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MUPS Tablets – A Brief Review

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ABSTRACT: Compaction of multiparticulates, commonly called 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 MUPS, properties of an ideal MUPS dosage form, mechanisms involved in their compaction, their disintegration and dissolution behaviour, objectives/rationale involved in the design of MUPS dosage form, challenges in their compaction and key variables to be considered in successful production of MUPS.
KEY WORDS: MUPS, multiparticulates, pellets, tablets, compaction, compression, tabletting.

INTRODUCTION

Tablets are indeed the most popular solid dosage form for oral administration. One category of tablet formulations that has gained remarkable importance in drug therapeutics owing to various benefits it offers is controlled or modified release formulations. Controlled release capsules often containing plurality of coated pellets is yet another category of solid oral formulation that offers analogous therapeutic benefits. 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. Such a system is known as MUPS tablets.

MUPS is abbreviation for **M**ultiple-**U**nit **P**ellet **S**ystem. However, from pharmaceutical industry and research perspective, the term in general refers to MUPS compacted into tablets. Thus, the resulting tablets prepared by compaction of modified release coated multiparticulates or pellets are called as MUPS.

Compaction of MUPS is a challenging area. Aggressive research but by few individuals and industries is being carried out worldwide in this area.

Advantages of Compaction of MUPS over Conventional Modified-Release Tablets and/or Pellet-Filled Capsules

1. ***Pharmacokinetic advantages***

i. Rapid but uniform transit of micropellets 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.[1]

ii. Uniform emptying of micropellets from stomach into small intestine facilitates rapid dissolution of enteric coating and drug release resulting in early t_{max} and C_{max} (peak time and peak plasma concentration) in case of delayed-release formulations. In case of controlled-release

preparations, drug release is more uniform and possibility of dose dumping is avoided with minimized tendency for inter-subject variations.[1]

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.[1]

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 minimized.

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, e.g. Prevacid SoluTab.

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, e.g. Prevacid SoluTab.

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 swallowing.[2]

v. Smaller volume/size of tablet leads to better patient compliance than capsules.[3]

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 tabletting facility.[4]

iii. Lower cost of processing owing to higher processing speed, elimination of capsule cost, etc.[4]

iv. The product is relatively tamper-proof.[4]

v. Unlike conventional tablets, there is reduction in dust problems during compression.[5]

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 tabletting. 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 tubes[6] or from highly lubricated compacts.[7]

6. ***Regulatory advantages***

i. Extension of patent life.

ii. Line extension of product.

iii. Possibility of patenting and registering the product in various markets globally.

Properties of an Ideal 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.[8]
2. The drug release should not be affected by the compaction process.[9]
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 rupture.[9]
4. Pellet compacts must possess optimum physical strength to withstand the mechanical shocks

encountered in their production, packaging, shipping and dispensing.[10]

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 MUPS

It is suggested that four mechanisms are involved in the compression process of granules namely – deformation, densification, fragmentation and attrition.[4,11] 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] It has been suggested that permanent deformation and densification are the major mechanisms involved in the compression of spherical units while fragmentation and attrition seem to be inexistent or to occur to a minute extent.[11-13]

Disintegration and Dissolution Behaviour of 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 pellets.

Objectives of Preparing 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 form.

Marketed MUPS Formulations

Table 1 enlists few of the marketed MUPS formulations.

Challenges in the Compression of 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 tablets.[3]
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 tabletting 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 achieved.[14] 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 tabletting blend to avoid segregation.[15] With use of higher amounts of pellets, variation may reduce but the tendency for damage to coating increases.
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 subunits.[16] Moreover,

formulation scientists must have a comprehensive knowledge of how that formulation will behave during tabletting, as well as how other excipients and/or process-related parameters will affect the performance of that formulation as a drug delivery system. The increase in the number of operations involving compaction of pellets have resulted in a growing need for new theories and methodologies, which describe the physical properties of pellets and their relation to the compression/consolidation processes. Development and refinement of methods for determination of physical properties of pellets and a more in-depth understanding of the compaction process are needed in order to predict more accurately the tabletting behaviour of the pellets and its optimisation. Bashaiwoldu has summarised the progress made in the development of measurement methods for mechanical properties of the pellets.[17]

Formulation Approaches to Prevent Destruction of Drug Release Characteristics and other Attributes of Compacted 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 categorised 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.[18] 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.

Hard, less porous and non-compressible materials such as inorganic salts are unsuitable for use as cushioning excipients. Homogeneous mixtures of pellets and filler-binders are crucial to obtain tablets of uniform weight and drug content, and thus to ensure a high reproducibility in production.

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, etc.[9] 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 coatings.[19]

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 coating.[20]

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 beneath.

Modulation of Core Pellet – Besides the role of polymer coating on the pellets, the nature of core drug pellet can dramatically influence the damage to its own structure and the coating on its surface. 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 rearrange.[11]

c. *Pellet size* – Larger pellets deform more easily than smaller pellets.[12]

d. *Pellet elasticity* – Findings of various researchers on elasticity 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 tabletting.[18] 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 ruptured.[21]

To sum up, pellets that are smaller in size, stronger mechanically, less porous and more uniform in size distribution are more suited for compaction without deformation than pellets with wide size distribution, greater porosity, larger size and mechanically soft. Further, the polymer coating on such core drug pellets should be thick and elastic.

Often a combination of above approaches can be employed to result in a MUPS that retains the desired drug release and product characteristics.

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 pellets[22] –

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.

Matrix pellets – pellets which inherently contain excipients that retard drug release by being contained within the matrix of pellet structure, for example matrix pellets of swellable polymers or waxes, retain their controlled release characteristics to a larger extent even on compression since the release of drug from such pellets depend upon swelling or erosion of matrix rather than by diffusion through the membrane.[23,24] However, an important point that needs consideration in the design of MUPS of such matrix pellets is fusion of pellets with each other during compaction which may not be obvious during compression of coated pellets. Fusion of matrix pellets as a result of compaction can be avoided by application of film coating on such pellets or excessive blending with a hydrophobic agent separately prior to mixing them other extragranular materials before compression into tablets.

Figure 1 illustrates the MUPS comprising of reservoir and matrix pellets, figure 2 represents the approaches adopted for preparation of MUPS without damaging the membrane coating while figure 3 portrays the impact of compaction on pellet deformation and drug release.

Processing of 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 increased.[21] Beyond this value, both disintegration and dissolution are delayed, which testifies the formation of undesired matrix tablets.[18]

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.

A summary of factors or key variables that needs consideration during compaction of MUPS is given in table 2.

Tabletting Equipment for Processing of MUPS

Any tablet compression machine with little modification can be used for preparing MUPS. Modifications are often required in the feed frame and forced feeders. The former designed to ensure uniform clearance from the turret throughout the compression process to prevent attrition and crushing of coated pellets. Design of forced feeders should also intend to prevent such eventualities as abrasion or grinding of pellets.

Future Directions

Evidently the challenges in developing a MUPS formulation are many. Albeit the number of MUPS formulations reaching the market is few, development of such formulations is being pursued actively by both industry and academia since the technology possesses the potential of providing certain distinctness in the designed formulation. A major edge that MUPS provides is a formulation which is difficult for potential competitors to replicate from a regulatory perspective and thus such a dosage form enjoys monopoly for a much longer duration.

TABLE 1: Marketed MUPS tablet 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

TABLE 2: Factors to be Considered in the Design of MUPS Tablets[3]

Formulation Variables

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

Membrane coating

Type of polymer – cellulosic or acrylic, etc.
Coating thickness
Type and amount of placticizer
Presence of pigments
Additional outer coat on polymer surface – plastic layer or powder layer

Cushioning excipients

Nature – deformable (plastic) or fracturable (brittle)

Size – powder or pellets
Amount – ideally 50 to 75%

Process variables

Compression force
Compression speed

Equipment variables

Design of tabletting machine, powder feeding mechanism, etc.

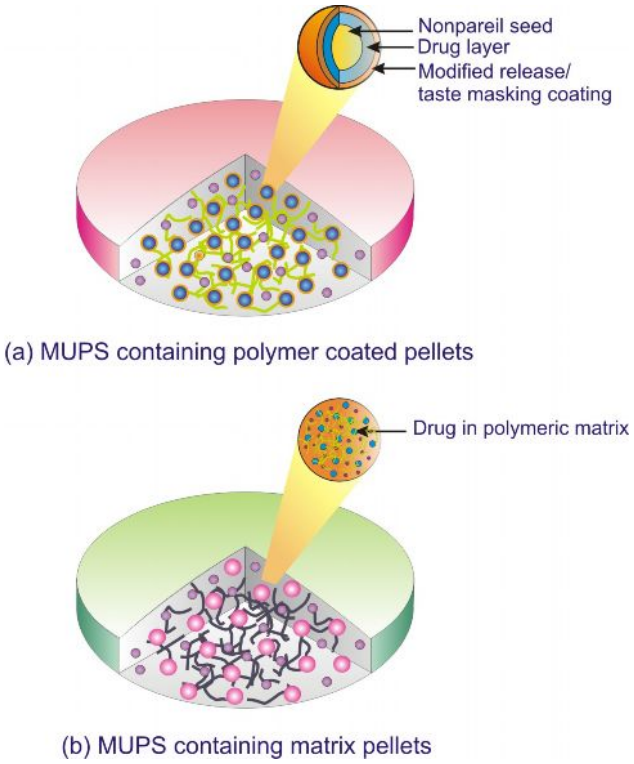

Figure 1. Types of MUPS – (a) MUPS containing polymer coated pellets, and (b) MUPScontaining matrix pellets

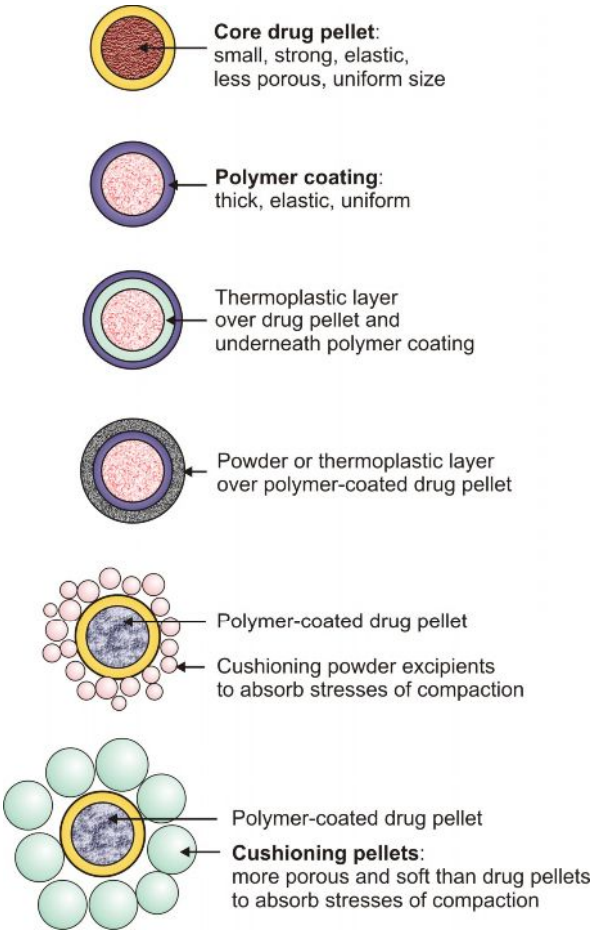

Figure 2. Schematic representation of the various approaches to prepare MUPS of coated pellets formulations

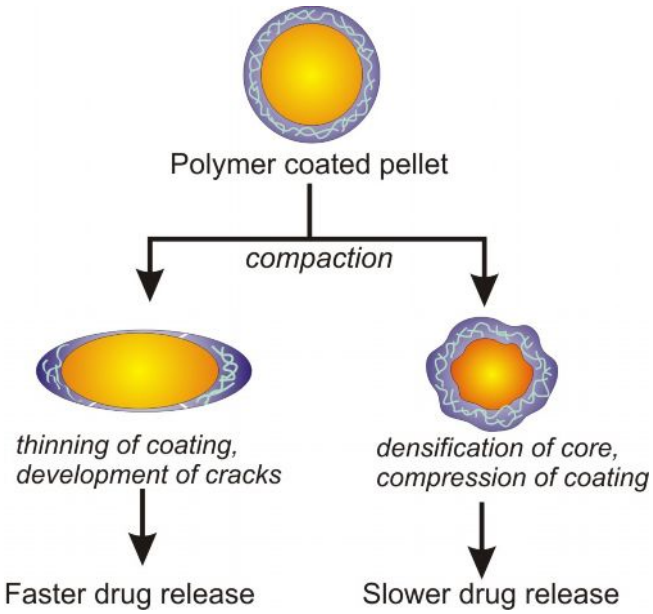

Figure 3. Impact of compaction on pellet deformation and drug release

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