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MEETING THE CHALLENGES OF PAEDIATRIC DOSING

Although paediatric drugs are traditionally administered in a liquid formulation, recent studies have suggested that orally disintegrating mini-tablets may be a more accurate, convenient and less messy dosage form. Don Barbieri, Technical Support Manager at SPI Pharma, explores the benefits of this method and reviews two case studies looking at whether quality standards can be met and the importance of taste in paediatric formulations.

A widely held belief in paediatric drug administration is that liquids are easier for children to take. In reality however, administering an accurate liquid dose has always been, and continues to be, an issue. Liquids can be messy and spill, possibly reducing the efficacy of the medication should the child be under-dosed as a result.

Dose variability has been greatly reduced through the use of calibrated measuring devices, but successful dosing with these devices completely depends on the caregiver's ability to measure the dose accurately and consistently and the patient's willingness to take the medication. Other concerns in paediatric liquid dosing include:

- The need to refrigerate reconstituted suspensions to ensure stability over the course of treatment
- The possibility of microbial contamination
- The inclusion of excipients, such as preservatives, that are not required in solid dosage forms.

NOVEL APPROACHES IN PAEDIATRIC DOSING

Recent studies have confirmed the preference of small tablets over syrups for children. Orally disintegrating mini-tablets (ODMTs) offer a promising alternative approach in paediatric dosing. This novel dosage form offers accurate and precise weight-based dosing, dose titration, fast disintegration, and, perhaps, enhanced dissolution and pharmacokinetic profiles. Since they are designed to disintegrate in the oral cavity in approximately 10 seconds or less there is no need for water, an important consideration where sources of clean water are limited. When it comes to dosing convenience and improved compliance, ODMTs offer some distinct advantages over traditional tablets and liquids, even children as young as six months of age have been shown to be able to swallow ODMTs effectively.[1, 2, 3]

> "Orally disintegrating mini-tablets offer a promising alternative approach in paediatric dosing."

In addition to ODMTs, sub-lingual (SL) tablets and orally dispersible powders (ODPs) are good approaches to consider when designing a paediatric dosage form. In all of these formulation approaches it's important to remember that good taste, convenient dosing and improved swallowability are key elements in achieving successful paediatric dosing regimens and successful therapeutic outcomes. These patient-friendly dosage forms play a significant role in meeting these objectives.

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ENHANCING PALATABILITY

Taste and mouthfeel are, of course, also major considerations in palatability. If the dosage doesn't have good mouth-feel, has an unpleasant odour and/or a bitter taste there is a reduced likelihood that the child will consume the medication. Therefore, taste masking of bitter actives is of the utmost importance. In many cases this can be achieved through the proper selection of flavours and sweeteners. In other cases however, taste masking can only be achieved through the application of an aqueous gelatin coating (e.g. Actimask®, SPI Pharma) to active drug particles or by the application of a functional polymer coat to active coated multi-particulates to produce multi-unit pellet system (MUPS) beads. Selection of the most appropriate taste-masking system and excipients is critical to ensure acceptable palatability and therefore patient acceptance.

CONSIDERATIONS FOR ORALLY DISPERSIBLE DOSAGE FORMS

Functionally coated MUPS multi-particulates are probably not a good fit for use with mini- or sublingual tablets and would be better formulated into more standard dosage forms. MUPS particles can be fairly large (approximately 300-400 µm), which increases the risk of blend and tablet non-uniformity, especially when compressing mini-tablets at very low weights. Consequently orally dispersible powders packaged in stick packs or sachets and standard size chewable or orally disintegrating tablets may be better options when formulating with MUPS-type systems, making them more suitable for use with older paediatric patients who can swallow or chew tablets.

Active drug particles coacervated with gelatin are also not a good fit for use with mini or sublingual tablets for the same blend and tablet non-uniformity and dosing concerns noted above. They are more appropriately used with standard-sized orally disintegrating or chewable tablets and orally dispersible powders or granules. Coacervated gelatin products are intended for direct administration into the oral cavity. They have a smooth mouthfeel and good palatability, making them ideal candidates for use with these dosage forms.

Formulation of orally dispersible tablet and powder blends containing taste-masked multi-particulates is not without its challenges. As is typical in most blending processes, particle size of the excipients, along with the particle size of the actives, must be comparable in size and density to ensure good blend and content uniformities. The use of "off-the-shelf", co-processed drug delivery platforms and excipients (e.g. SPI Pharma's Pharmaburst® 500 for orally disintegrating tablets, Compressol® SM and Advantol® 300 for chewable tablets, and Pharmasperse® 416 for orally dispersible powders) can facilitate formulation efforts and possibly increase a product's speed to market.

Test Performed	Trial 1 Phenylephrine HCl	Trial 2 Dextromethorphan HBr
Average Tablet Weight (mg)	10.0	10.1
Friability (%)	0.8	0.3
Hardness (N)	9	10
Disintegration (sec)	2.3	2.0
Assay (%)	103.3	99.0
Tablet Content Uniformity (Acceptance Value)	5.2	7.1

Table 1: Results from case study 1.

CASE STUDIES IN PAEDIATRIC DOSING

Two case studies that summarise practical approaches in paediatric formulation development follow:

1. Meeting Quality Standards & Demonstrating Proof of Concept in ODMTs

ODMTs of approximately 10 to 12 mg are typically compressed to a tablet with a diameter of approximately 3 mm. The intention of the study was to demonstrate the feasibility of formulating orally disintegrating mini-tablets using a co-processed off-the-shelf drug delivery platform (Pharmaburst 500, SPI Pharma) to address the challenges of meeting content uniformity and other quality requirements in such small tablets.

Phenylephrine HCl and dextromethorphan HBr – two active pharmaceutical ingredients (APIs) used extensively in paediatric liquid formulations – were utilised as model drugs in separate trials. In both trials the active was 25% of the formulation composition, the co-processed system comprised approximately 65% and the balance of the formulation consisted of sweeteners, flavours, a flow aid (colloidal silicon dioxide) and a lubricant (Lubripharm® – sodium stearyl fumarate). Taste-masking was achieved through the use of dry-blended flavours and sweeteners.

As with any dry-blend mixture, the order of mixing and identification of appropriate processing steps are critical. The formulators developed optimised blending procedures which included de-lumping/screening steps followed by ordered addition of the excipients and actives, and utilisation of appropriate blending steps and times.

Tablets were compressed to a total tablet weight of 10 mg using 2.5 mm multi-tip punches. In-process samples were tested and the tablets met accepted quality standards (Table 1).

Acceptance values (AV) of 5.2 and 7.1 were well below the limit of 15. Mini-tablet hardness results approximated 10 N, which helped to facilitate the rapid disintegration time of approximately two seconds, while the friability results of 0.3% and 0.8% indicated that tablets were sufficiently robust even at a low hardness.

The results of this proof of concept study demonstrate the feasibility of formulating ODMTs, using a commercially available drug delivery platform, that are intended

for administration to small children, possibly as young as six months of age. The applicability of this dosage form, however, could be limited to the use of lower dose actives that do not require taste masking or that can be taste masked using flavours and sweeteners.

2. The Importance of Taste Panel Evaluations to guide Formulation Decisions

A taste panel found two orally dispersible tablet formulations containing citrus flavours in combination with either citric or tartaric acid to have an unacceptable bitter taste, however formulations containing peppermint or menthol flavour had an acceptable taste without bitterness. The active drug particles were taste masked with a standard, reverse enteric polymer coating that solubilises at pH ≤ 5. Upon further review, the hypothesis was that the acidic nature of the tablet formulation dissolved the taste-masking barrier while still in the mouth, rendering the polymer coating ineffective.

To test this hypothesis, tablets containing citric or tartaric acid, as well as tablets without an acid, were dissolved in about 20 mL of water and the pH of each tablet solution was determined. Tablets containing an acid had a pH of approximately 4.3 whilst the tablets without an acidifying agent had a pH of approximately 8 or more. The solubility of the polymer coating at lower pH explains why bitterness was encountered in formulations containing an acid and not in those without. These findings, although expected and in no way surprising, stress the importance of using taste panel evaluations to help guide formulation decisions, increase patient acceptance and uncover potential organoleptic issues.

CONCLUSION

Traditionally the use of liquid formulations has been the go-to dosage form in paediatrics; however, accurate dosing with liquids has always been and continues to be challenging. The use of orally dispersible, patient-friendly dosage forms including ODMTs, sublingual tablets, orally dispersible powders and others, in combination with appropriate taste masking, offers promising alternative approaches to liquids for effective and accurate paediatric dosing.

The use of commercially available, preformulated drug delivery platforms helps to address some of the challenges faced by formulators as they develop these dosage forms, thereby facilitating product development and possibly increasing the speed of new patient-friendly paediatric products to market.

ABOUT THE COMPANY

SPI Pharma provides innovative solutions to global pharmaceutical and nutritional customers, solving the most challenging formulation problems efficiently, cost-effectively and with a focus on service. Serving over 55 countries in the manufacture and marketing of antacid actives, excipients, drug delivery systems for tablets and powders, taste-masked actives and vaccine adjuvants, SPI Pharma employs over 300 people globally and is backed by parent company Associated British Foods (ABF) also specialising in drug development services, having participated in over 60 commercially launched and marketed drugs globally.

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ABOUT THE AUTHOR

Don Barbieri has been with SPI Pharma since August of 2015 as the Technical Products Manager. He is responsible for managing SPI Pharma's excipient line and drug delivery platforms which include Mannogem® (mannitol), Actimask® (taste-masked APIs), Pharmaburst® 500, Advantol® 300 and the Pharmasperse® 416 product lines.

Mr Barbieri has worked in the pharmaceutical industry for over 30 years with responsibilities in a number of different areas including manufacturing, technical services, and process and formulation development. Prior to joining SPI Pharma in 2015, he was with Patheon in Cincinnati, OH, US, as the Associate Director of Formulation and Process Development.

Barbieri is a graduate of the Rutgers College of Pharmacy in (NJ, US) and is currently a registered pharmacist in New Jersey, Wisconsin and Pennsylvania.