properties of ODTs

Commonly, tablet dosage forms are exposed to various mechanical stresses during the manufacturing steps, transportation and handling by patients. Thus a successful tablet formulation must have a sufficient mechanical strength. The results for hardness of tablets made from quaternary mixtures of fixed concentrations of 30% w/w MCC, 64.5% (w/w) of D-mannitol, 5% w/w crospovidone and 0.5% w/w magnesium stearate showed similar results of hardness for all formulations ($p>0.05$) (Figure 4.20). The high crushing strength for all ODTs formulations (> 70 N) possibly due to the addition of MCC which could be explained by the microfibrillar structure of the MCC which has been exhibited to show mechanical interlocking, thus , preventing extensive stress relaxation (Bolhuis *et al.*, 1996).

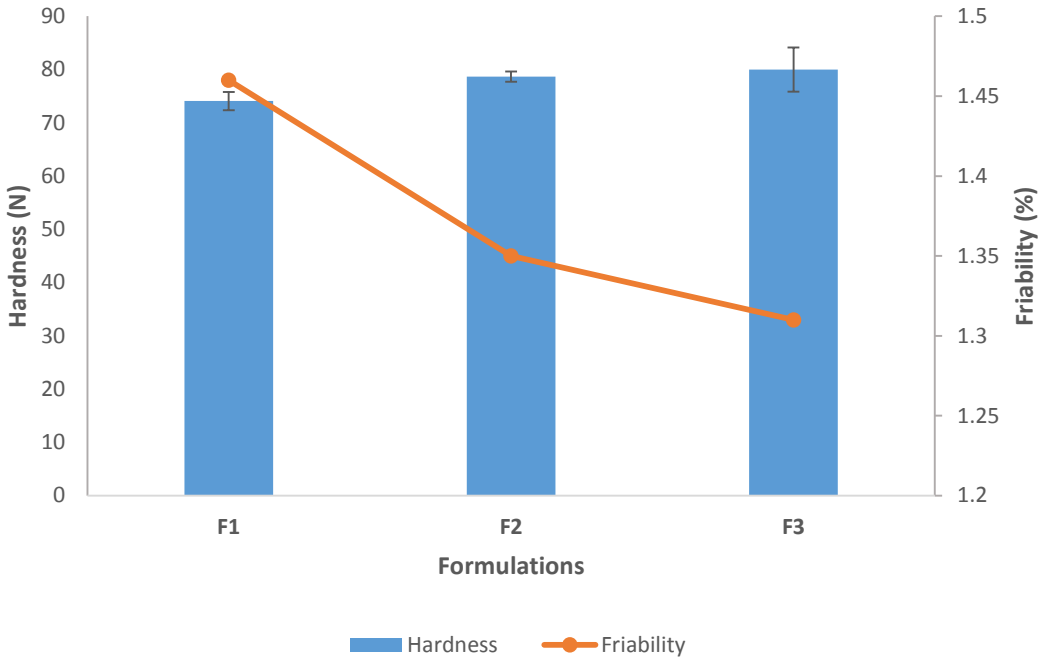

Figure 4.20: The hardness and friability profile of different order of blending of ODTs, 30% w/w MCC, 5% w/w crospovidone , 64.5% w/w mannitol and 0.5% magnesium stearate. (F1: Mannitol and MCC mixed first, crospovidone second, F2: mannitol and crospovidone mixed first, MCC second and F3: MCC and crospovidone mixed first, mannitol second. Magnesium stearate added at the end and mixed for 2 minutes then compressed at 10 KN. Values for hardness are represented as mean ± standard deviation (n=3).

Similarly, the results for friability for all batches did not achieve the pharmacopeial limit of <1% (Figure 4.20). Based on previous study a further increase of MCC concentration might yield lower friability due to the binding property of MCC. Furthermore, enhancement in friability of MCC based tablets is attributed to the high plasticity of MCC and mechanical interlocking ability which overcome the poor binding capacity leading to tablets with acceptable physico-mechanical properties. (Al-Khattawi *et al.*, 2014a).

4.3.5.2. Disintegration time and porosity studies

The assessment of disintegration time is considered an essential issue in optimising and developing orally disintegrating tablets. According to the U.S. FDA specification, the disintegration time of such tablets should not exceed 30 seconds (FDA, 2008).

Although, all formulations showed no significant difference in disintegration time (ANOVA, P>0.05), lower tablet disintegration time was observed with F2 which was approximately 22 seconds (Figure 4.21). It is possible that as MCC was added and mixed in the second stage (mannitol and crospovidone mixed first, then MCC) the surface access of MCC to water entering into the tablet promotes faster disintegration of the tablets. (Reier and Shangraw, 1966).

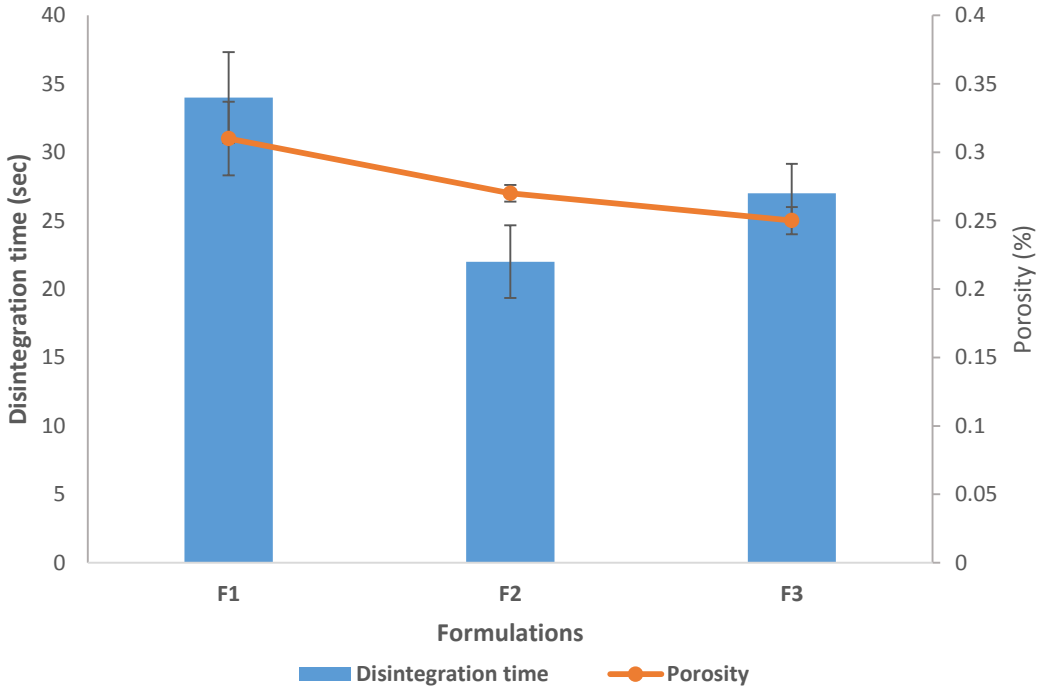

Figure 4.21: The disintegration time and porosity profile of different order of blending of ODTs, 30% w/w MCC, 5% w/w crospovidone, 64.5% w/w mannitol and 0.5% magnesium stearate. (F1: Mannitol and MCC mixed first, crospovidone second, F2: mannitol and crospovidone mixed first, MCC second and F3: MCC and crospovidone mixed first,mannitol second. Magnesium stearate added at the end and mixed for 2 minutes then compressed at 10 KN. Values are represented as mean ± standard deviation (n=3).

The porosity of the ODTs at various order of blending is summarised in (Figure 4.21). The results showed that produced tablets for all formulations with insignificant differences in their total porosity (p>0.05). However, as all tablets in this study were

produced using the same procedure and the same materials, any differences in their porosity would have been attributed to the change in the order of mixing.

4.4. Conclusion

The development of formulation with low API content is challenging and requires a proper understanding of API and excipients properties. In this study, it was found that flow properties improved as particle size increased, with the non-sieved, non-cohesive MCC and non-cohesive pregelatinised starch having excellent flow whereas the cohesive pregelatinised starch and starch had an angle of repose just outside the threshold of being considered to have poor flow properties. In case of geometric mixing technique for 1 minute all formulations failed to meet the required pharmacopeial standards for drug content uniformity. Therefore, an increase in mixing time to 5 minutes with geometric addition showed considerable uniformity improvements for all carrier types. Ordered mixing with the dry powder coater allowed for uniformity to be reached faster than hand order mixing, and was able to keep the blend containing cohesive powder within the acceptable uniformity range throughout the mixing period. The powder coater was also useful in obtaining good uniformities at 0.5% and 1% API using non-sieved carrier. All blends showed acceptable uniformity after the 32 minute mixing period, with the 1% API also achieving this only for MCC after 8 minutes of mixing, whereas the 0.5% API with MCC blend reached ideal uniformity at the end of 16 minutes mixing period. This study also highlighted the importance of excipient mixing order for (Mannitol, MCC, crospovidone and magnesium stearate) on tablet and powder properties. Although all formulations (F1-F3) demonstrated similar results for powder and tablets characterisations (no significance difference), powders flows were fair to passable for all batches whilst MCC alone showed excellent flow property. The inclusion of excipients with high plastic deformation proficiency (MCC) improved tablet hardness and reduced friability. The resultant mixture tablets exhibited good hardness and friability profile. Overall, it is critical to realize that mixing order has significant

impact on blend and tablet properties. The study concluded that MCC showed better % drug content uniformity in both the mixing techniques.

Chapter 5

Formulation, Optimisation and Characterisation of Pre-blend Excipients for direct compression of ODTs Based on D- mannitol, Starch1500 and Silica

5.1. Introduction

Tablets are extensively used as drug delivery system due to their suitability with respect to self-administration and ease of manufacture (Jivraj *et al.*, 2000). (Bhattacharyya *et al.*, 2006). Nonetheless, paediatric and geriatric patients experience difficulties in swallowing conventional tablets, which leads to poor patient compliance. To overcome this limitation, ODT formulations have been developed which provide the advantages of both a solid dosage form as well as a liquid preparation (Jonwal *et al.*, 2010). Regardless of the growing popularity and success of ODTs over the last decade, many challenges still face the development of these tablets. For example, the number of fillers/binders/glidants which can be selected for ODT formulations is limited because these bulk excipients have to fulfil special requirements, such as being soluble in water, pleasant taste, mouth feel, sweetness, hardness and rapid disintegration in the mouth (Gohel and Jogani, 2005). Consequently, novel co-processed excipients blends have been developed which satisfy the need of more than one excipient (summarized in Table 5.1).

Furthermore, the inclusion of these co- processed excipients alongside API in ODTs may provide a solution for the poor mechanical strength/high friability profile investigated for individual excipients such as mannitol (Al-Khattawi *et al.*, 2012). Hence, the incorporation of adjuvant excipients combined with mannitol, such as binders, disintegrants or combined systems of both is essential. For this reason, dry powder coating technique was developed in order to enhance the quality of material which resulted in introducing a strong adhesion of the fine particles on the surface of carrier particles, providing homogenous free flowing mixture (Alderborn *et al.*, 1988, Honda *et al.*, 1994, Pfeffer and Dave, 2001).

The work in this chapter aims to develop a novel co- processed blend including starch 1500, D-mannitol and silica for use in ODTs, that has the ability to disintegrate in a

matter of seconds (< 30 sec) with suitable tablet mechanical strength (Hardness > 50 N). It was hypothesised that starch 1500 powder coated with milled- mannitol and silica will overcome the significant challenge of very poor flow of milled mannitol.

- The objectives in this study were:

- To optimise the process parameters and mixing types using dry powder composite coating device.

- Investigate the effect of inclusion of API (Ibuprofen) and silica concentrations on the powder flow and ODT properties.

- Understanding the dry powder coating process using a range of quantitative and microscopic techniques.

Table 5.1: Overview examples of marketed co- processed excipients blend. Adapted from (Chaudhary *et al.*, 2010) (Kathpalia and Jogi, 2014).

Co-Processed Excipients	Manufacturer	Composition	Advantages
Ludiflash®	BASF (Germany)	Mannitol-90 Kollidon® CL-SF-5 Kollicoat®	Rapidly disintegration time Good mechanical strength Good flowability
ProSolv®	JRS (USA)	MCC- 98 Silicon Dioxide	Better flow Less sensitivity to wet granulation, better tablet hardness
StarCap1500®	Colorcon (UK)	Maize Starch, Pregelatinized Starch	Good flowability Excellent disintegration time
Pharmaburst ™ 500	SPI Pharma (USA)	Mannitol, Starch, Crosspovidone, Cross Carmellose Sodium, and Collidal Silica	Rapid disintegration for ODT tablets Good palatability
F-MELT	Fuji (Japan)	mannitol, xylitol, MCC, crospovidone	fast disintegration time good flow Less capping pleasant mouth-feel

5.2. Materials and Methods

5.2.1. Materials

D-Mannitol and Rhodamine B were obtained from Sigma-Aldrich (Dorset, UK). Magnesium stearate was purchased from Fischer Scientific (Loughborough, UK), while pregelatinised starch (starch 1500®) was obtained from Colorcon (Dartford Kent,UK). Ibuprofen was purchased from Discovery Fine Chemicals (Dorset, UK), whereas microcrystalline cellulose (PH-200) was donated by FMC BioPolymer Europe (Brussels, Belgium). Colloidal silicon dioxide (SiO_2) (AEROSIL® 200 Pharma) was used as received from Degussa AG (Düsseldorf, Germany).

5.2.2. Methods

5.2.2.1. Preparation of Ball Milled Mannitol

Milled mannitol samples were prepared using a Fritsch Pulverisette 7 planetary ball mill (Idar-Oberstein, Germany) according to parameters (speed 200 rpm, time 30 minutes and weight of powder 3.614 g) optimised by our team in a previous study (Koner *et al.*, 2015). Powders were accurately weighed, the weighed samples were transferred into agate vials (45 cm^3 volume) along with 13 agate balls (diameter 10 mm). The vials were sealed with a plastic ring to avoid atmospheric contamination.

5.2.2.2. Preparation and optimisation process of ODTs pre-blends using interactive and composite powder coating technique

The three key excipients studied included pregelatinised starch (starch 1500), mannitol and silica. Both D-mannitol (milled and un-milled) with starch1500 were composite mixed for 30 min followed by addition of various ratios of silica ranging from 0.5 to 2% w/w and continuous blending for 5 minute. The composite mixing process was carried out considering several critical operating parameters; speed of the mixer, mixing time

and the use of air flow. As for the materials used, the parameters considered were pertinent to the guest loading percentage, measured in weight per weight, and the type of carrier material in terms of particle size and shape. Samples were tested alongside interactive mixtures with the same content, but mixed at low speeds (200rpm) using cube mixer. The schematic in (Figure 5.1) illustrates the different mixing techniques used to optimise pre-blends.

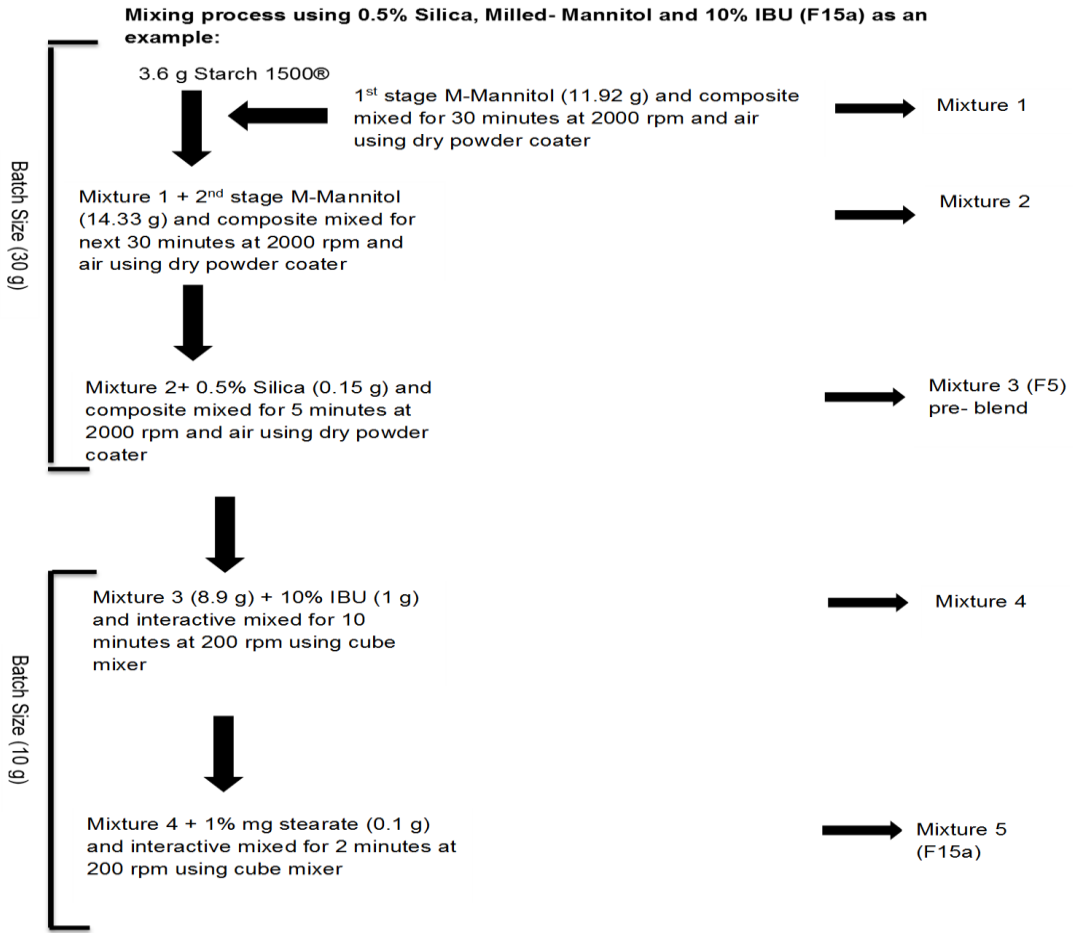

Figure 5. 1: A schematic representing an example of mixing process using 12% w/w starch 1500, 87.5% milled mannitol and 0.5% w/w silica.

5.2.2.3. Characterising pre-blend powder

5.2.2.3.1. Powder flow properties (angle of repose method)

The angle of repose measurement was performed using the recommended British Pharmacopeia procedure (Pharmacopoeia, 2012). Approximately 10 g of powder was

poured through a funnel into a base free from vibration to form a pile. The funnel was positioned 2 - 5 cm from the top of the powder pile as it was forming. Angle of repose was determined by measuring the height of the pile (h) and diameter of the base (d); then angle of repose (α) was calculated from the equation:

$$\tan\alpha = h \div (0.5 \times d)$$

5.2.2.3.2. Particle size analysis

Particle size of the powders was measured by the laser diffraction technique using HELOS/BR particles size analyser equipped with a RODOS dry disperser with VIBRI/L vibrating feeder, from Sympatec (Clausthal-Zellerfeld, Germany). The measuring range of the lens was 0 - 175µm. About 1 g of each powder was placed in the feeder tray and the run started at trigger condition of 2% Copt (optical concentration) for 10 sec with a powder dispensing pressure of 2bar. Volume mean diameter (VMD) was recorded for the powders and all the measurements were examined in triplicate.

5.2.2.3.3. Scanning electron microscopy (SEM)

The morphology of starch 1500, milled and un- milled D-mannitol, the mixture and the coated powder particles were examined using a Carl Zeiss EVO LS 15 from Cambridge Instruments (Crawley, UK) scanning electron microscope (SEM). Approximately 1-2 mg of each material was placed onto a double-sided adhesive strip on an aluminium stub. The specimen stub was coated with a 15nm of gold using a Quorum QR105S sputter coater from Polaron Equipment ltd. (Watford, UK) at 20 mA for 3 min followed by sample examination using SEM. The acceleration voltage (kV) and the magnification can be seen on each micrograph. Various magnifications were applied to identify characteristics of the powders.

5.2.2.3.4. Confocal laser scanning microscopy (CLSM)

This technique was used to confirm coating, 15% rhodamine B (a known fluorescent probe) was used as a guest material with 85% microcrystalline cellulose (MCC) as carrier material. MCC (mean particle size was sieved to be similar to starch 1500, 60 µm) was chosen due to auto- fluorescence of starch 1500 (discussed in results section). Dry coating process was run for 60 minutes in two stages at 2000 rpm and nitrogen gas pressure set at 3 bars. Rhodamine B was micronized using mortar and pestle and passed through sieve with mesh size of 38µm and the sample retained at sieves with pores size of 20µm was used. Confocal microscopy was carried out according to the method reported in (Korlach *et al.*, 1999), the samples (control, first coated sample and second coated) were then observed on a Leica Microsystem confocal microscope (TCS SP5 II) using a 10 X dry objective. Fluorescence micrographs of the labelled MCC particles were obtained using confocal microscope equipped with a Tunable Multiphoton Laser z-stacking and detector. The samples were measured at wavelength 543 nm and placed on a slide without any further treatment.

5.2.2.3.5. Quantitative analysis of fluorescence intensity particles using ImageJ

To quantify coated material (rhodamine B) levels in particles, a single in-focus smooth was acquired. Using ImageJ (v1.48, NIH), an outline was drawn around each particle and regions of interest included circularity, area, integrated density, mean fluorescence measured, along with several adjacent background readings (appendix 12). The total corrected fluorescence was calculated using equation below (McCloy *et al.*, 2014). For first and second coated samples, 0.3 µm z-sections were taken, de-convoluted, and shown as Interactive 3D Surface Plot maximum projections using ImageJ.

$$\text{CTF} = \text{Int Den} - (\text{Area of selected particle} \times \text{Mean fluorescence of background readings})$$

Where CTF is corrected total fluorescence and Int Den is integrated density.

5.2.2.3.6. Calculation of surface coverage

Surface coverage was calculated using the equation and method described in(Yang *et al.*, 2005). The amount of guest material in weight percentage required to achieve 100% coverage within the given parameters was as follows:

$$\text{Gwt\%} = \frac{\text{Nd}^3\ \text{Pd}}{(\text{D}^3\ \text{PD}) + (\text{Nd}^3\ \text{Pd})} \times 100$$

Here:

$$\text{N} = \frac{4(\text{D} + \text{d})^2}{\text{d}^2}$$

Where d is the diameter of guest particle, D is the diameter of the host particle, Pd is the density of the guest particle and pD is the density of the host particle.

5.2.2.4. Tablet preparation

Ternary mixture pre-blend were prepared using cube mixer or dry powder coater comprising of the excipients using different concentration of silica (0.5, 1, 1.5 and 2 % w/w), varying D-mannitol or milled mannitol concentration and fixed concentration (12% w/w) of pregelatinised starch. Ibuprofen was incorporated at concentration ranging from 10 to 50% w/w. Blending of the drug and excipients pre–blend was carried out by cube or composite mixer for 10 min followed by adding 1% w/w magnesium and continues blend for 2 min. The tablets (500 mg) were prepared using a bench-top hydraulic press from Specac ltd. (Slough, UK) equipped with flat faced dies of 13 mm

diameter at fixed compression force 20 KN for 6 sec. 15 tablets were prepared at each drug concentration; three were used for porosity, three for hardness, three for disintegration time and six for friability test.

5.2.2.4.1. Helium pycnometry for true density and porosity measurement

True density and porosity were measured for all the powders/tablets using a helium multipycnometer from Quantachrome Instruments (Syosset, USA). Each powder (1000 mg) or tablet (500 mg) was placed into a micro sample cell and assessed for true volume and in turn true density. True volume Vt was obtained using the equation:

$$V_t = V_C - V_R \left(\frac{P1}{P2 - 1}\right)$$

Where V_t is true volume of the sample, V_C is volume of the sample cell, V_R is the known reference volume, P1 is atmospheric pressure and P2 is pressure change during determination. V_t was used to calculate the true density of the tablet by weighing the tablet and substituting the values into:

$$True\ Density = \frac{Tablet\ Weight}{True\ Volume}$$

Porosity (ε) was calculated using the equation:

$$\varepsilon = 1 - \left(\frac{Bulk\ Density}{True\ Density}\right)$$

Bulk density was calculated from:

$$Bulk\ Density = \frac{Tablet\ Weight}{Bulk\ Volume}$$

Bulk volume was acquired by measuring the radius (r) and thickness (h) of the tablet using a digital calliper and substituting in the equation for volume of a flat-faced tablet:

$$V = \pi \times r^2 \times h$$

5.2.2.4.2. Tablet hardness

A tablet hardness tester from Schleuniger (Thun, Switzerland) was used to investigate the hardness of three tablets of each formulation. Hardness is the force required to break up the tablet from its original structure and was measured in Newton (N) for this study. All measurements were carried out in triplicate and the values reported as mean ± standard deviation.

5.2.2.4.3. Tablet friability

The friability test of the tablets was performed according to the USP <1216> method (2009) using tablet friability apparatus Sotax F2 Friabilator USP from Sotax AG (Basel, Switzerland). Six tablets were accurately weighed after careful de-dusting using soft brush, placed into the rotating drum and rotated for 100 revolutions with an average of 25 rounds per minute. The tablets were removed and de-dusted again and accurately weighed. The percentages loss in weight (% Friability) was calculated using the following equation.

$$\%\ \text{Friability} = \frac{\text{Initial Weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

5.2.2.4.4. Disintegration time of the tablets

The disintegration time of the tablets was investigated using a USP disintegration tester (Erweka, ZT3). Distilled water (800 ml) kept at 37 ºC was used as a medium and the basket was raised and lowered at a fixed frequency of 30 cycles/min. One tablet was tested at a time. All the formulations were evaluated in triplicate and standard deviation was calculated.

5.2.2.5. Statistical analysis

One way (ANOVA) followed by Tukey post-hoc test or student t-test were performed using GraphPad Prism 7 software (California, USA). Statistical significance was

considered at a p value <0.05. Where applicable, all results are presented as mean ± SD for triplicate measurements to account for the noise encountered within the experiments.

5.3. Results and Discussion

The work presented in this chapter provides a new formulation preblend for ODTs which consists of milled-mannitol, pregelatinised starch and silica. Pre-blend products were obtained by composite mixing using dry powder coater. Optimisation of process parameters, e.g. speed, time of mixing, inclusion of air were essential on product quality. Similarly, optimising the concentration of excipients was crucial to produce a fast disintegrating tablet with good mechanical properties. The study commenced with the evaluation of powder flow and was followed up with particle size analysis. Furthermore, co-processed excipients alongside different concentration 10-50%w/w of API (ibuprofen) and 1% magnesium stearate as the lubricant were assessed for their tableting functionality.

5.3.1. Flowability, particle size and morphological studies

Powders prepared by blending or processing for direct compression of ODTs usually have poor flowability due to their smaller particle size, cohesivity and possibly non-uniform shape (Castellanos, 2005). Initial attempts to examine dry powder coating technique were carried out by studying the flow properties of fine and cohesive API powder (ibuprofen) (Han *et al.*, 2013), as a model drug. Ibuprofen has low solubility and is available as a very cohesive powder with small particle size, volume mean diameter (VMD) was 38±0.89 microns. The study compared interactive powder mixes obtained from cube mixing to dry coated powders using composite blender.

The results showed extremely poor flowability (>50%) of non-processed and processed using cube mixer (i.e. interactive mixing of ibuprofen for 30 min), whilst composite ibuprofen showed a fair flowability (40.14 ±1.98) (Table 5.2). Analysis of particle size measurements for the processed ibuprofen (composite only) when compared to non-processed showed a significant increase in size (ANOVA, $p<0.05$).

Table 5.2: Processing technique, flow properties and particle size analysis of bulk/processed ibuprofen. Results reported as mean ± standard deviation (n=3).

Formulations Code	Ingredients & Process	Silica Conc. (% w/w)	Time of Adding Silica	Angle of Repose (°)	Flow property	VMD (µm)
F0a	Ibuprofen (bulk powder , un-processed)	N/A	N/A	56.73±1.97	Very poor	37.98±0.89
F0b	Processed Ibuprofen (interactive mixed for 30 minutes using cube mixer)	N/A	N/A	56.70±0.89	Very poor	37.66±1.08
F0c	Processed Ibuprofen (composite mixed for 30 minutes using dry powder coater)	N/A	N/A	40.14±1.98	Fair	40.18±0.89

To further support composite mixing, high speed air was introduced into the processing chamber which provided enhanced flow possibly due to de-agglomeration of fine and cohesive ibuprofen powder (Figure 5.2 iii).

Table 5.3: Formulation content (F1-F5), processing technique, flow properties and particle size analysis of pre-blend composed of un-milled mannitol or milled–mannitol 87.5% w/w, 12%w/w strach1500 and 0.5% w/w silica. Results reported as mean ± standard deviation (n=3).

Formulations Code	Ingredients & Process	Silica Conc. (% w/w)	Time of Adding Silica	Angle of Repose (°)	Flow property	VMD (µm)
F1	Cube Unmilled/Starch	0.5	Added at the start and mix for 30 min	24.11±2.49	Very excellent	45.54±2.31
F2	Composite Unmilled/Starch			22.94±2.03	Very excellent	43.05±0.51
F3	Cube Milled/Starch			50.62±3.04	Poor	16.72±0.83
F4	Composite Milled/Starch			38.90±1.27	Fair	16.32±0.75
F5	Composite Milled/Starch	0.5	Added at the end and mix for 5 min	43.64±0.82	Passable	17.49±1.20

Figure 5.2: Visual evaluation of bulk ibuprofen (i), processed using cube mixer (ii) and composite (iii) using dry powder coater, after processing for 30 min.

Based on the results obtained from the preliminary experiment, the next stage was to develop a pre-blend where mannitol was selected as guest material (un-milled or milled mannitol 41.3±0.19, 12.08±0.38 microns respectively) whereas starch1500 was used

as a carrier (60±0.98 microns). Additionally, a model glidant (silica) was chosen to provide a synergistic effect with composite mixing in order to enhance flowability. The processing parameters for obtaining the pre-blend were selected from a previous optimisation study carried out in our laboratory (Alyami *et al.*, 2016).

Irrespective of the processing technique (i.e. cube or composite), it is important to note that, pre-blend formulations containing un-milled mannitol (F1 and F2) showed excellent flowability (24.11±2.49 and 22.94±2.03 respectively) which was attributed to particle size. However, milled mannitol demonstrated poor to fair (50.62±3.04 and 38.90±1.27) flowability (F3 and F4) respectively (Table 5.3). It is possible that milled mannitol has a high degree of adhesion between particles due to increase in surface area which in turn results in poor flow. Although milled pre-blend showed very poor flowability, it was taken forward to the next stage as it improved tablet properties (Koner *et al.*, 2015).

Formulation and process strategies were investigated in order to enhance flowability and the first approach was to study the effect of increasing glidant concentration (0.5-2% w/w). Results as illustrated in (Table 5.4) (F6-F8) showed that increasing silica concentration resulted in significant improvement in flowability (ANOVA, $p<0.05$), for example, the flowability of composite/milled containing only 0.5% silica (F5) shifted from passable to good and excellent when 1 and 1.5% silica were added respectively. It was hypothesized that the fine glidant particles (19.37µm) adhere to the surface of the powders and increase the distance between particles, which in turn leads to a reduction of the forces of attraction between them. Additionally, it can be explained that composite mixing provides a ball bearing type effect whereby silica forms a mono layer on the powder particles causing them to roll over one another which reduces frictional and adhesive forces between the surfaces (Sheth *et al.*, 1980, Jonat *et al.*, 2004). SEM analysis was carried out to confirm the degree of silica particle coverage and distribution on the pre-blend powder as was evidenced in (Figure 5.5 e and f).

Table 5.4: Effect of increasing glidant concentration (silica) of formulation content (F6-F8), on flow properties of pre-blend composed of milled–mannitol 86-87.5% w/w, 12% w/w strach1500 and 1-2% w/w silica. F9 and F10 showed a strategy to enhance flow of formulation which contain 0.5 % silica by increasing composite mixing time to 15 and 30 min respectively. Results reported as mean ± standard deviation (n=3).

Formulations Code	Ingredients &Process	Silica Conc. (% w/w)	Time of Adding Silica	Angle of Repose (°)	Flow property	VMD (µm)
F6	Composite Milled/Starch	1	Added at the end and mix for 5 min	33.15±2.13	Good	17.08±0.16
F7	Composite Milled/Starch	1.5		26.17±1.46	Excellent	16.89±0.21
F8	Composite Milled/Starch	2		25.97±1.19	Excellent	17.01±0.13
F9	Composite Milled/Starch	0.5	Added at the end and mix for 15 min	37.31±1.66	Fair	18.99±0.86
F10	Composite Milled/Starch	0.5	Added at the end and mix for 30 min	37.18±2.11	Fair	19.76±1.52

The second approach was based on increasing composite mixing time of pre-blend containing 0.5% w/w silica from 5 min to 15 min. The results showed that processing the blend for 15 min improved the powder flow from passable to fair , similar trend was obtained with processing for 30 min (F5, F9 and F10) respectively (Table 5.3 and 5.4). It is worth mentioning that the guest particles were more de-agglomerated and better distributed, with the longer processing time.

Table 5.5: Formulation content (F11-F15), processing technique and flow properties of pre-blend composed of un-milled mannitol or milled–mannitol 87.5% w/w, 12%w/w strach1500 ,0.5% w/w silica and inclusion of ibuprofen 10-50% w/w . Results reported as mean ± standard deviation (n=3).

Formulations Code	Ingredients &Process	Ibuprofen Conc. (% w/w)	Silica Conc. (% w/w)	Adding Silica	Angle of Repose (°)	Flow property
F11a	Cube Unmilled/Starch	10	0.5	Added at the start	22.16±1.65	Excellent
F11b	Cube Unmilled/Starch	30			21.78±0.53	Excellent
F11c	Cube Unmilled/Starch	50			17.24±0.24	Excellent
F12a	Composite Unmilled/Starch	10			18.12±1.42	Excellent
F12b	Composite Unmilled/Starch	30			18.41±1.18	Excellent
F12c	Composite Unmilled/Starch	50			17.11±0.41	Excellent
F13a	Cube Milled/Starch	10			41.87±0.81	Passable
F13b	Cube Milled/Starch	30			42.75±1.97	Passable
F13c	Cube Milled/Starch	50			43.93±0.49	Passable
F14a	Composite Milled/Starch	10			35.68±2.63	Fair
F14b	Composite Milled/Starch	30			37.48±1.13	Fair
F14c	Composite Milled/Starch	50			38.41±0.91	Fair
F15a	Composite Milled/Starch	10	0.5	Added at the end and mix for 5 min	43.72±1.18	Passable
F15b	Composite Milled/Starch	30			45.14±0.75	Passable
F15c	Composite Milled/Starch	50			47.33±0.45	Poor

On the other hand, the flowablity results of the composite and interactive mixtures at various concentrations of ibuprofen ranging from 10% to 50% are depicted in (Table 5.5). The powder blend containing un-milled exhibited excellent flow when compared with milled powder batches which have poor to passable flow. Interestingly, a clear trend can be seen whereby increasing ibuprofen concentration decreased flowablity of the powders. It is possible that ibuprofen has high cohesivity and adhesivity (Liu *et al.*, 2008), and further support was obtained from SEM images of ibuprofen as it has a distinct needle shape with rough surface (Figure 5.4 i and j). However, the flowability of pre-blend powders were improved substantially by increasing glidant concentration (p value <0.05) (Table 5.6).

Table 5.6: Formulation content (F16-F20), processing technique and flow properties of pre-blend composed of milled–mannitol 86-87.5% w/w,12% w/w strach1500 , 0.5-2% w/w silica and inclusion of ibuprofen 10-50% w/w . Results reported as mean ± standard deviation (n=3).

Formulations Code	Ingredients &Process	Ibuprofen Conc. (% w/w)	Silica Conc. (% w/w)	Adding Silica	Angle of Repose (°)	Flow property
F16a	Composite Milled/Starch	10	1	Added at the end and mix for 5 min	33.98±2.11	Good
F16b	Composite Milled/Starch	30			37.25±1.64	Fair
F16c	Composite Milled/Starch	50			39.19±2.75	Fair
F17a	Composite Milled/Starch	10	1.5		27.76±0.94	Excellent
F17b	Composite Milled/Starch	30			30.19±2.06	Excellent
F17c	Composite Milled/Starch	50			33.26±1.44	Good
F18a	Composite Milled/Starch	10	2		27.34±1.58	Excellent

F18b	Composite Milled/Starch	30			29.21±2.19	Excellent
F18c	Composite Milled/Starch	50			32.98±1.64	Good
F19a	Composite Milled/Starch	10	0.5	Added at the end and mix for 15 min	37.66±0.88	Fair
F19b	Composite Milled/Starch	30			39.21±1.58	Fair
F19c	Composite Milled/Starch	50			41.08±0.64	Passable
F20a	Composite Milled/Starch (IBU+ pre-blend composite)	10	0.5	Added at the end and mix for 5 min (IBU+ Pre-blend were composite mixed for 10 minutes)	33.75±2.31	Good
F20b	Composite Milled/Starch	30			36.21±1.06	Fair
F20c	Composite Milled/Starch* (IBU was added on one stage)	50			39.32±0.98	Fair
F20d	Composite Milled/Starch** (IBU was added on two stages)	50			38.11±1.27	Fair

Table 5.7: Particle size distribution parameters for Un-milled/milled mannitol, strach1500, silica and ibuprofen, using laser diffraction technique, (mean ±SD, n=3).

Ingredient	X10 (µm)	X50 (µm)	X90 (µm)	VMD (µm)
Un-Milled Mannitol	6.93±0.16	34.66±0.14	84.97±0.51	41.31±0.19
Milled Mannitol	0.84±0.01	5.16±0.21	31.95±0.87	12.08±0.38
Starch 1500	12.09±0.37	47.66±1.12	129.22±1.42	60.00±0.98
Colloidal silicon dioxide	5.98±0.57	14.88±0.89	37.13±0.22	19.37±0.34
Ibuprofen	7.09±055	33.08±2.38	78.40±2.38	37.98±0.89

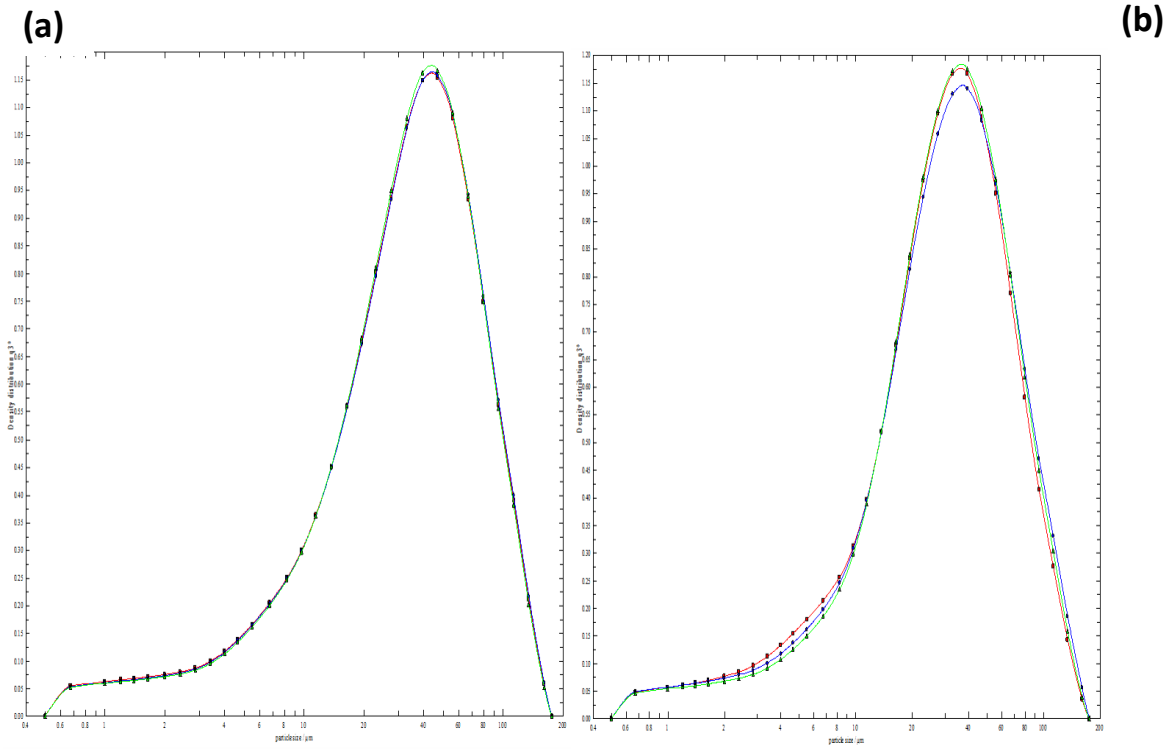

Figure 5.3: Particle size distribution of (a) Un-milled mannitol and (b) ibuprofen established by laser diffraction showing similar distribution between mannitol and ibuprofen.

Interestingly, when scanning electron microscopy (SEM) tests were carried out, it was recognized that the shape of the mannitol particles was similar compared to ibuprofen as well as particle size distribution (Figure 5.3).

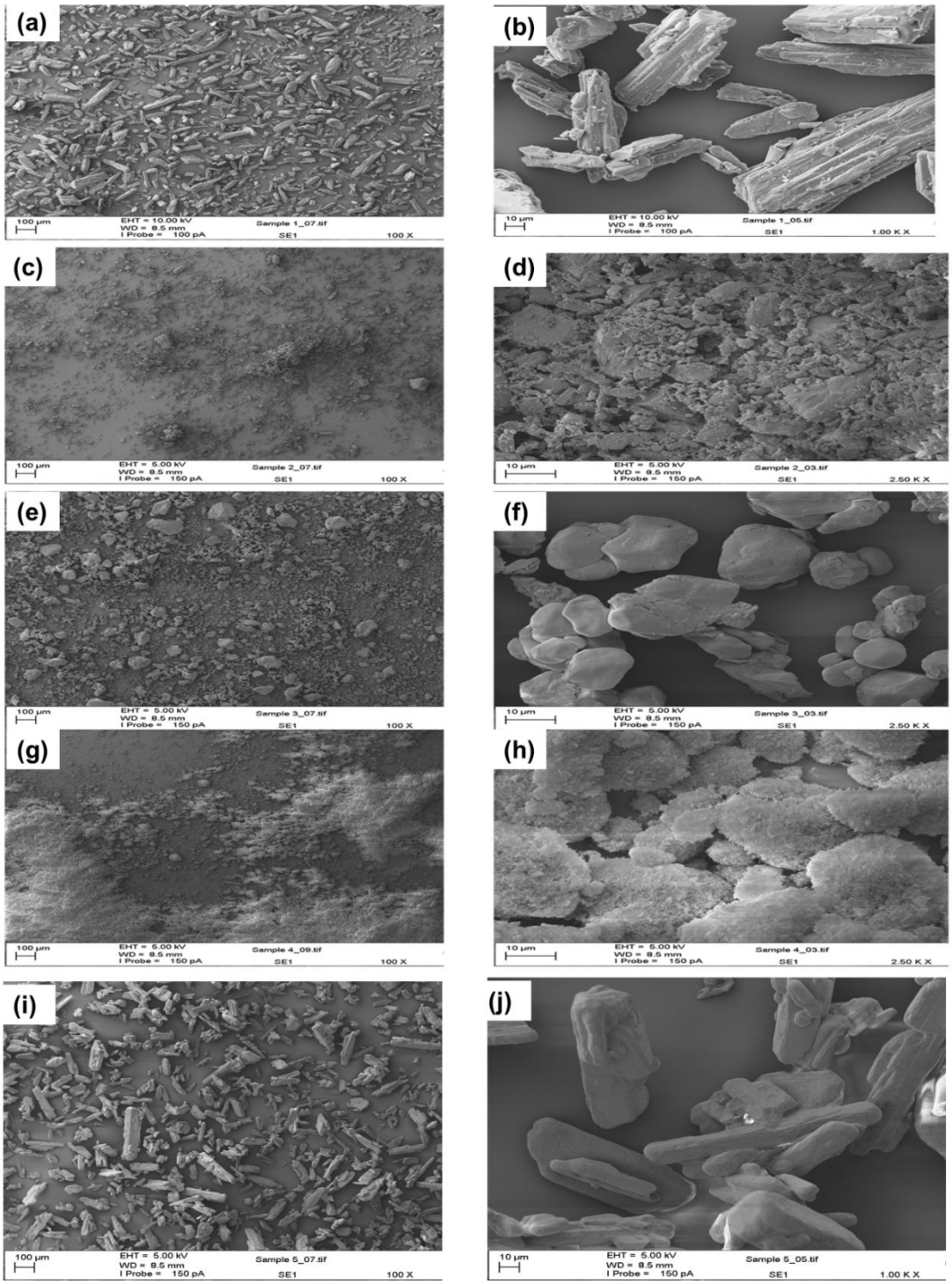

Figure 5.4: SEM images powder of (a and b) un-milled mannitol, (c and d) milled mannitol, (e and f) starch1500, (g and h) silica and (i and j) ibuprofen.

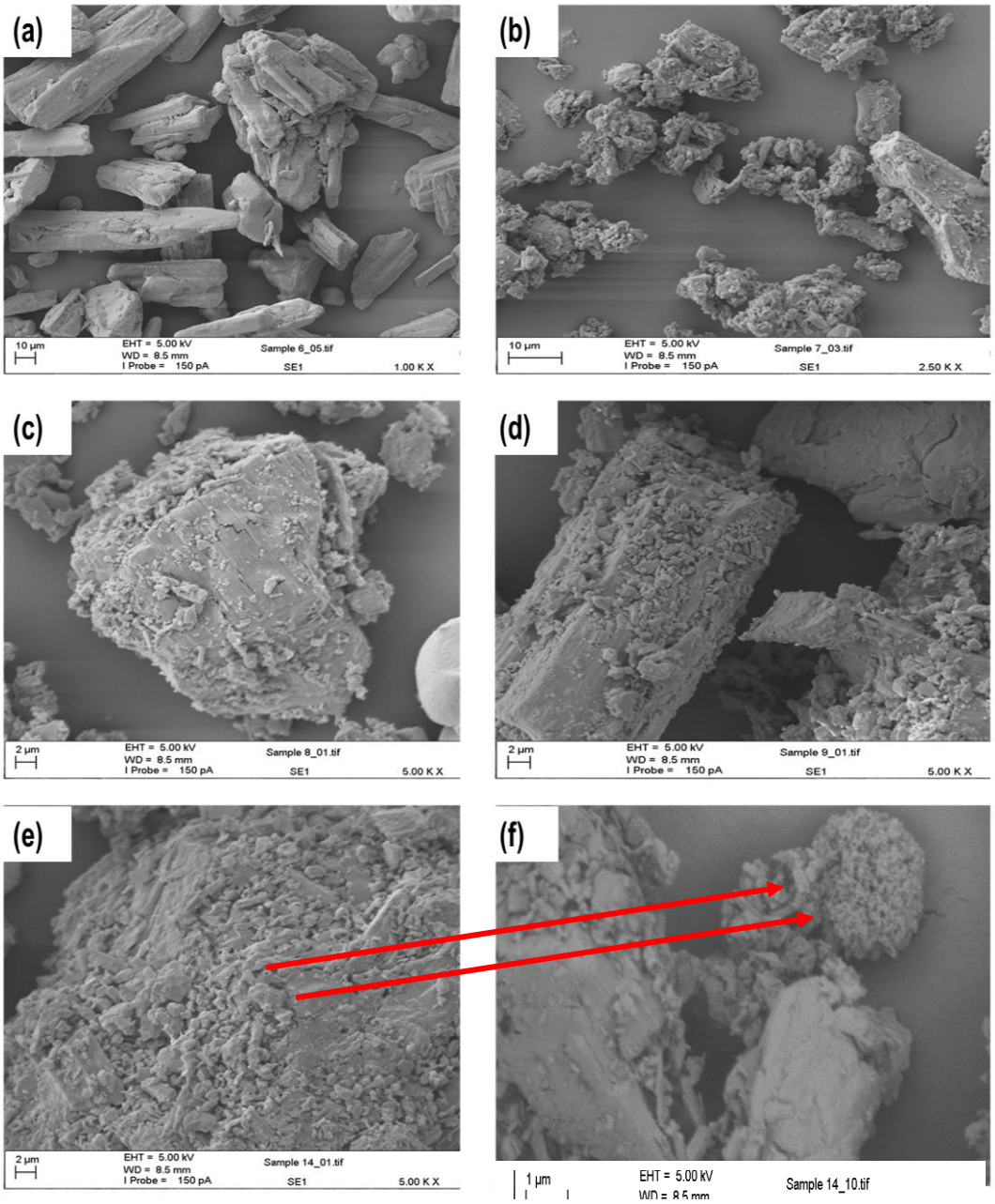

Figure 5.5: SEM images of (a) control 1 cube un-milled pre-blend, (b) control 2 cube milled pre-blend, (c) first coat of composite/milled ,(d) second coat of composite/milled alongside 0.5% w/w silica, (e) second coat of composite/milled alongside 2% w/w silica and (f) Zoomed area showing small particles of silica coating the surface of pre-blend powder.

5.3.2. Particle coating formation using confocal microscopy

Qualitative evidence aimed at examining the influence of dry particle coating and the extent of guest particle deposition as well as uniformity of coat over the carrier particles was analysed using confocal microscopy followed by quantitative investigation using ImageJ software. 15% w/w rhodamine B was selected as guest and micronized to be

similar to milled- mannitol particle size (mean diameter 10 µm) and used as a fluorescent probe. Starch 1500 was selected as a control, however it was fluorescent under confocal microscopy. Thus, 85% MCC was used as control and carrier (Figure 5.6 a). Furthermore, surface complete coverage was calculated using true density and particle size according to the equation mentioned in the methods section. MCC has a true density of 1.86 g/cm^3 whereas rhodamine B was 0.81 g/cm$^{3.}$ .14.33% w/w from guest amount (15% w/w) was required to produce complete coverage (first coat) however, in order to achieve second coat, remaining amount of guest was added and composite mixed for an additional 30 min.

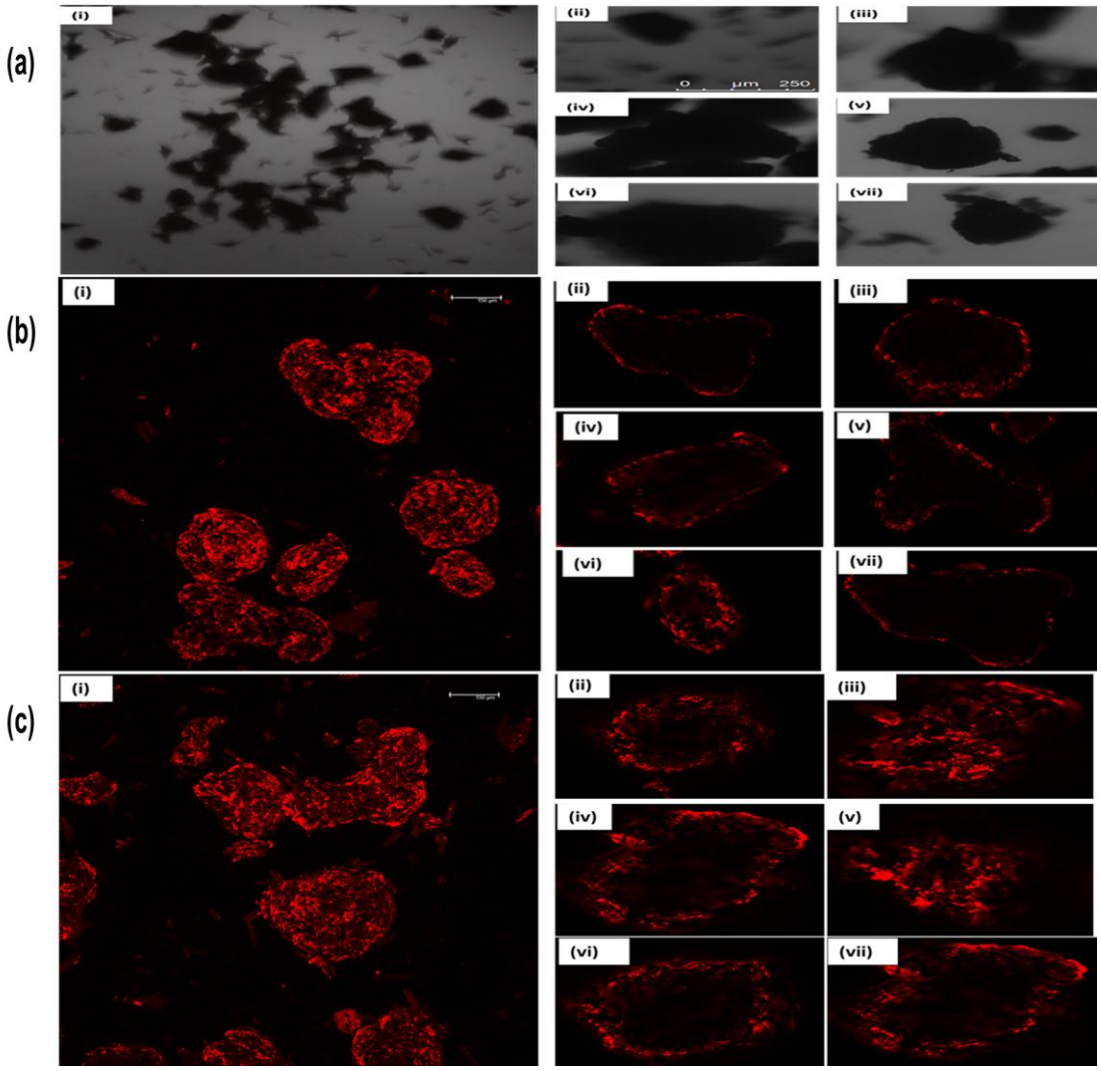

Figure 5.6: Confocal microscopy images of control, first coat and second coat samples with Z-stack slices A (i-vii), B (i-vii)-one coating and C (i-vii)-two coats respectively using a 10x objective (bars= 150 µm). The dry coated particles are shown by the red colour whereas carrier material (MCC) representing by the black internal region (non- florescent colour).

The results clearly demonstrated that rhodamine was deposited uniformly around the surface of MCC particles forming less bright and thinner layer for first coat whereas brighter continuous layer can be seen for second coat (Figure 5.6 b and c respectively). Further confirmation on the coating quality was performed using ImageJ software through 3D images of maximum projection for control, first coat and second coat samples (Figure 5.7). The results showed that less rhodamine (fluorescent) was presented in the first coat, as was shown by the dark areas (control) not fully coated by guest, however, second coat (Figure 5.7 iv and v) showed a fully coated particle surface.

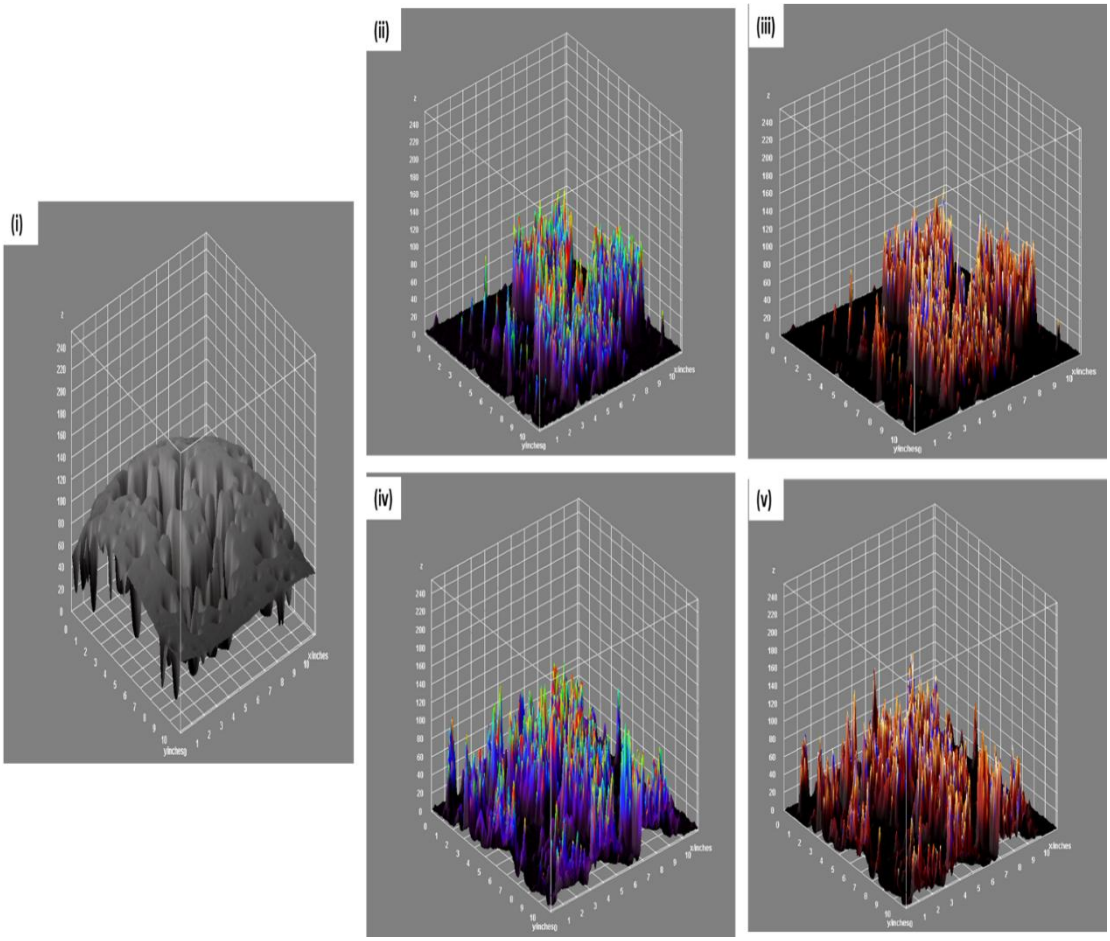

Figure 5.7: 3D images of group of particles (i) control, (ii-iii) first coat and (iv-v) second coat using plugins interactive 3D surface plot of ImageJ software. Black colour indicates control in i and non-coated area (ii-v) whereas different colours indicates coating layer.

Furthermore, ImageJ was used as another confirmative technique where first coat and second coat samples were taken forward in order to quantify fluorescence intensity. The results showed that a significant increase in average corrected total fluorescence was obtained for second coat sample when compared to single coat (increased by two fold compared to first coat) (ANOVA, $p<0.05$). Additionally, there was a similar trend for integrated density for both samples (Figure 5.8).

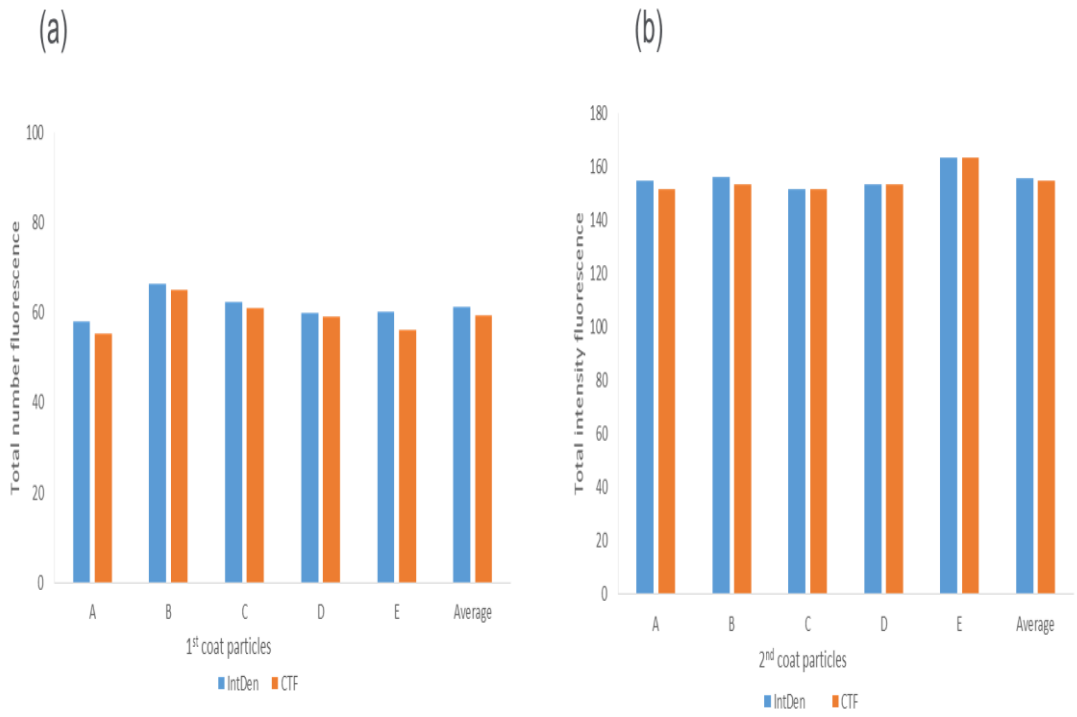

Figure 5.8: Quantitative total fluorescence (CTF) analysis was performed on MCC particles coated with Rhodamine B; (a) indicating first coated sample and (b) indicating second coated sample. Integrated density (IntDen) was applied using ImageJ software, analysis was carried out to the maximum projection images of samples. Average bar is the mean of A, B, C, D and E bars samples.

5.3.3. Tablet characterisation studies

In this section tablet properties of the different pre-blend of powders containing the different ibuprofen concentrations were investigated. Disintegration time and hardness were both affected by the increase in ibuprofen concentration possibly as a result of

the different densification mechanisms of the powder bed due to increase of cohesive bonding between ibuprofen particles (Al-Khattawi *et al.*, 2014a).

5.3.3.1. Mechanical properties results of ODTs

Generally, tablet dosage forms are exposed to various mechanical stresses during the manufacturing steps (e.g. packaging process), distribution and handling by patients. Consequently a successful tablet formulation must have an acceptable mechanical strength.

The results of the hardness and friability are shown in (Figure 5.9 and 5.10) respectively.

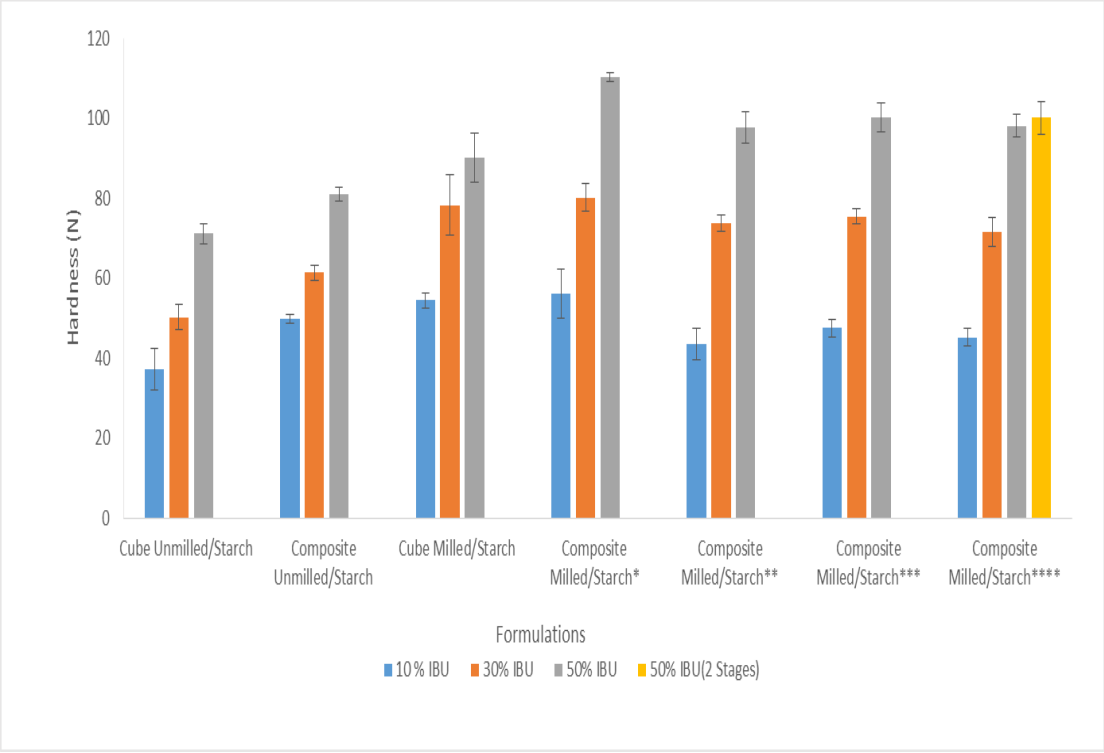

Figure 5.9: Comparison of hardness of ternary mixture pre-blend containing (12% w/w starch1500, 87.5% w/w milled or un-milled mannitol and 0.5% silica) tablets of ibuprofen. Tablets were compressed at 20 kN compression force. Data marked with a single asterisk (*) indicates results that are silica added at start & composite mixed for 30 min. (**) indicates the silica added at the end & composite mixed for 5 min, (***) indicates silica added at the end & composite mixed for 15 min and (****) indicates ibuprofen+ pre-blend (silica added at the end & composite mixed for 5 min) were composite mixed for 10 min. Results reported as mean ± SD (n=3).

The hardness of the tablets (Figure 5.9) increased significantly by increasing ibuprofen concentration (ANOVA, $p<0.05$). This could be explained by the domination of ibuprofen particles. Previous research carried out in our laboratory explained that the fragmentation of ibuprofen occurs on the surface followed by elastic/plastic deformation (Al-Khattawi *et al.*, 2014a). Furthermore, increased cohesive bonding between ibuprofen-ibuprofen particles and crystal habit might be the reasons for increasing hardness of the prepared tablets while increasing ibuprofen concentration (Garekani *et al.*, 2001). In accordance, our results are in line with findings from Inghelbrecht and Remon (1998) who stated that highest ibuprofen concentrations (75% w/w) result in increased hardness of tablets.

It can be predicted that particle shape affects mechanical properties of plastically deforming and none fragmenting materials (Alderborn *et al.*, 1988). Nevertheless, from this study we found that particle shape possibly plays a role in densification of fragmenting materials. This arises from the fact that mannitol which is categorised as a brittle material only undergoes fragmentation as observed from SEM images (Figure 5.4 a and b). On the other hand, it could be that inclusion of fractured mannitol (milled) as well as milled mannitol coated starch (as noticed from SEM image) (Figure 5.5 c) in tableting result in an enhancement in the compressibility of the excipient as more of the compaction energy would be utilised in the bonding of the compact (Koner *et al.*, 2015). Surprisingly, the results showed that there was no impact of processing technique (i.e. interactive or composite mixing) on the hardness of the tablets (ANOVA, $p > 0.05$).

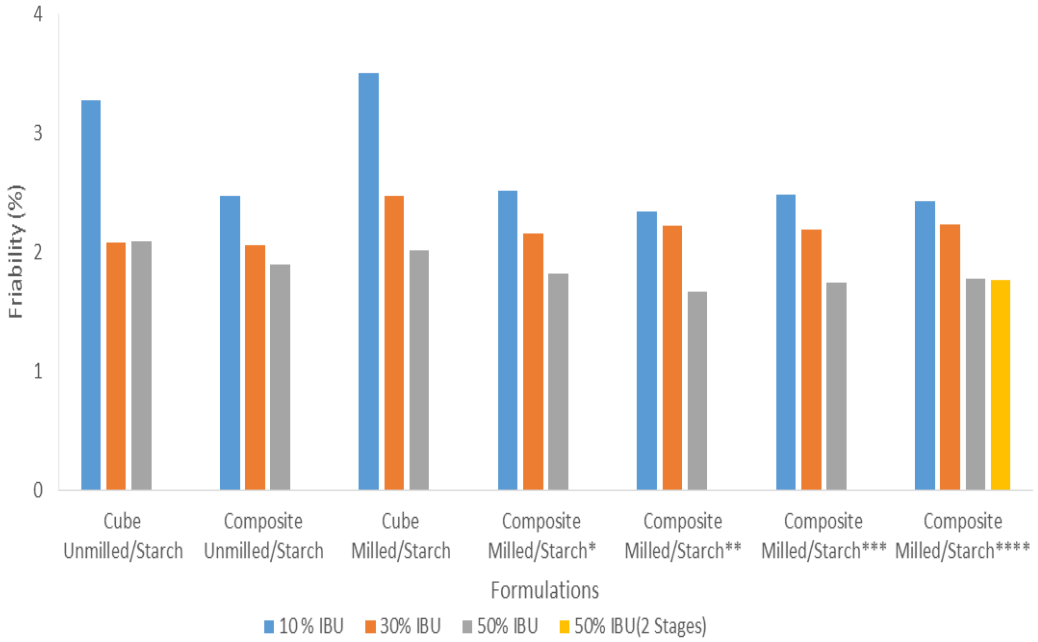

Figure 5.10: Comparison of friability of ternary mixture pre-blend containing (12% w/w starch1500, 87.5% w/w milled or un-milled mannitol and 0.5% silica) tablets of ibuprofen. Tablets were compressed at 20 kN compression force. Data marked with a single asterisk (*) indicates results that are silica added at start & composite mixed for 30 min. (**) indicates the silica added at the end & composite mixed for 5 min, (***) indicates silica added at the end & composite mixed for 15 min and (****) indicates ibuprofen+ pre-blend (silica added at the end & composite mixed for 5 min) were composite mixed for 10 min. Results reported as mean ± SD (n=3).

Results from friability testing were in line with the results obtained from hardness testing (Figure 5.10). The friability obtained for all formulation did not meet the Pharmacopeial requirement (1%) (Pharmacopoeia, 2012). However, the results obtained from 50% w/w ibuprofen were better than that of 10%w/w (≤ 2%, >2%) respectively. Consequently, composite milled-mannitol/ starch1500 will be taken forward to the next stage to investigate the influence of increased glidant (silica) concentration to improve flowability, hardness and reduce friability of tablets.

5.3.3.2. Effect of glidant (silica) concentration on tablet properties

The composite mixed formulation containing milled mannitol was taken forward into the next stage as it retained the best balance between hardness and disintegration among the formulations tested. The tablets were prepared at 20 kN from the blend

containing different concentrations of silica (0.5-2% w/w), the amount of silica was added at the end of pre-blend powder and composite mixed for 5 min. The purpose was to investigate the effect of glidant concentration on tablet's hardness, friability, disintegration time and porosity. The results showed a gradual increase in hardness upon increasing silica concentration irrespective of the concentration of ibuprofen. Moreover, the results showed significant difference in hardness (ANOVA/Tukey $p<0.05$) (Figure 5.11).

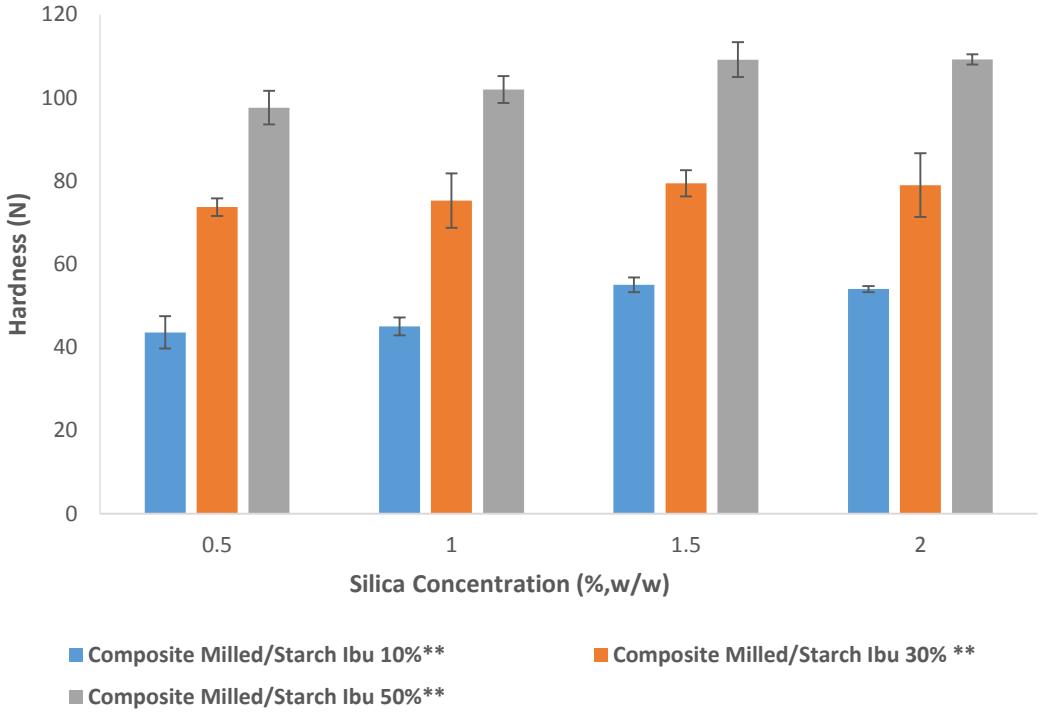

Figure 5.11: Hardness profile of tablets prepared using hydraulic tablet press at 20 kN from pre – blend containing 0.5 - 2% w/w silica, milled- mannitol, starch1500, ibuprofen at different concentration was incorporated to pre-blend and interactive mixed for 10 min, magnesium stearate was added at the end and mixed for 2 min . The results showed gradual increase in hardness upon increase in glidant (Silica) concentration. Each point represents mean ± SD (n=3).

The findings of the experiment are in agreement with previous research carried out by (Jonat *et al.*, 2005) who found that hydrophilic silica increased tablet strength for formulations containing starch1500. The increased mechanical strength could be attributed to the reduced destruction of antiparticle bonding due to a decrease in elastic

recovery. Elastic recovery is the enlargement of tablet during decompression stage which arises as a result of stored elastic energy in the compacted material (Haware *et al.*, 2010).

Investigation was continued to test the tablets for friability, disintegration, and porosity. Friability testing is significant as tablets are continuously exposed to abrasion and mechanical stresses during packaging and patient handling (Huynh-Ba, 2008). Friability of tablets prepared using different levels of silica (0.5-2% w/w) at a compression force (20 kN) was higher than 1% which is beyond the acceptable limit according to BP and USP (Figure 5.12).

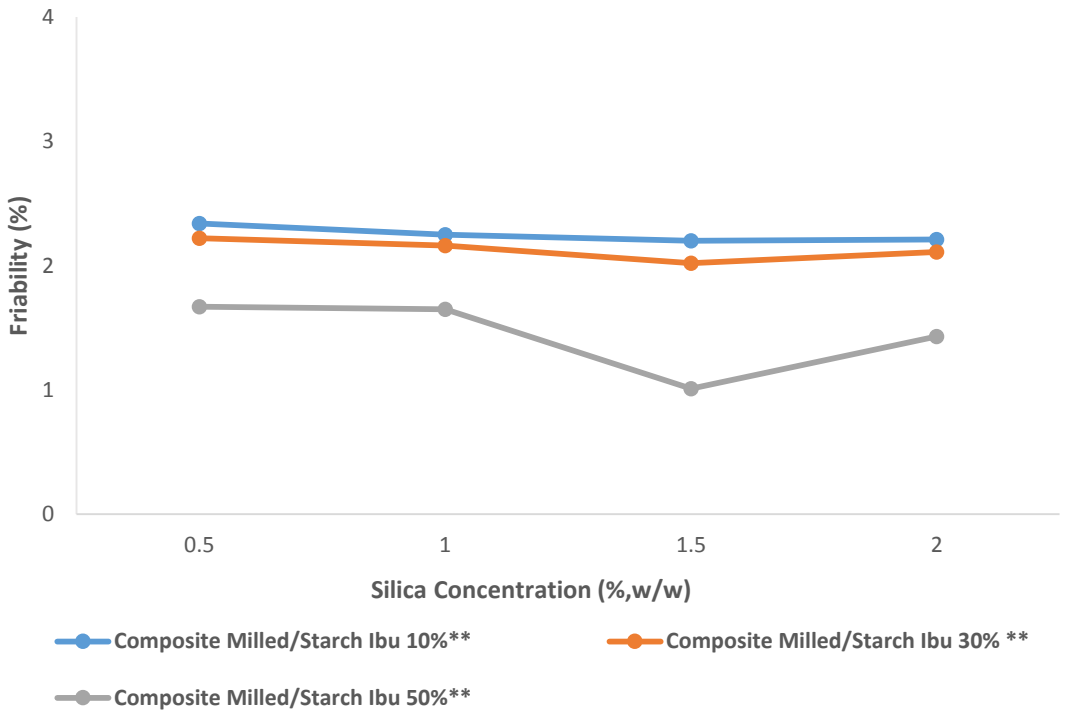

Figure 5.12: Friability profile of tablets prepared using hydraulic tablet press at 20 kN from pre – blend containing 0.5 - 2% w/w silica, milled- mannitol, starch1500, ibuprofen at different concentration was incorporated to pre-blend and interactive mixed for 10 min, magnesium stearate was added at the end and mixed for 2 min .The results showed gradual enhancement in friability upon increase in glidant (Silica) concentration.

Investigating the trend in (Figure 5.12), it is rational to assume that friability would decrease below 1% if the concentration of silica is increased beyond the levels tested,

though, this approach may not be practical as it will negatively impact on the mouth feel after tablet disintegration in the oral cavity. Inclusion of 1.5% w/w silica showed that tablet friability was higher than 1% (except for 50% ibuprofen where it was around 1%), but this slight increase can be controlled by adjusting the processing parameters such as increased compression force or change in the shape of the tablet (concave tablets instead of flat face).

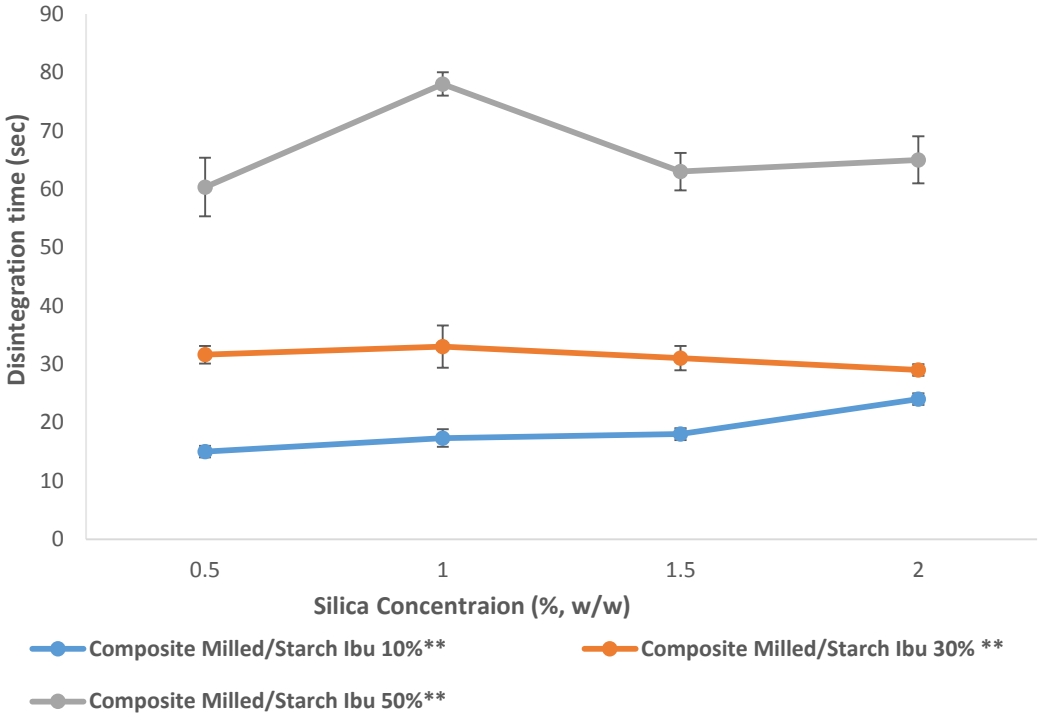

Figure 5.13: Disintegration time profile of tablets prepared using hydraulic tablet press at 20 kN from pre – blend containing 0.5 - 2% w/w silica, milled- mannitol, starch1500, ibuprofen at different concentration was incorporated to pre-blend and interactive mixed for 10 min, magnesium stearate was added at the end and mixed for 2 min . Each point represents mean ± SD (n=3).

Disintegration time was maintained upon increase the concentration of silica (Figure 5.13). It could be that silica resulted in the development of bi-functional materials exhibiting glidant-disintegrant properties (Rowe *et al.*, 2012). Furthermore, an optimised ratio of silica 1.5% w/w was required to create the balance that achieves suitable tablet hardness while maintaining fast disintegration and acceptable friability.

Similarly, results showed that varying silica concentration (0.5-2% w/w) did not have an impact on porosity of tablets (Figure 5.14).

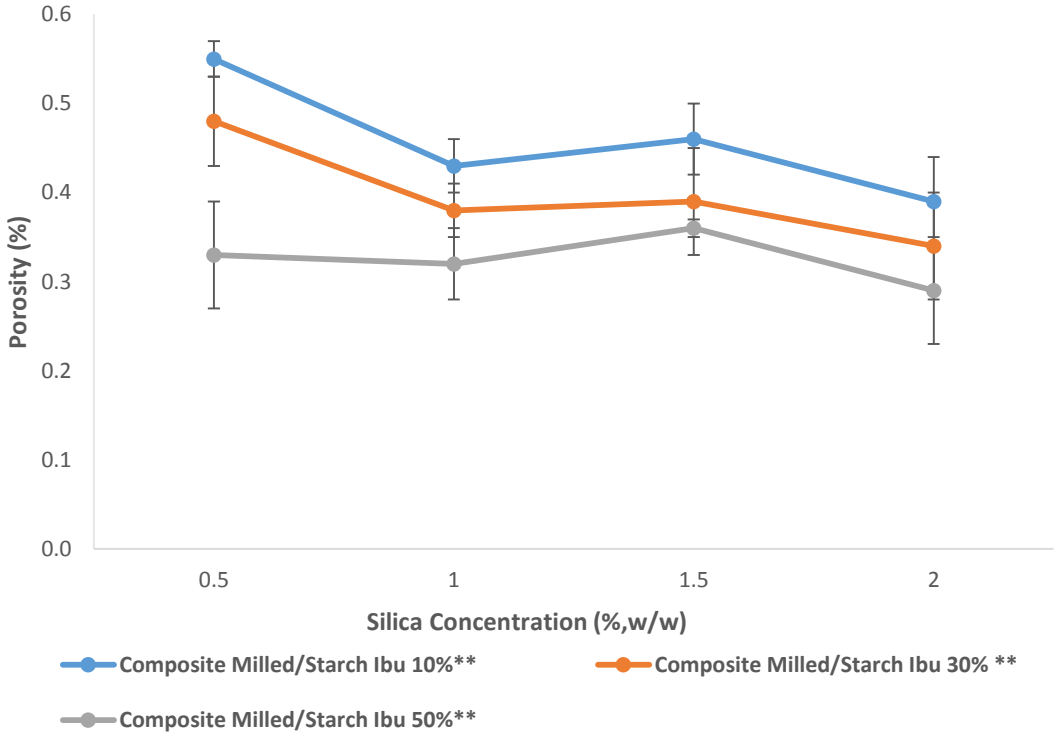

Figure 5.14: Porosity profile of tablets prepared using hydraulic tablet press at 20 kN from pre – blend containing 0.5 - 2% w/w silica, milled- mannitol, starch1500, ibuprofen at different concentration was incorporated to pre-blend and interactive mixed for 10 min, magnesium stearate was added at the end and mixed for 2 min . Each point represents mean ± SD (n=3).

5.3.3.3. Disintegration time and porosity studies

The assessment of the disintegration time is considered an important study in optimising and developing ODTs. The results for disintegration time and porosity of tablets made from ternary mixtures pre-blend (87.5 % w/w milled or un-milled mannitol, 12% w/w starch 1500 and 0.5%w/w silica) with 10-50% w/w ibuprofen and 1% w/w magnesium stearate showed that upon increasing concentration of ibuprofen, a significant increase (ANOVA, $p>0.05$) in disintegration time was noticeable (Figure 5.15) either because of increased cohesive bonding between ibuprofen-ibuprofen or due to fragmentation plastic behaviour of ibuprofen particles (Al-Khattawi *et al.*, 2014a).

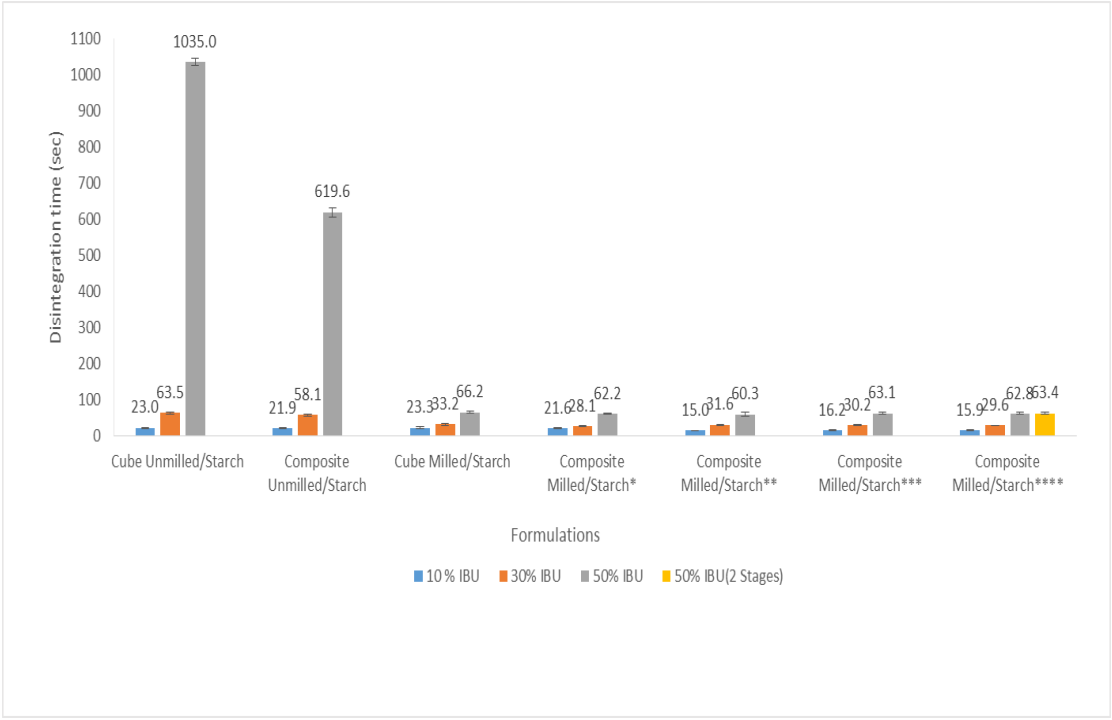

Figure 5.15: Comparison of disintegration time of ternary mixture pre-blend containing (12% w/w starch1500, 87.5% w/w milled or un-milled mannitol and 0.5% silica) tablets of ibuprofen. Tablets were compressed at 20 kN compression force. Data marked with a single asterisk (*) indicates results that are silica added at start & composite mixed for 30 min. (**) indicates the silica added at the end & composite mixed for 5 min, (***) indicates silica added at the end & composite mixed for 15 min and (****) indicates ibuprofen+ pre-blend (silica added at the end & composite mixed for 5 min) were composite mixed for 10 min. Results reported as mean ± SD (n=3).

Furthermore, disintegration time increased with increasing ibuprofen due to their lower porosity (ibuprofen powder porosity was 0.69±0.08) (Figure 5.18) and higher

densification, hence, increasing the ibuprofen concentration resulted in a decrease in porosity (Figure 5.16).

The tablets produced from composite un-milled mannitol at 10, 30, 50% w/w ibuprofen disintegrated in 22, 58 and 620 seconds respectively, whereas composite milled at similar ibuprofen concentration disintegrated at 23,33 and 66 seconds respectively. Statistically, milled mannitol provides a significantly faster disintegration time, (ANOVA, $p<0.05$). This was attributed to the tablets containing milled mannitol (fractured) had increased wettability due to the small size particle size which leads to increasing surface area of hydrophilic region of the crystal (Ho *et al.*, 2010, Koner *et al.*, 2015).

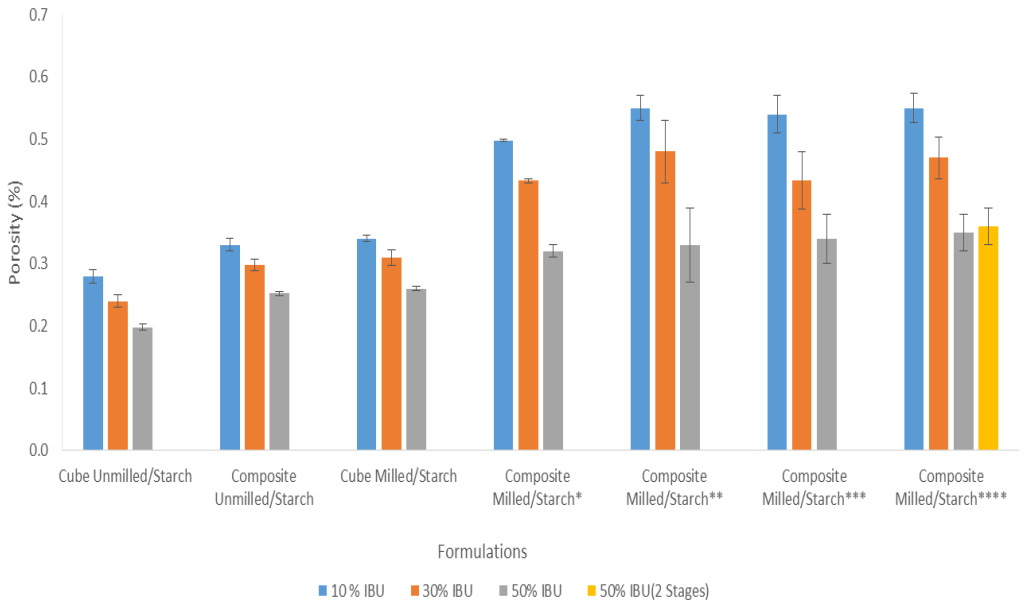

Figure 5.16: Comparison of porosity of ternary mixture pre-blend containing (12% w/w starch1500, 87.5% w/w milled or un-milled mannitol and 0.5% silica) tablets of ibuprofen. Tablets were compressed at 20 kN compression force. Data marked with a single asterisk (*) indicates results that are silica added at start & composite mixed for 30 min. (**) indicates the silica added at the end & composite mixed for 5 min, (***) indicates silica added at the end & composite mixed for 15 min and (****) indicates ibuprofen+ pre-blend (silica added at the end & composite mixed for 5 min) were composite mixed for 10 min. Results reported as mean ± SD (n=3).

Interestingly, investigation of the tablet porosity made from composite milled showed that it was higher than that of cube milled (Figure 5.16). This meant that composite milled tablets retained a high porosity compared with cube which is important in enhancing disintegration time of tablets. In fact, this was confirmed when powder porosity were carried out using helium pycnometer. Composite milled pre-blend powder showed 6% higher porosity (0.89± 0.09) than cube milled (0.83 ±0.03) (Figure 5.17).

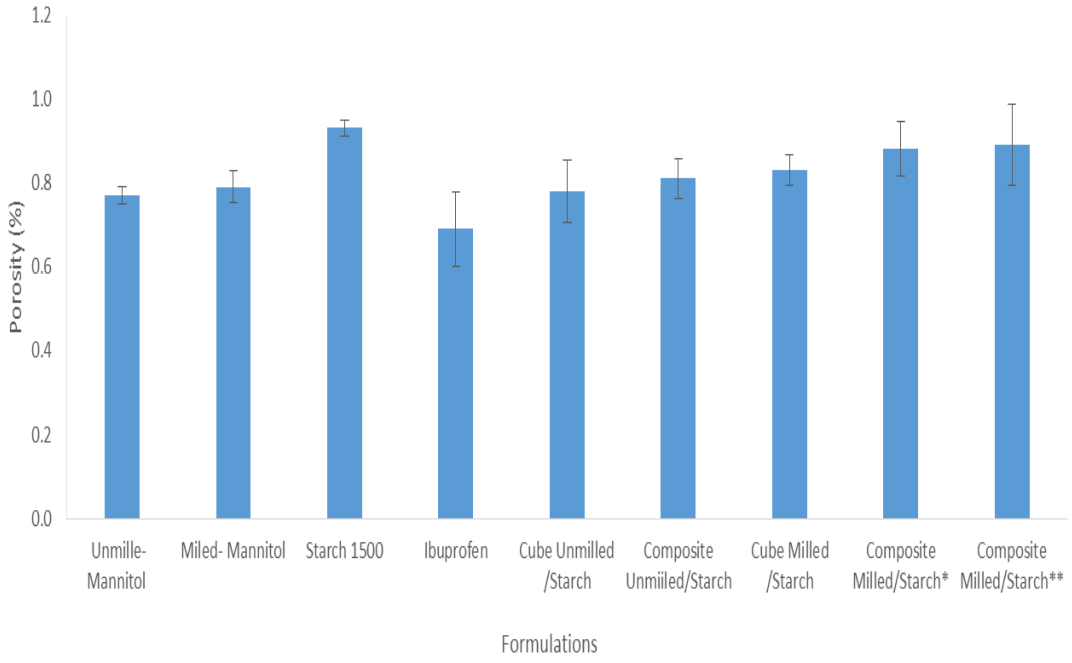

Figure 5.17: Powder porosity measurements of un-milled, milled mannitol, starch, ibuprofen and pre-blend cube or composite containing 87.5% w/w mannitol, 12% w/w starch1500 and 0.5% silica. Data marked with a single asterisk (*) indicates results that are silica added at start and composite mixed for 30 min. (**) indicates the silica added at the end and composite mixed for 5 min. Results reported as mean ± SD (n=3).

Overall, the results suggested that combining milled/ starch1500 using composite mixing produced pre-blend of ODTs with superior overall properties (disintegration time, hardness and porosity) than using cube mixed or un-milled formulations.

5.4. Conclusion

Pre-blend excipients play an important role in the development of ODTs. Formulation problems such as flowability, compressibility, compactability and disintegration time can be improved using co-processed excipients. This study was carried out to develop co-processing of milled mannitol with pregelatinised starch and silica using composite dry powder coating that offers an excellent multifunctional base for ODT formulations. The novel pre-blend excipient showed acceptable mechanical properties and fast disintegration. In addition, the pre-blend was able to accommodate a high amount (up to 50% w/w) of API without affecting its functionality.

Due to the high friability of mannitol based ODTs, replacement of proportion of powder mannitol with milled-mannitol was inevitable to enhance ODT mechanical strength and friability due to reduced fragmentation during compression and improved compressibility. Furthermore, milled-mannitol led to improve disintegration time due to increased wettability of the ODT.

Optimising silica concentration in ODT was also important to enhance flowability. Silica at 1.5% w/w was suitable as it achieved the required flowability without significantly prolonging disintegration time of ODTs. In summary, the co-processed excipients using composite dry powder coater containing 86.5% w/w of milled-mannitol, 12% w/w pregelatinised starch and 1.5% w/w silica can be used as a potential multifunctional directly compressible ODT pre-blend.

Chapter 6

Micro particle surface layering through dry coating: impact of moisture content and process parameters on the properties of orally disintegrating tablets

Publications relating to chapter 6

Hamad Alyami, Jasdip Koner, Eman Dahmash, James Bowen, David Terry and Afzal R Mohammed (2016). Microparticle surface layering through dry coating: impact of moisture content and process parameters on the properties of orally disintegrating tablets. Journal of Pharmacy and Pharmacology DOI: 10.1111/jphp.12623.

6.1. Introduction

In recent years, paediatric drug development has come to the forefront of research due to the incentives offered by regulatory bodies in the US and within the EU, including financial rewards and patent extensions for drug formulations (Turner *et al.*, 2014). In the past, big Pharma companies were more focused on developing adult friendly dosage forms due to the high profit margins and perceived lower risk of development. Children are a unique entity in the fact that they develop at a vast rate, from the day of birth to becoming adults, with the first 18 years of their lives sub classified in to several groups: Premature new-borns (<38 weeks gestational age); Term new-borns (>38 weeks gestational age); Neonate (0-30 days); Infant (1month-2 years); Young Child (2-6 years); Child (6-12 years) and Adolescents (12-18 years) (Kellie and Howard, 2008). This presents various formulation challenges, primarily pharmacokinetic and pharmacodynamic, as absorption, distribution, metabolism and excretion are highly varied throughout these years, and the dose for administration needs to be tailored throughout the paediatric age range (Ivanovska *et al.*, 2014).

For paediatric dosage forms to be acceptable there are a number of practical aspects that also need to be considered such as, risk of choking for solid dosage forms, elegance, palatability and acceptance of the dosage form by the child (Nunn and Williams, 2005). Historically oral liquid dosage forms, such as syrups, have been the dosage form of choice for many paediatric patients due to their ease of administration and dose flexibility. Nonetheless, oral liquid dosage forms have many disadvantages such as: poor taste of bitter drugs; drug stability, with many antibiotic formulations having 7-14 day expiry after reconstitution; storage conditions, with many being items that need to be kept in the fridge and transportability issues, with liquid bottles occupying large space. Consequently, the WHO recently stated that young children

may be treated with oral solid dosage forms, such as orally disintegrating tablets (ODTs) and as such there is a concerted effort in understanding and developing technologies to formulate these dosage forms (van Riet-Nales *et al.*, 2013).

ODTs are a dosage form designed to disperse on the tongue when it comes in to contact with saliva, thereby reducing the need for tablets to be swallowed whole without water, making them ideal dosage forms for paediatric populations. The standards for a dosage form to be classed as an ODT is that 'it must disintegrate rapidly in the oral cavity, with an *in vitro* disintegration time of approximately 30 seconds or less, and in general have a weight of no more than 500mg (Siddiqui *et al.*, 2011). ODTs combine the advantages of solid and liquid dosage forms with some novel ODT technologies allowing high drug loading whilst offering pleasant mouth feel with an acceptable taste.

Although ODTs present many advantages over other paediatric formulations, there are several challenges associated with these types of tablets. There are two common methods of manufacture; freeze drying, that produces rapidly disintegrating tablets which are often mechanically weak and require specialised packaging and equipment, and direct compression (Parkash *et al.*, 2011). Direct compression utilises traditional tableting equipment and requires no specialised processing techniques to form robust and fast disintegrating ODTs. Due to the simplicity of the method, excipient and bulk powder characteristics need to be considered. Flowability of the bulk powder is of particular importance as the powder needs to be able to flow in to the dies at a consistent rate to form uniform tablets that have a consistent weight and drug content. As the tablets disintegrate within the oral cavity, taste is a key factor that needs to be evaluated, as poor palatability of the dosage form would lead to poor medication adherence. This can often be solved using flavourings and sweeteners, with more complex systems such as film coating of granules and microencapsulation also used,

which can often increase development costs and also expose active pharmaceutical ingredients (APIs) to unfavourable conditions. One of the simplest ways to address this issue is the use of mannitol, a polyol isomer of sorbitol, which has a very sweet taste and cooling effect in the mouth and can often provide a palatable dosage form (Yoshinari *et al.*, 2002). It has dual functionality in that it is also a popular binder/filler used in ODTs due to its advantages in producing acceptable dosage forms. Other considerations specifically for ODTs include disintegration time, as this needs to be optimised to allow the dosage form to disintegrate within specified timeframes. This can often involve the use of superdisintegrants in the powder blend, such as crospovidone, which uses capillary action to induce water uptake in to the tablet through wicking mechanisms, resulting in a rapid volume expansion of the tablet and subsequent break-up of the tablet structure (Pabari and Ramtoola, 2012). Inclusion of superdisintegrants in to ODTs can increase moisture sensitivity in ODTs. High levels of moisture in the final dosage form can present difficulties particularly in ODTs, due to their ability to uptake moisture from the surroundings as well as their fast disintegrating properties (Hirani *et al.*, 2009) Including mannitol can often aid in reducing the hygroscopic nature of the ODT, due to mannitols non-hygroscopic nature (Yoshinari *et al.*, 2002). Alongside this, powder deformation processes need to be evaluated to minimise the elastic deformation properties of the powder, which could lead to capping and lamination of the tablet (Prescott and Barnum, 2000). MCC is a common excipient employed in ODTs as it has very high compactability due to its plastic behaviour, leading to robust dosage form manufacture (Vromans and Lerk, 1988).

The objective of this study was to study the effects of moisture content on MCC, which is a model filler/binder for ODTs, in order to optimise the moisture levels to produce the most beneficial powder/tablets. A novel composite coater developed in our

laboratory was used to investigate the effect of process parameters on the moisture content, as well as studying the effect of excipient addition on the resultant moisture. It was hypothesised that the powder coater could be used as a novel tool to optimise moisture levels within MCC to a desirable quantity, producing not only a favourable pre-processed material with good flowability and compaction properties, but also a suitable tableting excipient to formulate robust ODTs without a resultant compromise in disintegration time. The work involves developing a fast and robust technique in order to optimise varying moisture content ranges levels of MCC.

6.2. Materials and Methods

6.2.1. Materials

D-mannitol, magnesium stearate and sodium chloride salt (NaCl) were purchased from Sigma-Aldrich (Pool, UK), while microcrystalline cellulose (MCC) (Avicel PH-200) was obtained from FMC BioPolymer Europe (Brussels, Belgium). Crospovidone (CrosPVP, Polyplasdone® XL-10) was obtained from Ashland (Wilmington, USA). All the ingredients were of pharmaceutical grade.

6.2.2. Methods

6.2.2.1. Optimisation of Moisture Content

The first step of the moisture process began with weighing a precise amount of the original MCC powder (20g) (MCC1) which was spread evenly on a tray. In the next step, increments of distilled water were added at approximately 30 second intervals without any shaking. The moisture content was tested at intermittent durations until the desired moisture contents 11.2% (MCC 2) and 40% (MCC 3) were obtained. The amount of added water was approximately 5-10 ml providing moisture content between 10% and 40% for the MCC powder. The moist powders were transferred into a small airtight container and sealed using para film.

6.2.2.2. Sieving process, interactive and composite powder coating technique

The two key excipients studied included microcrystalline cellulose (MCC) and mannitol. Selected particle sizes of both D-mannitol and MCC were obtained by sieving. MCC was passed through sieve with mesh size of 355μm and the sample retained at sieves with pores size of 250μm was used. D-mannitol was sieved using 38μm sieve and particles retained on the 20μm sieve were used. The composite mixing process was carried out considering several critical operating parameters; speed of the mixer, mixing time and the use of air flow. As for the materials used, the parameters

considered were pertinent to the guest loading percentage, measured in weight per weight, and the type of carrier material in terms of particle size and shape. Samples were tested alongside interactive mixtures with the same content, but mixed at low speeds (300rpm) and a shorter time (10 minutes). The formulation and the processing parameters are listed in (Table 6.1) below.

Table 6.1: Formulation content and processing parameters of MCC (carrier) and D-mannitol (guest) (mannitol particle size <38 µm) used for composite and interactive mix.

No	Mannitol %,w/w	MCC %, w/w	Crosp %,w/w	Mg.st %,w/w	Mixing Tech	Duration min	Speed (rpm)	Air Pressure (PSI)	Batch size gm
F1	64.5	30	5	0.5	Interactive	10	300	NO	10
F2	64.5	30	5	0.5	Composite	60	1500	NO	10
F3	64.5	30	5	0.5	Composite	60	1500	YES	10

6.2.2.3. Characterising interactive and powder coating

6.2.2.3.1. Measurement of powder moisture content using TGA

A thermogravimetric analyzer, Pyris 1 TGA from Perkin Elmer (Massachusetts, USA) was used to measure the moisture content of all powders. 2-5 mg of each sample was loaded onto the TGA pan and heated between 30-300°C at a scanning rate of 30°C/min and held for 5 minutes at 100°C under a nitrogen stream. Pyris Manager Software (version 5.00.02) was used for analysing the obtained thermograms. Moisture content was obtained by calculating Δy for each run between 70°C and 130°C. All samples were analyzed in triplicate.

6.2.2.3.2. Assessment of powder flow properties by measurement of angle of repose

The angle of repose measurement was performed using the recommended British Pharmacopeia procedure (Pharmacopoeia, 2012). Approximately 10 g of powder was poured through a funnel into a base free from vibration to form a pile. The funnel was positioned 2 - 5 cm from the top of the powder pile as it was forming. Angle of repose

was determined by measuring the height of the pile (h) and diameter of the base (d); then angle of repose (α) was calculated from the equation:

$$\tan\alpha = h \div (0.5 \times d)$$

6.2.2.3.3. Scanning electron microscopy (SEM)

The morphology of MCC at different moisture contents, D-mannitol, the mixture and the coated powder particles were examined using a Stereoscan 90 from Cambridge Instruments (Crawley, UK) scanning electron microscope (SEM). Approximately 1-2 mg of each material was placed onto a double-sided adhesive strip on an aluminium stub. The specimen stub was coated with a thin layer of gold using a Polaron SC500 sputter coater from Polaron Equipment ltd. (Watford, UK) at 20 mA for 3 min followed by sample examination using SEM. The acceleration voltage (kV) and the magnification can be seen on each micrograph. Various magnifications were applied to identify characteristics of the powders.

6.2.2.3.4. Particle size analysis

Particle size of the powders was measured by the laser diffraction technique using HELOS/BR particles size analyzer equipped with a RODOS dry disperser with VIBRI/L vibrating feeder, from Sympatec (Clausthal-Zellerfeld, Germany). The measuring range of the lens was 0 - 175µm. About 1 g of each powder was placed in the feeder tray and the run started at trigger condition of 2% Copt (optical concentration) for 10 sec with a powder dispensing pressure of 2bar. Volume mean diameter (VMD) was recorded for the powders and all the measurements were examined in triplicate.

6.2.2.3.5. Atomic Force Microscopy (AFM)

Acquisition of topographical data was performed using a NanoWizard II AFM (JPK, UK) operating in force scan mapping mode under ambient conditions (18^{o}C, 50% relative humidity). This involved the use of a scanner with a maximum lateral range of

100 × 100μm and a maximum vertical range of 15μm. Data acquisition was performed using rectangular Si cantilevers (HQ:CSC17/noAl, MikroMasch, Estonia) having pyramidal tips with 10nm nominal radii of curvature. Cantilever spring constants were on the order 0.3N/m, calibrated according to the method reported by (Bowen *et al.*, 2010). Topography was assessed over a 2μm x 2μm area using a grid of 128 x 128 pixels. Data was acquired by driving the fixed end of the cantilever at a velocity of 50μm/s towards the sample surface, whilst monitoring the deflection of the free end of the cantilever using a laser beam. Upon making contact with a surface feature, the height of the contact point was recorded, representing one pixel in the image, which was converted into a map of surface topography. A maximum compressive load of 10nN was applied to the surface during data acquisition.

6.2.2.3.6. Nano-indentation

The hardness and Young's modulus of the powder wafer samples was measured using a Nanoindenter XP (MTS, USA) employing a diamond-coated Berkovich indenter. 36 indentations were performed perpendicular to the wafer surface, each in a different unperturbed area. Samples were indented at a strain rate of $0.05s^{-1}$ to a maximum depth of 500nm. The hardness and Young's modulus were calculated from analysis of the load-displacement data, fitting a second order polynomial to the unloading curve (Figure 6.1) (Zhu *et al.*, 2004). The Poisson's ratio of the powder was assumed to be 0.3. In this approach the total penetration depth is assumed by the sum of the plastic depth (contact depth), δ_c, and the elastic depth, δ_e, which represents the elastic flexure of the surface during loading. Thus the total penetration depth, δ, is given by

$$\delta = \delta_c + \delta_e$$

and

$$\delta_e = \varepsilon \, (P \div Su)$$

Where S_u is the slope of the unloading curve at maximum load (see figure 6.1), P is the indenter load and ε is a constant which depends on indenter geometry. So the hardness, H, is then given by equation

$$H = P \div A_c$$

Where A_c is an ideal Berkovich indenter constant .Young's modulus can be determined from the slope of the unloading curve using a modified form of Sneddon's flat punch equation where

$$S_u = \gamma\beta \frac{2}{\sqrt{\pi}} Er\sqrt{\mathrm{Ac}}$$

Where γ is the correction factor, β is the cone to pyramid indenter conversion factor and Er is the contact modulus which can be derived from Young's modulus E and Poisson's ratio (v) of the indenter and the test material via

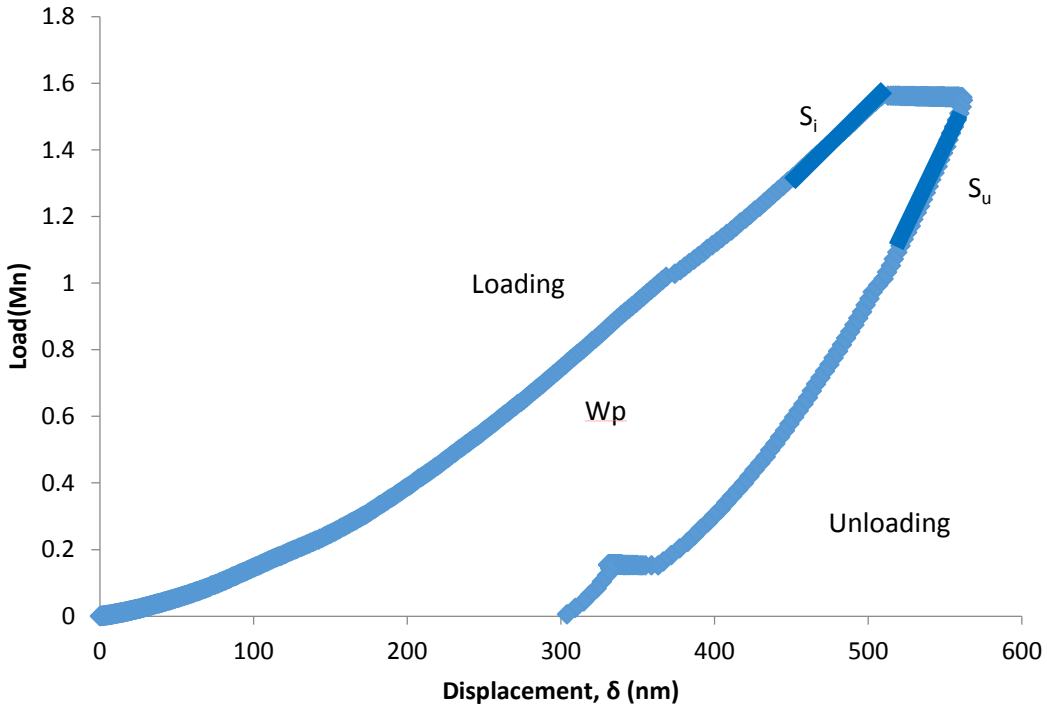

Figure 6. 1: The illustration graph represents load–displacement curve showing the unloading (Su) and loading (SI) slopes used in the calculation of hardness and Young's modulus. Besides indicated is the plastic work of indentation Wp which is the area bounded by the loading and unloading curves and the displacement on x-axis.

$$\frac{1}{Er} = \frac{1 - vm^2}{Em} + \frac{1 - vi^2}{Ei}$$

Where the m and i refer to the test material and indenter, respectively

6.2.2.3.7. Calculation of surface coverage

Surface coverage was calculated using the equation and method described in(Yang *et al.*, 2005). The amount of guest material in weight percentage (Gwt %) required to achieve 100% coverage within the given parameters was as follows:

$$Gwt\% = \frac{Nd^3\ pd}{(D^3\ pD) + (Nd^3\ pd)} \times 100$$

Where N is:

$$N = \frac{4(D + d)^2}{d^2}$$

Where d is the diameter of guest particle, D is the diameter of the host particle, pd is the density of the guest particle and pD is the density of the host particle.

6.2.2.4. Tablet Preparation and Characterization

Ternary mixture tablets were prepared comprising of the excipients at fixed quantities: 30% w/w of MCC, 5% w/w crospovidone, and 64.5% w/w mannitol and 0.5 % w/w magnesium stearate (lubricant). Powders were processed as interactive/composite mixes and compacted into 500 mg tablets under compression force of 10 KN, with a dwell time of 6s before compression force was released. The tablet press utilized for preparing the tablets was a bench-top semi-automatic hydraulic press from Specac Ltd. (Slough, UK) equipped with flat faced dies of 13 mm diameter. Tablets were

characterized for porosity, hardness, disintegration time and friability. All tests were carried out in triplicate (n=3).

6.2.2.4.1. Tablet hardness

A tablet hardness tester from Schleuniger (Thun, Switzerland) was used to examine the hardness of three tablets of each formulation. Hardness is the force required to break up the tablet from its original structure and was measured in Newtons (N) for this study. All measurements were carried out in triplicate and the values reported as mean ± standard deviation.

6.2.2.4.2. Tablet disintegration

The disintegration time was obtained using the standard USP moving basket apparatus (USP Convention, 2005). A ZT3 disintegration tester from Erweka (Heusenstamm, Germany) was used. A tablet was placed in the disintegration basket (without using a disk) which was raised and lowered at a constant frequency of 30 cycles/min in the disintegration medium. Distilled water (800 mL) maintained at 37°C was used as the disintegration medium while disintegration time was recorded for one tablet at a time to improve accuracy of recording. Time of disintegration was recorded when all the disintegrated fractions of tablet passed through the mesh at the base of the disintegration basket.

6.2.2.4.3. Tablet friability

The ability of the tablets to withstand mechanical stress, known as friability was measured using a Roche friabilator from J. Engelsmann AG (Ludwigshafen, Germany). 10 tablets were rotated at 25 rpm for 100 revolutions. Tablets were de-dusted before and after the test, and friability expressed as the percentage loss in weight. The percentages loss in weight (% Friability) was calculated using the following equation.

$$\%\ Friability = \frac{Initial\ Weight - Final\ weight}{Initial\ weight} \times 100$$

6.2.2.4.4. Tablet porosity

Tablet porosity was measured using a helium multipycnometer from Quantachrome Instruments (Syosset, USA). One tablet was placed in a micro sample cell of the instrument and the true volume V_t was obtained using the equation:

$$V_t = V_C - V_R \left(\frac{P1}{P2 - 1}\right)$$

Where V_t is true volume of the sample, V_C is volume of the sample cell, V_R is the known reference volume, P1 is atmospheric pressure and P2 is pressure change during determination. V_t was used to calculate the true density of the tablet by weighing the tablet and substituting the values into:

$$True\ Density = \frac{Tablet\ Weight}{True\ Volume}$$

Porosity (ε) was calculated using the equation:

$$\varepsilon = 1 - \left(\frac{Bulk\ Density}{True\ Density}\right)$$

Bulk density was calculated from:

$$Bulk\ Density = \frac{Tablet\ Weight}{Bulk\ Volume}$$

Bulk volume was acquired by measuring the radius (r) and thickness (h) of the tablet using a digital calliper and substituting in the equation for volume of a flat-faced tablet:

$$V = \pi \times r^2 \times h$$

6.2.2.5. Statistical analysis

One way ANOVA followed by Tukey post-hoc test or student t-test were performed according to the obtained results, using GraphPad Prism 6.02 software (California, USA). Statistical significance was considered at a p value <0.05. Where applicable, all results are presented as mean ± SD for triplicate measurements to account for the noise encountered within the experiments.

6.3. Results and Discussion

The work presented in this study provides a systematic investigation on the impact of moisture content of MCC on powder and tablet performance. Moisture content of the pre and post processed materials; MCC, D-mannitol, crospovidone, magnesium stearate and the ternary mixtures were analysed using TGA for loss on drying. These excipients were selected based on their role as binders, fillers, disintegrants or dual functional binder/disintegrant systems within ODTs. The majority of the work on moisture content was conducted with MCC as it is a hygroscopic excipient that is commonly employed within ODTs as a binder/filler (Rowe *et al.*, 2012).

6.3.1. Moisture content of the investigated excipients

Figure 6.2 shows the levels of moisture obtained from each of the studied excipients through TGA analysis. It was seen that D-mannitol had the lowest moisture content, at about 0.5% w/w compared to MCC, which had a moisture content of 3.8% w/w. This was in line with the literature findings where the moisture content of MCC was reported to be around 3-4% w/w (Khan *et al.*, 1981), with D-mannitol expected to have low moisture content due to its non-hygroscopic nature (Yoshinari *et al.*, 2002).

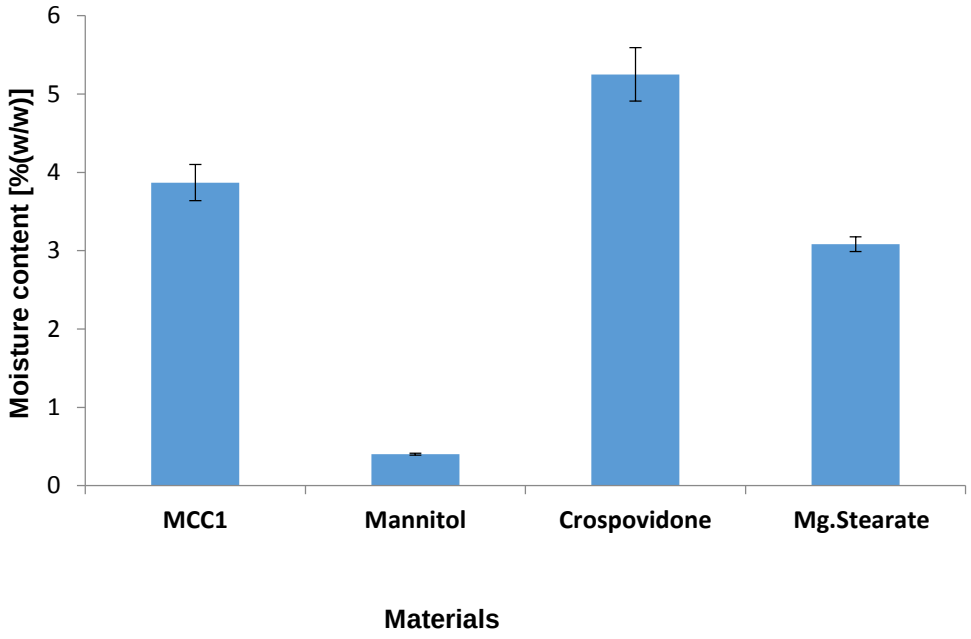

Figure 6. 2: Moisture content of the individual excipient, before blending, using TGA analysis. Results are presented as (mean ± SD, n=3).

In this study it was hypothesised that the levels of moisture within MCC influenced the physio-mechanical properties of the particles, including their hardness/tensile strength, flow and their compaction behaviour. In order to achieve different levels of moisture within MCC, the micro-spray method was used to increase levels of adsorbed water in the MCC to two different levels compared to the control MCC 4% (MCC 1), which had not been subjected to moisture addition. The moisture contents investigated were 11% w/w (MCC 2) and 40% w/w (MCC 3). The three MCC powders were then subjected to a range of investigations to ascertain the effect that the moisture had during processing, addition of further excipients and on the tablet properties of the ODTs.

6.3.2. Effect of moisture content on morphology and flow of MCC

Good flow properties are a requirement for the successful manufacture of tablets as it affects mixing, content uniformity, tablet compression and scale-up operations (Sarraguça *et al.*, 2010). Flow properties of the materials tested were primarily affected by the size and shape of the particles within the powder, which in turn affected the cohesivity and the mechanical interlocking between the particles (Al-Khattawi *et al.*, 2014a). Flow properties were evaluated before mixing/tableting was carried out for the different MCC powders. Powder flow properties of the different MCC powders were assessed by measuring the angle of repose. The results showed significant differences (ANOVA, $p<0.05$) between the angle of repose of the powders, with MCC 2, at 11%w/w moisture content, demonstrating the best flowability with a low angle of repose at 29.60±0.86°*,* as shown in (Figure 6.3) when compared to the control MCC, which had a fair flow, with the angle of repose of 38.52±0.67°. However at high moisture content of 40%w/w (MCC 3), poor flow was observed, with the angle of repose at 52±0.61°*,* indicating that high levels of moisture significantly worsened the flow properties of the powder (Al-Khattawi *et al.*, 2014b).

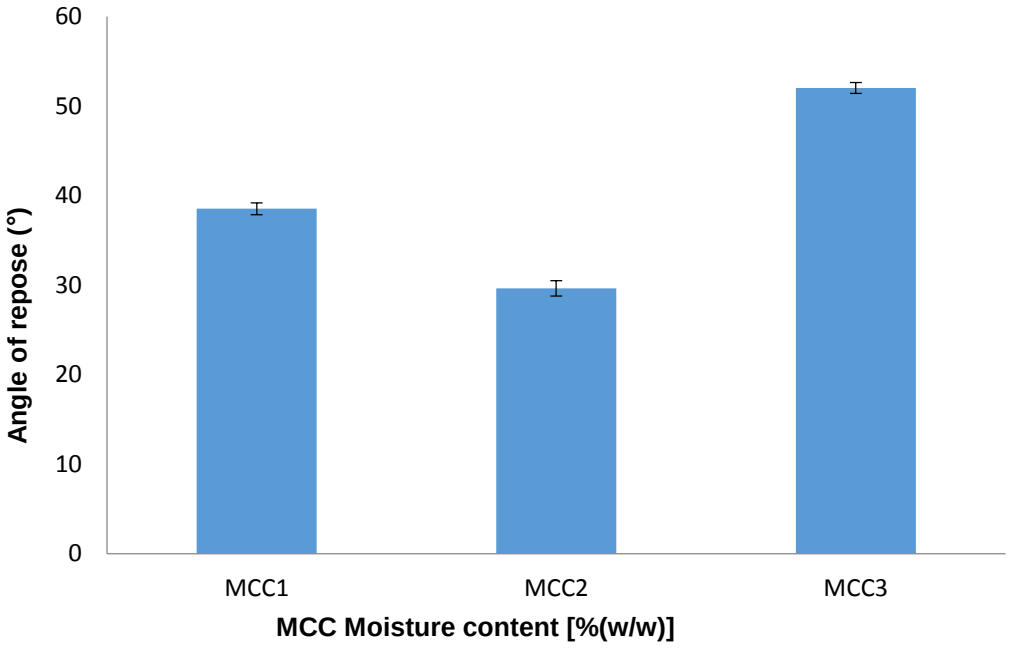

Figure 6. 3: Flow properties for MCC powders with different moisture content, test used was angle of repose. Results are presented as (mean ± SD, n=3).

At low moisture levels, water on the particle surface acted as a lubricant by decreasing friction and increasing the flowability of the powder thereby allowing the particles to move more easily over each other. For MCC2 it can be hypothesised that the moisture was able to act as a lubricant and increased the distance between the particles which also had the dual effect of reducing the effect of the van der Waals forces and reducing the cohesive forces. Once monolayer coverage was achieved, additional water did not significantly contribute to the lubricating and spacing effect and therefore further enhancements in flowability were minimal (Crouter and Briens, 2014).

On the other hand, MCC showed a sharp decrease in flowability with increasing moisture content up to 40% W/W. This was attributed to the increased cohesion from the stronger liquid bridges formed from the condensed water on the surface of the particles. At higher moisture levels, the water possibly increased cohesion through stronger liquid bridges thereby reducing flowability. Furthermore, water could primarily affect cohesion by increasing capillary forces through strengthening liquid bridges

between the particles (Dawoodbhai and Rhodes, 1989, Shi *et al.*, 2011). When the angle of repose test was carried out, it was also observed that MCC adhered to the funnel, (Figure 6.4 c), demonstrating that not only did the powder become more cohesive in nature, it also became more adhesive to external surfaces, indicating a worsening flow.

Analysis of SEM images after curing of MCC powder showed a slight enlargement in size with MCC 2 (at 11% moisture content), as shown in (Figure 6.4 e) which possibly was an additional factor for improved flowbaility, as the larger particle size results in a reduction in cohesivity of the particles due to lower electrostatic forces, thereby enhancing the flow of particles (Karner and Urbanetz, 2011). It could also be said that the fine particles contained within the powder were also able to agglomerate/coat the larger particles, resulting in an increased particle size, due to the increased cohesivity, which reduced the overall cohesiveness of the blend and synergistically worked with the lubricating effect of the surface adsorbed water to improve the flow of MCC.

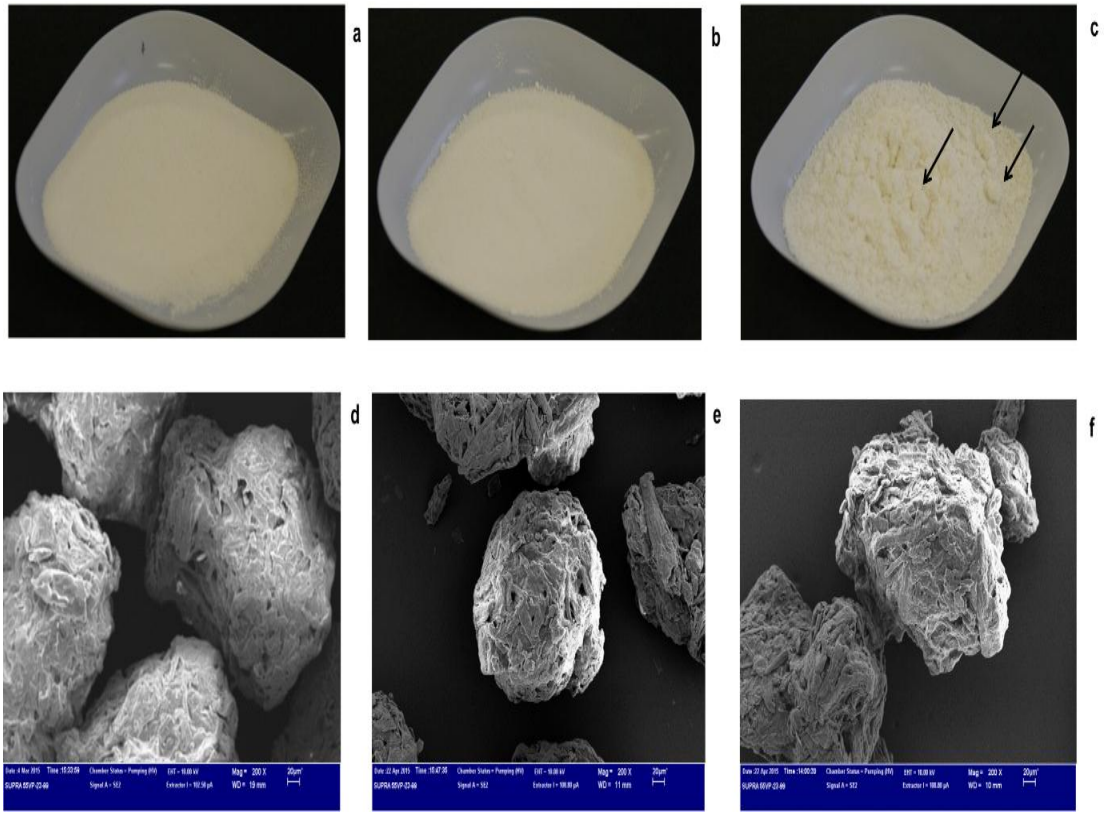

Figure 6. 4: (a-c) Visual structure features of different MCC moisture contents show images of MCC 1, MCC 2 and MCC 3 respectively. Arrows in (e) point to aggregated particles of MCC 3, (d-f) SEM showing morphology of MCC particles, (d) MCC 1(pure MCC powder, moisture content 4%w/w), (e) MCC 2(optimised MCC moisture content 11% w/w) and (f) MCC 3 (optimised MCC moisture content 40% w/w).

6.3.3. The effect of process parameters on MCC moisture content

To assess the effects of processing parameters on the moisture content of the MCC powders, three different parameters were used with each of the powders of MCC to analyse the effect on the resultant moisture content.

In this study a novel composite coater designed and built in our laboratory was used as the mixer of choice, and the effect of processing parameters within this device were assessed (Table 6.2). The first parameter was to mix the powder at a low speed of 300rpm for 10 minutes to achieve interactive mixture (10 minutes was chosen as previous work in the group had shown that this duration produced a homogenous interactive mix). The second processing parameter included the composite coater at a speed of 1500rpm for 60 minutes, which would be used to form composite dry coated

particles due to the high shear forces generated by the device. The third parameter had the device at the same speed and time as the second parameter (1500rpm for 60 minutes) but with the inclusion of air to increase the deagglomerating and shear forces during mixing and to aid and increase the dry coating capabilities of the excipients used in the mix. The resultant moisture content of the three MCC powders after undergoing the different processing parameters are displayed in (Table 6.2).

Table 6.2: Initial and final moisture contents for MCC at different processing parameters using powder coater (rpm: revolutions per minute).

Initial MCC Powder moisture content %	**Process Parameter**	**Final Moisture Content % Mean ± SD (n=3)**
MCC1 (4%)	300rpm	3.7 ± 0.53
MCC 2 (11%)		9.16 ± 0.84
MCC 3 (40%)		37.7 ± 3.74
MCC1 (4%)	1500rpm	3.41 ± 0.02
MCC 2 (11%)		7.33 ± 0.93
MCC 3 (40%)		35.31 ± 0.93
MCC1 (4%)	1500rpm + air flow	1.28 ± 0.14
MCC 2 (11%)		2.96 ± 0.22
MCC 3 (40%)		8.38 ± 0.622

The interactively mixed powders at 300rpm are shown in (Figure 6.5 a). The results showed no significant difference (ANOVA $p>0.05$) between the moisture content over time, indicating the mixing method had little effect on the moisture. Similarly, (Figure 6.5 b) shows that no significant difference in moisture content was observed using composite mixing without including air pressure (ANOVA $p>0.05$) in all three powders.

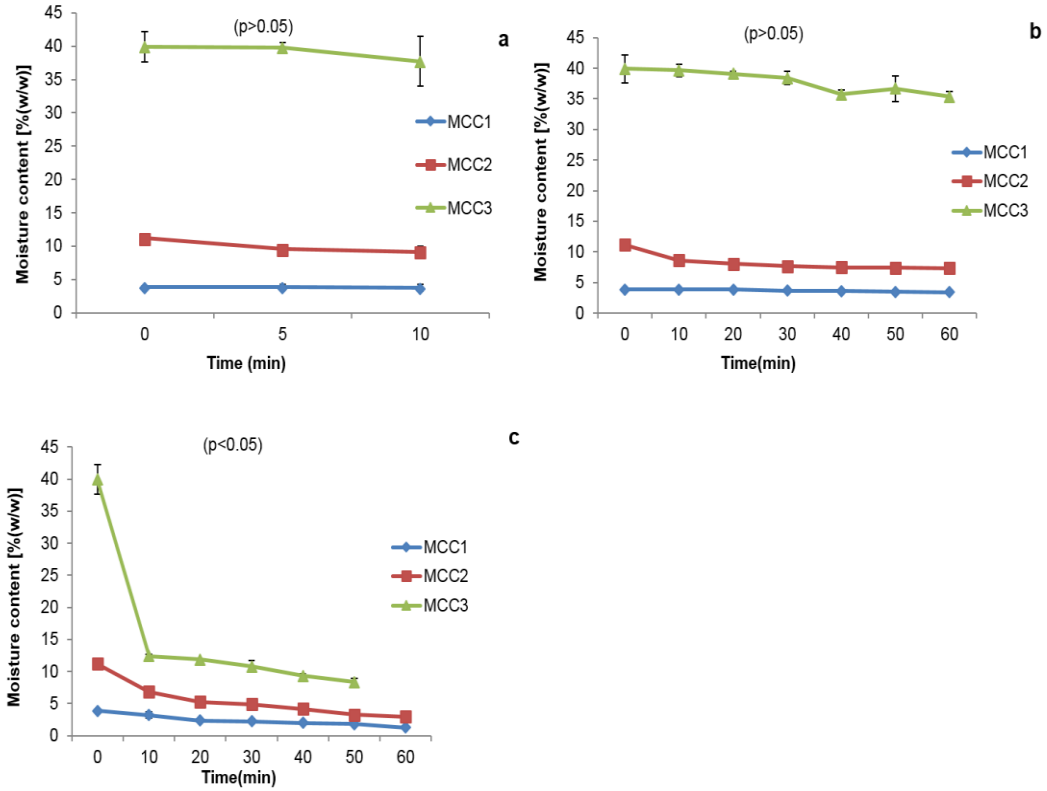

Figure 6. 5: (a) Moisture content profiles of different MCC batches using interactive mixing (ordered mixing) at 300 rpm. (b) Moisture content profiles of different MCC batches using composite mixing at 1500 rpm. (c) Moisture content profiles of different MCC batches using composite mixing at 1500 rpm with air. Results are presented as (mean ±SD, n=3).

Results of the moisture content over time using air in the mixing process are shown in (Figure 6.5 c) and demonstrated that the use of air at a mixing speed of 1500 rpm resulted in a significant decrease in the moisture content of MCC ($p<0.05$). This could possibly be attributed to the formation of vortexes/whirlpools within the system upon fluidisation of powder bed, which was demonstrated by computational fluid dynamics (CFD) (data not shown). This vortex was responsible for the fluid environment in the chamber resulting in the enhancement of the drying of the powder; hence there was a large reduction in moisture content of the powders when air was introduced during mixing. This led to the hypothesis that use of air in the processing of high moisture excipients could therefore be used to optimise levels of moisture within the excipient to the user's desired levels, with processing times altered according to the required final moisture content.

6.3.4. Mechanistic investigation of adding excipients and its effect on the moisture content of MCC

To assess the effects of excipient addition on moisture content, mannitol and crospovidone were added to the different MCC powders. For interactive mixing, all three materials were added together and mixed for 10 minutes (F1). For composite coating, excipients were added in a two-step process. Firstly to optimise the amount of mannitol added to form a full surface coverage around the MCC particles, surface coverage was calculated using equations by Yang et al (2005) with the following parameters; true density of MCC being 1.94g/cm$_3$ and D-mannitol 1.67 g/cm3; particle size of MCC being 250µm and D-mannitol 25.9µm, resulting in the percentage per weight of mannitol to achieve complete coverage calculated at 30.28%. This amount of guest particle (mannitol) was in agreement with the results stated in (Yang *et al.*, 2005) as with a volume ratio of 5 the average coverage was around 56%. The value for surface coverage would be significantly reduced upon the reduction in particle size of mannitol or increase in particle size of MCC. The second step involved the addition of the remaining portion of the mannitol, alongside the addition of the crospovidone which was mixed for a further 30 minutes to form the final mixture (F2 and F3).

(Figure 6.6 a-c) shows the moisture content profiles of the interactive against compositely mixed powders. All graphs indicated a reduction in the moisture content when the materials, in particular mannitol, were added to MCC, compared to MCC alone (ANOVA, $p<0.05$). With the interactive mix there was a large drop in the MCC moisture content for all three of the powders tested when the excipients were added to the powder blend and mixed over the 10 minute time period.

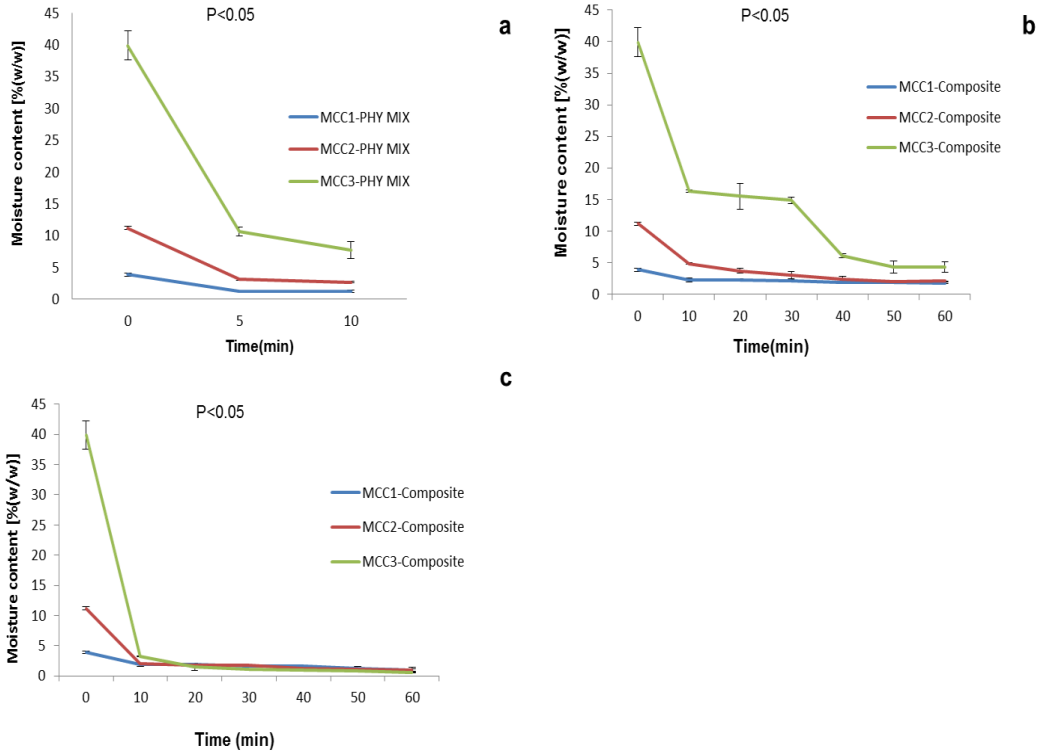

Figure 6. 6: (a) Moisture content profile of different physical mixtures using interactive mixing (ordered mixing) at 300 rpm, (b) Moisture content profile of different batches using composite mixing at 1500 rpm and (c) Moisture content profile of different batches using composite mixing at 1500 rpm with air. Results are presented as (mean ±SD, n=3).

In terms of the composite blends, SEM images, in (Figure 6.7b and c), showed that the mannitol was attached to the surface of MCC 2 particles and formed a coat around the MCC. (Figure 6.6 b and c) showed the moisture loss of the two composite coating processes, without air and with air respectively, and both indicated very large drops in moisture content after 60 minutes, due to the addition of the excipients. With the mixing that included air, as shown in (Figure 6.6 c), the moisture content was expected to reduce more dramatically as the air within the chamber aided in the drying of the MCC powder. Alongside the use of air, the addition of excipient resulted in around 35% of moisture being lost in the first 10 minutes for MCC 3. In comparison to the use of air alone (Figure 6.5 c) where the moisture loss after 10 minutes was around 25%, it showed that the addition of excipients was a key factor in the loss of moisture from the MCC particles. Comparing air and excipients, it was seen that the moisture loss of the

MCC at 1500 rpm with air was very similar to when the mannitol was added to the MCC without air at a 1500 rpm mixing speed, with the moisture content of MCC 3 dropping to around 15% in both cases.

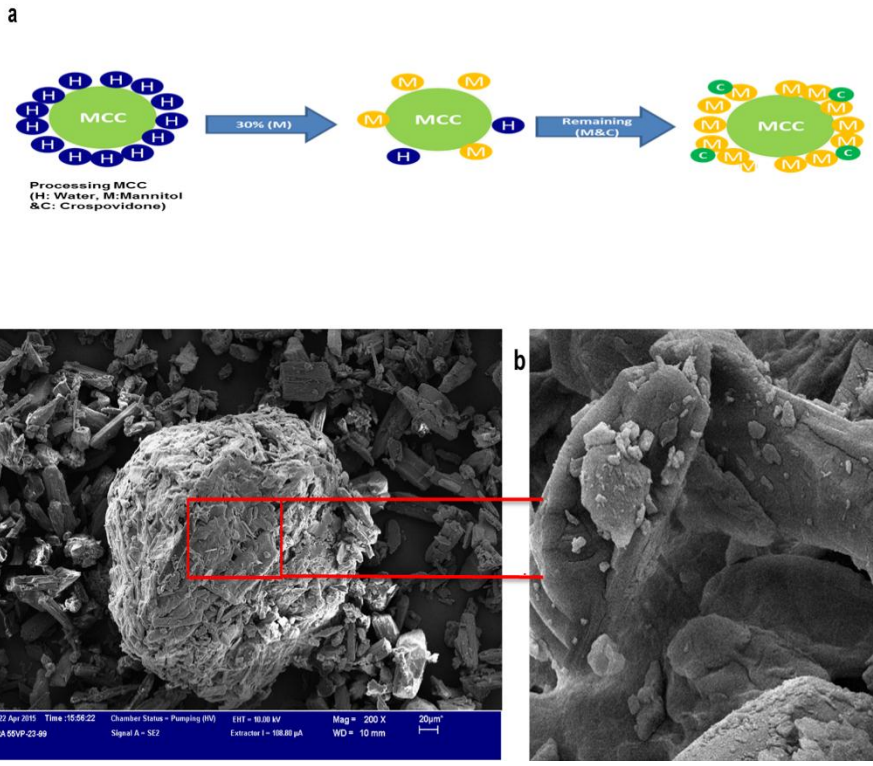

Figure 6. 7: (a) schematic illustrating microcrystalline cellulose (MCC) particles being partially coated by mannitol (guest), (b and c) scanning electron microscopy of MCC 2- composite particles (b) showing MCC 2 particles coated with mannitol 200x magnification & (c) Zoomed area showing small particles of mannitol coating the surface of MCC 2 1500x magnification.

It was hypothesised that the water particles acted as a guest molecule and surrounded MCC during the introduction of external moisture. However, once the mannitol was added to the mix, it attaches itself to the surface of the MCC during the coating process, to replace water molecules, as there was a difference in the densities between mannitol and water, with water having a relative density of 1g/cm^3 and mannitol density being 1.67g/cm^3. Therefore, it was assumed that water droplets were knocked out from the surface of MCC by mannitol, which resulted in the reduction in the moisture content

observed in (Figure 6.7 a). Of particular interest was the composite mix without air, shown in (Figure 6.6 b), where there was a large loss of moisture observed upon the addition of the first portion of mannitol, with around 25% moisture loss within 10 minutes of mixing followed by a plateau of moisture loss up until 30 minutes. However upon the second stage of excipient addition at 30 minutes, there was a further large drop in moisture content between 30-40 minutes by around 10%, which again plateaued. This indicated that the addition of other solid materials in to the powder blend clearly resulted in a loss in moisture as increased amounts of water were displaced from the surface of the MCC particles during the addition of further solid material. This supported the theory that water was substituted on the surface of MCC particles, as shown in (Figure 6.7 a), as the addition of the excipients in two stages resulted in further loss of water at each stage of excipient addition. To further understand these differences and to substantiate the above hypothesis, micro and macro properties of the materials were studied using a range of different techniques.

6.3.5. Investigation of the Micro and Macro properties of Ternary mixed powder blends

6.3.5.1. Micro Property assessment using AFM, Nano indentation and SEM

Nanoindentation was used to assess the micro-mechanical properties of the different MCC particles, with penetration resistance and hardness being two key features assessed. Wafers were prepared to give a uniform flat surface, as nanoindentation only tested local to the sample surface on to which the indents were performed. Wafers with the three different moisture contents of MCC and the interactive/compositely mixed powders were prepared and were subjected to the nanoindentation test, to examine viscoelastic behaviour and their elastic modulus and hardness. Modulus and hardness of the wafers prepared from the three MCC moisture contents and powders

compositely mixed at 1500 rpm with and without air were obtained and displayed in (Figure 6.8 a, b and c) respectively. With regards to the pre-processing materials, MCC 1, MCC 2 and MCC 3 pellets were subjected to the nanoindentaion test and the load penetration graph is shown in (Figure 6.8 d). The penetration of the nanoindenter on the surface of the pellet was governed by many features, for example the degree of compaction of the particles in the pellet and the structure and porosity of the particles (Das *et al.*, 2009). MCC 1 and MCC 2 showed similar profiles, indicating approximately the same absorption of energy during the loading/unloading cycle. In MCC 3 penetration was much less and the deformation predominantly showed an elastic profile. MCC 3 was found to have the lowest modulus at around 3.34 GPa and hardness around 17 Vickers, which could have been due to high moisture content and wide particle size distribution, giving rise to porous aggregates, which were subsequently confirmed by visual and SEM analysis in (shown in section 6.3.2). The results of the modulus and hardness of the different MCC powders showed a significant difference (ANOVA,$p<0.05$).

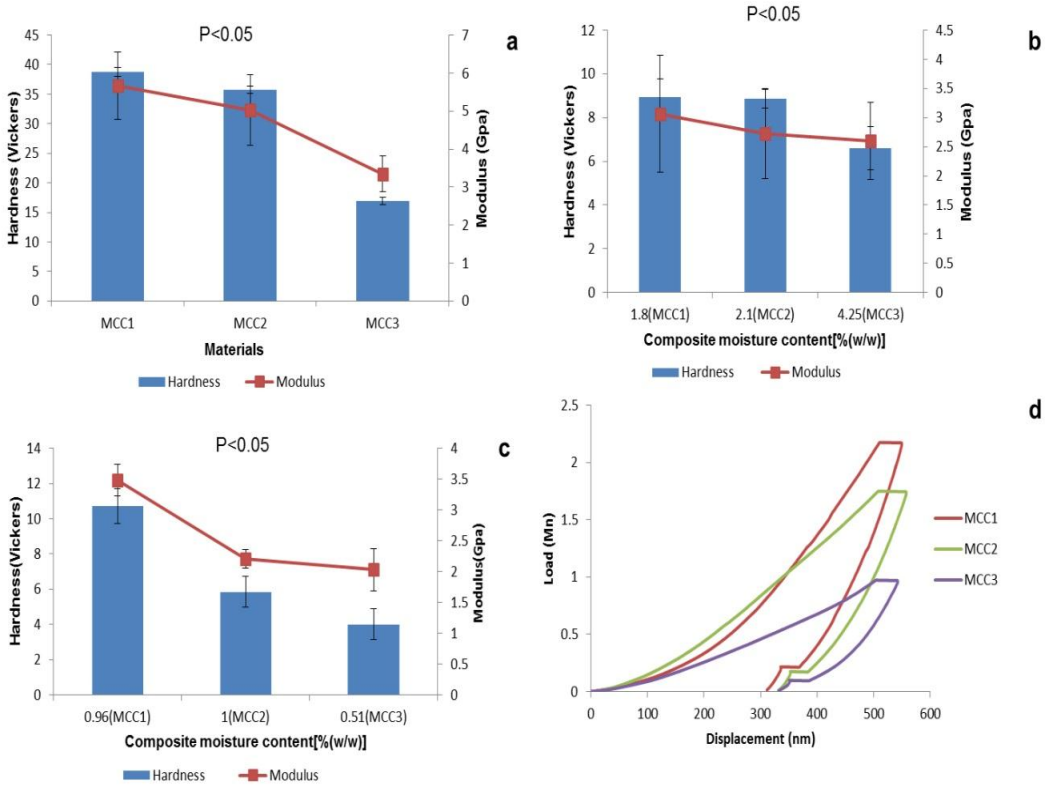

Figure 6.8: (a) The modulus and hardness of MCC1, cured MCC2 &MCC3 wafers as measured from nanoindentation test, (b) Effect of MCC composite moisture content (1.8 - 4.3% w/w) on modulus and hardness as measured from the nanoindentation test of ternary mixture wafers, (coating method, composite mixed at 1500rpm for 60 minutes without air), (c) Effect of MCC composite moisture content (0.5 – 1% w/w) on modulus and hardness as measured from nanoindentation test of ternary mixture wafers, (coating method, composite mixed at 1500rpm for 60 minutes with air), (d) Nanoindentation load–displacement curves for pre-processed materials (MCC1, MCC2and MCC3. The poor overlap of the loading curves shows the non-uniformity of properties and rough surface of the materials. Where applicable results reported as mean ± SD (n=3).

Data from AFM also showed that MCC 3 was composed primarily of smooth surface topography particles with the lowest average roughness Ra of approximately 35nm, as shown in (Figure 6.9 a). This was possibly due to the high levels of adsorbed moisture on the surface on the particles, which resulted in a smoother surface (Mujumdar *et al.*, 2004). The highest modulus and hardness was observed with MCC 2, and these values correlate to the AFM readings whereby particle roughness was highest.

A major change in hardness and modulus was observed in compositely mixed blends shown in (Figure 6.8 b and c) compared to pre-processing materials. This experiment

provided evidence that MCC was coated by mannitol as a sharp decrease in hardness and modulus of the particles was observed. The decrease in mechanical properties indicated that the surface of MCC was coated with mannitol. Mannitol has lower compactability when used in tablet formulation, giving tablets of a lower mechanical strength; hence, mannitol had undergone fragmentation under pressure, resulting in the formation of weak wafers (Koner *et al.*, 2015).

In addition, previous research from our group has stated that the needle shape of the particles of mannitol results in its low compactability (Al-Khattawi *et al.*, 2014a). To further support the fragmentation pattern, AFM topographical analysis was performed which showed a considerable number of asperities that were liable to damage when slight force was applied using the AFM cantilever. Additionally, morphological studies using SEM showed columnar/longitudinal particles for pure mannitol in comparison to MCC which was primarily composed of irregularly shaped particles with microfibrilar structure (Al-Khattawi *et al.*, 2014a). Using one way ANOVA, results of modulus and hardness demonstrated no significance difference between composite mix with/without air flow ($p>0.05$).

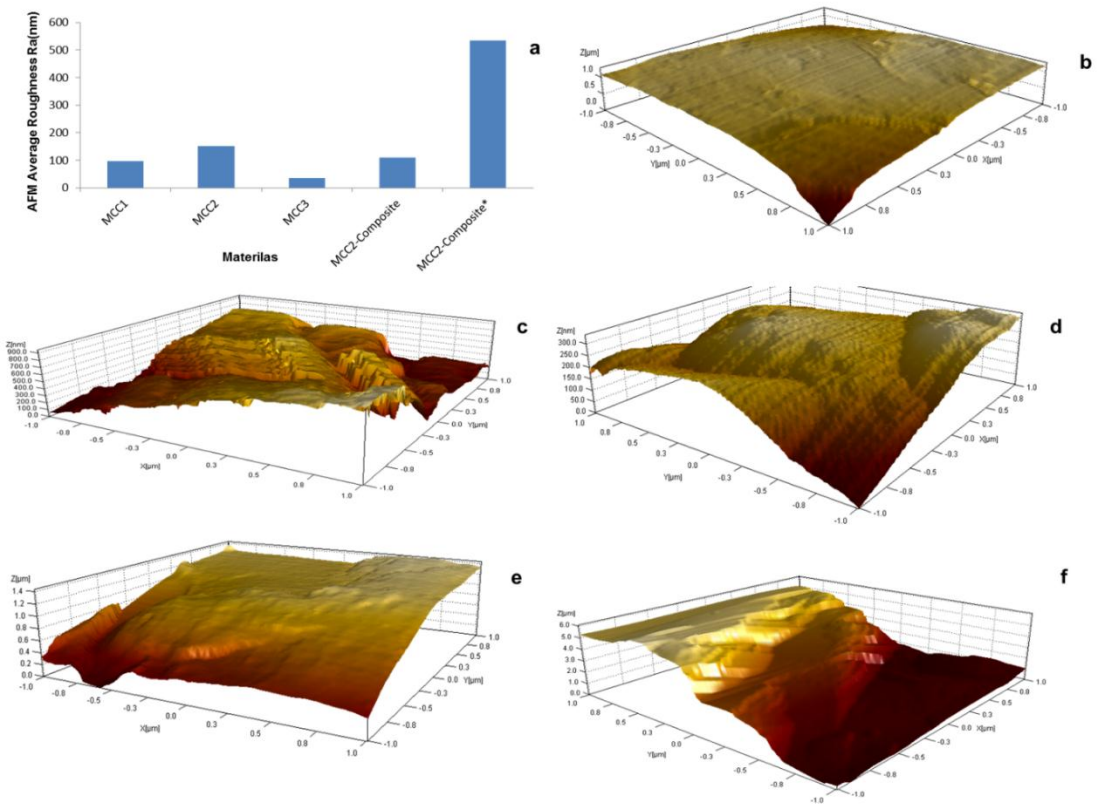

Figure 6.9: Nano structural features of MCC and MCC composite obtained from AFM. (a) AFM average surface roughness of MCC particles and MCC composite at different moisture contents. (b-f) show AFM topographical images of MCC1, MCC2, MCC3, MCC2-composite (at 1500rpm, no air) and MCC2-composite* (at 1500rpm and air).

Furthermore, AFM confirmed the smooth surface of particles when no air was included (Figure 6.9 e), whereas, the composite mixing with air presented a very high roughness (Ra was 534 approaching approximately five times that of composite mixing without air) (Figure 6.9 a).

6.3.5.2. Macro properties of ternary mixed powder blends

In this section tablet properties of the different ternary mixtures of powders containing the different MCC moisture content powders were investigated. Disintegration time, hardness and porosity were both affected by the increase in moisture content possibly as a result of the different densification mechanisms of the powder bed and particulate deformation due to the fragmentation of mannitol and plastic deformation of MCC (Tatavarti *et al.*, 2008).

6.3.5.2.1. Investigation of the effect of moisture content on mechanical properties of ODTs

The results of tablets made from ternary mixtures comprising of 64.5% w/w mannitol, 30% w/w MCC (different moisture contents), 5% w/w crospovidone and 0.5% w/w magnesium stearate showing the relationship between moisture content and hardness/friability, are depicted in (Figure 6.10 a-c). With regards to the interactive mixture, using MCC 2 where the final moisture content of the powder came to approximately 2.7% w/w, provided tablets with increased compact strength whereas at higher moisture contents, using MCC 3 (>4% w/w final moisture content) a dramatic reduction in tablets hardness was obtained as shown in (Figure 6.10 a and b). The initial increase in crushing strength of tablet compacts with increasing moisture content up to 2.7% w/w was possibly due to the hydrodynamic lubrication effect of moisture, which allowed a greater fraction of the applied force to be diffused through the compact on to the lower punch. Meanwhile, an initial increase in moisture content resulted in a higher crushing strength, due to increased particle-particle interaction. Consequently the increased moisture possibly improved plastic deformation (Nokhodchi *et al.*, 1995).

With regards to the composite blend without the inclusion of air, it was clear that increased moisture content up to 2% w/w resulted in an improvement of the tablet hardness. For example, the MCC 2 formulation (2.1% w/w moisture content) had a hardness of 52N, whereas the hardness of tablets with MCC 1 (1.8% w/w moisture content) was 29N. It is possible that the increased amount of moisture contributed to an increase in the initial consolidation rate as well as the final granule consolidation during compaction as the moisture acted as a low viscous binder (Iveson *et al.*, 2001).

The use of the composite dry powder coating process without air to form a final 2.1% w/w moisture content (MCC 2) resulted in enhancement of the hardness profile of the

tablets, up to 80%, when compared to 1.8% w/w moisture content powder (using MCC 1), as shown in (Figure 6.10 b). This was attributed to the strong adherence of the fine mannitol particles to the surface of MCC. Furthermore, the increase in hardness due to the moisture content and coating may have been due to the formation of a mono molecular layer of moisture around the powder particles. This film of moisture could enable the formation of interparticle hydrogen bonding and/or increased the van der Waals' forces, therefore smoothing out the surface micro irregularities and dropping interparticle separation (Malamataris and Pilpel, 1983).

The presence of excessive moisture decreased the compact strength, by reducing the hydrodynamic resistance and therefore increasing elastic recovery after ejection (Li and Peck, 1990). A high compaction force and high moisture content may have also led to a significant moisture squeeze out onto the particle surface, thus reducing interparticle bonding and thereby increasing elastic recovery resulting in a reduction of the crushing strength (Nokhodchi *et al.*, 1995). A previous study found that sodium chloride compacts containing higher moisture content had lower strength (Khan *et al.*, 1981). Another possible explanation for a decrease in hardness at high moisture content was the formation of multilayers of water at the particle surface. These layers may have disturbed or decreased inter molecular attraction forces and thus reduced tablet strength (Kristensen *et al.*, 1985).

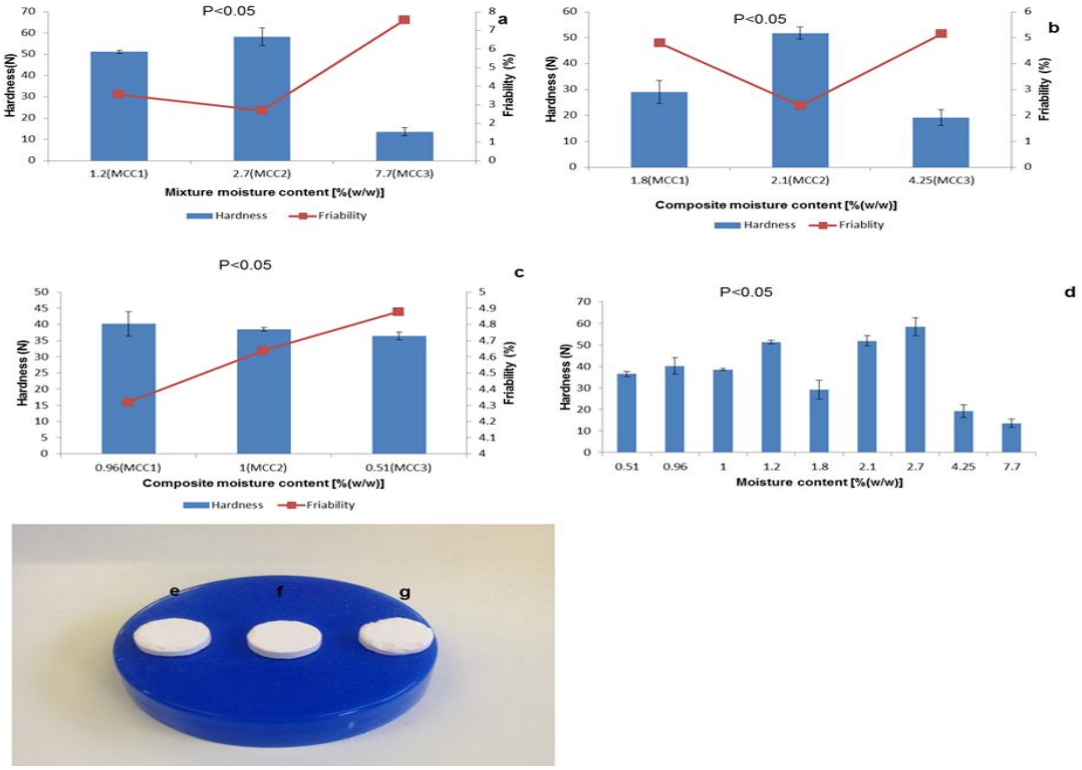

Figure 6.10: (a) Effect of MCC mixture moisture content (1.2 - 7.7% w/w) on hardness and friability of ternary mixture tablets (interactive method, mixed at 300 rpm for 10 minutes), (b) Effect of MCC composite moisture content (1.8 - 4.3% w/w) on hardness and friability of ternary mixture tablets (composite mixed at 1500rpm for 60 minutes without air), (c) Effect of MCC composite moisture content (0.51‑ 1% w/w) on hardness and friability of ternary mixture tablets (composite mixed at 1500rpm for 60 minutes with air), (d) Effect of MCC mixture/composite moisture content (0.51 - 7.7% w/w) on tablets hardness irrespective of process parameters and .Tablets were compressed at 10 kN compression force. Results reported as mean ±SD (n=3). (e-g) Moisture based tablet after friability test for compositely mixed powders at 1500rpm for 60 minutes without air, (e) Weight loss of 4.79% at 1.8% w/w moisture content, (f) weight loss of 2.38% at 2.1% w/w moisture content and (g) weight loss of 5.14% at 4.3% w/w moisture content.

Overall, a proportional relationship between the tablet hardness and friability was seen; as hardness increased the friability was improved in all approaches. For example, hardness in (Figure 6.10 a) showed that at 7.7% w/w moisture content, the tablets had the lowest hardness value at 13.57±3.32N and the highest friability percentage at 7.6%. While, the highest hardness of 51.9±2.35N with lowest friability of 2.38%, was found with 2.1% w/w moisture content as shown in (Figure 6.10 b).

It was also observed that post friability test, capping of prepared tablets increased with the increased moisture content (>4% using MCC 3) as shown in (Figure 6.10 g). The tendency to cap may have increased due to the weakening of the interparticle bonds as a result of the disruption of molecular forces and greater separation of the MCC particles by excess moisture (Nokhodchi *et al.*, 1995).

6.3.5.2.2. Effect of moisture content on disintegration time and tablet porosity

Figure 6.11 shows the effect of moisture content on tablet disintegration time and porosity. For example, at 7.7% w/w moisture content (with MCC 3) using interactive mixing at low speed (300 rpm), the tablets had a disintegration time of 7±1s whereas those prepared from 1.2% moisture powders (using MCC 1) had a longer disintegration time of 39±2s ($P<0.05$),(Figure 6.11 a).

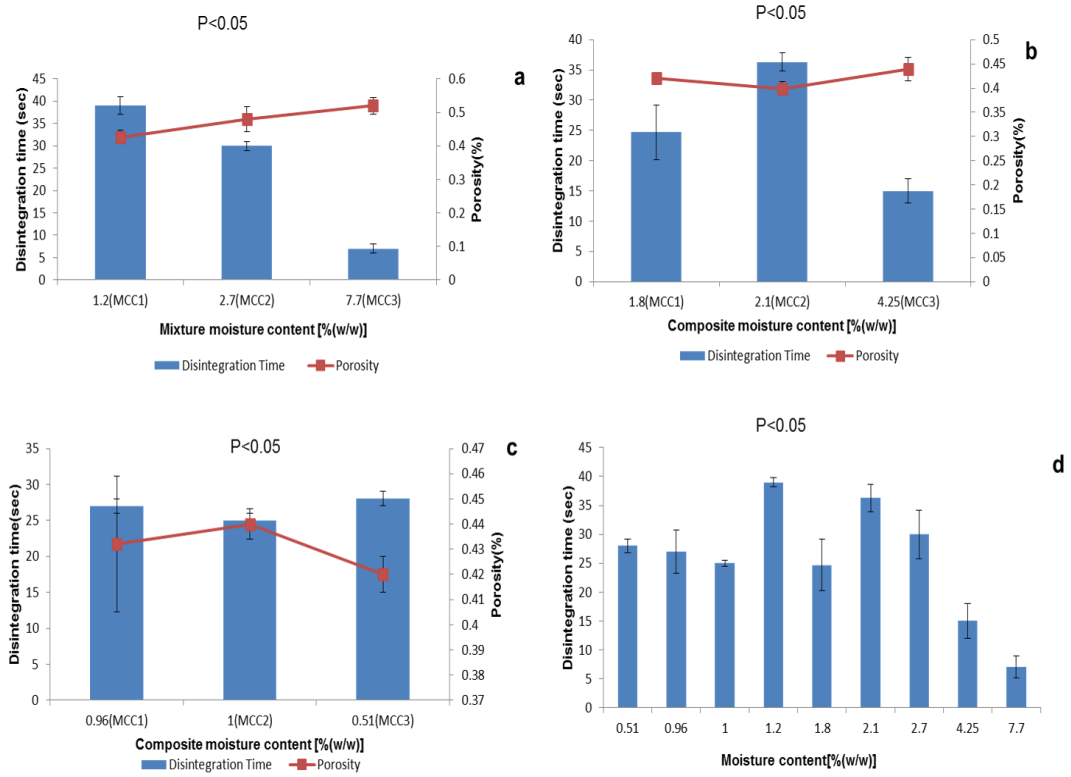

Figure 6.11: (a) Effect of MCC mixture moisture content (1.2 - 7.7% w/w) on disintegration time and porosity of ternary mixture tablets using interactive mixing at 300 rpm for 10 minutes, (b) Effect of MCC composite moisture content (1.8 - 4.3% w/w) on disintegration time and porosity of ternary mixture tablets compositely mixed at 1500rpm for 60 minutes without air , (c) Effect of MCC composite moisture content (0.51– 1% w/w) on disintegration time and porosity of ternary mixture tablets , compositely mixed at 1500rpm for 60 minutes with air &(d) Effect of MCC mixture/composite moisture content (0.51 - 7.7% w/w) on disintegration time irrespective of process parameters .Tablets were compressed at 10 kN compression force. Results reported as mean ±SD (n=3).

The porosity results during interactive mixing, shown in (Figure 6.11 a), were consistent with disintegration results as the increase in moisture content caused a significant increase in porosity and a sharp decrease in disintegration time (ANOVA, $p<0.05$). This suggested that the high amount of moisture content may have led to creating a freely moving environment of the particle that contributed to finding the most suitable compact configuration; while disintegration time was prolonged at low moisture content as the reduction of pores reduced the ability for water to penetrate and break up the tablet. Although tablets retained high porosity, which is important to enhance water penetration and disintegration of tablets, their hardness was insufficient

at 14±3.3 N (Figure 6.10 a). Additionally, increasing particle size range may have led to larger void spaces, which yielded a growth in porosity. Interestingly, when scanning electron microscopy (SEM) tests were carried out, it was recognized that a small increase in particle size of the MCC 2 moisture content particles was observed compared to MCC 1.

These increases in average particle size of the MCC 2 powders could be referred to as the coalescence process, at which the particles combined to form big clusters. Therefore, it is possible that the increased non-viscous binder (water) led to improved hardness, friability, disintegration time and porosity of tablets as the increased moisture created free movement for particles, increasing the consolidation process and decreasing the coalescence processes (Iveson *et al.*, 2001).

6.4. Conclusion

Manufacturing powders with differing levels of moisture content resulted in an alteration in the powder morphology as observed from SEM and AFM studies. This study showed that the amount of moisture content within MCC affected the mechanical properties of the subsequent powders and it was concluded that inclusion of 11% MCC moisture content resulted in the most flowable powder with favourable ODT characteristics, as tablets displayed increased hardness when formed using direct compression. Extreme moisture contents in pre-processing materials could be reduced using varying process parameters using composite dry coating, as well as mixing of the powders with excipients designed to dry coat the surface of the high moisture content carrier particles. The understanding of tableting performance of excipients at the particle level (nanoindentaion study) would facilitate the rational design of ODT formulations through consideration of the main factors that contribute to high hardness and fast disintegration which in turn would considerably accelerate product development.

Chapter 7

General Discussion and Future Work

7.1. General Discussion and Conclusions

The extensive use, in paediatrics, of off-label and unlicensed medicines formulated specifically for adults, caused the European Union to pass regulations that necessitate the formulation of medicines specifically targeted at the paediatric population. Reasons behind this move include, but are not limited to, the marked differences in organ development, metabolic competence and skin maturation in children; which produces vastly different pharmacokinetic and pharmacodynamics responses within this heterogeneous population; and when compared to adults. Therefore research into paediatric formulation has become a topical theme in the last few years. However, the stability issues associated with liquid dosage forms, which are commonly used in paediatric therapy, has caused the World Health Organisation (WHO) to advocate a paradigm shift from liquid dosage forms to solid dosage forms for paediatrics. This has become a great opportunity to explore the successful use of Orally Disintegrating Tablets (ODTs) in paediatric formulations, since these dosage forms which are seen as an intermediate between solid and liquid dosage forms can solve stability issues related to liquids, and reduce the risk involved in children swallowing conventional tablets, in cases of dysphagia. However, formulating paediatric doses as solid dosage form would require the consistent and uniform mixing of much smaller does into dosage forms. Blending requirements become more stringent for these low dose formulations. Because the final outcome of therapy in paediatric patients depends on the patients themselves, their careers and the prescribers, it became necessary to investigate the perceptions and motivations of these critical stakeholders, with regards the use of ODTs for children. Thus the aim of this work was to firstly, extract and understand the stakeholder (children/ carer and prescriber/ dispenser) preferences for ODT tablet characteristics that could ensure maximum patient compliance; and secondly to explore various mixing techniques that would deliver the highest quality of

pre-blended multifunctional excipients to facilitate the effective production of paediatric ODT formulations.

Acceptability studies were carried out across three international centres, to assess the ODT preference and acceptability amongst children of different age groups. The general outcome was that solid dosage forms are the preferred dosage forms with ODTs being the preferred dosage form for children and young adults. The preferences highlighted from this study included: pink or white colours, small size, round shape and strawberry flavour. Necessary physical attributes in terms of ODT acceptability revealed disintegration time and taste as having the highest priority, and importance reducing in the order of, size, flavour and shape. This study has identified the favoured medication characteristics as expressed by the participants. However it has not been tested whether these desirable characteristics are deliverable due to the physical properties of individual active pharmaceutical ingredients. Similarly the potential benefits in terms of patient adherence are implied only, and have not been tested in this present study. This leaves room for further onward research in this area.

Awareness of the critical role the prescriber plays in ensuring the appropriate choice and use of dosage forms for paediatric patients, coupled with the unavailability of data outlining the opinion and professional use of ODTs by prescribers, necessitated the conduction of a multifactorial study design across two hospital sites, to assess the opinions of different healthcare professionals in relation to ODTs. Results reaffirmed the popularity of liquids for prescribing in paediatrics, ODTs emerged as the second most popular dosage form, with healthcare practitioners indicating an increasing popularity in the use of this dosage form amongst patients in the hospital setting, and a clear indication that many liquid formulations could be substituted with a suitable ODT. The desired properties of an ideal ODT were also identified with healthcare practitioners preferring a small fast disintegrating tablet, with taste, flavour and disintegration time being the key attributes identified. This study provided a pragmatic

approach in assessing healthcare professional's opinions on ODTs, filling a clear gap in knowledge regarding the ideas and thoughts of practitioners who are on the frontline of paediatric prescribing and treatment.

To facilitate the formulation of ODTs containing very low doses of API, it was necessary to develop an understanding of API and excipients properties, under the processing conditions of various available blending techniques. Vitamin D was used as a potent low dose drug while MCC, starch and pregelatinised starch were investigated as model excipients. It was found that flow properties improved as particle size increased, with the non-sieved, non-cohesive MCC and non-cohesive pregelatinised starch having excellent flow whereas the cohesive pregelatinised starch and starch had an angle of repose just outside the threshold of being considered to have poor flow properties. In case of geometric mixing technique for 1 minute all formulations failed to meet the required pharmacopeial standards for drug content uniformity. Therefore, an increase in mixing time to 5 minutes with geometric addition showed considerable uniformity improvements for all carrier types. Ordered mixing with the dry powder coater allowed for uniformity to be reached faster than hand order mixing, and was able to keep the blend containing cohesive powder within the acceptable uniformity range throughout the mixing period. The powder coater was also useful in obtaining good uniformities at 0.5% and 1% API using non-sieved carrier. All blends showed acceptable uniformity after the 32 minute mixing period, with the 1% API also achieving this only for MCC after 8 minutes of mixing, whereas the 0.5% API with MCC blend reached ideal uniformity at the end of the 16 minutes mixing period. This study also highlighted the importance of excipient mixing order for (mannitol, MCC, crospovidone and magnesium stearate) on tablet and powder properties. Although all formulations (F1-F3) demonstrated similar results for powder and tablets characterisations (no significant difference), powder flow was fair to passable for all batches whilst MCC alone showed excellent flow property. The inclusion of excipients with high plastic

deformation proficiency (MCC) improved tablet hardness and reduced friability. The resultant mixture tablets exhibited good hardness and friability profile. Overall, it is critical to realize that mixing order has significant impact on blending and tablet properties.

Pre-blend excipients play an important role in the development of ODTs. Formulation problems such as flowability, compressibility, compactability and disintegration time can be improved using co-processed excipients. The next study was carried out to develop co-processedmilled mannitol with pregelatinised starch and silica using the composite dry powder coating that would offer an excellent multifunctional base for ODT formulations. The novel pre-blend excipient showed very good mechanical properties and fast disintegration. In addition, the pre-blend was able to accommodate a high amount (up to 50% w/w) of API without affecting its functionality. Replacement of proportions of mannitol powder (responsible for the production of highly friable ODTs) with milled-mannitol was found to enhance ODT mechanical strength and friability due to reduced fragmentation during compression and improved compressibility. Furthermore, milled-mannitol led to improve disintegration time due to increased wettability of the ODT. Optimising silica concentration in the ODT was also important to enhance flowability. Silica at 1.5% w/w was suitable as it achieved the required flowability without significantly prolonging disintegration time of ODTs. In summary, the co-processed excipients using composite dry powder coater containing 86.5% w/w of milled-mannitol, 12% w/w pregelatinised starch and 1.5% w/w silica can be used as a potential multifunctional directly compressible ODT pre-blend.

Finally, we found that manufacturing powders with differing levels of moisture content resulted in an alteration in the powder morphology as observed from SEM and AFM studies. This study showed that the amount of moisture content within MCC affected the mechanical properties of the subsequent powders and it was concluded that inclusion of 11% MCC moisture content resulted in the most flowable powder with favourable ODT characteristics, as tablets displayed increased hardness when formed using direct compression. Extreme moisture contents in pre-processed materials could be reduced using varying process parameters such as composite dry coating, as well as mixing of the powders with excipients designed to dry coat the surface of the high moisture content carrier particles. The understanding of tableting performance of excipients at the particle level (nanoindentation studies) would facilitate the rational design of ODT formulations through consideration of the main factors that contribute to high hardness and fast disintegration which in turn would considerably accelerate product development.

7.2. Future Work

The acceptability study of paediatric populations may bring to the attention of medical practitioners and other stakeholders, the need to accord more time and resources to ODTs as a form of paediatric drug administration. As the study was conducted in three countries, such future developments and expectations are required. This calls for putting in place measures that will streamline and present new avenues for making ODTs a success. Future work in this area would involve:

- Investigation and development of palatability studies for paediatrics since findings from healthcare professionals suggest that age-appropriate formulations should be developed to provide both suitable dose units and acceptable palatability for paediatric patients.
- The main issue raised after consultations with paediatric patients and healthcare professionals was related to the taste of specific medicines. Therefore, the development of a suitable taste masking technology for bitter tasting compounds, with significant potential for commercialisation in the near future, would be necessary.
- Development of a novel oral disintegrating granules formulation which convert small particles into physically stronger and larger aggregates. Aston Particle Technologies (APT) will be developed as a single and reproducible process, including high shear mixing granulation.

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Appendices

Appendix 1- Acceptability study survey (Chapter 2)

Evaluation the acceptability and palatability of solid oral dosage forms for paediatric

Section One: About You

1. Your Age

How old are you?

-

2. Your Gender

What is your gender? (Place a √ **only one**)

☐ 

☐ 

3. Your Education

What is your education level? (Place a √ **only one**)

☐ Are you at School
☐ Are you at higher education
☐ Are you working
☐ Others

Section two: About medicines

4. What experience do you have for taking medicine?

5. Which of the following dosage forms you prefer? (Place a √ only one)

☐ Big size

10. How thickness of tablets would you prefer? (Place a √ only one)

☐ Thick
☐ Thin

11. Which taste of tablets would you prefer? (Place a √ only one)

☐ Without taste ☐ Sweet taste

☐ Bitter taste

12. Which flavour of tablets would you like? (Place a √ only one)

☐ Strawberry
☐ Orange
☐ Cherry
☐ Vanilla
☐ Mint
☐ Lemon
☐ Chocolate
☐ Other (specify)

13. Which length of time for the tablets to dissolve would you prefer? (Place a √ only one)

☐ Very rapidly < 30 seconds
☐ Rapidly 30 - 1.30 minutes
☐ From 1.30 - 3 minutes

14. Which three are the most important characteristics of orally disintegrating tablets (ODTs)? (Place a √ only three)

☐ Colour
☐ Shape
☐ Size
☐ Thickness
☐ Taste
☐ Flavor
☐ The length to dissolve in mouth

15. Any feedback on the questionnaire, suggestions for any improvements?

Appendix2-The plan for agenda design (Chapter 2)

Number of event	Name of event	Duration (Minutes)
1	Welcome and discuss the aim of the event	2-5
2	Slide show for dosage forms and questions	10-15
3	Visual demonstrations comparing ODT and immediate release paracetamol tablet	10
4	Distribute Questionnaire	10
5	Feedback on questionnaire	5
6	Suggestions for any improvements	10
7	Distribution of ‘Thank You’ letter	5

Appendix 6- A question guide-Phase 1 (Chapter 3)

Current Opinions and Recommendations of Healthcare Professionals Regarding the Importance and their Preferences Concerning Paediatric Dosage Forms- Focus group question guide

Method/Question guide

Introduction
Hi everyone. Thank you for attending the focus group session. During this focus group session we will be discussing and finding out your opinions and views on the paediatric (age 6-18 yrs.) dosage forms.

Focus group ground rules
Before we start the focus group just some information and ground rules
Distribute PIS
I will be recording the focus group, however, in any transcripts and reports, all your details will be kept anonymous.
The session will be 40 minutes.
During this session we will be focusing on ODTs
Sign consent form

Opening questions (10 minutes)
Before we start on the key questions, I would like to ask you all to discuss
1) What dosage form of prescribed medication (e.g. liquids, tablets, capsules) would you prefer to prescribe for (doctors) / recommend (pharmacists) / give to (nurse) children and how does it affect your practice?

2) What are your views concerning the safety and dose accuracy of formulation types? What do you think about utility of dosage forms for children?

3) If ODTs were available for a medication, what would motivate you to prescribe this over unlicensed liquid for a child?

4) How do you feel cost would be affected as a result of a switch from unlicensed liquid to ODTs?

5) Do you receive any feedback from patients and their parents about the acceptability of the formulation? What are the views and comments that are fed back to them from patients who are prescribed and given ODTs?

Ok now that we have gathered the group member's views in terms of the definition and concerning paediatric dosage forms lets discuss the most preferred dosage forms and your views concerning physical characteristics of ODTs.

Key Question 1 (15 minutes) Discussion on the paediatric dosage forms

Now I would like to discuss your views and experience about prescribing/dispensing or administering medicine to children. What is the most common dosage forms that are given to patients?
What do you think the most preferred dosage forms to be given to children and why?
In particular, oral dosage forms including (Tablets, capsules, liquids and ODTs).
What do you think about dose frequency?

Key Question 2 (10 minutes) Discussion on the development of ODTS (physical characteristics)
Now that we have discussed the paediatric dosage forms (mainly ODTs), for the next session, let's discuss your views concerning the design and development of ODTs?
What do you think about taste, flavours, size and colour (in your opinion what most preferred)?

Ending questions (5 minutes)

That is very useful; we now need to draw the focus group to a close. Before we finish I would like to ask you to raise any other issues, suggestions, comments in general regarding the paediatric dosage forms, which we may not have discussed? We have 10 minutes left.
Once again I would like to thank you for attending the focus group, this has been very helpful.

Appendix 9- Online Survey-Phase 3 (Chapter 3)

Healthcare Professionals (HCPs) survey final

Page 1: Introduction

About the study

Thank you very much for taking time out to complete the survey. Completion of this survey will allow us to identify the current opinions and recommendations of healthcare professionals (HCPs) regarding the importance and their preferences concerning paediatric **(age group 6-18yrs)** dosage forms. In particular,this survey considers **Orally Disintegrating Tablets (ODTs) - tablets that melt and disintegrate when placed in the mouth**.

Data will be kept **confidential** at all times. All participants' data will be **deleted** as soon as the project is finished. By taking part in this study and completing this survey, you are agreeing to the use of the data that you provide in this survey for research purposes. This research has been approved by LHS Ethics Committee, Aston University Birmingham, Research and Development at BCH, Birmingham and Research and Development at Alder Hey Children's Hospital, Liverpool (reference number alyamihs project #917) .The survey should take 10-15 minutes to complete. All data will be **anonymised**.

If you have any questions, please contact Hamad Alyami at:-

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alyamihs@aston.ac.uk

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Page 2: About you

1. Which Hospital do you work at? ✱ *Required*

- Alder Hey Children's Hospital, Liverpool
- Birmingham Children's Hospital

2. What is your current profession? ✱ *Required*

- Consultant (Medical staff)
- Junior medical staff
- Nurse
- Pharmacist

3. In which year did you first register as a healthcare professional? ✱ *Required*

4. How many years' experience do you have as a healthcare professional working in paediatrics (please give your answer in accumulated years, if necessary including part years)? ✱ *Required*

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Page 3: About paediatric dosage forms

5. What types of dosage forms do you prescribe, supply or give to paediatric patients? From the list below please score each one according to how often you prescribe each form, with 1 being the most common and 5 being the least common. * *Required*

Please don't select more than 1 answer(s) per row.

Please select at least 3 answer(s).

	1	2	3	4	5	I don't prescribe/supply/give this to my patients
Capsules	☐	☐	☐	☐	☐	☐
Injections	☐	☐	☐	☐	☐	☐
Liquids	☐	☐	☐	☐	☐	☐
Orally disintegrating tablets (ODTs)	☐	☐	☐	☐	☐	☐
Powders	☐	☐	☐	☐	☐	☐
Suppositories	☐	☐	☐	☐	☐	☐
Tablets	☐	☐	☐	☐	☐	☐

6. In your opinion, which oral dosage forms do you prefer for paediatric patients? Please score each one in terms of preference (1 being the most preferred and 5 being least) * *Required*

Please don't select more than 1 answer(s) per row.

Please select at least 3 answer(s).

	1	2	3	4	5
Capsules	☐	☐	☐	☐	☐
Liquids	☐	☐	☐	☐	☐

Oral Disintegrating Tablets(ODTs)	☐	☐	☐	☐	☐
Tablets	☐	☐	☐	☐	☐

7. What factors influence your choice of formulations for paediatric patients? **(Select more than one answer if appropriate)** ✱ *Required*

- ☐ Age
- ☐ Weight
- ☐ Patient
- ☐ Parents
- ☐ Cost effectiveness
- ☐ Other

7.a. If you selected Other, please specify:

8. Have you ever prescribed (doctor)/dispensed and supplied (Pharmacist)/ given or administered (nurse) ODTs to paediatric patients? ✱ *Required*

- ○ Yes
- ○ No
- ○ Not applicable
- ○ I don't know

9. In the last 12 months, do you know how many ODTs formulations have you

prescribed, dispinsed or administered ? * *Required*

- None
- 1-5 Formulations
- 6-10 Formulations
- More than 10 Formulations
- I don't know

10. To what extent do you agree or disagree that liquid formulations could be substituted with ODTs in paediatric patients? * *Required*

- Strongly agree
- Agree
- Neither agree nor disagree
- Disagree
- Strongly disagree
- I don't know

11. What are your opinions concerning the safety ODTs formulations compared with liquids? * *Required*

11.a. What are your opinions concerning the the efficacy ODTs formulations compared with liquids? * *Required*

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11.b. What are your opinions concerning cost effectiveness ODTs formulations compared with liquids? * *Required*

11.c. What are your opinions concerning compliance and adherence ODTs formulations compared with liquids? * *Required*

Page 4: About Physical Characteristics of ODTs

12. In your opinion, which taste of ODTs would you accept for paediatric patients? **(Select more than one answer if appropriate)** * *Required*

- [ ] Bitter taste
- [ ] Neutral taste
- [ ] Sweet taste

13. In your opinion, which flavour of ODT would you prefer for paediatric patients ? From the list below please score each one according to your prefernces, with 1 being the mostly preferred and 5 being not preferred. * *Required*

Please don't select more than 1 answer(s) per row.

Please select at least 3 answer(s).

	1	2	3	4	5
Banana	☐	☐	☐	☐	☐
Cherry	☐	☐	☐	☐	☐
Chocolate	☐	☐	☐	☐	☐
Lemon	☐	☐	☐	☐	☐
Mint	☐	☐	☐	☐	☐
Orange	☐	☐	☐	☐	☐
Strawberry	☐	☐	☐	☐	☐
Vanilla	☐	☐	☐	☐	☐

14. In your opinion, which size of ODTs would you prefer for paediatric patients? * *Required*

- ○ Big size(≥ 13 mm)
- ○ Medium size (diameter 8-12 mm)
- ○ Small size (diameter 5-7 mm)

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15. In your opinion, which shape of ODTs would you prefer for paediatric patients ? * Required

- Oval
- Round
- Square
- Triangle
- Other

15.a. If you selected Other, please specify:

16. In your opinion, which colour of ODTs would you prefer for paediatric patients ? * Required

- Blue
- Pink
- White
- Yellow
- Other

16.a. If you selected Other, please specify:

17. In your opinion, which length of time for ODTs to be dissolved in the mouth would

you prefer for paediatric patients? * *Required*

- ☐ Very rapidly (≤ 30 seconds)
- ☐ Rapidly (30- 90 seconds)
- ☐ Between 90- 180 seconds

18. In your opinion, what are the most important characteristics of ODTs? * *Required*

Please don't select more than 1 answer(s) per row.

Please select at least 3 answer(s).

	VI= Very important	I=Important	N=Neutral	U=Unimportant
Colour	☐	☐	☐	☐
Disintegration time	☐	☐	☐	☐
Flavour	☐	☐	☐	☐
Shape	☐	☐	☐	☐
Size	☐	☐	☐	☐
Taste	☐	☐	☐	☐

Page 5: About your feedback

19. Please let us know if you have any additional comments regarding your preferences of oral dosage form choices for paediatric patients, in addition to the answers to the questions you have provided. * *Required*

20. To help us improve this survey for the future, do you have any other comments or recommendations? * *Required*

21. Would you like to be informed of the research outcomes? If yes, please provide your email: * *Required*

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Page 6: Thank you very much for taking time to complete this survey.

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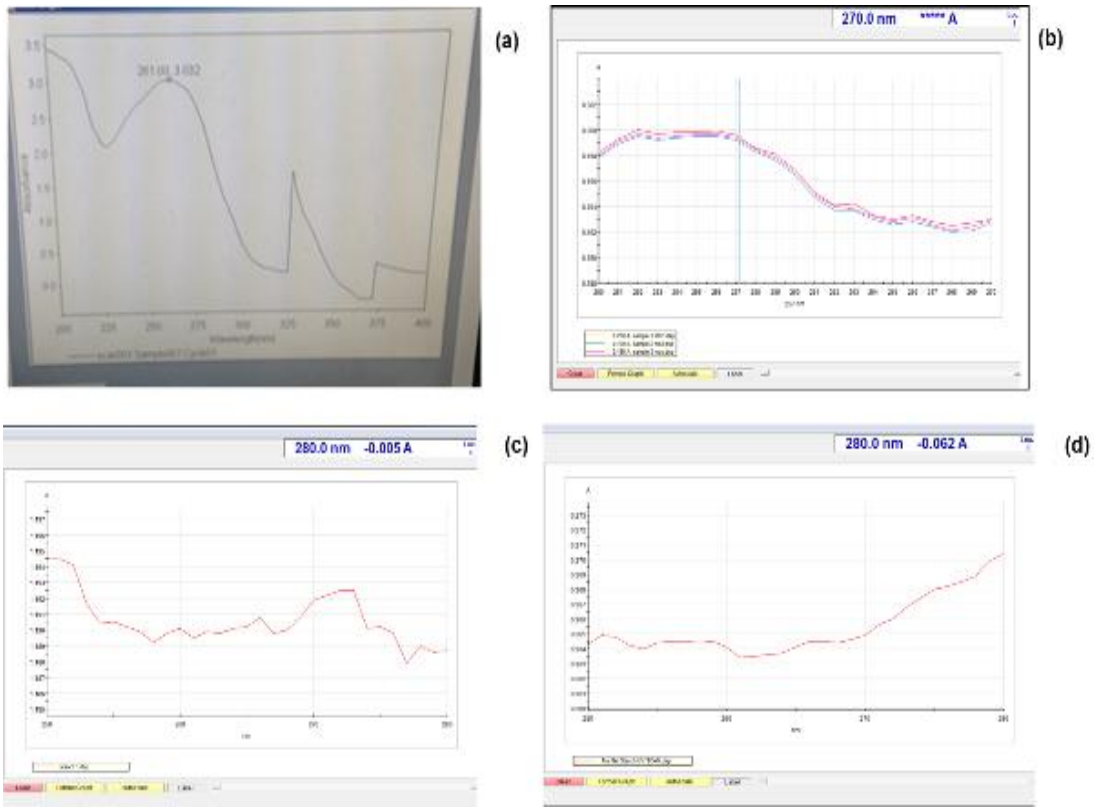
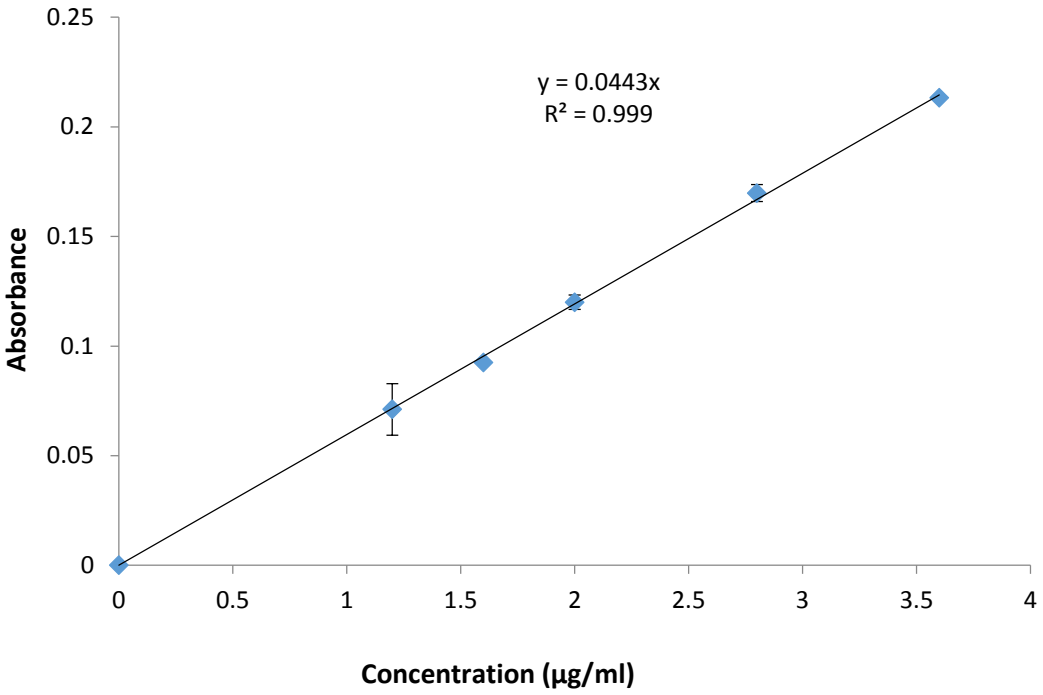
Appendix 10- UV spectrum scan (Chapter 4)



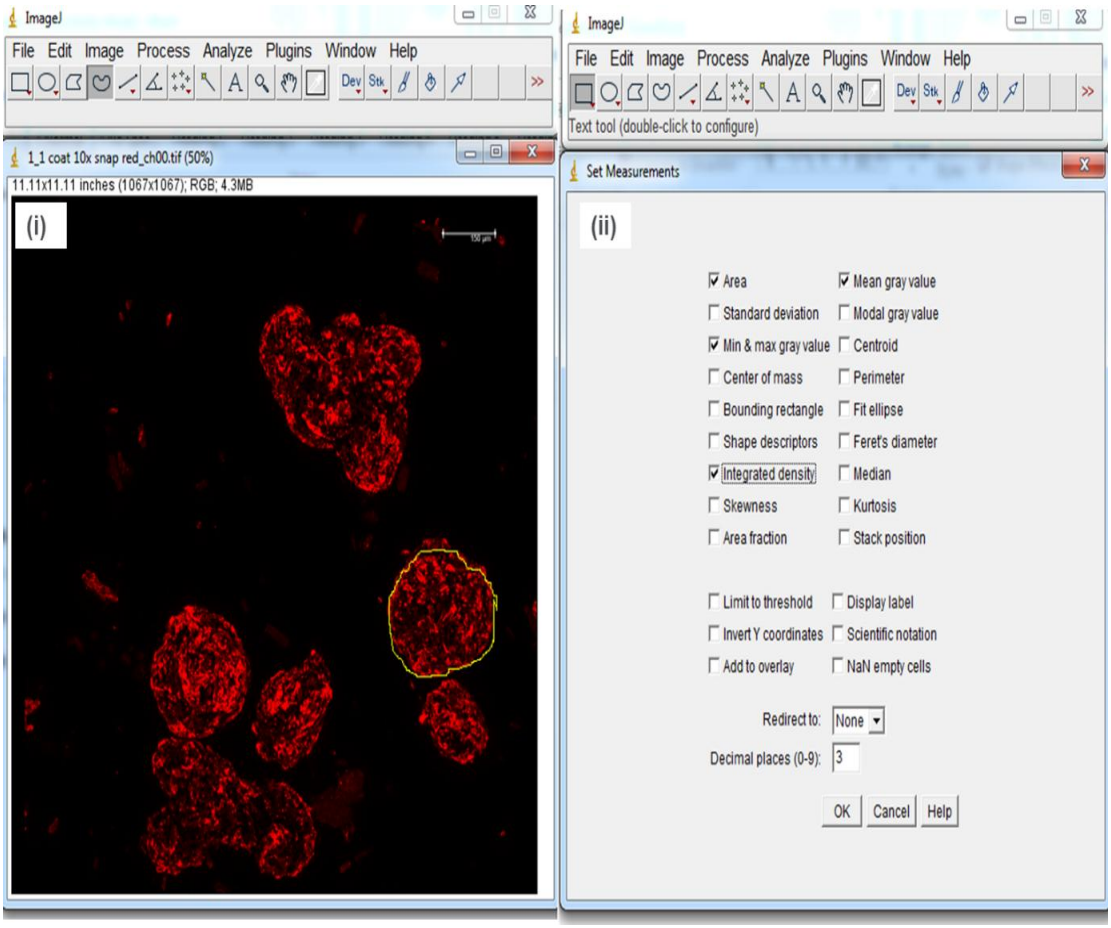
UV spectrum scan (a) absorption spectrum of ergocalciferol showing maximum absorbance at 261nm, (b) ,(c) and (d) UV spectrum scan performed for MCC, starch and pre gelatinised starch respectively between 250nm and 270nm showed no interference.

Appendix 11- Calibration curve (Chapter 4)



Calibration curve of ergocalciferol at 265 nm using UV spectrophotometer (Mean ±SD, n=3).

Appendix 12- Snap shot of ImageJ (Chapter 5)



Snapshot of ImageJ user guide showing selected region of interest (i) drawn on an image and set measurement feature (ii).