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Paediatric specific dosage forms: Patient and formulation considerations

Dilawar Khan [a], Daniel Kirby [a], Simon Bryson [b], Maryam Shah [b], Afzal Rahman Mohammed [a,*]

[a] Aston Pharmacy School, College of Health and Life Sciences, Aston University, Birmingham B4 7ET, UK
[b] Proveca Ltd., No.1 Spinningfields, Quay Street, Manchester M3 3JE, UK

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ABSTRACT

The total number of paediatric formulations available only account for a small proportion of the full therapeutic plethora required to effectively treat paediatrics and, therefore, the availability of high quality medicines designed specifically for children remains an ongoing challenge. Currently, the World Health Organisation (WHO) report that around 50% of medication issued for long-term conditions are not taken as advised, whilst it has also been established that, in general practice, around one tenth of medicines prescribed for children are either off-label or unlicensed. Such off-label and unlicensed use is owing to the considerable anatomical and physiological differences observed between paediatric subsets. Identifying such differences, is essential for better informing paediatric drug development and assisting regulatory reviews, whilst ensuring safe and effective therapeutic concentrations of pharmacological substances.

Points covered: The review discusses factors affecting the safety, toxicity and efficacy of paediatric drug delivery systems. The research highlights features of the gastrointestinal tract and reports anatomical and physiological differences between paediatrics and adults. Additionally, differences observed in paediatric pharmacokinetic profiles (absorption, distribution, metabolism and elimination) due to physiological differences are also discussed. Furthermore, this review considers the advantages and limitations of current paediatric specific dosage forms available and assesses the acceptability of innovative small flexible solid oral dosage forms. Lastly, this review highlights factors affecting paediatric medicine adherence and acceptability and discusses the techniques available to overcome barriers associated with non-adherence.

1. Introduction

At present, the (World Health Organisation) WHO report that around 50% of medication issued for long-term conditions are not taken as advised, whilst it has also been established that, in general practice, around one tenth of medicines prescribed for children are either off-label or unlicensed (NICE, 2009; Tomlin et al., 2009). Directed and effective pharmacotherapy has a significant impact on disease outcomes, where patients benefit from improved prognosis, better quality of life and fewer health related complications. Paediatrics are a distinct population, with differences observed between each subsets. Many factors differentiate children from one another and include anatomical and physiological changes and differences, as well as evolving competencies. Such features are inherent to the child and present many challenges in regards to medicine safety, toxicity and acceptability. It is therefore essential for formulators and researchers to have a good understanding of such variations in order to predict the fate of administered dosage forms within and across the paediatric age range, thereby limiting the potential of medicine related adverse effects.

Pharmacokinetic (PK) profiles (absorption, distribution, metabolism and elimination) measure the concentration of pharmacological substances in the body and are indicative of safe and toxic therapeutic levels. The consequence of anatomical and physiological changes observed within paediatrics may significantly alter the exposure of pharmacological substances, therefore, careful dose adjustments should be considered to limit the occurrence of any adverse effects (Batchelor

Abbreviations: PK, Pharmacokinetic; GI, gastrointestinal; OTT, Oesophageal transit time; GORD, Gastro oesophageal Reflux Disease; BCS, Biopharmaceutical classification system; SFB, Segmented Filamentous Bacteria; P-gp, P-glycoprotein; EMA, European Medicines Agency; IT, Intestinal transit; BBB, Blood Brain Barrier; CNS, Central Nervous System; CYPs, Cytochromes P450; GFR, glomerular filtration rate; ODT, orally disintegrating tablets; MDF, Multi-particulate dosage forms; WHO, World Health Organisation; FDA, The United States Food and Drug Administration.

* Corresponding author.
E-mail addresses: 139140185@aston.ac.uk (D. Khan), kirbydj1@aston.ac.uk (D. Kirby), simon@proveca.com (S. Bryson), maryamshah@proveca.com (M. Shah), a.u.r.mohammed@aston.ac.uk (A. Rahman Mohammed).

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and Marriott, 2015). This would also be true for any excipients added within the formulation, where the exposure and safety of excipients may change under influence of anatomical and physiological differences. Although excipients are considered 'inert', immature organs and lack of metabolising enzymes may lead to accumulation that may resulting in excipient toxicity (Rouaz et al., 2021).

From a formulation perspective, to enhance and maintain medicine-adherence and acceptability, it is necessary for paediatrics to have access to dosage forms that are capable of safely delivering the dose to the child in an easy and reliable fashion. Many paediatric specific drug delivery systems are present and include oral liquids, mini-tablets, chewable tablets and orodispersible technologies. Several studies have compared the acceptability of such dosage forms within the paediatric population, with small flexible solid oral dosage forms including mini-tablets proving to be most superior (Klingmann et al., 2013; van Riet-Nales et al., 2013; Spomer et al., 2012; Klingmann et al., 2015; Thomson et al., 2009). In contrast to adults, where conventional dosage forms are well accepted, the extent of acceptability of dosage forms in paediatrics greatly depends on individual child characteristics such as age, competency and developmental stage.

Ever since the introduction of the paediatric regulation in 2007, great collaborative effort has been made to better the health of children by encouraging the development and availability of medicines (EMA. Paediatric Regulation, 2007). This review paper intends to provide and improve the availability of information on the factors affecting safe and effective use of medicines, both from a patient and formulation perspective.

2. Anatomy and physiology of the paediatric gastrointestinal (GI) tract

Several routes of administration are possible within the paediatric population; however, the oral route is the most preferred, as it is simple, convenient and non-invasive. After oral administration, the drug/pharmacological substance is subjected to several processes before being eliminated from the body; the gastrointestinal (GI) tract is an organ system, composed of the oral cavity, oesophagus, stomach and intestines that serves to transport, digest, absorb and expel food and pharmacological substances (Yoder et al., 2010). In medicine, identifying the anatomical and physiological differences of components of the GI system between paediatrics and adults is paramount to achieve safe, non-toxic and effective therapeutic concentrations of pharmacological substances. Furthermore, the effect of physiological differences shall better inform paediatric drug development and assist regulatory reviews (Yu et al., 2014).

2.1. Oral cavity

The first stage of digestion starts from the mouth, where saliva is excreted to moisten the mouth and aid swallowability. In newborns, the tongue is short and broad, descending into the oropharynx by the age of 4 years (Singh, 2014). The larynx is situated at a higher position, while the soft palate touches the epiglottis. During development, this contact is lost, the larynx moves downwards and the pharynx associates with both the food way and airway, increasing the possibility of aspiration (Matsuo and Palmer, 2008). This developmental change, coupled with motor skill deficits, limits the use of solid oral dosage forms in the younger subsets of the paediatric population (EMA, 2006). Additionally, the size of the oral cavity would limit the size/volume of dosage possible.

2.2. Oesophagus

The oesophagus is a fibrous passageway that allows the transport of food from the mouth and into the stomach. The digestive process continues within the oesophagus through contractions. In neonates, the length of the oesophagus is 18 cm, increasing a further 2 cm by the age of three years and reaching adult measurements by the age of 10 years (25 cm) (Chai, 2018). Following the transportation through the oesophagus, the contents then enter the stomach where it is subjected to further digestion. The main physical oesophageal differences observed between children and adults is the length and diameter of the oesophagus, where size increases as the child gets older. Such differences may impact the total transit time, where content is emptied into the stomach quicker in younger children due to the shorter oesophagus. This may have a more significant affect when the patient is in a specific anatomical position, since it has been established that the oesophageal transit time (OTT) varies when in different anatomical positions (90°, 45° and 0°, respectively) (Cordova-Fraga et al., 2008). It would also be important to note that, although peristatic movements are present by the second trimester, the spread of peristalsis and the lower oesophageal sphincter is immature at birth, resulting in frequent symptoms of Gastro oesophageal Reflux Disease (GORD) during neonatal age (Margolis and Picoraro, 2017). This may not only vary transit time but also alter the total amount of drug actually reaching the stomach as some contents may be expelled out of the mouth when regurgitating.

2.3. Stomach

The stomach continues to digest and break the food down into a more liquid state before transferring the contents into the intestines; it is at this point where differences in stomach physiology (gastric pH, fluid volume and gastric emptying time) between paediatrics and adults may affect the absorption of pharmacological substances, especially those that are absorbed in the stomach (theoretically, weakly acidic drugs). Gastric acid secretion begins shortly after birth, gently increasing over several hours. In preterm infants, gastric acid secretion occurs more slowly, with the highest concentration observed by the fourth day of life (Bar-Shalom and Rose, 2014). The secretion of gastric acid during infancy is lower compared to adults, resulting in a higher gastric pH. At birth, gastric pH is neutral but drops to pH 1–3 within 24–48 h. The pH then slowly returns to neutral by day 8, thereafter gradually declining and reaching adult values only after the age of 2 years (Lu and Rosenbaum, 2014). Therefore, drugs (e.g. phenytoin and phenobarbital) that would fully be in its un-dissociated form and readily absorbed in the acidic gastric contents, may result in decreased bioavailability in children due to the higher gastric pH levels (Lu and Rosenbaum, 2014). In contrast, increased pH values may provide a protective effect on acid-labile drugs and encourage increased bioavailability of weak bases such as penicillin and ampicillin (Lu and Rosenbaum, 2014).

Although some absorption takes within the stomach, majority of the absorption takes place within the small intestines and therefore, gastric emptying and intestinal motility are rate limiting steps for absorption. Compared to adults, gastric emptying in new-borns and neonates is reduced and variable. This increase in gastric emptying time, alongside a shorter gut transit time and reduced intestinal absorption surface area may result in delayed absorption within the neonatal population (Lu and Rosenbaum, 2014). Furthermore, the duration of a drug's exposure to the highly acidic gastric environment is dependent on the gastric emptying time, this may also potentially alter the total drug absorption depending on its physicochemical properties.

In addition, the capacity of the stomach also increases with age from 10 to 20 mL in neonates, 200 mL by the age of 2 years and 1500 mL by the age of 16 years. This would be significant for BCS Class II and IV drugs that exhibits low solubility, since larger gastric fluid volumes result in enhanced dissolution values (Bar-Shalom and Rose, 2014; Nader et al., 2016).

2.4. Intestines

Post gastric digestion, the contents then enter the small intestines, where further digestion takes place before the nutrients/drug is absorbed into the systemic blood stream. Within the intestine, intestinal

transit time, intestinal permeability, bile secretion, intestinal microflora and active transport process are all physiological factors in which paediatrics differ from adults, leading to varied drug absorption capabilities between the two populations (Fernandez et al., 2011). The small intestine is classified into three parts; this includes the duodenum, jejunum and ileum. The duodenum makes up the first part of the small intestines and serves to combine food/nutrients with digestive enzymes from the pancreas and bile from the gallbladder. Moving forward, the jejunum is responsible for absorbing nutrients into the bloodstream, while the ileum (last section) connects to the large intestine and also contributes in absorbing nutrients into the bloodstream. At birth, the small intestine measure in around 300 – 350 cm, gradually increasing to 500 cm at age 10 and reaching adults level by the age of 20 years (Weaver et al., 1991).

In addition to the formation and secretion of faeces, the large intestine is also responsible for the absorption of water, electrolytes and vitamins. In children below the age of 2 years, the large intestine measures in around 52 cm, increasing to 73 cm at 4–6 years and 95 cm at 9–11 years (Mirjalili et al., 2017). In newborns, the small intestine measures between 300 and 350 cm, with quantitatively significantly reduced circular folds (plicae circulares) (Lander and Newman, 2013). These folds increase surface area for absorption and increase intestinal transit time by retarding the movement of semi digested food, allowing for effective digestion and sufficient absorption to occur.

Intestinal permeability describes the passage of material from the intestines into the rest of the body. At birth, the intestinal permeability is high, with rates three to four fold higher compared to adults (Ginsberg et al., 2004). This may be due to the immature intestinal mucosa that results in a defective mucosal barrier (Michielan and D'Incà, 2015). Permeability then begins to decrease in infancy and is expected to reach levels comparable to adults early in childhood (McOmber et al., 2010).

The GI tract is colonised by a wide range of microorganisms which affect various physiological process. Both metabolism and GI motility are under the influence of gut flora and changes in bacterial colonisation can result in altered bioavailability (Batchelor and Marriott, 2015). The composition of microbiota found in paediatrics is significantly different to that of adults, where microbial quantities vary as a result of physiological differences (Khonsari et al., 2016). A study by Hollister et al. (2015) concluded that the child's gut possessed greater quantities of microbes supporting the functions of development, where microbes relating to inflammation and obesity, such as Segmented Filamentous Bacteria (SFB) and bacterial species from the Firmicutes phylum were found at a higher concentration in adults (Hollister et al., 2015; Ericsson et al., 2014; Castaner et al., 2018). Levels of intestinal microbiota in paediatrics were thought to reach adult levels in between the ages of 1–3 years; however, more recent studies suggest otherwise and indicate an adult-like gut flora environment to establish at a later age of 4 years (Hollister et al., 2015; Ringel-Kulka et al., 2013).

Active transport systems involves the movement of substances across membranes and determines the absorption of molecules. At birth, these transport systems are immature, resulting in variable absorption values. Both active and passive transport systems completely mature at around the age of 4 months (Mulberg et al., 2013). P-glycoprotein (P-gp) is a plasma membrane protein that pumps drugs/substances out of the cell. P-gp is accountable for restricting cellular uptake and distribution of toxic substances; hence, its influence on drug absorption, metabolism, distribution and elimination is substantial (Amin, 2013). It has been reported that intestinal and hepatic p-gp expression at birth is limited, intensifying during the first few months of life and reaching adult levels by the age of 2 years (Lu and Rosenbaum, 2014; Maternal, 2017). However, within the paediatric population, the origin and development of P-gp expression is speculative, where contrasting results have emerged in which intestinal and hepatic P-gp expression values reaching adult levels are reported to be at the age of 0 and 12 months, respectively (Prasad et al., 2016; Fakhoury et al., 2005) (Table 1 and Fig. 1).

Table 1
An overview of the anatomical and physiological differences of components of the gastrointestinal tract observed between paediatrics and adults.

Anatomical and physiological differences of the gastrointestinal (GI) tract	Paediatrics	Adults
Oral cavity	Tongue: short and broad in newborns Tongue: Proportionally larger in young children Soft palate in contact with epiglottis Epiglottis: longer, floppy and U shaped Larynx: situated more anterior and superior	Tongue: proportionally smaller Soft palate and epiglottis contact lost Epiglottis: shorter and stiff Larynx: posterior and lower
Oesophagus	Neonates: measures at ≈ 18 cm Age 3: measures at ≈ 20 cm Vertebral column location: C4 – T9	Measures at ≈ 25 cm Vertebral column location: C6 – T11
Stomach		
Anatomical	Neonatal capacity: 10–20 mL Age 2 capacity: 200 mL	≥ 16 years capacity: 1500 mL
Physiological	Gastric pH: neutral at birth Gastric emptying rate: ↓ and linear (until 6–8 months)	Gastric pH: 2–3 Gastric emptying: ↑ and bi-phasic
Small intestine		
Anatomical	At birth: measures ≈ 300–350 cm Age 10: measures ≈ 500 cm Reduced number of circular folds Reduced absorptive surface area	≥ 20 years: measures at 575 cm Increased circular folds Higher absorptive surface area
Physiological	Intestinal permeability: 3–4 fold greater at birth Microbiota: Higher levels of microbes supporting developmental processes (e.g. mean bifidobacteria levels in infants: $4.4 \pm 8.6 \times 10^{10}$ CFU/g^{-1}) Transport system: P-gp limited during birth Intestinal transit time: ↑ in neonates and ↓during infancy Bile salt secretion and activity: ↓ in neonates and infants	Intestinal permeability: mature Microbiota: Mean levels of bifidobacteria: $1.03 \pm 1.7 \times 10^{9}$ CFU/g^{-1} Transport systems: mature Bile salt secretion and activity: mature

3. Paediatric pharmacokinetics

As the anatomy and physiology evolves in paediatrics with age so do the pharmacokinetic considerations; pharmacokinetic profiles are non-linear, where anatomical and physiological differences in children can affect the pharmacokinetic profile (Batchelor and Marriott, 2015). Pharmacokinetics (PK) studies the extent of absorption, distribution, metabolism and elimination of the pharmacological substance under review. The variance in pharmacokinetic profiles between children and adults can have a considerable effect on the resulting concentration of the pharmacological substance under review, whether that be a drug or an excipient. Careful dose titrations and adjustments must therefore be carried out accordingly in respect to all of the constituents involved in the formulation intended to be administered.

Although there has been a substantial increase of data available on pharmacokinetic drug profiles, the influence of certain age specific age-related effects on PK profiles and dose requirements is not well understood and continues to exist (Lu and Rosenbaum, 2014). Similarly, many

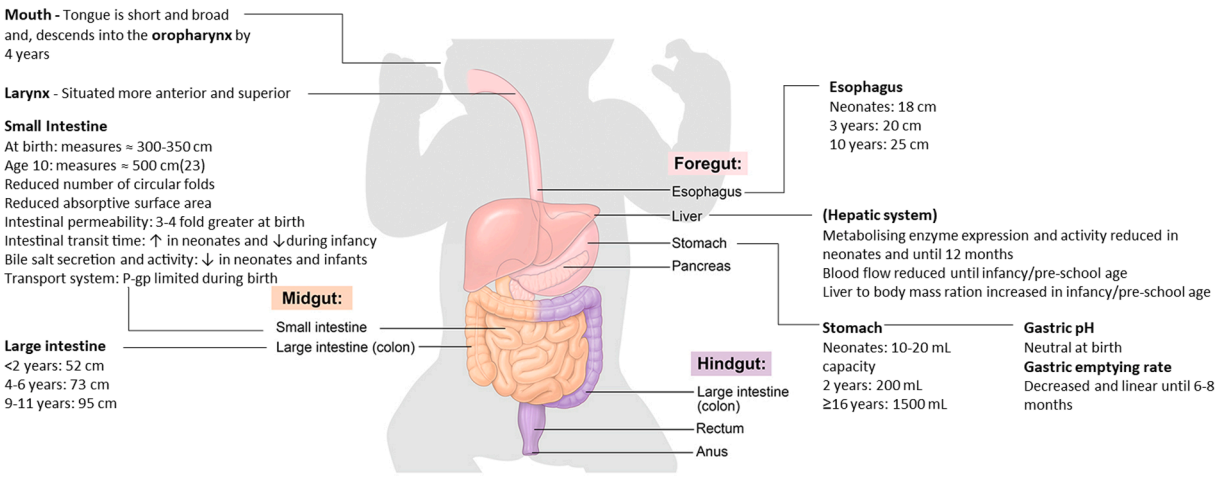

Fig. 1. Diagram showing the anatomical and physiological differences of the paediatric gastrointestinal tract when compared to that of an adult. Figure adapted from Leach, J. (2020), "Fetal development: your baby's digestive system.

commonly used pharmaceutical excipients have undergone comprehensive short and long term studies for safety and toxicity in adult population, but not in paediatrics, whilst it has also been established that pharmaceutical excipients are not inert and can lead to considerable adverse effects if administered in concentrations above specified values (Yochana et al., 2012). Therefore, selection of such excipients is encouraged to be based on research and guided by agencies such as the European Medicines Agency (EMA), where problematic excipients are identified and maximum daily intake values are specified. Furthermore, the dearth of authorised medicinal formulations available to paediatrics has led to the extensive use of unlicensed and off-label medicines, where excipient composition and load that is suitable and safe for paediatric patients is not guaranteed (Van Riet-Nales et al., 2017).

The anatomical and physiological differences observed between paediatrics and adults may significantly alter the pharmacokinetic profile of both drugs and excipients. Therefore, detailed understanding of implications of such differences is important in order to guide safe and acceptable daily intake values.

3.1. Absorption

Absorption – the first physiological process that governs the degree of bioavailability – can vary significantly due to differences in gastrointestinal (GI) tract development. Factors affecting extent of absorption include surface area available, intestinal permeability, gastric pH, gastric empting, GI motility and immaturity of intestinal mucosa, transport systems and secretion of bile (Fernandez et al., 2011). Gastric pH at birth is reported to be neutral (pH 7), where it then significantly decreases before returning back to neutral by the tenth day (Bartelink et al., 2006). Furthermore, gastric pH levels of 2–3, as observed in adults, are achieved in children by the age of 3 years (Stewart and Hampton, 1987). As a result of this change in gastric pH during growth and development, absorption and concentration of weakly basic, weak organic acids and/or acid labile pharmacological substances can significantly vary (Lange et al., 1997). The rate of gastric emptying in paediatrics up to the age of 6–8 months is slow and linear, where after this point proceeds to become bi-phasic, as observed in adults (Fernandez et al., 2011).

Intestinal transit (IT) is key for absorption and involves the travel of substances through the small intestine. In neonates, an increased IT time is observed owing to reduced GI motility and frequency of peristaltic waves, whereas during infancy, GI motility intensifies, resulting in a lower IT time (Strolin Benedetti and Baltes, 2003). As a consequence of short IT times, the pharmacological substance under review may not have sufficient time to fully absorb via active and passive transporters and, therefore, may result in decreased concentrations. Bile salts are manufactured in the liver from cholesterol and serve to solubilise dietary fats within the aqueous conditions of the small intestines. Bile salts are comprised of bile acids coupled with taurine/glycine, increasing the water solubilising power of the bile salts, suggesting a positive correlation between that of bile salt concentration and pharmacological drug/substance solubility (Moini, 2019). Within the lower subsets of the paediatric population (neonates and infants), the secretion of bile salts is hindered, resulting in a decreased ability to solubilise and absorb fat soluble substances and lipophilic drugs (e.g. carvedilol) (Arzani et al., 2015). Maturation of bile secretion and activity is achieved after 3–7 months post-natal. Therefore, careful dose determination and titration must be implemented (Shaffer et al., 1985).

3.2. Distribution

Following absorption, the substance then distributes relative to its physicochemical features. As a child grows and develops, total water (both intra and extracellular) concentration decreases, from around 80–90% v/w in neonates and infants, down to 55–60% v/w in adults (McLeod et al., 1992). Volume of distribution of hydrophilic substances (e.g. phenobarbital) would, therefore, vary as a consequence of body water content, with neonates (having the greatest volume of distribution) requiring larger doses per weight of such compounds to achieve an equivalent therapeutic response to that of an adult (Jailing, 1974). Additionally, the development of the blood brain barrier (BBB) in neonates is immature, thereby significantly increasing the risk of toxicity of substances (drugs and/or excipients) due to high levels entering the central nervous system(CNS) (Sanders et al., 2009). This is particularly common with several commonly used functional excipients, such as ethanol and propylene glycol (Valeur et al., 2018). Furthermore, the fraction of unbound drug found in neonates is higher compared to adults, due to the decreased plasma protein binding capacity, suggesting an increase in amount of pharmacological substance available for activity (Ku and Smith, 2015). Doses should, therefore, be determined with caution and in respect to the target age group to avoid toxicity.

3.3. Metabolism

The liver is predominantly the organ responsible for metabolism, where drug is metabolised into rather non-toxic and more water-soluble compounds, reducing toxicity and assisting excretion via urine and bile. In neonates, metabolising enzymes are immature, leading to supressed enzyme expression and activity, thereby increasing potential for substance accumulation (toxicity) (Zanger and Schwab, 2013).

Cytochromes P450 (CYPs) are a class of enzymes that serve to metabolise toxic substances and drugs through oxidation, so they may safely be excreted from the body. However, the amount of CYP metabolising enzymes in children aged between 6 and 12 months is around 50% to that of adults (de Wildt et al., 1999). Another factor influencing hepatic clearance is the amount of blood flow through the liver; the hepatic blood flow in a neonate is reduced, where it then reaches a rate comparable to adults by infancy/pre-school age. Nonetheless, the hepatic clearance of pharmacological substances during infancy/pre-school age is significantly increased due to a greater liver size to body weight ratio (Gibbs et al., 1997). Pharmacological substances undergoing high degree of metabolism are especially affected (e.g. allopurinol and benzyl alcohol) (Lammert et al., 2010; EMA, 2017).

3.4. Elimination

Elimination is the process in which the drug/substance and their metabolites are excreted from the body, predominately through the kidneys. Determinants affecting the rate and extent of elimination include glomerular filtration rate (GFR), tubular secretion and tubular reabsorption, which vary as a consequence of renal blood and plasma flow (Ku and Smith, 2015; Davis, 2018). In newborns, the renal excretion is at its lowest, gradually increasing as the renal system matures. Renal blood flow also increases with age, where values comparable to those of adults are achieved by the age of 2 years (Gandhi et al., 2011). These changes in blood flow can alter the rate of excretion; therefore, the dose of substance being administered needs to be adjusted. GFR describes how well the kidneys are working by measuring the rate of blood flowing through the glomeruli; at birth, the GFR is at its lowest, increasing rapidly during the first two weeks and reaching adult levels by the age of 1 years as a result of maturation (Muhari-Stark and Burckart, 2018). It is also important to mention that the rate of increase in GFR during early days of life also varies depending on whether the baby is born before or after the 37 weeks gestation (pre-term/term). Tubular reabsorption is an occurrence in which the filtrate is absorbed back into the systemic bloodstream; tubular reabsorption increases with age, with peak maturation taking place between the age of 1–3 years (Tayman et al., 2011). Similarly, active tubular secretion is also immature in newborns, with values comparable to adults achieved by the age of 7–12 months (Strolin Benedetti et al., 2005). Furthermore, the reabsorption of weak acids (e.g. citric acid) is under the influence of urinary pH, with a higher reabsorption of weak organic acids taking place at lower pH values, as in the case of neonates and infants (Alcorn and Mcnamara, 2008). The most common route of elimination of substances is through the kidneys; however, some are actively secreted into the bile by the liver before being excreted in faeces. Many factors determine the extent and route of excretion and include water solubility, molecular weight and plasma protein binding (Lu et al., 2019). As discussed, paediatrics and adults can have significantly varying PK profiles as a consequence of differences in hepatic and renal system anatomy and physiology; as a result, pharmacological substances intended for adult use cannot be assumed to be labelled as safe in paediatrics (Table 2).

4. Paediatric dosage forms- benefits and limitations

Pharmacokinetic profiles within the paediatric population are not only affected by the anatomical and philological differences but also by dosage form design which can affect adherence and compliance. This sections covers some examples of commercial dosage forms readily used in paediatric medicine, considering their benefits and limitations, especially with the perspective of safety, quality and efficacy.

4.1. Paediatric dosage forms

The current trend in paediatric formulation development is towards age-appropriate dosage forms, with considerations for acceptability, safety and capability of providing variable and accurate doses according to the child's specification. Furthermore, the dosage form must exhibit acceptable palatability, contain appropriate excipients and be regulatory compliant (Gerrard et al., 2019). Several oral dosage forms intended for paediatric oral administration exist and include both solid (tablet, capsules, orodispersible formulations, powder for reconstitution and chewable tablets) and liquid (solutions, suspensions, elixirs and syrups) dosage forms. Solid dosage forms remain as the preferred choice

Table 2
Differences in hepatic and renal system physiology between children and adults and subsequent pharmacokinetic effect on commonly used pharmaceutical excipients.

Differences in hepatic and renal system anatomy and physiology	Neonates (1 day to 1 month)	Infant (1 month to 2 years)	Adults	Effect on Pharmacokinetic profile	Types of Excipients affected	Example Excipient
Hepatic system *(metabolism)*						
Metabolising enzymes (CYPs) expression and activity	Immature	Reduced (until 12 months)	Increased	Reduced metabolism	Those metabolised through CYP enzyme family	Ethanol *(solvent)*
Blood flow through liver	Lowest	Adult levels	Increased	Reduced hepatic clearance until infancy/pre-school age	Those undergoing high degree of metabolism	Propylene Glycol *(solvent)*
Liver to body mass ratio	Smaller	Larger (in infants and pre-school children)	Smaller	Increased hepatic clearance in children (infants and pre-school) ↓ AUC (plasma drug concentration over time)	Those undergoing high degree of metabolism	Benzyl alcohol *(preservative)*
First pass metabolism	Decreased	Increased (due to liver to body mass ratio)	Increased	↑ Bioavailability	Those undergoing significant first pass metabolism	Fructose *(sweetener)*
Renal system *(elimination)*						
GFR	Reduced (up to the age of 12 months)	Adult levels reached by 12 months	Increased but decreases in the elderly	Slower elimination up to the age of 12 months ↑ Levels in blood	Those renal excreted	Cyclodextrins *(solubility enhancer)*
Maturation of tubular transport (reabsorption/ secretion) system	Reabsorption – Immature Secretion - Immature	Reabsorption- Adult levels reached by 1–3 year Secretion – Adult levels reached by 12 months	Increased	↑ Tubular reabsorption with age ↑ Tubular secretion with age	Disposed to tubular reabsorption/ secretion	Glucose *(sweetener)*, Sodium bicarbonate *(alkalizing agent)*, Propylene glycol
Urinary pH value	Decreased	Decreased	Increased	↑ Reabsorption at lower pH values	Weak acids/bases	Citric acid *(antioxidant)*

of formulation for pharmaceutical industry owing to its advantages of long-term stability, manufacturing flexibility (including the ability to film coat and control API release) and overall low production cost (Lopez et al., 2015).

4.2. Traditional tablets and capsules

Standard tablets and capsules have some major drawbacks within the paediatric population; having a fixed dose content means that only a small range of the target population can be treated, as most paediatric doses are based on child weight. The other key disadvantage arises simply from the inability of children to swallow such large dosage forms, although this is more of a concern in the lower sub-set of the population, where the risks of choking and aspiration are drastically increased (Kernell et al., 2018).

4.3. Chewable tablets

Chewable tablets are intended to be chewed before swallowing, making them a popular choice among individuals with phagophobia (fear of swallowing). Additionally, where possible, such tablets may also be swallowed whole considering, bioavailability is not affected (Batchelor and Marriott, 2015). However, the minimum age for safe use of chewable tablets is recommended from 2 years and above, due to the risk of choking in younger populations (Michele et al., 2002). As for standard tablets and capsules, chewable tablets are also limited by the lack of dose flexibility. In addition, since these tablets are designed to be chewed before swallowing, coating techniques to taste mask and control API release becomes a greater challenge (Walsh et al., 2014).

When developing chewable tablets, certain criteria must be met to ensure medicinal compliance and adherence is achieved. Palatability is of utmost importance in chewable tablets, as the tablets will fragment within the oral cavity and activate taste receptors upon contact with saliva (Mennella et al., 2013). Furthermore, chewable tablets must exhibit mechanical properties in which the tablet can easily be chewed without compromising its friability profile (FDA, 2018).

4.4. Orally disintegrating tablets (ODTs)/mini tablets (mini ODTs)

The term orodispersible tablet, refers to tablets that are intended to quickly disintegrate in the oral cavity in the presence of saliva. However, to label a tablet as an ODT, the FDA has suggested a disintegration time of 30 s and a maximum tablet weight of 500 mg (Parikh, 2016). ODTs are emerging as a popular choice amongst paediatrics and health care professionals, as they have proven to improve patient compliance (Dey and Maiti, 2010). After liquid preparations, ODTs are the dosage form of choice, with small size and fast disintegration times being identified as the most ideal characteristics (Alyami et al., 2018). Rapid disintegration times will reduce the administration process period and, therefore, encourage medicine adherence. Similar to chewable tablets, the palatability of ODTs is crucial, as children will associate the taste of the tablets each time they need to take their medication. ODTs improve swallowability and exhibit appropriate stability profiles without the use of functional excipients (e.g. preservatives), as in the case of liquid formulations. However, once again ODTs are limited due to their rigid dose content.

Since the European Medicine Authority (EMA) set up regulations for developing age-appropriate formulations, the development of orally disintegrating mini tablets (mini ODTs) has widely gained recognition (Lura et al., 2019). A mini tablet is referred to as a tablet with a diameter equal to/less than 4 mm (van Riet-Nales et al., 2016). The superiority of mini ODTs stems from their flexible dosing ability, where each unit dose incorporates a small concentration of active therapeutic substance, which can be taken either as a single tablet or as multiple tablets to fulfil higher dose requirements. Furthermore, for the upper end of the paediatric population, mini-tablets can be enclosed into capsules or compressed into a larger tablet to avoid the need to take multiple tablet units (Lopes et al., 2006). Mini ODTs hold advantages inherent to both liquid and solid dosage forms, while achieving dose flexibility, resulting in a dosage form that fulfils the definition of an age-appropriate formulation that can be utilised throughout the whole paediatric population (O'Brien et al., 2019).

4.5. Innovative solid dosage forms - Multi-particulate dosage forms (MDF)

Multi-particulate drug administration systems, usually presented in a sachet or encapsulated in a capsule, are tiny distinct units of pharmacologically active compounds, each demonstrating an extent of therapeutic response. Such dosage forms are usually intended to be reconstituted with liquid or sprinkled over soft foods, such as apple sauce, yogurt and pudding. Liquid vehicles include milk, water or juice. The discrete size of MDF improves swallowability, while their multi-particulate composition allows for increased dose flexibility. Additionally, owing to their small size, multi-particulates are evenly distributed along the GI tract, thereby improving bioavailability and minimising the occurrence of local irritation and toxicity (Martinez Teran et al., 2017). Due to their solid-sate, MDF do not require stabilising agents (e.g. preservatives and antioxidant), which have shown to be problematic excipients within the paediatric population. Co-administrating with food can promote medicine adherence by masking any unpleasant tastes; however, co –administration with foods and drinks may alter the absorption and potentially the bioavailability of the drug, leading to either reduced or increased therapeutic effects (Arcangelo et al., 2006). Moreover, reconstituting/mixing can at times lead to incomplete ingestion of the drug, if the entire quantity in which it is mixed is not administered. Lastly, while manufacturing technologies to produce such dosage forms are widely available, packaging and dosing requirements may call for more specialised equipment and accessories, significantly increasing cost (Lopez et al., 2015).

4.6. Liquid formulations

Liquid formulations comprise of solutions, suspensions, elixirs, syrups, drops and emulsions. Owing to their superior ability for dose flexibility and ease of swallowing, such dosage forms are most applicable and favoured in the lower subsets of the paediatric population (up to 8 years), who are incapable or find difficulty in swallowing solid dosage forms. The capability of flexible dosing in liquid formulations allows for administration throughout the whole paediatric population, from neonates up to adolescence (EMA, 2013).

Solutions are homogenous mixtures, where the solute is completely dissolved within the solvent. In contrasts, suspensions are heterogeneous, where the composition of components is non uniform and subject to separation and, therefore, require shaking prior to administration. Suspensions are chosen over solutions when the drug under review is insoluble in water and where use of solubilising agents is not possible (Edman, 1994). Emulsions are similar to suspensions; however, the mixture is comprised of two immiscible liquids and usually include an emulsifier such as polysorbates, lecithin and/or mono –and diglycerides. Syrups on the other hand are highly concentrated sugar solutions, with or without a medicinal substance that are usually directed for paediatrics and drugs with disagreeable taste. Paediatric drops are liquid preparations (either in the form of a solution or suspension) intended to be administered in minute doses using a calibrated dropper (Singh, 2007). Lastly, elixirs are similar to solutions, but differ due to the fact they are sweetened, clear hydro-alcoholic liquids, with varying degree of alcohol added to maintain and evenly distribute drug particles (Lowry, 2012).

The principal challenge associated with medicinal adherence in children is palatability, which includes and is influenced by taste, smell, texture and appearance (Sørensen et al., 2003). It has been revealed that

more than 90% of paediatricians linked non-adherence to drugs that are bitter and unpalatable (Milne and Bruss, 2008). Compared to solid dosage forms, this is more of a concern in liquid formulations, since simple taste masking techniques are at times not sufficient, resulting in bitter tasting formulations. Additionally, in regards to liquid preparations the dosing volume is also of significant importance when determining acceptability, where target volumes for children under 5 years is ≤5 mL, and ≤10 mL for children above the age of 5 years (Rose and Van den Anker, 2007). However, the EMA draft guidance suggests a maximum dose volume of 5 mL for children under 4 years of age and 10 mL in children between 4 and 12 years (EMA, 2013). Due to the complex nature of liquid formulations, several functional excipients are utilised to assist manufacturing processes and optimise the formulation to promote and enhance stability and palatability (Batchelor and Marriott, 2015). These include preservatives, solvents, solubilising agents, sweeteners, flavourings and colourants. However, such excipients are known to be 'problematic' and have undergone very few clinical/toxicity studies in paediatrics, resulting in unknown possibilities of observing potential adverse effects, such as hypersensitivity reactions, CNS effects and jaundice (Anna Burgess, 2017). As a result, the inclusion of such excipients should be justified and, where possible, limited/avoided. Furthermore, in comparison to solid dosage forms, the storage and handling cost of liquids is very high due to the bulky nature of the bottles and requirements of storing conditions, such as refrigerating and using high-density polyethylene bottles (Campbell and Vallejo, 2015). Additional, safety features such as child resistant caps and special amber type glass bottles further add to the cost. Lastly, very few controlled release liquid preparations are available, suggesting the need to dose several times a day. Certainly, an increase in dosing frequency leads to a decrease in adherence, as the administration process, which is found unenjoyable by many, would need to be repeated more times (El-Rachidi et al., 2017). A simpler dosing regimen (once or twice daily) would also limit the inconvenience caused to children and caregivers who have to carry their medicines to school.

Regarding stability, liquid preparations require many considerations. Other than the inclusion of antioxidants and preservatives, many liquid formulations require to be refrigerated at temperatures of 5 °C (±3 °C) (NHS PQAC, 2014). This may prove to be problematic in developing countries where access to refrigeration may not be possible. Moreover, such formulations may not be suitable in countries with a warmer climate as high temperatures may result in immediate product degradation when removed from storage conditions. This not only adds to medicine handling complications but leads to excess wastage where many products may need to be replaced owing to incorrect storage. Another disadvantage of liquid formulations, is their relatively short shelf life, with an even shorter in-use shelf life (e.g. Amoxicillin Oral Suspension only has a 7 day shelf life when reconstituted).

Liquid formulations have been perceived to be the most suitable dosage from type in paediatrics, since a flexible 'sweet tasting liquid' is thought to be preferred over solids in young children (Hoppu, 2016). Globally, this has been the norm, where pharmaceutical industries opt for liquid formulations when the medicine is to be given via oral cavity. However, as more studies have been carried out to assess acceptability, results show otherwise and flexible solid dosage forms show superiority.

4.7. Acceptability of innovative small flexible solid oral dosage forms

Small flexible solid oral dosage forms maintain the dose flexibility of liquid preparations, while exhibiting desirable characteristics of solid dosage forms, including stability and the ability to taste mask and modify drug release. Thus, such dosage forms suggest a promising alternative to the widely accepted liquid dosage forms.

A randomised cross over study carried out by van Riet-Nales et al. (2013) concluded the preference of small 4 mm tablets in domiciliary infants and preschool children over powders, suspensions and syrups. Kilingmann et al. conducted a series of randomised cross over studies comparing the acceptability of a 2 mm mini–tablet against sweet syrup; the first study compared an uncoated 2 mm tablet against 3 mL of syrup in a total of 306 children aged between 6 months and 5 years. No adverse events occurred and results showed that the uncoated 2 mm tablet was more accepted over the syrup (Klingmann et al., 2013). The second study compared the acceptability of a 2 mm uncoated mini-tablet and 0.5 mL of syrup in neonates (2–28 days). Out of 151 neonates, all showed competency in swallowing the mini-tablet, with increased levels of swallowability compared to the syrup (Klingmann et al., 2015).

Studies by Spomer et al. (2012) and Thomson et al. (2009) explored and assessed the acceptability and suitability of placebo mini-tablets for children up to the age of preschool (6 years); results showed that the acceptance of mini-tablets was higher or equal to that of the syrup Table 3.

These results suggest that small solid dosage forms are actually preferred in children over liquid formulations, shifting the paradigm to small flexible solid oral dosage forms, as proposed by the World Health Organization (Klingmann et al., 2015). In addition to preferring flexible solid paediatric formulations as mentioned earlier, a switch to such dosage forms also provides an opportunity to improve the availability of age-appropriate paediatric medicines in both first and third world countries. This would come as a result of reduced costs of manufacturing and logistics, which are usually associated with liquid formulations but not solid dosage forms.

4.8. Future of paediatric formulations

The World Health Organization (WHO) has considered flexible solid oral dosage forms as the most suitable dosage form for children (Kristensen, 2012). Preparations include orodispersible, chewable and soluble tablets. Such dosage forms relieve the stresses of swallowing, as the dosage form is intended to disperse in the mouth/liquid before swallowing. Flexible solid oral dosage forms hold advantages inherent to both liquid (flexible dosing capabilities and ease of swallowing) and solid (formulation stability and low production cost) dosage forms, while minimising their respective disadvantages (Lopez et al., 2015). Currently, the focus of developing age-appropriate formulations is with flexible solid dosage forms that are easy to swallow and well accepted throughout the whole paediatric population (EMA, 2006; Lajoinie et al., 2017). Progressively, paediatric oral formulations will be present as convenient and palatable single- use multi-particulate dosage forms (MDFs) including mini-tablets, orally dispersible tablets, mini-orally disintegrating tablets, granules, sprinkles and powders, with an excipient composition and load systematically elected for paediatrics (Strickley, 2019).

To encourage the development of flexible solid oral dosage forms, the LENA (Labelling of Enalapril from Neonates up to Adolescents) project was collaboratively initiated within Europe. The aim of the LENA project was to develop and clinically evaluate a novel age-appropriate solid oral drug formulation of enalapril. Subsequently, many developments of a novel formulation of enalapril orodispersible mini-tablets (ODMT) have taken place with a potential eligibility for a Paediatric Use Marketing Authorisation (PUMA) (Faisal et al., 2019; Thabet et al., 2018; Bajcetic et al., 2019).

5. Factors affecting paediatric adherence and acceptability

For safe and effective pharmacotherapy, it is vital for paediatrics to adhere and comply with their regimen, ensuring accurate quantities and volumes during administration. The dosage forms design is especially important since it will dictate the willingness and ability of children to take their medicines. In addition to formulation related factors, the adherence and acceptability of dosage forms is markedly under influence by patient and disease related factors including age and whether the treatment is for an acute or chronic condition.

The WHO suggests that around 50% of medication issued for long-

Table 3
Studies evaluating the acceptability of innovative small flexible solid oral dosage forms.

Author	Year	Study type	Population age (years)	Population size	Tablet size	Outcome/Acceptance of mini-tablet
Thomson et al.	2009	Randomised crossover study	2–6	100	3 mm	*Acceptance:* Age 2 years: 46% Age 3 years: 53% Age 5 years: 85%
Spomer et al	2012	Random two-way cross-over exploratory pilot study	0.5–6	60	2 mm	Mini-tablets preferred over sweet liquid formulation
van Riet-Nales et al	2013	Randomised crossover study	1–4	148	4 mm	Mini-tablet Preferred over powder, suspension and syrup
Kilingmann et al	2013	Randomised crossover study	0.5–5	306	2 mm	Mini-tablets more acceptable than liquid formulation
Kilingmann et al	2015	Randomised crossover study	2–28 days	151	2 mm	Level of swallowability higher for mini-tablets

term conditions is not taken as advised (Chisholm-Burns and Spivey, 2012). Medicine adherence assumes a consensus between the patient and the health care practitioner and can be defined as the extent to which the patient follows the agreed recommendations. High levels of medicine adherence ensures maximum possible therapeutic benefit, improves prognosis and overall condition (clinical output) and enhances quality of life. In contrast, consequences of non-adherence include treatment failure, deteriorating condition, related psychosocial effects and increased health care costs (Chisholm-Burns and Spivey, 2012). Apart from patient related factors, non-adherence may occur as a result of limitations in the drug delivery system or factors associated with the disease. Therefore, to improve adherence, paediatricians and pharmaceutical formulators should understand children's perspectives of medicines and collaboratively explore and address any limiting features in the delivery of the health care. In paediatrics, acceptability is not just limited to the child's ability and willingness to use the medicine, but also the ability and extent of compliance of the parent/caregiver to administer the drug as intended (Ranmal et al., 2018).

Non-adherence is usually described as either intentional or unintentional non-adherence. Intentional non-adherence is more common in older children and is when the child autonomously decides not to follow their agreed treatment recommendations; this is usually a consequence of patient related factors, such as social stigma and denial (Katz et al., 2013). Unintentional non-adherence is where the patient wants to follow the agreed recommendations, but is unable to do so and is limited by factors which are beyond one's control, such as unpalatability, level of development and required dose.

5.1. Patient related factors

The age of the child is a key factor when determining medicine adherence and acceptability. In the lower subsets of the paediatric population, children depend upon on their parents/caregivers; therefore, contributions and success are a direct reflection of the parents' ability to administer and follow treatment recommendations. Some reasons described by parents/caregivers for not following treatment advice include stopping medicine when symptoms improve, forgetfulness, misinterpretation of instructions and non-compliance of child (Burkhart and Sabaté, 2003). As the child grows and matures, they progressively begin to take ownership and responsibility of their treatment. This comes as a result of greater autonomy, where the child develops the capacity to make their own decisions. In regards to formulation acceptability, differences are observed between paediatric subgroups, where younger populations are unable to swallow solid dosage forms due to their immaturity and lack of motor and cognitive skills development (EMA, 2006). Other extensive differences observed between children that impact both adherence and acceptability include developmental changes/stages, disease perception, competency and biological changes (EMA, 2006). Due to the heterogeneity observed in children, the EMA has led to the grouping of the paediatric population into five subsets (preterm neonates, term neonates (2–28 days), infants and toddler (1–23 months), children (2–11 years) and adolescents (12–16/18 years))(15) (EMA, 2006). Each subset have unique requirements and, therefore, the age-appropriateness of a paediatric specific dosage form type should be assessed based on capability, suitability of the dosage form and incorporation of appropriate excipients in regards to the target paediatric subset (van Riet-Nales et al., 2011).

5.2. Formulation related factors

Palatability is the overall recognition of the dosage form in relation to its aesthetic appeal. Children have a reduced tolerance for displeasing taste that leads to unwillingness and non-adherence; therefore, as pharmaceutical manufacturers, it is important to effectively minimise any unpalatable and bitter formulations. Several taste masking techniques are available that mask unpleasant taste and include complexation, microencapsulation or addition of flavourings and sweetening agents (Zheng et al., 2018). However, many flavours and sweeteners have led to adverse effects, hence their inclusions within the formulation should be justified. Moreover, both the drug and the excipients can impact and influence the palatability of the final dosage form; therefore, careful consideration should be taken when selecting constituents for paediatric specific drug dosage forms. Taste and texture are regarded as the most important factors when determining medicine acceptability, due to their effects on the overall taste sensation and capacity of mastication (Shabir et al., 2012). Texture usually stipulates the relative content of different sized particles that result in a smooth, rough, gritty or slimy feel. Several studies have shown the influence of taste and texture on acceptability, where certain formulations were more acceptable than others due to taste and texture differences (van Riet-Nales et al., 2013; Gee and Hagemann, 2007). Palatability, as discussed, is crucial in both short-term and long-term paediatric medicine adherence; however, other crucial characteristics associated with long-term conditions include required dose (quantity/volume), excipient safety and convenience of dosage form.

The dose frequency and quantity should be tolerable, where once- and twice-daily regimens have shown to significantly improve patient adherence as compared to three to four times daily regimens (Doesch et al., 2010). For liquid formulations, acceptable dosing volumes are considered equal to the volume of a swallow, which is reported to be around 0.27 mL/kg (applicable from 15 months onwards) (Jones and Work, 1961). On the other hand, for soluble tablets, a volume of up to 20 mL is regarded acceptable in children under the age of 4 years, while 50 mL is acceptable in those above 4 years old (EMA, 2013). In regards to tablet size acceptability, the EMA had previously proposed certain measurements that were deemed acceptable in certain age groups (e.g. a 3–5 mm tablet is not acceptable under 2 years); however, these have since been updated and instead the EMA now suggests the acceptability of the size and shape of the tablet to be justified through appropriate studies/clinical evidence (EMA, 2013). Furthermore, since pharmaceutical excipients are not inert, the effect on the accumulation of such compounds should be taken into account and assessed during long-term

treatment to avoid potential adverse effects.

5.3. Disease related factors

Within the paediatric population, important features to be considered when assessing medication acceptability and adherence relating to the disease is whether the treatment is for an acute or chronic (lasting 3 months or more) condition (Lajoinie et al., 2017). It has been reported that children being treated for long-term conditions (such as asthma and HIV) acquire skills to swallow tablets and capsules safely, even from a relatively early age of around 3 years (Yeung and Wong, 2005). These swallowing capabilities arise from repetitive administration, where supporting strategies and practice encourages children, while minimising any psychological fears associated with swallowing. Nevertheless, from a social point of view, peer pressure and child reluctance are factors that may negatively affect medicine adherence in school going children that are being treated for chronic illnesses (Liu et al., 2014). It has been reported that up to approximately 70% of children with chronic conditions have poor medicine adherence because of prolonged treatment durations, symptomatic remission and increased number of medicines (Gardiner and Dvorkin, 2006). Furthermore, unsatisfactory treatment outcomes, toxicity (either due to drug or excipients) and increased frequency of medical complications further contribute to medicine non-adherence, leading to poor clinical outcomes and increased health care costs (Chappell, 2015).

5.4. Overcoming barriers in paediatric medicine non-adherence

Identifying factors affecting medicine non-adherence and acceptability authorises and opportunity to tailor design and production of paediatric specific dosage forms, guarantying appropriate dosage forms, in regards to child age and development, comorbidities and acceptable palatability.

Once- or twice-daily medication regimens have shown to increase compliance rates to more than 80% relative to three-times daily schedules (Eisen et al., 1990). Where possible, modified-release formulations are available and provide longer and patient friendly dosing intervals that improve adherence (Liu et al., 2014). The simplicity and convenience of such dosage forms are especially appreciated by elderly and children that take their medicines to school. However, their use is limited by their fixed dose content, since modified-release formulations cannot be crushed as the active ingredient is intended to be taken as a whole unit. Modified-release multi-particulate dosage forms that are available for flexible dosing include mini-tablets, pellets, beads, granules, microcapsules and microparticles (Al-Hashimi et al., 2018). Children taking multiple tablets (polypharmacy) as in the case of HIV patients have difficulty in adhering to their medication regimens; in such cases, fixed-dose combinations prove beneficial, where several drugs are incorporated into a single unit. However, this may increase the size of the tablet and cause swallowing difficulties (Liu et al., 2014).

Identifying the cause of non-adherence is key in improving adherence, as barriers identified can be individually tackled by physicians, parents and other health care practitioners. Medication adherence is not solely the responsibility of the child and encouraging a “blame-free” environment, improving patient education and assessing health literacy will positively impact medicine adherence (Brown and Bussell, 2011). Behavioural tailoring strategies aim to amend the child’s behaviour towards their treatment and promote positive changes (Costa et al., 2015). Interventions include cognitive–behavioural strategies (such as exposure and relaxation) and Emotion-focused therapy (EFT) (Clarke-smith et al., 2013). Although some reports of improved adherence have been noted with behavioural interventions, firm conclusions cannot be made as evidence is small and inconsistent (Costa et al., 2015; Clarke-smith et al., 2017). Instead, a combination of educational and behavioural techniques have been proposed to improve medication adherence (George et al., 2008). Table 4.

Table 4
Summary of factors affecting paediatric medication adherence and proposed actions to overcome non-adherence.

Barriers in paediatric medication adherence	Proposed actions to improve medication adherence
Patient related factors	
Disease perception	Education intervention
Age and development	Increase availability of age-appropriate formulations
Resistance	Behavioural tailoring strategies
Stigma and denial	Patient education/information counselling
Neurodevelopmental disorders (e.g. ADHD, autism, conduct disorders and cerebral palsy)	Cognitive adaptation training (CAT) Multisystemic therapy (MST) for conduct disorders
Formulation related factors	
Palatability (including taste, texture, appearance and smell)	Formulation based techniques (e.g. taste masking, film coating, inclusion of paediatric compliant excipients)
Dose quantity (including different strengths available for liquid formulations)	Accurate measuring device Ensure patient/parent have identified strength before administration
Dose frequency	Modified-release formulations Fixed-dose combinations Reminders/self-management plans

6. Conclusion

Around one tenth of medicines prescribed for children in general practice are unlicensed (Tomlin et al., 2009). Unlicensed medicines increase levels of non-adherence, as they present several problems such as unpalatability, difficulty in swallowing standard sized tablets and safety concerns with certain excipients (Chappell, 2015). Therefore, it is required that paediatric specific drug delivery systems are available that contain non-toxic excipients, are palatable, grant minimal dosage and frequency, are applicable to all ages and exhibit easy and reliable administration (Nunn and Williams, 2005). In 2007, the paediatric regulation came into force and aimed to improve the health of children in Europe by facilitating the development and availability of medicines for children and increase the number of off-patent medicines being developed and licensed for children. As part of the EU paediatric regulation, the paediatric use marketing authorisation (PUMA) was introduced, with an aim to stimulate research in existing compounds that are off-patent and/or to help transform known off-label use into authorised use. However, regardless of global policy reforms and recent advances in the development of paediatric specific dosage forms, success has been limited, with only 221 new paediatric medicines and indications becoming available in Europe since 2007 (EMA, 2016). The total number of paediatric formulations available only accounts for a small proportion of the full therapeutic plethora required to effectively treat paediatrics and, therefore, the availability of high quality medicines designed for children remains an ongoing challenge.

7. Expert opinion

Considering the extensive variability between the paediatric populations, a systematic approach to paediatric formulation development should be employed to ensure safe and effective treatment, where paediatric specific drug delivery systems are available which contain non-toxic excipients, are palatable, grant minimal dosage and frequency, are applicable to all ages and exhibit easy and reliable administration. Progressively, these will present as convenient and palatable single- use multi-particulate dosage forms (MDFs) including mini-tablets, orally dispersible tablets, mini-orally disintegrating tablets, granules, sprinkles and powders.

Author contributions

Conceptualisation, A.R.M., D.K. (Dilawar Khan), and D.K.; methodology, D.K. (Dilawar Khan); data curation, D.K. (Dilawar Khan); writing—original draft preparation, D.K. (Dilawar Khan); writing—review and editing, A.M., D.K., S.B., M.S., and D.K. (Dilawar Khan); visualisation, A.M., D.K., and D.K. (Dilawar Khan); supervision, A.M. and D.K.; funding acquisition, A.M., D.K., S.B., and M.S. All authors have read and agreed to the published version of the manuscript.

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