

A REVIEW ON PHARMACEUTICAL MINI TABLETS: NEW MODALITY TO ORAL DRUG DELIVERY

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ABSTRACT

The purpose of any selected drug delivery system (DDS) is to deliver drug to target site and to get the desired drug concentration for effective therapy. The main purpose of designing controlled or sustained DDS is to decrease the frequency of dosing and maximizing its efficiency by confining the area of action of the drug to a selected region. It is well-identified that solid oral dosage form, particularly tablets, is the most satisfactory form of delivering medication. In addition, some new variations are emerging such as mini tabs which offer more formulation flexibility. Oral controlled release DDS are classified into two categories like single unit dosage forms which include tablets, capsules, and multiple-unit dosage forms include pellets, granules, or mini tablets. Mini tablets are a new development in solid dosage forms and more beneficial and great substitute for granules and pellets. Mini tablets defined as tablets which are having diameter <3 mm and promising patient friendly drug delivery system and more acceptable in small children's and old age people as they are easy to swallow and offer therapeutic benefits such as manufactured relatively easy, dose and formulation flexibility, combination release pattern, coating, and less solvent requirement. Dose dumping and local irritation can be avoided using mini tablets. This review highlights the various advantages of mini tablets, manufacturing processes, formulation possibilities, and their challenges.

Keywords: Oral dosage forms, Pediatric drug delivery, Pellets.

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INTRODUCTION

The most convenient and popular route of administration among all drug delivery routes is oral drug delivery. The main goal of any dosage form is to keep up the therapeutic amount of drug to the targeted site with minimum toxicity and side effects by providing loading and maintenance dose. Tablets are most widely used solid dosage form and there is always a possibility for improving the confines of tablets like delay in onset of action and difficulty in swallowing and improves patient compliance and have many advantages when compared with other dosage forms such as ease of transportation, production and application, accurate dosing, stability, and controlled release patterns were achieved [1-4]. However, they also hold some disadvantages such as the ease of use in pediatrics or geriatric's difficulty in swallowing and desired release profile; expected therapeutic effect or concentration of the drug at the site of action cannot achieve due to first-pass metabolism [5-7].

The challenging aspect related to mini tablets is the development of pediatric dosage forms (PDF) and it is mainly due to the differences in swallowing abilities, dosage form requirements, and taste preferences of children's [8,9]. Till date, the most commonly prescribed dosage form for the pediatric population is liquid dosage form due to its ease of administration. Liquid dosage form is the most commonly prescribed form for pediatrics due to its easy ingests benefits. However, they have major disadvantages such as physical, chemical, microbial instability, palatability of the solution, lack of controlled release, and palatability of the solution. There also limits on which excipients, preservatives, and solvents used in PDF [10-12]. Recent reported studies have shown that mini tablets are superior to syrups for administration to children's including toddlers and it characterizes a flexible drug delivery tool for single or composite of multiple units. Hence, mini tablets represent a very promising alternative to liquid formulations administrated to children's of different age group.

The traditional solid dosage forms such as tablets and capsules considered as not proper due to swallowing difficulties in young children. Due to lack of its stability, dose accuracy, and dispensing faults, special attention is given to the progress of mini tablets to overcome

these problems, with the aim to improve drug delivery for pediatrics. Mini tablets symbolize a new development in solid dosage form design and can use as a flexible drug delivery tool for single or composite of multiple units. Furthermore, mini tablets with well-controlled quality features could be a practical choice for administrating solid dosage forms of low potency drug substances as capsules or stick packs [13].

The difference in tableting among regular size tablets and mini tablets is a type of tooling required. Usually, tablet press to manufacture mini tablets is made by standard reciprocating or rotary tablet press with single or multiple-tip tooling. Depending on tableting requirements, certain alterations to the press and tooling might be necessary. The multi-tip tooling must meet certain requirements of precision and mechanical stability. While handling mini tablet tooling as it can easily damage minimum care should be taken [14,15]. Any excessive force applied to the tooling can lead to damage of punches and due to the smaller diameter of the punches, they are easily deform and breakable. Multi-tip tooling must meet tighter requirements for machining and mechanical stability compared to larger tablet tooling. The multi-tip tooling lessens the time required for production.

ORAL CONTROLLED RELEASE DRUG DELIVERY SYSTEMS (DDS) CAN BE CATEGORIZED IN TWO GROUPS [16]

1. Tablets and capsules which come under a class of single unit dosage forms (SUDF's). In a single unit dose, for example, matrix or tablet surrounded in diffusion membrane is a depot which releases drug throughout the passage of entire gastrointestinal (GI) tract without disintegrating. The empty core or shell was discharged. To keep a depot, effect the dose unit to be administered should be intact as dividing dosage form before administration would result in unintended rapid release
2. Multiple unit dosage forms (MUDF's) such as granules, pellets, or mini tablets. A multiple unit's dose consists of several mini units, for example, pellets or mini tablets contained in a capsule or a tablet. These mini depots were dispersed and distributed throughout the GI tract with the disintegration of the tablet or capsule. The dose in (MUDF's) is divided into several subunits, each one containing the

drug. The extent of the drug in each subunit and the functionality of the complete dose are directly correlated to the functionality of the specific subunits.

MINI TABLETS

The term "mini tablets" usually refers to compressed tablets with a smaller size than typical tablets. These are plain or blended tablets which are having a diameter ranging between 3 and 6 mm and less than that. Mini-tablets also called as oral granules because of its small diameter which is less-than 2.5 mm but the preparation and production of mini tablets mainly focused at their size range to take benefits of the potential flexibility in dosage form administration [17]. Mini tablets were produced with multiple punches using peculiar or rotary tablet press machines. Mini tablets are great substitutes for granules and pellets since they can easily produce and converted into a controlled DDS. Controlling drug release is a significant point of investigation in case of oral controlled drug release system [18].

Mini tablets can easily divide and administrated without loss of activity. In the case of normal tablet, pediatric and elderly patients chew the tablets which release drug all at once and may cause toxicity, but in case of mini tablets, it can overcome as it can be chewable as here dose dumping may not occur because each mini depot in the formulation acts individually. For local irritating drugs, mini tablet formulation decreases the irritation effects than that of single unit formulations [19].

Many reported studies have shown that by applying a consistent layer of a retarding film coat, the release rate of the drug can be controlled with greater certainty. The mini tablets were formulated using different concentrations of hypromellose (HPMC) k100M offer a prolonged drug release rate. Based on the composition of mini tablets, the drug contained in the different mini tablets gets released at different rates and it is possible to meet various releases with one formulation by combining different doses of mini tablets [20]. Mini tablets helpful in reducing the intra and inter-subject variability and reproducible release profiles can be achieved. Preferably, the drug absorption is more in the upper part of small intestine for a drug to reach the small intestine and then it had to pass through stomach and the drug absorption depends on gastric emptying time. If the gastric emptying is too slow, it may get mix up with gastric contents or if it is fast drug may not absorb to the required level. These effects are more in the case of SUDFs because of their size, but in the case of mini tablets will not depend on gastric emptying and easily get distributed through pylorus. Hence, mini tablets are beneficial over the normal size tablets to lessen intra and inter-subject variability [21].

Advantages [22,23]

1. Problem of less dose dumping
2. High degree of dispersion in GI tract
3. Mini tablets can be easily manufactured
4. They have a regular shape and smooth surface, excellent size uniformity
5. Mini tablets eliminate systemic side effects and local side effects
6. Improve efficiency in treatment and minimize drug accumulation with chronic dosing.

Types of mini tablets

Enteric coating is a barrier applied to oral medication that controls the location in the digestive system where it is absorbed. Most enteric coatings work by presenting a surface that is stable at the highly acidic pH found in the stomach but breaks down rapidly at a less acidic (relatively more basic) pH. For example, they will not dissolve in the acidic juices of the stomach (pH ~3), but they will in the alkaline (pH 7-9) environment present in the small intestine. Materials used for enteric coatings include fatty acids, waxes, shellac, plastics, and plant fibers. Drugs that have an irritant effect on the stomach, such as aspirin, can be coated with a substance that will dissolve only in the small intestine. Likewise, certain groups of azoles (esomeprazole,

omeprazole, pan, and all grouped azoles) are acid-activated. For such types of drugs, enteric coating added to the formulation tends to avoid activation in the mouth and esophagus. Recently, some companies have begun to utilize enteric coatings on fish oil (omega-3 fatty acids) supplements. The coating prevents the fish oil capsules from being digested in the stomach, which has been known to cause a fishy reflux (fish burps). Sometimes the abbreviation "EC" is added beside the name of the drug mini tablets can be classified based on the target site, method of manufacturing, patient needs as follows.

TYPES OF MINI TABLETS

Mini tablets can be categorized based on the target site, process of manufacturing, which includes;

1. Bioadhesive mini tablets
2. Gastroretentive mini tablets
3. Pediatric mini tablets
4. Oral disintegrating mini tablets
5. Biphasic mini tablet.

Bioadhesive mini tablets

Bioadhesive mini tablets are mainly used for vaginal drug delivery to carry drug precisely and for a long time in mini tablets dose is distributed into multiple units which will spread uniformly in the vaginal cavity with improved exposure in vaginal epithelium. Bioadhesive mini tablets act by swelling and forming microgels and releasing the drug in controlled release method and thereby enhancing the bioavailability [24].

Most of the problems with the use of other dosage forms available for vaginal drug delivery are creams, ointments, gels, and tablets are leakage, messy, less patient compliance, and less retention time. To overcome the above problems, we can use bioadhesive or hydrophilic polymers which are readily soluble and adhesive on exposure to moisture and will rapidly adhere to surfaces as they have high viscosity at low concentrations. Solid dosage forms have long term stability and accuracy but in case of conventional vaginal tablets the process of disintegration is very slow and rapidly cleared due to self-cleaning action of vagina and this can be reduced by using bioadhesive polymers in the formulation [25].

Bioadhesive mini tablets prepared with hydroxypropyl cellulose and HPMC have reported adequate mechanical and bioadhesive properties. The pH of vaginal varies from women to women of different ages. To withhold those pH conditions, bioadhesive vaginal mini tablets are to be designed using non-ionic cellulose ethers with bioadhesive property [26].

Gastro retentive mini tablets

Gastro retentive mini tablets were manufactured with the aim of release of drug in stomach for prolonged time. Usually, for tablets to float on gastrointestinal fluid, mini tablets should be formulated with a composition containing gas generating agents and when they come in contact with food generate CO_2 and then produced gas will trap in swellable hydrocolloid which makes the tablet to float and stay in stomach. In single-unit tablets, drug loading is low as the polymer used for floating is high. In the case of mini tablets, coating with sodium bicarbonate or calcium carbonate can be done, which are gas generating agents and the swellable polymers were replaced with Eudragit coating to increase the drug loading efficiency. Fluid bed processor is generally used for coating mini tablets [27].

Pediatric mini tablets

There are various dosage forms available for children's and most commonly preferred dosage forms are liquid dosage forms (syrups) and solid dosage forms (tablets and capsules). Liquid dosage forms which are easy to administer but it hold many drawbacks like their stability and taste palatability issues. In case of tablets, their size is big and becomes a difficulty in swallowing and dose adjustment is also difficult and sometimes need to cut the size of the tablet by breaking into two halves which lead to loss of activity and nowadays patient

compliance is another issue with the conventional dosage forms, all these issues can overcome by formulating mini tablets which can result in good patient compliance. It is a convenient and easily acceptable dosage form for children's than other dosage forms such as syrups, tablets, and capsules [28,29].

Oral disintegrating mini tablets

The synonyms for orally disintegrating tablets are orodispersible tablets, melt-in-the-mouth, rapidly disintegrating tablets, fast-dissolving tablets, quick-dissolving tablets are some of generally used synonyms [30]. Moreover, defined it as a tablet that is placed in the mouth where it disperses rapidly before swallowing. The oral dispersible tablets (ODT's) should have the following advantages like it should disintegrate in the mouth without extra water. It has been proven statistically that ODTs have several advantages over conventional tablets to enhance patient compliance and acceptance because of its feasibility and convenience [31]. Almost 50% of the population pediatric and geriatric suffers from difficulty in swallowing while taking tablets and hard gelatin capsules, large tablets, to overcome these problems, orally disintegrating tablets mini tablets (ODT) developed as substitute oral dosage forms. Orally disintegrating tablets can prefer even who do not suffer from any swallowing problems. ODT technologies have emerged very rapidly over this past decade. There are new generations of ODT which have been progressive to overcome the limitations of the earlier products [32,33]. Another reason which makes ODTs highly promising is the route of administration that it has only administered by mouth. This unique factor allows other companies to get approval for a generic version of the drug. Composition of ODT mini tablets includes the composition of sodium salicylate, Prosolv ODT, and magnesium stearate. Sodium salicylate served as the model drug compound [34]. Excipients include microcrystalline cellulose, cross povidone, mannitol, colloidal silicon dioxide, and fructose.

Biphasic mini tablet

A biphasic mini tablet comprises two parts a fast releasing part and a slow-releasing part. The intention of biphasic delivery systems is to release drug at two different rates or at two different time periods: They are either quick/slow or slow/quick. A quick/slow-release system provides an initial burst of drug release followed in a controlled way of release over a defined period of time and in slow/quick release system provides release vice-versa. This type can helpful for drugs used in hypertension where repetitive dosing can be reduced. Different drugs can compact into mini tablets and filled in the same capsules to treat various diseases [35,36].

PROSPECTS OF FORMULATING MINI TABLET DOSAGE FORM

1. Encapsulated coated mini tablets
2. Compressed mini tablets
3. Compressed mini tablets offered as biphasic drug delivery system.

Encapsulated coated mini tablets

Encapsulated coated mini tablets are widely preferred as it improves drug tolerance and yields a dose regimen that is easier to manage for patients. Mini tablets in a hard gelatin capsule can be developed by incorporating rapid-release mini tablets, sustained release mini tablets, each with different release rates. Rapid release mini tablets allow the progress of rapid-acting encapsulated dosage forms for fast action [37,38]. However, several mini tablets can be placed into each capsule, which later disintegrates and releases the contents of mini tablets. This as a result improves patient compliance. Based on various combinations of mini tablets such as site-specific, multiplied pulsatile, slow/quick releases, and quick/slow release, zero-order DDS will be achieved [39].

Compressed mini tablets systems are offered as a biphasic delivery system

Compressed mini tablet systems offered as a biphasic delivery system intended for zero-order sustained drug release. The outward layer that fills the void spaces among the mini tablet is formulated to release the

drug in a very short time (fast release). Different compositions (HPMC or EC) used in mini tablets to get different drug release rates [40]. The *in vitro* performance of these systems shows the desired biphasic performance depends on formulation the drug contained in the fast releasing phase (powder enrobing the mini tablets) dissolved within the first 2 min, where the drug contained in the mini tablets were released at different rates. Based on the kinetic release limits, it can be concluded that mini tablets comprising HPMC were a predominantly suitable approach to meet zero-order release(constant) over 8 h time period [41].

Compressed mini tablets

It has been a growing emphasis in the development of multi unit dosage forms's compresses into tablets instead of filling into hard gelatin capsules, to overcome the higher production costs of capsules, mini tablets can be used to produce a biphasic delivery system, by combining a fast release form with a slow-release form of the drug [42-44]. Mini tablets, due to their uniformity in size, regular shape, smooth surface, high mechanical strength, and low porosity, mini tablets can keep up their uniformity in a more reproducible way than pellets or granules when they compressed into a tablet. Drugs usually suitable for this type of administration include non-steroidal anti-inflammatory, anti-hypertensive, antihistamines, and anti-allergic agents [45].

Evaluation of mini tablets

Evaluation of mini tablets is similar to that of normal tablets, official tests such as weight variation, hardness, friability, thickness, diameter, and *in-vitro* drug release characteristics were evaluated.

Weight variation test

Twenty tablets are selected randomly and weighed from the batch and the individual weight of each tablet is noted. From this, the average weight is calculated. According to United States Pharmacopeia (USP), none of the individual tablet weight should be <90% and more than 110% of the average weight [46,47].

From this, the average weight is calculated. According to USP, none of the individual tablet weight should be <90% and more than 110% of the average weight. The specification of weight variation is 10% From this, the average weight is calculated. According to USP, none of the individual tablet weight should be <90% and more than 110% of the average weight. The specification of weight variation is 10%.

Hardness

Pfizer hardness tester detects the hardness of the mini tablets and expressed in kg/cm². Six tablets were randomly chosen tested for hardness. From each formulation, the mean and standard deviation values were calculated [48].

Thickness

The tablet thickness is generally determined based on the diameter value. Tablet thickness is usually controlled to lessen appearance problems, to assure that tablets will fit into the container and to assure that they can precisely be counted by the filling equipment. Some filling equipment's be influenced by the uniform thickness of the tablets as a counting mechanism. A screw gauge and digital Vernier Calipers were used to measure the thickness of the mini tablets [49]. It is expressed in terms of mm [50]. Thickness limits should orderly within $\pm 5\%$ variation of standard value.

Friability

Using Roche Friabilator, friability test of mini tablets is carried out. For this, usually, 20 mini tablets were chosen randomly from each batch and their initial weight (W_0) was noted [51,52]. The mini tablets were firstly weighed and shifted into friabilator; the drum was subjected to rotation process for 4 min at 25 rpm after which the mini tablets were removed. Any loose powder leftover was removed from the mini tablets and the tablets are weighed again and considered as final weight (W_f).

Drug content uniformity

Five mini tablets weighed and crushed in a mortar then weighed powder contained equivalent to 10 mg of drug transferred into 100 ml of dissolution medium which gives the concentration of 100 µg/ml. Take 10 ml of this solution and diluted it up to 100 ml with the same solution to give a concentration of 10 µg/ml. Absorbance measured at a particular wavelength using ultraviolet (UV)-visible spectrophotometer [53,54].

In vitro dissolution studies

USP type II dissolution test apparatus used to carry out the *in vitro* release studies at specific rpm and temperature for a definite time period in suitable buffer solution. The dissolution medium selected for performing the experiment is phosphate buffer (900 ml), having a P^H of 6.8 and the process was carried out for 10 h. At different time intervals (0, 15, 30, 60, 90, 120, 240, and 360 min), 5 ml of samples were pipette out and replaced with 5 ml of drug-free dissolution medium. These withdrawn samples were analyzed by UV spectrophotometry at a particular wavelength [55-57].

Stability studies

During the drug development process, stability studies play an integral role in the formulation of pharmaceutical products. Stability studies help to find any change in the quality of the drug substance with time under the influence of many environmental factors such as temperature, pressure, humidity, and light. These studies were carried out as per ICH guidelines. The storage condition requirements are 40°C±2°C/75%RH ± 5%RH and 25°C±2°C/60% RH ± 5% relative humidity for the period of 3 months [58-60].

CONCLUSION

Pharmaceutical mini tablets have comparatively more advantages when compared with the SUDFs and it is suitable substituents for pellets and granules. Inter- and intra-subject variability, most toxic effects that usually face with conventional tablets can reduce using mini tablets. Dose dumping and local irritation and toxicity effects are minimized by use of mini tablets. They have defined size and shape and low degree of porosity and high mechanical strength. However, production factors should carefully be assessed, to make sure good flow. Bioadhesive mini tablets showed increased bioadhesion and increased effect than that of single unit bioadhesive tablet. Particularly in geriatric and pediatric patient groups, there is a great potential for accomplishing success in treatment. Many reported studies have shown that mini tablets acclimatize to a multitude of modified release patterns such as pulsatile, extended, delayed, bimodal release, and colon targeting. As discussed in the review, mini tablets have become an attention-grabbing topic for researchers because of their plentiful advantages. Eventually, mini tablets improve overall therapeutic outcome, patient compliance, and convenience. As they have significant advantages, they are formulated for most of the existing and suitable drugs.

AUTHOR'S CONTRIBUTION

The author has written the manuscript.

CONFLICTS OF INTEREST

There are no conflicts of interest.

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