Mini-Tablets as a Pharmaceutical dosage form: A Comprehensive Review

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ABSTRACT

The article "**Mini-Tablets as a Pharmaceutical dosage form:A Comprehensive Review**" presents a thorough analysis of the development of mini-tablets system. The review focuses on the challenges associated with the mini-tablet system offers a promising alternative for effective eradication. The current study aimed at developing a "tablets in capsule" technology that would enable sustained release &CRDD.The major objective of mini-tablets, a new trend in solid formulation design, is to get past certain therapeutic barriers. Mini tablets are a multiple unit dosage form that have less stability issues and are easier to manufacture than pellets or any other oral dosage form.It is emphasizing its ability to overcome issues such as poor patient compliance, antibiotic resistance, and adverse effects associated with conventional treatment regimens. The mini-tablets system is designed to enhance patient adherence through reduced pill burden, improved palatability, and convenience.Furthermore, the review discusses the formulation and manufacturing aspects of mini-tablets, emphasizing the need for precise control over size, shape, and drug dispersion to ensure therapeutic efficacy.

KEYWORDS: Oral controlled drug delivery systems, Mini-tablets, Methods of mini tablets, encapsulated mini tablets.

INTRODUTION

In view of the many benefits of administering medications orally, oral controlled drug delivery systems are the most widely used type of controlled drug delivery system.[1]With its convenience of activity, oral drug delivery is the most common method of administration.[2]Oral CRDDS have received a lot of attention in study conducted during the years due to their many benefits compared to traditional medication delivery methods.Among these are the reduction of medication plasma concentration variations, which maximizes therapeutic efficacy and minimizes adverse effects.

Furthermore, by decreasing the frequency of dose, these devices can improve patient compliance.[3]Multi-unit dosages form was initially introduced in the 1950. Several facts of the mini tablets are the subject of this review. Like other multiple unit dosage form, it can also be put into capsule form. As such, it's a great substitute for granules and pellets it can also be put into capsule form.[4]Mini-tablets can be hard-capsuled or pressed in large tablets. Levofloxacin floating mini-tablets in capsules, which is gastroretentive, was developed and evaluated to eradicate Helicobacter pylori.[5-6]As a result, novel tablet design trends including chewable, oral dissolving, and mini-tablets have attracted a lot of attention.[7]Oral CRDD methods may be classified as two primary classes: single-dose doses, like capsules or tablet form, as well as various unit dose forms, which means pellets, granules, or mini tablets.[8]In order to create orally disintegrating mini-tablets, a new solid oral formulations with pre-processed, readily usable excipients that may be delivered to young children (under two years old), the research integrated the fast-dissolving dosage form and the mini-tablet methodologies.[9]Parts of the gastrointestinal tract (GIT) are the primary focus of oral medication delivery formulation and technology.[10]

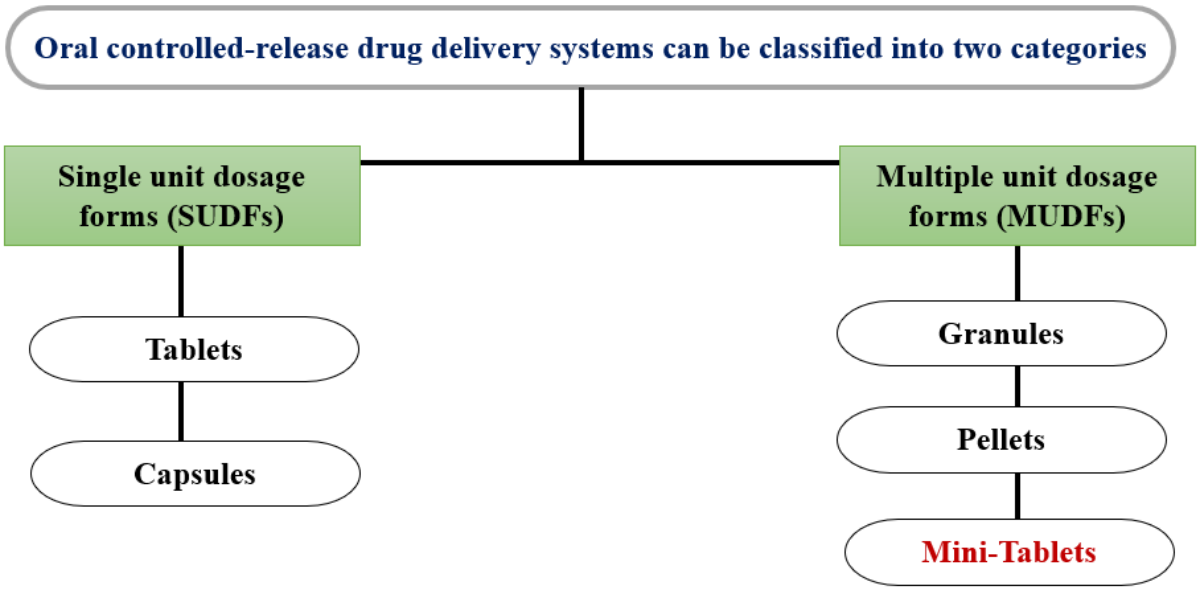

Fig.1: Oral controlled release drug delivery system

Multi-unit dosage helps to address this problem.When drugs have synergistic effects that make them more effective together than they are on their own it is possible to combine multiple drugs with similar therapeutic dosage into one dose. Making mini tablets dispersible aids in enhancing therapeutic efficacy and reduces possible side effects.[11]

Introduction to Novel Drug Delivery System:

An important factor influencing a drug's effectiveness is how it is administered. A multidisciplinary approach to the distribution of therapies to target tissues is becoming increasingly necessary. While certain drugs have an optimal concentration range within a maximal benefit, the efficacy of treatment for several diseases is progressing extremely slowly.From this novel concept to develop controls on pharmacokinetics, pharmacodynamics, non-specific toxicity, and immunogenicity. We refer to this new concept as a unique drug delivery mechanism.

Its goal is to continuously administer the drug over an extended period of time in circulation with kinetics that are predictable and repeatable. The combination of controlled release and sustained release properties in a delivery system would increase the effectiveness of treatment.[12]

MINI TABLETS

Tablet is in the lead in terms of being the most preferred pharmaceutical form, while solid appears to be the most familiar dosage form in terms of oral administration.[13]Mini-tablets are a solid formulation with several benefits greater stability (physical, chemical, and microbiological), and dose precision.[14]All of the components contained in the capsules are represented by mini tablets. Every single mini tablet within the capsule has an influence on how well it works as a therapeutic aid.[15]Tablets that have a diameter of 2-3 mm or less are known as mini-tablets. Hard gelatin capsules can be filled with these mini-tablets.[16]They are known as the innovative dosage forms.[17]The idea behind this technology is based on partitioning the amount into multiple subunits, each of them containing the medicine.[18]Mini-tablets, a novel tablet design approach that holds promise for well-defined populations, present enhanced, adjustable swallowing and offer different mixtures of active substances, which may be disease- specific.[19]The interaction between the API and excipient has been addressed by the development of innovations including mini-tablets, dry-coated tablets, bi-layered tablets, and pellet systems with numerous units.[20] Hydrophobic matrix tablets and mini-tablets might be made with the use of a less complicated industrial technique like direct compression.[21]These drugs are used as multi-unit drug delivery system:Ibuprofen,[22]Ranitidine,[23]KetorolacTromethamin,[24]Telmisartan,[25]levodopa,[26]Piretanide & Atenolol,[27]Terbutaline Sulphate,[28]Ketoprofen.[29]

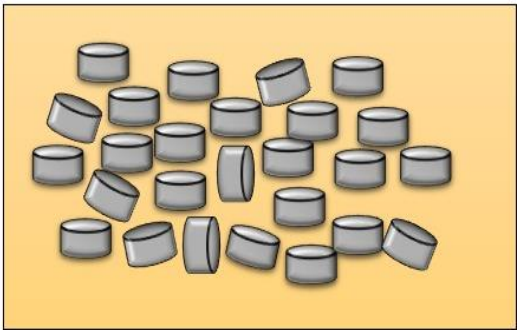

Fig.2: Mini Tablets

ADVANTAGES OF MINI TABLETS

- There is less variation between and within subjects with smaller tablets.
- The chance of dose dumping is lower for them.
- Compared to pellets, mini tablets are easier to make since they have uniform size, weight, and a smooth, consistent surface.
- They are able to be continuously and reliably produced.
- Due their outstanding size consistency, regular shape, and smooth surface, mini tablets make appropriate substrates for coating.
- They provide high drug loading, a variety of patterns for release rates, and the ability to fine-tune these release rates.[30]

BENEFITS OF THE TECHNOLOGY OF TABLETS IN A CAPSULE:

- It reduces treatment failure rates, case-fatality ratios, and treatment failure rates significantly.
- Regulated and multi-phase release is what some medications with regulated and multi-phase release are but they are available as a single formula or a number of them in combination and they are available as prescription as well as over-the-counter drugs.
- There is a possibility to have patient convenience and also good results for less money and also adherence to treatment.
- It is conceivable for conflicting APIs to be delivered.
- Late, pulsed, or sustained release characteristics are possible to attain.
- The GI tract can be divided into two sections for the purpose of drug distribution.
- It requires less money to produce new medicines for long-term therapy, because of its longer colonic residence period and more consistent stomach emptying.
- This model furnishes excellent calibration of release rates, various release signals, and a large drug load. High concentrations near the local tissues are avoided since the drug is widely spread throughout the gastrointestinal tract, which reduces the possibility of dose dumping and the degree of both inter- and intra-subject variability. A diverse number of therapeutic advantages can be brought about.[31]

TYPES OF MINI TABLETS

The following categories classify patient needs and manufacturing techniques based on the target site:

A. PH responsive MTs
B. Gastro retentive MTs
C. Pediatric MTs
D. Bio-adhesive MTs
E. Oral disintegrating MTs
F. Biphasic MTs

A. PH responsive mini tablets

Human GI tract pH levels fluctuate greatly. If the absorption of drugs is higher in one place than another, pH-responsive release polymers such as Eudragits can be coated to obtain appropriate pH responsive drug release. Most often the granules are coated before being put into capsules to full fill the necessary release at adequate pH.[32]

B. Gastro retentive Mini tablets

The gastroretentive mini-tablets retains for a longer time the drug dosage into the stomach and the gas generating agents must be present for the tablet to float on a gastric fluid filled with gas. These agents react with food to produce carbon dioxide which becomes entrapped by the swollen hydrocolloid thereby causing the tablet stay in the stomach. The raw materials should be selected taking into consideration a higher polarity.[33]

C. Pediatric Mini tablets

For many years, the advancement of paediatric medicine has been mainly overlooked [34]. A large number of paediatric medications are poorly tasting. The youngster refuses to take the prescription if it tastes harsh, metallic, or sour.

Film coating is a generic solution to this issue for solid oral dosage forms. On the other hand, flavouring chemicals are frequently required to cover up the unpleasant taste of a medication that is meant to be administered orally. Melt extrusion is another method that may be used to hide taste. In addition to the challenge of dose-specific oral medicine, young patients also face the challenge of bigger tablets or capsules being difficult for them to swallow.[35]

D. Bio-adhesive Mini tablets

Other being an important reproductive organ, the vagina can also be a possible route of drug administration.[36] Compared to semi-solid systems, solid formulations have the advantages of long-term stability and great dosage precision. However, due to gravity and the vagina's natural cleaning ability, traditional vaginal pills frequently dissolve slowly in the vagina and are quickly removed. Investigating bioadhesive mini-tablets for vaginal medication administration is in trend as current investigation. Tablets having a diameter of 1-3 mm are called mini-tablets. Minitablets showed its potential use in photodynamic treatment(PDT) for topical malignancies, including cervical carcinoma. Direct compression method is one best method for the preparation of mini tablets. The goal of the bioadhesive qualities was to increase how long the mini-tablets stayed on the vaginal mucosa.[37]

E. Oral disintegrating Mini tablets

Contrary to other solid oral dosage forms, the latest type of dosage dissolves immediately in the mouth after administration in 1-3 minutes without requiring mastication.The tablets have displayed diverse attributes when breaking down in the mouth without needing more water. Soon after the tablet degraded, it was transformed into some spongy paste or suspending liquid with high patient acceptability index (PAI). Upon analysis they conclude that MEl-Say is a paediatric drug expert “As discovered by the researchers”.

F. Biphasic mini tablets

A mini biphasic tablet comprises 2 sections: one that releases quickly and the other that releases gradually. As soon as the medication is administered, the first component releases it, and the second part releases it gradually and under regulated circumstances.When repeated dosage can be decreased, this kind of medication may be advantageous for hypertension treatments. To treat various ailments, multiple medications can be combined into mini pills and put inside of the same capsules.Mini tablets and the instant release portion can be compressed here. This instant release component fills in the empty areas found between the mini-tablets[38.]

MANUFACTURING METHODS FOR MINI TABLETS

The following techniques will be used in different ways to manufacture the mini tablets:

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

1. **Direct compression technique**

Excipients and active pharmaceutical components are combined into a powder combination, which is then compressed straight into mini-tablets form using the direct compression method. The degree to which the supplementary material is directly pressed determines its

hardness.The powdered mixture enters in a die, where it is compressed under high pressure by the tablet press's top and bottom punches to create mini-tablets. This procedure involves compressing a powder combination that includes lubricants, excipients, and active medicinal components.[39]

2. Dry granulation technique

The method of granulation performed without the use of liquids is simpler than that of wet granulation, and it does not require drying, among other benefits.In terms of manufacturing simplicity, dry granulation is positioned between wet granulation and direct compression in the past, milling was done after slugging to achieve dry granulation. In contemporary dry granulation, a loose powder is compressed into ribbons by roll compaction, which produces granules when further milled. Under the recently implemented manufacturing classification system.[40]

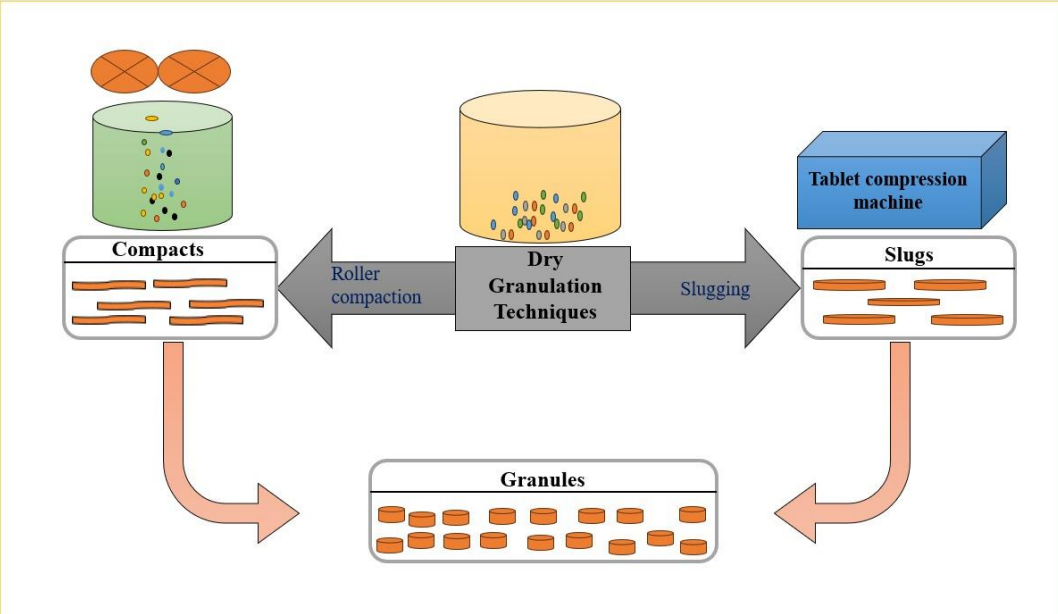

Fig. 3: Dry Granulation Technique

3. Wet granulation technique

Wet granulation, the most used method, produces granules by massing the mixture of excipients and API which are moist in granulation liquid, either with or without binder. The steps of the traditional wet granulation method.Wet granulation has seen a number of scientific and technical advancements.This innovation states that after preparing the binder solution, the addition of the dry powder excipientswhile the mixture was being mixed in a granulator.[41]

4. Melt-extrusion technique

Compared to previous pharmaceutical technologies, HME offers various additional advantages, including the removal of organic solvents and a reduction in the number of production steps.By generating various medications more soluble, HME has been used to create solid dispersions that boost the bioavailability of specific medications.[42]

Mini-tablets are placed within HPMC or hard gelatine capsules.
These are typically placed into hard gelatine capsules and then given out since the mini tablets are difficult to handle.[43]

Minitab lets formulation types for delivery
1. Direct Compressed mini tablets
2. Encapsulated mini tablet
3. Manufactured as a mini tablet for a biphasic drug delivery technique

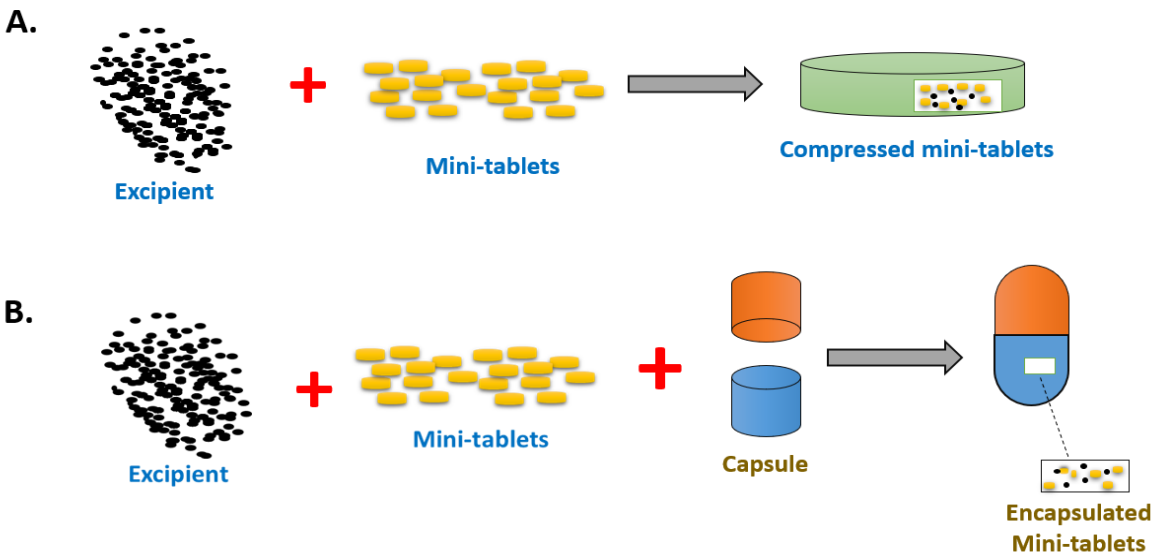

Fig. 4: Mini-tablets into different dosage A). Compressed mini-tabletB). Encapsulated Mini-tablets

1.Direct Compressed mini tablets

Oral tablets are the most common dosage form because they are small, simple to make, and convenient for self-administration.Another type of solid oral formulation that provides comparable therapeutic advantages is mini tablets.The direct compression approach makes it very easy to create mini tablets. These mini pills can be squashed into larger tablets, put into hard gelatine capsules, or given with a dose dispenser for personalized dosage.[44]

2. Encapsulated mini tablets

The reason why mini-tablets are so effective at boosting therapeutic efficacy, patient compliance with medication regimes, and dose administration is because they are coated capsules within which other coatings are enclosed rapidly-releasing micro tablets like rapid-release micro-tablets (RMTs), capsules containing mini-tablets capable of releasing drug in a sustained manner such as sustained-release mini-tablets (SMTs), capsules with mini-tablets designed to burst into blood stream due to pulsatile action as in pulsatile mini-tablets (PMTs) and capsules containing mini-tablets inside them releasing drug in a sustained manner after a predetermined lag like delayed-release sustained-release mini-tablets (DSMTs).[45]

Capsule size	Number of 2mm Mini-Tablets filled in to capsules
000	105
00	75
0	50
1	30
2	20
3	15
4	10

Table 1: Total Number of Mini Tablets Filled based on capsule size[46]

3. **Manufactured as a mini tablet for a biphasic drug delivery technique**

Biphasic delivery systems are designed to distribute a medication at two different rates or during two different durations. Additionally, there are swift/leisurely and leisurely/swift. A quick/slow release method releases the medication in an early burst followed by a steady rate of release (ideally) over a specific period of time, while a slow/leisure release technique releases the drug in reverse. Biphasic release scheduling is mostly utilized when the greatest amount of rest must be obtained quickly. Additionally, it is followed by a continuous release phase to avoid constant guidance. It supplied part of the entire medication dosage together with the excipient dust that seals the invalid seats in between the mini-tablets.This system can cause a rapid increase in plasmatic attentions for approximately the desired duration to sharply exercise the therapeutic outcome, followed by an extended-release phase in instruction to avoid repeat dosages.[47]

Tooling used in compression of mini tablets:

Mini-tablets can be produced using compaction simulators or traditional tablet presses. A primary distinction between the process of tableting standard-sized tablets and mini-tablets is the tooling system. Conventional tablets typically employ a single-tip punch set with different geometries, such as flat, concave, or round. More specialized tooling techniques are needed for the industrial manufacture of mini-tablets. Hershberg held a patent for the first mini-tableting tooling system. Since then, other companies have started offering bespoke tooling systems with a wide range of tips and geometries. Mini-tablets with the desired quality qualities are what are being produced during the production process. The yield during manufacture is obviously influenced by the quantity of tips used, since more tablets can be made with more tips. But as of yet, no research has been done on how the tooling system that is, the quantity of tips affects the qualities of mini-tablets.[48]

Sl/No	Generic Name	Brand Name
1	Pancrelipase	Ultresa
2	Galantamine HBr ER	Razadyne ER
3	Fenofibric Acid Capsules	Trilipix

Table 2: list of Encapsulated mini tablets available in market.[49]

EVALUTION

- **Pre formulation studies for Mini Tablets:**
  Pharmaceutical dosage forms that are stable are developed via the use of physical and analytical characteristics described in pre-formulation investigations.

- **Drug-excipient compatibility studies:**
  Drug-excipient compatibility studies is used check the compatibility of the drug with the various excipient. In this method the drug and excipient mixture in a ratio of 1:1 or 1:0.5 is filled in the glass vial (open and closed). The vials are kept in stability chamber at accelerated stability condition as per the ICH guidelines. The samples are taken different interval and performed the FTIR and DSC of the sample to check any change in the peaks of the drug.
  FTIR studies:
  Using a Fourier Tran form infrared (FTIR) spectrophotometer.IR spectra for pure drug and sample were recorded in a Fourier transform infrared (FTIR) spectrophotometer with Kbr.
  DSC studies:
  The pure drug and the sample were the subjects of a differential scanning calorimetry (DSC) investigation. Every sample utilized for analysis was placed in sealed, perforated aluminum pans. Using indium as the benchmark, temperature calibration was carried out. We utilized a reference pan, which was empty and sealed similarly to how the samples were sealed.With a maximum rate of 100°C/min, all samples were run between 50 and 3000°C .[50]

- **Tapped density**
  A mechanical tapper equipment is placed with a graduated cylinder carrying a specified mass of granules, and the tapper is operated for a specific number of taps until the powder bed volume reaches a minimum volume. This method determines the tapped density. The tapped density may be calculated using this minimal volume and the weight of the medication in the cylinder.[51]
- **Measurement of the compressibility of powders**
  The interaction might have an impact on the characteristics and flow of particles in a batch. Density of bulk and tapped could offer insight into powder flow as well as interactions among particles. This paper compares using Compressibility Index (Carr's Index) and Hausner's Ratio; two highly indicative traditional methods which are commonly employed for this purpose.
  Computation of the Compressibility Index and Hausner's Ratio can be done with Compressibility index:$100\ (V_0\text{-}V_F)/V_0$ Hausner's Ratio: $V_0/\ V_F$.[52]
- **Evaluation parameter for compressed Mini tablets:**
  Weight variation test
  A batch of twenty random tablets is picked and each tablet weighed separately. This helps to determine the mean mass. In the United States Pharmacopeia (USP) no tablet mass is to be more than 110% and no less than 90% of the average mass of tablets. A batch of twenty random tablets is picked and each tablet weighed separately. This helps to determine the mean mass. In the United States Pharmacopeia (USP) no tablet mass is to be more than 110% and no less than 90% of the average mass of tablets.[53]

Hardness test

A Pfizer hardness tester was used to measure the tablets' hardnes in kg/cm2.The weight of the material employed and the distance between the upper and lower punches at the moment of compression determine the tablet's hardness. The kind and amount of excipient utilized in the formulation affect the hardness as well.If the final tablet was too soft, it might not tolerate handling during packing and transit, and if it was too hard, it might not break down in the allotted amount of time. As a result, it was imperative to examine the tablet's hardness.[54]

Thickness, length and width measurement

The dimension of the tablet was controlled by the total quantity of filling which could go into the mold and the quantity of pressure that was applied during compression.Using a vernier calliper, the thickness, length, and width of each of the twenty tablets were measured. We estimated the standard deviation and mean.[55]

***In-vitro* drug release**

Mini-tablets were evaluated for their capacity to deliver the intended controlled drug delivery in in-vitro drug release assays using simulated gastric and intestinal fluids. Since the usual stomach emptying duration is around two hours, drug release studies were conducted using USP dissolving test equipment I at desired rpm, 37±0.5°C, and pH 1.2 buffer (900 ml) (i.e., 0.1 N HCL) for two hours. and then in simulated intestinal fluid (i.e. Phosphate buffer pH 6.8) for up to 12 hrs or as per the specific requirement of the dosage form. The drug release then calculate using the HPLC or UV Spectrophotometer.[56]

- **Evaluation Tests for Encapsulated Mini-tablets**

Disintegration test for capsule

Hard gelatin capsules: A maximum of 30 minutes should pass for the disintegration process. The disintegration period of soft gelatin capsules should not exceed 60 minutes. Stomach capsule: Capsules should dissolve in 30 minutes in an alkaline medium and should not dissolve in acidic media for two hours**.**

Weight Variation Test

This test involves the random selection of 20 undamaged capsules from each batch, each individual weight being recorded, and the average weight being computed. Per USP guidelines, no individual capsule should weigh less than 90% or more than 110% of the average weight.

In vitro dissolution studies

In vitro drug release experiments are performed in USP type II dissolution test apparatus with an appropriate buffer solution at a given temperature and rpm for a predetermined amount of time. Each of these elements is dependent upon that specific formulation. From this, 10 ml of the sample are taken out and subjected to the proper wavelength analysis with a UV spectrophotometer[43].

Stability study

When the improved formulation was stored for three months at room temperature and under accelerated circumstances, no appreciable changes were seen in terms of appearance, hardness, friability, drug content, or in vitro drug release.[57]

Drug content estimation

In a pestle and mortar, 20 tablets which were selected at random had been broken up. The exact weight of the powder was then added to a beaker containing 100 ml of 0.1 N HCl. After 30 minutes of stirring the mixture, absorbance was detected with a UV visible spectrophotometer.[58]

Conclusion

When compared to single unit dose forms, mini-tablets have a number of benefits, including improved accuracy, practicality, affordability, innovative research, and focused drug delivery. The formulator was able to create a biphasic delivery system for medications that were identical or different by using a unique tablet in capsule delivery system. Although the shape of the mini-tablets can be changed to meet the study's objectives, the medicine was released at the desired pace and pattern. They improve patient compliance by mixing medications with various release kinetics and permitting pharmaceuticals to coexist. There is a great chance that treatment will be successful, particularly in the case of elderly and young patients.

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