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Polymeric microspheres redefining the landscape of colon-targeted delivery: A contemporary update

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ABSTRACT

During recent times, the delivery of the medications to the colon has seen more interest by the researchers, as it proved to be providing both options for treating local colon-related conditions and a route for systemic delivery of the various other types of medications. For these to happen, the medication has to provide protection from severe conditions in the stomach and small bowel, which either degrade the medication or may cause its premature release and uptake in the upper part of the digestive track. This review describes the various roles of microspheres as a colon-targeted drug delivery device (CTDDD). Through these review, we try to provide thorough information about the effects of the physiology of the colon. Also, we made an effort to highlight different mechanisms of colon targeting. Along with these, we have pointed out some of the important evaluation factors for carrying out a thorough investigation about the physicochemical and pharmaceutical properties of microspheres for targeting the colon. Also, we exchange views about the applications of microspheres as CTDDD in different diseases and disorders of the colon. Plus, we discuss the different challenges that occur during the formulation and targeting of these microspheres. At last, we share our thoughts on the possibilities in the near future in these domains, which will help in changing the scenario of how we can treat colon-related problems.

1. Introduction

Colonic diseases are seen to be widely spreading, which obviously demands the development of adroit, targeted treatments to improve the safety and effectiveness of medication therapy [1,2]. Colorectal carcinoma (CRC) is reported as one of the three most rampant causes of cancer-related deaths on the planet, which brings about over 850,000 people to lose their lives annually [3]. Additionally, chronic inflammatory bowel diseases (CIBD) are seen to be more frequent in regions like Asia [4]. Therefore, colonic disease prevention is crucial for global public health. Colon-targeted drug delivery devices (CTDDD) are being sought after to address these concerns. These devices aim to inhibit release and uptake from the upper digestive tract while releasing medications in response to the colonic environment [5]. Non-targeted medicines may cause adverse reactions and lower efficacy due to systemic absorption before reaching the colon. Apart from that, colon-targeted drug delivery devices provide a technique to increase the bioavailability of medications, specifically large biomolecules like proteins and peptides, which are susceptible to breakdown in the acidic and enzymatic conditions of the upper gastrointestinal tract (GIT) [6]. Given its lesser variability and frequency of digesting enzymes than the small intestine, it has been presumed that the colonic part of the GIT provides an ideal place to absorb protein or polypeptide medicines. CTDDD prevents peptide medication hydrolysis along with breakdown by enzymes throughout the duodenum as well as the jejunum and allows release when they reach the ileum or colon, which will eventually lead to higher systemic bioavailability. Additionally, the colon can be susceptible to enhancers of absorption due to the extended residency period (a maximum of five days) [7]. Rectal delivery offers a quicker way to deliver medications to the colon than oral administration, yet it might be challenging to make it to the proximal colon and discomforting for those taking medications. Drug preparations for intra-rectal usage are available in a variety of types, including solutions, foam, and suppositories, to treat the large intestine both systemically and topically. Drug concentration is influenced by formulation variables, retrograde spreading, in addition to retention time. Topical application is principally responsible for the effectiveness of medications absorbed into the colon. Notably, enema solutions have a greater spreading capacity than foam and suppositories, which are primarily held in the rectum and sigmoid colon [8].

For the successful creation of CTDDD, both the changed

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Abbreviations

CRC	Colorectal Carcinoma
CIBD	Chronic inflammatory bowel disease
CTDDD	Colon targeted drug delivery device
GIT	Gastrointestinal tract
UC	Ulcerative colitis
SBS	Spastic Bowel Syndrome
HPMC	Hydroxypropyl methylcellulose
HPC	Hydroxypropyl cellulose
CTDD	Colon targeted drug delivery

microenvironment close to disease sites and the special physiological properties of the colon must be taken into account. Throughout the stomach and towards the intestine, the GIT undergoes dynamic fluctuations in pH, enzymatic levels, fluid matter, and motility. Additionally, the colon microenvironment near illness sites is very different from that in healthy areas. All individuals with colonic problems have injuries to the mucosa, elevated reactive oxygen species and inflammatory cytokine levels, and an unbalanced level of vital antioxidants in their bodies. Numerous formulation techniques have been investigated to enhance colonic medication delivery in light of these pathophysiological alterations. These consist of systems that are pH-sensitive, enzyme-activated, and magnetically-driven [9–11]. Receptor-mediated systems have also been researched with the aim of interacting selectively with particular receptors highly expressed around the site(s) of the disease. Microspheres can be made into variable sizes (between the scales of micrometers and millimeters). With their minute size, which leads to a greater surface area, microspheres have an upper hand in medication delivery as they bring forth the release of the medication in a controlled release profile by entrapping the medication as a perfect formulation for site-specific targeting in the large intestine [12–16]. Microspheres, designed as CTDDD, are formulated using pH-dependent and/or enzyme-responsive polymers, which prevent the medication from being released inside the stomach or even small intestinal regions and release the medication in colonic conditions by undergoing either pH-succeptible degradation or enzymatic degradation. Along with that, microspheres are coated with various pH-dependent polymeric coatings to retard medication release in the upper part of the GIT [17]. By means of this review, we want to provide an overview of the microsphere formulation considerations and methods, along with the influence of the colon's physiology over it [18]. These microspheres can be formulated to target the large intestine, utilizing the diverse types of approaches to targeting the large intestine [19,20]. Additionally, we discuss the challenges, recent trends, and possible developments in this domain in the near future [21].

2. Colon physiology and drug absorption

The large intestine, a crucial part of the digestive tract, has a substantial impact on medication absorption due to its unique anatomical and physiological characteristics, making understanding colon physiology essential for developing CTDDD, as perceived in Fig. 1.

2.1. Colon anatomy

Understanding the physiological features of the colon is crucial for customizing medications for it. The colon, which makes up 1.6 m of the typical GIT (6 m), assists in water, mineral, and vitamin uptake, as well as polysaccharide digestion and intestinal immunoregulation. Its distinct features are essential for a thorough comprehension of the digestive system [22].

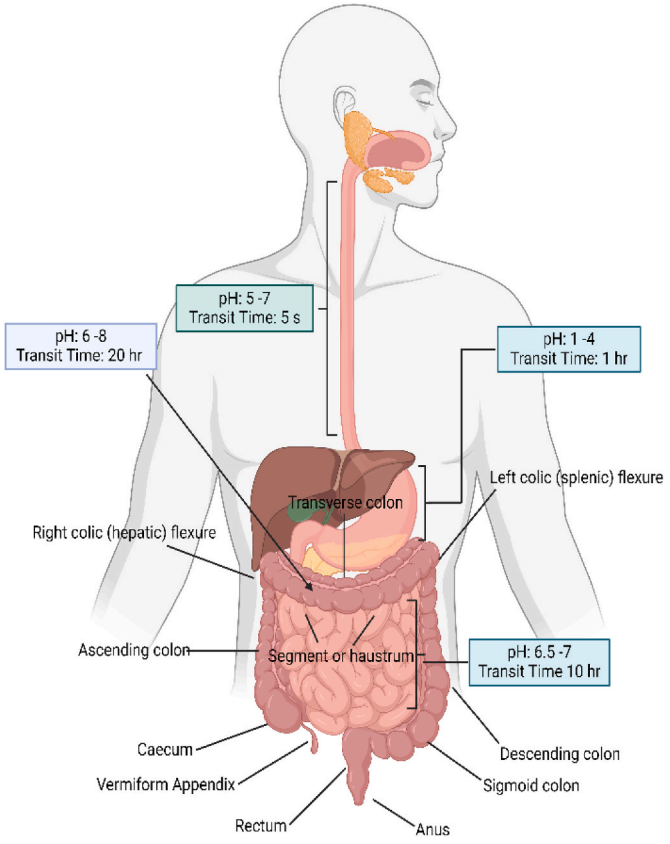

Fig. 1. Schematic representation of colon physiology including anatomy, pH variations and transit time.

2.2. Transit time and motility

Motility or movements inside the colon are important for the uptake of medication since they improve the period of contact between it and the surface mucosa, and understanding its role is critical for improving the delivery of medications and performance, particularly for medications that target colon conditions [23]. The transit time of medications through the colon is influenced by the intake of food, particularly fatty foods, the peristalsis phase, and dosage form. Medication emptying in the stomach is influenced by age, gender, and health issues such as diabetes, which can also affect how long it takes for the medication to reach the colon [24–28].

2.3. Colonic secretions and enzymes

When it comes to how our bodies absorb medications, the gut plays an important role. The colon has unique cells that produce a sticky substance known as mucus. This slimy substance forms a protective layer on the surface of the colon. This protective layer prevents medications from immediately contacting the inside of the colon, which may alter how the medicine enters our systems. In addition, there are numerous species of beneficial microorganisms in the colon. These bacteria can change some medications and make new substances that might affect how medicines get absorbed in our bodies [29,30].

2.4. pH variations in the colon

The pH gradient throughout the GIT has a significant impact on drug solubility and dissolution. While the stomach has an acidic pH, the small intestine has a gradually rising pH gradient due to bicarbonate-rich pancreatic secretions. Colonic pH: on the contrary, the proximal colon's is normally acidic, gradually shifting towards a near-neutral pH

near the distal colon. This pH gradient makes medication administration difficult, especially for pH-sensitive drugs [31].

2.5. Water absorption and drug concentration

Absorption of water, electrolytes, and vitamins via the luminal contents is one of the colon's main roles. A concentration effect is produced by this mechanism, which may raise the concentration of the medication in the colon. For fecal matter to remain at the proper consistency, effective water absorption through the colon is essential [32].

2.6. Drug absorption in the colon

Even though its surface area for absorption is comparatively smaller than that of the small intestine, the large intestine has significant importance for the uptake of drugs, especially for compounds with certain physicochemical characteristics. Absorption is more likely for drugs with low molecular weight, lipophilicity, and relative stability in the intestinal environment [33]. Although less effective compared to the small intestine, passive diffusion over the colonic epithelium facilitates absorption and can nonetheless result in considerable drug uptake [34,35].

2.7. Influence of disease states on colonic drug absorption

A variety of pathological conditions have the potential to profoundly impact colonic physiology and, in turn, medication absorption. CIBD's, including Crohn's disease, along with ulcerative colitis (UC), are typified by persistent inflammation and structural changes in the colonic mucosa. Spastic bowel syndrome (SBS), a syndrome requiring specialized medication administration, can significantly impact the well-being of patients due to changes in colonic motility [36,37].

2.8. Influence of gut microbiota on drug absorption

The gut microbiota, a complex ecosystem of bacteria in the GIT, significantly influences medication metabolism and absorption. This can affect the pharmacokinetics and therapeutic effectiveness of certain drugs, and certain bacterial species can alter the permeability and solubility of medications in the colon [30,38].

2.9. Considerations for colon-targeted drug delivery

Understanding the complex interaction between colon physiology and drug absorption is crucial to the creation of an effective colon-target medication delivery device. Customized formulations can enhance drug delivery to this region based on certain qualities of the colon, including prolonged transit times as well as improved water absorption.

3. Colon targeting approaches

In order to guarantee the release of drugs in exact regions of the colon, precise targeting mechanisms are required. To accomplish this aim, many ways have been proposed, each leveraging the particular physiological properties of the colon. These approaches include pH-dependent, time-dependent, and microbe-dependent methods, as shown in Fig. 2, as well as the application of certain polymers and coatings.

3.1. pH-dependent targeting

Because the pH value in the last segment of the ileum along with the colon (except the ascending colon) has a higher value compared to any of the other GIT parts, a drug formulation that breaks down, preferably with elevated pH values, possesses a strong likelihood of acquiring site-specific delivery in this part [39]. Despite the constraints of fluctuations within the luminal pH caused by disease states, these pH-dependent systems continue to be widely researched for colon targeting. Enteric-coated microspheres are one of the easiest techniques for constructing pH-controlled multiparticular systems for the colonic delivery of drugs. Traditionally, enteric coating has been utilized to inhibit the release of drugs over the upper GIT. Enteric coating polymers have been reported to be employed for binding alongside their use for coating granular components [40]. The effects of introducing organoacidic substances to microspheric frameworks on medication release have also been investigated [41]. The most extensively utilized pH-sensitive coat polymeric materials for oral administration include Eudragit L100, a methacrylic acid-containing polymer, along with Eudragit S100, and they undergo dissolution between pH ranges of 6.0 and 7.0. Changes over the proportions of the two aforementioned polymers when combined enable the control of drug release inside the pH value spectrum from 6.0 to 7.0. It has been observed that transferring medication colon-specifically using Eudragit S by itself doesn't seem suitable [42].

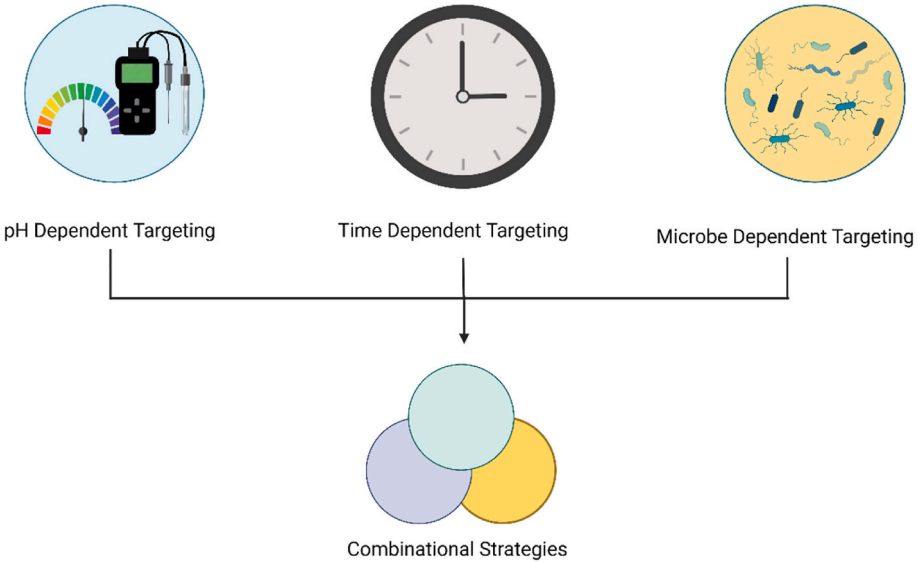

Fig. 2. Schematic representation of colon targeting strategies.

Trials on human volunteers have revealed that these kinds of systems sometimes do not succeed in releasing the medication when the intestinal pH drops to 6.0 in the ascending colon compared to 7.0 inside the terminal section of the ileum [43]. In order to solve this problem, the polymeric mixture belonging to Eudragit S100 alongside Eudragit L100 in proper combination guarantees that the drug will be released from the formulation even if the GIT's pH falls below 6.8.

3.2. Time-dependent targeting

The medication becomes available within the colon shortly after a certain duration in time-released formulations [44]. This method is based on the small bowel's transition period, and it is estimated to fall within three to 4 h [45,46]. The duration taken for gastric emptying varies across people and is also affected by meal consumption [47]. Furthermore, illnesses related to the colon, like SBS and UC, might affect the duration of transit via the large bowel [7]. Researchers had achieved colon-specific administration by combining pH-sensitive polymers with a method for timely release [48]. A drug-containing core was encapsulated between a total of three polymer coverings (a water-loving covering encased within two pH-responsive coverings). The dissolution experiment results demonstrated that the release of medications was sustained as a result of pH protection plus hydrogel formation.

3.3. Microbe-dependent targeting

Since a microbially controlled delivery system allows for more precise targeting and is dependent on the unique bioenzymatic capabilities possessed by the colon's microflora, it is an appropriate option for colon-specific targeting, despite the pH fluctuations along the GIT. The gut microbiota, particularly in the colon, produces enzymes that aid in the breakdown of certain substrates, which include glycosidases and azoreductases. Many natural polysaccharides, including dextran, chondroitin sulfate, guar gum, and pectin, among others, were investigated, considering their possible use in creating CTDDD [49]. The majority of non-starch polysaccharides have the disadvantage of having poor film-forming capabilities. They also tend to enlarge in the GIT and get porous, which leads to premature drug release. Milojevic et al. [50], in a landmark study, evaluated the capabilities of amylose in its role as a film-forming polymer. Amylose, the most abundant component of starch, has the capacity to gel and create films. Although amorphous amylose-based coatings can be broken down by colonic bacterial enzymes, they are resilient to the alpha amylase enzyme of the pancreas. The swelling capabilities of amylose in aqueous environments are one downside of employing it in this form. This might be regulated by adding insoluble polymers to the amylose film, such as acrylates and ethyl cellulose. Lorenzo-Lamosa et al. [51] proposed the method of covering the polysaccharide-based frameworks in pH-responsive polymers. Chitosan microspheres containing the medication had been produced and encased with polymers, Eudragit S100 and Eudragit L100, accordingly. Two approaches were used to create a multiparticulate framework that had been developed by combining two methods: pH-dependent administration plus breakdown by bacteria inside the colonic conditions. The framework was created using two stages: a spray drying approach was utilized to retain the medication contained inside the chitosan microspheres, and then a solvent evaporation method was used to microencapsulate those microspheres inside Eudragit polymers. Eudragit micro-encapsulated chitosan microcores did not show release of the drug in vitro after 3 h at stomach pH. Furthermore, no medication release occurred at a pH lower than the enteric covering polymers' solvability pH. When the exterior Eudragit covering was dissolved at the proper pH, the apparent chitosan microspheres got swollen and created a viscous layer around the basic pH that allowed the diffusion of medication. Furthermore, it has been hypothesized that this chitosan will degrade inside the colonic region, increasing the dissolution of the entrapped medication. A multiparticulate system composed of microspheres of chitosan encapsulated using Eudragit L100 or S100 coverings was proposed for the colonic delivery of metronidazole as an amoebiasis remedy in a similar manner [52]. The drug was predicted to be released when the enteric coating disintegrated in the small bowel and the polymer biodegraded inside the large intestine because of the occurrence of polysaccharides within the colonic fluids. Chitosan was crosslinked with glutaraldehyde to avoid early medication loss from microspheres. The effectiveness of these systems in impeding the release of medication before it reached the colon was established. Additionally, the increased medication release observed in the company of rat cecal contents highlights the vulnerability of the chitosan matrix to enzymatic breakdown in the colon.

3.4. Combination strategies

Integrating several targeting strategies provides a synergistic approach for enhancing drug delivery precision to the colon. These strategies aim to maximize drug release kinetics and targeting efficiency by combining pH sensitivity, time-dependent release, and microbial enzyme-dependent processes.

3.4.1. pH-dependent/time-dependent targeting

This combination entails creating microspheres with enteric coatings that are resistant to the stomach environment and the small intestine, as well as including time-dependent release properties. The microspheres stay unaffected inside the upper GIT to deliver the drug continuously after they reach the colon. Gupta et al. [53], for example, attempted to leverage the small intestine's relatively consistent transit period of 3–4 h and an elevated pH level of around 7–8 in the distally located area. Their goal was to design a dependable multiparticulate colonic delivery system by combining the pH-based dissolving properties of multiple Eudragit polymers with consistent transit duration in the small intestine. Utilizing a fluidized bed coating machine, the pellets have been coated using a combination of Eudragit RL/RS for the internal coating. During the fluidized bed processor, the outer coat was given using Eudragit FS 30D to the aforementioned pellets that dissolve at pH levels over 6.5. A system like this has the advantage of being simple to manufacture at an enormous level within an acceptable processing time using conventional powder layering and fluidized bed coating methods. The delivery system confirmed its promise of enabling colon targeted drug delivery (CTDD) by preventing medication release as high as pH 6.5, while the blend of Eudragit RS with RL demonstrated effectiveness for the sustained administration of mesalamine around large intestine pH. Coating of the pellets of mesalamine pellets, either including or without inulin, employing a time-sensitive polymer (Eudragit RS) and a bipolymeric mixture (Eudragit L and S), is another example [54]. These encased pellets outperformed the Pentasa formulation in an animal model of UC (pH-only triggered) in terms of therapeutic effects. It needs to be highlighted that there was no substantial therapeutic difference seen in comparison of the two types of pellets containing and excluding inulin, suggesting that the combination, as well as the pH- and time-responsive mechanisms, provided extra medicinal effect.

3.4.2. pH- and microbiota-activated integration methods

3.4.2.1. Phloral®. Phloral® devices were the pioneers in the commercial market as a dual-triggered technology for colonic medication administration. It is a single-coat coating mechanism formed by a homogeneous combination of Eudragit S with water-resilient starch [31,55]. Because of the distinct triggering systems, the two components work complementarily and thus may account for each other's activity if one fails to be engaged [56]. Eudragit S protects the formulation's integrity while it travels via the stomach and the small intestinal area in this system. Furthermore, it functions as a starch structuring agent, managing its expansion. On the contrary, resistant starch helps colonic

bacteria by providing a different pathway for medication release in the event that the Eudragit S pH limit is not reached. Regardless of patient eating conditions, the Phloral® technique has effectively demonstrated excellent effects for the therapeutic management of CIBD [56,57]. Phloral® was additionally effectively used to treat infections caused by *C. difficile* [58,59].

3.4.2.2. OPTICORE™. OPTICORE™, which stands for Optimized Colonic Release, is a newly invented hybrid combo method for quickly releasing medications at the ileocolonic site, in which the amount of fluid is greater compared to the middle and distal sections of the large intestine [60,61]. The technology comprises a pair of coating surfaces, the first of which is Eudragit® S, a neutral intestinal polymer mixed with a buffering agent in the first coat. This layer has an outer Phloral® coat covering it [61]. Given that the base layer seems alkaline, acidic drug formulation may necessitate the insertion of an extra Hydroxypropyl methylcellulose (HPMC) coat to separate these drugs from their alkaline foundation layer. The OPTICORE™ device achieves rapid ileocolonic release of the drug by boosting the breakdown of the specially designed Phloral® coating. The Phloral® layer develops pores once the formulation moves through the distal GIT, allowing lumen fluid to enter and enabling the intestinal foundation layer to dissolve. The pH value, strength of ionization, and buffering power of the interior face of the remaining Phloral® coat are all raised by this dissolving process, resulting in fast ionization and dissolution associated with the Eudragit® S segment of Phloral® [62–64]. So far, owing to its capacity to precisely administer measalamine to the colon inflammatory site, the OPTICORE™ system has been employed effectively in the therapeutic management of CIBD (61). AsacolTM is a commercial medication for the treatment of CIBD that was licensed within Europe upon the completion of its Phase III clinical testing. Its colon-targeting strategy is called OPTICORE™ [65]. Notably, 1.6 g of mesalamine can be delivered colonically using the multi-impetus device—the highest amount of medicine ever approved via oral administration. Due to the acidic nature of mesalamine, the foundation layer's buffering inside OPTICORE™ accelerates breakdown via the Phloral® coat, enabling quicker colonic release. The capacity to administer such high mesalamine dosages enhances patient compliance by reducing dossing frequency. Another study has looked at the OPTICORE™ strategy for treating *C. difficile* infection via ileocolonic delivery by delivering the acidic medication metronidazole benzoate [66].

3.4.3. Microbiota- and time-responsive integration methods

While microbiota- and time-dependent triggers for colonic drug delivery have been thoroughly investigated, their combination as concurrent pathways is uncommon [67]. An analogous approach is the use of pectin along with HPMC as a coating, which takes advantage of the pectin's breakdown by microbial activity and swelling of the HPMC inside GIT [68]. The coating was proven in a pilot trial to reliably carry payload through the ascending or transverse colons in six healthy male subjects. In another study, injection-molded capsule shells were made by integrating HPMC and high-amylose starch, and the dissolution studies of paracetamol from the capsule shells have been carried out [69]. Faster drug release occurs within the colonic conditions due to the efficient microbial metabolism of starch, while the existence of HPMC permits scheduled drug release during swelling. It has been proposed that the polymer proportions, shell thickness, and shell form might be altered to fine-tune the drug delivery. Because dosage form and shape may be altered to assist indication-specific release of medication, these discoveries have the potential to encourage the development of novel commodities that could help with release in certain locations of the colon.

3.4.4. pH-, microbiota-, and time-activated integration devices

A unique colon-targeted drug delivery device with multiple activation methods was proposed by Moutaharrik et al. [70]. This system's dual-layered coating consists of an interior, time-sensitive, swellable cellulose counterpart (HPMC or hydroxypropyl cellulose (HPC)), encircled by a mixture of a pH-sensitive polymer (Eudragit® S) and a microbiota-responsive polysaccharide (Amylo N460). In both in vitro and ex vivo settings, the cellulose derivatives Eudragit® S and Amylo N460 consistently demonstrated colon-targeting efficacy, making this the first time a triple colon-targeting method has ever been successful. Following this positive early evidence, the system's continuing development in vivo models seems promising.

4. Formulation considerations

4.1. Selection of drugs

Drugs intended for incorporation into a CTDDD must meet a minimum of one of the physicochemical or medicinal requirements listed below. To begin with, these drugs ought to have local actions within the colonic area for the purpose of managing bowel diseases. Drugs exhibiting such effects include peptides such as amylin along with non-peptidic drugs such as oxyprenolol. Subsequently, these drugs could suffer from lower absorption within the upper GIT. This involves antianginal medications such as isosorbide dinitrate. Treatments for colorectal cancer, such as 5-flurouracil along with capecitabine, also serve as excellent options for CTDDD. Other requirements comprise a substantial possibility of the medication being due to the stomach's acidic surrounding enzymes (for example, peptidic drugs such as gonadorelin and insulin) or an elevated risk of undergoing first-pass metabolism (for example, corticosteroids) [7,71–74].

4.2. Selection of crosslinking agent

The crosslinking agent must interact quickly with the polymers of choice to generate a firm matrix, ensuring the microspheres' integrity. To avoid any potential injury or unpleasant responses whenever the microspheres come into contact with the intestinal mucosa, the crosslinking agent needs to be biocompatible. In conditions where pH-sensitive crosslinking is intended, the drug should have increased reactivity under colon-specific pH circumstances. The crosslinking reaction is not supposed to produce any toxic byproducts that could compromise the drug's stability or safety [7,75,76].

4.3. Selection of coating material

The coating polymer should be pH-dependent, remaining unaffected throughout the acidic conditions of the stomach and small intestine while dissolving within the colon in more alkaline conditions. The polymer should have mucoadhesive qualities for extended interaction with the colonic mucosa, extending the residence period of microspheres in the colon. If the polymer is to disintegrate or erode over time, it must do so in a safe and compatible manner with the colonic environment. The coating polymer should be strong enough to protect the microspheres throughout passage within the GIT. The coating polymer should be compatible with all types of release modifiers or agents employed to further tailor drug release [32,77–80]. These selection criteria give a methodical strategy for developing colon-targeted microspheres, making sure the selected drug, crosslinking agent, and coating polymer correspond with the planned therapeutic aims and the physiological parameters within the GIT.

5. Formulation methods

5.1. Wax melting

The wax melting process principle, also known as the melt dispersion-condensation technique, includes heating wax till it becomes liquid, followed by emulsifying it with hot water while stirring

continuously. This emulsion is then pushed through a nozzle into a subsequent aqueous phase maintained at a lower temperature, where the wax droplets harden into spherical microparticles. Following solidification, the wax microspheres are removed from the aqueous phase and dried to eliminate any remaining moisture. This process is delineated in Fig. 3 [81–83].

5.2. Spray drying

This process required mixing the untreated product with a liquid coating solution to make drug-loaded polymer microspheres. After that, the resultant mixture was sprayed into the ambient air to encourage surface solidification and prompt solvent evaporation, as delineated in Fig. 4. Under controlled laboratory circumstances, drug-loaded microspheres were created by combining and spraying an organic solvent plus a polymeric solution in various weight ratios with the drug. Although this method is effective, it has the potential to cause crystallinity loss due to the quick drying process [84].

5.3. Coacervation

With this method, a fluid composed of macromolecules is simply split directly into two distinct kinds of materials that are unlikely to mix together: an exceedingly dense coacervate layer that is substantially condensed in macromolecules and an equilibrium-state refined layer. Whenever only a single kind of macromolecule is present, this process is known as basic coacervation. However, this can also be referred to simply as complex coacervation if more than two macromolecules with opposing charges are involved. The former causes macromolecular dehydration and is brought on by particular variables, such as changes in temperature or the addition of non-solvents or micro-ions. Through solvent interactions, these components support connections between polymers. This method can be modified to produce microspheres with different characteristics [85].

5.4. Solvent evaporation

In order to produce microspheres constructed from polylactic acid and poly (lactic-*co*-glycolic acid) carrying different medicines, the solvent evaporation approach has been widely used. The features of the microspheres are significantly influenced by a number of variables, which have been recognized as such. The medication's solvability, inner structure, loading capacity, solvent preference, rate of diffusing,

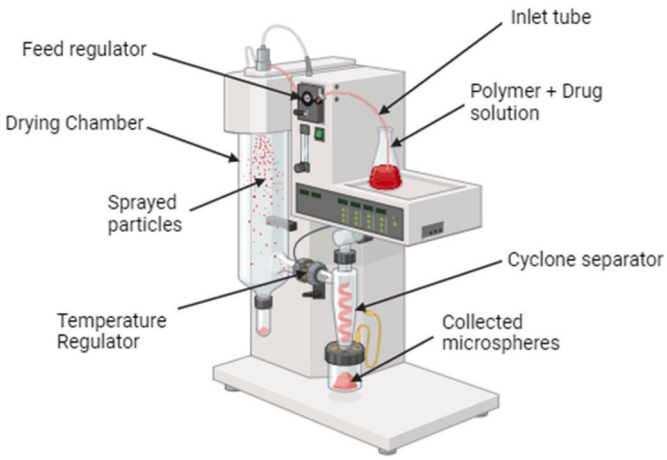

Fig. 4. Schematic representation of spray drying.

temperature, viscosity, and polymeric framework are a few of these. Efficient incorporation of an active chemical into the particles determines how well the solvent vaporization procedure produces microspheres. For medications that remain either insoluble or just partially dissolve in the liquid medium constituting the continuous phase, this approach is therefore shown to be very effective [86].

5.5. Precipitation

A different type of evaporation is used in this process. A non-polar liquid is used to disperse polar droplets during this operation. The solvent is easier to remove from these droplets when a co-solvent is added. An increase in polymer concentration follows, which causes precipitation and the development of a microspheric suspension [87–89].

5.6. Freeze drying

A very efficient technique for creating protein API microspheres is freeze-drying. There are four steps to the process: freezing, sublimation, primary drying, and secondary drying. The eutectic point for each of the constituents is carefully taken into account throughout freezing. Lyoprotectants or cryoprotectants work to stabilize API molecules throughout the process by drawing out water, resulting in the formation

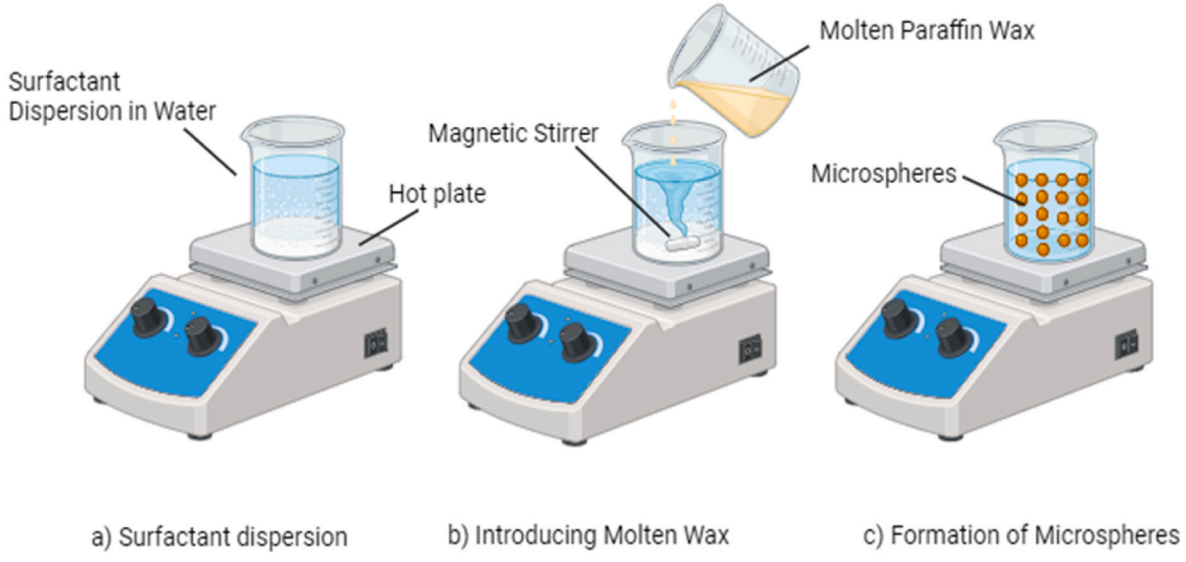

Fig. 3. Schematic representation of wax melting.

of a glass matrix. By encouraging hydrogen bonds or dipole-dipole interactions in molecules, this in turn lessens intermolecular interactions. This technique works well for molecules that can withstand heat, although it can be expensive. The solidification that results from freeze-drying enables the reconstruction of particles within the aqueous medium [90].

5.7. Single emulsion solvent evaporation technique

This procedure involves emulsifying an aqueous solution comprising an emulsifier while also dissolving the polymeric material in an organic solvent. To help the solvent evaporate, the resultant emulsion is agitated for a number of hours in the atmosphere. After that, it is cleaned, rinsed, and dried inside desiccators, as delineated in Fig. 5. Diffusion-evaporation is used in combination with emulsion solvents to produce microspheres that contain planned and produced medicines with polymers [91].

5.8. The double emulsion method

This technique involves the creation of a double emulsion through either oil-in-water-in-oil (o/w/o) or water-in-oil (w/o/w) processing, as delineated in Fig. 6. In this method, the aqueous solution of the product is scattered within a perpetual lipid-based organic phase. The perpetual phase, comprising a polymeric solution, ultimately envelopes the medication observed within the scattered aqueous layer, forming an initial emulsion. Before introducing the emulsion to the aqueous solution of alcohol to create the primary emulsion, the pre-formed emulsion undergoes homogenization or sonication. The resulting microspheres, loaded with the drug, exhibit prolonged release of the medication over a 24-h period and are observed to be regulated by both diffusion and erosion mechanisms [92,93].

5.9. Ionotropic gelation

Ionotropic gelation depends on polyelectrolytes' propensity to interact with one another and construct hydrogel beads, sometimes known as "gelispheres," when they are exposed to counter ions. Gelispheres are cross-linked, hydrophilic, spherical polymeric materials that can significantly thicken and gel in biological simulation fluids. Drug release is regulated by polymer relaxation inside the gelispheres. Such hydrogel beads are produced by mixing an aqueous solution with polyvalent cations with a drug-containing polymeric solution, as delineated in Fig. 7. The drug-containing hydrophilic molecules are penetrated by the cations, which create a three-dimensional framework that has been ionically crosslinked. These gelispheres can also contain biomolecules to maintain their three dimensional structure even in moderate environments [94].

6. Evaluation parameters

6.1. Entrapment efficiency

To guarantee full dissolution of the medicine, rigorously grind the weighed quantity of microspheres from each batch into a fine powder, blend it with methanol, and keep it at room temperature for 24 h with constant stirring. Following that, filter the samples through a 0.45 μ pore size. Following that, use high-performance liquid chromatography (HPLC) to assess the amount of drug content they possess, as explained below. The drug's entrapment efficiency (EE%) is then determined using equation (1):

$$\frac{Q_r}{Q_t} \times 100 = EE\% \tag{1}$$

In this case, Q_t represents the total amount of drug added during batch preparation, whereas Q_r reflects the amount of drug extracted from the microspheres [95].

6.2. Swelling index

Individually submerge 50 mg of microspheres without coating in either a simulated stomach fluid of pH value 1.2 or a simulated bowel fluid of pH 7.5. Subject the microspheres to the required amount of swelling in a dissolution apparatus for the required duration. Then, put these microspheres on the filter paper to dry at regular intervals and observe their weight change (corrected for any kind of drug loss) until equilibrium has been attained. Afterwards apply the following equation (2) to determine the swelling index (SI):

$$\frac{M_g - M_0}{M_0} = \%\ SI \tag{2}$$

The swelling index (SI), the microspheres' starting mass (M_0), and their final mass (Mg) are all defined in this equation [96].

6.3. Dissolution studies of medication

Use the horizontal shaking device technique to investigate the dissolution profiles of microspheres washed with water and those that were not washed, as well as capsules brimmed with microspheres covered by the coating. As part of the experimental setup, keep an operating temperature of 37 °C and a stirring velocity of 50 rpm. Fill the container containing simulated medium with a weighted quantity of the medication-entrapped microspheres. Collect the samples at prearranged time frames, and afterwards spin them in the centrifuge over a duration of 10 min while maintaining a velocity of 1000 rpm. After filtering, assess the acquired liquid supernatant using spectroscopic measurements. Assume the blank microspheres as a reference point. Carry out

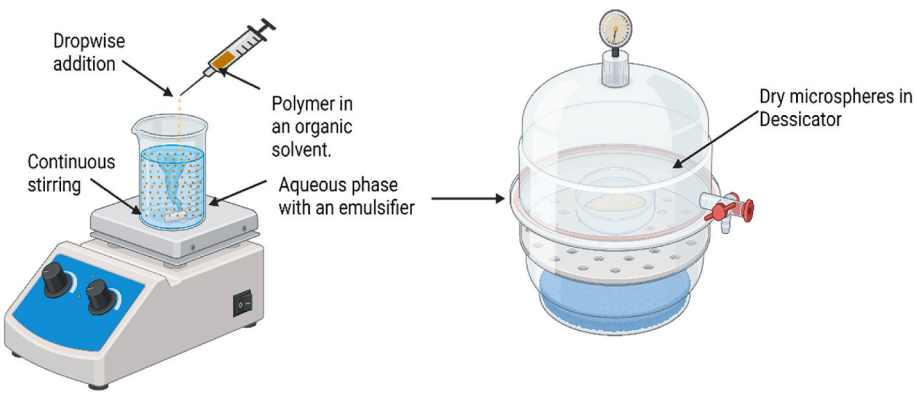

Fig. 5. Schematic representation single emulsion solvent evaporation.

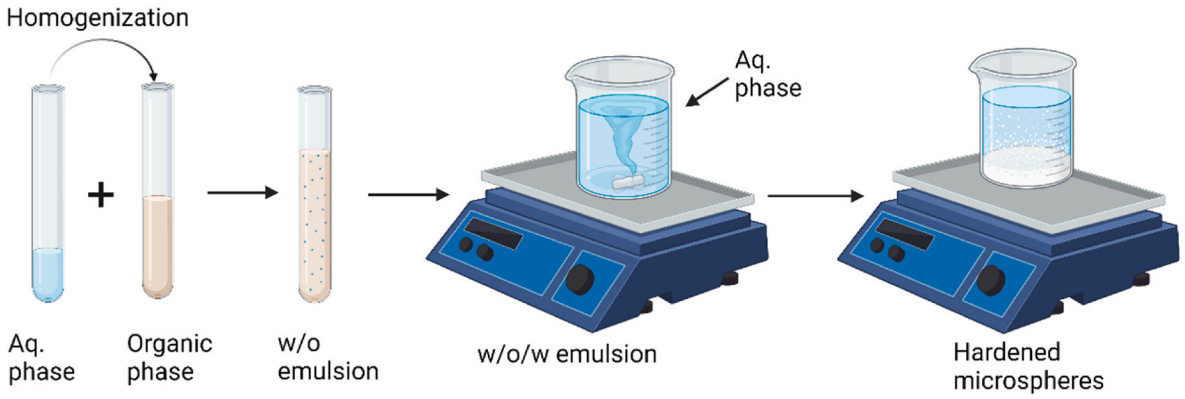

Fig. 6. Schematic representation of double emulsification.

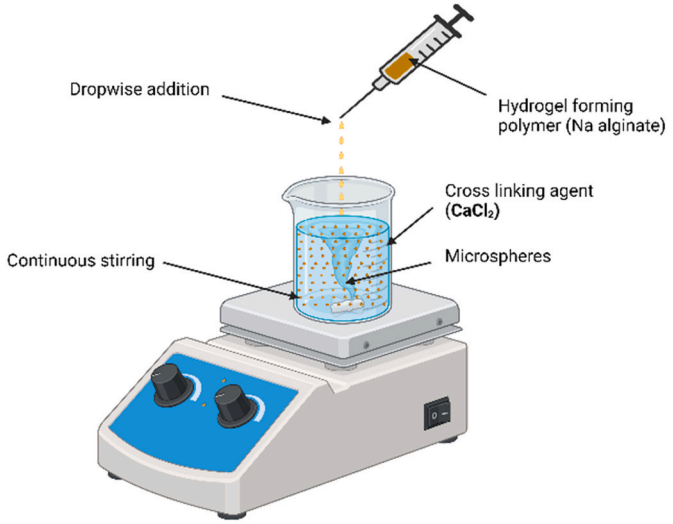

Fig. 7. Schematic representation of ionotropic gelation.

this entire technique at least three times. Measure the release from several formulations to investigate the effects of stomach and colon pH on the release rate at these two pHs. Next, apply the perpetual model to measure the dissolution profile generated by the optimal formulation, which simulates gastric pH values. The first hour at pH 1.5 represents the stomach media. The initial segment of the small bowel is represented by 2 h at pH 4.5, the second section by 2 h at pH 6.5, and the large intestine area by 4 h at pH 7.4. The dissolving medium used to validate the release profile with the microbial enzymes includes a phosphate buffer with a pH value of 7.4 and pectinase. Carry out the assay according to the preceding protocol [97].

6.4. Particle size

Assess the particle size of the produced microspheres using Zetasizer equipment. Vortex a tiny amount (10 mg) of microspheres into distilled ultrapure water, including Tween 80 (0.2 %, w/v). Following that, subject the material to sonication and transfer it to a cuvette for particle size measurement [98].

6.5. Surface characteristics

Assess the surface and cross-sectional properties of the microspheres produced by the specified formulation by employing an electron microscope for scanning. Place the microspheres on metallic slides using double-sided sticky tape during sample preparation. Following that, make the microspheres electrically conductive by depositing a light coating of gold plating under vacuum settings [99].

6.6. DSC studies

Perform the DSC assessment on a DSC METTLER equipped with a thermal analyzer. Precisely measure the samples, each weighing about 5 mg, and deposit them in a sealed aluminum pan. Subsequently, heat these samples with a 20 mL/min nitrogen flow at a scan rate of about 20 °C per minute, with temperatures spanning 40 °C–300 °C. Use an unfilled metal pan as a reference. Obtain DSC thermograms for pure chemicals, their physical mixes, and the drug-loaded microparticles [100].

7. Applications and therapeutic benefits

CTDDDs, which are centered on microspheres, have demonstrated great promise for a number of clinical applications. A wide range of applications with various therapeutic effects have been made possible by the special qualities of microspheres combined with precisely targeted strategies, as shown in Fig. 8.

7.1. Chronic inflammatory bowel diseases (CIBD)

Treating CIBD, which includes Crohn's disease and UC, can be quite difficult. These colon illnesses are ideally suited for targeted medicine administration due to their localized nature. Formulations based on microspheres provide a constant therapeutic effect within the inflamed colonic mucosa by delivering a regulated and prolonged release of anti-inflammatory drugs. By limiting systemic exposure, this focused strategy lowers the possibility of side effects from systemic treatment [101–103].

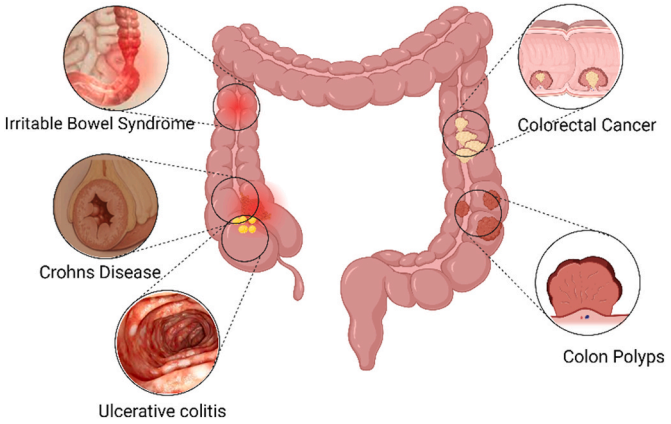

Fig. 8. Applications of colon targeted microspheres.

7.2. Colorectal carcinoma

Innovative therapeutic strategies are needed to address CRC, which is still a global health concern. One potential solution is to deliver high concentrations of drugs directly to the colon using microspheres loaded with chemotherapy drugs like 5-fluorouracil (5-FU). This localized delivery approach enhances the cytotoxic effects on malignant cells while limiting off-target effects and reducing systemic exposure [104,105].

7.3. Spastic bowel syndrome (SBS)

The symptoms of spastic bowel syndrome, which include bloating, changed bowel behaviors, and persistent abdominal discomfort, call for therapies that target specific regions of the GIT. Targeted delivery to the colon can provide localized relief from these symptoms. Localized relief from abdominal cramping and discomfort associated with SBS can be achieved through the use of microsphere-based formulations containing spasmolytic agents like dicyclomine [106].

7.4. Localized infections and colon-specific therapies

The colon is a major site for infections like bacterial overgrowth and amoebiosis. Targeted drug delivery can improve therapeutic efficacy by delivering high concentrations directly to the infection site, and antimicrobial agents like metronidazole are effective in colonic infections [107].

7.5. Treatment of colon polyps

Adenomatous polyps are early signs of colorectal cancer. Targeted drug delivery can reduce the progression of these polyps. Celecoxib-loaded microspheres have shown potential for reducing colon polyp quantity and size. This tailored approach could potentially delay malignancy development by applying chemopreventive drugs directly to the polyp formation site [108].

8. Recent advancements

Significant improvements have been achieved across the domain of CTDDD in recent years, with microspheres emerging as an appealing option for precise and controlled drug release. This developing field of study has seen an increase in studies aiming at optimizing microsphere compositions, investigating innovative materials, and improving manufacturing procedures. The complete review of current notable studies in the realm of CTDDD's based on microsphere is enlisted in Table 1.

9. Side effects of drug release from microspheres

Oral delivery of microspheres is not extensively utilized for medication delivery these days, despite the fact that they can enable long-acting drug release, because they have some drawbacks, such as bursts of large initial concentrations of medication release, extended drug release timeframes, and limited encapsulation efficiency. While delayed release at a later point might be therapeutically ineffective, the significant burst release of medication from these microspheres could lead to various side effects. Fast discharge of high quantities of a medication can cause gastrointestinal distress, interactions between medications, oscillating levels of medication, a higher possibility of adverse reactions, declined effectiveness for therapy, tolerance and dependence, and even overdosing manifestations. The consequences of an overdose could include toxicity, nausea, and vomiting. Fast medication release may cause drug levels to fluctuate, which could result in therapy failure or the recurrence of previously untreated symptoms. Variations in medicine dosage can lower the medication's overall therapeutic effectiveness. Abrupt drops in the concentration of the medication might lead to tolerance and dependency developing. Certain drugs may produce gastrointestinal discomfort when taken in high doses, which can result in symptoms including diarrhea, constipation, or abdominal pain. Medication interactions with other drugs can also happen, which could have a significant impact on the effectiveness of the medications [156–158].

10. Challenges

Microsphere-based colon-targeted delivery of drugs faces a number of challenges, which academics and pharmaceutical companies are actively working to overcome. The following list of key issues is followed by suggested solutions backed by pertinent sources.

10.1. Variable gastric emptying time

The inconsistency in gastric emptying time can lead to premature drug release prior to reaching the colon. Employing pH-sensitive or enteric coatings can effectively postpone drug release until the microspheres reach the colon [159].

10.2. Enzymatic degradation

Digestive tract enzymes might break down the microspheres, resulting in an early release of the medication. The medicine can be protected until it reaches the colon by including enzyme inhibitors in the microsphere system or by using biodegradable polymers tolerant to enzymatic breakdown [160].

10.3. Mucosal barrier

The mucosal layer of the colon may prevent microspheres from adhering to and penetrating the colonic epithelium. It is possible to improve the interaction of microspheres with the colonic mucosa by adding mucoadhesive polymers to the microsphere surface or by using targeted ligands (lectins, for example, or antibodies) [161,162].

10.4. Colon pH variability

The efficacy of pH-sensitive coatings can be impacted by shifting pH values in the colon. Stability in a range of pH settings can be achieved by creating microspheres with a substantial number of pH-sensitive coatings or simply by using more sophisticated pH-responsive materials [163].

10.5. Limited drug loading capacity

It can be difficult to achieve high drug loading into microspheres while maintaining the necessary physicochemical qualities [164]. In order to increase drug loading capacity without affecting microsphere integrity, innovative encapsulation strategies such as hot melt extrusion, coacervation, solvent evaporation, and supercritical fluid technology can be used [165–167].

10.6. Control drug release

For a treatment to be effective, it is essential to achieve a drug release profile of sustained and controlled release in the colon. The appropriate release pattern can be achieved by using polymers with particular release kinetics, for example, hydrogels or biodegradable matrices [168].

10.7. Safety and biocompatibility

Making sure the components used to create microspheres are safe, biocompatible, and do not cause adverse effects. Conducting thorough

Table 1
Recent advancements in CTDD via microspheres.

Fabrication Technique	Polymer	Medication	Size (μm)	Entrapment Efficiency	Mechanism of Medication release	Uses/Treatment	Study type	Reference
	Resistant Starch	Aspirin	–	68.96	Enzymatic degradation	CIBD	In vitro	[109]
	Eudragit S100	Lactobacillus rhamnosus GG	5.2–7.3	–	pH susceptible degradation	Probiotics therapy	In vitro	[110]
	Eudragit S-100	Mesalamine	4.91	7 ± 0.89	pH susceptible degradation	UC	In vitro	[111]
	Chitosan	Curcumin overloaded with ascorbic acid	–	91.2 ± 0.88	pH susceptible degradation	CRC	In vivo	[112]
	Inulin	Mesalamine	0.8–10	87	Enzymatic degradation	UC	In vitro	[113]
	Polyacrylamide-*graft*-gum karaya	Capecitabine	1.02–8.19	77.30–88.74	pH susceptible degradation	CRC	In vitro	[114]
	Chitosan	Meloxicam	–	65.5 ± 1.5–84.1 ± 1.7	pH susceptible degradation	CRC	In vivo	[115]
	Eudragit S-100	5-Fluorouracil	–	99	pH susceptible degradation	CRC	In vivo	[116]
	Zein (ZN) and Gantrez® AN119 (PVMMA)	Curcumin	10.15–25.64	89	pH susceptible degradation	CIBD	Ex vivo	[117]
	PGA-co-PDL	Indomethacin	–	63.16 ± 3.5	pH susceptible degradation	CIBD	In vitro	[118]
	Polyacrylamidegrafted-CMCNa copolymer	Capecitabine	1.00–7.34	70.98 ± 1.23–94.41 ± 0.45	pH susceptible degradation	CRC	In vitro	[119]
	Eudragit® FS 30D	Glutathione and S-nitrosoglutathione	5 ± 1–7 ± 1	74 ± 3–82 ± 2	pH susceptible degradation	Therapy for Crohns disease	In vitro	[120]
Ionic gelation	Inulin/Chitosan/Alginate	Quercetin	25.1 ± 1.8–79.4 ± 4.5	53.2 ± 1.2	Enzymatic degradation	CIBD	In vitro	[121]
	Sodium alginate	Gallic Acid	–	11.26–72.64	Enzymatic degradation	CRC	Ex vivo	[122]
	Alginate	Astaxanthin	0.5–3.2	–	Enzymatic degradation	UC	In vitro	[123]
	Gum odina - Sodium alginate	Capecitabine	568.33 ± 45.76	45.91 ± 2.94	Enzymatic degradation	CRC	Ex vivo	[124]
	Pectin/NaCMC	Progesterone	1031 ± 19	80.1–97.8 %	Enzymatic degradation	Hormone therapy	Ex vivo	[125]
	Sodium alginate	Meloxicam	109.16 ± 0.96–1025.12 ± 0.29	50.33 ± 0.40 to 74.93 ± 0.69	Enzymatic degradation	Rheumatoid arthritis management	In vivo	[126]
	Konjac glucomannan/ Sodium alginate/Graphene oxide	Ciprofloxacin	–	19.11 ± 1.39	Enzymatic degradation	CIBD	In vitro	[127]
	Arabinoxylan	Insulin	150–300	71.3 ± 2.7	Enzymatic degradation	Management of Diabetes	In vitro	[128]
	Locust bean gum	Mesalamine	1450	32.64 ± 0.57–57.42 ± 1.98	pH susceptible degradation	UC	In vitro	[129]
	Portulaca oleracea polysaccharide/Alginate/ Borax	5-fluorouracil	930–1140	53–88	Enzymatic degradation	CRC	In vitro	[130]
	Chitosan	Flurbiprofen	700–1300	20.3 ± 0.007–78.8 ± 0.003	pH susceptible degradation	Non steroidal anti-inflammatory drug (NSAID)	In vitro	[131]
	Pectin/NaCMC	Progesterone	1114 ± 36.9–1447 ± 35.7	82–99	Enzymatic degradation	Hormone therapy	Ex vivo	[132]
	Gelan gum	Ketoprofen	700.17–938.32	48.76 to 87.52	pH susceptible degradation	NSAID	In vitro	[133]
Double emulsion	Methocel E5/Eudragit L100	Captopril	110–128	95	pH susceptible degradation	–	In vitro	[134]
	PLGA/PVA	Fucoxanthin	2.01–10.95	33.09–34.87	pH susceptible degradation	CRC	In vitro	[135]
	Eudragit® RS100	Fluorescein isothiocyanate-dextran	31.1 ± 0.5	–	pH susceptible degradation	–	Ex vivo	[136]
	Gum Katira	5-fluorouracil	–	79.71 ± 6.01	pH susceptible degradation	CRC	In vivo/ Ex vivo	[98]
	Eudragit® FS 30D/ Eudragit® RS-PO	Enoxaparin sodium	80.64–165.00	62.38–94.89	pH susceptible degradation	Anticoagulant	In vitro	[137]

(*continued on next page*)

Table 1 (*continued*)

Fabrication Technique	Polymer	Medication	Size (μm)	Entrapment Efficiency	Mechanism of Medication release	Uses/Treatment	Study type	Reference
	PLGA/PVA	Fucoxanthin	3.93–17.12	–	pH susceptible degradation	CRC	–	[138]
	Tulsion® Thermocoat L 30 D55	Clarithromycin	52.0 ± 0.46	61.0 ± 3.1	pH susceptible degradation	–	In vivo	[139]
	PLGA	PEGylated apoptotic protein	14.4 ± 1.8	85.7 % ± 4.1	pH susceptible degradation	CRC	In vivo	[140]
Emulsion solvent Evaporation	Cellulose/Alginate	Mesalazine	–	–	pH susceptible degradation	CIBD	In vitro	[141]
	Halloysite nanotube/ Chitosan	Paeoniflorin	26.7 ± 7.5	–	pH susceptible degradation	UC	In vitro	[142]
	Eudragit® FS 100	Curcumin		98.26 ± 6.38	pH susceptible degradation	CIBD	In vivo	[143]
	Pectin	Lamivudine	–	30.31–66.32	Enzymatic degradation	Chronic Hepatitis B	In vitro	[144]
	Resistant Starch	Ciprofloxacin HCl	0.743–4.156	–	pH susceptible degradation	Antimicrobial	In vitro	[145]
	Pectin/Chitosan	Acetoaminophen	24.98 ± 13.67 and 0.62 ± 0.24	18.86–64.33	pH susceptible degradation	–	In vitro	[146]
	Eudragit L100–55 and S100	Celecoxib	–	72.67 ± 3.93–84.33 ± 2.12	pH susceptible degradation	UC	In vivo	[147]
	Chitosan	Curcumin	10.94 ± 0.16–24.13 ± 0.62	73.88 ± 0.54–83.37 ± 0.62	pH susceptible degradation	CIBD	In vivo	[148]
	Chitosan	5-fluorouracil/ Leucovorin	15 to 35	11.6 ± 0.09–21.8 ± 0.12	pH susceptible degradation	CRC	In vitro	[149]
	Pectin	Metronidazole	14.02 ± 1.03	80.61 ± 2.42–94.52 ± 2.25	Enzymatic degradation	Antimicrobial	In vitro	[150]
	PEG-cross-linked Chitosan	5-fluorouracil	316 ± 20	–	pH susceptible degradation	CRC	In vivo	[151]
Coacervation	NaCMC/Pectin	Potassium diformate	–	–	pH susceptible degradation	Bacteriostatic	In vitro	[152]
	Chitosan-Alginate	Quercetin	–	86.91 ± 1.10–93.11 ± 0.72	pH susceptible degradation	Antimicrobial	In vitro	[153]
	Chitosan-Alginate	Ruta graveolens L. Phytocomplex	–	31.99 ± 0.12–75.31 ± 0.96	pH susceptible degradation	Antioxidant	In vitro	[154]
	Agave Fructans	Ibuprofen	–	0.8–21.5	Enzymatic degradation	NSAID	In vitro	[155]

biocompatibility studies and using the polymers and excipients that are likely to be approved by the Food and Drug Administration helps address the safety concerns [169].

10.8. Manufacturing and scale-up challenges

It might be challenging to move microsphere manufacturing from laboratory scale to industrial scale. Scaling up can be accelerated while maintaining product quality by using cutting-edge production methods such as emulsion solvent evaporation, spray drying, or hot-melt extrusion [170].

11. Future perspectives

Microspheres offer a promising method for colon-targeted medication, providing regulated release and improved therapeutic results. Future developments in this field include nanotechnology integration, biodegradable polymers, functional coatings, multi-compartmental microspheres, combination therapy, personalized therapies, 3D printing, biological agent delivery, and enhanced imaging and monitoring. Microspheres ranging in nanosize can be made in the future using nanotechnological progression, which can provide precise control over drug release as nano-sized particles can be absorbed directly through intestinal mucosal barriers, which makes them ideal for personalized medicine techniques. Advancements in the search for biodegradable and bioresponsive polymers can increase security and minimize adverse effects as compared to non-biodegradable polymers. In the future, various types of new coatings and polymers will be made that can provide enhanced protection from gastric pH or media for microspheres as they move through the digestive system, which can be used for tailored release on the basis of physiological circumstances. Combination therapy, in which microspheres can be combined with immunotherapy medicines (encapsulating immunotherapeutic agents into microspheres), could revolutionize cancer treatment. Advancements in genetic profiling and biomarker identification can enable personalized therapies based on individual patients' unique physiological characteristics, so that microspheres solely designed for a particular individual can be designed. 3D printing techniques can be used to make microspheres in the future, allowing for precise design of microspheres, greatly enhancing microsphere characteristics, enabling personalized medication release patterns, and improving patient compliance. Biological agent delivery, such as peptides, proteins, and gene therapies, could also benefit from microspheres, as these agents will be encapsulated into microspheres as CTDDD, which will enhance the bioavailability and effectiveness of these agents.

12. Conclusion

Colonic drug delivery of medications has advantages over conventional delivery regarding lesser adverse effects, greater efficacy, and

approval by patients as it is more potent in curing local colonic issues. Any desirable CTDDD has to be designed to suit confronting the concerns raised within the GIT due to its complex anatomy and physiology. Also, it should have the ability to determine the disease locations and the healthy tissues. It should also be capable of targeting certain types of cells and releasing the medication as needed. There are several hindrances that have to be conquered while establishing an effective CTDDD. Microspheres, using different colon targeting approaches, offer a promising method for colon-targeted medication, providing regulated release and improved therapeutic results. In spite of these, only medication release must not be seen as the climax of these medication deliveries. Colon has a natural tendency to throw out the metabolites more than the uptake of the molecules. Due to this, more investigations must be carried out, which will be centered particularly on the uptake of specific medications in the colonic region. Future developments in this field include nanotechnology integration, biodegradable polymers, functional coatings, multi-compartmental microspheres, combination therapy, personalized therapies, 3D printing, biological agent delivery, and enhanced imaging and monitoring.

CRediT authorship contribution statement

Raosaheb S. Shendge: Writing – review & editing, Supervision. **Tejas S. Zalte:** Writing – original draft, Conceptualization. **Shubhangi B. Khade:** Investigation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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