REVIEW ARTICLE

Polyelectrolyte Complex-based Multiparticulate Drug Delivery System: A Special Emphasis on Chitosan and Alginate

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Abstract

Effective drug delivery systems play a pivotal role in optimizing therapeutic outcomes and minimizing side effects. This study explores the potential of a multiparticle drug delivery system incorporating chitosan, alginate, and polyelectrolyte as a versatile platform for controlled and targeted drug release. These materials offer distinct attributes that synergistically enhance drug bioavailability, stability, and release kinetics. With its bioadhesive properties and biocompatibility, chitosan promotes prolonged residence time in the gastrointestinal tract, thereby improving drug absorption. Alginate contributes to the system's stability and protection of encapsulated drugs, while also allowing modulation of release profiles. The inclusion of polyelectrolytes offers an additional layer of control over swelling behavior and encapsulation efficiency. The multiparticulate nature of the system addresses challenges associated with dose uniformity and release consistency. This approach provides advantages in terms of enhanced drug dispersion, reduced risk of dose dumping, and potential for tailored release patterns. Furthermore, the system's adaptability enables the design of complex delivery strategies, including sequential or combination therapies. However, formulation optimization remains a critical factor in achieving desired release profiles and therapeutic effects. Challenges in maintaining batch consistency and scaling up production also warrant consideration. As the field of pharmaceutical science continues to advance, this multiparticulate drug delivery system holds promise for revolutionizing drug administration, resulting in safer and more effective treatments for various medical conditions. Further research and development in this area are warranted to fully harness its potential.

Key words: Alginate beads, chitosan, multiparticulate drug delivery, polyelectrolyte complex

INTRODUCTION

The development of new drugs in pharmaceutical research continues to change the way drugs are used, increasing efficacy, safety, and patient compliance. Among these advances, the emergence of the delivery of multiple drugs has gained the popularity and attention of many due to its unique ability to provide controlled release, delivery, and enhanced drug bioavailability.[1] This approach encapsulates the drug as discrete particles, allowing for better release kinetics and further application in different clinical fields. This article explores the potential for multidrug delivery based on the integration of chitosan and alginate. Chitosan obtained from the shell of crustaceans is a versatile candidate for drug encapsulation with its biocompatibility, mucoadhesive, and controlled release.[2] Alginate extracted from brown seaweed creates a gel-like structure when interacting with different cations, allowing controlled release.[3] The inclusion of a polyelectrolyte complex adds a layer of customization by fine-tuning the release profile and drug focus. Through studies of the chemistry, formulation methods, quality, and challenges associated with this multiparticulate drug delivery system, this article aims to demonstrate the potential of using the

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three components to achieve effective therapeutic effects.[4] Understanding the interaction between chitosan and alginate assists researchers and clinicians develop new drug delivery techniques that tackle the drawbacks of drug formulation.[5] With the increasing demand for personalized medicine and drug therapy, the integration of chitosan and alginate into multiparticulate drug delivery systems must address the complex drug release kinetics, the specific purpose of action, and ultimately improve patient health.[6] This article aims to expand pharmaceutical research knowledge and guide future research and innovation in the search for more effective. Developing a patient-focused Polyelectrolyte Complex-based Multiparticulate Drug Delivery System (MCDDS), particularly leveraging Chitosan and Alginate, aims to enhance therapeutic efficacy and patient adherence. By optimizing drug bioavailability, controlling release profiles, and ensuring stability in varying physiological conditions, these systems offer improved treatment outcomes with reduced side effects. Targeted delivery capabilities further personalize treatment regimens, while considerations of biocompatibility and cost-effectiveness contribute to broader accessibility and patient satisfaction. Ultimately, integrating these advancements into MCDDS design underscores a commitment to meeting diverse patient needs effectively and safely. As mentioned in Figure 1.

SOME APPROACHES TO MULTIPARTICULATE FORMULATIONS

Certainly, here are some common approaches to multiparticulate formulation that can be used in the development of drug delivery systems:

1. Microspheres and microcapsules: Microspheres are small spherical particles that can encapsulate drug molecules. They can be formulated using techniques such as solvent evaporation, spray drying, or emulsification. Microcapsules, on the other hand, are microspheres that have a core-shell structure, where the core contains the drug and the shell provides controlled release.
2. Nanoparticles: Nanoparticles are ultra-small particles with dimensions on the nanometer scale. They can be engineered using methods such as nanoprecipitation, emulsion techniques, or high-pressure homogenization.[7] Nanoparticles can offer improved drug solubility and targeted delivery.
3. Beads and pellets: Beads and pellets are multiparticulate systems often used in controlled-release formulations. They can be prepared by layering drug and polymer coatings onto inert cores, providing flexibility in achieving desired release profiles.[8]
4. Extrusion-spheronization: Extrusion-spheronization is a technique where a wet mass of drugs and excipients is extruded through a mesh to form cylindrical extrudates.[9] These extrudates are then rounded into spheres through a spheronization process. This method is suitable for drugs with poor flow and compression properties.
5. Coating on inert cores: In this approach, inert cores such as sugar spheres or microcrystalline cellulose particles are coated with drug and polymer layers. This enables drug release to be modulated by changing the coating thickness and composition.[10]
6. Layered tablets: Layered tablets consist of multiple drug-containing layers compressed together. Each layer can be programmed to release the drug at a different rate, allowing for controlled and sequential drug administration.[11]
7. Fluidized bed coating: Fluidized bed coating involves suspending particles in an air stream and then applying layers of polymer onto the particles. This technique is useful for achieving uniform and controlled coatings on multiparticulate systems.
8. Hot-melt extrusion: Hot-melt extrusion involves mixing drugs and excipients at an elevated temperature and then extruding the mixture through a die.[12] This method is particularly useful for poorly water-soluble drugs and can produce multiparticulates with enhanced dissolution profiles.
9. Spray congealing: Spray congealing is a technique where a melted mixture of drugs and excipients is sprayed and rapidly cooled, resulting in solidified particles.[13] This method is advantageous for lipid-based drug delivery systems.
10. Multiple-unit pellet system (MUPS): MUPS involves blending drug-loaded pellets with other excipients and then compressing the mixture onto tablets. This approach allows for achieving controlled and tailored release profiles.

To develop an effective multiparticulate drug delivery system, these techniques can be designed and combined based on the specific properties of the drug, the desired release profile, and the intended route of administration.[14]

ADVANTAGES AND DISADVANTAGES OF MULTIPARTICULATE DRUG DELIVERY

Advantages

1. Uniform drug distribution: Multiparticulate systems ensure uniform distribution of the drug within each particle. This reduces the possibility of dose variability and ensures consistent drug delivery, resulting in more predictable therapeutic outcomes.[15]
2. Controlled release: These systems enable precise drug release control. By modifying particle properties, coatings, or formulations, it is possible to achieve various release profiles, such as immediate release, sustained release, or targeted release.
3. Lower risk of dose dumping: In contrast to monolithic dosage forms, a multiparticulate system lowers the risk of dose dumping, where a large amount of drug is released rapidly.[16] This is especially true for medications with a narrow therapeutic window.
4. Enhanced bioavailability: Particulates can improve drug solubility and dissolution rates, resulting in higher

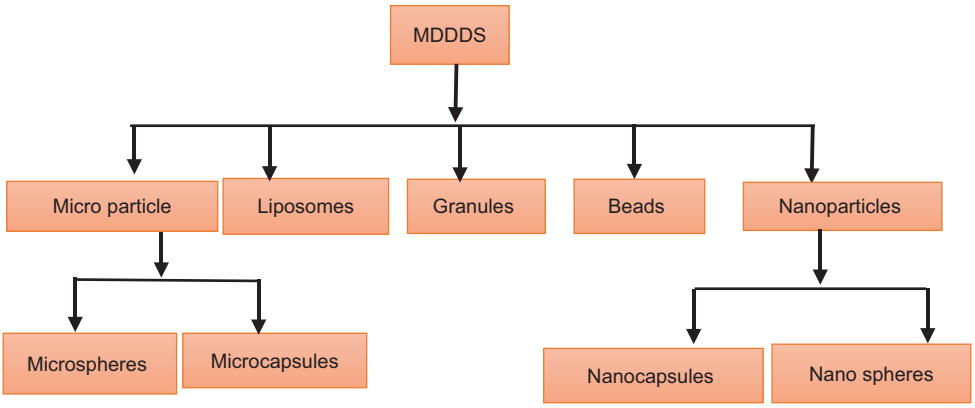

Figure 1: Various approaches to multiparticulate drug delivery system

bioavailability, especially for poorly water-soluble drugs.[17] The increased surface area of smaller particles facilitates faster dissolution.

5. Minimized gastrointestinal irritation: Smaller particles in multiparticulate systems can reduce gastrointestinal irritation, making them more tolerable for patients compared to large, single-unit dosage forms.[18]
6. Flexibility in dosage: Multiparticulate allows flexibility in dosing by enabling accurate adjustments of the dose through the combination of different-sized particles.[19] This is especially valuable when patients require specific or varied doses.
7. Combination therapies: Multiparticulate systems can encapsulate multiple drugs for combination therapies, potentially enhancing treatment efficacy.[20]
8. Targeted delivery: By modifying particle properties, coatings, or formulations, multiparticulate systems can be designed to deliver drugs to specific areas of the gastrointestinal tract, improving site-specific treatment.[21]
9. Reduced side effects: Controlled release provided by multiparticulate systems can lead to reduced fluctuations in drug concentrations, which may help minimize side effects associated with rapid fluctuations in drug levels.[22]
10. Enhanced patient compliance: Smaller particle sizes and the ability to adjust doses can improve patient compliance, as they may find it easier to swallow multiparticulate and adhere to their prescribed treatment regimen.
11. Improved stability: Multiparticulate systems can offer improved stability for certain drugs by protecting them from degradation, oxidation, or interaction with other ingredients.[23]
12. Efficient absorption: The small particle sizes and uniform distribution can facilitate efficient absorption in the gastrointestinal tract, contributing to consistent drug levels in the bloodstream.[24]

Disadvantages

- Complex formulation and manufacturing: Developing multiparticulate systems can be technically demanding and require specialized equipment and expertise.[25] The formulation process may involve multiple steps, which can increase the complexity of manufacturing and raise the risk of batch-to-batch variability.[26]
- Higher manufacturing costs: The complexity of formulation and manufacturing processes can lead to higher production costs compared to conventional dosage forms.[27] This can impact the overall affordability of the medication.
- Scale-up challenges: Transferring a successful laboratory-scale formulation to large-scale production can be challenging. Ensuring consistent quality and performance during scale-up requires careful optimization and control.[28]
- Regulatory considerations: Introducing multiparticulate systems may require additional regulatory testing and approval compared to traditional dosage forms.[29] This can extend the development timeline and increase regulatory compliance costs.
- Dissolution variability: Factors such as particle size distribution, coating uniformity, and interactions between particles can impact dissolution behavior.[30] Variability in dissolution can affect drug release consistency and bioavailability.
- Packaging and stability issues: Proper packaging is crucial to prevent particle agglomeration, moisture absorption, and potential stability problems.[31] Inadequate packaging can compromise the performance and shelf life of the multiparticulate system.
- Patient acceptability: Multiparticulate systems often involve ingesting multiple small particles, which may not be well received by all patients, particularly those who have difficulty swallowing or adhering to complex dosing regimens.[32]
- Taste and odor concerns: In some cases, the taste or odor of the multiparticulate system might be undesirable for patients, potentially affecting their willingness to continue treatment.[33]
- Compatibility issues: Some drugs may not be compatible with the excipients used in multiparticulate systems, leading to interactions that could impact drug stability, release, or effectiveness.[34]

- Limited applicability: While multiparticulate systems are advantageous for certain drugs and therapeutic purposes, they may not be suitable for all types of drugs or conditions.[35] The selection of the appropriate formulation approach depends on the specific drug characteristics and release requirements.
- Delayed onset of action: While multiparticulate systems with controlled release profiles might result in a delayed onset of action compared to immediate-release dosage forms.[36]
- Lack of clinical experience: New multiparticulate formulations may have limited clinical data and experience. Making it essential to conduct thorough studies to ensure safety, efficacy, and patient acceptability.[37]

MECHANISM OF DRUG RELEASE FROM MULTIPARTICULATES

The mechanism of drug release from particulate drug delivery systems varies according to the formulation and the desired release characteristics.[38] Here, I will outline the general mechanisms involved in drug release from such systems.

- Diffusion: This is the least widespread mechanism of drug release from particulate systems. It involves the movement of drug molecules that dissolve in the surrounding fluid and diffuse outward from the particles, following a concentration gradient.[39] The rate of diffusion is affected by factors such as the molecular weight of the drug, its solubility, and the characteristics of the surrounding environment (Figure 2).[40]
- Erosion or degradation: In some cases, the polymer matrix or coating around the particles can degrade or erode over time when exposed to the surrounding fluids.[41] As the polymer breaks down, it exposes the drug, allowing it to be released. This mechanism is prevalent in systems where the polymer is water soluble or undergoes enzymatic degradation.[42] As mentioned in Figure 3.
- Sweeling-controlled release: Hydrophilic polymers used in the formulation can absorb water and swell, leading to an increase in the particle size. This swelling can create pores or channels in the matrix, allowing the drug to diffuse out more readily.[43] The release rate is determined by the extent of swelling and the size of the channel formed.[44] As mentioned in Figure 4.
- Osmotic pressure: Osmatic drug delivery systems involve using an osmatic agent within the particle that attracts water into the system. As water enters, it creates pressure inside the particle, leading to the outward release of the drug through a pre-defined orifice.[45] As mentioned in figure 5.
- Ion exchange: Some particulate systems involve ion exchange resins that bind to drug ions and release them when exposed to ions in the surrounding fluid. This mechanism is particularly useful for drugs that are present in ionized form.[46]

The choice of mechanism depends on the intended release profile, the properties of the drug and polymer, the formulation method, and the desired pharmacokinetics.[47] Many formulations incorporate a combination of these mechanisms to achieve the desired release characteristics, making particulate drug delivery systems versatile tools for controlled drug administration. As mentioned in Figure 6.

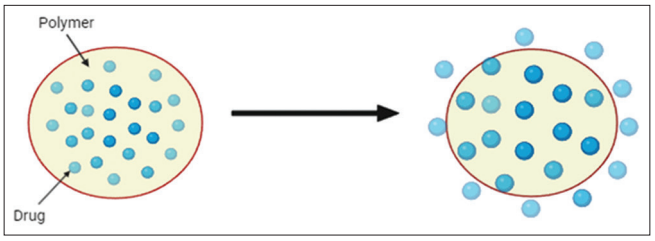

Figure 2: Mechanism of diffusion

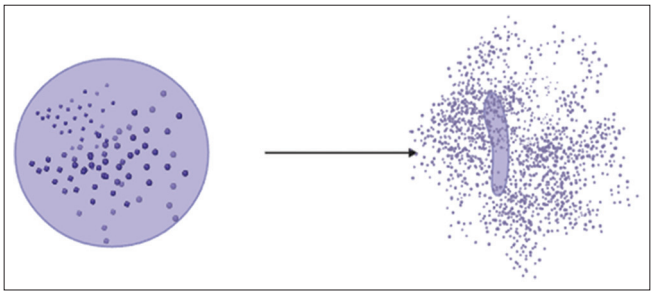

Figure 3: Mechanism of erosion

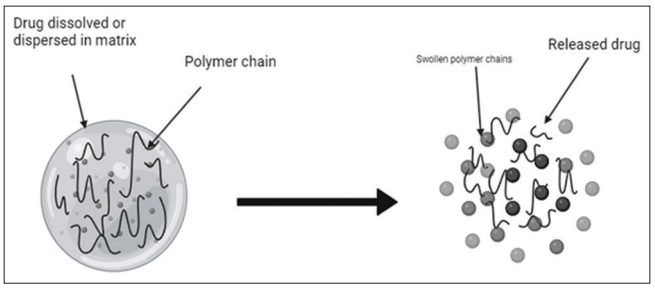

Figure 4: Mechanism of swelling controlled release

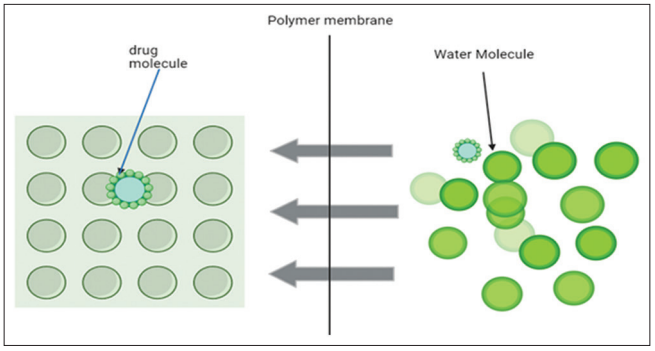

Figure 5: Mechanism of osmosis

ALGINATE BEADS FOR DRUG DELIVERY

Alginate beads are a widely used form of particulate drug delivery system that utilizes alginate, a natural polysaccharide derived from brown seaweed.[48] Due to their biocompatibility,

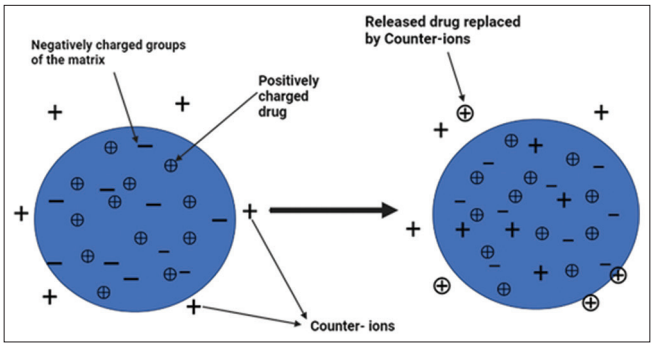

Figure 6: Mechanism of ion exchange

alginate beads have several advantages for drug delivery, ease of formulation, and versatility. Here is an overview of alginate beads for drug delivery:

Preparation

Alginate beads are typically prepared through a process called "ionotropic gelation." This involves the crosslinking of alginate chains in the presence of divalent cations, such as calcium ions (ca2+).[49] The steps include:

1. Droplet formation: Using techniques such as dripping or emulsification, an aqueous solution of the drug and alginate is formed into droplets.
2. Crosslinking: The droplets are then introduced into a solution containing divalent cations, usually calcium chloride ($CaCl_2$). The calcium ions form ionic bonds with the negatively charged alginate chains, resulting in the formation of a gel-like matrix around each droplet.[50]
3. Beads solidification: As the crosslinking reaction progresses, the alginate matrix solidifies, forming discrete beads that encapsulate the drug.[51]
4. Controlled release: By altering factors such as alginate concentration, crosslinking density, and bead size, the release rate of the drug can be controlled and tailored to achieve specific therapeutic goals.[52]
5. Versatility: Alginate beads can encapsulate a wide range of drugs, including small molecules, peptides, proteins, and even genetic materials such as DNA or RNA.
6. Site-specific delivery: Alginate beads can be engineered to release drugs at specific sites along the gastrointestinal tract by modifying the alginate composition or incorporating pH-sensitive coatings.[53]
7. Improved bioavailability: Alginate beads can enhance drug solubility and dissolution rates, potentially leading to improved bioavailability.
8. Ease of formulation: The ionotropic gelation method for alginate bead preparation is relatively simple and can be adapted to various drugs and formulations.[54]
9. Combination therapies: Different drugs with varying release kinetics can be encapsulated in separate alginate beads, allowing for combination therapies and controlled release of multiple agents.[55]

Challenges and considerations

1. Bead size and distribution: Controlling bead size and achieving a uniform size distribution can be challenging, as it can impact drug release and administration.
2. Bead stability: Alginate beads can be sensitive to environmental factors such as temperature and moisture, affecting their stability and performance.
3. Release kinetics: Achieving precise and consistent release profiles may require optimization of formulation parameters.
4. Mechanical strength: Alginate beads can sometimes be fragile, leading to potential breakage during handling or administration.[56]

ALGINATE CHEMISTRY

Alginate is a naturally occurring polysaccharide derived from brown seaweed. It consists of linear chains of two monosaccharides, β-D-mannuronic acid (M) and α-L-guluronic acid (G), which are arranged in different sequences.[57] The composition and arrangement of M and G monomers within the alginate chain give rise to its unique properties and functionality. Here is a brief overview of alginate chemistry:

1. Monomer units: Alginate is made up of M and G monomer repeating units. The arrangement of these monomers along the chain affects the physical and chemical properties of the alginate polymer.[58]
2. G and M blocks: Alginate chains can have regions of consecutive G or M monomers, referred to as "blocks."[59] G-blocks tend to form rigid and stable structures, while M blocks are more flexible.
3. Ionotropic gelation: This process involves the formation of a hydrogel matrix through the crosslinking of alginate chains by calcium ions. This is the basis for the preparation of alginate beads and other particulate systems used in drug delivery.[60]
4. Viscosity and gel formation: Alginate solutions have varying viscosities depending on factors such as the M/G ratio, molecular weight, and concentration.[61] When calcium ions are added, they bind to the alginate chains, causing them to crosslink and form a gel structure.
5. pH sensitivity: Alginate gels are generally stable over a wide pH range. However, some formulations can be pH changes in the surrounding environment.
6. Applications: Apart from drug delivery, alginate is widely used in various industries, including food, cosmetics, and biomedical fields, due to its gelling, thickening, and stabilizing properties.
7. Blend and modification: Alginate can be blended with other polymers or chemically modified to enhance specific properties, such as mechanical strength, controlled release, or targeting capabilities.
8. Biocompatibility: Alginate can be blended with other polymers or chemically modified to enhance specific

properties, such as mechanical strength, controlled release, or targeting capabilities.[62]

9. Biocompatibility: Alginate is biocompatible and is used in biomedical applications such as wound dressings, tissue engineering, and regenerative medicine.
10. Degradation: Alginate is naturally degraded by enzymes in the body, particularly alginate lyases, leading to a breakdown of the polymer and eventual elimination.[63]

Chemical structure

The chemical structure of alginate consists of repeating units of β-D-mannuronic acid (M) and α-L-guluronic acid (G) monomers.[64] These monomers are connected by glycosidic bonds, forming a linear polysaccharide chain. The arrangement of M and G monomers along the chain gives rise to the distinctive properties of alginate.[65] As mentioned in Figure 7.

GEL FORMATION MECHANISM

The gel formation mechanism of alginate involves the crosslinking of alginate polymer chains in the presence of divalent cations, typically calcium ions (Ca2+). This process is known as "ionotropic gelation" and is responsible for the formation of gels and three-dimensional networks in various applications, including drug delivery, food, and biotechnology.[66] As mentioned in Figure 8. Here is a step-by-step explanation of the gel formation mechanism:

1. Alginate solution: Alginate is a linear polysaccharide composed of alternating β-D-mannuronic acid (M) and α-L-guluronic acid (G) monomers. It is usually dissolved in water to create an alginate solution.
2. Divalent cations: The gelation process requires the presence of divalent cations, which have multiple positive charges. Calcium ions (Ca2+) are commonly used for this purpose due to their abundance and ability to crosslink alginate chains effectively.
3. Ion exchange: When the alginate solution is introduced to a solution containing divalent cations, the negatively charged carboxy groups of the G and M monomers interact with the calcium ions through ionic bonds. This ion exchange between the calcium ions and the carboxy groups leads to the formation of calcium-alginate complexes.[67]
4. Crosslinking: As the calcium ions bind to the carboxy groups along the alginate chains, the chains become interconnected, forming a three-dimensional network. This network is held together by the ionic bonds between the negatively charged carboxy groups of the alginate and the positively charged calcium ions.
5. Gel formation: The cross-linked network of alginate chains traps water within its structure, resulting in the formation of a gel. The gel has a stable and viscoelastic nature, allowing it to retain its shape and structure.
6. Gel strength and texture: The properties of the formed gel, such as its strength and texture, depend on various factors, including the concentration of alginate, the M/G ratio, the concentration of calcium ions, and the pH of the solution.[68]

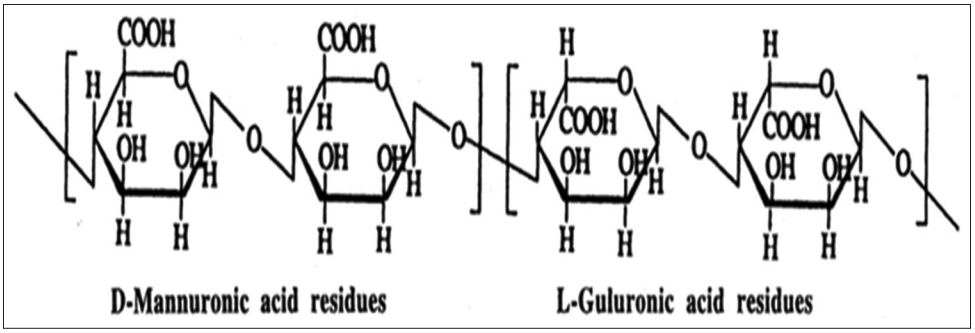

Figure 7: Structure of alginate showing both β-D-mannuronic acid and α-L-guluronic acid residues

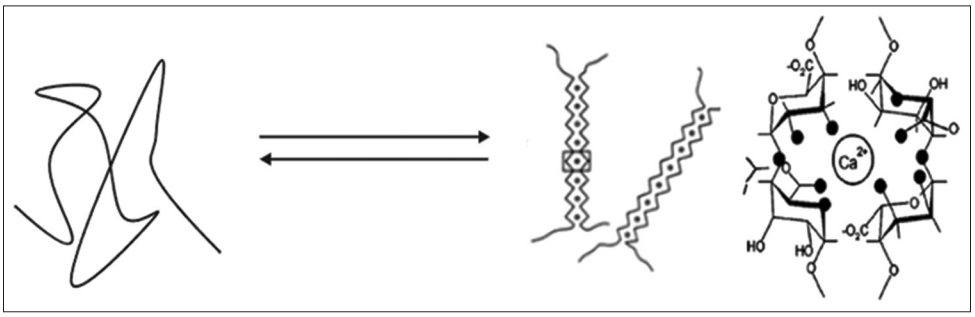

Figure 8: A schematic representation of the egg-box association of poly-L-guluronate alginate sequences cross-linked by calcium ions is shown

S.N.	Polyelectrolyte complex	Drug delivery system	Research finding	References
1.	Chitosan phthalate	Multiparticulate drug delivery system for diclofenac	The preparation of a specific antibiotic for diclofenac sodium using chitosan phthalate is investigated in this study. Use extrusion and spheroidization to create spherical multiparticle systems. The prepared products have a good spherical geometry with diameters ranging from 1.1 to 0.20 mm. The loading system has a maximum pH of 7.4 and the pH is reduced to 1.2. The formulation increased the maximum plasma concentration of DS Pellets compared to pure DS.	[74]
2.	Zinc–pectin–chitosan composite particles	Drug delivery to the colon	As carriers, zinc-pectin-chitosan composite microparticles were designed and manufactured. Due to its utility in intestinal diseases, resveratrol is used as a model drug. The formulation was created using a variety of techniques (cross-linking pH, chitosan molecular weight, and drug concentration). Contrast single-step formulation with multistep formulation technology.	[75]
3.	Chitosan-Tripolyphosphate and chitosan-polyphosphoric acid gel	Controlled drug delivery system for anti-cancer drug	Using a polyelectrolyte complexation method, chitosan-triphosphate and chitosan-polyphosphoric acid gel beads were created using enzymatically hydrolyzed chitosan for the sustained release of the anticancer agent. 6-Mercaptopurine. The enzymatically hydrolyzed chitosan's polyelectrolyte complexation mechanism and molecular weight influence the pH-responsive swelling ability, drug-release characteristics, and morphology of the chitosan gel bead. Chitosan beads were complexed through ionotropic crosslinking or interpolymer complexation after being gelled in penta-sodium tripolyphosphate or Polyphosphoric acid solution, respectively.	[76]
4.	Novel chitosan- based polyelectrolyte complex	Skin drug delivery	Skin-applied films with optimal functional properties (flexibility, resistance, water vapor transmission rate, and adhesion) were developed and optimized using novel chitosan-based polyelectrolyte complexes (PEC). The research was based on the combination of chitosan and two polyacrylic acid (PAA) polymers with varying crosslinkers and crosslinking densities. The interaction between the polymers was maximized by controlling the pH and forming the films at a pH close to the Ka of the respective components as determined by potentiometric and turbidimetric titrations.	[77]
5.	Chitosan sulfate-lysozyme hybrid hydrogels	Oral drug delivery	It is difficult to manipulate the properties and biological activities of chitosan-lysozyme hybrid hydrogels in order to benefit from their intriguing biomedical applications because chitosan acetylation pattern is a difficult parameter to manipulate. Sulfated chitosan-lysozyme hydrogels were created to be a versatile platform with fine-tuned degradability and long-term bactericidal and antioxidant properties. The advantage of using chitosan sulfates instead of chitosan is that the rate and mechanism of lysozyme release, as well as antibacterial and antioxidant activities, are all dependent on the sulfation profile, a structural parameter that is easily controlled through simple chemical modifications.	[78]

SN	Polyelectrolyte complex	Drug delivery system	Research finding	References
1.	Alginate-Neusilin US2 microcomposite beads	The oral administration of HES does not produce allergic reactions	The Alginate-Neusilin US2 microcomposite (MC) beads were developed and optimized for oral hesperidin (HES) administration. A 32-factorial design was used, with independent variables (factors) such as sodium alginate concentration (X1) and Neusilin US2 concentration (X2) and dependent variables (response) such as particle size (Y1), entrapment efficiency (Y2), and swelling degree (Y3) as the dependent variables.	[79]
2.	Alginate-Neusilin US2 Microcomposite hydrogel badges	Oral sustained release drug delivery system cilnidipine	The work presented here developed and optimized Alginate-Neusilin US2 microcomposite beads (MCBs) for oral delivery of cilnidipine (CIL). The optimized formulation of CIL-loaded MCB (BA-O) has a particle size of 1.55 0.05 mm, an entrapment efficiency of 82.35 1.5%, and a drug release after 12 h of 69.27 2.2%.	[80]
3.	Calcium alginate beads	Gastroretentive delivery systems	Gastroretentive delivery systems help improve absorption and, as a result, bioavailability of drugs with a narrow absorption window in a specific region of the gastrointestinal tract. A floatable multiparticulate system with the potential for intragastric sustained delivery is one method for achieving gastro retention. Cinnarizine (CNZ), an antihistaminic drug used to treat vertigo caused by Meniere's disease, was used as a model drug for non-effervescent floating beads.	[81]
4.	Assam Bora rice starch (ABRS) – alginate beads	Colon targeting drug delivery system	The study used an inotropic gelation technique and a 32 factorial design to formulate and optimize Assam bora rice starch (ABRS)-alginate beads containing a non-steroidal anti-inflammatory drug such as Naproxen for colon targeting against rheumatoid arthritis, inflammatory bowel disease, and colon cancer.	[82]
5.	Pectin vs. pectin–alginate beads	Multiparticulate colon drug delivery systems	He proposes a multiparticulate drug delivery system created by prilling in conjunction with an enteric coating in his research. Beads with a strong gelled matrix are produced by optimizing process variables such as feed viscosity at the nozzle, cross-linker selection, gelling solution pH, and cross-linking time. According to the findings, Dextran/piroxicam beads demonstrated high packaging efficiency, very narrow dimensional distribution, and high sphericity.	[83]

CHITOSAN-BASED POLYELECTROLYTE COMPLEX

Due to their unique properties and versatility, chitosan-based polyelectrolyte complexes (PECs) have received a lot of attention as potential carrier materials in drug delivery systems. Chitosan is a biocompatible and biodegradable polysaccharide derived from chitin, found in the shells of crustaceans. When combined with other polyelectrolytes, particularly oppositely charged polymers, chitosan forms complexes that offer various advantages in drug delivery applications.[69] An overview of the potential of chitosan-based PECs in drug-delivery systems is provided below:

Formation of chitosan-based PECs

1. Polyelectrolyte interaction: Chitosan possesses amino groups (-NH2) that can be protonated under acidic conditions, giving them a positive charge. When mixed with an oppositely charged polymer, such as alginate or hyaluronic acid, electrostatic interactions occur between the charged functional groups of the polymers. For instance, in negatively charged polymers like alginate or hyaluronic acid, these interactions play a crucial role in the formation of polyelectrolyte complexes.[70]
2. Complex formation: The electrostatic interactions between chitosan and the oppositely charged polymer lead to the formation of PECs. These complexes can

encapsulate drugs, genes, proteins, or other therapeutic agents within their structure.

Advantages of chitosan-based PECs in drug delivery

1. Enhanced stability and bioavailability: Chitosan-based PECs can protect encapsulated drugs from degradation in the physiological environment, enhancing drug stability and bioavailability.
2. Sustained release: The gradual diffusion of the drug through the polymer matrix allows for controlled drug release from PECs, prolonging therapeutic effects and minimizing side effects.
3. Targeted delivery: Surface modification of PECs can facilitate targeted drug delivery to specific tissues of cells, enhancing treatment efficacy and reducing off-target effects.
4. Biocompatibility and biodegradability: Chitosan is biocompatible and can be metabolized by the body's enzymes. This property reduces the risk of toxicity and long-term accumulation.
5. Versatility: Chitosan-based PECs can encapsulate a wide range of drug types, including hydrophobic and hydrophilic molecules, as well as biomolecules such as proteins and genes.
6. Muco-adhesion: The positive charge of chitosan allows it to interact with negatively charged mucosal surfaces, enhancing the residence time of drug-loaded PECs at target sites.
7. pH-sensitivity: Chitosan's charge can be pH sensitive, allowing for controlled drug release in response to changes in pH along the gastrointestinal tract.
8. Combination therapies: PECs can encapsulate multiple therapeutic agents with different release kinetics, enabling combination therapies.[71]

Challenges and considerations

1. Polymer compatibility: The choice of the oppositely charged polymer is crucial to achieve stable PEC formation. Compatibility and interactions between polymers should be considered.
2. Controlled complex formation: Achieving consistent and reproducible PEC formation requires precise control over polymer concentrations, pH, and mixing conditions.
3. Release kinetics: Tuning the release kinetics to meet therapeutic needs can be difficult and may necessitate optimization.
4. Scale-Up: Translating laboratory-scale PEC formulations to large-scale production can pose challenges in maintaining consistent quality and performance.
5. Regulatory considerations: The introduction of new materials like chitosan-based PECs in drug delivery systems requires regulatory testing and approval.[72]

Chitosan-based PECs offer a promising avenue for advancing drug delivery systems by providing controlled release, enhanced stability, and the potential for targeted therapy. However, careful formulation, characterization, and optimization are essential to harness their full potential in various biomedical applications.[73]

CONCLUSION

The development of a multiparticulate drug delivery system utilizing chitosan, alginate, and polyelectrolyte has shown significant promise in enhancing drug delivery efficiency, bioavailability, and targeted therapeutic outcomes. This innovative approach capitalizes on the unique properties of these materials, offering a versatile platform for the controlled and sustained release of various pharmaceutical compounds. Through the incorporation of chitosan, the system gains bioadhesive properties and biocompatibility, enabling prolonged residence time in the gastrointestinal tract and potentially improving drug absorption. Alginate, on the other hand, contributes to the system's stability and protection of encapsulated drugs from harsh stomach conditions, while also allowing for modulation of release kinetics. The addition of polyelectrolytes further fine-tunes the system's characteristics, influencing factors such as swelling behavior and overall encapsulation efficiency. The multiparticulate nature of this delivery system offers several advantages. It enhances drug dispersion, reduces the risk of dose dumping, and provides more consistent drug release profiles compared to single-unit dosage forms. This is particularly advantageous for drugs with narrow therapeutic windows or those requiring precise release profiles.

Moreover, the combination of these materials allows for the creation of complex drug delivery strategies, such as dual-drug delivery or sequential release of multiple therapeutic agents. This could find applications in combination therapies or treatments requiring phased drug administration. However, challenges still exist. Optimizing the formulation parameters, such as particle size, drug loading, and polymer rations, remain crucial for achieving desired release profiles and therapeutic outcomes. In addition, maintaining batch-to-batch consistency and scaling up production while preserving the system's performance pose engineering and manufacturing challenges. The multiparticulate drug delivery system utilizing chitosan, alginate, and polyelectrolyte represents a promising advancement in the field of pharmaceutical science. Its ability to enhance drug delivery efficiency, provide controlled release, and accommodate various drug compounds makes it an exciting avenue for further research and development. As technology advances and our understanding of these materials deepens, this system holds the potential to revolutionize drug delivery, leading to safer, more effective, and patient-centric treatments.

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