



ChemTech

International Journal of ChemTech Research

CODEN (USA): IJCRGG, ISSN: 0974-4290, ISSN(Online):2455-9555
Vol.12 No.05, pp 263-272, 2019

Multiple Unit Pellets (MUPS) as A Tablet for Novel Drug Delivery System: A Review

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Abstract : Oral drug delivery system becomes challenging when the drug product needs to be delivered in modified release pattern in especially since it is difficult to swallow for them. Compaction of multiparticulates, commonly called Multiple Unit Pellet System (MUPS), is one of the more recent and challenging technologies that combine the advantages of both tablets and pellet-filled capsules in one dosage form. This article reviews the advantages and drawbacks of multiple unit pellet system, properties of an ideal multiple unit pellet system dosage form, mechanisms involved in their compaction, their disintegration and dissolution behaviour, objectives/rationale involved in the design of dosage form, challenges in their compaction and key variables to be considered in successful production of multiple unit pellet system. Compressed multi-particulate system prepared by using pellets have several pharmacokinetic, pharmacodynamic, commercial and other advantages as mentioned henceforth in this review article. It includes not only different types of modified release pellets that can be compressed into multiple unit pellet system. This review also presents detailed explanation on physicochemical properties of pellets and formulation strategies of multiple unit pellet system. This unique feature of multiple unit pellet system (MUPS) makes them a suitable candidate for the delivery of different types of drug molecules for a variety of therapeutic purposes.

Key words : Oral drug delivery system, Multiple unit pellet system (MUPS), compressed multi-particulate, Pharmacodynamic.

Introduction

The current interest shown in novel drug delivery systems (NDDS) and the pioneering research to devise new strategies for effective delivery of drugs in the body or the fine tuning of the existing technologies

Rana Mazumder *et al* /International Journal of ChemTech Research, 2019,12(5): 263-272.

DOI= <http://dx.doi.org/10.20902/IJCTR.2019.120530>

to enhance their efficiency. Several strategies are being tried out currently to discover novel carriers for the drugs to be delivered specifically and effectively¹. Novel drug delivery system refers to the use of a delivery device with the objective of releasing at a predetermined rate, or at specific time or with a specific release profile, at a desired area of effect. The NDDS essentially efforts are now being made to devise carriers that can transport multiple drugs and release them on command.

Multi Unit Pellet System (MUPS)

Tablets are indeed the most popular solid dosage form for oral administration. A relatively more recent approach that has come into existence is the one that combines the features of both controlled release tablets and modified release capsules in one dosage form, known as MUPS tablets – an abbreviation for Multiple-Unit Pellet System.

Advantages of Compaction of Multi Unit Pellet System (MUPS) Over Conventional Modified-Release Tablets and/or Pellet-Filled Capsules

1. Pharmacokinetic Advantages

- i. Rapid but uniform transit of micro-pellets contained in MUPS from the stomach into small intestine owing to their small size and thus lesser possibility of localized irritation, better and more uniform drug absorption and greater bioavailability.
- ii. Uniform emptying of micropellets from stomach into small intestine facilitates rapid dissolution of enteric coating. In case of controlled-release preparations, drug release is more uniform and possibility of dose dumping is avoided with minimized tendency for inter-subject variations³.

2. Pharmacodynamic Advantages

- i. Owing to rapid and uniform gastric emptying and subsequently uniform drug dissolution of pellets in the gastrointestinal tract due to their small size and larger surface, uniform drug absorption is facilitated which results in consistent and controlled pharmacological action.
- ii. A further reduction in inter- and intra-subject variability in drug absorption and clinical response is facilitated since the number of pellets per MUPS dosage form is much more than a conventional pellet-filled capsule and possibility of dose dumping (in stomach) and incomplete drug release is further minimized³.

3. Patient Friendly Dosage form

Better patient compliance is expected from MUPS for following reasons :

- i. Mouth disintegrating MUPS dosage form having a palatable taste is suitable for paediatric and geriatric patients who cannot swallow tablet or capsule.
- ii. The orodispersible MUPS medication can be taken without water, especially while travelling since the dosage form can be designed as orally disintegrating preparation that contains flavours and sweeteners that stimulate salivation and swallowing.
- iii. Being tablets, quite unlike a capsule formulation, MUPS can be also designed into a divisible dosage form, without compromising the drug release characteristics of coated particles contained therein.
- iv. The MUPS have lesser tendency of adhering to oesophagus during swallowing⁴.
- v. Smaller volume/size of tablet leads to better patient compliance than capsules^{5,6}.

4. Processing Advantages

Since MUPS is a tablet dosage form, it offers all the advantages which a tablet has over capsule preparation. Some specific advantages are –

- i. Greater physicochemical and microbiological stability of pellets owing to their embedment in inert matrix.

- ii. Rapidity of processing in comparison to capsules using existing tableting facility.
- iii. Lower cost of processing owing to higher processing speed, elimination of capsule cost, etc⁶.
- iv. The product is relatively tamper-proof. 22 cimgadmr⁶.
- v. Unlike conventional tablets, there is reduction in dust problems during compression.
- vi. Pellets intended for compaction into MUPS demonstrate excellent flow properties owing to their near spherical nature and thus easy to process into a tablet as compared to conventional granules used for tableting. Such compositions also require lesser amount of lubricants for tablet processing

5. Research, Analysis and Evaluation

MUPS provide an opportunity to examine the change in size, shape and density of pellets after compaction by retrieving the pellets from disintegration tubes⁶ or from highly lubricated compacts⁷.

6. Regulatory advantages

- i. Extension of patent life.
- ii. Line extension of product.
- iii. Possibility of patenting and registering the product in various markets globally⁸.

Properties of an Ideal Multi Unit Pellet (MUPS) Tablet

Two categories of MUPS are possible, considering that the pellets to be compressed are modified release or have a specific dissolution profile –

1. MUPS comprising of coated pellets.
2. MUPS comprising of matrix pellets.

The former category of MUPS is common but the latter category is less frequently encountered, although it has definite advantages over compaction of polymer coated pellets. Ideally, MUPS being a tablet, it must possess all attributes of a conventional tablet prepared by compression. Additionally, a MUPS tablet should possess following characteristics –

1. The compacted pellets should not fuse into a non-disintegrating matrix during compaction. The dosage form must disintegrate rapidly into individual pellets in gastrointestinal fluids. The drug release should not be affected by the compaction process⁹.
3. With MUPS containing reservoir-type coated pellets, the polymeric coating must be able to withstand the compression force; it may deform, but it should not rupture⁹.
4. Pellet compacts must possess optimum physical strength to withstand the mechanical shocks encountered in their production, packaging, shipping and dispensing¹⁰.
5. Surface of compacted MUPS should be smooth and elegant and devoid of pinholes and other imperfections and should facilitate ease of film coating if needed.

Mechanisms Involved in Compression of Multi Unit Pellet(MUPS)

It is suggested that four mechanisms are involved in the compression process of granules namely – 1. Deformation 2. Densification 3. Fragmentation 4. Attrition

Owing to the irregular shape and to the surface roughness of granules, it is rather difficult to determine the degree of incidence of the suggested mechanisms. Recently, the use of nearly spherical units, here defined as pellets, brought new light into the mechanistic knowledge of the compaction process of porous particles and justified the use of these units as an alternative model system^{11, 12}.

Disintegration and Dissolution Behaviour of Multi Unit Pellet (MUPS)

Since MUPS are often designed to possess particulates having modified release characteristics, they are expected to disintegrate in one of the following ways –

1. Rapid disintegration in the oral cavity, if the MUPS contains taste-masked coated particles or modified-release coated particles but designed as a compact in an orodispersible base (orally disintegrating tablets) e.g. Prevacid SoluTab.
2. Rapid disintegration in the gastrointestinal tract after oral administration or swallowing.e.g. Losec MUPS.
3. Slow and gradual erosion of MUPS in the GIT to release polymer-coated particles slowly, e.g. Toprol XL. The dissolution behaviour of individual coated multiparticulates that separate out as a result of disintegration of MUPS, follows the one that is expected of such particles and is often dictated by the type of coating or matrix design of such pellets⁸.

Objectives of Preparing Multi Unit Pellet (MUPS) Tablet

Following are the various objectives of preparing MUPS tablets –

1. Designing controlled release drug delivery system.
2. Designing enteric release drug delivery system.
3. Designing colon targeted drug delivery system.
4. Mouth-melting taste-masked dosage form.
5. Combining drugs with different release characteristics in the same dosage form.
6. Increasing the drug dose administered in controlled release form as compared to that possible with capsules.
7. Enhancing stability of dosage form as compared to its capsule counterpart.
8. Obviating the need for specialized packaging such as that required for capsules making it a more cost effective dosage form⁸.

Factors to be considered in the Design of MUPS Tablets

1. Formulation Variables

a. Pellet core:

Type – matrix or reservoir

Composition – hard brittle e.g. sucrose or plastic, e.g. MCC

Size

Shape

Porosity

Elasticity – is directly related to pellet composition. Thermoplastic layer on surface of drug pellet

b. Membrane coating:

Type of polymer – cellulosic or acrylic, etc.

Coating thickness

Type and amount of plasticizer

Presence of pigments

Additional outer coat on polymer surface – plastic layer or powder layer

c. Cushioning excipients :

Nature – deformable (plastic) or fracturable (brittle/elastic)

Size – powder or pellets

Amount – ideally 50 to 75%

2. **Process variables**
 - a. **Compression force**
 - b. **Compression speed**
3. **Equipment variables**
 - a. **Design of tableting machine and powder feeding machine.**

Marketed Multi Unit Pellet (MUPS) Formulations

Table 1 Enlists Few of the Marketed Multi Unit Pellet (MUPS) Formulations

Product	Company	Drug	Therapeutic Category	Formulation type
Theodur	Key	Theophylline	Antiasthamatic	Extended release
Losec MUPS	Astra Zeneca	Omeprazole magnesium	Antiulcer	Delayed release
Prevacid SoluTab	Takeda	Lansoprazole	Antiulcer	Delayed release orodispersible tablet
Toprol XL	Astra Zeneca	Metoprolol tartrate	Antihypertensive	Extended release

Challenges in the Compression of Multi Unit Pellet (MUPS) Tablet

Some of the issues that need to be addressed during processing or compaction of MUPS are as under

1. Development of an electrostatic charge on pellet surfaces can interfere with their flow during tablet compression cycle. This problem is usually solved by adding talc at 1% concentration, although this excipient can decrease the tensile strength of tablets¹³.
2. MUPS may present higher variations in tablet weight and content due to the segregation phenomenon. De-mixing is usually due to differences in size, shape, surface and density between pellets and extragranular tableting excipients. If pellets with a narrow size distribution are compressed together with additives of similar size and shape, uniformity of mass and content can be achieved¹⁴. Besides addressing the role of particle and pellet size, shape and density, the ratio of excipients-to-pellets is equally important in obtaining an optimum MUPS. A threshold of at least 50% w/w pellet content has to be attained in any tableting blend to avoid segregation¹⁵.
3. Alteration of drug release characteristics after compaction into tablets. Amongst the problems listed above, the biggest challenge in compaction of reservoir pellets into MUPS tablets is damage to the coating with a subsequent loss of the controlled-release, delayed release, taste-masking or drug stabilizing properties. The type and amount of coating agent, selection of the external additives and the rate and magnitude of the pressure applied must be considered carefully to maintain the desired drug release properties of the subunits¹⁶ Moreover, formulation scientists must have a comprehensive knowledge of how that formulation will behave during tableting, as well as how other excipients and/or process-related parameters will affect the performance of that formulation as a drug delivery system.

Formulation Approaches to Prevent Destruction of Drug Release Characteristics and other Attributes of Compacted Multi Unit Pellet (MUPS)

Several approaches have been employed to prevent damage to the pellet coating membrane during compaction of MUPS and can be categorised into following means –

1. Modulation of fillers or cushioning excipients
2. Modulation of pellet coating
3. Modulation of pellet core

Cushioning fillers/excipients

Cushioning excipients are those that take up the pressures of compaction by re-arranging themselves within the tablet structure or by preferentially getting deformed and/or fractured thereby preventing damage to the coating on drug pellets. They can be categorized further into 2 classes –

- a. Conventional powder excipients** – these include excipients such as microcrystalline cellulose, lactose, etc. and their blends. Disintegrants are also used as part of such excipients. A proper blend of deformable materials, e.g. microcrystalline cellulose and material that fractures e.g. lactose is often required to provide optimum cushion.
- b. Cushioning pellets** – these are normally more porous and soft compared to coated drug pellets and normally made of excipients which are used as cushioning excipients. The drug pellets-to-cushioning excipient(s) ratio is very critical in preventing coating film damage – a ratio of 1:3 or 1:4 is considered most suitable. Ideally speaking, the amount of cushioning excipients used should be sufficient to –

Facilitate good cohesion of tablet ingredients, and produce mechanically strong tablets at low compression forces that can withstand subsequent stresses of further processing, transportation and handling,

Yield tablets having elegant surface topography, and when exposed to aqueous environment, aid rapid disintegration of tablets (preferably less than 15 minutes) that result in separation of discrete pellets free from fusion with other pellets.

Modulation of Pellet Coating –

After compaction into MUPS, maintenance of integrity of functional coating present on the surface of drug pellet is vital for preservation of desired product characteristics, which could be taste masking, sustained-release, delayed release or drug stability. Approaches adopted to retain the characteristics of applied membrane coating include –

a. Use of more elastic coating composition

Coating films have been made more elastic to withstand pressures of compaction by use of more elastic materials such as acrylic polymers instead of cellulosic polymers, use of more quantity of plasticizers or a more efficient plasticizer, etc¹⁷. However, there should not be tendency of coated pellets to fuse with each other. Fusion tendency of pellets during compaction can be reduced by incorporation of lubricants and pigments such as talc in the coating composition but such materials are known to reduce elasticity of coating.

b. Increased thickness of coating

Thicker but elastic polymeric coat can better withstand the deformation and rupturing forces of compression in comparison to thinner coatings¹⁸.

c. Elastic/thermoplastic layer on the outer surface of drug pellets

Presence of an outer coating comprising of thermoplastic material such as carbowaxes on the surface of drug pellets, on which is applied the functional polymer coating, is known to absorb the stresses that may otherwise tear or fissure the outermost surface coating¹⁹.

d. Powder layer over the surface of polymer coated pellets

Application of an integral but porous powder layer on the outside of polymer coated pellets results in preferential damage to the powder shell resulting in its breakage thus preventing/reducing transmission of compaction force to polymer coated core drug pellet present beneath²⁰.

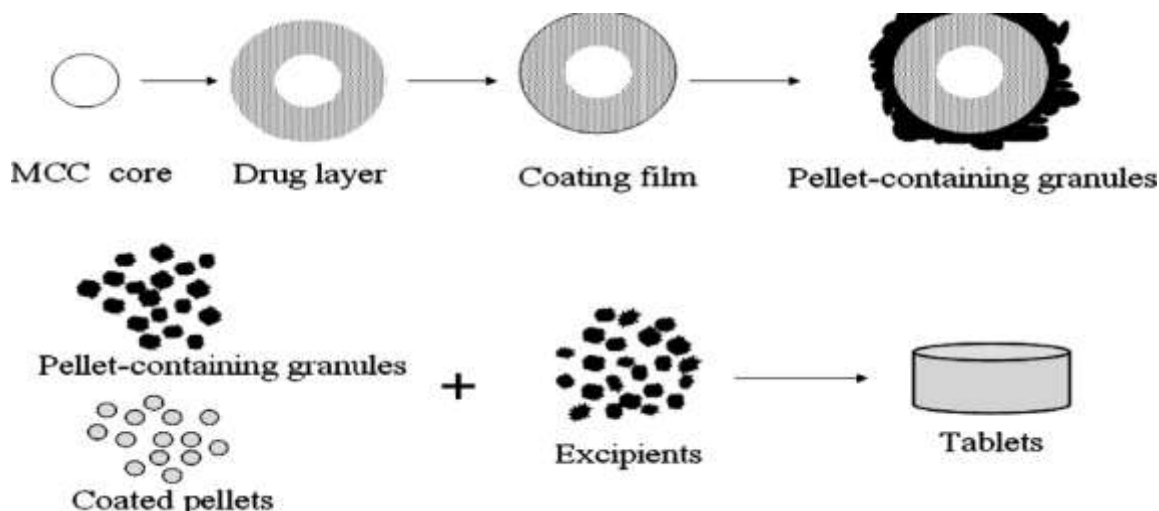


Figure 1 Compaction of Pellets with Cushioning Agents After Forming Pellet Containing Granules

Modulation of Core Pellet

Pellets core should have require plasticity besides the polymer coating on the pellets. Following pellet-related factors influence compaction characteristics –

a. Composition – Besides the inherent nature of drug, the other excipients that comprise core pellets can influence compaction characteristics. Presence of hard and brittle materials produce rigid pellet core that resists bulk deformation while elastic/plastic materials such as microcrystalline cellulose get easily deformed.

b. Pellet porosity – If the pellets being compacted are coated, during compaction, pellet deformation (change in shape of pellets) and densification (reduction in pellet porosity) occur to a larger extent while fragmentation is seen to a lesser extent. Porous pellets get more deformed during compaction, due to the higher freedom degree of rearrangement of the powder particles within them. On the other hand, more compact pellets are more intensively buffered during compaction by powder particles, because they cannot widely rearrange²⁰.

c. Pellet size – Larger pellets deform more easily than smaller pellets²⁰.

d. Pellet elasticity – Findings of various research ers on el.0asticity of core pellets are discordant. Bodmeier et al. claimed that the bead core should possess some degree of elasticity, in order to accommodate changes in shape and deformation during tableting²¹. Conversely, Opitz asserts that cores should possess characteristics such as high crushing strength so as to overcome the compression forces and the coated pellets are neither deformed nor ruptured²².

Even if compaction of coated particles do not result in destruction of coating, there still exist two possible outcome of compaction on drug release profile of coated pellets²³.

a. Faster drug release – The deformation of the substrate pellet may stretch out the coating, making it thinner or more permeable, which has a negative effect on the control of the drug release. This often explains that the release rate increases with increased irregularity of the compacted reservoir pellets.

b. Prolonged drug release – The densification of the substrate pellet may compress the coating, making it thicker or less permeable, and consequently prolong the drug release.

Processing of Multi Unit Pellet (MUPS)

Compaction factors that can influence preparation of MUPS include –

1. Compression force exerted - Opitz reports the effect of the compression force on the drug release from the MUPS. Increasing the compression force from the minimum required to have a compact till a certain value, which differs for each formulation, film ruptures are enhanced and the dissolution rate is increased²². Beyond this value, both disintegration and dissolution are delayed, which testifies the formation of undesired matrix tablets²⁴.

2. Compression velocity – is more related to dwell time (time period for which the punch head is in contact with the compression roller) during the compression cycle. MUPS are more prone to capping during compression. An increase in dwell time favours formation of strong bonds between particles being compressed and thus prevents capping and lamination.

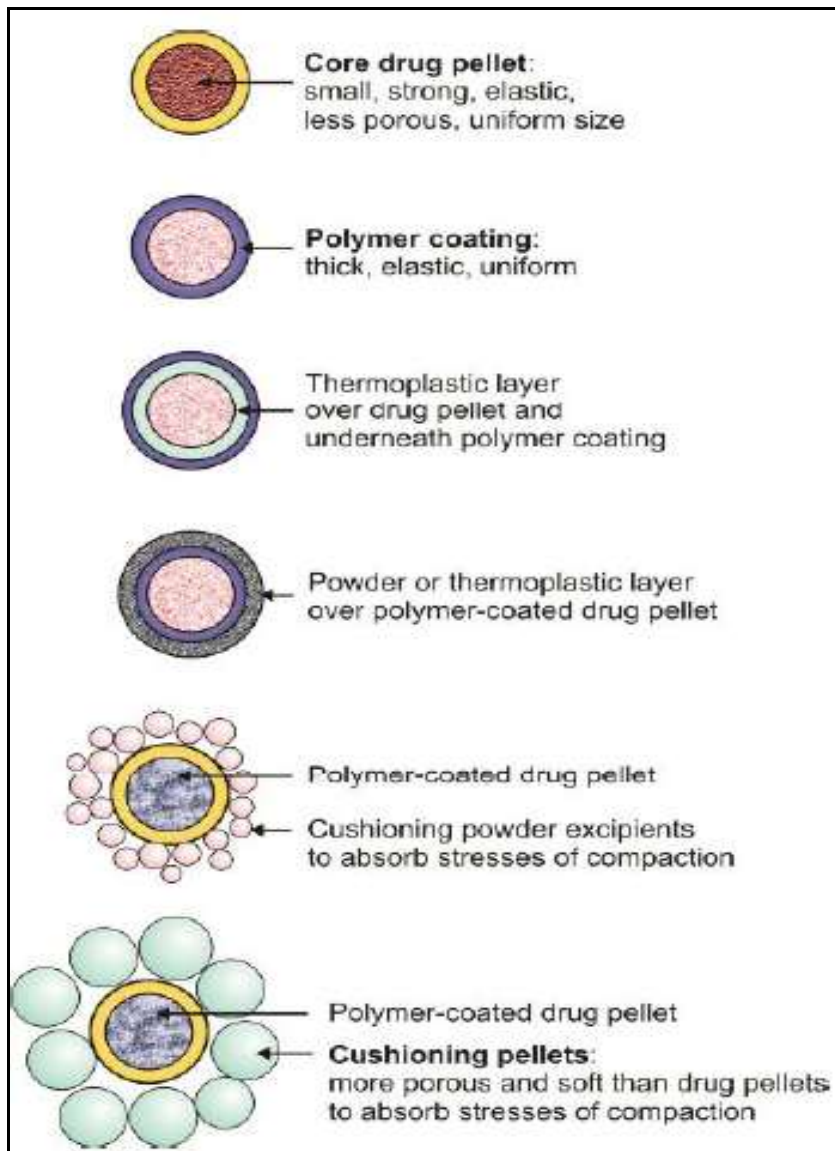


Figure 2 Represents the Approaches Adopted for Preparation of Multi Unit Pellet (MUPS) Without Damaging the Membrane Coating

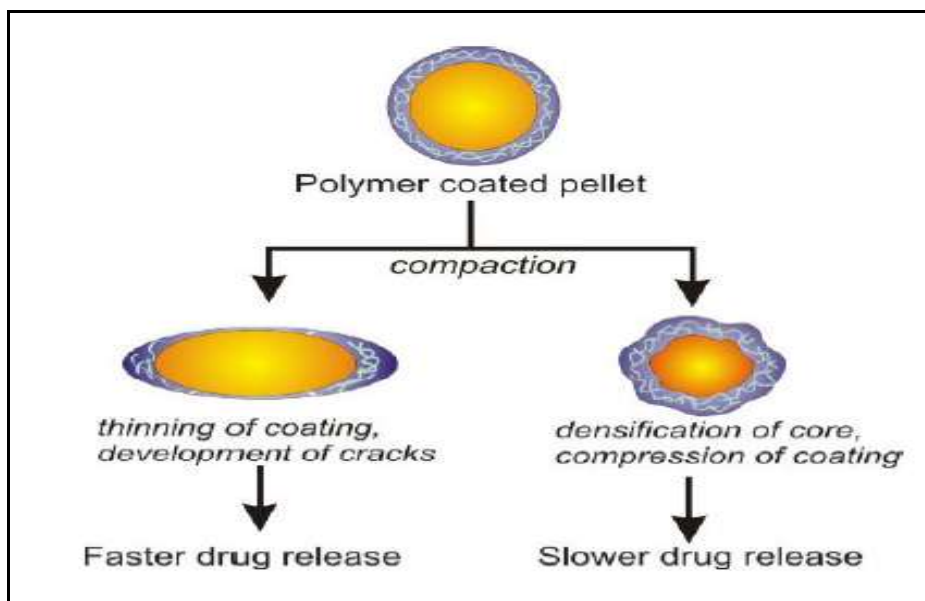


Figure 3 Portrays the Impact of Compaction on Pellet Deformation and Drug Release

Conclusion

The review research work is developed by multiple unit system which have a larger surface area than single unit systems, leading to more rapid release of drug with low production cost and also given good stability of drug with highest bioavailability. Multi-Unit particulate drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, each exhibiting some desired characteristics. The palletized product can freely disperse in the gastrointestinal tract as a subunit, thus maximizing drug absorption and reducing peak plasma fluctuation. The palletized products can improve the safety and efficacy of the active agent. It is helpful in achieving unique release pattern and Simultaneous administration of two or more incompatible drugs. Multi unit particulates system (MUPS) improves patient comfort and compliance.

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