How to Achieve Precise and Flexible Dosing with Multiparticulates

LUIGI BOLTRI • GIUSEPPE DE FRANZA
ADARE PHARMA SOLUTIONS | VANDALIA, OHIO USA

INTRODUCTION

Formulation and choice of delivery mechanism can make or break a drug product. For orally delivered medicines, developers often must balance a drug's "curb appeal"—its specific delivery mechanism, taste, ease of administration, and convenience—with safety and efficacy.

Pharmaceutical companies employ numerous strategies for achieving this equilibrium, among them are the use of excipients, modifiers, and taste agents to create products unique in both patient acceptance and pharmacology. One important technology that has incredible advantages for both patient centricity and drug formulation and development are orally delivered multiparticulate systems.

Multiparticulate systems are composed of numerous individual particulates in which the API is present; such particles can be delivered in capsules, sachets, or sprinkles. At Adare Pharma Solutions, proprietary technology platforms involving oral multiparticulate systems deliver taste masking, controlled release, and bioavailability enhancement.

Based on years of working with these technologies, Adare has found that multiparticulate systems have several advantages over conventional tablet or capsule formulations. Dividing the dose into multiple units homogenizes mucosal distribution of the drug with lower risk of local irritation. Having predictable, reproducible pharmacokinetics means that GI transit times are less dependent on gastric emptying. Although such formulations have high drug loading capacity, the risk of "dose dumping," which can happen in modified release systems, is minimized. Precisely metering drug delivery facilitates dosage titration, the creation of multiple-strength products from the same formulation, and the pursuit of development programs based on dose proportionality.

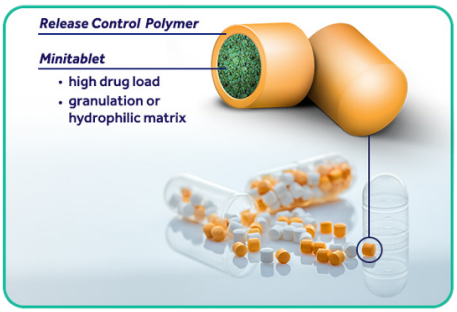
MMTS Minitabs: Flexible, Engineered Dosing

Adare's MMTS™ Multi Mini Tablet System platform is the embodiment of what is possible through multiparticulate technology, combining the simplicity and high drug loading capacity of tablets with the flexibility to generate a wide range of release profiles specifically suited to both patient and drug.

With this multiparticulate dosage form, as many as hundreds of cylindrical MMTS Minitabs (1.0–2.0 mm) can be delivered in convenient dosage forms like capsules, sachets, or sprinkles. MMTS Minitabs are composed of the active pharmaceutical ingredient (API) and excipients that are enveloped within specialized polymer coatings that control the drug's dissolution and diffusion.

For instance, Adare can use one or more functional polymer membrane layers to envelop a core consisting of an inert base material and the drug, resulting in a small, multi-layered bead with tailored release characteristics. Depending on the composition and placement of the layers, achieving classical immediate, pulsatile, and timed/sustained-release is possible by selecting from among available rate-controlling polymers. A combination of timed or pH-dependent polymers can also be used. Timed pulsatile delivery is a modification of immediate-release, which is achieved by adding a combination of slow-dissolving and pH dependent polymers as the outer layer. Once that layer dissolves, the

release is similar to the immediate pulse formulation. Timed/sustained delivery is also possible by timing the disintegration/dissolution of the outer layer and formulating the drug in a sustained-release format.



Because MMTS Minitabs are precisely engineered, two or more "desirables" may be combined to improve both taste and drug release. For example, MMTS Minitabs incorporating oral disintegration to improve palatability may also incorporate immediate, pulsatile, or delayed release to address the factors primarily affecting compliance and efficacy among younger patients: taste, swallowing, and reduced dosing frequency via drug release (modified or sustained release).

With MMTS Minitabs, API dosing may be adjusted by adding or subtracting individual units, allowing for precise, patient-specific dosages. This is particularly advantageous for titration studies in clinical trials as well as drugs intended for pediatric patients that are dosed by age and weight.

MMTS Minitabs in combination with dosing devices further demonstrates the dosing flexibility attainable by formulating drugs in minitablet dosage form.

Flexible dosing is an important advantage. Despite improved understanding of pharmacokinetics and pharmacodynamics, pharmaceutical dosing has been remarkably resistant to evolution. Drugs are often tested exclusively in adult subjects and approved for use, on that basis, in one or just a few dosages. This has hampered efforts to develop formulations suitable for children, a fact that concerns regulators.

The lack of pediatric clinical data raises issues of safety (through over-dosing) and effectiveness (under-dosing) when these drugs are prescribed to children, which they often are. Since 2000, the U.S. Food and Drug Administration has maintained that:

- Pediatric patients should have access to products that have been appropriately evaluated
- Product development programs should include pediatric studies when pediatric use is anticipated

In that vein, the 2002 U.S. Best Pharmaceuticals for Children Act provides financial incentives for conducting pediatric studies, and the 2004 Pediatric Research Equity Act requires drug developers to assess the safety and effectiveness of certain products in pediatric patients. In 2011 the World Health Organization and the European Medicines Agency followed suit. In its Guideline on Pharmaceutical Development of Medicines for Paediatric Use, EMA considered the acceptability of tablets in regard to children's age and tablet size.

MMTS Minitabs address these issues several ways. They are smaller and easier for children to swallow, leading to easier dosing and greater acceptance as will be shown in the next section. This benefit is also useful for any patient population affected by dysphagia such as geriatric patients or those with certain neurological conditions. Of note, Adare can combine MMTS Minitabs with its unique Parvulet® platform to further improve compliance and product acceptability. With this technology, a solid powder or tablet can be transformed into a semi-solid material in the presence of water within 30 seconds. The soft food like texture is ideal for pediatric and geriatric populations, and anyone with dysphagia. Moreover, precision dosing based on a child's age and weight is easily accomplished by simply adjusting the number of minitablets taken.

Pediatric Acceptance of MMTS Minitabs: Scientific Validation

The most effective, technologically advanced drug formulations and delivery systems do no good if patients reject them.

When German researchers compared acceptance of 2 mm uncoated minitablets vs. liquid formulations among pediatric patients, they expected conventional wisdom to hold, namely that children would prefer liquids. To their surprise, even children younger than 1 year of age could easily swallow the mini-tablets and many preferred them over the sweet liquid formulation. According to the authors, "acceptance rate of the mini-tablets in the different age groups was much higher than expected." The authors conclude that minitablet formulations were "a very promising alternative to liquid formulations and could be used at an earlier age in pediatric drug therapy than previously anticipated."

Another small study, from Poland, supported these findings in 50 two- and three-year-old children. Investigators found that 75% of two-year-old participants were capable of swallowing placebo minitablets (2mm or 3mm diameter) suspended in fruit jelly, while 93% of the older children could process the dose with or without chewing.

Finally, a much larger German study on acceptability and "swallowability" of minitablets, compared with an equivalent dose of syrup, confirmed that preferences for minitablets was

statistically highly significant. Children were randomized to two age groups: 6–23 months (N = 186) and 2–5 years (N = 186) in a three-way, single administration cross-over study. The first age group received 25 minitablets, 100 minitablets, and 5 mL syrup. Age group 2 received 100 minitablets, 400 minitablets, and 10 mL syrup. Researchers reported strong preference among younger patients for minitablets in terms of acceptability (age group 1: 25 minitablets, P < .017; 100 minitablets, P < .0001) and swallowability (25 minitablets and 100 minitablets, both P < .0001) compared with syrup. Similar results were obtained from age group 2, but acceptability was found only for the 400-minitablet dose (P < .0003), not for 100 minitablets.

Researchers concluded that this dosage form "is well-tolerated, feasible, and safe in children aged from 6 months, and was superior to the equivalent dose of syrup. Children aged >1 year accept ≤400 minitablets even better than the equivalent dose of syrup. Minitablets open the perspective for introducing small-sized solid drug formulations for all children, thus further shifting the paradigm from liquid toward small-sized solid drug formulations."

Case Study: Minitabs at Work

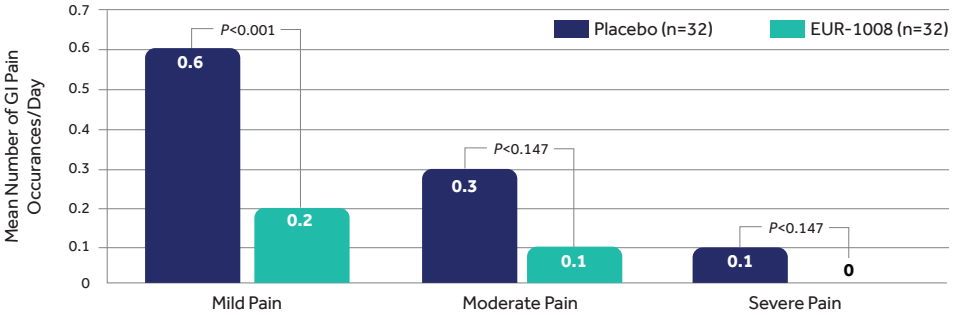
A European pharmaceutical company faced a difficult challenge: to improve delivery of their pancreatic enzyme product to patients who experience difficulty swallowing. This was indeed an important goal, as the recommended dosage of several capsules a day was challenging for this patient population.

The FDA-approved medicine, ZENPEP®, is indicated for treating exocrine pancreatic insufficiency due to cystic fibrosis (CF) or chronic pancreatitis. Flexible dosing options allow patients to get closer to their calculated dose, according to the manufacturer.

Many patient groups have difficulty swallowing, especially children with cystic fibrosis and other conditions. The prevalence of swallowing disorders among hospitalized patients, for example, may be as high as 13%.

Adare scientists paired the API with the company's MMTS Minitabs and even smaller Microtabs (which are 1.5 mm vs 2.0 mm for Minitabs) technology formulated with a gastroprotective coating and enabling opening of the capsule for sprinkling the dose onto soft, low-pH foods typically eaten by cystic fibrosis patients in the one to six-year age group (e.g., applesauce and many baby foods). This strategy turned out to be effective, safe, and well-tolerated when treating pediatric patients with the drug at doses ranging from 3,000 to 25,000 USP units *(see Figure 1)*. The lower doses were intended for the low end of the pediatric range and were delivered in the Microtab format. MMTS Minitabs and Microtabs are also compatible with delivery through gastric feeding tubes. Drug patency is maintained while the beads deliver their payloads without sticking or clogging the tube. The integrity of the coating protecting the enzyme from degradation in the gastric media is likewise maintained. Most notably, the MMTS Minitab formulation enabled expanding the dosage range up to 40,000 USP units.

Figure 1: *ZENPEP® – Positiive Phase III Pivotal Study*



Data are derived from daily patient or caregiver-reported diaries. Assessments were subjective and represent the mean number of GI pain occurrences per day. A pain occuurrence was defined as a 1-hour block of time in which the patient experienced pain.

	ZENPEP (n=32)	PLACEBO (n=31)
Mean CFA	88.3%	62.8%
Mean CNA	87.2%	65.7%

Commercial Manufacturing

While it is not difficult to manufacture mini/microtablets with simple tablet punches on a small scale, efficient commercial-scale production of 1.5, 2.0 and 3.0 mm minitablets is a different story. Certain process parameters must be carefully planned and would benefit from engagement of a third-party partner with expertise in the formulation and production of minitablets.

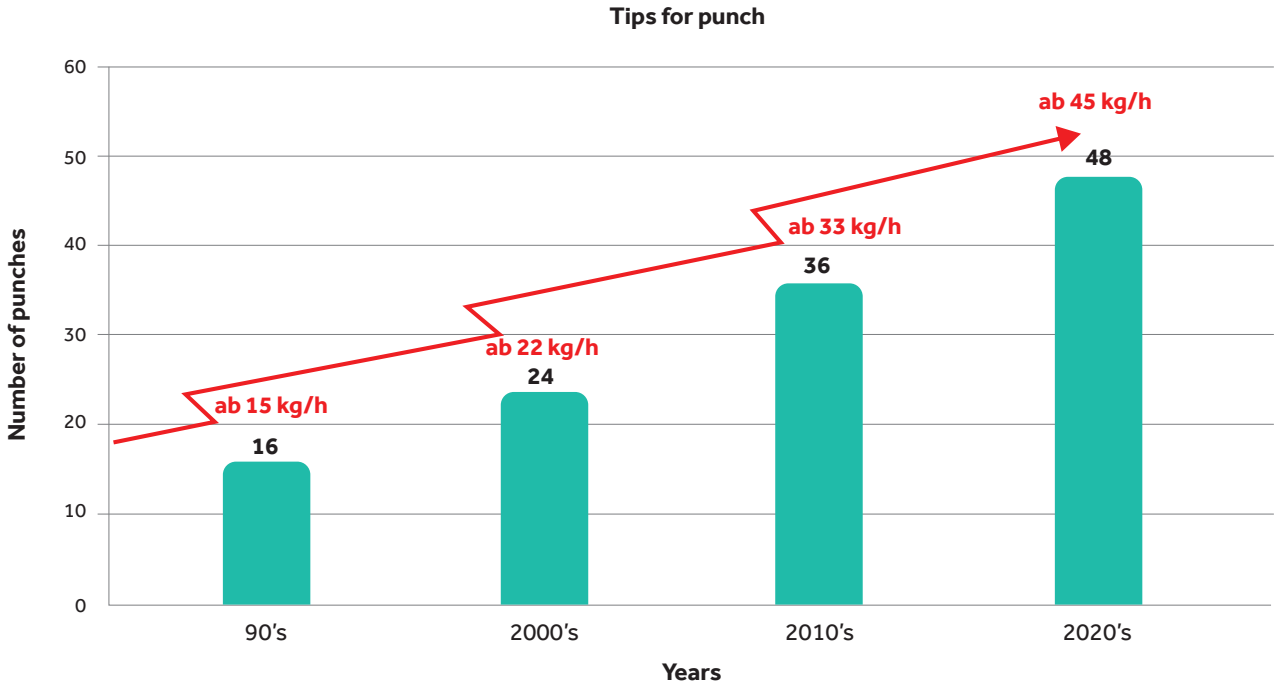
For instance, the production of 1.5 Zenpep Microtabs and 2.0 mm Zenpep Minitabs required dedicated process parameters such as low moisture condition to reduce the impact on pancreatic enzymes. Adare decided to use customized low-moisture HPMC capsules that were different than anything else on the market at that time in addition to the low-moisture environmental conditions. With these improvements, Zenpep can achieve up to three years of product stability without overage.

Adare also wanted to create more robust in-process controls for friability, an important tableting parameter along with weight, thickness, and hardness. The parameter developed was more challenging than Pharmacopeia guidelines because Adare wanted to have more accurate data about MMTS Minitabs brittleness under stressed conditions. In the end, the team tested 20 g for 30 minutes versus about 10 g for 4 minutes.

Tooling is another important consideration for efficient commercial-scale manufacturing. Adare worked closely with its supplier for punches and dies to gain space and increase minitablet production speed. In the 1990s, 16 punches per station were used to make the minitablets at 15 kg/hour. Adare has just validated the use of 48 punches on industrial scale for production speeds of 45 kg/hour *(see Figure 2)*. This offering is unique, and critical to efficient commercial-scale production.

Another example of Adare's operational excellence approach involves the definition of a dedicated screwing force for the screw on punches and die to standardize starting conditions for each batch with respect to the tableting step in order to reduce the variability.

Figure 2: *Adare Improvement: Tips for Minitablet Punch on Industrial Scale*



ADARE PHARMA SOLUTIONS is a global technology-driven CDMO providing end-to-end integrated services, from product development through commercial manufacturing and packaging, with small molecule expertise focusing on oral dosage forms. Adare's specialized technology platforms provide taste masking, controlled release, solubility enhancement, and patient-centric dosing solutions. With a proven history in drug delivery, Adare has developed and manufactures more than 65 products sold by customers worldwide.

THE ADARE EXPERTS

Luigi Boltri
Director, Technology Development

Dr. Boltri is a pharmaceutical chemist by training and completed his degree at the University of Turin. With almost 30 years of experience in the Pharmaceutical Industry, Dr Boltri has held leading positions as Department Head and Director.

Giuseppe De Franza
Senior Manager, Technical Services

Giuseppe has more than 20 years of experience in the pharmaceutical field. He is responsible for leading all activities related to Continuous Improvement Italian team. Giuseppe holds Bachelor's degree in Biology from the University of Milan, Italy

SUMMARY

Minitabs can offer versatile applications, including as a pediatric dosage form and cases where rapid or flexible dose adjustments are needed. Producing this dosage form is most successful when partners have deep experience with this technology so as to create high process robustness and reproducibility as well as production efficiency at commercial scales.

SOURCES:
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