

Pharmaceutical Mini-Tablets Overview

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Abstract

Oral dosage forms are considered as the most preferred dosage forms to various age groups of patients. However, conventional solid dosage forms (tablets and capsules) have been associated with some issues; such fluctuation in the plasma drug concentration and swallowing difficulty for some patients. This advocates the need for the continuous development and improvement of tablets and capsule to enhance therapeutic efficacy and increase patient acceptance. Mini tablets technology has been developed to minimize these problems. It aims to facilitate oral administration with minimal swallowing difficulty (especially in pediatrics and geriatrics) and deliver a therapeutic agent, selectively and effectively, to be targeted in a certain position in the body. The most benefit of this technique is the ease of production with facilitated control of stability problems. The size and shape uniformity, with smooth surface area, make minitables attractive to be incorporated with different medications for the efficient treatment of chronic diseases. This overview outlines properties, production requirements, formulation options and evaluation methods of mini tablets.

Keywords: Mini Tablets, multiple unit dosage forms, compressed mini tablets.

Introduction

Oral solid dosage forms have several advantages compared to other dosage forms. This includes; high patient contentment to administer the dosage, ease of transport, as well as the pattern of drug release, which can be comfortably managed and facily controlling of stability. Using conventional solid dosage forms, for example: capsules or tablets can cause fluctuation in the plasma drug concentration; thus reducing the therapeutic efficacy. Increasing the dosing frequency decreases patient's compliance and may end up with an adverse or toxic effect. In order to decrease fluctuation in the concentration, single unit or multi-unit dosage forms with varied release profiles are improved to obtain the desired pharmacological effect. In single unit

systems, the controlled drug release is achieved utilizing membrane or matrix systems. In multi-unit systems (mini tablets), drug dose is divided into small subunits. Problems of conventional tablets may be solved using mini-tablets system. Mini tablet technology aims to deliver a therapeutic agent effectively with minimal swallowing difficulty (especially in pediatrics and geriatrics) and reduced dosing frequency; and therefore the maximum therapeutic effect will be obtained as well as a minimum of possible adverse effect. Additionally, a controlled drug delivery system can be developed using mini-tablets systems for the selective and effective treatment of chronic diseases (Figure 1).

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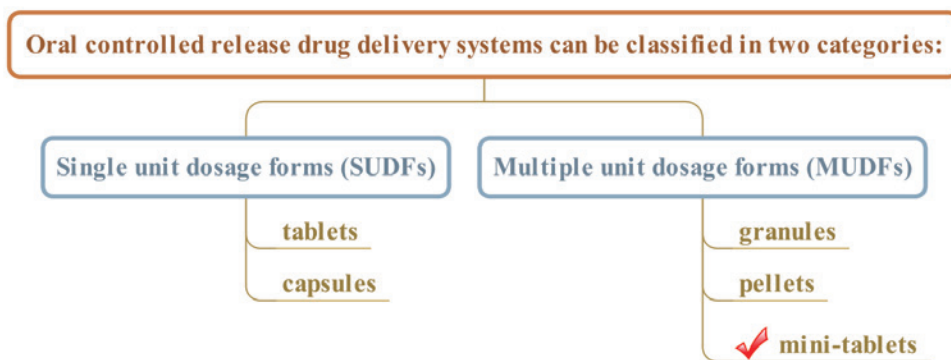


Figure 1: Oral controlled release drug delivery systems

Multiple unit dosage forms

Drug delivery systems aim to deliver a therapeutic agent, effectively and selectively, to a specific site in the body; thus minimizing dosing frequency, improving treatment efficiency and reducing potential toxicity. Conventional dosage forms have failed to achieve this and they have been associated with inconsistent plasma drug levels, which may be ineffective or toxic levels^[1]. Multi-unit dosage forms have shown the ability to conquer this obstacle, especially when the ingredients represent synergistic or additive impact, and reduce the therapeutic doses into a single unit dosage form. This advocates the advantage of preparing mini tablets dosage units to enhance the therapeutic efficacy and reduce potential side effects. Multi-unit dosage forms have greater bioavailability compared to single units due to the higher credible dissolution profile^[2]. Figure 2 shows a comparison among the characteristics of multi- and single- unit dosage forms^[3].

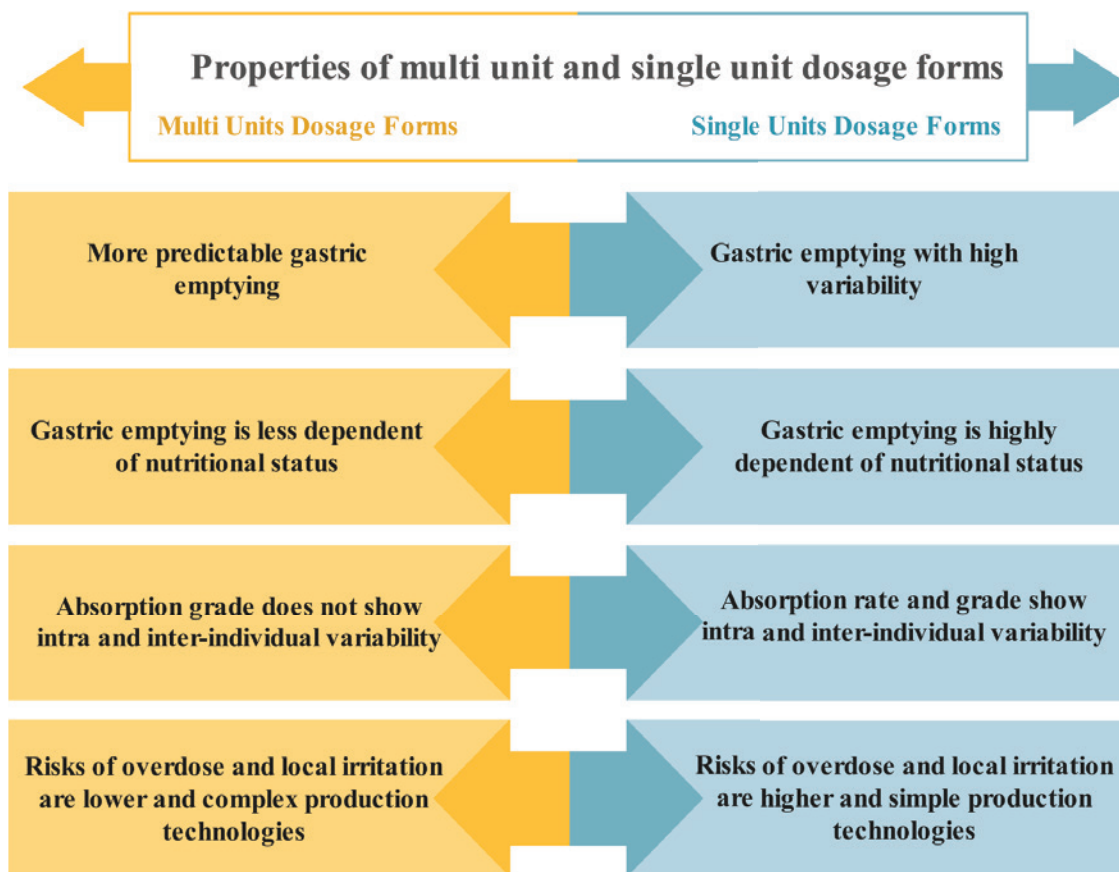


Figure 2: Multi- vs single- units' dosage forms

The definition, characteristics, and processing apparatus of mini-tablets

Mini tablet is an expression used to describe a tablet with small diameter, 3 mm or less (Figure 3). Mini tablets are described for many pharmaceutical applications, such as oral, controlled and targeted drug delivery systems. They can be loaded in capsules, sachets or pressed in large tablets^[1, 4]. Different dosages and sizes of Mini tablets are generally manufactured easily utilizing rotary tablet press machines with various punches^[1, 2].

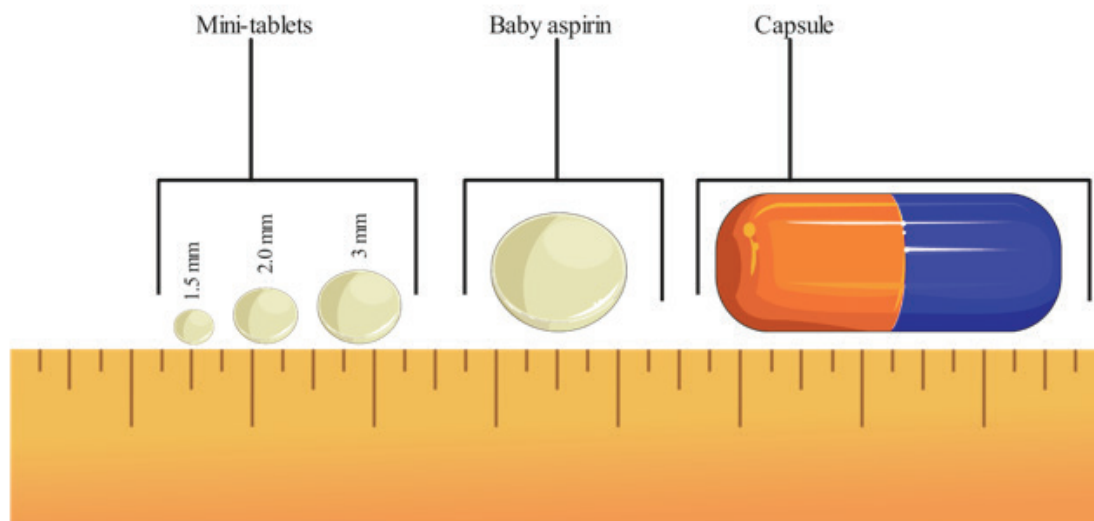


Figure 3: Comparison of the diameters of conventional tablets and mini tablets

The usage of multiple punches is advantageous as it shortens the filling time and thus reduces the possibility of powder segregation. The benefits of using multiple punches are presented in Figure 4^[4, 5].

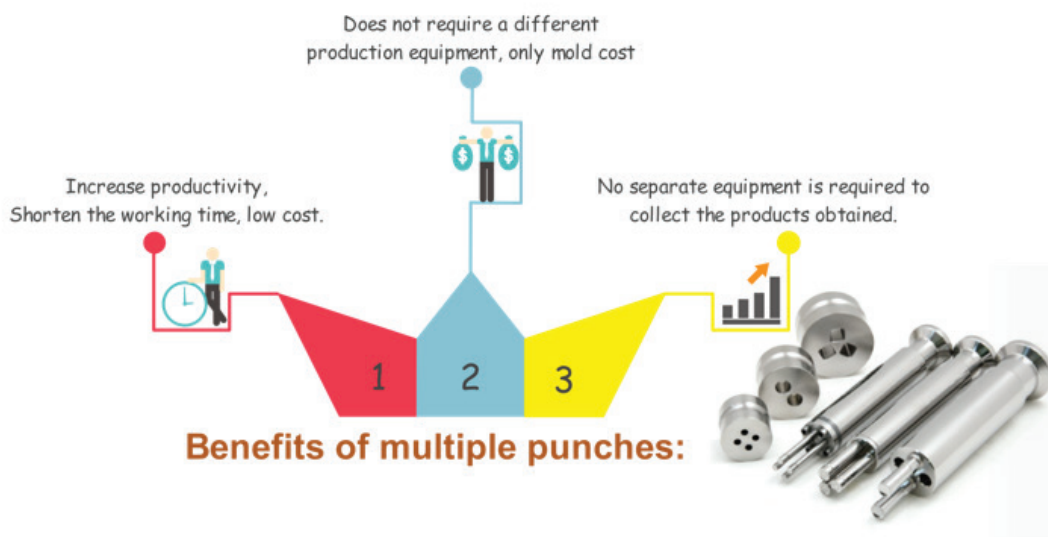


Figure 4: Advantages of multiple punches usage in mini tablets production.

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Multiple punches are available as multi-part associated or as monoblocks (Figure 5). Multi piece assemblies exhibit low risk of contamination and they are classified into two types; the first one is the internal cap fixing (Figure 5-1), which is immobilized into the punch body. The second type is the external cap fixing (Figure 5-2). The internal fixing contains fewer pins as well as provides comfortable disassembly and mounting compared to the external one. Monoblock punches (Figure 5-3) are simpler to clean and require less installation time.

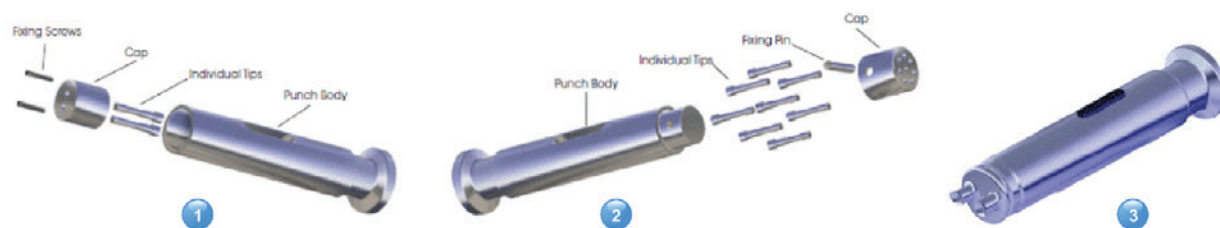


Figure 5: Types of staples used in mini tablet production

Additionally, they are stronger and more resistant against breakage and abrasion compared to multiple punches. The eroded edges can be easily renewed in multiple punches without any requirement to renew the punches. The improper installation is the main cause of eroding and punches damaging. The elevated ratio of length/diameter of the punches makes them nondurable to non-axial stresses. The device speed and length/diameter ratios should be adjusted carefully to minimize this risk. Mini tablets require fewer pressures compared to normal tablets. The process should begin with minimum pressure rates due to the durable diameter of a single punch, which is approximately 2-3 mm and may elevate to 2-3 kN axial force^[4]. Figure 6 presents the main advantages of mini tablets^[3, 6].

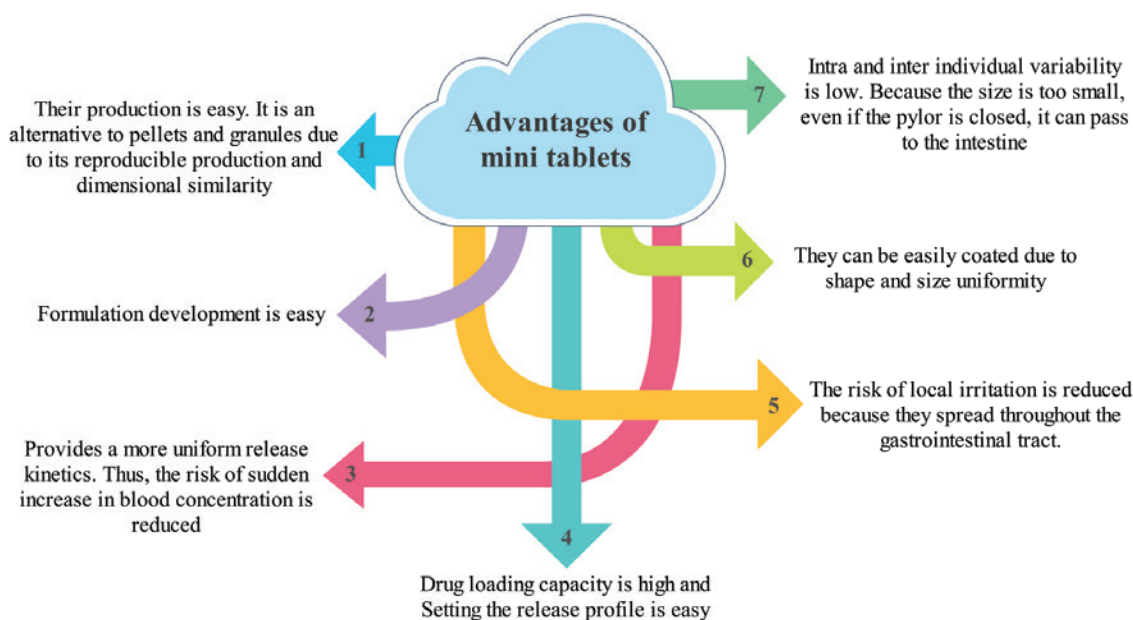


Figure 6: Advantages of mini-tablets

Formulation and production requirements

Mini tablets have different parameters compared to conventional tablets. These parameters include; cylindrical hole length, die diameter, size distribution, particle size, length-width ratio as well as bulk and tapped densities. The most important characteristics of mini tablets are the cylindrical hole length and die diameter. There is a proportional relationship between diameter size and bulk flow rate, if diameter is large (4 mm) therefore the bulk flow rate increases, and vice versa. The cause of the flow rate differences is the elevated negative pressure gradient in punch. The environmental factors, such as temperature and humidity, must be taken

into account during processing^[7]. It is very important to achieve good and reproducible followability, in order to ensure uniformity of content and die filling.

During tablet manufacturing, powders should be provided with mechanical resistance to facilitate the process of coating and capsule filling; this resistance can be obtained via good selection of formulation components such as binders and lubricants. Additionally, particle size plays an important role in mechanical resistance. A study carried out in 1998 by Lennartz and Mielck to improve the compact ability of paracetamol powder

mixtures, they discussed the role of tablet content, size and pressure on capping tendency and tensile strength. It was found that particle size reduction has increased the mechanical resistance and decreased capping tendency, which can be explained by the elevated ratio of surface area/volume in mini tablets compared to that in conventional tablets. Therefore, increasing amount of mixture will increase the friction in punch and die wall; thus leading to obtain a homogeneous distribution of densities^[8, 9].

Formulation types of mini-tablets

Mini tablets can be formulated into compressed mini tablets, encapsulated mini tablets and biphasic drug delivery systems^[1]. Mini tablets can be pressed into tablets or loaded within capsules (Figures 7-1 & 2).

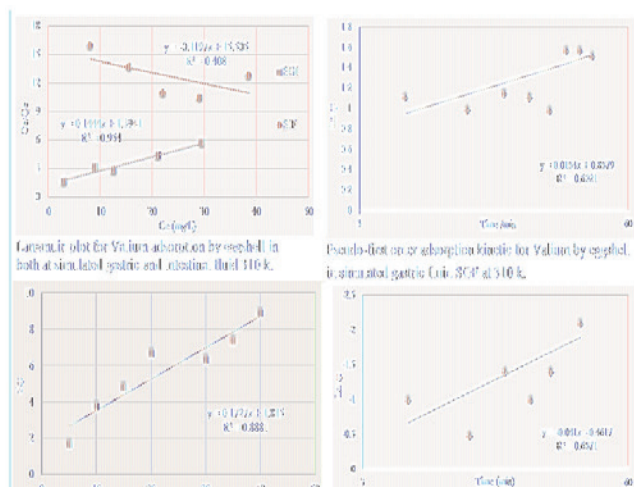


Figure 7-1: Compressed mini tablets formulation

Compressed mini tablets

Mini tablets can be easily proceeded into tablets; this will save the high cost of hard gelatin capsules. There are several characteristics of mini tablets, which make them more attractive than pellets and granules such as low porosity, smooth shapes, good mechanical resistance, uniform particle size and smooth surfaces. Release profile of mini tablet can be comfortably modified according to the external phase characteristics, which provide filling of the cavity. Biphasic drug delivery systems are improved via employing several release properties. The first phase in this system works for rapid action and immediate release, whereas the second phase sustains the drug release, which maintains continuous

action and decreases dose frequency^[1, 10, and 11].

Encapsulated mini tablets

Encapsulated coated mini-tablets (**Figure 7-2**) are developed due to their great ability to improve therapeutic efficacy, patient compliance and dosage regimen. Multifunctional systems, composed of gelatinized hard capsule of minitables, can be developed such as Rapid-release Mini-Tablets (RMTs), Sustained-release Mini-Tablets (SMTs), Pulsatile Mini-Tablets (PMTs), and Delayed-onset Sustained-release Mini-Tablets (DSMTs)^[12, 13].

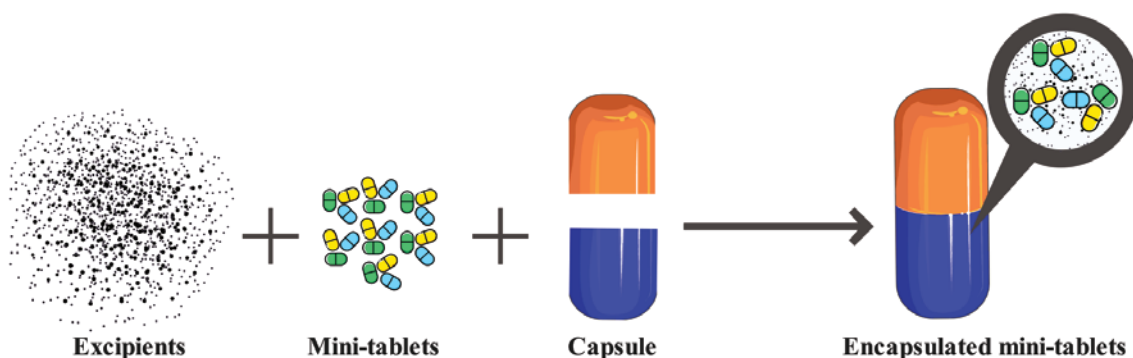


Figure 7-2: Encapsulated mini tablets formulation

Tablet coating

Coating is the final step of tablet manufacturing and it has a role in cost elevation (Figure 8). The advantages of coating tablets are illustrated in Figure 9. Tablet coating includes four operations; coating via sugar, film coating, coating with pressure and enteric coating.

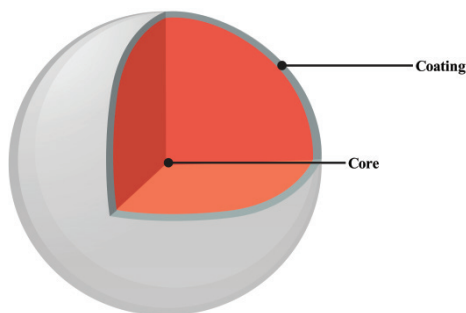


Figure 8: coating of table

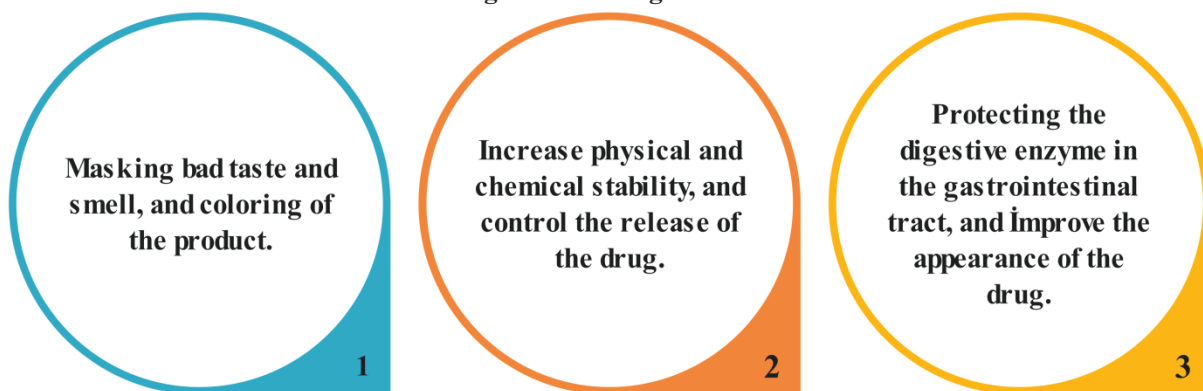


Figure 9: Benefits of tablet coating

Many factors determine the importance to carry out the coating step, such as tablet core strength, the cost of coating material and the desired therapeutic effect^[1]. It is complicated to manage the release pattern within the matrix systems in mini tablets because of the high surface area to volume ratio. A study was performed to examine the film-coated matrix mini-tablets for the extended release of a water-soluble drug. It is discussed the role of theophylline-containing mini matrix tablets

and non-matrix tablets using different concentrations of ethyl cellulose, and they concluded that it is able to extend the release of water-soluble drugs from mini matrix tablets employing a convenient quantity of film coating^[14].

Compressed mini tablets as biphasic drug delivery systems

The production of mini tablets as compressed tablets can reduce the production cost significantly compared to filling them within capsules. It is possible to merge among immediate and controlled release in the biphasic drug delivery systems, the immediate release provides rapid action at the beginning, whereas the controlled release ensures the continuous action in constant rate for certain period of time. Biphasic systems can be modified to be fast - slow or slow -fast^[15, 16]. The correlation between weight of the mini tablets and amount of powder that will surround them is very important to be considered, this ratio is recognized to be at least 3/1. Filling the gap among mini tablets requires high amount of powder, if small amounts are used, this will end up with fracture after compressing^[2].

Mini tablets and modified drug delivery

To modify the release of active ingredient from dosage form, several techniques can be used, for example: delayed release, targeted drug release, prolonged release as well as pulsatile and bimodal release^[4].

Extended release mini tablets

In this system, the active substance is gradually released for a long time. This can be achieved via extending transition time over the gastrointestinal tract or by modifying the drug diffusion from dosage form. The slow release in extended release tablets can be obtained via changing the dissolution and diffusion of the drug over barrier coating, or matrix system^[17].

Using lipid excipients is important to achieve extended release in tablets, hydrophobic substances follow diffusion principle (Fickian release) and hydrophilic substances follow diffusion and erosion principles

(Non-Fickian release). The release of extended-release mini tablets will be slow, increasing system hydrophobicity will slow down the drug release, hydroxypropyl methyl cellulose (HPMC) is a hydrophilic polymer, which performs an important role in forming a resistant or less permeable hydrogel layer^[18,19].

Drug solubility plays a critical role in the release profile. Weakly acidic and basic drugs exhibit pH-dependent solubility. This type of solubility tends to alter the ionic or non-ionic drug ratios according to pH in the release medium or the gastrointestinal fluid. In pharmaceutical production of extended release dosage forms, it is good to achieve solubility which is pH independent^[20]. In order to obtain pH independent solubility from pH dependent solubility, microenvironments should be created using a pH modifying substance. Immediate and extended release profiles can be easily controlled by pH modifiers.

If salt ingredients are introduced in the formulation of an immediate release dosage forms, it will decrease the dissolution of less soluble compounds. To achieve a pH-independent release for the extended release of weak acidic or basic drugs, pH modifiers may be introduced, which can be combined with a basic drug for example to enhance the solubility significantly at high pH values^[21].

Pulsatile and bimodal release

Fluctuations in drug concentration can occur because of the physiological factors (heart rate, blood pressure, hormone, enzymes and plasma proteins) and circadian rhythms in pathological situations. To solve this problem, several drug delivery systems are produced^[22]. To obtain a Chrono therapeutic effect, pulsatile drug release is used to delay release in a programmed manner. This system is known as a time controlled system^[23]. Pulsatile drug delivery is considered as a perfect choice for the treatment of diseases, which require a chronotherapy principle (such as bronchial asthma and angina pectoris). Pulsatile release is obtained using a controlled releasing polymer for coating tablets, which acts as a protective layer. Depending on the drug physicochemical characteristics, the release happens at certain times^[24, 25]. Pulsatile release coatings may be rupturable, erodible, permeable and semipermeable film coating (Figure 10).

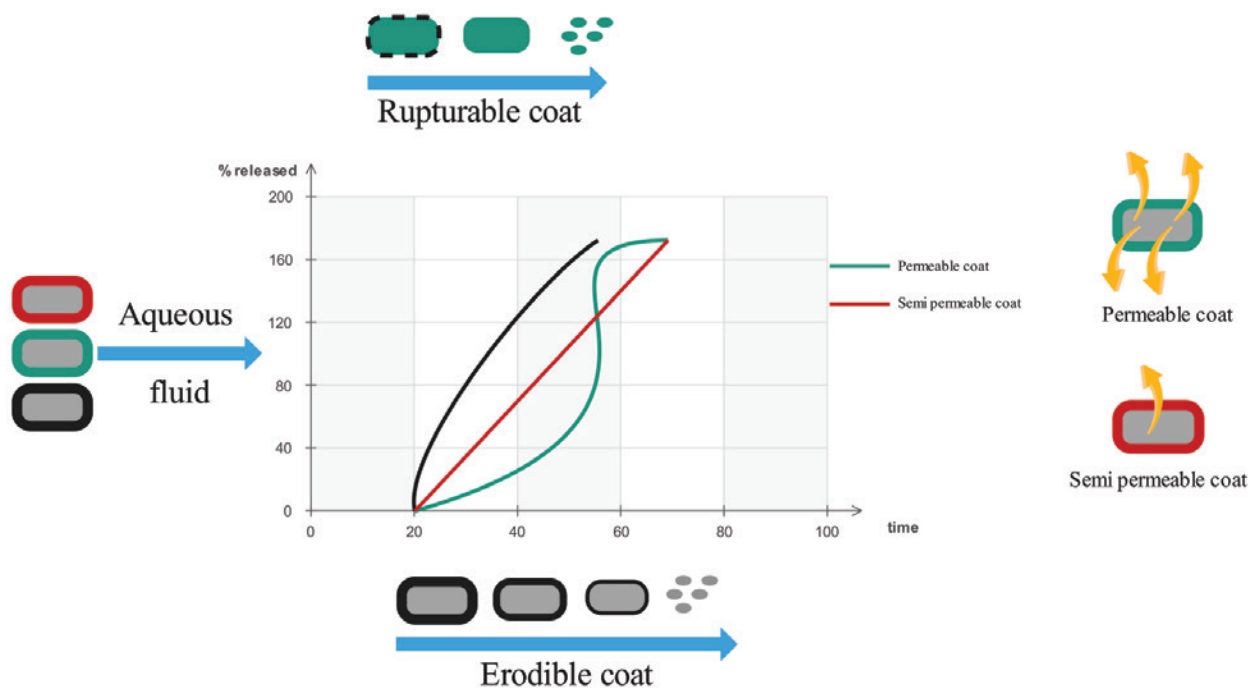


Figure 10: Performance of oral coated drug delivery systems with pulsatile release

In case of multiple release profiles, pulsatile release systems should be utilized, as in elevated metabolism with first pass effect and pharmacologically tolerated drugs. The advantages of drug administration in divided doses are reduction of bacterial resistance as well as enhancement of biological tolerance^[26].

Pulsatile release prevents the possible interaction between the dosage forms and the gastrointestinal tract^[27]. Coating a drug core with functional polymers results in multiple releases from pulsatile system (Figure 11).

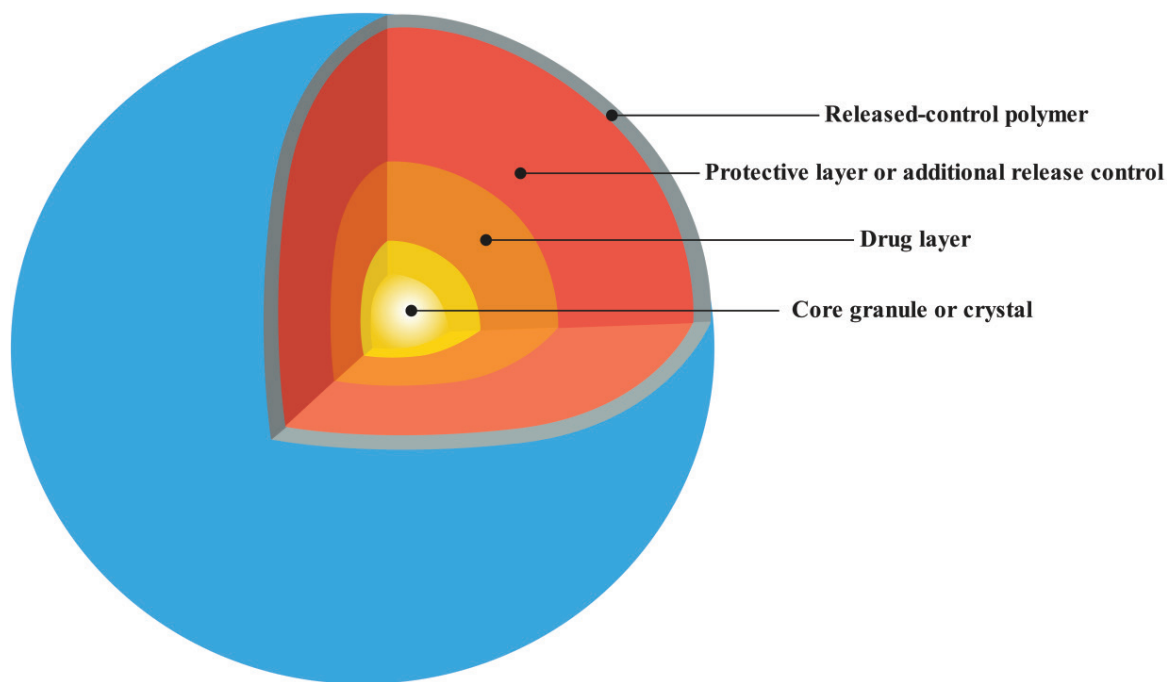


Figure 11: Multilayer coated pellets

Bimodal drug delivery systems exhibit several release properties within a single unit to enhance therapeutic efficacy and patient tolerance. It is possible to have multi delivery systems such as rapid, prolonged, extended and delayed release systems. The drug release rate in zero order kinetic system is independent of blood concentration; this system is recognized as a perfect condition to maintain the desired amount of drug in the blood. The absorption rate varies with different digestive parts; it is usually slow in the stomach, too slow in the distal part of the gut and high in the proximal part of the gut. This means that drug release rate should be changeable according to site of action to obtain a constant drug plasma concentration. Bimodal systems provide such a volatile release^[28, 29].

Floating mini tablets targeted to the gastrointestinal system

Drug absorption can be increased using floating systems in the stomach, which extend the drug's residence time. This system is beneficial for drugs, which have poor solubility and/or stability problem at intestinal pH. It is also beneficial for drugs act locally in stomach and it can decrease the possible local irritation that may occur as an adverse effect for certain drugs^[30, 31]. Medicines that have narrow absorption windows, low solubility at intestinal pH and high absorption rate in the stomach as well as the ones act locally in the stomach are considered as good candidates to be prepared as floating drug delivery systems. The density of this system is lower than that of the aqueous medium of the gastrointestinal tract (usually less than 1 g / ml) and therefore capable to float at the surface of the stomach fluid. Floating systems are classified into two subtypes: effervescent and non-effervescent systems and they can be single- or multi-units^[31,32]. Matrix-forming polymers are employed in non-effervescent systems such as polysaccharides and hydrocolloids. The result of adding these polymers is that the system swells once subjected to stomach fluid, whereas protecting the integrity shape. The drug release is controlled via the air, which introduces the swollen polymer and permits floating to occur. The external fluid introduces the dosage via swelling the system and permits drug dissolution. After that, the dissolved drug diffuses through the hydrated gel layer^[33].

Mucoadhesive mini tablets

Mucoadhesive systems are advantageous to achieve local and systemic effect. This system permits prolonged drug existence at the active site; thus increasing the local effect and enhancing the therapeutic efficacy^[34, 35]. Bioavailability can be increased by introducing mucoadhesive polymers, which adhere to the gastric mucosa surface; thus increasing drug residence in this site for long time^[36]. Highest mucoadhesive power had been shown with using thiolate polymers; they raised bioavailability more than penetration enhancers^[37, 38].

Evaluation of mini tablets properties

Evaluation of powder mixture is carried out using three measurements; bulk density, tapped density and powder compressibility (Carr's index and Hausner ratio).

Bulk density

It is the ratio of powder mass to the bulk volume of untapped powder; it involves the inter-particulate void volume. Many factors influence the bulk density, such as the powder density and the arrangement of the interstices among the particles in the powder bed. Measurement of bulk density is very sensitive, fine shaking of dust mass can alter density. The bulk density of a certain weight is discussed largely in the American Pharmacopoeia, using different methods (graded cylinder, volumetric method and a container measurement). The bulk density is usually represented by g/ml or g/cm³. In case of powder weight expressed by M and the initial powder volume is expressed by V₀, bulk density is represented as: M/ V₀. Calculating the average of at least three separated measurements is usually performed to have a representative correct value.

Tapped density

It is the ratio of powder mass to the volume occupied by the powder after it had been tapped for a certain time. After determining the initial powder volume, compression of powder is taking place. In case of powder weight is expressed by M and the compressed final powder volume is expressed by V_F, Tapped density is represented as: M/ V_F. Calculating the average of at least three separated measurements is usually performed to have a representative correct value.

Measurement of the compressibility of powders

Powder flow and batch characteristics are affected by possible particles interaction. Information about powder flow and particle interactions can be obtained from the bulk and tapped densities. This comparison is performed using the Compressibility Index (Carr's Index) and

Hausner Ratio (Table 1). The Compressibility Index and Hausner's Ratio can be calculated using the following formulas^[39]:

$$\text{Compressibility index: } 100(V_0 - V_F) / V_0$$

$$\text{Hausner's Ratio: } V_0 / V_F$$

Table 1: Flow propertied and Compressibility Evaluation of Powders

Compressibility Index (%)	Flow Properties	Hausner Ratio
≤ 10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Available	1.19-1.25
21-25	Acceptable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
> 38	Very very poor	> 1.60

Mini Tablets control**Weight Variation**

Depending on European Pharmacopoeia, 20 randomly samples are selected and weighed, then the weight average is calculated, percentage variation can be observed in up to two of these weights but it must not vary by more than twice that percentage (Table 2).

Table 2: Weight Variance Evaluation

Pharmaceutical Form	Average Weight	Percent Deviation
Tablets (Uncoated and Film Coated)	80 mg or less	10
	80-250 mg	7.5
	More than 250 mg	5
Capsules, Granules (coated and uncoated) and Powders	Less than 300 mg	10
	More than 300 mg	7.5

Uniformity of tablets

To ensure uniformity of content (uniformity of active pharmaceutical ingredients (API) in each tablet); thus obtaining the desired therapeutic effect without loss of efficacy or any possible toxic effect. There are two methods to recognize the uniformity of tablets: weight variation or content uniformity. The drug's contents are examined to define if the single contents are in limits; Content Uniformity (CU) and weight variability (MV) tests of various dosage forms are illustrated in Table 3.

Table 3: Content Uniformity and Weight Variability Tests for Dosage Forms

Dosage Form	Type	Subtype	Dosage and proportion of active substance	
			≥ 25 mg and $\geq \%25$	≤ 25 mg and $\leq \%25$
Tablets	Uncoated	-	MV	CU
	Coated	film coated	MV	CU
Capsules	Hard	-	MV	CU
	Soft	Suspension, Emulsion, Gel	CU	CU
		Solution	MV	MV
Solids in single dose container	One-component	-	MV	MV
	Multi-components	freeze-dried solution	MV	MV
Liquid in single dose container	-	-	MV	MV

Friability

This experiment is carried out under specific situations to confirm the existence of lamination or fractures in uncoated tablet or any surface damage. It is performed once and if there is any fracture or crack in a sample, this sample is considered to fail the friability test^[39].

Dissolution test

It is performed to define the dissolution rate of the active pharmaceutical ingredients (API) in solid dosage

forms (capsules or tablets). Many factors should be recognized to prepare a sample for this test:

The utilized device, rotating speed, sampling method, analysis method and amount of (API) required to be dissolved^[39].

Disintegration test

It is utilized to confirm if the solid dosage form (tablet or capsule) are dispersed in a specific time, when they are subjected to a liquid medium, under the test situations demonstrated in Figure 12^[40].

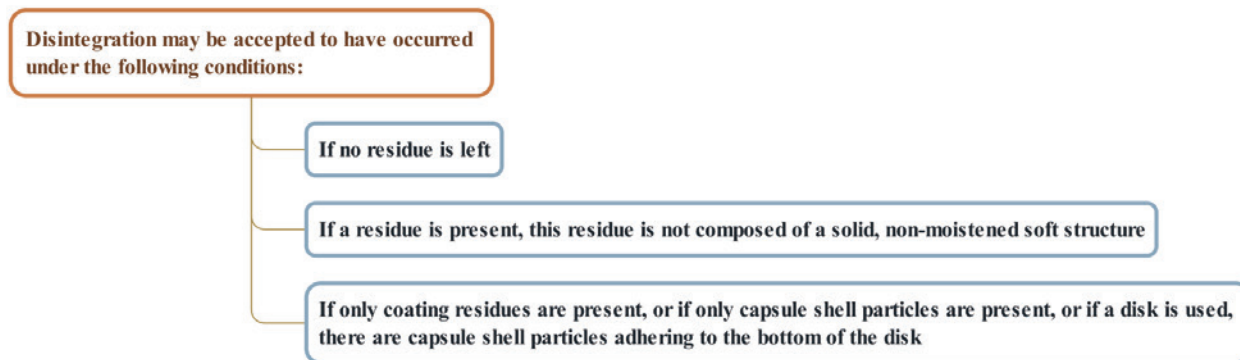


Figure 12: the conditions of disintegration occurrence

Mini-Tablet Drug Delivery System for Pediatric Dosage Form (PDF)

Pediatric have a problem of swallowing difficulty, and therefore the most prescribed dosage form for them is the liquid dosage form which provides ease of administration. Because of the lack of stability of the liquid drugs and inaccurate dosing intake; mini-tablet technique provides the facility of delivering drugs for pediatrics in an accurate dose as well as in high stability in a comparison with the bulk dosage form^[41].

Few drugs commercially available as mini-tablets, for examples: capsules of Propafenone HCl as antiarrhythmic, Sachet of Terbinafine HCl as Antifungal, capsules and sachet of Sodium Valproate for epilepsy, capsules of Fenofibric acid for cholesterol and Stick Pack of Ivacaftor for Cystic Fibrosis (CF)^[41].

Conclusion

Pharmaceutical mini-tablets provide several benefits compared to conventional tablets, which make them as excellent alternatives for granules and pellets. They have low porosity and high mechanical strength. They can be formulated into tablets or filled in capsules. Mini-tablets can be used to deliver incompatible drugs for the effective treatment of different chronic disorders. It enhances the therapeutic efficacy and patient compliance. As discussed in this review article, mini tablets technology represents a promising field, which requires high interest from pharmaceutical researchers because of the wide therapeutic applications. As such, mini-tablets seem best implemented for small volume, high value products, particularly for pediatric patient populations that would benefit by this unique dosage form.

Acknowledgements: The authors are grateful to the Philadelphia University, Amman, Jordan for the financial support granted to cover the publication fee of this paper.

Conflict of Interest: The authors declare they have no conflicts of interest to disclose.

Authors' contributions

MB organized the project and the article writing. HS is a student under MB supervision who prepared the manuscript. HS and MS contributed to the writing style

and proof reading. All authors have read and approved the manuscript.

Ethical Clearance: Not applicable.

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