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Playing hide and seek with poorly tasting paediatric medicines: Do not forget the excipients[☆]



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ABSTRACT

The development of paediatric medicines can be challenging since this is a diverse patient population with specific needs. For example, the toxicity of excipients may differ in children compared to adults and children have different taste preferences. Acceptable palatability of oral paediatric medicinal products is of great importance to facilitate patient adherence. This has been recognised by regulatory authorities and so is becoming a key aspect of paediatric pharmaceutical development studies. Many active pharmaceutical ingredients (APIs) have aversive taste characteristics and so it is necessary to utilise taste masking techniques to improve the palatability of paediatric oral formulations. The aim of this review is to provide an overview of different approaches to taste masking APIs in paediatric oral dosage forms, with a focus on the tolerability of excipients used. In addition, where possible, the provision of examples of some marketed products is made.

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1. Introduction

Acceptable palatability is paramount for paediatric formulations. A survey of over 800 paediatricians showed that unpleasant taste of medication is a key barrier to compliance for 90.8% of patients with acute illness and 83.9% of patients with chronic illness [1]. Compliance rates in children have been found to range from 11 to 93%, with major factors attributed to formulation and palatability [2]. Palatability is largely dictated by taste and this is a concern as a significant number of active pharmaceutical ingredients (APIs) on the market and in development have aversive taste. This is not considered to be a key issue when developing oral dose forms for adults who can swallow tablets since such products can be film or sugar-coated, thereby masking the taste of the API. In the paediatric population the issue is accentuated by dysphagia, leading to an increased use of oral dosage forms such as liquids, (oro-) dispersible and chewable tablets where taste masking becomes a greater challenge. In addition, differences in taste perception, sensitivity and tolerance between adults and children make taste assessment and development of palatable paediatric medications more complex.

The paediatric population represents a diverse group of patients, exhibiting differences in biological and physiological attributes compared to adults. Indeed, children are not merely miniature adults because sensory systems mature postnatally and their responses to certain tastes differ markedly from adults. Amongst these differences are heightened preferences for sweet-tasting and greater rejection of bitter-tasting foods [3]. In addition, APIs and excipients are metabolized differently by children of different ages compared to adults [4]. Therefore the use of certain excipients may not be appropriate or the levels will be restricted, which further complicates excipient selection.

Indeed, when designing an age-appropriate paediatric medicinal product, the excipients used should be selected using a benefit risk approach, encompassing all aspects of the proposed excipients in parallel, including:

- physico-chemical properties (stability, solubility, compatibility *etc.*)
- purity (identification and quantification of impurities)
- toxicity (quality and relevance of data)
- acceptable daily intake (ADI)
- tolerability (risk of allergies/sensitization, cariogenicity, gastrointestinal osmotic effects and metabolic fate, caloric contribution)
- the patient's age
- the patient's susceptibility (diabetic patients, patients with allergies *etc.*)
- dosage regimen/exposure (quantities, duration and frequency of administration)
- possible cumulative effect with excipients in concomitant medications
- regulatory status.

Acceptability is an overall ability of the patient and caregiver (defined as 'user') to use a medicinal product as intended (or authorised). Acceptability of a medicinal product is likely to have a significant impact on the patient's adherence and consequently on the safety and efficacy of the product.

Acceptability is driven by the characteristics of the user (age, ability, disease type and state) and by the characteristics of a medicinal product such as:

- palatability
- swallowability (volume/size and shape, integrity of dosage form, *e.g.* functional coating)
- complexity of manipulation if required
- the required dose *e.g.* the dosing volume, number of tablets *etc.*
- the required dosing frequency and duration treatment
- the selected administration device
- the primary and secondary container closure system
- the actual mode of administration.

Palatability is one of the main elements of the patient acceptance of a medicinal product. It is defined as the overall appreciation of an (often oral) medicine by organoleptic properties such as smell, taste, aftertaste and texture (*i.e.* mouthfeel), and possibly also vision and sound. It is determined by the characteristics of the components (API and excipients) and the way the API is formulated. Palatability is relevant for other routes of administration *e.g.* buccal, nasal, inhalation. Thus not only should a medicinal product not taste and smell (especially the aroma on first opening and during consumption) unpleasant, it should have acceptable mouthfeel (viscosity, grittiness) and appearance (visual aspect, size and shape, packaging). Thus palatability and indeed acceptability are key considerations when defining the target product profile.

The importance of acceptable palatability has been recognised by regulatory authorities, including the European Medicines Evaluation Agency (EMA) [5]. The French regulatory authorities (Afssaps) launched a study designed to determine the acceptability of oral liquid originator and generic antibiotics prescribed to ambulatory children [6]. The disparity in the acceptability of the different antibiotics prescribed, even for the same drug has been confirmed by Wollner *et al.* [7].

Moreover within the requirements of the European Union's Paediatric Regulation [8], paediatric investigation plan (PIP) guidelines state that the proposed studies of particular relevance to the development of paediatric products may include:

- Taste masking or palatability.
- Compatibility with administration systems *e.g.* medical devices.
- Compatibility and stability in the presence of relevant common foods and drinks.

As stated above, the majority of API's have an unpleasant taste. The pragmatic approach often taken by patients and carers to facilitate dosing is to dilute or obscure the taste of a medicinal product by mixing or sprinkling it in food/beverages. However, there are risks associated with using this approach. For example the entire dose of the medicinal product may not be consumed especially if the volume or quantity of food/beverage is too large or taste not appropriately masked. In addition, this approach may result in the child being put off the food/beverage used, which could be a particular issue for very young children and babies where milk is the main food source. Hence mixing with food or beverage should not be the primary means of taste masking a formulation. However, should mixing with food/beverages be recommended, appropriate *in vitro* compatibility testing should be conducted during

development to produce practical and robust mixing and administration instructions for users in the summary of product characteristics (SPC). The subject of taste masking APIs and medicinal products via pharmaceutical development means has been discussed by many authors in the past decade [9–11].

The aim of this review is to provide an overview of different approaches and pharmaceutical platform technologies that may be utilised for the taste masking of APIs in paediatric oral dosage forms, with a focus on excipients used together with the provision of examples of some marketed products. In addition, the tolerability of taste masking excipients will be discussed. Although there is a clear need for robust and reliable *in vitro* and *in vivo* taste assessment methodologies, this topic is out of scope of the current review.

The aim of taste masking techniques is to obscure the aversive taste of an API or formulation, or to prevent interactions of the dissolved API with the taste receptors in the mouth and throat. An overview of taste masking techniques is presented in Fig. 1.

2. Bitter blockers and taste modifiers

Although currently not widely preceded, some emerging technologies are discussed first as they interfere directly with the taste receptor or taste transduction mechanism. Bitter blockers work by biochemically interfering with the taste transduction from mouth to brain. Taste transduction is a complex process and different mechanisms for preventing bitter taste have been proposed depending on where the taste signal cascade is blocked.

2.1. Bitter receptor antagonists

At least 25 different bitter taste receptors have been discovered to date. These receptors are genetically extremely diverse, which explains different sensitivity to bitter tastes within the population. Taste genetics play an important role in a child's acceptance of oral liquid medications and experience with solid oral formulations. For example, children with bitter-sensitive TAS2R38 genotypes prefer sweeter formulations and are more likely to have had experience with (less bitter tasting) solid dosage forms [12].

Bitter receptor antagonists bind competitively to a specific bitter receptor site, thereby blocking the release of a G-protein, gustducin [13]. These antagonists are often tasteless compounds that are close structural analogues of known bitter compounds, hence binding to the same receptor [14].

Bitterness inhibition at the receptor level can only be achieved successfully if the bitter API molecule and the bitter blocker bind to exactly the same receptor. It is normally not known which bitter receptor an API

molecule interacts with, and likewise the receptor interaction of bitter blockers is often not fully understood. In practice, the selection of bitter receptor antagonists is therefore usually conducted with limited success via a 'trial and error' approach.

2.2. Taste transduction cascade blockers

Broad bitterness inhibition, with potential as a platform technology, is most likely to be achievable if a late stage in the taste transduction pathway can be blocked. As shown in Fig. 2 [15], certain 'bitter blocking' molecules can interact with taste transduction steps beyond the receptor interaction (1). Potential interactions can occur during the following steps: at the receptor–G protein (gustducin) interaction (2), at the activation of G protein (3), at the G protein effector (phospholipase C) interaction (4), at the generation of the second messenger (cAMP) (5), and at the ion channel activation step (6).

The ion channel, Transient Receptor Potential cation channel sub-family M member 5 (TRPM5), is an essential component of this cascade. By controlling the activity of TRPM5 it is thought that unwanted bitter tastes can be mitigated or even abolished, or desirable sweet and umami flavours can be enhanced. Compounds that specifically inhibit or enhance TRPM5 activity are currently under development as bitter blockers for both pharmaceuticals and foods such as processed soy and cocoa; however they are not expected to be commercialized for several years [16].

2.3. Gaps in current knowledge and technology limitations

The principle of bitter blockers is relatively new to taste masking of pharmaceutical dosage forms, and there is limited precedence of bitter blockers and other taste modifiers in marketed pharmaceutical products (see Table 1). Apart from sodium ions, no precedence for their use in paediatric products has been identified.

The transduction mechanism underlying bitter taste perception and the exact mechanism of action of bitter blockers are not yet fully understood. Therefore the selection of bitter blockers for taste masking purposes is often carried out by an empirical approach, with a limited likelihood of success. With progress in understanding the molecular mechanisms underlying bitter taste perception and with the help of recombinant DNA technology it may in the future be possible to predict the efficacy of bitter blockers for a drug of interest, and to determine the structure activity relationship (SAR) between taste modifiers and the proteins with which they interact [17]. An increased understanding of this relationship may in the future help in selecting the most appropriate bitter blocker for specific applications. However, the use of bitter blockers in taste masking applications is likely to remain challenging

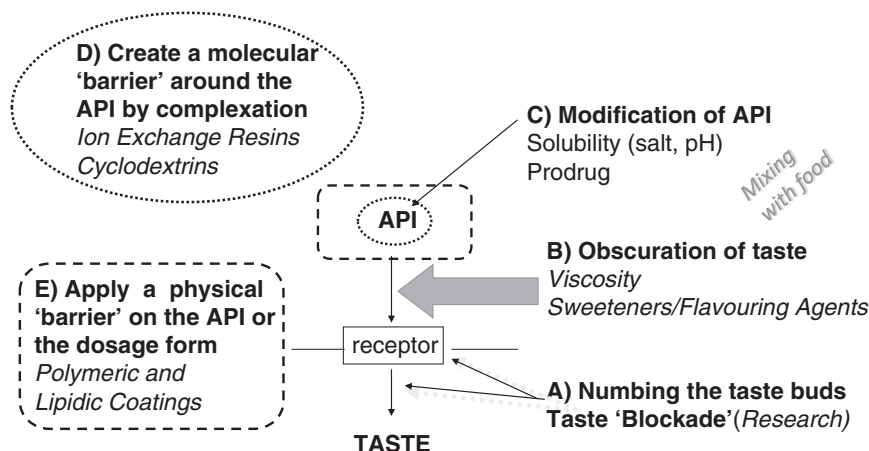


Fig. 1. Overview of taste masking methods.

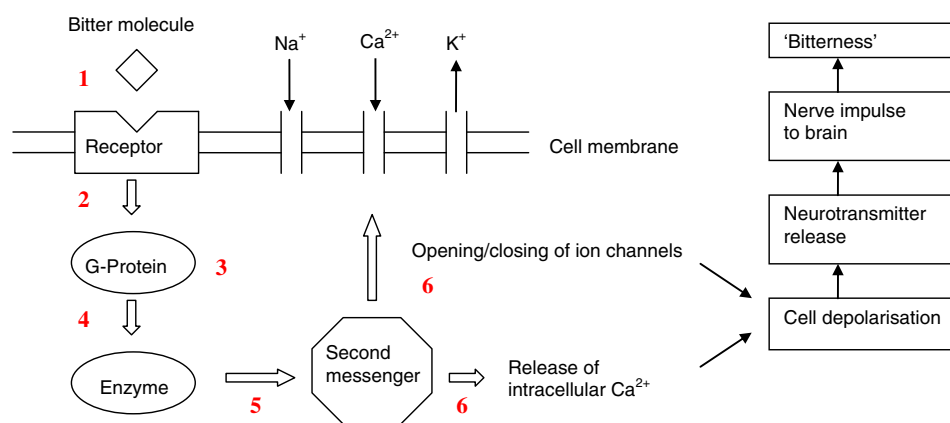


Fig. 2. Taste transduction (derived from McGregor, 2007 [15]).

because of the diverse number of receptors and multiple transduction pathways involved in bitterness perception.

Due to their mechanism of action, bitter blockers will require administration prior to dosing of a bitter medicinal product, resulting in challenges related to compliance (*i.e.* administration of additional formulation to paediatric patients) and increased cost. It is also not understood whether bitter blockers are able to remove or at least reduce the aftertaste caused by bitter APIs. Aftertaste is a major factor reducing compliance as it can often last for several hours following administration of a medicinal product.

Sensitivity to bitterness is age-related and is known to be different in adults and children. Methodologies to study the efficacy of bitter blockers in reducing the bitter taste of medicinal products need to be developed in paediatric and adult panels. Although there is a relatively large patent literature on bitter blockers and other taste masking technologies [9], few published studies investigated the efficacy of blockers in humans; and none in children, except for sodium chloride [18].

The safety and toxicology of bitter blockers in humans, and in particular in children, need to be investigated. Bitter receptors are not only found on the tongue, they also exist in the throat and lungs [19], and little is known about the impact of their action on these receptors. Due to their mechanism of action, taste modifiers may not be regarded as 'inactive' ingredients in pharmaceutical products, which in turn may have regulatory implications. Indeed, the regulatory status of most taste modifiers currently limits their use in pharmaceuticals.

In summary, broad bitterness inhibition, with potential as a platform technology for paediatric dosage forms, is difficult to achieve and requires blocking of the taste transduction process beyond the receptor level. Even if suitable molecules were to be identified, their use in pharmaceuticals, and especially in paediatric formulations, is likely to be limited due to toxicological, safety and regulatory concerns.

Some of the potential benefits and limitations of bitter blockers are summarised in Table 2.

3. Sweeteners and flavouring systems

Sensory based taste masking approaches have been commonly used for decades as it is the most intuitive approach to obscure aversive API tastes such as bitterness, excessive saltiness, astringency, and metallic taste. However as any compounds dissolved in the saliva will interact with the taste receptors and elicit a response, this approach does not work well for highly aversive APIs and for APIs with an intense lingering aftertaste. Moreover it is very difficult to predict whether this approach will actually work at all (unless conclusive taste data for API in water is available), and it is often a 'trial-and-error' approach (requiring several taste tests) to see which combinations and levels of flavours/sweeteners

may work. Nevertheless, the concept is versatile and can be applied to liquid or solid formulations that are applicable to younger patients (solutions/suspensions, soluble or dispersible tablets, oral wafers) or school age children (chewable tablets, orodispersible tablets (ODTs)). The use of flavours and/or sweeteners can be very effective (*e.g.* Diovan®, valsartan solution); however this is very much a non-platform technology and needs to be optimised on a case by case basis.

The usual taste masking development sequence, by which sweetener and flavouring agent compatibility with other excipients, stability and importantly tolerability needs to be taken in account, is to develop a sweetener blend, and then to add/complement with supporting flavours for aroma and taste [35].

3.1. Sweeteners

There are 2 main categories of sweeteners: bulk and intense sweeteners, as listed in Table 3. The former provides body and texture to the product (sucrose being the 'syrup' reference for pharmaceuticals) and the latter provides intense sweet taste at very low concentrations. The sweeteners used in medicinal products can be either artificial or natural.

It should be noted that not all sweeteners are globally acceptable from a regulatory perspective which limits the number of sweeteners that can be considered when developing a global commercial paediatric product. For example, cyclamates are not permitted in USA but are in Canada and in the EU, and neotame has been approved as a food additive in Australia since August 2001 and in the USA since July 2002, but has only been approved in the EU since 2010.

It is difficult to determine the prevalence and extent of sweeteners used. It may be considered that newer sweeteners and those not included in the US Food and Drug Administration (FDA) list of inactive ingredients [36] (*e.g.* alitame, neohesperidin dihydrochalcone, steviolosides and thaumatin), are less likely to be used in pharmaceutical products than those included in the FDA list.

Different sweeteners have advantages and disadvantages in terms of sensory qualities (taste, texture) and processability (temperature and pH stability). Fig. 3 represents sweetness intensity temporal profiles of acesulfame potassium (Ace-K), saccharin, aspartame, sucralose and neotame *versus* sucrose ranging from early-middle to middle-late onset of sweetness [37]. They provide a palette of sweetness choice to match the taste profiles of APIs. Compounds such as glucose and sorbitol have an early onset sweetness whilst that for thaumatin for example is late onset. A combination of sweeteners may be used in order to provide sufficient sweetness and intensity as a function of time to mask the unpleasant taste of an API in a particular oral dosage form, although concentrations required will depend upon the dose/strength of the product and properties of the drug (physical state, solubility). Indeed

Table 1
Examples of bitter blockers and other taste modifiers.

Bitter blocker/taste modifier	Mechanism	Applications	Limitations	Regulatory status	Precedence in pharmaceuticals
Adenosine 5'-monophosphate (AMP)	<ul style="list-style-type: none"> May bind to bitter-responsive taste receptors or interfere with receptor-G protein coupling to serve as naturally occurring taste modifier [20]. 	<ul style="list-style-type: none"> Reduces the bitter taste of potassium in low-sodium foods containing KCl. Reduces bitterness of selected drugs [21]. Reduces bitter aftertaste of artificial sweeteners, e.g. saccharin [17]. 	<ul style="list-style-type: none"> Likely to only block certain types of bitterness due to interaction with specific bitter taste receptors. Savoury (umami) taste may limit its use in pharmaceutical applications. 	<ul style="list-style-type: none"> GRAS status for use in foods, beverages and oral pharmaceutical dosage forms since 2004 [22]. 	<ul style="list-style-type: none"> No precedence in pharmaceuticals identified. Use in foods only.
<ul style="list-style-type: none"> Nucleotide found in RNA Natural constituent of many foods, including breast milk 	<ul style="list-style-type: none"> Sodium ions may act by shielding receptor proteins from bitter compounds, modulating ion channels or pumps, stabilising the cell membrane or interfering with second messenger systems after entering receptor cells [21]. 	<ul style="list-style-type: none"> In adults, sodium salts can suppress the bitter taste of some bitter compounds [4,21] 		<ul style="list-style-type: none"> Dependent on counter ion. 	<ul style="list-style-type: none"> Used in pharmaceuticals and foods.
Neohesperidin dihydrochalcone (E959)	<ul style="list-style-type: none"> Synthesised by hydrogenation of neohesperidin, a bitter flavonoid occurring naturally in Seville oranges (<i>Citrus aurantium</i>). (Also see Section 3.1). 	Low-calorie intense sweetener, flavour modifier and bitterness suppressor.	Optimum neohesperidin dihydrochalcone concentrations are API-dependent and need to be determined on a case-by-case basis.	<ul style="list-style-type: none"> GRAS listed Authorised sweetener in the European Parliament and Council Directive 94/35/EC of 30 June 1994 on Sweeteners for Use in Foodstuffs Authorised flavour enhancer in certain applications under the European Parliament and Council Directive 95/2/EC on Additives Other than Colours and Sweeteners. ADI of 0–5 mg/kg body-weight (Europe) Monographs in Ph. Eur (2001) and BP [23,25]. 	<ul style="list-style-type: none"> No precedence in pharmaceuticals identified.
Thaumatococcus daniellii (E957)	<ul style="list-style-type: none"> Mixture of five proteins isolated from the fruit of the African plant <i>Thaumatococcus daniellii</i>. 	<ul style="list-style-type: none"> The tertiary structure of the molecule may enable it to interact with bitter taste receptors. 	<ul style="list-style-type: none"> Used as a sweetening agent and flavour enhancer in food applications. It is claimed that thaumatococcus is effective at masking bitterness and off notes in foods, supplements and pharmaceuticals. Used in antibiotics, analgesics, antacids, cough syrups, common cold remedies, medicated gums, vitamin preparations and oral hygiene products [26]. 	<ul style="list-style-type: none"> Long (up to one hour) liquorice-like aftertaste. Optimum thaumatococcus concentrations are API-dependent and need to be determined on a case-by-case basis. 	<ul style="list-style-type: none"> Accepted for use in food products as a sweetener or flavour modifier in a number of areas including EU and Australia. In Europe, because of its lack of toxicity, an ADI of 'not specified' has been set. GRAS listed and included in nonparenteral medicines licensed in the UK.
Flavonones and structurally related compounds	<ul style="list-style-type: none"> Flavonones only partially block bitter reception. They may not compete with bitter molecules on taste receptors but bind to a second site common to all bitter receptors [27]. 	<ul style="list-style-type: none"> Used as a sweetening agent and flavour enhancer in food applications. It is claimed that thaumatococcus is effective at masking bitterness and off notes in foods, supplements and pharmaceuticals. Used in antibiotics, analgesics, antacids, cough syrups, common cold remedies, medicated gums, vitamin preparations and oral hygiene products [26]. 	<ul style="list-style-type: none"> Long (up to one hour) liquorice-like aftertaste. Optimum thaumatococcus concentrations are API-dependent and need to be determined on a case-by-case basis. 	<ul style="list-style-type: none"> No information found. 	<ul style="list-style-type: none"> No precedence in pharmaceuticals identified.
<ul style="list-style-type: none"> Eriodictyol, homoeriodictyol, its sodium salt and sterubin are flavanones extracted from <i>Eriodictyon californicum</i>, a plant native to N. America. 	<ul style="list-style-type: none"> Mechanism unknown. 	<ul style="list-style-type: none"> Homoeriodictyol sodium salt shows potent bitter-masking activity, reducing the bitterness of salicin, amarogentin, paracetamol and quinine [27]. 		<ul style="list-style-type: none"> No information found. 	<ul style="list-style-type: none"> No precedence in pharmaceuticals identified.
Derivatives of cinnamic acid	<ul style="list-style-type: none"> Caffeic acid is an organic compound that is found in plant cell walls Caffeic acid is a key intermediate in the biosynthesis of lignin. 	<ul style="list-style-type: none"> Caffeic acid, ferulic acid and their salts are patented as bitterness inhibitors in foods, to mask the bitter aftertaste of the artificial sweeteners acesulfame potassium and saccharin [28]. 		<ul style="list-style-type: none"> No information found. 	<ul style="list-style-type: none"> No precedence in pharmaceuticals identified.
Miraculin	<ul style="list-style-type: none"> Glycoprotein extracted from miracle berry, the fruit of the West African bush <i>Synsepalum dulcificum</i>. 	<ul style="list-style-type: none"> Miracle Fruit™ supplement has been reported to improve chemotherapy-associated taste changes [31]. 	<ul style="list-style-type: none"> Currently no standardised plant extract available. No secure source of material. No chemical synthesis at commercial scale. Rapid degradation following harvest of berries – freeze drying required to enhance stability. No toxicological data available. Impact on sour taste only [32,33]. 	<ul style="list-style-type: none"> No regulatory approval for use in pharmaceuticals or foods. 	<ul style="list-style-type: none"> No precedence in pharmaceuticals identified.
<ul style="list-style-type: none"> Lipoproteins Composed of phosphatidic acid and beta-lactoglobulin. 	<ul style="list-style-type: none"> No taste of its own but interacts with the taste receptors in the mouth and allows acidic foods to taste sweet for up to 2 hours [29]. The exact mechanism is unknown. Miraculin may distort the shape of sweetness receptors so that they become responsive to sour instead of sweet molecules [30]. 	<ul style="list-style-type: none"> Can mask target sites for bitter substances on the taste receptor membrane without affecting responses to sweet, salty or acidic tastes [34]. 	<ul style="list-style-type: none"> Phosphorylated amino acids have been found to inhibit unpleasant taste of ibuprofen, paracetamol, dextromethorphan HCl and other drugs [34]. 	<ul style="list-style-type: none"> No information found. 	<ul style="list-style-type: none"> No precedence in pharmaceuticals identified.

GRAS – generally regarded as safe, ADI – acceptable daily intake.

Table 2

Summary of benefits and limitations of bitter blockers.

Benefits	Limitations
Potentially more effective at controlling bitterness than conventional taste masking approaches such as use of sweetener and flavours.	Understanding of bitter blocker mechanism is currently limited. Selection often based on 'trial and error' approach.
Can overcome limitations of other technologies such as bioequivalence issues with coatings.	Limited regulatory acceptability for use in pharmaceuticals.
Useful for bitter APIs that are delivered buccally or sublingually. For these drugs suitable taste masking approaches are currently limited to use of sweeteners and flavours.	Safety and toxicology in adult and paediatric population largely unknown.
Effective at very low concentration, hence suitable for dosage forms where high levels of excipients are unsuitable, e.g. oral films.	May require administration of the bitter blocker prior to unpleasant tasting medicine – administration of two separate dosage forms will impact compliance and increase cost.

API – active pharmaceutical ingredient.

binary mixtures of sweeteners are frequently used synergistically, a typical mixture being aspartame–acesulfame K (E962) which has a synergistic sweetness which is 350 more than sugar alone [24,38].

3.2. Flavours

Natural and artificial flavours are available. Natural flavours have the advantage of better palatability over artificial flavours which are easier to characterise and more chemically stable [39] and therefore likely to overcome flavouring agents' batch to batch variability and potential changes in taste with time. This highlights additional issues such as the requirement to meet specification throughout product shelf life and the challenge of selection of methodologies (*in vivo*-human panels or *in vitro*-taste sensors) to evaluate taste stability over time. Furthermore, flavours are often complex mixtures and exact composition is usually not known, which can complicate the assessment of compatibility with other components within a formulation. Flavours may be available as liquids, some of which contain ethanol and/or propylene glycol usually in very small quantities which may not raise concern, or solids

whereby the flavouring is adsorbed onto excipients such as malto-dextrins. Safety concerns such as possible risk of toxicity, allergies and sensitization should be considered.

Two pieces of legislation adopted by the European Commission in October 2012 [40] have been introduced to harmonise and clarify the rules for using flavouring substances.

- Regulation (EU 872/2012) providing for a new EU wide list of flavouring substances which can be used in food will apply from 22 April 2013. All flavouring substances not in the list will be prohibited after a phasing out period of 18 months.
- Regulation (EU 873/2012) concerning transitional measures for other flavourings such as those made from non-food sources will apply from 22 October 2012.

The new list includes over 2100 authorised flavouring substances, which have been used for a long time and have already been assessed as safe by other scientific bodies. A further 400 will remain on the market until European Food Safety Authority (EFSA) concludes its evaluation.

Table 3

List of sweetening agents in pharmacopoeias and/or GRAS listed and/or in the FDA list of inactive ingredient for approved drug products and/or with an E number.

Sweetener	Origin	Sweetness (compared to sucrose)	GRAS status	In FDA list of inactive ingredients	E number	Pharmacopoeia
Acesulfame potassium ^a	Artificial sulfilimide	×130–200	–	+	E 950	PhEur; USP-NF; BP
Alitame	Artificial dipeptide	×2000	–	–	E 956	–
Ammonium glycyrrhizate	Natural glycoside	×30–50	+	+	–	PhEur; BP
Aspartame	Artificial dipeptide	×180–200	–	+	E 951	PhEur; USP-NF; BP
Aspartame–acesulfame potassium	Artificial mixed	×350	+	–	E 962	–
Cyclamate and calcium salt	Artificial sulfilimide	×30	–	+	E 952	–
Cyclamate sodium	Artificial sulfilimide	×30–50	–	+	E 952	PhEur; BP
Dextrose (glucose)	Natural monosaccharide	×0.74	+	+	–	PhEur; USP; BP; JP
Erythritol	Natural polyol	×0.7	+	–	E 968	PhEur; USP-NF; BP
Fructose	Natural monosaccharide	×1.73	+	+	–	PhEur; USP; BP; JP
Glycerin (glycerol)	Natural polyol	×0.6	+	+	E 422	PhEur; USP; BP; JP
Inulin	Natural polysaccharide	×0.1	+	–	–	USP
Isomalt	Natural polyol	×0.4	+	+	E 953	PhEur; USP-NF; BP
Lactitol	Natural polyol	×0.4	+	+	E 966	PhEur; USP-NF; BP
Maltitol	Natural polyol	×0.9	+	+	E 965	PhEur; USP-NF; BP
Maltose	Natural disaccharide	×0.3	+	+	–	USP-NF; JP
Mannitol	Natural polyol	×0.5	+	+	E 421	PhEur; USP; BP; JP
Neohesperidin dihydrochalcone	Artificial glycoside	×1500–1800	–	–	E 959	PhEur; BP
Neotame	Artificial derivated dipeptide	×7000–13,000	+	+	E 961	USP-NF;
Saccharin	Artificial sulfilimide	×300–500	–	+	E 954	PhEur; USP-NF; BP; JP
Saccharin sodium, calcium	Artificial sulfilimide	×300–500	–	+	E 954	PhEur; USP; BP; JP
Sorbitol	Natural polyol	×0.6	+	+	E 420	PhEur; USP-NF; BP; JP
Steviol glycosides	Natural glycoside derivated	×40–300	+	–	E 960	–
Sucralose	Artificial disaccharide	×400–800	–	+	E 955	USP-NF; BP
Sucrose (saccharose)	Natural disaccharide	×1	+	+	–	PhEur; USP-NF; BP; JP
Tagatose	Natural monosaccharide	×0.9	+	+	–	USP-NF;
Thaumatococin	Natural protein	×2000	+	–	E 957	–
Trehalose	Artificial disaccharide	×0.45	+	–	–	PhEur; USP-NF; BP; JP
Xylitol	Natural polyol	×0.95	–	+	E 967	PhEur; USP-NF; BP; JP

PhEur – European Pharmacopoeia, USP-NF – United States Pharmacopoeia National Formulary, BP – British Pharmacopoeia, JP – Japanese Pharmacopoeia.

^a Also known as acesulfame K.^b Rebudioside A.

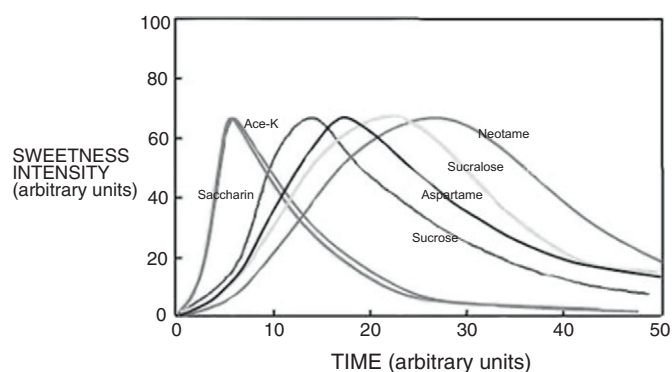


Fig. 3. Sweetness intensity of various sweeteners as a function of time (reproduced with permission from DeFer, 2010 [37]).

In general, a combination of flavours is used to complement the taste profile of an API, and the selection of flavours should be based upon the taste characteristics of the drug to be taste-masked. Table 4 provides a list of product character (flavour type) together with flavours that have been found to be most successful at taste masking, together with a list of flavours often used for different product types (indications) in Europe [41].

However the relevance of this information with respect to selection of flavours for paediatric formulations is debatable. It is a useful starting point, although it implies that the taste characteristics of the API are known which is rarely the case for drugs in early phase development. In addition, the information appears to be somewhat derived from adult marketing feedback and not according to age, gender and socio-cultural background which will influence recognition and preference of these flavours or by evidence-based proof of increased compliance in paediatric patients. Indeed, market research suggests that there are “favourite” flavours which vary from country to country [41]. During the development of Coartem® dispersible tablets for the treatment of uncomplicated *Plasmodium falciparum* malaria, three fruit flavours (cherry, orange, strawberry) were tested in Tanzanian children; the flavour, smell and sweetness of each were rated using a visual analogue scale with smiley faces. Other easily-recognized flavours such as banana and mango were not strong enough to mask the bitter taste of the drug. Cherry was the overall preferred flavour although unlike banana and mango, this fruit is not native to Africa [42]. In many cases, it is preferable to develop a “taste neutral” medicinal product to avoid specific flavour recognition and preferences.

In order to simplify flavour selection, the option of flavouring the medicinal product at the point of administration for each dose may be considered. This would offer flexibility (for example, day to day, region by region, acute versus chronic dosing) and address preference issues. However, compatibility of all the flavours with the product would need to be assessed including “in-use” shelf life.

Such an approach has been developed by FLAVORx [43] and is available in the USA, whereby commercial prescription liquid medicines can be re-flavoured (18 proprietary flavours available) in participating pharmacies. This is done either based on experience of successful flavourings or on patient choice. FLAVORx products are considered to be food-grade items by the FDA. However, it should be noted that the ingredients in the FLAVORx add-mixture have not been tested for compatibility with each and every drug product and hence drug product safety, efficacy and stability could potentially be affected. In addition, if the added volume of a premade liquid flavouring product is substantial, the concentration of API may become diluted. Another example of flavouring a medicinal product at point of dosing is Children's Tylenol with Flavor Creator™, where the cherry based original over the counter (OTC) paracetamol syrup can be customised at home with stickpacks of sugar free flavouring granules (apple, bubblegum, chocolate, or strawberry) to sprinkle in each dosing cup at the time of administration.

3.3. Safety and toxicity of sweeteners and flavouring agents

As for other excipients discussed in this review, a risk based approach should be used for the selection of sweeteners and flavouring agents and there should be a strategy in place with 1st line, 2nd line etc. choice.

For example, the use of cariogenic sweeteners can be balanced by length of treatment and severity of disease or simply oral hygiene (rinsing the mouth with water after dosing). The use of carbohydrates with potential to raise plasma glucose such as fructose, glucose or sucrose should be strictly limited or possibly totally avoided in diabetic children and adolescents [44]. When medicines are taken in small quantities for limited periods, the sugar content is unlikely to cause problems, as it is low in relation to the carbohydrate content of the whole diet. Sugar free alternatives should be recommended if the medicine is for long term use.

Sugar alcohols or polyols (Table 5) including hydrogenated monosaccharides (erythritol, xylitol, sorbitol, mannitol) and disaccharides (isomalt, lactitol, maltitol) are low-digestible carbohydrates; they have potential benefits such as reduced caloric content, reduced or no effect on blood glucose levels (low glycemic response) and a non-cariogenic effect.

Glycerol (glycerin), the simplest polyol with 3 carbon atoms is widely used as sweet vehicle or co-solvent (relative sweetness of 0.6) in various oral liquid pharmaceutical products. ADI levels for polyols have not been specified by the Joint Expert Committee on Food Additives (JEFCA), although in varying doses they can cause gastrointestinal symptoms such as bloating and laxation. Despite great variety in study designs, protocols, and types of results, Grabitske and Slavin [45] in a review of published studies reporting gastrointestinal effects of low-digestible carbohydrates estimated some ADI for sugar alcohols (Table 5). Nevertheless the limits for medicinal products are even more conservative: if the maximum oral daily intake exceeds 10 g for sorbitol, xylitol, mannitol, maltitol, isomalt, lactitol or glycerol, it is necessary to provide information on the labelling as per the European Commission guideline on Excipients in the Label and Package Leaflet of Medicinal Products for Human Use (CPMP/463/00) [46]. It is proposed that the current excipient labelling guideline, which was implemented before the European Paediatric Regulation, is updated as a number of safety concerns regarding excipients have not been addressed, including the paediatric population [47].

Fructose is formed via the metabolism of polysaccharides such as sucrose, and polyols such as sorbitol. Patients with rare hereditary fructose intolerance are missing aldolase B, a key enzyme in the further

Table 4
Potential flavours as a function of product character and product type (indication) (adapted from CHMP, EMEA, 2006. Reflection paper: Formulation of choice for the paediatric population [41]).

Product character	Suitable flavours
Acid	Lemon, lime, grapefruit, orange, cherry, strawberry
Alkaline	Aniseed, caramel, passion fruit, peach, banana
Bitter	Liquorice, aniseed, coffee, chocolate, peppermint, grapefruit, cherry, peach, raspberry
Metallic	Berry fruits, grape, peppermint
Salty	Butterscotch, caramel, hazelnut, spice, maple
Sweet	Vanilla, grape, cream, caramel, banana
Product type	Flavours often used
Anticleratives	Lemon, fresh and balsamic blends
Laxatives	Cherry, raspberry, liquorice, aniseed, orange/vanilla blends
Mucolytics	Orange/lemon blends, raspberry
Penicillins	Cherry, raspberry, woodberry, tutti frutti, blends
Sulphonamides	Vanilla, caramel, woodberry, apricot, cherry, blackberry, banana
Tranquillisers	Aniseed/mint blends
Vasodilators	Ginger, coffee, caramel
Vitamins	Orange, lemon, tangerine, grapefruit, pineapple, tropical fruits

Table 5

Solubility, cooling effect, hygroscopicity, estimated acceptable daily intakes, and caloric value of polyols.

Polyol	Number of carbons	Solubility in water 25 °C	Cooling effect	Hygroscopicity	ADI (g/day) ^a	Caloric value (kcal/g)
Erythritol	4	37%	Very strong	Low	40	0.2
Xylitol	5	64%	Very strong	High	30	2.4
Mannitol	6	20%	Strong	Low	20	1.6
Sorbitol	6	70%	Strong	High	30	2.6
Maltitol	12	60%	Weak	Low	40	2.4
Isomalt	12	25%	Weak	Low	40	2.4
Lactitol	12	57%	Weak	Low	30	2.4
Sucrose	12	67%	Weak	Low	~	4

ADI — acceptable daily intake.

^a Estimated by Grabitske and Slavin, 2009 [45].

metabolism of fructose, normally present in the liver, kidneys and small intestine. Patients with this condition should avoid medicinal products containing fructose, sucrose, lactitol, maltitol (4-O- α -glucopyranosyl-D-sorbitol), or sorbitol, in order to avoid fructose accumulation in these organs. This intolerance can cause major hypoglycaemic crises, liver damage, kidney malfunction, coma and death.

Very often intense sweeteners are needed to intensify the sweet taste of a formulation especially to taste mask very bitter compounds. Safety issues associated with intense sweeteners are different to those of bulk sweeteners as the quantities used are infinitesimal. Thus they do not provide a heavy calorific burden (e.g. sucralose is poorly absorbed), they elicit little or no glycaemic response and they do not promote dental caries. The ADIs of intense sweeteners are provided in Table 6 and specific safety concerns are discussed below.

Since aspartame is a methyl ester of the aspartic acid/phenylalanine dipeptide, it is a source of phenylalanine and so it can be harmful to patients with phenylketonuria. Although neotame is a derivative of aspartame, it is not metabolised to phenylalanine and has the advantage to be heat stable but with the same pH dependant stability (around pH 4). There is inconclusive evidence that aspartame causes hyperactivity in children.

“Sulfa allergy” is a term used to describe adverse drug reactions to sulphonamides. Cyclamate and saccharin are both sulphonamides and so should therefore be avoided in patients with sulphonamide allergy.

Despite critiques by Grotz and Munro [48] and Brusick et al. [49], a study by Abou-Donia et al. [50] showed that 100–1000 mg/kg of Splenda® (a proprietary sweetener based on sucralose) gavaged to male Sprague–Dawley rats for 12 weeks led to (1) reduction in beneficial faecal microflora, (2) increased faecal pH, and (3) enhanced expression levels of P-gp, CYP3A4, and CYP2D1, which are known to limit the bioavailability of orally administered drugs. Additional safety studies are warranted to determine the full impact of sucralose on drug bioavailability and to evaluate the biological effects of chronic sucralose usage particularly for special populations (e.g. children, elderly, nursing mothers, persons with diabetes, cancer patients). However the quantities of sucralose likely to be used in formulations (less than 0.25%–250 mg/100 ml in general) mean that the level of consumption mentioned above is very unlikely to be met.

A review of the safety of flavouring agents is out of scope of this document and readers are recommended to interrogate the EU Flavouring regulations previously described. When assessing a flavouring agent for its suitability for a paediatric patient, it is important to consider the solvents or carriers used within the material.

In summary, the use of sweeteners is the simplest and often the first approach for taste masking. It is applicable to a wide range of solid and liquid dosage forms and does not require specialist equipment for manufacture. Bioequivalence is generally not of concern, except where gastrointestinal transit may be accelerated. However it is not a platform approach and is not particularly successful for taste masking extremely bitter highly water soluble compounds. Flavours can have a complex composition and may not be universally acceptable from a regulatory and/or patient perspective. Flavours and sweeteners can be used in

conjunction with other taste masking techniques discussed later in this review.

4. Modification of API solubility

The taste of an API can only be evoked if the compound is in solution and able to interact with the taste receptors within the oral cavity. Oral dosage forms where the drug remains undissolved in the oral cavity, such as a suspension, can provide taste masking of aversive tasting compounds, since the drug remains predominantly undissolved in the formulation vehicle or saliva and binding to the taste receptors is greatly reduced. Maintaining solid status or driving the API out of solution by utilising the physico-chemical properties of the free form or various other solid forms (salt, cocrystal, polymorph), as well as use of prodrugs/softdrugs that have poor solubility in the formulation vehicle or saliva can, therefore, also provide taste masking of unpleasant tasting compounds. A number of patents describing these approaches are available and discussed below, whilst the use of prodrugs and softdrugs are not discussed, since these techniques go beyond the scope of this document.

4.1. Keeping the API unionised

For compounds that are ionisable, with pH-dependent solubility characteristics, utilising the pKa of the free form and fixing the pH of the formulation, so that the majority of the compound remains unionised, can 1) greatly limit the solubility of the compound in the formulation vehicle, 2) reduce rate of dissolution in saliva or 3) promote *in-situ* precipitation during reconstitution. This approach has been demonstrated by Wyley [51], who incorporated pH modifiers, such as L-arginine, into a reconstituted suspension formulation of quinolone carboxylic acid to maintain an alkaline pH once reconstituted in water, reduce the solubility of the drug in the formulation vehicle and consequently mask the bitter taste of the compound. A similar approach was used in an ondansetron ODT formulation where sodium bicarbonate was added to create an alkaline environment and reduce solubility and the consequent taste perception of the drug [52]. The alkalinising agent anhydrous trisodium phosphate was also added to a reconstituted suspension formulation for the antibiotic azithromycin to create a suspension formulation where azithromycin had limited solubility and thus reduced taste intensity [53]. To enable this technique to be used in medicinal products destined for children the pH modifying excipients and the concentrations used need to be appropriate and suitable for the intended paediatric population.

4.2. Alternative solid form

During formulation development the solid form of the API can vary and may only become fixed during market formulation development and when the drug substance synthesis is finalised. Selection of an alternative solid form, such as a salt, cocrystal or polymorph, with low solubility in the formulation vehicle or slower dissolution rate may, therefore, be a viable option to enable taste masking of an unpleasant

tasting API. Alternative solid forms of an API have also been reported as having differing tastes from one another and could therefore aid palatability of a formulation. This approach has been demonstrated with diclofenac [54], ibuprofen [55], and buspirone [56]. As per the buffer systems mentioned previously, to enable this technique to be used in medicinal products destined for children the counter ions and cofomers employed need to have acceptable safety in the paediatric population in which the formulation is intended for.

4.3. Challenges to consider for modifying an API

Applying modifications to the API, whilst being effective, does come with various challenges and points to consider. First and foremost pharmacokinetic (PK) performance and bioavailability utilising this technique need to be assessed when any modification to the API is employed, since integral physicochemical properties of the API may be altered that may alter the performance of the formulation. Keeping the API unionised or using a poorly soluble salt form cannot be employed successfully for unpleasant tasting compounds that have a low taste threshold – *i.e.* compounds that evoke their taste perception at low concentrations. This is because having a very small concentration

of drug dissolved in the formulation vehicle or saliva may be unavoidable and if the drug has a very low taste threshold it will still be tasted despite most of the drug remaining undissolved. Applying modifications to the API may also affect aftertaste – dissolution rates may alter in various buffered systems or with differing solid forms and, therefore, oral residence time might change. Modifications to the API may also affect particle morphology that might influence mouthfeel of these compounds in the oral cavity and should therefore be assessed where possible. Utilising a fixed pH to enable low solubility of an API in a suspension formulation may also jeopardise any preservative system that is being employed, since the majority of these systems are pH dependent. The use of various buffer systems also needs to be monitored for adverse effects. The low pH of oral liquid formulations has been associated with for example dental caries and tooth erosion [57].

In summary, modification of API solubility is a beneficial taste masking technique for applicable compounds that have a low/moderate level of bitterness, since commonly used excipients can be employed. Care should be maintained, however, that these common excipients have acceptable safety in the paediatric population. Despite numerous patents showcasing this technique, there is a lack of clarity on the approach used in marketed formulations and as such the benefit of this taste masking method in the paediatric population is not clear.

Table 6
Structures and acceptable daily intakes of intensive sweeteners.

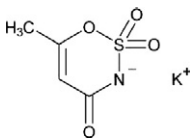
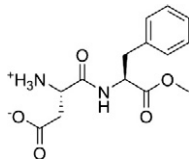
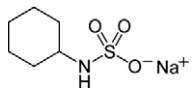
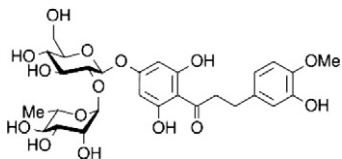
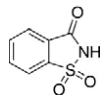
Intensive sweetener	ADI mg/kg	Structure
Acesulphame K	15 (FDA, EFSA)	
Aspartame	40 (EFSA) 50 (FDA)	
Cyclamate	5 (EFSA)	
Neohesperidin dihydrochalcone (NHDC)	5 (EFSA)	
Saccharin	5 (FDA, JEFCA)	
Steviol glycosides (expressed as steviol equivalents)	4 (EFSA)	

Table 6 (continued)

Intensive sweetener	ADI mg/kg	Structure

ADI — acceptable daily intake, FDA — United States Food and Drugs Administration, EFSA — European Food Safety Authority, JECFA — Joint Expert Committee on Food Additives, SCF — Scientific Committee on Food.

5. Create a 'molecular' barrier around the API by complexation

5.1. Ion-exchange resins

Ion exchange resins (IER) are a molecular tool to bind unpleasant tasting drugs and prevent interactions between the API molecule and the taste receptors. The solid IER particles may be suspended in a pleasant tasting vehicle and administered to the child as a liquid or the taste masked particles can be compressed into conventional tablets or ODTs. As ODTs directly disintegrate within the oral cavity they offer various advantages for example are easy to swallow without the need for water. Furthermore, IER may act as superdisintegrants for tablet formulations [58].

IER are high molecular weight polymers which are mostly insoluble in water and contain acidic or basic functional groups with capability to reversely exchange counter-ions within aqueous solution [59,60]. They can be divided into two groups; strong and weak ion exchange resins depending on the number and the chemical nature of ionic groups contained within the resin. Most drug–resin complexes (so called “resonates”) are prepared by the batch method whereby a certain amount of IER is dispersed in water and an excess of drug substance is added

while stirring (drug loading process). The batch is subsequently stirred for a specified time until reaching the equilibrium of drug adsorption and desorption which is pH dependent [61].

Some general considerations need to be made for choosing the appropriate resin. The ionic characteristic of the API should be opposite to the IER in order to obtain an anion–cation interaction. To ensure taste masking, the resinate needs to be stable in the drug formulation e.g. a suspension or a tablet formulation. In addition, the resinate must not dissociate in the mouth, hence the complex should be stable at pH 6–7 of the saliva [62,63]. However, at enteric pH conditions (pH < 5), the drug should be rapidly and almost entirely released in order to prevent reduced bioavailability.

5.1.1. Safety and toxicity of pharmaceutical grade ion exchange resins

The advantage of most resins is their high molecular weight and therefore very low absorption from the gastrointestinal tract. Oral toxicity is reported to be low for marketed IER (Table 7) and they are generally regarded as safe. However, studies with radio-labelled cationic exchangers showed remarkable particle uptake in pigs and distribution in several organs such as liver, kidney, spleen and skeletal muscle [64]. Moreover, it has to be considered whether the released counter-ion

may affect toxicology and safety data. Conversely, IER can be beneficial for reducing the acute toxicity of APIs or even detoxification from contaminants through binding. Becker and Swift [65] were able to show this for 13 different APIs (e.g. DL-amphetamine phosphate, dihydrocodeine bitartrate, ephedrine sulphate, pyrilamine maleate) bound to two strong acid cation exchange resins (Amberlite™). The anion exchange resin cholestyramine is widely used as an API at high doses for binding bile acids in the intestine in order to reduce cholesterol blood levels.

5.1.2. Formulations suitable for the paediatric population

Characterization of drug–resin complexes and the success of taste masking effect have been extensively described in the literature [9,11, 59,66–73]. Examples of successfully taste masked drugs by IER complexes and related drug dosage forms that are relevant for paediatric patients are provided in Table 8 and are discussed below.

Interestingly, most resins were formulated into an ODT or chewable tablet rather than into a liquid suspension. When developing a formulation with suspended resin, it is important that the resin does not interact with the excipients of the suspension base and the pH should be adjusted to prevent dissociation of the drug from the resin. Furthermore, the IER may act as a solid phase catalyst for API degradation. This has been recently shown for methylthionium chloride, also known as methylene blue [61], which underwent demethylation in the presence of the employed IER [74]. In contrast, a stable oral suspension of quinine sulphate complexed by Indion 234 has been developed [75].

For extremely bitter tasting tramadol hydrochloride, mechanically robust mouth-dissolving tablets (MDT) with rapid disintegration could be obtained. Shaking the drug resin (Tulsion 335) complex in phosphate buffer (pH 6.8) did not show any drug release after 300 s. Therefore, taste masking was assumed to be successful [76]. Puttewar et al. [77] prepared ODTs with a doxylamine-Indion 234 complex using crospovidone. Stability of the resin in a simulated saliva fluid could be shown and taste masking was confirmed by a human taste panel (n = 10). Risperidone taste masked ODTs were prepared and assessed *in vitro* by release studies in artificial saliva as well as *in vivo* by six human volunteers [78]. Mouth-dissolving pellets containing

taste masked fexofenadine hydrochloride bound to Indion 234s and 254 were developed and produced by extrusion–spheronisation [79]. Taste masking and smooth mouthfeel were confirmed for the Indion 234s resin by a human adult taste panel (n = 10), but not for Indion 254 which showed poor mouthfeel despite taste making capabilities. Metoclopramide resin was directly compressed or granulated by melt granulation with mannitol or xylitol and then compressed to ODTs [80]. Assessment of taste masking was not described. Ambroxol hydrochloride containing ODTs could be obtained by direct compression with mannitol. No bitter taste was rated by a panel of 6 healthy volunteers and a smooth mouthfeel was described [81]. Diphenhydramine hydrochloride was formulated into effervescent and dispersible tablets with improved palatability after binding to Indion 234 and Tulsion 343 as rated by 20 male volunteers [82].

These studies showed that unpleasant tasting APIs can be efficiently taste masked with different strong and weak IER and how these resins can be further processed into dosage forms in order to obtain a child-appropriate drug formulation. Challenges for ODTs are good mechanical strength with a rapid disintegration and a pleasant mouthfeel at the same time. Stability of the resin also has to be taken into account for both solid and liquid dosage forms.

5.2. Cyclodextrins

Cyclodextrins (CD) are cyclic oligosaccharides which have a cup-like structure and are able to form inclusion complexes with other molecules, in both aqueous solutions and the solid state. The nomenclature of CDs is derived from the number of glucose units, for example, α CD contains 6 units, β CD contains 7 units and γ CD contains 8 units of glucose. β CD is the most commonly used CD and is primarily used in oral formulations, whilst α CD is used mainly in parenteral formulations [84]. CDs are water soluble due to the large number of hydroxyl groups present, although solubility can be increased *via* chemical modification by for example the introduction of other functional groups. The inner cavity of CDs tends to be relatively polar and is therefore hydrophobic, whilst the exterior is hydrophilic. This means that CDs are capable of interacting with a variety of molecules whereby whole or part of the guest molecule fits into the CD cavity. This results in the physical and

Table 7
Toxicity data on pharmaceutical grade ion exchange resins.

Excipient name	Functional group	Counter ion	Brand name	Oral toxicity – LD 50 in mice (mg/kg)	Comment
<i>Strong acid cation-exchange resin</i>					
Styrene/divinyl benzene co-polymer	$-\text{SO}_3^-$	$-\text{H}^+$	Indion® 244	5500	Not absorbed by body tissues (non-toxic)
Sodium polystyrene sulfonate USP	$-\text{SO}_3^-$	$-\text{Na}^+$	Amberlite™ IRP69 Indion® 254 Tulsion® 344	10,000 (Indion 254)	Not absorbed by body tissues (non-toxic)
<i>Weak acid cation-exchange resin</i>					
Polacrilin potassium USP/NF	$-\text{COO}^-$	$-\text{K}^+$	Amberlite™ IRP88 Indion® 294 Tulsion® 339	3000 (Indion 294)	Not absorbed by body tissues (non-toxic)
Cross linked polyacrylic matrix	$-\text{COO}^-$	$-\text{K}^+$	Indion® 414	10,000 (Indion 414)	Not absorbed by body tissues (non-toxic)
Polacrilin resin	$-\text{COO}^-$	$-\text{H}^+$	Indion® 234 Amberlite™ IRP64 Tulsion® 335		Not absorbed by body tissues (non-toxic)
Cross linked polyacrylic matrix	$-\text{COO}^-$	$-\text{H}^+$	Indion® 204 Indion® 214	4500 10,000	Not absorbed by body tissues (non-toxic)
<i>Strong base anion-exchange resin</i>					
Cholestyramine resin USP/EP	$-\text{N}^+\text{R}_3$	$-\text{Cl}^-$	Duolite™ AP143/1083 Duolite™ AP143/1093 Tulsion® 412 (CHL) Indion® 454		Not absorbed by body tissues; used as API for detoxification or to treat hypercholesterin-aemia
<i>Weak base anion-exchange resin</i>					
Styrene/divinyl benzene co-polymer	$-\text{N}^+\text{R}_2$	$-\text{H}^+$	Amberlite® IR 4B		Not absorbed by body tissues (non-toxic)

Toxicity data provided by ion-exchange resin suppliers: Ion Exchange India Ltd, <http://www.ionresins.com/pharma.htm>; Rohm and Haas, <http://rohmmaas.com/ionexchange/pharmaceuticals/Tastemasking.htm>; Thermax, India, <http://www.thermaxindia.com/Chemicals/Ion-Exchange-Resins/Speciality-Resins/Pharmaceutical-Resins.aspx>.

Table 8

Ion exchange resins used for taste masked drug formulations.

Excipient	Drug	Dosage form	<i>In vitro</i> testing	<i>In vivo</i> testing	Reference
Indion 204, 234, Tulsion 335, 339	Quinine sulphate	Suspension	✓	✓	[75]
Indion 204	Etorocoxib	Suspension	✓	✓	[70]
Amberlite IRP 69F Dowex 50*8-100	Codeine phosphate	Suspension	✓	–	[83]
Indion 234, 234s, 254, 294 Amberlite IRP-64, IRP 69, IRP 88	Methylene Blue HCl	Suspension	✓	✓	[74]
Indion 234s, 254	Fexofenadine HCl	Melt-in-mouth pellets	–	✓	[79]
Tulsion 335	Tramadol HCl	Mouth-dissolving tablets	✓	–	[76]
Indion 234, Tulsion 343	Diphenhydramine HCl	ODTs	✓	✓	[82]
		Effervescent tablets			
Indion 204, 234	Ambroxol HCl	ODTs	✓	✓	[81]
Amberlite IRP64	Risperidone	ODTs	✓	✓	[78]
Indion 244	Metoclopramide HCl	ODTs	nd	nd	[80]
Indion 204, 234, 414	Doxylamine succinate	ODTs	✓	✓	[77]
Kyron T 134	Atomoxetine HCl	ODTs	✓	–	[72]
Amberlite IRP-69	Dextromethorphan HBr	ODT	✓	✓	[73]

nd – not done, ODT – oro-dispersible tablet.

chemical properties of the entrapped molecule being modified. It is for this reason that CDs have a variety of applications, *via* various routes of administration, including increasing bioavailability, solubility and stability as well as decreasing the taste perception of a drug. The size of the molecule to be complexed is a major factor that determines which CD is best suited for complexation. For example, α CD has a smaller cavity and thus preferentially forms inclusion complexes with slender guest molecules such as aliphatic chains whilst β CD is appropriate for aromatic rings [10,85–87].

It is believed that the extent of taste masking depends upon the amount of free drug available. Two theories have been reported; (i) the CD enwrap the bad tasting molecule impeding its interaction with the taste buds, and (ii) the CD interacts with the gate-keeper proteins of the taste buds, paralysing them [86]. However, it is believed that the latter theory is less likely since this would result in all taste sensations being blocked, which is not true. Furthermore, it has been reported that the bitter taste of an API only disappears in the presence of CD when it has formed a complex with it.

5.2.1. Oral safety and toxicity of cyclodextrins

Animal toxicity studies in mice, rats and dogs have shown that orally administered CDs are essentially non-toxic, which is believed to be due to a lack of absorption through the gastrointestinal tract. Indeed, β CD LD₅₀ for mice, rats and dogs have been reported as >12.5 g/kg, 18.8 g/kg and 5 g/kg respectively [88,89]. Administration of β CD at concentrations of up to 1.25% in the diet of rats did not cause any developmental toxicity. However, when given at a dietary concentration of 5%, treatment of lactating rats caused retarded pup growth. The cause of this is not known although it is postulated that it may have been due to a change in milk yield as the females consumed slightly less food during the lactation period. β CD was not excreted in the milk and indeed there were no differences in milk composition. There were no permanent defects to the pups and no adverse events were seen as a result of treatment with β CD during gestation [88].

The toxicity of hydroxypropyl (HP) β CD has been investigated and it is considered that this molecule has no mutagenic potential, no adverse effects on fertility nor peri and post natal development. However, an increase in the weight of the pancreas was reported following a 25 month carcinogenicity study in which HP β CD was dosed orally to rats at up to 5 g/kg per day. The authors believe, however that the hyperplastic effect observed is a rat-specific phenomenon, although additional studies are recommended [89]. Thackaberry et al. [90] have done further studies on HP β CD in mice, rats, dogs and cynomolgus monkeys. It was found that the oral administration of HP β CD to dogs and monkeys at a dose of 1000 mg/kg resulted in an increase in loose/soft stools, whilst this only increased minimally in male dogs at a dose of 500 mg/kg. When rats and mice were administered the same doses, a time and dose dependent increase in serum AST and ALT levels was observed in female

rats whilst four out of five male mice had minimally elevated ALT levels in the 1000 mg/kg group. These observations would suggest progression of hepatic toxicity although macroscopic and microscopic examinations of the livers were normal and similar to controls. The nature and toxicological significance of elevated transaminase levels in rodents is not known. However, this could have an impact on the interpretation of drug toxicity studies should HP β CD be used in pre-clinical formulations.

CDs are poorly absorbed in the human gastrointestinal tract and it is generally recognised that this is due to their bulky and hydrophilic nature [89]. β CD is poorly digested in the human small intestine and is almost completely degraded by the microflora in the colon. A daily consumption of 10 g in human adults increases the faecal excretion of bifidobacteria [91]. HP β CD is well tolerated in humans and considered to be non-toxic when administered orally [90]. Indeed, doses of 4–8 g daily for one to two weeks were well tolerated. However, an increase in the incidence of soft stools and diarrhoea has been observed when doses of 16–24 g were given for 14 days. Based on these findings, HP β CD is considered to be acceptable at daily doses below 16 g [89]. From a review of the literature, it has not been possible to determine the maximum tolerated dose of CDs for babies and children. Based on the above observations, it is considered likely that if CDs are given in large doses to paediatric patients they may experience diarrhoea.

5.2.2. Formulations containing cyclodextrins for taste masking

The effectiveness of CDs to mask the taste of an API will depend upon the dose and properties of the API, the CD selected and also the formulation type and composition. This technology needs to be optimised on a case-by case basis. Consideration needs to be given to the potential impact the formation of inclusion complexes may have on the PK and bioavailability of the drug and also any potential interactions with other excipients, for example preservatives, which may compete for complexation with the CD and alter the CD–drug inclusion complex equilibrium. Furthermore, the use of CDs may not be practical for high doses of API, especially if a high ratio of CD to API is required to achieve taste masking.

Despite these challenges, numerous examples of investigations into the development of taste-masked drug formulations using CDs exist in the literature, including patent applications. Products containing drug–CD complexes have also been marketed across the Globe, although the vast majority utilise CD ability to increase solubility instead of their taste masking properties [11,85,86].

Examples of bitter compounds that have been taste-masked using CDs are presented in Table 9, some of which are in formulations that may be suitable for paediatric patients. The utilisation of ternary complexes of CDs with various polymers has also been evaluated and in some cases has been found to have superior taste masking properties compared to CD–drug complexes. However it should be noted that the safety and tolerability of such complexes do not appear to have been

fully evaluated. Further examples of the application of CDs for taste masking are provided by Arima et al. [87].

Although there has clearly been research into the formulation of CD containing products that may be potentially administered to children, there do not appear to be many examples of the use of CDs for taste masking in licensed paediatric oral formulations. Nicorette® microtabs (McNeill Products Ltd) and Boots NicAssist® microtabs (The Boots Company) sub-lingual tablets utilise CDs for taste masking nicotine. These products are approved in some territories for adults and children over 12 years for the relief of nicotine withdrawal symptoms as an aid to smoking cessation. Children's Zyrtec® Chewable tablets (McNeill-PPC) contain taste masked cetirizine and are licensed for the relief of symptoms of hay fever and other upper respiratory allergies in children from the age of 6 years.

Due to the technical challenges associated with the use of CDs to achieve optimal taste masking, this is not considered to be a platform technology for taste masking in paediatric medicines.

6. Apply a physical 'barrier' on the API or the dosage form

A number of platform technologies may be utilised in order to create a physical "barrier" on the API or dosage form, some of which are discussed below.

6.1. Polymer film-coating

Multiparticulates, for example mini-tablets, granules or pellets, are multiple-unit dosage forms which are often presented in sachets or stick packs, and are preferred to conventional tablets in almost every age group according to the EMA reflection paper "formulations of choice for the paediatric population" [41]. These multiparticulate dosage forms offer the possibility of individual dosing with a low risk of dose dumping and there are also easy to swallow. In addition, they can be further dispersed in a pleasant tasting suspension base or administered with food.

Taste masking of these dosage forms can be achieved by introducing a saliva-resistant barrier onto the outside of a particle, pellet, or tablet. Therefore, the unpleasant API cannot directly interact with the taste buds on the tongue. Polymer coating of solid particles, pellets or (mini) tablets can be carried out using conventional coating processes, for example in fluidized bed systems or in a drum coater. Further coating can be achieved by granulation-spheronisation, by spray drying, or microencapsulation [10]. Coating may be achieved by using aqueous dispersions, organic solvents or solvent-free processes, depending on the properties of the coating material [9,34].

A major prerequisite to use a polymeric coating material as a taste masking excipient is its ability to act as an insoluble barrier at pH of saliva (pH 6–7) [62,63]. In general a number of polymeric excipients

Table 9
Examples of *in vivo* taste masking with cyclodextrins (human volunteers).

Drug/bitter compound	Cyclodextrin	Drug:cyclodextrin ratio	Preparation and formulation	Taste-masking properties	Reference
Diclofenac sodium	β CD	1:1	Freeze-dried aqueous solution (other taste masking techniques also evaluated)	Mostly acceptable but short lived	[92]
Artichoke extract, caffeine, gentian extract, aloe extract	α CD β CD γ CD (alone and linked to chitosan)	0.4 and 1.2% of CD and various drug concentrations	Chitosan, CDs and chitosan – CDs dissolved in solutions of the test compounds	1.2% chitosan – β CD most effective	[93]
Naringin, limonin, caffeine	Macromolecular derivatives of β CD and γ CD bound to carboxymethyl-chitosan and carboxymethyl cellulose-chitosan	0.4 and 1.2% of CD derivatives and various drug concentrations	CD soluble derivatives dissolved in solutions of the test compounds	1.2% γ CD carboxymethyl-cellulose and 1.2% β CD carboxymethyl chitosan most effective	[94]
Primaquine phosphate	β CD	1:1, 1:5, 1:10, 1:15, 1:20, 1:25	Physical mixing or kneading. Complex incorporated into dry suspension for constitution formulation	1:25 ratio by physical mixing best	[95]
Famotidine	β CD (also with HPMC as a ternary complex)	1:1	Freeze-dried aqueous solution. Physical mixture of drug, β CD and HPMC also prepared	Ternary complex best, drug-β CD complex better than physical mixture.	[96]
Artemether	β CD	1:1, 1:5, 1:10, 1:15, 1:18, 1:19, 1:20	Physical mixing or kneading. Complex incorporated into dry suspension for constitution formulation	1:20 ratio by physical mixing best	[97]
Levocetirizine dihydrochloride	HP β CD	1:3	Fast dissolving films of water soluble polymers prepared by solvent casting	Good	[98]
Famotidine	β CD SBE β CD ^a HP β CD (with and without povidone K30)	1:1	Freeze-dried aqueous solution, physical mixing, or kneading (with and without povidone K30).	SBE β CD-povidone > SBE β CD > HP β CD povidone > HP β CD > β CD povidone > β CD	[99]
Rizatriptan benzoate	β CD	1:1, 1:2, 1:4, 1:6, 1:8, 1:10, 1:12, 1:14, 1:16	Physical mixing or kneading. Aqueous dispersions prepared and tasted.	Optimized taste-masking observed with 1:10 kneading	[100]
Oseltamivir phosphate	β CD	1:1	Freeze-dried aqueous solution	Bitter taste of drug improved	[101]
Diphenhydramine hydrochloride	α CD	1.0 or 5.0 mM drug in 10, 20 and 30 mM solutions of CDs	Aqueous solutions	HP-β CD and β CD more effective than α CD and γ CD	[102]
Hydroxyzine dihydrochloride	β CD				
Cetirizine dihydrochloride	γ CD				
Chlorpheniramine maleate	HP-β CD				
Epinastine hydrochloride					

CD – cyclodextrin, HPMC – hydroxypropyl methylcellulose, SBE – sulfobutyl ether.

^a Brand name Captisol®.

could be used for taste mask coating. However, it is important that the intended API release profile should not be compromised and so the coating barrier should dissolve after passing the mouth at enteric pH (pH < 5). Consequently, water soluble films and pH dependent, acid-soluble films can be used. Stability and masking efficiency of a water soluble film can be controlled by the thickness of the film. The main advantage of pH dependent, salivary resistant films is that they only dissolve at enteric pH and can therefore be dispersed in suspension bases or sprinkled on food. Water soluble polymer coatings might release the API too early resulting in the detection of the bitter taste. This may be mitigated by using a mixture of water soluble and water insoluble polymers.

As stated previously, ODTs offer many advantages and may be especially suitable for paediatric and geriatric patients. However, a taste masking coating applied to the API or granulates may rupture during compression or if the tablet is chewed. To overcome this problem, microencapsulation has been developed for taste masking API particles. It has been reported that microparticles remained intact without undergoing merging or rupturing during tableting and hence taste masking was ensured when the microparticles were incorporated ODTs [103].

The small-sized taste masked particles (microparticles) can be prepared through spray drying, phase separation (coacervation) or through solvent evaporation. For spray drying, the polymer is dissolved in a suitable solvent and API added to form a solution or suspension and then the solvent is evaporated through spray drying. The phase-separation and solvent evaporation methods are based on an emulsion of an aqueous drug solution and a polymeric organic solution. This water in oil (w/o)-emulsion is then either dispersed in a large volume of a polyvinyl alcohol containing aqueous phase, which leads to coacervation, or a phase separator like silicon oil is added, which also leads to polymer coacervation of the API particles. Usually organic solvents have to be used and suitable techniques have to be applied to remove these from the formulations which is a clear disadvantage. The residual solvent levels need to be as low as possible, especially for children, which might be challenging. In the literature, the preparation of taste masked diclofenac sodium microcapsules has been described by Al-Omran et al. [104], and Hashimoto et al. [105] have described the taste

masking of salts of basic drugs using a water in oil in water (w/o/w) emulsion solvent evaporation method to produce microspheres. The production of taste masked famotidine microspheres by a spray drying [103] or the spray coating of diclofenac using Eudragit® EPO resulted in taste masked formulations [106]. Fast-disintegrating tablets containing microparticles with taste masking properties have been described in a patent by Dobetti [107]. The microparticles were prepared by a phase separation method and contained ibuprofen as a model drug.

Recently, the use of polymers in combination with lipids using hot-melt extrusion has been introduced as an alternative taste masking technique [108,109] where, for example, anionic active substances can interact with the functional groups of positively charged polymers. These interactions facilitate the creation of hydrogen bridge bonding and consequently mask the active's bitter taste. Paracetamol and ibuprofen have been successfully embedded within a Eudragit® EPO polymer matrix and the latter incorporated in ODT formulations [110, 111].

6.1.1. Safety and toxicity of coating materials

Table 10 shows commercially available pharmaceutical grade coating materials which can be used for taste masking.

Toxicity issues can be associated with polymers having an ionic structure. These polymers are of high molecular weight and therefore have limited absorption in the body. Nevertheless, ionic functional groups could randomly interact with body's tissues and therefore adverse effects could occur. Facts regarding the safety profiles of these polymers which are known today are summarised below.

According to the "WHO Food additives Series 26" [112] celluloses (including ethylcellulose (EC), hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPMC), (also known as hypromellose), methylcellulose (MC), and carmellose sodium) have low oral toxicity. Therefore the ADI was declared as "not specified" for food additives. The only adverse effect which was observed was laxative effects. Furthermore, HPMC (listed as hypromellose) and EC can be found on the FDA list of food additives that are generally recognized as safe. (GRAS) [36].

Table 10

Toxicity data on pharmaceutical grade coating excipients.

Excipient name	Brand name	Oral toxicity – LD50 (mg/kg body weight)	Comment
<i>Water soluble polymers</i>			
Macrogol poly(vinylalcohol) grafted copolymer Ph. Eur.	Kollicoat® IR	Rat: >2000	Oral bioavailability in rats < 1% (with dosages of 10 and 1000 mg/kg)
Ethylene glycol and vinyl alcohol graft copolymer USP/NF (draft)			
HEC (hydroxyethylcellulose Ph. Eur.)	Various	–	Increased food consumption in rats, no toxicity in man
HPC (Hydroxypropylcellulose Ph. Eur.)	Various	Rat: 10,200–15,000	–
HPMC (hydroxypropylmethylcellulose, hypromellose Ph. Eur.)	Various	Rat: >1000	Light laxative or constipation effect in men GRAS for general use in food at intake levels up to 20 g/p/d (GRAS Notice No. GRN 000,213)
MC (methylcellulose Ph. Eur.)	Various	–	Single oral doses of 5 and 10 g were well tolerated in man No toxic effects in man were observed
CMCNa (carboxymethylcellulose sodium, carmellose sodium Ph.Eur.)	Various	Rat: 15,000–27,000 Guinea-pig: 16,000	
<i>pH dependent soluble polymers</i>			
Basic butylated methacrylate copolymer Ph. Eur.	Eudragit® E (100; PO)	Mouse: >15,000 Rat: >3000	Loss of weight due to food absorption effects might occur
Amino methacrylate copolymer USP/NF aminoalkyl methacrylate copolymer E JPE	(soluble at pH < 5)		Influence on the water and electrolyte balance
Methacrylic acid – Ethyl acrylate copolymer (1:1) (L30 D-55 = Dispersion 30%) Ph.Eur.	Eudragit® L (30 D-55; 100-55)	Mouse: >2000 Rat: absence of toxic effects at 28,200 mg (LD50 therefore not determined) Dog: absence of toxic effects at 9100 mg (LD50 therefore not determined)	–
Methacrylic acid copolymer (L30 D-55 = Dispersion) – NF USP/NF Methacrylic acid copolymer LD JPE	(soluble at pH > 5.5)		
HPMCP (hydroxypropylmethylcellulose phthalate, hypromellose phthalate Ph. Eur.)	– (various) (soluble at pH > 5.5, but insoluble in saliva)	–	No toxic action has been found in rats and dogs [115]

Toxicity data on branded polymers provided polymer coating suppliers: Evonik Industries, <http://eudragit.evonik.com/product/eudragit/en/products-services/eudragit-products/Pages/default.aspx>; BASF, <http://www.pharma-ingredients.basf.com/Kollicoat/Home.aspx>.

Another group of polymers often used in pharmaceutical preparations are methacrylate copolymers. Various types and grades of Eudragit® are approved and listed in US FDA's "Inactive Ingredients for Approved Drug Products" list. However, as previously discussed, there are still safety concerns regarding polymers with ionic structure. The EFSA scientific opinion on the safety of neutral, basic and anionic methacrylate copolymers for use as food additives (glazing agents) concluded that the use of these materials in solid food supplements is not of a safety concern at the proposed levels. The estimated daily exposures were 46.7 mg/kg body weight/day for high adult consumers and 32 mg/kg body weight/day for children (4–17 years, 25 kg body weight) for neutral copolymer, and 23.4 mg/kg body weight/day for a 60 kg adult and 16 mg/kg body weight/day for children (4–18 years) for anionic and basic copolymer. The properties and toxicology of basic and neutral methacrylate copolymers have recently been reviewed [113,114], from which there appear to be different views between the authors and EFSA regarding estimated daily exposures for the neutral copolymers. The authors proposed an ADI level of 20 mg/kg body weight for basic polymethacrylate and an ADI of 18–20 mg/kg body weight for neutral polymethacrylate. Various new polymers are under development, for example Kollicoat Smartseal®, which is a methacrylate co-polymer. However, many of such new polymers have not been used in commercially available medicinal products. Although the majority of suppliers of these excipients appear to have conducted extensive toxicity studies in animals (mice, rats and dogs) as well as *in vitro* cell based studies, there is a lack of published data regarding safety and toxicity in humans, especially in the paediatric population.

It should be noted that coating formulations often contain additional excipients, for example pore formers, glidants and plasticizers. Therefore, safety and toxicity of the whole formulation needs to be considered. Due to differences in surface area and shape of particles, pellets and mini-tablets, the amount of polymer for coating is higher for pellets and granulates than for mini-tablets. Conversely, the amount of glidant needed to prevent sticking during the coating process might be different for pellet, granulate and mini-tablet coating. This has to be taken into account together with the intended dose to be administered when selecting the dosage form in relation to the total amount of coating excipients.

6.1.2. Formulations suitable for the paediatric population

Coating of solid dosage forms in order to mask the unpleasant taste of a drug has been described before by Douroumis [10], and a patent review considering coating materials used for taste masking has been conducted by Ayenew et al. [9]. Therefore, the coating of dosage forms that are age appropriate is considered in this section, as well as data on experiences with the administration of these dosage forms to paediatrics. Table 11 shows examples of taste masked child appropriate dosage forms.

Quinine sulphate, which is a very bitter tasting API, could be taste masked *via* coating of pellets (size: 300–700 µm), which were obtained by a wet-extrusion–spheronisation process [116,117]. 20% (w/w) of Eudragit® E PO was required to mask the bitter taste sufficiently and to obtain a homogeneous film. The API could be released immediately in acid medium after showing a different release rate in water compared to uncoated pellets. In a following bioavailability study in children < 5 years and adults, it could be shown that the bioavailability of the taste masked pellets was similar to that of commercially available tablets. Furthermore, no pellets were rejected by the patients due to unpleasant taste and all 56 children completed the 14-day follow-up.

Shirai et al. [118] prepared a fine granule system containing sparflaxacin, a bitter tasting antibacterial drug, and low-substituted hydroxypropylcellulose (L-HPC). Taste masking could be carried out by coating the granules containing 52% L-HPC with EC/HPMC (4/2) and a 10% coating level. Due to this excipient combination, taste masking was sufficient, whilst rapid dissolution of the drug was still possible and bioavailability, tested in dogs, was not affected compared to rapidly releasing tablets. Bitter tasting ibuprofen particles were coated with a mixture of EC and HPMC (2:3) in a fluidized bed process [119, 120] and healthy human volunteers evaluated particles with a film coating > 10% as well masked. Binding to an ion exchange resin was not sufficient enough for taste masking in the case of binding erythromycin and clarithromycin to carbopol (polyacrylic acid) [121] and taste masking by coating with hypromellose phthalate was achieved.

Eudragit® E PO pellets containing theophylline were prepared using a powder coating process [122]. Taste masking was confirmed by delayed dissolution at pH 6.8. At pH 1.0, simulating enteric pH, immediate release of the drug could be observed. No solvents or liquid plasticizers

Table 11
Examples of polymeric coating excipients used for formulations suitable for paediatrics.

Excipient	Drug	Dosage form	Paediatric use	Reference
Hypromellose/ethylcellulose	Ibuprofen	Core particles	–	[119,120]
Hypromellose phthalate	Erythromycin	Carbopol adsorbates	–	[121]
	Clarithromycin	incorporated in a suspension	–	
Hypromellose/ethylcellulose	Sparflaxacin	Fine granules	–	[118]
Macrogol poly(vinylalcohol) grafted copolymer Ph. Eur.	Paracetamol	Oral disintegrating tablet	–	[124]
Ethylene glycol and vinyl Alcohol Graft Copolymer USP/NF (draft)(Kollidon IR)				
Basic butylated methacrylate copolymer Ph. Eur. (Eudragit® E PO)	Theophylline	Tablets (powder coating process)	–	[122]
Basic butylated methacrylate copolymer Ph. Eur. (Eudragit® E PO)	Quinine sulphate	Pellets	Bioavailability study in children	[116,117]
Methyl methacrylate and diethylaminoethyl methacrylate co-polymer Kollicoat Smartseal	Ornidazole	Fine granules	–	[125]
Anionic methacrylate copolymer (Eudragit® L)	Esomeprazole	Oral granules for suspension	✓	Nexium®
Basic butylated methacrylate copolymer Ph. Eur. (Eudragit® E PO)	Terbinafine	Oral granules/minitables	✓	Lamisil®
Basic butylated methacrylate copolymer Ph. Eur. (Eudragit® E PO)	Dexmethylphenidate	Pellets	✓	Focalin®
Ethylcellulose	Tenovir	Oral granules	✓	Viread®
Ethylcellulose	Sodium valproate	Oral granules/minitables	✓	Orfiril®
Hypromellose/ethylcellulose	Ibuprofen	Oral disintegrating tablet	✓	Nurofen for Children Meltlets®
Polymethacrylate (Eudragit® E100)/polyacrylate dispersion 30 %	Paracetamol	Oral disintegrating tablet	✓	Calpol Six Plus Fastmelts®

were used in the powder coating process, offering the advantage to reduce safety and toxicity concerns for a child appropriate formulation. Pearnchob et al. [123] evaluated the ability of shellac as taste masking material in comparison to HPMC. Lower coating levels of shellac were needed compared to HPMC to obtain the same masking effect. In addition, drug release at gastric pH was not significantly decreased by thin shellac coatings.

In conclusion, taste masking *via* introduction of a barrier has already been undertaken for child appropriate dosage forms. Eudragit® EPO and Hypromellose (HPMC) in combination with other cellulose derivatives were the most commonly used materials as they offered the advantage of not influencing the immediate release of a drug.

6.2. Lipidic barrier system

Although lipid excipients may be used to confer controlled/delayed release properties on a medicinal product [126], they present an attractive alternative to standard polymer coatings for taste masking as they only require melting before application directly onto the substrate. Furthermore, solvent evaporation is not required and thus powders with very high specific surface areas can be coated rapidly. Also, since the lipid is not diluted with solvents, higher and more uniform application rates are feasible compared to other techniques. As the process is water-free this taste masking technology is suitable for moisture sensitive APIs and the risk of microbial contamination is reduced.

Triglycerides, mixtures of long chain mono-, di-, and triglycerides and waxes used as coating agents provide several noteworthy advantages: (i) the amount of excipient required to achieve the desired effect is generally less compared to polymers; (ii) usually only one excipient is required simplifying the formulation and hence the registration of the drug product with regulatory authorities; (iii) they are plastic compounds which do not crack during compression into tablets; (iv) they are not soluble in ethanol and drug release should therefore not be influenced by the presence of alcohol in the dissolution medium; and finally (v) they might be relatively inexpensive in comparison to polymer coatings resulting in lower production costs.

A number of different lipid excipients and technologies can be used for taste masking purposes, for example, hot-melt coating, spray congealing, melt extrusion or melt granulation. However, choosing the appropriate excipient for the application requires an understanding of their physico-chemical properties and its associated effect on API release and taste masking efficiency.

Hot-melt coating with lipid excipients offers an attractive alternative to polymer film coating since, as stated above, the lipid coating agent is directly applied onto the drug substance without any solvent. Thus there are no issues regarding residual solvent levels which can be of particular concern to young children. Jannin et al. [109] and Repka et al. [127] give a detailed overview of hot-melt technologies and application for pharmaceutical use.

In order to produce small solid taste masked lipid particles the molten lipid/API formula can be sprayed into a cooling chamber [128]. The so-called spray cooling or spray congealing technique uses the same lipids as hot-melt technology. Lipid particles produced in this way may be used for tableting to produce for example controlled release dosage forms [129]. One key parameter that needs to be considered is the API load of the formulations, as this influences the viscosity of the spray liquid, since dispersions generally tend to be more viscous than solutions. So far a maximum of 30% drug load has been reported [130]. Larger spherical pellets can be obtained using a similar process whereby a melted suspension is dropped onto a cooled surface [131].

Hot or cold extrusion offers the advantage to apply taste masking to APIs which are sensitive to moisture and in the case of cold extrusion, those sensitive to heat. Both technologies can be combined with a spherization process to produce pellets. Lipid pellets represent multiple unit (often sustained release) matrix dosage forms that combine

several advantages. As stated previously, multiple unit dosage forms are easy to swallow, and also possess more reproducible gastrointestinal transit times compared to monolithic dosage forms and so there is a lower risk for dose dumping [132].

Another technique for lipid-based taste masking is the preparation of solid lipid nanoparticles (SLN). However, SLN are generally utilised as a drug carrier system rather than a taste masking opportunity. Classic components of SLN are glyceryl dibehenate as the solid matrix and poloxamers or polysorbates as surfactants. SLN can be produced through hot or cold high pressure homogenization. For both techniques the drug is dissolved or solubilized in the molten lipid. Afterwards it is either dispersed in a hot surfactant solution and homogenized or it is cooled, ground and then dispersed in cold surfactant solution and then homogenized [133].

6.2.1. Commonly used lipidic excipients for taste masking

Lipids are naturally occurring compounds that are predominantly digestible and have GRAS status and therefore offer an advantage for use in paediatric formulations. Lipids commonly used for coating are glycerides, *i.e.* esters of glycerol and fatty acids and depending on the nature of the fatty acid and their degree of esterification, they are more or less digestible by lipases [134].

The main lipid excipients that are used in the pharmaceutical industry together with their ADI limits are provided in Table 12, including vegetable oil derivatives such as hydrogenated vegetable oils, partial glycerides, polyoxylglycerides, ethoxylated glycerides and esters of edible fatty acids and various alcohols (waxes). The common components are fatty acids.

6.2.2. Formulations containing lipidic excipients for taste masking

Examples of formulations that may be suitable for children where lipid excipients have been used for taste masking are provided in Table 13 and discussed below.

Chewable taste masked tablets containing bitter tasting acetaminophen (paracetamol) have been developed by Suzuki et al. [135,136]. A mixture of Witexsol H-15, (hydrogenated coco-glycerides, a hard fat), Benecoat BMI-40, (a commercial bitter-masking powder mixture made from lecithin), and sucrose was found to have the best taste masking properties without influencing the desired immediate release profile. The mouthfeel could be further improved by using Witocan H, (triglycerides based on coconut/palm kernel oil) instead, but the addition of the Benecoat BMI-40 bitterness suppressant was needed. As previously mentioned in Section 6.1, solid lipid extrusion with mixtures of hard fat (hydrogenated coco-glycerides) and PVA-PEG graft copolymer has been described as being successful for taste masking the poorly soluble model API NXP120 [108].

Paracetamol has also been successfully taste masked by hot melt coating using different combinations of lipids (for example Precirol® (glyceryl distearate) and Sterotex® HM (hydrogenated soybean oil)) with emulsifiers and disintegrants to improve dissolution [137,138]. Further examples of drugs that have been successfully taste masked using a hot melt coating technique include chloroquine and theophylline, using glyceryl dibehenate [132,139] and bromhexine hydrochloride and salbutamol sulphate using bees wax and cetyl alcohol [140]. In the latter, complete *in vivo* taste masking was achieved using a coating level of 5% w/w. Microparticles of indeloxazine hydrochloride have been successfully taste masked using a coating of a mixture of hydrogenated oil and surfactants [141].

The bitter and salty tasting drug sodium benzoate could be masked by producing pellets with hard fat (Witocan 42/44), glyceryl dibehenate (Compritrol® 888 ATO), glyceryl trimyristate (Dynasan 114) and glyceryl distearate (Precirol ATO5®). The obtained pellets, evaluated *via* a human taste panel and electronic tongue, had a better taste masking ability than saliva-resistant coated granules [142]. Although carnauba wax has been used to prepare delayed-release dosage forms [126], it may also confer taste masking properties to the API or product. It is

Table 12
Toxicity data on commonly used lipids for taste masking.

Excipient name	Brand name	Pharmacopoeia	Comment
<i>Hydrogenated vegetable oils</i>			
Hydrogenated cottonseed oil	Lubritab™		ADI: not established
Hydrogenated palm oil	Dynasan™ P60, Softisan™ 154	USP-NF: not listed	ADI: not established
<i>Partial glycerides</i>			
Glyceryl monostearate (GMS)	Imwitor® 191, Cutina™ GMS or Tegin™	USP-NF	ADI: not limited
Glyceryl distearate	Precirol® ATO 5	USP-NF, PhEur	ADI: not limited
Glyceryl dibehenate	Compritol® 888 ATO	USP-NF, PhEur	ADI: not limited
<i>Triglycerides (TAG)</i>			
Glyceryl trimyristate	Dynasan® 114	Not listed	ADI: Not limited
Glyceryl tristearate	Dynasan® 118	21 CFR §172.811 JClC	LD50 oral (rat) all types > 5 g/kg bw
<i>Polyoxyglycerides or macrogolglycerides</i>			
Lauroyl polyoxyglycerides	Gelucire® 44/14	USP-NF, PhEur	LD50 oral (rat) > 20 g/kg
Stearoyl polyoxyglycerides	Gelucire® 50/13	USP-NF, PhEur	LD50 oral (rat) > 20 g/kg
<i>Waxes/hard fat</i>			
Carnauba wax	–	USP-NF, PhEur	ADI: 7.0 mg/kg bw LD50 not established
Bees wax	–	USP-NF, PhEur	ADI: acceptable
Polyethylene glycol (PEG) ^a	Carbowax®; Macrogol 1500	USP-NF, PhEur	ADI: 10.0 mg/kg bw LD50 oral (rat) > 15 g/kg
Hydrogenated coco-glycerides	Witepsol W35 Witocan 42/44	USP-NF, PhEur, JP, DMF USP-NF, PhEur	LD50 oral (rat) > 2 g/kg

USP-NF – United States Pharmacopoeia National Formulary, PhEur – European Pharmacopoeia, JP – Japanese Pharmacopoeia, DMF – Drug Master File.

Source of toxicity data: Joint Expert Committee on Food Additives (JECFA).

^a PEG in molecular weights of 1500 and 6000 is chemically not a wax but has been included due to their use as excipient for *e.g.* solid lipid extrusion.

often used in tablet coatings to improve appearance and taste, for example Kalydeco™ and Colcrys® tablets.

Solid lipid extrudates with the bitter drug praziquantel are described by Witzleb et al. [143]. The taste of extrudates with diameter down to 0.2 mm, a drug load up to 70% and addition of up to 20% PEG were tested in a palatability study in cats. Since cats react very sensitively to bitter taste and generally reject food that is given together with a bitter tasting medicine this study suggests that there would also be sufficient taste masking for humans.

Lipid extrudates containing praziquantel or enrofloxacin with taste masking properties were investigated by Michalk et al. [144] using glyceryl dibehenate as the lipid component. The taste masking was indirectly measured by a special short time dissolution test. The release from the extrudates at pH 7.4 was low and increased with increasing diameter of extrudates.

These studies demonstrate that salty or bitter tasting APIs can be efficiently taste masked using lipids or combinations of different lipids alone or mixed with other excipients. The obtained granules, pellets or microspheres are already considered as age-appropriate dosage forms and offer the possibility to process them further into other child-friendly dosage forms. Due to the advantage of low safety concerns or ADI restrictions, lipids are an interesting and promising class of excipients for taste masking. However, effect on API bioavailability and the influence of storage (especially under accelerated conditions) on physico-chemical properties, need to be studied further.

7. Summary and conclusions

The taste of an oral paediatric product can have a huge impact on its acceptability and acceptable palatability is of great importance for paediatric medicinal products to facilitate patient adherence. The development of palatable oral dosage forms for children is challenging [145]; many APIs have an unpleasant taste, and so it is necessary to obscure or mask this property within the formulation. When developing medicines for children, the selection of suitable age-appropriate dosage form for the proposed paediatric population should be based on a benefit risk approach, taking into account safety, efficacy/ease of use and patient access [146]. Part of this process should consider the need for taste masking. Choice of taste masking technique should take into account the organoleptic properties of the API, in addition to its physico-chemical properties.

This review has provided an overview of different approaches that may be applied for the taste masking of APIs in oral paediatric medicinal products, with a focus on the excipients used. Fig. 4 proposes a tool/framework to help to summarise all the aforementioned reflection on taste masking approaches to age appropriate formulations. This is not intended to be a guidance as such but more a rational/practical proposal that may be applied during development.

More than one taste masking technique may be used, and each has advantages and disadvantages. In general, the use of sweeteners and flavours is often the first approach investigated. This is because a wide range of sweeteners and flavouring agents are available, special

Table 13
Lipid excipients used for taste masking of formulations suitable for children.

Excipient name	Drug	Dosage form	Paediatric use	Reference
Glyceryl distearate; hydrogenated soybean oil	Paracetamol	Granules	–	[137]
Glycerol trimyristate; glyceryl dibehenate; glyceryl distearate; hard fat	Sodium benzoate	Pellets	✓	[142]
Hydrogenated coco-glycerides	NXP120	Pellets	–	[108]
	Acetaminophen	Chewable tablet	–	[135,136]
Glycerol tristearate	Praziquantel	Pellets	–	[143]
Glyceryl dibehenate	Theophylline; Chloroquine	Granulates	–	[132,139]
	Praziquantel, Enrofloxacin	Pellets	–	[144]
Bees wax, cetyl alcohol	Bromhexine HCl	Pellets	–	[140]
	Salbutamol			

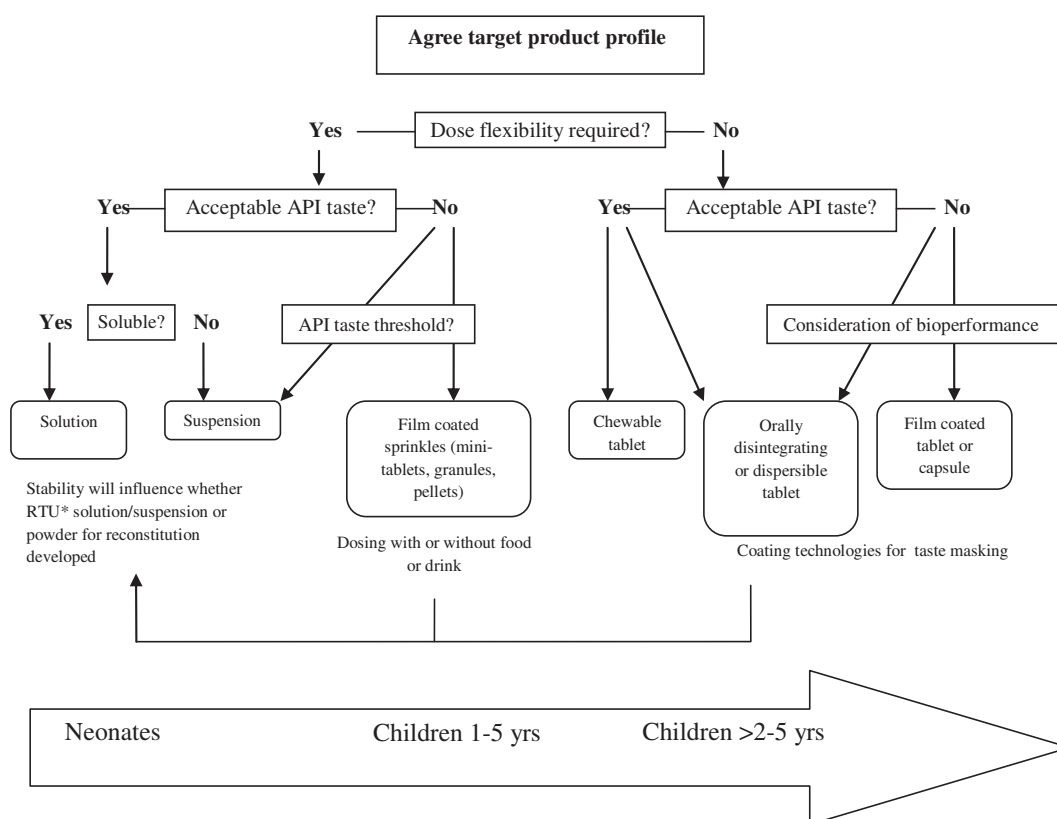


Fig. 4. Taste masking approaches for age-appropriate formulations.

manufacturing technologies or equipment are not required and API release rates are unlikely to be affected. Despite these advantages, the use of sweeteners and flavours is not the most effective means of taste masking and selection of sweeteners and flavours. Modification of an APIs solubility may improve its taste characteristics, although this approach is not suitable for all APIs and would often be used in combination with sweetener/flavour. Furthermore, potential effects on PK characteristics need to be considered.

The use of complexation with IERs or CDs is likely to be more effective than the use of flavours and sweeteners, although it is more technically challenging. Indeed, the suitability of complexation for taste masking depends upon the physico-chemical properties of the API and the dose required. Polymeric and lipidic coatings are considered to be the most effective techniques for taste masking. However, as for complexation, these approaches are more technically challenging than the use of flavours and sweeteners alone and specialist equipment may be required. In addition, coatings may have an impact on the bioavailability of the paediatric product.

Bitter blockers and taste modifiers offer an interesting alternative approach to taste masking. The use of these compounds is fairly new and unproven.

It can therefore be concluded that a range of techniques may be used for the taste masking of paediatric medicinal products. Selection of taste masking approach needs to be done on a case-by-case basis.

References

- [1] Periodic Survey #44 Patient compliance with prescription regimens, American Academy of Pediatrics, http://www.aap.org/en-us/professional-resources/Research/Pages/PS44_Executive_Summary_PatientComplianceWithPrescriptionRegimens.aspx 2000 (Last accessed 26 March 2013).
- [2] D. Matsui, Current issues in pediatric medication adherence, *Pediatr. Drugs* 9 (5) (2007) 283–288.
- [3] J.A. Mennella, M.Y. Pepino, D.R. Reed, Genetic and environmental determinants of bitter perception and sweet preferences, *Pediatrics* 115 (2) (2005) e216–e222 (Feb.).
- [4] J.A. Mennella, G.K. Beauchamp, Optimizing oral medications for children, *Clin. Ther.* 30 (2008) 2120–2132.
- [5] Committee for Medicinal Products for Human Use (CHMP), Paediatric Committee (PDCO), EMA/CHMP/QWP/805880/2012 Rev. Guideline on pharmaceutical development of medicines for paediatric use, http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/07/WC500147002.pdf August 2013 (Last accessed 23 January 2014).
- [6] R. Cohen, F. de La Rocque, A. Lécuyer, C. Wollner, M.J. Bodin, A. Wollner, Study of the acceptability of antibiotic syrups, suspensions, and oral solutions prescribed to pediatric outpatients, *Eur. J. Pediatr.* 168 (7) (2009) 851–857.
- [7] A. Wollner, A. Lécuyer, F. De La Rocque, G. Sedletzki, V. Derkx, M. Boucherat, A. Elbez, N. Gelbert-Baudino, C. Levy, F. Corrad, A. Cohen, Acceptability, compliance and schedule of administration of oral antibiotics in outpatient children, *Arch. Pediatr.* 18 (5) (2011) 611–616.
- [8] Regulation EC No. 1901/2006, <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:378:0001:0019:en:PDF> (Last accessed 26 March 2013).
- [9] Z. Ayenew, V. Puri, L. Kumar, A.K. Bansal, Trends in pharmaceutical taste masking technologies: a patent review, *Recent Pat. Drug Deliv. Formul.* 3 (2009) 26–39.
- [10] D. Douroumis, Practical approaches of taste masking technologies in oral solid forms, *Expert Opin. Drug Deliv.* 4 (2007) 417–426.
- [11] H. Sohi, Y. Sultana, R.K. Khar, Taste masking technologies in oral pharmaceuticals: recent developments and approaches, *Drug Dev. Ind. Pharm.* 30 (2004) 429–448.
- [12] S.V. Lipchick, D.R. Reed, J.A. Mennella, Relationship between bitter-taste receptor genotype and solid medication formulation usage among young children: a retrospective analysis, *Clin. Ther.* 34 (3) (2012) 728–733.
- [13] C. Biever, Bitter pills banished by taste-blocking compounds, *New Scientist*, <http://www.newscientist.com/article/dn3433-bitter-pills-banished-by-tasteblocking-compounds.html> Feb 2003 (Last accessed 10 Feb 2013).
- [14] Modifying Bitterness: Mechanism, Ingredients and Applications, in: G.M. Roy (Ed.), Technomic Publishing Company, 1997.
- [15] R. McGregor, Bitter blockers in foods and pharmaceuticals, in: A. Taylor, J. Hort (Eds.), *Modifying Flavour in Food*, Woodhead Publishing, 2007, pp. 221–231.
- [16] Redpoint Bio website, http://www.redpointbio.com/science_taste.shtml (Last accessed 10 Feb 2013).
- [17] R. McGregor, Future directions: using biotechnology to discover new sweeteners, bitter blockers and sweetness potentiators, in: W.J. Spillane (Ed.), *Optimising Sweet Taste in Foods*, CRC Press, 2006, pp. 404–414.
- [18] J.A. Mennella, M.Y. Pepino, G.K. Beauchamp, Modification of bitter taste in children, *Dev. Psychobiol.* 43 (2) (2003) 120–127 (Sep).
- [19] D.A. Deshpande, W.C.H. Wang, E.L. McIlmoyle, K.S. Robinett, R.M. Schillinger, S.S. An, J.S.K. Sham, S.B. Liggett, Bitter taste receptors on airway smooth muscle bronchodilate by localized calcium signaling and reverse obstruction, *Nat. Med.* 16 (2010) 1299–1304.

- [20] D. Ming, Y. Ninomiya, R.F. Margolskee, Blocking taste receptor activation of gustducin inhibits gustatory responses to bitter compounds, *PNAS* 96 (17) (1999) 9903–9908.
- [21] R.S.J. Keast, P.A.S. Breslin, Modifying the bitterness of selected oral pharmaceuticals with cation and anion series of salts, *Pharm. Res.* 19 (7) (2002) 1019–1026.
- [22] in-Pharma Technologist.com, Bitter blocker backed by FDA, <http://www.in-pharmatechnologist.com/Regulatory-Safety/Bitter-blocker-backed-by-FDA> Sept 2004 (Last accessed 10 Feb 2013).
- [23] P.J. Weller, Neohesperidan dihydrochalcone, in: R.C. Rowe, P.J. Shenskey, W.G. Cook, M.E. Fenton (Eds.), *Handbook of Pharmaceutical Excipients*, Pharmaceutical Press, London & Philadelphia, 2012, pp. 518–519.
- [24] H. Mitchell, *Sweeteners and Sugar Alternatives in Food Technology*, first edition Wiley-Blackwell, Oxford, 2006.
- [25] International Sweeteners Association, Neohesperidin DC Fact Sheet, http://www.isabru.org/pdf/Neohesperidine_DC_August_2009_EN.pdf 2009 (Last accessed 10 Feb 2013).
- [26] Naturex website, <http://www.thaumatococcus.com/> Last accessed 10 Feb 2013.
- [27] J.P. Ley, G. Krammer, G. Reinders, L.L. Gatfield, H.J. Bertram, Evaluation of bitter masking flavanones from *Herba Santa* (*Eriodictyon californicum* (H. and A.) Torr., Hydrophyllaceae), *J. Agric. Food Chem.* 53 (15) (2005) 6061–6066.
- [28] J.A. Riemer, Kraft General Foods, Bitterness inhibitors. United States Patent 5,336,513 (1994).
- [29] G.E. Inglett, B. Dowling, J.J. Albrecht, F.A. Hoglan, Taste-modifying properties of miracle fruit (*Synsepalum dulcificum*), *J. Agric. Food Chem.* 13 (3) (1965) 284–287.
- [30] Wikipedia, The Free Encyclopedia, *Synsepalum dulcificum*, http://en.wikipedia.org/wiki/Synsepalum_dulcificum (Last accessed 10 Feb 2013).
- [31] M.K. Wilken, B.A. Satiroff, Pilot study of “miracle fruit” to improve food palatability for patients receiving chemotherapy, *Clin. J. Oncol. Nurs.* 16 (5) (2012) 173–177.
- [32] A. Paladino, S. Costantini, G. Colonna, A.M. Facchiano, Molecular modelling of miraculin: structural analyses and functional hypotheses, *Biochem. Biophys. Res. Commun.* 367 (1) (2008) 26–32.
- [33] J. Piao, B.C. Min, K. Sakamoto, Study of evoked potentials induced by stimulus of four basic tastes under the influence of miracle fruit, *Jpn. J. Taste Smell Res.* 5 (3) (1998) 391–394.
- [34] A.S. Mundada, N.O. Chachda, J.G. Avari, Taste masking approaches – a review: part II, *Am. Pharm. Rev.* 11 (6) (2008) 74–82.
- [35] D.A. Tisi, The taste of success, *Pharm. Formul. Qual.* 11 (2) (2009) 14–18.
- [36] Food and Drug Administration (FDA), List of food additives that are generally recognized as safe (GRAS), <http://www.accessdata.fda.gov/scripts/cfn/cfnNavigation.cfm?rpt=scogsListing> (Last accessed 28 March 2013).
- [37] B. DeFer, Food ingredients – sweetener technical overview and allowable daily intake (ADI), The NutraSweet Company, Chicago, 2010, 22.
- [38] R. Wilson, et al., (Eds.), *Sweeteners, Leatherhead Ingredients Handbook*, third ed., John Wiley & Sons, New York, 2007.
- [39] A.S. Mundada, S. Jain, N.O. Chachda, J.G. Avari, Taste masking approaches – a review: part I, *Am. Pharm. Rev.* 11 (4) (2008) 94–102.
- [40] Regulation EU/872/2012 and EU/873/2012, <http://eur-lex.europa.eu/JOhtml.do?uri=OJ:L:2012:267:SOM:EN:HTML> (Last accessed 18 March 2013).
- [41] CHMP, EMEA, Reflection paper: Formulation of choice for the paediatric population, <http://www.emea.europa.eu/pdfs/human/paediatrics/19481005en.pdf> 2006 (Last accessed 28 March 2013).
- [42] S. Abdulla, B. Amuri, A.M. Kabanywany, D. Ubben, C. Reynolds, S. Pascoe, S. Fitoussi, C.M. Yeh, M. Nuorti, R. Séchaud, G. Kaiser, G. Lefèvre, Early clinical development of artemether-lumefantrine dispersible tablet: palatability of three flavours and bioavailability in healthy subjects, *Malar. J.* 3 (9) (2010) 253.
- [43] FLAVORx, <http://flavorx.com/> (Last accessed 18 March 2013).
- [44] C.P. Aires, C.P. Tabchoury, A.A. Del Bel Cury, H. Koo, J.A. Cury, Effect of sucrose concentration on dental biofilm formed in situ and on enamel demineralization, *Caries Res.* 40 (1) (2006) 28–32.
- [45] H.A. Grabitske, J.L. Slavin, Gastrointestinal effects of low-digestible carbohydrates, *Crit. Rev. Food Sci. Nutr.* 49 (4) (2009) 327–360 (Apr).
- [46] EC Notice to applicants. Volume 3B Guidelines, Medicinal products for human use. Safety, environment and information. Excipients in the label and package leaflet of medicinal products for human use, http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003412.pdf July 2003 (Last accessed 18 March 2013).
- [47] EMA/CHMP/SWP/888239/2011 Concept paper on the need for revision of the guideline on excipients in the label and package leaflet of medicinal products for human use, http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/03/WC500123804.pdf (Last accessed 18 March 2013).
- [48] V.L. Grotz, I.C. Munro, An overview of the safety of sucralose, *Regul. Toxicol. Pharmacol.* 55 (2009) 1–5.
- [49] D. Brusick, J.F. Borzelleca, M. Gallo, G. Williams, J. Kille, A.W. Hayes, F.X. Pi-Sunyer, C. Williams, W. Burks, Expert panel report on a study of Splenda in male rats, *Regul. Toxicol. Pharmacol.* 55 (2009) 6–12.
- [50] M.B. Abou-Donia, E.M. El-Masry, A.A. Abdel-Rahman, R.E. McLendon, S.S. Schiffman, Splenda alters gut microflora and increases intestinal P-glycoprotein and cytochrome P-450 in male rats, *J. Toxicol. Environ. Health A* 71 (21) (2008) 1415–1429.
- [51] G.J. Wyley, MXP008720 (2004).
- [52] Y.J. Park, D.S. Kang, WO2004096214 (2004).
- [53] T.A. Hagen, CN1697648, 2005.
- [54] A. Reiner, G.Reiner, US Patent 7 482,377 (2009).
- [55] S. Motola, A.R. Branfman, G.R. Agisim, D.J. Quirk, US Patent 502862 (1991).
- [56] J.W. Rayburn, WO2000012067A1 (2003).
- [57] B.G. Neves, A. Farah, E. Lucas, V.P. de Sousa, L.C. Maia, Are paediatric medicines risk factors for dental caries and dental erosion? *Community Dent. Health* 27 (1) (2010) 46–51 (Mar).
- [58] R.V. Keny, C. Desouza, C.F. Lourenco, Formulation and evaluation of rizatriptan benzoate mouth disintegrating tablets, *Indian J. Pharm. Sci.* 72 (2010) 79–85.
- [59] I. Singh, A.K. Rehni, R. Kalra, G. Joshi, M. Kumar, H.Y. Aboul-Enein, Ion exchange resins: drug delivery and therapeutic applications, *FABAD J. Pharm. Sci.* 32 (2007) 91–100.
- [60] M.V. Srikanth, S.A. Sunil, N.S. Rao, M.U. Uhumwangho, K.V. Ramana Murthy, Ion-exchange resins as controlled drug delivery carriers, *J. Sci. Res.* 2 (2010) 597–611.
- [61] F. Gut, W. Schiek, W.E. Haefeli, I. Walter-Sack, J. Burhenne, Cation exchange resins as pharmaceutical carriers for methylene blue: binding and release, *Eur. J. Pharm. Biopharm.* 69 (2008) 582–587.
- [62] H. Ben-Aryeh, S. Lapid, R. Szargel, A. Benderly, D. Gutman, Composition of whole unstimulated saliva of human infants, *Arch. Oral Biol.* 29 (1984) 357–362.
- [63] D. Cogulu, E. Sabah, N. Kutukculer, F. Ozkinay, Evaluation of the relationship between caries indices and salivary secretory IgA, salivary pH, buffering capacity and flow rate in children with Down's syndrome, *Arch. Oral Biol.* 51 (2006) 23–28.
- [64] H.J. Schneider, W. Dedek, R. Grah, B. Mothes, J. Uhlemann, H. Schwarz, G. Schwachulla, H. Reuter, M. Möhring, Studies of the persorption of large particles from radio-labelled cation exchangers, *Urol. Int.* 38 (1983) 116–120.
- [65] B.A. Becker, J.G. Swift, Effective reduction of the acute toxicity of certain pharmacologic agents by use of synthetic ion exchange resins, *Toxicology* 1 (1959) 42–54.
- [66] R. Agarwal, R. Mittal, A. Singh, Studies of ion-exchange resin complex of chloroquine phosphate, *Drug Dev. Ind. Pharm.* 26 (2000) 773–776.
- [67] V.K. Chatap, D.K. Sharma, P.T. Deshmukh, V.B. Gupta, Taste masking property of ion exchange resin: a review, *Pharmatimes* 40 (2008) 22–26.
- [68] R.B. Shah, M.A. Tawakkul, V.A. Sayeed, M.A. Khan, Complexation between risperidone and Amberlite resin by various methods of preparation and binding study, *Drug Dev. Ind. Pharm.* 35 (2009) 1409–1418.
- [69] V.D. Wagh, S.V. Ghadlinge, Taste masking methods and techniques in oral pharmaceuticals: current perspectives, *J. Pharm. Res.* 2 (2009) 1049–1054.
- [70] S. Patra, R. Samantaray, S. Pattnaik, B.B. Barik, Taste masking of etoricoxib by using ion-exchange resin, *Pharm. Dev. Technol.* 15 (2010) 511–517.
- [71] M.R. Bhalekar, S.J. Bidkar, T.K. Shete, A.R. Madgulkar, Taste masking of cefuroxime axetil by ion exchange resin complex, *Lat. Am. J. Pharm.* 29 (2010) 198–204.
- [72] I.S.G. Huda, S.S. Toshinwal, Taste masked orodispersible tablet of atomoxetine hydrochloride, *Lat. Am. J. Pharm.* 30 (2011) 1785–1791.
- [73] W. Samprasit, P. Opanasopit, P. Akkaramongkolporn, T. Ngawhirunpat, K. Wongsermsin, S. Panomsuk, Preparation and evaluation of taste-masked dextromethorphan oral disintegrating tablet, *Pharm. Dev. Technol.* 17 (2012) 315–320.
- [74] E. Schornick, Entwicklung und Herstellung geschmacksmaskierter Zubereitungen von Methyleneblau-Resinaten zur Behandlung von Kindern mit Malaria, (Ph.D. thesis) Heinrich Heine University Düsseldorf, Germany, 2011.
- [75] C.G. Geetha Rao, A.V. Motiwale, D. Satyanarayana, E.V.S. Subrahmanyam, Formulation of taste masked oral suspension of quinine sulphate by complexation, *Indian J. Pharm. Sci.* 6 (2004) 329–331.
- [76] A.R. Madgulkar, M.R. Bhalekar, R.R. Padalkar, Formulation design and optimization of novel taste masked mouth-dissolving tablets of tramadol having adequate mechanical strength, *AAPS PharmSciTech* 10 (2009) 574–581.
- [77] T.Y. Puttevar, M.D. Kshirsagar, A.V. Chandewar, R.V. Chikhale, Formulation and evaluation of orodispersible tablet of taste masked doxylamine succinate using ion exchange resin, *J. King Saudi Univ. Sci.* 22 (4) (2010) 229–240.
- [78] D. Shukla, S. Chakraborty, S. Singh, B. Mishra, Fabrication and evaluation of taste masked resinate of risperidone and its orally disintegrating tablets, *Chem. Pharm. Bull.* 57 (2009) 337–345.
- [79] S.P. Jain, D.C. Mehta, S.P. Shah, P.P. Singh, P.D. Amin, Melt-in-mouth pellets of fexofenadine hydrochloride using croscopolone as an extrusion-spheronisation aid, *AAPS PharmSciTech* 11 (2010) 917–923.
- [80] S. Malke, S. Shidhaye, V. Kadam, Novel melt granulation using sugars for metoclopramide hydrochloride orally disintegrating tablet, *Asian J. Pharm. Clin. Res.* 2 (2009) 68–72.
- [81] D.P. Venkatesh, C.G. Geetha Rao, Formulation of taste masked orodispersible tablets of ambroxol hydrochloride, *Asian J. Pharm.* 2 (2008) 261–264.
- [82] K. Bhise, S. Shaikh, D. Bora, Taste mask, design and evaluation of an oral formulation using ion exchange resins as drug carrier, *AAPS PharmSciTech* 9 (2008) 557–562.
- [83] E. Roblegg, P. Dittrich, K. Halmeyer, A. Zimmer, Reformulation of a codeine phosphate liquid controlled-release product, *Drug Dev. Ind. Pharm.* 36 (2010) 1454–1462.
- [84] W. Cook, Cyclodextrins, in: R.C. Rowe, P.J. Shenskey, W.G. Cook, M.E. Fenton (Eds.), *Handbook of Pharmaceutical Excipients*, Pharmaceutical Press, London & Philadelphia, 2012, pp. 229–233.
- [85] M.E. Davis, M.E. Brewster, Cyclodextrin-based pharmaceuticals: past, present and future, *Nat. Rev.* 3 (2004) 1023–1035.
- [86] J. Szejtli, D. Szenté, Elimination of bitter, disgusting tastes of drugs and foods by cyclodextrins, *Eur. J. Pharm. Biopharm.* 61 (3) (2005) 115–125.
- [87] H. Arima, T. Higashi, K. Motoyama, Improvement of the bitter taste of drugs by complexation with cyclodextrins: applications, evaluations and mechanisms, *Ther. Deliv.* 3 (5) (2012) 633–644.
- [88] P.C. Barrow, P. Olivier, D. Marzin, The reproductive and developmental toxicity profile of beta-cyclodextrin in rodents, *Reprod. Toxicol.* 9 (4) (1995) 389–398.
- [89] T. Irie, K. Uekama, Pharmaceutical applications of cyclodextrins. III. Toxicological issues and safety evaluation, *J. Pharm. Sci.* 86 (2) (1997) 147–162.
- [90] E.A. Thackaberry, S. Kopytek, P. Sherratt, K. Trouba, B. McIntyre, Comprehensive investigation of hydroxypropyl methylcellulose, propylene glycol, polysorbate 80 and hydroxypropyl-beta-cyclodextrin for use in general toxicology studies, *Toxicol. Sci.* 117 (2) (2010) 485–492.
- [91] B. Flourie, C. Molis, L. Achour, H. Dupas, C. Hatat, J.C. Rambaud, Fate of β -cyclodextrin in the human intestine, *J. Nutr.* 123 (1993) 676–680.

- [92] M.F. Al-Omran, S.A. Al-Suwaych, A.M. El-Helw, S.I. Saleh, Taste masking of diclofenac sodium employing four different techniques, *Saudi Pharm. J.* 10 (3) (2002) 106–113.
- [93] A. Binello, G. Cravotto, G.M. Nano, P. Spagliardi, Synthesis of chitosan-cyclodextrin adducts and evaluation of their bitter-masking properties, *Flavour Fragrance J.* 19 (2004) 394–400.
- [94] A. Binello, B. Robaldo, A. Barge, R. Cavalli, G. Cravotto, Synthesis of cyclodextrin-based polymers and their use as debittering agents, *J. Appl. Polym. Sci.* 107 (2008) 2549–2557.
- [95] P.P. Shah, R.C. Mashru, Formulation and evaluation of taste masked oral reconstitutable suspension of primaquine phosphate, *AAPS PharmSciTech* 9 (3) (2008) 1025–1030.
- [96] A.R. Patel, P.R. Vavia, Preparation and evaluation of taste masked famotidine formulation using drug/ β -cyclodextrin/polymer ternary complexation approach, *AAPS PharmSciTech* 9 (2) (2008) 544–550.
- [97] P.P. Shah, R.C. Mashru, Palatable reconstitutable dry suspension of artemether for flexible pediatric dosing using cyclodextrin inclusion complexation, *Pharm. Dev. Technol.* 15 (3) (2010) 276–285.
- [98] A. Mahesh, N. Shastri, M. Sadanandam, Development of taste masked fast disintegrating films of levocetirizine dihydrochloride for oral use, *Curr. Drug Deliv. J.* 7 (2010) 21–27.
- [99] F.M. Mady, A.E. Abou-Taleb, K.A. Khaled, K. Yamasaki, D. Iohara, T. Ishiguro, F. Hirayama, K. Uekama, M. Otagiri, Enhancement of the aqueous solubility and masking the bitter taste of famotidine using drug/SBE- β -CyD/povidone K30 complexation approach, *J. Pharm. Sci.* 99 (10) (2010) 4285–4294.
- [100] S.T. Bihade, V.H. Bankar, P.D. Gaikwad, S.P. Pawar, Preparation and evaluation of cyclodextrin based binary systems for taste masking, *Int. J. Pharm. Sci. Drug Res.* 2 (3) (2010) 199–203.
- [101] M. Sevukarajan, T. Bachala, R. Nair, Novel inclusion complexes of oseltamivir phosphate with β cyclodextrin: physico-chemical characterization, *J. Pharm. Sci. Res.* 2 (9) (2010) 583–589.
- [102] N. Ono, Y. Miyamoto, T. Ishiguro, K. Motoyama, F. Hirayama, D. Iohara, H. Seo, S. Tsuruta, H. Arima, K. Uekama, Reduction of bitterness of antihistaminic drugs by complexation with β -cyclodextrins, *J. Pharm. Sci.* 100 (5) (2011) 1935–1943.
- [103] J. Xu, L.L. Bovet, K. Zhao, Taste masking microspheres for orally disintegrating tablets, *Int. J. Pharm.* 359 (1–2) (2008) 63–69.
- [104] M.F. Al-Omran, S.A. Al-Suwaych, A.M. El-Helw, S.I. Saleh, Taste masking of diclofenac sodium using microencapsulation, *J. Microencapsul.* 19 (1) (2002) 45–52.
- [105] Y. Hashimoto, M. Tanaka, H. Kishimoto, Preparation, characterization and taste-masking properties of polyvinylacetate diethylaminoacetate microspheres containing trimebutine, *J. Pharm. Pharmacol.* 54 (2002) 1323–1328.
- [106] M. Guhmann, M. Preis, F. Gerber, N. Pollinger, J. Breitzkreutz, W. Weitschies, Development of oral taste masked diclofenac formulations using a taste sensing system, *Int. J. Pharm.* 438 (1–2) (2012) 81–90.
- [107] L. Dobetti, Fast disintegrating tablets, US Patent 6,596,311 (2003)
- [108] J. Vaassen, K. Bartscher, J. Breitzkreutz, Taste masked lipid pellets with enhanced release of hydrophobic active ingredient, *Int. J. Pharm.* 429 (2012) 99–103.
- [109] V. Jannin, Y. Cuppok, Hot-melt coating with lipid excipients, *Int. J. Pharm.* (2012), <http://dx.doi.org/10.1016/j.ijpharm.2012.10.026>.
- [110] M. Maniruzzaman, J.S. Boateng, M. Bonnefille, A. Aranyos, J.C. Mitchell, D. Douroumis, Taste masking of paracetamol by hot-melt extrusion: an in vitro and in vivo evaluation, *Eur. J. Pharm. Biopharm.* 80 (2) (2012) 433–442.
- [111] A. Gryczke, S. Schminke, M. Maniruzzaman, J. Beck, D. Douroumis, Development and evaluation of orally disintegrating tablets (ODTs) containing Ibuprofen granules prepared by hot melt extrusion, *Colloids Surf., B* 80 (2) (2011) 275–284.
- [112] Joint expert committee for food additives (JECFA), Toxicological evaluation of certain food additives and contaminants. WHO Food Additives Series, No. 26, nos 680–693, <http://www.inchem.org/pages/jecfa.html> 1990 (Last accessed 29 March 2013).
- [113] J. Eisele, G. Haynes, T. Rosamilia, Characterisation and toxicological behaviour of basic methacrylate copolymer for GRAS evaluation, *Regul. Toxicol. Pharm.* 61 (2011) 32–43.
- [114] J. Eisele, G. Haynes, K. Kreuzer, T. Rosamilia, Characterisation and toxicological assessment of neutral methacrylate copolymer for GRAS evaluation, *Regul. Toxicol. Pharmacol.* 67 (2013) 392–408.
- [115] H.C. Hodge, The chronic toxicity of cellulose acetate phthalate in rats and dogs, *J. Pharmacol. Exp. Ther.* 80 (1944) 250–255.
- [116] P.C. Kayumba, N. Huyghebaert, C. Cordella, J.D. Ntawukulirayao, C. Vervaeke, J.P. Remon, Quinine sulphate pellets for flexible pediatric drug dosing: formulation development and evaluation of taste-masking efficiency using the electronic tongue, *Eur. J. Pharm. Biopharm.* 66 (2007) 460–465.
- [117] P.C. Kayumba, M. Twagirumukiza, N. Huyghebaert, J.D. Ntawukulirayao, L. van Bortel, C. Vervaeke, J.P. Remon, Taste-masked quinine sulphate pellets: bioavailability in adults and steady-state plasma concentrations in children with uncomplicated *Plasmodium falciparum* malaria, *Ann. Trop. Paediatr.* 28 (2008) 103–109.
- [118] Y. Shirai, K. Sogo, K. Yamamoto, K. Kojima, H. Fujioka, H. Makita, Y. Nakamura, A novel fine granule system for masking bitter taste, *Biol. Pharm. Bull.* 16 (1993) 172–177.
- [119] T. Hamashita, Y. Nakagawa, T. Aketo, S. Watano, Granulation of core particles suitable for film coating by agitation fluidized bed I. Optimum formulation for core particles and development of a novel friability test method, *Chem. Pharm. Bull.* 55 (2007) 1169–1174.
- [120] T. Hamashita, M. Matsuzaki, T. Ono, M. Ono, Y. Tsunenari, T. Aketo, S. Watano, Granulation of core particles suitable for film coating by agitation fluidized bed II. A proposal of a rapid dissolution test for evaluation of bitter taste of ibuprofen, *Chem. Pharm. Bull.* 56 (2008) 883–887.
- [121] M.F. Lu, S. Borodkin, L. Woodward, P. Li, C. Diesner, L. Hernandez, M. Vadnere, A polymer carrier system for taste masking of macrolide antibiotics, *Pharm. Res.* 8 (1991) 706–712.
- [122] M. Cerea, W. Zheng, C.R. Young, J.W. McGinity, A novel powder coating process for attaining taste masking and moisture protective films applied to tablets, *Int. J. Pharm.* 279 (2004) 127–139.
- [123] N. Pearnchob, J. Siepmann, R. Bodmeier, Pharmaceutical applications of shellac: moisture-protective and taste-masking coatings and extended-release matrix tablets, *Drug Dev. Ind. Pharm.* 29 (2003) 925–938.
- [124] K. Kondo, T. Niwa, Y. Ozeki, M. Ando, K. Danjo, Preparation and evaluation of orally rapidly disintegrating tablets containing taste-masked particles using one-step dry-coated tablets technology, *Int. J. Pharm.* 39 (10) (2011) 1214–1224.
- [125] A. Chivate, V. Sargar, P. Nalawade, V. Tawde, Formulation and development of oral dry suspension using taste masked Ornidazole particles prepared using Kollicoat-Smartseal 30D, *Drug Dev. Ind. Pharm.* 39 (7) (2013) 935–935.
- [126] A.G. Balducci, G. Colombo, G. Corace, C. Cavallari, L. Rodriguez, F. Buttini, P. Colombo, A. Rossi, Layered lipid microcapsules for mesalazine delayed-release in children, *Int. J. Pharm.* 421 (2) (2011) 293–300.
- [127] M.A. Repka, S. Shah, J.N. Lu, S. Maddineni, J. Morott, K. Patwardhan, N.N. Mohammed, Melt extrusion: process to product, *Expert Opin. Drug Deliv.* 9 (1) (2012) 105–125.
- [128] W. Erni, M. Zeller, N. Poit, Die Eignung von Fettpellets als Zwischenform für perorale depotarzneiformen, *Acta Pharm. Technol.* 26 (1980) 165–171.
- [129] M. Savolainen, J. Herder, C. Khoo, K. Lovqvist, C. Dahlqvist, H. Glad, A.M. Jupp, Evaluation of polar lipid-hydrophilic polymer microparticles, *Int. J. Pharm.* 262 (1–2) (2003) 47–62.
- [130] N. Passerini, B. Albertini, B. Perissutti, L. Rodriguez, Evaluation of melt granulation and ultrasonic spray congealing as techniques to enhance the dissolution of praziquantel, *Int. J. Pharm.* 318 (1–2) (2006) 92–102.
- [131] E. Pallagi, K. Vass, K. Pintye-Hodi, P. Kasa, G. Falkay, I. Eros, P. Szabo-Revesz, Iron(II) sulfate release from drop-formed lipophilic matrices developed by special hot-melt technology, *Eur. J. Pharm. Biopharm.* 57 (2) (2004) 287–294.
- [132] A. Faham, P. Prinderre, N. Farah, K.D. Eichler, G. Kalantzis, J. Joachim, Hot-melt coating technology. I. Influence of Compritol 888ATO and granule size on theophylline release, *Drug Dev. Ind. Pharm.* 26 (2000) 167–176.
- [133] R.H. Müller, K. Mäder, S. Göhl, Solid lipid nanoparticles (SLN) for controlled drug delivery: a review of the state of the art, *Eur. J. Pharm. Biopharm.* 50 (2000) 161–177.
- [134] J.C.B. N'Goma, S. Amara, K. Dridi, V. Jannin, F. Carriere, Understanding the lipid-digestion processes in the GI tract before designing lipid-based drug-delivery systems, *Ther. Deliv.* 3 (1) (2012) 105–124.
- [135] H. Suzuki, H. Onishi, Y. Takahashi, M. Iwata, Y. Machida, Development of oral acetaminophen chewable tablets with inhibited bitter taste, *Int. J. Pharm.* 251 (2003) 123–132.
- [136] H. Suzuki, H. Onishi, S. Hisamatsu, K. Masuda, Y. Takahashi, M. Iwata, Y. Machida, Acetaminophen-containing chewable tablets with suppressed bitterness and improved oral feeling, *Int. J. Pharm.* 278 (2004) 51–61.
- [137] S. Bold, A. Boegershausen, O. Ruch, O. Graner, S. Klein, Hot Melt Coating with Fast Release as an Innovative Taste Masking Concept AAPS, <http://abstracts.aapspharmaceutica.com/Verify/AAPS2012/postersubmissions/W4090.pdf> 2012 (Last accessed 28 March 2013).
- [138] P. Krahs, S. Bold, L. Fahsel, EP 2 198 859 A1, 2012.
- [139] A. Faham, P. Prinderre, P. Piccerelle, N. Farah, J. Joachim, Hot melt coating technology: influence of Compritol (R) 888 Ato and granule size on chloroquine release, *Pharmazie* 55 (6) (2000) 444–448.
- [140] A. Patil, S. Chafle, D. Khobragade, S. Umathe, J. Avari, Evaluation of hot melt coating as taste masking tool, *Int. Res. J. Pharm.* 2 (2011) 169–172.
- [141] H. Sugao, S. Yamazaki, H. Shiozawa, K. Yano, Taste masking of bitter drug powder without loss of bioavailability by heat treatment of wax-coated microparticles, *J. Pharm. Sci.* 87 (1) (1998) 96–100.
- [142] J. Krause, Novel paediatric formulations for the drug sodium benzoate, (Ph.D. Thesis) Heinrich-Heine-University, Duesseldorf, Germany, 2008.
- [143] R. Witzleb, V.R. Kanikanti, H.J. Hamann, P. Kleinbude, Solid lipid extrusion with small die diameters – electrostatic charging, taste masking and continuous production, *Eur. J. Pharm. Biopharm.* 77 (1) (2011) 170–177.
- [144] A. Michalk, Taste masking by solid lipid extrusion, (Ph.D. Thesis) Heinrich-Heine-University, Duesseldorf, Germany, 2007.
- [145] A. Cram, J. Breitzkreutz, S. Desset-Brethes, T. Nunn, C. Tuleu, Challenges of developing palatable oral paediatric formulations, *Int. J. Pharm.* 365 (1–2) (2009) 1–3.
- [146] T. Sam, T.B. Ernest, J. Walsh, J.L. Williams, A benefit/risk approach towards selecting appropriate pharmaceutical dosage forms – an application for paediatric dosage form selection, *Int. J. Pharm.* 435 (2) (2012) 115–123.