

REVIEW ARTICLE

Carbohydrate polymer derivatives as gastrointestinal pH-responsive oral drug delivery systems: A review

Diego E. Boldrini^{1,2*} ¹Pilot Plant of Chemical Engineering, National University of The South, National Scientific and Technical Research Council, Bahía Blanca, Buenos Aires, Argentina²Department of Chemical Engineering, National University of The South, Bahía Blanca, Buenos Aires, Argentina

Abstract

PH-responsive carbohydrate polymers have gained significant attention as promising candidates for next-generation oral drug delivery systems. This review focuses on the use of pH-sensitive carbohydrate polymers as a platform for controlled drug delivery. The unique ability of these polymers to undergo a conformational or structural change in response to specific pH ranges makes them ideal for targeted drug release. The gastrointestinal tract, with its distinct pH environments ranging from the highly acidic stomach to the neutral small intestine, presents a perfect scenario for these intelligent delivery systems. The design principles of these systems, including the chemical modification of natural carbohydrate polymers and the synthesis of new pH-sensitive materials, are explored. Furthermore, this review summarizes recent advancements and challenges in the application of carbohydrate polymers for oral drug delivery, particularly in enhancing drug bioavailability, protecting acid-labile drugs, and enabling site-specific release in the colon. The review concludes by highlighting the immense potential of these biocompatible and biodegradable materials in developing advanced, patient-friendly pharmaceutical formulations. In addition, the primary limitations of these materials are discussed with respect to enzymatic degradation, scaling up, cost-effectiveness, and regulatory approval.

***Corresponding author:**Diego E. Boldrini
(dboldrini@plapiqui.edu.ar)

Citation: Boldrini DE. Carbohydrate polymer derivatives as gastrointestinal pH-responsive oral drug delivery systems: A review. *Innov Med Omics*. 2026;3(1):1-14. doi: 10.36922/IMO025390049

Received: September 24, 2025**Revised:** November 13, 2025**Accepted:** December 9, 2025**Published online:** December 23, 2025

Copyright: © 2025 Author(s). This is an Open-Access article distributed under the terms of the Creative Commons Attribution License, permitting distribution, and reproduction in any medium, provided the original work is properly cited.

Publisher's Note: AccScience Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Keywords: Carbohydrate polymer derivatives; Drug delivery systems; pH-sensitivity

1. Introduction

The field of drug delivery has seen a paradigm shift from conventional formulations to sophisticated systems that can precisely control the release of therapeutic agents. This evolution is driven by the need to enhance drug efficacy, minimize side effects, and improve patient compliance. Among the various materials explored for this purpose, carbohydrate polymers have emerged as a highly promising class of biomaterials. Their unique properties, including biocompatibility, biodegradability, and a wide array of functional groups, make them ideal for designing advanced drug delivery systems.¹ Carbohydrate polymers, also known as polysaccharides, are naturally abundant and structurally diverse macromolecules that play crucial roles in biological systems. Their inherent non-toxicity and lack of immunogenicity make them exceptionally

well-suited for biomedical applications. Unlike synthetic polymers, which can sometimes pose concerns regarding long-term toxicity and environmental impact, these natural polymers are recognized by the body, leading to predictable degradation into non-toxic byproducts. This biological compatibility allows for their use in various routes of administration, including oral.² Furthermore, the presence of numerous hydroxyl groups on their backbone provides multiple sites for chemical modification. This versatility allows for the fine-tuning of their physical and chemical properties, such as solubility, swelling behavior, and hydrophobicity, to achieve a desired release profile. This has led to the development of a new class of materials known as stimulus-responsive polymers. These smart polymers are highly sensitive to their environment, designed to detect subtle physicochemical shifts and react by self-assembling or drastically altering their properties. This inherent responsiveness makes them an excellent tool for controlled drug delivery, where a specific trigger can release a therapeutic agent from the carrier.³ Stimuli used for drug release can be classified as either internal (endogenous) or external (exogenous). Internal stimuli are those that occur naturally within the human body, such as changes in pH, the presence of enzymes, specific biomolecules, or the redox microenvironment. External stimuli, on the other hand, are applied artificially, including physical cues such as light, magnetic or electric fields, and temperature. In particular, temperature is a physical stimulus that can be both internal and external.⁴ Among the various strategies, systems that respond to pH changes have garnered considerable attention. The human body presents a diverse range of pH environments, from the highly acidic stomach to the near-neutral small intestine and the slightly alkaline colon. These natural pH gradients provide an ideal trigger for smart delivery systems. By designing carriers that are stable at one pH and dissolve or swell at another, it is possible to protect drugs from harsh environments, enable site-specific release in the gastrointestinal tract (GIT), and improve the bioavailability of sensitive compounds. Consequently, pH-responsive systems are at the forefront of research for oral drug delivery, offering a powerful approach to optimize therapeutic outcomes.⁵⁻⁸ In summary, the sophisticated design of pH-responsive carbohydrate polymer derivatives offers a powerful solution to overcome the challenges associated with oral drug delivery. By leveraging the body's natural pH gradients, these systems can protect labile drugs from specific environments in the GIT, ensuring targeted release at the desired site of absorption, thereby improving therapeutic outcomes and patient compliance. As the industry shifts toward personalized medicine and biologics, these systems provide adaptive platforms

that can respond to pathological microenvironments, such as the acidic pH characteristic of tumor tissues or inflamed regions, thereby enhancing therapeutic efficacy while minimizing systemic side effects. Furthermore, their natural origin aligns with the growing demand for sustainable and biobased materials in pharmaceutical manufacturing. Despite significant progress in the development of pH-responsive carbohydrate-based drug delivery systems, several limitations still hinder their translation into clinical use. The inherent variability of physiological pH along the GIT and between patients often leads to inconsistent release profiles and limited site-specific targeting.⁹ Furthermore, the structural heterogeneity of natural polysaccharides, such as chitosan, pectin, and alginate, results in batch-to-batch variations in molecular weight, degree of substitution, and charge density, which complicate reproducibility and large-scale manufacturing.² Another major challenge lies in the stability of these systems under physiological conditions, where enzymatic degradation and ionic strength can alter polymer conformation and drug-polymer interactions, affecting release kinetics.¹⁰ From a regulatory standpoint, carbohydrate-based matrices are often classified as combination products, subject to dual evaluation under pharmaceutical and medical device frameworks, which significantly prolongs approval timelines.^{11,12} In addition, the lack of harmonized protocols for assessing *in vitro*–*in vivo* correlation in pH-responsive formulations further limits the predictive power of pre-clinical data and their clinical translation.¹³ Addressing these issues requires standardized characterization methods, advanced modeling of release mechanisms, and coordinated regulatory guidance tailored to stimuli-responsive biomaterials. This review provides a comprehensive overview of the design principles, synthesis methods, and key mechanisms of these innovative GIT drug delivery systems. We also discuss recent advancements, limitations, and future perspectives of these biocompatible materials in the development of next-generation oral pharmaceuticals. The structure of this manuscript is designed to provide a comprehensive and logically organized discussion of pH-responsive carbohydrate-based drug delivery systems. Section 2 describes the pH gradient along the GIT, emphasizing its physiological relevance for the design of site-specific drug delivery platforms. Section 3 outlines the regulatory framework governing pH-sensitive and polysaccharide-based delivery systems, referencing key international guidelines, such as International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q8–Q10, International Organization for Standardization (ISO) 10993, U.S. Food and Drug Administration (FDA), and

European Medicines Agency (EMA) recommendations for nanomaterials and combination products. Section 4 summarizes the fundamental characteristics of pH-responsive polymers, focusing on their ionization behavior, network dynamics, and physicochemical parameters that influence drug release. Section 5 presents a detailed analysis of carbohydrate polymer derivatives as pH-responsive gastric drug delivery systems, subdivided into four mechanistic categories: Swelling-controlled systems (Section 5.1), dissolution-controlled systems (Section 5.2), drug-polymer interactions (Section 5.3), and combined mechanisms (Section 5.4), highlighting their structure-function relationships and release kinetics. Section 6 discusses the broader implications of the findings, integrating molecular mechanisms with translational and clinical perspectives. Finally, Section 7 provides the concluding remarks, summarizing key insights, realistic challenges, and future directions for advancing carbohydrate-based smart delivery technologies toward clinical application.

2. pH gradient along the human GIT

The human GIT (Figure 1) is a highly dynamic and heterogeneous environment, characterized by distinct regions with significant pH variations. This natural pH gradient is a key physiological factor that is widely exploited in the design of smart drug delivery systems.

The oral route begins from the mouth, where the pH is around 6.8–7.0, and the transit time is negligible. After that, the stomach is a highly acidic environment, with a pH typically between 1.2 and 2.0. With a transit time of 3–4 h, the stomach's condition can protect against pathogens but also degrade acid-sensitive drugs. As gastric contents move into the small intestine, they are progressively neutralized by pancreatic secretions, with the pH gradually increasing from approximately 6.0 in the duodenum to around 7.4 in the ileum. This region is the primary site for drug

absorption. Finally, the material reaches the large intestine (colon), which maintains a slightly acidic to near-neutral pH, generally in the range of 6.0–6.7, influenced by the metabolic activity of the resident microbiota. This unique physiological sequence of pH changes provides an ideal trigger for controlling the release of therapeutic agents at a specific site along the GIT.¹⁹ Table 1 summarizes the pH gradient and transit time along the human GIT.^{20–22}

The values reported in Table 1 represent average physiological conditions of the human GIT. It is important to note that these parameters can vary considerably due to physiological variability associated with the fasted/fed state, age, disease status, co-medications, antacid use, and the presence of *Helicobacter pylori*.^{15,23,24} These variations are particularly relevant for the design and *in vitro* evaluation of pH-responsive drug delivery systems, as they directly influence polymer ionization, swelling-dissolution kinetics, and site-specific drug release behavior. Therefore, when interpreting the data in Table 1, it should be understood that the listed values correspond to mean estimates and should be contextualized within the expected physiological variability observed *in vivo*. In the particular case of the broad range reported for colonic transit time (6–70 h), it is worth mentioning that the variability well reflects the documented interindividual and physiological differences. Specifically, the shorter values correspond to healthy adults under normal or accelerated motility conditions, whereas the longer durations are associated with slower transit, often observed in older individuals or those with constipation.²⁵

3. Regulatory framework

Despite the rapid progress of pH-responsive carbohydrate-based drug delivery systems at the pre-clinical level, their translation into clinical applications remains limited due to stringent regulatory and practical constraints.^{2,26–29} To enter clinical evaluation, such systems must comply with international standards, such as ICH Q8-Q10 (pharmaceutical development and quality systems), ISO 10993 (biological evaluation of medical devices), and the FDA's Guidance for Industry on Nanotechnology in 2022, which emphasizes safety, reproducibility, and quality-

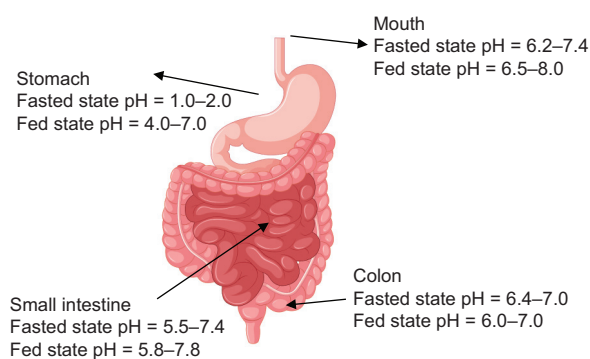


Figure 1. Schematic representation of the human gastrointestinal tract showing the typical pH gradient (fed and fasted states)^{14–18}

Table 1. pH gradient and transit time along the human gastrointestinal tract

Organ	pH	Transit time (h)
Mouth	6.8–7.0	Negligible
Stomach	1.2–2.0	3–4
Small intestine	6.0–7.4	2–6
Large intestine (colon)	6.0–6.7	6–70

by-design principles. Clinical trials for nanocarriers or bioresponsive polymers must follow Good Manufacturing Practice (GMP) and Good Clinical Practice standards, with extensive documentation on pharmacokinetics, biodegradation, immunogenicity, and long-term toxicity. However, a major challenge arises from the inherent variability of natural carbohydrate sources and the lack of harmonized protocols for characterizing their pH sensitivity, stability, and release kinetics under physiological conditions. Moreover, both EMA and FDA currently evaluate bioresponsive systems on a case-by-case basis, leading to uncertain regulatory pathways. Overcoming these barriers demands standardized analytical frameworks, cross-disciplinary collaboration, and early regulatory engagement to ensure that innovative biopolymer-based systems meet safety and efficacy criteria suitable for clinical translation.³⁰⁻³⁴

4. Characteristics of pH-responsive polymers

Drug delivery systems designed to release their payload in response to a specific pH often incorporate ionizable groups into the carrier's structure. These groups are essential because their protonation or deprotonation alters the polymer's hydrophobicity, thereby triggering a change in system behavior.^{35,36}

These polymers contain either acidic or basic functional groups that can donate or accept protons depending on the pH of their environment. For instance, acidic (anionic) polymers feature ionizable acidic side chains, such as carboxylic ($-\text{COOH}$), sulfonic, or phosphonic acids. Conversely, basic (cationic) polymers are characterized by basic groups, such as amines, which can be located in the main chain or as side groups. The ionization of these functional groups in response to pH creates a net charge on the polymer chains, thereby altering their interactions.^{37,38} This process is schematically represented in Figure 2, which illustrates how the state of an acidic or basic polymer changes based on the degree of ionization of its groups.

The ionization process is what enables swelling in cross-linked systems or dissolution in other polymer matrices. For acidic polymers, the chains repel one another when the surrounding pH is greater than the polymer pK_a , while they attract each other at pH values below the pK_a . Conversely, for a basic polymer, the chains attract each other at pH values above the pK_b but repel at pH values below the pK_b . In both scenarios, the ionization of the functional groups generates a net charge on the polymer chains, leading to their mutual repulsion and a subsequent change in the material structure. In addition to these mechanisms, drug release can occur in systems that involve

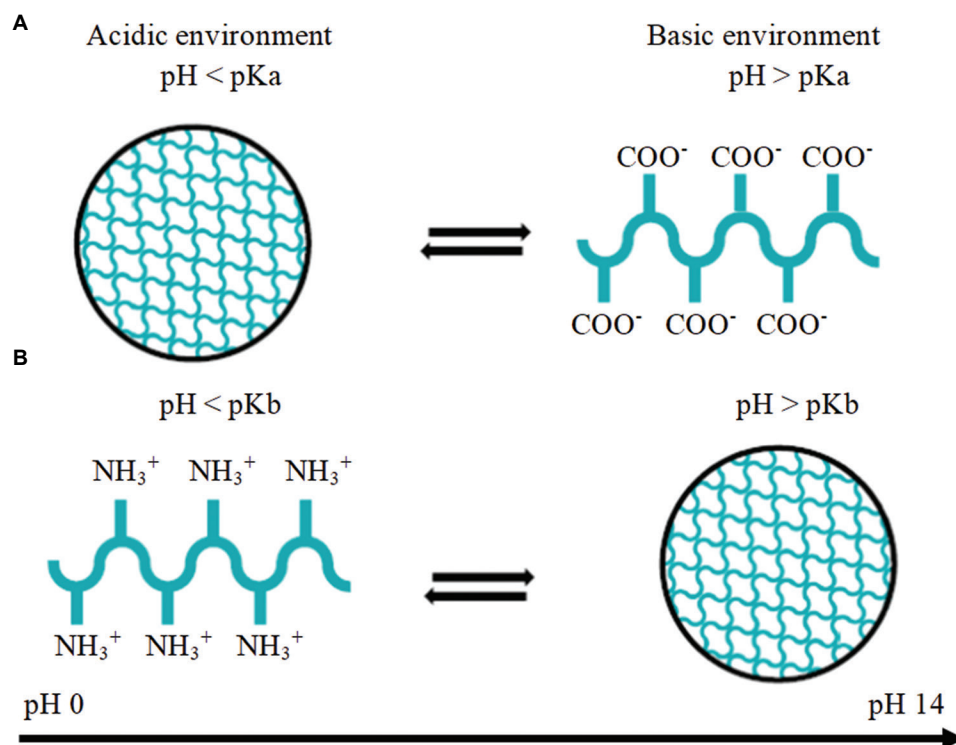


Figure 2. The state of the polymeric chain based on the ionization degree. (A) Acidic polymeric chain. (B) Basic polymeric chain. Image created by the authors.

an interaction between the drug and the polymer. In this case, the hydrogen bond between the drug and the polymer is influenced by the environmental pH because the drug can exist in protonated, neutral, or deprotonated forms. On the other hand, in some systems, these release mechanisms may be combined.⁴ Determining the effective pKa of ionizable groups within polymeric networks is essential for predicting their pH-responsive behavior. In carbohydrate-based systems, several complementary methods are employed. Potentiometric titration is the most common approach, in which titration curves of polymer solutions or hydrogels are recorded, and inflection points correspond to the apparent pKa values. Ultraviolet–visible spectroscopy can also monitor protonation–deprotonation equilibria through absorbance or band-shift changes, offering insight into specific functional groups. In cases where direct titration is hindered by low solubility or crosslinking, model monomeric compounds (e.g., glucosamine and galacturonic acid) are often used to estimate intrinsic pKa values, later corrected for polymeric effects. The apparent pKa in polymer matrices often deviates from that of corresponding small molecules due to the microenvironmental effects of the polymer network. Factors such as electrostatic interactions, polymer chain density, hydration degree, and dielectric constant alter proton activity around ionizable sites. For example, strong intramolecular hydrogen bonding or dense crosslinking can restrict solvent access, thereby increasing the apparent pKa, whereas high hydration and charge repulsion may decrease it. These effects must be considered when designing pH-responsive carbohydrate carriers, as they directly influence the onset of swelling or dissolution under physiological conditions.^{39–41}

A prime commercial example of a pH-responsive polymer family is the Eudragit® series, a non-biodegradable, poly(methacrylate)-based copolymer.⁴² Their basic chemical structure, shown in Figure 3, can be modified to achieve different functionalities.

For instance, a product sensitive to acidic pH, such as Eudragit E, has tertiary amine groups as side chains

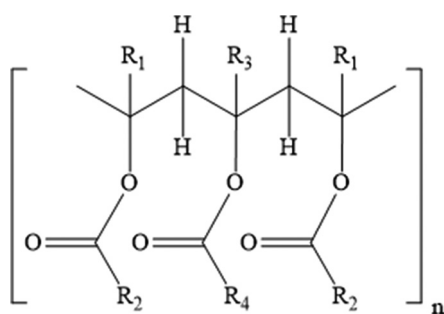


Figure 3. Basic structure of the Eudragit® compounds

($R_2 = \text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$) and methyl or butyl esters ($R_4 = \text{CH}_3$ or C_4H_9), whereas for a product sensitive to basic pH (Eudragit L or S), the side chains contain carboxylic acid groups ($R_2 = \text{H}$) and methyl esters ($R_4 = \text{CH}_3$). Furthermore, a pH-independent material that swells and is permeable can be created by incorporating hydrophilic quaternary ammonium groups ($R_4 = \text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_3^+\text{Cl}^-$), as is the case with Eudragit RL and RS. This specific modification allows for water uptake, which gives the polymer its swelling and permeability properties. While Eudragit copolymers are among the most established pH-responsive materials in oral dosage forms, they are non-biodegradable polymethacrylates. Upon administration, these polymers resist enzymatic and microbial degradation and are excreted largely unchanged in feces. From a regulatory perspective, Eudragit grades (e.g., L100, S100, and EPO) are classified as pharmaceutically safe excipients and are included in both the FDA Inactive Ingredient Databases and the European Pharmacopoeia monographs.^{43,44} However, their lack of biodegradability raises increasing concerns regarding long-term environmental persistence and residual accumulation, particularly in high-dosage or chronic therapies. In contrast, natural polysaccharides, such as alginate, chitosan, and pectin, are enzymatically and microbially degradable, providing a sustainable and biocompatible alternative with favorable regulatory perception in current green-pharma initiatives.⁴⁵ From a processing standpoint, synthetic polymers, such as Eudragit, exhibit excellent compatibility with manufacturing techniques, including hot-melt extrusion and three-dimensional (3D) printing, due to their defined thermal stability and rheological behavior.⁴⁴ In contrast, carbohydrate-based polymers (e.g., chitosan, alginate, and starch derivatives) often exhibit limited processability due to a narrow processing window between their glass transition temperature and the onset of thermal degradation temperature. Consequently, adapting carbohydrate matrices for hot-melt extrusion or 3D printing often requires chemical modification or processing under solvent-assisted or low-temperature conditions to maintain functionality and achieve consistent drug release behavior.⁴⁶ These differences are crucial for translating pH-responsive formulations into scalable manufacturing processes.

In summary, the acid-base dissociation constant (pKa or pKb) of a polymer's functional groups is a critical determinant of its pH-responsiveness and thus its suitability for gastrointestinal drug delivery. In pH-sensitive carbohydrate-based systems, ionizable groups, such as $-\text{COOH}$ group, amino group, and hydroxyl group, undergo protonation–deprotonation equilibria depending on the luminal pH. The design principle involves matching the polymer's pKa to the target region's pH within the GIT: for

instance, polymers with pKa values around 4.0–5.0 (e.g., alginate, chitosan-citrate) respond to the acidic-to-neutral transition of the small intestine, whereas polymers with pKa around 6.5–7.0 (e.g., carboxymethyl cellulose and pectin derivatives) activate in the colonic environment. When the environmental pH exceeds the polymer's pKa, ionization induces electrostatic repulsion and osmotic swelling, facilitating drug diffusion or polymer erosion. Conversely, in pH below pKa, the polymer remains collapsed and less permeable, protecting the drug in acidic media, such as the stomach. Therefore, rational pKa selection enables spatially controlled release and optimization of swelling-dissolution kinetics in carbohydrate-based matrices.^{13,47,48}

5. Carbohydrate polymer derivatives as pH-responsive gastric drug delivery systems

The pH-responsive drug delivery systems based on carbohydrate polymers can exhibit distinct release mechanisms, including swelling-controlled, dissolution-controlled, or a combination of both, depending on the polymer structure, crosslinking density, and environmental pH. In swelling-controlled systems, drug release is primarily governed by the diffusion of the therapeutic agent through a hydrated polymer matrix, where the rate of swelling dictates the release kinetics, often following Fickian or anomalous diffusion behavior. Conversely, dissolution-controlled systems rely on the gradual solubilization or erosion of the polymer network under specific pH conditions; this mechanism typically results in zero-order or erosion-controlled kinetics, allowing sustained and predictable release profiles. The combination of swelling and dissolution mechanisms introduces complex, often biphasic kinetics, an initial diffusion-driven burst phase followed by a slow degradation-dependent release, offering fine-tuned control over therapeutic delivery. The interplay between these processes can be modulated by adjusting polymer composition and degree of crosslinking, or by incorporating pH-labile linkages, enabling the design of systems optimized for site-specific and time-dependent drug release under physiological or pathological pH gradients.⁹

It should be noted that the behavior of pH-responsive carbohydrate-based systems is highly dependent on several experimental variables, including buffer composition, ionic strength, temperature, and the degree of crosslinking. However, such parameters are not uniformly reported across studies. Consequently, the data summarized in [Tables 2–5](#) represent the most commonly reported pH conditions (typically pH 1.2 for gastric and pH 6.8–7.4 for intestinal media) and reflect generalized qualitative

trends rather than standardized quantitative comparisons. Experimental details, such as media composition or United States Pharmacopeia apparatus type, are mentioned only when explicitly provided in the original publications. This approach ensures internal consistency and avoids introducing sporadically available methodological data.

In general terms, for drugs with limited solubility but good chemical stability, swelling-controlled matrices are preferred because gradual water uptake supports diffusion-driven release. Conversely, drugs that are highly soluble or unstable in gastric conditions benefit from dissolution-controlled carriers or polymer–drug ionic complexes. The combination approach is suitable when dual responsiveness (swelling and erosion) is required to balance protection and release kinetics. Patient-related factors, such as gastric pH variability, fed or fasted state, and co-medications, should also be considered, as they may significantly shift the effective pH triggers and hence the performance of these delivery systems.

5.1. Swelling-controlled systems

Cross-linked carbohydrate polymers represent a highly promising class of biomaterials for the development of pH-sensitive drug delivery systems. By crosslinking natural polymers, a stable 3D network is formed that, unlike its linear counterparts, does not readily dissolve in solvents. This network structure, combined with the ionization capacity of some functional groups on the polymer chains (Section 3), allows the material to swell or contract in response to changes in the surrounding pH while maintaining its structural integrity. This characteristic is crucial for controlled drug release in the GIT. This ensures targeted and efficient drug delivery, preventing premature degradation and enhancing bioavailability. [Table 2](#) shows examples of pH-responsive controlled-release systems based on cross-linked carbohydrate polymers.

5.2. Dissolution-controlled systems

Unlike their cross-linked counterparts, uncross-linked carbohydrate polymers are linear or branched structures that rely on their pH-dependent solubility for controlled drug release. These materials can undergo a reversible transition from a solid or viscous state to a soluble one in response to specific pH values, depending on the ionizable groups in the polymer chains (Section 3). For instance, the low pH of the stomach protonates the amine groups on chitosan, causing the polymer to dissolve and facilitating drug release in the stomach. Conversely, the carboxylic acid groups on alginate remain protonated and insoluble in acidic media, but deprotonate and become soluble as the pH increases in the intestine. This mechanism of controlled dissolution provides a straightforward

Table 2. Examples of carbohydrate polymer-based carriers responding to the pH changes in the gastrointestinal tract (swelling)

Carbohydrate polymer	Encapsulated compound	Behavior	References
Anionically modified starch	N/D	Swelling considerably augments with the increase of pH from 1.0 to 5.5 because the carboxyl groups are ionized	49
Starch-poly (sodium acrylate-co-acrylamide)	Ibuprofen	Drug delivery is faster at pH 7.4 than at pH 1.2 due to the ionization of carboxylate groups at basic pH	50
Poly (starch/acrylic acid)	Rutin	Swelling is greater at pH 7.4 than at pH 2.0 due to the carboxylic groups	51
Methyl methacrylate-g-starch/hydroxypropylated starch	Esomeprazole magnesium	Drug delivery is higher at pH 6.8 than at pH 1.2 due to the presence of carboxylic groups	52
Starch cross-linked with poly (aspartic acid)	5-fluorouracil	Swelling is greater at high pH media than at low pH media due to the presence of carboxylic groups	53
Carboxymethyl sago pulp/carboxymethyl sago starch	Ciprofloxacin hydrochloride and diclofenac sodium	Swelling is greater at high pH media than at low pH media due to the presence of carboxylic groups	54
Starch-g-poly (sodium-2-acrylamido-2-methyl-1-propane sulfonate-co-methacrylic acid)	Amoxicillin trihydrate	Drug release is higher at alkaline pH than at neutral or acidic pH due to the carboxylic groups	55
Chitosan cross-linked starch	Insulin	Drug release is higher at high pH than at low pH due to the presence of carboxylic groups	56
Carboxymethyl starch grafted with poly (methacrylic acid)	5-aminosalicylic acid and salicylic acid	An increase in the content of methacrylic acid results in less swelling in SGF, but greater swelling in SIF	57
Carboxymethyl starch grafted with poly (methacrylic acid)	Sodium diclofenac	An increase in the content of methacrylic acid results in less swelling in SGF, but greater swelling in SIF	58
2-hydroxyethyl methacrylate and acrylic acid grafted on starch	-	Swelling is greater at pH 7.4 than at pH 1.0 due to the presence of carboxylic groups	59
Corn starch/ethylene-co-vinyl alcohol thermoplastic blend	-	The maximum hydration degree is at pH=7.4, and the lowest is observed at an acidic pH due to the presence of carboxylic groups	60
Starch cross-linked with acrylic acid	Paracetamol	Drug release from the polymer is less at pH 1.2 compared to pH 7.4 due to the presence of carboxylic groups	61
High amylose cross-linked with pectin	-	Samples with a higher pectin proportion have greater swelling ability because pectin is more hydrophilic than starch. Besides, the swelling of the polymer increases at high pH values because of the presence of carboxylic groups, which ionize at basic pH	62
Cross-linked starch	Curcumin	Drug delivery is greater in the SGF than in SIF because the solubility of the curcumin is greater at acidic pH. Polymer swelling is not evaluated	63
Cross-linked alginate	N/D	Cross-linked alginate demonstrates pronounced swelling at alkaline pH and contraction in an acidic environment due to the presence of carboxylic groups. The authors propose the use of these compounds as a targeted delivery vehicle	64
Xanthan gum cross-linked with starch	Aspirin and paracetamol	Drug release is significantly higher in pH 7.4 than in pH 1.2 due to the presence of carboxylic groups in xanthan gum	65
Sodium carboxymethyl cellulose cross-linked with fumaric acid	N/D	The polymers show pH-sensitivity due to the presence of carboxylic groups	66
Quaternized cellulose cross-linked with carboxymethyl cellulose	N/D	The polymer exhibits pH-sensitivity due to the presence of $-\text{COO}^-$ and $-(\text{CH}_3)_3\text{N}^+$ groups	67
Chitosan cross-linked with glutaraldehyde	Chlorhexidine acetate	Drug release is higher at low pH values due to the presence of amino groups, which causes swelling in this pH range	68
Citrate cross-linked chitosan	Riboflavin	Drug release is higher at low pH values due to the presence of amino groups, which causes swelling in this pH range	69

(Cont'd...)

Table 2. (Continued)

Carbohydrate polymer	Encapsulated compound	Behavior	References
Chitosan cross-linked with hydroxypropyl methylcellulose phthalate	Insulin	Crosslinking avoids chitosan dissociation in the stomach, thus protecting the drug	70
Chitosan cross-linked with polyvinyl pyrrolidone	Cefixime	Drug release is higher at low pH values due to the presence of ionizable groups, which causes swelling in this pH range	71
Bone ash-reinforced cross-linked chitosan-grafted-glycidyl methacrylate and poly (ethylene glycol) diacrylate	Amoxicillin	Drug release is higher at low pH values due to the presence of amino groups, which causes swelling in this pH range	72
Acrylate-grafted-carboxymethyl starch-2-isobutyl-acrylic acid copolymer	Insulin	The copolymer exhibits pH-dependent swelling/deswelling behaviors due to the ionization/deionization transition of the carboxyl groups	73

Abbreviations: N/D: No data; SGF: Simulated gastric fluid; SIF: Simulated intestinal fluid.

Table 3. Examples of carbohydrate polymer-based carriers responding to the pH changes in the gastrointestinal tract (dissolution)

Carbohydrate polymer	Encapsulated compound	Behavior	References
Starch grafted poly (L-glutamic acid)	Insulin	Drug release is higher at basic pH because of the ionization of carboxylic groups on poly (L-glutamic acid), which allows the dissolution of the aggregates	74
High-amylose starch-pectin blend	Diclofenac sodium	Drug release is higher at basic pH because of carboxylic group ionization in pectin, which solubilizes at these pH values. Starch incorporation into the blend delays drug release since it hinders pectin solubilization	75,76
Hyaluronic acid grafted 3-diethylaminopropyl groups	Doxorubicin	The drug is delivered due to nanoparticle destabilization related to the protonation of 3-diethylaminopropyl when the pH decreases	77
Cellulose acetoacetate cross-linked with cystamine dihydrochloride	Rhodamine B	Drug delivery is achieved by a sol-gel transition due to the presence of an enamine moiety in the polymer	78
N-naphthyl-N, O-succinyl chitosan and N-octyl-N, O-succinyl chitosan	Curcumin	Drug delivery increases at high pH values due to polymer dissociation caused by the ionization of the carboxyl groups from the succinic acid moiety	79
High surface area silica-loaded chitosan	Curcumin	Drug delivery increases at low pH values due to polymer dissociation caused by the ionization of the amino groups in the chitosan	80
Chitosan-poly(γ -glutamic acid) complex	Insulin	Drug delivery increases at low pH values due to polymer dissociation caused by the ionization of the amino groups in the chitosan	81
Cellulose acetate phthalate-ethyl cellulose mixture	Ibuprofen	Drug release rate increases in alkaline medium due to the high solubility of cellulose acetate phthalate at basic pH	82
Chitosan-O-carboxymethyl chitosan mixture	Doxorubicin hydrochloride	At high pH values, NH_3^+ ions on chitosan and O-carboxymethyl chitosan are deprotonated, allowing polymer disaggregation	83

Table 4. Examples of carbohydrate polymer-based carriers responding to the pH changes in the gastrointestinal tract (drug-polymer interaction)

Carbohydrate polymer	Encapsulated compound	Behavior	References
Soluble starch	Curcumin	Release in SIF is faster than that in SGF. The different pH values may be responsible for the observed release speed difference, as hydrogen bonding between curcumin and starch is highly influenced by the environmental pH value	85
Methacrylated carboxymethyl cellulose cross-linked with poly (N-isopropylacrylamide)	Hen egg white lysozyme	At pH 7.4, lysozyme is positively charged, and the polymer is negatively charged, which causes a strong attraction between them, resulting in slow release	86

Abbreviations: SGF: Simulated gastric fluid; SIF: Simulated intestinal fluid.

Table 5. Examples of carbohydrate polymer-based carriers responding to the pH changes in the gastrointestinal tract (combined mechanisms)

Carbohydrate polymer	Encapsulated compound	Behavior	References
Alginate-starch blend	Salicylic acid	Drug release is maximal at pH 7.4 and minimum at pH 1.0 due to the presence of carboxylic groups on alginate. Besides, drug release increases as starch content is augmented because it dissolves, leaving pores that accelerate drug release from the polymer	87
Chitosan-starch blend	Antofloxacin	Drug delivery is favored at acidic and basic pH because hydrogen bonds are weakened, caused by ions' interference. At neutral pH, drug release is moderate. Besides, drug delivery is higher at acidic pH than at basic pH because the protonation of amine groups in chitosan makes the polymer swell	88

approach to developing oral drug delivery systems that can protect drugs from harsh environments and achieve targeted release at specific sites in the GIT. Table 3 presents examples of pH-responsive controlled-release systems based on uncross-linked carbohydrate polymers.

5.3. Drug-polymer interactions

In carbohydrate polymer-based drug delivery systems, the direct interaction between the drug and the polymer is a key mechanism for achieving controlled, pH-sensitive release. Instead of relying on polymer dissolution or swelling, these systems leverage hydrogen bonds or ionic interactions between the drug molecules and the polymer chains. The strength of this interaction is directly influenced by the environmental pH. A change in pH can modify the protonation state of either the drug or the polymer, thereby altering the affinity between the two. The interplay between the ionization constants of the drug and the polymer matrix (drug pKa vs. polymer pKa) is a critical determinant of loading efficiency and release performance in pH-responsive systems. For weakly acidic drugs (e.g., ibuprofen, pKa $\approx$ 4.4), encapsulation within matrices bearing weakly basic or neutral groups can minimize premature ionization in the stomach (pH 1.2–2.0) and promote release in the intestine (pH 6.0–7.4), where deprotonation enhances solubility and diffusion. Conversely, weakly basic drugs (e.g., propranolol, pKa $\approx$ 9.5) tend to be protonated in acidic media, favoring ionic interactions with negatively charged polysaccharides, such as alginate or carboxymethyl cellulose; drug release is then triggered by polymer deionization at higher pH. Therefore, selecting a polymer whose pKa closely matches the target intestinal pH enables a balance between drug-polymer affinity (for stability) and repulsion (for release), optimizing both loading and responsiveness.⁸⁴ Table 4 shows examples of carbohydrate polymers used for pH-sensitive controlled drug release through a drug-polymer interaction mechanism.

5.4. Combined mechanisms

The design of advanced drug delivery systems has increasingly moved toward combining multiple

mechanisms to achieve superior control over drug release. This strategy allows a single formulation to leverage the advantages of different approaches, creating a robust, versatile system. Table 5 shows examples of carbohydrate polymer-based carriers that respond to pH changes in the GIT through combined mechanisms.

6. Discussion

Despite significant advances at the laboratory scale, the clinical translation of pH-responsive carbohydrate-based drug delivery systems remains limited due to several regulatory and practical challenges. Most studies demonstrating precise pH-triggered release, biocompatibility, and efficacy are still confined to *in vitro* or small animal models, with only a few progressing to early-phase clinical trials. A major barrier lies in the complexity and variability of biological environments, which can alter the expected release kinetics observed under controlled conditions. Moreover, the regulatory framework for nanocarriers and bioreactive materials requires extensive data on long-term safety, biodegradation pathways, and potential immunogenicity, parameters that are challenging to standardize across different carbohydrate sources and modification methods. Manufacturing scalability and reproducibility further complicate approval, as minor changes in polymer purity or crosslinking chemistry can significantly affect performance. Addressing these issues requires harmonized characterization protocols, improved predictive models linking physicochemical parameters to *in vivo* behavior, and closer collaboration among academia, industry, and regulatory agencies to accelerate the clinical validation of these intelligent drug delivery systems.^{89,90}

Beyond classical pH-triggered release, recent research trends emphasize multi-stimuli-responsive strategies that integrate physiological and microbial cues for enhanced site specificity. Mucoadhesive coatings have demonstrated improved retention in the intestinal mucosa, reducing premature drug loss during transit. Enzyme-triggered colon delivery systems incorporating azo-linkers or glycosidic bonds exploit the reductive or hydrolytic

activity of colonic bacteria to achieve selective cleavage and release. Furthermore, hybrid systems combining pH-sensitivity with microbiota responsiveness, such as pectin–Eudragit or chitosan–inulin matrices, represent promising platforms for achieving synchronized responsiveness to both pH and enzymatic environments. These emerging approaches align with the growing interest in personalized and microbiota-informed drug delivery strategies.^{91–93}

7. Conclusion

This comprehensive review has highlighted the significant role of carbohydrate polymers as a versatile and effective platform for pH-controlled drug delivery. The inherent biocompatibility, biodegradability, and structural tunability of these materials make them an exceptional choice for the design of sophisticated oral delivery systems. We have explored the various mechanisms of pH-responsive release, from the dissolution of uncross-linked polymers to the structural integrity and controlled diffusion offered by cross-linked matrices. Furthermore, we have examined how direct drug-polymer interactions, such as those mediated by hydrogen bonds, can be leveraged to achieve highly precise, on-demand release.

The successful application of these systems in protecting acid-labile drugs from the harsh stomach environment and ensuring targeted release in the small intestine or colon has been well documented. Future research should focus on developing advanced formulations that combine these mechanisms, creating multi-responsive systems that can adapt to the complex physiological conditions of the GIT. In addition, greater emphasis on enzymatic degradation, scale-up, cost-effectiveness, and regulatory approval will be critical for translating these promising biomaterials from laboratory research into widely available pharmaceutical products. Agencies such as the FDA and EMA currently assess such systems on a case-by-case basis, guided by frameworks including ICH Q8–Q10, ISO 10993, and the FDA Nanotechnology Guidance, all of which emphasize safety, immunogenicity, and long-term biocompatibility. Realistic progress will depend on developing standardized characterization methods, particularly for pH-triggered swelling and dissolution kinetics, alongside GMP-compatible synthesis routes. Integration of *in silico* modeling and machine learning to predict release profiles and biological fate may accelerate translation, but the field must first address regulatory and reproducibility gaps before achieving large-scale clinical validation. Ultimately, continued innovation in this field holds immense potential to develop effective, patient-friendly, and personalized therapeutic solutions.

Acknowledgments

None.

Funding

The author acknowledges the financial support of the Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET) (grant number PIBAA 2022-2023 28720210100304CO) and Agencia Nacional de Promoción Científica y Tecnológica (ANPCyT) (grant number PICT-2021-I-INVI-00116).

Conflict of interest

The author declares no conflict of interest.

Author contributions

This is a single-authored article.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

References

- Shukla RK, Tiwari A. Carbohydrate polymers: Applications and recent advances in delivering drugs to the colon. *Carbohydr Polym.* 2012;88(2):399–416. doi: 10.1016/j.carbpol.2011.12.043
- Di X, Liang X, Shen C, Pei Y, Wu B, He Z. Carbohydrates used in polymeric systems for drug delivery: From structures to applications. *Pharmaceutics (Basel)*. 2022;14(4):739. doi: 10.3390/pharmaceutics14040739
- Bruschi, ML. *Strategies to Modify the Drug Release from Pharmaceutical Systems*. United Kingdom: Woodhead Publishing; 2015.
- Boldrini DE. Starch-based materials for drug delivery in the gastrointestinal tract-A review. *Carbohydr Polym.* 2023;320:121258. doi: 10.1016/j.carbpol.2023.121258
- Ofridam F, Tarhini M, Lebaz N, Gagnière É, Mangin D, Elaissari A. pH-sensitive polymers: Classification and some fine potential applications. *Polym Adv Technol.* 2021;32(4):1455–1484. doi: 10.1002/pat.5186
- Zhuo S, Zhang F, Yu J, Zhang X, Yang G, Liu X. pH-sensitive

- biomaterials for drug delivery. *Molecules*. 2020;25(23):5649. doi: 10.3390/molecules25235649
7. Balamuralidhara V, Pramodkumar TM, Srujana N, *et al*. pH sensitive drug delivery systems: A review. *Am J Drug Discov Dev*. 2011;1(1):24-48. doi: 10.3923/ajddad.2011.24.48
8. Zhu YJ, Chen F. pH-responsive drug-delivery systems. *Chem Asian J*. 2015;10(2):284-305. doi: 10.1002/asia.201402867
9. Vegad U, Patel M, Khunt D, Zupančič O, Chauhan S, Paudel A. pH stimuli-responsive hydrogels from non-cellulosic biopolymers for drug delivery. *Front Bioeng Biotechnol*. 2023;11:1270364. doi: 10.3389/fbioe.2023.1270364
10. Abbasi YF, Bera H, Cun D, Yang M. Recent advances in pH/enzyme-responsive polysaccharide-small-molecule drug conjugates as nanotherapeutics. *Carbohydr Polym*. 2023;312:120797. doi: 10.1016/j.carbpol.2023.120797
11. FDA. *Drug Products, Including Biological Products, that Contain Nanomaterials: Guidance for Industry*. United States: U.S. Food and Drug Administration; 2022.
12. EMA. *Reflection Paper on Nanotechnology-based Medicinal Products for Human Use*. Netherlands: European Medicines Agency; 2021.
13. Singh J, Nayak P. pH-responsive polymers for drug delivery: Trends and opportunities. *J Polym Sci*. 2023;61(22):2828-2850. doi: 10.1002/pol.20230214
14. Humphrey SP, Williamson RT. A review of saliva: Normal composition, flow, and function. *J Prosthet Dent*. 2001;85(2):162-169. doi: 10.1067/mpd.2001.113991
15. Kalantzi L, Goumas K, Kalioras V, Abrahamsson B, Dressman JB, Reppas C. Characterization of the human upper gastrointestinal contents under conditions simulating bioavailability/bioequivalence studies. *Pharm Res*. 2006;23(1):165. doi: 10.1007/s11095-006-8311-2
16. Dressman JB, Berardi RR, Dermentzoglou LC, *et al*. Upper gastrointestinal (GI) pH in young, healthy men and women. *Pharm Res*. 1990;7(7):756-761. doi: 10.1023/a:1015941724040
17. Koziolok M, Grimm M, Becker D, *et al*. Investigation of pH and temperature profiles in the GI tract of fasted human subjects using the Intellicap® system. *J Pharm Sci*. 2015;104(9):2855-2863. doi: 10.1002/jps.24474
18. Nugent SG, Kumar D, Rampton DS, Evans DF. Intestinal luminal pH in inflammatory bowel disease: Possible determinants and implications for therapy with aminosalicylates and other drugs. *Gut*. 2001;48(4):571-577. doi: 10.1136/gut.48.4.571
19. Evans DF, Pye G, Bramley R, Clark AG, Dyson TJ, Hardcastle JD. Measurement of gastrointestinal pH profiles in normal ambulant human subjects. *Gut*. 1988;29(8):1035-1041. doi: 10.1136/gut.29.8.1035
20. Hua S. Advances in oral drug delivery for regional targeting in the gastrointestinal tract-influence of physiological, pathophysiological and pharmaceutical factors. *Front Pharmacol*. 2020;11:524. doi: 10.3389/fphar.2020.00524
21. Klein S. Polysaccharides in oral drug delivery-recent applications and future perspectives. *Expert Opin Drug Deliv*. 2009;6(10):1037-1052. doi: 10.1517/17425240903173429
22. Madni A, Kanwal R, Tariq M, *et al*. Devising interactive dissolution experiment for pharmacy students (part I): Use of USP type II apparatus for comparison of immediate release and enteric coated tablets in time varying pH conditions. *PSM Biol Res*. 2016;1(2):83-87.
23. Fallingborg J. Intraluminal pH of the human gastrointestinal tract. *Dan Med Bull*. 1999;46(3):183-196.
24. Koziolok M. Gastrointestinal transit and hydrodynamics under fasting and fed conditions. In: Kerc J, editor. *Oral Drug Delivery for Modified Release Formulations*. Berlin: Springer; 2022. p. 25-38. doi: 10.1007/978-3-030-97771-3_2
25. Nandhra GK, Chaichanavichkij P, Birch M, Scott SM. Gastrointestinal transit times in health as determined using ingestible capsule systems: A systematic review. *J Clin Med*. 2023;12(16):5272. doi: 10.3390/jcm12165272
26. Damiri F, Fatimi A, Santos ACP, Varma RS, Berrada M. Smart stimuli-responsive polysaccharide nanohydrogels for drug delivery: A review. *J Mater Chem B*. 2023;11(44):10538-10565. doi: 10.1039/d3tb01426k
27. Liu L, Yao W, Rao Y, Lu X, Gao J. pH-Responsive carriers for oral drug delivery: Challenges and opportunities of current platforms. *Drug Deliv*. 2017;24(1):569-581. doi: 10.1080/10717544.2017.1309858
28. Ghitman J, Voicu SI. Controlled drug delivery mediated by cyclodextrin-based supramolecular self-assembled carriers: From design to clinical performances. *Carbohydr Polym Technol Appl*. 2023;5:100266.

- doi: 10.1016/j.carpta.2023.100266
29. 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.
doi: 10.1002/bip.23632
30. Çetintaş HC, Tonbul H, Şahin A, Çapan Y. Regulatory guidelines of the US food and drug administration and the european medicines agency for actively targeted nanomedicines. In: *Drug Delivery with Targeted Nanoparticles*. United States: Academic Press; 2021. p. 725-741.
doi: 10.1016/B978-0-12-818274-1.00017-9
31. Bhavyasri K, Vishnumurthy KM, Rambabu D, Sumakanth M. ICH guidelines-“Q” series (quality guidelines)-A review. *GSC Biol Pharm Sci*. 2019;6(3):89-106.
doi: 10.30574/gscbps.2019.6.3.0033
32. Northup SJ. Safety evaluation of medical devices: US food and drug administration and international standards organization guidelines. *Int J Toxicol*. 1999;18(4):275-283.
doi: 10.1080/109158199225721
33. Metselaar JM, Lammers T. Challenges in nanomedicine clinical translation. *Drug Deliv Transl Res*. 2020;10(3):721-725.
doi: 10.1007/s13346-020-00727-x
34. Peng C. Nanomedicine development and clinical translation. *Front Chem*. 2024;12:1458690.
doi: 10.3389/fchem.2024.1458690
35. Foster S, Duvall CL, Crownover EF, Hoffman AS, Stayton PS. Intracellular delivery of a protein antigen with an endosomal-releasing polymer enhances CD8 T-cell production and prophylactic vaccine efficacy. *Bioconjug Chem*. 2010;21(12):2205-2212.
doi: 10.1021/bc100269x
36. Liu J, Huang Y, Kumar A, et al. pH-sensitive nano-systems for drug delivery in cancer therapy. *Biotechnol Adv*. 2014;32(4):693-710.
doi: 10.1016/j.biotechadv.2014.02.008
37. Joseph X, Akhil V, Arathi A, Mohanan PV. Nanobiomaterials in support of drug delivery related issues. *Mater Sci Eng B*. 2022;279:115680.
doi: 10.1016/j.mseb.2022.115680
38. Kocak G, Tuncer C, Bütün V. pH-Responsive polymers. *Polym Chem*. 2017;8(1):144-176.
doi: 10.1039/C6PY01671A
39. Titration P. Ionization equilibrium and potentiometric titration of weak polyelectrolytes. *Phys Chem Polyelectrolyte Solut*. 2015;158:67.
doi: 10.1016/B978-0-12-800188-2.00004-9
40. Saeidi M, Khasreji SN. Spectrophotometric determination of the pKa, isosbestic point and equation of absorbance vs. pH of methyl red indicator. *J Chem*. 2015;2015:1-6.
doi: 10.1155/2015/347621
41. Settimo L, Bellman K, Knegetel RM. Comparison of the accuracy of experimental and predicted pKa values of basic and acidic compounds. *Pharm Res*. 2014;31(4):1082-1095.
doi: 10.1007/s11095-013-1200-4
42. Dos Santos J, da Silva GS, Velho MC, Beck RCR. Eudragit®: A versatile family of polymers for hot melt extrusion and 3D printing processes in pharmaceuticals. *Pharmaceutics*. 2021;13(9):1424.
doi: 10.3390/pharmaceutics13091424
43. European Medicines Agency. *Guideline on Excipients in the Dossier for Application for Marketing Authorisation of a Medicinal Product for Human Use (Revision 2)*. Amsterdam: European Medicines Agency; 2006.
44. Food and Drug Administration. *GRN 710 Amendments - Basic Methacrylate Copolymer (Eudragit®) Monograph*. United States: Food and Drug Administration; 2017.
45. Thakral S, Thakral NK, Majumdar DK. Eudragit®: A technology evaluation. *Expert Opin Drug Deliv*. 2013;10(1):131-149.
doi: 10.1517/17425247.2013.737604
46. Zamboulis A, Michailidou G, Koumentakou I, Bikiaris DN. Polysaccharide 3D printing for drug delivery applications. *Pharmaceutics*. 2022;14(1):145.
doi: 10.3390/pharmaceutics14010145
47. Peppas NA, Bures P, Leobandung WS, Ichikawa H. Hydrogels in pharmaceutical formulations. *Eur J Pharm Biopharm*. 2000;50(1):27-46.
doi: 10.1016/S0939-6411(00)00090-4
48. Meng Y, Qiu C, Li X, et al. Polysaccharide-based nano-delivery systems for encapsulation, delivery, and pH-responsive release of bioactive ingredients. *Crit Rev Food Sci Nutr*. 2024;64(1):187-201.
doi: 10.1080/10408398.2022.2081510
49. Dragan ES, Apopei DF. Multiresponsive macroporous semi-IPN composite hydrogels based on native or anionically modified potato starch. *Carbohydr Polym*. 2013;92(1):23-32.
doi: 10.1016/j.carbpol.2012.08.064
50. Sadeghi M, Hosseinzadeh H. Synthesis of starch-Poly (sodium acrylate-co-acrylamide) superabsorbent hydrogel with salt and pH-responsiveness properties as a drug delivery system. *J Bioact Compat Polym*. 2008;23(4):381-404.
doi: 10.1177/0883911508093122

51. Ghaffar AA, Radwan RR, Ali HE. Radiation synthesis of poly (starch/acrylic acid) pH sensitive hydrogel for rutin controlled release. *Int J Biol Macromol*. 2016;92:957-964.
doi: 10.1016/j.ijbiomac.2016.08.026
52. Kumar P, Ganure AL, Subudhi BB, Shukla S. Preparation and characterization of pH-sensitive methyl methacrylate-g-starch/hydroxypropylated starch hydrogels: *In vitro* and *in vivo* study on release of esomeprazole magnesium. *Drug Deliv Transl Res*. 2015;5(3):243-256.
doi: 10.1007/s13346-014-0238-7
53. Liu C, Gan X, Chen Y. A novel pH-sensitive hydrogels for potential colon-specific drug delivery: Characterization and *in vitro* release studies. *Starch-Stärke*. 2011;63(8):503-511.
doi: 10.1002/star.201000155
54. Tan HL, Wong YY, Muniyandy S, Hashim K, Pushpamalar J. Carboxymethyl sago pulp/carboxymethyl sago starch hydrogel: Effect of polymer mixing ratio and study of controlled drug release. *J Appl Polym Sci*. 2016;133(28):43697.
doi: 10.1002/app.43697
55. Clara I, Natchimuthu N. Hydrogels based on starch-g-poly (sodium-2-acrylamido-2-methyl-1-propane sulfonate-co-methacrylic acid) as controlled drug delivery systems. *Starch-Stärke*. 2017;69(7-8):1600177.
doi: 10.1002/star.201600177
56. Mahkam M. Modified chitosan cross-linked starch polymers for oral insulin delivery. *J Bioact Compat Polym*. 2010;25(4):406-418.
doi: 10.1177/0883911510373204
57. Saboktakin MR, Maharramov A, Ramazanov MA, Mahkam M. Modification of carboxymethyl starch as nano carriers for oral drug delivery. *Nat Sci*. 2007;5(3):67.
58. Saboktakin MR, Maharramov A, Ramazanov MA. pH-sensitive starch hydrogels via free radical graft copolymerization, synthesis and properties. *Carbohydr Polym*. 2009;77(3):634-638.
doi: 10.1016/j.carbpol.2009.02.016
59. Gils PS, Ray D, Mohanta GP, Manavalan R, Sahoo PK. Designing of new acrylic based macroporous superabsorbent polymer hydrogel and its suitability for drug delivery. *Int J Pharm Pharm Sci*. 2009;1:43-54.
60. Elvira C, Mano JF, San Roman J, Reis RL. Starch-based biodegradable hydrogels with potential biomedical applications as drug delivery systems. *Biomaterials*. 2002;23(9):1955-1966.
doi: 10.1016/S0142-9612(01)00331-5
61. Shaikh MMM, Gramopadhye NS, Wardole AA, Lonikar SV. Starch-acrylic acid hydrogel: Synthesis, characterization and drug release study. *World J Pharm Pharm Sci*. 2015;4:942-954.
62. Soares GA, Carbinatto FM, Cury BS, Evangelista RC. Effect of drying technique on some physical properties of cross-linked high amylose/pectin mixtures. *Drug Dev Ind Pharm*. 2013;39(2):284-289.
doi: 10.3109/03639045.2012.673895
63. Pereira AG, Fajardo AR, Nocchi S, Nakamura CV, Rubira AF, Muniz EC. Starch-based microspheres for sustained-release of curcumin: Preparation and cytotoxic effect on tumor cells. *Carbohydr Polym*. 2013;98(1):711-720.
doi: 10.1016/j.carbpol.2013.06.079
64. Chan AW, Whitney RA, Neufeld RJ. Semisynthesis of a controlled stimuli-responsive alginate hydrogel. *Biomacromolecules*. 2009;10(3):609-616.
doi: 10.1021/bm801047v
65. Sethi S, Saruchi S, Kaith BS, Kaur M, Sharma N, Kumar V. Cross-linked xanthan gum-starch hydrogels as promising materials for controlled drug delivery. *Cellulose*. 2020;27(8):4565-4589.
doi: 10.1007/s10570-020-03079-y
66. Akar E, Altınışık A, Seki Y. Preparation of pH-and ionic-strength responsive biodegradable fumaric acid crosslinked carboxymethyl cellulose. *Carbohydr Polym*. 2012;90(4):1634-1641.
doi: 10.1016/j.carbpol.2012.07.034
67. Chang C, He M, Zhou J, Zhang L. Swelling behaviors of pH-and salt-responsive cellulose-based hydrogels. *Macromolecules*. 2011;44(6):1642-1648.
doi: 10.1021/ma1027137
68. Yao KD, Peng T, Feng HB, He YY. Swelling kinetics and release characteristic of crosslinked chitosan: Polyether polymer network (semi-IPN) hydrogels. *J Polym Sci Part A Polym Chem*. 1994;32(7):1213-1223.
doi: 10.1002/pola.1994.080320703
69. Shu XZ, Zhu KJ, Song W. Novel pH-sensitive citrate cross-linked chitosan film for drug controlled release. *Int J Pharm*. 2001;212(1):19-28.
doi: 10.1016/S0378-5173(00)00574-6
70. Makhlof A, Tozuka Y, Takeuchi H. Design and evaluation of novel pH-sensitive chitosan nanoparticles for oral insulin delivery. *Eur J Pharm Sci*. 2011;42(5):445-451.
doi: 10.1016/j.ejps.2011.01.012
71. Ata S, Rasool A, Islam A, et al. Loading of Cefixime to pH sensitive chitosan based hydrogel and investigation of controlled release kinetics. *Int J Biol Macromol*. 2020;155:1236-1244.
doi: 10.1016/j.ijbiomac.2020.04.053
72. Aycan D, Alemdar N. Development of pH-responsive chitosan-based hydrogel modified with bone ash for

- controlled release of amoxicillin. *Carbohydr Polym.* 2018;184:401-407.
doi: 10.1016/j.carbpol.2017.12.052
73. Liu L, Zhang Y, Yu S, *et al.* pH-and amylase-responsive carboxymethyl starch/poly (2-isobutyl-acrylic acid) hybrid microgels as effective enteric carriers for oral insulin delivery. *Biomacromolecules.* 2018;19(6):2123-2136.
doi: 10.1021/acs.biomac.8b00288
74. Zhang Z, Shan H, Chen L, He C, Zhuang X, Chen X. Synthesis of pH-responsive starch nanoparticles grafted poly (l-glutamic acid) for insulin controlled release. *Eur Polym J.* 2013;49(8):2082-2091.
doi: 10.1016/j.eurpolymj.2013.05.008
75. Desai KGH. Preparation and characteristics of high-amylose corn starch/pectin blend microparticles: A technical note. *AAPS PharmSciTech.* 2005;6(2):30.
doi: 10.1208/pt060230
76. Desai KG. Properties of tableted high-amylose corn starch-pectin blend microparticles intended for controlled delivery of diclofenac sodium. *J Biomater Appl.* 2007;21(3):217-233.
doi: 10.1177/0885328206064503
77. Kim SW, Oh KT, Youn YS, Lee ES. Hyaluronated nanoparticles with pH-and enzyme-responsive drug release properties. *Colloids Surf B Biointerfaces.* 2014;116:359-364.
doi: 10.1016/j.colsurfb.2014.01.026
78. Liu H, Rong L, Wang B, *et al.* Facile fabrication of redox/pH dual stimuli responsive cellulose hydrogel. *Carbohydr Polym.* 2017;176:299-306.
doi: 10.1016/j.carbpol.2017.08.106
79. Woraphatphadung T, Sajomsang W, Rojanarata T, Ngawhirunpat T, Tonglairoum P, Opanasopit P. Development of chitosan-based pH-sensitive polymeric micelles containing curcumin for colon-targeted drug delivery. *AAPS PharmSciTech.* 2018;19(3):991-1000.
doi: 10.1208/s12249-017-0941-0
80. Gaware SA, Rokade KA, Kale SN. Silica-chitosan nanocomposite mediated pH-sensitive drug delivery. *J Drug Deliv Sci Technol.* 2019;49:345-351.
doi: 10.1016/j.jddst.2018.11.029
81. Sung HW, Sonaje K, Liao ZX, Hsu LW, Chuang EY. pH-responsive nanoparticles shelled with chitosan for oral delivery of insulin: From mechanism to therapeutic applications. *Acc Chem Res.* 2012;45(4):619-629.
doi: 10.1021/ar200231h
82. Chandran S, Asghar LF, Mantha N. Design and evaluation of ethyl cellulose based matrix tablets of ibuprofen with pH modulated release kinetics. *Indian J Pharm Sci.* 2008;70(5):596.
doi: 10.4103/0250-474X.45970
83. Feng C, Wang Z, Jiang C, *et al.* Chitosan/o-carboxymethyl chitosan nanoparticles for efficient and safe oral anticancer drug delivery: *In vitro* and *in vivo* evaluation. *Int J Pharm.* 2013;457(1):158-167.
doi: 10.1016/j.ijpharm.2013.08.058
84. Hillery A, Park K. *Drug Delivery: Fundamentals and Applications.* United States: CRC Press; 2016.
85. Li J, Shin GH, Lee IW, Chen X, Park HJ. Soluble starch formulated nanocomposite increases water solubility and stability of curcumin. *Food Hydrocoll.* 2016;56:41-49.
doi: 10.1016/j.foodhyd.2015.12.001
86. Dutta S, Samanta P, Dhara D. Temperature, pH and redox responsive cellulose based hydrogels for protein delivery. *Int J Biol Macromol.* 2016;87:92-100.
doi: 10.1016/j.ijbiomac.2016.02.049
87. Wang Q, Hu X, Du Y, Kennedy JF. Alginate/starch blend fibers and their properties for drug controlled release. *Carbohydr Polym.* 2010;82(3):842-847.
doi: 10.1016/j.carbpol.2010.06.014
88. Huo W, Xie G, Zhang W, *et al.* Preparation of a novel chitosan-microcapsules/starch blend film and the study of its drug-release mechanism. *Int J Biol Macromol.* 2016;87:114-122.
doi: 10.1016/j.ijbiomac.2016.02.056
89. Verkhovskii RA, Ivanov AN, Lengert EV, *et al.* Current principles, challenges, and new metrics in pH-responsive drug delivery systems for systemic cancer therapy. *Pharmaceutics.* 2023;15(5):1566.
doi: 10.3390/pharmaceutics15051566
90. Wang Z, Wang X, Xu W, *et al.* Translational challenges and prospective solutions in the implementation of biomimetic delivery systems. *Pharmaceutics.* 2023;15(11):2623.
doi: 10.3390/pharmaceutics15112623
91. Ghodrati AD, Çomoğlu T. Mucoadhesive polymers in colon targeted drug delivery systems: A comprehensive review. *J Fac Pharm Ankara Univ.* 2023;48(2):696-713.
doi: 10.33483/jfpau.1206584
92. Jain A, Gupta Y, Jain SK. Azo chemistry and its potential for colonic delivery. *Crit Rev Ther Drug Carr Syst.* 2006;23(5):373-401.
doi: 10.1615/critrevtherdrugcarriersyst.v23.i5.30
93. Kumari A, Singh B. Emerging trends in designing polysaccharide based mucoadhesive network hydrogels as versatile platforms for innovative delivery of therapeutic agents: A review. *Int J Biol Macromol.* 2025;293(Pt 2):140229.
doi: 10.1016/j.ijbiomac.2024.140229