CHAPTER

6

Pharmaceutical mini-tablets: a revived trend

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1. Introduction

Pharmaceutical mini-tablets are novel solid dosage forms that can be as small as 1 mm in diameter. However, the World Health Organization defines them as no bigger than 4 mm in diameter. These mini-tablets are conventional compressed tablets, only smaller in size, i.e., between 1 and 4 mm in diameter and sometimes also referred to as micro-tablets. Mini-tablets with a size of around 2.5 mm meet the Food and Drug Administration guidance for industry "Size of beads in drug products labeled for sprinkle," Rev. 1, published in May 2012.

Mini-tablets combine the advantage of both solid and liquid formulations. Mini-tablets are viable options that can be successfully adopted for pediatric and geriatric populations. Currently, liquids are the most frequently used dosage forms for administering pediatric formulations. The reason for this is because liquids are easy to administer and the dose can be changed as needed. However, they have major disadvantages of chemical, physical, and microbial stability, palatability of the solution, inaccuracy of dosing, lack of controlled release, and elevated toxicological risks. There are also limitations on which excipients, preservatives, and solvents can be used in pediatric formulations. This makes mini-tablets a very promising alternative to liquid formulations administered to children of different age groups.

In general, tablets are very rarely developed for use in infants and preschool children because historic opinions suggest that young children cannot swallow tablets that are intact [1]. A study in 2009 with 100 children, 2–6 years of age, demonstrated the potential use of mini-tablets as large as 3 mm in diameter for the treatment of preschool-aged children. There is increasing evidence that mini-tablets can be swallowed safely by children from a very young age [2]. More recent studies show that the acceptance of 2-mm diameter mini-tablets defined as immediate swallowing or chewing first with subsequent swallowing was higher or at least equal to that of syrup for 0.5–6-year-old children. An overview of the current evidence is provided by Liu et al. [3] and Aleksovski [2]. For example, Klingmann et al. found that uncoated and coated 2-mm tablets are well accepted in children from 6 months onward

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and that the uncoated mini-tablets were even better accepted than a syrup [4]. The same authors also showed that rapidly dissolving uncoated 2-mm tablets were well taken by (pre) term neonates. The tablets were placed in the cheek pouch and swallowing was facilitated by offering the child a drink of the parents' choice (breast milk, milk, tea, water, maltodextrin). Actually, the tablets were even better accepted than 0.5 mL of an oral syrup [5]. In addition, Kluk et al. showed that children from 2 years on are able to swallow several 2-mm mini-tablets as a single dose, eventually with the help of a gliding agent [6]. Although the repeatability of these findings in the domiciliary setting remains to be investigated, we showed that 4-mm uncoated placebo mini-tablets are well accepted in children older than 1 year when given by their parents at home [7]. It has been observed that the 4-mm mini-tablets were generally better accepted than an oral powder, suspension, and solution [8]. Based on this evidence, mini-tablets may also be developed to provide modified release. A comparison of size of mini-tablets to that of a conventional tablet and capsule [9] is provided in Fig. 6.1.

2. Advantages of mini-tablets

2.1 Dosages

Due to the ease of administration, liquid formulations are most commonly prescribed to patients with swallowing difficulties. To eliminate problems related to liquid dosage forms—such as chemical and microbial instabilities and lack of accuracy in dosing—and with the aim of improving drug delivery for pediatric and geriatric populations, pharmaceutical companies have developed mini-tablets as a patient-friendly dosage form.

Coated or uncoated mini-tablets are more appropriate than traditional tablets or capsules for pediatric and geriatric patients because they offer improved swallowing and flexible dosing, combining various release kinetics, doses, and active compounds in a single dosage form.

2.2 Customized delivery

Mini-tablets allow customized delivery in terms of a combination of release rates and mechanisms as well as targeted release to

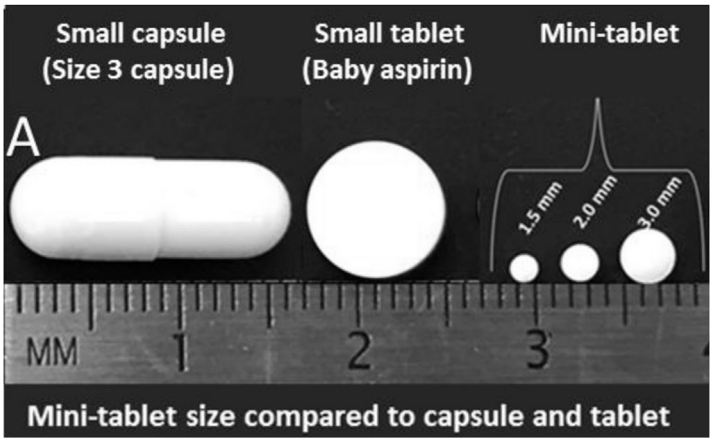

FIGURE 6.1 Comparison of size of mini-tablet to that of a capsule and tablet.

different segments of the gastrointestinal (GI) tract. One dosage form can incorporate a number of mini-tablets, each one formulated individually and programmed to release a drug at a different site in the GI tract.

These combinations can include immediate release (IR), delayed release, and/or extended release (ER) mini-tablets. For instance, in one study, Butler et al. filled a final capsule product with nine mini-tablets combining three intermediate components: IR mini-tablets, ER mini-tablets targeted to release a drug in the upper small intestine, and ER mini-tablets targeted to release a drug in the lower small intestine [10].

An illustration of a capsule filled with only mini-tablets, then a combination of mini-tablets filled into capsules and pellets, and mini-tablets in combination with powder filled into a capsule, is provided in Fig. 6.2.

2.3 Improving patient compliance

Rapid release mini-tablets allow the development of rapid-acting encapsulated dosage forms for fast action. However, several mini-tablets can be placed into a capsule, which disintegrates and releases these mini-tablets. Different mini-tablets of different coatings and different combinations of active pharmaceutical ingredients (APIs) can be placed into one capsule to obtain the required release profiles and therapeutic activities. This helps to improve patient compliance.

FIGURE 6.2 Example of a hard gelatin capsule containing (A) mini-tablets, (B) mini-tablets with pellets, and (C) mini-tablets with powder.

2.4 Combination therapy

Mini-tablets also provide the opportunity to create a multiparticulate dosage form that can include more than one API and be used as a combination therapy. To create this form, formulators can incorporate each API into its own mini-tablet and then place all mini-tablets in one capsule, sachet, or stick pack dosage form. By combining different mini-tablets into one capsule, incompatible compounds can be administered in the same dosage form.

2.5 Dose range finding

Mini-tablets can be useful in dose range-finding clinical trials because the number of mini-tablets can be altered in the capsules being administered to the patients. This provides flexible options for scientists and innovator companies to just increase/decrease the number of mini-tablets to cater for the required dose without having to develop new formulations for each dosage strength.

2.6 Disintegration times

Additionally, the small size of mini-tablets enables rapid disintegration times. This permits their use as an orally disintegrating dosage form when properly formulated and allows their dispersion in a liquid prior to administration, which is appropriate for young children or infants who can swallow only disintegrated particulates.

2.7 Product design

From a product-design perspective, mini-tablets offer potential advantages. For instance, Guggi et al. prepared mucoadhesive mini-tablets containing a peptide-structured calcitonin compound, targeted to the stomach. This formulation used thiolated chitosan as a mucoadhesive polymer, glutathione as a penetration enhancer, and chitosan–pepstatin conjugate as a peptide-protecting agent. The researchers administered the peptides orally to determine the pharmacological effects [11].

In another study, Goole et al. developed floating mini-tablets using high-viscosity hydroxypropyl methylcellulose (HPMC) as a swellable hydrocolloid to trap the carbon dioxide that the gas-generating agents created and to extend the release of the drug. These mini-tablets remained buoyant until their complete erosion, which ensured their floating capabilities, until the end of drug release [12].

Similarly, Iannuccelli et al. designed multiunit floating systems with air compartments, separated by a calcium alginate core and a membrane of calcium alginate or calcium alginate/polyvinyl alcohol. These systems showed improved in vitro and in vivo performance compared to a single-unit system [13].

Additionally, researchers have used mini-tablets as controlled-release ophthalmic inserts containing timolol maleate, where the researchers applied a thin, rate-controlling membrane over the devices by spraying aqueous dispersions of acrylic copolymers (Eudragit RS and Eudragit RL) [14].

2.8 Caregivers

In addition to better adherence and patient compliance, mini-tablets as a dosage form can reduce the time and energy required of caregivers to administer medication. Caregivers can easily spill liquid medications, and it is time consuming for them to measure an accurate dose. Innovations such as sprinkles, dissolvable mini-tablets, mini-tablet dispensers, and sachets of mini-tablets can decrease the mess and reduce the time it takes to prepare medications by allowing caregivers simply to mix the drug product with soft foods like sauces, purees, or yogurts.

2.9 Excipients

Stoltenberg and Breitkreutz studied orally disintegrating mini-tablets (ODMTs) as a suitable dosage form for pediatric patients. In their study, the researchers examined the suitability of five commercially available, ready-to-use, coprocessed tableting excipients based on mannitol—Ludiflash, Parteck ODT, Pearlitol Flash, Pharmaburst 500, and Prosolv ODT—that they directly compressed into 2-mm mini-tablets. They investigated drug-free ODMTs and ODMTs with a child-appropriate dose and found that they could produce ODMTs with all investigated excipients. These promising results indicated that ODMTs may serve as a novel platform technology for pediatrics in the future [15].

2.10 Marketed mini-tablets

Development of mini-tablets was initiated in the 1980s. Pharmaceutical companies have invested a lot of time and effort in developing mini-tablets to be administered either from a capsule or sachet/stick pack. As a result, there are several marketed dosage forms containing mini-tablets. Two examples of commercially available mini-tablets for pediatric use include Lamisil oral granules (Novartis) and Orifil long (Desitin). Both these products contain 2-mm mini-tablets and are dispensed in stick packs and capsules. They are recommended to be administered to children by sprinkling on food.

Table 6.1 presents examples of commercially available marketed mini-tablet formulations as compiled by Shah et al. [16].

2.11 Packaging

The target product profile or the required product-design criteria determine the packaging

TABLE 6.1 Examples of commercially available formulations containing mini-tablets.

Brand Name	Drug name	Indication	Manufacturer	Dosage form
Rythmol SR	Propafenone HCl	Antiarrhythmic	GlaxoSmithKline	Capsule
Enzym-Lefax	Pancreatin	Indigestion	Bayer	Capsule
Lamisil oral granules	Terbinafine HCl	Antifungal	Novartis	Capsule, sachet
Orfiril long	Sodium valproate	Epilepsy	Desitin	Capsule, sachet
Pankreatan	Pancreatin	Pancreatic insufficiency	Novartis	Capsule
Trilipix	Fenofibric acid	Cholesterol	Abbott	Capsule
Kalydeco	Ivacaftor	Cystic fibrosis	Vertex	Stick pack

configuration of mini-tablets. Selection of the correct packaging configuration also depends on the drug product's performance in a particular packaging configuration upon long-term storage. The delivery of core or coated mini-tablets to patients can include encapsulation or unit-dose packaging, such as stick packs or sachets.

Since most mini-tablets are oral medications for pediatric and geriatric populations, an ideal dispensator is key. The Stevanato Group, previously Balda Medical, developed a number of mini-tablet dispensers that provide the convenience to patients to take their medication accurately and safely. The smart Mini Tablet Dispenser system is a reusable dispenser with a flexible and open design, which allows modification according to a tablet's characteristics and customer requirements. The patient, caretaker, or nurse can easily adjust the number of mini-tablets per dosage at home or prefixed by the pharmacist based on the dose required, with space for up to 20 units. The device can also include additional features such as child-proofing. This device supports the acceptance of mini-tablets at home by patients and caregivers (Fig. 6.3).

3. Manufacturing

Mini-tablets are manufactured using standard rotary tablet presses. However, minor modifications to the press or to the instrumentation may be needed. Manufacture of mini-tablets will require special tooling, which is generally more expensive when compared to the tooling used in the manufacture of normal tablets. All major tooling companies supply what is called stepped tooling, where punches have shorter stems to

FIGURE 6.3 A smart mini-tablet dispenser system. *sMTS*, Smart Mini Tablet Dispenser system. *Courtesy: Stevanato group.*

reinforce the tooling tip strength and reduce the risk of potential damage to the punches.

A few potential challenges exist in working with mini-tablets as an age-appropriate dosage form. The most notable issue with mini-tablets is their small size, which makes them difficult to handle individually during a manufacturing operation or during analytical testing in the lab. The large number of units per batch and the number of units required for testing are significantly higher compared to those of traditional tablet development.

From a manufacturing perspective, pharmaceutical companies must package multiple mini-tablets together to provide a single dose, which lowers the dose-based production rate. As such, mini-tablets seem best implemented for small-volume, high-value products, especially for specific patient populations that can benefit from their distinguishing features.

Fig. 6.4 provides details on punch tooling used in the manufacture of mini-tablets.

There are advantages of solid multitip tooling over assembly multitip punches:

1. Reduced risk of cross-contamination
2. Minimized assembly time
3. Significant increase in tablet production
4. Decreased tool rusting
5. Simplified tool cleaning

4. Types of mini-tablets

Mini-tablets are classified based on the target site, method of manufacturing, and patient needs as follows:

1. Pediatric mini-tablets
2. Gastroretentive mini-tablets
3. Oral disintegrating mini-tablets
4. Ocular mini-tablets
5. Bioadhesive mini-tablets
6. pH-responsive mini-tablets
7. Biphasic mini-tablets

4.1 Pediatric mini-tablets

Syrups, tablets, and capsules are commonly used dosage forms for children. Syrups are liquid dosage forms that are simple to administer and the dose can be easily altered to the patient's needs. The disadvantages of these liquid dosage forms are chemical, physical, and microbial instability, taste issues, lack of controlled release, and formulation problems. In the case of tablets, because they are big, swallowing and dose adjustment are difficult. Sometimes the tablets have to be broken for ease of administration, which causes loss of activity of the tablets. Patient compliance is

FIGURE 6.4 Mini-tablet tooling: punch and die combination (left); different designs exist for mini-tablet multitip tooling, such as multiple part cap-and-pin design and solid multitip design (right). In a monoblock design, all tips are machined from one piece of stainless steel. Mini-tablet tooling can also be produced with different shapes and varying number of tips. The upper punch for mini-tablet tooling is keyed to maintain its rotational orientation. *Pictures are courtesy of Natoli.*

another issue with conventional dosage forms. To overcome all of these issues, formulating mini-tablets can result in good patient acceptance. Mini-tablets are more easily accepted by children than other dosage forms like tablets, syrups, capsules, etc.

4.2 Gastroretentive mini-tablets

Gastroretentive tablets are intended to release the drug in the stomach over a prolonged time. Generally, for tablets to float on the GI fluids content are formulated by using gas-generating agents in them. When they come into contact with food these tablets generate CO_2 and the generated gas is trapped in swellable hydrocolloid, which makes the tablet float and remain in the stomach. In normal single unit tablets, drug loading is low because the polymer used for floating is high. In mini-tablets one can use a coating with sodium bicarbonate or calcium carbonate (gas-generating agents), or a Eudragit coating in place of swellable polymers used in formulations to increase drug loading. Fluidized-bed processors can be used for the coating of mini-tablets.

Goole et al. developed sustained release floating mini-tablets of levodopa. They used a 3-mm mini-tablet core formulated with gas-generating agent and coated the core with Eudragit RL30 D to achieve the required release [17].

4.3 Orally disintegrating mini-tablets

Oral dispersible tablets (ODTs) are the novel dosage form that rapidly disintegrates in the mouth (1−3 min) without chewing and without the need for water, unlike other conventional oral solid dosage forms. ODTs are also known as "fast-dissolve," "rapidly disintegrating," "quick-dissolve," "crunch-melt," "bite-dispersible," "mouth-dissolve," and "oro-dispersible" tablets. ODMTs are more suitable for pediatric patients because of their small size, pleasant mouth feel, and fast disintegration in the mouth.

ODTs should disintegrate in the mouth without additional water. The disintegrated tablet should become a soft paste or liquid suspension, which can provide good mouth feel and smooth swallowing. Because ODTs dissolve or disintegrate in the mouth cavity, the drug will be partially dissolved in close proximity to the taste buds. A pleasant taste inside the mouth becomes critical for patient acceptance. Unless the drug is tasteless or does not have an undesirable taste, taste-masking techniques should be used. The taste-masking technology should also be compatible with ODT formulations. For example, if drug particles are coated to minimize unpleasant taste, the coating should not be broken during compression or dissolved during wet granulation. Taste masking of bitter-tasting drugs is critical to the success of ODT formulations. For ideal ODT technology, the drug properties should not significantly affect the tablet properties. Because ODTs are designed to have a quick dissolution/disintegration time, tablet porosity is usually maximized to ensure fast water absorption into the tablets. In addition, low-compression pressure causes fast-dissolving dosage forms to be soft, friable, and unsuitable for packaging in conventional blisters or bottles. Stoltenberg et al. worked on placebo and active (hydrochlorothiazide) ODMT formulations with commercially available excipients. They were successful in obtaining orally disintegrating mini-tablets with all the excipients that were investigated in the study. ODMTs with a crushing strength of more than 7 N and low friability (<1%), as well as short simulated wetting testing time (<5 s), have been reported [15]. A strategy to increase tablet mechanical strength without sacrificing tablet porosity or requiring special packaging to handle fragile tablets should be provided. A good package design or other strategy should be created to protect ODTs from various environmental conditions, especially from moisture.

4.4 Ocular mini-tablets

To overcome the disadvantages of various ocular drug delivery systems, mini-tablets as a new dosage form can be formulated for ocular administration. Ocular mini-tablets are mucoadhesive tablets of sizes ranging from 2 to 4 mm in diameter, from which drug release may occur either by erosion of the outer layer or by converting the tablet into a gel form upon instillation into the lower cul-de-sac.

Advantages of ocular mini-tablets are:

1. Increased bioavailability
2. Extended duration of action
3. Reduced number of instillations
4. Minimized systemic side effects
5. Accurate dosing
6. Increased shelf life with respect to aqueous solutions
7. Exclusion of preservatives, thus reducing the risk of sensitivity reactions

Researchers have demonstrated the potential of mini-tablet dosage forms for ocular delivery of compounds for the treatment of bacterial keratitis and conjunctivitis. Dhumane et al. worked on mini-tablets for the ocular delivery of norfloxacin [18]. These mini-tablets (4 mm diameter) were sterilized using gamma radiation before being administered to rabbits.

4.5 Bioadhesive vaginal mini-tablets

The vagina is an important application site for local drug delivery in different diseases like bacterial, fungal and protozoal infections, HIV prevention, delivery of contraceptives, spermicides or labor inducers, and for the treatment of pancreatic lesions and an alternative route for systemic drug delivery.

The dosage forms intended for vaginal drug delivery should be easy to administer without irritation or discomfort and should have even distribution and long retention time, thereby increasing patient compliance and adherence to therapy.

The current available dosage forms for vaginal drug delivery are creams, gels, ointments, and tablets.

The problems with these dosage forms are leakage, mess, less patient compliance, and less retention time. Nanopharmaceuticals can be used but the problem associated with them is low residence time because they are liquid in nature. Bioadhesive polymers provide a solution to these problems.

Bioadhesive polymers or hydrophilic polymers are readily soluble and act as an adhesive on exposure to moisture. These polymers will rapidly adhere to surfaces because they have high viscosity at low concentrations.

Solid dosage forms have higher dose accuracy than semisolid systems. The problem in solid dosage forms is slow vaginal disintegration and they are rapidly cleared due to gravity and the self-cleansing action of the vagina. Bioadhesive polymers can be used to overcome this but in the case of large size tablets, loss is reported.

Bioadhesive mini-tablets can be used for vaginal drug delivery to deliver drug accurately and over a long period of time. In mini-tablets, dose is divided into multiple units, which will spread evenly in the vaginal cavity with improve coverage in vaginal epithelium. Bioadhesive mini-tablets act by swelling and form into microgels, thereby releasing drug in a controlled manner. Thus by using bioadhesive polymers, maximum bioavailability can be achieved.

Marianne Hiorth et al. prepared bioadhesive mini-tablets of hexyl ammonium hydrochlorodium (HAL), which is used for the photodynamic therapy of cervical cancer [19]. A thermogel of HAL is already available; however, HAL is unstable in moist environments. Bioadhesive mini-tablets were investigated as a dosage form to address the stability issues of HAL. Mini-tablets prepared by direct compression with HPMC and HPC were observed to

have adequate mechanical and bioadhesive properties. Vaginal pH varies among women of different ages. To withstand those pH conditions, bio-adhesive vaginal mini-tablets should be designed using nonionic cellulose ethers with bioadhesive properties.

4.6 pH-responsive mini-tablets

pH of the human GI tract varies greatly (stomach 1.5–3.0, upper part of small intestine, i.e., duodenum 4.0–5.0, lower parts of the small intestine, i.e., jejunum and ileum 6.5–7.5, and colon 5.6–6.9). pH-responsive drug release is required when absorption of drug is increased at a particular site; this can be achieved by coating with pH-responsive release polymers like Eudragit. Generally, granules are coated, which are then placed into capsules to achieve the required release at the required pH. In the case of pellets, control of size and size distribution are important before coating. To achieve reproducible results, desirable pellet size and narrow particle size distribution are required, which are difficult to achieve.

Mini-tablets are easy to manufacture and coat when compared to pellets because they have smooth surfaces. Uniform size can be obtained so there is less variation with each unit. Reproducible results can be achieved by uniform coating. So, mini-tablets can be used as an alternative to pellets.

Researchers formulated pH-responsive mini-tablets for colonic drug delivery of naproxen, which is used for the treatment of rheumatoid arthritis. Eudragit L100 and Eudragit S100 are used as pH-responsive polymers so that the required dosage is released.

4.7 Biphasic mini-tablets

A biphasic mini-tablet contains two parts: a fast-releasing part and a slow-releasing part. The first part releases drug immediately after administration and the second part releases drug slowly in a controlled manner.

This type can be beneficial for drugs used for hypertension where repetitive dosing can be reduced. Different drugs can be compressed into mini-tablets and can be filled in the same capsule to treat different diseases.

Lopes et al. prepared biphasic mini-tablets of ibuprofen with ideal release characteristics [20].

5. Methods of manufacturing mini-tablets

Some of the techniques for manufacturing pharmaceutical mini-tablets are:

1. Direct compression
2. Dry granulation
3. Wet granulation
4. Melt extrusion

5.1 Direct compression

Direct compression is the process by which tablets are compressed directly from powder blends containing API and excipients. Excipients used for this process are direct compression grades, which have optimum flow properties and that can be compacted well to achieve the required hardness. Stability problems are less compared to those of tablets prepared by wet granulation.

5.2 Dry granulation

Dry granulation is the technique of choice for the manufacture of tablets containing thermolabile and moisture-sensitive drugs. This technique employs processing equipment known as a roller compactor or chilsonator. The roller compactor functions by compacting premixed powders between two counterrotating rollers under extreme pressure. The resultant material is in the form of a brittle ribbon, sheet, or piece depending on the configuration of the roller.

The compacted material is reduced to an optimum size to form granules that are mixed with other inactive excipients to obtain the final blend. The lubricated blend is compressed on a rotary compression machine to obtain tablets. An alternative method to brittle ribbon sheets are slugs that can be formed by forcing the initial blend of powders into dies of a large capacity tablet press, which is then compacted by means of flat-faced punches. The formed compacted masses are called "slugs" and the process is referred as "slugging." The slugs are then screened or milled to produce granules. These granules are mixed with other excipients and finally subjected to compression.

5.3 Wet granulation

Wet granulation involves the use of binder solution to form granules. The granules obtained from wet granulation are then blended with excipients (in some cases) and lubricated before loading the blend onto a compression machine. The lubricated blend is compressed with optimum force to produce mini-tablets. Polyvinyl pyrrolidone of different grades and HPMC are generally used as binding agents. The binding agent can be added to the granulator bowl or can be sprayed into the granulator bowl via premixed solution.

5.4 Hot melt extrusion

In the hot melt extrusion technique, the powder (API+ excipients) is premixed and is then transferred to a melt extruder. In a melt extruder, parameters like screw speed, feed rate, and temperature are set in the melting point range of the material. After the process the extrudates are then milled and sieved. The obtained granules are then compressed into mini-tablets using a compression machine.

De Brabander et al. [21] and Verhoeven et al. [22] used a corotating twin screw extruder equipped with a 3-mm cylindrical die. The extrudates were cut into mini-tablets of 2 mm in length. The researchers demonstrated that hot melt extrusion may be a viable method for the production of ER inert mini-tablets based on thermoplastic polymers like ethyl cellulose. In a separate study, De Brabander et al. milled the extrudates based on a combination of microcrystalline wax and a starch derivative and compressed the obtained granules into 2-mm hydrophobic mini-tablets [23].

6. Challenges in the manufacturing of mini-tablets

Pharmaceutical mini-tablets are processed in similar way to conventional tablets. On account of the miniature size of the mini-tablets, there are a number of challenges that can be encountered during compression. The flow of the final blend for tableting is critical for the successful production of mini-tablets. In the case of a pharmaceutical blend where the API is electrostatic in nature, sticking to the walls of the blender or hopper can be envisioned. This situation can be worsened if the drug load is high and the flow properties of the blend are dominated by the characteristics of the drug substance. This can lead to weight variation in tablet weights and result in high relative standard deviation. On the other hand, if the active is in low proportion within the blend, this can lead to low assay and blend uniformity issues. In these scenarios, techniques like wet or dry granulation will be required to produce granules that are capable of improving flow properties of the blend, thereby alleviating the blend flow issue. An important point to note is to avoid very large granules that could also cause inadequate flow by blocking the space within the die during compression. The ideal flow of blend should be such that it supports consistent die filling during the tableting step. Typically, smaller mini-tablets have higher weight variation due to their

narrower die orifices. Multivariate and univariate analyses suggest that gravity fill influences weight variation of 3-mm mini-tablets, while suction fill is associated with that of 1.8-mm mini-tablets [24].

Sticking is another problem due to inherent characteristics of the active molecule. This can be avoided by adequate lubrication during a premixing step. Early development work related to excipient screening based on particle size and selection of processing parameters for granulation determines the quality of the final blend, which ultimately controls blend uniformity. So, proper characterization and optimization of powder blends should include densities (bulk density and tapped density), flow properties, and segregation potential. The selection of different grades of excipients is also important to evaluate critical material properties required for successful development of mini-tablets with specifically small sizes (1.0−2.0 mm).

Small tablets might not be appropriate for patients with motor impairment, unless administered in clinical settings or with the help of a caregiver or a dosing device. Due to their small size, mini-tablets can be more easily dropped or lost by patients and caregivers compared to traditionally sized tablets, which may lead to an accidental loss of dose.

7. Coating of mini-tablets

Film coatings are frequently applied when it comes to solid oral dosage pharmaceutical drug delivery. The purpose for coating can vary depending on the properties of the active. Some of the reasons for coating mini-tablets may include aesthetic appeal, marketing requirements and patient acceptance (color, gloss), improved stability (light protection and moisture), and taste masking. Moreover, functional coatings can be used to modify the drug release behavior of the dosage form. It is possible to delay the release of the drug (such as in enteric coatings) or sustain the release of the drug over an extended period of time, depending on the polymers used. The drug can also be layered as a functional coating material to produce an IR effect of the same drug or a different drug or a combination of drugs. The equipment used to employ coatings on the surface of a tablet core are pan coaters and fluidized bed. Many believe that pan coating is mainly designed to coat regular-sized tablets because of the large opening in the pans, which are not suitable for mini-tablets. However, mini-tablet pans are available with smaller openings or when they need to be fabricated to suit the purpose. Thus both pan coating and fluidized-bed coating are suitable methods.

8. Fluidized-bed coating of mini-tablets

The coating of mini-tablets is typically carried out by fluidized-bed technology. In this process, the mini-tablets are in a fluidized state using air coming from the bottom and a spray gun delivers the coating solution. The bottom spray set-up is also known as Würster coating; the mini-tablets are circulated in a vertical expansion chamber equipped with the column, while the coating solution is sprayed from the bottom of the bed near the distributor plate through an upward-pointing gun. A number of design modifications on the conventional fluidized bed have been adopted to improve the coating process for mini-tablets. To coat mini-tablets using the fluidized-bed process, a specially designed “D” plate is required. Careful evaluation of optimum fluidized-bed critical processing parameters—fluidizing air flow, bed temperature, spray rate, atomization pressure, and filter bag mesh size used—are imperative to the mini-tablet coating process. The processing parameters will differ depending on the size of the mini-tablet, equipment, batch size, and the type of coating formulation used. Fluidized-bed technology is used as an alternative approach to pan coating because it

helps to achieve a fast and uniform coating using fluidized hot air to mix, coat, and dry the substrate (mini-tablet) at the same time. A major concern during fluidized-bed mini-tablet coating is high attrition of substrates (frequent collisions, high friction) due to fluidization, increased moisture, and high temperature. This may compromise the core tablet appearance due to the physical stress that the tablets are subjected to. Pan coating is a much gentler process. Hence, mini-tablet coating by fluidized-bed technology requires higher mechanical strength for mini-tablet cores, and a high standard for tablet formulation design. In general, high fluidization of substrates, with low bed temperature, lead to the formation of fines and the breaking of substrates (mini-tablets/pellets) during the fluidized-bed coating process. Moreover, lower fluidization with respect to bed load leads to nonuniform coating and formation of doublets during the coating process. Therefore the mini-tablets should have sufficient high mechanical strength and low friability to avoid physical damage during the coating process. Vuong et al. investigated the enteric coating efficiency of mini-tablets using either a perforated pan or a fluidized-bed coating machine. For both types of equipment, good enteric coating efficiency was obtained and the results were comparable [25]. Despite the processing challenges, Würster coating is a preferred method for the coating of mini-tablets. However, the main benefit of using the perforated pan instead of a fluidized-bed is a shorter process time.

9. Pan coating of mini-tablets

A pan coater is the most common equipment used for coating mini-tablets. The main challenge when using a perforated pan coater to coat mini-tablets is fabrication of the pan to prevent mini-tablets from falling through the perforations. A simple and economical way to pan coat mini-tablets is to use a mesh insert [26]. It was also observed during such trials that due to the small size of mini-tablets they tend to jump out of the coating pan increasing the residual loss. A Perspex shield plate is typically placed at the front of the pan to prevent loss of tablets during the coating process. The coating of mini-tablets was found to be faster and more reproducible due to uniform shape, size, smooth surface, low porosity, and high attainable strength. It was found that one-third reduction of functional coating of mini-tablets was needed compared to coating of granules because of lower surface-to-volume ratio. Mini-tablets have also been successfully coated in a solid wall pan machine using GS (IMA) coating equipment where drying air was delivered to the core tablet bed by means of two immersed perforated swords. Researchers successfully demonstrated the coating efficiency of 10 kg of mini-tablets of 2 mm size (9 mg each) in a GS 25l pan. These mini-tablets had satisfactory mechanical strength (16−19 N breaking force and low friability of 0.09%−0.17%) that enabled their successful coating in a pan coater. From a commercial standpoint, coating of mini-tablets in a perforated pan can be more efficient due to higher production volumes, lower waste of coating material, and faster equipment cleaning time compared to conducting the process in a fluidized bed.

10. Novel coating technology for mini-tablets

Pan coating and fluidized-bed coating technologies are widely applied for the coating of mini-tablets. However, these conventional coating methods are considered labor intensive, expensive, and require technical expertise for material selection and process development. As a result, formulators and process experts are constantly looking for novel, efficient, economical, and simple coating techniques. Atomic layer deposition (ALD) is one such novel technique

that has been investigated for coating mini-tablets, and for masking the bitter taste of drug substances [27]. ALD is a surface-controlled, self-limiting layer-by-layer coating method for depositing ultrathin, high-quality, and conformal thin films. Hautala et al. investigated the influence of coating processes (conventional fluidized-bed coating and ALD coating) on masking the bitter taste of denatonium benzoate-containing mini-tablets. Mini-tablets containing bitter-tasting denatonium benzoate were coated by ALD using three different TiO_2 nanolayer thicknesses (number of deposition cycles). The established coating of mini-tablets was performed in a laboratory-scale fluidized-bed apparatus using four concentration levels of aqueous Eudragit E coating polymer. The coated mini-tablets were studied with respect to the surface morphology, taste-masking capacity, in vitro disintegration and dissolution, mechanical properties, and uniformity of content. The ALD thin coating resulted in minimal increase in the dimensions and weight of mini-tablets in comparison to original tablet cores. Interestingly, ALD coating with TiO_2 nanolayers decreased the mechanical strength and accelerated the in vitro disintegration of mini-tablets. The authors summarize that the studied levels of TiO_2 nanolayers on tablets were inadequate for effective taste masking and need to be investigated further. The concept of ALD seems attractive, because ALD coatings are not only continuous, ultrathin, dense, and smooth, but also most importantly pinhole free, very conformal to the substrate, and provide good diffusion barriers with low gas and moisture permeability. As compared to the conventional pan or fluidized-bed coating, the ALD process is very different and does not involve certain limitations because tablet cores are stationary, and are coated during separate surface saturation (deposition) cycles involving chemical interactions in a reactor.

11. Packaging of mini-tablets

The packaging to be chosen for mini-tablets is decided based on the product design or on the target product profile. The selection of correct packaging configuration also depends on drug product stability in a particular packaging configuration for long-term storage. There are number of ways to deliver mini-tablets to patients; these include encapsulation in capsule shells, unit-dose packaging such as stick packs or sachets, or prefilling a container for disintegration.

12. Encapsulation of mini-tablets into capsules

Among the possible packaging configurations, including filling in sachets/stick packs, encapsulation of mini-tablets is the most common and preferred option. Mini-tablet shapes and sizes vary widely and require different technical approaches to enable their filling into capsules. The scope of requirement ranges from volume dosing to a precisely counted dosing of the mini-tablets. The controls, which are designed to ensure the correct filling of the number and type of mini-tablets into capsules, are essential to support the validation and regulatory approval of the product for marketing.

The encapsulation machines are capable of filling mini-tablets, pellets, powder, and granules using direct or indirect filling operation mechanisms. In the case of direct filling operation, the mini-tablets are fed into the body until it is completely full. An encapsulator such as the Qualifill TM Pellet filler works on a direct filling operation mechanism. For indirect filling, the encapsulates have modified dosators that use either suction to hold the material in the tube during transfer or are pushed through the material bed as seen in the Zanasi 40 E encapsulator.

However, most advanced encapsulation equipment currently on the market are units such as the Bosch GKF 2500. These machines offer filling of mini-tablets based on the number of individual mini-tablets per capsule. Modern filling equipment like the Zanasi Lab 16 are designed to fill mini-tablets and also combinations of mini-tablets with multiparticulates like pellets or with powder. Inside one capsule, it is possible to combine mini-tablets of varying formulations and coatings to obtain customized release profiles, something that is not easily achievable with tablets or capsules.

Tables 6.2 and 6.3 shows the number of mini-tablets of 2-mm size that can be filled into different capsule sizes.

The maximum number of mini-tablets that can be filled into each capsule depends on the size of the capsule and that of the mini-tablets.

Custom-designed dosing discs with cavities filled with mini-tablets are used. Each dosing disc is designed to accommodate the specific size of the mini-tablets and number required per capsule. A variable thickness dosing disc can slide underneath to hold the material prior to transfer to allow only one mini-tablet per cavity. The mini-tablets are held in position on the wheel by vacuum, and this is electronically monitored by a webcam sensor that checks the disc for the presence of mini-tablets. All insufficiently filled capsules are automatically rejected in the finished product discharge chute.

TABLE 6.2 Differences between dosage forms of mini-tablets and pellet formulations.

	Mini-tablets	**Pellets**
Definition	Mini-tablets are conventional tablets that are smaller in size (1–4 mm)	Pellets are bead-like structures and are generally filled into capsules or compressed into tablets along with other excipients
Physical characteristics	Mini-tablets have defined size and shape. They have superior mechanical strength because they are compressed to optimum hardness to withstand stress.	Pellets are ideally spherical in nature. However, they are inferior to mini-tablets with respect to mechanical strength. Therefore they might not be of uniform size and shape.
Processing	Manufactured via simple tableting (direct blend being compressed into mini-tablets)	Time taken and labor-intensive processes like fluidized-bed granulation or extrusion/spheronization are required to manufacture pellets
Solvents	The use of solvents is not required for producing mini-tablets. Thus problems with stability can be avoided.	The use of solvents is needed to manufacture pellets during extrusion/spheronization and fluidized-bed granulation
Coating	Mini-tablets can be coated using Würster coating technology or in a perforated pan coater (depending on the size of the tablets). They are easier to coat compared to pellets due to their even surface and because they are more uniform in nature.	Pellets are coated using Würster coating technology. Due to the possibility of pellets with lower mechanical strength, it might be challenging to achieve uniform distribution of coating on pellets, thus relying more on the experience of the operating personnel.
Final packaging	Mini-tablets are typically packaged in capsules or sachets/stick packs	Pellets are filled into capsules.

TABLE 6.3 The number of 2-mm mini-tablets that can be filled into capsules of different sizes.

Capsule size	Approximate number of 2-mm capsules that can be filled into the capsules
000	105
00	75
0	50
1	30
2	20
3	15
4	10

The dosing discs are intended to count mini-tablets in an accurate manner across a wide range of target fills.

A pilot-scale encapsulator such as the Zanasi 40 E is capable of filling capsules at a relatively moderate speed of around 40,000 capsules per hour, whereas the Bosch GKF 2500 can be used at a commercial scale and is capable of filling capsules at speeds of 150,000 capsules or more per hour. Moreover, modern encapsulators are capable of filling combination products, such as mini-tablets with different release profiles (ER component and IR component) of the same drug, or different types of mini-tablets, or mini-tablets combined with pellets or powder. A drug delivery system like this can produce a sharp rise in plasma concentrations for some drugs: analgesic, antihypertensive, antiinflammatory and antihistaminic agents, which are required to promptly produce the therapeutic effect, followed by the ER phase to avoid repeated administrations. Lopes et al. [20] demonstrated such a system where a capsule is filled with powder as an IR component and coated mini-tablets as the ER part of the combination therapy. A recent study by Mitra et al. concluded that the number of mini-tablets dispensed is critical when more than one mini-tablet is needed to achieve a target dose within a 15% content uniformity limit. Hence, the ability to accurately dispense varying mini-tablet quantities using different encapsulators can cover a wide dose range and such dosing flexibility is beneficial in clinical trials.

13. Unit-dose packing of mini-tablets into sachets

Unit-dose packaging of mini-tablets has been receiving attention recently, especially for pediatric formulations. Unit-dose packaging can be referred to as stick packs or sachets depending on the fill volume: stick packs have smaller fill volumes, whereas sachets have larger fill volumes. The main advantage of unit-dose packaging is that it is suitable for packaging relatively large numbers of mini-tablets, which can be beneficial for high-dose drugs. With increasing complexity, more options can be included, such as an increased number of mini-tablets per dose, or the possibility of dispensing two or more products simultaneously.

Stick packing requires specific equipment and there are a number of stick-packing machines available. They usually work on the same vertical intermittent-motion principle. Specifically, a

packaging machine such as the SBL-50 from Merz System is a vertically operating, fully automatic forming, filling, and sealing machine for the production of very small tubular bags, referred to here as "stick packs." During stick packing, the machine processes flexible composite films (often including foil) from the flat laminate reel, cut lengthwise, formed into a tube during transportation, and sealed lengthwise. It is then filled, sealed transversally, and cut. At the same time, photocell control assures the exact positioning of the print. The filling of stick packs is dependent on multiple factors, including the size of the dose, type of laminate/sachet material, and type of adhesive/polymer used to seal the sachet. In early process optimization, supplier recommended sealing criteria of the laminate/sachet material can be used but eventually critical process parameters need to be identified, and then the range has to be established through development work. The critical process parameters related to stick packing are sealing temperature, sealing pressure, sealing dwell time, and size of the stick pack, which depends on fill volume. The changing of parts is required depending on the selection of products, meaning powder dosing versus mini-tablets dosing. In the case of mini-tablet dosing, a specifically fabricated dosing disc is selected based on the number of mini-tablets per stick pack. By means of air pressure or vacuum, mini-tablets are removed from the dosing disc. The physical characteristics of mini-tablets such as thickness, length, width, diameter, and diagonal length are very critical when ordering a dosing disc. With increasing complexity, more options can be included, such as an increased number of mini-tablets per dose, or the possibility of dispensing two or even more products simultaneously.

14. Conclusion

Mini-tablets are miniature versions of conventional tablets. Therefore the decades of knowledge associated with the manufacturing of conventional tablets can be directly applied to the production of mini-tablets. This combines the simplicity of producing tablets with the advantages of multiparticulate systems in terms of in vivo applicability. Mini-tablets allow for good patient compliance due to their size, which helps in ease of swallowing. Mini-tablets provide a promising alternative to liquid dosage forms (syrups and solutions) administered to children of different ages. Additionally, mini-tablets offer the unique advantage of combination therapy that it is not easily achievable with conventional tablets or capsules. One disadvantage is the difficulty in handling mini-tablets, i.e., mini-tablets can be more easily dropped or lost compared to larger tablets. However, these risks can be mitigated by the selection of appropriate measuring aid. Due to their unique size, some adjustments to the manufacturing process steps may be needed. Earlier development work related to flow property assessment can provide useful insights to help guide the development efforts. The manufacturing process typically involves unit operations such as dry or wet granulation to improve flow properties, compression using multitip tooling, Würster or pan coating, and encapsulation or stick packing. These manufacturing processes have a number of technological challenges when producing mini-tablets when compared to conventional tablets, but careful evaluation of each unit operation can produce a better-suited and more robust mini-tablet-based dosage form. As such, mini-tablets seem best implemented for small-volume, high-value products, particularly for pediatric patient populations that would benefit from this unique dosage form.

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