AN EVALUATION OF PHARMACEUTIC MINI TABLETS: A NEW MODEL FOR ORAL DRUGS

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ABSTRACT

Every drug delivery system (DDS) must deliver drug to target region and achieve drug concentration for therapy. Controlled or sustained DDS limits pharmaceutical activity to a specified location to reduce dosage frequency and increase efficacy. It's commonly known that pills are the best way to provide medication. Little tabs that offer formulation flexibility are also emerging. Tablets, capsules, and pellets, granules, and small tablets are all oral controlled release DDS. Small tablets are better than granules and pellets. Tiny tablets, with a diameter <3 mm, are patient-friendly drug delivery systems that are easier to swallow and provide therapeutic advantages such dosage and formulation flexibility, combined release pattern, coating, and reduced solvent demand. Little tablets reduce dosage dumping and local pain. This study discusses micro tablet advantages, manufacturing methods, formulation alternatives, and constraints.

Keywords: *Oral dose forms, pediatric medication administration.*

INTRODUCTION

Oral medicine administration is most convenient and popular. Every dosage form aims to keep the therapeutic amount of medication at the desired area with minimal toxicity and side effects by administering a loading and maintenance dose. Tablets are the most common solid dose form, although their late start of action and swallowing difficulties might be improved to boost patient compliance. Tablets are easier to travel, produce, apply, dose, and manage [1-4]. Nevertheless, ingestion, pediatric and geriatric usage, and desired release profile are limitations. First-pass metabolism also reduces therapeutic efficacy and medication concentration at the site of action [5-7].

As children have different swallowing abilities, dosage needs, and taste preferences than adults, creating pediatric dosage forms (PDF) for micro pills is problematic [8,9]. Liquid dose formulations are still suggested for children due to their ease of administration. Liquid dose is suggested for youngsters due to its ease of use. Nevertheless, the solution's palatability, lack of controlled release, and physical, chemical, and microbiological instability are negatives. PDF excipients, preservatives, and solvents are limited [10–12]. Recent studies have demonstrated that tiny pills are better than syrups for administering medicine to children, even toddlers. Hence, mini tablets are potential alternatives to liquid formulations for children of different ages.

As small children can't swallow tablets and capsules, they're improper. Little pills address stability, dosing accuracy, and dispensing problems to enhance medication administration for children. Solid dosage form design has advanced with micro pills, which may deliver single or many units of medicine. Little

tablets with well-controlled quality may also be used to provide low-potency solid dosage forms such capsules or stick packs [13].

Different gear is needed to tablet large and small tablets. A reciprocating or rotating tablet press with a single or multiple tip tooling is used to make tiny tablets. The press and tooling may need to be adjusted for tableting. Mechanical and accuracy parameters must be met by multi-tip tooling. Because to its fragility, micro tablet tooling should be handled with care [14,15]. Punches may be damaged by excessive force due to their smaller diameter. Multi-tip tooling has higher machining and mechanical stability requirements than bigger tablet tooling. Multi-tip tooling reduces production time.

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

1. Single unit dose forms (SUDFs), which include tablets and capsules. The matrix or tablet in a single unit dosage, for instance, is a depot that distributes medicine during the transit of the whole gastrointestinal (GI) tract without dissolving. The shell or core that was empty was released. The dose unit to be supplied should be whole in order to maintain a depot since separating the dosage form before administration would cause an unexpected fast release.

1. MUDFs, or multiple unit dosage forms, such granules, pellets, or little pills. Many micro units, such as pellets or small tablets enclosed in a capsule or tablet, make up a multiple unit's dosage. After the dissolution of the tablet or capsule, these tiny depots were spread throughout the GI tract. Each of the many components that make up the dosage in (MUDFs) contains the drug. The functioning of the individual subunits is closely associated with the amount of medication present in each subunit and the efficacy of the whole dosage.

MINI TABLETS

Mini tablets are often compressed tablets that are smaller than standard tablets. These tablets are either plain or mixed, and their diameters range from 3 to 6 mm and smaller. Due to their tiny diameter, which is less than 2.5 mm, mini-tablets are also known as oral granules. Nevertheless, the manufacture and manufacturing of mini-tablets was primarily focused on this size range to take advantage of the possible flexibility in dosage form administration [17]. Using unusual or rotational tablet press machines, little tablets were created with many punches. Because to their ease of production and conversion into a controlled Dosage, mini tablets are excellent alternatives to granules and pellets. In the case of an oral controlled drug release device, controlling drug release is an important area of inquiry [18].

Small pills can readily split and administrated without loss of action. Children and elderly patients swallow conventional tablets, which may induce toxicity since the medication is released all at once. However, micro tablets are chewable and may prevent dosage dumping because each small depot in the formulation works independently. Mini tablet formulations for locally irritating medicines had less of an irritating impact than single unit formulations [19].

Several published investigations have shown that the release rate of the medicine may be more precisely regulated by using a constant layer of a retarding film coat. The micro tablets were created employing various hypromellose (HPMC) k100M concentrations to provide a sustained

medication release rate. It is feasible to fulfill varied releases with one formulation by mixing different dosages of micro tablets since the medicine included in individual mini tablets releases at varying rates depending on their composition [20]. Small tablets may assist produce repeatable release patterns and lower intra- and inter-subject variability. For a medicine to enter the small intestine, it must first pass through the stomach, and the drug absorption relies on the gastric emptying time. Ideally, the drug absorption is greater in the upper section of the small intestine. It may mix up with stomach contents if the gastric emptying is too slow, and if it is too quick, the medicine may not absorb to the necessary amount. Because to their smaller size, SUDFs are more likely to have these effects; nevertheless, tiny tablets do not rely on gastric emptying and may readily be absorbed via the pylorus. Mini tablets are thus preferable to regular tablets in order to reduce intra- and inter-subject variability [21].

Advantages [22,23]

1. Less dosage dumping issue
2. Severe dispersion in the Gastrointestinal tract
3. Tiny tablets are simple to produce
4. They feature good size consistency, a regular shape, a smooth surface, and
5. Tiny pills reduce local and systemic negative effects.
6. Increase therapeutic effectiveness and reduce drug buildup with prolonged dosing.

Types of mini tablets

The region in the digestive tract where oral medications are absorbed is controlled by a barrier called an enteric coating. The majority of enteric coatings function by providing a surface that is stable at the stomach's extremely acidic pH but quickly decomposes at a less acidic (relatively more basic) pH. For instance, they won't dissolve in the stomach's acidic contents (pH 3), but they will in the small intestine's alkaline environment (pH 7-9). Fatty acids, waxes, shellac, polymers, and plant fibers are some examples of the materials utilized for enteric coatings. Aspirin and other stomach-irritating medications may be coated with a material that will only dissolve in the small intestine. Esomeprazole, omeprazole, pan, and all grouped azoles are examples of azoles that are acid-activated. With these kinds of medications, the formulation's use of an enteric coating helps prevent activation in the mouth and esophagus. Lately, several businesses have started using enteric coatings on supplements that include fish oil (omega-3 fatty acids). The coating stops the stomach from breaking down the fish oil capsules, which has been known to result in fishy reflux (fish burps). Miniature tablets may be categorized depending on the target location, production process, and patient requirements as follows, with the acronym "EC" sometimes appearing next to the drug's name.

TYPES OF MINI TABLETS

Based on the target location and production technique, mini tablets may be divided into the following categories:

1. Bioadhesive mini tablets
2. Miniature gastro-resistant pills
3. Children's little tablets
4. Little pills that dissolve in the mouth
5. Miniature biphasic tablet.

Bioadhesive mini tablets

Bioadhesive micro tablets are primarily used for vaginal drug administration to transport medication accurately and for a long time. The dosage is divided into several units that will spread evenly in the vaginal cavity with enhanced

exposure in the vaginal epithelium. When they expand and produce microgels, bioadhesive mini tablets work to increase bioavailability by releasing the medication in a controlled manner [24].

The main issues with using alternative vaginal medication administration dosage forms, such as creams, ointments, gels, and tablets, include leakage, mess, lower patient compliance, and shorter retention times. We may employ bioadhesive or hydrophilic polymers, which are easily soluble and adhesive when exposed to moisture and will quickly cling to surfaces because they have high viscosity at low concentrations, to solve the aforementioned issues. While typical vaginal pills disintegrate slowly and are quickly cleaned by the vagina's self-cleaning activity, solid dose forms have long-term stability and accuracy [25].

Using bioadhesive polymers in the formulation might reduce this.

HPMC and hydroxypropyl cellulose were used to create bioadhesive micro tablets, which have been shown to have sufficient mechanical and bioadhesive qualities. Women of various ages and genders have varying vaginal pHs. Bioadhesive vaginal micro pills with bioadhesive properties are to be developed utilizing non-ionic cellulose ethers to withstand such pH conditions [26].

Gastro retentive mini tablets

Gastro retentive micro pills were created with the intention of prolonging the duration of medication release in the stomach. Little tablets should typically be made with a composition that contains gas-generating agents. When these agents come into contact with food, they release CO2, which subsequently traps in swellable hydrocolloid, causing the tablet to float and remain in the stomach. Drug loading is low in single-unit tablets because a lot of polymer is needed to make them float. To improve the effectiveness of medication loading, swellable polymers were swapped out for Eudragit coating when coating tiny tablets with sodium bicarbonate or calcium carbonate, which are gas-generating agents. Little tablets are typically coated using a fluid bed processor [27].

Pediatric mini tablets

There are many different dose forms for children, but the two that are most often used are liquid dosage forms (syrups) and solid dosage forms (tablets and capsules). While liquid dosage forms are simple to use, they have a number of disadvantages, including stability and taste concerns. In the case of tablets, their size is large and makes swallowing difficult. Dose adjustment is also challenging, and sometimes it's necessary to cut the size of the tablet by breaking it into two halves, which results in a loss of activity. Nowadays, patient compliance is another problem with conventional dosage forms. All these problems can be resolved by formulating mini tablets, which can lead to good patient compliance. Compared to alternative dose forms for kids including syrups, pills, and capsules, it is more practical and well accepted [28, 29].

Oral disintegrating mini tablets

Orally disintegrating tablets are often referred to as orodispersible tablets, melt-in-the-mouth tablets, quickly disintegrating tablets, fast-dissolving tablets, and quick-dissolving pills [30]. Moreover, described it as a tablet that is taken by placing it in the mouth, where it quickly dissolves before being sucked down. The oral dispersible tsblets (ODTs) should offer the following benefits, such as the ability to dissolve naturally in the mouth without the need for additional water. Because to their practicality and

simplicity, ODTs have been statistically shown to offer a number of benefits over traditional tablets in terms of improving patient compliance and adoption [31]. Orally disintegrating tablets micro tablets (ODT) were created as an alternative oral dose form since over 50% of children and older people have trouble swallowing tablets and firm gelatin capsules, huge tablets. Even those without swallowing issues may choose orally dissolving pills. During the last ten years, ODT technologies have developed at a breakneck pace. In order to alleviate the shortcomings of the prior products, new generations of ODT have been developed [32,33]. The fact that ODTs have only been given orally is another factor that makes them very promising. Because of this distinctive feature, other businesses may successfully apply for a generic version of the medication. Magnesium stearate, Prosolv ODT, and sodium salicylate are all components of ODT small pills. The model medicinal molecule was sodium salicylate [34]. Microcrystalline cellulose, cross-polyvinyl alcohol, mannitol, colloidal silicon dioxide, and fructose are excipients.

Biphasic mini tablet

Two parts—a quick and a slow-releasing part—make up a biphasic micro tablet. Biphasic delivery methods either release drugs slowly or quickly, depending on the case, at two separate rates or times. A quick/slow release system releases the medication in a controlled manner over a predetermined amount of time after an initial burst, while a slow/quick release system releases the drug in the opposite manner. Drugs used to treat hypertension that may benefit from less frequent doses include those of this kind. To treat a variety of disorders, diverse medications may be compressed into tiny tablets and placed within identical capsules [35,36].

PROSPECTS OF FORMULATING MINI TABLET DOSAGE FORM

Little pills with coating and encapsulation

2. Miniature compressed pills

3. A technique for biphasic medication administration is proposed using compressed micro tablets.

Encapsulated coated mini tablets

Encapsulated coated micro pills are often chosen because they increase medication tolerance and provide a dosing schedule that is simpler for patients to follow. Rapid-release and sustained-release mini tablets with various release rates may be combined to create small tablets in a hard gelatin capsule. Rapid-acting encapsulated dose forms may be developed with rapid release micro tablets for quick action [37,38].

Each capsule, however, may hold several small tablets, which subsequently fall apart and release their contents. As a consequence, patient compliance is improved. Zero-order DDS will be accomplished via a variety of micro tablet combinations, including site-specific, multiplied pulsatile, slow/quick releases, and quick/slow releases [39].

Compressed mini tablets systems are offered as a biphasic delivery system

Biphasic compressed micro tablet delivery devices are available and designed for zero-order sustained medication release. The outer layer, which fills the crevices between the small tablets, is designed to release the medication quickly (fast release). In order to achieve varied drug release rates, alternative compositions (HPMC or EC) are utilized in micro tablets [40]. The in vitro performance of these systems demonstrates that the formulation is what determines whether the drug contained in the fast releasing phase (the

powder encasing the mini tablets) dissolves within the first two minutes, where the drug contained in the mini tablets was released at various rates. According to the kinetic release restrictions, tiny tablets containing HPMC were a mostly appropriate method to achieve zero-order release (constant) during an 8-hour period [41].

Compressed mini tablets

In order to get around the higher manufacturing costs of capsules, there has been an increasing focus on developing multi-unit dosage forms that compress into tablets rather than hard gelatin capsules [42–44]. Mini tablets can be used to create a biphasic delivery system by combining a fast release form with a slow release form of the drug. Due to their consistent size, regular shape, smooth surface, strong mechanical strength, and low porosity, micro tablets are better able to maintain their homogeneity when compacted into a tablet than pellets or granules. Non-steroidal anti-inflammatory, anti-hypertensive, antihistamine, and anti-allergic drugs are often acceptable for this form of delivery [45].

Evaluation of mini tablets

Miniature tablets were tested using methods identical to those used for regular tablets, including measurements of weight variation, hardness, friability, thickness, diameter, and in-vitro drug release properties.

Weight variation test

Twenty pills are chosen at random from the batch, weighed, and the specific weight of each tablet is recorded. The average weight is determined from this. None of the individual tablet weights shall fall between 90% and 110% of the average weight, under the United States Pharmacopeia (USP) [46,47].

The average weight is determined from this. None of the individual tablets shall weigh less than 90% or more than 110% of the average weight, per USP. Weight fluctuation is specified to be 10%. The average weight is determined from this. None of the individual tablets shall weigh less than 90% or more than 110% of the average weight, per USP. 10% is the maximum allowed weight fluctuation.

Hardness

The hardness of the small pills is measured by the Pfizer hardness tester and is given in kg/cm2. Randomly selected six pills were assessed for hardness. The mean and standard deviation values for each formulation were computed [48].

Thickness

Typically, the diameter value is used to calculate the tablet thickness. Tablet thickness is often regulated to reduce aesthetic issues, ensure that they will fit into the container, and ensure that the filling machinery can properly count them. The consistent thickness of the tablets may have an impact on certain filling equipment's counting process. The thickness of the tiny tablets was measured using a screw gauge and digital Vernier Calipers [49]. It is stated in units of millimeters [50]. Thickness limits should consistently vary by no more than 5% from the average value.

Friability

The friability of micro pills is tested using the Roche Friabilator. Typically, 20 micro pills were selected at random from each batch for this purpose, and their initial weight (W0) was recorded [51, 52]. The tiny tablets were first weighed before being placed in the friabilator. The drum was then rotated for 4 minutes at 25 rpm before the small pills were taken out. The micro pills were emptied of any loose powder, and their ultimate weight was

determined by weighing them once again (Wf).

Drug content uniformity

A concentration of 100 g/ml is achieved by weighing five miniature tablets, crushing them in a mortar, and then weighing the resulting powder, which included 10 mg of medication put into 100 ml of dissolving media. To get a concentration of 10 g/ml, dilute 10 ml of this solution with 100 ml of the same solution. UV-visible spectrophotometer used to measure absorbance at a certain wavelength [53,54].

In vitro dissolution studies

The in vitro release experiments were conducted using a USP type II dissolution test device at a given speed and temperature for a predetermined amount of time in an appropriate buffer solution. Phosphate buffer (900 ml) with a PH of 6.8 was chosen as the dissolving media for the experiment, and the procedure took place over the course of 10 hours. 5 ml of the samples were pipette out and replaced with 5 ml of drug-free dissolving media at various time intervals (0, 15, 30, 60, 90, 120, 240, and 360 min). These samples were extracted, and UV spectrophotometry was used to examine them [55-57].

Stability studies

Stability studies are crucial to the formulation of pharmaceutical products throughout the medication development process. Stability studies aid in identifying any changes in the medication substance's quality over time due to a variety of environmental influences, including pressure, humidity, light, and temperature. The ICH guidelines were followed for conducting these research. For a duration of three months, the required storage conditions are 40°C2°C/75%RH 5%RH and 25°C2°C/60%RH 5%RH [58-60].

CONCLUSION

Pharmaceutical micro tablets replace pellets and granules better than SUDFs. Small tablets may reduce inter- and intra-subject variability and most harmful effects of regular pills. Little tablets prevent dose-dumping, local toxicity, and irritation. They have precise dimensions, low porosity, and great mechanical strength. Manufacturing parameters should be reviewed to optimize flow. Mini-bioadhesive tablets had better bioadhesion and effectiveness than single-unit tablets. Therapeutic effectiveness is likely in geriatric and pediatric patients. According to various studies, mini tablets may adapt to pulsatile, extended, delayed, bimodal, and colon-targeted release patterns. According to the report, researchers are interested in small tablets because of their advantages. Little tablets improve patient compliance, convenience, and therapeutic success. Due to their advantages, most accessible and acceptable drugs have them.

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