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Delivering scents and flavours - lessons from the pharmaceutical industry

Active pharmaceutical ingredients (API) are most frequently administered in oral formulations which must demonstrate an acceptable degree of palatability in addition to the obvious therapeutic value. Oral drug delivery constitutes 70 to 80 percent of the drug delivery market and tablets and capsules, in existence since the nineteenth century, are the most frequently used solid dosage formulations. The drug substance's physicochemical characteristics, the manufacturing method and the excipients added to the formulations all contribute to ensuring therapeutic activity. Many APIs, however, have a bitter, disagreeable taste and may also have an unpleasant odour so whenever drug administration requires the patient to taste the drug, palatability becomes a critical factor in driving patient compliance, prescribing practices, the perceived quality of the drug product, and ultimately its success. Within the pharmaceutical industry, taste masking techniques are employed to prevent the drug substance exhibiting a bitter or unpleasant taste. This is especially relevant in the paediatric market as drug products are typically chosen on the basis of texture, taste and ease of use. Poor organoleptic properties will have a negative influence on paediatric compliance. Palatability can also play an important factor in a product's perceived quality and in differentiating products in the market. Many taste-masked products are dispensed in oral formulations such as tablets and capsules but also gels, syrups, solutions, emulsions, lozenges and films. In addition to the taste concerns, the formulation needs to survive the high temperatures, high moisture and/or high pressure treatment which may be encountered during processing, and, once manufactured, appropriate storage conditions need to be defined. Striking a balance between attaining palatability by masking undesirable tastes and imparting a pleasant flavour and mouth feel, all within the context of an effective, stable dosage form, presents a unique formulation challenge. The more pleasurable the taste, the more opportunity for abuse or accidental overdosing especially with respect to paediatric formulations, therefore the aim is for somewhere between not being attractive, and not feeling unpleasant taking the medicine. Regardless of the flavour system used, the challenge is how to deliver unpleasant compounds, usually the API, while maintaining patient acceptability, efficacy and compliance. There are two strategies used in order to reduce the detrimental effects of a bitter-tasting drug: either to cover the bitter taste by administering simultaneously some very intense flavour to 'mask' the bitter taste (flavour enhancers) or to prevent the contact between drug and the taste receptors.

Using flavour enhancers is the simplest approach for taste-masking, especially for liquid formulations but is not particularly useful for very bitter, water-soluble drugs (1). The primary taste-masking excipients used in pharmaceutical formulation are sweeteners, flavouring agents and amino acids. In addition to palatability, the chosen enhancer has to be compatible with the other excipients added to the formulation to add processing or to ensure bioavailability and will be different for each active and each formulation. Chemical modification, including prodrug design or selection of a lipophilic counter-ion, is an effective method for reducing solubility, and thereby improving taste. The pH of a formulation can also be manipulated to reduce drug solubility and lipophilic vehicles such as lecithins can also be employed to coat the buccal cavity (including the taste buds) and reduce the flavour threshold of bitter tasting molecules. Similarly, common technologies involving applying coating layers of hydrophilic polymers, such as celluloses, provide one of the most straightforward approaches to taste masking. The coating, along with additional flavours, if required, can be applied to the whole tablet or to particulate material prior to compression into tablets. Recent innovations include the use of gelatine and non-animal derived coatings for tablets that are tamper-evident and can be designed with different colours for branding purposes. They are reported to be preferred by patients due to their ease of swallowing and superior taste- and odour-masking properties (2, 3). Bitter tasting granules can be coated with water-soluble polymers of hydroxypropyl methylcellulose and sugars such as sucrose and lactose to decrease the bitter perception at the time of administration (1). Coating drug particles with appropriate polymers will improve the taste but will also modulate release and improve stability. Prolamines, extracted from ceral grains and flour, such as zein, gliadin and hordein can also be used and the resultant masking is effective over a prolonged storage period without reducing onset of action or bioavailability (1).

Sustained release is possible
Minimising or eliminating side effects
Environmental protection, protection of drug contents from moisture and /or oxygen,
Gastric irritation reduction
Liquid-solid conversion
To allow the combination of incompatible constituents by the protection of one or more components
Taste masking

Table 1. Advantages of microencapsulation for drug delivery.

Recent progress in taste masking technologies has enabled development of novel dosage forms such as fast dissolving tablets, fast dissolving films and chewable tablets. Oral dispersible tablets (ODTs), for example, are designed to disintegrate and/or dissolve rapidly in the saliva without the need for water, within seconds to minutes. They are therefore convenient and may have an altered absorption profile resulting in a faster onset of action. Microencapsulation and complexation with ion-exchange resins or cyclodextrins can be used along with other flavours

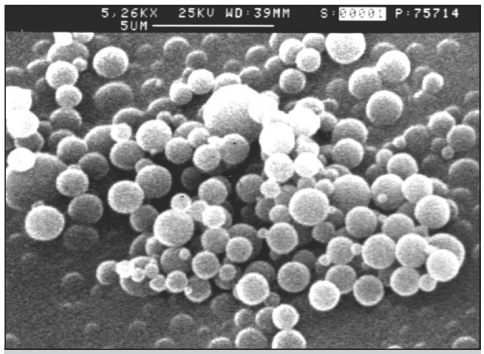

Figure 1. PLGA microspheres formed using a double emulsion solvent evaporation method.

and sweeteners for taste-masking of bitter drugs in these formulations. Taste masking is very often an essential feature of ODTs and can also be the rate-determining mechanism for dissolution/release. s. Cyclodextrins (CDs) are cyclic oligosaccharides derived from starch containing six (αCD), seven (βCD), eight (γCD), nine (δCD), ten (εCD) or more (α-1,4)-linked α -d-glucopyranose units. Beta-cyclodextrin is the most widely used complexing agent for inclusion type complexes and is suitable for use with potent substances (4). Ion-exchange resins are high molecular weight polymers with cationic and anionic functional groups used in drug formulations to mask taste and these agents can also can stabilize the sensitive components, sustain release of the drug and aid disintegration. Drugs are attached to the oppositely charged resin substrate, forming insoluble adsorbates or resonates, through weak ionic bonding so that dissociation of the drug-resin complex does not occur under the salivary pH conditions thus masking unpleasant tastes or flavours.

Microencapsulation is a method of wrapping small entities in individual coatings designed to protect, separate or aid in storage. Controlled-release microparticulate dosage forms offer a number of distinct advantages over many conventional dosage forms and the technique has numerous applications for pharmaceuticals in addition to taste masking (Table 1). It can be used to protect labile constituents from degradation or to allow combination of incompatible ingredients. Polymers used can be natural or synthetic, and typical polymers used for miroencapsulation of pharmaceuticals are polypeptides and proteins, such as albumin, and gelatine and polysaccharides, such as starch and chitosan. Synthetic polymers that have been used successfully in marketed products are polylactide (PLA) and polylactide-co-glycolide (PLGA) and polyanhydrides. Two main types of encapsulated systems are prepared, microcapsules or microspheres. In microspheres, the drug is distributed throughout the polymer matrix and thus must dissolve, melt or erode to provide drug release. The polymers used will often biodegrade within the body, thuds eliminating the need for removal after release. Coating of microparticles, or formation of a shell surrounding the drug, results in the formation of microcapsules and normally the drug will diffuse slowly across the membrane. The rupture of the outer polymeric membrane will provide release of drug. Different triggers can be used to initiate release of the encapsulated product such as pH changes, time, enzymatic activity or osmotic forces.

Frequently used encapsulation techniques include spray-drying, coacervation and phase separation, interfacial polymerization and extrusion and conditions can be varied to control the rate of release of active ingredient (Figure 1). Extrusion microencapsulation has been used is useful for the encapsulation of volatile and unstable flavours in glassy carbohydrate matrices, although the particles do tend to be larger than those made by corresponding methods (5).

Up to recent times, the most widely used method for measuring the taste characteristics of pharmaceutical preparations were in vivo approaches including human taste panel studies, electrophysiological methods and even animal preference studies (6). Within the pharmaceutical industry, biomimetic taste sensing systems (BMTSSs), such as multichannel taste sensors or electronic tongues with global selectivity, have been adopted and the further acceptance of these emerging in vitro approaches for assessing taste characteristics of taste masked drug and drug products will result in a decreased reliance on human panel tests. Electronic sensing instruments such as an electronic nose and tongue can quantify, qualify and compare chemical properties of both the raw materials (flavours, excipients or APIs) prior to formulation and various formulations according to their origins, qualities, shelf life or stability, reactions during aging under various storage conditions or packaging (7). Such technologies require minimal sample preparation and can objectively and safely characterize many chemical properties of ingredients and formulations. They enable screening of a larger library of ingredients, additives or taste screening of formulation candidates to speed up and optimise the formulation process development, especially for pharmaceutical formulations that cannot be safely tasted by a human panel. This has benefits for development time, development costs, subjectivity, bias, and safety concerns (8). These techniques can also be used to assay the flavour concentration during release testing of formulations and to monitor flavour shelf-life in the marketed container. They can also be implemented for selection of appropriate packaging for the formulation in order to ensure the flavour shelf-life (9). In vitro approaches to study taste are useful in the development of effective taste-masking procedures and the development of palatable formulations but will also be useful in high-throughput taste assessment for testing of flavour release. Encapsulation technology from the pharmaceutical industry can be used to entrap sensitive ingredients, such as volatile and labile flavours, into solid carriers to increase their protection, reduce evaporation, promote easier handling, and control their release during storage and application. In addition to preventing degradation of the agents, the encapsulation may provide controlled release, leading to a different pattern of flavour release, e.g. delayed onset or pulsatile delivery. The controlled release of ingredients at the right place and the right time can improve their effectiveness. As modern perfumes include components blended to produce a combination of scents designed to last for several hours and provide a combination of notes the ability to control the rate of release of the lingering notes will be an advantage.

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