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Multi-Unit Pellet System Tablets: A Review

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Abstract:
Oral route of drug administration is the commonest form of drug administration. Multi-unit pellet system tablet involves is a tablet that contains either coated or uncoated pellets. This system confers so many advantages to the tablet when compared to the conventional tablets. Multi-Unit Pellet system technique has some challenges that when optimized yields an excellent tablet with wonderful pharmacodynamics profile. This article reviews the advantages, ideal properties of multi-unit pellet system, production of multi-unit pellet system tablets and challenges of compressing multi-unit pellet system tablets. Multi-unit pellet system has been utilized in the production of some pharmaceuticals whose pharmacodynamics effect always stands out from the rest conventional tablets.

Keywords — **Multi-unit pellet system, extrusion, spheronisation, multi-particulate, compression.**

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I. INTRODUCTION

The essence of formulating different dosage forms is to administer them to the patients to prevent, diagnose or treat any existing illness. It is of essence that whatever dosage form administered to the patient is absorbed in the right proportion that would exert the desired pharmacological action. For each of the dosage forms, tablets, powders and parenteral, they have their different pros and cons. With the development of multi pellet drug delivery systems, most of the challenges of some dosage forms have been avoided. The Multiple-Unit Pellet System (MUPS) tablets are a kind of multiparticulate system that has become an important and successful dosage form for immediate or modified drug release. These Multiple Units are composed of tablets containing uncoated or coated pellets allowing modified drug release [1]. Different techniques have been used in the manufacture of multi-unit pellet system. The manufacturing process of these tablets is tough and constitutes a challenge when considering all the steps involved in the process [1]. Some studies have been carried out on the advantages of MUPS, challenges and techniques of MUPS production. This study is inspired by patient's testimonies about some products used in the management of Gastroesophageal Reflux Disease (GERD) and ulcer which have been produced as MUPS tablet. This study involves a literature review on MUPS system as a form of drug delivery. This study covers the advantages of MUPS, techniques of production, challenges of production.

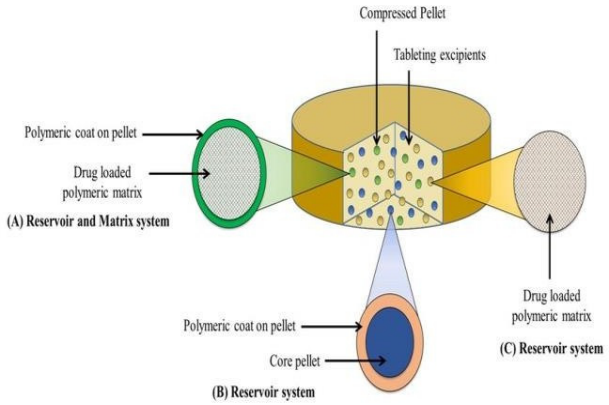

Fig I. Pictorial diagram of multi-unit pellet system tablet [11]

II. ADVANTAGES OF MULTI-UNIT PELLET SYSTEM TABLET DRUG DELIVERY

- The MUPS technology is used successfully as an alternative to conventional tablets. Enteric coated pellets containing different drugs and packed into tablets are commonly used to protect drugs from gastric media. It has been shown that Omeprazole MUPS have increased bioavailability and improved pharmacological response [2].
- Smaller pellets contained in MUPS passes from the stomach into the small intestine rapidly and uniformly resulting in the lesser chances of localized irritation, uniform drug absorption, and more bioavailability [4]
- Uniform emptying of pellets from the stomach into small intestine supports faster dissolution resulting in early tmax (peak time) and Cmax (peak plasma concentration). In the case of controlled release preparations, drug release is more identical, and the chances of dose dumping are avoided with minimized tendency for inter-subject variations [4]
- The MUPS have a lesser tendency of adhering to esophagus during swallowing [5].
- 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 [7]
- Compressing coated pellets into tablet 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 [7]
- MUP form rather than filling them into capsules is helpful to avoid use of gelatin [6].
- Greater physicochemical and microbiological stability of pellets owing to their embedment in inert matrix [8].

III. IDEAL PROPERTIES OF MULTIPARTICULATE TABLETS

In addition to all the properties of a conventional tablets, it should also possess the following attributes [9].

- The polymer-coated pellets must be able to withstand the pressure during compaction with little deformation.
- The drug release from pellets should not be affected by compaction operation.
- The surface of the compacted MUPS tablets must be smooth and elegant to facilitate the film coating.
- The compacted MUPS should disintegrate rapidly into individual pellets within the G.I.T fluids.
- The physical strength of the pellet structure must be efficient to withstand the mechanical shocks that are applied in their production, packaging, transport, and dispensing.

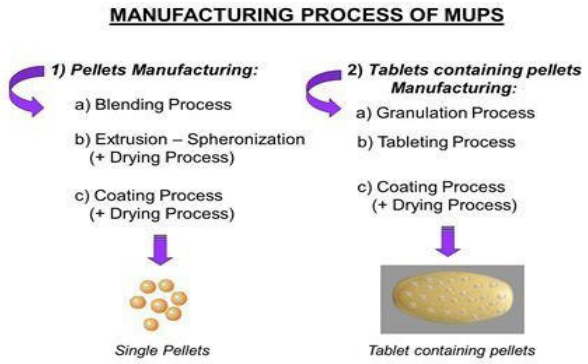

Fig. II. (1) Diagram of Pellet manufacturing (2) Tablet containing pellet manufacturing [1].

IV. MANUFACTURING PROCESS OF MUPS

The manufacturing process of MUPS can be divided into two steps

1. Pellet manufacture
2. Manufacturing of tablets containing pellets

First, the drug-pellet manufacturing process begins with the blending of pellet components such as drug, cushioning excipients like microcrystalline cellulose, Glyceryl Monostearate (GMS) and Lactose Monohydrate (LM) are widely used in this kind of formulation. A binder liquid must be used for wet mixing. The mass obtained continues through the extrusion: shaping the wet mass into cylinders. Then spheronisation process: breaking up the exudates and rounding of the particles into spheres. Afterwards, the drying of pellets recently formed can be performed in a fluid bed dryer. The next step, pellet coating, requires a careful selection of the excipients that will form the coating film in order to obtain the desired drug release [10].

The tableting process will be performed by a rotary tablet press machine and tableting parameters like main compression force or speed constitute important issues. Pellets and cushioning excipients will be added for tableting, taking into account the excipients' adequate properties in order to withstand high compression forces [1].

Tablets containing pellets with specific features of shape, weight, thickness, and hardness then continue through the tablet film coating process. The tablet film coating is applied to improve the stability and appearance of the pharmaceutical composition, and has no significant influence on drug release

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upon tablet disintegration, as it is one of the functions of pellet coating film [1].

Compression of Multi-Unit Pellet System Tablet

Each discrete particle in a MUPS product incorporates its own release characteristics and further contributes to the product's therapeutic activity. Compressing these subunits without affecting their individual release profiles is a major challenge of MUPS technology because compacting subunits may lead to structural changes in the coating and consequently alter drug-release behavior [12]. Compressing coated pellets to achieve more than one aim presents a huge challenge hence, thorough process optimization is needed for the compaction of coated pellets. The main variables involved are the compression force and the velocity of the punches. The hardness, thickness, and porosity of the tablets must be maintained. Other important factors concerning the preparation of multiunit tablets are the properties of the barrier coating and the inclusion of protective excipient particles in the tablet formulation [13].

Pellet core

The selection and study of the material used to manufacture pellets is important to achieve the desired release pattern [14]. Salako confirmed the advantages of softening materials during compression. On application of initial compaction pressure, the soft beads ruptured. On further application of pressure, the beads deformed and formed a network. Because of the soft nature of the beads, the material readily underwent deformation and rearrangement. Harder pellets are compact, and upon the application of compaction pressure, they underwent reduction in volume by particle rearrangement, not because of bond formation, compared with soft pellets (15).

Pellets undergo structural modifications during compaction. They need elasticity and flexibility to withstand compaction pressure. The ideal pellets are strong, not brittle, and have a low elastic resilience. They should deform under load application and load recovery without fracture (16). Knowledge of the compression behaviour of uncoated pellets can provide a basis for the manufacture of multiunit tablets from barrier-coated pellets without damaging their coating [13].

Size and Shape

Small pellets are stronger than large ones; they withstand compression pressure with less deformation [17]. Ragnarsson found that the compaction of small pellets had less effect on drug release than the compaction of large pellets. He also concluded, however, that the effect of pellet size depended on the choice of coating material, as well as on the amount and properties of the pellets and the excipients forming the tablet [18]. The shape of pellets affects the compression behaviour and tablet-forming ability of granular materials. Irregular shapes induce complex compression behaviour in granules. They increase the attrition of the granules, thus resulting in increased deformation [19,20].

Density and Porosity

Pellets with a narrow size distribution and excipients of similar sizes, shapes, and densities can prevent segregation [21]. The critical density for achieving prolonged gastric residence may be between 2.4 and 2.8 g/cm^3 [22]. The amount and choice of material used for binding or granulating the powders during palletisation, and the compaction pressure, have a direct effect on the porosity. A study by Bodmeier revealed that an increased proportion of water as granulating fluid in the mixture led to hard and less porous tablets with a slow drug-release pattern. Similarly, pellets prepared using 95% ethanol as a granulating fluid showed good compressibility in contrast with pellets prepared with water [12]. Porosity also can affect drug release. Tuton showed that pellets of high porosity were densely packed and deformed, and that the drug release from these pellets was not affected. But upon compaction of pellets with low porosity, the pellets were compressed with slight densification and deformation, leading to increased drug release. Using highly porous pellets did not alter the drug release after compression, in comparison with pellets with low porosity [23].

Compression force

Several studies investigated the compression force required for compressing pellets and found that 15 KN was sufficient for tablets with smooth surfaces [13]. Flament studied the compression of theophylline-loaded pellets with acrylic polymer. Upon the application of compression pressure, the pellets were compacted by deformation at 6 KN. Further investigation revealed that increasing the compaction force to 20 KN did not alter the dissolution rate significantly [24].

Protective Particle

Protective particles, also known as cushioning agents, help prevent damage to the drug–polymer-loaded core pellets [13]. Preferred excipients are agglomerates (e.g., pellets or granules) that lower the risk that pellets will separate by size or density during processing, thus leading to weight variation or dose non-uniformity [13]. Several studies proved MCC and polyethylene glycol to be good excipients for compaction because of their plastic deformation [21,25,26,27]. Studies also proved that lactose, which undergoes fragmentation upon compression, offers better protection than MCC [28]. Studies of 14 excipients proved that excipients that show good plastic deformation during compression give the best protection to the coating material [29]. Particle size is an important factor in preformulation, and some studies suggested that particles smaller than 20 µm prevent damage to the coating. Increased dissolution rate was observed with particles bigger than 20 µm [22,30]. Using wax as a cushioning agent during pellet compression also is of great help to the formulator because it prevents damage to the coating during compression [31].

Nature of Polymer

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Polymers play an important part in any controlled- or modified-release dosage form. The final release of the drug from the formulation depends on the polymer used [13]. A polymer must have appropriate plastic and elastic properties to withstand the shear of compression and compaction [13]. Various polymers currently used to modify the release of pellets are either cellulosic polymers (e.g., ethyl cellulose) or acrylic polymers (e.g., Divakar's Polex, Evonik's Eudragit, or BASF's Kollicoat). The most frequently used polymers to extend the release of water-insoluble drugs are ethyl cellulose and ammonio methacrylate copolymers [32]. Film-forming polymers have satisfactory elastic properties that prevent the rupture of the coating polymer, and good plastic properties that prevent deformation during compression [13]

Thickness of polymer coating

Applying a thick polymeric coating to the surface of pellets imparts good elasticity and crushing strength to them [25]. Bodmeier observed increased elastic and plastic deformation upon application of thick coating [12]. To prevent the coatings from rupturing during compaction, the coating should have good elasticity and flexibility and be able to undergo structural changes and adapt to the deformation process [16,25,33,34].

Plasticizer

Plasticizers are added to polymeric dispersions, especially to water-dispersions, to lower their glass-transition temperature and expedite the coalescence of the distinct polymer particles in the dispersion [13]. The flexibility of the aqueous-based coatings was improved by adding plasticizers, but Aulton observed that plasticizers led to a reduction in tensile strength [35]. Felton proposed that increasing plasticizer content would increase the tensile strength of film-coated beads. The increased degree of plasticization of the polymer made the film more elastic and allowed it to withstand the deformation process during compression [36].

V.CONCLUSION

Multi-unit pellet system tablets prevent different side effects that comes with the conventional tablets. The process of manufacturing is challenging and several factors needs to be optimized in order to get a dosage form with a high bioavailability. When all the factors are optimized, the result is an excellent dosage form with a wonderful pharmacokinetic and pharmacodynamics profile.

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