Multiparticulate approach: an emerging trend in colon specific drug delivery for Chronotherapy

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ABSTRACT

Colonic targeting has gained increasing interest over the past years. A considerable number of patents and publications dealing with the colon specific drug delivery system indicate a growing focus of research activities in this field, not just for the delivery of the drugs for the treatment of the local pathologies associated with the colon but also for its potential for the systemic delivery of the protein and peptides. Currently because of the inherent potential to delay or avoid systemic drug absorption from the small intestine, colonic formulations can be utilized for chronotherapy of the diseases which are affected by the circadian biorhythms (e.g., asthma, hypertension and arthritis). Diverse approaches, like osmotic, capsular, single and multiparticulate systems can be used for colonic delivery. Multiparticulate systems enabled the drug to reach the colon quickly and retained in the colon for a relatively prolonged period of time. Because of their smaller particle size as compared to single unit dosage forms these systems are capable of passing through gastrointestinal tract (g.i.t.) easily. The current article focuses on the multiparticulate formulation approach for colon specific delivery of medicament.

Key words: Circadian biorhythm, hypertension, asthma, arthritis, crystalline composition, IPDAS, PRODAS, SPDS.

INTRODUCTION

The challenge of delivering drugs specifically to the colonic region of the g.i.t. is one that has been embraced by scientists over past two decades. Although considered by many to be an innocuous organ that has simple functions in the form of water and electrolyte absorption and temporary storage of stool. Research interest area of colonic drug delivery has been fuelled by the need to better treat not only the diseases associated with the colon but also used as a means of achieving chronotherapy for diseases that are sensitive to circadian biorhythms, such as asthma, arthritis and arrhythmia (Basit et al., 2003; Ibkwie et al., 2004). These diseases are characterized by night time or early morning onset. For treatment of these diseases it is therefore highly desirable to have a delayed – release delivery system that can provide nocturnal release of a drug, which in turn may provide considerable relief to the patient while they are in resting (Singh et al., 2002; Patel et al., 2008). The foremost confront while designing the colon specific drug delivery system is to prevent the formulation during its passage through the stomach and about 6 m of the small intestine (Ashford et al., 1994). In order to develop a reliable colonic drug delivery system the transit time of dosage forms through the g.i.t. needs to be understood well (Ali et al., 2006). Thus to mimic the function of living systems and in view of emerging chronotherapeutic approaches, multiparticulate delivery, has attracted increasing interest in recent years. The focus of this review is aimed at collating and understanding novelty and feasibility of different multiparticulate...
formulation design approaches for chronotherapy, and upcoming technologies being exploited on an industrial scale.

**CRITERION FOR DESIGN OF COLONIC FORMULATION**

The proper selection of a formulation approach is dependent upon several important factors which are as follows:

i. Pathology and pattern of the disease, especially the affected parts of the lower GI tract or, physiology and physiological composition of the healthy colon if the formulation is not intended for localized treatment.

ii. Physicochemical and biopharmaceutical properties of the drug such as solubility, stability and permeability at the intended site of delivery, and the desired release profile of the active ingredient.

iii. The pH of the intestinal fluids affects the efficacy of the colon specific drug delivery systems hence it is the most common physiological factor that considered in the design of delayed release colonic formulation. In normal healthy individual there is a progressive increase in the luminal pH from the duodenum (pH = 6.6 ± 0.5) to the terminal ileum (pH = 7.5 ± 0.4), a decrease in the cecum (pH = 6.4 ± 0.4), and there is a slow rise from the right to left colon with a final value of (pH = 7.0 ± 0.7) (Evans et al., 1988).

**PHARMACEUTICAL APPROACHES FOR FORMULATION OF COLON SPECIFIC DRUG DELIVERY SYSTEMS**

Nevertheless, a variety of approaches have been used and system have been developed in past for the purpose of achieving colonic delivery. These approaches are either drug specific (prodrugs) or formulation – specific (coated or matrix preparations). The must commonly used mechanisms are (Kinget et al., 1998):

i. pH – dependent delivery

ii. Time – dependent delivery

iii. Pressure – dependent delivery

iv. Micro flora – dependent delivery

Ideally, the approach based on combination of pH dependent and time – controlled release mechanism seems encouraging (Ali et al., 2009). The approaches of colonic delivery mentioned above have been summarized in Table 1.

Colon specific drug delivery systems may be formulated either as single – unit or multiparticulate drug delivery systems, which are described in the following section. Overall, they work on the same basic principles of erosion or dissolution; swelling and rupturing; and system based on change in membrane permeability.

**SINGLE – UNIT SYSTEMS**

Single- unit systems are formulated either as capsule – based or osmosis – based systems. Single – unit systems are designed by coating the system either with eroding/soluble or rupturable coating (Ashford et al., 1994; Shidhaye et al., 2010).

**Advantages**

Ease of manufacturing due to less number of formulation steps.

**Shortcomings**

Such kind of delivery systems may suffer from the following limitations:

i. Unintentional disintegration of the formulation (most probably due to manufacturing deficiencies or unusual gastric physiology) may lead to compromised systemic drug bioavailability or loss of therapeutic action in the colon (Kramer et al., 2003).

ii. Variable gastric residence time.

**MULTIPARTICULATE DRUG DELIVERY SYSTEMS:**

Multiparticulate drug delivery systems are reservoir type of oral dosage forms consisting of a collection of small discrete units, each exhibiting some desired characteristics. In these systems, the dosage of the drug substances is divided in a plurality of subunits, typically consists of thousands of spherical particles (12). Thus multiparticulate dosage forms are pharmaceutical formulations in which the active ingredient is present as a number of minute independent subunits. To deliver the recommended total dose, these subunits are filled into a capsule or compressed with additional excipients to form a tablet (Daumesnil et al., 1994; Ueda et al., 1989).

These systems show various advantages as well as disadvantages over single – unit systems, which are as follows (Roy et al., 2009):

**Advantages**

i. Predictable, reproducible and short gastric residence time.

ii. Less inter- and intra-subject variability.

iii. Improve bioavailability.

iv. Reduced adverse effects and improved tolerability.

v. Limited risk of local irritation.

vi. No risk of dose dumping.

vii. Flexibility in design.

viii. Ease of combining pellets with different compositions or release patterns.

ix. Improve stability.

x. Improve patient comfort and compliance.

xi. Achieve a unique release pattern.

xii. Extend patent protection, globalize product, and overcome competition.

**Shortcomings**

i. Low drug loading.

ii. Proportionally higher need for excipients.

iii. Lack of manufacturing reproducibility and efficacy.

iv. Large number of process variables.
v. Multiple formulation steps.
vi. Higher cost of production.
vii. Need of advanced technology.
viii. Trained/skilled personal needed for manufacturing.

Rationale behind designing the multiparticulate drug delivery systems

There are many reasons for designing and delivering drug as a multiparticulate system e.g.

i. To facilitate disintegration in the stomach. Shows better reproducible pharmacokinetic behaviour then conventional (monolithic) formulations.

ii. After disintegration, the individual subunit particles pass rapidly through the g.i.t. If these subunits have diameter of less than 2 mm, 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.

iii. Drug safety may also increased by using multiparticulate dosage forms.

DESIGN OF MULTIPARTICULATE DRUG DELIVERY SYSTEM

The purpose of designing multiparticulate dosage forms is to develop a reliable formulation that has all the advantages of a single unit formulations and yet devoid of the danger of alteration in drug release profile and formulation behaviour due to unit to unit variation (Rot et al., 2009).

Multiparticulate approaches tried for colonic delivery includes formulations in the form of pellets, granules, microparticles, nanoparticles, and beads. Because of their smaller particle size as compared to single unit dosage form these systems are capable of passing through the g.i.t. easily. Moreover, multiparticulate systems are to be more uniformly dispersed in the g.i.t. and also ensure more uniform drug absorption (Davis et al., 1989; Meyer et al., 1985; Rodriguez et al., 1998). As the units of multiparticulate systems are distributed freely throughout the g.i.t., their transport is affected to a lesser extent than single – unit formulations by the transit time of food (Syan et al., 2010; Bechgaard et al., 1978).

Multiparticulate systems are formulated as:

A. Reservoir system with rupturable polymeric coating:

In these multiparticulate systems the reservoir devices are coated with a rupturable polymeric layer. Such systems comprised of many layers some layer contain drug substance, while others are rate – controlling polymers. The rupturing effect is achieved by coating the individual units with osmotic or swelling agents. Numerous release – profiles can be achieved using this approach – including sustained release of active pharmaceutical ingredients for absorption throughout the g.i.t. Time – delayed release of the drug as either a burst or sustained release profile can be achieved over a period of 1 – 12 h, with a lag – time of 4 – 10 h. The duration of drug release following the lag – time depends on the composition and thickness of the polymer barrier and the lag – time coating itself. The multiparticulate system provides an optimal release profiles for either single drugs or for a combination of drugs (Roy et al. 2009).

The first attempt to develop a time – dependent system for colon delivery was made by Ueda et. al. (Ueda et al., 1989; Ueda et al., 1994; Ueda et al., 1994, Ueda et al., 1994). These inventors developed a time – controlled explosion system (TES) in which drug release is caused by explosion of a membrane after a definite time period (i.e. lag times), which is precisely programmed. TES were developed for both single and multiple – unit dosage forms. In both cases, a core contains drug (model drugs used were metoclopramide hydrochloride, tiapride hydrochloride, sodium diclofenac and nilvadipine) plus an inert osmotic agent and suitable disintegrants. Individual units can be coated by a protective layer and then by a semipermeable layer, which is the rate controlling membrane for the influx of water into osmotic core. The osmotic pressure buildup by water ingress causes the core to explode, with an immediate release of the drug. The explosion of formulation can also be achieved through use of swelling agents.

Hata et. al., 1994 describes a similar time – controlled formulation. A four layered TES was developed where, drug was layered on an inner core (polystyrene balls or non – pareil sucrose beads), followed by a swappable layer (hydroxypropyl cellulose) and an insoluble polymeric top layer (ethyl cellulose). An In – vivo study was carried out with this system for a new vasodilator drug (FK409) in conscious dogs. The drug appeared in the blood at 3 h and the maximum level was attained at 5 h was in accordance with In – vitro release profile. In bioavailability studies in human volunteers a 3h lag time to peak concentration at 5 h was obtained. These studies prove the system suitability for use in treatment of nocturnal symptoms of diseases.

Blum (Blum et al., 2003; Kalantzi et al., 2009) described a controlled release oral dosage form of acetylsalicylic acid (aspirin) capable of delaying the release of the drug until a predetermined time interval after ingestion. The following is prepared in such a manner that, after ingestion, there will be no release for a preset time interval (5-8 hours). Thus, if taken at bedtime it reaches optimal therapeutic blood levels at a time in the early morning when the events leading up to a vascular obstruction culminating in a heart attack or stroke are most commonly occurring after the drug is taken in the evening. The formulation comprises of an aspirin core together with a swelling agent and a fragile coating protecting aspirin from dissolution by gastrointestinal fluids having water soluble and insoluble properties.

B. Reservoir systems with soluble or eroding polymer coatings

Another class of reservoir-type multiparticulate pulsatile systems is based on soluble / erodible polymer coatings in which, barrier dissolves or erodes 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. The basic principle employed in these systems is that of pH – sensitive polymers complimenting to their large increase in solubility at same point in the g.i.t. this sensitivity has been utilized to prevent release in the stomach affording complete release in intestine. 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.

Kao et al., 1997 studied the lag times delayed by the hydration of various thicknesses of polymer (Eudragit RS) films in an attempt to deliver drugs (Diltiazem hydrochloride) to various sites in the g.i.t. In a theoretical simulation, it was found that the lag time could be controlled by varying the thickness of the coated polymer, which was equivalent to the amount of the dry polymer in coating. The relationship between the lag time and the square of the amount of polymer coated, as well as that between the release rate at steady state and the inverse of the amount of polymer coated well predicted.

Gazzaniga et al., 1994 developed a multi-unit system with a reservoir drug coated with a high viscosity polymer (HPMC 4000) and an outer enteric coating. The outer film protects the system from the stomach fluids and dissolves on entering the small intestine. HPMC layer delays the release of drug for 3-4 h when the system is transported through small intestine.

Pawar et al., 2007 developed a system comprised of multicoated multiparticulates for time controlled pulsatile release. One of the coating membranes is an enteric polymer and the second membrane barrier is a mixture of a water-insoluble polymer an enteric polymer. An organic acid, such as fumaric acid, citric acid, succinic acid, tartaric acid, or malic acid, may be provided between the first and second membrane layers to provide for the time-separated pulses. The acids in between the membranes may delay the dissolution of the enteric polymer in the inner layer, thereby increasing the lag time as well as decreasing the rate of release of the active ingredient from the coated microparticulates. This type of system has been utilised for the weakly basic drugs (which shows pH – dependent solubility and hence insoluble at intestinal pH) because the system contains pH adjusters which maintains the local acidic environment within the system.

C. System with changed membrane permeability

Abundant pharmaceutical forms with delayed release for oral administration are available. The release of the drug must be controlled according to therapeutical rationale and the pharmacological properties of the active ingredient. In consequence, it is not always desirable the blood levels to be steady. On the contrary, in order to avoid any habituation and in order to limit the side effects aggravated by the active ingredient, it would be absolutely beneficial for the plasmatic rate to follow the metabolic rhythm and the specific needs of the patient during certain periods. For instance, in order to diminish the nocturnal symptoms or the symptoms upon awakening in the case of certain chronic diseases which are affected by the circadian biorhythms (ischemic heart disease, asthma and arthritis), the drugs should be administered in such a way that the desired therapeutic plasma level is reached only at the desired moment, i.e. during sleep or at the moment of awakening (Kalanzi et al., 2009).

The release profile in this system depends on physical – chemical properties of drug and its interaction with the membrane. Chen et al., 1996 designed osmotic multiparticulate delivery systems in which the drug released in divided doses over timed intervals throughout the day to produce pulsatile blood concentration curve with time. Each pellet contains a drug (Diltiazem) containing core, and a water soluble osmotic agent (NaCl) enclosed in a water permeable, water-insoluble polymer film. Incorporated into the polymer film is a hydrophobic, water insoluble agent which alters the permeability of the polymer film. The film coating of each population of pellets differs from the coating of every other population of pellets in the dosage form in the rate at which water passes through to the core and the rate at which drug diffuses out of the core. The osmotic agent dissolves in the water, causing the pellet to swell and regulating the rate of diffusion of drug into the environment of use.

Sigmoidal release pattern is therapeutically beneficial for timed release and colonic drug delivery, and is observed in coated systems. A Sigmoidal release pattern obtained is based on the permeability and water uptake of polymers and influenced by the presence of different counter – ions in the release medium (Bodmeire et al., 1996). Narisawa et. al. (Narisawa et al., 1993; Narisawa et al., 1996) developed a system with such type of ion exchange. Eudragit RS 30D is reported to be a polymer of choice for this purpose. It typically contains positively polarized quaternary ammonium group in the polymer side chain, which is always accompanied by negative hydrochloride counter-ions. The ammonium group being hydrophilic it facilitates the interaction of polymer with water, thereby changing its permeability and allowing water to permeate the active core in a controlled manner. They found that a core of theophylline coated with Eudragit RS 30D showed very slow release in pure water but a significant increase in the release rate when immersed in an organic acid solution containing succinic, acetic, glutaric, tartaric, malic or citric acid. This is due to higher hydration of the film containing quaternary ammonium groups on interaction with the acids.

ENCROACHMENT IN TECHNIQUES OF ORAL TIME CONTROLLED TECHNOLOGY

Currently, pharmaceutical companies have been focused on developing and commercializing programmable drug delivery systems that fulfill unmet medical needs in the treatment of various diseases. Table 2 describes some of the novel technologies.

FUTURE PROSPECTS

Recent information indicates a growing interest in colon as a site for chronotherapeutics, which seems to be quite promising as in certain disease states (which are affected by circadian
Acknowledgement

Authors are thankful to Management of Shree Kambhat Taluka Sarvajanik Kelavani Mandal for supporting the study.

Declaration of Interest

The authors report no declarations of interest.

References


Biorhythms. From the technological point of view, multiparticulate systems seems to be more efficient than single unit dosage forms provides several all the advantages including greater flexibility and adaptability of multiparticulate systems, which gives researchers powerful new tools to optimize therapy. An increasing number of multiparticulate systems would possibly become commercially available in the near future.