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# Mini - Tablets Technology: An Overview

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## ABSTRACT

It is well known that solid oral dosage forms, particularly tablets, are the most acceptable form of delivering medication. However, some new variations are beginning to emerge such as mini-tablets, which offer formulation flexibility. A multifunctional and multiple unit system for oral use are developed by filling versatile mini-tablets in a hard capsule. Multipulsatile DDS, site-specific DDS, zero-order DDS, slow/quick DDS, and quick/ slow DDS are designed in different ways and are investigated. Mini-tablets are small tablets with a diameter typically equal to or less than 3 mm that are typically filled into a capsule, or occasionally, further compressed into larger tablets. It is possible to incorporate many different mini-tablets, each one formulated individually and programmed to release drug at different sites within the gastrointestinal track, into one capsule. These combinations may include immediate release, delayed release, and/or controlled release mini-tablets. It is also possible to incorporate mini-tablets of different drugs to treat concurrent diseases or combinations of drugs to improve overall therapeutic outcome, while delivering distinct release rates of each according to disease requirements. Mini-tablets combine the advantages of multiparticulate dosage forms with the established manufacturing techniques of tableting. Additional benefits of mini-tablets include excellent size uniformity, regular shape and a smooth surface, thereby offering an excellent substrate for coating with modified release polymeric systems. From this, study it can be concluded that, granules-mini-tablets filled in HPMC capsule systems and coated mini-tablet-in-HPMC capsule system sulphate shows both sustained release as well as immediate release may improve the bioavailability and efficacy of any drugs.

**Keywords:** Mini-tablets, immediate-release, delayed-release, controlled-release, multiparticulate dosage forms.

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## INTRODUCTION:

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 [1]. The most convenient and commonly employed route of drug delivery has historically been by oral ingestion[2].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[3].

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[4]. 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[5]. 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[6,7].

**Chronotherapeutic: Right drugs at right time can heal effectively[8-11]:**

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-HS$^{TM}$), osmotic pump mechanisms (COER-24$^{TM}$), and matrix systems (Geminex$^{TM}$ ) 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. 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[12] is the synchronization of medication levels in time with reference to need, taking into account biologic rhythms in the patho physiology of medical conditions, and/or rhytmodependencies in patient's tolerance for given chemical interventions. It is based on importance of biologic rhythms in the patho physiology 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[13]. 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[5,14].

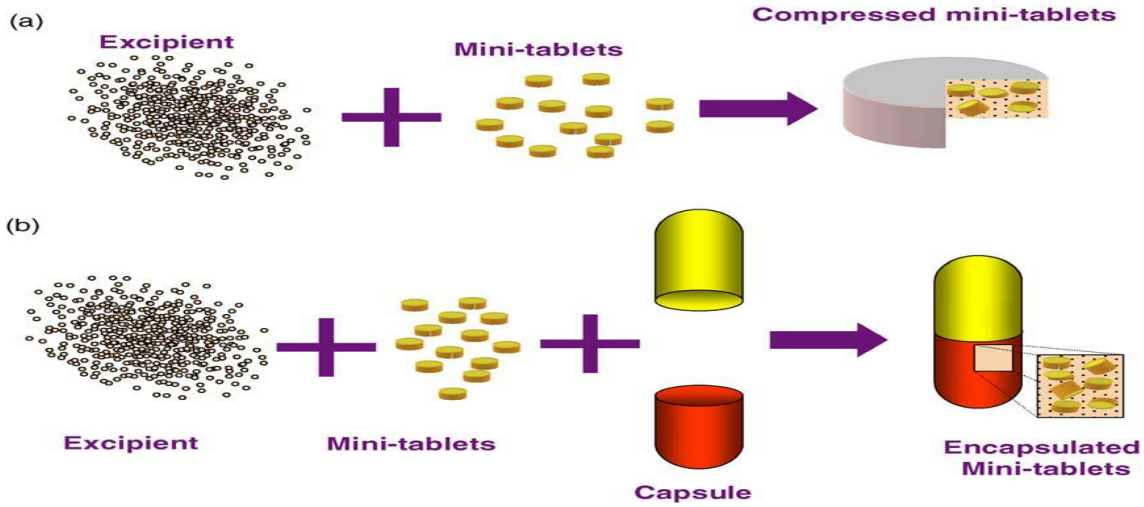


**Figure 1: Mini-tablets delivered as a tablet (a) or a capsule (b).**

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[15].

**Advantages of mini-tablets[16- 19]:**

- 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[5, 20, 21]. 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[22]. 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[20.] 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[23].

**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. 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[24].

**Tablet coating principles[25]:**

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[25, 26]:**

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. Three main types are used in the pharmaceutical industry today: Sugar coating, Film coating, Compression coating.

The encapsulated mini-tablet (EMT) system (Figure 2 and 3). 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.

**Figure 2: Encapsulated coated mini-tablets systems.**

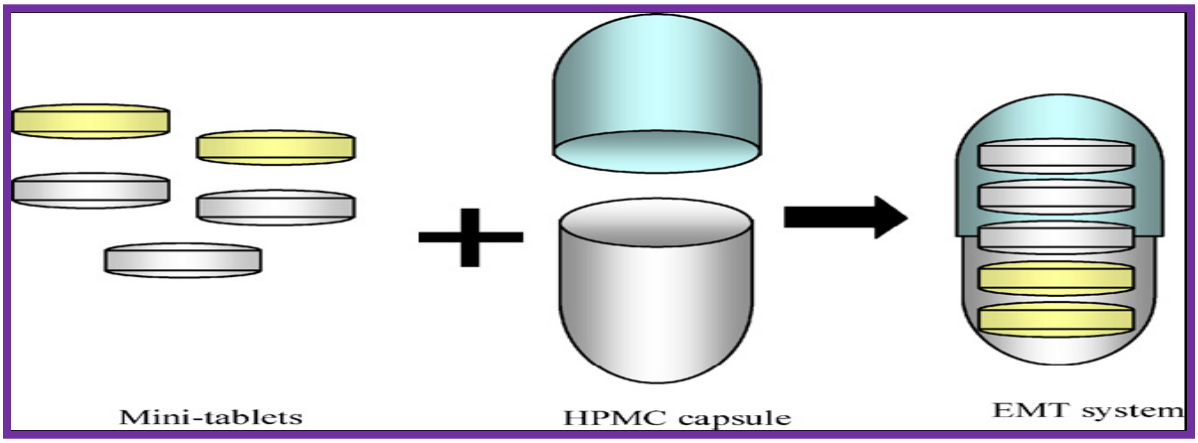


**Figure 3: Schematic diagram of the EMT system contains 2 IRMT 3 SRMT placed.**

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).

To ensure immediate release, the IRMT contained low substituted hydroxy propyl cellulose as a disintegrant, and were prepared simply by coating MT with HPMC. HPMC is a non-ionic, non-toxic, water-soluble substance that is easy to handle, relatively easy to manufacture, and has a minimal influence on processing parameters. In contrast, the SRMT were coated with a mixture of Ethyl cellulose (a water-insoluble polymer) and HPMC. Mixtures of two polymers are often used in controlled release drug delivery systems[27, 28] to allow pore-mediated diffusion through the polymer film.

ETHOCEL ethylcellulose products have long been used as a solvent-based tablet coating. Ethocel resins form strong films with good adhesion. Because ethylcellulose is water insoluble, it is often used in conjunction with other water and organic-solvent soluble polymers such as Methocel cellulose ethers. Sustained or delayed release coatings can be achieved by varying the ratios of Ethocel and Methocel cellulose ether products. As water insoluble

excipients, Ethocel polymers can effectively control the release of an active by modifying the size and length of the diffusion path. In this role, an Ethocel polymer is typically used in combination with water-soluble active and/or water-soluble excipients such as Methocel cellulose ether and/or polyethylene glycols. By varying the type and amount of insoluble/soluble excipients ratio and the particle size, a wide variety of release rate profiles can be achieved [29 - 31].

**Table 1: Summary of key variables affecting drug release from ethyl cellulose coated Multiparticulate systems:**

| Key Variable | Effect on drug release |
|---|---|
| Film thickness | As film thickness increases, drug release decreases. |
| Viscosity | As viscosity increases, drug release decreases. |
| Drug solubility | As the solubility increases, drug release increases. |
| Plasticizer | Drug release is faster if water soluble plasticizer is used. Change in plasticizer level may change the drug release. |
| Pore former | As pore former increases, drug release decreases. |
| Solvent | Faster release from aqueous than organic coated at equivalent thickness. |

**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[32].

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[33]. 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[34]. 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[35]. 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[36].

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[37]. Prepared immediate release granules and sustained release mini tablets are filled in the HPMC capsule. The main advantage of HPMC capsules over gelatin capsules could be because of their vegetable source which has wider customer acceptance. Hindu or Buddhist for example rely on vegetable sources for their nutrition[31-35]. The drug contained in the fast releasing phase (Granular powder) dissolved within the first 5 min, whereas the drug contained in the mini-tablets was released at different rates, depending upon composition of mini tablets [38, 39].

**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. Hard gelatin capsules do have some drawbacks, so that the in the present work HPMC capsules are preferred. The principal drawback of hard gelatin capsules is that the capsule shells have 13 to 16% water content and therefore may not be suitable for use with readily hydrolysable drugs. Some drugs react with amine group of gelatin, causing formation of cross-link between gelatin molecules and reducing the solubility of the

capsule shell. Furthermore gelatin products are avoided by many as a result of religious, cultural or vegetarian restrictions. In addition, recent safety report suggests theoretical risks of transmitting spongiform encephalopathy via gelatin capsules.


| Size | 00 | 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|---|
| Volume | 0.95 | 0.68 | 0.50 | 0.37 | 0.30 | 0.21 |

**Figure 4: Size of the capsule to fill weight**

To overcome these problems, pharmaceutical scientists has been working for decades to develop capsules made of starch, cellulose derivatives and polyvinyl alcohol copolymer. In 1998, shionogi qualicep successfully manufactured HPMC capsules, QUALI-V with the properties suitable for pharmaceutical products and dietary supplements. QUALI-V is the first HPMC capsule developed for pharmaceutical market, can be filled with many kinds of liquid or semi-solid dosage forms. HPMC capsules are available in a wide range of sizes- 00, 0, 1, 2, 3, 4. It comes in crystal clear or colored as per the needs including a range of natural colors to complement the brand(Figure 4)

HPMC[40-42] capsules can be manufactured by the same dipping and forming method that is employed for the manufacture of classic hard gelatin capsules. HPMC capsules are odorless, flexible and exhibit similar dissolution character to the hard gelatin capsules. The main difference in their physicochemical properties from the gelatin capsules is that their water content is less, 2 to 5 % as opposed to 13 to 16 % of gelatin, and water does not act as a plasticizer for the HPMC shells and thus maintain integrity under low moisture conditions. Dissolution profiles of gelatin and HPMC capsules are comparable over a wide range of pH values. Among the long list of advantages, perhaps one of the most significant is that non-animal sources capsule allow consumers for addressing a variety of cultural and dietary requirements. These capsules avoid concerns about the spread of animal originated disease. Increasing commercial availability, offer of overcoming problems inherent with gelatin capsules coupled with their rapid progress in manufacturing; make HPMC capsules an ideal alternative to classic gelatin capsules.

**Preparation of mini-tablets-in capsule system and granules-mini-tablets-in-capsule systems:**

**Formula used for the calculation of immediate-release dose[43]:** The pharmacokinetic parameters of drug were utilized for the calculation of theoretical drug release profile for coated mini-tablet-in-capsule system. The immediate-release part of drug was calculated using the following equation.

$$D_L = C_{max}\ V_d$$

Where $C_{max}$ is maximum plasma concentration, and $V_d$ is volume of distribution.

**Preparation of immediate release component (Granules):** Calculated amount of immediate-release dose drug and other suitable excipients [Microcrystalline cellulose (Avicel PH 102)] were used because of its good compaction and disintegration properties. Any suitable superdisintegrants was used to obtain an immediate release of the drug. The granules were prepared by wet granulation method.

**Preparation of immediate-release coated mini-tablet (IRCMT)[44]:** The IRCMT was prepared using the wet granulation method. The ingredients consisting of calculated amount of immediate-release dose drug, other excipients [D-mannitol, anhydrous dibasic calcium phosphate, hydroxyl propyl cellulose] and intragranular portion of any suitable superdisintegrants in proportions varying according to the experimental design were passed through 60 mesh (250µm) separately and dry mixed. The dry mixing was carried at a slow speed for 10 min and the blend was granulated with ethanol. The resulting wet mass was immediately passed through a 16 mesh screen (1000µm). The granules obtained were dried for 1 hr in a thermostatic hot air oven maintained at 30-35$^{o}$C to moisture content of 2 to 3 %. The dried granules were passed through the same sieve (1000µm) to break the lumps and blended with extra granular portion of any suitable superdisintegrants, Aerozil and magnesium stearate. The lubricated granules were compressed into mini-tablets weighing 80 mg using 6.3 mm round convex punches in a rotary tablet press (Rimek mini press, model RSB-4, M/S: Karnavati engineering, Ahmadabad).

A Coating suspension was prepared from HPMC (5cps/15cps), magnesium stearate, plasticizer, ethyl alcohol and water**.** Magnesium stearate was first dispersed in water, and the HPMC was first dispersed in an ethanol/water mixture. With gentle stirring, the magnesium stearate suspension was added to the HPMC dispersion, and the aqueous ethanolic HPMC solution was plasticized with polyethylene glycol. The mixture was stirred for 2 hrs to ensure sufficient plasticization of the polymer.

The mini-tablets were coated with an aqueous ethanolic solution of HPMC using a pan coating system (United technologies, Mumbai.) to yield a 5 % increase in weight.

Percentage weight gain calculated by following equation:

$$\text{Percentage weight gain} = [(Wt - Wo)/Wo]*100$$

Where,

Wt = Weight of tablet after coating,

Wo= Initial weight of tablet.

**Preparation of sustained-release coated mini-tablet (SRCMT)[44]:** The SRCMT was prepared using the same method as used for preparing the IRCMT. However, the SRCMT did not contain the any superdisintegrants.

A coating suspension was prepared from HPMC (5cps/15cps), ethyl cellulose, magnesium stearate, ethyl alcohol and water. Magnesium stearate was used in the coating preparation to minimize friction between the surfaces of mini-tablets, the mini-tablets-filling system and the HPMC capsules. HPMC, ethyl cellulose and magnesium stearate were dispersed in an ethanol/water mixture. Aqueous ethanol solutions of HPMC and ethyl cellulose were mixed at the desired ratios (65:35, 70:30, 75:25, 80:20) based on the experimental design. The mini-tablets were coated using a similar method to that used for coating the IRCMT, using an aqueous ethanolic solution of HPMC and ethyl cellulose to yield 5 % increase in weight. A coating load of 5 % was used to test the effect of the various ratios of HPMC and ethyl cellulose.

**Preparation of coated mini-tablet-in-capsule system[45]:** To prepare the CMTICS, two IRCMT and three SRCMT were placed in each HPMC capsule (size1). Both similar/different ratios of SRCMT were placed in each HPMC capsule to achieve various sustained release profiles of the CMTICS. The qualitative and quantitative composition of the different formulations of the CMTICS can be seen below Figure-5.

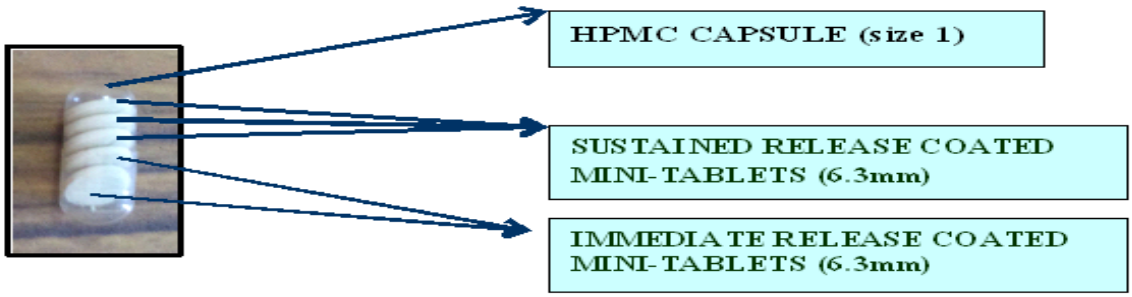


**Figure 5: Coated mini-tablet-in capsule system**

**Preformulation studies mini-tablets**[46]:

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. Relationship between angle of repose and flow properties was shown in Table 2. With r being the radius, of base of conical pile, angle of repose can be determined by following equation:

$$\theta = \tan^{-1} (h/r)$$

Where, θ is the angle of repose, 'h' is height of pile, 'r' is radius of base of the pile.

**Table 2: Relationship between angle of repose (θ) and flow properties.**

| Angle of Repose (θ) | Flow |
|---|---|
| <25 | Excellent |
| 25-30 | Good |
| 30-40 | Passable |
| >40 | Very poor |

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.

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.(Table 3)

$$\text{Carr's index (\%)} = [(TBD-LBD) * 100] / TBD$$

Where, LBD: Weight of the powder/volume of the packing.

TBD: Weight of the powder/Tapped volume of the packing.

**Table 3: Grading of the powders for their flow properties according to Carr's Index**

| Consolidation Index (Carr %) | Flow |
|---|---|
| 5 – 15 | Excellent |
| 12 – 16 | Good |
| 18 – 21 | Fair to passable |
| 23 – 35 | Poor |
| 33 – 38 | Very poor |
| >40 | Very very poor |

4. **Hausner's ratio:**

Hausner's ratio can be determined by the following equation,

$$\text{Hausner's ratio} = TBD / LBD$$

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.

**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.

**Evaluation of mini-tablets:**

1. **Weight variation [47]:** 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%.(Table 4)

**Table 4: Percentage deviation in weight variation**

| Average Weight of Tablet | % Deviation |
|---|---|
| 80 mg or less | ± 10 |
| More than 80 mg but less than 250 mg | ± 7.5 |
| 250 mg or more | ± 5 |

2. **Hardness:** The hardness of the tablets was determined using Pfizer hardness tester. It is expressed in kg/cm$^2$. Six tablets were randomly picked from each formulation and the mean and standard deviation values were calculated.
3. **Thickness[48]:** 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.
4. **Friability (F)[48]:** 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 ($W_{initial}$) 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 ($W_{final}$). The percentage friability was then calculated by,

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} x100$$

% Friability of mini-tablets less than 1% is considered acceptable.

5. **Drug content uniformity[49-51]:** 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.

6. ***In-vitro* disintegration[52]:** 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. 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 $37^0$ C. 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.
7. **In-vitro drug release[53]:** 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[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. 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.

**Treatment of dissolution data with different kinetic equations [56-63]:**

To analyze the mechanism of release and release rate kinetics of the dosage form, the data obtained were fitted into Zero order, First order, Higuchi matrix, and Korsmeyer-Peppas. Based on the r-value, the best-fit model was selected.

The suitability of several equations, which are reported in the literature to identify the mechanism(s) for the release of drug, was tested with respect to the release data. Some diffusion models (Korsmeyer–Peppas) are expected to be valid only up to approximately 60% cumulative drug released and the data for analysis were therefore restricted to that range excluding also the lag time. The data were evaluated according to the following equations:

❖ Zero-order model:

$$Mt = M_0 + K_0t \quad (1)$$

❖ Higuchi model:

$$Mt = M_0 + K_H t^{0.5} \quad (2)$$

❖ Korsmeyer–Peppas model:

$$Mt = M_0 + K_K t^n \quad (3)$$

Where Mt is the amount of drug dissolved in time t, M0 the initial amount of drug, $K_0$ the zero-order release constant, $K_H$ the Higuchi rate constant, $K_K$ the release constant and n is the release exponent, which characterizes the mechanism of drug release. The magnitude of the exponent n indicates the release mechanism as Fickian diffusion, as case II transport, or as anomalous transport. In the present study (cylindrical shape) the limits considered were $n = 0.45$ (indicates a classical Fickian diffusion-controlled drug release) and $n = 0.89$ (indicates a case II relaxational release transport: polymer relaxation controls drug delivery). Values of *n* between 0.45 and 0.89 can be regarded as indicators of both phenomena (transport corresponding to coupled drug diffusion in the hydrated matrix and polymer relaxation) commonly called anomalous non-Fickian transport. Values of *n* greater than 0.89 indicates a super case II transport, in which a pronounced acceleration in solute release by a film occurs toward the latter stages of release experiments, resulting in a more rapid relaxation-controlled transport.

**Stability studies[64, 65]:**

Stability of a drug has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specifications.

❖ The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity an light and enables recommended storage conditions, re-test periods and shelf lives to be established.

❖ Generally stability studies were carried out at $40^0$ C ± $2^0$C / 75 ± $5^0$C % RH for 6 months as per ICH Guidelines for the selected formulations.

❖ The tablets were evaluated for any change in physical appearance and percent cumulative drug release after one, three and six months. The obtained results were compared with the stability data for zero time and room temperature ($25^0$C ± $2^0$C) and relative humidity (60% ± 5%RH) as per ICH guidelines.

## CONCLUSION:

A multifunctional and multiple unit system for oral use is developed by filling versatile mini-tablets in a hard capsule. Multipulsatile DDS, site-specific DDS, zero-order DDS, slow/quick

DDS, and quick/ slow DDS are designed in different ways and are investigated. A quick/slow novel and multifunctional drug delivery system can be developed by compressing mini-tablets into a tablet dosage form or by encapsulating mini-tablets. The two different release phases can be easily adjusted in a wide range of values of both delivery rate and ratio of the dose fractions, on the basis of the pharmacokinetics and therapeutic needs, to perform the desired *in-vivo* profile. In compressed mini-tablets dosage form the release profile is strongly dependent on the number and/or composition of subunits, making up the drug sustained dose. In encapsulated coated mini-tablets dosage forms choice and level of molecular weight grade (viscosity grade), plasticizer, solvent for coating and pore former influence drug release. By selecting right combination of all these parameters can offer drug release profile flexibility and robustness of the overall formulation.

A novel biphasic granules and mini-tablets filled in HPMC capsule system was developed by filling granules and mini-tablets into an empty HPMC capsule shell. And formulations containing coated mini-tablet-in- HPMC capsule system**.** From this, study it can be concluded that, granules and mini-tablets filled in HPMC capsule systems and coated mini-tablet-in- HPMC capsule system sulphate shows both sustained release as well as immediate release may improve the bioavailability and efficacy.

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