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MULTIPARTICULATE DRUG DELIVERY SYSTEM: MINI TABLETS

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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 by localization. In oral controlled drug delivery systems, multiple unit dosage forms (MUDFs), like granules, pellets and mini tablets effectively control the release of the drug when compared to single unit dosage forms (SUDFs) like tablets and capsules. Among all MUDFs, mini-tablets offer several advantages like they can be manufactured relatively easily, they do not require any solvent for their production, can be coated reproducibly, and also requires less coating material. Also, there is a great flexibility during their formulation development. In this context, last few decades have witnessed some major advancement. 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.

Among all MUDFs, mini tablets represent a new trend in solid dosage form design, with the main aim of overcoming drug-excipients or drug-drug interactions. They also offer an alternative for pellets and granules because of their relative ease of manufacturing and dosage forms of equal dimensions, weight with smooth regular surface can be produced in a reproducible and continuous way. Therefore, they resemble good substitutes for pellets and granules. They can also be filled in capsules like other multiple unit dosage forms. Focused on how mini tablet formulation become effective in targeted and modified drug delivery system. This review emphasizes the various advantages of mini-tablets, formulation possibilities, general evaluation tests, and brief insight to marketed drugs.

Keywords: *Single unit dosage form, Multi unit dosage form, Mini tablets, pellets, granules.*

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INTRODUCTION:

Oral administration of medicines has an advantage for patient's compliance. Most of the solid dosage forms administered orally are tablets and capsules. Tablets have many advantages over other dosage forms, such as ease of transportation, application and production, high patient's compliance, accurate dosing, control of drug release and stability. Problems related to conventional tablet is desired drug release profile, therapeutic effect, in use of pediatrics or geriatrics, difficulties in swallowing and repeated dosing leads to toxic concentrations. The main aim in designing sustained or controlled drug delivery systems is to reduce the frequency of dosing and to increase the effectiveness of the drug by localization at the specific site of action.

Oral controlled release id mainly classified into two types: Single unit dosage form (SUDFs): tablets or capsules and Multiple unit dosage form (MUDFs): like granules, pellets or mini tablets [1].

Multiple unit dosage form contain number of subunits, each subunit contain drug. The Overall dose is equal to the sum of the quantity of the drug in each subunit. Functionality of the individual dose related to functionally of the overall dose [2]. MUDFs is beneficial when the selecting agents possing different mechanism of action that providing synergistic effect. MUDFs offers advantages like reduce the risk of high local drug concentration; reduce the risk of local irritation after disintegration rapidly distributed in gastrointestinal tract, more uniform bioavailability. MUDFs is comes under the controlled drug release and shown reproducibility of the drug release profile. MUDFs may seem costlier than SUDFs in the short term; but due to, lower treatment failure rate, reduction in development of resistance, higher colonic residence time, and more predictable gastric emptying, results in significant savings [3].

Table 1: Properties multi unit and single unit dosage form

Multi units Dosage forms	Single Units Dosage forms
More predictable gastric emptying	Gastric emptying with high variability
Gastric emptying is less dependent on nutritional status	Gastric emptying is highly dependent on nutritional status
Absorption grade does not show intra and inter-individual variability	Absorption rate and grade shows intra and inter-individual variability
Risk of overdose and local irritation are lower	Risks of overdose and local irritation are higher
Complex production technologies	Simple production technologies

Mini tablets

Mini tablets are tablets with diameters ≤ 3 mm and have a wide range of application area for ease of use, they are usually filled in capsules, or they can be compressed in larger tablet of filled into sachets [4,5]. This combination may include immediate release, sustained release or control release. It is possible to incorporate mini-tablets of different drugs to improve overall therapeutic outcomes and also for the treatment of concurrent diseases.

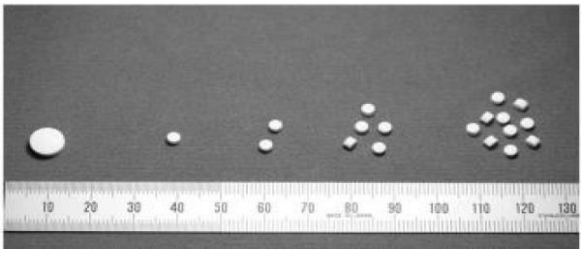

Figure 1: Mini tablets

Advantages of mini tablets [6,7,8]

- Minitablets can be easily manufactured.
- They have regular shape and smooth surface, excellent size uniformity.
- 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.
- 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.
- It also offers the high drug loading, a wide range of release rate designs, and fine-tuning of these release rates.
- 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.
- Mini tablets are easy to manufacture compared to pellets as they have equal proportions, weight with smooth regular surface.
- Mini tablets are good coating substrates as they have excellent size uniformity, regular shape and a smooth surface.
- Unlike pellets, mini tablets do not require any solvents for its production; as a result problem with stability can be avoided.
- Mini tablets eliminate local side effects and eliminate systemic side effects.
- Minimize drug accumulation with chronic dosing and Improve efficiency in treatment.

- Make use of superior properties, e.g. sustained release aspirin for morning relief of arthritis by dosing before bed time.

Advantages of mini tablets over pellets

- Pellets are small bead like structures, usually with medium to high uniformity and are usually filled into capsules (Figure 2) or compressed into tablets.
- Technically demanding process like fluid bed granulation, extrusion or spheronization are required for the production of pellets. Whereas, mini tablets can be manufactured via simple tabletting procedures [9].
- Unlike pellets, mini tablets does not require any solvents for its production, as a result problems with stability can be avoided [10].
- As mini-tablets have well designed size, shape, smooth surface, low degree of porosity and high mechanical strength, they are easy to coat than pellets, which usually have an uneven surface and are very porous. Hence, tablets with defined size, shape and surface can be easily produced with good batch to batch uniformity [11].

Figure 2: Encapsulated pellets

Advantages of mini tablets over pellets

- Mini-tablets offer several advantages when compared to irregularly shaped units like granules (Figure 3). Due to their smooth surface, constant surface area and high mechanical strength, mini-tablets can be coated reproducibly, and also requires less coating material compared to granules [12].
- Hence, mini-tablets are good substitutes for granules and pellets because they can be manufactured relatively easily.
- In addition, dosage forms containing mini-tablets can be smaller than those containing granules and pellets. So, the development of mini-tablets for controlling drug release is an important focus of research in oral controlled solid dosage forms.

Figure 3: Granules

METHODOLOGY:

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.

1. API 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.

a. Physical Appearance: The physical characteristics of the drug are usually studied by visual inspection.

b. 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.

Procedure: Accurately weighed amount of drug is taken and transferred to the top most sieves. The sieves are then shaken for about 5-10 minutes, depending on the nature of the drug. Then the amount retained on each sieve is collected, weighed separately and is expressed in terms of percentage.

2. 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 [13].

Drug-excipient compatibility studies by force degradation method:

For this binary mixtures of drug and excipients (1:1) are prepared and packed properly to avoid any contact with external environment. These are then stored in accelerated conditions (25°C/60% RH and 40°C/75% RH) for definite time periods. At the end

of this, all the samples are collected and observed physically for any incompatibility [15].

3. 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].

4. Differential scanning colorimetry (DSC) Studies: DSC studies were carried out for pure drug and Optimize mini-tablets formulations [8].

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

a. Determination of maximum absorption wavelength of the drug:

The drug sample in the respective medium is scanned using U.V spectrophotometer for the determination of its absorption maxima.

c. Development of calibration curve:

Accurately weighed amount of drug is taken and added to the respective buffer solution, from this primary stock solution is prepared, and then serial dilutions are developed. These samples are analyzed using UV Spectrophotometer.

Evaluation of the blend

a) Bulk density
b) Tapped density
c) Compressibility index
d) Hausner's ratio

a) Bulk Density [16,17]

Bulk density is determined as per the standards of USP method-I. Weighed amount of the blend is taken and transferred to a measuring cylinder. Bulk volume of the blend is noted as per the reading on the measuring cylinder, and the bulk density is calculated using the following formula:

Bulk density= Mass of the blend/Bulk Volume of the blend.

b) Tapped Density [16,17]

Tapped Density is determined using the tapped density tester. Weighed amount of the blend is poured into the graduated cylinder of the tester, which is then operated for 500 taps. Tapped density is calculated by the following formula:

Tapped density= Mass of blend/ Tapped Volume of the blend.

c) Compressibility Index (Carr Index)

Compressibility index is an important measure and is calculated from the readings of bulk and tapped densities.

It indicates the flow properties of the blend. Low percentage of Carr index indicates free flowing powder, whereas high Carr index represents poor flowing powder [16,17].

CI= (TD-BD)*100/TD

Where,

CI= Carr Index
TD= Tapped density
BD= Bulk density

d. Hausner's Ratio

Even Hausner's ratio indicates the flow properties of the powder blend and is measured by the ratio of tapped density to bulk density [16,17].

Hausner's ratio=Tapped density/Bulk density

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 [14].

Figure 4: Punch fitting several mini-punches [8]

Manufacturing Methods for Mini Tablets [18]

A techniques that can be utilized for the manufacturing of mini tablets are: A. Direct compression, B. Dry granulation, C. Wet granulation, D. Melt- extrusion.

A. Direct Compression Method: In direct compression method, powder blends containing excipients and active pharmaceutical ingredients are directly compressed the powder blends into mini tablets. Hardness is depending on the excipients direct compression grade. A powdered blend flow into a die, the upper and lower punches of the tablet machine compress, the material under a high pressure to produce a mini tablets. In this process, powder blend containing Active pharmaceutical ingredient, excipients, lubricants followed by compression, which makes the product simple and easier process, no other additional processing steps are required. Direct compression method is most commonly used because it requires less time, most effective and least complex way to produce mini tablets. Stability problems are lower compared to wet granulation method.

B. Dry Granulation Method: Dry granulation method is a logical approach for the manufacturing mini tablets. In these method granules are formed by slugging. Thermo labile and moisture sensitive

drugs are suitable for manufacturing mini tablets by this method. Roller compactor is used as processing equipment in this method. In this method premixed powders between two counter rotating rollers under extreme pressure, mini tablets are compressed.

C. Wet Granulation Method: In wet granulation method active ingredient, diluents, disintegrates are well mixed to form granules, which are further compressed in compression machine to produce mini tablets. In this method, binding agents are different grades of polyvinyl pyrrolidine are used.

D. Melt-Extrusion Technique: In Melt-Extrusion Technique, the powder (Drug + excipients) were premixed this premixed powder is then moved to dissolve extruder. In melt-extruder parameters like temperature, screw speed and feed rate are set in the scope of melting point scope of material. After the procedure extrudes are then processed and sieved. The acquired granules are then compressed to mini tablets utilizing compression machine.

Evaluation of Mini tablets [19,20]

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.

- **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.
- **Hardness:** The hardness of the Mini tablet is determined using Pfizer hardness tester and expressed in kg/cm^2. Six tablets were randomly picked tested for hardness. From each formulation and the mean and standard deviation values were calculated.
- **Thickness:** Thickness of the Mini tablet is measured using a digital caliper (Mitutoyodigimatic caliper,) and screw gauge. It is expressed in terms of mm.
- **% 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 (W_0) 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 help of soft brush and mini tablets were weighed again (W_1).
- **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.
- ***In-vitro* disintegration:** The in-vitro disintegration of the core mini-tablets were determined using disintegration test apparatus as per I.P specifications.
- **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 UV spectrophotometer.
- **Stability Studies:** 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. It gives an idea regarding the recommended storage conditions and re-test periods. Stability assessment of a substance helps in the determination of its degradation products. In this, the tablets are stored in suitable containers and analyzed at specific intervals for various parameters like appearance, assay of API, determination of degradation products, hardness, disintegration time, dissolution time etc., Stability studies are conducted at following conditions.
- Storage conditions: 40°C ± 2°C /75%RH ± 5%RH, 25°C ±2°C /60% RH ± 5% RH
  Period: 1, 2, 3 months

Tablet coating processes

In most cases, the coating process is the last critical step in the tablet manufacturing process. Successful 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.

Generally, four main types of coating procedures are used in the pharmaceutical industry:

- Sugar coating,
- Film coating,
- Compression coating, and
- Enteric coating.

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. As several mini-tablets can be placed in each capsule, tablets with different dose, content and release characteristics can be included. 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 [21]. 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 [22].

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

Table 2 : List of various mini tablets available in the Market

Generic name	Brand name
Pancrelipase	Ultresa
Zafirlukast	Accolate
Donepezil HCL	Aricept
Galantamine HBr ER	Razadyne ER
Fenofibric Acid capsule	Trilipix
Levonorgestrel and Ethinyl Estradiol	Alesse
Prasugrel Tablet	Effient
Olanzapine	Zyrexa,Zyprexa Zydis
Sumatriptan and Naproxen Sodium tablets	Treximet
Warfarin Sodium	Coumadin
Vorapaxar tablets	Zontivity
Hydromorphone Hydrochloride Extended Release tablet	Exaigo

Table 3: List of encapsulated Mini-tablets available in the market

Generic name	Brand name
Pancrelipase	Ultresea
Galantamine HBr ER	Razadyne ER
Fenofibric Acid Capsule	Trilipix

Basic formulation approach of mini-tablet dosage form

1) Compressed mini-tablets [23]

There has been an increasing focus in the development of MUDFs compressed into tablets (Figure 5) instead of filling 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.

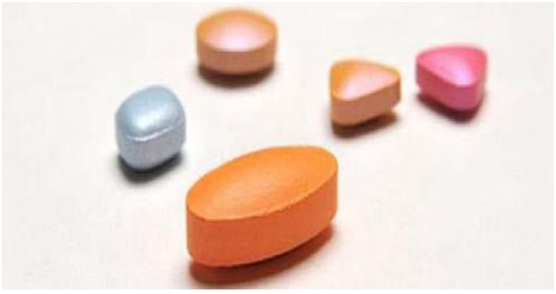

Figure 5: Compressed mini tablets

Advantages: It is easy and low-cost. It is utilized to distinct incompatible ingredients. It may be utilized to generate modified release products. It is not dangerous to nature meanwhile it does not require the utilization of high measures of organic solvents [27].

2) Encapsulated coated mini-tablets systems

Among all the possible formulations, encapsulated coated mini-tablets (Figure 6) are widely used as it

improves drug tolerance 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 [25,26]. 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.

Figure 6: Encapsulate coated mini-tablets systems

Advantages: It causes lower treatment failure rate, huge savings. Broad therapeutic applications can be accomplished. This offers both multi-phase and controlled release for combination or single prescription and over the counter medicines. Sustained, delayed or pulsed release profiles can be accomplished. Drug delivery can be targeted to two dissimilar regions of the GI tract. It has more predictable gastric emptying, higher colonic residence time and subsequently less money required for the development of new products in long-term therapy. Delivering of incompatible drugs is also possible. Cost effective therapy and patient compliance can be accomplished [27].

3) Compressed mini-tablets presented as a biphasic drug delivery system

Biphasic delivery systems release the drug at two different rates and/or in two different time periods, that is either quick/slow or slow/quick. A quick/slow system provides an initial burst of drug release followed by a constant release rate over a defined time period, whereas opposite is the case of slow/quick release systems. These systems are used primarily when maximum relief needs to be achieved quickly, followed by a sustained release rate in order to reduce the dosing frequency [28]. Drugs suitable for biphasic drug delivery include analgesics, anti-inflammatory drugs, antihypertensive, antihistaminic and anti-allergic agents.

In simpler words, biphasic drug delivery is a combination of conventional controlled and immediate release systems. As controlled delivery systems delay the release of the drug into the system and as a result do not provide rapid onset of action. Whereas immediate release systems provide fast release and rapid onset of action, but fails to provide longer duration of action. Considering all these factors a new oral drug delivery system, double component model is developed. In this, one component is formulated to provide fast release of the drug to achieve a high serum concentration in a short period of time. The other portion is a sustained release component, which is developed to maintain constant plasma levels over defined periods of time. Hence, this concept can be used to develop a biphasic delivery, by combining a fast release component with a slow release one. Compressed mini-tablets can be effectively formulated into a biphasic drug delivery system. In this, the outer layer that fills the void spaces between the mini-tablets is developed to release the drug in a short span, whereas layer usually contains a superdisintegrant that is crospovidone; mini-tablets are formulated using different concentrations of HPMC and Ethyl cellulose along with other basic ingredients [29].

Approaches of mini tablets in various dosage form:

1) Extended release mini tablets:

In extended release formulations, the active ingredient is slowly released over a wide period of time from the dosage form. This is accomplished by altering the diffusion from the dosage form of the drug or by prolonging the time of transition through the gastrointestinal tract. In extended release tablets, release slowing is achieved by altering the dissolution and diffusion of the drug through barrier coating, matrix system or chemical interaction / reaction [30]. As with conventional tablets, the drug release profile is also greatly influenced by formulation parameters in mini tablets. In general Hydophobic drug compound exhibit Fickian (diffusion) and Hydophilic drug compound shows non-Fickian (diffusion + erosion). It is expected that drug release will be slow in all extended release mini tablets. The difference in size between standard tablets and mini tablets affects the effectiveness of the release. As long as tablet size decreases, the rate of release

increases due to increased surface area / volume ratio and
reduced distance that the drug will diffuse [5].

2) Pulsatile drug release:

Pulsatile drug release is delayed release within a programmed time period to meet the chronotherapeutic need. These systems are time controlled systems and site-specific systems. While site specific systems are provided by environmental factors such as pH, enzymes, time-controlled drug delivery is provided by the drug delivery system. Pulsatile release coatings may be rupturable, erodible, permeable and semipermeable film coating. Tablets are often coated by spray coating, but pressure coating or dipping coating methods can also be used. Pulsatile release is achieved by coating a tablet with controlled releasing polymer. When the drug is compared to an aqueous medium, the coating acts as a protective layer. The release occurs at a defined time, depending on the physicochemical properties of the drug. Pulsatile release coatings may be rupturable, erodible, permeable and semipermeable film coating. Tablets are often coated by spray coating, but pressure coating or dipping coating methods can also be used. Multiple release in pulsatile systems is achieved by coating the drug core with functional polymers. These systems can be multi unit or single unit. Pulsatile drug release may be useful in the treatment of diseases that require chronotherapy, such as bronchial asthma, angina pectoris, and sleep disorders.

3) 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.

4) Floating Mini tablets:

Floating systems in the stomach increase the absorption of the drug by prolonging the duration of the drug's retention. It is also an advantageous system for drugs that do not dissolve in the intestinal pH or that is effective locally on the stomach, and reduce side effects of drugs that cause local irritation. Floating systems are divided into two types, these are effervescent and non-effervescent systems and they can be single unit or multi unit. With multi unit floating systems, the fluctuation in absorption and release of the drug can be reduced [31-33]. In Floating non-effervescent systems, polymers such as polysaccharides, hydrocolloids, or gel-forming or high swelling substances or matrix-forming polymers are used. Floating effervescent systems include an effervescent component such as citric acid and sodium bicarbonate.

Multi-unit floating systems with air compartments. Each unit comprises an air compartment separated by a calcium alginate core and calcium alginate or calcium alginate / polyvinyl alcohol (PVA) membrane. The flow of the system depends on the presence of the air chamber and the porosity of the membrane. porous structure is provided by the addition of a water-soluble material to the PVA composition, thereby preventing shrinkage of the system. It has been observed that the ability of the system to float increases with increasing molecular weight and quantity of PVA.

5) Oral disintegrating Mini Tablets:

Oral Dispersible Tablets (ODTs) are the unique dosage form which promptly disintegrates in the mouth i.e., 1-3 minutes without the required of water, chewing upon oral administration and dissimilar other conventional oral solid dosage form. ODTs are also known as bite-dispersible, mouth-dissolve, rapidly disintegrating, fast dissolve, crunch-melt, quick-dissolve, and oral dispersible tablets. ODTs are additional proper for pediatric patients since pleasant mouth feel, fast disintegration in mouth and their lesser size. The ODTs must have the following characters they must disintegrate in the mouth without additional water. The disintegrated tablet turn into a fluid suspension or soft paste which can give smooth swallowing and great mouth feel. Because ODTs break down or deteriorate in the patient's mouth, the drug will be mostly dissolved in nearness to the taste buds. A pleasant taste inside the mouth ends up basic for patient acceptance. Unless the drug is tasteless or does not have an unwanted taste, taste-masking methods to be utilized. The taste-masking innovation should likewise be perfect with ODTs formulations [34].

6) Colon targeted mini tablets:

Targeting of drugs to cola increases the rate of treatment especially for local bowel diseases such as Chron's disease, irritable bowel syndrome, and ulcerative colitis. The specificity and local effect of drugs on a particular site reduces systemic side effects. The enzyme activity at the end is low. This allows protein and peptide structured drugs to be successfully used with colon targeted systems. Targeting of drugs to colon can be achieved in different ways. For example, coating with enteric polymer showing pH dependent dissolution provides colon targeting. In areas with low pH, such as in the proximal part of the stomach and small intestine, the polymer will not dissolve, dissolve in the proximal part of the small intestine and in the stomach, as a result the drug will be released [35,36]. When single-unit drug delivery systems are targeted to the colon, problems may arise such as an unexpected disintegration of the system and loss of drug along the gastrointestinal tract. Colon targeting systems may be single unit or multi unit such as mini tablet, microparticle, pellet, granules.

5-Aminosalicylic acid, water-soluble dextrin and Nutriose® containing mini tablets that sensitive to enzymes secreted by colon bacteria were prepared, and as a result it was found that this system prevented the drug from being released in the acidic medium and continued to release in the colon for 8 hours [37].

7) Mucoadhesive mini tablets:

It is possible to obtain local and systemic effect by using mucoadhesive systems. They allow the drug to remain in the area of action for a long time, thereby providing the local effect due to increase the duration of the absorption in the absorption zone [38, 39]. Mucoadhesive polymers can adhere to the surface of the gastric mucosa, thus allowing the drug to remain in this area for a longer period of time, thereby increasing bioavailability [40]. The use of thiolated polymers as a mucoadhesive agent has gained importance in recent years. The thiolated polymers have higher mucoadhesive power. They increase bioavailability through penetration enhancing effects [41,42]. Guggi et al., (2003) [43], prepared mucoadhesive mini tablets containig peptide-structured calcitonin compound and targeted to the stomach. Thiolated chitosan is used as a mucoadhesive polymer and glutathione is used as a penetration enhancer. Chitosan-pepstatin conjugate acts as a peptide-protecting agent. With this system, the peptides are administered orally to show the pharmacological effect.

8) 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.

9) 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. Bimodal drug delivery systems have different release characteristics within a single unit. Systems such as rapid release / prolonged release, extended release / delayed release may be combined to increase therapeutic efficacy and patient compliance. Bimodal or combined release can be provided by single-unit systems such as layered tablets, as well as by multi unit systems such as pellets and mini tablets. In zero order release systems, the release rate of the drug is independent of blood concentration and is considered to be the ideal system for keeping the amount of drug in the plasma constant. In these systems, the absorption of the drug is assumed to be rapid and uniform throughout the entire gastrointestinal tract. However, the absorption of most drugs is partially slower at the stomach, faster at the proximal part of the gut, and too slow at the distal part of the gut. For this reason, the rate of release from the dosage form of the drug should be increased or decreased in certain regions to achieve a constant drug blood concentration. Thus, it can be considered that the release rate in varying proportions is more favorable than the zero-order constant release. Bimodal systems provide such a volatile release. It consists of initial rapid release and a constant and slow release period followed by a second rapid release phase. That is, with a sigmoidal release profile [44, 45].

10) 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.

Release profile of Mini tablets

Due to increased surface in relation to volume, 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 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.

Future Prospective

Mini-tablets could offer a solution to the current issue in the pharmaceutical industry that is lack of dosage forms for paediatrics. Mini-tablets can be considered as a potential new formulation for paediatric use, as they meet the requirements of child-friendly drug delivery [46]. In paediatric use, mini-tablets offer many benefits such as, the delivery of an accurate dose and the opportunity of dose flexibility by administering multiple mini-tablets [47].

CONCLUSION:

From this review it can be concluded that Pharmaceutical mini tablets offer numerous advantages over single unit dosage forms. Precise dose of drug can be assumed to patients to expand the efficiency. Mini tablets are alternative to pellets and granules when compared to single unit dosage forms. Local irritation and dose dumping can be avoided by utilize of mini tablets. Bio adhesive mini tablets express improved bio adhesion and improved effect than that of single unit bio adhesive tablets. They increase patient compliance by allowing coexistence of drugs with each other and by combining drugs with different release kinetics. Studies have shown that mini tablets adapt to a multitude of modified release patterns such as extended, delayed, pulsatile, bimodal release and colon targeting. They are fit for pediatric and geriatric patient groups compare to single unit dose forms and also good substitutes for pellets and granules. 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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