

Multi Particulate Drug Delivery System

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Abstract

Multiparticulate drug delivery system is increasing desire effect over single unit dosages forms because of their potential benefits. Multiparticulate systems provide predictable gastric emptying, no risk of dose dumping, flexible release pattern and increased bioavailability with less inter and Intra subject variability. The aim of this review is to provide the main multiparticulate pulsatile delivery system, for which the swelling and rupturing and changed permeability of the coating membrane is primarily involved in the control of release. Ulcerative colitis is the chronic relapsing multifactorial gastrointestinal inflammatory bowel disease, which is characterized by bloody diarrhea, bowel dysfunction, anaemia. The main aim is to overcome ulcerative colitis is appropriate local targeting and drug-related side-effects. To overcome these problems, microparticulate systems seems to be a promising approach for controlled and sustained drug release after oral administration, with this drug delivery system increasing immense importance for the local targeting drug to the colon at a controlled and sustained rate.

Prior to the development of any system, due consideration must be given to the physiological changes that occur in the disease state that might affect the performance of such a system. In spite of such physiological constraints to drug delivery to the colon, several colon-targeted formulations have been successfully commercialized in US and European markets. Few of the commercialized products are listed in Table 1. Several reviews have been published reporting the research that has gone into the development of

perorally delivered single unit colon targeted drug delivery systems (24-30). In general, four primary approaches have been proposed for colon targeted delivery, namely prodrugs, pH-dependent system, time-dependent systems and colonic microflora activated systems (27). A brief summary of some of the colon targeted formulations based on the above mentioned conventional approaches is given in Table 2. Single unit colon targeted drug delivery system may suffer from the disadvantage of unintentional disintegration of the formulation due to manufacturing deficiency or unusual gastric physiology that may lead to drastically compromised systemic drug bioavailability or loss of local therapeutic action in the colon. Recently, much emphasis is being laid on the development of multiparticulate dosage forms in comparison to single-unit systems because of their potential benefits like increased bioavailability, reduced risk of systemic toxicity, reduced risk of local irritation and predictable gastric emptying (31). Multiparticulate approaches tried for colonic delivery include formulations in the form of pellets, granules, microparticles and nanoparticles. The use of multiparticulate drug delivery systems in preference to single unit dosage forms for colon targeting purposes dates back to 1985 when Hardy and co-workers (32) showed that multiparticulate systems enabled the drug to reach the colon quickly and were retained in the ascending colon for a relatively long period of time. Because of their smaller particle size as compared to single unit dosage forms, these systems are capable of passing through the GI tract easily, leading to less inter-and intra-subject variability. Moreover, multiparticulate systems tend to be more uniformly dispersed in the GI tract and also ensure more uniform drug absorption (33-35).

Table 1: Marketed drug products for the treatment of inflammatory bowel disease

Drug	Trade Name	Formulations	Dose
Mesalamine	Asacol	Eudragit-S coated tablets (dissolves at pH 7)	0.8 -2.4 g/day
Mesalamine	Salofac	Eudragit-L coated	1.0-4.0 g/day

		tablets (dissolves at pH 6)	
Mesalamine	Claversal Mesazal Calitoflak	Eudragit-L coated tablets	1.0-4.0 g/day
Budesonide	Entocort	Eudragit-L coated tablets	9 mg/day

Table 2: Examples of colon targeted formulations based on conventional techniques

TECHNIQUE EMPLOYED	POLYMERS USED	DRUG USED
pH dependent	Eudragit L100 & S100 Eudragit L100 & S100 Eudragit L100 & S100 Eudragit S, Eudragit FS, Eudragit P4134F Eudragit L30 D-54 & Eudragit FS 30D	Mesalazine NS Diclofenac sodium & 5-ASA Prednisolon Paracetamol
Time dependent	Hydroxy propyl methyl cellulose Hydroxyethyl cellulose Ethyl cellulose micro crystalline cellulose Lactose /behinic ā Hydroxy propyl methyl cellulose Hydroxy propyl methyl cellulose	Pseudo ephedrine HCL Theophylline Indomethacin NS Diltiazem
Bacterial dependent/ Polysaccharide based	Christon Pectin Guar gum Chondroitin sulfate Amylose Alginates	Diclofenac sodium Indomethacin Dexamethasone Indomethacin 5-Acetyl salicylic ā 5- Acetyl salicylic ā

Keywords: - Multiparticulate drug, colon, ulcerative colitis, gastric emptying, dumping, inter and intra.

INTRODUCTION

In research aiming towards underlying principles to bring both commercial and therapeutic values to health care products are contributing to a novel drug delivery system.[1] Based on these premises, the aim of the present review is to survey the main multiparticulate pulsatile delivery systems, for which the swelling and rupturing dissolution or erosion; and changed permeability of the coating membrane is primarily involved in the control of release [1]. The dependence of several diseases and body function on circadian rhythm is well known. Genetic control of a "master clock" located in the nucleus suprachiasmatic has been recently proposed [2]. In recent pharmaceutical applications involving pulsatile delivery, multiparticulate dosage forms are gaining much favor over single-unit dosage forms [9].

The potential benefits as shown in Table 1 include increased bioavailability; predictable, reproducible and generally short gastric residence time; no risk of dose dumping; reduced risk of local irritation; and the flexibility to blend pellets with different compositions or release patterns. Because of their smaller particle size, these systems are capable of passing through the GI tract easily, leading

to less inter-and intra-subject variability. Limitation of process variables caused by multiple formulation steps can act as technical hurdles in manufacturing reproducibility and lack of safety and efficacy; true reservoir devices have not yet succeeded. Pharmaceutical invention and research are increasingly focusing on delivery systems that 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, the flexibility of blending to attain different release patterns, as well as reproducible and short gastric residence time. The release of drugs 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.

ADVANTAGES AND DRAWBACKS OF MULTIPARTICULATE PULSATILE DRUG DELIVERY SYSTEMS

Advantages

1. Predictable, reproducible and short gastric residence time
2. Less inter-and intra-subject variability
3. Improve bioavailability
4. Reduced adverse effects and improved tolerability
5. Limited risk of local irritation
6. No risk of dose dumping
7. Flexibility in Design
8. Ease of combining pellets with different compositions or release patterns.
9. Improve stability
10. Improve patient comfort and compliance

11. Achieve a unique release pattern

12. Extend patent protection, Globalize product, Overcome competition.

Drawbacks

- Low drug loading
- Proportionally higher need for excipients
- Lack of manufacturing reproducibility and efficacy
- Large number of process variables
- Multiple formulation steps
- Higher Cost of production
- Need for advanced technology
- Trained/skilled personal needed for manufacturing.

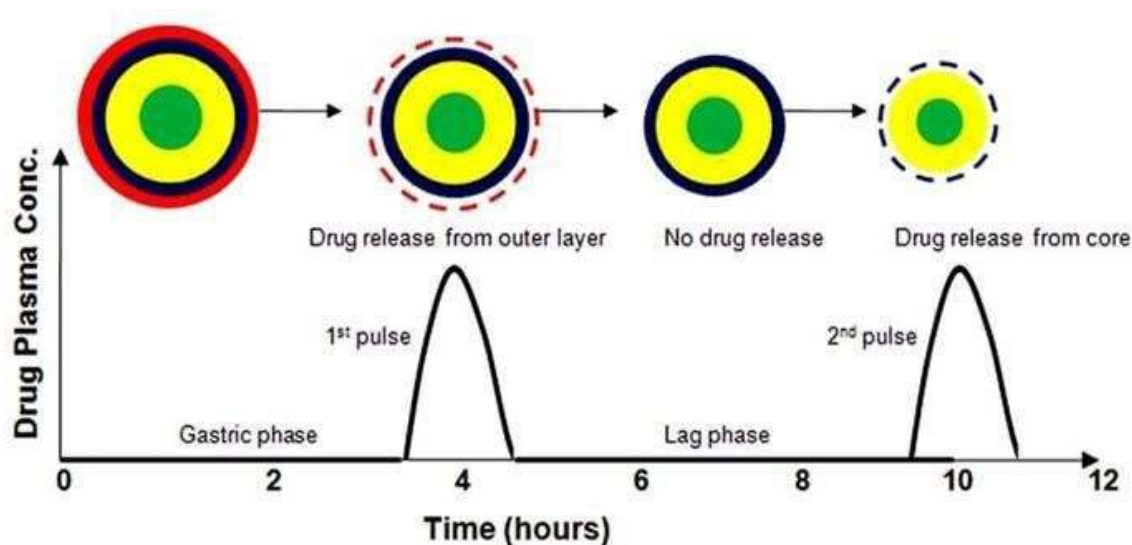


Figure 1: Hypothetical design and plasma drug profile of a multiparticulate pulsatile system. A. Design of a pellet with multiple coatings, and B. Predicted bi-modal plasma

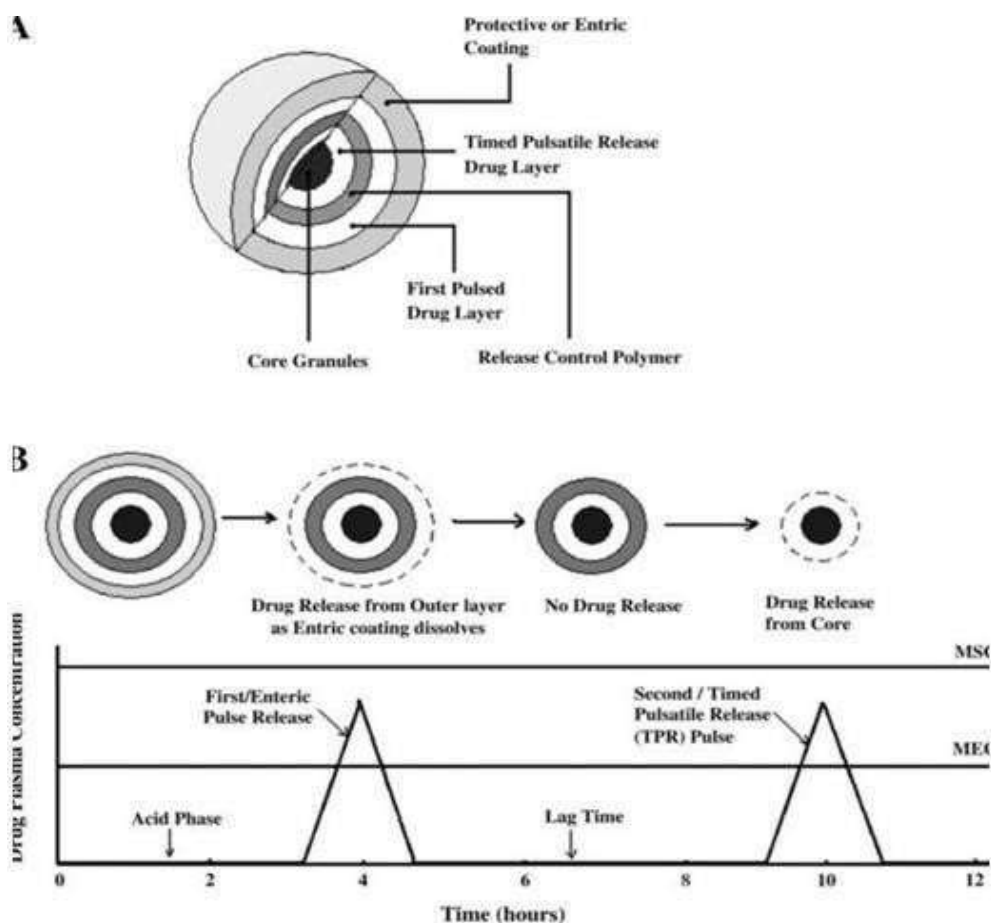


Figure 2: Hypothetical design and plasma drug profile of a Diffucaps multiparticulate pulsatile system. A. Design of a pellet with multiple coatings, and B. Predicted bi-modal plasma concentration profile

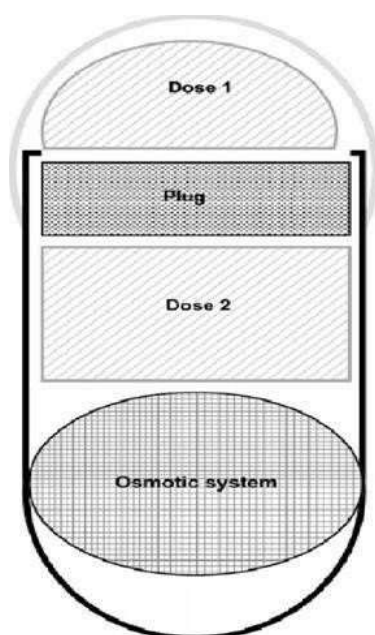


Figure 3: Pulsatile capsule

The pulsatile capsule is designed for two drug doses. The first is placed into the capsule cap, while the second dose is released from an insoluble capsule body. Lag time is determined by an osmotic system that presses an insoluble plug out of the capsule body.

PHARMACEUTICAL MULTIPARTICULATES

The present invention generally relates to a method of manufacturing pharmaceutical dosage forms for human or veterinary use, preferably Sustained release particles, Such as particles having diameters ranging from 0.1 to 3.0 mm. Such particles may contain analgesics, Such as morphine, or other active ingredients. The present invention also relates to dosage forms obtained by processing of the aforesaid particles, such as tablets, Suppositories or pessaries. Patent Application PCT/SE93/00225 published under No. WO 93/18753 describes a process for the preparation of Sustained release pellets, which comprises pelletizing a mixture containing the drug in finely divided form and a binder; the process is characterized in that: (a) the binder is in particle form consisting of one or more water-insoluble or water-soluble, wax-like binder Substance(s) with a melting point above 40° C. and (b) the pelletization step is

performed by mechanically working the mixture, in a So-called high-shear mixer, under the input of a Sufficient amount of energy for the binder to melt and pelletization to take place. Patent Application PCT/SE92/06679 describes a similar process. Processes of this kind are sometimes referred to as —melt-pelletization processes. We have found that operating according to these processes using commercial manufacturing equipment with a Standard Stainless Steel interior, which is also the method described in Schaefer et al. (Drug Development and Industrial Pharmacy, 16(8), 1249-1277 (1990) and Taggart et al. (International Journal of Pharmaceutics 19 (1984) 139-148), results in yields of pellets in the preferred size range of only about 30 to 60% compared with the theoretical. Use of a wider particle size range to improve the yield results in an erratic in vitro release rate and irreproducible performance. There is, therefore, a need for a commercial process for producing Satisfactory controlled release particles, which has a much higher yield. Therefore, one object of the invention is to provide a process that has an improved yield and preferably produces a product with reproducible controlled release characteristics. The present invention thus includes in one aspect a process for the

manufacture of particles, preferably Sustained release particles, which comprises (a) mechanically working in a high-speed mixer, a mixture of a particulate drug and a particulate, hydrophobic and/or hydrophilic fusible carrier or diluent having a melting point from 35 to 150° C. and optionally a release control component comprising a water Soluble fusible material or a particulate, Soluble or insoluble organic or inorganic material, at a Speed and energy input which allows the carrier or diluent to melt or Soften, whereby it forms agglomerates, (b) breaking down the larger agglomerates to give controlled release particles, optionally (c) continuing mechanically working optionally with the further addition of a low percentage of the carrier or diluent; and (d) optionally repeating Step (c) and possibly (b) one or more, e.g., up to five, times.

This process is capable of giving a high yield (over 80%) of particles in the desired size range, with a desired in Vitro release rate and uniformity of release rate. The resulting particles may be Sieved to eliminate any oversized or undersized material then formed into the desired dosage units by for example, encapsulation into hard gelatin capsules containing the required dose of the active Substance or by

tableting, filling into Sachets or molding into Suppositories, pessaries or forming into other Suitable dosage forms. The drug may be water-soluble or water-insoluble. Water Soluble drugs will usually be used in amounts giving, for example, loading of up to about 90% w/w in the resulting particles; water-insoluble drugs may be used in higher amounts, e.g., up to 99% W/w of the resulting particles. Examples of water-soluble drugs which can be used in the method of the invention are morphine, hydromorphone, diltiazem, diamorphine and tramadol and pharmaceutically acceptable Salts thereof; examples of water-insoluble drugs which can be used in the process of the invention are naproxen, ibuprofen, indomethacin and nifedipine. Among the active ingredients which can be used in the process of the invention are the following:

Analgesics:- Dihydrocodeine, Hydromorphone, Morphine, Diamorphine, Fentanyl, Alfentanil, Sufentanyl, Pentazocine, Buprenorphine, Nefopam, Dextropropoxyphene, Flupirtine, Tramadol, Oxycodone, Metamizole, PropyphenaZone, Phenazone, Nifenazone, Paracetamol, Phenylbutazone, OxyphenbutaZone, Mofebutazone, Acetyl Salicylic acid, Diflunisal, Flurbiprofen, Ibuprofen, Diclofenac, Ketoprofen,

Indomethacin, Naproxen, MeptaZinol,
Methadone, Pethidine, Hydrocodone,
Meloxicam, Fenbufen, Mefenamic acid,
PiroXicam, Tenoxicam, AZapropaZone,
Codeine.

Antiallergics:-

Pheniramine,
Dimethindene, Terfenadine, Astemizole,
Tritoqualine, Loratadine, Doxylamine,
Mequitazine, Dexchlorpheniramine,
Triprolidine, Oxatomide.

Antihypertensive:-

Clonidine,
Moxonidine, Methyldopa, Doxazosin,
Prazosin, Urapidil, Terazosin, Minoxidil,
Dihydralazin, DeSerpentine, Acebutalol,
Alprenolol, Atenolol, Metoprolol,
Bupranolol, Penbutolol, Propranolol,
Esmolol, Bisoprolol, Ciliprolol, Sotalol,
Metipranolol, Nadolol, Oxprenolol,
Nifedipine, Nicardipine, Verapamil,
Diltiazem, Felodipine, Nimodipine,
Flunarizine, Quinapril, Lisinopril,
Captopril, Ramipril, Fosinopril,
CilaZapril, Enalapril.

Antibiotics:-

Demo clocycline,
Doxycycline, Lyme cycline, Mino cycline,
Oxytetracycline, Tetra cycline,
Sulfametopyrazine, Ofloxacin,
Ciproflaxacin, AeroSoxacin, Amoxycillin,
Ampicillin, Becampicillin, Piperacillin,
Pivampicillin, Cloxacillin, Penicillin V,

Flucloxacillin, Erythromycin,
Metronidazole, Clindamycin,
Trimethoprim, Neomycin, Cefaclor,
Cefadroxil, Cefixime, Cefpodoxime,
Cefuroxime, Cephalexin, Cefradine.

Bronchodilator anti-Asthmatic:-

Pirbuterol, Orciprenaline, Terbutaline,
Fenoterol, Clenbuterol, Salbutamol,
Procaterol, Theophylline,
Cholintheophyllinate, Theophylline-
ethylenediamine, Ketofen.

Antiarrhythmics:-

Vicquidil,
Procainamide, Mexiletine, Tocainide,
Propafenone, Ipratropium.

Centrally Acting Substances:-

Amantadine, Levodopa, Biperiden,
Benztropine, Bromocriptine,
Tranlycypromine, Tranlycypromide,
Clomipramine, Maprotiline, Do Xepin,
Opipramol, Amitriptyline, Desipramine,
Imipramine, Fluvoxamin, Fluoxetine,
Paroxetine, TraZodone, Viloxazine,
Fluphenazine, Perphenazine,
Promethazine, Thioridazine, Triflu-
promazine, Promethazine, Thioridazine,
Chlorprothixene, Haloperidol,
Pipamperone, Pimozide, Sulpiride,
Fenethylline, Methylphenidate,
Trifluoperazine, Thioridazine, Oxazepam,
Lorazepam, Bromazepam, Alprazolam,

Diazepam, Clobazam, Clonazepam, BuSpirone, Piracetam.

MULTIPARTICLE PHARMACEUTICAL DOSAGE FORM FOR A LOW-SOLUBLE ACTIVE SUBSTANCES AND METHOD FOR PRODUCING SAID PHARMACEUTICAL DOSAGE FORM

Describes pharmaceutical forms for sublingual active-substance application in the form of bioadhesive microspheres. The microspheres have a mean diameter of less than 50 μm and contain a non-crystalline active Substance in a micro matrix embedded in a bioadhesive polymer. The bioadhesive polymer can be, e.g., a cellulose, a chitosan or an acrylic copolymer. Describes some formulations with a lipophilic matrix and a large amount (over 70%) of monoglycerides, which permit a more efficient release of the active substance. Some formulations with a muco polysaccharide, together with a process for their preparation. The mucopolysaccharide, e.g., heparin, is first combined with an adsorption intensifier, such as a chitosan. Then, given a coating that only dissolves in the intestinal fluid so that the active substance can be released in the middle or lower sections of the small intestine.

The material used for the coating that dissolves in the intestinal fluid can be, e.g., an anionic acrylic copolymer of the type of Eudragit(R) L, S or L100-55. The formulations can comprise capsules, tablets and granules. Describes oral pharmaceutical formulations for active substances in the form of physiologically active peptides. These formulations contain the active substance coupled to a carrier that takes it across the cell membrane, a pH-lowering agent, and/or a protease inhibitor, and also an acid-stable transport vehicle. The latter protects the pharmaceutical formulation as it passes through the patient's stomach, preventing contact with the proteases present in the stomach. The transport vehicle can be a capsule that is coated with acid-resistant Eudragit (RL30 D-55).

There is a special problem in the case of low-solubility active substances in a sense defined in German Pharmacopeia DAB 10. For purposes of the present invention, these are taken to be active substances whose water-solubility according to DAB 10 is such that at least 30 parts by volume of water are needed to dissolve 1 part by weight of the active substance. Active substances that are peptides or proteins, or peptide and protein derivatives or conjugates are explicitly ruled out in the

present invention, for this forms the subject of a different invention. Low-solubility active substances and those which are even less soluble in water present certain problems in the formulation of the pharmaceutical form, but they mainly suffer from having a low bioavailability. Therefore, many active substances of this type can be developed further only as parenteral formulations, e.g., as implants or injections. These have the appreciable disadvantage of low patient compliance, or they are not developed further to the stage of marketable products at all, despite their demonstrable pharmacologic activity. When an oral dosage form of such an active Substance is prepared with the well-known excipients, it can happen that the body does not absorb a large part of the active substance from the resulting formulation.

The residual bioavailability depends to a great extent on the circumstances in each individual case, e.g., on the Surrounding conditions and presumably also on the receiving organism itself and so may be subject to large variations. A therapeutically reliable administration is therefore impossible in many cases. There is hence a need for pharmaceutical forms

with which low-solubility active substances can be better administered.

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 meloxicam (15). 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 1multiparticulate system consisting of drug-loaded cellulose acetate cores encapsulated within Eudragit S-100 microcapsules was designed for chronotherapeutic delivery of ketoprofen (16).

The site-specific delivery of drugs to the colon has implications in many therapeutic areas, including topical treatment of colonic disorders such as Crohn's disease, ulcerative colitis, constipation, colorectal cancer, spastic colon and irritable bowel syndrome (17). Multiparticulate approaches tried for colonic delivery include 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 -intrasubject variability. (19) 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 palletization, 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. 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 process (20). In comparison with the sodium chloride free formulation the inclusion of the osmotically active ingredient results in a completely different dissolution behavior (21).

Most commonly studied multiparticulate systems for colon-specific drug delivery include pellets, granular matrices, beads, microspheres, and nanoparticles (33-39).

This review is aimed at collating and understanding the novelty and feasibility of the multiparticulate formulation design approach in the development of successful colon-specific drug delivery systems.

DESIGN OF MULTIPARTICULATE DRUG DELIVERY SYSTEMS

Multi-particulate drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, each exhibiting some desired characteristics. Thus multiparticulate dosage forms are pharmaceutical formulations in which the active substance is present as a number of small independent subunits.

1. 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.

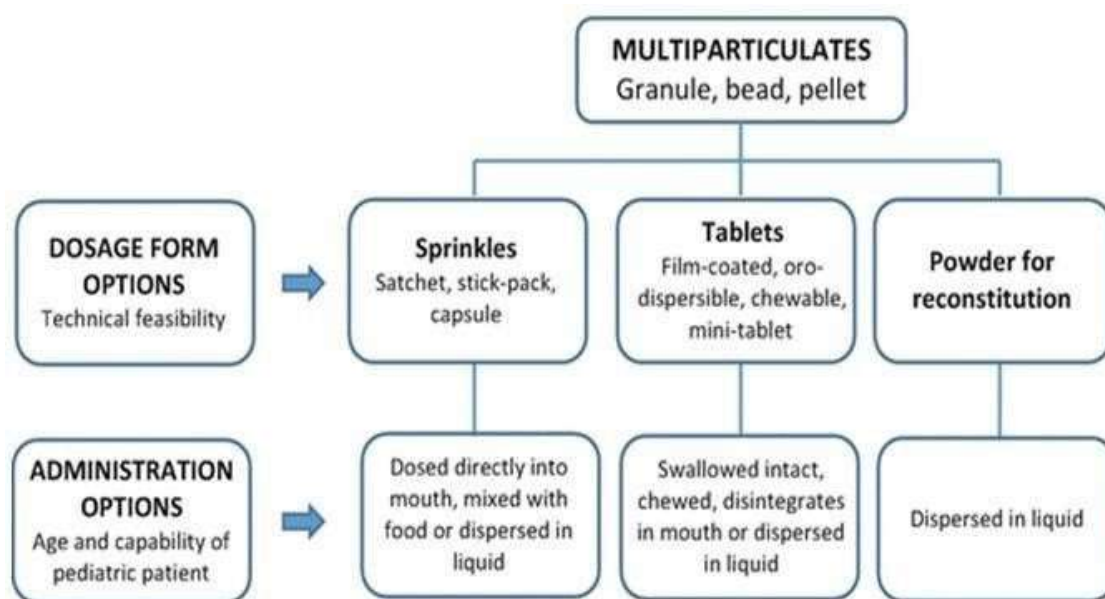


Figure 4

2. 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 an NDDS, an existing drug molecule can get a new life, thereby increasing its market value and competitiveness and even extending patents life.

Technology Description	Lipid Multiparticulates	Spray Layered Dispersions	Pellets	Mini Tablets
MP Image				
Primary Process(es)	Melt Spray Congeal	Fluid Bed Coating & Drying	Wet Granulation & Spheronization	Dry Granulation & Compression
Nominal Particle Sizes	0.1 – 0.4 mm	0.2 – 1.0 mm	0.5 – 1.5 mm	1.5 – 3 mm
Typical Drug Loadings	5 – 60%	1 – 40%	10 – 80%	10 – 80%

Primary multiparticulate technologies with common design attributes

Figure 5

Minitabs

The Eurand MINITABS technology 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 the drug release rate. Additional membranes may be added to further control the release rate. The small size of Eurand minitabs means that they can be filled into capsules as a final dosage form.

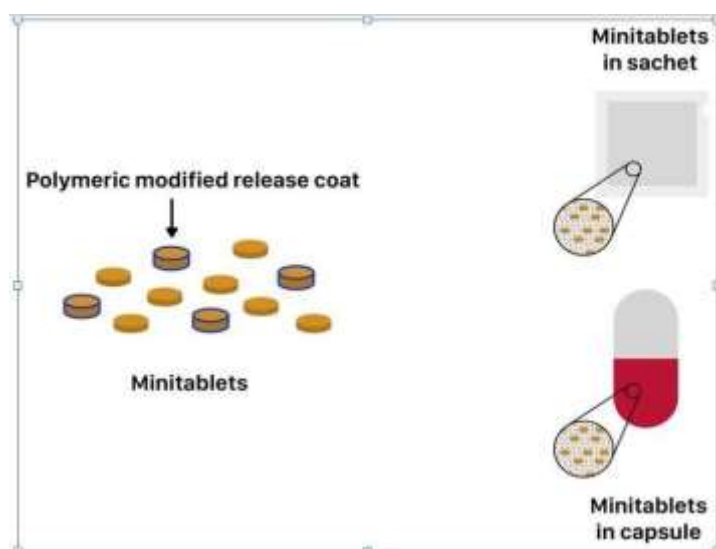


Figure 6: Mini tab in capsules



Figure 7: Different novel drug delivery system for RA

3. Multiparticle Drug Dispersing Shuttle

Multiparticle drug dispersing shuttle 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.

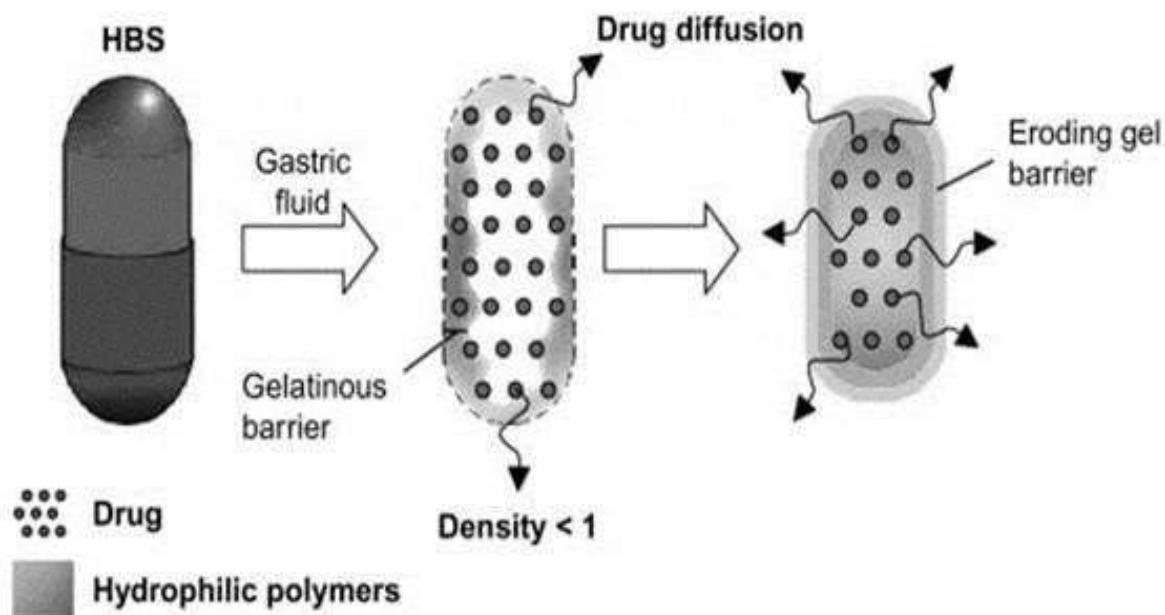


Figure 8: Shuttle of drug dispersing

4. Multiparticulate Mucoadhesive Formulations

Mucoadhesion will be able to outline and it is concerned with molecular interactions. The interaction between two molecules is composed of repulsion as well as attraction. The attractive interface would be superior to that of non-specific repulsion.

The appropriate occurrence of mucoadhesion, these diverse forces of interactions is entirely narrated by the subsequent theories. (23)

ROLE OF MICROPARTICULATE CARRIER FOR TARGETED DRUG DELIVERY TO COLON FOR ULCERATIVE COLITIS

Polymeric microparticles have turned out to be a promising approach as a targeted drug delivery system for the treatment of ulcerative colitis. The main aim of the targeted drug strategy is to target the maximum concentration of active agents in inflamed intestinal tissues by using selective delivery to achieve therapeutic efficacy while simultaneously reducing adverse effects. In addition to this, such a targeted delivery system must meet the

conditions for complete biodegradation and high biocompatibility without pro-inflammatory properties (Christian et al., 2013). In recent years, Particulate drug carriers include microparticulate; nanocarriers have been gaining immense importance due to their wide advantages over existing systems (Ritu et al., 2009).

These particulate systems are unique in terms of their particle size, as the optimum particle size of the carrier for localization of drug should be in the range of 5 to 15µm to increase the residence time of the drug in the colonic region. The particle size of this range is able to adhere to the site of action and get accumulated in the targeted region. But in some studies, it has been reported that for IBD therapy, microparticles should be in the size range of 10–300 µm to target specifically the inflamed region of the colon (Collnot et al., 2012). Selection of carrier is very important for a particular drug, i.e., either hydrophilic or lipophilic.

VARIOUS MICROPARTICULATES POLYMERIC APPROACHES USED FOR TARGETING DRUGS TO COLON FOR THE TREATMENT OF ULCERATIVE COLITIS

Colon targeted drug delivery via pH-dependent, time-dependent, microflora or

enzyme-activated system, mucoadhesive and pressure-controlled based system have attracted great interest for the treatment of systemic as well as local disease (Patel et al., 2007).

VARIOUS METHODS OF PREPARATION OF MICROPARTICLES

Microparticles should be biocompatible and biodegradable and have the ability to deliver drugs specifically to the confined area rather than other sites. It depends upon the properties of the polymer used, method of preparation and various other factors that affect its surface properties. There are various methods used for the preparation of microparticles, as mentioned below.

FUTURE PROSPECTS

Recent reports indicate interest in the colon as a site where poorly absorbed drug molecules may have improved bioavailability. The distal colon is considered to have a less hostile environment as well as enzyme activity compared to the stomach and small intestine. 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 challenges for oral peptide delivery in the pharmaceutical field. Colon targeted multiparticulate systems like microspheres and nanoparticles can provide a platform for spatial delivery of candidates like peptides, proteins, oligonucleotides and vaccines. However, drug release is not the endpoint of oral delivery. The bioavailability of protein drugs delivered at the colon site needs to be addressed. The use of drug absorption enhancers in drug delivery systems is likely to enhance therapeutic efficacy. Studies on drug absorption by the intestinal system have focused on drug transporters that mediate drug influx and efflux and agents, which can enhance drug absorption. The colon segment is designed by nature, mainly to expel metabolism products rather than to absorb nutrients. Therefore, more research that is focused on the specificity of drug uptake at the colon site is necessary. Such studies will be significant in advancing the cause of colon targeted delivery of therapeutics in the future.

CONCLUSION

The market for the 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 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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