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REVIEW ARTICLE
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MICROSPHERE-BASED COLON-SPECIFIC DELIVERY SYSTEMS: A NOVEL APPROACH FOR DIHYDROARTEMISININ

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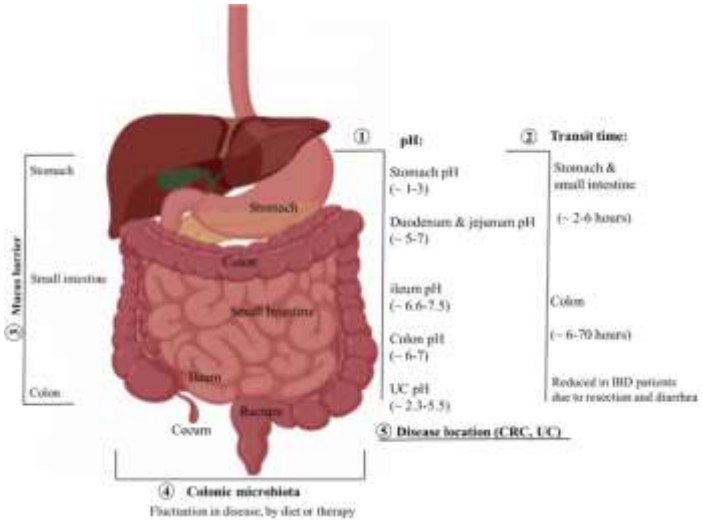
Abstract
Colon-targeted drug delivery has become an important strategy for improving the treatment of diseases that affect the large intestine, as well as for enhancing the systemic availability of drugs that are unstable in the upper gastrointestinal tract. Microspheres have drawn particular attention because they can protect sensitive drugs, provide controlled release, and deliver them precisely where needed. Dihydroartemisinin, a key antimalarial drug, is limited in its use due to poor solubility, rapid clearance, and instability in normal physiological conditions. Incorporating this drug into polymer-based colon-targeted microspheres offers a way to overcome these barriers, leading to better stability, prolonged release, and improved bioavailability. This review summarizes the importance of colon-targeted systems, the barriers and mechanisms of targeting, the role of microspheres, and the polymers used in their formulation. It also highlights how such approaches can specifically benefit Dihydroartemisinin therapy, while pointing toward future directions in research and clinical translation.

Key words: Colon-targeted drug delivery, Microspheres, Dihydroartemisinin (DHA), Controlled release, Bioavailability enhancement, Polymer-based drug carriers, Site-specific delivery, pH-sensitive polymers, Nano carrier innovations

2. Introduction

Oral medication is still the most common and easy-to-use way to give medicine. But this pathway is very difficult for drugs that are meant to work in the colon. The stomach's acidic environment can break down medications, the small intestine can start metabolism, and the liver can do a lot of first-pass elimination, all of which lower the drug's effectiveness and availability throughout the body (1).

Colon-targeted drug delivery systems (CDDS) provide an effective way to deal with these problems. By skipping the upper gastrointestinal tract and sending drugs straight to the colon, CDDS get the most out of local therapeutic concentrations, make them work better, and lower systemic side effects. This is especially important for treating inflammatory bowel disease, colorectal cancer, and ulcerative colitis (2).



Utilizing the colon's distinct physiology, which sets it apart from the stomach and small intestine due to its longer transit time, unique microbial population, and near-neutral pH, is essential to designing an efficient CDDS (3). Because of their biocompatibility and selective biodegradation by colonic microflora, which allows for site-specific drug release, natural polysaccharides like chitosan, alginate, pectin, inulin, and guar gum have become important carriers [4,5].

Modern formulation technologies, such as 3D printing and hot melt extrusion (HME), have transformed dosage design by providing exact control over drug distribution, release kinetics, and geometry. These customized platforms enhance CDDS's individualization, scalability, and reproducibility.

Even with these advancements, it is still difficult to convert these technologies into clinically useful CDDS. Widespread adoption is hampered by patient differences in colon physiology and microbiota, strict regulatory frameworks, and manufacturing difficulties [6]. However, new developments are still being made, such as intelligent pH-sensitive coatings and carriers based on polysaccharides or inulin that react to triggers unique to the colon [7].

The necessity of colon targeting, formulation techniques, especially microsphere-based carriers, and future directions will all be covered in this review, with a focus on the innovative use of Dihydroartemisinin in colon-targeted systems.

3. Colon-Targeted Drug Delivery Systems (CDDS)

3.1 The Critical Need for Colon Targeting

By delivering high concentrations of the therapeutic agent precisely where it is needed while preserving healthy tissues elsewhere, targeting drug release to the colon can significantly improve treatment for diseases like ulcerative colitis, Crohn's disease, and colorectal cancer [8]. This localized strategy reduces systemic side effects while increasing therapeutic effect.

Furthermore, sensitive molecules like peptides and proteins that would otherwise break down quickly can be delivered to the colon because of its special physiological conditions, which include a quasi-neutral pH, decreased activity of digestive enzymes, and a slower transit time [9]. Bypassing the upper gastrointestinal tract also lowers first-pass metabolism, which enables medications to maintain higher systemic levels after absorption. This can lower dosage needs and enhance patient outcomes [10].

The ability of CDDS to administer drugs in a delayed-release fashion, which corresponds with the colon's transit timetable and allows for prolonged therapeutic coverage, is an additional advantage. This is especially important in chronic, relapsing conditions [11]. Colon targeting is a key component of advanced oral drug therapy because of these benefits taken together.

3.2 Barriers to Colon Targeting

Despite the compelling advantages, delivering drugs precisely to the colon remains technically challenging:

- **Variable GI Transit Times:** The rate at which a drug passes through the stomach and small intestine can be affected by a number of factors, including food consumption, stress, and illness, which makes the timing of colon release uncertain [12].
- **pH Variability:** The pH of the human gastrointestinal tract varies significantly; the stomach is extremely acidic, the small intestine is neutral, and the colon is slightly alkaline. pH-triggered release systems may be compromised by these variations [13].
- **Enzymatic instability:** Drugs and their carriers may be broken down by digestive enzymes in the upper tract, which lowers payload effectiveness before it reaches the colon [9].
- **Microbiome Variability:** Although certain delivery methods use microbial degradation to release medications, differences in a person's gut microbiota, particularly in diseased conditions, can result in irregular release profiles [14, 15].

3.3 Mechanisms of Colon Targeting

A variety of innovative strategies have emerged to enhance targeting precision:

3.3.1 Systems Sensitive to pH

These employ enteric polymers, such as Eudragit S100, which ensure localized release by dissolving in the colon's higher pH but remaining intact in acidic and neutral environments [16].

3.3.2 Release Dependent on Time

These formulations, also referred to as chronotopic systems, are designed to release the drug after a predefined lag time, typically ~5–6 hours, which corresponds with transit to the colon [9].

3.3.3 Systems Triggered by Microbes

Utilizing the metabolic activity of the microbiome, polysaccharide-based carriers like pectin, inulin, and guar gum withstand digestion until they get to the colon, where bacterial enzymes break them down and release the medication [9].

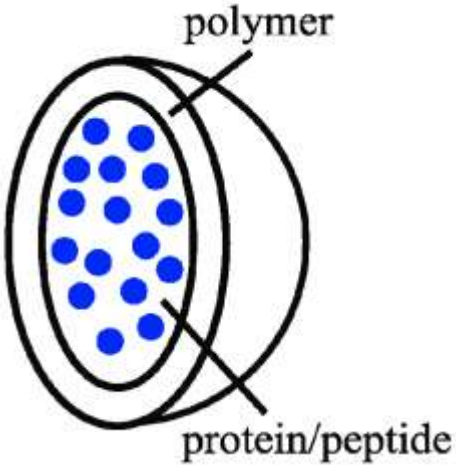
3.3.4 Systems That Are Hybrid

Innovations like 3D printing and hot-melt extrusion are also showing promise in creating precise, customizable colon-specific formulations [10].

Colon-targeted delivery exemplifies a merge of physiology, smart materials, and engineering. Current advances in manufacturing techniques—like 3D printing and stimuli-responsive systems—promise increasingly personalized and effective CDDS. Yet, realizing their full potential will require overcoming regulatory, manufacturing, and individual physiological variability challenges.

4. Microspheres as a Drug Delivery System

Because of their remarkable adaptability in drug delivery applications, microspheres are gaining traction in pharmaceutical research. These spherical carriers, which usually have a diameter of 1 to 1000 µm, provide a matrix-based system in which medications are evenly distributed, guaranteeing consistent and repeatable release kinetics [20]. In contrast to microcapsules, which enclose a drug core in a shell, they permit full matrix embedding, providing improved drug stability and more consistent release.



4.1 Classification of Microspheres

Microspheres can be categorized in several ways based on their physicochemical and functional properties:

- **Biodegradability**

o Biodegradable polymers, like PLA and PLGA, can be used for injectable and sustained drug delivery because they break down into nontoxic byproducts [21].

o While non-biodegradable alternatives (like ethyl cellulose) offer longer retention, their biocompatibility in long-term therapy may raise questions[22].

- **Mechanism of Release**

o Diffusion-controlled systems: the medication slowly permeates the matrix.

o Systems that are controlled by erosion or degradation: polymer breakdown controls release [24].

o Stimuli-responsive systems: perfect for colon-targeted therapy, these systems release when external factors like pH, pressure, or enzymatic activity are met.

4.2 Advantages of Microspheres in Drug Delivery

Microspheres bring a suite of benefits across different therapeutic areas:

- Longer therapeutic levels and fewer adverse effects are guaranteed by controlled and sustained release [21].
- Preventing the stomach and upper intestines from breaking down sensitive medications, such as peptides [26].
- decreased frequency of dosing, which improves patient compliance and is particularly helpful for long-term illnesses like Crohn's disease or ulcerative colitis [27].
- Particularly when intended for colon-specific delivery, improved bioavailability and targeted delivery lessen systemic toxicity [28].
- They provide formulation flexibility and can transport biological, hydrophilic, or hydrophobic molecules.

4.3 Preparation Methods of Microspheres

1. Solvent Evaporation Method

This popular technique entails dissolving the drug and polymer in an organic solvent, such as ethyl acetate or dichloromethane. An oil-in-water (O/W) emulsion is produced when this organic phase is emulsified into an aqueous phase that contains a stabilizer such as polyvinyl alcohol (PVA). The polymer then precipitates and forms solid microspheres encasing the drug as the solvent evaporates, either with stirring or at lower pressure.

- Important variables include temperature, stirring speed, emulsifier concentration, solvent type, and polymer concentration.
- Benefits include high encapsulation efficiency and good control over particle size (1–1000 μm).

• Restrictions: incompatible with hydrophilic medications unless a double emulsion (W/O/W) is utilized; residual solvent issues.

A double emulsion solvent evaporation method (W/O/W) is recommended for hydrophilic drugs. In this method, the drug dissolves in the inner aqueous phase, is emulsified in the polymeric organic phase, and is emulsified in an outer aqueous phase[21].

2. Foam-Phase Evaporation

This method, a novel take on solvent evaporation, creates microspheres by using foamed emulsions rather than straightforward liquid phases. Higher yields and quicker solvent evaporation are made possible by the foamed nature's increased surface area.

• Mechanism: A foam is created by aerating the polymer-drug solution and dispersing it throughout the aqueous phase. Porous microspheres are stabilized by the foam's quick solvent removal.

• Benefits include increased production speed, energy efficiency, and high porosity for prolonged release.

• Uses: appropriate for hydrophobic medications that need porous matrices for regulated dispersion [25].

3. Spray Drying

This technique uses a nozzle to atomize a polymer-drug solution or suspension into tiny droplets that are then sent into a hot drying chamber. The high surface area causes the solvent to evaporate almost immediately, resulting in dry, spherical microspheres[29].

• Process variables include solvent volatility, atomization pressure, feed rate, and inlet/outlet temperature.

• Benefits: narrowly distributed particles, scalable for industrial production, and continuous process.

• Restrictions: limited application for heat-labile biomolecules; possible thermal degradation of sensitive medications.

4. Ionotropic Gelation

Ionotropic gelation, which uses ionic crosslinking to create microspheres in mild aqueous conditions, is primarily utilized for natural polymers such as chitosan and alginate [30].

• Method: Sphere formation and instantaneous gelation occur when a polymer solution is dropped into a solution containing multivalent cations (for example, Ca2+ for alginate).

• Benefits: great for encapsulating delicate proteins and peptides, requires neither heat nor organic solvents.

• Constraints: frequently generates particles larger than 10 μm, occasionally with reduced mechanical strength.

5. Electrospraying & Microfluidic Techniques

Modern techniques for fabricating microspheres employ electric fields or microfluidic chips to produce monodisperse microspheres with exact control over shape and size [24].

• Electrospraying: A polymer-drug solution is run through a charged needle to create a fine spray of charged droplets, which, when the solvent evaporates, solidify into microspheres.

• Microfluidics: Uniform droplets that solidify into microspheres are formed by precisely controlling fluid streams in microscale channels.

• Uses: beneficial for creating stimuli-responsive carriers, encapsulating several medications, and creating core-shell structures.

5. Polymers Used in Microsphere Formulation

The choice of polymer largely determines the **degradation rate**, **mechanical strength**, and **drug release profile**.

- **PLGA&PLA**

Injectable sustained-release formulations frequently use these synthetic biodegradable polymers, which hydrolyze to break down[21].

- **Chitosan,Alginate,Dextran**

Due to their microbial sensitivity, natural, biocompatible, and biodegradable substances are particularly helpful for colon-targeted systems[23,26].

- **Eudragit-S100**

Drug release is guaranteed only after the formulation reaches the colon thanks to a pH-sensitive polymer that dissolves at pH > 7. extensively utilized in systems that target the oral colon [28].

- **Gellan Gum & Guar Gum**

Plant-based polysaccharides that create robust hydrogels; they are helpful in formulations that are microbially degradable and mucoadhesive [30].

5.1 Polymeric Carriers for Colon-Targeted Microspheres

Choosing the right polymer is foundational to the success of colon-targeted microsphere systems, especially for delicate drugs like dihydroartemisinin (DHA). The polymer not only determines where and how the drug is released but also impacts stability, manufacturability, and therapeutic efficacy.

Natural Polymers: Biodegradable and Biocompatible

Because of their biodegradability and ability to be selectively broken down by colonic microflora, natural polysaccharides such as chitosan, alginate, and pectin are highly valued in formulations that target the colon. Pectin was actually the most commonly used polymer studies)in colon-targeted drug delivery research, followed by chitosan and alginate, according to a recent systematic review [31]. By electrostatically interacting with colonic mucin, chitosan, alginate, and pectin improve drug retention and may increase local bioavailability, according to another open-access review that highlighted their mucoadhesive qualities [32].

Synthetic Polymers: pH- and Time-Responsive Release

Methacrylic acid copolymers, such as Eudragit S100, are frequently used to prevent medications from releasing too soon in the upper gastrointestinal tract because they are pH-sensitive. These polymers dissolve when the pH rises above 6.0–7.0, making them perfect for release in the terminal ileum or colon, but they stay intact in acidic and early intestinal pH [33]. It has also been demonstrated that a targeted formulation that combines microbial triggers and pH sensitivity (e.g., starch + Eudragit S) can overcome physiological variability and improve site-specific release.[34]

Hybrid Systems: Combining Strengths

The most effective systems frequently use a mix of polymers to take advantage of bacterial degradation and pH sensitivity. An excellent illustration is the enteric coating of Eudragit S100 over pectin microspheres, which prevented drug release in the stomach or intestines and allowed release only in the colonic environment when enzymes were active [35].

6. Limitations of Dihydroartemisinin in Conventional Delivery and the Potential of Colon Targeting

Dihydroartemisinin (DHA), the most active metabolite of artemisinin derivatives, has demonstrated potent antimalarial and anticancer effects. However, its clinical translation has been limited due to several drawbacks associated with conventional oral delivery.

Physicochemical properties

Because DHA is poorly soluble in water, the gastrointestinal tract has a much harder time dissolving and absorbing it[36]. Additionally, it shows chemical instability in acidic environments,

which results in stomach degradation and decreased therapeutic effectiveness[37, 38]. Furthermore, DHA's sustained activity is limited by its brief plasma half-life of 1-2 hours. [39]

Pharmacokinetic issues

Traditional oral DHA formulations have a low and inconsistent bioavailability due to their extensive first-pass metabolism and quick elimination [40,41]. Particularly for long-term diseases like cancer or parasitic infections that need constant treatment, this pharmacokinetic behavior results in inadequate systemic exposure [42].

Therapeutic drawbacks

DHA requires frequent dosing because of its short half-life and poor stability, which lowers patient compliance [36]. Additionally, rapid clearance can result in sub-therapeutic plasma levels, which can cause incomplete tumor inhibition in cancer therapy and recrudescence in malaria treatment.

Potential of Colon Targeting

By shielding DHA from deterioration in the stomach and upper intestine, colon-targeted delivery systems can aid in overcoming these difficulties and enhancing stability [44]. Additionally, the colon has a lower enzymatic activity and a more favorable pH environment, which may improve DHA's absorption and residence time [45,46,47]. Moreover, colon-targeted carriers' prolonged release can increase systemic exposure, lower dosage requirements, and enhance therapeutic results [48]. By delivering DHA locally at the disease site, this method may also increase its effectiveness in treating colonic conditions like colorectal cancer [49].

7. Future Perspectives and Challenges

Manufacturing & Scalability

Unexpected difficulties frequently arise when moving from lab-scale techniques like emulsion-solvent evaporation or spray-drying to large-scale production. It is difficult to maintain batch-to-batch reproducibility, drug loading, and particle size at industrial volumes. Although they come with higher material and validation costs, recent reviews show that cutting-edge methods like hot-melt extrusion (HME) and 3D printing could improve uniformity and scalability [50].

Regulatory Landscape

Colon-targeted systems, like delivery platforms that are pH-sensitive or microbiota-triggered, are in a regulatory "grey zone." Regulators require solid proof of manufacturing quality, safety, and predictable in vivo release. The 2024 review by AAPS PharmSciTech emphasizes how new processing technologies could make regulatory scrutiny worse, particularly for systems that depend on physiology unique to each patient [51].

Colon Variability Among Patients

Individual differences in colon physiology, particularly between healthy and diseased states, are significant. These differences include pH, transit time, and microbiome composition. This variability is described as a significant barrier to standardizing colon-targeted formulations in a 2022 J Control Release review. This obstacle might be addressed with the use of customized dosing plans and predictive in vitro models [52].

Stability and Storage Challenges

Under normal storage conditions, microspheres must maintain their stability, especially in humid or tropical climates that are typical in areas where malaria is endemic. Real-world viability depends on formulation parameters, such as drug content, particle integrity, and release profile, remaining constant despite variations in temperature and humidity [53].

Clinical Translation

There are still few clinical trials examining microsphere-based colon-targeted drug delivery, despite encouraging preclinical data. In order to close this gap and eventually enable human studies, collaborations, funding, and early regulatory framework alignment are necessary.

Advanced Materials and Future Innovations

Stimuli-responsive polymers, hybrid nanomicrospheres, and intelligent microdevices that can adjust to the specific surroundings of each patient are examples of the next frontier. Precision therapeutics may be made possible by incorporating artificial intelligence to model release kinetics using individualized data [(54)].

8. Conclusion

A promising answer to many of the problems with traditional drug delivery is provided by colon-targeted microspheres. They increase stability, prolong drug release, and lessen undesirable side effects by shielding the medication until it reaches the large intestine. This method offers a useful way to increase the therapeutic benefits of dihydroartemisinin, which has poor solubility and breaks down quickly in the body. Although the potential of these systems has been enhanced by recent developments in polymers and formulation techniques, problems like large-scale manufacturing, regulatory acceptance, and patient-specific variability still require attention. In order to move these systems from research to practical use, more thorough clinical studies and the creation of intelligent, colon-responsive polymers will be necessary. All things considered, colon-targeted microspheres mark a significant advancement in site-specific drug delivery technologies as well as a new delivery method for dihydroartemisinin.

9. References

1. Ghosh S, Majumdar S, Ganguly D. A brief review on colon-specific drug delivery system for targeting to colonic region. *J Appl Pharm Res*. **2021**;9(4):9–15.
2. McCoubrey LE, Favaron A, Awad A, Orlu M, Gaisford S, Basit AW. Colonic drug delivery: Formulating the next generation of colon-targeted therapeutics. *J Control Release*. **2023**;353:1107–26.
3. Yamamura R, Inoue KY, Nishino K, Yamasaki S. Intestinal and fecal pH in human health. *Front Microbiomes*. **2023**;2:1192316.
4. Kulkarni N, Jain P, Shindikar A, Suryawanshi P, Thorat N. Advances in the colon-targeted chitosan-based multiunit drug delivery systems for the treatment of inflammatory bowel disease. *Carbohydr Polym*. **2022**;288:119351.
5. Udaipuria N, Bhattacharya S. Novel carbohydrate polymer-based systems for precise drug delivery in colon cancer: Improving treatment effectiveness with intelligent biodegradable materials. *Biopolymers*. **2025**;116(1):e23632.
6. "Advancements in Colon-Targeted Drug Delivery: A Comprehensive Review on Recent Techniques with Emphasis on Hot-Melt Extrusion and 3D Printing Technologies." *AAPS PharmSciTech*. **2024**;25:236.
7. Yecheng L, et al. Inulin-based colon targeted drug delivery systems: Advancing site-specific therapeutics. *Discover Mater*. **2025**;5:114.
8. Bertin L, et al. Polysaccharide-based drug delivery targeted approach for colon cancer treatment: A comprehensive review. *Therap Adv Gastroenterol*. **2024**;17:17562848241303651.
9. Cui, M., Zhang, M., & Liu, K. Colon-targeted drug delivery of polysaccharide-based nanocarriers for synergistic treatment of inflammatory bowel disease: A review. *Carbohydrate polymers.* **2021,***272*, 118530.
10. Deljavan Ghodrati A, Çomoğlu T. Mucoadhesive polymers in colon targeted drug delivery systems: A comprehensive review. *J Fac Pharm Ankara Univ*. **2024**;48(2):696–713.

11. Alshammari ND, Elkanayati R, Vemula SK, et al. Advancements in Colon-Targeted Drug Delivery: A Comprehensive Review on Recent Techniques with Emphasis on Hot-Melt Extrusion and 3D Printing Technologies. *AAPS PharmSciTech*. **2024**;25:236.
12. Dos Santos AM, Carvalho SG, Meneguin AB, et al. Oral delivery of micro/nanoparticulate systems based on natural polysaccharides for intestinal disease therapy: challenges, advances, and future perspectives. *J Control Release*. **2021**;334:353–366.
13. McCoubrey LE, Favaron A, Awad A, et al. Colonic drug delivery: Formulating the next generation of colon-targeted therapeutics. *J Control Release*. **2023**;353:1107–1126.
14. Ghodrati A, Çomoğlu T. An overview on recent approaches for colonic drug delivery systems. *Pharm Dev Technol*. **2024**;29(5):566–581.
15. Kumari B, Upadhyay PK, Kumar M, et al. An updated overview of recent advances on formulation development for colon targeting. *Int J Pharm Sci Res*. **2020**;11(4):1571–1580.
16. Zheng B, Wang L, Yi Y, et al. Design strategies, advances and future perspectives of colon-targeted delivery systems for the treatment of inflammatory bowel disease. *Asian J Pharm Sci*. **2024**;19:100943.
17. Hu S, Zhao R, Xu Y, et al. Orally-administered nanomedicine systems targeting colon inflammation for the treatment of inflammatory bowel disease: Latest advances. *J Mater Chem B*. **2023**;12(1):13–38.
18. Ray S, Shukla S, Singhai AK, et al. Colon drug delivery system and their benefits and the carriers for delivery of drugs to colon: a review. *Asian J Pharm Educ Res*. **2020**;9:15–26.
19. Hua S, Marks E, Schneider JJ, et al. Advances in oral nano-delivery systems for colon-targeted drug delivery in inflammatory bowel disease: selective targeting to diseased versus healthy tissue. *Nanomedicine (Lond)*. **2015**;11(5):1117–1132.
20. Ábrómez-Gálvez R, et al. Microparticles, microspheres, and microcapsules—a review. *Pharmaceutics*. **2020**;12(3):209.
21. Butreddy A, Gaddam RP, Kommineni N, et al. PLGA/PLA-based long-acting injectable depot microspheres in clinical use. *Int J Mol Sci*. **2021**;22(16):8884.
22. Zhang M, et al. Ethyl cellulose-based microparticles: A comprehensive review. *J Drug Deliv Sci Technol*. **2022**;67:102911.
23. Petrovici AR, et al. Dextran formulations as delivery systems of therapeutic agents. *Molecules*. **2023**;28(3):1086.
24. Feng T, et al. Microfluidic fabrication of microspheres for drug delivery. *Front Bioeng Biotechnol*. **2025**;13:1551199.
25. Yang Y, Li G, Han W, et al. Efficient porous microspheres by foam-phase evaporation. *Chin J Chem Eng*. **2021**;29(1):409–16.
26. Prajapati ST, et al. Chitosan-based colon-targeted microparticles: preparation and characterization. *AAPS PharmSciTech*. **2023**;24(2):73.
27. Awasthi R, et al. Colon-specific drug delivery for inflammatory bowel disease. *Drug Discov Today*. **2022**;27(2):586–97.
28. Momin M, et al. Colon-targeted Eudragit-coated microspheres: formulation and evaluation. *J Microencapsul*. **2021**;38(7):579–92.
29. Patil SA, et al. Advances in spray drying for microsphere fabrication. *J Control Release*. **2023**;361:297–313.
30. Vyas D, et al. Ionotropically gelled gellan gum microparticles for colon targeting. *Pharmaceutics*. **2025**;17(5):569.
31. Patil S, Parmar D, Amin A, et al. Carbohydrate polymer-based carriers in colon-targeted pharmaceutical formulations: a systematic review. *Carbohydr Polym*. **2023**;299:120310.
32. Tas C, Calıskan Ö, Celebioglu A, et al. Mucoadhesive polymers for oral drug delivery: Mechanisms and design strategies. *Int J Biol Macromol.* **2023**;234:123–138.
33. Shendge RS, et al. Polymeric microspheres redefining the landscape of colon-targeted delivery. *Eur J Med Chem Rep.* **2024**;11:100156.

34. Kang J, Zhang J, Gao Y et al. Strategic approaches for colon-targeted drug delivery: pH-triggered and microflora-mediated release. *Pharmaceutics*. **2020**;12(2):154.
35. Vilar G, Tulla-Puche J, Albericio F. Polymers and drug delivery systems. *Curr Drug Deliv.* **2012**;9(4):367–94.
36. Ahmadi E, Sadrjavadi K, Mohammadi G, Fattahi A. De-Esterified tragacanth microspheres in Eudragit S100 capsules for colon-targeted delivery. *Iran J Pharm Res.* **2018**;17(2):e124822.
37. Dos P, et al. Smart hydrogels of Eudragit S100 and acrylic acid for colon-specific delivery of losartan. *Drug Deliv.* **2021**;28(1):1234–1246.
38. Zhang C, et al. Core–shell curcumin microparticles for site-specific release in ulcerative colitis (electrospray). *Chin Med.* **2021**;16:92.
39. Alshammari ND, Elkanayati R, Vemula SK, et al. Advancements in colon-targeted drug delivery: Hot-melt extrusion and 3D printing. *AAPS PharmSciTech.* 2024;25(7):236.
40. MDPI Editorial Team. In vitro methodologies for colon-targeted drug delivery evaluation. *Pharmaceutics.* **2022**;14(2):291.
41. Xu Y, Xu S, Li Y. Improving the solubility and bioavailability of dihydroartemisinin using solid dispersions and inclusion complexes. *Drug Dev Ind Pharm.* **2021**;47(8):1231–8.
42. Olliaro P, Navaratnam V. Stability of the antimalarial drug dihydroartemisinin under physiologically relevant conditions; implications for clinical treatment and pharmacokinetic studies. *Antimicrob Agents Chemother.* **2015**;59(11):7140–4.
43. Morris CA, Duparc S, Borghini-Fuhrer I, Jung D, Shin CS, Fleckenstein L. Review of the clinical pharmacokinetics of artesunate and its active metabolite dihydroartemisinin following various routes of administration. *Malar J.* **2011**;10:263.
44. Sriwongjanya M, Mallick B, Swanson BD, et al. Development of nanoscale drug delivery systems of dihydroartemisinin for cancer therapy: A review. *Asian J Pharm Sci.* **2022**;17(4):475–90.
45. Wong KH, Yang D, Chen S, He C, Chen M. Development of nanoscale drug delivery systems of dihydroartemisinin for cancer therapy: A review. *Asian J Pharm Sci.* **2022**;17(4):475–90.
46. Qian S, et al. Encapsulating DHA in gelatin or hyaluronic acid nanoparticles enhanced bioavailability in lung cancer cells. *J Nanobiotechnology.* **2020**;18:69.
47. Morris CA, et al. Clinical PK review of artesunate and DHA, pointing to short half-life and frequent dosing. *Malar J.* 2011;10:263. Alshammari ND, et al. Colonic drug delivery: Formulating the next generation of colon-targeted therapeutics. *AAPS PharmSciTech.* **2024**;25(7):236.
48. Lv Y, et al. Colon-specific delivery of methotrexate using hyaluronic acid-modified pH-responsive nanocarrier for colitis therapy in mice. *Carbohydr Polym.* **2021**;269:118325.
49. Frontiers Editorial Office. Targeted lipid nanoparticles encapsulating dihydroartemisinin and chloroquine phosphate for suppressing colorectal cancer metastasis. *Front Pharmacol.* **2021**;12:720777.
50. Alshammari ND, Elkanayati R, Vemula SK, Al Shawakri E, Uttreja P, Almutairi M, Repka MA. Advancements in Colon-Targeted Drug Delivery: A Comprehensive Review on Recent Techniques with Emphasis on Hot-Melt Extrusion and 3D Printing Technologies. *AAPS PharmSciTech*. **2024**;25(7):236. doi:10.1208/s12249-024-02965-w
51. Wang L, Guo B. Colonic drug delivery: Formulating the next generation of colon-targeted therapeutics. *J Control Release*. **2023**;353:1107–1126.
52. Hussain A, Bhagat M. Challenges and advances in colon-targeted nano-drug delivery systems. *Nanomedicine*. **2020**;15(11):951–970.
53. Iswandana R, Putri KS, Gunawan M, Larasati SA. Challenge and development strategy for colon-targeted drug delivery system. *Pharm Sci Res.* **2022**;9:17–27.
54. Dos Santos AM, Carvalho SG, Meneguin AB, Sábio RM, Gremião MPD, Chorilli M. Oral delivery of micro/nanoparticulate systems based on natural polysaccharides for intestinal diseases therapy: Challenges, advances and future perspectives. *J Control Release.* **2021**;334:353–366.