Polysaccharide hydrogels for colon-targeted drug delivery

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Keywords: polysaccharide, hydrogels, drug delivery, colon

Introduction

Hydrogels are three dimensional, hydrophilic, polymeric networks capable of imbibing large amounts of water or biological fluids**.** Since the pioneering work of Wichterle and Lim in the 1960s on the crosslinked three-dimensional polymers obtained by the copolymerization of hydroxyethylmethacrylate (HEMA) with ethylene dimethacrylate (EDMA), polymeric hydrogels have attracted tremendous research interest.[1] Stimuli-responsive hydrogels, which are also called intelligent, smart or environmentally sensitive hydrogels, are defined as polymer networks able to respond to small environmental changes resulting in abrupt changes in their swelling behaviour, network structure, permeability and/or mechanical strength.

Applications of hydrogels in drug delivery

Controlled release systems were first used in medical research in the 1960s. The earliest drug delivery systems were first introduced in 1970s and were based on polymers formed from lactic acid.

With conventional dosing formulations, the drug level in the blood often exceeds the toxic level immediately after each administration of the drug and then declines sharply below the minimum therapeutic level until the next administration.[2] This bolus administration of drugs is therefore far from ideal, not least of all in pain relief therapies. Controlled drug delivery systems are designed for long term administration where the drug level in the blood remains constant, between the desired maximum and minimum, for an extended period of time (Fig. 1).

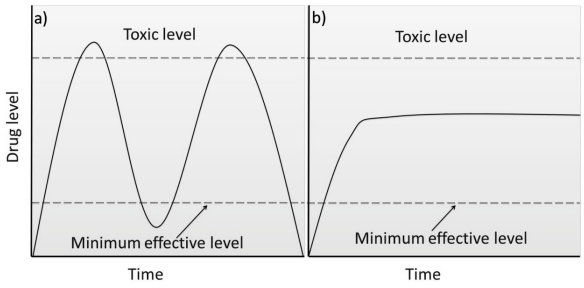

Fig. 1. Drug level in blood with a) traditional drug administration and b) controlled drug delivery.

Due to their attractive physicochemical and biological characteristics, hydrogels have attracted a lot of attention as they are excellent candidates for delivery systems of therapeutic agents. Hydrogel-based delivery devices can be used for ocular, transdermal, subcutaneous, rectal and oral delivery (Table 1).[3-9]

Oral drug delivery

Administering drugs orally is by far the most widely used route which helps eliminate the pain caused by injection, psychological barriers associated with multiple daily injections and possible infection from injection sites.[10] Almost 90% of all medicines are oral formulations. However, it is important for oral drug administration to overcome several different obstacles during delivery through the gastrointestinal tract (Fig. 2). The barriers can be morphological barriers such as mucus layers and microvilli as well as physiological factors such as a wide range of pH conditions and enzymatic activities.[11]

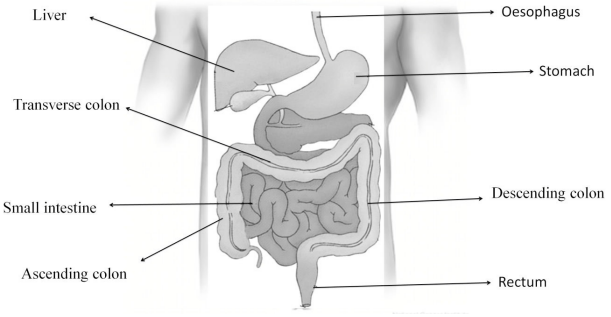

Fig. 2. Anatomy of gastrointestinal tract.

Site-specific drug delivery

Drug discovery and development involves highly challenging, laborious, and expensive processes which take an average of 15 years and a cost of about US $1 billion for a drug to travel from the research lab to the patient. However, most of the drugs fail to achieve favourable clinical outcomes because they do not have the ability to reach the intended targets.[12] Therefore, aggressive research efforts have recently focused on development of new strategies for delivering drugs to the required site of action.[13]

Table 1. Examples of stimuli-responsive hydrogel systems used for drug delivery

Hydrogel	Stimuli	Application	Drug
Poloxamers[3]	Temperature	Ocular delivery	Liposomes
Xyloglucan[4]	Temperature	Ocular delivery	Timolol/pilocarpine
Chitosan[5]	pH	Ocular delivery	Ofloxacin
Ethylene-co-vinyl acetate[6]	Magnetic field	Oral drug delivery	Insulin
Poly(2-hydroxyethyl methacrylate)[7]	Electric field	Oral drug delivery	Propranolol hydrochloride
Polyethylene glycol[8]	Temperature	Nasal drug delivery	Mucin
Carboxymethyl Chitosan[9]	pH	Intestinal drug delivery	Methyl prednisolone

Colon-specific drug delivery

Absorption and storage are the two main functions of the colon which lead to a lower water content and fluid mobility than other areas of the gastrointestinal (GI) tract. These conditions mean drugs can have higher residency times which will allow for the maximum possible drug uptake efficiency in patients. Therefore, the colon as a site for drug delivery has received a good deal of interest for the treatment of localised diseases such as irritable bowel syndrome, colon cancer, and inflammatory bowel disease (IBD) including Crohn's disease and ulcerative colitis.[14-17] Oral colon-specific drug delivery of protein and peptide drugs has also attracted the attention of worldwide drug delivery scientists due to the relatively low proteolytic enzyme activity in the colon compared to the small intestine.[18]

Factors affecting the design of colon-specific drug delivery systems

a) pH of the colon

The pH of the GI tract is subject to both inter- and intra-subject variations. The highest pH levels were measured by radiotelemetry and were found to be 7.5 ± 0.5 in the terminal ileum. On entry into the colon, the pH drops to 6.4 ± 0.6. The pH in the transverse colon was measured at 6.6 ± 0.8.[19]

b) Transit time to colon

Arrival time of a drug or drug composite in the colon depends on the rate of gastric emptying and intestinal transit time. The movement of materials through the colon is slow, tends to be highly variable and influenced by a number of factors such as diet, stress, disease state and presence of drugs.[20]

c) Colonic microflora and their enzymes

The sluggish movement of material through the colon provides perfect conditions for bacterial growth with over 400 resident species and a range of 1011-1012 colony-forming units (CFU)/g in comparison to the stomach (102 CFU/g) and the small intestine (104-107 CFU/g).[21] The colonic microflora are able to break down polysaccharides by producing a large number of reductases and carbohydrases.[22]

Polysaccharide-based colon-targeted drug delivery systems

Polysaccharides have gained much attention in developing colon-specific drug release systems because of their flexibility in obtaining a desirable drug release profile, cost effectiveness, ease of modification, biocompatibility, biodegradability and ability to form hydrogels (Table 2). Polysaccharides are widely distributed natural polymers. They are formed by condensation reactions of monosaccharides that result in glycosidic linkages. Hydrolysis of the glycosidic linkages on arrival in the colon triggers the release of the entrapped bioactive.

The death rate from bowel cancer in New Zealand is one of the highest in the developed world. At least 2,700 people are diagnosed with bowel cancer every year and more than 1,200 die each year as a result, equivalent to more than 100 New Zealanders every month. Because a high intracolonic drug concentration is required for the treatment of diseases associated with the colon, a considerable amount of research work has been carried out to develop colon-targeted drug delivery systems.

The main benefits of colonic delivery as a site for drug delivery are:

a) Proteolytic activity of colon mucosa is less than that observed in the small intestine, thus the colon may be helpful in achieving a reasonable absorption of certain drugs that are enzymatically labile in the small intestine

b) The colon provides a longer retention time and appears highly responsive to agents that enhance the absorption of generally poorly absorbed drugs

c) The colon is rich in lymphoid tissue which can take absorbed antigens into the mast cells of the colonic mucosa. This leads to rapid local production of antibodies which can help in efficient vaccine delivery.[19]

d) The colon continues to attract interest as a site where poorly absorbed drug molecules may have an improved bioavailability

e) The colonic region has a somewhat less hostile environment with less diversity and less intensity of activity as compared to the stomach and small intestine.

To achieve successful oral colonic delivery, a drug needs to be protected from the absorption and degradation pathways of the upper gastrointestinal tract and then achieve abrupt release into the colon.

References

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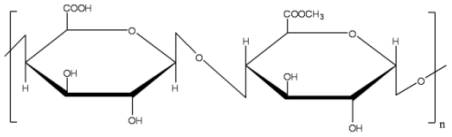
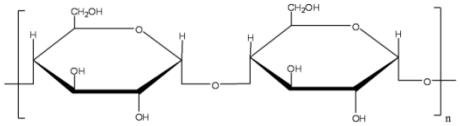
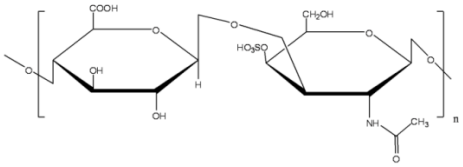
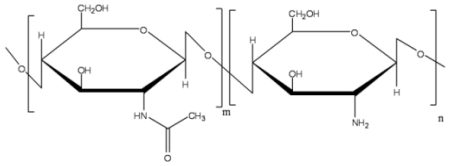
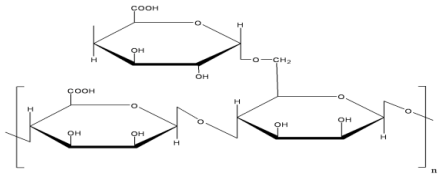
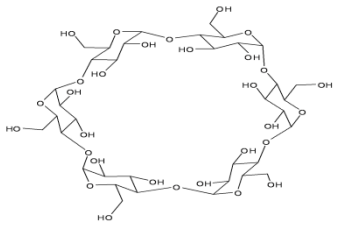
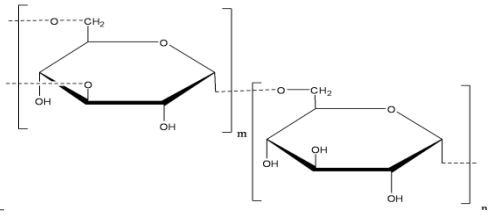
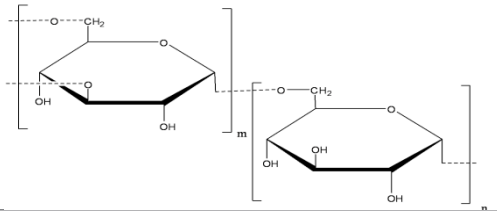
Table 2. Polysaccharide-based colon-targeted drug delivery systems

Polysaccharide	Structure	Source	Bacterial species that degrade polysaccharide
Pectin		Citrus peel and apple pomace	Bacteroids, Bifidobacterium, Eubacterium
Amylose		Plant	Bacteroids, Bifidobacterium
Chondroitin sulfate		Animals and humans	Bacteroids
Chitosan		Exoskeleton of crustacean and insects	Bacteroids
Guar gum		Seeds of plants	Bacteroids, Ruminococcus
Cyclodextrin		Plant	Bacteroids
Dextran		Microbial (bacterium Leuconostoc mesenteroides)	Bacteroids
Cellulose		Plant, microbial (Acetobacter xylinum)	Bacteroids

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