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eye on excipients

Alen Guy
IMCD

Guest columnist Alen Guy addresses the use of excipients in pediatric formulations, especially non-liquids, such as granules and mini-tablets, two forms that are gaining acceptance.

It seems the pharmaceutical industry is constantly addressing regulatory and ethical issues. Harmonization, Quality-by-Design, investment and innovation, and clinical trials are among the issues up for discussion today. Yet another is pediatric medicine, which generates much discussion and, more often than not, disharmony.

In 2007 the European Medicines Agency (EMA) implemented the Paediatric Regulation, which requires that companies seeking marketing authorization for new products 1) submit results according to a pediatric investigation plan or 2) seek a waiver or deferral. The reward for submitting results was a combination of patent and market protection. In the USA, the history of exclusivity and incentives for drug products approved for pediatric use is much longer, but the uptake of clinical efforts has still been slow. This can be ascribed to many causes, a good number relating more to ethical and commercial considerations than to specific ingredients. Nonetheless, there are important issues related to ingredients, some of which I address here.

Age-appropriate dosage forms

People's ages vary and age-appropriate formulation is key to the success of many products, especially those designed for children. This entails considering not only the dosage form of pediatric medicines, but also their administration, which is typically performed by a parent or another caregiver.

Among the factors that determine the ease and accuracy of dosing are route of administration, dose level, excipient load, palatability, and stability. The vast majority of pediatric drug products are administered orally via liquids, granules/powders, and rapidly dispersing and traditional tablets. There is a great variety of useful excipients for all of these dosage forms.

Unfortunately, barriers are too often placed on formulators. The most common include, "It is bad practice to make children's medicine taste good because it will seem like candy." And: "We should not give tablets to young children."

As recently as 2010, I heard both notions frequently cited as reasons that some products were unsuitable for pediatric reformulation. In fact, such notions hamper the development of age-appropriate formulations that would improve medicines for children and their access to them.

Nachman et alia [1] demonstrated that point in their study of a clinical trial involving children aged 2 to 5. It showed that a chewable tablet (for an HIV indication) appeared to help the children, even after previous regimens had failed to keep the virus in check. Indeed, 71 percent of the young patients achieved a successful response to treatment. The study concluded that "proper" dosing with liquids or with broken/crushed large tablets was "imprecise," and that a chewable tablet taste-masked with an orange-banana flavoring elicited not one complaint from the children. The researchers concluded that chewable pills are needed for children, and that children have difficulty swallowing pills. Thus, children "have to rely on liquids or crushed pills." This last point seemed to be a warning.

According to the Nachman study of the Boston trial and the graph in Figure 1 on the following page, the vast majority of dosage forms given to children aged 2 to 5 are liquid. However, the need for precise administration and a better understanding of what children of all age groups can actually tolerate are vital to fostering the development of better products. I cited just two references, but many others have highlighted the challenges of what these dosage forms require.

To begin, look at approved products for good examples of candidates that allow simple formulations, ones with a minimal number and load of excipients. Examples include mini-tablets, rapidly dispersing forms (orally disintegrating tablets (ODTs) and thin films), chewable tablets, and oral granules and powders.

Dosage forms that may be considered tricky or difficult include suspensions and syrups, the traditional liquid forms. Their difficulty arises from the necessity of using stabilizers, rheology modifiers, and complex taste masking. Worst, of course, is the inability to taste-mask effectively, resulting in a largely unpalatable product.

Two regulators recently commented on pediatric dosage forms and excipients [3]. One was Catherine Tuleu, chair of the EMA's Paediatric Formulation Innovation Committee. "Don't use big volumes, then you can't overdose easily," she said. "Consider who will administer the treatment, often the parents, rather

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than a trained physician." She said children aged 2 to 3 have been shown to prefer placebo tablets to syrup. The parents did, too. "Preparing medications, such as mixing it with food products, is tricky and easy to get wrong," she said. The other regulator was Mansoor Khan, the FDA's director of the Division of Product Quality Research. He suggested looking at drug products already on the market to identify how excipients can be used safely. "If it has been used before and is safe, then use it."

Their statements indicate that regulators in Europe and the USA agree: All excipients approved for use should be investigated and incorporated into future formulations. All other elements of pediatric formulation should ensure the safety of the patient group. That's paramount. Furthermore, excipients should be used to maximum potential at minimal usage levels. One thing very evident about excipients: On the whole, they taste better than APIs, so their function should be obvious to most people.

Role of excipients in pediatric dosage forms

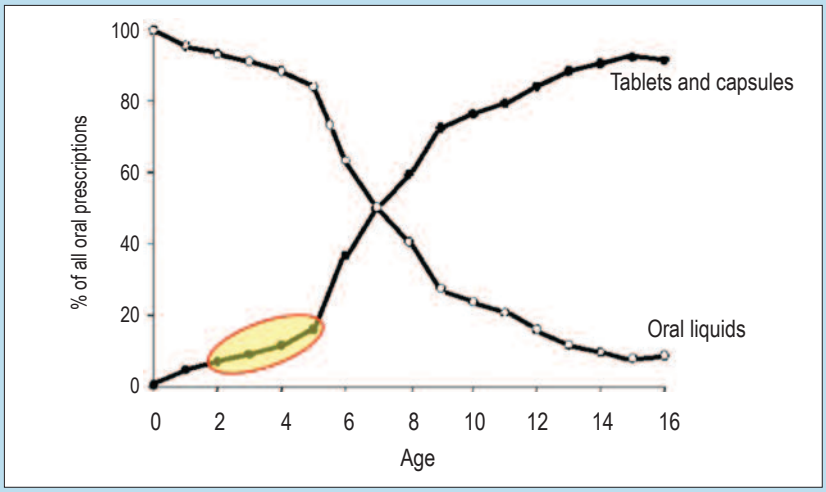
Less discussed than dosage forms are the availability, suitability, and flexibility of today's excipients and technologies in this area. There is general agreement, however, that pediatric formulations should be as simple as possible when it comes to excipients, because minimizing the excipient loads will also minimize the potential for adverse responses. While a blanket exclusion of specific excipients from pediatric formulations is not necessarily useful [4], examples of the potential for undesirable outcomes include

- Sugar and dental caries;
- Mannitol or lactose and diarrhea;
- Lactose and lactose/dairy intolerance;
- Preservatives and allergic response/hypersensitivity; and
- Propylene glycol and serious neurotoxicity.

Clearly, some valuable studies have been conducted on the use of these excipients, but other evidence appears anecdotal. Therefore, it is wise to consider pediatric development from first principles and to consider the targets more clearly. Evidence should trump opinion.

FIGURE 1

Available dosage forms of medicine by age. The red circle highlights the 2- to 5-year-old age group [2].



Taste masking. For instance, there are safe taste-masking technologies—barrier methods—that can achieve low-level excipient loads. And with bitterness the most commonly stated physical characteristic of APIs, it's no surprise that taste is a primary factor in the success of any oral dosage form for children.

There are several techniques for masking off-tastes, but identifying one that lasts from administration through swallowing is often a challenge. Figure 2 illustrates how coatings can be applied to API crystals, micro-granules, or API-excipient pellets. Not only must these coatings mask tastes, they must also achieve rapid—or at least acceptable—dissolution. That is not trivial. It is entirely possible to retard API release with excessive coating. Furthermore, tablet manufacturing (compression) can severely test the integrity of the applied coating film, even those that are quite flexible. Even the fracture of relatively few coated granules can release sufficient API into the oral cavity to trigger a very bitter taste response.

Mini-tablets. Mini-tablets are receiving a lot of attention, having shown their utility in dosing young children. Excipients worthy of study in this area must be conducive to high-speed manufacturing, which requires materials with good flow characteristics, either inherent or obtained by granulation. Microcrystalline cellulose (MCC) comes to mind. Those skilled at formulating tablets will also turn to disintegrants and lubricants. Perhaps less obvious are the techniques of wet granulation that can be applied, making binders more important.

Granulation, however, tends to increase the number of excipients compared to direct compression, which is counter to the intent of pediatric formulation guidance and regulations. Nonetheless, some mini- and micro-tablets on the market contain many excipients. There is a pancrelipase product for cystic fibrosis indications that has undergone clinical studies in children aged 6 to 30 months. It contains such excipients as lactose, croscarmellose sodium, MCC, silicon dioxide, stearic acid, and talc.

Rapidly dispersing forms and chewable tablets. There are several rapidly dispersing forms and chewable tablets for children on the market, including lyophilized mannitol, thin-film extrudates, ODTs, even lollipops. Chewable tablets have long been available, and now there are also mini-ODTs. These forms are favored because they are fairly easy to administer and can be flavored to improve compliance significantly.

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Dosing with rapidly dispersing forms and mini-tablets is more accurate than liquid forms and do not rely heavily on a parent or caregiver to measure the dose.

Oral granules and powders. By delivering the dose in a granule or powder form, you eliminate the risk of compression-induced fractures. You can also optimize taste masking, with more freedom in selecting flavoring elements. In fact, taste-masking excipients would dominate, and the bulk would comprise neutral to sweet, rapidly dispersing excipients. Granules and powders also minimize the need for disintegrants and lubricants. They also facilitate the development of controlled-release products for pediatric administration because they reduce the potential for choking by eliminating the tablet. In its place is a good-tasting powder that can be delivered directly to the mouth or sprinkled over food.

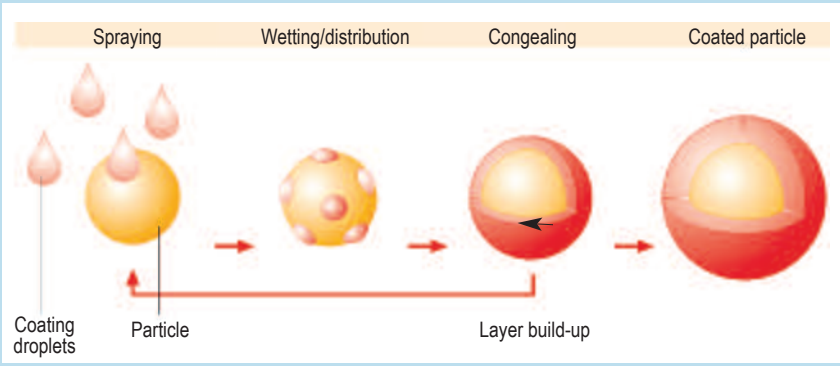
One example is Singulair, a brand-name prescription product available as a chewable tablet or granules for pediatric use. The labels of the two reveal the simplicity of their formulations. The 4- and 5-milligram chewable tablets contain "mannitol, microcrystalline cellulose, hydroxypropyl cellulose, red ferric oxide, croscarmellose sodium, cherry flavor, aspartame, and magnesium stearate." The granular formulation is simpler yet. It contains "mannitol, hydroxypropyl cellulose, and magnesium stearate" [5].

Artequin, another prescription product, is supplied as an oral powder in a stick pack intended for administration in areas where infection risk among children is high and clean water is frequently unavailable. While the granulated APIs of these products are relatively complex, their exteriors comprise polyol, sweetener, and flavoring, as well as excipients to improve flow and mouth-feel.

Another example is over-the-counter Mucinex in powder form, which Reckitt Benckiser offers in a stick pack. The company also offers a stick pack that contains a very high load of paracetamol and phenylephrine for adults. In both products, the dominant excipient is polyol-based to promote good mouth-feel and rapid dispersion.

FIGURE 2

Adding a barrier coating to API crystals or API-excipient pellets masks their bitterness.



Courtesy of Glatt Air Techniques, Ramsey, NJ

Conclusion

Pharmaceutical companies understand the therapeutic need for safer and better understood pediatric medicines. They are also recognizing that the need can be met with solid dosage forms, even for age groups normally associated with less precise and problematic liquid doses.

As the acceptance of excipients with proven safety profiles improves in Europe and the USA, the potential for formulators to deliver age-appropriate and safe dosage forms will expand. These good-tasting drug products—be they tablets or powders—need not resemble candy, and child-resistant packaging is available to minimize the risk of misuse and accidents.

Today's excipients and technology can provide fit-for-purpose taste masking while easing dose administration. It's now only a matter of tapping the imaginations and expertise of formulators and product managers to develop products so that children can receive the treatment they deserve when they are ill. *T&C*

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Alen Guy, Ph.D., is technical director of pharmaceuticals at the UK office of IMCD Group, Times House, Throwley Way, Sutton, Surrey, SM1 4AF UK. Tel. +44 208 770 7090, fax +44 208 770 7295. E-mail: alen.guy@imcd.co.uk. The Netherlands-based company distributes specialty chemicals and food ingredients.