A Current Technology for Modified Release Drug Delivery System: Multiple-Unit Pellet System (MUPS)

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ABSTRACT

Pelletization is a technique to convert drugs or excipients to small free flowing, spherical or semi spherical units, which are produced by agglomerating fine powdered drug/excipients with a binder solution. Pellets range in size, typically, between 0.5 – 2.0 mm. MUPS (Multiple Unit Pellet Systems) are multi-particulate in nature and are administered as tablets. These tablets disperse in stomach and intestine allowing constant drug release in systemic circulation. This article reviews the advantages, disadvantages, common industrial technique for preparation of pellets and challenges in manufacturing of MUPS.

Key words: MUPS, Pellets, Tablets, Compaction, Compression, Tableting, Spheronization.

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INTRODUCTION

The oral route of drug administration is the most important and most user-friendly route of administration. In recent years, Multiple Unit Pellet Systems (MUPS) tablets are widely used in solid dosage form design. MUPS is considered to provide pharmacokinetic advantages compared to monolithic dosage forms. Typically, modified release pellets are contained in MUPS tablets. Modified release drug delivery systems have acquired very important role in pharmaceutical research and development.[1] Pellets are produced primarily for the purpose of oral modified release forms having gastro resistant, sustained-release properties and the capability of Pulsatile Drug Delivery Systems. For such purposes, coated pellets are administered in the form of hard gelatin capsules or disintegrating tablets that quickly disperse in the stomach. The safety and efficacy of the formulation is higher than that of other dosage forms. Pellets provide high degree of flexibility during the design and development of oral dosage forms. They can be divided into desired dose without formulation or process changes, and can also be blended to deliver

incompatible agents simultaneously or particles with different release profiles at the same site or at different sites within the gastrointestinal tract. Orally administered pellets generally disperse freely in the gastrointestinal tract and maximize the drug absorption, minimize local irritation of the mucosa for certain irritant drugs.[2]

Pellets may be produced by different methods based on their application and the choice of manufacturer. The most widely used processes are extrusion and spheronization, solution or suspension layering, and powder layering. Other processes with limited application in the development of pharmaceutical pelletized products include globulation, balling, and compression. The compression of pellets into tablets is a novel technology and is much more ideal than filling them into capsule.[3,4]

MUPS Tablets:

MUPS tablets are widely used in solid dosage form design[5, 6,]. 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 [7, 8.]

Objectives for the preparation of MUPS Tablets

Following are some of the objectives and current application areas of MUPS tablets:

1. For controlled release drug delivery system.
2. For enteric release and colon targeted drug delivery system.
3. Designing of Mouth-melting taste-masked dosage form.
4. Combining of drugs with different release patterns in the same dosage form.
5. Increasing the drug dose administered in controlled release form as compared to that possible with capsules.
6. Enhancing stability of dosage form as compared to its capsule counterpart.
7. Obviating the need for specialized packaging.

Advantages of Pellets

Following are some of the advantages of using pellets:

- Possibility of developing different dosage strengths without process/formulation changes[9].
- Pellets have stable therapeutic effects over single unit dosage forms[10-11].
- Pellets can also be used to provide different release profile at the same or different sites in the gastrointestinal tract.
- Pellets offer high degree of flexibility in the design and development of oral dosage form like suspension, sachet, tablet and capsule[12-13].
- Pellets disperse freely in gastro intestinal tract, increasing drug absorption, and reducing local irritation of the mucosa by certain irritant drugs[14].
- Pellet-released active ingredients may offer a greater bioavailability than usual drugs.
- 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 [15].
- 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 SoluTab.

METHODS OF PELLETIZATION [16, 17, 18]

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.

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.

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.

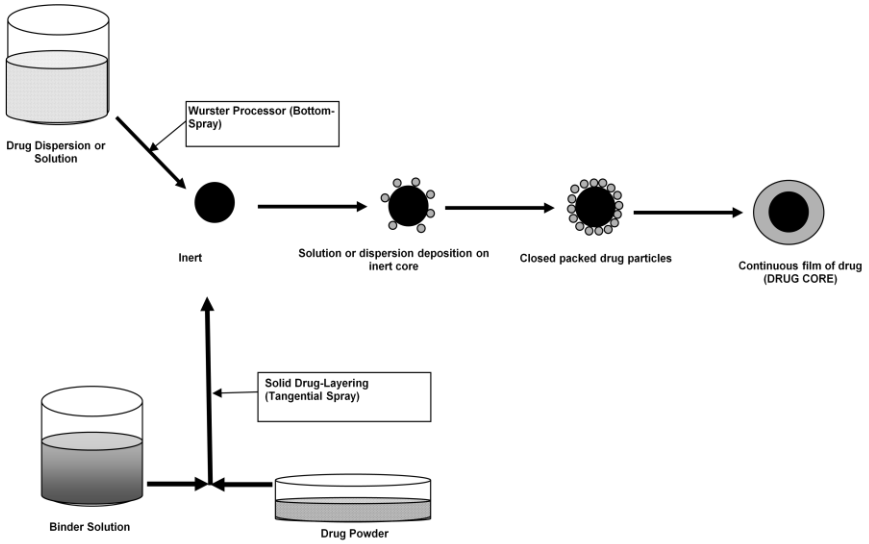

Fig 1: Principle of Powder Layering and Solution/Suspension Layering

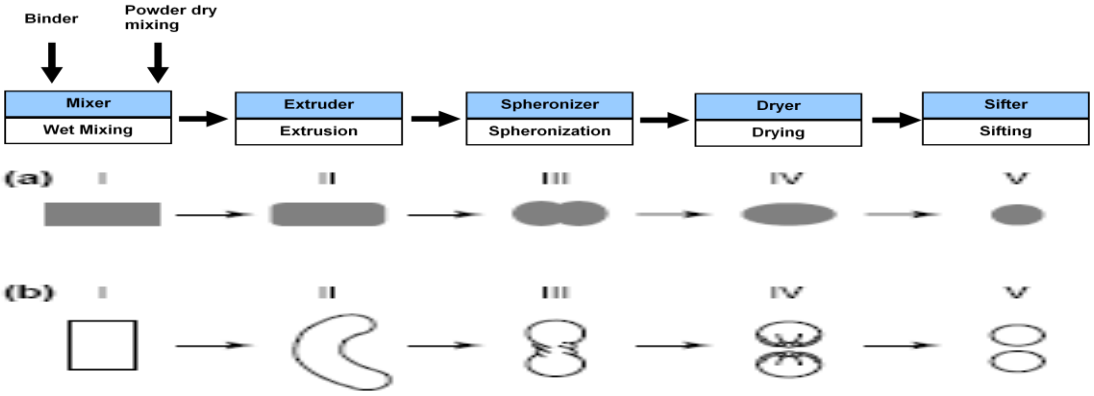

Fig 2: Principle of extrusion and spheronization process

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.

TYPES 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.

Fig 3: Flexibility of pellets in development of dosage form

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.[19]

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.[20]

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. [21, 22]

Compression of MUPS[23-25]

It is recommended that four mechanisms are involved in the compression process of granules namely – deformation, densification, fragmentation and attrition. Recently, the use of nearly spherical units, here defined as pellets, brought new insights 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.

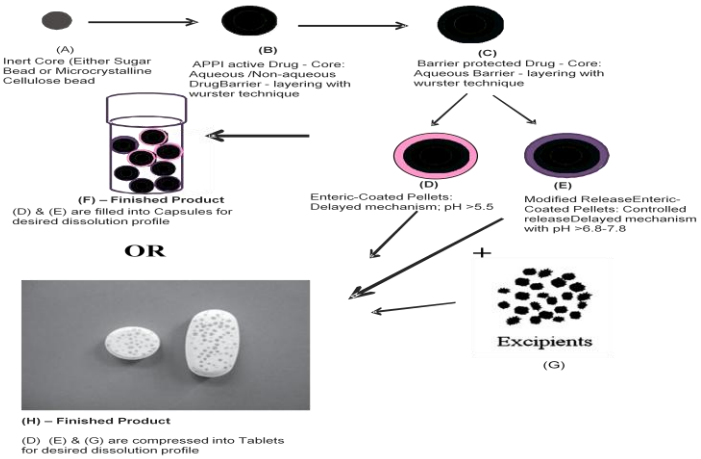

Fig 4: Representation of Formulation Design

CHALLANGES TO DEVELOP MUPS TABLETS [26, 27]

Following factors to be considered during design and manufacture of MUPS to avoid deformation, densification, fragmentation and attrition of pellets:

- Robustness of coated pellets to maintain the drug release profile after compression.
- Compactibility of heterogeneous mass of pellets and tabletting excipients.
- Mechanical strength of compacted tablets for further processing such as film or functional.
- Coating and packing.

Solutions to overcome challenges in MUPS [28-31]

- Granulation: The tabletting mixture with good flow and narrow particle size distribution prevent de-mixing of pellets and extra-granular material. In case of big sized coated particles, size adaptation (managed by granulation) may be considered.

- **Pellet shape:** The shape of the pellets should be spherical or nearly spherical for good uniform distribution. A more deviation in spherical shape does not result of characteristic release due to flaws and cracks during compression.
- **Pellet size:** The size of the coated pellets can be maximum upto 2 mm to withstand compression pressure. Large sized pellets cause rupture to the coating of pellets due to segregation with tabletting excipients and there by direct exposure of the transmitted force by the upper punch to lower punch. Thus influences content uniformity of the final tablet.
- **Pellet Density:** Pellets of density about 1.5 g/cm^3 shows faster gastric emptying than pellets with higher density of > 2 g/cm^3. Pellets with < 2 mm in diameter and < 2 g/cm^3 density can pass through pyloric sphincter both in fasted and fed state which is similar to liquids in terms of gastric emptying.
- **Pellet core and Core material:** Pellets should have low surface to volume ratio as this may result in a decreased area of contact between the particles as they consolidate. In favor of this, pellet core should have some degree of plasticity to have deformation in shape during compression without any damage to the coated film. An extensive study has been carried out on microcrystalline cellulose by many researchers both as powdered and granulated forms, and revealed that microcrystalline cellulose shows plastic deformation during compression and offers better protection to the coated particles as powder and granules. Core material should not be too hard eg. Dicalcium Phosphate pellets, which obstructs the flow of pellets. In such case, compression force shows impact on the surface and results in deformation of the surface and alters the release characteristics.[32]
- **Porosity:** Porosity of pellets plays a major role in compression thereby relates to deformation. The deformation of pellets was much in favor of medium and high porous pellet because of high porous nature pellets become denser due to the applied compression force and forms as deformed coherent units due to the non interfering excipients. Compaction of less porous pellets results in significant increase in the release rates of the drug which is due to comparatively low densification and deformation. The excipients used should not interfere with the pellets which alter the drug release profile. The extragranular material must form closest packing with the deformed pellets.[33]
- **Polymer coating and Film flexibility:** Polymers widely used in attaining specific release profiles are cellulose derivatives and polyacryls. Cellulose and its derivatives like HPMC,

HPMCP forms hard and brittle films that fractures during compression whereas polyacryls and copolymers of acrylics form flexible film deforms easily on compression. Plasticizers like triethyl citrate, triacetin and polyethylene glycol also helps in the formation of flexible films. During compression a highly flexible film ensures elastic properties and prevents cracking of coating. Polymers like Eudragit along with plasticizers triethyl citrate provide greater flexibility to the film in required quantity.

- **Selection of Solvents:** Both aqueous and non-aqueous coatings can be done. Though aqueous coating is eco-friendly, a certain drawbacks such as degradation of the drug due to entrapped moisture; when pellets are cured for more time to evaporate moisture, the temperature also results in degradation. Whereas, non-aqueous coatings show thixotropy of polymer solution as sol-to-gel; helps to coat the polymeric solution and the solvent evaporate much earlier than aqueous solvents.[33]
- **Mechanical resistance:** Film flexibility provides mechanical stability to pellets during compaction. During compression, high mechanical resistance support film integrity by preventing deformation of pellets. Larger particle size supports mechanical stability and leads to less interparticle contacts which also support less film damages.[34]
- **Coating thickness:** The thickness of coating layer is related to mechanical resistance of pellets during compaction. Greater thickness supports elastic properties, whereas below a certain thickness even highly flexible films tend to break. The manner in which deformation of the coated pellets occurs during compaction alters the thickness of the coating layer which has an impact on the release profile of the drug.
- **Extra-granular material and cushioning agents:** Film stability is influenced by extra-granular material during compression. Sharp-edged and abrasive crystalline materials may damage the coating as compression force increases. This alters the drug release characteristics after compaction into tablets. Type and amount of the coating agent, selection of additives like plasticizers, use of cushioning excipients and rate of pressure applied must be monitored carefully to maintain the drug release properties of the sub units helps in the protection of the film. Cushioning agents are waxy in nature take up the pressures of compaction by re-arranging themselves within the tablet structure or by preferentially getting deformed and/or fractured thereby provides protection to the coated pellets. The best choice of cushioning agent is polyethylene glycol preferably polyethylene glycol 6000. Cushioning

pellets are normally more porous and soft compared to coated drug pellets and normally made of excipients which are used. 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. [35, 36]

- **Electrostatic charges:** Development of an electrostatic charge on the pellet surfaces can interfere with their flow during tablet compression cycle. This problem is usually solved by adding talc, which acts as a glident.[37, 38] During development of multiparticulate tablets comparative dissolution tests should be conducted to identify the possible differences between the release rates of the uncompressed tabletting mixture versus the tablets. In order to ensure reproducible drug releases the difference between the two dissolution profiles should not exceed 10%.

MARKETED PRODUCTS OF MUPS

Losec MUPS is the second highest selling pharmaceutical drug product in Sweden in the year 2002. Another patent is of European Patent Office by Astrazeneca EP 723437 for Nexium and Losec for compression of proton pump inhibitor to tablets for MUPS into the market. Various marketed products are tabulated in Table I.

Table 1: Marketed Products of MUPS

Product	Company	Drug	Therapeutic Category	Formulation type
Losec MUPS	Astra Zeneca	Omerprazole Magnesium	Antiulcer	Antiulcer
Esomeprazole	Astra Zeneca	Esomeprazole Magnesium	Antiulcer	Antiulcer
Troprol XL	Astra Zeneca	Metoprolol tartrate	Antihypertensive	Extended release
Prevacid SoluTab	Takeda	Lansoprazole	Antiulcer	Delayed release Orodispersible tablet
Theodur	Key	Theophylline	Antiasthmatic	Extended release

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. [39, 41]

CONCLUSION

Formulation of different drugs to MUPS tablets offers a significant role because Pellet-released active ingredients may offer a greater bioavailability than usual drugs. Present scenario of MUPS finds a greater advantage due to its flexible design in target drug release properties, stability, patient compliance and cost effectiveness when compared to other dosage forms. For a pharmaceutical industry, the innovation of new products and techniques, creation of line extension, expansion of patent protection, achieving globalized product and thereby overcome competition are key strategies with respect to profit perspective. MUPS meet all these with medical, health care, and business benefits.

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