

Review Article

Multiparticulate Drug Delivery Systems for Controlled Release

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Abstract

Pharmaceutical invention and research are increasingly focusing on delivery systems which enhance desirable therapeutic objectives while minimising side effects. Recent trends indicate that multiparticulate 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 microparticles depends on a variety of factors including the carrier used to form the multiparticles and the amount of drug contained in them. Consequently, multiparticulate drug delivery systems provide tremendous opportunities for designing new controlled and delayed release oral formulations, thus extending the frontier of future pharmaceutical development.

Keywords: *Dose dumping, Microparticles, Multiparticulate delivery system, Delayed release*

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INTRODUCTION

Multi-particulate drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, each exhibiting some desired characteristics. In these systems, the dosage of the drug substances is divided on a plurality of subunit, typically consisting of thousands of spherical particles with diameter of 0.05-2.00mm¹. Thus multiparticulate dosage forms are pharmaceutical formulations in which the active substance is present as a number of small independent subunits. To deliver the recommended total dose, these subunits are filled into a sachet and encapsulated or compressed into a tablet⁴. Multiparticulates are discrete particles that make up a multiple-unit system. They provide many advantages over single-unit systems because of their small size. Multiparticulates are less dependent on gastric emptying, resulting in less inter and intra-subject variability in gastrointestinal transit time. They are also better distributed and less likely to cause local irritation². Recently much emphasis is being laid on the development of multiparticulate dosage forms in preference to single unit systems because of their potential benefits such as increased bioavailability, reduced risk of systemic toxicity, reduced risk of local irritation and predictable gastric emptying³.

There are many reasons for formulating a drug as a multiparticulate system for example, to facilitate disintegration in the stomach, or to provide a convenient, fast disintegrating tablet that dissolves in water before swallowing which can aid compliance in older patients and children. Multiparticulate systems show better reproducible pharmacokinetic behavior than conventional (monolithic) formulations. After disintegration which occurs within a few minutes often even within seconds, the individual subunit particles pass rapidly through the GI tract. If these subunits have diameters of less than 2mm, they are able to leave the stomach continuously, even if the pylorus is closed. These results in lower intra and inter individual variability in plasma levels and bioavailability.

Drug safety may also be increased by using multiparticulate dosage forms, particularly for modified release systems. For example, if the film coat of a single-unit (monolithic) enteric coated tablet is damaged, the complete dose will be released into the stomach where it may cause pain or ulceration or reduced efficacy, depending on the reason for choosing the protection of the enteric coating. Equally, if there is damage to the film coating of a monolithic tablet with a sustained release formulation, this can lead to "dose dumping" and result in dramatic side effects. By contrast, in multiparticulate formulation, the release characteristics are incorporated into every single subunit and any damage only affects the release behavior of the subunit involved, which represents a small part of the total dose, reducing the likelihood of safety problems⁴.

SOME APPROACHES TO MULTIPARTICULATE FORMULATION

A multiparticulate floating-pulsatile drug delivery system was developed using porous calcium silicate [RE(R)] and sodium alginate, for time and site specific drug release of meloxicam⁵.

An oral controlled onset extended release dosage form intended to approximate the chronobiology of rheumatoid arthritis was proposed for site specific release to the colon. The multiparticulate system consisting of drug loaded cellulose acetate cores encapsulated within Eudragit S-100 microcapsules was designed for chronotherapeutic delivery of ketoprofen⁶. The site-specific delivery of drugs to the colon has implications in a number of therapeutic areas, which include topical treatment of colonic disorders such as Crohn's disease, ulcerative colitis, constipation, colorectal cancer, spastic colon and irritable bowel syndrome⁷.

Multiparticulates approaches tried for colonic delivery includes formulations in the form of pellets, granules, microparticles and nanoparticles. Because of their smaller particle size compared to single unit dosage forms these systems are capable of passing through the GI tract easily, leading to low inter

and -intra subject variability. Moreover, multiparticulate systems are to be more uniformly dispersed in the GI tract and also ensure more uniform drug absorption³. A multiparticulate system of chitosan hydrogel beads has been investigated for colon-specific delivery of macromolecules using fluorescein isothiocyanate-labeled bovine serum albumin as a model protein⁸.

Multiparticulates may be prepared by several methods. Different methods require different processing conditions and produce multiparticulates of distinct qualities. Some of these methods may be broadly classified as pelletization, granulation, spray drying, and spray congealing. Drug particles may be entrapped within the multiparticulates or layered around them. Subsequently, these multiparticulates may be modified in many ways to achieve the desired drug release profile.

One approach to the modification of drug release profile in multiparticulates is to coat them. Reasons for the application of coating onto multiparticulates are to obtain functional coats, provide chemical stability, improve physical characteristics and enhance patient acceptance. Coats are formed from various polymeric coating materials broadly classified as aqueous polymer dispersions, polymer solutions, molten polymers and dry powders. Depending on the type of coating material used, functions such as sustained release (SR), targeted release, delayed release, and pulsatile release can be achieved.

The most common method used for the application of coating onto multiparticulates is air suspension coating. Other methods include compression coating, solvent evaporation, coacervation, and interfacial complexation. It is also possible to form coated multiparticulates by spray drying and spray congealing². A multiparticulate composition may allow controlled release of the drug over a wide range of release rates, and permit the release rate to be set at a predetermined rate, such a formulation may be formed using a melt-congeal process which maintains the crystallinity of the drug during the melt-congeal process⁹. A multiparticulate delayed

release system based on coated pellets containing an osmotic active ingredient has been prepared. The coating consisted of a semi permeable membrane of cellulose acetate. Following ingestion water penetrates into the core and forms a saturated solution of the soluble components. The osmotic pressure gradient induces a water influx resulting in a rapid expansion of the membrane leading to the formation of pores. The osmotic ingredient and the drug are released through these pores according to zero order kinetics. In comparison with the sodium chloride free formulation the inclusion of the osmotically active ingredient results in a completely different dissolution behavior. Lag time and dissolution rate were dependent on the coating level and the osmotic properties of the dissolution medium¹⁰.

MECHANISM OF DRUG RELEASE FROM MULTI-PARTICULATES

The mechanism of drug release from multiparticulates can be occur 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 coating¹.

DESIGN OF MULTIPARTICULATE DRUG DELIVERY SYSTEMS

The purpose of designing multiparticulate dosage form is to develop a reliable formulation that has all the advantages of a



Fig 1: Intestinal Protective Drug Absorption System



Fig 2: Spheroidal Oral Drug Absorption System



Fig 3: Programmable Oral Drug Absorption System

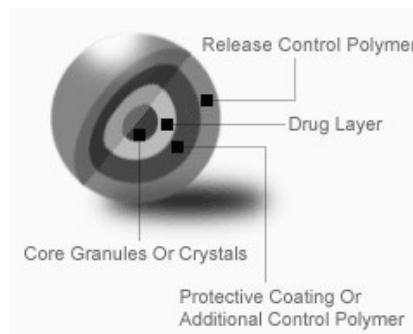


Fig 4: Diffucaps

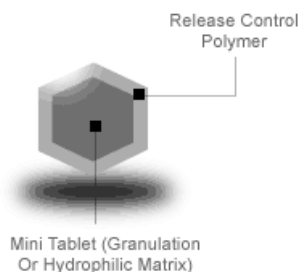


Fig 5: Minitab

single unit formulations and yet devoid of the danger of alteration in drug release profile and formulation behavior due to unit to unit variation, change in gastro-luminal pH and enzyme population. A generally accepted view is that multiparticulate systems perform better in vivo than single unit system, as they spread

out through the length of the intestine cause less irritation, enjoy a slower transit through the colon and give a more reproducible drug release. As in the case of single unit dosage forms, for the purpose of the designing multiparticulate colon specific drug delivery system, the presence of specific bacterial

populations in the colon and increasing pH gradient have been extensively explored as triggering mechanism in order to initiate colon specific drug release.

Multiparticulate crystalline drug compositions

A multiparticulate for controlled release of a drug comprises a crystalline drug, a glyceride having at least one alkylate substituent of not less than 16 carbon atoms, and a poloxamer, wherein at least 70 wt % of the drug in the multiparticulate is crystalline. The multiparticulate comprises crystalline drug particles embedded in the glyceride/poloxamer mixture. The poloxamer 16 is substantially homogeneously distributed throughout the glyceride 14 and is present as a separate phase from the glyceride 14¹¹.

Multiparticulates 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 life¹.

Intestinal Protective Drug Absorption System

Intestinal protective drug absorption system (IPDAS) (Figure 1) is a multiparticulate tablet technology that has been developed to enhance the gastric tolerability of potentially irritant or ulcerogenic drugs such as the NSAIDs. It consists of high density controlled release beads that are compressed into a tablet form. The beads may be manufactured by techniques such as extrusion spherulization and controlled release can be achieved with the use of different polymer systems to coat the resultant beads. Alternatively, the drug can also be coated into on an inert carrier such as non-pareil seeds to produce instant release multiparticulates. Controlled release can be achieved by the formation of a polymeric membrane onto these instant release multiparticulates. Once an IPDAS tablet is ingested, it rapidly disintegrates and disperses beads containing

the drug in the stomach which subsequently pass into the duodenum and along the gastrointestinal tract in a controlled and gradual manner, independent of the feeding state. Release of active ingredient from the multiparticulates occurs through a process of diffusion either through the polymeric membrane and /or the micro matrix of the polymer/active ingredient formed in the extruded/spherulized multiparticulates. The intestinal protection of IPDAS is by virtue of the multiparticulate nature of the formulation which ensures wide dispersion of irritant drug throughout the gastrointestinal tract. Naprelan®, which is marketed in the United States, employs IPDAS technology. This innovative formulation of naproxen sodium is a unique controlled release formulation indicated both for acute and chronic pain^{1,12}.

Spheroidal oral drug absorption systems

Spheroidal Oral Drug Absorption System (SODAS) (Figure 2) is a multiparticulate technology that enables the production of customized dosage forms and responds directly to individual drug candidate needs. It can provide a number of tailored drugs release profiles including immediate release of drug followed by sustained release to give rise to a fast onset of action which is maintained for 24 hours. Alternatively, the opposite scenario can be achieved where drug release is delayed for a number of hours^{1,13}.

Programmable Oral Drug Absorption System

Programmable Oral Drug Absorption System (PRODAS) (Figure 3) is presented as a number of mini tablets contained in hard gelatin capsule. It thus combines the benefits of tableting technology within a capsule. It is possible to incorporate many different minitables, each one formulated individually and programmed to release drug at different sites within the GIT. These combinations may include immediate release, delayed release, and/or controlled release mini tablets. It is also possible to incorporate mini tablets of different sizes so that high drug loading is possible. Their size ranges usually from 1.5 – 4 mm in diameter^{1,14}.

Diffucaps

In this multiparticulate system, drug profiles are created by layering an active drug onto a neutral core such as sugar spheres, crystals or granules followed by the application of a rate-controlling, functional membrane (Figure 4). The coating materials can be water soluble, pH dependent or independent or water insoluble depending on the individual needs of compound. The resultant beads are small in size approximately 1mm or less in diameter. By incorporating beads of differing drug release profiles into hard gelatin capsules, combination release profiles can be achieved. It is possible to customize any combination of sustained release, pulsatile release and immediate release profiles depending on the specific needs of the product.

The drug layering process can be conducted either from aqueous or solvent based drug solutions. Eurand has also developed a formulation technology that combines the customized drug release offered by Diffucaps with technologies that enhance the solubility of insoluble drugs in the gastrointestinal tract. Eurand is using this technology to provide a degree of delivery control that goes beyond that of single technology systems.

Diffucaps beads are small in size, approximately 1mm in diameter, and are filled into a capsule to create the final dosage form. Beads of differing drug release profiles can be easily combined in a single capsule providing high levels of control over release profiles. Diffucaps beads of different drugs can be combined to make convenient single dose units for combination therapies^{1, 15}.

Minitabs

The Eurand MINITABS technology (Figure 5) is unique in that it offers the advantages of a tablet combined with those of a multiparticulate drug form. Eurand MINITABS are tiny (2mm x 2mm) tablets containing gel-forming excipients that control drug release rate. Additional membranes may be added to further control release rate. The small size of Eurand minitabs means that they can be filled into capsules as a final dosage form.

As a result, combination products can be developed to allow for two or more release profiles within a single capsule. Eurand minitabs offer high drug loading, the ability to fine tune release rates for targeted delivery and content uniformity for more accurate dosing. Eurand Minitabs offer high drug loading, a wide range of release rate designs, and fine tuning of these release rates. The capsules can be opened and the contents used as a "sprinkle" formulation^{1, 16}.

Stabilized Pellet Delivery System

Stabilized pellet delivery system technology uses functional polymers or a combination of functional polymers and specific additives, such as composite polymeric materials to deliver a drug to a site of optimal absorption along the intestinal tract. The active drug is incorporated in multiparticulate dosage forms such as DIFFUCAPS or Eurand MINITABS, which are then subsequently coated with pH dependent/independent polymeric membranes that will deliver the drug to the desired site. These are then filled into hard gelatin capsules. This technology is designed specifically for unstable drugs and incorporates a pellet core of drug and protective polymer outer layer(s)¹.

Pelletized Delivery System

Pelletized Delivery System (PDS) is a sustained release system using pellets or beads manufactured using marumerization/ pheronization/pelletization techniques or by layering powders or solutions on nonpareil seeds. Release modulating polymers are sprayed on the beads using various coating techniques. The coated beads are filled in to hard gelatin capsules. Drug release occurs by diffusion associated with bioerosion or by osmosis via the surface membrane. The release mechanism can be pH-activated or pH-independent. The beads can be formulated to produce first order or zero order release¹.

Pelletised tablet

Pelletised tablet (Peltab[®]) system utilizes polymer-coated drug pellets or drug crystals, which are compressed into tablets. In order to provide a controlled release, a water insoluble

polymer is used to coat discrete drug pellets or crystals, which then can resist the action of fluids in the GIT. This technology incorporates a strong polymer coating enabling the coated pellets to be compressed into tablets without significant breakage¹.

Multiparticle Drug Dispersing Shuttle

Multiparticle drug dispersing shuttle (Multipart[®]) consists of a tablet carrier for the delivery of controlled release beads or pellets through the GIT which preserves the integrity and release properties of the beads. The distribution of the beads is triggered by the disintegration of the tablet carrier in the stomach. Drug release from the beads is triggered by super disintegration of the tablets. It can be pH-activated or pH-independent and can occur by disintegration or osmosis. The beads can be formulated to produce first or zero order release¹.

Macrocap[®]

Macrocap[®] consists of immediate release beads made by extrusion/ spheronization/ pelletization techniques or by layering powders or solutions on nonpareil seeds. Release modulating polymers are sprayed on the beads using various coating techniques. The coated beads are filled in hard gelatin capsules. Drug release occurs by diffusion associated with bioerosion or by osmosis via the surface membrane. The release mechanism can be pH-activated or pH-independent. The beads can be formulated to produce first or zero order release¹.

Orbexa[®]

Orbexa[®] technology is a multiparticulate system that enables high drug loading and is suitable for products that require granulation. This technology produces beads that are of controlled size and density using granulation, extrusion and spheronization techniques. This process is unique in that it allows for higher drug loading than other systems, is flexible and is suitable for use with sensitive materials such as enzymes¹.

KV/24

KV/24 is a patented, multiparticulate drug delivery technology that encapsulates one or more drug compounds to achieve release in a pre-determined fashion over a 24-hour period after oral administration. KV/24 technology is based upon coating a neutral core (non-pareiled bead) with a drug substance, then sequentially coating with one or more polymers to achieve a once-a day release profile. The drug can either be combined with the neutral core or incorporated into the coating process¹.

Flashtab

Flashtab technology is a fast dissolving/disintegrating oral tablet formulation. It is a combination of taste masked multiparticulate active drug substances with specific excipients compressed into tablets. A disintegrating agent and a swelling agent are used in combination with coated drug particles in this formulation to produce a tablet that disintegrates in the mouth in less than one minute. These oro-dispersible tablets disperse rapidly before the patient swallow them¹.

InnoHerb

This technology is used coating the pellets inside of the capsule, InnoHerb Phytogranules. The multiparticulate is made up of many micropellets or small beads containing active herbal compounds. The special coating for each plant extract contains top quality standardised dried extracts which assures efficacy and safety of the semi-permeable membrane, improves stability, mask taste/smell and affords gastro-protection as well as promote controlled release of actives, optimal availability and better absorption¹⁷.

Layering process for multiparticulate dosage form

Layering processes involve loading solid inert cores with drugs and/or excipients. Inert cores, placed in a suitable vessel such as a coating pan or a fluid bed, may be layered according to different methods. Some methods consist of spraying onto the cores a

solution/suspension containing both drug and binding agent. Others are based on layering the drug directly in powdery form where drug loading occurs by gravity and adhesion is ensured by a liquid binder sprayed onto the cores.

The layering process is particularly suitable for production of small drug loaded units, multiples of which are placed into capsules for patient delivery. In the case of spherical inert cores such as non-pareils, the layering techniques from solution/suspensions produce homogeneous drug loaded particles, which retain an approximately spherical shape. They are therefore particularly suitable for successively film coating to build up the particle with the aim of providing a desired drug release profile¹⁸.

Delayed release oral polypeptides

In one embodiment, the composition further includes an inert core. The inert core can be, e.g., a pellet, sphere or bead made up of sugar, starch, microcrystalline cellulose or any other pharmaceutically acceptable inert excipient. A preferred inert core is a carbohydrate, such as a monosaccharide, disaccharide, or polysaccharide, i.e., a polymer including three or more sugar molecules. An example of a suitable carbohydrate is sucrose. In some embodiments, the sucrose is present in the composition at a concentration of 60-75%.

When the bioactive polypeptide is IL-11, the IL-11 layer is preferentially provided with a stabilizer such as methionine, glycine, polysorbate 80 and phosphate buffer, and/or a pharmaceutically acceptable binder, such as hydroxypropyl methylcellulose, povidone or hydroxypropyl cellulose. The composition can additionally include one or more pharmaceutical excipients. Such pharmaceutical excipients include, e.g., binders, disintegrants, fillers, plasticizers, lubricants, glidants, coatings and suspending/ispersing agents. In some embodiments, the composition is provided as a multiparticulate system that includes a plurality of enteric coated, IL-11 layered pellets in a capsule dosage form. The enteric coated IL-11 pellets

include an inert core, such as a carbohydrate sphere, a layer of IL-11 and an enteric coat. The enteric coat can include, e.g., a pH dependent polymer, a plasticizer, and an antisticking agent/glidant. Preferred polymers include e.g., methacrylic acid copolymer, cellulose acetate phthalate, hydroxyl propyl methylcellulose phthalate, polyvinyl acetate phthalate, shellac, hydroxypropyl methylcellulose acetate succinate and carboxymethylcellulose. Preferably, an inert seal coat is present in the composition as a barrier between the IL-11 layer and enteric coat. The inert seal coat can be e.g. hydroxyl propyl methyl cellulose, povidone, hydroxypropyl cellulose or another pharmaceutically acceptable binder.

Suitable sustained release polymers include, e.g., amino methacrylate copolymers (Eudragit RL, Eudragit RS), ethylcellulose or hydroxypropyl methylcellulose. In some embodiments, the methacrylic acid copolymer is a pH dependent anionic polymer solubilizing above pH 5.5. The methacrylic acid copolymer can be provided as a dispersion and be present in the composition at a concentration of 10-20% wt/wt. A preferred methacrylic acid copolymer Eudragit[®] L30D-55¹⁹.

Multiparticulate mucoadhesive formulations

In a preferred embodiment, illustrated by way of example, there is provided a supply of gas-developing components as well as a number of film-like, stacked individual particles which consist of a mucoadhesive, active substance-containing layer and of a backing layer controlling the direction of active substance release, these components being located within a polymer enclosure which is resistant to gastric juice but permeable to intestinal juice. Here, the active substance may be present embedded in the film-like component. The process for the production of a gastric juice-resistant device, consisting of at least one active substance in the form of a multiparticulate preparation with mucoadhesive properties, and of a blowing agent which on contact with liquid produces gas individual particles being enclosed by a gastric juice-resistant, intestinal juice-soluble polymer

enclosure, is as follows: (a) transfer of a polymer material in web form to a moulding board provided with bores, and applying a vacuum to form the compartments of the polymer enclosure; (b) alternately filling-in the active substance-containing preparation and the blowing agent-containing preparation; (c) superposing a second polymer web, and closing the compartments by sealing with application of heat and pressure; and (d) separating the individual devices by punching or cutting²⁰.

CONCLUSION

The market for drug delivery system has come a long way and will continue to grow at an impressive rate. Today's drug delivery technologies enable the incorporation of drug molecules into a new delivery system, thus providing numerous therapeutic and commercial advantages. Multiparticulate drug delivery systems provide several all the advantages including greater flexibility and adaptability of microparticulate dosage forms which gives clinicians and those engaged in product development powerful new tools to optimize therapy. It is little wonder therefore, that such systems are growing rapidly in popularity.

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