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MULTIPLE UNIT PELLETS SYSTEM (MUPS) – REVIEW

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ABSTRACT

Compressed multiple unit pellet tablets/multiple unit particulate or pellet system commonly called MUPS are composed of polymer coated subunits namely pellets; which are embedded in an inert excipients matrix designed to overcome the difficulties in administering capsules and improved Physico-chemical stability compared to suspensions. The functional coating like drug coating, barrier coating, enteric polymer coating is usually applied in a fluid bed coating processor provides each subunit with the characteristic desired drug release properties. The size, shape and surface morphology of the pellets to be coated are the prequisite for coating of pellets. Design of MUPS involves formulating pellets by different techniques and further compression of these pellets into rapidly disintegrating tablets; disintegrate rapidly in the oral cavity for the delivery of coated pellets into the gastrointestinal tract or the site of release of the drug. In spite of the challenges like content uniformity of the compressed tablets, ability of the film to withstand compression force; MUPS occupy a prominent role in formulating drugs due to their greater patient compliance, process, formulation and therapeutic advantages.

KEYWORDS

MUPS (Multiple unit pelley system), Multiple unit pellets tablets, Multiple unit pellets compressed Tablets, Disintegrating tablets, Cushioning excipients, compression velocity, pelletization.

INTRODUCTION

A design principle of increasing importance for sustained, controlled, delayed, site specific or pulsatile release preparations is the compaction of coated particles into disintegrating

multiple unit tablets. One challenge in the production of disintegrating multiple unit tablets is maintaining the modified drug release after compaction, as the application of the compaction pressure can lead to deformation of film coating and, consequently, altered drug release, as reviewed by Bodmeier. To protect the coating from such changes, excipients with so-called cushioning or protective properties are usually incorporated in the tablet formulation in addition to fillers. The compression-induced changes in the structure of a film coating may depend on physical factors of pellets such as the size, shape, density, porosity and formulation factors such as type and amount of coating, the properties and structure of the substrate pellets and the incorporation of excipient particles. The demand for MUPS tablets has been increasing due to its greater advantage over other dosage forms. The present review focuses on compaction and characteristics of multiple unit pellets to tablets. 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. 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 pellets are called as MUPS (Multiple Unit Pellet System).[1,2]

Compression of Pellets to Tablets (MUPS)

Multi particulates are filled into hard-shell gelatin capsules, compressed into tablets Figure 1, suspended in liquids or packed in sachets. Compaction of single units results in disintegrating tablets illustrated in Figure 2; becoming more and more important on the pharmaceutical market, as they provide several advantages compared to single-unit dosage forms and pellet-filled capsules.[2]

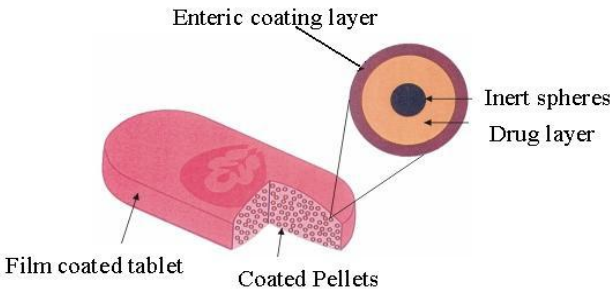

Fig 1: MUPS - Multiple Unit Pellets compressed to Tablet.

Fig 2: MUPS showing rapid Disintegration in Water.

MUPS Tablets

MUPS tablets are widely used in solid dosage form design. MUPS is advantageous in comparison to monolithic dosage forms. Combination of drug substances and release profiles can be provided by formulating the MUPS tablets with different pellet qualities or combining pellets with drugs in powder or granulated form. MUPS tablet contains several hundred of coated pellets of active pharmaceutical ingredients which delivered the drug at predetermined rate and absorption to provide constant blood profile. MUPS are easily administered as disintegratable tablet which disperse into their subunits across the stomach and the small intestine, leading to predictable oral transition and constant bioavailability.[1,2,3]

Rationale of Formulating MUPS

The rationale in formulating MUPS is to design chased on the release rates such as designing controlled release, sustained release, delayed release and colon targeted drug delivery system; oral disintegrating taste-masked dosage form; combining drugs with different release characteristics in the same dosage form. The drug dose administered in modified release form can be increased as compared to that possible with capsules and enhance the stability of dosage form as compared to its capsule counterpart. It also helps in obviating the need for specialized packaging such as that required for capsules making it a more cost effective dosage form.[2]

Advantages

1. Possibility of developing different dosage strengths without process/formulation changes.
2. Pellets have stable therapeutic effects over single unit dosage forms.
3. Pellets can also be used to provide different release profile at the same or different sites in the gastrointestinal tract.

4. Pellets offer high degree of flexibility in the design and development of oral dosage form like suspension, sachet, tablet and capsule.
5. Pellets disperse freely in gastro intestinal tract, increasing drug absorption, and reducing local irritation of the mucosa by certain irritant drugs.
6. Pellet-released active ingredients may offer a greater bioavailability than usual drugs.
7. Good tolerability - It reduces side effects by maintaining plasma levels within the therapeutic zone. It delivers steady plasma levels hour by hour for day and night control.
8. Better patient compliance - Orally disintegrating MUPS tablet having a palatable taste which is suitable for pediatric and geriatric patients who cannot swallow tablet or capsule. e.g. Prevacid Solu Tab.[1,2,3,4]

Disadvantages

1. Dosing by volume rather than number and splitting into single dose units as required.
2. Involves capsule filling which can increase the costs or tabletting which destroy film coating on the pellets.
3. The size of pellets varies from formulation but usually lies between 1 to 2 mm^2.

Ideal Characteristics of MUPS

1. Should maintain all the tablet properties.

2. Pellets should not show any interaction like developing electrostatic charges; during compression.

3. The pellets should not show any deviation in its release even after compression.

4. The coated pellets during the process of compression should not fuse into a non-disintegrating matrix and should not lose its coating integrity either by breaking or cracking or rupturing the coating layer (s) or pinholes and other imperfections.

5. Like tablets, MUPS should have ease to withstand physical parameters, stability, packing storage and transportation. The dosage form must disintegrate rapidly into individual pellets in gastrointestinal fluids.[5]

Types of MUPS Formulations

MUPS formulations are broadly classified into two types illustrated in Figure 3.

- **MUPS with matrix pellets.**
- **MUPS with pellets coated.**

MUPS with matrix pellets used generally in controlled release formulations. These pellets are coated with Swellable or Erodable polymers than diffusible polymers. The main problem of matrix pellets in compression is fusion of polymer coating of pellets with other pellets and also polymer coating with extra-granular material. This can be counteracted by coating with any non interfering coating agent. For example hydrophobic coating agent prevent fusion of pellets-pellet and pellet-tabletting excipients. 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. 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 extra-granular materials before compression into tablets.

MUPS with pellets coated using different pelletization techniques with all the desired characteristics for compression of pellets.

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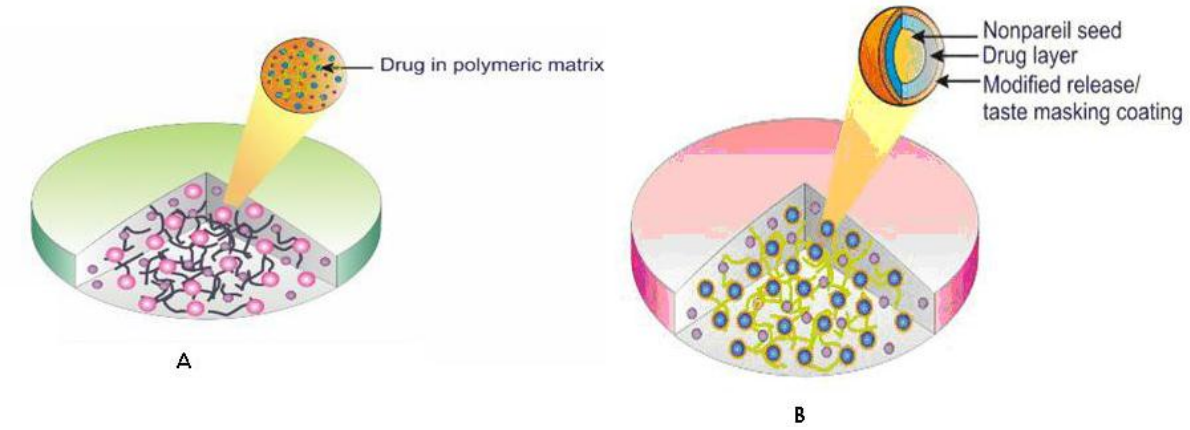

Fig 3: A) MUPS with matrix pellets. B) MUPS with polymer coated pellets.

Mechanisms involved in Compression of MUPS

It is suggested that four mechanisms are involved in the compression process of granules namely

- Deformation,
- Densification,
- Fragmentation,
- 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. 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.[10]

Deformation of Pellets During Compression

Deformation of the aggregates was found to depend on three deformation characteristics, namely, capacity, mode and the resistance to deformation. The mode of deformation of pellets depends on the material composition of the pellets and extra-granular material used for compression. This is of two types. The former is surface oriented deformation, a local change in the geometry of the external surface of a pellet making the pellet conform to the external surfaces of adjacent pellets (*i.e.* there is no change in the bulk dimensions). Later one is bulk oriented deformation, a change in the main dimensions of the pellets, primarily

expressed as a flattening of their bulk. High surface deformation refers to the great ability of the pellets to conform to the surfaces of surrounding pellets. In pellets containing a soft component, the primary particles can reposition within the agglomerate and hence the ability to fill the inter-granular pore space is increased. For pellets consisting of a hard material, on the other hand, the compaction stress may give local failure at pellet surfaces. Thus, the material properties of the primary particles constituting the pellets are important for the compression behavior of pellets.[8,9,10,11]

Challenges in Formulating MUPS

1. To ensure uniformity of content and weight.
2. To compress the coated subunits to tablets with sufficient hardness and low friability without damaging the film coatings.[2,11]

Disintegration and Dissolution Behaviour of MUPS

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 orally dispersible 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.[1,2,12,13]

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.

1. Modulation of fillers or cushioning 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 two classes.

1. Conventional powder excipients.

2. Cushioning pellets.

1. 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, Lactose is often required to provide optimum cushion.

2. 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. 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.

2. 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

1. Use of more elastic coating composition.
2. Increased thickness of coating.
3. Elastic/ Thermoplastic layer on the outer surface of drug pellets.
4. Powder layer over the surface of polymer coated pellets.

1. 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. 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.

2. Increased thickness of coating

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

3. 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.

4. 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.

3. 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.

1. Composition.

2. Pellet porosity.

3. Pellet size.

4. Pellet elasticity.

a. Faster drug release.

b. Prolonged drug release.

1. 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.

2. 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.

3. Pellet size

Larger pellets deform more easily than smaller pellets.

4. Pellet elasticity

Findings of various researchers on elasticity of core pellets are discordant. Claimed that the bead core should possess some degree of elasticity, in order to accommodate changes in shape and deformation during tabletting. Conversely, possess should characteristics such as high crushing strength so as to overcome the compression forces and the coated pellets are neither deformed nor ruptured. 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.

1. Faster drug release.

2. Prolonged drug release.

1. 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.

2. 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.[14,15]

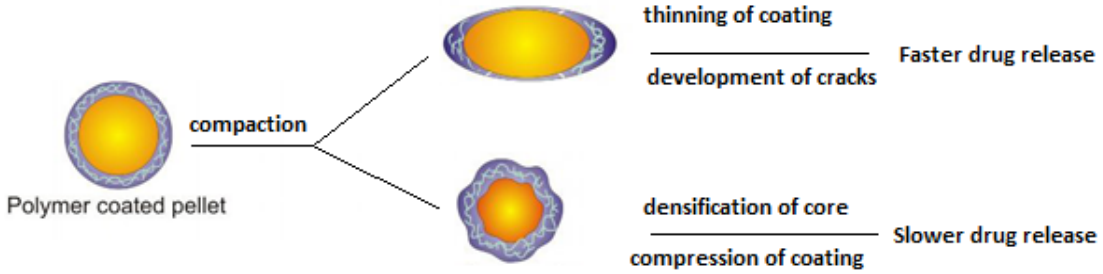

Fig 4: Impact of compaction on pellet deformation and drug release.

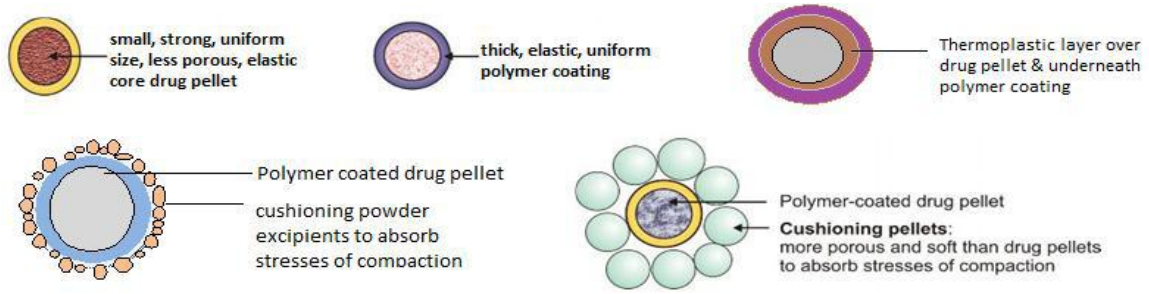

Fig 5: Schematic representation of various approaches to prepare MUPS of coated pellet formulations.

Tablet Press for Preparing MUPS

Tablet press designed MUPS have a modification in the hopper, feed frame and forced feeders compared to normal tablet press. The hopper for feed consists of a butterfly valve to modulate the flow of blend to feed frame. The feed frame designed is continuous to ensure uniform clearance from the turret and prevent attrition/ segregation of pellets from extra-granular material and also crushing of coated pellets throughout the compression process, which is not possible with the regular rotary tablet press. The forced feeder used is gravity feeder, designed to prevent abrasion or grinding of pellets.[14,15]

Processing of MUPS

Compaction factors that can influence preparation of MUPS include.

1. Compression force exerted.

2. Compression velocity.

1. Compression force exerted

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. Beyond this value, both disintegration and dissolution are delayed, which testifies the formation of undesired matrix tablets.

2. Compression velocity

It 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.[15]

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.[15]

Methods of Pelletization

Compaction and drug layering are the most widely used pelletization techniques. Other methods such as globulation, balling are also used in development of pellets in a limited scale. Some of the desirable properties of the pellets include pellets shape should be near spherical and have a smooth surface; both considered important characteristics for subsequent film coating. Additionally, the particle size of pellets should be as narrow as possible. The optimum size of pellets for pharmaceutical use is considered to be between 0.5 and 1mm.

1. Powder layering.

2. Solution / suspension layering.

3. Extrusion and Spheronization.

1. Powder layering

Powder layering involves the deposition of dry powders of drugs and excipients on neutral spheres with the help of binding liquids. Powder layering involves simultaneous addition of binding agents and dry powders; hence it requires specialized equipments like spheronizer. If the process is set-up properly, hourly weight gains up to 300% are possible, which indicates the processing option is very fast and efficient.

2. Solution / suspension layering

Solution/suspension layering involves the deposition of solution or suspensions of drug substances and binder over the neutral spheres. Consequently conventional coating pans, fluid bed processor, centrifugal granulators, wurster coaters have been used successfully to manufacture pellets by this method. To achieve uniform layers the bottom spray method should be the processing option of choice. Average weight gain per processing hour is about 15-20%, because 80 - 85% liquid vehicle have to be evaporated.

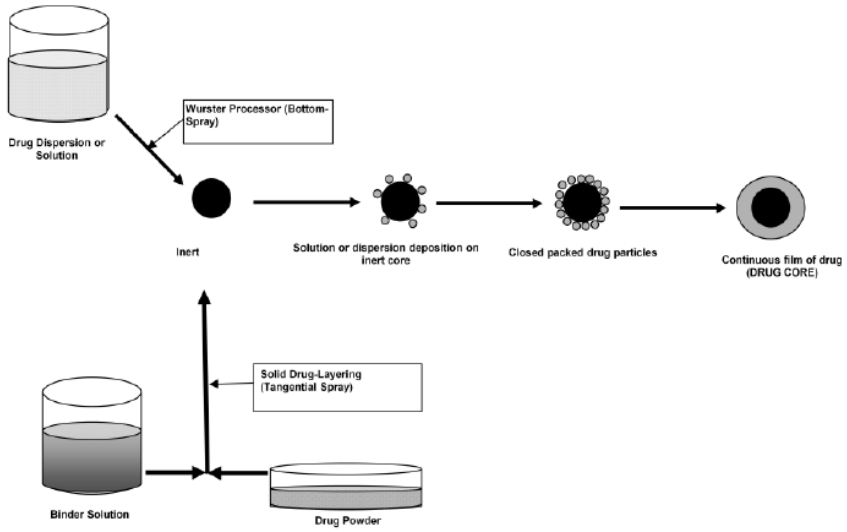

Fig 6: Principle of Powder Layering and Solution/Suspension Layering.

3. Extrusion and Spheronization

This processing option is the oldest known industrial pelletizing technique. First all ingredients are blended, then by adding liquid a wet dough is formed, which is passed through an extruder with defined dye sizes. Other pelletization methods such as globulation, cryopelletization, spray drying, spray congealing, balling, and compression are used, although on a limited scale in the preparation of pharmaceutical pellets.[16]

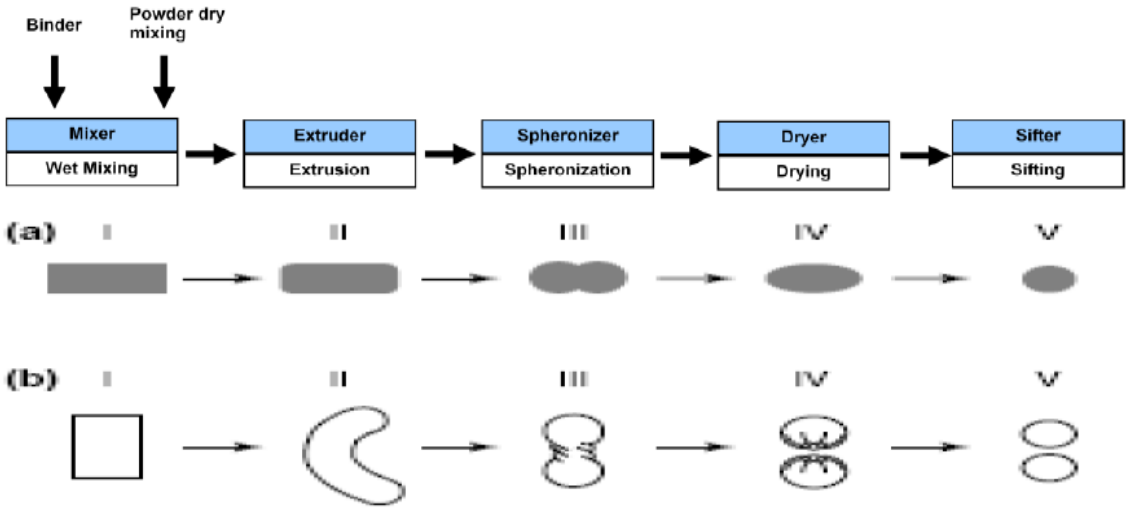

Fig 7: Principle of Extrusion and Spheronization process.

Type of Multi Unit Dosage Forms

With regards to the final dosage form, the multiparticulates are usually formulated into single-unit dosage forms such as filling them into hard gelatin capsules or sachets or

compressing them into tablets or suspended in a suspending media with suitable suspending agent at an appropriate pH.[17,18]

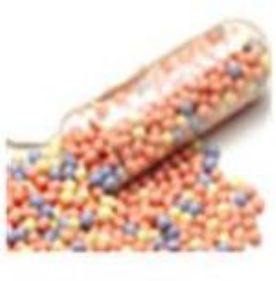

Fig 8: Capsules.

Fig 9: MUPS Tablets.

Application of MUPS

1. To protect drugs that are unstable in acid from disintegrating in the gastric juice e.g. antibiotics enzymes, peptides proton pump inhibitors.
2. pH Dependent controlled release of drugs for optimal absorption.
3. GI targeting of different sections of small intestine or of the colon (absorption window, targeting localized effects).
4. Colon targeting for local treatment and systemic therapies. The key to controlling the release of the drug is the pH dependent dissolution of the film coating, which takes advantage of the different pH values that exist along the gastrointestinal tract. Since the coatings dissolution is controlled by pH, or by gradually permeability, the drug is release in a precise manner in specific sections of the digestive tract, or at specific times after intake.
5. Combination of drug substances and release profiles can be provided by formulating the MUPS tablets with different pellet qualities or combining pellets with APIs in powder or granulated form.[19]

Future Directions

There are numerous challenges in developing a MUPS formulation. The number of MUPS formulations reaching the market is one; 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.[19]

CONCLUSION

Formulation of different drugs to MUPS tablets has a prominent role because dissolution profiles tailor-made to biopharmaceutical requirements are a key therapy success factor. Present scenario of MUPS find a greater advantage which is the compaction of pellets coated with drug and polymer due to its flexible design in variable release properties, stability, patient compliance and economic compared to other dosage forms. For the pharmaceutical industry, not only the innovation of new products and techniques, creation of line extension, expansion of patent protection, achieving globalized product and thereby overcome competition are also key strategies with respect to profit perspective. MUPS meet all these with medical, health care, and business benefits.

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