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Commentary

Challenges of developing palatable oral paediatric formulations

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1. Introduction

The development of paediatric medicines can be very challenging. This was recognised by the European Paediatric Formulation Initiative (EuPFI), a group consisting of paediatric formulation experts predominantly from industry, as well as academia and clinical pharmacy. EuPFI was founded in 2007 with the aim of raising awareness of paediatric formulation issues. The current focus areas of the group include excipients, taste assessment, delivery devices for the administration of medicines, and extemporaneous preparations. This commentary, paper written in response to the recent editorial (Florence, 2008) entitled 'Neglected diseases, neglected technologies, neglected patients?' highlights, on behalf of this group, some of the challenges related to masking the taste of poorly palatable drugs that are encountered on a regular basis during development of oral paediatric medicines.

The development chart (Fig. 1) illustrates the differences between the drug development processes for adults and children. Since the new Paediatric Regulation came into force in the European Union in January 2007 (EMEA, 2006), a Paediatric Investigation Plan (PIP) outlining the paediatric drug product strategy needs to be agreed with the EMEA's Paediatric Committee at an early stage of development (no later than completion of the relevant human pharmacokinetic studies in adults). At this early development stage, only very limited data are likely to be available to guide paediatric formulation development. Taste data would not usually be available at time of writing the PIP, and final paediatric dose(s) may not be defined until later in the development programme. Therefore any information about paediatric dosage form(s) of choice, whose selection will be influenced by taste masking potential and palatability, is likely to be limited in the PIP.

2. Discussion of challenges of developing palatable formulations

Palatability of paediatric oral medications is crucial for adherence to therapeutic regimens (Matsui, 2007). However, development of a palatable formulation can be associated with significant challenges that are discussed in the following paragraphs.

2.1. Challenges related to drug and formulation development

During early development of new drugs intended for the oral route of administration, the main emphasis is on suitability of compound properties for adult dosage forms, with the intention of developing tablet or capsule formulations. Although solid dosage forms are widely accepted by older children and adolescents, younger children and their carers tend to prefer liquid formulations (CHMP, EMEA, 2006).

The taste of a drug is not considered when nominating new compounds for development. Reasons include:

- The most relevant selection criteria are safety, tolerability and efficacy of the compound which are based on non-clinical testing, and physico-chemical properties such as solubility, permeability, stability and crystallinity.
- Adult dosage forms can be easily taste masked by encapsulation or film coating techniques, if required.
- There is a lack of robust and reliable techniques for early taste screening of compounds with limited toxicity data. Such

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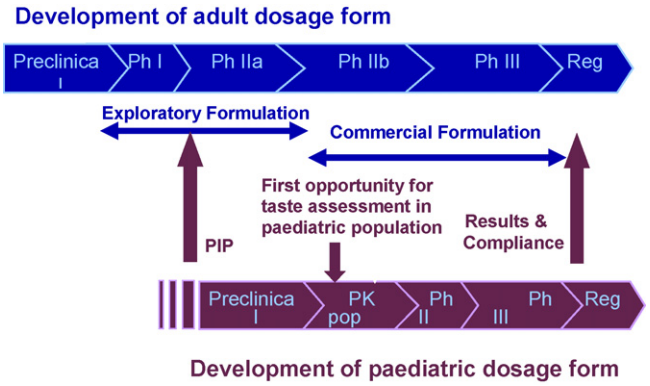

Fig. 1. Dosage form development in adults and in children.

techniques would need to be efficient and cost effective in order to allow assessment of relatively large numbers of compounds and formulations at a development stage where the attrition rate is very high.

- The current understanding of the structure–taste relationships of pharmaceutically active molecules is limited.

However, many drugs are extremely bitter, and as a result of the above, taste is later often found to be unpleasant during the development of paediatric dosage forms. Certain in vitro and in vivo taste prediction techniques such as the electronic tongue technology (Anand et al., 2007) and animal models have shown some early promise and optimisation of these techniques should be encouraged. Assessing the taste properties of drugs at an early stage could facilitate later stage drug product development activities (Worthington, 2007).

In addition, the molecule's solubility characteristics may not be ideal for the liquid dosage form approaches preferred by young children. Compounds with high solubility can be difficult to taste mask in liquid preparations, as they often cannot be easily formulated as suspensions. Even suspensions of poorly soluble compounds can exhibit poor palatability characteristics if the small amount of solubilised drug exceeds the human taste threshold, or if mouthfeel is compromised by the suspended drug substance.

Taste masking of certain solid paediatric dosage forms such as chewable tablets or fast dissolving preparations (e.g. orodispersible tablets and films) can also be challenging, especially for high solubility drugs which may dissolve rapidly in the mouth. Alternative approaches to facilitate taste masking of paediatric solid preparations include coating of drug substance prior to incorporation into formulations, or film-coating of small dosage forms such as pellets or mini tablets.

Compliance of paediatric patients can also be improved by taking into account individual taste preferences of the child. Examples include Children's Tylenol® with Flavour Creator, where a cherry flavoured liquid is supplied together with sachets of different flavouring agents (bubble gum, chocolate, strawberry and apple) that may be added to the liquid prior to administration.[1] A similar concept is the FLAVORx™ system which is widely used in North America and Australia.[2] It consists of 42 dye and sugar free flavours that can be added to oral medications by either the pharmacist, or by the patient or carer to improve palatability (Bunupuradah et al., 2006). The caveat of this approach is that compatibility of the flavours with the medication is often unknown, potentially impacting formulation stability.

A different example is the SIP technology by Grünenthal, a drug delivery system for the precise and easy administration of an antibiotic (Clarosip®) to children. A drinking straw contains the already premeasured dose as coated taste-masked granules and can be used with a beverage of the patient's choice.[3] However, many technologies are protected by patents which restrict their wider use or result in the requirement for royalty payments, making the cost of using the technology more prohibitive.

When designing paediatric dosage forms, formulators need to consider potential excipient-related adverse effects that can occur in children. Therefore excipient types and levels available to the formulator may be restricted which can increase challenges when developing a taste masked dosage form for paediatric use. Regulatory guidance on use of excipients, e.g. avoidance of cariogenic sweeteners and certain colouring and flavouring agents, also needs to be considered. The intention to develop paediatric products with global regulatory acceptability can lead to additional restrictions in excipient types and levels.

In some instances, masking the taste of drugs whilst retaining the original pharmacokinetic profile for the dosage form of choice can also be challenging. Some taste masking approaches such as binding of the drug to ion exchange resins or use of prodrugs or alternative salt forms may alter a drug's in vivo performance. Complex non-standard taste masking techniques could potentially also increase the development time and cost, delaying progress of paediatric medicine to market and exposing paediatric patients to potential risks associated with off-label use of medicines (EMEA, 2004).

2.2. Challenges related to taste assessment

When starting paediatric formulation development, the formulator usually has no or very limited information about the taste of the drug. It is therefore difficult to assess whether and what kind of taste masking will be required. This emphasises the need to generate taste data at an early stage during the development programme, to direct paediatric formulation development. However, as the available experience base of in vitro methods for taste prediction is currently limited, the only way to reliably assess palatability of formulations is a taste study in humans.

The perception of taste of medicines has been shown to be different between adults and children and will probably differ between healthy and sick children (Doty et al., 2008; Schiffman, 2007). Thus, ideally taste should be assessed in children, but there may be some ethical concerns to perform taste studies in healthy children unless the study is a 'swill and spit' one with drugs known to have a good safety profile. The EU ad hoc committee considering ethical aspects of clinical trials in children has stated: 'In principle, healthy children should not be enrolled as healthy volunteers, because they cannot consent and are vulnerable like children with a disease or condition. Studies should not be performed in children when they can be performed in adults. Exceptions could be where healthy children participate in palatability testing such as swill and spit taste testing for a new flavoured medicine' (EMEA, 2008). For many drugs, e.g. cytotoxics, it would be considered unethical to enroll healthy volunteers, even in 'swill and spit' tests. These should have taste assessed when administered to children with the illness to be treated and the study should preferably be imbedded within another clinical study. An advantage is that taste can be assessed during multiple

[1] http://www.tylenol.com.
[2] http://www.flavorx.com/human/default.asp.
[3] http://www.grunenthal.com.

dosing where results may differ from single administration studies in volunteers. Informed consent to taste studies must be obtained from the person with legal responsibility for the child and assent of the child should be obtained wherever possible.

The need for taste tests of new medicines was also recognised by the French Health Products Safety Agency, AFSSAPS, who is proposing paediatric taste acceptability studies for liquid antibiotic preparations (AFSSAPS, 2008). Carrying out taste tests in children is associated with a variety of practical and technical challenges, including questionnaire design and reliability of paediatric responses (Davies and Tuleu, 2008). Interpretation of study results can be difficult as well, as a standard definition of 'acceptable taste' does not exist. Whilst it is important that the taste of the formulation does not impact compliance, the scenario of a 'too pleasant', 'candy-like' formulation with its potential risks (e.g. overdosing and poisoning) also needs to be considered.

In order to obtain early taste data prior to the start of paediatric studies, taste studies in adult volunteers or patients need to be considered. In certain instances, it may be possible to generate adult taste data as part of Phase 1 trials. However, results are not directly transferable to children due to different taste preferences and perception of adults and children (James et al., 1997, 1999; Mennella et al., 2005). In fact, even within the paediatric population, taste preferences differ between age groups as well as culturally and geographically, which creates additional challenges when designing taste studies and developing paediatric products.

It would be extremely useful to the formulator if adult taste tests could be designed and validated in a way that allows results to be transferred to the paediatric population, whilst also being acceptable to the regulatory authorities. One way of achieving this may be to identify adults with a particular taste palate which is more akin to children's. Identifying testers with specialist sensory abilities is an approach commonly used in the food and cosmetics industry.

In practice, due to lack of adequate taste assessment techniques, it is likely that paediatric studies will often be initiated with an enabling dosage form which requires taste optimisation at a later stage of development when paediatric taste data are available. In this case, a bridging strategy, including assessment of bioequivalence between enabling and commercial dosage form, needs to be put in place.

3. Conclusion

Palatability of paediatric oral medications is one of the most crucial factors influencing adherence to therapeutic regimens and therapeutic outcomes. Following implementation of the new European Paediatric Regulation, there is a real incentive for palatability research to be progressed. Indeed the PIP guidelines list taste masking and palatability as proposed studies of particular relevance to the development of paediatric products (EMEA, 2007).

Development of palatable paediatric formulations can be associated with considerable challenges. However, certain areas have been identified where further research may considerably simplify and accelerate the formulation development process:

- Development or optimisation of robust and reliable taste assessment or prediction techniques suitable for early drug product development, where limited toxicological information is available.
- Validation of adult taste panels, allowing transfer of results to the paediatric population.
- Development of platform technologies with universal taste masking capabilities, e.g. encapsulation or complexation. A thorough review of appropriate and available technologies would be beneficial. Taste enhancement approaches used in the food industry should not be overlooked when developing pharmaceutical products.
- Development of 'flexible' dosage forms that take into account the taste preference of the paediatric patient, such as Children's Tylenol® with Flavour Creator or the Grünenthal SIP technology.

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