

Renewable Biopolymer-based Excipients for Colon Drug Delivery System: an Overview

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Abstract

Most of the colonic drugs, peptides and proteins have been reported to be unstable in the gastric environment and prone to absorption in the upper gastrointestinal tract (GIT), and as a result, cause lowering of drug bioavailability and reduction of their efficiency against inflammatory bowel diseases (IBD). Therefore, to protect drugs from an undesired release in the upper GIT and to deliver it to the colon, pharmaceutical industries have made an endeavor to develop renewable biopolymer-based excipients. Thus the present review includes an overview on the development of various approaches for colon drug delivery system (DDS).

Key words: pH-dependent formulations; enteric coatings; microbially triggered approaches; colon drug delivery system

1. INTRODUCTION

Drugs have maximum activity within optimum range of concentration and values of their concentration, beyond the minima or maxima of this range, may be toxic or produce no therapeutic efficacy. Thus, a multidisciplinary approach has become an essential requirement for drug delivery, at appropriate site of interest. In order to achieve the above goal, new ideas on controlling the pharmaco-kinetics, pharmaco-dynamics, non-specific toxicity, immunogenicity, bio-recognition, and efficacy of drugs have been generated. These new strategies, often called drug delivery systems, are based on interdisciplinary approaches that combine polymer science, pharmaceuticals, bio-conjugate chemistry, and molecular biology [1].

Drug delivery systems particularly for colon have been developed, for the treatment of several inflammatory bowel diseases (IBD) such as crohn's disease, ulcerative colitis, colon cancer and other infectious diseases, where it is necessary to achieve optimum concentration level of active ingredient such as drug. Most of the drugs have been reported to be unstable in the gastric environment and prone to absorption in the upper GIT. This causes lowering of drug bioavailability and reduction of their efficiency against IBD, hence drug delivery to the colon, via GIT, requires their protection from an undesired release in stomach and small intestine, while administered orally [2]. In order to resolve the above challenging problems, scientists have begun to focus on physiology and anatomy of human GIT such as variations in (1) gastric emptying time, and small and large intestinal transit time [3-5] (2) pH of GIT [6, 7], and (3) staying microflora [8], etc., as shown in Table 1. These are the three most important factors which have to be considered during successful formulation of drugs.

Thus scientists have been concentrating themselves to develop a well-orchestrated system by taking into consideration the above three factors to protect drugs from gastric environment and thereby transferring them to the lower GIT. The well-orchestrated system not only reduces the dose of administration, but also reduces the incidence of possible adverse effects associated with this active

ingredient. Therefore, the various DDS, developed for targeting drug delivery to the colon, include multi-coating time-dependent formulations, coating with pH-sensitive polymers, and the use of biodegradable polymers. Several objectives, such as, attainment of required concentration of drugs, to minimization of drug loss, prevention of harmful side effects and enhancement of drug bioavailability can be achieved through above mentioned DDS for targeting colon [9, 10].

2. MULTI-COATING TIME-DEPENDENT FORMULATIONS

Time dependent formulations are designed to resist the release of drug in the stomach with an additional non-disintegration or lag phase included in the formulation (which is equal to the small intestinal transit time) and thereby release of drug takes place in the lower bowel. This can be achieved by designing the system to deliver drugs after 5-6 h of lag time. The lag time prior to rupture is mainly controlled by (i) the permeation and mechanical properties of the polymer coating and (ii) the swelling behavior of the swelling layer.

Pulsincap® [12-14] is a time-dependent formulation that consists of non-disintegrating body having an enteric coated cap. The enteric coated cap dissolves in the small intestine and a hydrogel plug swells up to create a lag phase. This plug ejects on swelling and releases the drug from the capsule as designed in Fig. 1. Low substituted hydroxypropylmethyl cellulose (HPMC) formulation [15] was prepared for the expulsion system of propranolol release over a time period of 2-10 h. This could be controlled by using compressed erodible tablets made of lactose and HPMC.

Sarkar et al., (2011) showed that release of drug from the Time Clock® formulation depends mainly on the thickness of hydrophobic layer and it is independent from pH of gastrointestinal (GI) environment [16]. Thus, the basis behind all time-released DDS is valid only when, small intestinal transit times remain constant. Alternatively, our GIT vary in the gastric emptying time and, small and large intestinal transit time (Table 1), and thereby, the time dependent release formulations are not supposed to be

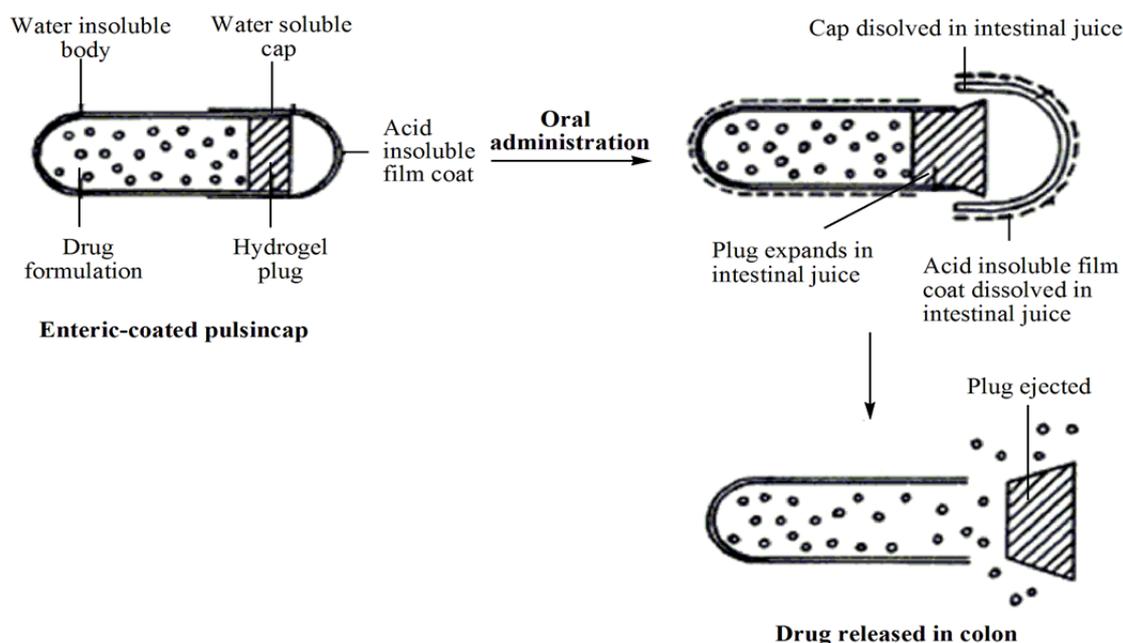


Fig. 1. Schematic design of pulsincap system

Table 1. Transit time, pH and microfloral distribution in human GIT [3-8, 11]

Segment of GIT	Oral cavity	Oesophagus	Stomach		Small intestine				Large intestine	
			Fed	Fasted	Duodenum		Jejunum	Ileum	Colon	
					Fed	Fasted			Mid	Left
pH	6.8±0.6	5.5±0.5	4.0±1.0	1.8±0.3	3.0±1.3	4.5±1.5	6.6±0.5	7.5±0.5	6.6±0.8	7.0±0.7
GIT Transit (h)	Negligible		>3	<1	3 to 4				20 to 30	
Micro-floral Concentration (CFU/ml)	10 ¹¹	10 ² to 10 ⁴	0 to 10 ³		10 ³		10 ³	10 ³ to 10 ⁸	10 ¹¹ to 10 ¹²	
Existing microflora			<i>Streptococcus</i> <i>Lactobacillus</i> <i>Candida</i> <i>Staphylococci</i> <i>Helicobacter pylori</i> <i>Peptostreptococcus</i>		Gram-positive cocci e.g., <i>Streptococcus</i> and <i>Lactobacillus</i>				<i>Bacteroides</i> Clostridium IV and XIV <i>Bifidobacterium</i> <i>Enterobacteriaceae</i> Cellulytic species	

suitable for colon DDS [4]. This can be overcome using enteric coating system however; drug release from these systems is not pH-controlled. The lag time of coated dosage forms that is designed for time-controlled release formulations, usually depends on the coating thickness whereas; drug release can also be triggered either by a change in pH or by disruption of the coating by swelling of the core [9, 17]. Therefore, researchers would have to concentrate themselves to design pH-dependent formulations for colonic DDS.

3. PH-DEPENDENT FORMULATIONS

GI pH of healthy human varies from stomach to small and even to large intestine as shown in Table 1. Large intestine of GIT has lower pH than small intestine. Fall in pH on entry into the large intestine due to the formation of short chain fatty acids arising from bacterial fermentation of the polysaccharides. Therefore, scientists are trying to resolve

the problem through various innovative experimental approaches, in such a way that active ingredient, i.e., drug, must appropriately reach to the site of interest. Researchers have made an attempt to coat the drug using different combinations of pH-sensitive polymers for colon DDS. The combination of two methacrylic acid copolymers such as Eudragit® L 100-55 (anionic copolymer based on methacrylic acid and ethyl acrylate) and Eudragit® S 100 (anionic copolymers based on methacrylic acid and methyl methacrylate) were used to coat the drug. Co-polymers of methacrylic acid and methyl methacrylate have dissolution property at pH ≥ 6.0, hence it has been used extensively to protect the active ingredient from acidic environment of stomach. Dissolution or degradation rate of drug-coated pH-sensitive polymers are dependent upon the ratios of combinations of two co-polymeric systems as well as on thickness of the coating. The schematic representation of pH-dependent formulation is shown in Fig. 2.

The pH-sensitive polymer, e.g., Eudragit[®] has been used in delayed release tablet such as Asacol[®] and Salofalac[®] for colon drug delivery. Davis et al., (1986) showed through in-vitro evaluation that Eudragit[®]FS (co-polymer of methyl acrylate, methyl methacrylate and methacrylic acid) coating material would be more appropriate than Eudragit[®]S (co-polymer of methacrylic acid and methyl methacrylate) for drug delivery to the ileo-colonic region [3]. Their result was also verified by Rudolph et al., (2001) [18]. Khan et al., (1999) used Eudragit[®] L100-55 and Eudragit[®] S100 as a film-coating material for mesalazine (5-aminosalicylic acid) tablets [19]. The release study showed that the proposed combination system is superior to the tablet coat as compared to the coat either with Eudragit[®] L 100-55 or with Eudragit[®] S 100 alone for targeted delivery. Similarly, Vijay et al., (2011) used copolymer of acrylic acid (AA) and methyl methacrylate (MMA) as an enteric coating material for prolonged release of NSAIDs, e.g., Flurbiprofen [20]. They showed that release of drug takes place only at pH ≥ 6.8 .

Although, pH-sensitive polymers have been used by researchers to coat the drug for colon targeted DDS hitherto, these formulations have some limitations because pH of upper GIT is slightly more than that of lower GIT and thereby it could not be neglected the drug release in the small intestine. Moreover, pH of GIT also depends upon inter and intra individual variations such as diet, disease, age, sex, and fed or fasted state [9, 21]. In addition, coated tablets with pH-sensitive polymers show an abrupt drug release and furthermore, pH-sensitive polymers used as carriers may accumulate in the body on prolonged use [9, 10, 22]. These limitations encourage to scientists to bring into play an alternative substrates, e.g., biodegradable polymers, either in combination with pH-sensitive polymers or in separate layers.

Van den Mooter et al., (1992) prepared azo-linked film-coating with 2-hydroxyethyl methacrylate and methyl methacrylate in presence of bis-(methacryloylamino) azobenzene [23]. The prepared film coatings were found to be insoluble in simulated gastric and intestinal juice. However, *in-vitro* and *in-vivo* tests proved that the films containing azo-linkage can be degraded by intestinal microflora. This may gave an opportunity to search other bacterially triggered biopolymer for successful delivery of drug. As colon of our lower GIT has bacterial microflora of the order of 10^{11} - 10^{12} CFU/ml, consisting chiefly of anaerobes (including more than 400 bacterial strains) help in degrading the polymers. Colonic anaerobic bacteria, such as, *Bacteroides*, *Bifidobacteria*, *Eubacteria*, *Clostridia*, *Enterococci*, *Enterobacteria* and other Cellulytic species [24-26] full-fill their energy requirements by fermenting various types of undigested residual substrates, e.g., di-, tri- and poly-saccharides, available from upper GIT [9], in the proximal colon [27], through the production of vast number of enzymes. These enzymes are functional in degrading the coatings/matrices, as well as in breaking bonds between an inert carrier and an active ingredient (i.e., release of a drug from a prodrug) ultimately results in, drug release from the formulations. Since,

production of these enzymes are localized only in colon, and therefore, the use of bacterially triggered biodegradable polymers for colon-specific drug release, seems to be a more targeted approach as compared to the others, such as, timed-release system and pH dependent system [28-30].

Thus, scientists initiated bacterially triggered biopolymer in combination with pH-sensitive polymer and observed the promising results. Colonic drugs namely, theophylline [31] and 5-ASA [32, 33] were coated to different film thickness, by blend of chitosan and kollicoat SR30D. The swelling behavior and the resulting drug release were dependent on the composition of the coatings as well as on the ratios of kollicoat SR30D to chitosan. The extent of digestion of the film was directly proportional to the amount of chitosan present in the film. The *in-vivo* pharmacokinetic studies of theophylline coated tablets showed delayed T_{max} , decreased C_{max} and prolonged MRT indicating the coated tablets didn't release drug in the stomach or small intestine, however, it delivered to the colon for the local action.

Drug release profiles of pectin/ethylcellulose film-coated pellets containing 5-Fluorouracil (5-FU) were studied in rats [34]. Release of 5-FU from uncoated and coated pellets mainly distributes in the upper and lower GIT respectively. The relatively high local drug concentration with prolonged exposure time provides a potential to enhance anti-tumor efficacy with low systemic toxicity for the treatment of colon cancer. Pharmacokinetics in dogs also revealed that mixed film coated pellets could provide sufficient time delay, might be related to more effective drug delivery to the colon. The cross linked HPMC/pectin/calcium matrix tablet could provide sufficient time delay in the release of Indomethacin, indicated more effective drug delivery to the colon, instead of HPMC/pectin tablet only [35]. Similarly, dextran-based pH-sensitive hydrogels for bovine serum albumin (BSA) [36] were prepared by activation of dextran with 4-nitrophenyl chloroformate followed by conjugation of activated dextran with 4-aminobutyric acid and subsequently cross-linking with 1, 10-diaminodecane. The release kinetics of BSA from these dextran-based pH-sensitive hydrogel was primarily determined by the swelling extent, which in turn depends upon the content of carboxylic acid and the degree of cross-linking. Release kinetics was further predominantly enhanced by addition of enzyme, dextranase, in the dissolution media.

Recently, McConnell et al., (2008) have carried out a comparative study between pH-responsive and microbially triggered colonic release in order to establish the better and more reliable one [29]. They chose Theophylline as a model drug and coated with pH-responsive polymer (Eudragit S) or microbially triggered polymer (amylose/ethylcellulose). *In-vivo* Eudragit S coated Theophylline pellets showed premature release in the small intestine, however, microbially-triggered polymer coated Theophylline pellets showed no release in the upper bowel and release sustained only after reaching the colon. Thus, *microbially-triggered systems behave more reproducibly and consistently, and provide superior colonic targeted DDS.*

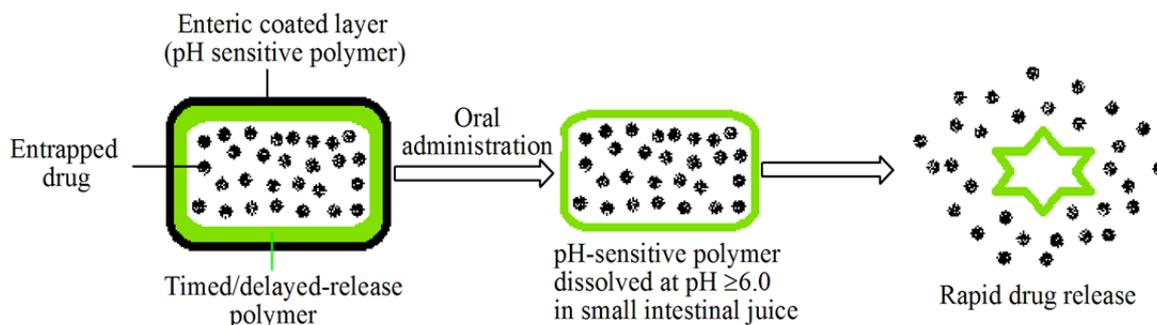


Fig. 2. Schematic representation of pH-dependent formulation system

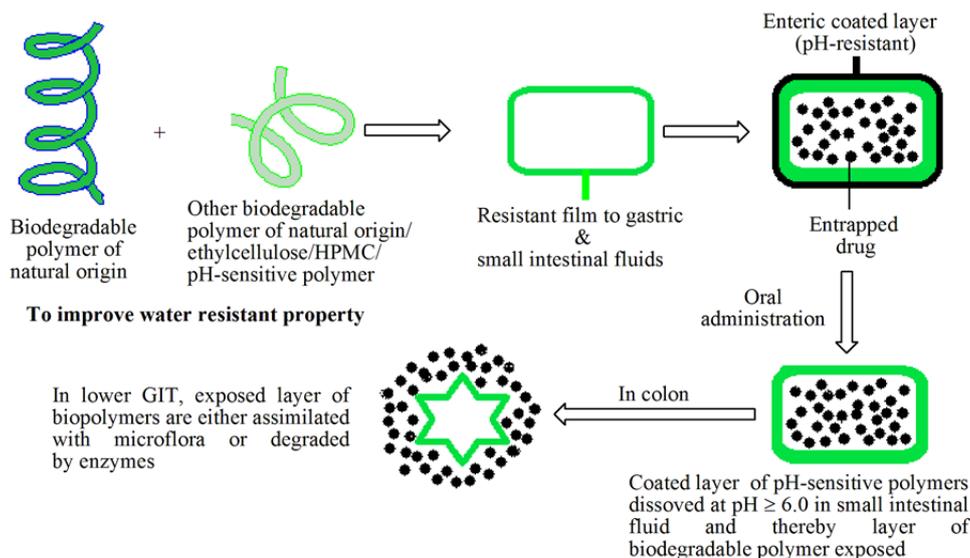


Fig. 3. Schematic representation of microbially-triggered formulation system

4. MICROBIALLY-TRIGGERED SYSTEM

Enzymes produced by colonic microflora, help to degrade coatings/matrices and participate in breaking the bonds between an inert carrier and an active ingredient, resulting in drug release from the formulations. Therefore, scientists started to choose those biodegradable polymers/materials, which can easily be degraded by the colonic microflora without altering the side effects either by the inert carriers or by the active ingredients. These biopolymers protect drug from the gastric environment of stomach and also exhibit competence in delivering the drug to the colon. On reaching the colon, they undergo assimilation by microorganisms or degradation by enzymes, resulting in breakdown of the polymeric backbone, which leads to a subsequent reduction in their molecular weight and mechanical strength. Thus, due to conditions prevailing in the colon, these biopolymers are unable to hold the drug entity anymore and thereby release the drug in the colonic part of GIT [9, 37, 38].

Biodegradable polymer of natural origin such as amylose, pectin, guar-gum, dextran, cyclodextrin, alginate and chitosan are either soluble or swell up extensively in water. Therefore, scientists have made an endeavor to improve water resistant derivatives without affecting their degrading property by colonic microflora as summarized below. Illustration of common microbially-triggered formulation is shown in Fig. 3.

4.1. Amylose-based

Plant polysaccharide for instance amylose consists of D-glucopyranose units linked by α -(1, 4) linkage, has an ability to form water swellable films that are potentially resistant to pancreatic α -amylase [39]. However, amylose films are degraded by enzymes, produced by colonic microflora [40]. Film coating system with such biodegradable polymer has been investigated as a potential vehicle for colonic DDS. Coatings with such biodegradable polymers that contain major fraction of starch have an ability to form film through the process of gelation. When coatings made exclusively by amylose, they swell and become porous and consequently drug is released. Thus to make a film, that is resistant to gastric and small intestinal fluids, amylose was mixed with ethocel[®] (1:4 w/w). Ethocel[®] mixed amylose coating formulations of 5-ASA showed optimum drug release retarding properties in gastric and intestinal fluids. On the other hand, it has been investigated that the coated pellets of 5-ASA were fermented in simulated colonic environment, resulting in drug release [41]. Further studies showed that amylose-ethylcellulose coating (1:4) was also suitable to deliver a highly water soluble drug, e.g., Glucose, to the colon [42, 43]. Freire et al., (2010) made films-coat by dispersion of high amylose-starch (Hylon VII) with ethylcellulose (Surelease) (1:2 w/w) [44]. The retrieval of the coated pellet from the rabbit faeces suggested that film coating had been digested by bacterial amylases of the colon and drug

was released specifically in the colon. Similarly, amylose and Surelease[®] grade EA-7100 showed good release in human faecal slurry, i.e., simulated colonic conditions [45]. Scientists also showed that drug release from the coated pellets depends upon the thickness of the coating and ratios of the two components such as amylose and ethylcellulose within the film. The experimental investigations revealed that ratio of amylose and ethylcellulose was the predominant factor and responsible for controlled release of drug, as compared to the coat thickness [46]. Under simulated colonic conditions, drug release was more pronounced from coating formulations containing higher proportions of amylose. Coat thickness containing 1:1 ratio of both amylose and ethylcellulose, resisted the release of 5-ASA in upper GIT successfully, although relatively rapid onset drug release occurs in the simulated colonic conditions. Such plant polysaccharide-based systems offer a practical means of drug delivery to the colon, particularly those that are water-sensitive and/or thermolabile.

4.2. Pectin-based

Water soluble, non-starch linear plant polysaccharide for example pectin, couldn't hold the drug effectively during its passage through stomach and small intestine. An experimental study showed that a coat of high methoxy pectin of a considerable thickness was required to protect the drug core in simulated *in-vivo* condition [47]. Moreover, the focus shifted towards the development of such derivatives of pectin which are less water soluble but degradable by the colonic microflora [9, 48]. Pectin derived as a calcium salt, has shown reduced solubility due to formation of egg box configuration [49]. The presence of calcium in formulations, controlled the optimum drug delivery [50] and increased the susceptibility to enzyme attack [9, 10]. Rubinstein et al., (1993) developed colon specific DDS using calcium pectinate for Indomethacin as a model drug [48]. Calcium pectinate gel (CPG) beads containing drug namely, 5-FU were also prepared by ionotropic gelation method followed by an enteric coating with Eudragit S-100 [51]. *In-vivo* data showed that Eudragit S-100 coated calcium pectinate beads delivered most of its loaded drug to the colon, which reflects its promising target. Another modified form of pectin, e.g., amidated-pectin, was considered for colonic delivery because of its biodegradability, high tolerance to pH variations and fluctuations in calcium levels [52]. To reduce the solubility of pectin, it was also mixed with ethylcellulose resulted in mixed film coating material for colon-specific DDS [34, 53, 54]. Results showed that films possess excellent protective properties in water, along with degradation property of pectin. Release profile of Paracetamol could be decreased either by increasing the content of ethylcellulose in the film or by increasing the coat thickness and vice versa. The films that were degraded in the presence of enzymes produced by colonic microflora showed the characteristics of an efficient carrier for colon DDS. Compression coated core tablets of 5-ASA were also prepared using pectin and HPMC [54]. Meshali and Gabr, (1993) did concentrate to develop inter-polymer complex of pectin and chitosan [55], and potential *in-vitro* studies of this mixture was further investigated for colon-specific

delivery [56]. *In-vitro* studies using pectin and chitosan as a compression coat showed that this coat could offer greater protection at a lower coat weight in the upper GIT than pectin alone (in which a substantially thick coat is required for protection). Results were better with water insoluble drug as compared to water soluble one [9]. Pectin cross-linked with epichlorohydrin showed that the release rate increases in the presence of enzymes highlights the suitability of cross-linkage, for targeting drugs to the colon [57]. The applicability of pectin, singly or in combination with other polymers has been studied for colon-specific DDS. Pectin, when used alone, was needed in large quantities or substantially thick coat to control the release of drug through the core. A coating composition of a mixture of pectin, chitosan and HPMC proved to be very efficient as coating for tablets [9].

4.3. Guar gum-based

Guar gum, a naturally occurring galactomannan polysaccharide, derived from seeds of *Cymopsis tetragonolobus*. It is made up of a linear chain of β -D-mannopyranose joined by β -(1, 4) linkage with D-galactopyranosyl units attached by 1, 6-links at every second mannopyranose, forming short side branches. Guar gum hydrates and swells in cold water, resulting in viscous colloidal dispersions or sols [58-60] and thereby gelling property retards the drug release from the tablets [61, 62]. It is being used to deliver drug to the colon due to its drug release retarding property in the upper GIT and susceptibility to microbial degradation in the large intestine [63]. Guar gum-based matrix tablets of Dexamethasone and Budesonide [64] have shown very encouraging results as colon carriers. The study demonstrated that galactomannanase (0.1%) accelerates the dissolution of Dexamethasone and Budesonide from guar gum matrix tablet. It was observed that extent of drug dissolution depends on concentration of galactomannanase. Guar gum has also been evaluated as a compression coating to protect the drug core of 5-ASA in upper GIT [65]. The release kinetics of 5-ASA depends upon compression thickness of guar gum was investigated [9]. Phosphated cross-linked hydrogel of guar gum were also prepared and analyzed *in-vitro* and *in-vivo* for colon drug carrier [66, 67]. The phosphated hydrogels showed low swelling property and thus hydrocortisone loaded hydrogels were able to resist the release of 80% of the drug for 6 h in phosphate buffer at pH of 6.4. *In-vivo* studies in rat showed that the modified guar gum was degraded enzymatically. This finding highlights the suitability of phosphated cross-linked guar gum for colon targeted delivery of drug.

4.4. Dextran-based

Dextran are a class of natural polysaccharides with a linear polymer backbone of mainly α -(1, 6)-D-glucopyranosidic linkages. It is obtained from bacterial cultures of *Leuconostoc mesenteroides* NRRL B-512. The glycosidic linkages of dextrans are hydrolyzed by the mammalian cells [68]. Dextranases are the enzymes which hydrolyze these glycosidic linkages. Dextranase activities of the colon are shown by anaerobic gram-negative intestinal bacteria especially the *Bacteroides*. Dextran has also been found to degrade in human faeces due to bacterial action [9].

Biodegradable dextran macromolecule was prepared as a hydrogels using di-isocyanate as a crosslinking agent [69], have been found to degrade completely by dextranases *in-vitro* and *in-vivo* in the rat ceacum [70] and even in the human colonic fermentation model [71]. This would however cause a delay release of drug which would take place in the distal colon where conditions for absorption are much reduced. In another approach, glutaraldehyde cross-linked dextran capsules were used for colon-specific drug delivery [72]. These capsules were loaded with Hydrocortisone and drug release studies were conducted *in-vitro*. Dextranase enzymes enhance the release of Hydrocortisone by rapid degradation of the capsule. Films of dextran fatty acid esters that are insoluble in gastric and small intestinal fluids were also synthesized for the utilization in colon DDS [73]. Lauroyl dextran esters were applied to prepare a film for coating of theophylline, showed that release rate was inversely proportional to the amount of ester applied on the coating [74]. Addition of dextranase degrades the coating and thereby leads to release of the drug. However, further studies showed that dispersion of lauroyl dextrans were not suitable as degradable coating material [75] as they didn't display ideal zero order dissolution before and quick disintegration after enzyme addition [9]. Due to thermoresponsivity and biodegradable nature dextran may also led to the potential use as a controlled release devices in addition to drug carrier [76]. Recently, 5-ASA, a colonic drug, was entrapped in super paramagnetic chitosan-dextran sulfate hydrogel, resulting in a significant increase in size of hydrogels and which gives a good induction of the incorporation. Release study showed their role as a good carrier for colon DDS [77].

4.5. Cyclodextrin-based

Cyclodextrins are cyclic oligosaccharide consists of 6-8 glucopyranose units linked through α -(1, 4)-glycosidic bonds. Cyclodextrins are neither hydrolyzed nor absorbed from the stomach and small intestine however, it is degraded by vast anaerobic microflora, stay alive in the lower bowel [78]. This property of being able to be degraded by colonic bacteria especially *Bacteroides* led to its use as a colon targeting carrier.

4.6. Alginate-based

Alginate is an anionic polysaccharide isolated from cell wall of brown algae. It is a linear polymer which has 1, 4-linked- β -D-mannuronic acid and α -L-guluronic acid residues, arranged as blocks of either type of unit or as a random distribution of each type. Alginates do not gel, as they have poly (L-guluronic acids) which are rigid and thereby Ca^{2+} ions are induced for gelation. Calcium alginate beads were made as a core carrier for delayed dissolution followed by burst release to the potential site of colon [79]. 5-ASA was spray-coated on dried calcium alginate beads and then coated with different percentage of enteric co-polymer or sustained release polymers. They showed that beads coated with 6% (w/w) methacrylic copolymer on the top of 4% (w/w) ethylcellulose polymer didn't release the drug in 2 h of acidic treatment or the next three hour of simulated intestinal fluid treatment. Thus it might be assumed that this dosage form provides the

suitability to deliver drug to the lower GIT with minimal early release, followed by sustained release in the colon.

4.7. Chitosan-based

Natural polysaccharide of animal origin, such as chitosan is obtained by removing enough acetyl groups from chitin. It is a linear polysaccharide consists of β -(1, 4)-D-glucosamine units. Chitosan has interesting properties, e.g., antimicrobial and biocompatible nature, led to its various applications. Its rigid nature can be overcome by blending of PEG (polyethylene glycol) which leads to the development of flexible membrane as required in dressing fabrication [80, 81]. Lately, drug loaded nanohybrids scaffold of chitosan-g-lactic acid with montmorillonite [82] and chitosan-g-glycolic acid with gold nanoflower [83] were prepared by freeze drying process. It has also been investigated that montmorillonite and gold nanoflowers were found to control the drug release rate in the release medium of pH 7.4 in the respective scaffold.

Chitosan has also an ability to get soluble in dilute acid and hence it requires an enteric layer over the chitosan for successful delivery of drug to the site of interest, i.e., colon. As formulation reaches the intestine, the pH increases and the enteric layer dissolves releasing the chitosan coated core. These cores are acted upon by microflora of the colon, which degrade the chitosan and release the drug. Chitosan capsules, coated with an enteric layer of HPMC phthalate have been evaluated for colon DDS [9, 84]. Chitosan microcores entrapped Diclofenac sodium efficiently, using spray-drying method and entrapped Diclofenac sodium within chitosan microcores was further encapsulated by Eudragit L-100 and Eudragit S-100 using an *oil-in-oil* solvent evaporation method [85]. Eudragit coating gave a pH-dependent release profile because it has dissolution property at pH 6 or above. To protect the cores of acetaminophen (N-acetyl-p-aminophenol) in the small intestine, chitosan has been used as an inner coat and gastric fluid resistant material such as phytin used as an outer coat. Phytin protect the core from gastric pH and dissolve in the small intestine whereas chitosan protect the core in the small intestine and release the core upon biodegradation in the colon [86]. To reduce the dissolution property in acidic medium and to improve it in the basic medium, derivative of chitosan, such as, chitosan-succinate and chitosan-phthalate were also prepared using succinic and phthalic anhydrides. Dispersal of Diclofenac sodium in the matrix of these chitosan derivatives showed that these matrices resist dissolution under acidic conditions and undergo improved dissolution under basic conditions, suggest their suitability for colon-specific DDS [87].

4.8. Xylan-based

Xylan is the most common hemicelluloses and considered to be the major non-cellulosic components after cellulose one. Indeed, xylan is made up of Poly β -(1, 4)-D-xylopyranose units with various side groups or chains attached to the hydroxyl groups of C-2 and/or C-3 carbon atoms. These side chains mainly consist of α -D-glucuronic acid, 4-O-methyl- α -D-glucuronic acid, acetyl groups, phenolic, ferulic and coumaric acids, and some neutral sugar units, e.g., α -L-arabinofuranose, α -D-xylopyranose or α -D-galactopyranose also [88-92]. Inimitable properties of

xylan such as biocompatibility, non-toxicity, biodegradability [93], flexible methods of synthesis, range of constituents, and desirable physical characteristics [91] provide an innovative platform for researchers towards its use in the biomedical area. Xylan has limited application in the biomedical area; even they have a lot of inimitable properties as described above. Thus, scientists have been deliberating themselves towards its novel use as a carrier either in the form of hydrogel, film or in a form of prodrugs in the pharmaceutical industries. Pure xylan yielded brittle aggregates and thereby it is unable to form free-standing films [94]. Magnetite microparticles intended for oral intake and applied as magnetic markers for monitoring gastrointestinal motility were coated with corn cob xylan without altering its superparamagnetic properties [94, 95]. Recently, xylan derivatives-based hydrogels are prepared using polyvinyl alcohol (PVA) [96], N,N'-diallyldiamides (DA) [97], N,N-methylene bisacrylamide [98] and 2-hydroxyethyl methacrylate (HEMA) [91] as a cross-linkers. The prepared hydrogel showed biodegradability and pH-sensitivity [98], and noncytotoxic behavior [96] which leads to its use as a promising carrier for sustained and targeted DDS. Scientists also reported previously that acetylated xylan-based hydrogel show enhanced drug release profile than non-acetylated one [91]. The presence of acetyl groups introduced compactness and high stiffness to the hydrogels which ultimately reduced their water swelling capacity and moreover, significantly enhanced their drug release properties. Hydrogels of xylan can also be developed by selective removal of arabinose side chains from oat spelt xylan by recombinant α -L-arabinofuranosidase (AbfB) for encapsulation and sustained release of horse radish peroxidase [99, 100].

4.9. Cellulose-based

Polysaccharide of natural origin, e.g., cellulose, obtained either from plants or from gram-negative bacteria, *Acetobacter xylinum* [101, 102]. It is the most abundant naturally occurring plant polysaccharide consists of long chains of anhydro- β -D-glucopyranose units (AGU). It has three hydroxyl groups per AGU units, with exception of the terminal ends [103, 104]. Cellulose biopolymer benefits from extensive evidence of non-toxicity, biocompatible nature and non-absorbable from GIT led to its use in the pharmaceutical applications. As a consequence, cellulose derivatives, e.g., hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), sodium carboxymethyl cellulose (Na-CMC), methylcellulose and ethylcellulose, etc., can be made by different processes for their proper pharmaceutical applications. Functionalized cellulose have different chemical properties from pure cellulose, as their substituent groups disrupt the hydrogen bonding and consequently, compounds are more soluble [105]. Therefore, the modified cellulose derivatives have enhanced water retention capacity and film forming properties.

HPMC is used as a time-dependent release formulation for propranolol HCl. Propranolol HCl containing matrices were prepared by compressing a homogeneous mixture of the drug and the polymer powder. Studies investigated that

drug release strongly dependent on the matrix swelling ratio [106]. HPMC [107] or ethylcellulose [53, 108], etc., can also be used to overcome the dissolution property of pectin/chitosan. Therefore, they can be used in combination with pectin/chitosan to produce film coat for colon DDS. Scientists reported that drug release was controlled mainly by combination ratios and film thickness. Drug release can be reduced either by increasing the proportion of these derived polymers or by increasing the coat thickness. Cellulose derivative, e.g., methylcellulose, is not absorbed by the intestines but passes through the digestive tract unchanged when it is administered orally. It draws large amount of water into the colon, producing a softer and bulkier stool. As a consequence, it is widely used to treat constipation and IBD [109]. Other derived compounds, e.g., HPC and Na-CMC, can be used as thickening agent, film coating and tablet binder. Na-CMC can be used in the preparation of microspheres using glutaraldehyde as a cross-linker. An anti-inflammatory drug, e.g., Ketorolac tromethamine (KT), was successfully encapsulated into these microspheres. This encapsulated drug showed non-fickian controlled release [110]. In the recent time, regenerative cellulose matrix was used to immobilize the Indazole derivatives. This polymer-drug blend system was obtained as medical benefit [111].

Cellulose has exceptional properties, e.g., non-toxicity, biocompatibility and passes through digestive tract unchanged, hitherto, its applications are very limited in the pharmaceutical industry. In one of the experimental studies it had been revealed that cellulosic fibers were largely excreted in feces and therefore, were fermented to only a small extent by the intestinal microbes [112]. Alternatively, other literature reported that ingested cellulose may be digested, absorbed and metabolized up to a significant level. However, digestion of cellulose may also be depending upon its purity, i.e., more purified cellulose is being less readily digested. Usually, it is more readily digested in younger person [113, 114]. As a consequence, these fibers increased fecal output and fecal frequency, but did not cause gases, produced as a result of fermentation. On the other hand, cellulose degrading microflora or cellulytic bacteria, e.g., *Ruminococcus albus*, *Ruminococcus bromii*, *Ruminococcus obeum* and *Ruminococcus callidus* were also isolated from the human feces as reported [26, 115]. Thus, cellulose molecules may give an opportunity to explore its wide pharmaceutical applications specifically in targeted DDS.

CONCLUSION

There are various formulations/systems have been developed to deliver drug to the lower GIT using synthetic as well as microbially-triggered biopolymers. Microbially-triggered system one of them, behaves more reproducibly and consistently, and provides superior colonic targeted DDS. Most of the microbially-triggered polymers of natural origin are either soluble or swell up extensively in water. Therefore, they are used by improving their water resistant property either in combinations with other polymers or as derivatives, without affecting their degrading property by colonic microflora. However, the most and the second most

abundant microbially-triggered polymers of natural origin, e.g., cellulose and xylan, have a lot of inimitable properties, hitherto, their applications are very limited in the pharmaceutical industry. Thus, both of the biopolymers may give an opportunity to explore their wide pharmaceutical applications specifically in targeted DDS.

ACKNOWLEDGEMENT

One of the authors, Dr. Samit Kumar, would like to express his sincere thanks to the Ministry of Human Resource Development (MHRD), New Delhi, India; for the financial research grant during PhD research work. We also would like to express our sincere thanks to Late Professor Jugendra Sain Upadhyaya for his valuable suggestions during preparation of the manuscript.

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