MULTI UNIT DOSAGE FORMS

The goal of any drug delivery system is to deliver a therapeutic amount of drug to the specific site and then to maintain the desired drug concentration at that particular site. Usually conventional dosage forms result in wide range of fluctuations in drug concentration in the blood stream with consequent toxicity as a result of poor efficiency. These factors, such as 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. In oral controlled drug delivery systems, multiple unit dosage forms (MUDFs), like granules, pellets and mini-tablets 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. This review emphasizes the various advantages of mini-tablets, formulation possibilities, general evaluation tests, and brief insight to marketed drugs.

Keywords: Biphasic delivery systems, Compressed mini-tablets, Encapsulated coated systems, Granules, Mini-tablets, Pellets.

MINI-TABLETS

Mini-tablets (Figure 1) are flat or slightly curved tablets with a diameter ranging between 1.0-3.0 mm. They are usually filled into a capsule, occasionally compressed into larger tablets, or sometimes placed in sachets for easy administration.

Constituents of Mini-tablets

Different mini-tablets can be formulated and designed individually, incorporated into a capsule to release the
drug at different sites and at different rates. Different combinations of mini-tablets include immediate release, delayed release, and/or controlled release formulations. Also, combining different mini-tablets together, incompatible drugs can be administered.

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

Release profile

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.

Outlook

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.6

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.7

Advantages of Mini-Tablets

✓ They can be manufactured relatively easily.
✓ They offer flexibility during the formulation development.8
✓ They have excellent size uniformity, regular shape and a smooth surface, thereby acts as an excellent coating substrate.
✓ They are a great 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.
✓ They have less risk of dose dumping.
✓ They have less inter and intra- subject variability.
✓ They offer high degree of dispersion in the GI tract, thus minimizing the risks of high local drug concentrations.9
✓ They offer high drug loading, a wide range of release rate patterns, and also fine tuning of these release rates.

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 tableting procedures.10
✓ Unlike pellets, mini tablets does not require any solvents for its production, as a result problems with stability can be avoided.11

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.12

Figure 2: Encapsulated Pellets

Advantages of Mini Tablets over Granules

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.13

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.
Possibilities Of Formulating Mini-Tablet Dosage Forms (Figure 4):
1. Compressed mini-tablets
2. Encapsulated Coated mini-tablets
3. Compressed mini-tablets presented as a biphasic drug delivery system

Compressed mini-tablets

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. Mini-tablets can be used to produce a biphasic delivery system, by combining a fast release form with a slow release form of the drug. Biphasic release system is used when relief needs to be achieved quickly, and followed by a sustained phase to avoid repeated administration of the drug. Drugs suitable for this type of administration include non-steroidal anti-inflammatory drugs (NSAIDs), antihypertensive, antihistaminic and anti-allergic agents.

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 mini-tablets, multiplied pulsatile DDS, site-specific DDS, slow/quick DDS, quick/slow DDS, and zero-order DDS could be obtained. Rapid-release Mini-Tablets allows the development of rapid acting encapsulated dosage forms for fast action. However, several mini-tablets can be placed into each capsule, which later disintegrates and releases the mini-tablets. As different mini-tablets can be placed into each capsule, tablets with various combinations of drugs, dosage and drug release profiles can be obtained. This as a result, improves patient compliance.

Tablet coating principles

Coating of tablets, which is an additional step in the manufacturing process, increases the overall cost of the product. Therefore, the decision to coat a tablet is usually based on one or more of the following requirements:
- To mask the taste, odor or sometimes the color of the drug.
- In order to provide physical and chemical protection to the drug.
- To control the release rate of the drug or to provide sequential drug release from the formulation.
To protect the drug from the gastric environment of the stomach by applying an acid-resistant enteric coating.

To improve the overall elegance of the formulation by using special colors and contrasting printing.

**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 mini-tablet 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.18

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.19

**Composition of enteric coatings**

- 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

**Formulation of mini-tablet-in-capsule systems:** The formulation process of mini-tablet-in-capsule systems can be divided into three important steps:

- The formulation/production of mini-tablets,
- Coating of these mini-tablets with appropriate coating polymer, and
- Filling of coated mini-tablets into hard gelatin or HPMC capsules (Mini-tablet-in-capsule systems).

**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.20 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 system, 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...
the mini-tablets provides a sustained drug release. Outer 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.21

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

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancrelipsase</td>
<td>Ultesa</td>
</tr>
<tr>
<td>Zafirlukast</td>
<td>Accolate</td>
</tr>
<tr>
<td>Donepezil Hydrochloride</td>
<td>Aricept</td>
</tr>
<tr>
<td>Galantamine HBr ER</td>
<td>Razadyne ER</td>
</tr>
<tr>
<td>Fenofibric Acid Capsules</td>
<td>Trilipix</td>
</tr>
<tr>
<td>Levonorgestrel and Ethinyl Estradiol</td>
<td>Alesse</td>
</tr>
<tr>
<td>Prasugrel Tablets</td>
<td>Effient</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Zyprexia, Zyprex 2yzis</td>
</tr>
<tr>
<td>Sumatriptan and Naproxen Sodium Tablets</td>
<td>Treximet</td>
</tr>
<tr>
<td>Warfarin Sodium</td>
<td>Coumadin</td>
</tr>
<tr>
<td>Vorapaxar Tablets</td>
<td>Zontivity</td>
</tr>
<tr>
<td>Hydromorphone Hydrochloride</td>
<td>Exalga</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Brand name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancrelipsase</td>
<td>Ultesa</td>
</tr>
<tr>
<td>Galantamine HBr ER</td>
<td>Razadyne ER</td>
</tr>
<tr>
<td>Fenofibric Acid Capsules</td>
<td>Trilipix</td>
</tr>
</tbody>
</table>

METHODOLOGY

Preformulation Studies

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

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.

Drug - Excipient Compatibility Studies

Compatibility studies are performed in order to study the possible interactions of the active drug with excipients/inactive ingredients.

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.22

Analytical Method Development

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

a. Determination of maximum absorption wave length of the drug

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

b. 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

Evaluation of the blend

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

a. Bulk Density23,24

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:

\[ \text{Bulk density} = \frac{\text{Mass of the blend}}{\text{Bulk Volume of the blend}}. \]

b. Tapped Density\textsuperscript{23,24}

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:

\[ \text{Tapped density} = \frac{\text{Mass of blend}}{\text{Tapped Volume of the blend}}. \]

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.\textsuperscript{23,24}

\[ \text{Carr Index} = \frac{(\text{Tapped density} - \text{Bulk density})}{\text{Tapped density}} \times 100 \]

Where,

- \( \text{Carr Index} \)
- \( \text{Tapped density} \)
- \( \text{Bulk density} \)

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.\textsuperscript{23,24}

\[ \text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \]

Evaluation Tests for Coated Mini-tablets

a. Weight variation

b. Hardness

c. Thickness

d. Diameter

Weight Variation Test

For this test, 20 tablets are selected randomly 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.\textsuperscript{25}

Hardness

The hardness of the tablet is determined using Pfizer hardness tester and expressed in kg/cm\textsuperscript{2}.\textsuperscript{26}

Thickness

Thickness of the tablet is measured using a digital calipers and screw gauge. It is expressed in terms of mm.\textsuperscript{27}

Friability (F)\textsuperscript{28}

Friability test is conducted using Roche friabilator. For this, usually 20 mini-tablets are selected randomly from each batch and their initial weight (\( W_0 \)) is noted. These tablets are then transferred to the drum of friabilator and rotated at appropriate rpm for definite time period. After which the mini-tablets are collected and weighed again (W). The percentage friability is then calculated by the following formula:

\[ F = \left(1 - \frac{W}{W_0}\right) \times 100 \]

Evaluation Tests for Encapsulated Mini-tablets

a. Weight Variation Test

b. In-Vitro Drug Release

a. Weight Variation Test

For the weight variation test, 20 intact capsules are selected randomly from each lot and their individual weight is noted. From this, the average weight is calculated. According to USP, none of the individual capsule should weigh less than 90\% and more than 110\% of the average weight.\textsuperscript{29}

b. 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 particular 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.\textsuperscript{30}

Stability Studies\textsuperscript{31}

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 help 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

CONCLUSION

From this review, it can be concluded that pharmaceutical mini-tablets offer several advantages when compared to single unit dosage forms and are also good substitutes for granules and pellets. They have well defined size, shape, surface, low degree of porosity and high mechanical strength. By combining different mini-tablets, incompatible drugs can be administered and concurrent diseases can be treated effectively. Also, mini-tablets serve as a potential new formulation for pediatric use, as they meet all the requirements of pediatric drug delivery. Ultimately, mini-tablets improves overall therapeutic outcome, patient compliance and convenience. As they have significant advantages, they can be formulated for most of the available and suitable drugs. 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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