PHARMACEUTICAL MINI TABLETS, ITS ADVANTAGES AND DIFFERENT ENTERIC COATING PROCESSES

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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. 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.

INTRODUCTION

MULTI UNIT DOSAGE FORMS

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration. The most convenient and commonly employed route of drug delivery has historically been by oral ingestion. Usually conventional dosage form produce wide ranging fluctuation in drug concentration in the blood stream and tissues with consequent undesirable toxicity and poor efficiency. This factor such as repetitive dosing and unpredictable absorption led to the
concept of controlled drug delivery systems. The goal in designing sustained or controlled
delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the
drug by localization at the site of action, reducing the dose required or providing uniform
drug delivery.[1] Oral controlled release drug delivery systems can be classified in two broad
groups: single unit dosage forms (SUDFs), such as tablets or capsules, and multiple unit
dosage forms (MUDFs), such as granules, pellets or mini-tablets. The concept of MUDFs
was initially introduced in the early 1950s. The production of MUDFs is a common strategy
to control the release of a drug, as shown by the reproducibility of the release profiles when
compared to the ones obtained with SUDFs. These MUDFs is characterized by the fact that
the dose is administered as a number of subunits, each one containing the drug. The dose is
then the sum of the quantity of the drug in each subunit and the functionality of the entire
dose is directly correlated to the functionality of the individual subunits.[2] The concept of
MUDFs is beneficial when the selected agents posses differing mechanism of action that
provide additive or synergistic efficacy, reducing the required doses of individual agents as
compared with monotherapy and potentially limiting side effects. MUDFs may seem costlier
than SUDFs in the short term; but causes significant savings, lower treatment failure rate,
lower case-fatality ratios, reduction in development of resistance, higher colonic residence
time, more predictable gastric emptying and consequently less money needed for the
development of new products in long-term therapy.

**Chronotherapeutic**

**Right drugs at right time can heal effectively**

Chronotherapy coordinates drug delivery with human biological rhythms and holds huge
promise in areas of pain management and treatment of asthma, heart disease and cancer. The
coordination of medical treatment and drug delivery with such biological clocks and rhythms
is termed chronotherapy. The goal of chronotherapeutic is to synchronize the timing of
treatment with the intrinsic timing of illness. Theoretically, optimum therapy is more likely to
result when the right amount of drug is delivered to the correct target organ at the most
appropriate time. In contrast, many side effects can be minimized if a drug is not given when
it is not needed. Unlike homeostatic formulations, which provide relatively constant plasma
drug levels over 24 hrs, chronotherapeutic formulations may use various release mechanisms.
e.g., time-delay coatings (Covera-HSTM), osmotic pump mechanisms (COER-24TM), and
matrix systems (GeminexTM) that provide for varying levels throughout the day. A major
objective of chronotherapy in the treatment of several diseases is to deliver the drug in higher
concentrations during the time of greatest need according to the circadian onset of the disease or syndrome.\textsuperscript{[3]} The chronotherapy of a medication may be accomplished by the judicious timing of conventionally formulated tablets and capsules. In most cases, however, special drug delivery technology must be relied upon to synchronize drug concentrations to rhythms in disease activity. Chronotherapeutics is the synchronization of medication levels in time with reference to need, taking into account biologic rhythms in the pathophysiology of medical conditions, and/or rhytmodependencies in patient’s tolerance for given chemical interventions. It is based on importance of biologic rhythms in the pathophysiology of medical conditions and uses the timing of medication to provide maximal efficacy and minimal toxicity. For chronotherapy treatment we require modified release drug delivery system like formulation of coated mini-tablets-in capsule system and granules-mini-tablets-in-capsule systems.(Figure 1) Mini-tablets are tablets with a diameter equal to, or smaller than, 2–3mm. Like other MUDFs, several mini-tablets can be either filled into hard capsules or compacted into bigger tablets that, after disintegration, release these subunits as multiple dosage forms. Mini-tablets are good substitutes for granules and pellets because they can be manufactured relatively easily, and are amenable to coating in order to sustain drug release. 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 into oral controlled-release solid dosage forms.\textsuperscript{[4]}

**MINI-TABLETS**

Mini-tablets (Figure 1) are flat or slightly curved tablets with a diameter ranging between 1.0-3.0 mm.\textsuperscript{4} They are usually filled into a capsule, occasionally compressed into larger tablets, or sometimes placed in sachets for easy administration.

![Figure 1: Mini-tablets](image-url)

**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.\textsuperscript{[5]}

**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. 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.\textsuperscript{[6]}

**Advantages of mini-tablets**

- They can be manufactured relatively easily.
- They have excellent size uniformity, regular shape and smooth surface.
- They offer a substrate which is easy to coat with polymeric membranes for modified release purposes.
- They combine the advantages of MUDFs with the established manufacturing techniques in tableting and have fewer constraints compared to extrusion/Spheronization.
Mini-tablets also offer an alternative for pellets because of their relative ease of manufacturing and because dosage forms of equal dimensions and weight with smooth regular surface are produced in a reproducible and continuous way.

They offer high drug loading, a wide range of release rate designs, and fine tuning of these release rates.

They have less risk of dose dumping, less inter- and intra-subject variability, high degree of dispersion in the digestive tract thus minimizing the risks of high local drug concentrations.

Possibilities for formulating the mini-tablets dosage forms

1. Compressed mini-tablets systems
2. Encapsulated Coated mini-tablets systems
3. Compressed mini-tablets systems are presented as a biphasic delivery system

There has been an increasing interest in the development of MUDFs incorporated into tablets instead of 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 attainable strength, mini-tablets can maintain their structure and shape in a more reproducible way than usual pellets or granules, once they have been compressed into a tablet system. It can be hypothesized that when shape irregularity and surface roughness of the mini-particles (pellets and granules) increases, the compression behavior changes towards a more complex process that, besides deformation and densification, includes also fragmentation and attrition of the subunits. This concept can be used to produce a biphasic delivery system combining a fast release together with the slow release period of the drug, provided that the excipients powder that fills the void spaces between the mini-tablets incorporates a part of the total drug dose. Different composition (hydrophilic or hydrophobic polymers) and number (10 or 21) of mini-tablets can be used to obtain different drug release rates. Biphasic release system is used primarily when maximum relief needs to be achieved quickly, and it is followed by a sustained release phase to avoid repeated administration. Suitable candidate drugs for this type of administration include non-steroidal anti-inflammatory drugs (NSAIDs) antihypertensive, antihistaminic, and anti-allergic agents. The pharmacokinetic advantage relies on the fact that drug release from fast releasing component leads to a sudden rise in the blood. However, the blood level is maintained at steady state as the drug is released from the sustaining mini-tablets. Many approaches have been trialed, and matrix mini-tablets have
been developed based on hydroxy propyl methylcellulose, ethyl cellulose, poly vinyl
acetate/polyvinylpyrrolidone, calcium alginate, HPMC/guar gum, poly vinyl acetate,
cellulose acetate propionate, xanthan gum, karaya gum and starch/microcrystalline wax.

Figure 2: Compressed Mini-tablets
Encapsulated coated mini-tablets systems
Coated oral sustained-release forms of drugs are widely used to improve drug tolerance or to
yield a dosing regimen that is easier to manage for patients. However, little published
information is available on sustained-release systems using coated mini-tablets.

Figure 3: Encapsulated Pellets

In particular, it has proven challenging to develop one dosage form with sustained and
immediate-release properties. A multifunctional and multiple unit system, which contains
versatile mini-tablets in a hard gelatin or HPMC capsule, can be developed by preparing
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 lag times of release. Based on the combinations of mini-tablets, multiplied pulsatile
drug delivery system (DDS), site-specific DDS, slow/quick DDS, quick/slow DDS, and zero-
order DDS could be obtained. Inclusion of RMTs permits the development of rapid-acting
encapsulated dosage forms with optimal pharmacokinetic profiles for fast action. The size of the tablet can be reduced such that it could be enclosed in a capsule, then deploy tablets with different release properties within the one capsule. Several mini-tablets can be placed into each HPMC capsule, which later disintegrates and releases these subunits. Because several mini-tablets can be placed into each capsule, tablets with different combination of drugs, dose and drug-release profiles can be included. Hence, patient compliance can be improved.[8]

**Compressed mini-tablets systems are presented as a biphasic delivery system:**

Biphasic delivery systems are designed to release a drug at two different rates or in two different periods of time: they are either quick/slow or slow/quick. A quick/slow release system provides an initial burst of drug release followed by a constant rate (ideally) of release over a defined period of time and in slow/quick release system provides release vice versa.[39] Biphasic release system is used primarily when maximum relief needs to be achieved quickly, and it is followed by a sustained release phase to avoid repeated administration. Suitable candidate drugs for this type of administration include non-steroidal anti-inflammatory drugs (NSAIDs) antihypertensive, antihistaminic, and anti-allergic agents. Generally, conventional controlled dosage forms delay the release of therapeutic systemic levels and do not provide a rapid onset of action. While immediate release granules give fast release to provide rapid onset of action, but fails to provide longer duration of action. A relatively constant plasma level of a drug is often preferred to maintain the drug concentration within the therapeutic window. However, it is difficult to achieve, especially for once-daily dosage forms, partly because the environment for drug diffusion and/or absorption varies along the gastrointestinal (GI) tract. On the basis of these considerations, we have proposed a new oral delivery device, in the form of a double-component tablet and granules, in which the one portion is formulated to obtain a prompt release of the drug, with the aim of reaching a high serum concentration in a short period of time. The second portion is a sustain release matrix, which is designed to maintain an effective plasma level for a prolonged period of time. This concept can be used to produce a biphasic delivery system combining a fast release together with the slow release period of the drug, provided that the excipients powder that fills The void spaces between the mini-tablets incorporate a part of the total drug dose. This system can produce a rapid rise in the plasmatic concentrations for some drugs (such as analgesic, anti-inflammatory, anti hypertensive and antihistaminic agents) that are requested to promptly exercise the therapeutic effect, followed by an extended release phase in order to avoid repeated administrations.[9] Compressed mini-tablets systems are
presented as a biphasic delivery system. The outer layer that fills the void spaces between the mini-tablets was formulated to release the drug in a very short time (fast release), while the mini-tablets provided a sustained release. Fast releasing component comprises superdisintegrant crospovidone, while mini-tablet was formulated using different concentration of HPMC and Ethyl cellulose. The In-vitro performance of these systems showed the desired biphasic behavior.

**Tablet coating principles**
The application of coating to tablets, which is an additional step in the manufacturing process, increases the cost of the product; therefore, the decision to coat a tablet is usually based on one or more of the following objectives:

1. To mask the taste, odor or color of the drug.
2. To provide physical and chemical protection for the drug.
3. To control the release of the drug from the tablet.
4. To protect the drug from the gastric environment of the stomach with an acid-resistant enteric coating.
5. To incorporate another drug or formula adjuvant in the coating to avoid chemical incompatibilities or to provide sequential drug release.
6. To improve the pharmaceutical elegance by use of special colors and contrasting printing.

**Tablet coating processes**
In most cases, the coating process is the last critical step in the tablet production cycle. The successful application of the coating solution formula to a tablet provides the visual characteristics to the product; thus the quality of the product may be judged on this final production step. The type of process chosen depends on the type of coating that is to be applied the durability (toughness) of the tablet core, and the economics of the process.\(^{[10]}\)

Three main types are used in the pharmaceutical industry today:

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

We aimed to reduce the size of the tablet such that it could be enclosed in a capsule, and then deploy tablets with different release properties within the one EMT, which to the best of our
knowledge has not been achieved previously. Our EMT system comprises immediate-release mini-tablets (IRMT) and sustained release mini-tablets (SRMT) in a capsule made from HPMC, a water-soluble polymer. Several MT can be placed into each HPMC capsule, which later disintegrates and releases these subunits. Because several MT can be placed into each capsule, tablets with different content, dose and release characteristics can be included. Inclusion of IRMT permits the development of rapid acting EMT dosage forms with optimal pharmacokinetic profiles for fast action. EMT systems can be designed to yield various sustained drug-release profiles by combining different types or quantities of MT, and can include combinations of different drugs, thereby improving patient compliance. This concept of drug release may be modulated at the core level by using different release retardant polymers and further modified by coating the mini-tabs similar to multiparticulate. Mini-tablets are coated in fluid bed process and in modified coating pans (to handle small sizes of the mini-tablets).

**Enteric coating** is a barrier applied to oral medication that controls the location in the digestive system where it is absorbed. Most enteric coatings work by presenting a surface that is stable at the highly acidic pH found in the stomach, but breaks down rapidly at a less acidic (relatively more basic) pH. For example, they will not dissolve in the acidic juices of the stomach (pH ~3), but they will in the alkaline (pH 7-9) environment present in the small intestine. Materials used for enteric coatings include fatty acids, waxes, shellac, plastics, and plant fibres. Drugs that have an irritant effect on the stomach, such as aspirin, can be coated with a substance that will dissolve only in the small intestine. Likewise, certain groups of azoles (esomeprazole, omeprazole, pan and all grouped azoles) are acid-activated. For such types of drugs, enteric coating added to the formulation tends to avoid activation in the mouth and oesophagus. Recently, some companies have begun to utilize enteric coatings on fish oil (omega-3 fatty acids) supplements. The coating prevents the fish oil capsules from being digested in the stomach, which has been known to cause a fishy reflux (fish burps). Sometimes the abbreviation "EC" is added beside the name of the drug to indicate that it has an enteric coating.
Parameters for fluid-bed coating

Table 1: List of various parameters of fluid-bed coating

<table>
<thead>
<tr>
<th>Process parameters</th>
<th>Seal-coat</th>
<th>Enteric coat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablet charge (kg)</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Fluidizing air volume (m³/h)</td>
<td>98 – 105</td>
<td>98 – 110</td>
</tr>
<tr>
<td>Inlet air temperature (°C)</td>
<td>64 – 67</td>
<td>51 – 53</td>
</tr>
<tr>
<td>Exhaust air temperature (°C)</td>
<td>45 – 48</td>
<td>32 – 36</td>
</tr>
<tr>
<td>Atomizing air pressure (bar)</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Spray rate (g/min)</td>
<td>5 – 6</td>
<td>7 – 10</td>
</tr>
<tr>
<td>Process time (min)</td>
<td>53</td>
<td>136</td>
</tr>
<tr>
<td>Total weight gain (%)</td>
<td>5</td>
<td>60</td>
</tr>
</tbody>
</table>

Parameters for perforated pan coating

Table 2: List of various parameters for perforated pan coating

<table>
<thead>
<tr>
<th>Process parameters</th>
<th>Seal-coat</th>
<th>Enteric coat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablet charge (kg)</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Air volume (m³/h)</td>
<td>250</td>
<td>250</td>
</tr>
<tr>
<td>Inlet air temperature (°C)</td>
<td>65</td>
<td>40 – 45</td>
</tr>
<tr>
<td>Exhaust air temperature (°C)</td>
<td>48 – 58</td>
<td>33 – 45</td>
</tr>
<tr>
<td>Product temperature (°C)</td>
<td>47 – 57</td>
<td>29 – 33</td>
</tr>
<tr>
<td>Atomizing air pressure (bar)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Spray rate (g/min)</td>
<td>6 – 11</td>
<td>10 – 11</td>
</tr>
<tr>
<td>Process time (min)</td>
<td>30</td>
<td>114</td>
</tr>
<tr>
<td>Total weight gain (%)</td>
<td>5</td>
<td>60</td>
</tr>
</tbody>
</table>

Composition of enteric coatings

- methyl acrylate-methacrylic acid copolymers.
- cellulose acetate succinate.
- hydroxy propyl methyl cellulose phthalate.
- hydroxy propyl methyl cellulose acetate succinate (hypromellose acetate succinate).
polyvinyl acetate phthalate (PVAP).
- methyl methacrylate-methacrylic acid copolymers.
- Sodium alginate and stearic acid.

Formulation of mini-tablet-in-capsule systems

The formulation process of mini tablet-in-capsule systems can be divided into two steps:

- The formulation/production of mini-tablets and
- Filling of these mini-tablets into hard gelatin or HPMC capsules.
- Filling of granules-mini-tablets-in-capsule systems.

A capsule is a solid dosage form in which the active ingredients and diluents are contained in a two-piece hard shell, usually made of gelatin. The success achieved by the hard gelatin capsules, popularly known as HGC, is well known and is reflected by the fact that hard gelatin capsules shells have been used in the pharmaceutical field for more than 100 years and continue to grow in acceptance as the preferred oral dosage form.\[^{12}\]

![Figure 4: Punch fitting several mini-punches](image)

Advantages of Capsules

- Ease of use due to the fact that it is smooth, slippery and easy to swallow.
- Suitable for substances having bitter taste and unpleasant odor.
- As produced in large quantities it is economic, attractive and available in wide range of colors.
- Minimum excipients required.
- Little pressure required to compact the material.
- Unit dosage form.
- Easy to store and transport.
Disadvantages of Capsules

- Not suitable for highly soluble substances like potassium chloride, potassium bromide, ammonium chloride, etc.
- Not suitable for highly efflorescent or deliquescent materials.
- Special conditions are required for storage.

TYPES OF CAPSULES

1. Hard gelatin capsules
2. Soft gelatin capsules.

1. Hard gelatin capsules

These sizes are designed by in numbers.

Table 3: Capsules sizes and their fill weights

<table>
<thead>
<tr>
<th>S.No</th>
<th>Size of capsules</th>
<th>Volume in ml</th>
<th>Fill weight in mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>000</td>
<td>1.37</td>
<td>615-1370</td>
</tr>
<tr>
<td>2</td>
<td>00</td>
<td>0.95</td>
<td>430-950</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>0.68</td>
<td>305-680</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>0.50</td>
<td>225-500</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>0.37</td>
<td>165-370</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>0.30</td>
<td>135-300</td>
</tr>
<tr>
<td>7</td>
<td>4</td>
<td>0.21</td>
<td>95-210</td>
</tr>
<tr>
<td>8</td>
<td>5</td>
<td>0.13</td>
<td>60-130</td>
</tr>
</tbody>
</table>

2. Soft gelatin capsules

These are classified depending upon the sizes and capacities.

The number represents capacities in minims

1) Round-1,2,3,4,5,6,7,8,9,28,40,40T,80T and 90T.
2) Oval-1,2,3,4,5,6,7,5,10,12,16,20,40,60,80,85 and 110.
3) Obolong-3,4,5,6,8,9,5,11,14,16,20,90 and 360.
4) Tube-5,6,8,17,5,30A,30B,35,45,55,65,90,160,250,320 and 480.
5) Misc-6, 17, 30, 35, 60 and 80.

Capsules Standards and limits

a) Description

It should comply with specifications of product.
b) Content of active ingredients
Limit: 90 to 110% of label claim or as per In house limit.

c) Uniformity of weight
Table 4: Content uniformity limits

<table>
<thead>
<tr>
<th>Average weight of capsules content</th>
<th>Percentage deviations allowed</th>
</tr>
</thead>
<tbody>
<tr>
<td>less than 300mg</td>
<td>10%</td>
</tr>
<tr>
<td>300mg or more</td>
<td>7.5%</td>
</tr>
</tbody>
</table>

d) Disintegration test
a. Hard gelatin capsules
   Disintegration time shall not be more than 30 min.
b. Soft gelatin capsules
   Disintegration time shall not be more than 60 min.
c. Enteric capsule
   Acidic media – shall not disintegration 2hrs and in alkaline medium capsules shall disintegrate within 30 min.

e) Standard lock length for hard gelatin capsules in mm
Table 5: Capsules lock length in mm.

<table>
<thead>
<tr>
<th>Size</th>
<th>Cap</th>
<th>Body</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>10.68-11.68</td>
<td>18.22-19.22</td>
</tr>
<tr>
<td>1</td>
<td>9.51-10.51</td>
<td>16.22-17.22</td>
</tr>
<tr>
<td>2</td>
<td>8.67-9.67</td>
<td>14.84-15.84</td>
</tr>
<tr>
<td>3</td>
<td>7.73-8.73</td>
<td>12.98-13.98</td>
</tr>
<tr>
<td>4</td>
<td>6.97-7.97</td>
<td>11.84-12.84</td>
</tr>
</tbody>
</table>

F) In-vitro drug release
Mini-tablets were subjected to in-vitro drug release studies in simulated gastric and intestinal fluids to assess their ability in providing the desired controlled drug delivery. Drug release studies were carried out using USP dissolution test apparatus I at 100 rpm, 37±0.5°C, and pH 1.2 buffer (900 ml) (i.e. 0.1 N HCl) for 2 hours, since the average gastric emptying time is about 2 hours. The dissolution medium was replaced with pH 6.8 phosphate buffer (900 ml) and experiment continued for another 10 hours. At different time intervals, 5ml of the samples were withdrawn and replaced with 5ml of drug-free dissolution medium. The
samples withdrawn were analyzed by UV spectrophotometer using multi component mode of analysis at required wave length.

Preformulation studies mini-tablets
Preformulation study relates to pharmaceutical and analytical investigation carried out proceeding and supporting formulation development efforts of the dosage form of the drug substance. It gives information needed to define the nature of the drug substance and provide frame work for the drug combination with pharmaceutical excipients in the dosage form. Hence, the following preformulation studies were performed on the obtained sample of drug.

1. Angle of repose
2. Bulk density and Tapped density
3. Carr’s index
4. Hauser’s ratio

1. Angle of repose
The angle of repose is determined by fixed funnel and free standing cone methods employ a funnel that is secured with its tip at a given height, h, which was kept 2 cm above graph paper that is placed on a flat horizontal surface.

2. Bulk density and tapped bulk density
Bulk density and tapped bulk density was determined. A quantity of 2gm of granules from each formula, previously light Shaken for the break of any agglomerates formed, was introduced into the 10 ml of measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall down its own weight from the hard surface from a height of 2.5cm at 2 sec Intervals. The tapping was continued until no further change in the volume was noted LBD and TBD were calculated using the following formulas: LBD: Weight of the powder/volume of the packing.\[13\] TBD: Weight of the powder/Tapped volume of the packing.

3. Compressibility index
The compressibility index of the granules was determined by Carr’s Compressibility index. Carr’s index (%) = \([(TBD-LBD) * 100] / TBD\]
Where, LBD: Weight of the powder/volume of the packing. TBD: Weight of the powder/Tapped volume of the packing.\[14\]
4. Hausner’s ratio

Hausner’s ratio can be determined by the following equation, Hausner’s ratio = TBD / LBD

Where, TBD - Tapped bulk densities & LBD - Loose bulk densities

1. <1.25 – Good flow = 20% Carr
2. 1.25 – Poor flow = 33% Carr’s

Drug excipients Compatibility study

Compatibility of the drug with excipients was determined by FT-IR spectral analysis DSC thermal analysis, this study was carried out to detect any changes on chemical constitution of the drug after combined it with the excipients. The samples were taken for FT-IR and DSC studies. [15]

a) 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 pellets.

b) DSC studies

DSC studies were carried out for pure drug and best mini-tablets formulations. DSC scan of about 5mg accurately weighed montelukast and optimized formulations were performed by using an automatic thermal analyzer system (DSC60 Shimadzu Corporation, Japan). Sealed and perforated aluminium pans were used in the experiments for all the samples. Temperature calibrations were performed using indium as standard. An empty pan sealed in the same way as for the sample was used as a reference. The entire samples were run at a scanning rate of 10° C/min from 50-300° C. [16]

Evaluation of mini-tablets

1. Weight variation

The weight variation test was conducted by weighing 20 randomly selected mini-tablets individually, calculating the average weight and comparing the individual mini-tablet weights to the average. The specification of weight variation is 10 %

2. Hardness

The hardness of the tablets was determined using Pfizer hardness tester. It is expressed in kg/cm2. Six tablets were randomly picked from each formulation and the mean and standard deviation values were calculated. [17]
3. Thickness
The thickness of ten randomly selected core/coated tablets from each batch was individually recorded in mm using a digital caliper (Mitutoyo digimatic caliper, Mitutoyo Corporation, Japan) and screw gauge. The mean and standard deviation values were calculated from each value recorded.[18]

4. Friability (F)
A friability test was conducted on the mini-tablets using a veego friabilator. Twenty mini-tablets were selected from each batch and any loose dust was removed with the help of a soft brush. The mini-tablets were initially weighed (Winitial) and transferred into friabilator. The drum was rotated at 25 rpm for 4 minutes after which the mini-tablets were removed. Any loose dust was removed from the mini-tablets as before and the tablets were weighed again (Wfinal). The percentage friability was then calculated by,

5. 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 dissolution medium to give a concentration of 100 μg/ml. Take 15 ml of this solution and diluted it up to 100 ml with same solution to give a concentration of 15μg/ml. Absorbance measured at respective wave length using UV-Visible spectrophotometer.[19]

6. In-vitro disintegration
The in-vitro disintegration of the core mini-tablets of IRCMT were determined using disintegration test apparatus as per I.P specifications. Place one tablet in each of the six tubes of the basket.[20] Add the disc to each tube and run the apparatus using 900ml of dissolution medium as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in dissolution medium maintained at 370 C.[21] The time in sec for complete disintegration of the tablet with no palable mass remaining in the apparatus was measured and recorded. For the determination of content uniformity five tablets weighted and crushed in a mortar then weighed powder contained equivalent to 10 mg of drug transferred in 100 ml of dissolution medium to give a concentration of 100 μg/ml. Take 15ml of this solution and diluted it up to 100ml with dissolution medium to give a concentration of 15μg/ml. Absorbance measured at required wave length using UV-visible spectrophotometer.[22]
7. In-vitro drug release

Mini-tablets were subjected to in-vitro drug release studies in simulated gastric and intestinal fluids to assess their ability in providing the desired controlled drug delivery.\textsuperscript{123} Drug release studies\textsuperscript{3,54, 55} were carried out using USP dissolution test apparatus I at 100 rpm, 37±0.5°C, and pH 1.2 buffer (900 ml) (i.e. 0.1 N HCl) for 2 hours, since the average gastric emptying time is about 2 hours. The dissolution medium was replaced with pH 6.8 phosphate buffer (900ml) and experiment continued for another 10 hours.\textsuperscript{24} At different time intervals, 5ml of the samples were withdrawn and replaced with 5ml of drug-free dissolution medium. The samples withdrawn were analyzed by UV spectrophotometer using multi component mode of analysis at required wave length.\textsuperscript{25}

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.

REFERENCES


