Drug targeting: approaches to colonic drug delivery

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Abstract

The challenge of targeting drugs specifically to the colonic region of the gastrointestinal tract is one that has been embraced by scientists over the past two decades. Research interest in the area of colonic drug delivery has been fuelled by the need to better treat pathologies of the colon that range in seriousness from constipation and diarrhoea to the debilitating inflammatory bowel diseases (ulcerative colitis and Crohn's disease) through to colon carcinoma, the third most prevalent form of cancer in both men and women. Furthermore, colonic drug delivery may also be used as a means of achieving chronotherapy for diseases that are sensitive to circadian rhythms, such as asthma and arthritis. Targeted drug delivery to the colon would therefore ensure direct treatment at the disease site, lower dosing and a reduction in systemic side effects. In spite of potential difficulties, a variety of approaches have been used and systems have been developed for the purpose of achieving colonic targeting. Targeted drug delivery is reliant on the identification and exploitation of a characteristic that is specific to the target organ. Successful colonic delivery requires careful consideration of a number of factors, including the properties of the drug, the type of delivery system and its interaction with the healthy or diseased gut. Although a number of formulations have been proposed as colonic delivery vehicles, most lack the necessary site specificity. In the context of colonic targeting, the exploitable gastrointestinal features include pH, transit time, pressure and bacteria.

Key Words: Targeting, Drug delivery, Colon

Introduction

The challenge of targeting drugs specifically to the colonic region of the gastrointestinal tract is one that has been embraced by scientists over the past two decades. Previously thought of as a relatively innocuous organ, concerned solely with the absorption of water and electrolytes, and the formation and temporary storage of stool, the colon has recently become accepted as an increasingly important site for drug delivery. Research interest in the area of colonic drug delivery has been fuelled by the need to better treat pathologies of the colon that range in seriousness from constipation and diarrhoea to the debilitating inflammatory bowel diseases (ulcerative colitis and Crohn's disease) through to colon carcinoma, the third most prevalent form of cancer in both men and women. Targeted drug delivery to the colon would therefore ensure direct treatment at the disease site, lower dosing and a reduction in systemic side effects. Aside from local treatment, the colon can also be utilized as a portal for the entry of drugs into the bloodstream for the purpose of systemic therapy. Drugs that are degraded and/or poorly absorbed in the upper gut may be preferentially absorbed from the colon because of the lower levels of luminal and mucosal digestive enzymes, as compared with the small intestine. Furthermore, colonic drug delivery may also be used as a means of achieving chronotherapy for diseases that are sensitive to circadian rhythms, such as asthma and arthritis.

The rectal route has traditionally been used to administer medicaments in the form of suppositories and enemas to the distal gut, although such formulations rarely succeed in spreading beyond the descending colon. Also, the rectal route is not convenient or acceptable for most patients and hence the oral route is the preferred route of drug administration. However, colonic drug delivery via the oral route is not without its challenges. The colon constitutes the most distal segment of the gastrointestinal tract and so an orally administered formulation must retard drug release in the upper gastrointestinal regions but release the drug promptly

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on entry into the colon. Retardation of drug release in the diverse and hostile conditions of the stomach and small intestine is not easily achieved, since the dosage form will be subjected to a physical and chemical assault that is designed to breakdown ingested materials. While in the colon, the low fluid environment and viscous nature of luminal contents may hinder the dissolution and release of the drug from the formulation. Moreover, the resident colonic microflora may impact on the stability of the released drug via metabolic degradation (Basit and Lacey, 2001). In spite of these potential difficulties, a variety of approaches have been used and systems have been developed for the purpose of achieving colonic targeting. Targeted drug delivery is reliant on the identification and exploitation of a characteristic that is specific to the target organ. In the context of colonic targeting, the exploitable gastrointestinal features include pH, transit time, pressure and bacteria.

Approaches to colonic drug delivery via the oral route

Time Responsive Delivery

Time dependent dosage forms are formulated to release their drug load after a predetermined lag time. While not site-specific delivery systems *per se*, it has been suggested that colonic targeting can be achieved by incorporating a lag time into the formulation equivalent to the mouth to colon transit time. A nominal lag time of 5 hours is usually considered sufficient, since small intestinal transit has been considered relatively constant at 3 to 4 hours. A number of systems have been developed based on this principle, with one of the earliest being the somewhat complex Pulsincap® device (Wilding *et al*., 1992). This device consists of a non-disintegrating half capsule shell sealed at the open end with a hydrogel plug. The plug hydrates on contact with gastrointestinal fluids and swells to an extent that it is expelled from the capsule body, thus releasing the drug. Usually the time it takes the hydrogel plug to hydrate and eject from the capsule shell defines the lag time prior to drug release and hence by altering the composition and size of the hydrogel plug, it is possible to achieve drug release after lag times. Hebden *et al.,* 1999 have reported variable release positions in man from such a device, partly due to variability in gastric emptying, and others have noticed a distinct lack of spread of the drug from the capsule shell after plug ejection. The problem of variable gastric emptying rates was addressed by the use of an outer enteric coating on the Pulsincap® that delays the hydration of the hydrogel plug until post gastric emptying of the device. However, aside from gastric emptying, and colonic transit are also subject to considerable inter-and intra-subject variability, as well as diurnal variability. This clearly limits the utility of the timed-release approach for colonic delivery.

Pressure Responsive Delivery

A pressure-controlled colon delivery capsule (PCDC) has recently been described (Takaya *et al*., 1995). This novel delivery system utilizes the increase in pressure of the luminal contents of the colon resulting from the reabsorption of water in the region. The PCDC is composed of drug, dispersed in suppository base coated with the hydrophobic polymer ethyl cellulose. Once swallowed, the temperature of the body causes the suppository base to melt and increase in volume, and the system resembles a liquid-filled ethyl cellulose balloon. The balloon is able to withstand the luminal pressure of the small intestine resulting from muscular contraction of the gut wall (peristalsis), but will rupture when subjected to the pressure of the more intense haustral contractions of the colon and contents of thicker viscosity. Such systems have been assessed for their ability to deliver model drugs in beagle dogs and humans. The authors have shown that the thickness of the ethyl cellulose coating can be manipulated to effect drug release in vivo. However, none of the in vivo studies have followed the transit of the capsules by gamma scintigraphy, which would allow the time and location of capsule disintegration to be accurately determined, but have compared the appearance of drug in the plasma with reported values for colon arrival times in dogs and in man. As small intestinal transit time is known to be variable, it has not been conclusively shown that the capsules have disintegrated in the colon.

So far, this method has only been used to produce single-unit systems. There is a generally accepted view that multi-unit systems perform better in vivo the single-unit systems, as they spread our throughout the length of the intestine causing less irritation, enjoy a slower transit through the colon and give a more reproducible drug release. Also, there is no data on the luminal pressures of different regions of the gastrointestinal tract, and whether these are subject to inter and intra-subject variation as is pH and intestinal transit time. Therefore, it remains to be seen whether the PCDC represents a viable means of colon specific delivery.

Bacteria Responsive Delivery

These systems utilize substrates that are degraded by bacteria present in the colonic region. The bacterial count has been estimated to be 10^{11} per gram in the colon (compared with 10^4 per gram in the proximal small intestine) and consists of around 400 species being predominantly anaerobic in nature. The first bacterially activated system marketed to maintain remission in ulcerative colitis patients was sulphasalazine, a pro-drug consisting of the active ingredient 5-aminosalicylic acid consisting of the active ingredient 5-aminosalicylic acid (5-ASA) linked by an azo bond to sulphapyridine (Khan *et al*.,1977). 5-ASA alone is well absorbed from the small intestine, but when administered as a pro-drug is not released until it reaches the colon where the azo bond undergoes a reduction reaction to liberate the active ingredient at the site of inflammation.

Researchers have long since realized the benefits of producing a universal system based on a bacteria-dependent system, and Saffran *et al*., 1986 were the first to demonstrate this principle by using polymers cross-linked with azo-aromatic groups to coat pellets and deliver insulin and vasopressin to the rat colon. However, the use of azo polymers has so far been hindered as some azo-aromatic compounds are known to be potential carcinogens. Nevertheless, a universal delivery system would be able to transport any drug molecule to the colon, and as a further advantage would not be subject to the same stringent regulation that pro-drugs are, being new chemical entities.

Polysaccharides offer an alternative substrate for the bacterial enzymes present in the colon. Many of these polymers are already used as excipients in drug formulations, or are constituents of the human diet and are therefore generally regarded as safe. Although specifically degraded in the colon, many of these polymers are hydrophilic in nature, and swell under exposure to upper gastrointestinal conditions, which would result in premature drug release. To overcome this problem the natural polysaccharides are either chemically modified or mixed with hydrophobic, water insoluble polymers. This has the effect of limiting the swelling in the upper gastrointestinal tract, but still permitting a partial solubilisation of the matrix or coating in the colon due to bacterial degradation resulting in drug release. The number of polysaccharides investigated to date is large, and a comprehensive review is not possible here, but materials used include amylase, chitosan, chondroitin sulphate, dextran, guar gum, insulin and pectin.

One polysaccharide that has been rigorously investigated is amylase. Amylose is one of the major components of starch, accounting for 15-25% of the total weight. The glassy from of amylase has good film forming properties and is resistant to pancreatic enzymes in the small intestine but will undergo degradation due to fermentation by a broad range of bacterial enzymes present in the colon. In combination with the water-insoluble polymer ethyl cellulose, amylase has been exploited as film coating for colonic drug delivery (COLAL™, Alizyme, Cambridge, UK). This single coating can be applied directly to tablets or pellets by conventional coating methods with equipment that is widely available, and so is amenable to industrial scale up.

pH Responsive Delivery

There is a pH gradient in the gastrointestinal tract with values ranging from 1.2 in the stomach through 6.6 in the proximal small intestine to a peak of about 7.5 in the distal small intestine (Evans *et al*., 1988). This pH differential between the stomach and small intestine has historically been exploited to deliver drugs to the small intestine by way of pH sensitive enteric coatings. These polymer coatings are recalcitrant to the acidic conditions of the stomach but ionize and dissolve above a certain threshold pH found in the small intestine. Thus, it is also possible to apply this concept to deliver drugs to the terminal ileum/colon by use of enteric polymers with a relatively high threshold pH for dissolution. The most commonly utilized polymer for this purpose is Eudragit®S, a copolymer of methacrylic acid and methyl methacrylate, which dissolves at a pH of greater than 7 (Rohm Pharma, Darmstadt, Germany). This concept is based on the assumption that gastrointestinal pH progressively increases through the gastrointestinal tract, akin to that found in the upper gut. However, pH in the proximal colon is of the order of 6.4, lower than that of the distal small intestine. This poses the risk of premature drug release from such formulations in the terminal ileum especially in view of the delayed transit through this region. Nevertheless, distal gut targeting is still attainable using this approach, and in fact the Eudragit®S polymer forms the basis of proprietary 5-aminosalicylic acid

formulations for the treatment of ulcerative colitis (Asacol®, Ipacol®, Claversal®). However, there is anecdotal evidence to suggest that in some patients the Asacol® formulation passes through the gut intact. This led the authors to conclude that gastrointestinal pH was not a reliable trigger for colon specific drug release, a view that has since then been widely held.

A copolymer of methacrylic acid, methyl methacrylate and methyl acrylate (Eudragit® FS) has recently been developed to overcome the inherent problems with the other enteric polymers. Although this polymer has a threshold pH similar to that of Eudragit®S, it dissolves at a slower rate. Eudragit®FS was superior to Eudragit®S in terms of retarding drug release in the small intestine, although there was some inter and intra subject variability in the site of drug release in the distal gut. It would seem therefore, that Eudragit®FS is more appropriate for colonic drug delivery than the erstwhile enteric polymers. However, one must question the impact of gastrointestinal disease on targeting performance since patients with ulcerative colitis are known to have a markedly lower colonic pH (Nugent *et al*., 2001).

Conclusions

Successful colonic delivery requires careful consideration of a number of factors, including the properties of the drug, the type of delivery system and its interaction with the healthy or diseased gut. Although a number of formulations have been proposed as colonic delivery vehicles, most lack the necessary site specificity. Time dependent systems are not a feasible solution due to variable gastric and small intestinal transit times, but may have a role in the treatment of diseases that are subject to circadian rhythm. Pressure controlled delivery systems hold some promise but currently little is known about the luminal pressures of different regions of the gastrointestinal tract, and at present the manufacturing methods are not suitable for future scale-up. The only universal systems currently marketed for distal bowel delivery are those based on pH, but it has been shown that these systems may deliver the active ingredient as proximally as the duodenum, or in some individuals not at all. This is perhaps not surprising given the inter- and intra-individual variation in gastrointestinal pH, although the advent of the next generation of enteric polymers and the relative ease of fabricating pH systems may sustain interest in this approach. At present, the bacterially activated delivery systems possible have the greatest potential for colonic targeting as the levels of bacterial enzyme activity in the colon is the characteristic that is most unique and exploitable in this region. The amylase-based COLAL™ system perhaps shows the most promise of all the bacterial activated systems, having successfully come through phase II clinical trials, and being most suitable for large scale manufacture.

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