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Review Article

MULTIPLE UNIT PELLET SYSTEM (MUPS TECHNOLOGY) FOR DEVELOPMENT OF MODIFIED RELEASE FAST DISINTEGRATING TABLETS: 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 elderly patients, especially since it is difficult to swallow for them. Multiparticulates are the choice of dosage form when fast disintegration is desirable without loss of original release profile. 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 (MUPS) but also factors regulating the compression behavior of pellets including properties of pellets, core material, and compressible excipients. This review also presents detailed explanation on physicochemical properties of pellets and formulation strategies of MUPS.

Keywords: Multi-particulates, Multiple Unit Pellet System (MUPS), sustained-release, delayed-release, pellet compression, drug layering.

INTRODUCTION

As our society has a significant number of geriatric patients, so an appropriate dosage form for elderly patients is most anticipated. Because of the slower physiological functions, such as swallowing, the conventional dosage forms are not useful in a broad way. The easiness in swallowing a tablet depended on its size. Studies indicate that the tablet with the size of 7-8 mm is easiest to swallow, but the size of 8 mm is easiest to handle. Therefore, since a tablet size that is both easy to swallow and handle is hard to achieve; tablets have some inherent problems as dosing formulations for the geriatric patients.[1]

Considering easy to swallow and handle tablets are most desirable in geriatric patients, attempts have been made to develop a fast-disintegrating tablet.[2] Such a tablet can disintegrate in a less amount of water in the oral cavity and is convenient to take at any time, place or any age patient.

Orally Disintegrating Tablets (ODT) are usually meant to disintegrate in the oral cavity and release drugs instantly. In this case, certain dosage forms are required to design which can deliver drug at pre-determined manner. A fast-disintegrating drug delivery tablet dissolves or disintegrates quickly in the oral cavity when comes in contact with saliva, hence resulting in solution or suspension of the drug to be administered.[3] In the case of suspension, particles which are disintegrating from the tablets are made up with modified release profile.

In this case, multi-particulates are the choice of dosage for modified release system. These are dosage forms having small discrete particles having identical release profile and form a therapeutic dose using such identical particles called multi-particulate system.[4] Most widely used multi-particulates are pellets filled in the capsules. Granules, mini-tablets, powder crystals and ion-exchange resin particles are orally administered multi-particulates. Nanoparticles, nanosphere, nanocapsules, microparticles, microsphere, liposomes and other vesicular formulations are parenterally administered multi-particulates.

FEATURES OF MULTIPARTICULATE DOSAGE FORM

Multiparticulate drug delivery is beneficial over single unit dosage form in following aspects.[5]
When multiple-unit systems are taken orally, the subunits of these multiple-unit preparations distribute over a large surface area of the gastrointestinal tract. These small particles (<2 mm) act as liquids which leave the stomach within a short period. The small size of multi-particulates enables uniform distribution in the gastrointestinal tract that potentially improves bioavailability resulting in reduced local drug concentration. Therefore, helps reduce the risk of toxicity and side-effects.[6] Variation in bioavailability due to reduced food effect or premature drug release from enteric-coated dosage forms in the stomach potentially results in degradation of drug or irritation of gastric mucosa. Such symptoms can be minimized or eliminated with coated pellets because of more rapid transit time when compared to enteric-coated tablets.[7, 8]

In the multiple-unit systems, the total drug dose gets divided into multiple units. Failure of few units in the system would not significantly impact the dose, unlike single-unit system. This phenomenon is apparent in sustained-release single-unit dosage form, where a failure may lead to dose-dumping of the drug.[5] Other advantages of this divided dose include ease of adjustment of the strength of a dosage unit, administration of incompatible drugs in a single dosage unit by separating them in different multi-particulates and combination of multi-particulates with different drug release rates to obtain the desired overall release profile.[9]

COMPRESSED MULTIPARTICULATE SYSTEM

Individual discrete particles with desired release property can either be filled in capsules or compressed into tablets. Compression into tablet form is advantageous over filling into capsule owing to higher industrial productivity and economic viability. Compressed tablet using super disintegrant can disintegrate in water easily and can be swallowed by patient easily as compared to capsule. Dusting during manufacturing is also reduced using the compressed multi-particulate system.

MULTIPLE UNIT PELLETS SYSTEM (MUPS)

MUPS is the compressed system of pellets having identical release properties like uncompressed pellets. They are formed using some cushioning excipients (which aid the compression of pellets). Drugs which are incompatible can be combined as one of the units of the dosage form. Different release profiles of the same drug or different drugs can be achieved using MUPS.

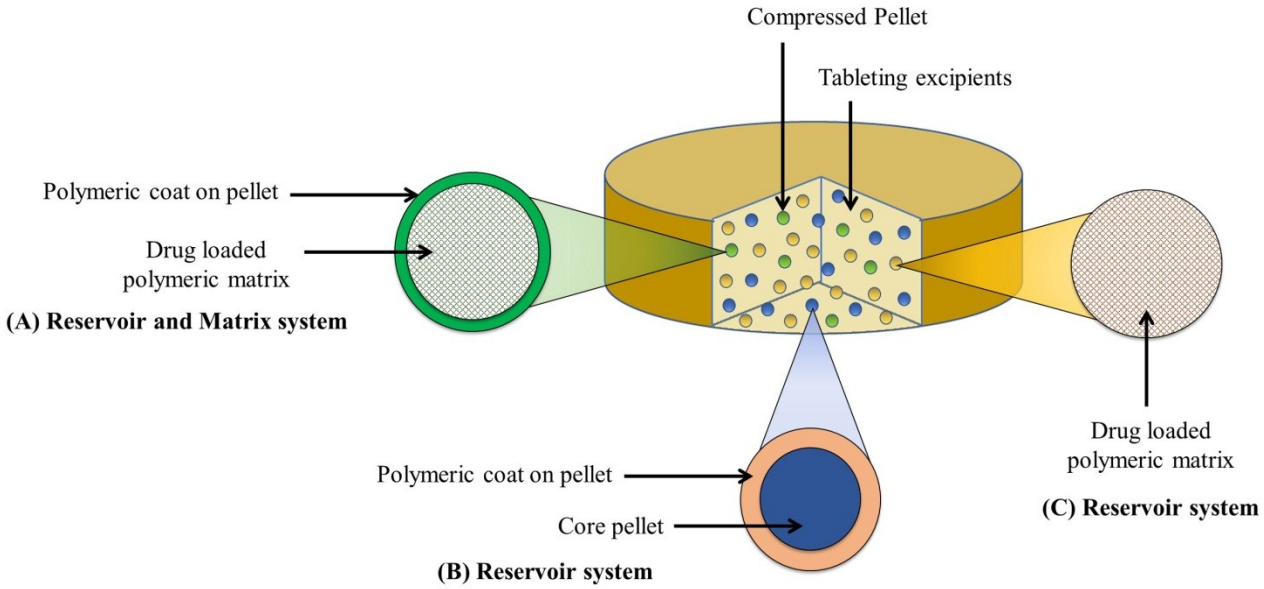

Figure 1: MUPS consisting pellets prepared by reservoir, matrix and combined pellets system

Advantages of MUPS

Modified release dosage forms such as extended release and delayed release dosage forms with multiple units such as pellets offer various advantages over other conventional dosage forms such as tablet and capsule. 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.[10] Uniform emptying of pellets from the stomach into small intestine supports faster dissolution resulting in early t_{max} (peak time) and C_{max} (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.[10] Uniformity in gastric emptying and subsequently drug dissolution of pellets in the GIT with their small size and larger surface area, uniform drug absorption occurs which results in consistent and controlled pharmacological action. The number of pellets in MUPS dosage form is more than conventional pellet filled capsule which significantly reduces inter- and intra-subject variability in drug absorption and clinical response. As a result, the possibilities of dose dumping or incomplete drug release gets reduced.

The pediatric and geriatric population, who cannot swallow tablet or capsule as such, are more beneficial from dosage form like MUPS, e.g. Prevacid SoluTab.[11] Such medication can be taken without any fluid such as water, especially during traveling since the formulation is designed as the orally disintegrating preparation that contains flavors and sweeteners which stimulate salivation and swallowing. MUPS tablets can be designed into a dividable dosage form, without compromising the drug release characteristics of coated particles contained therein. The MUPS have a lesser tendency of adhering to esophagus during swallowing.[12] Smaller volume/size of tablet can be formulated with intact release profile because of compression.[13] Compressing coated pellets into tablet form rather than filling them into capsules is helpful to avoid use of gelatin.[14]

MUPS is a tablet dosage form, so it offers all processing advantages which a tablet has over capsule preparation. Pellets are physicochemically and microbiologically stable because of their entrapment of drug into matrix. Processing cost can be minimized by rapid manufacturing process because capsule manufacturing is a longer process than making MUPS.[15] The MUPS dosage forms are relatively tamper-proof. Because of pellets, dust problems can be reduced which can be observed in tablet manufacturing.[16] Pellets are of a near-spherical shape which shows excellent flow properties and easy to process for compaction as compared to non-uniform sized granules. These compositions usually require lesser amounts of lubricants for improving flow. Product life cycle can be extended by MUPS technology by extending patent life and line extension of the product. MUPS is a very flexible dosage form but at the same time very difficult to formulate which cannot be easily copied by other competitors. The possibility of patenting and registering the product in various markets globally.

Characteristics of MUPS

MUPS is a tablet dosage form and possesses all properties of a conventional compressed tablet. During the process of compression, the compressed pellets should not fuse into a matrix which is difficult to disintegrate. This results in a faster disintegration and disaggregation into individual pellets in gastrointestinal fluids.[17] The process of compression must not affect the final drug release profile. MUPS made up of reservoir-type coated pellets; the polymeric coating must withstand the compression force; coating should not break even if deformed. Tablet with compressed pellets must possess the optimum physical strength to withstand the mechanical shocks encountered in their processing such as production, packaging, shipping and dispensing.[6] Compressed MUPS have very uniform and smooth surface without pinholes and other imperfections and should facilitate ease of film coating if required. Compression of small coated particles is easier than the larger one. However, the coating is difficult for smaller particles.[18] Smaller particles can be coated efficiently by side spray on swirling flow of particles specifically when the particles are irregular shaped.[19]

Pellets: A Potential Candidate for Multi-Particulate System

Different attributes of the pellets such as density, porosity, composition, and size can affect the properties of the multiple-particulate system. An understanding of the compression behavior of uncoated pellets can provide a basis for the formulation of multiple unit tablets. Compaction and consolidation behavior of pellets show the difference as compared to the power of same material upon compression.[20] Film formation from aqueous dispersions, however, is a complex process.[4] In aqueous dispersions, polymer particles come into contact with each other in a closed packed order during drying. Due to high interfacial surface tension between air and water, there is the formation of a layer of polymer spheres filled with water.

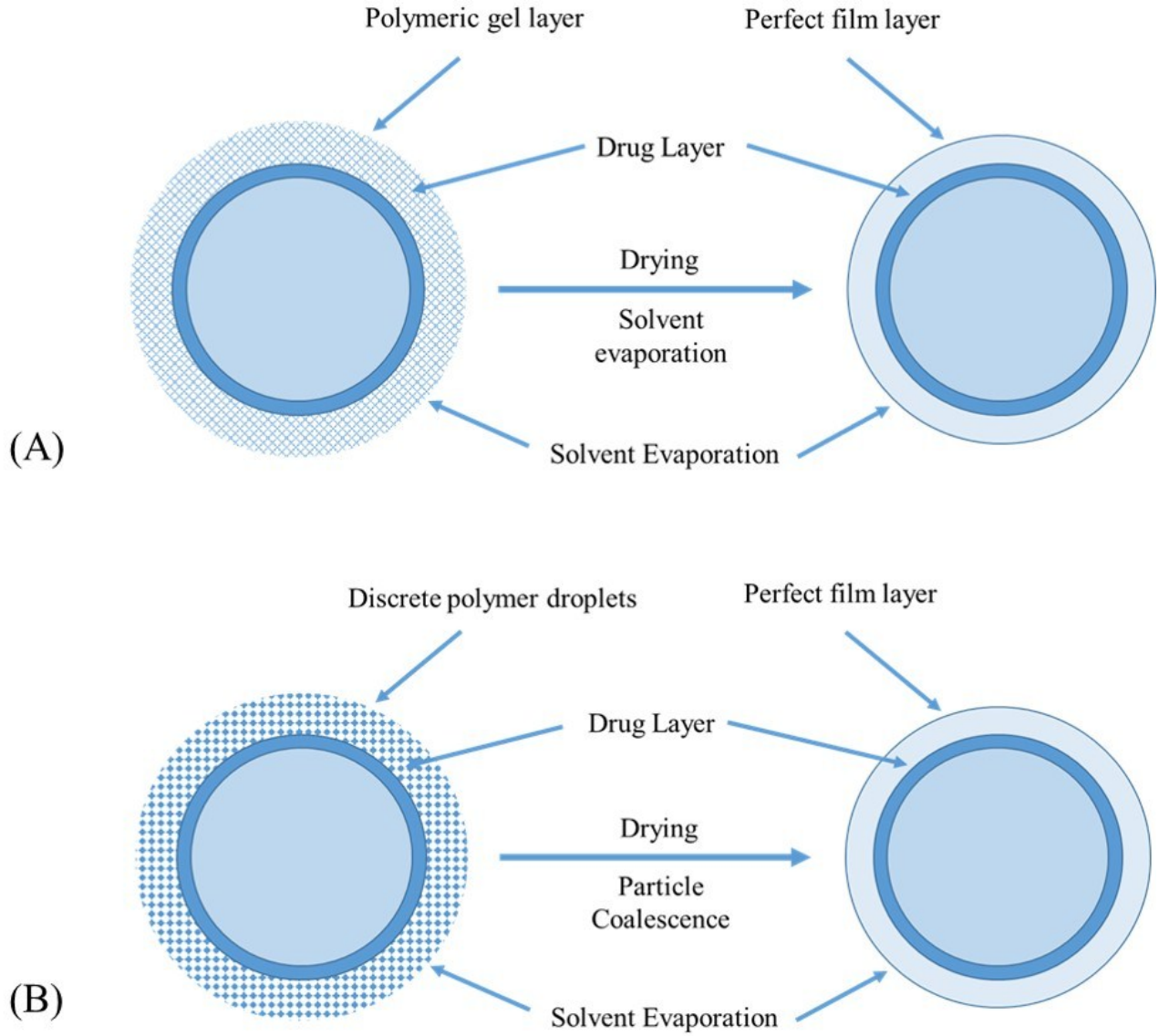

Figure 2. (A): Schematic presentation of the film forming mechanism from organic polymer solution. (B): Schematic presentation of the film forming mechanism from aqueous polymer dispersions

The aqueous dispersions also consist of additional ingredients such as surfactants that act as stabilizers during the production process. Other compounds such as plasticizers and anti-tacking agents are also used to enhance the coating process and film properties. Plasticizers are added to promote the polymer particle coalescence, softening the particles and reducing minimum film formation temperature (MFT).[21] Polymer film formation depends on the glass transition temperature (Tg) of the polymer or minimum film formation temperature of the aqueous dispersion. The MFT is the minimum temperature to form a continuous film during drying under standardized conditions.[22] Below MFT; the dry latex is opaque and powdery; however, these conditions are different from drying during coating. In fact, water can decrease T_g of some polymers (due to its plasticizing effect), and so MFT is lower than the T_g of the polymer. Lippold and group showed a linear relationship between the T_g and MFT for different polymer/plasticizer concentrations.[23]

Methods of Preparing Pellets

Extrusion and Spheronization

Basic steps for extrusion and spheronization include four steps as below.

- Wet Granulation – preparation of the wet mass/granules or dough
- Extrusion – transforming the wet dough into cylindrical extrudes;
- Spheronization - breaking up the extrudate and rounding off into round spheres;;
- Drying – drying of the spheres/pellets

Powder materials along with drug are transformed into the dough using granulating liquid and extruded from an extruder. Extrudates are spheronized into spherical shape beads called as pellets. Extrudates undergo series of transformations to form pellets (described in Table 1) and subsequently dried.

Table 1: Stages of pellet formation in spheronization process

	Extrudate	It is the product of Extrusion process subjected to spheronization.
	Chopped Cylinders	Extrudates are broken into smaller Cylinder parts.
	Round-ended Cylinders	Due to Hatch plate, the end portion of cylinder becomes round shape
	Dumbbells	Subsequent form of cylinder due to spheronization
	Ellipsoids	Ellipsoidal shaped product
	Pellets	Final stage product has round spherical shape.

Hot Melt Extrusion (HME)

In this method, the mixture is exposed to high temperature, and pressure and the drug is dispersed in the matrix at a molecular level by forming solid solution and extrudates. Extruded material can then further processed into pellets. Hot melt extrusion is commonly used in the delivery of poorly soluble drugs as it increases the dissolution, absorption, and therapeutic efficacy of the drugs by the mechanism of a solid solution.[24]

Powder Layering

This technique involves deposition of successive layers of dry powder of drug and excipients on preformed nuclei like sugar spheres and MCC spheres with the help of binding liquids. Powder layering involves simultaneous application of binding agent and dry powders; hence it requires specialized equipment like Spheronizer. A key requirement for this process is that the product container should have solid walls without any perforations to avoid powder loss in product chute before the powder is picked up by the wet mass of pellets being layered.[25, 26]

Solution/suspension Layering

Drug or coating materials are sprayed on the cores or pellets using Fluid Bed Coater. Coating liquid may be in the form of solution or dispersion and solvents used are either organic or aqueous. Layering by solid dispersion requires curing after completion of coating at its glass transition temperature. Wurster technique is widely used for a solution or suspension layering.[27]

Globulation

It is a process that forms the droplets and subsequently transforms into solid beads or pellets.[25, 28]
Two processes are related to globulation:

Spray Drying: It is the process in which drug in the suspension or solution without excipients is sprayed onto a hot stream to produce dry and more spherical particles. This process is commonly used for improving the dissolution rates and bioavailability of poorly water-soluble drugs.

Spray Congealing: Here, the drug is dissolved or dispersed in a hot melt of gums, waxes or fatty acids and then sprayed into an air chamber with the temperature below the melting point of the formulation components, to produce spherical congealed pellets.

Compression of Uncoated Pellets

Several mechanisms have been proposed for the compression behavior of uncoated pellets. The most prominent mechanism involves five steps namely; repositioning, deformation (change in the shape of individual pellet), densification (a reduction in the pellet porosity), fragmentation (fracturing of pellets into small particles) and attrition of small particles.[10, 29, 30, 31]

Compression of pellets is four stage process which involve (1) volume reduction of the pellets by rearrangement of pellets to fill inter-particle voids (2) volume reduction of pellet bed by local surface deformation involving surface flattening of pellets (3) bulk deformation of pellets (change in pellet dimensions) in parallel with densification of pellets and (4) cessation of the volume reduction owing to low inter- and intra-granular porosity.[32]

Compression of Coated Pellets

The coating is applied to pellets to mask the taste, improve stability, elegance, and mechanical integrity. Coated pellets can be compressed into tablet dosage form if the coat has certain properties. The coat must remain attached to pellets and unbroken during compression. Coating polymer must have enough flexibility and deformability to be compressed. Coated pellets either go plastic deformation or withstand with compression. Soft pellets undergo plastic deformation while hard pellets withstand with compression. Flexibility and plastic deformability is measured by elongation value.[33]

Factors Regulating the Compression Behavior of Pellets

Type of coat: Eudragit NE 30 D and Eudragit NM 30 are found to be the most flexible polymer in the class of acrylic acid polymer. Ethyl cellulose is very brittle in nature even after plasticizing it. Aquacoat ECD has <5% elongation after plasticizing with triethyl citrate.[34]

The thickness of coat: Thicker film coat can withstand with pellets after compression but after certain level of thickness the polymer-polymer binding increases than polymer-substrate binding which leads to the breaking of coat.[35]

The flexibility of coat: Plasticized coat has good elongation property which aids the plastic deformation of pellets during compression. Kollicoat® SR 30 D (Polyvinyl acetate dispersion stabilized by Sodium dodecyl sulfate) is polymer for sustained release formulations, is brittle in nature and least elongation value <1%. After plasticizing it with 20 %, triethyl citrate enhances the elongation value up to 150% and support in the compressibility of pellets.[17] Top coated beads with highly bonding polymer enabled the manufacturing of MUPS in reported study. Moisture activation followed by silica coating of polymer top coated beads were developed with enough mechanical strength and desired release profile.[36]

Pellet size: Larger pellets easily break during compression while smaller pellets don't break until more force is applied. Smaller pellets also avoid the segregation of pellets and subsequently the content uniformity problems.[37]

Pellet porosity: Highly porous pellets can easily undergo deformation but also densification which leads to change in the release profile. Dense pellets are less porous and lower tendency for densification. Smaller dense pellets can withstand with compression without alteration of release property.[10]

The mechanical crushing strength of pellets: Incorporation of a higher amount of binder forms the hard pellets but produce the dissolution problem. Mechanically strong pellets can withstand the higher force of compression.

Tableting excipients: Ideal tableting excipient should prevent the direct contact of pellets during compression. Tableting excipient could be any of powder of material, agglomerates or granules or soft pellets which can be compressed along with the pellets. Another requirement of tableting excipient is to have flow property. The difference in the density of tableting excipient and pellets should be minimal to avoid the segregation during filling into compression press and maintain uniformity of dosage units. The protective effect of tableting excipient

depends on the compressibility characteristics. Material that can deform plastically is the best excipient to use as tableting excipients.[38] Pellets used for compression can be mixed with other excipients that can help the compression of pellets. Glyceryl Behenate, Glyceryl Monostearate, higher molecular weight Polyethylene glycol (PEG 3350, PEG 6000), Cellactose and granular grade excipients like Avicel PH 200 can be used as tableting excipients.[39]

Cushioning pellets and granules: Cushioning pellets are either deforming or disintegrating in nature. Disintegrating pellets tends to break during compression with pellets while deforming pellets not break but undergo deformation and help the drug loaded pellets in the compression.[40] Cushioning excipients are developed using different techniques such as co-spray drying using stearic acid for the protection of pellets during compression.[41] Novel cushioning excipient developed using co-spray dried micronized lactose with different polymers such as Hydropropylcellulose (HPC), Hydroxypropylmethylcellulose (HPMC) and polyvinylpyrrolidone (PVP). Such excipients help reducing yield pressure and improve compressibility.[42] Microcrystalline based cushioning layer on extended release ethylcellulose coated pellets showed intact release profile after compression. Researchers reported that addition of glidants drastically decreased coat rupturing during compression.[43] Co-spray dried micronized lactose with mannitol was studied for the compression of ethylcellulose coated pellets using rotary tablet press. The increase in dwell time during compression resulted in significantly improved mechanical strength of MUPS tablet. However, increasing compression force reduced the mean dissolution time of MUPS.[44]

Compression force: Compression force applied for the tableting of pellets depends on the property of pellets. Some pellets have elastic recovery after compression, and such tablet has very low tensile strength. Compression force must be optimized for soft pellets to get desired tensile strength.

Compression speed: High compression speed for pellets produce attrition and tends to break during the process.

Characterization of MUPS

Release profile should be assessed by dissolution of MUPS in media. Hardness, friability, and disintegration should be evaluated and should be comparative to conventional tablets. Scanning electron microscopy can be done to characterize the pellets coat to assess the intactness of coating material.

Marketed MUPS Formulations

Table 2. Marketed MUPS formulations [9]

Brand name	Drug content	Manufacturer
Beloc ZOK	Metoprolol	Ozay Pharma
Toprol XL	Metoprolol	Astra Zeneca
Antra MUPS	Omeprazole	Astra Zeneca
Tylenol	Paracetamol, Diphenhydramine	Johnson & Johnson
Prevacid Solutab	Lansoprazole	Novartis
Theodur	Theophylline	Key
Losac MUPS	Omeprazole magnesium	Astra Zeneca

CONCLUSION

A fast disintegrating tablet made by compressing multi-particulates with intact release profile is challenging task. Selection of the type of pellets based on dose and type of excipients used for a tablet compression play very critical role in getting dosage form. The pellets must be hard enough which can withstand with compression force. The coat on pellets must be flexible enough which cannot rupture during compression. Selection of tableting excipient must be done carefully to get better protection to pellets during compression and good flow property which prevent segregation of pellets.

REFERENCES

1. Sugihara M, Hidaka M, Saito A. Discriminatory features of dosage form and package. Japanese Journal of Hospital Pharmacy. 1986;12(4):322-328.
2. Chang RK, Guo X, Burnside BA, Cough RA. Fast dissolving tablets. Pharm Tech. 2000;24:52–58.
3. Que L, Wu W, Cheng X, Hu T. Evaluation of Disintegrating Time of Rapidly Disintegrating Tablets by a Paddle Method. Pharmaceutical Development and Technology. 2006;11(3):295-301.
4. Celik M, Multiparticulate oral drug delivery. 1st ed. New York: Informa healthcare; 1994. Chapter 9. Compaction of multiparticulate oral dosage forms; p. 181–215.
5. Bechgaard H, Nielsen G. Controlled-Release Multiple-Units and Single-Unit Doses a Literature Review. Drug Development and Industrial Pharmacy. 1978;4(1):53-67.
6. Bashaiwoldu A, Podczeck F, Newton J. The application of non-contact laser profilometry to the determination of permanent structural change induced by compaction of pellets - II. Pellets dried by different techniques. European Journal of Pharmaceutical Sciences. 2004;22(1):55-61.
7. Collett J, Moreton C. Pharmaceutics: The Science of Dosage Form Design. 2nd ed. Churchill Livingstone; 2002. Modified-release per oral dosage forms, p. 289-305
8. Dechesne J, Delattre L. A new enteric tablet of acetylsalicylic acid. II. Biopharmaceutical aspects. International Journal of Pharmaceutics. 1987;34(3):259-262.
9. Abdul S, Chandewar A, Jaiswal S. A flexible technology for modified-release drugs: Multiple-unit pellet system (MUPS). Journal of Controlled Release. 2010;147(1):2-16.
10. Johansson B, Alderborn G. The effect of shape and porosity on the compression behaviour and tablet forming ability of granular materials formed from microcrystalline cellulose. European Journal of Pharmaceutics and Biopharmaceutics. 2001;52(3):347-357.
11. Shimizu T, Morimoto S, Tabata T. Orally disintegrating tablets. US 6328994 B1, 2001.
12. Marvola M, Rajaniemi M, Marttila E, Vahervuo K, Sothmann A. Effect of Dosage Form and Formulation Factors on the Adherence of Drugs to the Esophagus. Journal of Pharmaceutical Sciences. 1983;72(9):1034-1036.
13. Augsburger L, Hoag S, Torrado J. Pharmaceutical Dosage Forms - Tablets. 2nd ed. Hoboken: Taylor and Francis; 2008. Chapter 3. Rational Design and Formulation. p. 509-533.
14. Xu M, Heng P, Liew C. Evaluation of coat uniformity and taste-masking efficiency of irregular-shaped drug particles

coated in a modified tangential spray fluidized bed processor. Expert Opinion on Drug Delivery. 2015;12(10):1597-1606
15. Clelik M, Maganti L. Formulation and Compaction of Microspheres. Drug Development and Industrial Pharmacy. 1994;20(20):3151-3173.
16. Conine J, Hadley H. Preparation of small solid pharmaceutical spheres. Drug and Cosmetic Industry. 1970;106:38-41.
17. Dashevsky A, Kolter K, Bodmeier R. Compression of pellets coated with various aqueous polymer dispersions. International Journal of Pharmaceutics. 2004;279(1-2):19-26.
18. Wang L, Heng P, Liew C. Cluster Formation and Drag Reduction—Proposed Mechanism of Particle Recirculation within the Partition Column of the Bottom Spray Fluid-Bed Coater. Journal of Pharmaceutical Sciences. 2015;104(4):1303-1310.
19. Xu M, Heng P, Liew C. Evaluation of coat uniformity and taste-masking efficiency of irregular-shaped drug particles coated in a modified tangential spray fluidized bed processor. Expert Opinion on Drug Delivery. 2015;12(10):1597-1606.
20. Asa T. Preparation of Tablets from Reservoir Pellets with an Emphasis on the Compression Behaviour and Drug Release [Ph.D.]. Uppsala University; 2003.
21. MacGinity J, Felton L. Aqueous polymeric coatings for pharmaceutical dosage forms. 3rd ed. New York: Taylor & Francis; 2008.
22. Wagner K. Aqueous polymer dispersions for extended release dosage forms [Ph.D.]. Freie Universitaet Berlin; 2002.
23. Lippold B, Monells P. Control and stability of drug release from diffusion pellets coated with the aqueous quaternary polymethacrylate dispersion Eudragit RS 30 D. Pharmazie. 2001;56(6):477-483.
24. Chokshi R, Zia H. Hot-Melt Extrusion Technique: A Review. Iranian journal of pharmaceutical research. 2004;3(1):3-16.
25. Pearnchob N. Evaluation of new film coating processes and materials [Ph.D.]. Freie Universitaet Berlin, Berlin; 2002.
26. Nastruzzi C, Cortesi R, Esposito E, Genovesi A, Spadoni A, Vecchio C et al. Influence of formulation and process parameters on pellet production by powder layering technique. AAPS PharmSciTech. 2000;1(2):14-25.
27. Kovacevic J, Mladenovic A, Djuris J, Ibric S. Evaluation of powder, solution and suspension layering for the preparation of enteric coated pellets. European Journal of Pharmaceutical Sciences. 2016;85:84-93.
28. Ghebre-Sellassie I. Pharmaceutical pelletization technology. 1st ed. New York: M. Dekker; 1989. Chapter 1. Pellets – A general overview; p. 1-14.
29. Johansson B, Wikberg M, Ek R, Alderborn G. Compression behaviour and compactability of microcrystalline cellulose pellets in relationship to their pore structure and mechanical properties. International Journal of Pharmaceutics. 1995;117(1):57-73.
30. Johansson B, Nicklasson F, Alderborn G. Effect of pellet size on degree of deformation and densification during compression and on compactability of microcrystalline cellulose pellets. International Journal of Pharmaceutics. 1998;163(1-2):35-48.
31. Nicklasson F, Johansson B, Alderborn G. Occurrence of fragmentation during compression of pellets prepared from a 4 to 1 mixture of dicalcium phosphate dihydrate and microcrystalline cellulose. European Journal of Pharmaceutical Sciences. 1999;7(3):221-229.
32. Johansson B, Alderborn G. Degree of pellet deformation during compaction and its relationship to the tensile strength of tablets formed of microcrystalline cellulose pellets. International Journal of Pharmaceutics. 1996;132(1-2):207-220.
33. Ghebre-Sellassie I, Kramer J, Blume H. Multiparticulate oral drug delivery. 2nd ed. New York: M. Dekker; 1995. Chapter 12. Biopharmaceutical aspects of multiparticulates; p. 307-332.
34. Bodmeier R, Paeratakul O. Mechanical properties of dry and wet cellulosic and acrylic films prepared from aqueous colloidal polymer dispersions used in the coating of solid dosage forms. Pharmaceutical Research. 1994;11(6):882-888.
35. Clelik M, Maganti L. Formulation and Compaction of Microspheres. Drug Development and Industrial Pharmacy. 1994;20(20):3151-3173.
36. Osei-Yeboah F, Lan Y, Sun C. A top coating strategy with highly bonding polymers to enable direct tableting of multiple unit pellet system (MUPS). Powder Technology. 2017;305:591-596.
37. Béchard S, Leroux J. Coated pelletized dosage form: Effect of compaction on drug release. Drug Development and Industrial Pharmacy. 1992;18(18):1927-1944.
38. Torrado J, Augsburger L. Effect of different excipients on the tableting of coated particles. International Journal of Pharmaceutics. 1994;106(2):149-155.
39. Beckert T, Lehmann K, Schmidt P. Compression of enteric-coated pellets to disintegrating tablets. International Journal of Pharmaceutics. 1996;143(1):13-23.
40. Vergote G, Kiekens F, Vervaet C, Remon J. Wax beads as cushioning agents during the compression of coated diltiazem pellets. European Journal of Pharmaceutical Sciences. 2002;17(3):145-151.
41. Li X, Xu D, Li M, Liu L, Heng P. Preparation of co-spray dried cushioning agent containing stearic acid for protecting pellet coatings when compressed. Drug Development and Industrial Pharmacy. 2015;42(5):788-795.
42. Lin X, Chyi C, Ruan K, Feng Y, Heng P. Development of potential novel cushioning agents for the compaction of coated multi-particulates by co-processing micronized lactose with polymers. European Journal of Pharmaceutics and Biopharmaceutics. 2011;79(2):406-415.
43. Hosseini A, Körber M, Bodmeier R. Direct compression of cushion-layered ethyl cellulose-coated extended release pellets into rapidly disintegrating tablets without changes in the release profile. International Journal of Pharmaceutics. 2013;457(2):503-509.
44. Xu M, Heng P, Liew C. Formulation and process strategies to minimize coat damage for compaction of coated pellets in a rotary tablet press: A mechanistic view. International Journal of Pharmaceutics. 2016;499(1-2):29-37.

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