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NOVEL DRUG DELIVERY SYSTEM: MUPS

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ABSTRACT

The Compaction of Multiparticulates are commonly called as MUPS. This article reviews the advantages, an ideal characteristics, mechanisms, types, techniques and characterization of MUPS. Various techniques used to prepare MUPS are extrusion-spheronization, solution or suspension layering, cross-linking, polymerization, single or double emulsion technique. MUPS are designed for controlled release as well as targeted release like colon targeted, floating drug delivery system or mucoadhesive system. Pharmaceutical invention and research are increasingly focusing on delivery systems which enhance desirable therapeutic objectives while decreasing side effects. Recent trends indicate that MUPS drug delivery systems are especially suitable for achieving controlled or delayed release oral formulations with low risk of dose dumping, flexibility of blending to attain different release patterns as well as reproducible and short gastric residence time. The release of drug from MUPS depends on a variety of factors including the carrier used to form the MUPS and the amount of drug contained in them. Consequently, MUPS drug delivery systems provide tremendous opportunities for designing new controlled and delayed release oral formulations, thus extending the frontier of future pharmaceutical development. Now a days the novel technologies are used in development of MUPS like Cryo-pelletization, Ultrasonic spray-congealing and Prilling technique.

INTRODUCTION

The concept of the multiple unit dosage form was initially introduced in the early 1950s. These multiple units are also referred to as pellets, spherical granules, spheroids, mini or micro tablets, beads, microspheres. Together, these characteristic units provide the overall desired CR of the dose. To deliver the recommended total dose, these subunits are filled into a sachet and encapsulated or compressed into a tablet. Pellets or spherical granules are produced by agglomerating fine powders with a binder solution. These pellets usually range in size from 0.5-1.5 mm and in some applications may be as large as 3.0 mm.[(1)] Mini-tablets are tablets with a diameter equal to, or smaller than, 2-3mm. The production of mini-matrices using a tableting technique is an attractive alternative to the production of pellets, as the presence of solvents (e.g. water) is avoided and high production yields are obtained.[(3)] Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers which are biodegradable in nature and ideally having a particle size less than 200μm.[(4)] Multiple unit dosage forms provide many advantages over single-unit systems. For example, more predictable gastric emptying, a high degree of dispersion in the digestive tract, increased bioavailability, reduced risk of systemic toxicity, reduced risk of local irritation, decrease dosing frequency and increase patient compliance, less absorption variability, a lesser risk of dose dumping, more suitable for formulations with acid-sensitive drugs (i.e., erythromycin), accurate dosing, increased shelf life. Multiparticulates composed of different drug entities can be blended and formulated in a single dosage form which allows the combined delivery of two or more bioactive agents; they may or may not be chemically compatible, at the same site or at different sites within the GIT. It also permits the combination of multiparticulates viz. pellets of different release rates of the same drug in a single dosage form. In addition, multiple unit dosage forms have an enough surface area-to-volume ratio and provide an ideal shape for the application of film coatings. On the other hand, multiple-unit preparations exhibit several disadvantages like, their manufacturing is more complicated and more expensive, the filling of multiple units in gelatin capsules is difficult to accomplish especially in the case where different subunits are involved. The preparation process of multiparticulates necessitates extra care and fine adjustments of various equipment's like tableting machines for the preparation of minitablets, the volume per dose is usually higher than for tablets because of the lower bulk densities of pellets compared to compressed tablets, Compared to larger single unit dosage forms, the specific surface area per dose of multiple units

is higher and more coating material is necessary to obtain coatings of the same thickness for controlled release.[2, 6, 7, 8]

MUPS as NDDS

Incorporating an existing medicine into a novel drug delivery system (NDDS) can significantly improve its performance in terms of efficacy, safety and improved patient compliance. In the form of a NDDS, an existing drug molecule can get new life, thereby increasing its market value and competitiveness and even extending patent life.[11, 16]

Advantages of MUPS

Pharmacokinetic Advantages

- Rapid but uniform transit of micro pellets contained in MUPS from the stomach into small intestine owing to their small size and thus lesser possibility of localized irritation, better and more uniform drug absorption and greater bioavailability.[12]
- Uniform emptying of micro pellets from stomach into small intestine facilitates rapid dissolution of enteric coating and drug release resulting in early tmax and Cmax (peak time and peak plasma concentration) in case of delayed-release formulations. In case of controlled-release preparations, drug release is more uniform and possibility of dose dumping is avoided with minimized tendency for inter-subject variations.[12]

Pharmacodynamic Advantages

- Owing to rapid and uniform gastric emptying and subsequently uniform drug dissolution of pellets in the gastrointestinal tract due to their small size and larger surface, uniform drug absorption is facilitated which results, controlled pharmacological action.[12]
- 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.

Patient Friendly Dosage Form

Better patient compliance is expected from MUPS for following reasons:-

- Mouth disintegrating MUPS dosage form having a palatable taste is suitable for paediatric and geriatric patients who cannot swallow tablet or capsule, e.g. Prevacid SoluTab.

- The orodispersible MUPS medication can be taken without water, especially while travelling since the dosage form can be designed as orally disintegrating preparation that contains flavours and sweeteners that stimulate salivation and swallowing, e.g. Prevacid SoluTab.
- 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.
- The MUPS have lesser tendency of adhering to esophagus during swallowing.[13]
- Smaller volume/size of tablet leads to better patient compliance than capsules.[14]

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.[15]

Ideal Characteristics of MUPS

- Should maintain all the tablet properties.
- Pellets should not show any interaction like developing electrostatic charges; during compression.
- The pellets should not show any deviation in its release even after compression.
- The coated pellets during the process of compression should not fuse into a nondisintegrating matrix and should not lose its coating integrity either by breaking or cracking or rupturing the coating layers or pinholes and other imperfections.
- 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.[15]

Mechanism of Drug Release From MUPS

The mechanism of drug release from multiparticulates can be occurring in the following ways:

Diffusion

On contact with aqueous fluids in the gastrointestinal tract (GIT), water diffuses into the interior of the particle. Drug dissolution occurs and the drug solutions diffuse across the release coat to the exterior.

Erosion

Some coatings can be designed to erode gradually with time, thereby releasing the drug contained within the particle.

Osmosis

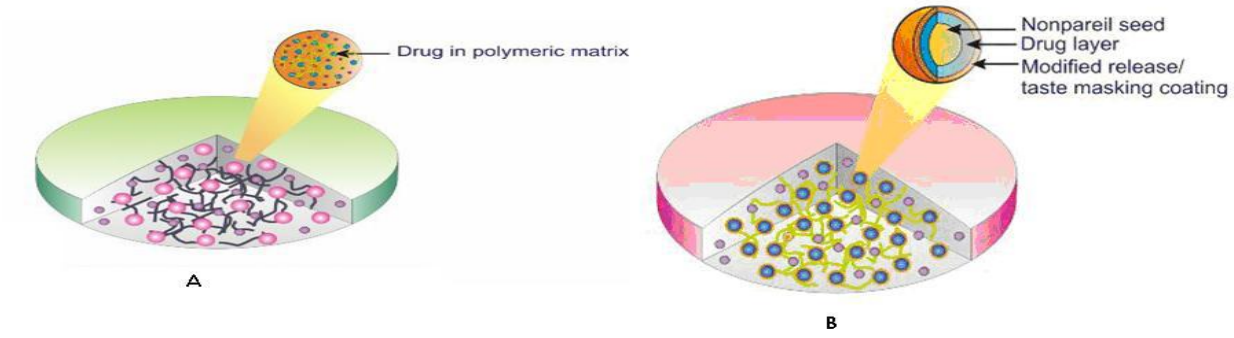
In allowing water to enter under the right circumstances, an osmotic pressure can be built up within the interior of the particle. The drug is forced out of the particle into the exterior through the coating.[11,16]

Types of MUPS Formulations

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

A) **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- tableting excipients.

B) **MUPS with pellets coated** using different pelletization techniques with all the desired characteristics for compression of pellets. [15]



Design/ Approaches of MUPS

1. Pellets

Mucoadhesive polymer-coated pellets

Mucoadhesive pellets can be prepared by layering technique using mucoadhesive polymers like HPMC, sodium alginate, HPMC/ Carbopol, and sodium carboxylmethylcellulose (Na- CMC) etc. This result in increase in gastric residence time and hence improve bioavailability of the drug.[18, 19]

Time-Controlled Explosion based Rupturable coating System

This is a multiparticulate system in which drug is coated on non-pareil sugar seeds followed by a swellable layer and an insoluble top layer. Upon ingress of water, the swellable layer expands, resulting in rupture of film with subsequent rapid drug release. The release is independent of environmental factors like pH and drug solubility.[19]

Osmotic-Based Rupturable Coating Systems

Permeability Controlled System

This system is based on a combination of osmotic and swelling effects. The core containing the drug, a low bulk density solid and/or liquid lipid material (e.g., mineral oil) and a disintegrant is prepared. This core is then coated with swellable polymer like cellulose acetate. Upon immersion in aqueous medium, water penetrates the core displacing lipid material. After the depletion of lipid material, internal pressure increases until a critical stress is reached, which results in rupture of coating. In another system each pellet has a core that contains the therapeutic drug and a water-soluble osmotic agent. Water-permeable, water-insoluble polymer film encloses each core. A hydrophobic, water insoluble agent that alters permeability (e.g., a fatty acid, wax, or a salt of fatty acid) is incorporated into the polymer film. The osmotic agents dissolve in the water causing the pellets to swell, thereby regulating the rate of drug diffusion. This system was used for the delivery of antihypertensive drug, diltiazem. It has also proposed a system containing a core of drug and osmotically active agent (sodium chloride) coated with an insoluble permeable membrane. The coating materials reported include different types of poly (acrylate-methacrylate) co-polymers and magnesium stearate, which reduces water permeability of the membrane, thus allowing for use of thinner films. Using ethyl cellulose as a coating material, it was possible to affect lag time of enteric polymer to achieve rupturing after a predetermined time.[17]

Pulsatile Delivery by Change in Membrane Permeability

The permeability and water uptake of acrylic polymers with quaternary ammonium groups can be influenced by the presence of different counter-ions in the medium. Several delivery systems based on this ion exchange have been developed. In one such attempt cores were prepared using

theophylline as model drug and sodium acetate. These pellets were coated using Eudragit RS30D (10% to 40% weight gain) in four different layer thicknesses. It was found that even a small amount of sodium acetate in the pellet core had a dramatic effect on the drug permeability of the Eudragit film. After the lag time, interaction between the acetate and polymer increases the permeability of the coating so significantly that the entire active dose is liberated within a few minutes. The lag time increases with increasing thickness of the coat, but the release of the drug was found to be independent of this thickness and depended on the amount of salt present in the system.[20]

2. Minitablets

A biphasic gastro retentive floating drug delivery system with multiple-unit mini-tablets based on gas formation technique was developed to maintain constant plasma level of a drug concentration within the therapeutic window. The system consists of loading dose as uncoated core units, and prolonged release core units are prepared by direct compression process; the latter were coated with three successive layers, one of which is seal coat, an effervescent (sodium bicarbonate) layer, and an outer polymeric layer of polymethacrylates. A novel approach in which pseudoephedrine hydrochloride (PSE) sustained-release dosage form was prepared which comprises immediate-release mini-tablets (IRMT) and sustained-release minitablets (SRMT) contained in a hydroxypropyl methylcellulose (HPMC) capsule. The IRMT contained PSE, excipients and low-substituted hydroxypropyl cellulose (a disintegrant), and the tablets were coated with HPMC, a water-soluble polymer. The SRMT contained only PSE and excipients, and were coated with a mixture of HPMC and the water-insoluble polymer ethylcellulose. The PSE release profile for the SRMT could be controlled by varying the thickness of the coat, and the lag time could be controlled by varying the amount of ethylcellulose present in the polymer coat. PSE was released immediately from encapsulated mini-tablet system and release was sustained over an extended period of time.[21]

3. Microspheres

Gastro retentive Microspheres Micro balloons (Hollow microspheres)

This system involves low density materials; entrapping oil or gas.General techniques involved in their preparation include simple solvent evaporation, and solvent diffusion and evaporation. Kawashima and coworkers prepared hollow microspheres (‘microballoons’) with a drug loaded in their outer shells by an emulsion-solvent diffusion method. The ethanol /dichloromethane

solution of a drug and an enteric acrylic polymer was poured into an aqueous solution of polyvinyl alcohol (PVA) that was maintained at 40°C with continuous stirring. The gas phase generated in the dispersed polymer droplet by the evaporation of dichloromethane formed an internal cavity in the microsphere of the polymer with the drug. During *in vitro* testing, the microballoons floated continuously over the surface of an aqueous or an acidic dissolution medium containing surfactant for more than 12 h. Floating microspheres can be prepared by the ionotropic gelation method with use of gas-forming agent. Chitosan- alginate microspheres have been prepared using calcium carbonate as a gas forming agent. Formed microspheres were coated with enteric polymer Eudragit RS to extend the drug release. Floating microspheres were prepared by nonaqueous emulsification solvent evaporation technique. Drug and ethyl cellulose were mixed in acetone at various ratio. This slurry was added slowly in to liquid paraffin with constant stirring. Formed microspheres were filtered and tested for the size, size distribution, drug content, yield, drug release of microspheres and floating time.[17]

Bio/Mucoadhesive system

Mucoadhesive microspheres of atenolol and propranolol were prepared by an inter-polymer complexation of poly (acrylic acid) (PAA) with poly (vinyl pyrrolidone) (PVP) and also using only PVP to increase gastric residence time using solvent diffusion method. A mixture of ethanol/water was used as the internal phase, corn oil was used as the external phase of emulsion, and span 80 was used as the surfactant. New positively charged biodegradable mucoadhesive microspheres were prepared using aminated gelatin (modified gelatin) by surfactant free emulsification in olive oil, followed by a cross-linking reaction with different concentration of glutaraldehyde. Gelatin microspheres were also prepared by same method except that cross linking reaction was carried out in an aqueous solution containing 0.1% Tween 80. The modified gelatin microspheres demonstrated a greater gastric mucoadhesiveness than the gelatin microspheres in an isolated rat stomach.[22]

Colon targeted microspheres

Colon-specific alginate microspheres of 5- fluorouracil were prepared by the modified emulsification method in liquid paraffin and by cross-linking with calcium chloride. The core microspheres were coated with Eudragit S-100 by the solvent evaporation technique to prevent drug release in the stomach and small intestine. The microspheres were characterized by shape, size, surface morphology, size distribution, incorporation efficiency, and *in vitro* drug release

studies. Coated chitosan microspheres were prepared for colon specific delivery of 5-ASA by an emulsionsolvent evaporation technique based on a multiple w/o/w emulsion. Chitosan solution in dilute acetic acid containing 5-ASA was dispersed into solution of cellulose acetate butyrate (CAB) in methylene chloride. The primary induced w/o emulsion was dispersed into a PVA aqueous solution to produce a w/o/w multiple emulsion and was stirred for approximately 2.5 h. The produced microspheres were separated, washed and dried. Hydroxycamptothecin (HCPT) loaded fast release microspheres were prepared and then coated with a layer of Eudragit S100 by air suspension spraydrying method to obtain colon-specific microspheres.[23, 24, 25]

4. Beads

Most common method for the preparation of beads is the polymer cross linking method. Beads so formed can be coated with different polymers to tailor the release of the drug from beads. Chitosan hydrogel beads for colon-targeted delivery of satranidazole have been prepared by the cross-linking method followed by enteric coating with Eudragit S100. Multi-unit floating dosage forms have been developed from freeze-dried calciumalginate. Spherical beads can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing the precipitation of calcium alginate. The beads are then separated, snap-frozen in liquid nitrogen, and freeze-dried at -40ºC for 24 hours, leading to the formation of a porous system, which can maintain a floating force for over 12 hours. Ion-exchange resin beads loaded with drug and effervescent agent is coated with a semi permeable membrane. CO2 is released on contact with the acid gastric juice. Such system has been developed for theophylline. Oil entrapped crosslinked beads can be prepared by emulsion gelation method. Polymer is dissolved in water with stirring. Oils and drug are added to polymer solution. The homogenized or nonhomogenized mixture is extruded into solution containing crosslinking agents with gentle agitation. The formed beads are allowed to stand in the solution, filtered, and dried at room temperature. Alginate gel beads have been prepared by this approach and result showed that increase in concentration of oil caused increase in size and sphericity. The release profile indicates that the sustaining action was more pronounced with liquid paraffin followed by groundnut oil> castor oil> mentha oil> conventional alginate beads.[17, 26]

PROCESS VARIABLES IN FORMULATING MUPS

Compression force, to a greater extent leads to damage of polymeric functional coating and alters dissolution profile based of the designed type of formulation. In case of delayed release

formulation rupture of polymer coat leads to release of drug in acidic media and thereby, degradation of the drug.

Compression speed, probably be optimum for the formulation. High speed may cause improper die fill. Capping and lamination can be prevented by increasing the contact between punch heads and compression rollers.[15]

Techniques to Prepare MUPS

Given the enormous advantages of multiparticulate systems over single-unit oral dosage forms, extensive research has focused recently on refining and optimizing existing manufacturing techniques as well as on the development of novel manufacturing approaches that use innovative formulations and processing equipment. Different methods require different processing conditions and produce multiparticulates of distinct quality. Various production techniques used for manufacturing of multiple units have been discussed here briefly.[17]

A. Production techniques for preparation of pellets

Spherical agglomeration, or balling, is a pelletization process in which powders, on addition of an appropriate quantity of liquid or when subjected to high temperatures, are converted to spherical particles by a continuous rolling or tumbling action. Over the years, spherical agglomeration has been carried out in horizontal drum pelletizers, inclined dish pelletizers, and tumbling blenders; more recent technologies use rotary fluid-bed granulators and high-shear mixers. Spherical agglomeration can be divided into two categories-liquid-induced and melt-induced agglomerations. During liquid-induced agglomeration process, liquid is added to the powder before or during the agitation step. As powders come in contact with a liquid phase, they form agglomerates or nuclei, which initially are bound together by liquid bridges subsequently replaced by solid bridges, derived from the hardening binder or any other dissolved material within the liquid phase. The nuclei formed collide with other adjacent nuclei and coalesce to form larger nuclei or pellets. Melt-induced agglomeration processes are similar to liquid-induced processes except that the binding material is a melt. Therefore, the pellets are formed with the help of congealed material without having to go through the formation of solvent-based liquid bridges.[17]

2. Compaction

Compaction is a general pelletization process which produces denser pellets. Compaction technique can be subdivided into compression and extrusion spheronization.

a) Compression

In this technique, particles, that are prepared trough dry blending or wet granulation followed by drying, rearrange themselves to form a closely packed mass. During this phase, the original particles retain most of their properties.

b) Extrusion-Spheronization

It is most popular in pharmaceutical industries for the manufacturing of pellets. This process was first reported by Reynolds (1970) and by Conine and Hadley (1970) and involves four steps.

(1) Granulation: Preparation of the wet mass using binding solution or hot melt wax.

(2) Extrusion: shaping the wet mass into cylinders using different types of extruders.

(3) Spheronization: breaking up the extrudate and rounding of the particles into spheres in spheronizer and

(4) Drying- drying of the pellets at room temperature or at an elevated temperature in the fluidized-bed drier, in an oven, in a forced circulation oven or in a microwave oven.[27]

3. Globulation

Spray drying and spray congealing, known as globulation processes, involve atomization of hot melts, solutions, or suspensions to generate spherical particles or pellets.

a) Spray drying

During spray drying, drug entities in solution or suspension are sprayed, with or without excipients, into a hot air stream to generate dry and highly spherical particles. As the atomized droplets come in contact with hot air, evaporation of the application medium is initiated. This drying process continues through a series of stages whereby the viscosity of the droplets constantly increases until finally almost the entire application medium is driven off and solid particles are formed. Generally, spray-dried pellets tend to be porous.

b) Spray congealing

During spray congealing, a drug substance is allowed to melt, disperse, or dissolve in hot melts of waxes, fatty acids, etc., and sprayed into an air chamber, where the temperature is below the melting temperatures of the formulation components, to provide spherical congealed pellets under appropriate processing conditions. A critical requirement in a spray congealing process is that the formulation components have well-defined, sharp melting points or narrow melting zones. Because the process does not involve evaporation of solvents, the pellets produced are dense and non-porous.

4. Layering technique

Layering results in heterogeneous pellets with a core and a shell. For this process, seed or starting core material is required. Often, sugar spheres, nonpareils or spheres made from microcrystalline cellulose are used as core material.

a) Powder layering

During powder layering, a binding solution and a finely milled powder are added simultaneously to a bed of starter seeds at a controlled rate. In the initial stages, the drug particles are bound to the starter seeds and subsequently to the forming pellets with the help of liquid bridges originated from the sprayed liquid. Today fluidized bed equipment is used in order to ensure rapid drying. The core particles (seeds) are fluidized in a warm or hot air stream. A binding liquid is sprayed and simultaneously add the drug substance as a powder. The particles stick to the wetted surface of the seed material and form a layer together with the binder after drying.

b) Solution/ Suspension layering

Solution/suspension layering involves the deposition of successive layers of solutions and/or suspensions of drug substances and binders on starter seeds, which may be inert materials or crystals/granules of the same drug. The process continues until the desired quantity of drug substance and thus the target potency of the pellets are achieved.

5. Production techniques for preparation of microspheres

1. Single emulsion technique

In single emulsion technique, natural polymers are dissolved or dispersed in aqueous medium followed by dispersion in non-aqueous medium like oil. Next cross linking of the dispersed globule is carried out either by means of heat or by using the chemical cross linkers like glutaraldehyde, formaldehyde, acid chloride etc. Heat denaturation is not suitable for thermolabile substances. The amount of chemical and the period and intensity of heating are critical in determining the release rates and swelling properties of the multiparticulates formed.

2. Double emulsion technique

Double emulsion method involves the formation of the multiple emulsions or the double emulsion of type w/o/w and is best suited to water soluble drugs, peptides, proteins and the vaccines. This method can be used with both the natural as well as synthetic polymers. The aqueous protein solution is dispersed in a lipophilic organic continuous phase. This protein solution may contain the active constituents. The continuous phase is generally consisted of the

polymer solution that eventually encapsulates of the protein contained in dispersed aqueous phase. The primary emulsion is subjected then to the homogenization or the sonication before addition to the aqueous solution of the poly vinyl alcohol (PVA). This results in the formation of a double emulsion. The emulsion is then subjected to solvent removal either by solvent evaporation or by solvent extraction.

3. Polymerization techniques

The polymerization techniques conventionally used for the preparation of the microspheres are mainly classified as Normal polymerization and Interfacial polymerization.

a) Normal polymerization

It is carried out using different techniques such as bulk, suspension, precipitation, emulsion and micellar polymerization processes. In bulk polymerization, a monomer or a mixture of monomers along with the initiator or catalyst is usually heated to initiate polymerization. Polymer so obtained may be moulded as microspheres. Drug loading may be done during the process of polymerization. Suspension polymerization also referred as bead or pearl polymerization. Here it is carried out by heating the monomer or mixture of monomers as droplets dispersion in a continuous aqueous phase. The droplets may also contain an initiator and other additives. Emulsion polymerization differs from suspension polymerization as due to the presence initiator in the aqueous phase, which later on diffuses to the surface of micelles.

b) Interfacial polymerization

It involves the reaction of various monomers at the interface between the two immiscible liquid phases to form a film of polymer that essentially envelops the dispersed phase.

4. Coacervation

Coacervation is the simple separation of a macromolecular solution into two immiscible liquid phases, a dense coacervate phase, which is relatively concentrated in macromolecules, and a dilute equilibrium phase. Coacervates may be described as liquid crystals and mesophases. In the presence of only one macromolecule, this process is referred to as simple coacervation. When two or more macromolecules of opposite charge are present, it is referred to as complex coacervation. Simple coacervation is induced by a change in conditions, which results in dehydration of the macromolecules. This may be achieved by the addition of a non-solvent, the addition of microions, or a temperature change, all of which promote polymer– polymer

interactions over polymer–solvent interactions. Complex coacervation is driven by electrostatic interactive forces between two or more macromolecules.

5. Solvent evaporation

The solution containing the polymer and the drug in organic solvent may be dispersed in an aqueous phase to form droplets. Continuous mixing and elevated temperatures maybe employed to evaporate the more volatile organic solvent and leave the solid polymer–drug particles suspended in an aqueous medium. The particles are finally filtered from the suspension and dried.

6. Precipitation

Precipitation is a variation on the evaporation method. The emulsion consists of polar droplets dispersed in a non-polar medium. Solvent may be removed from the droplets by the use of a cosolvent. The resulting increase in the polymer drug concentration causes precipitation forming a suspension of micro particulates.

7. Freeze drying

This technique involves the freezing of the emulsion; the relative freezing points of the continuous and dispersed phases are important. The continuous phase solvent is usually organic and is removed by sublimation at low temperature and pressure. Finally, the dispersed phase solvent of the droplets is removed by sublimation, leaving polymer-drug particles.[17, 26, 28, 29]

Characterization of MUPS

1. Characterization of pellets

Determination of the size

Particle size analysis is in most cases carried out by a simple sieve analysis, although the more advanced method of computer-aided image analysis has also been reported.

Shape analysis

At least 50 pellets from each batch are randomly selected for shape analysis. The pellets were mounted on a light microscope fitted to a Camera Lucida and the images of the pellets were drawn manually on a graph paper. The area of the images and the maximum and minimum radius are calculated.

Friability

The tendency of the pellets to flake off during handling resulting in the formation of dust is assessed by rotating the pellets in a friabilator or by shaking the pellets in a Turbula mixer for a

fixed period of time. Both techniques make use of glass beads to increase the mechanical stress on the pellets.

Volume, Density, and Compressibility

A 50 g sample is taken into a 250 ml graduated cylinder of a volume and density apparatus. The volume is noted as being bulk volume. The cylinder is then tapped 1250 times until the volume of the sample is reduced to a constant or consolidated one. Bulk density, tapped density, and Carr's index and Hausner's ratio are calculated. The true density of pellets evaluates the porosity of the pellets and can be determined by the displacement with He or Hg or by a pycnometer.[31]

Flow Properties

Flow properties of pellets are determined by measuring angle of repose according to the standard method using standard trigonometric relationship.[32]

Wettability

Pellet is fixed on clean glass slide. A 15 µl drop of distilled water is placed carefully with the help of a micro-syringe on the pellet. Photographic impressions of the water drop in contact with the pellet are recorded in the static stage.[31]

Scanning electron microscopy (SEM)

The morphology of pellets is examined by scanning electron microscopy. Samples are freeze dried, cross sectioned and then placed onto aluminum stubs coated with adhesive. The cross-sections of the pellets are coated with gold under vacuum and examined under the microscope to visualize the surface characteristics of the pellets.[33]

Moisture Content

Moisture content is determined by means of Karl Fisher titration.

Content uniformity

Content uniformity (assay) is performed for each batch as per the procedure given in the official pharmacopoeia.

***In vitro* dissolution testing**

In vitro dissolution study is preformed according to the specifications and conditions given in the official monograph.

1. Characterization of microspheres and beads

Microspheres are characterized for size, shape analysis, friability, volume, density, and, Compressibility, flow properties, scanning electron microscopy (SEM), *in vitro* dissolution

testing. Apart from these, microspheres are characterized for other parameters like % entrapment efficiency, drug loading, and % yield.

1. Characterization of minitablets

Minitablets are characterized for it size and size distribution, weight variation, hardness, % friability, angle of repose, Carss's index, Hauser's ratio, flowability, disintegration, *in vitro* dissolution testing and SEM.[34]

Novel Technologies In Development of MUPS

Cryo-pelletization

A new technique-Cryopelletization has been introduced in which droplets of a liquid formulation are converted into solid spherical particles or pellets by using liquid nitrogen as the fixing medium. The procedure permits instantaneous and uniform freezing of the processed material owing to the rapid heat transfer that occurs between the droplets and liquid nitrogen. The frozen pellets are transported out of the nitrogen bath into a storage container at - 60˚C before drying. The pellets are dried in conventional freeze dryers.[28]

Ultrasonic spray-congealing technique

Drug particles are suspended in a polymeric aqueous solution and the system is then freeze-dried. A suspension is prepared from the co-freeze dried drug/ polymer powder into molten wax material that is then atomized into small droplets using ultrasound. Solidification in air produced microparticles having regular macroscopic morphology and coated by a thin external film of wax. This technique gives uniform distribution of drug in the final particles.[35]

Prilling technique for microencapsulation

Among the different physical methods for microencapsulation such as the well-known spray drying, fluid bed coating, extrusion, etc., an innovative technique known as prilling or laminar jet breakup is able to produce microparticles or beads with very narrow dimensional range and high encapsulation efficiency by breaking apart a laminar jet of polymer solution into a row of mono-sized drops by means of a vibrating nozzle device. The resultant droplets fall into a polymer gelation solution in which they are solidified as beads.[36]

CONCLUSION

The brief review on MUPS concludes MUPS dosage forms as one of the most promising and efficient pathway of novel and multiparticulate drug delivery systems. Formulation of different drugs to MUPS has a prominent role because of dissolution profiles and biopharmaceutical

requirements. Present scenario of MUPS find a greater advantage due to its flexible design in variable release properties, stability, patient compliance and economic compared to other dosage forms. MUPS meet all these with medical, health care, and business benefits and hence the market for these dosage forms is growing rapidly and gaining popularity in an impressive rate.

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