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Paediatric dosage forms

Proposal of a versatile platform technology

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ABSTRACT *Recent legislation has highlighted the need to develop medicines for the paediatric population, which requires the assessment of efficacy and safety of these products in children. Amongst the challenges of developing paediatric medicines, pharmaceutical companies are obliged to provide age-appropriate dosage forms, which are acceptable to children across the paediatric age range. This article describes the technical considerations for the design of paediatric dosage forms and discusses the available technologies used in administration of drugs to children. The use of multi-particulate dispersible systems is recommended and details of an emerging platform technology are given. Systems of this type can be produced inexpensively, are acceptable in children of all ages, and allow adjustment of doses to provide safer and more effective therapies.*

INTRODUCTION

Prior to the creation of current legislation (1), limited attention had been focussed on the development of medicinal products for the paediatric population. Ethical considerations together with limitations in the availability of funding and constraints in clinical development timelines had restricted the majority of clinical studies to the adult population. As a consequence, the availability of medicines licensed for use in children has been inadequate. In order to address the burden of disease in the paediatric population, off-label and un-licensed adult medicines have often been used despite the lack of clinical evidence demonstrating their long term safety and efficacy. Differences in the pharmacokinetics of drugs in adults and children (2), provides risk of adverse events or reduced efficacy. Children should not be considered small adults and demonstrate age related variations in anatomy and physiology which can impact drug disposition and consequent biological response. In addition to clear differences in body size, children are also subject to inter subject variation in fat mass, extra cellular water, gastrointestinal pH and enzyme activity (3). The delivery of precise and accurate doses of drugs to children is further complicated through the limited availability of dosage forms in age appropriate formats. Most therapeutic agents are marketed as adult products and so the manipulation of these dosage forms is typically required to provide drugs in acceptable form for administration.

The majority of marketed medicines are given orally, although inhaled, topical and injectable products are also available.

Oral medicines are typically presented as tablets and capsules which can be difficult to swallow and are often disliked by children. Ideally, age-appropriate formulations for this route should be easy to swallow and should have acceptable taste, appearance and mouth-feel. Dosage forms should also require minimal instruction and need few subsequent processing steps. The manipulation of adult dosage forms by crushing, reconstitution or division is however often required and provides additional risk to the safety and well-being of patients. The extemporaneous processing of adult dosage forms can lead to the inaccurate apportionment of the unit dose, degradation of drug and loss of active agent. It is clear therefore that provision of formulations suitable for use in children is critical to the safe and effective treatment of disease. The development of commercially available paediatric formulations is however not always considered, owing to low prevalence of some diseases in children. The marked cost of clinical studies and the expense of establishing a robust supply chain for low volume products can also limit the attractiveness of paediatric formulations. This article therefore explores the ethical, supply chain and regulatory drivers for development of a global paediatric platform technology. A cost-effective, robust and versatile formulation approach to alleviate the current limitations in age-appropriate dosage forms is recommended with references made to a prototype preparation.

Regulatory drivers

Since the end of the 20th century, governments and regulatory bodies led by initiatives in the USA have introduced a mixture of legislation and incentives in order to encourage the evaluation of therapeutic agents in the paediatric population. In 1998 "The Paediatric Rule" was established in the US, which required the provision of data from paediatric studies at the time of first marketing submission (4). Although some resistance to these requirements was experienced at the time, the request to substantiate the use of medicines in children remains. To encourage investment of resources in the development of paediatric medicines, financial incentives were also introduced by the US Food and Drug Administration (FDA) in the form of the FDA Modernization Act (1997)-(5). As part of this act, additional exclusivity was offered on new chemical entities (NCEs) licensed in the USA in return for delivery of a paediatric clinical programme in a predetermined indication. Although age-appropriate products were required in these clinical studies, there was no commitment to commercialise these formulations.

Following the lead by the USA, similar initiatives were pursued in the European Union (6), with companies developing drugs for use in Europe now mandated to provide a paediatric investigation plan (PIP) at the conclusion of Phase I studies in man (1). Additional financial incentives were also established to encourage new clinical development programmes in children. Additional exclusivity of 6 months can be obtained for NCEs, whilst orphan drugs receive a supplementary protection certificate (SPC) giving a further 24 months exclusivity. Incentives also exist for marketed drugs through acquisition of paediatric use marketing authorisations (PUMAs).

Ethical and logistical drivers

In addition to the economic and regulatory imperatives for the development of paediatric formulations, considerable ethical and logistical drivers also exist. Medicines intended for use in the paediatric population must demonstrate adequate stability under the climatic conditions to which they are exposed. This is particularly critical when dispensing these products at high temperature and humidity typically experienced in tropical climates (7). Liquid formulations are often the platform of choice, but can be prone to stability issues, particularly for labile drugs. Greater storage and transportation costs can also be encountered for large volume liquids relative to denser solid dosage forms. Minimisation of costs is essential in developing countries, where patients often rely on charities and non-governmental organisations for provision of medical care. Simple, inexpensive solid formulations, suitable for direct administration or reconstitution prior to dosing are therefore required.

A further dilemma in the development of paediatric formulations is the selection of dosage strength. Levels of exposure required to elicit a therapeutic response are likely to differ considerably between children of different age and maturity (3). These issues become increasingly complex when considering requirements for combination products such as those used in treating HIV and malaria (8, 9). A flexible dosing platform, which enables provision of appropriate doses at the point of use and which provides maximal chemical stability is therefore required. The manufacturing processes for these formulations should ideally use conventional technologies where possible, preferably located in production plants local to the patient population. This article is therefore focussed on technology for administration of paediatric medicines and makes recommendation of a formulation platform with potential global appeal and vitality.

Formulation technologies for paediatric drug administration

In recent years considerable attention has been paid to the development of age appropriate formulation technology with suitable attributes for administration to neonates through to adolescents. This has included conventional liquid systems such as oral suspensions and solutions through to thin film technology (10), oro-dispersible tablets (11) and dose sipping technology (12). Oral liquids include suspensions, solutions and emulsions. Despite difficulties in developing oral liquids, they are still the most common medicinal preparations for children in the age range 0-9 years in the US and EU. Liquid formulations are typically easy to administer to infants, toddlers and young children, assuming appropriate taste-masking has taken place and enable

adjustment of doses to account for changes in body mass and surface area across a wide age range. However, the unpleasant taste associated with dissolved drug in these products cannot often be overcome easily and requires the use of artificial sweeteners and flavouring agents. As noted earlier, the stability of drugs in solution is also often inferior to that of the solid state. Recent technological advances have therefore seen a move towards solid dosage forms which can be delivered directly to the patient or those which are suitable for reconstitution prior to administration.

Owing to the limited acceptability of oral liquids, much attention has turned to mini-tablets and miniature capsules with longest dimension below 3 mm. It is likely however, that difficulties in swallowing these systems will still restrict their use to older age groups, with larger tablets only being suitable for adolescent usage. The principle benefits of developing miniature solid dosage forms is that commercialised adult products can be scaled down to provide the appropriate paediatric doses. Considerable difficulties are however likely to be encountered when relatively high tablet strengths are required. Chewable, dispersible and oro-dispersible solids can address this problem and are becoming increasingly common in the US and EU. The increased complexity and cost of manufacturing these systems, especially the complex freeze-dried formats such as those presented in blister packs can however prohibit their adoption particularly in developing countries.

Owing to the relative complexity and cost of oro-dispersible systems, notable attention has now been given to oral granules and multiple unit pelletised systems for simple and convenient age-appropriate dosing. These systems can be produced at low cost using well established and widely available processing technology which increases their attractiveness to developing countries. Preparations of this type can be either taken directly,

be incorporated into food or fluids prior to consumption or be delivered using dose sipping technology. The use of granules also allows adjustment of dosage strength,



which can be important in neonates, infants, toddlers and young children where doses can differ markedly from those used in adults.

Although granular products can be used to provide different strengths of active agent, the co-administration of these products with food stuffs such as apple sauce have raised issues about the accuracy of doses provided. The direct administration of granules into the buccal cavity however reduces the risk of drug losses. The reconstitution of drug product directly into a known volume of dispersion medium also reduces the potential for dosing errors. It is essential however that a suitable taste-masking strategy is employed to enhance the palatability and acceptability of these preparations when given to children across the paediatric age range.

Taste acceptability of oral dosage forms used in the paediatric population is often critical to compliance. A number of approaches for masking unpleasant tasting drugs have been established, which range from the use of sweeteners and flavouring agents, through to cyclodextrin complexes (13), ion exchange resins (14) and particle coating technologies (15). Taste-masking can also be achieved by coating of multiple unit systems and granules (16) or through direct encapsulation of the active pharmaceutical ingredient (17). The barrier properties and release rate of drug from these formulations can be achieved through application of different membrane polymers. Permeability of the coating should be sufficiently low to prevent release in the buccal cavity yet enable adequate release in the gastro-intestinal tract.

Conventional processing technology such as fluidised bed coating is typically used to apply barrier membranes on to multi-particulate systems such as granules, pellets and spheroids, whilst potential also exists to encapsulate micron sized drug particles (18). This approach together with hot-melt coating (19) has demonstrated greatest potential to mask the taste of powders and enables coatings to be applied prior to granulation or pelletisation. The cost and relative complexity of these processes however prohibits their use in developing countries.

GLOBAL PLATFORM TECHNOLOGY

Of the different formulation strategies described in this article, the use of multi-particulate fast dispersing systems which can be delivered to the buccal cavity or which can be mixed with food or fluids prior to administration is probably the most globally acceptable and inexpensive option considered for administration of drugs to children. Systems of this type, when used appropriately have the potential to be adopted as a generic solution for paediatric drug administration and have the capacity to address issues of dose content and drug ratio. Problems of transportation and stability often observed with liquid preparations can also be alleviated. The technology involved is well established and in operation worldwide by pharmaceutical companies at full scale under GMP control. The versatility of the proposed strategy enables sets of pellets or granules containing a single drug component to be manufactured. Facile titration of doses can be achieved whilst combination therapies can easily be prepared by blending appropriate quantities of two or more sets of pellets, thus providing total flexibility in dose(s) and dose ratio requirements. The final granule/pellets will be sized at <1.0mm, will be suitable for administration to children in solid form and will provide smooth mouth feel when dispersed. Undesirable taste will be masked through application of barrier membranes to primary drug particles and through addition of flavourings and sweeteners. These systems will be designed to disperse rapidly

in the mouth. Alternative formulation designs will provide the opportunity to sprinkle the granules onto/into solid and semi-solid foods, while the granules will also be designed to disperse rapidly in liquids. Progress towards such an approach has already been made at the University of Bradford (UK) in partnership with the University of Lagos (Nigeria). Anti-malarial therapies combining artesunate and amodiaquine hydrochloride have been designed which have been shown to overcome issues of incompatibility previously observed with the two agents.

Fast disintegrating, orodispersible granules containing either artesunate or amodiaquine were formulated by wet granulation to produce agglomerates with size in the range 350 µm to 1000 µm. Fixed-dose formulations were then produced by mixing these systems at relevant ratios. The production of blended granular products of the individual active agents gave rise to products, which were markedly more stable than formulations containing both agents combined into a single granular product (see Figure 1). The entire combined dose presented as sachets was shown to disperse rapidly (<1 minute) in a low volume (10 ml) of water (see Figures 2a and 2b) and appeared to be stable even under stressed accelerated conditions. Not only do these granular systems provide opportunity to adjust the size of dose administered to children, they provide a flexible dosing platform, whereby a common granule can be filled into sachets, dose sipping straws or even capsules for use in adults. Although further research and development is required to substantiate the wider use of this generic approach, significant momentum has already been gained in justifying the need for this strategy.

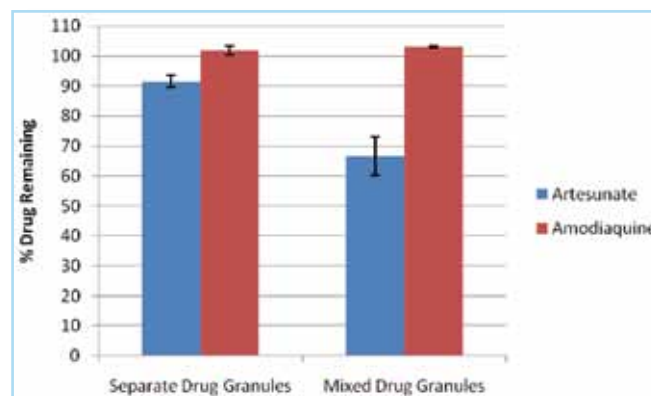


Figure 1. 26-week drug stability at 40°C/ 75 percent RH for blends of granules containing individual drugs (separate drug granules) and for granules containing an intimate mix of both agents (mixed drug granules).




Figure 2. Photographs showing granule dispersibility in 10 ml of water (a) undispersed and (b) dispersed after 30 seconds.

CONCLUSIONS

It has been shown that considerable drivers exist for the development of a globally acceptable platform for the delivery of therapeutic agents to children across the

paediatric population. Although a plethora of acceptable options exist to administer medicines safely and effectively, it is necessary to select a versatile platform which can be manufactured and distributed cost-effectively, and which can be used across a wide age range, potentially including adults. The use of multi-particulate granular or pelletised systems provides marked opportunity to address this global need and has been recognised by several observers as a suitable approach to the issues of paediatric drug administration. Further research and development is however required to demonstrate the vitality of these systems in delivering a range of therapeutic molecules.

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