ABSTRACT

Controlled drug delivery systems are pivotal in enhancing the therapeutic efficacy and safety of medications by ensuring targeted and sustained release, thereby minimising side effects to healthy tissues. This thesis focuses on the innovative development of biopolymeric nanoparticles for the oral delivery of two potent anti-diabetic agents, curcumin and α-lipoic acid, which are traditionally limited by poor bioavailability due to their hydrophobic nature and rapid metabolism. Employing natural polymers such as chitosan, carrageenan, alginate, gelatin and soy flour, this research aims to overcome these challenges through advanced formulation strategies.

The study utilises drug-loaded polymeric systems, employing crosslinkers and reinforcing agents to optimise drug release profiles and enhance particle stability. The formulations are designed to target the gastrointestinal tract effectively by integrating therapeutic approaches, maximising drug absorption, and minimising premature degradation.

The main objectives of this investigation are:

I. To develop and optimise delivery systems capable of controlled release of curcumin and α-lipoic acid using natural, biodegradable polymers;

II. To assess the impact of various formulation parameters such as polymer type, crosslinker concentration, and concentration of reinforcing agent on the bioactivity, yield, loading, encapsulation, and release dynamics of the encapsulated drugs;

III. To characterise the drug-loaded polymeric systems using Fourier transform infrared spectroscopy, x-ray diffraction, field emission scanning electron microscopy, etc.;

IV. To evaluate the *in vitro* effectiveness and safety of the nanoparticles in delivering therapeutic agents for diabetes management.

The thesis consists of four chapters, namely

Chapter 1: Introduction

This chapter presents an introduction and a literature review. It discusses the concept of controlled drug delivery, the role of nanotechnology in such systems, key components involved in controlled drug delivery, and oral drug therapy for diabetes treatment. Additionally, it addresses natural polymers essential for transporting active agents and the

fabrication methods utilised for creating drug-loaded polymeric nanoparticles. The chapter also examines the roles of reinforcing agents, crosslinkers, and surfactants in drug delivery systems. A general overview of the structure, properties, and applications of soy flour, chitosan, carrageenan, alginate, montmorillonite, halloysite, glutaraldehyde, α-Lipoic acid, and curcumin is also included. Furthermore, this chapter outlines the aims and objectives of the current study.

Chapter 2: Materials and Methods

This chapter details the experimental approaches and methodologies used to develop biopolymeric complexes for the controlled delivery of α-lipoic acid (LA) and curcumin. Key materials outlined include chitosan, sodium alginate, carrageenan, gelatin A, and reinforcing agents such as montmorillonite nano-clay, halloysite nanotubes, and magnesium oxide nanoparticles. The synthesis section describes the preparation of drug-loaded polyelectrolyte complexes, with an emphasis on the role of glutaraldehyde (GA) as a cross-linking agent. Characterisation techniques such as Fourier Transform Infrared Spectroscopy (FTIR), X-ray Diffraction (XRD), Scanning Electron Microscopy (SEM), Field Emission Scanning Electron Microscopy (FESEM), and Energy Dispersive X-ray Spectroscopy (EDX) are employed to analyse the chemical integrity, crystalline structure, and microstructural morphology of the complexes. *In vitro* release studies assess the drug release kinetics under simulated physiological conditions, which is critical for determining the system's efficacy in controlled release. Additionally, biological assays, including glucose uptake and cell viability tests, are used to evaluate the therapeutic potential and cytocompatibility of the formulations.

Chapter 3: Results And Discussion

Chapter 3 comprehensively evaluates biopolymeric complexes designed for the controlled oral delivery of hypoglycaemic agents, curcumin and α-lipoic acid. The chapter is structured into four main sections, each focusing on different biopolymeric systems and their modifications to enhance controlled drug delivery and overall therapeutic efficacy.

Section 3.1 details the optimisation of the Chitosan-Alginate (Ch/Alg) complex using MMT and GA. Results show that increased concentrations of both MMT and GA reduce encapsulation and drug loading efficiencies. This is attributed to the restrictive effect of MMT’s silicate layers and the GA-induced polymer rigidity, which limits the flexibility of the polymer chain and internal volume, thereby reducing the potential for drug entrapment.

The *in vitro* release of LA from these complexes demonstrated clear pH dependence, with enhanced drug release in alkaline conditions (pH 7.4) due to increased swelling and reduced polymer interactions. Characterisation via FTIR, XRD, and SEM confirmed the successful formation of polymer-drug interactions, with FTIR spectra revealing the presence of hydrogen bonds and amide linkages between chitosan and alginate, and SEM images highlighting surface morphology changes resulting from crosslinking and the inclusion of MMT. The glucose uptake assay demonstrated improved glucose uptake, and cytotoxicity assays showed non-toxicity, indicating the therapeutic potential of these formulations.

Section 3.2 explores the Gelatin-Halloysite Nanotube-Carrageenan complex for pH-responsive delivery of LA. Increased HNT content notably improved encapsulation and drug loading due to enhanced polymer-drug interactions provided by HNT's large surface area. However, GA's higher concentrations negatively impacted these efficiencies by creating a dense polymer matrix. The release studies again highlighted pH responsiveness, with higher release rates under alkaline conditions due to reduced gelatin-carrageenan interactions and increased swelling. FESEM analysis revealed that the structural complexity induced by HNT and GA is beneficial for modulating adhesion and drug release. Glucose uptake and cytotoxicity assays confirmed the balance between structural stability and biocompatibility necessary for therapeutic effectiveness.

Section 3.3 evaluates the role of the MgO-doped Chitosan-Carrageenan complex in delivering curcumin. MgO incorporation mildly reduced encapsulation and loading efficiencies due to interactions that reduced available drug entrapment spaces. GA crosslinking further limited these efficiencies by creating rigid, less permeable structures. Drug release studies showed pronounced pH dependency, favouring alkaline conditions, with sustained drug release attributed to increased porosity from MgO doping. Characterisation techniques supported these observations, indicating molecular dispersion of curcumin and confirming MgO incorporation through XRD and EDX analyses. Biological assays revealed that these nanoparticles effectively enhanced glucose uptake, with optimised MgO and GA levels essential for maximising therapeutic efficacy and minimising cytotoxicity.

Section 3.4 addresses the development of a pH-responsive Soy Flour–Montmorillonite–Magnesium Oxide complex tailored for the sustained release of curcumin. This system

optimally integrates the structural advantages and pH-responsive properties of both MMT and MgO to enhance the encapsulation and controlled release kinetics of curcumin. Increased concentrations of MgO negatively impacted encapsulation and loading efficiency by occupying a significant amount of space within the polymer matrix and interacting strongly with soy flour, thereby reducing the entrapment of the drug within the matrix. Similarly, higher MMT concentrations reduced encapsulation and loading efficiencies by restricting the movement of polymer chains due to interactions with their silicate layers. Careful optimisation of component ratios resulted in improved structural integrity and optimal drug release profiles under varying pH conditions, demonstrating the complex's significant potential for effectively managing diabetes through sustained therapeutic delivery. Glucose uptake and cytotoxicity assays confirmed the efficacy and biocompatibility of the system.

Chapter 4: Conclusion And Future Scopes

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.