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Pharmaceutical Mini Tablets

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Abstract: Solid oral dosage forms are most acceptable dosage forms especially tablets are most widely accepted by people of different age groups. Mini tablets are tablets with a diameter equal to or smaller than 2–3 mm. 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 mini tablets, pH responsive mini tablets, gastro retentive mini tablets, paediatric 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.
Key words: Mini Tablets, multiple unit dosage forms, encapsulated mini tablets.

Introduction:

The main aim of any drug delivery is to deliver therapeutic amount of drug to the specific site and then to maintain the desired drug concentration at that particular site[1]. Usually conventional dosage forms result in wide range of fluctuations in drug concentration in the blood stream which results in poor efficiency[2]. Repetitive dosing, unpredictable absorption and undesirable toxicity lead to the development of controlled drug delivery system. The main aim in designing sustained or controlled drug delivery systems is to reduce the frequency of the dosing and to increase the effectiveness of the drug by localization at the specific site of action[3]. Sustained release, prolonged action, and repeated action are the names which are given to oral pharmaceutical formulations which follow slow release, timed release or delayed release which are commonly called as controlled release dosage forms. The term controlled release includes both single unit dosage forms and multiple unit dosage forms[4].

A single unit dose e.g. Matrix or tablet enclosed 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[4].

A multiple 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. A multiple units tablet may thus be divided before ingestion without loss of depot effect, as the subunits act as self-contained depots. The dose in multiple unit dosage forms 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[4].

Table No. 1 Comparison of Single unit dosage forms and Multi unit dosage forms[4]

Single unit dosage form	Multiple unit dosage forms
Definitions	
Oral pharmaceutical dosage form consisting of one un disintegrating unit	Oral pharmaceutical dosage form consisting of a unit which disintegrates in GIT into large number of sub units.
Example	
Enteric coated tablets passing un disintegrated through stomach	Capsule containing pellets or mini tablets individually coated being dispersed upon disintegration.

Mini tablets:

Mini tablets are tablets with a diameter equal to or smaller than 2–3 mm (Lennartz and Mielck, 1998). These mini-tablets can be filled into hard gelatin capsules or can be compressed as normal tablets. Mini-tablets also offer an alternative for pellets because of their relative ease of manufacturing and because dosage forms of equal dimensions and weight with smooth regular surface are produced in a reproducible and continuous way. Mini-tablets are very suitable for coating in order to sustain the drug release but the coating process is expensive, time consuming and sometimes associated with reproducibility problems of release during storage[5].

Mini tablets reduce intra and inter subject variability and also reproducible release profiles can be obtained. Majority of the drugs absorption is more in upper part of small intestine (duodenum), for a drug to reach the small intestine it had to pass through stomach. So, drug absorption depends on gastric empting time. If the gastric emptying is too fast drug may not absorb to required level or if it too slow it may get mix-up with gastric contents and may adsorb to food which gives unintended effects. These effects are more in case of single unit dosage forms because of their size but in case of mini tablets will not depend on gastric emptying and easily get passed through pylorus. So mini tablets are beneficial over the normal size tablets to reduce intra and inter subject variability[4].

Mini tablets will give reproducible plasma drug concentrations. Plasma drug concentration is directly proportional to the absorption. Absorption is more and even with mini tablets as they are distributed all over the surface which is not in case of single unit dosage forms3. So by formulating multiple unit dosage forms like mini tablets better plasma drug profiles can be obtained[4].

Mini tablets can be easily divided and administered without loss of activity. Elderly and paediatric patients who sometimes chew the tablets which releases drug all at once and may cause toxicity in case of normal tablet but in case of Mini tablets, they can be chewed as here each mini depot in the formulation act individually dose dumping may not occur[5]. For local irritating drugs, mini tablet formulation decreases the irritation effect than that of single unit formulations.

Advantages:

Some of the advantages of mini tablets are[6]

- 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 with smooth 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 a smooth surface.
- They offer high drug loading, a wide range of release rate patterns, and also fine tuning of these release rates.
- They offer high degree of dispersion in the GI tract, thus minimizing the risks of high local drug concentrations.
- Unlike pellets, mini tablets do not require any solvents for its production, as a result problems with stability can be avoided.

- Complex manufacturing steps can be minimized in case of mini tablets when compared to pellets which may require fluid bed granulator for granulation or coating as mini tablets can be manufactured easily by simple tableting techniques.

Types of Mini tablets:

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

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

Paediatric mini tablets:

Syrups, tablets and capsules are commonly used dosage forms for children. Syrups are liquid dosage forms which are simple to administer and dose can be easily altered to the patient needs on the other side disadvantages 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 in swallowing 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. To overcome all the above issues formulating mini tablets can result in good patient acceptance. Mini tablets are easily accepted by children than other dosage forms like tablets, syrups, and capsules etc[7].

Gastro retentive mini tablets or Floating mini tablets:

Gastro retentive tablets are intended to release the drug in stomach for prolonged time. Generally for tablets to float on the GI fluids content we formulate tablets by using gas generating agents in them. These tablets when come in contact with food generate $CO_2$and the generated gas is trapped in swellable hydrocolloid which makes the tablet to float and retain in stomach. In normal single unit tablets drug loading is low as the polymer used for floating in high. In mini tablets we can use coating with sodium bicarbonate or calcium carbonate (gas generating agents), eudragits coating in place of swellable polymers used in formulation to increase the drug loading. Fluid bed processor can be used for coating of mini tablets[8].

Goole et al developed sustained release floating mini tablets of levodopo. Here they used 3mm mini tablets core formulated with gas generating agent and coated the core with eduragit RL30 D to get the required release.

Bio Adhesive Vaginal Mini Tablets:

Vagina is an important application site of drug delivery for local therapy of different diseases like bacterial, fungal and protozoal infections, HIV prevention, delivery of contraceptives, spermicides or labor inducers and for treatment of Pancreatic lesions and an alternative route of systemic drug delivery[9,10].

The dosage forms which are aimed for vaginal drug delivery should be easy to administer without irritation or discomfort and should have even distribution and long retention time there by increasing patient compliance and adherence to therapy[11].

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. Nano pharmaceuticals can be used but the problem associated with them is low residence time as they are liquid in nature. To overcome the above problems we can use bio adhesive polymers[11].

Bio adhesive polymers or hydrophilic polymers are readily soluble and adhesive on exposure to moisture and will rapidly cohere to surfaces as they have high viscosity at low concentrations[11].

Solid dosage forms have high dose accuracy than semisolids systems. The problem in solid dosage forms is vaginal disintegration is slow and they are rapidly cleared due to gravity and self-cleansing action of vagina. Bio adhesive polymers can be used to overcome this but in large size tablets loss is reported[11].

Bio adhesive mini tablets can be used for vaginal drug delivery to deliver drug accurately and for long period of time. In mini tablets dose is divided into multiple units which will spread evenly in vaginal cavity with improved coverage in vaginal epithelium. Bio adhesive Mini tablets act by swelling and forming micro gels and releasing drug in controlled release manner and there by maximum bioavailability can be achieved[11].

Marianne Hiorth et al Prepared Bio adhesive mini tables of hexyl ammonium hydro chlorodium (HAL), which is used for the photodynamic therapy of cervical cancer. Thermo gel of HAL is already there but HAL is unstable in moist environment, to prevent or to eliminate the stability issues bio adhesive mini tablets were prepared by direct compression. Mini tablets prepared with HPMC and HPC have shown adequate mechanical and bio adhesive properties. Vaginal pH varies from women to women of different ages. To withstand those pH conditions bio adhesive vaginal mini tablets are to be designed by using non-ionic cellulose ethers with Bioadhesive property[11].

pH responsive mini tablets[12]:

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). pHresponsive drug release is required when absorption of drug is more at a particular 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.

M AHadi et al. formulated pH responsive mini tablets for ileo colonic drug delivery of naproxen which is used for the treatment of rheumatoid arthritis. Eudragit L100 and Eudragit S100 are used as pH responsive polymers to get the required release.

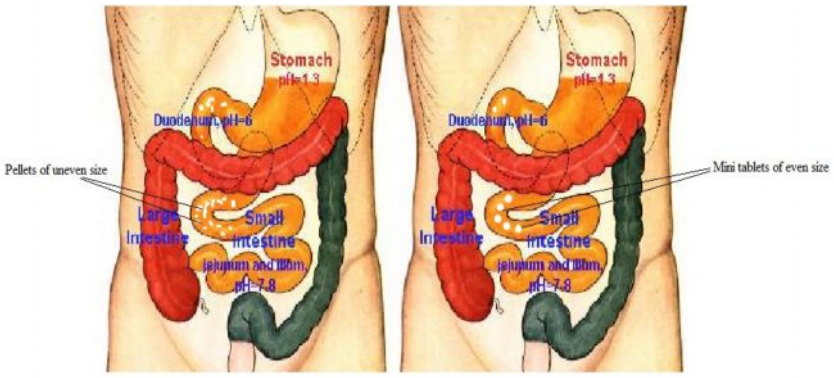

Fig No. 1: Pellets and Mini tablets size and Distribution

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 beneficial 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. Here immediate release part can be compressed along with mini tablets this immediate release part fills in void spaces present in between mini tablets[13].

Carla M. Lopes prepared biphasic mini tablets of ibuprofen where they got required release characteristics for biphasic mini tablets.

Oral disintegrating mini tablets:

Oral dispersible tablets (ODTs) are the novel dosage form which rapidly disintegrates in the mouth (1-3 min) without chewing upon oral administration and without the need of water, unlike other conventional oral solid dosage form[14]. Oral Dispersible Tablets (ODTs) are also known as "fast dissolve", "rapidly disintegrating", "quick-dissolve", "crunch-melt", "bite-dispersible", "mouth-dissolve", and "orodispersible" tablets . Oral dispersible mini tablets (ODMTs) are more suitable for paediatric patients because of their small size, pleasant mouth feel and fast disintegration in mouth[15].

The ODT should have the following characters they should disintegrate in the mouth without additional water. The disintegrated tablet should become a soft paste or liquid suspension, which can provide good mouth feel and smooth swallowing. Because ODTs dissolve or disintegrate in the patient's mouth, the drug will be partially dissolved in close proximity to the taste buds. A pleasant taste inside the mouth becomes critical for patient acceptance. Unless the drug is tasteless or does not have an undesirable taste, taste-masking techniques should be used. The taste-masking technology should also be compatible with ODT formulations. For example, if drug particles are coated to minimize unpleasant taste, the coating should not be broken during compression or dissolved during wet granulation. Taste masking of bitter tasting drugs is critical to the success of the ODT formulations. For the ideal ODT technology, the drug properties should not significantly affect the tablet property. Because ODTs are designed to have a quick dissolution/disintegration time, the tablet porosity is usually maximized to ensure fast water absorption into the tablets. In addition, low compression pressure causes fast dissolving dosage forms to be soft, friable, and unsuitable for packaging in conventional blisters or bottles. A strategy to increase tablet mechanical strength without sacrificing tablet porosity or requiring a special packaging to handle fragile tablets should be provided. A good package design or other strategy should be created to protect ODTs from various environmental conditions especially from moisture[15].

Methods of manufacturing mini tablets:

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

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

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[16].

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[16].

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[16].

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[17].

Tooling used in compression of mini tablets:

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

Fig No. 2:Showing various multi tip punches used for compression of mini tablets (Source:http://notter.com/en/tablettierwerkzeuge/mehrfach_und_pellets-werkzeuge/)

Coating of mini tablets:

Application of the coating solution to a tablet improves the visual characteristics of the product, based on which the quality of the product can be judged. The type of coating process chosen usually depends on the type of coating material that has to be applied, whereas the durability of the tablet core depends both on the coating material and application process.

Encapsulated mini-tablets system usually comprises immediate-release mini-tablets (IRMT) and sustained release mini-tablets (SRMT) in a capsule made from HPMC, a water-soluble polymer. HPMC capsule which contains the mini-tablets later disintegrates and releases these subunits into the system. Inclusion of IRMT permits the development of rapid acting dosage forms for fast action. Encapsulated minitablet systems can be designed to yield various sustained release drug profiles by combining different types, quantities and combinations of mini-tablets, thereby improving patient compliance. Mini-tablets are usually coated with enteric 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 alkaline environment of the small intestine. That is, they will not get dissolved in the acidic juices of the stomach, but breaks down in the alkaline environment of the small intestine. Materials used for enteric coatings mostly include fatty acids, waxes, phthalates, shellac, plastics, and plant fibres. Drugs that cause irritation to gastric mucosa or inactivated in the stomach, can be coated with a substance that will dissolve only in the small intestine. Abbreviation "EC" along with the name of the drug indicates that the drug has an enteric coating[18].

Polymers used for enteric coating of mini tablets[18]

- 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

Fig No 3: Compressed and coated mini tablets
(Source:http://www.ritter-pharma-technik.de/english/minitablettierung.html)

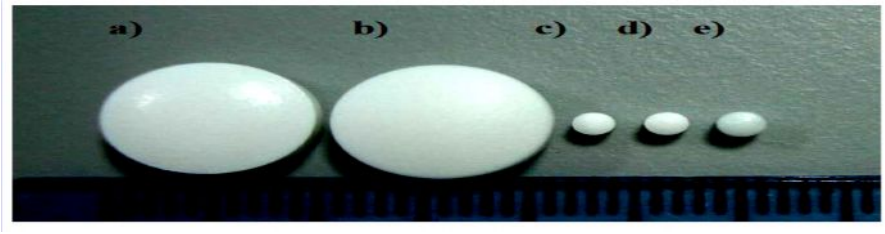

Fig No. 4: Different type of Tablets with and without coatinga) 10mm uncoated tablet b)10mm enteric coated tablet , c)2mm uncoated tablet , d) 2mm seal coated tablet and e) 2mm enteric coated tablet
(Source:http://www.colorcon.com/literature/marketing/mr/Delayed%20Release/Acryl-EZE/English/ent_coat_minitabs.pdf)

Mini tablets can be administered by following methods[13]:

- Directly administered as single units.
- Filled in hard gelatine capsules.
- Use of automatic Dose dispensing device.

Directly administered as single units:

Mini tablets can be directly administered as such. Required dose can be easily taken and these are packed in bottles. Sometime compressed mini tablets are again compressed to get tablets of normal size.

Filled in hard gelatine capsules:

As it is difficult to handle the mini tablets these are usually filled in hard gelatine capsules and then administered.

Fig No. 5: Mini tablets filled in a capsule

(Source:http://www.qualicaps.co.jp/en/capsule/medical/index.html)

Automatic dose dispensing device:

Dose is decided on the basis of patient population average dose individualization is important as administration of right drug in wrong dose will result in adverse effects of decreased efficiency. Generally tablets are most commonly used but limited strengths available for administration. Dividing tablets for getting required dose or combining different strengths will not give the desired therapeutic effect so an automatic dose dispensing device can used to dispense tablets of required dose[19].

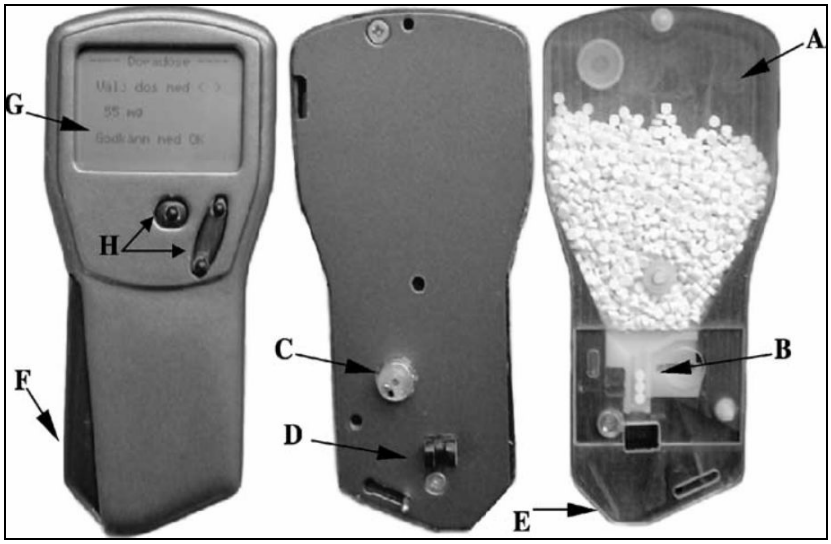

Fig No. 6:The dose dispensing device, consisting of

(A) a cassette filled with micro tablets,
(B) Plastic components,
(C) Electronic motor,
(D) a photocell which monitors the number of micro tablets transported from the cassette to the receiving compartment
(E) Actuator
(F) Releases the micro tablets into a collecting vessel or a glass of water.
(G) The digital display and
(H) The buttons used to adjust the dose.

The dose dispensing device comprises a cassette filled with micro tablets, buttons operated by the patient (with an associated digital display) for dose adjustment, a battery-driven electronic motor, a photocell monitoring the number of micro tablets dispensed from the cassette to a receiving compartment, and an actuator, by which the micro tablets are emptied from the receiving compartment into a collector or a glass of water. The usefulness of the automatic dose dispenser and patient acceptance of the device were evaluated in patients with Parkinson's disease[19].

Table No. 2: List of various mini tablets available in the Market[18]

Generic Name	Brand name
Pancrelipase	Ultresa
Zafirlukast	Accolate
Donepezil Hydrochloride	Aricept
GalantamineHBr ER	Razadyne ER
Fenofibric Acid Capsules	Trilipix
Levonorgestrel and EthinylEstradiol	Alesse
Prasugrel Tablets	Effient

Evaluation of Mini tablets:

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

Conclusion:

Mini Tablets offer great advantage over single unit dosage forms. 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 duodenum independent of gastric emptying and intestinal motility. Bio adhesive mini tablets show increased bio adhesion and increased effect than that of single unit bio adhesive tablets. Mini tablets are more acceptable in children and elderly people as they are easy to swallow. Mini tablets can be used as a solution for the shortcomings of single unit dosage forms.Although manufacturing cost is more and problems like sticking, handling may arise during manufacturing of mini tablets, they are effective alternative solution for single unit dosage forms.

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