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PHARMACEUTICAL MINI TABLETS-A BEST ALTERNATIVE OF OTHER DOSAGE FORMS: AN OVERVIEW

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ABSTRACT

Solid oral dosage forms are most acceptable dosage forms especially tablets aremost widely accepted by people of different age groups. A multifunctional and multiple unit system for oral use are developed by filling versatile mini-tablets in a hard capsule. Some new variations are beginning to emerge such as mini-tablets, which offer formulation flexibility. The objective of controlled drug delivery systems is to reduce the frequency of the dosing and to increase the effectiveness of the drug by localization. Mini tablets can be used as a solution for the short coming of single unit dosage forms. Mini tablets are multiple unit dosage forms and are advantageous than pellets or any other oral dosage forms as they are easy to manufacture and stability problems are less. Many types of mini tablets are there like bio adhesive minitablets, pH responsive mini tablets, gastro retentive mini tablets, pediatric mini tablets, oral disintegrating mini tablets. These mainly reduce the variation among subjects. The review emphasises on advantages of mini tablets, types, methods of manufacturing and modes of administration and evaluation of mini tablets.

KEYWORDS: Mini-Tablet, type, method, tooling, encapsulated mini tablet, evaluation parameter.

INTRODUCTION [1-9]

Oral dosage forms occupy the largest and the most significant place among all pharmaceutical dosage forms, and it considered one of the most popular drug delivery systems. The use of a glass of water to take the dosage form orally is considered to be the easiest and most suitable technique of administration of the drug to a patient.

Usually conventional dosage forms result in wide range of fluctuations in drug concentration in the blood stream with consequent toxicity as a result of less amount of efficiency. To increase the effectiveness of drug by localization at the specific site of action and To decrease the frequency of the dosing, these main reasons behind the designing sustain or controlled drug delivery. The oral controlled release drug delivery system included two types of dosage forms:

- Single unit dosage forms (SUDFs) e.g. Tablet, Capsule

- Multiple unit dosage forms (MUDFs) e.g. Mini tablet, Pellets, granules

In single unit dosage forms (SUDFs), Tablet or matrix enclosed in different membrane. Without disintegrating, it is depot which release drug during passage of entire GI tract. The shell or empty core is discharged. The dose unit to be administered should be intact as dividing dosage from to retain a depot effect. Because of these, it should result unintended rapid release before administration.

In multiple unit dosage forms (MUDFs), multiple unit dosage form contained in capsule or tablet. These Mini depot are dispersed and distributed thought the GI tract when capsule or tablet disintegrate. Mini tablet may be divided before ingestion without loss of depot effect as the subunit act as self-contained depots. In MUDFs, the dose is divided into number of sub units, each one containing drug. The dose is then the sum of the quantity of the drug in each sub unit. And the functionally of the entire dose is directly correlated to the functionality of the individual sub unit.

MINI TABLET[10, 11]

Mini-tablets are flat or slightly curved tablets with a diameter ranging between 1.0-3.0 mm.4 They are usually filled into a capsule, occasionally compressed into larger tablets, or sometimes placed in sachets for easy administration. Different mini-tablets can be formulated and designed individually, incorporated into a capsule to release the drug at different sites and at different rates. Different combinations of mini-tablets include immediate release, delayed release, and/or controlled release formulations. Also, combining different mini-tablets togetherincompatible drugs can be administered. This, as a result, improves overall therapeutic outcome, and also concurrent diseases can be treated effectively.

CONSTITUENTS OF MINI-TABLETS[12]

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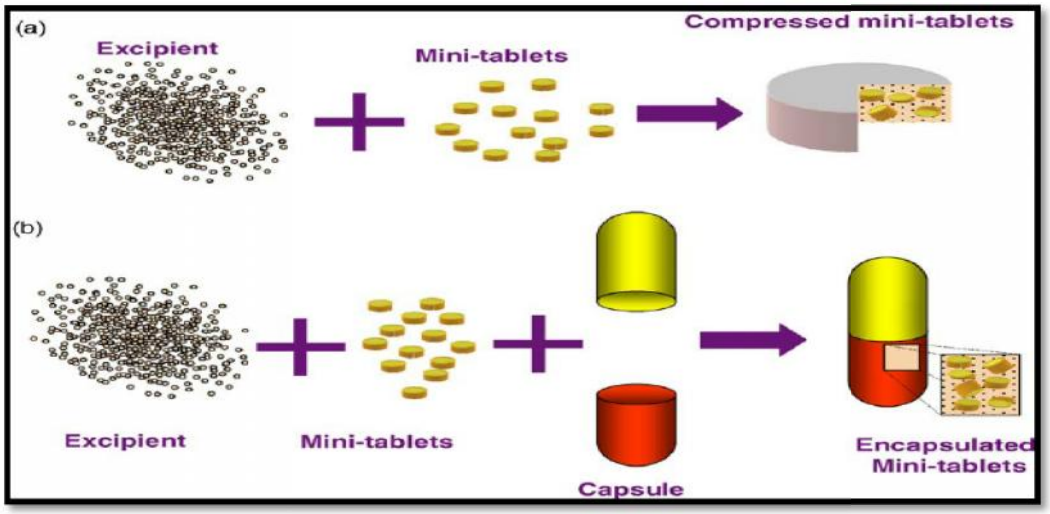
result, improves overall therapeutic outcome, and also concurrent diseases can be treated effectively.

RELEASE PROFILE[13]

Due to increased surface in relation to volume, the drug can be released more efficiently incase 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 rates. 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.

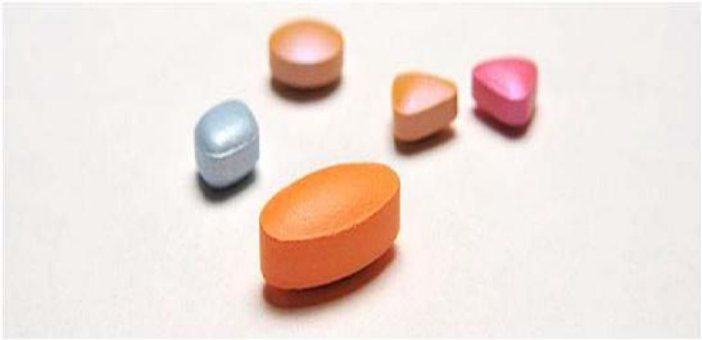
ADMINISTRATION OF MINI-TABLETS DONE BY FOLLOWING METHODS[14-24]

1. As a single unit
2. Filled in hard gelatin capsule
3. Compressed mini-tablets presented as a biphasic drugdelivery system



Compressed mini-tablets

There has been an increasing focus in the development of MUDFs compressed into tablets instead offilling into hard gelatin capsules, in order to overcome the higher production costs of capsules. Because of their size uniformity, regular shape, smooth surface, low porosity and high mechanical strength, mini-tablets can maintain their uniformity in a more reproducible way than pellets or granules, once they have been compressed into a tablet. Different compositions like hydrophilic and/or hydrophobic polymers and number of mini-tablets can be used to obtain different drug release rates. 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. Biphasic release system is used when relief needs to be achieved quickly, and followed by a sustained phase to avoid repeated administration of the drug. Drugs suitable for this type of administration include nonsteroidalanti-inflammatory drugs(NSAIDs), antihypertensive, antihistaminic and anti-allergic agents.

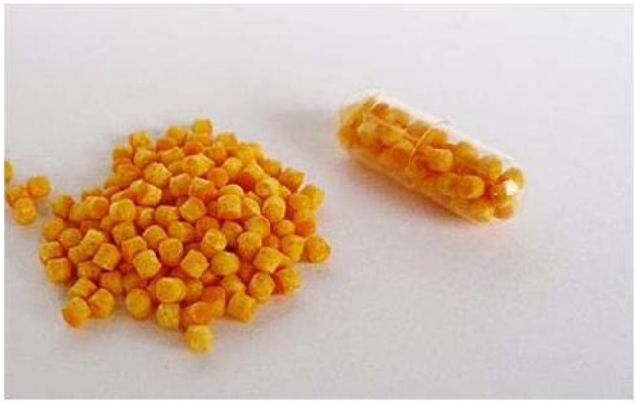


Compressed Mini-tablets

Encapsulated coated mini-tablets systems

Among all the possible formulations, encapsulated coated mini-tablets are widely used as it improves drugtolerance and also yields a dose regimen that is easier to manage for patients. A multifunctional and multiple unit system, containing different mini-tablets in a hard gelatin capsule, can be developed by incorporating Rapid-release Mini-Tablets (RMTs), Sustained-release Mini-Tablets (SMTs), Pulsatile Mini-Tablets (PMTs), and Delayed-onset Sustained-release Mini-Tablets (DSMTs), each with various release rates. Based on the combinations of minitablets, multiplied pulsatile DDS, site-specific DDS, slow/quick DDS, quick/slow DDS, and zero-order DDS could be obtained. Rapid-release Mini-Tablets allows the development of rapid

acting encapsulated dosage forms for fast action. However, several mini-tablets can be placed into each capsule, which later disintegrates and releases the mini-tablets. As different mini-tablets can be placed into each capsule, tablets with various combinations of drugs, dosage and drug release profiles can be obtained. This as a result, improves patient compliance.



Encapsulated mini tablet

ADVANTAGES OF MINI TABLETS[25-28]

- Mini tablets have less inter and intra- subject variability.
- They have less risk of dose dumping.
- Mini tablets are easy to manufacture compared to pellets as they have equal dimensions, weight withsmooth regular surface. They can be produced in a reproducible and continuous way
- Mini tablets are good coating substrates as they have excellent size uniformity, regular shape and asmooth surface.
- They offer high drug loading, a wide range of release rate patterns, and also fine tuning of these releaserates.
- They offer high degree of dispersion in the GI tract, thus minimizing the risks of high local drugconcentrations.
- Unlike pellets, mini tablets do not require any solvents for its production, as a result problems withstability can be avoided.
- Complex manufacturing steps can be minimized in case of mini tablets when compared to pellets whichmay require fluid bed granulator for granulation or coating as mini tablets can be manufactured easilyby simple tableting techniques.

COMPARISON OF MINI TABLET WITH OTHER DOSAGE FORMS[29-32]

Multiple unit dosage form MINI-TABLET	**Single unit dosage form TABLET**
Non-dependent on gastric emptying easily get pass through pylorus.	**Dependent on gastric emptying.**
Distributed all over surface,which result absorption is more.	**Not distributed all over surface.**
In this, "Each mini-tablet depot in formulation act individually" So, Less chance of toxicity. Dose dumping may not occurs.	**In this, "Drug all at once" So, May cause toxicity Dose dumping may occurs.**

MINI TABLETS	**PELLETS**
Manufacturing by single tableting procedure	**Demanding process like, fluid bed granulation.extrusion &spheronization require for production**
Not required any solvent so stability problem avoided.	**Require solvents for production, it may be caused stability problem.**

MINI TABLETS	GRANULES
Compare to granules require less coating material.	**Require more coating material.**
Regular shaped smooth surface constant surface, high mechanism strength.	**Irregular shaped**
Dosage form of mini tablet is smaller than granules.	**Dosage form of granules are larger**

Because mini-tablets offer many advantages, their future exploration seems to be a rich field for both pharmaceutical and medical researchers.

TYPES OF MINI-TABLET[33-38]

Mini tablets can be classified based on the target site, method of manufacturing, patient needs as follows,

1. Gastro retentive mini tablets
2. Pediatrics mini tablets
3. Bio-adhesive mini tablets
4. pH responsive mini tablets
5. Biphasic mini tablets
6. Oral disintegrating mini tablets

Gastro retentive mini tablets or Floating mini tablets:

Gastro retentive tablets are intended to release the drug in stomach for prolonged time. Generally fortablets to float on the GI fluids content we formulate tablets by using gas generating agents in them. Thesetablets when come in contact with food generate $_{CO2}$and the generated gas is trapped in swell able hydrocolloidwhich makes the tablet to float and retain in stomach. In normal single unit tablets drug loading is low as thepolymer used for floating in high. In mini tablets we can

use coating with sodium bicarbonate or calciumcarbonate (gas generating agents), Eudragits coating in place of swell able polymers used in formulation toincrease the drug loading. Fluid bed processor can be used for coating of mini tablets. sustained release floating mini tablets of levodopo. Here they used 3mm minitablets core formulated with gas generating agent and coated the core with eduragit RL30 D to get the requiredrelease.

Pediatric mini tablets:

Syrups, tablets and capsules are commonly used dosage forms for children. Syrups are liquid dosageforms which are simple to administer and dose can be easily altered to the patient needs on the other sidedisadvantages with these liquids dosage forms are chemical, physical, and microbial instability, taste issues,lack of controlled release and formulation problems. In case of tablets as they are big in size difficulty inswallowing and dose adjustment is difficult. Some time we have to break the tablets and administer which causes loss of activity of the tablets. Patient compliance is another issue with the conventional dosage forms. Toovercome all the above issues formulating mini tablets can result in good patient acceptance. Min tablets areeasily accepted by children than other dosage forms like tablets, syrups, and capsules etc.

Bio Adhesive Vaginal Mini Tablets:

Vagina is an important application site of drug delivery for local therapy of different diseases likebacterial, fungal and protozoal infections, HIV prevention, delivery of contraceptives, spermicides or laborinducers and for treatment of Pancreatic lesions and an alternative route of systemic drug delivery. The dosage forms which are aimed for vaginal drug delivery should be easy to administer withoutirritation or discomfort and should have even distribution and long retention time there by increasing patientcompliance and adherence to therapy.The various available dosage forms for vaginal drug delivery are creams, gels, ointments and tablets.The problems with these are leakage, messy, less patient compliance and less retention time. Bio adhesive mini tablets can be used for vaginal drug delivery to deliver drug accurately and for longperiod of time. In mini tablets dose is divided into multiple units which will spread evenly in vaginal cavitywith improved coverage in vaginal epithelium. Bio adhesive Mini tablets act by swelling and forming microgels and releasing drug in controlled release manner and there by maximum bioavailability can be achieved.

pH responsive mini tablets:

The pH of human Gastro Intestinal Tract varies greatly (Stomach 1.5-3.0, upper part of small intestineDuodenum 4.0-5.0, lower parts of SI jejunum and ileum 6.5-7.5, and colon 5.6-6.9). pHresponsive drug releaseis required when absorption of drug is more at a particular site this can be achieved by coating with pHresponsive release polymers like Eudragits. Generally coating is done to granules and then they are filled intocapsules to achieve the required release at required pH. In case of pellets control of size and size distribution isimportant before coating. To get reproducible results, desirable pellet size and a narrow particle size distributionare required in pellets which are difficult to achieve.

Biphasic mini tablets:

A biphasic mini tablet contains two parts a fast releasing part and a slow releasing part. First partreleases drug immediately after administration and the second part releases drug slowly in a controlled manner. This type can be beneficial for drugs used for hypertension where repetitive dosing can be reduced. Differentdrugs can be compressed in to mini tablets and can be filled in same capsules to treat different diseases. Hereimmediate release part can be compressed along with mini tablets this immediate release part fills in voidspaces present in between mini tablets. Biphasic mini tablets of ibuprofen where they got required releasecharacteristics for biphasic mini tablets.

Oral disintegrating mini tablets:

Oral dispersible tablets (ODTs) are the novel dosage form which rapidly disintegrates in the mouth (1-3min) without chewing upon oral administration and without the need of water, unlike other conventional oralsolid dosage form. Oral Dispersible Tablets (ODTs) are also known as “fast dissolve”, “rapidlydisintegrating”, “quick-dissolve”, “crunch-melt”, “bite-dispersible”, “mouth-dissolve”, and “orodispersible”tablets . Oral dispersible mini tablets(ODMTs) are more suitable for pediatric patients because of their smallsize, pleasant mouth feel and fast disintegration in mouth.

METHODS OF MANUFACTURING MINI TABLETS[39, 40]

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

1. Direct compression 2. Dry granulation3. Wet granulation 4. Melt- extrusion

Direct compression technique:

Direct compression is the process by which tablets are compressed directly from powder blends containing API and excipients directly compressed the powder blend into biconvex 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.

Dry granulation technique:

Dry granulation is rational technique of choice for the manufacture of tablets containing thermo labile and moisture-sensitive drugs. This technique employs processing equipment known as roller compactor or chilsonator. This machine compress as premixed powders between two counter rotating rollers under extreme pressure. The resultant material is in the form of a brittle ribbon, sheet, or piece-depending on the configuration of the roller. The compressed material is reduced to the proper size to form granules that are mixed with other in-active excipients and finally compressed on a rotary compression machine. There is another method instead 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 is referred as ‘slugging’. The slugs are then screened or milled to produce granules. These granules are mixed with other excipients and finally subjected to compression

.

Wet granulation:

Wet granulation involves the use of binder solution to form granules which then compressed in compression machine to get mini tablets. Polyvinyl pyrrolidone of different grades is generally used as a binding agent.

Melt-Extrusion technique:

In melt-extrusion technique, the powder (API+ 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 sieved. The obtained granules are then compressed to mini tablets using compression machine.

TOOLING USED IN COMPRESSION OF MINI TABLETS[41-44]

Compression of mini tablets can be done by using different tooling when compared to tooling's thatused for compression of conventional tablets. Compression of normal tablets is normally done by using singletip tooling which are be interchangeable according to the requirement. Compression of mini tablets involves theuse of multi tip tooling i.e., several number of tips to the same punch which allows us to compress more numberof tablets at a time. The use of multi tip tooling also reduces the time required for production.

Showing various multi tip punches used for compression of mini tablets

COATING OF MINI TABLETS[45, 46]

Application of the coating solution to a tablet improves the visual characteristics of the product, basedon which the quality of the product can be judged. The type of coating process chosen usually depends on thetype of coating material that has to be applied, whereas the durability of the tablet core depends both on thecoating material and application process.Encapsulated mini-tablets system usually comprises immediate-release mini-tablets (IRMT) andsustained release mini-tablets (SRMT) in a capsule made from HPMC, a water-soluble polymer. HPMC capsulewhich contains the mini-tablets later disintegrates and releases these subunits into the system. Inclusion ofIRMT permits the development of rapid acting dosage forms for fast action. Encapsulated minitablet systemscan be designed to yield various sustained release drug profiles by combining different types, quantities andcombinations of mini-tablets, thereby improving patient compliance. Mini-tablets are usually coated withenteric coating polymers in fluid bed

coater or in modified coating pans. Enteric coating is a polymer barrier,which when applied to a drug protects it from the acidic pH of the stomach, and releases the drug in the alkalineenvironment of the small intestine. That is, they will not get dissolved in the acidic juices of the stomach, butbreaks down in the alkaline environment of the small intestine. Materials used for enteric coatings mostlyinclude fatty acids, waxes, phthalates, shellac, plastics, and plant fibers. Drugs that cause irritation to gastricmucosa or inactivated in the stomach, can be coated with a substance that will dissolve only in the smallintestine. Abbreviation "EC" along with the name of the drug indicates that the drug has an enteric coating.

Polymers used for enteric coating of mini tablets

- Methacrylic acid/ethyl acrylate
- Cellulose acetate succinate
- Cellulose acetate trimellitate
- Cellulose acetate phthalate (CAP)
- Hydroxy propyl methyl cellulose phthalate
- Hydroxy propyl methyl cellulose acetate succinate
- Polyvinyl acetate phthalate (PVAP)
- Sodium alginate and stearic acid
- Shellac

MARKETED PRODUCT

Table 1: List of various mini tablets available in the Market

Generic Name	Brand Name
Pancrelipase	**Ultresa**
Zafirlukast	**Accolate**
Donepezil Hydrochloride	**Aricept**
Galantamine HBr ER	**Razadyne ER**
Fenofibric Acid Capsules	**Trilipix**
Levonorgestrel and Ethinyl Estradiol	**Alesse**
Prasugrel Tablets	**Effient**
Olanzapine	**Zyprexa, Zyprexa Zydis**
Sumatriptan and Naproxen Sodium Tablets	**Treximet**
Warfarin Sodium	**Coumadin**
Vorapaxar Tablets	**Zontivity**

Table 2: List of encapsulated Mini-tablets available in the market

Generic name	Brand name
Pancrelipase	**Ultresa**
Galantamine HBr ER	**Razadyne ER**
Fenofibric Acid Capsules	**Trilipix**

EVALUATION

Evaluation of mini tablets were evaluated, with general tests like weight variation, hardness, friability, thickness, diameter, *in-vitro* drug release characteristics etc. which issimilar to that of normal tablets specified in different pharmacopeias.

CONCLUSION

From this review, it can be concluded that pharmaceutical mini-tablets offer several advantages when compared to single unit dosage forms and are also good substitutes for granules and pellets. They have well defined size, shape, surface, low degree of porosity and high mechanical strength. A multifunctional and multiple unit system for oral use is developed by filling versatile mini-tablets in a hard capsule. Accurate dose of drug can be given to patients to increase the efficiency. Inter and intra subject variability can be decreased by using mini tablets. The toxic effects of potent drug overdose while using conventional dosage forms can be reduced by mini tablets. Dose dumping and local irritation can be avoided by the use of mini tablets. For those drugs whose absorption is more in small intestine mini tabletdosage form is beneficial as they can easily pass through the duodenumindependent of gastric emptying and intestinal motility.Minitablets 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. So, the development of mini-tablets for controlling drug release is an important focus of research in oral controlled solid dosage forms.

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