Advances in Bioresearch
Adv. Biores., Vol 7 (2) March 2016: 05-10
©2015 Society of Education, India
Print ISSN 0976-4585; Online ISSN 2277-1573
Journal's URL:http://www.soeagra.com/abr.html
CODEN: ABRDC3
ICV Value 8.21 [2014]

Advances in Bioresearch

REVIEW ARTICLE

Mini-Tablet: A Review

Shoaeb Mohammad Syed*, Marathe R P, Shahi S R, Mourya V K
*Research Scholar, Govt. College of Pharmacy Aurangabad 431005
Email: ybccpsh@gmail.com

ABSTRACT
Oral drug delivery system is most desirable and preferred method of administering therapeutic agent. Drugs are administered by oral route in variety of pharmaceutical dosage form. The most common are tablet, capsule, suspension and solutions. Among the drugs that are administered orally solid dosage form represent the preferred class of product. Conventional dosage form suffers certain disadvantages hence sustained release dosage form is preferred to maintain the therapeutic concentration over a long period of time. Oral solid sustained release dosage forms are classified as single unit and multiple unit dosage forms. Some of the formulating and clinical problems (free flowing property, dose dumping, dysphagia, etc) comes along the with the single dose formulations. This soon led to the dividing of monolithic dosage forms into multiples. Multiple Unit Dosage Forms (MUDFs) are formulated as granules, pellets or mini tablets. The current review gives brief discussion of mini-tablets, advantages, disadvantages and formulation technologies.
KEY WORDS: *Oral drug delivery, Sustained release, Single & multiple unit dosage form,Mini-tablet*

Received 22/12/2015 Accepted 27/02/2016

How to cite this article:
Shoaeb Mohammad S, Marathe R P, Shahi S R, Mourya V K. Mini-Tablet: A Review . Adv. Biores., Vol 7 [2] March 2016: 05-10**.** DOI: 10.15515/abr.0976-4585.7.2.510

INTRODUCTION

Oral drug delivery

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects. In addition, the oral medication is generally considered as the first avenue investigated in the discovery and development of new drug entities and pharmaceutical formulations, mainly because of patient acceptance, convenience in administration, and cost-effective manufacturing process. For many drug substances, conventional immediate-release formulations provide clinically effective therapy while maintaining the required balance of pharmacokinetic and pharmacodynamic profiles with an acceptable level of safety to the patient [1]. For sustained as well as for controlled-release systems, the oral route of administration has received the most attention [2].

Drugs are administered by the oral route in a variety of pharmaceutical dosage forms. The most popular are tablets, capsules, suspensions and various pharmaceutical solutions. Among the drugs that are administered orally, solid dosage forms represent the preferred class of products. They are versatile, flexible in dosage strength, relatively stable, present lesser problem in formulation, packaging and it is convenient to manufacture, store and sale. Solid dosage form provides best protection to the drug against light, temperature, humidity, oxygen, and stress during transportation. Amongst the solid oral dosage forms, tablets are widely used [3].

All the pharmaceutical products formulated for systemic delivery via the oral route of administration irrespective of the mode of delivery (immediate, sustained or controlled release) and the design of dosage forms (either solid dispersion or liquid), must be developed within the intrinsic characteristics of GI physiology, pharmacokinetics, pharmacodynamic and formulation design is essential to achieve a systemic approach to the successful development of an oral pharmaceutical dosage form [4].

In many instances, conventional method is more preferred to deliver the drug, but some drugs are unstable and toxic by frequently dosing. These kinds of drug have narrow therapeutic range and face solubility difficulties. In such cases, sustained drug delivery system is used, which maintain the drug plasma level in the therapeutic index [5].

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SUSTAINED RELEASE SYSTEMS

Over the past decades, the treatment of illness has been accomplished by administering drugs to the human body via various pharmaceutical dosage forms like tablets, capsules, pills, powders, parenteral preparations, solutions, emulsions, suspensions, creams, ointments, and aerosols. These conventional drug delivery systems and associated dosage forms are still commonly used today in the prescription and over the counter drug market place. When such a conventional dosage form is administered, the concentration of drug in systemic circulation gradually rises to attain a therapeutic range in short time, and this concentration is maintained for some time and finally decreases to sub-therapeutic value rendering the drug pharmacologically inactive. Ideally the drug concentration should be continuously maintained within therapeutic level. However, for drugs with short half life, it is not possible to maintain the drug concentration within therapeutic range without frequent dosing. Frequent dosing may lead to patient non-compliance and drug toxicity and hence suitable alternative is sustained release product [6].

Over the past 30 years, as the expense and complications involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of controlled drug-delivery, greater attention has been focused on development of sustained or controlled release drug delivery system. The goal in designing sustained or controlled delivery system is to reduce the frequency of dosing or to increase the effectiveness of the drug by localization at the site of action, reducing the doses required or providing uniform drug delivery.

Sustained release constitutes any dosage form that provides medication over an extended time [7].

The sustained drug delivery is to ensure safety and enhancement of efficacy of drug with improved patient compliance. Hence, the use of these dosage forms is increasing in treatment of acute and chronic diseases as they maintain the concentration of drug in plasma above minimum effective concentration and below the minimum toxic level for extended period of time. Thus, sustained drug delivery results in optimum drug therapy with reduced frequency of dosing and side effects [6-8].

SINGLE UNIT AND MULTIPLE UNIT DOSAGE FORM

Traditionally oral dosage forms are classified as single unit and multiple unit dosage forms. Multiparticulate dosage forms are receiving an immense attention as alternative drug delivery system for oral drug delivery even though single unit dosage forms have been widely used for decades. The most commonly used pharmaceutical solid dosage forms today include granules, pellets, tablets and capsules, out of which tablets being the most popular dosage form, accounting for 70% of all ethical pharmaceutical formulations [9].

But soon it was sensed that some of the formulating and clinical problems (free flowing property, dose dumping, dysphagia, etc) comes along the with the single dose formulations. This soon led to the dividing of monolithic dosage forms into multiples. Multiple Unit Dosage Forms (MUDFs) are formulated as granules, pellets or mini tablets [10-11]. The concept of this multiple unit dosage forms answers many formulating problems and is common strategy to control the release of drug as showing the reproducible release profiles when compared to SUDFs. These MUDFs can either be filled into capsules or compacted into a bigger tablets or can be dispensed in a dose pouches or packets [9].

MUDFs are 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 [12].

The concept of MUDFs is beneficial when the selected agents possess 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 [13-15].

MINI TABLETS

Mini-tablets are compact dosage forms which can be produced via traditional tableting methods, such as direct compression. The defined size of mini-tablets is varied in the literature. For example, Lennartz and Mielck stated that mini-tablets have diameters equal to or smaller than 2–3 mm, whilst Thomson et al

defined their size as 2–5 mm in diameter; Kachrimanis et al. used dies with diameters of 2–4 mm to assess the flow of excipients through orifices relevant to mini-tableting and Flemming and Mielck referred to tablets with diameter equal or less than 2 mm, although in the case of latter the term micro tablets was used to describe the small sub-units [16-20].

The production of mini-matrices using a tabletting technique is an attractive alternative to the production of pellets, as the presence of solvents (e.g. water) is avoided and high production yields like the ones observed in extrusion and spheronization are obtained. Furthermore, due to the manufacturing process, defined size and strengths can easily be produced, with small variability within and between batches [12].

Matrix Tablets are normally single unit dosage forms (SUDFs), but multiple unit dosage forms (MUDFs) have distinct advantages over SUDFs (11, 21). MUDFs are usually comprised of coated pellets, beads, granules and mini-tablets enclosed in a hard gelatin capsules. Technological processes in production make MUDFs more expensive than SUDFs. Therefore, mini-matrices were produced to combine the physiological advantages of MUDFs with the economic advantage of SUDFs [22].

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 also known as "Micro Tablets", as described by C. De Brabander [23].

Mini tablets can be used as a potential new formulation for pediatric oral drug delivery. In pediatric use, mini tablets present many benefits over orally administrated liquids, including the delivery of an accurate dose without any manipulation before administration and the opportunity of dose flexibility(for different patients ages and weights) through administration of multiple mini tablets [24].

Advantages

1. They can be manufactured relatively easily.
2. They have excellent size uniformity, regular shape and smooth surface.
3. They offer a substrate which is easy to coat with polymeric membranes for modified release purpose.
4. They combine the advantages of MUDFs with the established manufacturing techniques in tableting and have a fewer constraints compared to extrusion/spheronization.
5. 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.
6. They offer high drug loading, a wide range of release rate designs and fine tuning of these release rates.
7. 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 [25-27].
8. Sustained-release mini-tablets may offer distinct advantages over many conventional dosage forms used in paediatric medicine. In addition to their small size helping overcome issues associated with dysphagia, they may be designed to mask unpleasant tastes to improve palatability whilst also modifying the release of the active drug substance from the formulation [20].
9. The small diameter of the mini-tablets permits 0.5- to 6-year-old children to swallow them without any complications [28].

Possibilities for formulating the mini-tablets dosage forms

- Tablet in tablet systems
- Compressed mini-tablets systems are presented as a biphasic delivery system
- Tablet-in-capsule systems

Tablet in tablet systems

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 [15].

Although less popular, tablet-in-a-tablet technology gained increased interest in the recent years for creating modified released products. This type of tablet has two parts, internal core and surrounding coat. The core is small porous tablet and prepared on one turret. After tablet core manufacture it is transferred (centrally positioned) to another slightly larger die that is partially filled with coating powder. More coating powder is filled on the top of the core and compressed again resulting in tablet with in tablet. Mechanically, it is a complex process, as the tablet may be tilted when transferred to the second die cavity. Mostly, the coat is water soluble and disintegrates easily after swallowing, in order to achieve

immediate release product. This tablet readily lend itself in to a repeat action tablet as the outer layer provides the initial dose while the inner core release the drug later on. But, when the core quickly releases the drug, entirely different blood level is achieved with the risk of over dose toxicity. To avoid immediate release of both the layers, the core tablet is coated with enteric polymer so that it will not release the drug in stomach while, the first dose is added in outer sugar coating. Even so, coating operation requires interpretation while manufacturing and dawdling the manufacturing process. Sometimes, inner core may be of liquid formulation to provide immediate release of core after the coat gets dissolved [29].

Advantages of tablet-in-a-tablet technology

1. It is simple and inexpensive.
2. It is used to separate incompatible materials (one in the core and the other in the coat).
3. May be used to create modified-release products such as Delayed Release (Release in intestinal).
4. It is not hazardous to the environment since it does not require the use of high amounts of organic solvents.
5. It can also be used to avoid pharmacokinetic drug–drug interactions between concomitantly administered medications, creating a time interval between their releases into the gastrointestinal tract [30].

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 [29, 31].

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 [29].

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
- Filling of these mini-tablets into hard gelatin or HPMC capsules.

Drugs are usually encapsulated in one way or another within a barrier material, which is composed of an erodible or biodegradable polymer. Depending on the barrier material structure and thickness, different release lag times can be achieved. After the barrier material is dissolved, eroded or degraded, drugs are rapidly released from the inner reservoir core. Based on the concept that a formulation given once a time daily, a multifunctional and multiple unit system for oral use can be developed by filling versatile tablets in a hard capsule. This 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. This system can be used for achieving the selective delivery of drugs at appropriate time, which is a chronopharmaceutical approach for the better treatment of disease with circadian rhythms. This novel system is a so-called “tablets in capsule device”. The designed capsule device consists of an impermeable capsule body and a soluble cap. The multi-layered tablets formulation prepared is filled within the capsule body and sealed with the water soluble cap [32].

In this technology we can reduce the size of the tablet such that it could be enclosed in a capsule, and then deploy tablets with different release properties, within one single dosage form. This technology may be achieved by fast/slow delivery system. The proposed fast/slow delivery devices show a wide flexibility in the modulation of the delivery program. 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 [15, 26].

The concept of this technology 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.(12)

Advantages of tablets-in-a-capsule technology:

1. It causes significant savings, lower treatment failure rate and lower case fatality ratios.
2. Provides both controlled and multi-phase release for single or combination prescription and over the counter medicines.

3. Delivering of incompatible APIs are possible.
4. Patient convenience, compliance and cost effective therapy can be achieved.
5. Sustained, pulsed or delayed release profiles can be achieved.
6. Drug delivery can be targeted to two different regions of the GI tract.
7. It has higher colonic residence time, more predictable gastric emptying and consequently less money needed for the development of new products in long-term therapy.
8. It offers high drug loading, a wide range of release rate designs, and fine tuning of these release rates. It has 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.
9. Broad therapeutic applications can be achieved [33].

CONCLUSION

From the current review it can be concluded that formulation of mini-tablet can be a promising tool for oral drug delivery. The controlled release of drug required in various conditions can be achieved by using either tablet in tablet or tablet in capsule technology also the delivery of drug in the form of mini-tablet may be helpful in chronotherapy as well as for separating the incompatible material for combined drug delivery.

ACKNOWLEDGEMENT

We are thankful to Ministry of Minority Affairs Govt. of India New Delhi and University Grant Commission New Delhi for providing financial assistance. We are also thankful to Govt. College of Pharmacy Aurangabad for providing facility to carry out the present work.

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