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Review article

Polymers in Colon Targeted Drug Delivery Systems; A Review

Akshit Sharma, Ritesh Rana*, Parshuram Rai, Priyanka Devi

Himachal Institute of Pharmaceutical Education and Research (HIPER) Nadaun-177033 (H.P.), India.

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Corresponding author *
Ritesh Rana
Associate Professor,
Himachal Institute of Pharmaceutical Education and Research (HIPER) Nadaun-177033 (H.P.), India

ABSTRACT:

In A lot of interest has been shown in colon-targeted drug delivery systems as possible means of improving oral delivery of a variety of medications susceptible to enzymatic and acidic breakdown in the upper gastrointestinal tract, as well as for the local treatment of colonic diseases with fewer systemic side effects. The importance of colonic drug delivery as a non-invasive method of delivering macromolecules is highlighted by the rise in the worldwide pharmaceutical industry for biologics and the growing patient-friendly drug administration system demand. Colon-targeted drug delivery systems for macromolecules have the potential to reduce costs and improve patient compliance because to their painlessness and self-administering nature. An attempt has therefore been made to review the various polymers utilized in colon-targeted medication delivery systems in this review.

Keywords: Biodegradable polymers, colon targeted delivery, controlled delivery.

1. INTRODUCTION

Standard controlled-release oral medications typically don't have any unique characteristics that would help them target the medicine to a particular location in the gastrointestinal tract [1, 2]. Recently there has been a lot of interest in targeted medicine delivery to the colon for both systemic absorption of protein and peptides and local therapy of various colonic diseases [3].

The colon is a perfect location for local and systemic medication administration. A colon-targeted drug delivery system can help treat conditions of the large intestine where a high concentration of active medication is needed, such as Crohn's disease, irritable bowel syndrome, ulcerative colitis, and colon cancer [4-5]. Because the mucosa of the colon has far less proteolytic activity than that of the small intestine, the colon is also utilized for the systemic absorption of proteins and peptides. Medication that targets particular sites of action has several benefits over non-targeted medication, including dose reduction and adverse effect prevention. Due to its almost neutral pH and prolonged transit time, the colon has several therapeutic benefits when used as a medication delivery site [6].

A dosage form must be designed to account for the many barriers the gastrointestinal tract introduces for the medicine to reach the colon and release it. Drugs must be shielded from deterioration or release in the stomach and then released into the colon under controlled conditions for colon delivery to be successful [7, 8]. Given that polymers are now known to potentially affect drug release and absorption rates and to play a significant role in the formulation of colon-targeted drug delivery systems, it is possible to achieve the desired properties of these systems by utilizing some polymers alone or in combination [9].

Several kinds of natural, synthetic, and semisynthetic polymers have been studied to overcome the strong physiological variations in the upper gastrointestinal tract and focus drug release in the colon [10]. These polymers can be employed to develop a great variety of colon drug delivery systems, ranging from classical matrix tablets to more complex and sophisticated osmotic pressure drug delivery systems. Unarguably, nanotechnology represents a promising approach to specific colon drug delivery. Among all the polymers employed, polysaccharides and their derivatives are the most common in the development of matrix tablet formulations [11]. Natural polysaccharides are well known and have low toxicity and low cost, making them perfect candidates for industrial production [12]. They can also be easily modified to produce semisynthetic polymers by enhancing and changing a few of their physicochemical characteristics.

2. DRUG CRITERIA FOR A COLON-SPECIFIC DELIVERY

The following physicochemical/therapeutic requirements should be met by medications intended for integration into a colon-specific delivery system [13]. To treat intestinal illnesses, these medications should first show up locally in the colon. Agents with these effects include peptide medications like amylin and non-peptide medications like oxyprenolol. Secondly, it is possible that these medications are not absorbed as well as they may be in the upper gastrointestinal system. This includes antianginal medications like isosorbide dinitrate [14]. Medications like

capecitabine and 5-fluorouracil, which are used to treat colon or rectal malignancies, are also excellent choices for CDDS. The remaining requirements include a high probability that the medication will be broken down in the stomach by enzymes or an acidic environment (this includes peptide medications like insulin and gonadorelin) or a high risk of first-pass metabolism (this includes corticosteroids).

3. BIODEGRADABLE POLYMERS

Solid oral dose formulations for colonic medication administration are frequently developed using natural polysaccharides [15]. In an acidic pH, biodegradable polymers typically exhibit limited swelling properties and are hydrophilic. Numerous enzymes, including β-D-galactosidase, amylase, pectinase, β-D-glucosidase, dextranase, and α-D-xylosidase, are secreted by different bacteria that are found in the colon. These polymers come in a wide array of forms and are reasonably priced. The human colon's bacteria break down linear polysaccharides, which makes them potentially beneficial in colon-targeted drug delivery systems even while they remain intact in the stomach and small intestine [16].

3.1. Guar gum:

Guar gum is a polysaccharide made up of mannose and galactose sugars chemically. Guar gum's ability to delay medication release and its vulnerability to microbial destruction in the large intestine make it a useful ingredient in colon-targeted drug delivery systems [17].

Using a reciprocating cylinder dissolving apparatus (USP Dissolution Apparatus III), Wong et al. investigated the dissolution of dexamethasone and budesonide from guar gum-based formulations and found that the drug release in simulated colonic fluid was significantly increased at galactomannanase concentrations >0.01 mg/ml [18].

In a study conducted on guar gum matrix tablets with human participants, Krishnaiah et al. used technetium-99m-DTPA as a tracer for gamma scintigraphy. The majority of the tracer contained in the tablet mass was transported to the colon, according to the scintigraphy, whereas a small quantity was released in the stomach and small intestine from the tablets' surface. Based on these findings, guar gum as directly compressed matrix tablets may be a viable delivery system for drugs targeted at specific colon regions [19].

Six healthy human volunteers were used in the pharmacokinetic investigation by Krishnaiah et al. of colon-targeted mebendazole tablets made of guar gum vs an immediate-release tablet. When comparing colon-targeted tablets to immediate-release tablets, they displayed a delayed tmax (9.4±1.7 h), absorption duration, and lower Cmax (25.7±2.6 µg/ml) and absorption rate constant. The study's findings showed that the colon-targeted mebendazole tablets made of guar gum carried the medication to the colon, where it was slowly absorbed and available for local action in the colon instead of releasing the medication in the stomach and small intestine [20]. 5-aminosalicylic acid (5-ASA) was made into core tablets by wet granulating starch paste, and then the tablets were compressed and coated with various amounts of guar gum [21]. By applying guar gum as a carrier in the form of a compressive coating over the drug core, the study verified that it is possible to deliver 5-ASA to the colon selectively.

3.2. Pectin:

Galactose and its methyl ester make up the majority of pectin, a linear, heterogeneous polysaccharide. It is taken out of fruit and vegetable cell walls and is one of the main sources of dietary fiber [22].

Using diltiazem hydrochloride and indomethacin as model medicines and pectin as a carrier, a novel colon-targeted tablet formulation has been designed. According to an in vitro investigation, prepared dosage forms released the most medication in the colon and the least amount in the stomach and small intestine. Pectin is an excellent colon-targeting agent for both water-soluble and insoluble medicines, according to the study [23].

A less water-soluble pectin salt called calcium/zinc pectinate is employed to make colonic delivery devices. By using extrusion-spheronization, Sriamornsak et al. created cores that contained microcrystalline cellulose, calcium acetate, and theophylline. They then coated the uncoated cores with calcium pectinate through interfacial complexation, and they observed that the release of theophylline from the uncoated cores was quick and linear with the square root of time [24]. Drug release occurred over approximately 4 hours for the big coated cores and 2 hours for the small coated cores.

When comparing zinc pectinate beads to calcium pectinate in hard capsules for colonic distribution of ketoprofen, Dupuis et al. found identical performance; however, there were notable variations when the same pellets were tested and encapsulated in enteric hard capsules. The results of this investigation showed that pharmaceuticals adequately entrapped in zinc pectinate beads could be protected from circumstances in the upper gastrointestinal tract, and that pectin breakdown with colonic microbiota will influence drug release[25]. Enteric hard capsules containing zinc pectinate beads show promise as a vehicle for targeted colonic delivery of medications following oral intake.

Pectin microspheres for indomethacin oral colon administration have been prepared using a spray drying technique. Calcium chloride was used to crosslink the produced microspheres. Indomethacin's release from cross-linked pectin microspheres was reduced more than that of non-cross-linked microspheres [26]. The inclusion of pectinase improved drug release from pectin microspheres. While indomethacin release from the pectin microsphere was enhanced at neutral pH 7.4, it was less acidic at pH 7.4. The study's findings showed that pectin microspheres made by crosslinking and spray drying could be used as possible delivery systems for medications targeted at specific colon regions.

Colonic targeting with pectin/ethylcellulose film-coated 5-fluorouracil pellets was investigated in vivo and in vitro by Wei et al. Three distinct pectin: ethylcellulose compositions were applied to the pellet cores to achieve varying film thicknesses. More suitable drug-release profiles were obtained in simulated stomach, intestinal, and colonic fluids using pectin:ethylcellulose-coated pellets with a 1:2 ratio and 30% total weight gain (TWG-30%). After being removed from the stomach in two hours, the majority of the coated pellets passed into the small and large intestines in two to four hours, respectively [27]. Concerning uncoated pellets, the TWG-30% formulation exhibited a longer mean residence time, a lower Cmax, and a delayed Tmax.

3.3. Chondroitin Sulfate:

Bacteroides species mainly B. thetaiotaomicron and B. ovatus employ chondroitin sulfate, a soluble mucopolysaccharide, as a substrate in the large intestine. Since natural chondroitin sulfate is extremely water soluble and cross-linked, it presents a barrier to the formulation of colon-targeted medication delivery. Chondroitin sulfate was cross-linked by Rubinstein et al. using 1, 12-diamino dodecane. For the large bowel specifically, indomethacin was delivered via cross-linked chondroitin sulfate.

Chondroitin sulfate dimers were created when the carboxyl group in chondroitin and the amino group in diaminododecane underwent cross-linking. Measuring the amount of methylene blue adsorbed as a result of cation exchange allowed researchers to measure the degree of cross-linking. Doxethacin was combined with the cross-linked polymer and crushed into tablets. After incubating with rat cecal contents, an increased release was seen [28].

Using chondroitin sulfate and chitosan as binders and carriers, Amrutkar et al. have created matrix tablets for the colon-specific delivery of indomethacin. Polyelectrolyte complexes (PEC) were formed with chitosan and chondroitin sulfate, and their potential as a colon-targeted drug carrier was explored. The study verified that cross-linked chitosan and chondroitin sulfate polysaccharides can be used to selectively deliver medications to the colon [29].

3.4. Dextran:

A polymer made up of α-1,6 D-glucose and the side chain of α-1,3 D-glucose units is called dextran. These commercially accessible, highly water-soluble polymers come in a variety of molecular weights with a relatively narrow molecular weight distribution [30]. Sodium periodate was utilized to oxidize dextran, and the α-amino group of 5-amino salicylic acid (5-ASA) was linked with the aldehyde product.

A degree of swelling equilibrium and mechanical strength were observed in the produced dextran hydrogels. Dexttranase was used in an in vitro study, rat in vivo studies, and human fermentation model studies to investigate the hydrogels' breakdown. According to the study, it is possible to modify the hydrogels' chemical composition to manage their equilibrium degree of swelling, mechanical strength, and degradability. There is evidence that dextran hydrogels can be utilized as drug carriers for colon-specific drug administration because they broke down in vivo in the rat cecum but not in the stomach [31].

McLeod et al. synthesised conjugates of glucocorticoids and dextran by attaching dicarboxylic acid linkers (succinate and glutarate) to dextran, hence methylprednisolone and dexamethasone. In the contents of the upper GI tract, dextran conjugates withstood hydrolysis, but in the cecal and colonic contents, where the bacterial count was high, they were quickly broken down [32]. According to the study's findings, glucocorticoids may be delivered to the large intestine with selectivity using dextran conjugates to cure colitis.

3.5. Chitosan:

Chitosan is a useful linear polymer that is produced when chitin is alkaline deacetylated. Because it tends to disintegrate in the stomach's acidic pH but swells in the intestine pH, chitosan is employed for colon-targeted medication administration [33].

For the colonic administration of sodium diclofenac, Lorenzo-Lamosa et al. developed a method using chitosan microcores encased in acrylic microspheres. Using spray drying, the medication was effectively encapsulated within chitosan microcores, which were subsequently microencapsulated into Eudragit. By altering the chitosan molecular weight or the kind of chitosan salt, the release rate could be controlled.

Moreover, ideal pH-dependent release profiles were obtained by applying Eudragit to the chitosan microcores. A combination method of release is suggested, taking into account the evaporation of the Eudragit covering, the expansion of the chitosan microcores, and the breakdown of the sodium diclofenac and subsequent diffusion through the chitosan gel cores. A chitosan film was made and citrate was used to cross-link it. In neutral settings, the medication is released slowly, while it is released swiftly in acidic ones. The chitosan/citrate film was once more coated with alginate to regulate the drug's release. According to the study, drugs can be targeted to particular areas by using chitosan and citrate. Tripolyphosphate was used to create chitosan hydrogel beads, and various in vitro conditions were examined for protein release. Because of the beads' breakdown, it was shown that there was a high level of protein release in a colonic environment [34].

3.6. Cyclodextrin:

Cyclodextrins are slowly hydrolyzable in the upper gastrointestinal system, where colonic bacteria ferment them into tiny saccharides, which are then absorbed in the large intestine. Drug qualities including solubility, stability, and bioavailability are enhanced by the use of cyclodextrins. Through an ester or amide bond, the anti-inflammatory medication was conjugated with the main hydroxyl groups of alpha, beta, and gamma cyclodextrins. Rats were used to study the in vivo drug release behavior of these drug-cyclodextrin conjugates. These conjugates were found to be stable in the small intestine and stomach, according to the

data. According to the study, cyclodextrins can be employed to transport medications specifically to the colon [35].

3.7. Inulin:

When D-fructose is connected β 2-1 and has a glycosyl unit at the reducing end, it forms inulin, a naturally occurring glucofructan. The upper gastrointestinal system is unable to hydrolyse or break it down. The microorganisms in the colon can ferment inulin. Researchers looked into the swelling property of inulin hydrogels, which Vervoort et al. produced for the colonic delivery of medications [36]. Numerous factors were examined for their impact on the swelling property of hydrogels, including the degree of substitution, the feed concentration of methacrylate inulin, the effect of pH and ionic strength, and variable concentrations of the initiators of the polymerisation reaction.Vervoort and Rombaut used an inulinase preparation generated from Aspergillus Niger in a different investigation to examine the in vitro enzymatic digestibility of the inulin hydrogels. It was determined that the hydrogels may degrade as a result of the inulinase enzyme diffusing into them.

3.8. Amylose:

An ingredient of starch, amylose is a polysaccharide that is extracted from plants. Tablet coating applications can make use of the film that amylose forms through gelation. However, in settings that mimic the gastrointestinal tract, a coating composed only of amylose becomes porous and releases the medicine. The amylose swelling is controlled by the addition of water-insoluble polymers to the amylose layer, which helps to avoid this issue. This polymer mixture is appropriate for colon targeting when ethylcellulose is added to amylose [37]. It was determined that amylose: ethylcellulose coat (1:4) resists these circumstances for a whole 12-hour period during the in vitro disintegration of different coated pellets under simulated gastric and simulated intestinal conditions.

By utilising glucose as a model medication, pellets were created by the processes of extrusion and spheronization. This amylose-Ethocel® mixture (ratio 1:4 w/w)-coated glucose-containing pellets were evaluated in vitro38. The formulation's in vitro dissolution release profile demonstrated its resilience to gastric and small intestinal transit. Bacterial enzymatic attack susceptibility was shown by an in vitro fermentation investigation. By treating epichlorohydrin to create cross-linked amylose, Lenaerts et al. utilized the resulting matrix to deliver medicines with precise release timing.

3.9. Locust bean gum:

The natural polysaccharides found in locust bean gum have a molecular weight of 310000. Due to its origin in the endosperm of the "Carob" seed (Ceratonia Siliqua Linne, Fam: Leguminosae), locust bean gum is also referred to as "Carob gum." It is a molecule having a branching β-1,4-D-galactomannan unit and an uneven shape[38]. The content of locust beans is around 88% D-galactose-D mannoglycan, 4% pentane, 6% protein, 1% cellulose, and 1% ash.Research conducted by Raghavan and colleagues on polysaccharides demonstrated that chitosan and locust bean gum, when used as a covering material, can effectively shield the mesalazine-containing core tablet from damage while simulating the transit of food from the mouth to the colon [39]. The colonic bacterial enzymes that released the medication were able to penetrate the covering. The formulation with a 4:1 ratio of locust bean gum to chitosan was found to have a better-dissolving profile, higher bioavailability, and therefore potential as a drug carrier for the colon.

4. SYNTHETIC POLYMERS IN COLON TARGETING

The polymers utilized for colon targeting, however, must be able to dissolve at the neutral or slightly alkaline pH of the terminal ileum, ideally near the ileocecal junction, as well as tolerate the lower pH values of the stomach and the proximal portion of the small intestine. By distributing the medication throughout the large intestine, these procedures enhance the efficacy of colon-targeted delivery methods. Colon-targeted medication delivery employs a variety of synthetic polymers [40]. They also go by the name of pH-dependent polymers. Acrylic and cellulose derivatives are the most widely utilized pH-dependent polymers. pH-sensitive polymers are used to cover the medication core for colonic administration. The medication comes in granules, tablets, capsules, pellets, micro-particles, and nanoparticles. At low pH values, the pH-dependent colon-specific drug delivery is insoluble; however, as pH rises, it becomes more soluble.

4.1. Eudragit:

Eudragit products are polymers of methacrylic acid that include carboxyl groups and are pH-dependent. The pH at which dissolution occurs depends on the quantity of esterified carboxyl groups [41]. There exist three distinct forms of Eudragit: Eudragit L, Eudragit S, and Eudragit RS. Above pH 7, Eudragit S becomes soluble, and above pH 6, Eudragit L does as well. Colon-specific formulations have been prepared using Eudragit S coatings, which offer good protection against drug liberation in the upper gastrointestinal tract.

Using a gamma camera, the sites of disintegration of Eudragit S-coated single-unit tablets were located between the ileum and splenic flexure. Both single- and multiple-unit Eudragit S formulations often have low site specificity. Eudragit S coatings have been applied to the large intestine in single-unit formulations of the anti-inflammatory medication 5-aminosalicylic acid (5-ASA). Single-unit tablets containing eudragit L coatings have been utilized to target 5-ASA on the colon in individuals suffering from Crohn's disease or ulcerative colitis [42].

4.2. Shellac:

The natural resin lac, produced by the little parasitic bug Kerria Lacca, also referred to as the "lac insect," is refined to produce shellac. To date, there is no other commercial resin derived from animals. It is a solid that is resinous, brittle,

and hard. When it becomes heated and melts, it releases a distinct scent that makes it almost odorless in the cold.

It is not soluble in water. Typically, ethanolic solutions are used to apply shellac coatings for culinary applications. Although it is interesting for formulations that target the colon, shellac is not appropriate for a traditional enteric coating [43].

As the food passes through the stomach and small intestine and enters the colon, which has a higher pH, the shellac covering layer does not break. For the topical treatment of colonic disorders, this permits the passage of medications into the colon. Oral administration of peptide medications, like insulin, is made possible by the colon's reduced peptidase activity compared to the upper GI tract.

Approaches Used for Site-Specific Drug Delivery to Colon (CDDS) [44, 43, 44, 45, 46]

Several approaches are used for site-specific drug delivery.

1Primary Approaches for CDDS

a. pH-Sensitive Polymer Coated Drug Delivery to the Colon

b. Delayed (Time Controlled Release System) Release Drug Delivery to Colon

c. Microbially Triggered Drug Delivery to Colon

i) Prodrug Approach for Drug Delivery to Colon

(ii) Azo-Polymeric Prodrugs

iii) Polysaccharide Based Delivery Systems

2. Newly Developed Approaches for CDDS

a. Pressure Controlled Drug-Delivery Systems

b. Novel Colon Targeted Delivery System (CODESTM)

c. Osmotic Controlled Drug Delivery (ORDS-CT)

5. EVALUATION TESTS

a) In vitro dissolution test

The dissolution process of controlled-release formulations used for colon-specific drug administration is typically complicated, and the USP's dissolution procedures are unable to accurately replicate in vivo factors like pH, bacterial habitat, and mixing forces. The traditional basket approach can be utilized for CDDS dissolution tests. To characterize the behavior of formulations at different pH values, parallel dissolution studies in various buffers can be conducted. A colon-specific formulation has been subjected to dissolution studies in a variety of media that mimic different pH levels and times that are likely to be experienced at different points in the gastrointestinal system [47]. For example, pH 1.2 was used to represent gastric fluid, pH 6.8 to represent the jejunal area of the small intestine, and pH 7.2 to represent the ileum section. A gradient dissolution study in three buffers has been conducted to examine enteric-coated capsules for CDDS. The pH levels of the capsules were measured for two hours at 1.2, one hour at 6.8, and then at 7.4.

b*) In vitro enzymatic tests*

Streptococcusfaccium and B. ovatus are two types of bacteria that are suited for the fermenter in which the carrier drug system is incubated. The amount of medication released at various periods is calculated [48]. Drug release is studied in a buffer media containing enzymes (ezypectinase, dextranase), or the cecal contents of rabbits, rats, or guinea pigs. The amount of medication released in a specific amount of time depends on the rate at which the polymer carrier breaks down.

c) In vivo evaluation

The anatomical, physiological, and microbiology of the human gastrointestinal tract are similar in some species, including dogs, guinea pigs, rats, and pigs, which is why these animals are used to assess drug delivery to the colon. Colonic disease-related models should be taken into account while selecting a model for CDDS testing. Models of experimental IBD frequently involve guinea pigs. In the gastrointestinal tracts of rats and rabbits, the distribution of azoreductase and glucuronidase activity is similar to that observed in humans [49].

A unique paradigm has been presented for the quick evaluation of CDDS. The human foetal bowel is implanted in this model into a subcutaneous tullel on the back of thymic nude mice. The tullel grows and becomes capable of producing a host-derived mucosal immune system after vascularization in four weeks.

Drug Delivery Index (DDI) and Clinical Evaluation of Colon-Specific Drug Delivery Systems

DDI is a calculated pharmacokinetic parameter, following single or multiple doses of oral colonic prodrugs. DDI is the relative ratio of RCE (Relative colonic tissue exposure to the drug) to RSC (Relative amount of drug in blood i.e. that is relative systemic exposal to the drug). High drug DDI value indicates better colon drug delivery [50]. Absorption of drugs from the colon is monitored by colonoscopy and intubation. Currently, gamma scintigraphy and high-frequency capsules are the most preferred techniques employed to evaluate colon drug delivery systems.

Complementary Tools for Designing Effective Colonic Drug Delivery Systems

In vitro and in vivo testing are among the several investigations needed to optimize drug formulations using the conventional method; these are frequently expensive, time-consuming, and laborious procedures. Furthermore, a lot of drug delivery systems show promise in vitro but frequently fall short in vivo, primarily because trial-and-error experiments lack mechanistic knowledge [51]. In order to speed up the rational formulation design process, computational techniques like as data mining, molecular modeling and simulation, and artificial intelligence are helpful. The identification of essential parameters for formulation optimization and the selection of good candidates for additional experimental confirmation, it can save a significant amount of time and effort during testing.

Metwally and Hathout, for instance, have demonstrated that the combined application of multiple chemo/bioinformatics and statistical tools could reliably forecast the loading efficiency of pharmaceuticals in a carrier and clarify the

impact of specific drug molecular descriptors on their docked binding energies on carriers [52]. As a result, precise loading capacities and entrapment efficiencies in medication delivery systems might be estimated without the need for laborious lab testing.

Computer modeling techniques generally facilitate the identification of critical variables for formulation optimization and also furnish comprehensive details on molecular interactions between the drug and the carrier, entrapment efficiency, drug distribution/localization in delivery systems, stability, drug release behavior, and so forth [53]. As a result, these computational techniques can support more logical formulation design and optimization while also serving as a supplement to tests. A new era of revolutionary drug delivery systems, including electronic and radiofrequency drug delivery devices, has also been brought about by the combination of such computational tools with other technologies for targeted drug delivery. Below is a discussion of a few chosen instances of how computational and device-based methods are used to support the design of colon-specific formulations.

Computer-Assisted Formulation Design

Statistical techniques and chemo/bioinformatics tools help support the thoughtful design of experiments and helping to formulate them. When examining the effectiveness of drug delivery systems and the impact of several environmental factors including pH, temperature, salt content, external stimuli, and interactions with other biomolecules in the body, the computational approach can also be used. For the colon-specific administration of metronidazole and ciprofloxacin, Patra et al. synthesized a luminous gel based on biopolymeric glycogen [54]. They conducted an ab initio molecular dynamics analysis in addition to the experimental evaluation to look into the potential molecular interactions between medicines and hydrogel. To look into the pH-responsive swelling and drug release from the created hydrogel, they also conducted quantum mechanical and molecular mechanics computations.Along with confirming the pH-dependent drug release patterns in line with experimental observations, the results demonstrated the physical contact between drug molecules and hydrogel during its swelling. Targeting phospholipase A2 (PLA2), the PL-prodrug activating enzyme overexpressed in the inflammatory colonic tissues, is a novel phospholipid (PL)-based prodrug strategy for colon-specific drug delivery, as proposed by Markovic et al. They started by using the model chemical Fmoc (fluorenylmethyloxycarbonyl) and creating PL-Fmoc conjugates with various linker lengths between the PL and the drug moiety [55]. The activation of the PL-Fmoc conjugates mediated by PLA2 was then experimentally assessed by them.

To ascertain the ideal linker length for the therapeutically important medication in ulcerative colitis, such as methotrexate, scientists also carried out a unique molecular dynamics simulation of the conjugate's transition state in the PLA2 enzyme complex [56]. Based on the simulation results, the rate of PLA2-mediated activation was determined by the free energy of the PL-prodrug binding to the transition state geometry of the enzyme. The results also showed that shorter linkers activated less than longer linkers and that a linker length of 6 should be optimal for the highest level of PLA2-mediated activation. According to this study, the amount of chemical synthesis required to develop efficient prodrugs for colon-specific delivery can be decreased, and the chemical structure of the molecular linker between the drug moiety and PL can be optimized [57].

It is now possible to replicate the microbiota in the colon and simulate the physiological processes in the GI tract using SIMGI (SIMulator Gastro-Intestinal), an automated in silico model. Food impacts on gut microbiota modulation and its metabolic activities can be investigated using this computer model. With its short history and several shortcomings that are still being worked out, this model could prove useful in the rapid and cost-effective construction of a more effective colon-targeted delivery system [58]. When combined, the computational method can provide a useful toolkit for building the best colon-targeted drug delivery systems and forecasting the efficacy of the created formulations in vivo.

Electronic Device-Assisted Formulation Design

Pharmacological absorption across the GI tract must be characterized in vivo to successfully create colon-specific drug delivery devices. Determining if the tested formulation is valid for modified drug release hence calls for a fast, easy, and reliable method of evaluating the drug release qualities within the GI tract. That is to say, using electronics introduces a fresh method for integrating data from several sources. Controlled drug release, patient monitoring, and real-time wireless communication are all combined in IntelliCap®, the world's first intelligent electronic drug administration and monitoring device [59].

This electronic capsule allows carers to track the capsule's advancement in the GI tract thanks to its real-time wireless data recording capability. In addition, the ability to precisely target drug delivery and evaluate pH and transit simultaneously provides in vivo data for formulation design. As a result, IntelliCap® technology offers a quick and practical solution for the GI tract's targeted controlled drug release. Maurer et al. verified the ileo-colonic drug release of ColoPulse tablets in people using the Intellicap® system, indicating that the ColoPulse system is a viable colonic drug delivery technology.

While electronic capsules have numerous advantages, there are drawbacks as well, such as high cost, challenges in manufacturing, problems with biocompatibility, and a possible danger of device failure [60]. To increase the widespread compatibility of electronic delivery systems, ongoing efforts should be made to address these drawbacks. When it comes to regulated drug release at the intended target areas, electronic drug delivery systems are a potentially innovative solution.

6. CONCLUSION

One of the most important strategies for improving the efficacy of local treatment for colonic disorders is colon-targeted medication administration. In terms of patient compliance, safety, and effectiveness, it might provide several advantages over traditional dosage forms. Because biodegradable polymers are inexpensive, non-toxic, safe, and chemically compatible with the other excipients in the formulation, interest in them is growing daily. The several kinds of biodegradable polysaccharides that have already been employed in the first methods of colon-specific medication delivery have been covered in this article. Excellent microorganisms found in the colon are abundant and can be used to target the release of drugs into the colon. The medication is released in the colon by the formulation that contains the microbially degradable polymers after it passes through the upper gastrointestinal tract intact.

7. REFERENCES

1. Krishnaiah, Y S et al. Gamma scintigraphic studies on guar gum matrix tablets for colonic drug delivery in healthy human volunteers." Journal of controlled release: Official Journal of the Controlled Release Society vol. 55,2-3 (1998): 245-52.
2. Keum, N.; Giovannucci, E. Global burden of colorectal cancer: Emerging trends, risk factors and prevention strategies. Nat. Rev. Gastroenterol. Hepatol. 2019, 16, 713–732.
3. Ng, S.C.; Bernstein, C.N.; Vatn, M.H.; Lakatos, P.L.; Loftus, E.V.; Tysk, C.; O'morain, C.; Moum, B.; Colombel, J.F.; Epidemiology and Natural History Task Force of the International Organization of inflammatory Bowel Disease (IOIBD). Geographical variability and environmental risk factors in inflammatory bowel disease. Gut 2013, 62, 630–649.
4. Patole, V.C.; Pandit, A.P. Mesalamine-loaded alginate microspheres filled in enteric coated HPMC capsules for local treatment of ulcerative colitis: In Vitro and in vivo characterization. J. Pharm. Investig. 2018, 48, 257–267.
5. Rahier, J.F.; Magro, F.; Abreu, C.; Armuzzi, A.; Ben-Horin, S.; Chowers, Y.; Cottone, M.; de Ridder, L.; Doherty, G.; Ehehalt, R.; et al. Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. J. Crohns. Colitis. 2014, 8, 443–468.
6. Wang, X.; Yu, D.G.; Li, X.Y.; Bligh, S.W.; Williams, G.R. Electrospun medicated shellac nanofibers for colon-targeted drug delivery. Int. J. Pharm. 2015, 490, 384–390
7. Vats, A.; Pathak, K. Exploiting microspheres as a therapeutic proficient doer for colon delivery: A review. Expert Opin. Drug Deliv. 2013, 10, 545–557.
8. Hua, S.; Marks, E.; Schneider, J.J.; Keely, S. Advances in oral nano-delivery systems for colon targeted drug delivery in inflammatory bowel disease: Selective targeting to diseased versus healthy tissue. Nanomedicine 2015, 11, 1117–1132
9. Guo, Y.; Zong, S.; Pu, Y.; Xu, B.; Zhang, T.; Wang, B. Advances in pharmaceutical strategies enhancing the efficiencies of oral colon-targeted delivery systems in inflammatory bowel disease. Molecules 2018, 23, 1622.
10. Newton, A.; Prabakaran, L.; Jayaveera, K. Pectin-HPMC E15LV vs. pH sensitive polymer coating films for delayed drug delivery to colon: A comparison of two dissolution models to assess colonic targeting performance in-vitro. Int. J. Appl. Res. Nat. Prod. 2012, 5, 1–16.
11. Nidhi; Rashid, M.; Kaur, V.; Hallan, S.S.; Sharma, S.; Mishra, N. Microparticles as controlled drug delivery carrier for the treatment of ulcerative colitis: A brief review. Saudi Pharm. J. 2016, 24, 458–472.
12. Naik, J.B.; Waghulde, M.R. Development of vildagliptin loaded Eudragit® microspheres by screening design: In vitro evaluation. J. Pharm. Investig. 2018, 48, 627–637.
13. Hua, S. Orally administered liposomal formulations for colon targeted drug delivery. Front. Pharmacol. 2014, 5, 138.
14. Maroni, A.; Zema, L.; Loreti, G.; Palugan, L.; Gazzaniga, A. Film coatings for oral pulsatile release. Int. J. Pharm. 2013, 457, 362–371.
15. Maroni, A.; Moutaharrik, S.; Zema, L.; Gazzaniga, A. Enteric coatings for colonic drug delivery: State of the art. Expert Opin. Drug Deliv. 2017, 14, 1027–1029.
16. Bak, A.; Ashford, M.; Brayden, D.J. Local delivery of macromolecules to treat diseases associated with the colon. Adv. Drug Deliv. Rev. 2018, 136–137, 2–27.
17. Ibekwe, V.C.; Liu, F.; Fadda, H.M.; Khela, M.K.; Evans, D.F.; Parsons, G.E.; Basit, A.W. An investigation into the in vivo performance variability of pH responsive polymers for ileo-colonic drug delivery using gamma scintigraphy in humans. J. Pharm. Sci. 2006, 95, 2760–2766.
18. Ibekwe, V.C.; Fadda, H.M.; McConnell, E.L.; Khela, M.K.; Evans, D.F.; Basit, A.W. Interplay between intestinal pH, transit time and feed status on the in vivo performance of pH responsive ileo-colonic release systems. Pharm. Res. 2008, 25, 1828–1835.
19. Ibekwe, V.C.; Khela, M.K.; Evans, D.F.; Basit, A.W. A new concept in colonic drug targeting: A combined pH-responsive and bacterially-triggered drug delivery technology. Aliment. Pharmacol. Ther. 2008, 28, 911–916.
20. Liu, F.; Moreno, P.; Basit, A.W. A novel double-coating approach for improved pH-triggered delivery to the ileo-colonic region of the gastrointestinal tract. Eur. J. Pharm. Biopharm. 2010, 74, 311–315.
21. Varum, F.J.; Hatton, G.B.; Freire, A.C.; Basit, A.W. A novel coating concept for ileo-colonic drug targeting:

Proof of concept in humans using scintigraphy. Eur. J. Pharm. Biopharm. 2013, 84, 573–577.
22. Hashem, F.M.; Shaker, D.S.; Nasr, M.; Ragaey, R. In Vitro and in vivo evaluation of combined time and pH-dependent oral colonic targeted prednisolone microspheres. Br. J. Pharm. Res. 2013, 3, 420–434.
23. Patel, M.M. Cutting-edge technologies in colon-targeted drug delivery systems. Expert Opin. Drug Deliv. 2011, 8, 1247–1258.
24. Zeeshan, M.; Ali, H.; Khan, S.; Khan, S.A.; Weigmann, B. Advances in orally-delivered pH-sensitive nanocarrier systems; an optimistic approach for the treatment of inflammatory bowel disease. Int. J. Pharm. 2019, 558, 201–214.
25. Ma, X.; Williams, R.O. Polymeric nanomedicines for poorly soluble drugs in oral delivery systems: An update. J. Pharm. Investig. 2018, 48, 61–75.
26. Mutalik, S.; Suthar, N.A.; Managuli, R.S.; Shetty, P.K.; Avadhani, K.; Kalthur, G.; Kulkarni, R.V.; Thomas, R. Development and performance evaluation of novel nanoparticles of a grafted copolymer loaded with curcumin. Int. J. Biol. Macromol. 2016, 86, 709–720.
27. Sahu, K.K.; Pandey, R.S. Development and characterization of HBsAg-loaded Eudragit nanoparticles for effective colonic immunization. Pharm. Dev. Technol. 2019, 24, 166–175.
28. Naeem, M.; Choi, M.; Cao, J.; Lee, Y.; Ikram, M.; Yoon, S.; Lee, J.; Moon, H.R.; Kim, M.S.; Jung, Y.; et al. Colon-targeted delivery of budesonide using dual pH- and time-dependent polymeric nanoparticles for colitis therapy. Drug Des. Devel. Ther. 2015, 9, 3789–3799.
29. Seo, J.; Kim, M.J.; Jeon, S.O.; Oh, D.H.; Yoon, K.H.; Choi, Y.W.; Bashyal, S.; Lee, S. Enhanced topical delivery of fish scale collagen employing negatively surface-modified nanoliposome. J. Pharm. Investig. 2018, 48, 243–250.
30. Han, S.M.; Na, Y.G.; Lee, H.S.; Son, G.H.; Jeon, S.H.; Bang, K.H.; Kim, S.J.; Lee, H.J.; Cho, C.W. Improvement of cellular uptake of hydrophilic molecule, calcein, formulated by liposome. J. Pharm. Investig. 2018, 48, 595–601.
31. Yoon, S.W.; Shin, D.H.; Kim, J.S. Liposomal itraconazole formulation for the treatment of glioblastoma using inclusion complex with HP-β-CD. J. Pharm. Investig. 2019, 49, 477–483.
32. Lee, M.K. Clinical usefulness of liposomal formulations in cancer therapy: Lessons from the experiences of doxorubicin. J. Pharm. Investig. 2019, 49, 203–214.
33. Zhao, M.; Lee, S.H.; Song, J.G.; Kim, H.Y.; Han, H.K. Enhanced oral absorption of sorafenib via the layer-by-layer deposition of a pH-sensitive polymer and glycol chitosan on the liposome. Int. J. Pharm. 2018, 544, 14–20.
34. Gupta, B.; Yong, C.S.; Kim, J.O. Solid matrix-based lipid nanoplatforms as carriers for combinational therapeutics in cancer. J. Pharm. Investig. 2017, 47, 461–473.
35. Pokharkar, V.; Patil-Gadhe, A.; Kaur, G. Physicochemical and pharmacokinetic evaluation of rosuvastatin loaded nanostructured lipid carriers: Influence of long-and medium-chain fatty acid mixture. J. Pharm. Investig. 2018, 48, 465–476.
36. Singh, D.; Tiwary, A.K.; Bedi, N. Canagliflozin loaded SMEDDS: Formulation optimization for improved solubility, permeability and pharmacokinetic performance. J. Pharm. Investig. 2019, 49, 67–85.
37. Nekkanti, V.; Rueda, J.; Wang, Z.; Betageri, G.V. Comparative evaluation of proliposomes and self micro-emulsifying drug delivery system for improved oral bioavailability of nisoldipine. Int. J. Pharm. 2016, 505, 79–88.
38. Rahman, M.A.; Mujahid, M.; Hussain, A.; Iqbal, Z. Development and pharmacokinetic evaluation of spray-dried self-nanoemulsifying drug delivery system of sertraline. J. Pharm. Investig. 2017, 47, 325–333.
39. Madhav, K.V.; Kishan, V. Self microemulsifying particles of loratadine for improved oral bioavailability: Preparation, characterization and in vivo evaluation. J. Pharm. Investig. 2018, 48, 497–508.
40. Ahsan, M.N.; Verma, P.R.P. Enhancement of in vitro dissolution and pharmacodynamic potential of olanzapine using solid SNEDDS. J. Pharm. Investig. 2018, 48, 269–278.
41. Zhang, L.; Zhu, W.; Yang, C.; Guo, H.; Yu, A.; Ji, J.; Gao, Y.; Sun, M.; Zhai, G. A novel folate-modified self-microemulsifying drug delivery system of curcumin for colon targeting. Int. J. Nanomed. 2012, 7, 151–162.
42. Yoshida, T.; Lai, T.C.; Kwon, G.S.; Sako, K. pH- and ion-sensitive polymers for drug delivery. Expert Opin. Drug Deliv. 2013, 10, 1497–1513.
43. Lin, C.; Ng, H.L.; Pan, W.; Chen, H.; Zhang, G.; Bian, Z.; Lu, A.; Yang, Z. Exploring different strategies for efficient delivery of colorectal cancer therapy. Int. J. Mol. Sci. 2015, 16, 26936–26952.
44. Park, H.J.; Jung, H.J.; Ho, M.J.; Lee, D.R.; Cho, H.R.; Choi, Y.S.; Jun, J.; Son, M.; Kang, M.J. Colon-targeted delivery of solubilized bisacodyl by doubly enteric-coated multiple-unit tablet. Eur. J. Pharm. 2017, 102, 172–179.
45. Foppoli, A.; Maroni, A.; Moutaharrik, S.; Melocchi, A.; Zema, L.; Palugan, L.; Cerea, M.; Gazzaniga, A. In Vitro and human pharmacoscintigraphic evaluation of an oral 5-ASA delivery system for colonic release. Int. J. Pharm. 2019, 572, 118723.
46. Nguyen, M.N.U.; Tran, P.H.L.; Tran, T.T.D. A single-layer film coating for colon-targeted oral delivery. Int. J. Pharm. 2019, 559, 402–409.

47. Maurer, J.M.; Schellekens, R.C.; van Rieke, H.M.; Stellaard, F.; Wutzke, K.D.; Buurman, D.J.; Dijkstra, G.; Woerdenbag, H.J.; Frijlink, H.W.; Kosterink, J.G. ColoPulse tablets perform comparably in healthy volunteers and Crohn's patients and show no influence of food and time of food intake on bioavailability. J. Control. Release 2013, 172, 618–624.
48. Maurer, J.M.; Schellekens, R.C.; van Rieke, H.M.; Wanke, C.; Iordanov, V.; Stellaard, F.; Wutzke, K.D.; Dijkstra, G.; van der Zee, M.; Woerdenbag, H.J.; et al. Gastrointestinal pH and transit time profiling in healthy volunteers using the IntelliCap system confirms ileo-colonic release of ColoPulse tablets. PLoS ONE 2015, 10, e0129076.
49. Gareb, B.; Dijkstra, G.; Kosterink, J.G.W.; Frijlink, H.W. Development of novel zero-order release budesonide tablets for the treatment of ileo-colonic inflammatory bowel disease and comparison with formulations currently used in clinical practice. Int. J. Pharm. 2019, 554, 366–375.
50. Gareb, B.; Posthumus, S.; Beugeling, M.; Koopmans, P.; Touw, D.J.; Dijkstra, G.; Kosterink, J.G.W.; Frijlink, H.W. Towards the oral treatment of ileo-colonic inflammatory bowel disease with Infliximab tablets: Development and validation of the production process. Pharmaceutics 2019, 11, 428.
51. Barbosa, J.A.C.; Al-Kauraishi, M.M.; Smith, A.M.; Conway, B.R.; Merchant, H.A. Achieving gastroresistance without coating: Formulation of capsule shells from enteric polymers. Eur. J. Pharm. Biopharm. 2019, 144, 174–179.
52. Kotla, N.G.; Rana, S.; Sivaraman, G.; Sunnapu, O.; Vemula, P.K.; Pandit, A.; Rochev, Y. Bioresponsive drug delivery systems in intestinal inflammation: State-of-the-art and future perspectives. Adv. Drug Deliv. Rev. 2019, 146, 248–266.
53. Morales-Burgos, A.M.; Carvajal-Millan, E.; Rascón-Chu, A.; Martínez-López, A.L.; Lizardi-Mendoza, J.; López-Franco, Y.L.; Brown-Bojorquez, F. Tailoring reversible insulin aggregates loaded in electrosprayedarabinoxylan microspheres intended for colon-targeted delivery. J. Appl. Polym. Sci. 2019, 136, 47960.
54. Zhu, J.; Zhong, L.; Chen, W.; Song, Y.; Qian, Z.; Cao, X.; Huang, Q.; Zhang, B.; Chen, H.; Chen, W. Preparation and characterization of pectin/chitosan beads containing porous starch embedded with doxorubicin hydrochloride: A novel and simple colon targeted drug delivery system. Food Hydrocoll. 2019, 95, 562–570.
55. Barclay, T.G.; Day, C.M.; Petrovsky, N.; Garg, S. Review of polysaccharide particle-based functional drug delivery. Carbohydr. Polym. 2019, 221, 94–112.
56. Jain, V.; Shukla, N.; Mahajan, S. Polysaccharides in colon specific drug delivery. J. Transl. Sci. 2015, 1, 3–11.
57. Wen, Y.; Oh, J.K. Recent strategies to develop polysaccharide-based nanomaterials for biomedical applications. Macromol. Rapid. Commun. 2014, 35, 1819–1832
58. Shaikh, R.; Singh, T.R.R.; Garland, M.J.; Woolfson, A.D.; Donnelly, R.F. Mucoadhesive drug delivery systems. J. Pharm. Bioallied. Sci. 2011, 3, 89–100.
59. Song, Q.; Jia, J.; Niu, X.; Zheng, C.; Zhao, H.; Sun, L.; Zhang, H.; Wang, L.; Zhang, Z.; Zhang, Y. An oral drug delivery system with programmed drug release and imaging properties for orthotopic colon cancer therapy. Nanoscale 2019, 11, 15958–15970.
60. Sookkasem, A.; Chatpun, S.; Yuenyongsawad, S.; Wiwattanapatapee, R. Alginate beads for colon specific delivery of self-emulsifying curcumin. J. Drug Deliv. Sci. Technol. 2015, 29, 159–166.

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