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Mini-Review: Potential of Nanocarriers 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: Nanomedicine, Bioavailability, Absorption, 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 proteins 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. 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. In particular, nanoparticles such as liposomes, micelles, polymer nanoparticles, and inorganic nanomaterials, which are typically in the range of 10 nm-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. Nanostructure delivery systems are prepared from different materials. Among them, polymeric nanomaterials have been widely used for the preparation of targeted and controlled release drug delivery system. 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 [1,2].

LITERATURE REVIEW

Potential nanocarriers approaches

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

Microsphere

The microspheres are prepared from biodegradable polymers, have an appropriate size ranging from 1 μm-100 μm and can be easily injected subcutaneously as a parenteral depot. 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. The key factor of microsphere formulation is polymer selection. Both natural and synthetic polymers 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. 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. Some of the marketed formulations of proteins based on biodegradable microspheres are as follow [2-7].

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. 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. 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.

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. Nanoemulsions are kinetically well built isotropic dispersed systems of two immiscible liquids that is droplets with sizes in the range between 100 nm 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. 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. Whey protein peptides are potential emulsifiers in food nanoemulsions. Bioactive peptides can act as functional and nutraceuticals agent. Peptides play a dual-functional role when consumed as emulsifiers and bioactive compounds in food. Protein extracted from medicinal leech tissue based nanoemulsion has shown a stable and successful topical drug delivery for treating various skin disorders.

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. 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. 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. 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.

Liposomes

A liposome is lipid-based nanoparticles which is spherical-shaped vesicle composed of one or more phospholipid bilayers, similar in structure to cell membranes. 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. 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 GIT. 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. But it is susceptible to gastro-intestinal enzyme hydrolysis which limits its oral bioavailability. To overcome these restrictions, lactoferrin encapsulation in liposomes has been studied. Some investigations have been reported for the successful dermal delivery of liposomes bound protein such as superoxide dismutase, tissue growth factors and interferons.

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 has favoured the use of protein nanoparticles. They include various nanomedicine classes where drugs are conjugated to protein carriers, recombinant protein where active therapeutic is the protein itself. 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. The most commonly used animal proteins and plant proteins in the field of bioactive molecules delivery are classified as Figures 1 and 2 respectively.

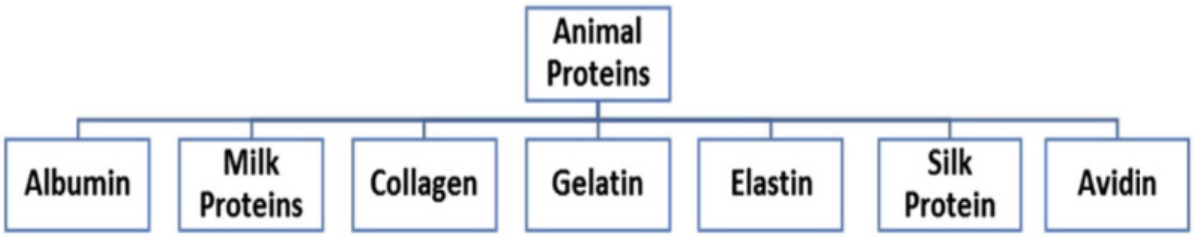

Figure 1: Animal proteins which are used in the field of bioactive molecules synthesis of nanoparticles.

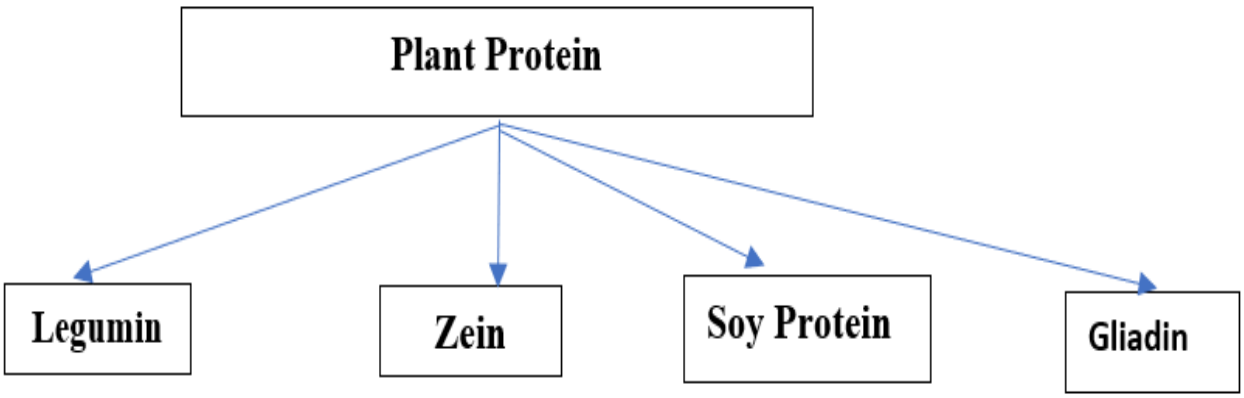

Figure 2: Plant proteins which are used in the field of bioactive molecules synthesis of nanoparticles.

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. 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.

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

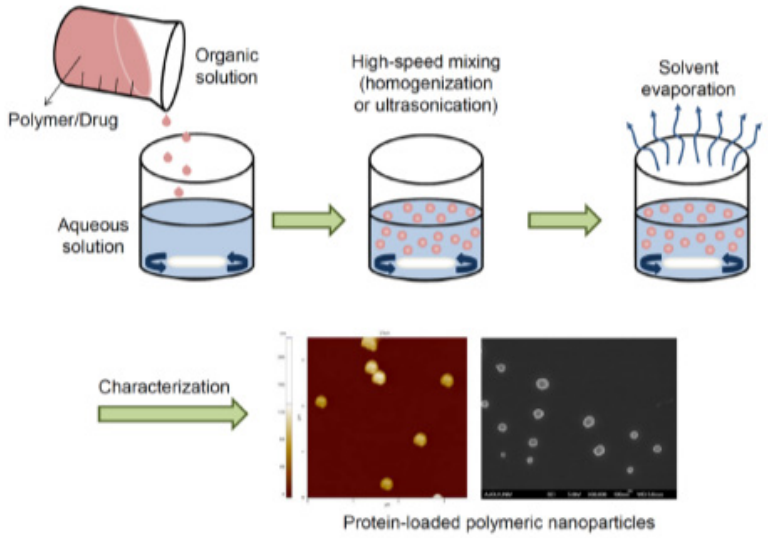

Figure 3: Schematic diagram of the conventional process for protein integrated polymeric nanoparticles.

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. 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. 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. 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 and encapsulate with proteins and antibodies.

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. It boosts drug delivery efficiently through dermal, ocular, rectal and pulmonary routes and provides greater drug stability and safety with its controlled release. Solid lipid nanoparticles composed of a solid lipid matrix, or nanostructured lipid carriers composed of mixture of liquid and solid lipids as a matrix. 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. Two main ways 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™.

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. 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.

DISCUSSION AND CONCLUSION

Mucoadhesive nanocarriers for protein delivery are methylcellulose, hydroxyethyl cellulose, thiol group and carboxymethyl cellulose. 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.

Proteins are very important therapeutic molecules that are used in the treatment of various diseases. Therefore, its delivery to the biological site is must for the therapeutic action. Since these molecules are very complex in structure, large in size and high molecular weight, it is very difficult to easily transport these molecules to the site. Its unfavourable physicochemical properties such as hydrophilicity, stability and macro size have limited its use. Various nanocarriers have been developed to overcome these problems. Some of the approaches discussed in this article focused on the safe, easy and efficient delivery of the proteins and peptides of interest. The combination of technologies can be productive for solving the challenges of peptide/protein-based drug delivery in the modern era. In the near future, it would be excellent to have a safe and effective nanocarriers system that can be used for the delivery and systemic stability of different proteins and peptides.

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