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Review Article

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A Review on Modern Formulation Approaches for Protein Based Drug Delivery

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Abstract

Protein and Peptide drugs have great emerging applications as healing agents because they have higher efficacy and less toxicity than chemical drugs. However, difficulty in their delivery has limited their use. In particular, their oral bioavailability and stability is very low, and non-invasive drug delivery route such as nasal, pulmonary and transdermal delivery faces absorption limitations. Therefore, the promising way of protein-based drug delivery is parenteral route. However, this route also has some problems like poor patient compliance, pain, and dermal discomfort. So, structure based nanocarriers design for drug delivery is developing nowadays and has illustrated the fewer side effects and better usefulness in disease treatment than free drug molecules. A modish nanocarriers offer site specific drug delivery in controlled fashion against all the physiological barriers and is ultimately metabolized in the body. This review will discuss the various nano-formulation strategies for biomacromolecules delivery.

Keywords: Nanocomposite, Nanotube, Polymer composite, Peptide and Protein drug delivery, Permeability.

Introduction

Proteins and Peptides are very vital biomolecules of today because of their versatile application in diagnostic field. Many proteins and peptide such as vaccine, insulin, antibodies and various recombinant protein cannot be administered orally because they are degraded inside the gastrointestinal tract (GI tract) frequently due to their short half-life in the body fluids. Therefore, most of the protein and peptide-based drugs are administered by the parenteral and non-invasive topical route [1] . However, it has also some set of drawbacks like permeability, local allergic and skin barriers. Nanotechnology has shown great promise for medical applications. To date, dozens of nanomedicines have been approved for clinical use, and many are in clinical research. Nanoscale drug delivery systems have generally been characterized by some physical and chemical properties such as the high surface to volume ratio as well as the size of nanoparticles, which plays an important role in the characteristics of the nanocarriers due to the passive targeting strategy [2]. In particular, nanoparticles such as liposomes, micelles, polymer nanoparticles, and inorganic nanomaterials, which are typically in the range of 10–150 nm in size, have considerable advantages as drug carriers. In protein delivery, nanoparticle technologies can: i) prevent proteins from premature degradation or denaturation in biological environment; ii) enhance in vivo half-life of proteins with poor pharmacokinetic properties; iii) control sustained release which can maintain drug concentration in the therapeutic range; and iv) target diseased tissues, cells, and intracellular compartments, thus improving the safety and efficacy of biologic therapeutics [3]. Nanoformulations are prepared from various biomaterials. However, polymeric nanomaterials have been widely used for the preparation of targeted and controlled release drug delivery systems. Synthetic polymers are toxic and very less biocompatible. In this regard natural biodegradable polymer including proteins are suitable alternatives due to their safety and biocompatibility properties. Thus, natural protein-based nanoparticles are preferentially used as biological therapy [2].

Potential Nanocarriers Approaches

Pharmaceutical formulations with colloidal particulate carriers have been widely used to enhance peptide/protein activity. Microemulsion, Nanoemulsion, Microspheres, Nanoparticles, Mucoadhesive polymers and Clay Nanotubes are exciting approaches [4]. Strategies to deliver protein and peptides can be successfully achieved using various carrier systems as follow.

I) Microsphere

The microspheres are prepared from biodegradable polymers, have an appropriate size ranging from 1µm – 100 µm and can be

easily injected subcutaneously as a parenteral depot [5]. It can also be administered orally but its oral bioavailability is very low as they are poorly absorbed and easily degraded by proteolytic enzyme in the gastrointestinal tract. Thus, subcutaneous mode of delivery is in great demand offering controlled drug delivery and the avoidance of routine invasive dosing [5, 6]. The key factor of microsphere formulation is polymer selection. Both natural and synthetic polymer are used for the preparation based upon their release profile. The release profile from the microspheres depends on diffusion through the polymer matrix and polymer degradation. Polyester has found the most extensive use among all the polymers [1, 7]. It can be prepared using various methods such as double emulsification, spray drying and phase separation- coacervation. They are physically and chemically more stable than liposomes and also act as important vehicle for proteins drug delivery system in pulmonary delivery [4, 6]. Some of the marketed formulations of proteins based on biodegradable microspheres are as follow [1].

Drug	Trade Name	Company	Route	Application
Leuprolide acetate	Lupron	Takeda- Abott	3-monthdepot suspension	Prostate Cancer
Goserelin acetate	Zoladex	I.CI.	S/c implant	Prostate cancer
Octreotide acetate	Sandostatin	Novartis	Injectable s/c suspension	GH suppression anticancer
Triptorelin recombinant bovine somatropin	Posilac	Monsanto	Oil based injection	To increase milk production in cattle
Minocycline	Arestin	Orapharma	Unit dose cartridge	N/A
Buserelin	Suprecur	Sanofi- Aventis		N/A

Table 1: Some of the Marketed Formulations of Proteins Based on Biodegradable Microspheres

II) Microemulsion

Microemulsion is a stable, isotropic, thermodynamically safe clear liquid consisting of water, oil and surfactant. Water in oil type of microemulsions offer unique advantages. Protein and peptide are water soluble in nature, this property supports the loading capacity of proteins within the hydrophilic core [8, 9]. This protects the protein from external denaturation and peptide degradation. The outer phase is surrounded by a lipophilic environment that mimics with the outer layer of the skin and helps in the easy absorption of bioactive molecules through the skin [9, 10]. This resemblance makes microemulsions ideal for application on the skin surface. The particle size of this micro emulsion composition is 0.15 µm. The W/O/W methodology of multiple emulsions was further researched using insulin encapsulation and found to be a very promising drug delivery system [11].

III) Nanoemulsion

Nanoemulsion is playing a very important role for both topical and oral delivery of proteins and peptides. Recent studies have shown that nano-technology has improved the pharmacokinetic and biopharmaceutic profile of bioactive molecules [12]. Nanoemulsions are kinetically well built isotropic dispersed systems of two immiscible liquids that is droplets with sizes in the range between 100 and 500 nm. They can appear either as oil-in-water (O/W) or water-in oil (W/O) particles, whose center is either oil or water, respectively[12,13]. Most proteins are insoluble in oil due to their hydrophilic nature. Its solubility and physical properties play a key role in structuring nanosystem and additives selection. The best way to increase the absorption of bioactive molecules such as proteins for topical delivery is to load them into the oil phase [13]. Whey protein peptides are potential emulsifiers in food nanoemulsions [14]. Bioactive peptides can act as functional and nutraceuticals agent. Peptides play a dual-functional role when consumed as emulsifiers and bioactive compounds in food [15]. Protein extracted from medicinal leech tissue based nanoemulsion have shown a stable and successful topical drug delivery for treating various skin disorders [14].

IV) Nanoparticles

The rapid advancement of nanotechnology provides a revolutionary approach to the design of drug delivery systems based on nanoparticles to protect proteins and deliver them to desired locations. Nanoparticles have been extensively used as carriers for the delivery of chemicals and biomolecular drugs, such as anticancer drugs and therapeutic proteins [7]. Natural biomolecules, such as proteins, are an attractive alternative to synthetic polymers commonly used in nanoparticle formulation because of their safety. Several approaches are deployed for the formulation of nanoparticle and its delivery at the target site. Nanoparticle delivery systems are prepared from different materials [4, 6]. Lipid based nanoparticles (Liposomes, micelles), solid lipid nanoparticles, protein-based nanoparticles, Inorganic and polymer-based nanoparticles (both natural and synthetic) are used for protein delivery based upon their characteristics [16]. In general, protein nanoparticles offer many advantages, such as biocompatibility, biodegradability and ability to be modified over other nanosystem. It has been reported that mesoporous silica nanoparticles (MSNs) are of particular interest for protein delivery due to their excellent biocompatibility, high stability, rigid structure, well-defined pore structure, easily controllable morphology and tuneable surface chemistry[17].

a) Liposomes

A liposome is a lipid-based nanoparticles which is spherical-shaped vesicle composed of one or more phospholipid bilayers, similar in structure to cell membranes [16]. The ability of

liposomes to encapsulate hydrophilic or lipophilic drugs has allowed these vesicles to become useful drug delivery systems but the stability of such structures and release profile of encapsulated agents are not easily controlled. To mitigate these problems, researchers are adopting various strategies such as coating vesicles [18]. There has been extensive research on liposomes-based delivery systems for their application in the delivery of proteins or peptides, primarily via oral delivery. The benefits of liposomes in oral delivery are mainly protecting protein (e.g., Insulin, Lactoferrin) from enzymatic hydrolysis in the gastrointestinal tract. Lactoferrin is a peptide that has gained a lot of attention due to its important role on the immune system, as well as its antioxidant, anti-inflammatory, anti-viral and anti-bacterial properties [15]. But it is susceptible to gastro-intestinal enzyme hydrolysis which limits its oral bioavailability. To overcome these restriction, lactoferrin encapsulation in liposomes has been studied [15, 18]. Some investigations have been reported for the successful dermal delivery of liposomes bound protein such as superoxide dismutase, tissue growth factors and interferons [19].

b) Protein based nanoparticles

Protein nanoparticles are nanocarriers of great interest in research due to their safe biological properties, metabolizable and biodegradability. Its wide range of drug encapsulation capacity and solubility natures have favoured the use of protein nanoparticles [6]. They include various nanomedicine classes where drugs are conjugated to protein carriers, recombinant protein where active therapeutic is the protein itself [20]. Both animals based and plant-based proteins are used for protein nanocarrier formulation. Animal based proteins are derived from meat, fish, dairy, eggs and other animal derived tissue whereas plant proteins are derived from natural foodstuffs [2]. The most commonly used animal proteins and plant proteins in the field of bioactive molecules delivery are classified as Fig. 1 and Fig. 2 respectively.

Figure 1: Animal Proteins

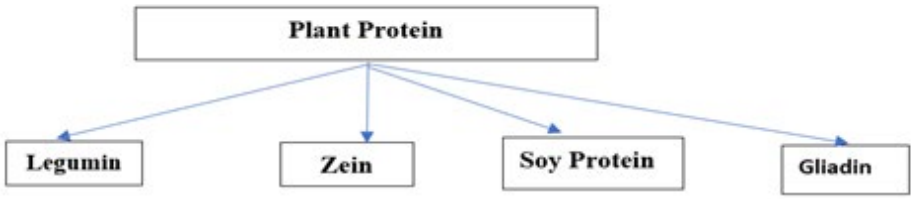

Figure 2: Plant Proteins

c) Polymeric Nanoparticles

Polymeric nanocarriers provide suitable environment for the targeted delivery of therapeutic proteins to a specific site and also protects from any physiological changes caused by external stimuli. Nanoparticles with charged surfaces are preferred for many applications because they provide gentle protection through electrostatic interactions [7]. Polymeric nanoparticles are prepared from natural and synthetic polymers via different strategies. Some of the commonly used synthetic biodegradable polymers and natural polymers are mentioned in the following table 2 [2, 7, 21].

Natural Polymers		Synthetic Polymers
Polysaccharides	Protein based polymers	Poly (ethylene glycol)
Chitosan	Fibrin	Polylactides (PLA)
Alginate	Gelatin	Polyglycolides (PGA)
Dextran	Elastin	Polycaprolactone (PCL)
Hyaluronic Acid	Corn Zein	Poly (hydroxy butyrate) (PHB)

Pectin	Keratin	Poly (vinyl alcohol) (PVA)
Xanthan Gum	Silk	poly(lactide-co-glycolides) (PLGA)
Cyclodextrins	Albumin	poly (methyl methacrylate) (PMMA),

Table 2: Some examples of Natural polymers and Synthetic polymers.

Several factors are important in choosing an appropriate polymer for the preparation of polymeric nanoparticles, such as biocompatibility, safety, and immunogenicity [22]. Basic conventional way of protein conjugated polymeric nanoparticle is shown in figure 3.

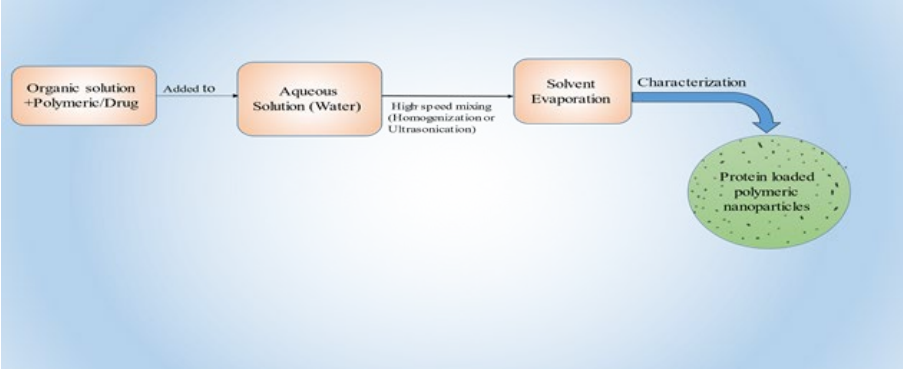

Figure 3: Schematic Diagram of the Conventional Process for Protein Integrated Polymeric Nanoparticles.

d) Inorganic Nanoparticles

Inorganic nanoparticles are receiving more attention in the development of a protein or peptide carrier due to certain properties. The protein and peptides macromolecules are encapsulated inside the nanoparticles which protects from enzymatic degradation of proteins. Porous inorganic nanoparticles are particularly attractive for applications in API delivery because they offer API loading inside the nanoparticles structure [6, 16]. Pores allow an additional control of drug release kinetics, where pore size, surface chemistry and pore capping or filling strategies can be used to tailor bioactive molecules release from this structure. Inorganic nanomaterials come in many varieties, such as gold nanoparticles, carbon nanotubes, quantum dots, calcium phosphate, porous silicon and mesoporous silica nanoparticles [23]. Above all mesoporous silica nanoparticles have been used extensively because they are inert, non-immunogenic and convertible as a therapeutic agent due to the advantage of cargo loading efficiency over large surface area and pore volume [6]. The unique properties of inorganic nanoparticles have begun to inspire researchers to incorporate them into biomaterials to create multifunctional hybrid materials with a greater degree of control of API release. Kane et al. reported the silica nanoparticle successfully delivered antibodies into intracellularly. Silica nanoparticles were surface modified with n-octadecyltrimethoxysilane (n-ODMS) and encapsulate with proteins and antibodies [24].

e) Solid Lipid based Nanoparticles

In 1990 solid lipid nanoparticles were introduced as an alternative drug delivery system to liposomes and emulsion. Solid Lipid Nanoparticles were developed to address deficiencies in liposomal drug delivery [25]. It boosts drug delivery efficiently through dermal, ocular, rectal and pulmonary routes and provides greater drug stability and safety with its controlled release [25, 26]. Solid lipid nanoparticles composed of a solid lipid matrix, or nanostructured lipid carriers composed of mixture of liquid and solid lipids as a matrix [26]. These carriers constitute a hydrophobic core that is solid at body temperature and is stabilized by surfactant layer encapsulated in their surface. The most commonly used lipids are complexes of purified tri-acyl-glycerol, waxes and acyl-glycerol mixtures [15]. Two main way of production techniques are high - pressure homogenisation and the microemulsion based technique. SLN has already reached the market as a topical formulation by Dr. Rimpler with the name NanoRepair™ [25].

V) Mucoadhesive Polymeric Systems

Mucoadhesive polymeric systems of protein delivery are a very innovative approach that utilizes the bioadhesive properties between polymeric materials and the mucosal surface. The polymers, with certain structural features, become adhesive to mucus layer upon hydration [27]. This adhesion provides additional residence time leading to higher concentration of the therapeutic molecules. The exact mechanism of adhesion varies with the types of polymers used in the formulation [28].

Some of the possible interaction theory and its mechanism are mentioned in the table 3.

Theory	Mechanism
Electronic	Electron transfer occur between mucus and polymer that leads to formation of a double layer of electrical charge.
Adsorption	Hydrogen bonding and Van der Waals interaction

Wetting	Ability of polymers to swell and spread on mucus layer.
Diffusion	Interpenetration and physical entanglement of the mucoadhesive polymer with mucus layer.

Table 3: Some of the possible interaction theories and its mechanism.

Mucoadhesive nanocarriers for protein delivery are methylcellulose, hydroxyethyl cellulose, thiol group and carboxymethyl cellulose [29]. Other used polymers are polyacrylic acid derivatives such as carbapol and polyacrylate. Some of the latest types of polymers such as anionic alginate and cationic chitosan are mucoadhesive polymers whose adhesive properties are better than unmodified polymers due to tight disulphide bonding with mucus layer [7, 15, 30].

VI) Halloysite Clay Nanotube

It is an aluminosilicate tubular natural material with proven biocompatibility and are available in abundant form at low price. It is a tubular hollow structure having external diameter of 50 nm and an inner lumen of 15 nm [31]. They have a nanoscale organization and show various properties for various application. Halloysite clay nanotube is a versatile, safe, green nanomaterials used for drug encapsulation for numerous clinical applications [32]. Because of its dual ion properties, it has dual nature of carrying both low water-soluble drugs and poor lipid soluble drugs. It is highly recommended nowadays for the delivery of both positive protein and negative protein like DNA. The versatile surface properties of halloysite nanotubes are increasingly being taken advantages in the food industry and nutraceuticals for protein based canned formulation [32, 33]. Hence, Nanotube is acting as a potent platform for protein-based drug loading and sustained release to the site of its application

Importance of Nanocarriers in Protein Based Drug Delivery

1. Enhanced Bioavailability: Proteins are macromolecules having high molecular weight in nature and often have poor bioavailability, meaning they are unable to reach their target sites in the body effectively [34]. Nanocarriers can improve the bioavailability of proteins by protecting them from rapid clearance, enzymatic degradation, and immune recognition. By encapsulating proteins, nanocarriers can prolong their circulation time in the body, allowing for increased uptake and accumulation at the desired site of action [35].

2. Controlled release: Nanocarriers offer precise control over the release kinetics of proteins. They can be designed to release proteins in sustained or triggered manner, providing a controlled and prolonged release profile. This controlled release is particularly beneficial for therapeutic proteins, as it allows for optimal dosing, reduces side effects, and ensure a therapeutic level of protein is maintained over an extended period [36].

3. High Drug Loading Capacity: Nanocarriers offer high aspect ratios for surface functionalization and have the potential for substantial drug loading for both low water and poorly lipid soluble drugs [32]. Mesoporous silica nanocomposite and Halloysite clay nanotubes are some of the ideal examples of nanocarriers known for high drug loading capacity [32, 33].

4. Formulation Versatility: Nanocarriers offer flexibility in terms of formulation design. They can be tailored to accommodate proteins of various sizes, charges and hydrophobicities [33]. Additionally, nanocarriers can be composed of different materials, such as lipid, polymers or inorganic nanoparticles, allowing for customization of their physicochemical properties [36]. This versatility enables the development of protein delivery systems suitable for different administration routes, including oral, parenteral, transdermal and inhalation [37].

5. Combination Therapy: Nanocomposite facilitate the co-delivery of proteins with other therapeutic agents, such as small molecules, nucleic acids or imaging agents. This capability enables combination therapies, where multiple agents can act as synergistically to enhance therapeutic outcomes [38].

Conclusion And Future Trends

Proteins play a crucial role as therapeutic molecules in the treatment of diverse diseases. Consequently, their successful delivery to the intended biological site in imperative for achieving effects. However, due to the complex nature, large size and high molecular weight of these molecules, transporting them to the desired site poses significant challenges. Their unfavourable physicochemical properties, including hydrophilicity, stability and macro size, further restrict their use. To address these issues, several nanocarriers have been developed to facilitate the transportation of proteins and peptides. This article explores various approaches aimed at achieving safe, efficient and easy delivery of specific proteins and peptides. Integrating different technologies holds promise in overcoming the obstacles associated with peptide/protein-based drug delivery in the present era. Looking ahead, the ideal scenario would involve the development of a reliable and effective nanocarrier system capable of ensuring the delivery and systemic stability of diverse proteins and peptides, thereby revolutionizing the field.

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