



Smart Nanomaterials for Bioencapsulation

1st Edition

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Elsevier
Radarweg 29, PO Box 211, 1000 AE Amsterdam, Netherlands
The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, United Kingdom
50 Hampshire Street, 5th Floor, Cambridge, MA 02139, United States

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ISBN: 978-0-323-91229-7

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Publisher: Matthew Deans
Acquisitions Editor: Ana Claudia Garcia
Editorial Project Manager: Samuel Young
Production Project Manager: Manju Paramasivam
Cover Designer: Greg Harris



Typeset by Aptara, New Delhi, India

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Delivery of bioencapsulated proteins

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4.1 Introduction

Proteins and peptides are multifunctional biomolecules that are involved in various biochemical reactions in the body, steering inflammatory responses, regulating cell multiplication and differentiation, and controlling metabolic and signaling pathways (Moreira et al., 2021). The increasing various medical conditions concerning endogenous protein functions has driven the application of proteins and peptides as therapeutic biological agents. Proteins and peptides are large molecules with multiple active sites and function specifically on targeted site, thus, makes it preferred as therapeutic agents than the small molecule drugs. The complexity and specificity of the protein function is not reproducible by other compounds (Moreira et al., 2021). Among proteins that are currently used as therapeutic biological agents are enzymes, hormones, coagulation factors, growth factors, cytokines, monoclonal antibodies, antibody-drug conjugates, and fusion proteins. The diverse biological functions performed by proteins in the body has initiated the development of therapeutic proteins for treatment of diabetes, cancer, AIDS, genetic disorders, myocardial infarction, autoimmune diseases, and many others (Kupikowska-Stobha et al., 2021).

The clinical application of protein and peptide as therapeutic agents are restrained due to a few setbacks related to its formulation and administration methods. Although the oral delivery of protein drug allows self-administration and high patient compliance, the degradation in gastrointestinal tract leads to low systemic bioavailability of the protein. The nature of proteins which are high molecular weights and usually display several ionisable groups shows difficulty in

crossing biological membranes such as the intestinal epithelium. Consequently, these therapeutic agents have to be administered through parental injections. This approach however exposes proteins to the risk of eradication by immune cells, liver, or kidneys, depending on their physicochemical, and structural characteristics, therefore shortening their half-lives. Other than that, protein drug administration also faces the problem of structural changes, due to several factors like hydrolysis, proteolysis, endocytosis, endosomal entrapment, and exocytosis of the remaining entrapped proteins or molecules (Kupikowska-Stobha et al., 2021; Gilleron et al., 2013). These modifications could affect the protein structure and integrity, resulting in denaturation, misfolding or aggregation which ultimately causes bioactivity loss, immunogenicity, and higher toxicity (Butreddy et al., 2021). The decrease in bioavailability of these therapeutics thus forces the requirement of higher and more regular doses which subsequently reduce patient acceptance and the emergence of other detrimental side effects. Another issue is the protein stability, for which it is susceptible to denaturation during processing, storage, and distribution. To maintain its stability, maintenance in cold temperature (near 0°C) from manufacturer to end consumer is necessary and this results in significant economic and logistic burden. Considering all the impediments in the administration of protein and peptide therapeutics, there is an urgent need for a new delivery systems that are capable to not only preserve protein bioactivity and protect against degradation, but also provide sustained release. These could reduce the applied dose or minimize the regularity of administration and improve the bioactivity of the protein.

The efficacy of protein drugs is determined by its stability and interaction with targeted molecules in the cell. Administering oral drugs as capsules or tablets has been a common approach that is well accepted by most patients. However, these capsules and tablets only confer macroscale protection. For the particular control of drug release on a molecular scale, the active therapeutic protein requires additional layers of encapsulation that permits controlled diffusion into the environment and targeted delivery site (Schwestka and Stoger, 2021). The encapsulation of protein drugs into nanoparticles, microparticles or polymer-based carriers is essential to protect them from environmental effects, stomach acid, and digestive enzymes reactions, as well as avoiding off-target effects. Among the advantages of this encapsulation include protection, controlled release, targeted delivery, adjuvant properties, and multivalent antigen display (Schwestka and Stoger, 2021).

4.2 Protein bioencapsulation development

Encapsulation is a method of enclosing bioactive materials into capsules prior to delivery into a system. Encapsulation can be categorized according to particle size, for which microencapsulation ranges from 3 μm to 800 μm and nanoencapsulation ranges from 10 nm to 1000 nm. Encapsulation protects the bioactive materials from unfavorable surrounding, thus preserving its bioactivity until it is delivered to the targeted site (Reque and Brandelli, 2021). Aside from that, encapsulation also enhances the oxidative, thermal and photo stability, enables sustained and controlled release, and increases ease of handling of the of the bioactive agents (Sharif et al., 2020). The encapsulated materials then can be released from the capsule by several mechanisms, for instance, changes of temperature and pH, biodegradation, medium solubility, mechanical rupture, and diffusion (Razavi et al., 2021).

Steps in the encapsulation involve the incorporation of bioactive compounds in a matrix, preparation of microcapsules, and stabilization of the microcapsules. Encapsulation matrix can be liquid or solid. During preparation, liquid matrix is dispersed while solid matrix is spray-dried. Stabilization process can be done through a physical, chemical, or physical-chemical process (Reque and Brandelli, 2021). Capsule size varies depending on the encapsulation technique. Spray drying produces 5–150 μm capsule, spray cooling produces 20–200 μm capsule, spray coating produces 5 μm –1 mm capsule, coacervation produces 1 μm –1 mm capsule, emulsification produces 200 μm –1 mm capsule and extrusion produces 300 μm –3 mm capsule (Reque and Brandelli, 2021).

Solvent evaporation and extraction, coacervation, poly-electrolyte complexation/ionotropic gelation, and spray drying are the common protein encapsulation techniques employed. Recently, electrohydrodynamic (EHD) technique shows a growing attention for protein drug delivery. This technique produces highly surface area fibers or particles using an electric field during polymer solidification. For instance, electrospinning that produces nano- or microfibers and electrospraying that generates nano- or microparticles (Moreira et al., 2021; Rostamabadi et al., 2021). Although EHD techniques demonstrate huge potential in the drug delivery and tissue engineering fields, extensive medical and operational research is imperative before clinical application takes place.

The nanocarrier systems have been quickly and popularly developed owing to its superiority in improving the bioavailability of encapsulated materials by providing high surface-to-volume ratio. This results in greater tendency for the microcapsule to attach to the intestinal mucosa and interact with enzymes and other metabolic factors. Due to its nanoscale size, nanoencapsulation enables entrance and permeation into living tissues and cells, thus providing target delivery of the protein therapeutics into the intracellular compartments (Noor et al., 2021; Reque and Brandelli, 2021). Nanotechnology has improved drug delivery systems in terms of enhancing thermal stability, oral bioavailability, and water solubility of the bioactive compounds (Noor et al., 2021). Nanocarrier systems such as liposomes, nanosuspensions, and nanoemulsions are among nanoencapsulation techniques that have been studied in designing nanocapsules. Among inclusion complexes used for nanoencapsulation are amylose and cyclodextrins, nanotransporters like yeast cells, nanogels, nanofibres, and nanosponges fabricated from polysaccharides and lipids (Noor et al., 2021). Research on nanomaterials and its application in pharmaceutical has been intensively growing. However toxicological effect when administered to human body is still a big concern when it comes to drug delivery application (Reque and Brandelli, 2021).

4.3 Challenges in protein and peptides bioencapsulation

The production of therapeutic agents and different metabolites could be more effective with the emergence of protein and peptide bioencapsulation technology. However, there are various challenges that must be addressed until this method is truly ready for clinical application, for example protein stability, matrix selection, retention or release properties, absorption, and storage condition (Fig. 4.1).

The selection of a suitable matrix to encapsulate protein and peptide is crucial. According to McClements (2018),

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