

MULTIPARTICULATE COMBINED APPROACHES FOR COLON SPECIFIC DRUG DELIVERY

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This article is available online at www.ssjournals.com

ABSTRACT

In order to achieve a successful colon targeted drug delivery system, a drug needs to be protected from degradation, release and/or absorption in the upper portion of the gastrointestinal tract (GIT) and then ensure abrupt or controlled release in the proximal colon. Such a system can be formulated by utilizing microbial triggering degradation of polymer coating/ gastro intestinal (GI) transit time (time dependent)/ pH dependent approach etc. But unfortunately it has been found that colonic microflora, GI transit time and pH varies considerably inside a human system by several factors, in addition to this the native biodegradable polysaccharides which are used widely for the microbial triggering colonic drug delivery system (CDDS), are having high aqueous solubility on account of which a single unit colon targeted drug delivery systems may suffer from dose dumping due to overall catastrophic failure of the film around a monolith, which would then release the whole drug, that may lead to drastically compromised systemic drug bioavailability or loss of local therapeutic action in the colon. This review emphasizes some of the causes which make a single unit dosage form unsuitable for targeting to colon by using microbial triggering/GI transit time/pH dependent approach, and at the same time discusses researches which have been carried out to alleviate these problems by utilizing multiparticulate combined approaches.

KEY WORDS: Microbial triggering, Time dependent, pH dependent, Colonic drug delivery system, Multiparticulate combined approach

1. INTRODUCTION

Oral administration of different dosage forms is the most commonly used method due to greater flexibility in design of dosage form and high patient acceptance. Among oral dosage forms, increasing interest has currently turned to systems designed to achieve time specific and site specific delivery of drugs^{1, 2}. Colon has large amount of lymphoma tissue, negligible brush boarder membrane activity, near neutral pH, reduced digestive enzymatic activity and high

responsiveness towards the action of absorption enhancers^{3, 4} and a much longer transit time as compared to small intestine⁵ due to which many benefits achieved. Some of which are mentioned below:

- i. For treating colonic diseases, i.e. ulcerative colitis, crohn's disease and constipation etc., the optimal drug delivery system, is colonic drug delivery system, because it selectively delivers the drug to the colon, but not to the upper GIT⁶. For this reason, the drug

concentration was significantly lessened in the upper part of GIT, while increased considerably in the colon, resulting in alleviated GI side effects.

- ii. Colon is referred to as the optimal absorption site for proteins and polypeptides after oral administration, because of the existence of relatively low proteolytic enzyme activities and quite long transit time in the colon^{7,8}.
- iii. Colon has a large amount of lymphoma tissue which facilitates direct absorption in to the blood and uptake of antigens into the mast cells of the colonic mucosa produces rapid local production of antibodies and this helps in efficient vaccine delivery³.
- iv. CDDS would be advantageous when a delayed pulsatile release⁹ is desirable as a means of achieving chronotherapy¹⁰ for the treatment of diseases that have peak symptoms in the early morning and that exhibit circadian rhythms, such as nocturnal asthma, angina and rheumatoid arthritis¹¹.

Although large intestine is difficult to reach by peroral delivery, is still deemed to be the ideal site for the delivery of agents to cure the local diseases of the colon^{12, 13} by using rectal dosage forms such as suppositories and enemas, which are always not effective since a high variability in the distribution of these forms is observed¹⁴. Irrespective of therapy desired for local (colonic) or systemic delivery of drug, the development and aim of the drug delivery to colon remain same¹⁵, that is

- The drug must not absorb from other regions of the GIT.
- It should only suffer negligible degradation in the small intestine lumen.
- The release of the drug in the colon should be at quantitatively controlled rate and the released drug in the colon should be

absorbed from the lumen of the large intestine without any appreciable degradation.

The most critical challenge in such drug delivery approach is to preserve the formulation during its passage through the stomach and about first six meters of the small intestine¹⁶. In order to achieve this, each colon-specific drug delivery system has been designed based on one of the following mechanisms or a combination of them with varying degrees of success: (1) prodrugs, (2) pH-sensitive polymer coating, (3) time-controlled dissolution, (4) microflora-activated drug release, and (5) pressure-dependent delivery¹⁵. However, a CDDS is primarily dependent on the microbial environment, transit time and pH level in the colon, governing the release of drug from different designs of CDDS^{15, 17} but these conditions may vary depending on various factors, which limit the success of a CDDS. In addition, a 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 colon¹⁸.

1.1 Causes of variation of colonic

microbe: The bioenvironment inside the human GIT is characterized by presence of complex microflora, especially the colon is rich in microorganisms¹⁹, consisting mainly of anaerobic bacteria, e.g. bacteroides, bifidobacteria, eubacteria, clostridia, enterococci, enterobacteria and ruminococcus etc²⁰. The microbial environment which is responsible for degradation of polymeric coating by producing a vast number of enzymes²¹ like glucuronidase, xylosidase, arabinosidase, galactosidase, nitroreductase, azareducatase, deaminase,

and urea dehydroxylase differs among individuals, and also during life within the same individual. Many factors, such as diet or climate, aging, medication (especially antibiotics), illness, stress, pH, infection, geographic location, race, socioeconomic circumstances, lifestyle can upset this balance, some of which are given below.

a. *Administration of chemotherapeutics:* Administration of other drugs changes the colonies of colonic microflora e.g., Gemifloxacin (Fluoroquinolone) suppresses Enterobacteria, Enterococci, Streptococci, Anaerobic cocci, Lactobacilli²².

b. *Age:* Recent studies suggest that age affects the intestinal microflora with a decrease in anaerobes and bifidobacteria population and an increase in enterobacteria of the aged²³. Polyphasic analysis of faecal bacteria showed that significant structural changes occur in the microbiota with aging and the principal microbiological difference between adults and children was the occurrence of higher numbers of enterobacteria in the latter group and this was especially evident with respect to putatively protective bifidobacteria²⁴.

c. *GI diseases:* GI diseases also affect the microflora population e.g., high number of facultative anaerobes and low levels of bifidobacteria, and bacteroids were found in *Clostridium difficile* associated diarrhea²⁴.

d. *Probiotics:* Probiotic bacteria are generally, though not exclusively, lactic acid bacteria and include *Lactobacillus acidophilus*, *L. casei*, *L. bulgaricus*, *L. plantarum*, *L. salivarius*, *L. rhamnosus*, *L. reuteri*, *Bifidobacterium bifidum*, *B. longum*, *B. infantis* and *S. thermophilus*. Probiotic bacteria are used in the production of yoghurt, various fermented milk products and dietary supplements.

Studies have demonstrated that probiotics sift significantly the bacterial counts by increasing health promoting genera (*Lactobacillus* and *Bifidobacterium*) and decreasing harmful ones (*Helicobacter pylori*, *Salmonella sp.*, *C. difficile*)²⁵.

1.2 Causes of variation of GI transit

The transit of perorally administered formulation through the GI tract is highly variable and depends on various factors²⁶.

a. *Co-administration of drugs:*

Concomitant administration of other drugs like domperidone, cisapride, metoclopramide etc, alters GI transit e.g., codein slow down transit.

b. *Age:* Aging is frequently associated with increased cholecystokinin levels, which can inhibit distal gastric contractions and slow gastric emptying²⁷.

c. *Disease state of lumen:* Various diseases like diarrhea, constipation, diabetes, peptic ulcer etc alter GI transit e.g., diarrhea increases colonic transit and constipation decreases it e. g., Small intestinal transit time reduces significantly in crohn's disease with ileocecal-resection²⁸.

d. *Body posture:* Vertical body posture increases GI transit while supine posture decreases.

e. *Diet:* Dietary fiber increases faecal weight, partly by retention of water and partly by increasing bacterial mass and reduces colonic transit times but ingestion of food accelerates colonic activity.

1.3 Causes of variation of GI pH

a. *Administration of anti-peptic ulcer drugs:* A number of drugs which are used to cure peptic ulcer reduce the gastric pH to a significant extent e. g., omeprazole²⁹, ranitidine³⁰.

b. *Age:* Increasing age is associated with changes in GI pH³¹ some concepts are, the incidence of achlorhydria is approximately 10–20% among elderly

patients, compared to less than 1% in younger subjects³², hypochlorhydria may be present in approximately 20% of individuals over the age of 70 years³³ and also the postprandial pH differs significantly between young and adult³⁴.

c. *Disease state*: Alterations in gastric pH are seen in gastric disorders^{35, 36, 37} such as chronic gastritis, gastro duodenal ulcer disease, gastric neoplasm etc. Chronic pancreatitis and cystic fibrosis seem to decrease pH of the proximal small intestine³⁸. Very low colonic pH values have been observed in severe active ulcerative colitis, crohn's disease^{38, 39}, inflammatory bowel disease^{39, 40, 41}.

d. *Food*: After taking meal the gastric pH climbs to a peak value of 6.7, and then gradually declines back over a period of 2h. In contrast to the pH behavior in the stomach, feeding a meal caused a reduction in the median duodenal pH to 5.4³¹. In addition, there was considerable fluctuation in the postprandial duodenal pH on an intra subject basis³¹.

1.4 Unsuitability of a CDDS utilizing microbial triggering/GI transit time/pH dependent approaches: The great challenge in using native degradable polysaccharides for the development of drug delivery systems is their high aqueous solubility⁴², which may contribute to the undesirable premature/burst release⁵⁵ of drug, in addition polysaccharide based CDDS are effective when they are precisely activated by the physiological conditions of the colon and absence of enzymes during colonic disorders might hinder the activation of the delivery system^{43, 44}. Reports suggest that pH of colon is more acidic than that in the small intestine, especially in inflammatory bowel disease,^{39, 40, 41} ulcerative colitis⁴⁴. Thus, the pH-

based CDDS, which are designed to release drug at a higher pH, fail to release drug completely upon encountering the more acidic colonic pH. It has also been shown that pH based approach lack site-specificity⁴⁰ because of inter/intra subject variation and the similarity of the pH between the small intestine and the colon^{40, 45}. Gastric transit time of single-unit non-disintegrating dosage forms has been reported to vary from 15 min to more than 3h⁴⁶ but timed-release systems depend on the relative consistency of intestinal transit times, therefore the high variability¹⁸ in gastric retention times makes prediction of the accurate location of drug release difficult⁴⁷ and any variation in gastric emptying time may lead to drug release in small intestine before arrival to colon.

Therefore, it is accepted that a CDDS utilizing only polysaccharide based microbial triggering/GI transit time/pH dependent approach would not be reliable^{18, 44}.

2. COMBINED APPROACHES UTILIZING MULTIPARTICULATE SYSTEMS:

2.1 Why multiparticulate systems?

Recently, much emphasis is being laid on the development of multiparticulate (MP) 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 emptying⁴⁸. The long lag times at the ileocaecal junction and fast transit indicate that a single unit may not be the best dosage form for a colon targeted drug delivery system. Also the late disintegration of a single unit dosage form creates a particular problem due to the abnormal release of contents and will result in loss of much of opportunity for local action or absorption in the proximal

colon. This can be partially rectified by targeting MP dosage forms because these systems enabled the drug to reach the colon quickly and were retained in the ascending colon for a relatively long period of time^{49, 50}. Hence, additional retention of a dosage form within the colon could be achieved by the use of a multi particulate formulation rather than a large single unit thus ensuring that it does not pass too rapidly through the colon and be excreted before the entire drug has been released. On account 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 variability⁵¹. Moreover, multiparticulate systems tend to be more uniformly dispersed in the GI tract and also ensure more uniform drug absorption^{49, 52}. Most commonly studied multiparticulate systems for colon specific drug delivery include pellets, granular matrices, beads, microspheres, and nanoparticles^{53, 54}.

2.2 Combination of microbially triggered and pH dependent systems:

To guarantee delivery of the drug to the colon and to prevent its premature release, it is preferable to combine polysaccharides with enteric or cellulosic polymers. It was shown that (Hydroxypropyl methyl cellulose) HPMC capsules coated with Eudragit FS 30D for the delivery of 5-fluorouracil disintegrated in the distal portion of small intestine and proximal colon. Capsules of this type could, therefore ensure spatial delivery of drug preferentially in colon without substantial release in the upper GI tract up to the ileum. The matrices were coated by Eudragit S100 and were then covered by a layer of chitosan HCl and loaded inside these capsules. Upon hydration, the capsule shell dissolves and the chitosan layer forms a gel (internal pH of 4.5),

which generates an acidic environment around the Eudragit film so that it does not dissolve in the ascending colon. In the ascending colon, the chitosan HCl gel is degraded by the colonic micro flora, thereby exposing the Eudragit film to the colonic environment. But since the ascending colon is weakly acidic where pH is less than 7.0, the film coat still remains intact. However, on arrival in the descending colon where pH is greater than 7, the Eudragit film coat dissolves and the drug is released in a controlled fashion from the matrices. In vitro release studies conducted in simulated GIT environment provided good evidence for the proof of concept that successful targeting to the descending colon could be achieved⁵³. In order to avoid the burst release pattern of ondansetron from chitosan microspheres Jose et al., encapsulated the optimized chitosan microspheres with Eudragit S-100 by solvent evaporation technique. From the drug release study they found that formulations which contains 1:10 core/coat ratio released lesser amount of drug in the upper gastro intestinal conditions⁵⁵.

In another study a multiparticulate system was prepared by coating cross linked chitosan microspheres exploring Eudragit L-100 and S-100 as pH sensitive polymers and metronidazole as the model drug. In-vitro drug release study showed no release of drug at acidic pH and higher drug release was found in presence of rat caecal contents⁵⁶. In a study by Alonso et al., sodium diclofenac, was entrapped within chitosan microcores and then microencapsulated into Eudragit L-100 and Eudragit S-100. The drug release from microcores was delayed and a combined mechanism of release is proposed, which considers the dissolution of the Eudragit coating, the swelling of the chitosan microcores and the dissolution of drug and its further

diffusion through the chitosan gel cores⁵⁷. Multiparticulate systems showing simultaneously specific biodegradability and pH-dependent drug release were prepared based on chitosan, amidated pectin, calcium ions, and using triamcinolone as model drug. Hydroxypropyl methyl cellulose phthalate (HPMCP) and cellulose acetate phthalate (CAP) were successfully incorporated into the system and aided the target action of the carbohydrates. The addition of CAP and HPMCP resulted in the highest control over the drug release in all media. CAP-Triamcinolone formulation presented the slowest drug release rate, of only 1.33%, in acidic medium after 2h, while the control formulation released 45.52% after the same time⁵⁸. Nanoparticulate colloidal carriers composed of natural or synthetic polymers have also been investigated for colon targeting⁵⁹. These particles for CDDS are known for their specific accumulation in the inflamed tissue in the colon because a strong cellular immune response occurs in the inflamed regions due to presence of increased amount of neutrophils; Natural Killer cells, macrophages etc. and nanoparticles could be efficiently taken up by these macrophages⁶⁰. They offer the excellent possibility of surface modification with targeting ligands, leading to a specific accumulation in the targeted tissue⁶¹. Recently Jain et al., developed Hyaluronic acid-coupled chitosan nanoparticles bearing oxaliplatin encapsulated in Eudragit S100-coated pellets. In therapeutic experiments the pellets of free drug and hyaluronic acid-coupled and uncoupled chitosan nanoparticles bearing oxaliplatin were administered orally at the dose of 10 mg oxaliplatin/kg body weight to tumor-bearing Balb/c mice. In vivo data showed that hyaluronic acid-coupled chitosan nanoparticles delivered 1.99

± 0.82 and 9.36 ± 1.10 μg of oxaliplatin /g of tissue in the colon and tumor, respectively after 12 h, reflecting its targeting potential to the colon and tumor. These drug delivery systems show relatively high local drug concentration in the colonic milieu and colonic tumors with prolonged exposure time, which provides a potential to enhance antitumor efficacy with low systemic toxicity for the treatment of colon cancer⁶².

2.3 Combination of pH and time dependent systems: Appropriate combination of pH sensitivity and time release functions in a dosage form may improve the site specificity of drug delivery to the colon as discussed below. Akhgari *et al.*, evaluated the combination of pH-dependent and time-dependent polymers as a single coating for design of colon delivery system of indomethacin pellets. Eudragit S100 and Eudragit L100 were used as pH-dependent polymers and Eudragit RS was used as a time-dependent polymer. The results of in vitro experiments indicated that the proposed combined time-dependent and pH-dependent polymethacrylate polymer coating is a suitable method to provide specific release of indomethacin to colon⁶³. Gupta et al., made an attempt to combine pH based dissolution characteristics of different Eudragit polymers and that of constant transit time in the small intestine to develop a reliable multiparticulate colonic delivery system. The drug, 5-ASA was layered onto non-pareil beads. For the inner coat, the pellets were coated with a combination of Eudragit RL/RS. For the outer coat, the above pellets were further coated with Eudragit FS 30D. He suggested that the delivery system demonstrated its potential for colonic delivery by resisting drug release up to pH 6.5 and the combination of Eudragit RL and RS proved successful

for the sustained delivery of 5-ASA at the pH of the colon⁶⁴.

Recently a novel pH and time controlled nano-particulate colon drug delivery systems was developed by Kshirsagar et al., He used nanoprecipitation method to prepare polymeric nanocapsules (NC) of prednisolone (PD) with pH responsive polymer Eudragit S100. The optimized formulations lead to the preparation of PD-NC with a mean size of 567.87 nm, high encapsulation efficiency of 90.21%. In vitro studies reveal that NC releases the drug after 4.5-h lag time corresponding to time to reach colonic region, and in vivo studies show that NC release drug after 3-h lag time in rat corresponds to arrival in colon⁶⁵.

CONCLUSION

Targeting drugs and delivery systems to the colonic region by multiparticulate formulations has received considerable interest because of many advantages over single unit products e.g., poorly absorbed drug molecules may have improved bioavailability, enhanced drug uptake by targeted cells thus the dose required is reduced, reduced side effects, reduced risk of systemic toxicity, reduced risk of local irritation, predictable gastric emptying and retained in the ascending colon for a relatively long period of time, passes through the GI tract easily, leading to less inter- and intra subject variability. Moreover, when multiparticulate systems are developed using combined approaches, minimize the risk of unpredicted release of medicaments by overcoming the demerits individual approaches owing to the variability microbial flora, gastric transit time and pH. Thus multiparticulate systems prepared utilizing combined approaches for CDDS provide numerous advantages and give a powerful tool to optimize therapy.

SOURCE OF SUPPORT

Nil

CONFLICT OF INTEREST

Nil

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