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Review Article

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POLYMER-BASED MICROENCAPSULATION OF PEPTIDYL DRUGS: FROM BENCH TO BEDSIDE

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ABSTRACT
Peptides and proteins are the fastest-growing class of therapeutics due to their high specificity and potency. However, their widespread use is limited by enzymatic degradation, short circulation half-lives, and poor stability during storage and administration. Microencapsulation has emerged as a potential strategy in overcoming these barriers by protecting biomolecules, enabling sustained and targeted release, and improving patient compliance. This review highlights both natural and synthetic polymers, such as poly (lactic-co-glycolic acid) (PLGA), chitosan, alginate, and hybrid systems in terms of encapsulation efficiency, release kinetics, and clinical safety. Marketed products, including Lupron Depot®, Sandostatin LAR®, and Bydureon®, are discussed as successful examples of regulatory-approved microsphere formulations. Furthermore, emerging trends such as stimuli-responsive and multifunctional microspheres are presented as future directions that may lead to personalized and precision medicine. By integrating insights from marketed products and ongoing innovations, this review provides an updated framework for the design and development of peptide- and protein-based microencapsulation systems with the potential to enter therapeutic applications and improve clinical outcomes.

INTRODUCTION

In the current era of biotechnology and biomedical innovation, researchers have developed a wide range of recombinant proteins and peptide-based drugs that not only have lifesaving potential but also offer significant improvements in quality of life for many patients. In-depth research on the identification and production of therapeutically active proteins and peptides has been conducted over the past few decades, resulting in a significant increase in the stockpiles of these agents and making them among the top-selling pharmaceutical products in the modern era [1,2]. But mainly due to their poor stability, delivery via conventional routes is often overlooked, with administration mostly via vascular routes, which, furthermore, entails a high dosing frequency. These challenges are frequently thoroughly evaluated, and various developmental steps have been undertaken to formulate novel drug delivery systems that enable delivery of this bioactive macromolecule, thereby increasing stability and reducing dosing frequency [3, 4]. Peptides and proteins have high molecular weight, and they are also prone to degradation because they are susceptible to changing environmental conditions, such as pH, temperature, etc., hence conventional oral administration of these peptidyl drugs isn't

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possible due to the acid degradation in the gastrointestinal tract and also due to the degradation caused by the proteolytic enzymes. Also, due to its large size, this molecule undergoes poor gastric absorption via passive diffusion into the systemic circulation. To date, only a handful of these macromolecules have been approved by the FDA for oral administration, as the IV route is the most preferred [5]. But when administering simple IV formulations containing peptidyl or protein drugs, some exhibit toxic effects at higher doses, and others have short half-lives and limited permeability across biological membranes, which restrict their IV administration and lead to inadequate utilisation [6,7]. It has been a primary focus for researchers to overcome these limitations through novel approaches and to develop methods for the efficient delivery of peptidyl or protein drugs [8]. For utilizing the maximum therapeutic potency of the protein or peptidyl drugs, significant efforts have been made in the field of novel drug delivery systems including development of micro delivery systems using polymers such as alginate, carrageenan, chitosan, poly (lactic-co-glycolic acid) polycaprolactone, etc which are having biodegradable property which resulted in conservation of the peptidyl drugs within the system during pre- and post-delivery phases [9 – 11]. Niosomes, Aquasomes, and Liposomes have also been utilised to develop protein/peptidyl drug delivery systems [12]. In the field of peroral delivery of peptides and proteins, the most significant challenge is reduced bioavailability due to proteolytic hydrolysis by proteases present in GI fluids. Still, researchers have also addressed this problem using enzyme inhibitors [13]. Another notable route of administration for peptidyl drugs is transdermal delivery, an alternative to oral administration. This topical pathway offers the advantage of bypassing enzymatic degradation commonly encountered in the gastrointestinal tract. However, the transdermal absorption of peptides and proteins remains limited, primarily because of their large molecular sizes. To overcome this challenge, a range of strategies, including permeation enhancers, microneedle systems, sonophoresis, iontophoresis, and electroporation, have been explored to facilitate more efficient penetration of peptidyl drugs through the skin [14 – 16]. Recently, the pulmonary route has also been widely studied and utilized for the delivery of peptidyl drugs. Still, due to the large particle size and polar nature of peptidyl drugs, and the functional defence mechanisms of the airways, achieving optimal delivery is challenging; therefore, non-conventional and novel delivery systems enable efficient pulmonary delivery [17-18]. The US FDA has approved a limited number of pulmonary systems for the delivery of peptidyl drugs; among them is the dry powder inhaler (DPI) used for insulin delivery, developed by spray-drying [19]. Because proteins and peptides must be structurally stable to exert their therapeutic effects in the body, many environmental conditions, as discussed earlier, such as pH changes, light exposure, and temperature fluctuations, can influence the biological and physicochemical stability of protein or peptide drugs [20]. To maintain the structural integrity of these agents, they can be encapsulated in a protective polymeric coating and converted into micron-sized microcapsules through microencapsulation [21-22]. This review synthesizes established and recent advances in the microencapsulation of peptides and proteins. It not only summarizes the role of PLGA but also explores alternative and hybrid polymers, giving a broader perspective on available options. Linking marketed products with experimental systems provides a balanced view of what is already possible and what lies ahead. The work stands out by highlighting the translation of laboratory research into clinically relevant therapies and identifying gaps that need to be addressed for the next generation of peptide and protein delivery systems.

Process of microencapsulation

Microencapsulation is a process in which solid, liquid, or gaseous materials are enclosed within a coating to form micron-sized capsules, commonly referred to as microcapsules, typically ranging from 1 μm to several hundred micrometres in diameter. This technique offers the fundamental advantage of shielding the encapsulated drug from environmental factors that may cause degradation, while also enabling controlled and sustained release of the active ingredient from the formulation [23-24]. The particles being encapsulated are termed the core, and the continuous polymeric film used to coat or encapsulate them is known as the shell/coat [25]. The microencapsulation process was first used in the mid-1900s, when a dye was developed using two polymers, namely gelatine and gum arabica, via the coacervation process [26]. Similarly, after a decade, cholesteric liquid-crystal microcapsules were produced and utilised as a special display material, using acacia and gelatine by the same coacervation technique [27]. Microencapsulation was also utilised in developing specially fabricated clothes for military personnel to safeguard them against chemical damage during war. Microencapsulation gained its popularity in the pharmaceutical industry during the 1970s [28]. After this technique gained popularity among industrial pharmacists and

formulators, it has since been a valuable tool for fabricating delivery systems with specific attributes. One of the most fascinating attributes, among others, is the ability of these systems to convert a liquid into a free-flowing solid, which exhibits altered surface and colloidal properties, resulting in a positive change in the overall physical characteristics of the encapsulated substance [29-31] as the microencapsulated product will be separated from the external environment by the special polymeric coating, allowing physical and chemical protection of the core or encapsulated material from the changing extreme external conditions [32]. As discussed earlier, microcapsules obtained via microencapsulation have two distinct parts: the core and the coat. A wide range of materials, including flavours, pharmaceuticals, peptides, proteins, pesticides, dyes, and others, can be incorporated into microcapsules as cores using various coating materials [33].

Microcapsules or microspheres can be prepared using various microencapsulation techniques. To date, various prominent microencapsulation techniques have been developed for a range of core materials. Generally, three types, namely chemical, physical, or mechanical entrapment techniques, are utilised, and along with other factors, the size and the properties of the microcapsule are dependent upon the type of method utilised for the microencapsulation process [34]. Among the various techniques, widely used methods include spray drying, in which a dispersion, emulsion, or mixture of the core material and the film material is atomised in a chamber and subsequently dried [35-36]. The other one is spray cooling, in which cool air replaces hot air after the mixture is atomized [37]. Another prominent technique is the coacervation phase-separation method for microencapsulation. Here, the polymeric film encapsulates the core material, with the encapsulation influenced by factors such as pH, ionic strength, and thermal changes. An essential aspect of this coacervation technique is the phase-separation process to form a three-immiscible phase system comprising three components (core material, coating material, and the solvent in which the coating material is dissolved) before the actual microencapsulation. This phase separation is influenced by various factors, as mentioned earlier [38-39]. Air-suspension is another reliable technique for microencapsulation. Here, the particles to be encapsulated are suspended in an air stream (typically inert), and the coating material is sprayed onto them, thereby achieving continuous mixing and microencapsulation. This method is suitable for producing relatively large micron-sized microparticles rather than smaller ones [40-41]. Centrifugal extrusion and the multi-orifice centrifugal process are other methods that utilise centrifugal forces to coat the core material [42]. Among various techniques, microfluidics (Figure 1) has emerged as a precise and versatile approach for preparing nano and microcapsules, enabling controlled size, uniform morphology, and efficient encapsulation of bioactive agents [43].

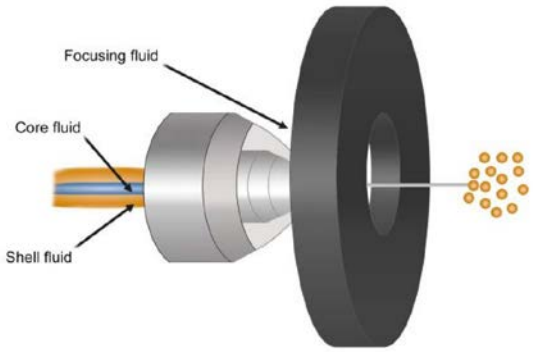

Figure 1: Microfluidic technique (Figure obtained and reused from Li et al. [43] under the CC-BY licence)

Microencapsulation of peptides and proteins

A wide range of peptides and proteins, including antimicrobials, enzymes, vaccines, and hormones, holds significant therapeutic potential and can be administered not only via invasive routes but also via non-invasive oral routes. However, their clinical use via the oral route is limited mainly by their inherent instability and susceptibility to degradation in the gastrointestinal tract [44-46]. For example, enzymes such as lactase can be utilized to break down lactose in lactose-intolerant people [47], pancrelipases can be used in individuals with pancreatic exocrine insufficiency [48], and insulin, the peptide of concern in diabetic patients, can be used in the management of diabetics via a non-invasive oral route [49]. A wide variety of peptides and proteins also have antimicrobial properties that can be utilised as therapeutic agents in infectious diseases [50]. These are only a handful of examples cited; many more proteins, peptides, enzymes, hormones, and vaccines can be utilised as therapeutic agents. Peptides and proteins must retain their original three-dimensional structures to be utilised as therapeutic agents [51-52]. Changes in this structure over time, before or after administration, resulting from factors such as changes in pH, temperature, ionic strength, or enzyme activity, can lead to inactivation. More commonly, these agents are unstable and denature easily in the acidic, protease-rich environment of our stomach [53, 54]. Another problem specific peptides and proteins face is poor absorption from the Gastrointestinal tract

[55]. Hence, encapsulating these highly susceptible agents in a protective envelope is a promising strategy to overcome these problems and enable their protection, delivery, and retention, thereby achieving optimal therapeutic efficacy [56, 57]. The loss of biological activity of this peptidyl or protein drug, along with a significant immune response, leads to inactivation. Some strategies can be employed to stabilise these protein drugs, such as chemical modification, immobilisation (for enzymes), the inclusion of additives, and lyophilisation (freeze-drying) before or after microencapsulation. Critical factors to consider when delivering peptides and proteins include the delivery method, retention of therapeutic activity, stability, and the amount of the agent or dosage for optimal therapeutic efficacy. Depending on these factors, one can estimate or determine the polymers and excipients that can be utilised, along with the loading dose to be incorporated into the dosage form, to achieve an optimal therapeutic effect [58-60]. Converting protein or peptidyl drug into micro-polymeric encapsules, known as microcapsules by the method microencapsulation, so far is the most reliable technique used for the preservation, stabilization, and optimization of the protein or peptidyl drug delivery, as microencapsulation can protect the protein/peptide from the proteolytic enzymes and make them structurally more stable [61, 62]. The encapsulation method has gained increased attention in recent years due to its growing demand in the food and nutraceutical industries, where it is used to fortify food products with peptides and bioactive substances [63, 64]. They are also utilised to mask the bitter taste and preserve hygroscopic bioactive peptides. In general, microencapsulation is a promising method for protecting fragile peptides and releasing them in a controlled manner, thereby enhancing bioavailability [65]. We now discuss polymeric systems used for the microencapsulation of peptides and protein drugs.

Alginate-based microcapsules

Alginate is a naturally occurring group of polysaccharides belonging to the family of linear binary copolymers of alternative units of β-D-mannuronic acid and α-L-glucuronic acid [66]. A versatile, biocompatible polymer derived from brown seaweed is widely utilised in drug delivery and the food industry due to its exceptional properties [67]. Due to the notable advantages of alginate derivatives, such as biocompatibility and exceptional gel-forming capability, various bioactive agents, including enzymes, proteins, vaccines, antigens, and cells, are functionalized using alginate-based microcapsules [68-70]. Recently, alginate-based cross-linked microcapsules for the encapsulation of bioactive agents, utilising spray-drying, have been developed, demonstrating industrial-scale capability [71]. Environment-friendly polyanionic polymer, sodium alginate, which shows thermal stability and biodegradability, has been widely utilized to entrap various peptides and protein drugs to be therapeutically used, like bioactive peptides from silkworm, Plantaricin EF (PlnEF), red-garlic peptides (nutritional peptides), some probiotics, and several other similar agents [72-75]. Microparticles developed using alginate have not only been studied and used for vascular routes but also investigated for non-vascular routes, including nasal, pulmonary, and oral delivery. When combined with other mucoadhesive polymers, the alginate-based system also exhibits strong mucoadhesive properties, which can be utilised for ocular drug delivery. The most common combination is alginate/chitosan, which is generally produced by emulsification; in this process, various therapeutically active agents, including peptidyl drugs, have been successfully encapsulated and evaluated for efficacy [76].

Chitosan microparticles

Chitosan is another linear polysaccharide, a copolymer of glucosamine and N-acetylglucosamine residues, generally derived from chitin. Chitin, on the other hand, is also a polysaccharide by itself, made up of (1-4)-N acetyl-D-glucosamine residues that is chitosan's parent molecule, obtained from various sea creatures such as prawns, lobsters, crab, crayfish, octopus & also from common household insects and some species of fungus such as *Agaricus volvaceus, Colletotrichum lindemuthianum, Pleurotussajo, Penicillium notatum, Mucor rouxii, Aspergillus niger*, etc [77-78]. Due to its exceptional capability, chitosan is frequently utilised for drug delivery. Challenges such as poor solubility and instability of therapeutic agents can be overcome by utilising chitosan alone or in combination with other compatible biomaterials [79]. Another advantage of naturally derived polymers over synthetic ones is that they are low-toxicity, relatively inexpensive, and readily available [80]. For decades, chitosan has been utilised in numerous studies to produce and fabricate microparticles for peptidyl and protein drugs. Due to its exceptional ability to deliver reliable, scalable microparticles, it is used in both invasive and non-invasive delivery systems. Bioactive agents such as β-Galactosidase, antimicrobial peptides, peptidyl supplements (e.g., fish peptides), probiotic bacteria, and many other therapeutic agents and supplements have been successfully

microencapsulated using chitosan as a coating material [81-85]. González-Chavarría et al. [86] fabricated chitosan-based microparticles by spray drying for the encapsulation of recombinant peptides. The microparticles exhibited a narrow size distribution within the micrometer range (Figure 3(A)) and a predominantly spherical morphology with smooth surfaces, as confirmed by SEM analysis (Figure 3(B)). Such structural features are advantageous for protecting peptides from gastric degradation and ensuring controlled release in the intestinal environment.

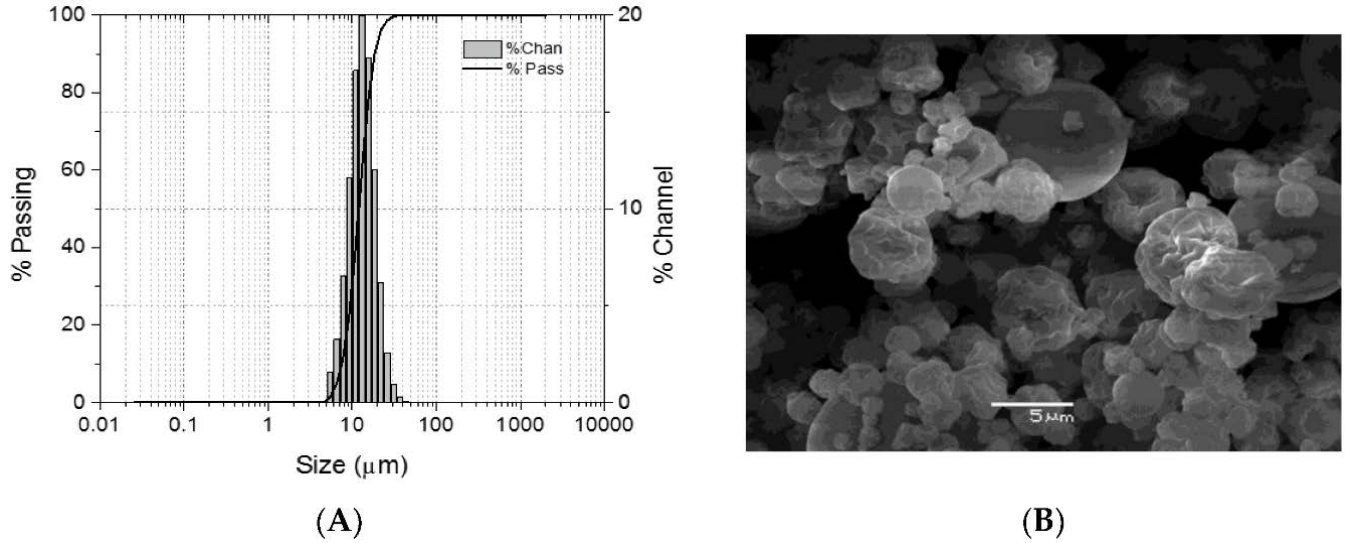

Figure 3: Chitosan microparticles (A) showing narrow size distribution within the micrometre range and (B) showing spherical morphology with smooth surfaces through SEM analysis. (Figure obtained and reused from González-Chavarría et al. (2023) [86] under the CC-BY licence)

Carrageenan-based microcapsules

Like the previous two polymers, carrageenan is another highly useful naturally occurring polysaccharide. It comes from a family of high-molecular-weight sulphated galactans, which is obtained from a particular seaweed belonging to the Rhodophyceae group. It consists of a linear structure consisting of D-galactose and 3,6 3,6-anhydro-D-galactose. Among six types of carrageenan found, namely Mu (μ), Iota (ι), Lambda (λ), Nu (ν), Theta (θ) and Kappa (κ), which has been differentiated based on the structural positioning of its sulphate group, carrageenan Iota (ι), Lambda (λ) and Kappa (κ) has been widely utilised in pharmaceutical application [87-90]. Although not used as frequently as other polymers such as alginate, carbomer, HPMC, and chitosan, it has exceptional properties. It has been utilised as an emulsifying, thickening, gelling, and stabilising agent [91]. Some researchers have shown that carrageenan can be used to preserve the functional properties of enzymes during delivery, as it is well suited for immobilizing enzymes such as trypsin, β-galactosidase, esterase, lipase, and glucose oxidase [92-95]. Carrageenan is utilised alone in delivery systems but performs best when combined with other biocompatible polymers. The chitosan-carrageenan complex can be utilised to develop a delivery system that releases entrapped or immobilised therapeutic agents in a controlled manner [96]. A study where sodium alginate and carboxymethyl starch were combined with carrageenan for the preparation of a capsule matrix system showed enhanced gelling characteristics, and this system, after preparation, had excellent mechanical strength [97]. Another study combining carrageenan with pectin to encapsulate *Lacticaseibacillus rhamnosus* resulted in the formation of a strong, spherical matrix system/beads [98]. Many therapeutic agents, peptides, and proteins from the pharmaceutical, nutraceutical, or food industries can be microencapsulated using carrageenan as an excipient, either alone or, more preferably, in combination with other biocompatible polymers, thereby increasing their stability and efficacy [99-101]. Vaishna et al. (2025) [102] fabricated carrageenan-based microcapsules for encapsulating snail protein hydrolysates. This study demonstrated that increasing carrageenan concentration improved encapsulation efficiency and colloidal stability (zeta potential up to 33.8 mV). The microcapsules exhibited more uniform spherical shapes and smooth, cohesive surfaces as the carrageenan concentration increased (Figure 4), indicating effective encapsulation and protection of snail protein hydrolysates against environmental stress.

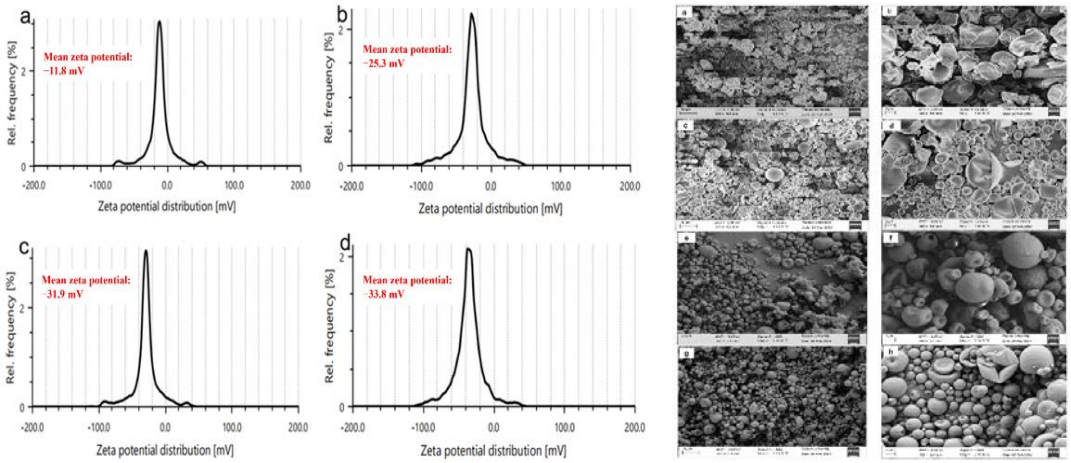

Figure 4: Zeta potential and SEM images of carrageenan-based microcapsules for the encapsulation of snail protein hydrolysates (This image was obtained from Vaishna et al. (2025) [102] under the CC-BY licence)

Gellan gum-coated microcapsule systems

Gellan gum is another natural polysaccharide. It is a biodegradable polymer widely utilised in the pharmaceutical, nutraceutical, biomedical, and food industries. An anionic linear polymer, which structurally is a tetrasaccharide consisting of repeating units of D-glucose, D-glucuronate, and L-rhamnose. Gellan gum is produced commercially by fermentation of the *Sphingomonas elodea* species. It is a promising polymeric material that can be utilised for targeted and controlled drug delivery through various routes of administration. In addition to being biodegradable, gellan gum exhibits other notable properties, including mechanical, thermal, and acid-stability, mucoadhesive properties, and a lower cost than other polymers used in the food and drug industries [103-104]. Gellan gum, due to its structural properties, is used as a gastroprotective and cryoprotective agent. Macromolecular materials, such as probiotics, can be delivered to the body's extreme environments, including the stomach, using gellan gum [105]. Due to its unique structural properties, gellan gum is well suited to the targeted, precise delivery of peptides and proteins. As discussed earlier, this polymer's mucoadhesive properties enable it to be combined with other mucoadhesive polymers, such as chitosan, to deliver drugs to specific mucosal sites, resulting in retention, stability, and controlled release of the drugs from the system [106, 107]. A study carried out by utilizing gellan gum-coated microparticles carrying insulin as a therapeutic agent was delivered orally to a diabetic rat, which showed enhanced stability of insulin in the gut, and it was also observed that the delivery system containing insulin contributed to the decrease in the blood glucose level in that experimental diabetic rat [108]. Yang et al. (2013) [109] investigated the gellan gum-based microcapsules for controlled delivery of proteins. This study demonstrated that the swelling ratio and release behaviour of the beads were strongly dependent on gellan gum concentration, with higher polymer concentrations resulting in reduced swelling and slower release profiles across simulated gastric, intestinal, and colonic pH conditions (Figure 5). These findings showcased the potential of gellan gum formulations to provide pH-responsive protection and sustained release of encapsulated proteins.

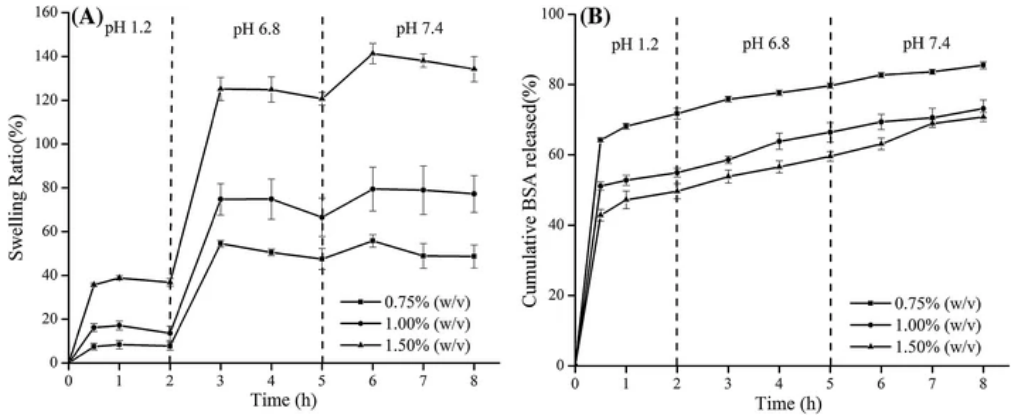

Figure 5: The swelling ratio (A) and release behaviour (B) across different pH conditions of gellan gum-based formulation (This image was obtained and used from Yang et al. (2013) [109] under CC-BY licence).

Gelatine-based systems

Gelatine is a complex natural polymer made up of a sequence of 19 amino acids, mainly hydroxyproline, proline, and glycine. It is generally obtained by hydrolytic degradation of proteins derived from bones, skin, and collagen of various animals, birds, and fish. Owing to its composition, the polymeric quality of mammalian gelatine is considered the best, followed by poultry and marine sources. Mammalian sources include bovine and pig skin and bones. Gelatine is commercially produced in large quantities from pigskin. Gelatin is a versatile material due to its exceptional and promising properties. For decades, it has been utilised as a gelling agent, thickener, emulsifier, and enveloping agent for soft and hard gelatine capsules. In pharmaceutical applications, in addition to its use in the production of conventional dosage forms (e.g., soft and hard gelatine capsule shells), gelatine has been utilised in novel drug delivery systems and formulations that can significantly control drug release kinetics. Additionally, due to its biodegradability and biocompatibility, gelatine can be best utilised in microdelivery systems to preserve drugs in extreme environments or to optimise drug release from the system [110-113]. Many literatures have explained that several proteins or peptidyl compounds like bovine serum albumin (BSA), bone morphogenetic protein 2 (BMP-2) different types of growth factors like transforming growth factor beta 1 (TGF-β1), vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF) can be encapsulated in a gelatine based microparticles for optimal delivery [114-116]. Microparticles and microcapsules made using gelatine alone as a wall material, or in combination with other polymers or resins such as shellac and gum arabica, can be produced by chemical methods (desolation, coacervation, or precipitation) or mechanical methods (emulsion technique, spray-drying technique, or electrospray method). During the synthesis of the carrier system, crosslinkers such as glutaraldehyde, formaldehyde, formalin, diisopropylcarbodiimide, dialdehyde carboxymethyl cellulose, and calcium chloride are used to stabilize the system and to adjust the release and degradation rates of the gelatin systems [117-120].

Furcellaran-based microcapsules

Polysaccharides, among other biopolymers, are considered ideal for the production of delivery vesicles or carriers because they are inexpensive and stable in a vast range of environmental conditions [121]. Furcellaran is one of the most utilised naturally occurring sulphated anionic polysaccharides, generally sourced from red algae (*Furcellaria lumbricalis*). Its properties resemble those of carrageenan and agar. Ferulic acid exists naturally in the sodium, magnesium, calcium, and potassium salts. Among red algal polysaccharides and other naturally occurring polymers, Furcellaran, due to its exceptional properties such as non-toxicity, hydrophilicity, biocompatibility, and excellent film-forming capability, is one of the most commonly used biocompatible polymers among formulators [122-124]. Generally, polymers containing hydroxyl, amide, carboxyl, or sulphate groups are considered optimal candidates for use in drug delivery systems [125]. Fucosylated, among others, includes a sulphate group and can form functional bonds with proteins and other biomolecules, making it a suitable candidate for microencapsulating proteins and peptides. Furcellaran-coated microcapsules are widely used as carriers, either alone or in combination with other polymers such as albumin and chitosan. Various literature reports that peptides, such as carp skin gelatine hydrolysate (CSGH), glutathione, and antimicrobial peptides such as cantharidin and lactoferricin B, have been successfully encapsulated using furcellaran as a coating material, either alone or in combination with other biocompatible polymers [126-129]. Drozdowska et al. (2024) [129] fabricated furcellaran-based glutathione microcapsules using a layer-by-layer assembly approach. The alternating deposition of chitosan and furcellaran produced systematic shifts in zeta potential, confirming the formation of multilayers. It was also revealed that well-formed spherical microcapsules with smooth morphology were formed (Figure 6). These structural and electrostatic characteristics demonstrate the potential of furcellaran as a natural polyelectrolyte for protein encapsulation.

Phthalate-based microcapsules.

Phthalates are common compounds found in cosmetics, pharmaceuticals, perfumes, food packaging, and dyes. Chemically, they are esters of 1,2 1,2-benzenedicarboxylic acid, also known as phthalic acid [130]. These compounds tend to dissolve only in a basic environment, not in an acidic one, making this material suitable for enteric coating. The enteric coating process is a protection method used to encapsulate or coat acid-sensitive agents that tend to deteriorate at acidic pH (stomach pH) [131, 132]. Cellulose acetate phthalate, a common phthalate derivative, is widely used as an enteric-coated material [133]. Some therapeutically significant peptides, such as insulin, can also be delivered orally using this phthalate-based system,

most commonly via a modified version such as the chitosan-phthalate polymer. Several other peptides, such as peptidyl growth factor, trefoil peptide, and pancreatic trypsin inhibitor, play crucial roles in metabolism and in the function of the gastrointestinal tract wall. These peptides have been considered for incorporation into microcapsules, especially trypsin, which is coated with cellulose acetate phthalate to prevent gastric degradation. Cellulose acetate phthalate microparticles containing thermally inactivated *Vibrio cholerae*, used for immunisation against cholera, have also been successfully formulated, potentially enabling enhanced oral delivery of powdered cholera and other vaccines [134-138]. Sun et al. [139] fabricated multifunctional composite microcapsules by encapsulating insulin PLGA nanoparticles into pH-sensitive hydroxypropyl methyl cellulose phthalate, which provided enteric protection, enhanced encapsulation efficiency & achieved controlled pH-dependent insulin release.

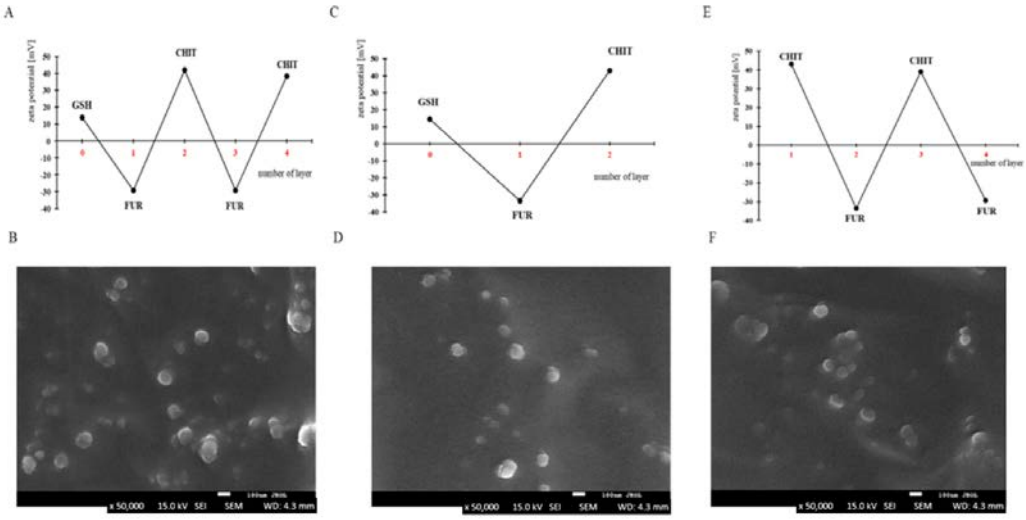

Figure 6: Zeta potential (GSH- glutathione, CHIT- chitosan, FUR- furcellaran) and SEM images of furcellen/chitosan multilayer microcapsules. (This image was obtained from Drozdowska et al. (2024) [129] and used under CC-BY licence)

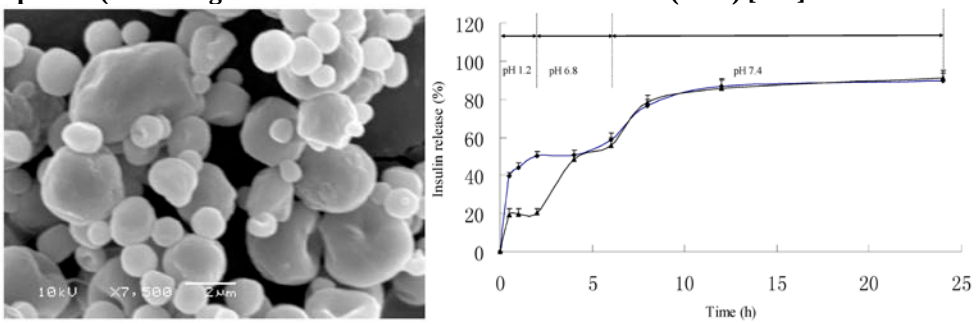

Figure 7: SEM image and insulin release profile from phthalate-based multifunctional composite microcapsules (This image was obtained from Sun et al. (2016) [139] and used under CC-BY licence).

Poly (methyl methacrylate) (PMMA) microparticles

Poly (methyl methacrylate) (PMMA) is a synthetic, biocompatible polymer with a glass transition temperature of around 100°C-130°C & was first used in the mid-1970s to develop nanoparticles carrying a vaccine. A hydrophobic, non-biodegradable, hard but brittle type of polymer with good thermal stability, which can withstand temperatures up to 100°C [140, 141]. Due to its non-biodegradable nature, it is rarely used in biomedical applications. It has been largely neglected; nevertheless, its use remains essential for the fabrication of carrier molecules, such as microcapsules and microspears, and for insulin delivery due to its biocompatible nature [142-144]. Not only as a carrier, but PMMA is also widely used in dentistry and orthopaedics as a prosthetic material [145, 146]. As carriers, they have been used as antibiotic delivery systems for the treatment of osteomyelitis and fractures [147].

Poly Lactic-co-Glycolic Acid (PLGA) based drug delivery microcarrier

PLGA remains the dominant polymer in FDA-approved microsphere vehicles for peptides and proteins, with over 10 marketed formulations [148]. Poly Lactic-co-Glycolic acid

(PLGA) is a biocompatible and biodegradable polymer, generally produced by the random polymerisation of lactic acid and glycolic acid, either via polycondensation or ring-opening polymerisation. It is a hydrophilic polymer that hydrolyses in water at its ester linkage [149, 150]. PLGA, in terms of performance and design, is one of the optimal biomaterials for the controlled delivery of drugs and other therapeutic agents, such as active peptides and protein drugs [151]. PLGA has recently been utilised for the production of injectable microspheres containing peptidyl and protein drugs, which have been shown to have longer-lasting effects than other conventional delivery methods. This PLGA-based microsphere enables targeted drug delivery and increases the local concentration of the peptidyl drug at the site of action, thereby reducing unnecessary systemic exposure [152]. It has gained popularity among formulators due to its ability to control drug release by simply changing the copolymer ratio (poly (lactic acid): poly (glycolic acid) and by utilising a differently structured PLGA copolymer. Due to their ability to control drug release, PLGA-based microparticles are considered among the most successful and functional polymers in novel drug delivery systems [153, 154]. Various drugs and peptides can be incorporated into a PLGA-based carrier system and delivered via parenteral routes to avoid GI-related metabolism and degradation. Among other biodegradable polymers, PLGA is among the most investigated for sustained drug delivery systems. Because the PLGA system can control drug release in biological systems, various peptides, including therapeutic and diagnostic agents such as human growth hormone, insulin, and tetracosactide, have been encapsulated in this system, providing enhanced control over the agents' release from the delivery system [155-157].

Poly (vinyl alcohol) (PVA) based microspears

Poly(vinyl alcohol) (PVA) is a synthetic, highly biocompatible, biodegradable, hydrophilic, and non-toxic polymer. Unlike other synthetic polymers, PVA can't be directly polymerised for vinyl alcohol (its monomer) due to some instability issues. Still, it is produced by the hydrolysis of poly(vinyl acetate) (PVAc) [158, 159]. PVA has been utilised to produce microcapsules that carry various peptidyl drugs and bacterial cells. When combined with other natural polymers such as chitosan, alginate, and starch, an excellent encapsulating material can be formed that has been shown to deliver therapeutic agents, including antimicrobial peptides, antioxidant peptides, peptidyl anticoagulants, bacterial cells, and islet cells [160-163]. Some marketed microparticulate products are illustrated in Table 1.

Table 1: Marketed microparticulate formulation of peptides and proteins

Product	Therapeutic agent	Delivery system	Use	Reference
Lupron Depot®	Leuprolide acetate (GnRH analog; peptide)	PLGA/PLA microspheres	Endometriosis, uterine fibroids, prostate cancer palliation	**[164]**
Sandostatin® LAR	Octreotide acetate (somatostatin analog; peptide)	PLGA glucose-star polymer microspheres	Carcinoid-syndrome diarrhea/flushing; acromegaly	**[165]**
Bydureon®	Exenatide (GLP-1 analog; peptide)	PLGA microspheres	Type 2 diabetes mellitus	**[166]**
Signifor® LAR	Pasireotide pamoate (somatostatin analog; peptide)	PLGA microspheres	Acromegaly; Cushing's disease; NET symptoms (regional)	**[167]**
Trelstar®	Triptorelin pamoate (GnRH analog; peptide)	PLGA microgranules / microspheres	Advanced prostate cancer palliation	**[168]**
Nutropin Depot®	Somatropin (recombinant human GH; protein)	PLGA microspheres	Pediatric growth hormone deficiency (later withdrawn)	**[169]**

CONCLUSION

Microencapsulation has emerged as a transformative strategy for peptide and protein drug delivery, addressing long-standing challenges such as instability, enzymatic degradation, and short systemic half-lives. By enabling sustained release, enhancing therapeutic efficacy, and reducing dosing frequency, it not only improves clinical outcomes but also contributes significantly to patient adherence and quality of life. The success of marketed formulations such as Lupron Depot®, Sandostatin LAR®, and Bydureon® underscores the clinical relevance and regulatory acceptance of polymer-based microsphere systems, setting benchmarks for translating laboratory innovations into clinical practice. Yet, despite these milestones, critical hurdles remain. The encapsulation process often exposes sensitive biomolecules to stress conditions that may compromise bioactivity, while achieving reproducible large-scale manufacturing with consistent release kinetics remains technically demanding. Furthermore, designing delivery systems that balance

biodegradability, safety, and precise pharmacokinetics remains a challenge for researchers. Future progress in this field will be driven by interdisciplinary innovation. The integration of novel biomaterials such as smart and stimuli-responsive polymers, hybrid polymer biopolymer matrices, and surface-engineered carriers promises to expand the functional scope of microsphere-based systems. Coupling these advances with microfluidic technologies, computational modelling, and artificial intelligence could allow for unprecedented precision in formulation design and performance prediction. In parallel, regulatory frameworks must evolve to accommodate these advanced delivery systems, ensuring a smooth transition from bench to bedside. In essence, microencapsulation is not merely a supportive technology but a pivotal enabler of the peptide and protein therapeutic revolution. Its continued evolution will shape the future of biologics, opening new avenues for safer, smarter, and truly patient-centred therapies.

FINANCIAL ASSISTANCE
Nil

CONFLICT OF INTEREST
The authors declare no conflict of interest.

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