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Review Article

Current Scenario of Multiple Unit Particulate System: A Review

VISHAL YADAV *, S SATHESHKUMAR

Department of Pharmaceutics, School of Pharmaceutical Sciences, Vels Institute of Science, Technology and Advanced Studies (VISTAS), Pallavaram, Chennai-600117, India.

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ABSTRACT

Pharmaceutical research is achieving and focusing new goals within the field of delivery systems, that square measure helpful to aggravate therapeutic objectives while alleviating side effects. Multiparticulates are discrete particles that make a multiple unit system. Pelletization is the technique to convert drugs or excipients into small free flowing, spherical or semi spherical units, which are produced by agglomerating fine powdered drug or excipients with a binder solution. Pellets range in a size, typically between 0.5-2.0mm. Multiple Unit Particulate System (MUPS) are multi-particulate in nature and are administered as tablets. These tablets gets disperse in the stomach and intestine, allowing constant drug release in systemic circulation. In comparison with single traditional dosage form, in the Micro particulate system dosage form of the drug has been divided among various discrete delivery entities. This article reviews the classification, advantages, disadvantages, common industrial technique for preparation of pellets.

INTRODUCTION

Microparticles are small free flowing particles consisting of natural or synthetic polymers having particle diameter ranging from 1 to1000 µm. With the advancement in biotechnology, genomics lots of potent and specific therapeutics have been formed. Because of the various issues like low solubility, poor stability, narrow therapeutics index of many new drugs, there is corresponding need for safer drug delivery [1]. Multiparticulates are discrete particles that are combined to Single dosage unit to form a multiple-unit dosage system. They will exist as pellets, granules, sugar seeds, mini-tablets, ion-exchange resin particles, powders and crystals with drugs being entrapped in or layered around cores. Multiparticulates are commonly filled into capsule shells and less commonly compressed into tablets [2]. Multiparticulates drug delivery systems are the most extensively used dosage than unit dosage forms for their improved bioavailability because of increased surface area, reduced inter-subject variation, good distribution and transportation [3]. Multiparticulates drug delivery system might will increases drug safety because the film of enteric coating on single unit or monolithic is damaged it will release whole drug in stomach and which cause irritation or ulceration due to this will cause loss of complete dose or dose dumping but equally if the damage of film coating of multi-unit dosage form occur it will release drug of that small subunit and affect the release behaviour of that specific sub unit which represent small part of total dose [4]. In multiple-unit systems, the total drug dose is split over many units. Failure of some units may not be as consequential as failure of a single-unit system. Other advantages of the divided drug dose include easy adjustment of the strength of a dosage unit by changing the number of multiparticulates in the dosage unit, administration of incompatible drugs in a single dosage unit by changing the number of multiparticulates in the dosage unit, administration of incompatible drugs in a single dosage unit by separating them with a totally different multiparticulates and combination of multiparticulates with a different drug release rates to obtain the desired overall release profile [5].

Author for Correspondence:
Email: v.yadavagcop@gmail.com

Classification of Multiparticulate Drug Delivery Systems

Non-effervescent Systems:

Colloidal Gel Barrier Systems:

Hydrodynamically balanced system (HBS), that contains drugs with gel forming hydrocolloids. These systems incorporate a high level (20-75%w/w) of one or more gel forming, highly sellable, cellulose type hydrocolloids, polysaccharides and matrix forming polymers. When it comes in contact with gastric fluid, the hydrocolloids in the system hydrate and form a colloidal gel barrier around its surface. This gel barrier is used to control the rate of fluid penetration into the device and accordingly release of the drug.

Micro Porous Compartment Systems: This method is based on the encapsulation of a drug reservoir inside a micro porous compartment with apertures along its top and bottom walls. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of the gastric mucosal surface with the undisclosed drug.

Multiparticulates System:

Floating beads is one of the most common methods for the preparation of beads is the polymer cross linking method. Beads which are formed coated with different polymers are used to release of the drug from beads. Spherical beads are prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, it causing the precipitation of calcium alginate. For the formation of a porous system the beads are then separated, snap-frozen in liquid nitrogen, and freeze-dried at -40ºC for 24 hours. Effervescent agent and Ion- exchange resin beads loaded with drug and is coated with a semi permeable membrane. In contact with the acid gastric juice CO_2 is released. Oil entrapped cross linked beads may be prepared by emulsion gelatin method.

Micro Balloons:

This system used low density materials for entrapping oil or gas. Techniques involved in their preparation include simple solvent evaporation, solvent diffusion and evaporation. Kawashima and co-workers prepared hollow microspheres (micro balloons) with a drug loaded in their outer shells by an emulsion solvent diffusion method. The mixture of drug with ethanol /dichloromethane solution and an enteric acrylic polymer was poured into an aqueous solution of polyvinyl alcohol (PVA) which was maintained at 40°C with continuous stirring. By the evaporation of dichloromethane formed the gas phase with dispersed polymer droplet gives an internal cavity in the microsphere of polymer with the drug.

Effervescent Systems:

In the stomach a floating drug delivery systems can be prepared by incorporating the floating chamber, which may be filled with vacuum, inert gas or air.

Volatile Liquid Containing Systems:

These have an inflatable chamber it contains a liquid e.g. ether, cyclopentane which cause the inflation of the chamber in the stomach because these gases gasifies at body temperature. This systems are osmotically controlled floating systems containing a hollow deformable unit There are two chambers in the system first contains the drug and the second chamber contains the volatile liquid.

Gas Generating Systems:

These buoyant delivery systems utilizes carbonate/ bicarbonate salts and citric acid /tartaric acid to liberate CO_2,which causes effervescent reaction and gets entrapped in the jellified hydrocolloid layer of the system, thus decreasing its specific gravity and making it float over time. These are formulated by boon mixing the CO_2 generating agents and the drugs in the matrix tablet. These have a bulk density that drops the gastric fluid and remains floating in the stomach unflattering the gastric emptying rate for prolonged period. The drug is slowly released at desired rate from the floating system and after the complete release the residual system is removed from stomach. This leads to an increase in the GRT and a better control over fluctuations in plasma drug concentration [6].

Objectives for the Preparation of Mups Tablets

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

- For controlled release drug delivery system.
- For enteric release and colon targeted drug delivery system.
- Designing of Mouth-melting taste-masked dosage form.
- Combining of drugs with different release patterns in the same dosage form.
- Enhancing stability of dosage form as compared to its capsule counterpart.
- Obviating the need for specialized packaging [7]

Advantages of Multiparticulates (Pellets) [8]

- Pharmacokinetic advantages
- Pharmacodynamic advantage
- Patient friendly dosage form
- Processing advantages
- Regulatory advantages
- Formulation Advantages
- Therapeutic Advantages

Disadvantages of Multiparticulates (Pellets)

- Low drug loading Low drug loading
- Proportionally higher need for excipients
- Lack of manufacturing reproducibility and efficacy
- Large number of process variables
- Multiple formulation steps
- Economically high cost
- Need of advanced technology
- Trained or skilled personal required for manufacturing [10].

Rationale of Formulating MUPS

The rationale of 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 forms; combining the 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 improves the stability of dosage form as compared to its capsule counterpart. It also helps to prevent the need for specialized packaging that for capsules making it more cost effective [11].

Types of MDDS [12 - 14]

There are different types of MDDS depending on the drug release mechanism and they are mentioned and explained below. As shown in Fig. 1.

Reservoir Coated Systems:

Such systems consist of a drug layered core surrounded by a polymer. The mechanism of controlling the drug release from reservoir type systems is often complex and depends on coating type, thickness, drug type and core type.

Those mechanisms include:

- Diffusion through the continuous polymer with film surrounding the drug loaded core. Firstly, water penetrates through the coating due to the concentration gradient inside pellet versus outside the pellet [Fig. 1 (A)].
- Drug release can occur through water filled pores. These pores can be due to leaching of water soluble compounds into the release medium or due to cracks formed by high hydrostatic pressure generated inside these systems upon water uptake [Fig. 1 (B and C)].
- For this mechanism to occur an osmotic active core is surrounded by semi-permeable membrane. Upon water uptake and under right circumstances, an osmotic pressure is built within the interior of the core and drug is pushed out via pores in the coating [Fig.1 (D)].

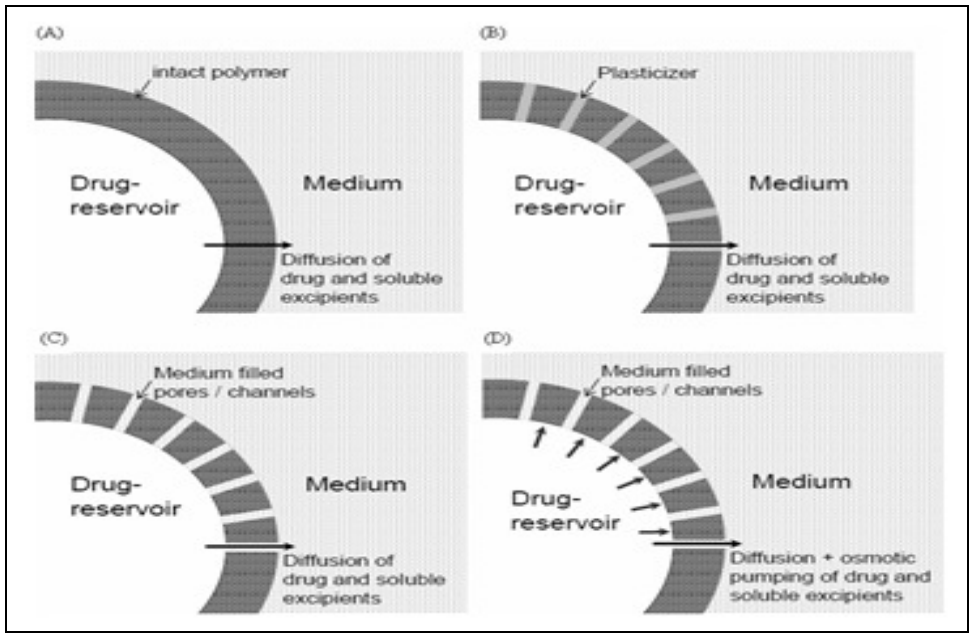

Figure 1: Schematic Representation of Typical Release Mechanism (A) Nucleation (B) Coalescence (C) Layering (D) Abrasion Transfer [20].

Matrix Coated Systems:
In these systems a polymer: drug solution or dispersion is sprayed on pellets in order to achieve controlled drug release. The drug and polymer are dissolved or dispersed in a common solvent and on solvent evaporation, a solid Dispersion solution (drug dispersed in the polymer) (polymer) or a solid dispersion (drug dissolved in the dispersion) or a combination of both is obtained. If the first drug concentration is below drug solubility in the polymer, drug is dissolved and drug release is mainly controlled by drug diffusivity in polymer.

Specialized Systems:
The MDDS can be specially designed into various types.

Pulsatile system is based on rupturable coating: This is a multiparticulates system in which the drug is coated on the non-pareil sugar seeds followed by a swellable layer and top layer as insoluble. The release is independent of environmental factors like P^H and drug solubility. The lag time can be differing by change in coating thickness or adding high amounts of lipophilic plasticizers in the outermost layer.

Low density floating multiparticulates pulsatile systems: These systems resides only in stomach, are not affected by variability of pH local environment or gastric emptying rate. The core is further coated with cellulose acetate [15]. These are advantageous for drugs either absorbed from the stomach or requiring local delivery in stomach.

Time controlled expulsion systems: This system is based on a combination of osmotic and swelling effects. This systems is based on a combination of osmotic and swelling effects. The core containers the drug, low density solid, liquid lipid material and disintegrant.

Reservoir systems with soluble or eroding polymer coatings: The barrier get dissolves after a specific lag time followed by burst release of drug from the reservoir core. In general, for this kind of systems, the lag time prior to drug release can be controlled by the thickness of the coating layer. However, since from these systems release mechanism is dissolution, a higher ratio of drug solubility relative to the dosing amount is essential for rapid release of drug after the lag period [16].

Sigmoidal release system: This consists of pellet cores comprising drug and succinic acid coated with ammonia-methacrylate copolymer USP/NF type B. The time lag is controlled by the rate of water influx through the polymer membrane. Acid and the drug in the core dissolve in Water. The acid solution in turn increases permeability of the hydrated polymer film.

Application of MUPS

- To protect drugs that are unstable in acid from disintegrating in the gastric juice e.g. antibiotics enzymes, peptides proton pump inhibitors.
- P^H Dependent controlled release of drugs for optimal absorption. GI targeting of different sections of the colon (absorption window, targeting localized effects) and small intestine.
- Colon targeting for local treatment and systemic therapies. The key to control 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 GI track. Since the coating dissolution is controlled by pH, by gradually permeability, the drug is released in a precise manner in specific of the digestive tract, or at specific times after intake.
- Combination of drug substances and release profiles can be provided by formulating the MUPS tablets with different pellet qualities or combining pellets with Active pharmaceutical ingredients in powder or granulated form [17].

Pellets
Pellets are small, free flowing, spherical particulate manufactured by the agglomeration of fine powder or granules. The pellet is used to describe a variety of systematically product geometrically defined agglomerates obtained from diverse starting material. In the pharmaceutical industry, pellets can be defined as agglomerates of fine powders or granules of bulk drugs and excipients. They consist of small, free-flowing, spherical or semi-spherical solid units, typically about 0.5 mm to 1.5 mm, and are intended usually for oral administration. It consist of small discrete unit and exhibits some derived characteristics produced by agglomeration of fine powder with binder solution normally the size of the pellets varies from 0.5 – 1.5 mm for oral dosage forms.

Advantages of Pellets

- Pellets can be divided into desired dosage strength without process/formulation changes.
- When pellets contains the active ingredients are in the form of suspension, capsules, or disintegrating tablets, they offer significant therapeutic advantages over single unit dosage forms.
- They can also be mixed to deliver inconsistent bioactive agents. They can also be used to provide different release profiles at the same or different sites in the gastrointestinal tract.
- Pellets offershigh degree of flexibility in designing and development of oral dosage form like suspension, sachet, tablet and capsules [18].

Theory of Pellet Formation And Growth

The pellet growth mechanism as shown in Fig. 2.

A) Nucleation
B) Coalescence
C) Layering
D) Abrasion transfer [19, 20]

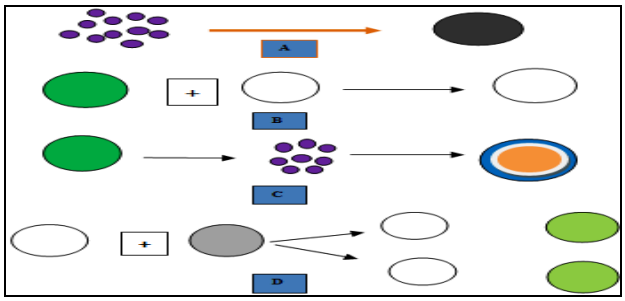

Figure 2: Schematic Representation of Pellet Growth Mechanism

Different Pelletization Techniques

Direct Pelletizing:

Powder is mixed and moistened. A solvent or binder can also be added. (Fluid Bed Pelletizing in the rotor)The powder bed is set for centrifugal motion. The impact and acceleration forces that occur in this process results in the formation of agglomerates, which get rounded out into uniform and dense pellets. The speed of rotation has a direct effect on the density and size of the pellets. The moist pellets are eventually dried in the fluid bed. If it is necessary then systems can be made inert for applications with organic solvents. Spray Granulation is another alternative for direct pelletizing. By using suitable additives, pellets can be converted into tablets or used to fill capsules.

Powder Layering:

Powder layering prepared by the deposition of successive layers of dry powders of drugs and excipients on preformed nuclei or cores with the help of binding liquids. As powder layering necessitates simultaneous application of binding agents and dry powders, hence it requires specialized equipment's like Spheronizer. The prime requirement in this process is the product container should be solid walls with no stab to avoid powder loss beneath the product.

Suspension or Solution Layering:

Solution or suspension layering involves the deposition of successive layers of solution and/or suspensions of drug substances and binder over the starter non-peril seeds, which is an inert material or crystals or granules of the same drug. In fact the coating process, involves in general is applicable to solution or suspension layering technology. Accordingly conventional coating pans, fluidized beds, centrifugal granulators, Wurster coaters have been used successively to manufacture pellets by this method [21].

Extrusion and Spheronization:

Extrusion-spheronization is widely used in formulation of immediate release, extended release and controlled release delivery systems. Pelletization by extrusion-spheronization is a process where pellets are produced from mixture of solid and liquid by the involvement of forming and shaping forces.

Extrusion and Spheronization Involves Four Steps:

- Preparing the wet mass (Granulation)
- Shaping the wet mass into cylinders (Extrusion)
- Breaking of the extrudates and rounding of the particles into spheres
- Drying of pellets.

Cryopelletization: In Cryopelletization droplets of liquid formulation are converted into solid spherical particles or pellets by utilizing liquid nitrogen as the fixing medium. The pellets are dried in conventional freeze dryer. The small size of droplets and hence the large surface area simplify the drying process. The most critical step in Cryopelletization is droplet formulation which is affected not only by formulation related variables, but also by equipment design and corresponding processing variables. The diameter and design of the shearing edge of the holes on the container plates are very critical [22].

Melt Spheronization:
It is a process where a drug substance and excipients are changed into a molten or semi molten state and eventually shaped using suitable equipment to provide solid spheres or pellets. The drug is blended with excipients, polymers, and waxes and void at predetermined temp. The temp of extrusion must be high to melt at least one of the components. The extrudates is cut into uniform cylindrical segments with cutter. Then they are spheronised and the resulting pellets are dried.

Globulation or Droplet Formation:
Consists of two related processes, primarily spray drying and second spray congealing. Spray drying is the process in which drugs in suspension or solution without excipients are sprayed into a hot stream to produce dry and more spherical particles. This process is often used to enhance the dissolution rates, hence bioavailability of poorly soluble drugs.

Compression:
For the preparation of pellets compression is one type of compaction technique .pellets of definite sizes and shapes are prepared by compacting mixtures or blends of active ingredients and excipients under pressure. The formulation and process variables controls the quality of prepared pellets are much same to those used in tablet manufacturing.

Fluid bed coating
Top spray coating: For enteric coating top spray coating process is used. With top spray Coating in the fluid bed (batch and continuous), particles are fluidized in the flow of heated air, which is introduced into the product container via a base plate. The coating liquid is sprayed in the fluid bed from overhead against the air flow (counter current) by means of a nozzle. As the particles continue to move upwards in the air flow drying takes place.

Bottoms spray coating (Wurster coating):
For a controlled release of active ingredients bottoms spray coating process is useful. In the Wuster process, a complete sealing of the surface can be achieved with a low usage of coating substance. The spray nozzle is fitted in base plate resulting in a spray pattern that is simultaneous with the air feed. By using a Wurster cylinder and a base plate with different gouges, the particles to be coated are accelerated inside the Wurster tube and fed through the spray cone simultaneously. As the particles continue travelling upwards, they dry and fall outside the Wruster tube back towards the base plate.

Bottom Sprays Coating (Continuous Fluid Bed):
Particularly suitable for protective coatings, colour coatings where the products throughout rates are high. The product is fed into one side of the machine and is transported onwards continuously via the sieve bottom by means of the air flow. Depending on the application, the system is sub-divided into pre-heating zones, spray zones and drying zones where spraying can take place from below in the form of a bottom spray. The dry, coated particles are withdrawal continuously.

Tangential Spray Coating (Rotor Pellet Coating)
Ideally used for coatings with high solid content. The product arrangeas a spiral motion by means of a rotating base plate, which has air fed into the powder bed at its edge. The spray nozzle is arranged tangentially to the rotor disc and also sprays coincidentally into the powder bed. Thick film layers can be applied by means of the rotor method [23].

Spray-Drying:
Drug solution or suspension is sprayed, with or without excipients, into a hot-air stream generating dry and highly spherical particles in spray drying. Though this technique is suitable for development of controlled release pellets, it is generally implemented to improve the dissolution rates and hence improve the bioavailability of poorly soluble drugs.

Spray Congealing:
Spray congealing is a process in which a drug is allowed to melt, disperse or dissolves in hot melts of gums, waxes, fatty acids etc. and is sprayed into an air chamber where the temperature is below the melting point of the formulation components, to provide, under appropriate processing condition, spherical congealed pellets [24].

Freeze Pelletization
Freeze Pelletization technique is a novel technique for producing spherical matrix pellets containing active ingredients. In this technique, a molten solid carrier along with a dispersed active ingredient is introduced as droplets into an inert and immiscible column of liquid. These droplets

can move either in upward or downward directions, depending on their density with respect to the liquid in the column and solidify into spherical pellets.

Factors Affecting on Pelletization Technique
Moisture Content:
It is a major critical parameter for pellet growth in Pelletization technique .Moisture in the wet mass bring cohesiveness to the powder so that the wet mass can be extracted and spheronised to give spherical shape. High moisture contents leads to agglomeration of pellets during process of spheronization which is one of the techniques of Pelletization due to excess water in the surface of pellets and low moisture content leads to generation of fine with large variation in size distribution.

Rheological Characteristics:
The Rheological condition of the wet mass determines the flow ability in extruder optimum Rheological condition leads to a good flow ability in order to extrude the wet mass variation in rheology make improper and non-uniform extrusion.

Solubility of Excipients and Drug in Granulating Fluid:
Granulating liquid is used to get dissolve soluble drug. Thus increasing the volume of liquid phase lead to over wetting of system of agglomeration of pellet sand increase in wetting liquid increases plasticity but induces sticky mass.

Composition of Granulating Fluid:
Alcohol, water/alcohol mixture, Ethyl Ether, Dilute Acetic Acid, Isopropyl alcohol is also used as a granulating liquid besides water,. According to researcher like Millili and Schwartz, a minimum of 5 % of granulation liquid should be water in order to produce pellets containing Avicel P^H (101) and theophylline. Some researchers used water and dilute acetic acid in different powders to liquid ratio and concluded that mass fraction can be increased up to 100% by using dilute acetic acid for granulation step in place of demineralised water. Aqueous polymer dispersion containing Eudragit, Hydroxypropyl methylcellulose (HPMC), Poly vinyl pyrrilodine (PVP) and Gelatin are used in the moistening liquid.

Physical Properties of Starting Material:
Formulation variable which have an effect on the Pelletization process, such as type and content of starting material, type of filler and particle size of constituent. Quality of pellets not only depends on composition but also on different grades of the same product.The swelling property of materials used in Pelletization technique decides the release rate of the drug in pellets.

Speed of the Spheronizer:
The speed of the Spheronizer affects the size, hardness, spherecity and density of pellets, high speed gives high Sphericity, lower friability, and smooth surface and high crushing strength.

Drying Technique and Drying Temperature:
It is important to get proper size, shape and flow of pellets and it must be reproducible and consistent in all batches. Difference in physicochemical properties of final dosage form like weight variation, improper filling etc. is due to Variation in pellet's size, shape and flow, which will further affect the therapeutic efficiency of the delivery system. Wider particle size distribution may lead to variation in the dose of drug delivery and Variation in shape may lead to variation in flow and compressibility.

Extrusion Screen:
The quality of the extrudateor pellets is greatly influenced by the characteristics of the orifice of screen. An increase in orifice dimension results in increased mean pellet size. The increase in orifice depth decrease with the presence of water at the extrudates surface, increasing the extrusion force, and then has a negative effect on granulometric distribution and on shape [25].

Technologies
Capsule-In-A-Capsule Technology:
Multispectrum of therapeutic applications can be attained by using single oral capsule dosage form based on capsule in capsule technology. In this, it is also possible to insert a prefilled capsule of smaller size into a liquid filled capsule of larger size. Coated or uncoated gelatin or hydroxypropyl methylcellulose (HPMC) may be used to develop such formulations. To attain multiple release profiles, immediate and sustained/controlled release formulations may be filled in outer larger and inner smaller capsules respectively. In addition to modifying release profiles, with appropriate coating, inner and outer capsules can target diverse regions of the GIT (small intestine or colon).

Various advantages of Capsule-in-a-capsule technology are as follows:

- This technology is helpful to provide controlled as well as multi-phase release for single and combination dose regimen even for over the counter drugs.
- By taking it in consideration, patient convenience and compliance and cost effectiveness can be overruled.
- Two independent compartments are comprised in one single unit oral dosage form.
- Delivery of various incompatible APIs is possible.

Tablets-In-A-Capsule Technology:

A new approach which comes into existence consist of combination of features of both modified and controlled release tablets in one dosage forms. Usually, drugs are encapsulated by either biodegradable or erodible polymer within a barrier material by one or other method. A wide variety of lag times can be obtain in release profile only by varying the thickness and structure of barrier material concentrating on the barrier material, structure and thickness. Erosion or degradation of inner reservoir core results in rapid release of drug that is incorporated. By filling versatile tablets in a hard capsule, multifunctional and multiple unit systems with various lag times for oral use, for e.g., sustained-release mini-tablets (SMTs), Rapid release mini tablets, pulsatile mini-tablets, and delayed- onset SMTs can be developed by filling versatile tablets in a hard capsule, by using various combinations of mini- tablets, multiple pulsatile DDS, site-specific DDS, slow/ quick DDS, quick/slow DDS, and zero-order DDS could be formulated easily.

Tablets-in-a-capsule technology offers wide variety of benefits. Some of them are as follows:

- Lower treatment failure rate and lower case-fatality ratios have been increased significant saving.
- Mutually controlled and multi-phase release profile could be attained for both unit or combined prescription as well over the counter dosages.
- Promising delivery of incompatible APIs. Multiple release profile could be attained as sustained, pulsed or delayed.
- Cost effective as well patient compliance therapy could be targeted with patient convenience.
- Drug delivery can target two different regions of GIT.

Programmable Oral Drug Absorption System (PRODAS):

PRODAS tool is believed to equally signify MP and hydrophilic matrix tablet technology and thus can provide all the related benefits of both Drug delivery system in single dosage form. Normally size ranges from 1.5 to 4 mm (in diameter) in controlled-release mini- tablets. Single dosage form can be designed of desirable characteristics by using mini-tablets with different release rates can be combined and formed to give the desired release rates.

Spheroidal Oral Drug Absorption System (SODAS):

SODAS are beads of 1-2 mm in diameter having controlled release pattern produced by MP technique. The drug in a bead is embedded in internal inert core consisting of multiple layers of polymers with other excipients so as to have controlled release of drug. These beads perform release by a diffusion mechanism. Polymer dissolves in GIT which leads to formation of pores in the outer membrane of the bead which are gateway for fluid which enter into the bead to dissolve the drug. The solution of drug formed inside the beads diffuses in a controlled manner causing prolonged absorption. Excipients used for the various purposes like to ensure optimal stability and solubility may also influence sudden environment of the drug within the inert core.

Programmed Multiple-Action Delivery System (PMDS):

In contrast to particularly controlled release technologies, PMDS technology can be helpful to provide for the multiphase delivery of any active ingredient and hence designed accordingly for delivery in a more controlled fashion, so that release of the active ingredient can be achieved at predetermined time intervals and their appropriate levels on a consistent basis.

Time Multiple Action Delivery Systems (TMDS):

Time TMDS is a technology to control release rate in a planned manner of multi-excipient within a single tablet over an extended period of time.

Dividable Multiple Action Delivery Systems (DMDS):

This technology has considerable dosing flexibility which is supposed to upgrade product efficacy and minimize the side effects and hence specially designed to serve the similar purposes.

Once the traditional controlled release tablet is broken, it usually loses its controlled release mechanism of delivery. DMDS technology is always helpful to achieve the exact same release profile on each respective portion of the tablet whenever broken down in two equal parts will as the whole tablet is getting.

Intestinal Protective Drug Absorption System (IPDAS):

In the IPDAS technology, major components are high density controlled release beads, which are compressed into a tablet form. After ingestion of these drugs, they disintegrated at a rapid pace and get dispersed into the beads containing drug molecules which finally enter to the duodenum and are released in the GIT in a controlled and cautious manner, independent of the feeling state. The active ingredient from the MPs is released via diffusion which is a general phenomenon either through the polymeric membrane and or the micro- matrix of polymer/active ingredient formed in the extruded/ sprouted MPs. The wide dispersion of irritant drug throughout the GIT has also been ensured by the intestinal protection of IPDAS technology. [26]

OROS Technology:

OROS technology is based on osmotic mechanism to give pre- programmed, controlled drug delivery to the gastrointestinal tract. Osmotic systems employ the principle of osmotic pressure for the delivery of drugs. Drug release pattern of these systems is independent of pH and other physiological parameter to a large extent and it is possible to adjust the release characteristic by optimizing the properties of drug and system Chronoset is proprietary OROS (Osmotic-controlled Release Oral delivery System) developed by Alza Corporation (now part of Johnson and Johnson). The drug vessel and the osmotic engine cap are the compartment present in System. When the system is open to the elements to an aqueous medium, water permeates into the osmotic engine cap via a rate-controlling membrane. Osmotic engine leads to its expansion due to hydration, which exerts a driving force against the ridge of the drug vessel.

DIFFUCAPS technology:

Is the most popular and versatile approach for chrono therapy for delivering drugs into the body in a circadian release manner. It is made of multiparticulates one or more populations of drug-containing particles.

Diffucaps technology involves the preparation of:

- Drug-containing cores by drug-layering on inert particles.
- Customized release (CR) beads by coating immediate release (IR) particles with one or more functional dissolution rate controlling polymers or waxes.
- Combining one or more functional polymer coated Diffucaps® bead populations into hard gelatin or hydroxypropylmethylcellulose (HPMC) capsules [27].

Characterization of Pellets

Pellets are evaluated for certain quality purpose, which reflect the suitability and use of material during various operations like filling, handling and transportation.

Pellet Size and Size Distribution:

Pellet size and its distribution is determined by sieve analysis which is very simple and economical; microscopy methods like Scanning electron microscopy (SEM) and laser diffraction are characteristic features of pellets which affect coating and rate of drug release.

Shape:

During coating, filling into capsules and dies Shape of pellets is important which influences flow of pellets. Ring gap analyser; scanning electron microscopy (SEM) is the most common method of analysis is by for qualitative and quantitative analysis. For optimum size pellets, stained with dye solution in a petri dish and dried on a hot air oven is another method to determine spherical shape. With the help of camera Lucida, each pellet is recorded for two dimensional image i.e., length and width which is fixed to an optical microscope and circulatory factor(s) was calculated using the equation:

$$\mathbf{S} = P2/(12.56 * A)$$

Where; P is the perimeter (cm), A is the area (cm^2) of circular tracing. Another parameter to determine shape is Circularity, calculated as $4\pi A/P2$, where A is projection area and P is projection perimeter.

Surface Area:

For drug release and results in batch to batch variability Surface area is important parameter to be considered. To ensure the production of consistent shape pellets, surface area is analysed by particle size distribution, gas adsorption (BET method- Brunauer, Emmett and Teller) and air

permeability method. by using fractal geometry of particle obtained by microscopy with image analysis and SEM, which effect on flow and packing of pellets.

Porosity:
Porosity affecting on rate of drug release from the pellets by affecting the capillary action of the dissolved drug; analysed quantitatively by mercury porosimetry and qualitatively by scanning electron microscopy. The sample is firstly introduced into the chamber, degassedit, and then completely covered with mercury. Pressure is applied in to chamber and the volume of mercury that penetrates into the pores is recorded. Pore radius is given by Washburn equation:

$$\mathbf{R} = 2\ g\ [\cos q]\ /\ P$$

Where; q= 140o, g = 480 ergs/cm3,r = pore radius, p = mercury-intrusion pressure.

Bulk Density and Tap Density:
Bulk Density and tap density affects the potency of finished product, produces segregation during mixing and leads batch to batch variation. The ratio of weight to the occupied volume is used to calculate bulk density and is measured by automated tapper or a pycnometer.

True Density:
True density indicates extent of densification or compactness. Air- comparison pycnometer, helium pycnometer or solvent displacement method are different methods of analysis [28].

Hardness and Friability:
Hardness and friability determination of pellets is important because the pellets have to withstand during Shipping, handling, storage and other processing such as coating. Relative hardness value is determined by the instrument such as the Kaul pellet hardness tester and by using Erkewa type tablet friabilator or turbula mixer for a fixed period of time combined with glass beads of certain diameter in order to generate abrasion friability of pellets to be determined.

Tensile Strength:
By using tensile apparatus the tensile strength of the pellets is determined with a 5 kg load cell, the pellets are strained until failure occurs. The load is recorded and the tensile strength is calculated applying the value for the failure load and the radius of the pellets [29].

Flowability:
Flowability is determined by angle of repose. If $\theta<30°$-excellent Flowability and $\theta>40°$- poor Flowability.

***In-Vitro* Dissolution Testing:**
In-vitro Dissolution Testing most commonly is by USP I (basket) and USP II (paddle) apparatus to study the release pattern of the coated pellets [30]. Some examples of marketed products of MUPS are given in Table 1.

Table 1: Marketed Products of MUPS

Product	Company	Drug
Losec MUPS	Astra Zeneca	Omerprazole Magnesium
Esomeprazole	Astra Zeneca	Esomeprazole Magnesium
Troprol XL	Astra Zeneca	Metoprolol tartrate
revacidSoluTab	Takeda	Lansoprazole
Theodur	Key	Theophylline
Bontril SR	Carnick laboratories, Inc	Phendimetrazine Tartrate
Brexin L.A	Savage Laboratories, Bangalore	Chlorpheniramine Pseudoephedrine
Compazine	Smith & French, Mumbai	Prochlorperazine
Cymbalta	Eli Lilly and Company, USA	Duloxetine Hydrochloride
Dilgard XL 180	Smith kline& French, Mumbai	Diltiazem hydrochloride
Fastin	Berlex Laboratories, USA	Phentermine

CONCLUSIONS AND FUTURE PERSPECTIVES
During the developing a MUPS there are numerous challenges. Importance of MUPS which provides 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. The development of a dosage form that improves the oral absorption of peptide and protein drugs whose bioavailability is very low because of instability in the GI tract due to pH or enzymatic degradation is one of the greatest scopes for oral peptide delivery in the pharmaceutical field. Multiparticulates systems like microspheres and nanoparticles can provide a platform for spatial delivery of candidates like peptides, proteins, oligonucleotides and vaccines.

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