PEDIATRIC DOSAGE FORM CONSIDERATIONS FOR HIGHLY POTENT COMPOUNDS

WHITE PAPER

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The development of pediatric medicine poses numerous challenges to pharmaceutical formulators, particularly products intended for infants and very young children. The EU Regulation 1901/2006 on medicinal products for pediatric use[1] rightly states that children are not simply small adults and that pediatric treatments must thus be tailored to the specific needs of children of various age groups. This means that developers must carefully select a dosage form that is appropriate for young patients in terms of administration and palatability, especially in the case of highly potent medicines used for various indications such as oncology.

CordenPharma Plankstadt, near Frankfurt, Germany, specializes in the development and manufacturing of oral solid dosage forms for highly potent compounds, with extensive experience in pediatric formulations. This white paper describes special considerations for selecting appropriate pediatric dosage forms and the benefits of choosing mini-tablets (e.g., orodispensible) for pediatric formulation, particularly for highly potent compounds.

CONSIDERATIONS for Selecting Pediatric Dosage Forms

Age-Appropriate Dosage Forms

When drug companies are determining the best child-friendly delivery mechanism for their pediatric formulation, finding a combination that works as successfully for infants as it does for older children is essential.

Mini-tablets truly shine in this regard, as they are compressed round or cylindrical tablets that are a fraction the size of conventional tablets (2.5 mm in diameter or smaller), offering formulation flexibility in a variety of ways. Orodispersible mini-tablets, for instance, are a particularly child-friendly format because they disintegrate rapidly (i.e., within 30 seconds) in the mouth, and thus can be easily consumed by patients as young as six months old. Adding to the flexibility, orodispersible mini-tablets can be dispersed easily in water, juice, and baby formula or sprinkled on food, depending on the needs and preferences of the patient.

Flexible Dosing

Dosing of mini-tablet formulations according to the child's age, weight and body surface area is significantly more flexible than with fixed systems. For instance, one can determine a dosage of 5 mini-tablets for children of one given weight range, and 10 mini-tablets for another weight range. This simple incremental dosing of mini-tablets is advantageous for many applications, including therapeutic applications designed for smaller patient populations, as it would be cost prohibitive to offer a variety of finely adjusted, fixed doses with other oral delivery methods. This is especially the case when dealing with newer highly potent compounds that require advanced containment solutions during manufacturing.

Accurate Dosing

Accuracy of dosing is another important consideration. Developers often rely on liquid formulations such as syrups, emulsions, suspensions, and solutions as the go-to delivery mechanism for pediatric drugs. While liquid formats certainly have benefits for pediatric patients, they also have limitations, including the possibility of incomplete or inaccurate dosing. This mostly arises from the fact that some amount of the medication will inevitably remain in the dispensing cup or oral syringe after consumption. Moreover, it is impossible to ascertain whether an infant swallows a complete liquid dose without some external loss of medicine outside their mouth. These challenges are particularly problematic when dosing life-saving medications with a low therapeutic index.

Conversely, mini-tablets offer excellent dosing accuracy, which is enhanced through dose-counting devices and stick packs that assist greatly with dispensing accuracy.

Excipients & Taste Masking

The selection of effective excipients for pediatric drugs is an important and often undervalued aspect of the pharmaceutical development process. Since pediatric patient safety is of paramount importance, toxicologically harmless excipients are required, especially in highly potent formulations. Formulators must additionally consider whether the therapeutic is intended for short or long-term use, as well as whether the excipient's safety profile for the target age group is based on single or daily exposure. Here, it can be very useful to transfer compatibility knowledge from existing adult formulations.

Masking bitter-tasting APIs is, of course, another important consideration for manufacturing effective pediatric dosage forms. Poor taste and texture are big deterrents to younger patients, and a common complaint of liquids. Mini-tablets can easily accommodate various typical excipients for taste masking such as sweeteners (e.g., sucralose), bitter blockers, cyclodextrins, flavors, and many more. In fact, several studies suggest that both children and caregivers find mini-tablets more palatable than other dosage forms, which benefits the patient, as well as associated compliance concerns.[2,3]

Manufacture & In–Process Control Testing

If drug developers need to demonstrate they have a means to transition their traditional tablet formulation for adults to mini–tablets for children as part of a pediatric investigation plan, they can draw upon much of the data gained from stability and other similar studies of the adult formulation. For example, the excipients used in both formulations may be similar. Other areas, however, will be quite different, making the move from an adult formulation to smaller tablets less straightforward than one might realize. Thus, the development of pediatric mini–tablet formulations can benefit greatly from collaborating with knowledgeable CDMO experts like those at CordenPharma, who bring proven experience in the area of oral solid dosage formulation development & manufacturing, specializing in highly potent compound handling.

For example, some level of reformulation work is often necessary for successful tablet compression of mini–tablets. In an ideal scenario, the manufacturing technologies used to make both traditional and mini–tablets would be quite similar (e.g. wet & dry granulation, and tablet compression). While the same conventional tablet presses may be used to produce both traditional and mini–tablets, multi–tip tooling is usually used for the compression of mini–tablets to achieve a higher throughput.

In particular, when using multi–tip tooling, adequate flowability of the powder blend is essential to allow adequate filling of the dies, thereby ensuring low mass variation and good content uniformity.

Another area where drug developers may run into challenges when transitioning from a traditional to mini–tablet is with standard tablet tests.

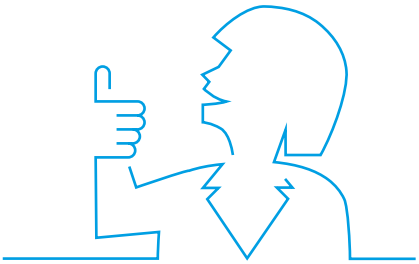
Challenges Transitioning from Tablets to Mini–Tablets

- Tablet hardness testing requires special equipment for mini–tablets that allows for the measurement of very small breaking forces. For instance, a hardness tester that can measure below 10 Newton is required, an amount that is too small to register on a typical hardness tester or multi–check tester.
- In terms of dissolution testing, the large amount of media typically required to perform the tests is often inappropriate for pediatric formulations.
- Moreover, the typical mesh aperture used in disintegration systems is usually 1.8–2.2 mm, which is too large for mini–tablets, causing them to slip right through the mesh. Thus, disintegration testing must be adapted for smaller tablet sizes.
- Even tablet dimension testing is challenging because the normal multi–check testing is inappropriate for mini–tablets.
- Friability testing must also be adjusted for smaller tablets, as the typical Pharmacopoeial tests were originally designed for larger tablets. An effective alternative are small glass beads in a bottle that can be used to mimic the stress inside the friabilator.

Highly Potent Oral Solid Dose early development facility at CordenPharma Plankstadt (DE).

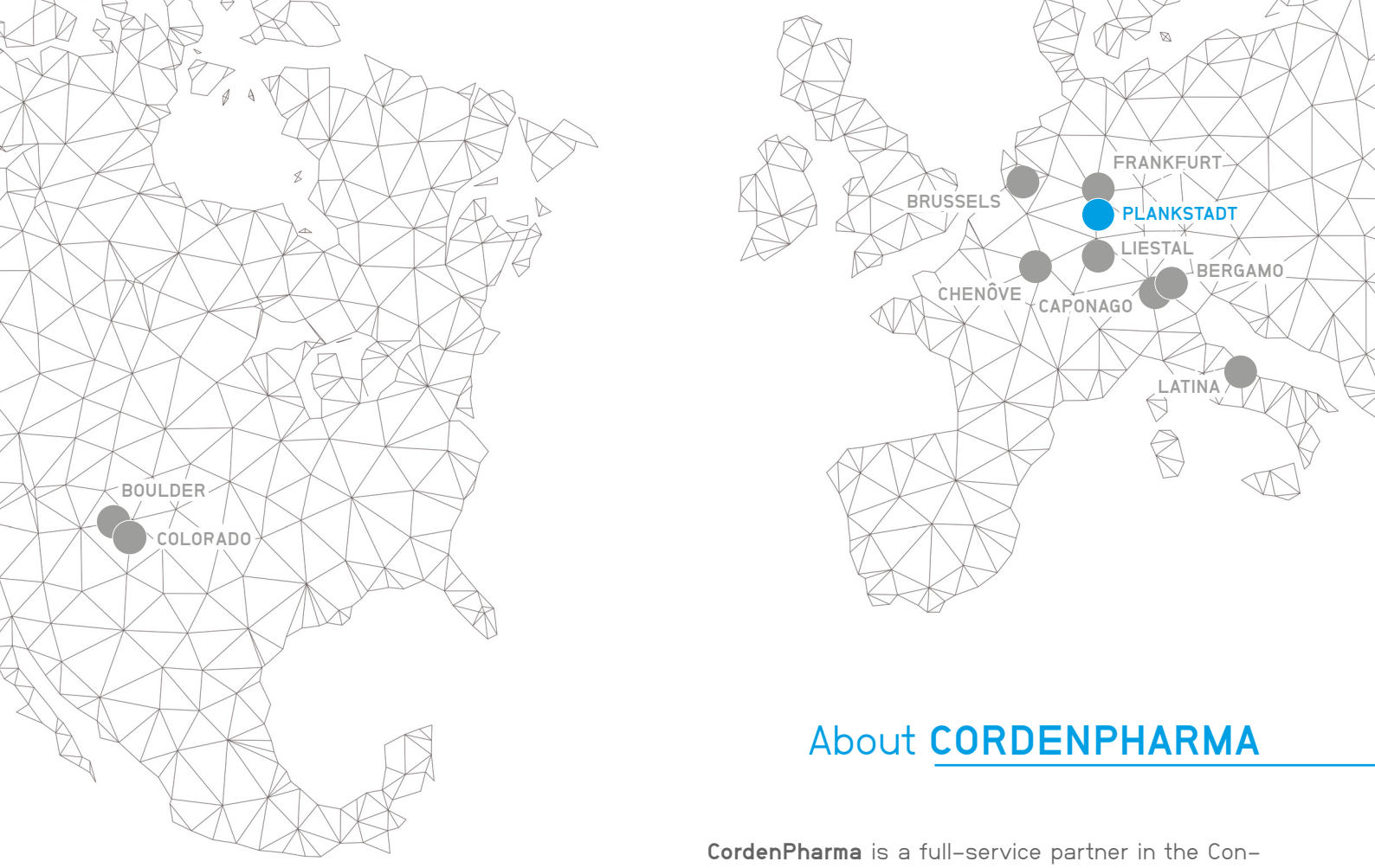
SPECIAL CONSIDERATIONS for Highly Potent Compounds

The use of pediatric mini–tablets for highly potent compounds has some specific challenges because the formula often requires a much lower dose when compared with other drugs. A special skillset is therefore needed to work with these very low–dose formats in order to ensure the highly potent APIs are distributed homogenously within the mini–tablets. While content uniformity is always a priority, the issue is even more challenging for mini–tablets with a low drug load.



CONCLUSION

The development of pediatric formulations requires special considerations to ensure compliance. Mini–tablets are an elegant way of delivering APIs to not only pediatric populations, but also other patient groups (e.g., geriatric) that would benefit from their advantages, such as age–appropriate & accurate dosing and better patient acceptability. This delivery system, however, requires special expertise in terms of developing a suitable tableting process and adapting analytical methods to analyze these tiny tablets. Thus, working with a partner that is experienced in developing mini–tablet formulations will benefit innovators looking to offer this patient–friendly dosage form in their portfolio.



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CordenPharma is a full-service partner in the Contract Development & Manufacturing (CDMO) of APIs, Drug Products, and associated Packaging Services. Through a network of cGMP facilities across Europe and the US organized under four Technology Platforms – Peptides, Lipids & Carbohydrates – Highly Potent & Oncology – Injectables – Small Molecules – CordenPharma experts translate complex ideas, processes, and projects at any stage of development into high-value products.

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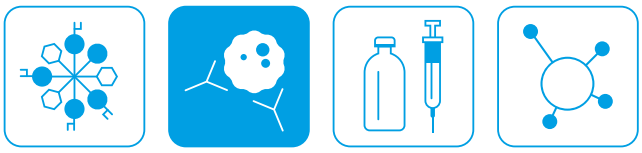

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