DEVELOPMENT OF BIOPOLYMERIC SYSTEMS FOR THE CONTROLLED DELIVERY OF ANTI-DIABETIC AGENTS

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Dikshita Sharma

Registration no: TZU18997 of 2025

School of Sciences

Department of Chemical Sciences

Tezpur University

Tezpur-784028

Assam, India

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CHAPTER 4

CONCLUSION AND FUTURE SCOPE

This chapter presents summaries of the thesis chapters and provides a brief discussion of the findings. The chapter also discusses the future scope of the work done in the thesis.

4.1. Conclusion

Oral drug delivery for chronic conditions, particularly type 2 diabetes mellitus (T2DM), remains a challenge due to the multifactorial nature of disease progression, the necessity for sustained therapeutic plasma concentrations, and patient adherence concerns. In this thesis, four distinct but complementary biopolymeric systems were developed and investigated to improve the oral bioavailability and controlled release profiles of antidiabetic compounds (lipoic acid and curcumin). By systematically exploring various polymeric matrices, crosslinkers, and inorganic dopants, this work has contributed novel insights into designing pH-responsive, nanostructured drug delivery carriers with enhanced therapeutic efficacy and safety profiles.

Chapter 1 discussed the study's background, significance and objectives. In developing advanced drug delivery systems, biopolymers such as chitosan, alginate, and carrageenan have proven indispensable due to their biocompatibility, biodegradability, and ability to facilitate controlled drug release. Chitosan is particularly valued for its mucoadhesive properties and pH-responsive gelation, which protect drugs through the gastric environment and enable targeted intestinal release. Alginate's gel-forming capabilities upon interaction with calcium ions make it an ideal material for creating robust drug delivery systems that respond dynamically to pH variations, thereby enhancing site-specific drug release in the small intestine. Similarly, carrageenan utilises its pH-sensitive properties to modulate drug release in response to the gastrointestinal tract's varying pH levels. Gelatin, with its mucoadhesive properties and thermal reversibility, facilitates the formation of stimuli-responsive drug delivery matrices. Soy flour enhances stability and promotes drug-polymer interactions through its functional groups. Additionally, integrating inorganic materials like montmorillonite, magnesium oxide nanoparticles, and halloysite nanotubes into these biopolymeric matrices addresses mechanical strength and stability challenges, further optimising the therapeutic efficacy of drug delivery systems. Crosslinking strategies, utilising agents such as glutaraldehyde and calcium ions, are crucial for enhancing the structural integrity and release profiles of these systems, underscoring the sophisticated interplay between materials science and chemistry in the quest for more effective and efficient drug delivery solutions.

Chapter 2 describes the experimental design and methodologies employed to formulate

and characterise the biopolymeric complexes for delivering α-lipoic acid and curcumin. It outlines the materials, cross-linking techniques, analytical procedures, and instrumentation that validate the preparation and performance of these controlled-release systems.

Chapter 3 discusses the formulation and systematic evaluation of biopolymeric complexes designed for controlled oral delivery of curcumin and α-lipoic acid. This chapter was divided into four sections. *Section 3.1* focused on synthesising lipoic acid-loaded chitosan–alginate complexes, with glutaraldehyde and montmorillonite (MMT) serving as functional additives. Characterisation using FTIR and XRD verified that drug encapsulation and transitioning from crystalline to amorphous states improve solubility and bioavailability. The pH-responsive release profile showed minimal drug release under acidic conditions and a higher release at alkaline pH, with more pronounced crosslinking reducing overall drug release. Cell-based assays revealed enhanced glucose uptake and cell viability, underscoring the system's potential as a controlled delivery platform. In *Section 3.2,* a novel gelatin-halloysite nanotube-carrageenan polyelectrolyte complex was developed to address the solubility and stability challenges associated with lipoic acid. Analytical techniques confirmed successful drug encapsulation and reduced crystallinity, which improves dissolution. The system demonstrated minimal drug release at acidic pH values and a considerably higher release at pH 7.4, indicating reliable pH responsiveness. Glucose uptake assays further validated the formulation's metabolic efficacy, and viability tests showed no significant cytotoxicity, indicating a good safety profile for potential *in vivo* applications. *Section 3.3* presented a novel system in which curcumin was encapsulated in MgO-doped chitosan-carrageenan polyelectrolyte complexes crosslinked by glutaraldehyde. Comprehensive characterisation confirmed effective drug loading and a decrease in crystallinity. The release behaviour indicated that curcumin remained stable in acidic environments while releasing more in alkaline conditions—an ideal property for targeting the small intestine. Additionally, MgO doping boosted glucose uptake in L6 myotubes, and the controlled release pattern maintained therapeutic concentrations over time, thus highlighting the formulation's promise for managing type 2 diabetes. *Section 4.4* discussed the synthesis and investigation of a soy flour matrix fortified with montmorillonite and magnesium oxide nanoparticles to achieve a sustained, pH-sensitive release of curcumin. Although higher dopant and crosslinker levels enhanced matrix rigidity and controlled release, they reduced encapsulation efficiency and, in some cases,

affected cell viability. Nevertheless, optimised formulations successfully balanced robust release control and biocompatibility, highlighting their potential for maintaining therapeutic curcumin levels in the small intestine. This work highlights the importance of fine-tuning dopant concentrations in designing effective oral delivery systems.

The thesis demonstrates how the strategic use of biopolymers, crosslinkers, and inorganic additives can improve the stability, solubility, and controlled release of antidiabetic agents. Drug release in the stomach is minimised through carefully tuned matrices, while sustained release in the intestine enhances therapeutic efficacy. The findings establish a foundation for future *in vivo* investigations and pave the way for innovative oral delivery systems in the management of chronic diseases. Hence, the subsequent conclusions can be drawn from the current work.

- **Polyelectrolyte Complexes as Robust Encapsulation Platforms**

All four studies demonstrated that naturally derived polymers—such as chitosan, alginate, carrageenan, gelatin, and soy flour—can be electrostatically assembled into polyelectrolyte complexes (PECs) capable of effectively encapsulating and stabilising bioactive compounds. This finding is consistent with broader evidence in polymer science, suggesting that polyelectrolyte interactions can enhance drug loading, confer structural stability, and enable tuneable drug release kinetics. Glutaraldehyde (GA) was used as a crosslinking agent throughout these studies to further strengthen the matrix, thereby minimising premature drug leakage and degradation. However, increased crosslinking density correlated with reduced encapsulation efficiency and slower release, underscoring the importance of optimising GA levels to balance stability with sufficient drug release rates.

- **Inorganic Nanoparticle Doping for Enhanced Functionality**

A recurring theme was the strategic introduction of inorganic additives—namely, montmorillonite (MMT), magnesium oxide (MgO), and halloysite nanotubes (HNTs)—to impart beneficial properties to the biopolymer matrices. These dopants improved mechanical rigidity, provided additional binding sites for drug molecules, and offered pH-sensitive responses. Halloysite nanotubes, for example, have been reported to enhance

drug encapsulation due to their high aspect ratio and natural lumen structure. Meanwhile, magnesium oxide nanoparticles contribute to metabolic regulation, as indicated by augmented glucose uptake in diabetic models. Nevertheless, the thesis also underscores that excessive dopant concentrations can lead to reduced drug loading, possible oxidative stress, and diminished cell viability, highlighting the delicate balance between functional enhancement and biocompatibility.

- **Suppression of Crystallinity and Amorphous Drug Dispersion**

X-ray diffraction (XRD) analyses consistently revealed a reduction in the crystallinity of curcumin and lipoic acid when incorporated into the polymeric matrices. Suppression of crystallinity is significant from a pharmaceutical standpoint, as drugs in an amorphous form often exhibit superior solubility and bioavailability. Fourier transform infrared (FTIR) spectra across all studies confirmed successful loading and the establishment of intermolecular interactions (e.g., hydrogen bonding, electrostatic interactions) between the drug, the polymer, and the dopants. By stabilising drug molecules in an amorphous state, the polyelectrolyte systems could address the inherently low solubility of specific antidiabetic agents, thereby improving their potential clinical efficacy.

- **pH-Responsive, Sustained Release for Targeted Delivery**

A notable achievement of these formulations was their pronounced pH-dependent release behaviour: minimal drug release at highly acidic gastric pH (1.2) and significantly enhanced release under near-neutral to alkaline intestinal conditions (pH 7.4). This aligns with the established principle that polyelectrolyte carriers can utilise physiological pH gradients to facilitate site-specific drug release. Such selectivity protects drugs like lipoic acid and curcumin from premature stomach degradation and maximises their absorption window in the small intestine. The sustained release kinetics, modulated further by crosslinking density and dopant concentrations, prevent a burst release effect and maintain therapeutically relevant drug levels over extended periods, particularly advantageous for the long-term management of T2DM.

- ***In Vitro* Validation of Therapeutic Efficacy and Safety**

Biocompatibility and therapeutic efficacy are paramount for clinical translation. MTT

assays across all four studies demonstrated that moderate-to-low concentrations of glutaraldehyde and inorganic additives minimised cytotoxic effects, sustaining high cell viability. Furthermore, the 2-NBDG glucose uptake assays in L6 myotubes consistently showed enhanced glucose uptake by cells treated with these formulations compared to controls, implying direct relevance to insulin sensitivity and glycaemic control in T2DM management. Such outcomes underscore that these polyelectrolyte-based systems are safe and capable of positively modulating metabolic pathways, offering encouraging prospects for clinical application.

4.2. Future Scopes

Building on the promising results of this thesis, several avenues can be pursued to advance further the development and application of biopolymer-based oral delivery systems for nutraceuticals and drugs:

- **Comprehensive *In Vivo* Evaluation**
  While the *in vitro* results are promising, extensive animal studies are necessary to elucidate pharmacokinetic and pharmacodynamic profiles, toxicity, and long-term biocompatibility under physiological conditions. This includes evaluating the systems' efficacy in diabetic animal models to confirm improved glycaemic control, insulin sensitivity, and overall metabolic health.
- **Scale-up and Industrial Translation**
  Transitioning from bench-scale to large-scale production is crucial for achieving clinical success. Future work should investigate established industrial processes, such as spray drying, electrospinning, or extrusion, to manufacture these nanocomposites in bulk. Process parameters (e.g., temperature, shear stress) and formulation variables (e.g., polymer ratio, dopant concentration) will need optimisation to maintain batch-to-batch consistency and meet regulatory standards.
- **Expansion to Other Bioactives and Therapeutic Areas**: The platform design can be adapted to carry other bioactive compounds with poor oral bioavailability. Many nutraceuticals (e.g., resveratrol, quercetin, or catechins) and even conventional drugs (e.g., certain anti-inflammatory or anticancer agents) face similar challenges related to low solubility or stability. Applying the current encapsulation strategy to these molecules could improve their therapeutic index. Likewise, the approach

could be extended to peptide and protein drugs (such as oral insulin or incretin mimetics) by modifying the polymers or adding enzyme inhibitors to protect against gastrointestinal degradation. Demonstrating the versatility of the delivery system across different therapeutic areas (beyond diabetes) would broaden its impact and utility.

- **Advanced Characterisation Techniques**

  Additional characterisation methods, including small-angle X-ray scattering (SAXS) and *in situ* rheology, could provide deeper mechanistic insights into how biopolymers and nanoparticles interact and self-assemble. Furthermore, advanced imaging techniques such as live-cell fluorescence microscopy or near-infrared (NIR) tracking could show how these formulations behave in biological systems in real-time.

- **Combination Therapeutic Approaches**

  Given the complexity of type 2 diabetes mellitus and its frequent comorbidities (e.g., hyperlipidemia, hypertension), integrating multiple therapeutic agents—such as antihyperlipidemic drugs, peptides, or antioxidants—within the same carrier could offer synergistic benefits. Future studies might explore dual- or even triple-drug encapsulation strategies to address multiple metabolic pathways simultaneously.

- **Personalised and Precision Medicine**

  The inherent tunability of biopolymeric PECs allows tailoring the matrix composition, crosslinking density, and nanoparticle content to meet individual patient needs. For instance, patients with differing gastric pH profiles or comorbid gastrointestinal disorders may benefit from fine-tuned release characteristics. Leveraging computational modelling and machine learning to predict patient-specific responses to oral drug delivery systems could be a step forward in precision medicine.

- **Exploration of Alternative Crosslinkers and Polymers**

  Although glutaraldehyde has proven practical, concerns about residual aldehyde groups and potential cytotoxicity remain. Investigating alternative crosslinkers such as genipin, oxidised polysaccharides, or enzyme-mediated systems may improve safety profiles without compromising mechanical stability. Likewise, exploring emerging biodegradable polymers (e.g., nanocellulose, poly(glycerol

sebacate)) could expand the versatility and sustainability of these drug carriers.

- **Closed-loop delivery system for hypoglycaemic agents**
  Building on biopolymeric approaches offering pH-sensitive, sustained-release profiles, future research could incorporate glucose-responsive polymers or embedded sensors into these matrices. Such platforms would detect fluctuations in blood glucose levels and modulate the release of antidiabetic agents—such as lipoic acid, curcumin, or insulin—without requiring continuous patient intervention. Advances in nanotechnology, microfluidics, and biosensing technology suggest extending this concept to wearable or implantable devices that communicate with external monitors, thereby maintaining tight glycaemic control while reducing the burden of multiple daily injections or oral doses. Ultimately, developing multifunctional polymers capable of real-time responsiveness to glucose could bring fully autonomous, closed-loop therapeutics closer to clinical implementation, significantly improving patient quality of life and long-term disease outcomes.
- **Regulatory and Clinical Validation**
  Eventually, any promising formulation must undergo rigorous clinical testing to validate its safety and efficacy in humans. Establishing robust metrics for quality control and engaging in early dialogues with regulatory agencies can help streamline the path from pilot studies to clinical trials.

In conclusion, the findings of this thesis provide a framework for enhancing the oral delivery of bioactive compounds using biopolymer-based controlled release systems. Pursuing the future research directions outlined above can deepen the scientific understanding of such delivery platforms and accelerate their progress toward clinical application. The ultimate vision is to develop **patient-friendly, effective, and safe oral therapies** for diabetes and other chronic diseases, leveraging the power of biomaterials to overcome pharmacokinetic barriers and unlock the full potential of promising therapeutic agents.