CHAPTER 1

INTRODUCTION

This chapter briefly outlines the global significance of diabetes mellitus and introduces hypoglycaemic active agents such as curcumin and α-lipoic acid as promising therapeutic agents. It then highlights how biopolymer-based drug delivery systems address key challenges in drug delivery, thereby underscoring the rationale for controlled-release strategies. Additionally, the chapter delineates the specific objectives and scope of the present study, laying the groundwork for the subsequent experimental investigations.

1.1. Background and Significance

Diabetes mellitus (DM) is a long-lasting metabolic condition marked by chronic high blood sugar levels due to insufficient insulin production, ineffective insulin action, or a combination of both. This condition can be classified into three main types: Type 1 diabetes (T1DM), Type 2 diabetes (T2DM), and gestational diabetes mellitus (GDM). Of these, T2DM represents the majority of cases globally, highlighting its significant clinical and epidemiological importance [1].

Recent projections from the International Diabetes Federation suggest that the worldwide prevalence of diabetes might surpass 700 million by the year 2045, indicating a concerning growth trend [2]. The rising rates of diabetes significantly impact morbidity through complications related to microvascular issues such as nephropathy (kidney disease), retinopathy (eye disease), and neuropathy (nerve damage), which can lead to serious health issues including blindness, kidney failure, and limb amputations. Additionally, diabetes increases the risk of macrovascular issues such as cardiovascular disease, which can lead to heart attacks and strokes, and also increases mortality risks [3]. Additionally, the economic burden is considerable, driven by rising healthcare expenses, diminished workforce productivity, and the difficulties in managing the disease over the long term [4]. As a result, diabetes has emerged as a crucial global health challenge, underscoring the need for the development of more effective and accessible treatment options**.**

Current treatments for diabetes consist of sulfonylureas (such as glibenclamide and glipizide), biguanides (like metformin), various insulin formulations, and other oral hypoglycaemic drugs [5, 6]. Although these medications can often provide adequate glycaemic control, several issues, including side effects like hypoglycaemia, weight gain, and gastrointestinal discomfort, limit their long-term effectiveness. Additionally, complicated dosing schedules and the risk of drug interactions can lead to reduced patient adherence, further hindering optimal blood sugar management [7–9]. These limitations emphasise the urgent need for new, patient-centred treatment strategies that improve therapeutic outcomes, reduce side effects, and enhance patient compliance, ultimately leading to better clinical results.

1.2. Rationale for Nutraceutical-Based Oral Therapy

Nutraceuticals—derived from the combination of "nutrition" and "pharmaceutical"—refer to products sourced from foods that offer both nutritional advantages and therapeutic effects [10]. In diabetes management, various nutraceuticals have shown potential in reducing blood sugar levels through mechanisms like modulating glucose metabolism, improving insulin sensitivity, and lowering oxidative stress. Key examples include curcumin (extracted from turmeric), α-lipoic acid, resveratrol (found in grapes and berries), cinnamon extract, and fenugreek seeds, all of which have been researched for their ability to enhance glycaemic control and lessen complications related to diabetes [11]. Since these bioactive substances primarily come from food sources or traditional medicinal plants, they are often considered safer and more approachable alternatives to traditional synthetic medications.

Utilising nutraceuticals as supplementary treatments for diabetes presents several benefits [12, 13]. Firstly, they can offer a broader range of therapeutic effects beyond just managing blood sugar levels, exhibiting antioxidant and anti-inflammatory properties that can help reduce complications arising from diabetes. Secondly, their generally positive safety records and fewer side effects can improve patient adherence and long-term use, addressing a significant limitation of specific standard anti-diabetic treatments. Thirdly, many nutraceuticals are affordable and can be easily added to standard diets, potentially alleviating the financial strain of managing chronic illnesses. These characteristics underscore nutraceuticals' potential as complementary or alternative treatment options, highlighting the necessity for ongoing research into their effectiveness, safety, and applicability within diabetes care.

Curcumin and α-lipoic acid stand out due to their well-documented pharmacological effects in managing diabetes and related complications. Curcumin, the principal bioactive compound in Curcuma longa (turmeric), enhances insulin signalling, reduces inflammation, and protects pancreatic β-cells from oxidative stress [14]. Similarly, α-lipoic acid, a mitochondrial antioxidant, plays a role in glucose uptake, insulin sensitivity, and neuroprotection against diabetic complications [15].

1.2.1. Therapeutic Potential of Curcumin

Curcumin, the primary active compound found in the rhizome of Curcuma longa (turmeric), consists of phenolic groups and α,β-unsaturated carbonyl functionalities that provide potent antioxidant and anti-inflammatory effects. Structurally, curcumin exists in keto-enol tautomeric forms, with the enolic configuration being the predominant form in physiological conditions. This molecular structure supports curcumin's diverse pharmacological properties, including the ability to influence various cell signalling pathways [16–18].

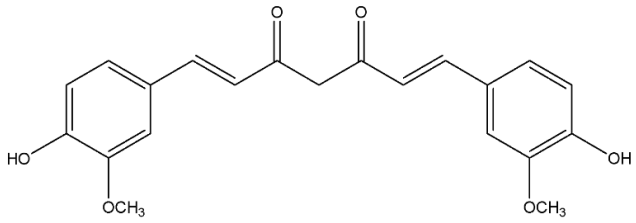

Figure 1.1. Structure of Curcumin

A significant component of curcumin's potential in managing diabetes is its ability to reduce hyperglycaemia and fight against insulin resistance. On a mechanistic level, curcumin targets key molecules such as nuclear factor-kappa B (NF-κB), peroxisome proliferator-activated receptors (PPARs), and inflammatory cytokines (like tumour necrosis factor-alpha and interleukins), thus diminishing chronic inflammation and oxidative stress—two important contributors to the development of type 2 diabetes mellitus (T2DM) [19]. Additionally, curcumin improves insulin receptor function and promotes glucose uptake in peripheral tissues by advancing downstream signalling pathways that support effective glycaemic management. Its significant antioxidant function also helps mitigate oxidative stress, often exacerbating insulin resistance and endothelial dysfunction in diabetic individuals [20, 21].

Preclinical research has shown that curcumin effectively lowers hyperglycaemia, enhances insulin sensitivity, and protects pancreatic β-cells from damage in diabetes animal models [22, 23]. Early human clinical studies also indicate that curcumin supplementation may

reduce fasting blood glucose levels and improve insulin resistance, though variability in bioavailability presents an ongoing challenge [24, 25]. These observations highlight the potential of curcumin as a supportive therapeutic option for managing diabetes, leading to continued research to enhance its oral bioavailability and pharmacokinetic properties for better clinical results.

1.2.2. Therapeutic Potential of Lipoic Acid

α-Lipoic acid (LA or ALA), a naturally occurring organosulfur compound, primarily exists in two redox states: the oxidised form (lipoic acid) and the reduced form (dihydrolipoic acid). This dual nature is fundamental to its significant antioxidant capabilities, encompassing the direct neutralisation of reactive oxygen species (ROS) and the renewal of endogenous antioxidants like glutathione and vitamins C and E [26]. By supporting redox balance, lipoic acid alleviates oxidative stress, which is commonly linked to the development and progression of diabetes and its complications.

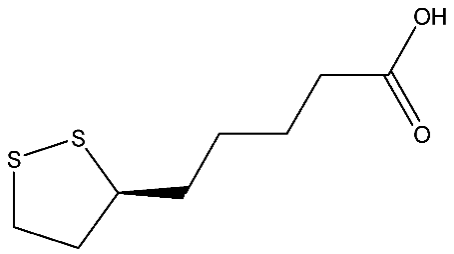

Figure 1.2. Structure of α-Lipoic acid

Beyond its antioxidant properties, LA exhibits noteworthy potential for enhancing insulin sensitivity and glucose metabolism. It is believed to boost insulin signalling and promote the translocation of glucose transporters (GLUT), thereby aiding glucose absorption in peripheral tissues [27]. Research on animal models has consistently indicated that LA supplementation can decrease hyperglycaemia, lower insulin resistance, and improve neuropathic and vascular diabetes-related issues [28]. Initial clinical investigations also imply that LA may help reduce neuropathic pain, enhance endothelial function, and improve glycaemic control in patients with type 2 diabetes mellitus [29]. Together, these results underscore the significant therapeutic potential of lipoic acid as a supportive or

complementary resource in managing diabetes. They instil optimism about its future role and prompt ongoing efforts to refine its formulation and delivery for more widespread clinical use.

1.3. Challenges in Oral Delivery of Curcumin and Lipoic Acid

1.3.1. Limited Bioavailability and Stability

Curcumin and lipoic acid have inherently low oral bioavailability (about 1% only), mainly due to their poor solubility in water (about 11 ng/mL), chemical instability, and significant first-pass metabolism. Curcumin's hydrophobic character and rapid metabolic conjugation in the gastrointestinal tract greatly limit its systemic absorption, requiring relatively high doses to achieve therapeutic effectiveness. Although lipoic acid has better solubility than curcumin, it still shows low bioavailability (approximately 30%) and faces rapid metabolic breakdown after oral intake, reducing its effective concentration in plasma. The pharmacokinetic profile of ALA is such that it demonstrates a short half-life, necessitating frequent dosing to maintain therapeutic levels [30, 31].

Several additional factors affecting oral absorption and systemic bioavailability include the pH within the gastrointestinal tract, the activity of enzymes and microbiota present in the gut, and the physicochemical characteristics of the formulation (like particle size, surface charge, and hydrophilicity). These factors highlight the necessity for innovative delivery methods to stabilise and improve curcumin and lipoic acid's solubility, permeability, and retention in the gastrointestinal tract.

1.3.2. Approaches to Address Bioavailability Challenges

Numerous strategies have been explored to improve the bioavailability of curcumin and lipoic acid. These strategies include chemical modifications (such as pro-drug formation or derivatisation), co-administration with bio-enhancers like piperine, nanoencapsulation, and the creation of liposomal or micellar formulations [32]. Chemical modifications typically alter functional groups to enhance water solubility or decrease metabolic degradation. Nanoencapsulation and liposomal systems involve encapsulating the bioactive agent within nanoscale structures or lipid vesicles, thereby increasing dissolution rates, facilitating targeted delivery, and reducing rapid clearance [33].

Despite these advancements, many current methods only partially address solubility, chemical instability, and first-pass metabolism challenges. Therefore, there is an increasing demand for biopolymer-based delivery systems that leverage the innate biocompatibility and biodegradability of natural polymers such as chitosan, alginate, and gelatin. By crafting formulations that react to specific physiological triggers (like pH or enzymes), researchers can achieve stable, targeted, and controlled release of curcumin and lipoic acid, which enhances therapeutic effectiveness while minimising systemic side effects. This emphasis on biopolymeric carriers is in harmony with contemporary trends in functional drug delivery, which stress the importance of patient-centric, sustainable, and highly effective treatments. Additionally, the versatility of these biopolymeric systems allows the incorporation of multiple therapeutic agents, potentially enabling synergistic effects and broadening their clinical applications. Moreover, ongoing research continues to refine these materials for enhanced mechanical stability, improved drug loading efficiency, and optimised release profiles, further advancing the scope of patient-centric treatments.

1.4. Overview of Biopolymer-based Systems for Controlled Oral Delivery

Biopolymers, defined as polymers sourced from biological materials, present a flexible platform for drug delivery applications. They can be divided into three categories: natural, synthetic, and semi-synthetic. Natural biopolymers like chitosan, alginate, gelatin, and carrageenan are often favoured in the biomedical field due to their biocompatibility, biodegradability, and low toxicity [34]. Synthetic biopolymers are usually designed with specific molecular weights and predictable degradation rates but may require further modifications to enhance their biological interactions. Semi-synthetic biopolymers are created by chemically altering natural polymers, which allows them to retain beneficial natural characteristics while gaining improved mechanical strength, solubility, or stability [35].

Among their various benefits, biopolymers demonstrate biocompatibility, which helps reduce adverse immune reactions, biodegradability, which lessens long-term environmental and physiological impacts, and often mucoadhesive properties that promote extended retention at targeted locations, such as the gastrointestinal lining [36]. Additionally, their structural flexibility—evidenced by adjustable mechanical strength, pH sensitivity, and controllable cross-linking density—renders them highly suitable for

developing drug delivery systems. This adaptability enables researchers to create nanoparticles, hydrogels, microspheres, and other drug-laden structures to improve therapeutic agents' stability and sustained release. As a result, biopolymer-based delivery systems have emerged as a compelling option for orally administering complicated compounds like curcumin and lipoic acid, for which conventional formulations frequently struggle to reach optimal bioavailability and therapeutic effectiveness.

1.4.1. Criteria for Selecting Biopolymeric Carriers

Choosing the right biopolymer to deliver therapeutics like curcumin and lipoic acid depends on several essential characteristics, including mechanical strength, swelling properties, pH responsiveness, and the potential for chemical modifications [37, 38]. Mechanical integrity is crucial to ensure the delivery system can endure physiological challenges, such as peristaltic movements and variations in osmotic pressure, especially during oral delivery. The swelling behaviour is also important since it affects the drug's release kinetics: polymers that expand in response to digestive fluids can enable quick or prolonged release, depending on the level of cross-linking and the interactions between the solvent and the polymer. In addition, pH sensitivity facilitates controlled release based on the site or timing, enhancing therapeutic efficacy and minimising off-target effects.

A further set of considerations influencing the efficacy of biopolymeric carriers encompasses cross-linking density, molecular weight, and the degree of chemical modifications [39, 40]. Cross-linking—whether through ionic interactions, covalent bonds, or other intermolecular forces—can substantially modify pore size, mechanical strength, and swelling rates, ultimately governing drug loading and release patterns. Molecular weight is also a significant factor: polymers with lower molecular weight typically degrade more swiftly, whereas those with higher molecular weight can offer more stable and enduring structures. Furthermore, chemical modifications (such as adding functional groups or the conjugation of ligands) can improve mucoadhesion, enhance targeting to specific areas of the gastrointestinal tract, or adjust pH responsiveness. By carefully balancing these factors, researchers can fine-tune the formulation of biopolymer-based delivery systems to enhance therapeutic efficacy for compounds with low bioavailability, such as curcumin and lipoic acid.

1.4.2. Need for Controlled Drug Release

Accomplishing a reliable and sustained release profile poses a significant challenge in oral drug delivery, particularly for compounds with low bioavailability or narrow therapeutic windows. Traditional immediate-release formulations often result in substantial variations in plasma drug concentrations, leading to subtherapeutic and potentially harmful cycles. These fluctuations can result in reduced efficacy, heightened side effects, and lower patient adherence. In contrast, controlled-release systems are designed to keep drug levels in the bloodstream consistent and prolonged, which can decrease the frequency of dosing and improve patient compliance [41].

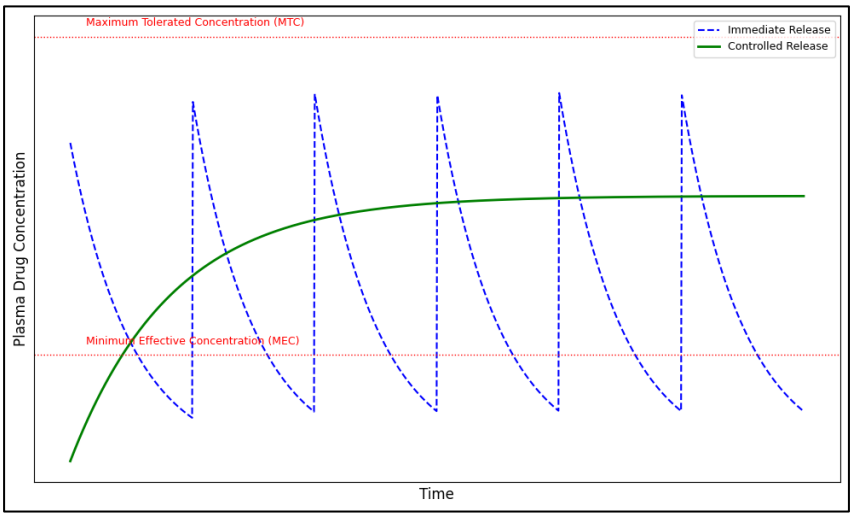

Figure 1.3. Pharmacokinetic profiles for immediate-release versus controlled-release dosage form

Moreover, controlled drug release provides the benefit of targeted delivery, where the formulation is designed to release its active ingredient at a particular location or over a set timeframe (for example, in response to pH changes or enzymatic activity in the gastrointestinal tract). This accuracy can be especially advantageous for bioactive compounds such as curcumin and lipoic acid, susceptible to degradation or rapid elimination in the gastrointestinal environment. Encapsulating these substances within polymeric carriers that react to environmental stimuli maximises their absorption potential and therapeutic effectiveness while minimising systemic adverse effects [42]..

Consequently, advancing sophisticated controlled-release strategies is vital for effectively converting promising drug candidates into clinically applicable treatments.

1.4.3. Advantages of Oral Route of Delivery

The oral route of drug delivery has long been recognised as the most widely used and patient-friendly approach for administering therapeutic agents. Its non-invasive nature, ease of administration, and cost-effectiveness confer considerable advantages over parenteral methods. Moreover, advances in formulation science, nanotechnology, and device fabrication have enhanced the oral route's ability to overcome physiological, biochemical, and mechanical barriers in the gastrointestinal (GI) tract.[43, 44]

A primary advantage of the oral route lies in its high patient compliance, particularly for individuals who require repeated doses over an extended period. Rather than relying on clinical interventions, most oral dosage forms—tablets, capsules, suspensions—allow self-administration, thereby minimising discomfort and the risk of infections [45]. Additionally, oral solid dosage forms typically exhibit long shelf lives, do not require cold-chain maintenance, and can be mass-produced through established manufacturing processes. These considerations collectively lower production costs and expand global access to medicines, particularly in resource-limited settings.

From a formulation perspective, multiple strategies address the GI tract's acidic and enzymatic environment. For instance, polymer-based nanoparticles and microparticles can be engineered to protect drugs from gastric acidity and enzymatic degradation. Moreover, pH-sensitive coatings are often employed to ensure that the drug remains encapsulated during transit through the stomach and is only released upon encountering the higher pH of the intestine [45, 46]. Encapsulation also benefits macromolecules like insulin, which are otherwise easily degraded by gastrointestinal enzymes [47]. By mitigating degradation, these advanced carriers can improve bioavailability for a broader range of active compounds, including proteins and peptides.

The oral route can also leverage natural GI physiology to target specific areas. For example, gastro-retentive systems keep dosage forms in the stomach for extended periods, capitalising on local treatment needs or ensuring drugs are released in the upper GI tract for enhanced absorption. Similarly, colon-targeted formulations can release their cargo in response to local bacterial enzymes, benefiting conditions such as inflammatory bowel

disease [43]. These location-specific strategies exemplify how the oral route can combine drug delivery precision with convenience and reduce systemic toxicity.

Another key advantage is the potential to induce mucosal and systemic immune responses when formulating oral vaccines. Although achieving robust immunogenicity via oral vaccination remains challenging, using mucoadhesive carriers and adjuvants to deliver antigens to gut-associated lymphoid tissues has shown promising results [48]. Such progress underlines the versatility of oral delivery in catering to therapeutic and prophylactic interventions.

Beyond patient adherence and manufacturing efficiency, the oral route supports controlled and sustained release profiles that can significantly improve therapeutic outcomes. By gradually releasing active molecules, these systems limit fluctuations in plasma concentration, thus reducing side effects and preventing subtherapeutic drug levels [45]. Extended-release tablets, microfabricated patches, and mucoadhesive platforms are some examples that illustrate how novel engineering approaches refine the temporal and spatial aspects of oral drug delivery.

In conclusion, the oral route of administration offers a powerful combination of patient convenience, manufacturing scalability, and increasingly sophisticated targeting capabilities. Through microencapsulation, nanoparticle design, pH-sensitive polymers, and mucoadhesive technologies, researchers continue to broaden the scope of drug classes that can be administered orally [47]. These advances enhance bioavailability and therapeutic efficacy and open new frontiers for vaccines and complex biomolecules. As innovation in formulation and materials science continues, oral drug delivery will likely maintain its prominence as a cornerstone of modern medicine.

1.4.4. Mechanisms of Controlled Release in the Gastrointestinal (GI) Tract

Biopolymer-based oral delivery systems can be designed to achieve controlled and targeted drug release through various mechanisms, such as pH-dependent release, swelling-controlled release, enzymatic degradation, and diffusion-driven release [5, 35, 36]. In pH-dependent release, the polymer matrix changes its conformation in response to the differing pH levels within the GI tract, enabling drug release in areas where absorption is most effective. Swelling-controlled systems use polymers that absorb fluids when they encounter GI secretions, which causes an increase in volume and regulates the rate at

which the drug is released from the polymer. Enzymatic degradation, often seen with natural polymers like chitosan and alginate, facilitates drug release in the presence of particular microbial or endogenous enzymes. In contrast, diffusion-based release primarily depends on concentration gradients to expel the drug from the carrier matrix.

These specifically designed release methods are especially advantageous for enhancing the therapeutic effectiveness of curcumin, lipoic acid, and other bioactive substances with low stability or bioavailability. GI-targeted systems enhance localised uptake and reduce unintended effects while maintaining drug levels over prolonged periods, lowering the frequency of doses and improving patient compliance. This combination of improved efficacy and increased patient convenience has made controlled-release formulations a key area of advancement in oral drug delivery research.

1.5. Recent Advances in Biopolymeric Controlled Release Platforms

1.5.1. Polysaccharide Based Systems

1.5.1.1. Alginate

Alginate is an anionic polysaccharide primarily derived from brown seaweed, widely recognised in pharmaceuticals and biomedicine for its unique beneficial properties. Structurally, alginates are salts of alginic acids comprising linear polysaccharide chains with varying proportions of 1,4-linked β-D-mannuronic acid (M-blocks) and α-L-guluronic acid (G-blocks). Alginate's popularity in biomedical applications stems from low toxicity, biocompatibility, ease of mild gelation via divalent cations like Ca^{2+}, and relatively low-cost [49, 50]. Variable factors such as the type of divalent cation used, the length of polymer chains, and the distribution and abundance of G-blocks can precisely modulate the gel properties. These G-blocks form stable cross-linked networks through ionic interactions with calcium ions, creating the characteristic "egg-box" structure that imparts significant mechanical strength and resistance to mechanical stress [51–53].

Moreover, alginate hydrogels exhibit pH-responsive behaviours driven by the ionisation states of their carboxylic acid groups. Specifically, alginate shrinks under acidic conditions due to reduced ionisation, while it expands in alkaline environments resulting from electrostatic repulsion between negatively charged chains. This pH-sensitive characteristic

has significant implications for targeted drug delivery, facilitating controlled drug release at specific physiological sites [54, 55].

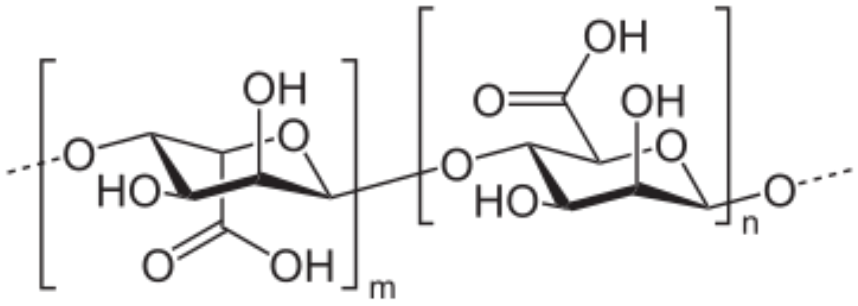

Figure 1.4. Structure of Alginate

Despite these advantages, pure alginate hydrogels often demonstrate limited drug retention capability due to their inherently large pore sizes. To overcome this limitation, alginate is frequently combined with other biopolymers, enhancing encapsulation efficiency and controlled release properties [56, 57]. Mukhopadhyay et al. developed chitosan-alginate nanoparticles by ionotropic pre-gelation of an alginate core encapsulating insulin, followed by chitosan polyelectrolyte complexation. This formulation significantly improved insulin bioavailability (~8.11%) and demonstrated substantial hypoglycemic effects in vivo, highlighting the efficacy of such core-shell systems for oral insulin delivery [58]. A novel study developed alginate-based nanoparticles hydrophobically modified with stearic acid or alkyl (C18) chains and compacted using polyethene glycol (PEG) via nanospray drying for intestinal-specific delivery of vitexin, an antidiabetic bioflavonoid. The PEG-compacted formulation significantly minimised premature drug release in gastric conditions, effectively targeting the intestinal tract. *In vivo* testing confirmed enhanced intestinal localisation of vitexin and improved blood glucose regulation in diabetic rats, underscoring the system's potential as a sophisticated intestinal-targeted antidiabetic therapy [59].

Similarly, George and Shrivastav created a pH-sensitive hydrogel of sodium alginate-chitosan complexes coated with κ-carrageenan to facilitate controlled metformin delivery. Characterisation techniques, including FTIR, XRD, DSC, and SEM, confirmed successful

drug encapsulation within the polymeric network. Coating the hydrogels with 3% κ-carrageenan significantly reduced premature release in simulated gastric fluid, effectively preserving approximately 50% of the drug for targeted intestinal absorption. In simulated intestinal fluid, the hydrogel exhibited sustained drug release following Higuchi kinetics, suggesting a diffusion-controlled mechanism. This formulation is promising for enhancing oral antidiabetic drug efficacy through targeted and sustained intestinal delivery [60].

Further highlighting its broad applicability, alginate has been extensively utilised for encapsulating various antidiabetic agents such as metformin, glibenclamide, repaglinide, vildagliptin, liraglutide, and bioactive phytochemicals including curcumin, berberine, quercetin, and mangiferin. Alginate-based formulations substantially improve oral bioavailability, enable sustained and controlled release, reduce dosing frequency, and minimise adverse effects, effectively addressing significant limitations associated with conventional diabetes treatments. Preclinical studies have demonstrated that oral insulin encapsulated in alginate-chitosan nanoparticles exhibits significantly enhanced stability, intestinal absorption, prolonged hypoglycemic effects, and improved overall bioavailability. Collectively, these findings reinforce alginate's potential as a robust and versatile biopolymeric platform for advancing therapeutic strategies in diabetes management [61].

1.5.1.2. Carrageenan

Carrageenan is a natural sulfated polysaccharide predominantly extracted from various species of edible red seaweeds belonging to the class Rhodophyceae, notably abundant along the coasts of Europe, North America, and the Atlantic shores of Britain. Chemically, carrageenan consists of alternating disaccharide units, specifically D-galactopyranose and 3,6-anhydro-D-galactopyranose, with sulfate ester groups attached. The distribution and quantity of these sulfate groups (approximately 18–40%) confer carrageenan's characteristic anionic properties, enabling electrostatic interactions with positively charged polymers such as chitosan, thereby facilitating the formation of stable polyelectrolyte complexes (PECs) [62].

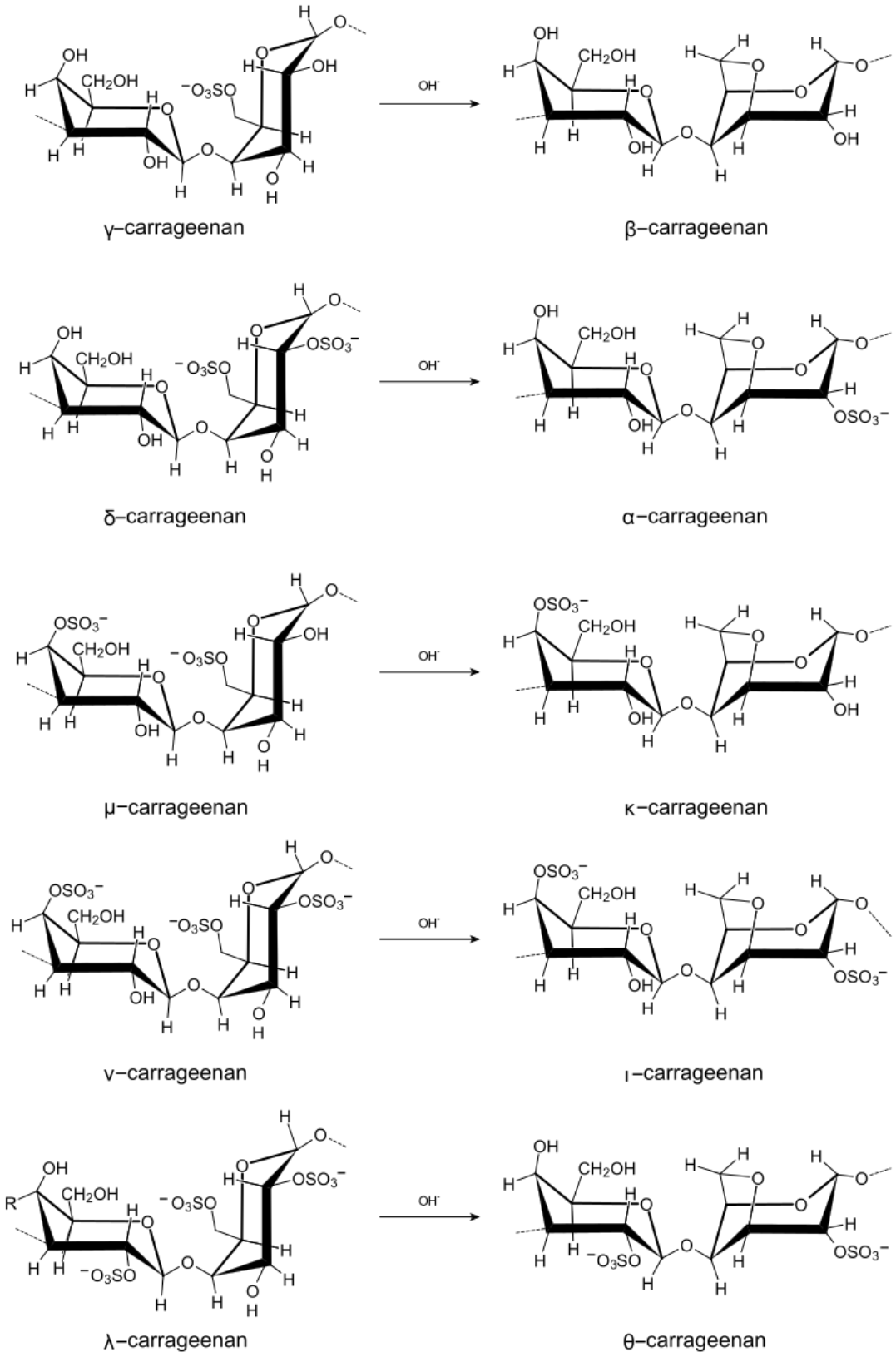

Figure 1.5. Structure of different types of Carrageenan

The ability of carrageenan-based PECs to encapsulate therapeutic molecules such as insulin is particularly advantageous due to their inherent biodegradability, biocompatibility, and minimal toxicity compared to synthetic polymers traditionally used in pharmaceutical applications. Once administered, carrageenan-based drug delivery systems can undergo metabolic breakdown or excretion, thereby reducing the risk of long-term toxicity. Furthermore, carrageenan demonstrates a unique pH-sensitive swelling behaviour, maintaining stability under acidic gastric conditions while swelling and progressively degrading in neutral to alkaline environments typical of the intestinal tract [63]. This intrinsic property is particularly beneficial for targeted drug delivery. It allows drugs to be released precisely at desired intestinal sites, enhancing therapeutic efficacy and minimising systemic side effects.

Among the various types of carrageenan, κ-carrageenan is predominantly utilised in biomedical and pharmaceutical formulations due to its superior gel-forming properties, low toxicity profile, and ability to achieve controlled, sustained drug release.[64] κ-carrageenan forms strong, brittle gels, while ι-carrageenan yields softer, more elastic gels. Conversely, λ-carrageenan lacks gelation capabilities and exhibits primarily viscous behaviour unless crosslinked by trivalent ions [65]. The physicochemical characteristics of κ-carrageenan, such as its gel strength, solubility, and reactivity towards proteins and other biomolecules, significantly influence its suitability for diverse biomedical applications.

Recent studies have highlighted the potential of carrageenan-based formulations for oral delivery of sensitive therapeutic agents like insulin. Leong et al. successfully synthesised carboxymethylated κ-carrageenan microparticles conjugated with lectin, achieving high insulin encapsulation efficiency (94.2 ± 2.6%) and substantial drug-loading capacity (13.5 ± 0.4%). The functionalisation with lectin significantly enhanced the microparticles' resistance to the gastrointestinal tract's harsh acidic and enzymatic conditions, facilitating protection and controlled insulin release. *In vivo* studies on diabetic rats demonstrated prolonged hypoglycaemic effects lasting 12 to 24 hours post-administration, underscoring the formulation's promise for developing effective oral insulin delivery platforms [66].

Recent research emphasises carrageenan’s multifunctional bioactivities, including antiviral, antibacterial, immunomodulatory, antihyperlipidemic, antioxidant, and antitumor properties. Das and Bal highlighted carrageenan’s potential in advanced

biomedical applications, including drug delivery, wound healing, and tissue engineering. They emphasised the promising application of carrageenan hydrogels and scaffold formulations for tissue repair and regeneration [67]. Guan et al. further elaborated on the utility of carrageenan in pharmaceutical formulations, showcasing carrageenan-based drug complexes and matrices. They reported that the ionic interactions between carboxymethylated κ-carrageenan and insulin amino acids significantly improved insulin loading efficiency and bioavailability. Additionally, κ-carrageenan was effectively utilised as a stabiliser for nanosuspensions of poorly water-soluble drugs, enhancing their dissolution rates and absorption profiles [65].

Furthermore, carrageenan-drug complexes significantly enhanced various pharmaceuticals ' controlled release and bioavailability. For instance, the complexation of λ-carrageenan with doxazosin mesylate led to sustained drug release, significantly prolonging its therapeutic effects. Similarly, complexes of λ-carrageenan with poorly soluble drugs containing pyridine and piperidine groups markedly improved their water solubility by 15 to 30-fold compared to the free drug form [65]. Moreover, Sathuvan et al. developed a κ-carrageenan-curcumin composite, which demonstrated significant cytotoxicity against lung cancer cells (A549) by inducing apoptosis and reducing mitochondrial membrane potential (Δψm), highlighting the therapeutic potential of carrageenan-based composites for targeted cancer treatment [68].

These recent advancements underscore carrageenan's broad applicability in biomedicine, not merely as a carrier but as an essential component of hybrid biomaterials. Despite these promising characteristics, ongoing safety evaluations are critical due to potential inflammatory responses associated with prolonged exposure, emphasising the necessity for continued toxicological assessments in biomedical applications [65].

1.5.1.3. Chitosan

Chitosan (CS) is a natural, linear polysaccharide obtained by partial deacetylation of chitin, the second most abundant natural biopolymer after cellulose, primarily found in crustacean shells, insect exoskeletons, fungi, and molluscs. Structurally, chitosan consists of randomly repeating units of β-linked D-glucosamine and N-acetyl-D-glucosamine [69, 70]. The degree of deacetylation (DD) significantly affects its physicochemical properties, including solubility, bioavailability, and mucoadhesion. A higher degree of deacetylation

typically results in increased solubility in acidic solutions and enhanced mucoadhesive properties. At acidic pH, chitosan exhibits a net positive surface charge due to the protonation of its amino groups, facilitating strong electrostatic interactions with negatively charged mucosal surfaces. These characteristics contribute to its enhanced mucoadhesive properties, enabling improved cellular uptake and drug permeation via the reversible opening of tight junctions between epithelial cells, thus increasing paracellular and transcellular drug transport [71].

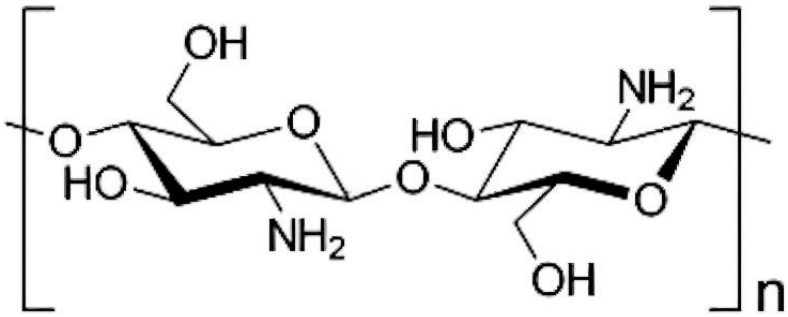

Figure 1.6. Structure of chitosan

The physicochemical characteristics of chitosan, such as molecular weight, viscosity, and crystallinity, also significantly influence its biomedical applications. The molecular weight of chitosan critically impacts its solubility, biodegradation rate, and bioactivity, thus determining its suitability for specific applications. Lower molecular weight chitosan often exhibits higher solubility and enhanced biological activity, making them particularly suitable for oral drug delivery systems. Additionally, chitosan's hydrophilic nature facilitates hydration and swelling, characteristics essential for controlled drug release formulations. Its ability to form films, gels, beads, and nanoparticles broadens its versatility in pharmaceutical applications, enabling tailored drug delivery approaches [69, 70, 72].

Chitosan is highly valued in the pharmaceutical and biomedical fields due to its biocompatibility, biodegradability, relatively low toxicity, and oral LD50 value, which exceeds sucrose. Its degradation is mediated through lysosomal pathways, further underscoring its safety profile [72]. Chitosan's inherent biological activities, including

antimicrobial, antiviral, anti-inflammatory, and antioxidant properties, have driven its application across various biomedical fields, including drug delivery, tissue engineering, regenerative medicine, and wound healing [70, 72].

Compared to synthetic polymers, chitosan-based systems offer significant advantages such as reduced cytotoxicity, enhanced biocompatibility, and improved biodegradability, making them more suitable for biomedical applications. This has driven extensive exploration into chitosan-based formulations for oral drug delivery, particularly in managing diabetes mellitus (DM). The beneficial role of chitosan in protecting and proliferating pancreatic beta cells, lowering hyperglycaemia, and preventing impaired lipid metabolism has been reported [72].

The self-assembly of nanoparticles via ionic gelation between cationic chitosan and anionic polymers or proteins has shown promise in protecting sensitive drugs from gastrointestinal degradation, enhancing drug stability, and improving intestinal absorption. Chellathurai et al. extensively reviewed various self-assembled chitosan-insulin nanoparticles, highlighting their effectiveness in shielding insulin from enzymatic degradation and improving intestinal uptake due to mucoadhesion and reversible tight junction opening [73]. Similarly, Li et al. developed a promising oral delivery vehicle for insulin using chitosan as the nanocarrier backbone [74] .They used a grafting reaction to modify chitosan with L-valine and Phenylboronic acid (PBA). Here, L-valine was used as a targeted ligand to facilitate the absorption in the small intestine, and PBA was designated as a glucose-responsive hydrophobic unit. The drug release was designed to be triggered by pH and glucose *in vitro.* The insulin-loaded NPs were stable in both simulated intestinal and gastric fluid. The modification of chitosan using L-valine here prolonged the gastrointestinal retention time and promoted insulin uptake. *In vivo* studies showed that the NPs showed a prolonged hypoglycaemic effect compared to subcutaneous injection, thus making such systems a good candidate for controlled oral delivery.

El-Dakroury et al. explored the potential of O-carboxymethyl chitosan (O-CMC) nanoparticles loaded with glipizide, achieving enhanced solubility, prolonged release, and improved pharmacokinetic profiles. These nanoparticles exhibited superior therapeutic efficacy, significantly impacting serum glucose levels, insulin sensitivity, lipid profiles, oxidative stress markers, and inflammatory cytokine levels [71].

Chitosan oligosaccharides (COS) have also garnered attention due to their potent antidiabetic effects. COS supplementation effectively reduced hepatic gluconeogenesis, enhanced skeletal muscle glucose uptake, and mitigated insulin resistance by decreasing lipid accumulation and inflammation in liver and adipose tissues. Clinical studies further indicate improved insulin sensitivity, reduced body weight, and lower triglyceride levels following chitosan administration [71].

Overall, chitosan and its derivatives continue to demonstrate significant promise for developing innovative drug delivery systems. Ongoing research into novel functionalisation methods, advanced blending strategies, and hybrid nanocarrier formulations continues to expand their therapeutic applications, offering enhanced patient compliance and improved clinical outcomes for managing diabetes mellitus and other chronic metabolic disorders.

1.5.2. Protein-based Systems

1.5.2.1. Gelatin

Gelatin is a natural, water-soluble protein derived from the partial hydrolysis of collagen, which is abundantly found in mammalian connective tissues such as skin, bones, and tendons. Its primary sources are generally bovine or porcine, although alternative origins, including fish, have also been explored to mitigate ethical and religious constraints. Structurally, gelatin comprises repeated glycine, proline, and hydroxyproline sequences, forming triple-helical segments that unravel under controlled hydrolysis conditions [75]. Because of this distinctive composition and hierarchical structure, gelatin demonstrates several physicochemical properties that render it highly suitable for pharmaceutical and biomedical applications, notably in drug delivery systems.

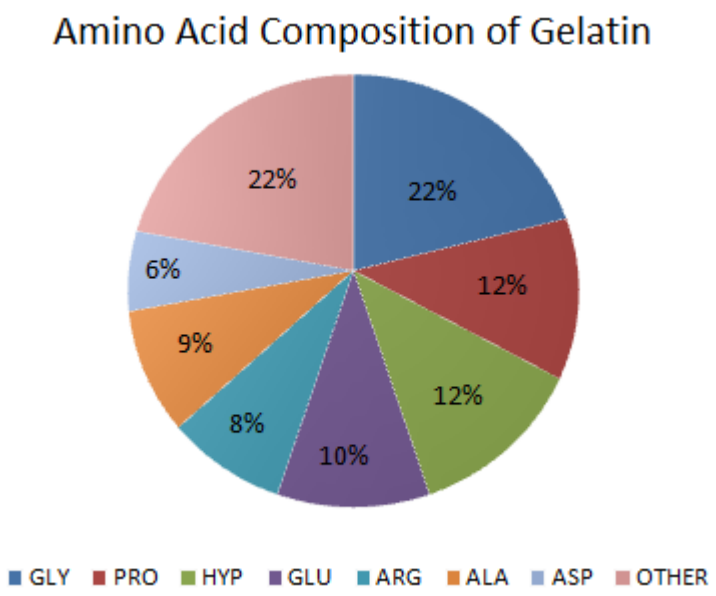

Figure 1.7. Amino Acid Composition of Gelatin

One of gelatin's most significant advantages is its biodegradability and biocompatibility. Once administered, gelatin is enzymatically broken down into amino acids that can be readily resorbed and metabolised by the human body, minimising toxicological risks. Gelatin also exhibits excellent film-forming capacity, gelation behaviour, and minimal immunogenicity, which collectively facilitate its use in micro- and nanoparticulate drug carriers, hydrogels, and scaffolds [76]. Furthermore, gelatin's amphoteric nature—containing both acidic (carboxyl) and basic (amino) side groups—enables it to be chemically modified via crosslinking agents or functional moieties. These modifications help tailor gelatin-based materials' mechanical strength, degradation rate, and drug-release kinetics, improving their performance for controlled-release applications [77].

Despite these benefits, gelatin also presents limitations that may impede its use as an oral delivery vehicle for labile therapeutics, such as peptide and protein drugs. Notably, gelatin can rapidly dissolve under physiological conditions, leading to premature drug release and reduced therapeutic efficacy [78]. To address these shortcomings, various crosslinking strategies—chemical crosslinking (e.g., glutaraldehyde, genipin) or physical crosslinking (e.g., dehydrothermal treatment)—have been employed to enhance gelatin's structural stability and control its degradation profile. Additionally, gelatin can be combined with

other polymers or functionalised with responsive moieties (e.g., pH or enzyme-sensitive groups) to improve its mucoadhesion, site specificity, and overall drug delivery performance. These strategies underscore gelatin's versatility in developing robust, biocompatible platforms for controlled, targeted, and effective drug delivery.

Mostofizadeh et al. explored a dual-drug delivery system using gelatin/poly(lactic-co-glycolic acid) (PLGA) core-shell fibres fabricated via coaxial electrospinning to treat diabetic neuropathic wounds. The system incorporates gabapentin (GBP) in the shell for immediate pain relief and ciprofloxacin hydrochloride (CipHCl) in the core for sustained antibacterial action. Structural characterisation confirmed the formation of core-shell fibres with amorphous drug dispersion, ensuring controlled drug release. Drug release studies demonstrated a rapid GBP burst release (57% within the first day) for early pain management, while CipHCl showed an initial burst followed by sustained release over 64 days for prolonged infection control. The biodegradation rate of drug-loaded fibres (60% over 32 days) was significantly higher than drug-free fibres, improving their suitability for wound healing applications. Although drug incorporation slightly reduced mechanical strength, the fibres maintained adequate durability. Antibacterial tests confirmed potent inhibition of *Staphylococcus aureus* and *Escherichia coli*, effective in both dry and wet conditions. Overall, the gelatin/PLGA core-shell fibres present a promising wound dressing solution by simultaneously addressing pain management and infection control, supporting their potential clinical use for diabetic ulcer treatment.

Bahoor et al. developed a controlled-release oral drug delivery system using cross-linked gelatin nanoparticles (GNPs) to sustain Gliclazide (GLI), a second-generation sulfonylurea for treating type 2 diabetes. To address the rapid dissolution of gelatin in aqueous media, they utilised glutaraldehyde as a cross-linking agent, which modified the polymer structure and reduced the burst release effect. The nanoparticles were synthesised via a two-step dissolution method, and characterisation techniques, including FTIR, XRD, SEM, and DLS, confirmed the successful cross-linking, amorphous nature, and nanoscale particle size (~88 nm). The drug release profile showed that GNPs cross-linked with 8% glutaraldehyde released 70% of GLI within 480 minutes, while those with 25% cross-linking released only 34%, demonstrating a controlled and tunable release mechanism dependent on the swelling index. Additionally, MTT cytotoxicity assays revealed 94.5% cell viability, suggesting high biocompatibility of the delivery system. Compared to

commercial GLI formulations such as Diabezide 80 mg and Diamicron MR 30 mg, the GNP-based system showed slower and more controlled drug release, offering a promising alternative for sustained oral drug administration in diabetes treatment [79].

1.5.2.2. Soy Flour

Soy flour is a protein-rich biomaterial derived from defatted soybeans. It offers economic viability and nutritional advantages for diverse applications within the food and pharmaceutical industries. In contrast to isolated soy protein, which undergoes extensive purification, soy flour retains integral components such as soluble carbohydrates, dietary fibres, and bioactive compounds, including isoflavones. These inherent constituents impart multifunctional properties such as emulsification capability, water-binding capacity, and film-forming ability, positioning soy flour as a promising candidate for developing biodegradable matrices, coatings, and other advanced materials [80].

A significant attribute of soy flour is its substantial protein content, primarily consisting of glycinin and β-conglycinin. These globular proteins possess reactive amino and carboxyl groups, enabling chemical or enzymatic modifications, such as crosslinking or grafting. Such modifications can effectively tailor mechanical strength, degradation kinetics, and swelling characteristics, which are crucial for developing controlled and targeted drug delivery systems [81]. These modifiable protein structures facilitate controlled and targeted release profiles in drug delivery contexts. For instance, the physicochemical characteristics of soy flour can be fine-tuned by adjusting pH, temperature, or ionic strength—factors that affect protein denaturation, aggregation, and hydrolysis [82]. Moreover, soy flour-based hydrogels, films, or micro/nanoparticles can be engineered to encapsulate and protect labile bioactive molecules from harsh gastrointestinal conditions, thereby preserving their therapeutic efficacy [83].

Despite these advantageous features, soy flour faces several challenges in pharmaceutical and biomedical contexts. Like other plant-derived proteins, soy flour is susceptible to enzymatic degradation and microbial contamination. Additionally, inherent variability in soybean genetics and processing parameters such as temperature and extraction methods can result in batch-to-batch inconsistencies, potentially compromising reproducibility and efficacy in drug delivery applications. To mitigate these limitations, formulation strategies include blending soy flour with natural or synthetic polymers such as chitosan, gelatin, or

polyvinyl alcohol, enhancing mechanical properties and consistency in drug release profiles [83]. Crosslinking soy flour proteins using agents such as genipin, glutaraldehyde (under strictly controlled conditions), or enzymatic catalysts has also been found to enhance structural stability and prolong drug release kinetics [84].

In recent studies using electrospraying techniques, Gao et al. successfully employed soy protein-derived amyloid fibrils (SAFs) to stabilise aqueous two-phase systems (ATPS). Their findings demonstrated that higher concentrations of soy protein isolate (SPI) or SAFs improved diffusion within the system and promoted effective adsorption at aqueous interfaces, underscoring the potential for food proteins in the biocompatible stabilisation of drug delivery systems [85].

Additionally, Probosari et al. evaluated the impact of a sorghum-soybean flour-based enteral formula on fasting blood glucose (FBG), lipid profiles, and albumin levels in hyperglycaemic Wistar rats [86]. The randomised control study revealed significant reductions in FBG levels (up to 29.89%), triglycerides (up to 31.85%), cholesterol (up to 13.94%), and LDL cholesterol (up to 38.44%), alongside increases in HDL cholesterol (up to 35.04%) and albumin levels, suggesting enhanced protein metabolism and nutritional status. These findings highlight soy flour-based formulations' hypoglycaemic and hypolipidemic potential, reinforcing their suitability for diabetic nutritional management.

These insights highlight soy flour's potential as an economically viable, environmentally sustainable biomaterial for drug delivery platforms. Strategic modifications and targeted formulation approaches can further optimise soy flour-based systems, broadening their applicability to various therapeutic domains, including oral administration, transdermal delivery, and tissue engineering applications.

1.5.3. Enhancing Stability and Performance with Inorganic Materials

The incorporation of inorganic fillers such as montmorillonite (MMT), magnesium oxide (MgO) nanoparticles, and halloysite nanotubes (HNTs) has become an increasingly popular strategy in the design of polymeric drug delivery systems for treating metabolic disorders (e.g., diabetes). These fillers address multiple challenges—such as burst release, limited mechanical strength, and diminished stability in the gastrointestinal tract—by leveraging their distinctive physicochemical properties.

1.5.3.1. Montmorillonite (MMT): Layered structure and high surface area.

Montmorillonite (MMT) is a layered silicate clay mineral renowned for its high cation exchange capacity, distinctive layered structure, and extensive specific surface area. Structurally, MMT is composed of an alumina octahedral sheet positioned between two silica tetrahedral sheets, forming a characteristic 2:1 layer structure. This unique arrangement results in negatively charged clay layers balanced by exchangeable cations, typically sodium (Na+), facilitating robust electrostatic and hydrogen-bonding interactions with polymers and therapeutic agents. Additionally, the interlayer spacing of MMT can be precisely tuned, enabling the effective intercalation or exfoliation of polymer chains into its interlamellar spaces, forming stable polymer-clay nanocomposites.

When exposed to polymer solutions, MMT undergoes swelling due to the ingress of polymer molecules into its interlayer galleries. This process forms a more structured nanocomposite system characterised by improved mechanical integrity and homogeneous distribution of polymeric chains. Polymer molecules intercalated within MMT layers modify the diffusion pathways, resulting in a significantly extended and more tortuous diffusion path for entrapped drugs. Consequently, the drug release rate is notably reduced, minimising the initial burst release phenomenon commonly observed in conventional delivery systems [87].

Incorporating MMT into polymer matrices such as chitosan or alginate yields composite systems with enhanced mechanical properties, improved drug encapsulation efficiency, and superior drug stabilisation against harsh gastrointestinal environments [88]. Kamari et al. developed montmorillonite-based hybrid nanocomposites encapsulating insulin coated with TiO_2 [89]. Their findings indicated that this porous inorganic coating markedly enhanced insulin entrapment efficiency and sustained its release for up to 22 hours in neutral pH conditions, compared to only 60 minutes observed for uncoated composites. Furthermore, the TiO_2-coated composites exhibited enhanced stability under acidic conditions, underscoring their capability to protect insulin from gastrointestinal degradation.

Shabir et al. demonstrated further advancements by creating novel insulin-loaded nanocomposite hydrogels using montmorillonite sodium complexes (I-MT) embedded within fenugreek seed mucilage-based hydrogels [90]. These nanocomposite hydrogels

significantly improved their thermal stability and sustained insulin release, achieving a relative bioavailability 50.65-fold higher than conventional oral insulin solutions.

Further, montmorillonite-PLGA nanocomposites have demonstrated effective insulin encapsulation with controlled release under acidic gastrointestinal conditions. These nanocomposites possess remarkable mucoadhesive properties, enhancing intestinal retention and systemic insulin absorption. The presence of MMT significantly improves the composite's biocompatibility, insulin stability, and overall bioavailability. Montmorillonite has also been extensively validated for biocompatibility and biodegradability through detailed haematological, biochemical, and histopathological analyses in animal studies, underscoring its suitability for biomedical applications [91].

In summary, montmorillonite's exceptional layered architecture, high specific surface area, and unique physicochemical properties offer significant advantages in the design of advanced drug delivery systems. The strategic intercalation or exfoliation of polymer chains within MMT's layered structure enhances mechanical integrity, sustained-release performance, and therapeutic efficacy, rendering it highly suitable for oral drug delivery, particularly for sensitive bioactive macromolecules such as insulin.

1.5.3.2. Magnesium Oxide (MgO) Nanoparticles: Matrix reinforcement and putative antidiabetic effects.

Magnesium oxide (MgO) nanoparticles have garnered considerable interest due to their dual functionality in reinforcing polymeric scaffolds mechanically and demonstrating significant bioactivity relevant to diabetes management. With intrinsically high Young's modulus values, MgO nanoparticles enhance the mechanical properties of biodegradable polymer matrices, such as poly(lactic-co-glycolic acid) (PLGA) and natural biopolymers including chitosan, providing composites with improved tensile strength and resilience against premature degradation in gastrointestinal conditions [92]. The resulting composite displays improved tensile strength and better resistance to premature degradation in the GI environment. Recent studies have highlighted the efficacy of MgO nanoparticles as reinforcement agents that significantly increase polymer matrices' strength and thermal stability, particularly when incorporated into biopolymeric composites such as polyvinyl alcohol (PVA) [93].

Beyond its role as mechanical reinforcements, MgO nanoparticles have promising applications in glucose regulation. *In vitro* studies indicate that MgO nanoparticles effectively lower serum glucose levels and enhance lipid metabolism, demonstrating their potential as antidiabetic agents [94]. For instance, MgO nanoparticles have been reported to ameliorate insulin resistance in diabetic models, improving cellular glucose uptake in diabetic 3T3-L1 adipocyte cells. The therapeutic mechanism is hypothesised to involve modulation of intracellular magnesium levels, which may subsequently influence insulin receptor functionality and GLUT-4 transporter translocation [95].

Recent advances in drug delivery have demonstrated that MgO nanoparticles also play a crucial role in reducing the initial burst release from polymeric hydrogels, leading to a more controlled and sustained drug release profile. Incorporating MgO nanofillers in hydrogel matrices has been shown to significantly decrease the initial burst effect by modifying the polymer network and surface morphology, thereby improving the bioavailability and stability of encapsulated drugs. This property is beneficial in oral and injectable drug delivery systems where controlled release is essential for maintaining therapeutic efficacy while minimising side effects [93].

Moreover, MgO nanoparticles have been explored for their multifunctional biomedical applications beyond drug delivery, including antimicrobial, antioxidant, and tissue engineering applications [36]. Their potent antibacterial effects are attributed to reactive oxygen species (ROS) generation and disruption of bacterial membranes. At the same time, their antioxidant properties stem from their ability to neutralise oxidative stress, a key factor in diabetes progression [36]. Additionally, MgO nanoparticles have been incorporated into scaffolds for tissue regeneration, particularly in bone healing, due to their biocompatibility and osteoinductive potential [96].

Additionally, novel composite systems incorporating MgO nanoparticles, such as polyvinyl alcohol/Arabic gum/MgO nanobiocomposites, have demonstrated considerable potential in targeted oral drug delivery applications. These systems exhibit pH-responsive behaviour that ensures selective and efficient drug release in the colon (pH 7.4) compared to limited release in gastric environments (pH 1.2), making them advantageous for colon-specific treatments. Such composites also show high biocompatibility and low cytotoxicity, confirming their suitability for biomedical applications [93].

Despite these promising outcomes, the exact molecular mechanisms by which MgO nanoparticles exert antidiabetic effects remain under investigation. Detailed mechanistic studies are required to thoroughly elucidate interactions between MgO nanoparticles, biological membranes, and cellular signalling pathways, ensuring optimised efficacy and safety profiles for clinical translation.

1.5.3.3. Halloysite Nanotubes (HNTs): Tubular architecture and versatile drug loading.

Halloysite is a naturally occurring aluminosilicate with a hollow, nanotubular morphology. This unique architecture confers several advantages. The tubular lumen and outer surface can encapsulate drug molecules with a wide range of hydrophobicities, providing dual-loading opportunities (e.g., loading hydrophilic drugs in the inner lumen while adsorbing hydrophobic drugs on the outer surface).[97] Like montmorillonite (MMT), halloysite nanotubes (HNTs) create a more convoluted diffusion route within polymeric matrices. The nanotube walls can further modulate drug release via electrostatic interactions or hydrogen bonding, fine-tuning the release kinetics. The rigid, inorganic halloysite rods reinforce the composite, enhancing its mechanical integrity and helping it withstand gastric acidity. Studies investigating HNT–chitosan or HNT–alginate composite beads have observed extended release of small and macromolecule drugs [98]. Moreover, the pH-responsive behaviour of certain biopolymers in conjunction with HNTs can enable selective release in the intestinal region, which is highly relevant for oral antidiabetic therapies to avoid premature degradation in the stomach [99].

Halloysite nanotubes are composed of multiple-rolled aluminosilicate kaolin sheets with an external diameter of 40–70 nm, an internal lumen diameter of 10–20 nm, and a length typically ranging from 500 nm to 1.5 μm [97]. This nanotubular structure provides a high aspect ratio, significant surface area, and dual-surface chemistry—characteristics make HNTs promising candidates for controlled and sustained drug delivery applications. One of the defining features of HNTs is their dual-charged surfaces. The outer layer comprises a negatively charged SiO_2 sheet, whereas the inner lumen contains a positively charged $Al(OH)_3$ layer. This difference in charge allows for the selective adsorption and encapsulation of a wide variety of drugs, including both hydrophilic and hydrophobic molecules [98]. The ability to modify the surface properties of HNTs through chemical functionalisation further enhances their application in drug delivery. For instance, surface

coatings such as polyethylene glycol (PEG) and polyelectrolyte layers have been reported to increase circulation time and reduce protein adsorption, thereby improving the biocompatibility of HNT-based carriers [97].

HNTs facilitate drug loading through three primary mechanisms: tubular entrapment via vacuum-assisted techniques, which draw drug molecules into the lumen under vacuum pressure and encapsulate them upon vacuum release. [99]; adsorption onto the external surface, where hydrophobic drugs interact with the negatively charged SiO_2 outer surface via van der Waals forces, hydrogen bonding, or electrostatic interactions [98]; and intercalation between layers, modifying release kinetics based on molecular interactions [97]. The sustained drug release from HNTs is governed by diffusion through the nanotubular structure, electrostatic interactions, and polymeric modifications, making them ideal candidates for sustained and controlled drug release [99]. Studies have demonstrated that HNTs can effectively encapsulate and deliver various pharmaceutical compounds, including antibiotics (e.g., tetracycline, metronidazole, oxytetracycline HCl), non-steroidal anti-inflammatory drugs (NSAIDs) (e.g., diclofenac, ibuprofen, aspirin), anticancer agents (e.g., doxorubicin, curcumin, paclitaxel, methotrexate), as well as proteins and enzyme-based therapeutics. For instance, diclofenac-loaded HNTs exhibited an extended-release profile compared to free diclofenac sodium, reducing systemic toxicity while enhancing therapeutic efficacy [98, 99] .

By incorporating MMT, MgO nanoparticles, or HNTs into biopolymeric carriers, researchers address three critical concerns in oral drug delivery: (1) the undesired “burst” or early release of drugs, (2) insufficient mechanical strength of purely organic matrices and (3) low stability in the harsh pH and enzymatic conditions of the gastrointestinal (GI) tract. Each of these inorganic fillers offers distinct advantages—layered structures (MMT), multifunctional oxide properties (MgO), and nanotubular architectures (HNTs)—that synergistically improve both the mechanical robustness of the matrix and the control over drug release kinetics. Although preliminary evidence suggests additional therapeutic benefits for MgO nanoparticles, the finer details of these interactions warrant further investigation to elucidate their mechanisms and fully optimise clinical outcomes.

HNTs are often combined with biocompatible polymers such as chitosan, gelatin, or alginate to enhance their drug-carrying efficiency and create a nanocomposite system. HNT–chitosan composites, for example, have been shown to improve drug encapsulation

efficiency, mechanical stability, and controlled release.[98] Chitosan-functionalized HNT composites enhance the mucoadhesive properties of drug carriers and facilitate pH-sensitive release, making them suitable for oral drug delivery applications such as antidiabetic therapies [97]. *In vitro* diffusion studies have confirmed that drug-loaded HNT–chitosan nanocomposites can significantly prolong drug release profiles while maintaining high biocompatibility. Additionally, integrating HNTs with polymers like polycaprolactone (PCL) and polylactic-co-glycolic acid (PLGA) has demonstrated promising applications in wound healing and localised drug delivery, further underscoring their versatility [99]. Electrospun nanofiber scaffolds incorporating HNTs have also been explored for transdermal drug delivery. Studies indicate sustained drug release over extended periods while preserving mechanical strength and flexibility [97].

Incorporating HNTs into biopolymeric drug delivery systems represents a significant advancement in nanomedicine, particularly for oral and targeted drug delivery applications. While extensive research has validated their efficacy in sustained-release formulations, further studies are required to optimise HNT-based nanocarriers for clinical applications. Future research should focus on enhancing drug-loading efficiencies via surface functionalisation strategies, investigating the long-term biocompatibility and biodegradability of HNT–polymer composites, and developing multifunctional HNT-based systems that integrate targeted drug delivery, imaging, and therapeutic functionalities. In addition, studies evaluating the pharmacokinetics and biodistribution of HNT-based drug carriers *in vivo* are essential to fully elucidate their therapeutic potential and safety profiles. Some preliminary studies suggest that HNTs can be excreted without significant accumulation in vital organs, indicating a promising safety profile. However, more comprehensive toxicological assessments are needed before clinical translation.

By leveraging the unique properties of HNTs, researchers can develop next-generation drug delivery systems that offer improved stability, controlled release, and enhanced therapeutic outcomes. The continued exploration of halloysite-based drug carriers, particularly in combination with advanced nanotechnologies such as smart drug release systems and stimuli-responsive nanocarriers, holds immense potential for revolutionising controlled drug delivery.

1.5.4. Crosslinking Strategies for Tuneable Release

Crosslinking is the core of designing polymeric carriers with controllable drug release profiles. Researchers can tailor the material's mechanical strength, swelling behaviour, and degradation rate by introducing physical or chemical linkages within a polymeric matrix. These parameters, in turn, govern the release kinetics of the encapsulated agent.

1.5.4.1. Physical (Ionic) Crosslinking

Physical crosslinking relies primarily on electrostatic interactions between oppositely charged species, creating a network without covalent bond formation. This mild ionic crosslinking can be performed under aqueous conditions and neutral pH. The absence of harsh chemicals helps preserve the biological activity of sensitive molecules (e.g., proteins or peptides). Moreover, the networks formed are generally reversible because physical crosslinks are typically weaker than covalent bonds. They can respond to external stimuli, such as pH or ionic strength changes, leading to stimulus-responsive swelling or de-swelling.

Recent research has demonstrated that combining electrostatic interactions with additional physical crosslinking strategies, such as coordination bonds with metal ions (e.g., Ag^{+}, Cu^{2+}), significantly enhances the mechanical properties of hydrogels. For instance, chitosan/poly(acrylic acid) hydrogels initially formed through electrostatic interactions showed enhanced mechanical performance upon further crosslinking with Ag^{+} ions, achieving tensile strengths up to 24.0 MPa and toughness of 84.7 MJ m^{-3} due to the dynamic and reversible nature of these physical crosslinks [100].

Examples of physical crosslinking agents include divalent and trivalent metal ions such as Ca^{2+}, Fe^{3+}, Zn^{2+}, and Ag^{+}. Ag^{+} ions have shown particularly strong interactions with amino and carboxylic groups. Other forms of physical crosslinking include hydrogen bonding, hydrophobic interactions, and van der Waals interactions, each providing unique mechanical properties and responsiveness suitable for various biomedical applications [101].

The softness and porosity of physically crosslinked gels make them particularly attractive for biomedical applications requiring close interaction with biological tissues—notably in oral, transdermal, or parenteral delivery. Softer matrices may release therapeutics more quickly, whereas denser matrices formed by higher ionic crosslinker concentrations can slow down drug diffusion, thus prolonging the release. Additionally, reversible ion-

exchange mechanisms enable these materials to respond dynamically to environmental stimuli such as pH or ionic strength, enhancing their suitability for controlled and targeted drug delivery systems.

However, exclusively physically crosslinked hydrogels often lack long-term mechanical stability. This instability may result in rapid erosion or disintegration in dynamic environments such as the gastrointestinal tract, potentially limiting their effectiveness for sustained oral delivery. Therefore, physical crosslinking alone may be insufficient for certain drug delivery applications, necessitating complementary strategies such as chemical crosslinking or composite approaches to ensure stability and controlled release in physiological conditions.

1.5.4.2. Chemical Crosslinking

Chemical crosslinking is an essential approach employed in the development of biopolymeric drug delivery systems, offering significant advantages in controlling the physicochemical properties and drug release characteristics of polymers. This process involves forming covalent or ionic bonds between polymer chains, enhancing structural integrity, and imparting desirable functionalities such as stimuli responsiveness and controlled drug release.

Various crosslinking agents, ranging from synthetic to natural origin, have been extensively investigated. Common synthetic agents like glutaraldehyde, formaldehyde, glyoxal, and epichlorohydrin effectively modify polymeric networks. However, concerns over cytotoxicity and health hazards associated with synthetic crosslinkers have directed research towards exploring natural, biocompatible alternatives such as genipin, glyceraldehyde, and citric acid.

Glutaraldehyde (GA) is widely recognised for its efficient crosslinking properties, primarily due to its high reactivity, affordability, and ease of handling under mild conditions. GA can form stable acetal linkages through interactions between its aldehyde and hydroxyl groups in hydrophilic polymers such as poly(vinyl alcohol), chitosan, gelatin, alginates, carrageenan, and various natural gums. GA-crosslinked polymers exhibit decreased crystallinity and increased amorphousness due to the disruption of hydrogen bonding, significantly impacting their swelling behaviour and drug release profiles[102].

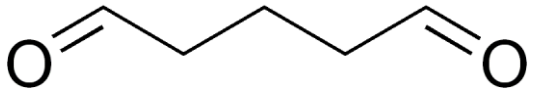

Figure 1.8. Structure of Glutaraldehyde

Recent advancements have further elucidated the role of chemical and physical crosslinking in hybrid hydrogel systems. Hybrid hydrogels, combining both covalent and noncovalent (physical) crosslinking, exhibit exceptional mechanical properties due to the synergistic effects between the two cross-linking types. Physical crosslinking significantly contributes to energy dissipation during initial deformation, while chemical crosslinking sustains the hydrogel structure during more significant deformations. This synergy greatly enhances toughness, stretchability, and durability, making hybrid hydrogels promising materials for biomedical applications requiring robustness, such as drug delivery scaffolds and tissue engineering matrices [103].

Gelatin-based hydrogels, extensively employed across food, pharmaceutical, medical, and biomedical applications, often utilize GA for crosslinking due to its effectiveness in strengthening hydrogel structures. However, GA's potential toxicity in biomedical applications necessitates the exploration of safer alternatives such as glyceraldehyde. Recent research has demonstrated that by altering experimental conditions, including cross-linker type and concentration, significant variations in hydrogel properties, such as swelling, dissolution behaviour, mechanical strength, and micro- and nanostructure, can be achieved. These modifications enable precise tuning of gelatin-based hydrogels, enhancing their thermal stability, biodegradability, and biocompatibility, and providing an optimal balance between mechanical strength and biocompatibility.

Natural crosslinkers like genipin, extracted from Gardenia jasminoides Ellis, also present a safer and biocompatible alternative to GA. Genipin crosslinking has been widely explored for biomedical and pharmaceutical applications due to its considerably lower cytotoxicity than synthetic crosslinkers. It efficiently crosslinks biopolymers containing primary amine groups, forming stable covalent networks that exhibit significantly improved mechanical strength, controlled swelling properties, and prolonged degradation rates, crucial for sustained drug delivery applications [104].

Another promising natural crosslinker is citric acid (CA), which has been extensively investigated due to its nontoxic, economical, and environmentally friendly nature. CA is

commonly utilised for crosslinking polysaccharides such as glucuronoxylans derived from Mimosa pudica seeds. Crosslinked glucuronoxylans exhibit stimuli-responsive swelling-deswelling behaviours under varying physiological conditions, such as different pH environments and saline solutions, making them particularly attractive for targeted drug delivery [105].

Moreover, drug release kinetics from crosslinked systems often follow zero-order release profiles, indicating a constant and predictable release rate. The drug release mechanism frequently exhibits non-Fickian diffusion (anomalous transport), involving both diffusion and polymer swelling. These properties make chemically crosslinked polymers suitable candidates for advanced drug delivery applications, significantly contributing to improving therapeutic outcomes and patient compliance.

Overall, the ongoing shift from synthetic to natural crosslinkers reflects the broader trend toward greener and safer pharmaceutical practices, with significant attention given to biocompatibility, sustainability, and patient safety.

1.5.4.3. Optimisation of Crosslinking Parameters

Optimising the number of crosslinkers is a delicate balance. Excessive crosslinking can lead to networks that are too rigid or non-biodegradable, which may pose challenges for controlled drug release and eventual clearance from the body. Conversely, insufficient crosslinking can result in weak gels that are prone to premature drug leakage. Optimal crosslinker concentrations must be empirically determined for each polymer-drug combination, considering factors such as polymer chain flexibility, drug molecule size and properties, and desired release kinetics [106]. A critical parameter in crosslinked systems is their capacity to absorb fluids (e.g., water or simulated physiological fluids) and swell. The degree of swelling not only affects the mechanical properties of the matrix but also governs the diffusion-driven release of the encapsulated drug. Biodegradability is equally important for systems intended for tissue engineering or biomedical implants. Biopolymers like chitosan, alginate, and gelatin are favoured for their enzymatic or hydrolytic degradation profiles, which can be modulated by adjusting crosslinking density [107].

Crosslinking density influences how the matrix swells or degrades under varying pH in pH-responsive systems, which is particularly relevant for oral drug delivery targeting different gastrointestinal tract regions. This allows site-specific therapeutics to release and

protect the active compound from harsh gastric conditions. Meanwhile, in systems designed for local injection or hydrogel-based implants, the gelation time and stiffness via crosslinker concentration ensure that the polymeric matrix solidifies appropriately at the target site.

1.5.5. Role of Particle Size in Controlled Oral Drug Delivery Systems

The size of drug delivery particles plays a crucial role in determining the efficacy of controlled oral drug delivery systems (DDS) by influencing absorption, bioavailability, release kinetics, stability, and targeting efficiency. Advances in nanotechnology and biomaterials have enabled researchers to optimise drug performance through size-dependent approaches that enhance permeability, reduce first-pass metabolism, and enable site-specific release. Several recent studies have highlighted the importance of modulating particle size to improve drug solubility, stability, and controlled release mechanisms.

A significant challenge in oral drug delivery is achieving efficient absorption across the gastrointestinal (GI) tract. Smaller particles (<500 nm) demonstrate superior mucosal penetration, particularly through transcellular absorption (via enterocytes) and transcytosis (via M cells in Peyer's patches). Chaurasiya et al. highlighted that nanoparticles below 200 nm significantly enhance intestinal permeability, making them particularly effective for the oral administration of peptide-based drugs such as insulin [108]. In contrast, microparticles (>1 μm) exhibit prolonged retention in the GI tract and are predominantly absorbed through paracellular transport or endocytosis. A study by Mohseni et al. demonstrated that chitosan-coated nanoliposomes improve the oral bioavailability of hydrophobic drugs, with particles smaller than 200 nm showing greater permeability and stability in simulated intestinal environments [109].

The rate and extent of drug release in oral DDS are significantly influenced by particle size. Nanoparticles (10–200 nm) are particularly effective for diffusion-controlled release, enabling sustained drug delivery over extended periods. In contrast, microparticles (>1 μm) are often used for site-specific drug delivery, particularly when formulated with pH-sensitive polymers. Research by Elsayyad et al. demonstrated that pH-responsive casein/hyaluronic acid nanoparticles effectively targeted the colon for metformin delivery, with particle size and surface charge playing a significant role in drug release dynamics across different GI segments [110]. Similarly, Qi et al. found that mesoporous silica nanoparticles could significantly enhance drug dissolution, ensuring sustained release of poorly water-soluble drugs [111].

In addition to controlled release, particle size is a critical factor in drug stability and protection against degradation. Many orally administered drugs, especially biopharmaceuticals, suffer from degradation due to enzymatic activity and acidic conditions in the stomach. Reducing particle size can protect these drugs from premature breakdown, thus preserving their therapeutic efficacy. Dubashynskaya et al. developed chondroitin sulfate/chitosan polyelectrolyte complexes for oral drug delivery and found that particles around 450 nm improved drug stability and controlled release while also enhancing absorption and mucosal adhesion [112]. Similarly, Rehman et al. demonstrated that solid lipid nanoparticles (SLNs) significantly enhanced the oral bioavailability of poorly soluble drugs, effectively protecting them from degradation in the harsh gastric environment [113].

Another critical advantage of particle size modulation is site-specific drug targeting within the GI tract. Smaller nanoparticles (<500 nm) are often preferred for peptide and protein-based drugs, as they enable direct uptake through M cells, bypassing enzymatic degradation. Microparticles (1–5 μm) are commonly employed in floating drug delivery systems, allowing for prolonged gastric retention and sustained drug release in the stomach. Larger microparticles (>10 μm) are often designed for colon-targeted delivery, where pH-sensitive polymer coatings regulate drug release in response to the alkaline environment of the large intestine. Research by Elsayyad et al. confirmed that pH-responsive nanoparticles could be utilised to release metformin in the colon, minimising systemic side effects and enhancing therapeutic efficacy [110].

With continuous advancements in nanotechnology, stimuli-responsive nanoparticles are emerging as a powerful tool in oral DDS. These smart nanocarriers can be engineered to respond to pH, enzymatic activity, or temperature changes, allowing for precise, on-demand drug release. Despite these innovations, several challenges remain in the field of oral DDS, including biocompatibility concerns, large-scale manufacturing difficulties, and ensuring consistent drug release profiles across diverse patient populations. Future research should focus on developing next-generation nanocarriers that address these challenges while optimising therapeutic outcomes.

The optimisation of particle size in oral DDS is fundamental to achieving improved drug bioavailability, stability, and controlled release. Recent studies have demonstrated that nanoparticles (<500 nm) are particularly beneficial for enhanced intestinal permeability, sustained release, and enzymatic protection, while microparticles (>1 μm) provide

superior site-specific delivery in the stomach or colon. By integrating nanotechnology and biomaterial innovations, researchers are paving the way for more efficient, targeted, and patient-friendly oral drug formulations. The future of oral DDS will continue to be shaped by advances in particle engineering, smart nanocarriers, and precision-controlled drug delivery strategies.

1.5.6. Surfactants

Surfactants are widely utilised in pharmaceutical formulations due to their unique chemical structure and versatile functional properties. The term "surfactant" originates from "surface-active agent," highlighting their ability to reduce surface and interfacial tension between two immiscible phases, such as oil and water. Structurally, surfactants possess amphiphilic properties, containing both hydrophilic (water-loving) and hydrophobic (water-repelling) regions. This molecular architecture enables them to self-assemble into organised structures known as micelles when dissolved in aqueous media above their critical micelle concentration (CMC).

Surfactants fulfil several key roles in pharmaceutical drug delivery systems (DDS). Surfactants can significantly increase drug solubility and facilitate efficient delivery through micelle formation.

They stabilise emulsions, nanoparticles, and other colloidal formulations by preventing aggregation and ensuring uniform particle distribution. Surfactants modify the drug and polymer matrix interactions, controlling drug release kinetics. Certain surfactants increase intestinal permeability by disrupting epithelial tight junctions, promoting the absorption of drugs that otherwise exhibit poor gastrointestinal uptake.

Various surfactants have been employed in polymeric-controlled drug delivery systems (DDS), categorised mainly as non-ionic, anionic, cationic, and zwitterionic. Examples include non-ionic surfactants such as Polysorbate (Tween series), polyvinyl alcohol (PVA), and Pluronic (Poloxamer) series; anionic surfactants like sodium dodecyl sulfate (SDS); cationic surfactants such as cetyltrimethylammonium bromide (CTAB); and zwitterionic surfactants like lecithin. Each type of surfactant has distinct functionalities and applications in polymeric DDS formulations.

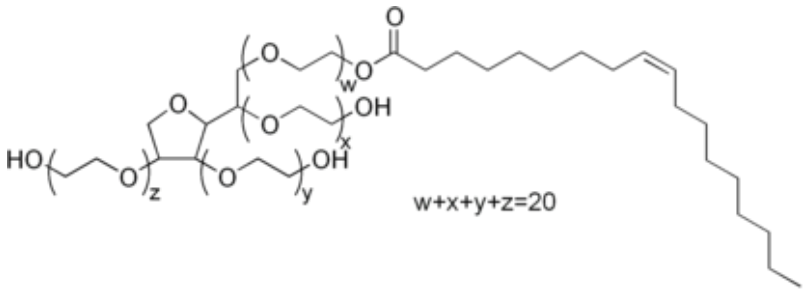

Figure 1.9. Structure of Tween 80

Among these surfactants, Tween 80 (polyoxyethylene sorbitan monooleate), a non-ionic surfactant, has been extensively studied and applied due to its exceptional micellar solubilisation capacity, biocompatibility, and ability to enhance the bioavailability of poorly water-soluble drugs significantly. Tween 80 effectively stabilises various formulations, including nanoparticles, nanoemulsions, microemulsions, and microsponge systems, critically influencing particle size, surface charge, encapsulation efficiency, and release kinetics [114, 115].

Recent investigations into microsponge-based formulations, such as those by Shahzad et al., have highlighted Tween 80's significant role in controlling the release of therapeutic agents. Specifically, Shahzad and colleagues demonstrated that Tween 80 markedly influenced the porosity, drug loading efficiency, and controlled release properties of ketoprofen-loaded ethyl cellulose/hydroxypropyl methylcellulose microsponges [116]. Higher concentrations of Tween 80 correlated with enhanced porosity and altered release kinetics, showcasing its capability to optimise DDS performance.

Tween 80 also plays a crucial role in self-microemulsifying drug delivery systems (SMEDDS), which spontaneously form acceptable emulsions upon contact with gastrointestinal fluids, significantly enhancing drug dissolution and absorption [115]. Additionally, Tween 80 improves gastrointestinal absorption by disrupting epithelial tight junctions, thereby increasing the permeability and bioavailability of orally administered drugs.

Thus, surfactants, particularly Tween 80, have become integral components in the successful development of oral controlled DDS, and research continues to uncover their profound impact on drug delivery efficacy, stability, and therapeutic performance.

1.6. Fabrication Techniques for Polymeric Controlled Release Vehicles

Polymeric complex systems used in oral controlled drug delivery systems (DDS) are fabricated using advanced techniques to achieve controlled release, stability, and improved bioavailability. Polymeric complex systems used in oral controlled drug delivery systems (DDS) are fabricated using advanced techniques to achieve controlled release, stability, and improved bioavailability. The following are prominent fabrication techniques for preparing polymeric complexes for oral controlled drug delivery systems.

1.6.1. Ionic Gelation Method

Ionic gelation is a widely utilised technique for synthesising polymeric nanoparticles. It is primarily based on the electrostatic interactions between oppositely charged functional groups in biopolymers. This method frequently employs polysaccharides such as chitosan, a positively charged (cationic) biopolymer, and negatively charged (anionic) agents like sodium tripolyphosphate (TPP), sodium alginate, or carrageenan [117]. The formation of nanoparticles occurs spontaneously upon mixing aqueous polymeric solutions under mild conditions, circumventing the need for harsh chemicals or organic solvents, thereby enhancing the biocompatibility of the prepared delivery systems.

The ionic gelation approach offers numerous advantages: simplicity, low cost, mild reaction conditions (typically conducted at room temperature and neutral or slightly acidic pH), and no toxic organic solvents. Such gentle conditions are beneficial in preserving the structural integrity and bioactivity of encapsulated therapeutic molecules, especially proteins, peptides, and other sensitive agents [118].

Moreover, the physicochemical properties of nanoparticles prepared by ionic gelation, such as size, surface charge (zeta potential), and encapsulation efficiency, can be systematically controlled by adjusting parameters like polymer concentration, polymer-to-crosslinker ratio, pH, ionic strength, and stirring speed during synthesis [119, 120]. This flexibility has made ionic gelation particularly advantageous for biomedical and pharmaceutical applications, notably in the controlled and sustained delivery of anti-diabetic drugs, peptides, and nutraceuticals [121].

The stability of ionic gelation-based nanoparticles is critical for practical drug delivery applications. Factors influencing nanoparticle stability include surface electrostatic charge, solution pH, ionic strength, and concentrations of reactive species. Non-ionic stabilisers and freeze-drying methods have been employed successfully to enhance

stability, ensuring prolonged storage and maintaining the therapeutic efficacy of encapsulated drugs [122].

Recent advances have expanded the scope of ionic gelation through hybrid and multipolymeric systems. For example, the alginate-chitosan complexation enhances mechanical stability and provides controlled release profiles by forming a robust polyelectrolyte complex on nanoparticle surfaces. Alginate, widely utilised for its biocompatibility and biodegradability, forms gel networks via the "egg-box" model in the presence of divalent cations like calcium, which are instrumental in encapsulating pharmaceuticals for sustained release [123, 124].

However, despite these advantages, the ionic gelation method presents particular challenges, primarily related to the heterogeneity in particle size distribution, indicated by relatively high polydispersity indices (PDIs), which can impact drug loading efficiency and uniformity in biological interactions [122]. Moreover, the limited exploration of alternative polymers and ionic species poses another limitation, although this simultaneously opens opportunities for discovering novel polymeric pairs and improving formulation outcomes [122, 123].

Characterisation techniques such as dynamic light scattering (DLS), scanning electron microscopy (SEM), transmission electron microscopy (TEM), and Fourier-transform infrared spectroscopy (FTIR) play pivotal roles in assessing particle size, surface morphology, and chemical interactions within nanoparticles. These methodologies optimise ionic gelation processes, ensuring nanoparticles meet precise biomedical criteria [122].

In conclusion, the ionic gelation technique remains highly beneficial for developing biocompatible, biodegradable, and effective polymeric nanoparticle systems for drug delivery. Continued research into optimising formulation conditions and exploring novel polymeric interactions will further enhance the therapeutic potential and applicability of ionic gelation-derived nanoparticles in clinical medicine

1.6.2. Polyelectrolyte Complexation (PEC)

Polyelectrolyte complexation (PEC) is a versatile, spontaneous assembly process driven primarily by electrostatic interactions between oppositely charged polymers in aqueous environments. This phenomenon typically involves interactions between polycationic polymers, such as chitosan or gelatin, and polyanionic counterparts, like carrageenan or alginate, forming polyelectrolyte complexes (PECs). PEC formation results from associative phase separation, producing polymer-rich phases distinct from the surrounding solvent, characterised by structures ranging from water-rich viscous coacervates to solid-like precipitates, depending upon polymer molecular weight, charge density, environmental conditions (e.g., pH, ionic strength), and polymer concentrations [125].

PEC formation's mechanisms include electrostatic attraction and entropic factors such as counterion release. Strong Coulombic interactions occur between charged groups along the polymer backbones after mixing solutions of oppositely charged polymers. Simultaneously, releasing counterions initially bound to polymer chains into the bulk solution markedly increases entropy, providing significant thermodynamic impetus for complex formation. Thus, enthalpic (electrostatic attraction) and entropic (counterion release) components synergistically drive PEC assembly [125].

Classical theoretical descriptions, notably the Voorn–Overbeek (VO) model, provide foundational insights into the complexation process. This model combines the entropy of mixing (via Flory–Huggins theory) and electrostatic free-energy contributions (Debye–Hückel approximation), thereby predicting phase separation conditions, critical polymer concentrations, and ionic strength effects. More advanced theoretical treatments, such as Random Phase Approximation (RPA), Field-Theoretic Simulations, and PRISM-based Liquid-State Theory, have addressed limitations in the VO model by explicitly considering factors such as finite chain connectivity, excluded volume effects and the detailed distribution of charged species. These advanced approaches significantly enhance understanding of PEC structures, stability, counterion partitioning, and physicochemical properties under various environmental conditions [125].

PEC-based biopolymeric systems offer substantial advantages for biomedical applications, particularly in developing controlled drug delivery platforms. Such complexes exhibit highly tuneable physicochemical properties—particle size, surface charge, swelling

behaviour, and biodegradation rates—allowing precise control over drug encapsulation efficiency and release kinetics. For oral delivery of sensitive bioactive agents, PEC systems notably improve therapeutic efficacy through sustained drug release and robust protection against gastrointestinal conditions, including enzymatic degradation and low pH environments, thereby significantly enhancing oral bioavailability [126].

Furthermore, due to their charged nature, PEC matrices often display inherent mucoadhesive properties, facilitating prolonged retention and improved absorption at mucosal surfaces—an essential consideration for the effective oral delivery of anti-diabetic agents [126]. In particular, biopolymers such as chitosan and carrageenan have attracted attention due to their biocompatibility, biodegradability, low immunogenicity, and regulatory approval status, making them highly suitable for pharmaceutical formulations [125, 126].

Characterisation of PEC-based biopolymeric systems includes assessing structural, morphological, and physicochemical attributes through techniques such as Fourier Transform Infrared Spectroscopy (FTIR), Nuclear Magnetic Resonance (NMR), Dynamic Light Scattering (DLS), Zeta Potential measurements, and electron microscopy (FESEM). These analytical methods provide crucial insights into polymer interactions, drug-polymer compatibility, encapsulation efficiency, and release mechanisms [126].

In conclusion, polyelectrolyte complexation represents a promising strategy for designing sophisticated, responsive biopolymeric systems that effectively deliver therapeutic agents for managing chronic conditions such as diabetes. Ongoing research, including theoretical advancements and empirical studies, continues to refine our understanding of PEC formation, stability, and performance in drug delivery applications, paving the way for developing optimised, patient-compliant formulations for improved diabetic care.

1.6.3. Emulsification-Solvent Evaporation Method

The emulsification-solvent evaporation method is widely adopted for fabricating polymeric vehicles in controlled-release drug delivery. Fundamentally, this approach involves dissolving a polymer and therapeutic agent in a volatile organic solvent and then emulsifying this solution into an aqueous phase containing a stabiliser to form droplets. Solid polymeric microparticles or nanoparticles encapsulating the drug are formed upon

solvent evaporation [127]. The underlying principle involves the formation of an emulsion that acts as a template, with subsequent solvent removal leading to the polymer precipitation and solidification, thus entrapping the drug within the polymer matrix. The method typically employs either single-emulsion (oil-in-water, o/w) or double-emulsion (water-in-oil-in-water, w/o/w) processes. Single emulsions are suitable for hydrophobic drugs, while double emulsions are ideal for encapsulating hydrophilic drugs, including proteins and peptides, due to better retention within the inner aqueous droplets.

Poly(lactic-co-glycolic acid) (PLGA), polylactic acid (PLA), polycaprolactone (PCL), and polymethacrylates are commonly employed polymers chosen based on their biodegradability, biocompatibility, and drug release properties [128]. Organic solvents such as dichloromethane, ethyl acetate, or acetone facilitate polymer dissolution and subsequent removal, whereas surfactants like polyvinyl alcohol (PVA) or polysorbates stabilise the emulsion droplets [129, 130].

Critical parameters influencing particle size and uniformity, encapsulation efficiency, and drug release kinetics include the polymer type and concentration, solvent choice, emulsification intensity (stirring or sonication), stabiliser type, and evaporation condition [129]. Typically, higher polymer concentrations yield larger particles and higher encapsulation efficiencies, whereas increased emulsification intensity or higher surfactant concentrations produce smaller, more uniform particles [130]. Additionally, the choice of solvent can influence particle morphology and drug encapsulation, as solvents with partial water miscibility tend to yield smaller particles due to faster diffusion into the aqueous phase.

Drug release profiles are adjustable through formulation parameters, allowing targeted therapeutic outcomes. For example, modifying polymer molecular weight, hydrophilicity, particle size, and drug-polymer ratio can tailor the release rate. Smaller particles generally demonstrate a higher initial burst release due to increased surface area-to-volume ratios. In comparison, larger particles or higher polymer content formulations typically result in sustained drug release over extended periods.

This method’s advantages include simplicity, versatility, mild processing conditions suitable for sensitive drugs, scalability, and effective control over particle characteristics. It also allows the encapsulation of hydrophilic and hydrophobic drugs, providing extensive

applicability. However, challenges include potential residual organic solvents, stabiliser residues, initial burst release phenomena, and particle aggregation during processing or storage. Despite these limitations, emulsification-solvent evaporation remains a cornerstone for preparing polymeric controlled-release systems, which have been extensively utilised in pharmaceutical research and industry [128, 129].

1.6.4. Spray Drying Method

Spray drying is an extensively utilised technique in the pharmaceutical, nutraceutical, and food processing industries, renowned for its effectiveness in fabricating polymeric microparticles and nanoparticles. This method converts liquid feed solutions or suspensions into dried particulate matter through rapid solvent evaporation under heated conditions. The core principle involves the atomisation of the polymer-drug or polymer-bioactive solutions into fine droplets within a heated drying chamber, leading to quick solvent removal and the formation of uniform, spherical particles [131, 132].

Polymeric microparticles and nanoparticles produced via spray drying have numerous pharmaceutical applications, including enhancement of oral bioavailability, protection of bioactive agents from environmental degradation, and controlled release of therapeutic agents. This versatility makes spray drying particularly beneficial for formulating oral drug delivery systems, such as sustained-release or targeted-release microparticles. The physicochemical characteristics of the spray-dried products, including particle size, morphology, encapsulation efficiency, and drug release profile, are significantly influenced by parameters like inlet and outlet air temperature, atomisation pressure, feed flow rate, polymer concentration, and solvent properties [132].

Notably, Murugesan and Orsat emphasise the effectiveness of spray drying for microencapsulation, underscoring its role in stabilising bioactive compounds against oxidative damage and light and temperature fluctuations. They highlight that spray drying is highly suitable for encapsulating vitamins, antioxidants, and fatty acids, essential in nutraceutical and functional food products. Also, spray-drying microencapsulation is economically advantageous to other encapsulation methods due to its single-step process and scalability [131].

Moreover, Nandiyanto and Okuyama illustrated that spray drying is adept at producing particles with diverse morphologies, ranging from solid spheres to hollow or doughnut-shaped structures, through precise control over processing parameters. They demonstrated that varying atomisation conditions and adjusting the physical properties of the precursor solution could yield controlled particle morphologies suitable for specific applications, including drug delivery and diagnostics [132].

Furthermore, comparative studies, such as those conducted by Karthik and Anandharamakrishnan, reinforce the utility of spray drying by comparing it with alternative methods like freeze-drying and spray-freeze drying. While spray-freeze drying showed superiority in minimising the thermal oxidation of sensitive compounds like docosahexaenoic acid (DHA), spray drying exhibited higher encapsulation efficiency, emphasising the method's robustness and practicality for heat-stable applications.

Spray drying's capacity to enhance the stability and bioavailability of drugs and bioactive molecules is extensively documented. The encapsulation process effectively shields sensitive compounds from harsh conditions, preserving their bioactivity during storage and gastrointestinal transit. The resulting spray-dried particles are usually spherical, providing improved flowability and facilitating easy incorporation into various pharmaceutical formulations, including tablets and capsules [131].

Regarding formulation stability, the rapid evaporation of solvents during spray drying ensures that the resultant particles have low residual moisture content, significantly reducing microbial growth risks and improving long-term product stability. Additionally, encapsulated compounds in spray-dried particles often exhibit controlled and predictable release kinetics, which can be finely tuned through formulation optimisation [132].

In conclusion, spray drying is a powerful, flexible, and scalable method for creating polymer-based microparticles and nanoparticles for controlled drug delivery. Its advantages, including cost-effectiveness, ease of particle property manipulation, and suitability for large-scale production, make it an indispensable technique in pharmaceutical and nutraceutical industries. Future developments and optimisations in spray drying parameters and materials science will likely further expand its capabilities and applications, enhancing therapeutic efficacy and consumer product stability.

1.6.5. Coacervation Method

Coacervation is a liquid-liquid phase separation technique extensively used in fabricating drug delivery systems, particularly in encapsulating pharmaceuticals, proteins, and bioactive compounds. It involves the self-assembly of oppositely charged polyelectrolytes into spherical droplets or coacervates, which encapsulate active ingredients and offer controlled and sustained release characteristics [133, 134]. This method is driven primarily by electrostatic interactions between oppositely charged polymers and entropic factors such as counterion release. This results in the spontaneous formation of polymer-rich dense phases and polymer-poor dilute phases [135].

The fabrication of coacervates involves two primary mechanisms: simple and complex coacervation. Simple coacervation involves the desolvation of a single polymer solution induced by changes in parameters such as pH, temperature, or ionic strength [135]. On the other hand, complex coacervation requires the interaction of two oppositely charged macromolecules, typically polycations and polyanions, which associate due to electrostatic attractions, leading to the formation of coacervate droplets [133, 134]. Complex coacervation has found broader application among these two due to its versatility and controllable encapsulation efficiency [134].

In a typical complex coacervation process, charged polymers such as chitosan (positively charged) and alginate (negatively charged) are dissolved separately in aqueous solutions. These polymers interact upon mixing under suitable conditions, forming tiny droplets through electrostatic interactions and eventually coalescing into larger coacervate droplets [135, 136]. Several critical factors, including polymer concentration, mixing ratio, molecular weight, ionic strength, temperature, and pH influence droplet formation. For example, coacervation between chitosan and alginate often occurs optimally at a slightly acidic pH, enabling sufficient protonation of chitosan's amino groups to facilitate strong ionic interactions with alginate [136].

Furthermore, structural design factors significantly impact the morphology and stability of coacervates. Polymer architecture—linear, branched, or block copolymers—can dramatically influence the phase separation behaviour. Linear polymers typically yield well-defined spherical droplets, whereas branched polymers or block copolymers might

form micelles or vesicular structures, providing distinct encapsulation and release profiles suitable for various therapeutic applications [134].

Recent research highlights polyzwitterions, which carry both positive and negative charges within the same molecule. These offer unique pH-responsive behaviours beneficial in gastrointestinal drug delivery. Such coacervate systems remain stable under acidic conditions in the stomach but dissociate rapidly upon reaching the neutral pH environment of the small intestine, releasing the encapsulated drug precisely where absorption is most efficient [135]. This pH-triggered mechanism enhances drug bioavailability and protects sensitive compounds from premature degradation in the harsh gastric environment.

Several studies have demonstrated the utility of coacervate-based drug delivery systems. For example, elastin-like peptides (ELPs) coacervates show temperature-responsive behaviours, facilitating targeted drug release within solid tumours [133]. Heparin-polycation coacervates exhibit extremely high loading efficiencies and prolonged growth factor release profiles, enhancing therapeutic angiogenesis and tissue regeneration. Similarly, alginate-based coacervate systems are commonly employed for oral drug delivery, effectively protecting the encapsulated drugs from acidic gastric conditions and releasing them at specific locations in the gastrointestinal tract [136].

Moreover, coacervate droplets can be easily functionalised with targeting ligands or stabilising agents, allowing targeted delivery to specific cells or tissues. Functionalisation improves the stability and biodistribution of the coacervates and enhances therapeutic outcomes by reducing systemic side effects. Additionally, due to their liquid-like nature and small droplet size, coacervates can be administered via minimally invasive routes such as fine gauge needle injections, greatly enhancing patient compliance and clinical applicability [133, 134].

In conclusion, the coacervation method is a highly versatile and promising approach in drug delivery research, owing to its ease of fabrication, tuneable physicochemical properties, and excellent biocompatibility. Continued advancements in understanding the underlying mechanisms governing coacervation and innovations in polymer chemistry will likely expand their therapeutic potential significantly, paving the way for more effective and precise biomedical applications.

1.6.6. Nano-precipitation (Solvent Displacement) Method

Nano-precipitation, or solvent displacement, is widely used for fabricating nanoparticles (NPs). It is particularly suitable for encapsulating hydrophobic molecules, including drugs, within polymer matrices. This method involves dissolving hydrophobic solutes in a water-miscible solvent, followed by their controlled precipitation upon addition to an antisolvent, like water, resulting from the rapid decrease in solute solubility upon mixing [137]. This method is particularly advantageous due to its simplicity, cost-effectiveness, and ability to precisely control particle size, distribution, and surface properties without requiring external energy inputs such as sonication or milling [138].

A modification of traditional nanoprecipitation involves using various miscible organic solvents, such as dimethyl sulfoxide (DMSO) and ethanol, instead of the standard acetone-water system. This provides an environment suitable for both hydrophilic and hydrophobic compounds [129]. Compared to emulsion-based encapsulation techniques, nanoprecipitation can lead to more homogeneous and smaller nanoparticles, typically ranging from approximately 130 to 560 nm. Notably, the encapsulation efficiencies for specific proteins like lysozyme can reach above 90%, demonstrating its effectiveness in drug loading [139].

Different nanoprecipitation techniques include traditional nanoprecipitation, flash nanoprecipitation (FNP), and microfluidic-based nanoprecipitation. Traditional nanoprecipitation, although straightforward, often suffers from limited control over mixing conditions, potentially leading to broader particle size distributions. Conversely, flash nanoprecipitation employs rapid micro-mixing through turbulence in confined impinging jets or multi-inlet vortex mixers, achieving superior control over nucleation and growth phases, resulting in nanoparticles with smaller sizes and narrower distributions [138, 140].

Microfluidic-based nanoprecipitation further advances particle control by utilising laminar flows in hydrodynamic focusing devices. This drastically reduces diffusion paths and achieves particle formation with precise size, charge, and morphology control. Although offering significant advantages in reproducibility and material utilisation, this technique can face challenges in scalability due to small production volumes [138].

Recent studies have extensively analysed the kinetic and thermodynamic factors influencing nanoprecipitation. For instance, selecting appropriate solvents and antisolvents, polymer concentration, and mixing conditions critically influence nanoparticle formation and stability [140]. Computational fluid dynamics (CFD) coupled with population balance models (PBM) have provided valuable insights into the roles of solvent interactions and mixing dynamics. They emphasise the importance of solvent choice on particle size and distribution and underscore the role of solvent-polymer affinity described by Flory-Huggins interaction parameters and Hansen solubility parameters [140].

Overall, nanoprecipitation remains a highly favourable method for preparing drug-loaded nanoparticles, offering controlled particle characteristics essential for efficient drug delivery applications. Continuous development and refinement in understanding the underpinning mechanisms promise further advancements in nanoparticle-based therapeutics and drug delivery systems.

1.6.7. Supercritical Fluid (SCF) Technology

Supercritical Fluid (SCF) technology represents an innovative and sustainable pharmaceutical and biomedical research approach. It is primarily utilised in drug particle formation, micronisation, and dispersion. This technique employs fluids, such as carbon dioxide (CO_2), maintained above their critical pressure and temperature, adopting unique properties advantageous for pharmaceutical applications.

One primary benefit of SCF technology is its ability to address common limitations associated with traditional pharmaceutical processing methods, such as thermal degradation, poor particle size uniformity, and solvent residues. Traditional techniques like milling, crystallisation, and spray drying typically involve high temperatures and organic solvents, leading to potential instability and toxicity issues. Conversely, SCF provides gentle processing conditions, reducing drug degradation and maintaining therapeutic efficacy [141–143].

Several methodologies under SCF technology include the Rapid Expansion of Supercritical Solutions (RESS), Gas Antisolvent (GAS), Supercritical Antisolvent (SAS),

and Precipitation from Gas Saturated Solutions (PGSS). Each method has specific applications:

- RESS dissolves drug substances in supercritical fluids, rapidly depressurizing through a nozzle, resulting in homogeneous fine particles due to the rapid change in solubility.
- GAS involves using supercritical fluids as antisolvents to precipitate substances dissolved in traditional solvents, producing particles with controlled morphology and size.
- SAS utilizes supercritical fluids as antisolvents that mix with solvent solutions of drug substances, leading to controlled particle formation through atomization.
- PGSS mixes supercritical fluids with drug solutions, which are rapidly depressurized to induce precipitation, creating drug particles with tailored characteristics.

SCF technology significantly enhances drug bioavailability and solubility, crucial for improving therapeutic outcomes. For instance, Super-stable Homogeneous Intermix Formulating Technology (SHIFT) has been developed to facilitate the dispersion of hydrophilic drugs within hydrophobic carriers, overcoming poor drug solubility and stability[141]. Indocyanine Green (ICG), a diagnostic tracer, exemplifies the application of SHIFT, enhancing dispersion within iodine oil for improved imaging and surgical outcomes in hepatocellular carcinoma (HCC) treatments.

Additionally, SCF technology proves beneficial in developing macromolecular drugs, such as proteins, nucleic acids, and polysaccharides. It effectively maintains biomolecule integrity, bioactivity, and stability, thereby significantly advancing the preparation of biomacromolecular nanomedicines for targeted drug delivery, gene therapy, and tissue engineering applications. This approach also enables precise particle size control, which is essential for optimising pharmacokinetics, biodistribution, and drug efficacy. Industrial scalability is another significant advantage of SCF technology. It promises reproducibility and low environmental impact, attributable to its use of non-toxic solvents like CO_2. The reduced reliance on harmful organic solvents minimises environmental contamination and enhances product safety [143].

Clinically, SCF technology has demonstrated its potential in various therapeutic contexts, including tumour therapy, vaccine development, and therapeutic protein delivery. Its applications extend to enhancing the efficacy of drug-loaded nanoparticles, which exhibit improved cellular uptake and intracellular transport, maximising therapeutic effects while minimising side effects [138].

Challenges persist, primarily in scaling up laboratory methodologies for commercial production, controlling cost, and ensuring consistency in drug particle characteristics [143]. Future research and development must focus on overcoming these hurdles, refining SCF methods, and expanding their applications in medicine and biotechnology [142].

In conclusion, SCF technology presents a transformative platform in pharmaceutical manufacturing. It addresses significant limitations of traditional methods and offers substantial improvements in drug formulation, stability, and therapeutic efficacy. Its eco-friendly, precise, and versatile characteristics hold significant promise for the future of sustainable drug development and advanced therapeutic solutions.

1.7. Scope and Objectives

Building upon this growing research, the present thesis investigates the design, fabrication, and evaluation of novel biopolymeric platforms for delivering antidiabetic agents—primarily α-lipoic acid and curcumin—under controlled and sustained-release conditions. The work encompasses:

1. Formulation and Characterisation: Developing and characterising pH-responsive networks using a range of biopolymers (e.g., chitosan, alginate, carrageenan, gelatin, and soy flour) and inorganic fillers (e.g., MMT, MgO, and HNTs).

2. Crosslinking and Stability Optimisation: Evaluating physical and chemical crosslinking strategies (e.g., calcium-mediated ionic and glutaraldehyde-mediated covalent bonding) to tailor mechanical robustness and drug release profiles.

3. Mechanistic Insights: Investigating the molecular interactions that underlie drug encapsulation, stability, and release, including ionic binding, intercalation within clay layers, and chemical crosslink formation and their effect on the physicochemical and functional properties of the systems.

4. Therapeutic Efficacy: Assessing the capacity of the developed systems to preserve bioactive compounds (curcumin and α-lipoic acid) under gastric conditions and deliver them to the intestinal region to enhance glycaemic control and mitigate diabetic complications.

Ultimately, this thesis aims to contribute a comprehensive framework for the rational design of biopolymer-based controlled-release carriers that address the pharmacokinetic and pharmacodynamic challenges in T2DM therapy. By integrating robust polymer networks, strategic crosslinking, and inorganic fillers with proven biocompatibility, these systems seek to elevate the clinical potential of promising antidiabetic agents, offering new directions for improved patient adherence and long-term disease management. The main objectives of this research work 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

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