RESEARCH PAPER

Development of pH-Sensitive Polymeric Nanoparticles for Colon-Targeted Drug Delivery: A Comprehensive Review

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ABSTRACT

Colon-targeted drug delivery has become an important strategy for improving the treatment of colonic disorders such as inflammatory bowel disease, colorectal cancer, colonic infections and local inflammatory conditions, while also offering opportunities for the oral delivery of labile biomolecules. Conventional oral dosage forms often release drugs in the stomach or small intestine, causing premature degradation, poor therapeutic concentration at the disease site and increased systemic adverse effects. pH-sensitive polymeric nanoparticles are advanced smart nanocarrier systems designed to exploit physiological pH changes along the gastrointestinal tract. These systems remain comparatively stable in the acidic gastric environment and trigger drug release in the near-neutral to alkaline conditions of the distal intestine and colon. The nanoscale architecture further improves drug protection, mucosal interaction, controlled release and cellular uptake. This review discusses the rationale, mechanisms, polymers, preparation techniques, characterization tools, therapeutic applications, limitations, recent advances and future perspectives of pH-sensitive polymeric nanoparticles for colon-specific delivery. The article also highlights the need for reproducible formulation design, clinically relevant evaluation models, safety assessment and scalable manufacturing to support successful translation from experimental research to patient care.

Keywords: Colon-targeted drug delivery; pH-sensitive nanoparticles; polymeric nanoparticles; Eudragit; chitosan; alginate; inflammatory bowel disease; colorectal cancer; nanomedicine; controlled release.

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1. INTRODUCTION

Oral administration remains the most preferred route for drug delivery because it is convenient, non-invasive, economical and highly acceptable to patients. However, conventional oral dosage forms frequently fail to deliver therapeutic agents selectively to the colon. Drugs may dissolve or degrade in the stomach and small intestine before reaching the target region, which can reduce local efficacy and increase systemic toxicity. Colon-specific delivery is therefore highly valuable for diseases requiring local action in the large intestine, including ulcerative colitis, Crohn's disease, colorectal cancer and microbial infections.[1,2]

The gastrointestinal tract possesses a distinct physiological pH gradient. The stomach is strongly acidic, the small intestine gradually becomes less acidic, and the terminal ileum and colon usually maintain a comparatively higher pH. This natural variation provides a useful trigger for designing pH-sensitive delivery systems. Polymers containing ionisable functional groups can remain intact at gastric pH and dissolve, swell or erode when exposed to the higher pH of the colon, thereby promoting site-specific drug release.[3,4,5]

Polymeric nanoparticles offer additional advantages over conventional pH-dependent tablets and capsules. Their small size, high surface area, modifiable surface properties and capacity to encapsulate both hydrophilic and hydrophobic drugs allow controlled release, improved mucosal residence and better protection against enzymatic degradation. By combining pH responsiveness with nanoscale drug carriers, it becomes possible to design systems that protect the drug during transit and release it preferentially at the colonic site.[6,7,8]

The present review provides a consolidated discussion of pH-sensitive polymeric nanoparticles for colon-targeted drug delivery. It covers the scientific rationale, gastrointestinal pH considerations, release mechanisms, polymer selection, formulation methods, characterization requirements, therapeutic applications, limitations, recent advances and future opportunities in this growing area of pharmaceutical nanotechnology.[9,10]

2. RATIONALE FOR COLON-TARGETED DRUG DELIVERY

Colon-targeted delivery is mainly intended to concentrate the drug at the large intestine while minimizing unnecessary exposure to the upper gastrointestinal tract and systemic circulation. This approach is especially important in inflammatory bowel disease, where direct delivery of anti-inflammatory drugs to inflamed mucosa can improve therapeutic response and reduce adverse effects associated with systemic treatment.[11,12]

In colorectal cancer, localised delivery can increase drug availability at tumour sites and reduce off-target toxicity. A colonic delivery system may also support sustained exposure of anticancer agents, molecularly targeted drugs or herbal bioactives at the tumour microenvironment. In addition, the colon has lower levels of certain digestive enzymes than the stomach and small intestine, making it a potential site for the delivery of peptides, proteins and nucleic acid-based therapeutics.[13,14,15]

Colon targeting is also relevant for chronotherapy. Some diseases, such as arthritis, asthma and bowel inflammatory symptoms, show time-dependent worsening. Delivery systems with delayed or triggered release can be designed to match drug release with the period of greatest disease activity. Thus, colon-targeted drug delivery provides benefits in local therapy, systemic delivery of labile molecules and time-programmed pharmacotherapy.[16,17,18]

3. GASTROINTESTINAL pH VARIATION AND ITS ROLE IN COLON TARGETING

The principle of pH-sensitive colon delivery depends on the ability of a formulation to remain stable in acidic gastric conditions and release its payload after reaching the more neutral or slightly alkaline environment of the distal intestine and colon. However, gastrointestinal pH is not constant; it varies with food intake, disease status, age, microbial activity and inter-individual physiology. Therefore, pH sensitivity should ideally be combined with additional mechanisms such as enzyme sensitivity, mucoadhesion or time-dependent release for improved reliability.[19,20,21]

GI region	Approximate pH range	Formulation implication	Desired nanoparticle behaviour
Stomach	1.0-3.0	Risk of acid degradation and premature release	Compact, unionised or insoluble polymer matrix
Small intestine	4.0-6.8	Possible partial polymer swelling or leakage	Limited release and preserved drug protection
Terminal ileum/colon	6.5-7.5	Target site for release	Ionisation, swelling, erosion or dissolution leading to drug release

Table 1. Gastrointestinal pH variation and expected behaviour of pH-sensitive polymeric nanoparticles.

4. MECHANISM OF pH-SENSITIVE DRUG RELEASE

pH-sensitive polymeric nanoparticles release the drug through one or more interrelated mechanisms. The first mechanism is ionisation of functional groups. Polymers containing carboxylic acid or amino groups undergo

changes in charge depending on environmental pH. At low pH, many acidic polymers remain unionised and less soluble, whereas at higher pH they become ionised and more hydrophilic. This transition promotes swelling, pore formation and drug diffusion.[22,23]

The second mechanism is polymer swelling. Ionisation generates electrostatic repulsion between polymer chains, causing expansion of the polymeric network. Swelling increases water penetration and creates channels through which the entrapped drug can diffuse. The degree of swelling depends on polymer composition, cross-linking density, drug loading, particle size and the pH of the surrounding medium.[24,25]

The third mechanism is dissolution or erosion of the polymer coating. Methacrylic acid copolymers such as Eudragit derivatives are widely used because they remain intact in acidic conditions but dissolve at specific pH thresholds. For example, Eudragit L100 dissolves above pH 6, whereas Eudragit S100 dissolves above pH 7, making them suitable for distal intestinal and colonic delivery. Natural polysaccharides such as pectin, guar gum and chitosan derivatives may also undergo degradation by colonic microbiota, creating a combined pH- and enzyme-responsive system.[26,27,28]

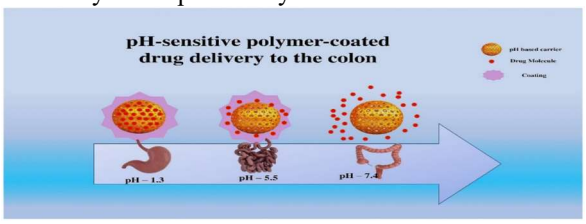

Figure 1. Schematic representation of pH-sensitive polymeric nanoparticles remaining intact in the stomach and releasing drug in the colon by ionisation, swelling, erosion or microbiota-assisted degradation.

5. POLYMERS USED IN pH-SENSITIVE NANOPARTICLES

Polymer selection is the most critical factor in the design of pH-sensitive colon-targeted nanoparticles. The polymer should protect the drug in the upper gastrointestinal tract, respond predictably at colonic pH, be biocompatible, non-toxic, reproducible and compatible with the selected drug. Both synthetic and natural polymers are used, and many modern systems combine two or more polymers to improve targeting precision and release control.[29,30,31]

Polymer class	Examples	Main pH-responsive behaviour	Major advantages	Key limitations
Methacrylic acid copolymers	Eudragit L100, Eudragit S100	Dissolve above specific pH thresholds	Predictable release, widely used, good film-forming property	Variable GI pH may cause incomplete or premature release
Biodegradable synthetic polymers	PLGA, PLA, PCL	Controlled degradation; can be coated with pH-sensitive polymers	Good safety profile and sustained release	May require organic solvents and careful process control
Cationic natural polymers	Chitosan and derivatives	Protonation/deprotonation and mucoadhesion	Biocompatible, mucoadhesive, useful for biomolecules	Poor solubility at neutral pH unless modified
Anionic polysaccharides	Alginate, pectin	Gel formation and microbial degradation	Natural, biodegradable and colon-responsive	Batch variability and weak mechanical strength
Microbiota-degradable polysaccharides	Guar gum, dextran, inulin	Degradation by colonic enzymes	High colon specificity when combined with pH polymers	Variable microbiota composition may affect release

Table 2. Common polymers used for pH-sensitive and colon-targeted polymeric nanoparticles.

6. METHODS OF PREPARATION

The method used for nanoparticle preparation strongly influences particle size, polydispersity index, zeta potential, entrapment efficiency, drug release profile and physical stability. Selection of the method depends on the solubility of the drug, polymer type, desired release behaviour, sensitivity of the active ingredient and scale-up feasibility.[32,33]

6.1 Emulsion-solvent evaporation method

In this method, the drug and polymer are dissolved in a volatile organic solvent and emulsified into an aqueous phase containing a stabiliser. Solvent evaporation leads to polymer precipitation and nanoparticle formation. The

method is suitable for hydrophobic drugs and provides good control over particle size, but residual solvent removal and scale-up require careful validation.[34,35]

6.2 Nanoprecipitation method

Nanoprecipitation, also called solvent displacement, involves dissolving the polymer and drug in a water-miscible solvent followed by addition into an aqueous phase. Rapid diffusion of solvent produces nanosized particles. It is simple, rapid and suitable for heat-sensitive drugs; however, it is more efficient for drugs with suitable solubility balance between solvent and non-solvent phases.[36,37]

6.3 Ionic gelation method

Ionic gelation is commonly applied for chitosan, alginate and related natural polymers. Nanoparticles are formed through electrostatic interaction between oppositely charged polymeric species or cross-linking agents. This method is mild, avoids harsh organic solvents and is useful for proteins, peptides and nucleic acids, but particle stability may depend strongly on pH and ionic strength.[38,39]

6.4 Spray drying

Spray drying converts a polymer-drug solution or suspension into dry particles by atomisation into a hot drying chamber. It is attractive for industrial production and dry powder formulations. Nevertheless, high inlet temperature and process parameters must be optimized to avoid drug degradation, low yield and broad particle size distribution.[40,41]

6.5 Microfluidics and advanced fabrication

Microfluidic preparation provides precise control over mixing, nucleation and particle growth. It may improve reproducibility, narrow size distribution and scalability through continuous manufacturing. Such techniques are increasingly explored for complex nanomedicines requiring strict quality-by-design control.[42,43]

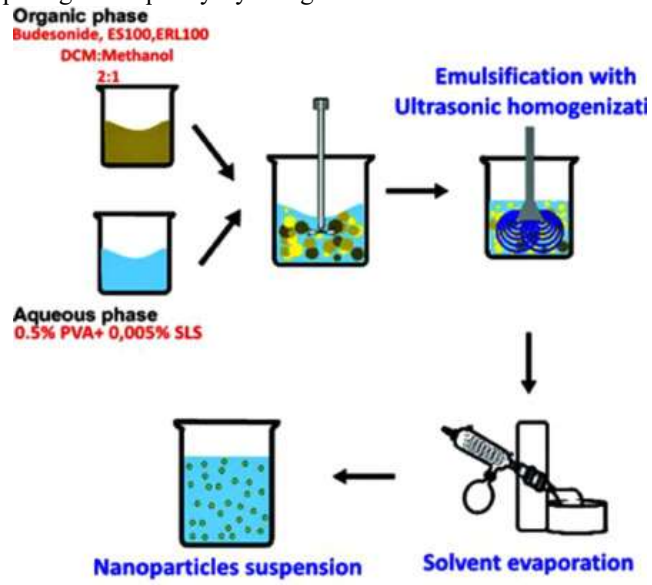

Figure 2. General preparation workflow of pH-sensitive polymeric nanoparticles: polymer-drug selection, nanoparticle fabrication, purification, drying and evaluation under simulated gastrointestinal pH conditions.

7. CHARACTERIZATION AND EVALUATION PARAMETERS

Comprehensive characterization is required to confirm that pH-sensitive polymeric nanoparticles possess suitable physicochemical, pharmaceutical and biological properties. Evaluation should not be limited to particle size; it must include drug loading, morphology, solid-state behaviour, compatibility, pH-dependent release, stability and in vivo targeting performance.[44,45]

Evaluation category	Parameters	Common techniques	Importance
Particle properties	Size, PDI, zeta potential	DLS, electrophoretic mobility	Predicts stability, aggregation and mucosal interaction
Morphology	Shape and surface structure	SEM, TEM, AFM	Confirms nanostructure and surface smoothness
Drug incorporation	Drug loading and entrapment efficiency	UV, HPLC, LC-MS	Ensures dose uniformity and formulation efficiency
Compatibility	Drug-polymer interaction	FTIR, DSC, TGA	Detects chemical interaction or thermal instability
Solid-state nature	Crystallinity or amorphous dispersion	XRD, DSC	Influences dissolution and release performance
pH-dependent release	Release at pH 1.2, 6.8 and 7.4	Dialysis, dissolution apparatus	Confirms protection in stomach and release in colon
Biological performance	Cell uptake, cytotoxicity, mucoadhesion	Cell culture assays, microscopy	Supports safety and targeting potential
In vivo	Pharmacokine	Animal	Demonstra

targeting	tics and biodistribution	models, imaging, tissue assay	tes colon-specific delivery

Table 3. Key characterization parameters for pH-sensitive polymeric nanoparticles.

8. DESIGN CONSIDERATIONS FOR FORMULATION DEVELOPMENT

An effective colon-targeted nanoparticle should possess optimal size, narrow size distribution, sufficient surface charge for colloidal stability, high entrapment efficiency, minimal burst release in gastric pH and predictable release at colonic pH. Excessive particle size may reduce mucosal penetration, while very small particles may undergo rapid transit or systemic uptake. Therefore, particle engineering must balance protection, release and residence time.[46,47,48]

Surface properties are equally important. Mucoadhesive systems may prolong colonic residence, whereas PEGylation or hydrophilic coatings can improve stability and reduce nonspecific interactions. Ligand conjugation may enhance uptake by inflamed tissues or tumour cells. In addition, formulation scientists must consider polymer-drug compatibility, manufacturing reproducibility, residual solvents, sterilization feasibility and long-term storage stability.[49,50]

Quality-by-design principles can be applied to identify critical material attributes and critical process parameters. Factors such as polymer concentration, organic-to-aqueous phase ratio, stabilizer concentration, stirring or homogenization speed, cross-linker amount and drying conditions can significantly affect nanoparticle performance. Systematic optimization improves product robustness and supports future regulatory acceptance.[51,52]

9. THERAPEUTIC APPLICATIONS

pH-sensitive polymeric nanoparticles are relevant for a broad range of colonic diseases and systemic delivery applications. Their ability to protect drugs in the upper gastrointestinal tract and release them in the colon makes them suitable for both conventional small molecules and sensitive biological therapeutics.[53,54]

Therapeutic area	Drug types	Formulation objective	Expected clinical benefit
Inflammatory bowel disease	Mesalamine, corticosteroids, immunomodulators, herbal anti-inflammatory agents	Local release at inflamed colonic mucosa	Improved efficacy with reduced systemic adverse effects
Colorectal cancer	Chemotherapeutic agents, phytoconstituents, targeted drugs	Higher drug concentration at tumour site	Enhanced anticancer response and reduced off-target toxicity
Colonic infections	Antibiotics and antimicrobial phytochemicals	Drug release at infection site	Better local concentration and lower dose requirement
Protein and peptide delivery	Insulin-like peptides, enzymes, vaccines, biologics	Protection from acid and enzymes	Improved oral stability and potential absorption
Gene and nucleic acid delivery	siRNA, plasmids, antisense oligonucleotides	Protection and intracellular delivery	Potential for advanced molecular therapy

Table 4. Therapeutic applications of pH-sensitive polymeric nanoparticles in colon-targeted drug delivery.

10. ADVANTAGES OF pH-SENSITIVE POLYMERIC NANOPARTICLES

1. They provide site-specific delivery by preventing or reducing drug release in the stomach and upper small intestine.
2. They protect acid-labile and enzyme-sensitive drugs during gastrointestinal transit.
3. They support controlled and sustained release, reducing dosing frequency and improving patient compliance.
4. They can increase local drug concentration at the colonic disease site and reduce systemic toxicity.
5. They can be surface-modified for mucoadhesion, active targeting or improved mucus penetration.
6. They are suitable for small molecules, phytoconstituents, peptides, proteins and nucleic acid-based therapeutics.[55,56]

11. LIMITATIONS AND CHALLENGES

Despite strong research interest, pH-sensitive polymeric nanoparticles face several translational challenges. The most important limitation is variability in gastrointestinal pH. The pH of the colon may be altered by diet, disease state, medication, microbial composition and individual physiology. In inflammatory bowel disease, local pH may differ significantly from healthy colon, potentially affecting polymer dissolution and release behaviour.[57,58]

Premature drug release is another concern. Some pH-sensitive polymers may begin to swell or dissolve in the distal small intestine, resulting in incomplete colon specificity. Conversely, insufficient pH elevation may delay or reduce drug release at the intended site. These problems can be reduced by using dual-trigger systems that combine pH responsiveness with enzyme-mediated

degradation, time-dependent release or ligand-mediated targeting.[59,60]

Manufacturing and regulatory barriers also remain significant. Nanoparticle preparation must be reproducible at industrial scale, with acceptable batch-to-batch consistency, low residual solvent content, stable storage properties and validated analytical methods. Regulatory agencies require detailed safety, biodistribution, toxicity and quality data, especially because nanocarriers may interact with biological systems differently from conventional dosage forms.[61,62]

12. RECENT ADVANCES

12.1 Dual-trigger and multi-stimuli responsive systems

Recent research has moved beyond single pH-triggered systems toward dual- or multi-responsive carriers. These systems combine pH sensitivity with enzyme responsiveness, redox sensitivity, microbiota-triggered degradation, temperature responsiveness or ligand-mediated uptake. Such strategies improve selectivity and reduce the risk of premature release in the upper gastrointestinal tract.[63,64]

12.2 Microbiota-responsive nanoparticles

The colon contains a dense microbial population capable of producing enzymes that degrade specific polysaccharides. Nanoparticles based on pectin, guar gum, dextran, inulin or chitosan derivatives can exploit this enzymatic environment. When combined with pH-sensitive coatings, microbiota-responsive materials offer improved colonic specificity and are particularly promising for inflammatory bowel disease and colorectal cancer.[65,66,67]

12.3 Targeted and multifunctional nanoparticles

Surface functionalization with ligands such as folic acid, peptides, antibodies or lectins can enhance binding to receptors overexpressed on inflamed or cancerous colonic cells. Multifunctional nanoparticles may combine drug delivery, imaging and diagnostic functions, allowing theranostic applications in precision therapy.[68,69,70]

12.4 Biodegradable and clinically acceptable polymers

Greater emphasis is being placed on biodegradable, biocompatible and regulatory-acceptable polymers such as PLGA, chitosan, alginate and methacrylic acid copolymers. These materials can be engineered into hybrid nanocarriers that combine the advantages of synthetic precision and natural polymer biocompatibility.[71,72]

13. FUTURE PERSPECTIVES

Future development of pH-sensitive polymeric nanoparticles should focus on clinically realistic design. Because gastrointestinal physiology differs among patients, personalized delivery strategies may be needed, especially for patients with inflammatory bowel disease, altered microbiota or abnormal intestinal transit time. Formulations that respond to more than one colonic trigger are likely to provide greater reliability than pH-only systems.[73,74]

Artificial intelligence, computational modelling and quality-by-design tools can accelerate nanoparticle optimization. Predictive models may help select polymers, estimate release behaviour, optimize process parameters and reduce experimental trial-and-error. Integration of continuous manufacturing and microfluidic technology may further support reproducible production.[75,76]

Successful clinical translation will require stronger in vivo evidence, standardized dissolution models that better simulate gastrointestinal transit, long-term toxicity studies and well-designed clinical trials. Collaboration among formulation scientists, clinicians, toxicologists and regulatory experts will be essential to convert promising laboratory systems into safe and effective patient-ready products.[77,78,79,80]

14. CONCLUSION

pH-sensitive polymeric nanoparticles represent a highly promising platform for colon-targeted drug delivery. By exploiting gastrointestinal pH gradients, these systems can protect drugs from premature release in the stomach and small intestine and enhance drug availability in the colon. Their nanoscale structure enables improved drug loading, controlled release, mucosal interaction and potential cellular uptake. They are particularly useful for inflammatory bowel disease, colorectal cancer, colonic infections and delivery of sensitive biomolecules. However, challenges related to variable gastrointestinal pH, premature release, scale-up, stability, safety and regulatory approval must be addressed. Future progress will depend on hybrid polymers, dual-trigger mechanisms, advanced characterization, quality-by-design optimization and clinically relevant evaluation. With continued research, pH-sensitive polymeric nanoparticles can become an important tool for precise, effective and patient-friendly colon-specific therapy.

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