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Review

Dissolution methodology for taste masked oral dosage forms

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ABSTRACT

Conventional adult dosage forms are often not suitable for the paediatric and geriatric populations due to either swallowing difficulties or patient repulsion and a requirement for tailored dosing to individual compliance or physiological needs. Alternative formulations are available; however these often require the incorporation of more complex taste masking techniques. One approach to taste masking is to reduce contact between the bitter Active Pharmaceutical Ingredient (API) and oral cavity taste bud regions. This is achieved by hindering release in the oral cavity, or including competitive inhibition of bitter sensation for example by using flavours or sweeteners. There may also be other sensational complications from the API such as residual burning, reflux or metallic taste sensations to deal with. *In vitro* dissolution testing is employed to elucidate taste masking capability by quantifying release of the drug in simulated oral cavity conditions. Dissolution testing approaches may also be used to potentially predict or quantify the effect of the taste masking technique on the resultant pharmacokinetic profile. The present review investigates the anatomy and physiology of the oral cavity and current approaches to taste masking. *In vitro* dissolution methodologies adopted in the evaluation of taste masked formulations are discussed for their relative merits and drawbacks. A vast array of methodologies has been employed, with little agreement between approaches, and a lack of biorelevance. Future directions in dissolution methodology such as TNO Intestinal Model (TIM) and the Artificial Stomach and Duodenum model (ASD) are also discussed.

Contents

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1. Introduction

The paediatric and geriatric populations present numerous challenges to the pharmaceutical industry. Changes in pharmacokinetic parameters such as metabolism and excretion [1,2] and difficulty swallowing in these populations results in the insufficiency of conventional oral dosage forms such as tablets and capsules [3,4]. However, the oral route is by far the most popular due to its convenience and greater compliance [5]. The requirement for an oral dosage form which is easy to swallow and can undergo manipulation to tailor dosing to individual needs is paramount [6].

There is an extensive range of paediatric formulations currently marketed, whose use is often translated to the geriatric population. In 2007, there were 17 different types of oral paediatric formulation available [7]. These included liquid formulations such as solutions, suspensions, and syrups, as well as tablets and powders for reconstitution into a liquid formulation. Tablet formulations included orally disintegrating tablets, chewable tablets, scored dividable tablets and effervescent tablets. Other formulations such as films, drops, minitabs, bulk granules or powders and sprinkle capsules were also available.

Many drugs have undesirable organoleptic properties such as a bitter or metallic taste or burning sensation which reduces compliance, resulting in therapeutic failure. Taste masking is therefore critical for the therapeutic and commercial success of these oral formulations. Unlike tablets and capsules for adult formulations, paediatric formulations tend to be more complex and require advanced taste masking techniques. The secondary need for enhanced physical delivery mechanisms and constructed packaging, to improve accuracy and dose compliance, can further complicate the approaches necessary with paediatrics and geriatrics.

2. Taste masking techniques

Broadly, approaches to taste masking aim to use strong flavours, maskers and sweeteners to overpower the bitter Active Pharmaceutical Ingredient (API), reduce contact between the API and the taste buds, or to reduce release of the API in the oral cavity [8]. Specifically, methods of taste masking include use of flavours and sweeteners [9–13], lipophilic vehicles [14–18], coating with polymers [19–31], carbohydrates [32–35], lipids [36–38] or proteins [8], complexation with cyclodextrins [39–45] or ion-exchange resins [46–59], formation of salts [8], use of salting out layers [60,61], and solid dispersions [62–67]. In practice, combinations of these techniques are often employed, for example ibuprofen orally disintegrating tablets were manufactured using a lipid matrix, coated with a film forming agent and formulated with a sweetener in order to achieve taste masking [10].

Whilst flavours and sweeteners are straight forward techniques, many excipients are subject to regulatory restrictions which limit their use, particularly in the paediatric population. For example, sucrose is a common sweetener but can cause dental caries, whilst certain flavours have been associated with hypersensitivity, toxicity or allergy and should also be kept to a minimum [7].

When the alternative method of inhibiting contact between API and taste buds by reducing release in the mouth is used, the manufacturing processes become more complex compared to the simple addition of a flavour or sweetener. These require sophisticated and advanced technologies and are subsequently more costly to develop and manufacture [6].

In addition, flavours and sweeteners, although simple, may not sufficiently mask the taste of extremely bitter compounds. Lipophilic vehicles increase the viscosity in the mouth and coat the taste buds with the oil, surfactant or lipid. On the other hand polymeric, carbohydrate or protein coatings act as a physical barrier surrounding the drug particle. Coatings are commonly used as an initial approach to taste masking and thus are widely used, whereas complexation with cyclodextrins or ion exchange resins is less common. Formation of salts or use of ion exchange resins is particularly suitable for highly soluble, ionisable drugs which form less soluble complexes at salivary pH. However, cyclodextrin complexation is generally reserved for low dose drugs which are shielded from taste buds in the central pore of the cyclodextrin molecule. A detailed review of taste masking technologies for oral pharmaceuticals was carried out by Sohi et al. which describes these methods in greater depth [8].

Numerous manufacturing processes are employed to generate taste masked microparticles. The manufacturing process used will depend on the taste masking technique. For example, lipophilic vehicles and solid dispersions may be manufactured by spray congealing [68], spray chilling [16], extrusion–spheronisation [14], hot melt extrusion [18] or solvent evaporation [66], whilst coatings may be applied by spray drying [36], fluidised bed coating [22], solvent evaporation [31] or coacervation [26]. Several other processes are also used within the pharmaceutical industry such as granulation [9], physical mixtures [44], freeze drying [55] and ionotropic gelation [69] amongst others. Meanwhile, the most common method of taste masking for adult oral formulations is simplistic coating of the final tablets, with many tablets employing a simple cellulosic based polymeric coating to provide a short "mouth time barrier" [70].

The taste masking technique and method of manufacture can have a great impact on the physiochemical characteristics and performance of the taste masked formulation. Commonly, performance is initially measured by *in vivo* taste analysis panels. Additionally, it is measured by prediction of the pharmacokinetic profile using *in vitro* dissolution testing, which is confirmed using *in vivo* studies. Occasionally *in vitro* taste sensors are also employed in the prediction of formulation performance.

3. Taste evaluation

The most common method of taste evaluation is by human taste panels. These are typically small groups (<20 people) of healthy volunteers who hold the formulation in their mouth for a set time before spitting it out. They then rate the formulation using different adjectives on an intensity scale. Taste panels are usually composed of lay members rather than trained, professional taste testers thus results are subjective with high inter-individual variability. It is also questionable whether results can be translated into the paediatric population whose preferences and perceptions of taste may differ. However, paediatric testing is minimal and generally limited to controlled needed clinical studies. Other *in vivo* tests include animal preference tests, where the animal avoids the bitter tasting compounds, and electrophysiological models, where electrodes measure the nerve response to stimuli in an anaesthetised animal [71]. *In vivo* testing is expensive and subject to ethical considerations and inter-subject variability, therefore *in vitro* taste assessments are becoming increasingly popular. Recently, there have been several reports of the use of electronic tongues (e-tongues or taste sensors) for taste assessment [11,18,22,28,36,40,51,72,73]. These models contain electrochemical sensors which can detect a range of substances of different tastes and intensities, thus generating electrical signals which are interpreted by the accompanying chemometrics software. One example is the Insent Taste Sensing System TS-5000Z as shown in Fig. 1.

There are several types of e-tongue in existence, differing by their receptor type and selectivity, required sample properties and handling requirements [71]. *In vitro* assay methods involve measurement of activation of G-proteins found in taste buds based on activation of receptors in an *in vitro* membrane. This method has many limitations outlined elsewhere and is not widely used [71]. Finally, *in vitro* drug release studies (dissolution tests) are employed to evaluate taste masking properties of a formulation. This approach removes the subjectivity found in *in vivo* taste testing, replacing it with robust analytical data.