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An updated review on pharmaceutical mini tablets: Formulation and it's evaluation

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Abstract

The objective of controlled drug delivery systems is to reduce the frequency of the dosing and to increase the effectiveness of the drug. In oral controlled drug delivery system, multiple unit dosage forms (MUDF's), like pellets, granules and mini tablets are most popular as compare to single unit dosage forms(SUDF's), as it can control the release of drug and could offer a solution to the current issue in pharmaceutical industry. Mini tablets offer many benefits such as the delivery of an accurate dose and can be manufactured relatively easily, they do not require any solvent for their production, so it helps to maintain the stability of product and it has great flexibility during their formulation and development. Mini tablets are more acceptable in children and elderly people as they are easy to swallow. Mini tablets are effective and alternative solution for single unit dosage forms. Dose dumping and local irritation can be avoided by the use of mini tablets. This review focus on various aspects of Mini tablets. They can also be filled in capsules like other multiple unit dosage forms. Therefore, they resemble good substitutes for pellets and granules. In this framework, last few eras, have witnessed some major advancement. This review highlights the several advantages of mini-tablets, types, methods of manufacturing, formulation possibilities, and general evaluation tests of mini tablets.

Keywords: Multiple unit dosage forms (MUDF's), Single unit dosage forms (SUDF's), Mini-tablets, Pellets.

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1. Introduction

The solid dosage forms of drugs are marketed all over the world are used orally and are classified according to their drug release behavior as conventional or modified release [1]. Despite grate development in drug delivery, oral route is the preferred route for the administration of therapeutic agent [2]. Most of the solid dosage forms are administered orally are tablets, capsules etc. Tablets have many advantages over other dosage forms, such as the low cost of treatment and ease of administration and cause to higher levels of patient compliance and ease of transportation, application and production, high patient compliance, accurate dosing, control of drug release and stability [3].

The modified-release dosage forms are designed as massive or multiparticulate systems, and their function is to modify the bioavailability of the drug and extend the release or control the beginning of the drug dissolution in the gastrointestinal tract.

In a massive system the total administered drug is concentrated in a single release unit (tablets, capsules and in multiparticulate forms the drug is divided into several convenient subunits, such as granules, pellets or mini-tablets, contained within a final dosage form (tablet or soft gel) that disintegrates rapidly after administration releasing the subunits into the gastrointestinal tract. This reduces the risk of a high local drug concentration and the potential effect of localized irritation of the gastric mucosa.

1.1 Oral controlled release drug delivery systems can be classified in two broad groups

i) Single unit dosage forms (SUDF's), such as tablets or capsules [4].In a single unit dose e.g. Matrix or tablet is bounded in diffusion membrane, is a depot which release drug during the passage of entire GI tract without disintegrating. The empty core or shell is discharged. To retain a depot, effect the dose unit to be administered should be intact as dividing dosage form before administration would result in unintended rapid release [5].

ii) Multiple unit dosage forms (MUDF's), such as granules, pellets or mini-tablets. Amultiple unit's dose consists of many mini-units, e.g. Pellets or mini tablets contained in a capsule or a tablet. These mini-depots are dispersed and distributed throughout the gastro intestinal tract when the capsule or tablet disintegrates. The dose in (MUDF's) is divided into number of subunits, each one containing the drug. The dose is then the sum of the quantity of the drug in each subunit and the functionality of the entire dose is directly correlated to the functionality of the individual subunits.

1.2 Mini tablets

Mini-tabs are smaller tablets with a diameter equal to or less than 3 mm that are filled into a capsule, or rarely, it can be compressed into larger tablets. These combinations may include immediate release, sustain release, or control release. It is also possible to incorporate mini-tabs of different drugs to treat concurrent diseases and combinations of drugs to improve overall therapeutic outcome. Mini-tablets are very small tablets compared to other normal tablets. Mini tablets offer many benefits such as the delivery of an accurate dose and can be manufactured relatively easily, they do not require any solvent for their production, so it helps to maintain the stability of product, and it has great flexibility during their formulation and development.

Mini tablets are more acceptable in children and elderly people as they are easy to swallow. Mini tablets are effective and alternative solution for single unit dosage forms. Dose dumping and local irritation can be avoided using mini tablets they are more uniform in size so very less unit-to unit variation in drug occur and accurately weighed amounts of drug can be loaded into mini-tablets. It is relatively easy to manufacture mini-tablets and is even possible to coat them in order to delay the drug release because of their excellent smooth surface area. They can also be filled in capsules like other multiple unit dosage forms. Therefore, they resemble good substitutes for pellets and granules [6].

Fig. 1: Mini tablets [7]

Mini tablets reduce inter and intra subject variability and can help in obtaining a reproducible release profile. Majority, the absorption of drug is more in upper part of small intestine i.e. (duodenum), for a drug it has to pass through stomach to reach the small intestine. So, drug absorption depends on gastric emptying time. If the gastric emptying is too fast drug it may not absorb to required level or if it is too slow it may get mix-up with gastric contents and may adsorb to food which gives unintended effects. These effects are more in single unit dosage forms (SUDF's) because of their size but in case of mini tablets it will not depend on gastric emptying and easily get passed through pylorus. So mini tablets are useful over the normal size tablets to reduce inter and intra subject variability. It gives reproducible plasma drug concentrations (PDC). The Plasma drug concentration is directly proportional to the absorption. Absorption is more in mini tablets as they are distributed all over the surface which is not in case of single unit dosage forms (SUDF's).

The release profile for mini tablet is due to increased surface in relation to volume, and the drug can be released more efficiently in case of mini-tablets. By applying uniform layer of a retarding film coat, the release rate of the drug can be controlled with greater certainty. Also, mini-tablets that are formulated using different concentrations of HPMC K100M, provides a prolonged drug release rate. The drug contained in the mini-tablets gets released at different rates, depending upon composition of mini tablets. Based on the release kinetic parameters calculated, it can be concluded that mini-tablets containing HPMC K100M are particularly suitable to release the drug over hours of time periods. By combining different doses of mini tablets, it is possible to achieve various releases with one formulation. Due to significant smaller dimensions of the mini tablets, when compared to normal tablets, they pass through the stomach at a more even rate. As a result, the concentration of the drug in the blood can be easily reproduced [8].

1.3 Advantages of Mini-tablets [2, 3, 8]

i) Minitablets can be easily manufactured.

ii) They have regular shape and smooth surface, excellent size uniformity.

iii) They combine the advantages of multiple unit dosage forms with the well-known manufacturing techniques in tableting and have fewer constrictions compared to extrusion or Spheronization.
iv) Mini-tablets also offer a substitute for pellets because of their relative ease of manufacturing and because dosage forms of equal proportions and weight with smooth regular surface are produced in a reproducible and continuous way.
v) It also offers the high drug loading, a wide range of release rate designs, and fine-tuning of these release rates.
vi) Mini tablet has less risk of dose dumping, high degree of dispersion in the digestive region thus minimizing the risks of high local drug concentrations.
vii) Mini tablets are easy to manufacture compared to pellets as they have equal proportions, weight with smooth regular surface.
viii) Mini tablets are good coating substrates as they have excellent size uniformity, regular shape and a smooth surface.
ix) Unlike pellets, mini tablets do not require any solvents for its production; as a result problem with stability can be avoided.
x) Mini tablets eliminate local side effects and eliminate systemic side effects.
xi) Minimize drug accumulation with chronic dosing and Improve efficiency in treatment.
xii) Make use of superior properties, e.g. sustained release aspirin for morning relief of arthritis by dosing before bed time.

1.4 Types of Mini tablets [5]

Mini tablets can be classified based on the targeted sites and the method of manufacturing, patient requirements as follows,

1.4.1 Pediatric mini tablets

The most common dosage forms for children are Syrups, tablets and capsules. Syrups are liquid dosage forms which are easy to administer, and dose can be easily changed to the patient needs on the other side drawbacks with these liquids' dosage forms are physical, chemical, and microbial instability problems and taste issues. In case of tablets, their size is big and becomes difficulty in swallowing and dose adjustment is also difficult. Sometimes we have to break the tablets and administer which may causes loss of activity of the tablets and nowadays Patient compliance is another issue with the conventional dosage forms, to overcome all the above issues formulating mini tablets can result in good patient compliance. It is easily accepted by children than other dosage forms like tablets, syrups, and capsules etc.

1.4.2 Floating mini tablets or Gastro retentive mini tablets

Gastro retentive tablets are intended to release the drug in stomach for long time. Generally, for tablets to float on the Gastro intestinal fluids, we had to formulate tablets by using gas generating agents in them. These tablets when meets food generate CO2and the generated gas is trapped in swellable hydrocolloid, it makes the tablet to float and retain in stomach. Drug loading is low as the polymer used for floating is high in normal single unit tablets. In mini tablets, Eudragits coating in place of swellable polymers is used in formulation to increase the drug loading and it can be coated with sodium bicarbonate or calcium carbonate as gas generating agents, Fluid bed processor can be used for coating of mini tablets.

1.4.3 Bio Adhesive Vaginal Mini Tablets

Vagina is an important application site of drug delivery for local treatment of different diseases like bacterial, fungal and protozoal infections, HIV prevention, delivery of contraceptives, and for treatment of Pancreatic lesions and an alternative route of systemic drug delivery. The dosage forms which are meant for vaginal drug delivery should be easy to administer without irritation or discomfort and should have uniform distribution and long maintenance time there by increasing patient compliance. The various available dosage forms for vaginal drug delivery are creams, gels, ointments and tablets. The problems with these are leakage, untidy, less patient compliance and less retention time. Nano pharmaceuticals can be used but the problem related with them is low residence time as they are liquid in nature. To overcome the above problems, we can use bio adhesive Vaginal Mini Tablets.

1.4.4 pH responsive mini tablets

The pH of human Gastro Intestinal Tract varies greatly (Stomach 1.5-3.0, upper part of small intestine Duodenum 4.0-5.0, lower parts of SI jejunum and ileum 6.5-7.5, and colon 5.6-6.9). The pH responsive drug release is required when absorption of drug is more at a site this can be achieved by coating with pH responsive release polymers like Eudragits. Generally coating is done to granules and then they are filled into capsules to achieve the required release at required pH. In case of pellets control of size and size distribution is important before coating. To get reproducible results, desirable pellet size and a narrow particle size distribution are required in pellets which are difficult to achieve. To overcome this problem in place of pellets Mini tablets can be used. Mini tablets are easy to manufacture and coating them is easy when compared to pellets as they have smooth surfaces. Uniform size can be obtained so less variation with in unit to unit. Reproducible results can be achieved by uniform coating. So, mini tablets can be used as an alternative to pellets.

1.4.5 Biphasic Mini tablets

A biphasic mini tablet contains two parts a fast releasing part and a slow releasing part. First part releases drug immediately after administration and the second part releases drug slowly in a controlled manner. This type can be advantageous for drugs used for hypertension where repetitive dosing can be reduced. Different drugs can be compressed in to mini tablets and can be filled in same capsules to treat different diseases.

1.4.6 Oral disintegrating Mini tablets

Oral dispersible tablets (ODTs) are the innovative dosage form which quickly disintegrates in the mouth (1-3 min) without need of water and without chewing on oral administration, unlike other conventional oral solid dosage form. Oral Dispersible Tablets (ODTs) are also known as "fast dissolving", "Rapidly disintegrating", "quick-dissolving", "bite-dispersible", "mouth-dissolving", and "Orodispersible" tablets. Oral dispersible mini tablets (ODMTs) are more suitable for pediatric patients because of their small size and pleasant mouth feel with fast disintegration in mouth. The Oral dispersible tablets (ODTs) should have the following characters like it should disintegrate in the mouth without additional of water. The disintegrated tablet should become a soft paste or liquid suspension, which can provide good mouth feel and smooth swallowing. ODTs are designed to have a quick disintegration time; the tablet porosity is usually maximized to ensure fast water absorption into the tablets.

2. Methodology

2.1 Pre-formulation Studies [8]

The objective of Pre-formulation studies is to make useful information, in order to develop a stable formulation. The use of Pre-formulation parameters greatly improves the chances of formulating an acceptable, safe and efficient and bioavailable product.

2.1.1API Characterization

To formulate any drug substance into a dosage form, it is necessary to study the physicochemical properties of the active drug like physical appearance, particle size determination, solubility, melting point and its compatibility with other excipients.

2.1.2 Physical Appearance

The physical characteristics of the drug are usually studied by visual inspection.

2.1.3 Sieve Analysis

Sieve analysis is performed to determine the different sizes of drug particles present in the sample. A series of standard sieves are arranged one above the other in a mechanical sieve shaker. Sieve with larger pore size is placed at the top followed by sieves with smaller pore size that is in the order of decreasing pore diameter.

2.2 Procedure

2.2.1 Drug excipients Compatibility study

Compatibility of the drug with excipients was determined by Fourier transform infrared (FT-IR) spectral analysis and differential scanning colorimetry (DSC) thermal analysis, this study was carried out to distinguish any changes on chemical constitution of the drug after united it with the excipients. The samples were taken for FT-IR and DSC studies for spectral analysis which was employed to check the compatibility of drugs with the excipients used [9].

2.2.2 FTIR studies

IR spectra for pure drug and best mini-tablets formulations were recorded in a Fourier transform infrared (FTIR) spectrophotometer (Shimadzu Corporation 8600, Japan) with KBr [8].

2.2.3 Differential scanning colorimetry (DSC) studies

DSC studies were carried out for pure drug and best mini-tablets formulations [8].

2.2.4 Analytical Method Development

Analytical method development for any drug is performed to determine the absorption maxima and quantification prior to formulation [8].

2.3 Methods of manufacturing Mini tablets [5]

Some of the methods that can be used for the manufacturing of mini tablets are:

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

2.3.1 Dry granulation technique

It is balanced technique for the manufacturing of mini tablets containing thermolabile and moisture-sensitive drugs. This technique serves as processing equipment known as Roller compactor or Chilsonator. This machine compresses as premixed powders between two counter rotating rollers under exciting pressure. The compressed material is reduced to the proper size to form granules that are mixed with other inactive excipients and finally compressed on a rotary compression machine. There is an alternative method of making brittle ribbon sheets, the slugs can be formed by forcing the initial blend of powders into the dies of a large capacity tablet press and is compacted by means of flat faced punches. The formed compacted masses are called 'slugs' and the process are called as 'slugging'. The slugs are then separated or milled to produce granules. These granules are mixed with other excipients and finally subjected to compression.

2.3.2Direct compression technique

It is the process by which mini tablets are compressed directly i.e. API and excipients directly compressed the powder blend into mini tablet. Excipients of

direct compression grade are used here to get the required hardness. Stability problems are less compared to that of tablets prepared by wet granulation.

2.3.3 Wet granulation

This technique involves the use of binder solution to form granules which then compressed in compression machine to get mini tablets. Different grades of binding agents are used.

2.3.4Melt-Extrusion technique

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

3. Tooling used in compression of mini tablets

Compression of normal tablets is normally done by using single tip tooling for conventional tablet which are be interchangeable according to the requirement. Compression of mini tablets involves the use of multi tip tooling i.e. several numbers of tips to the same punch which allows us to compress a greater number of tablets at a time. The use of multi tip tooling also reduces the time required for production. [5]

Fig. 2 Punch fitting several mini-punches [8]

4. Coating of mini tablets [9]

In oral controlled drug delivery systems, multiple unit dosage forms like (MUDF's), like mini tablets, pellets, are effectively control the release of the drug when it is compared with single unit dosage forms (SUDF's) like capsule and tablets. Polymers used for enteric coating of mini tablets.

i) Methacrylic acid or ethyl acrylate
ii) Sodium alginate and stearic acid.
iii) Cellulose acetate succinate
iv) Cellulose acetate trimellitate
v) Cellulose acetate phthalate (CAP)
vi) Hydroxy propyl methyl cellulose phthalate
vii) Hydroxy propyl methyl cellulose acetate succinate

4.1 Tablet coating principles for mini tablet [9]

The application of coating to mini tablets, which is an additional step in the manufacturing process, therefore, the decision to coat a tablet is usually based on the following objectives:

i. To mask the taste and odor of the drug.
ii. To provide physiochemical protection for the drug.
iii. To control the release of the drug from the tablet.
iv. To protect the drug from the gastric environment of the stomach with an acid-resistant enteric coating.
v. To combine another drug or formula adjuvant in the coating to avoid chemical incompatibilities.
vi. To provide sequential drug release.
vii. To improve the pharmaceutical elegance by use of special colors and contrasting printing.

4.2 Tablet coating processes for mini tablet

The coating process is the last critical step in the tablet production cycle. The successful application of the coating solution formula to a Mini tablet provides the visual characteristics to the product; so, the quality of the product may be judged on this final production step. The type of process depends on the type of coating that is to be valuable the durability (toughness) of the tablet core, and the economic process.

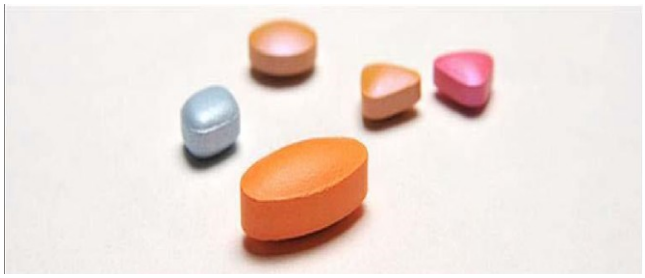

Fig. 3 Compressed coated mini tablets [8]

Table 1: List of various mini tablets available in the Market are as follows [6]

Generic name	Brand name
Donepezil Hydrochloride	Aricept
Zafirlukast	Accolate
Prasugrel Tablets	Effient
Olanzapine	Zyprexa, Zyprexa Zydis

Table 2: List of encapsulated Mini-tablets available in the market are as follows [6]

Generic name	Brand name
Pancrelipase	Ultresa
Fenofibric Acid Capsules	Trilipix

5. Evaluation of Mini tablets [10, 11]

Evaluation of mini tablets is like that of normal tablets, general tests like weight variation, hardness, friability, thickness, diameter, *in-vitro* drug release characteristics etc. were evaluated.

5.1 Weight Variation Test

20 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 USP, none of the individual tablet weight should be less than 90% and more than 110% of the average weight.

5.2 Hardness

The hardness of the Mini tablet is determined using Pfizer hardness tester and expressed in kg/cm2. Six tablets were randomly picked tested for hardness. From each formulation and the mean and standard deviation values were calculated.

5.3 Thickness

Thickness of the Mini tablet is measured using a digital caliper (Mitutoyodigimatic caliper,) and screw gauge. It is expressed in terms of mm.

5.4 % Friability

Friability test of Mini tablets is conducted using Roche friabilator or veego friabilator. For this, usually 20 minitablets are selected randomly from each batch and their initial weight (W0) is noted and transferred into friabilator. The drum was rotated at 25rpm for 4 mins after which the tablets were removed. Any loose dust was removed with the helpof soft brush and mini tablets were weighed again (W1).

5.5 Drug content uniformity

Five mini-tablets weighted and crushed in a mortar then weighed powder contained equivalent to 10 mg of drug transferred in 100 ml of wave length using UV-Visible spectrophotometer.

5.6 *In-vitro* disintegration

The *in-vitro* disintegration of the core mini-tablets were determined using disintegration test apparatus as per I.P specifications.

5.7 *In vitro* dissolution studies

In vitro drug release studies are carried out in USP type II dissolution test apparatus at specific rpm and temperature for definite time period in suitable buffer solution. All these factors depend on that formulation. From this, 10 ml of sample is withdrawn and analyzed using UV spectrophotometer at appropriate wavelength. After this, drug release is tested for definite time period, at same temperature and same rotational speed. At all the time points (15, 30, 60, 90, 120, 240 and 360 minutes), 10 ml of the sample is withdrawn, and analyzed using UVspectrophotometer.

6. Stability Studies [12]

Stability studies are an integral part of the drug development process and they play an important role during the registration of pharmaceutical products. They are conducted as per the ICH guidelines. Stability studies helps to identify the changes in the quality of a drug substance with time under the influence of environmental factors like temperature, humidity and light. Storage conditions: 40°C ± 2°C /75%RH ± 5%RH, 25°C ±2°C /60% RH ± 5% RH for the period: 1, 2, 3 months.

7. Conclusion

From this review, it can be concluded that pharmaceutical mini-tablets offer numerous advantages when compared to single unit dosage forms. Mini tablets can be made into tablets or they can be filled with capsules or used as a sachet, which is advantageous, both in terms of ease of production and cost and are also good alternatives for granules and pellets. They have well defined size, shape, surface, low degree of porosity and high mechanical strength. By combining different mini-tablets, incompatible drugs can be administered, and concurrent diseases can be treated effectively. Especially in geriatric and pediatric patient groups, there is a very high potential for achieving success in treatment. Ultimately, mini-tablets improves overall therapeutic outcome, patient compliance and convenience. As they have significant advantages, they can be formulated for most of the available and suitable drugs. Studies have shown that mini tablets adapt to a multitude of modified release patterns such as extended, delayed, pulsatile, bimodal release and colon targeting So, the development of mini-tablets have become an interesting topic of research in oral controlled solid dosage forms.

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