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## Protein and peptide drug delivery system

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### ABSTRACT

In the last three decades therapeutic uses of peptides and proteins has risen in prominence as potential drug of future. Proteins are polymers consisting of amino acids covalently linked by peptide bonds. Peptides are small proteins composed of upto a few dozen amino acids proteins are rapidly degraded by digestive enzymes. Till recently injections (i.e., intra venous, intra muscular, subcutaneous route) remain the most common for administering these proteins and peptide drugs. The alternate routes that have been tried with varying degrees of success the oral, buccal, intranasal, pulmonary, transdermal, ocular and rectal. In this review the aim is to focus on the various approaches for delivery of peptide and protein drugs. With the discovery of insulin in 1922, identification and commercialization of potential protein and peptide drugs have been increased. Since then, research and development to improve the means of delivering protein therapeutics to patients has begun.

**Keywords:** Protein, Peptide, Pharmaceutical Approaches, Immunoglobulins

### INTRODUCTION

Proteins are chains of amino acids, each joined to it neighbor by a specific type of covalent bond. The polymerization of L- $\alpha$ -amino acids by peptide bonds from the structural frame work of proteins. The term protein is used for molecules composed of over 50 amino acids. The term peptide is used for molecules composed of less than 50 amino acids.

The chemical and structural complexities involved demand an effective delivery system in which the physicochemical and biological

properties, including molecular size, conformational stability, solubility, sensitivity to light, moisture and heat, biological half life, immunogenicity, dose requirements, susceptibility to break down in both physical and biological environments requirement for specialized mechanisms for transport across biological membranes are to be considered [1,2].

## PEPTIDE AND PROTEIN STRUCTURE

It is essential to have an idea about structure of protein and peptide. In order to overcome the various problems during developing of drug delivery system. Proteins are large molecules with complex structure. The peptide chains in peptides and proteins are seldom linear and adapt a variety of specific folded three-dimensional patterns and conformations. All peptides and proteins are polymers of amino acids connected to amide linkages referred to as peptide bonds [3].

- Primary structure: Denotes the number and specific sequence of amino acids.
- Secondary structure: Arrangement of individual amino acids along the polypeptide backbone.
- Tertiary structure: Three-dimensional arrangement of a single protein molecule
- Quaternary structure: Proteins that contain two or more polypeptide chains associated by non-covalent forces.

## NEED OF PROTEIN AND PEPTIDE DRUG DELIVERY SYSTEM

- The proteins and peptides are very important in biological cells [4]
- Lack of proteins and peptides causes diseases like diabetes mellitus.
- Diabetes mellitus is caused due to lack of protein called "INSULIN" [5]
- Now a day's R-DNA technology and hybridoma techniques also used in protein and peptide-based pharmaceuticals [6].

## ADVANTAGES OF PROTEIN AND PEPTIDE DRUG DELIVERY SYSTEM

- Erythropoietin is mainly used for production of RBC [7].
- Tissue plasminogen activator is used for heart attack, stroke [8].
- Oxytocin maintains labor pain [9].
- Bradykinin increases the peripheral circulation [10].
- Somatostatin decrease gastric bleeding in gastric ulcer [11].
- Gonadotropin induces ovulation [12].

- Insulin maintains blood sugar level [13].

## FUNCTIONS OF PROTEIN AND PEPTIDE DRUG DELIVERY SYSTEM

- Transport and storage of small molecules and biological molecules [14].
- Coordinated motion via muscle contraction [15].
- The mechanical support from fibrous protein [16].
- Generation and transmission of nerve impulses [17].
- Enzymatic catalysis in biochemical reactions [18]
- The immune protection through antibodies [19]
- The control of growth and differentiation via hormones [20]

## PROPERTIES OF PROTEINS AND PEPTIDES

The proteins are the most abundant biological and organic molecule they are soluble in water and it can be formed a colloidal solution with water. Protein and peptides are the physicochemically and metabolically stable system. In case of oral administration in protein and peptide drug delivery system several properties can affect the rate of absorption of protein and peptide in oral drug delivery system [21].

The properties such as absorption properties includes molecular weight and size of the particle, conformational studies, stereospecification of three dimensional arrangements in space and immunogenicity of drug molecules affected the rate of absorption of protein and peptide in oral drug delivery systems. Another one is physicochemical properties such as, solubility and Lipophilicity of drug is major criteria of absorption of drug. The aggregations and hydrogen bonding of drug in oral administrations. The physiochemical properties are the major criteria for the drug absorption in oral drug delivery systems, the drug absorption oral drug delivery system it an mainly arises two main problems are the metabolic degradation of various forms protein and peptides by interaction with the various proteolytic enzymes, and it is having less membrane penetration abilities. This all is required

for determination of various problems associated in oral administration and has to be present basic idea on the basis properties to the prevent the problems in drug administration in oral protein and peptide in oral drug delivery systems [22,23].

## PHARMACEUTICAL APPROACHES

The protein and peptides are having four approaches they has follows [24]

1. Chemical modification
2. Enzyme inhibitors
3. Penetration enhancers
4. Formulation vehicle
5. Mucoadhesive polymeric system

### Chemical Modification (Prodrug Approach)

A chemical modification of protein and peptide drugs improves their enzymatic stability and membrane permeation. It also can be used for minimizing the immunogenicity.

#### Prodrug approach includes,

Amino acid modification:-

Modification of individual amino acids by the substitution of D- amino acids with the L- amino acids can significantly alter physiological properties of proteins and peptides.

Eg:- Desmopressin and Deaminovasopressin.

Application: The Amino acid modification is important to enhance the membrane permeability and maintain the Enzymatic stability.

Hydrophobization:

The surface modification using the Lipophilicity moieties.

Eg: NOBEX INSULIN by the palmitoylations.

### Enzyme inhibitors

The whole GIT and liver tend to metabolize proteins and peptides into smaller fragments of 2-10 amino acids with the help of variety of proteolytic enzymes. So, protease inhibitors are co-administered with proteins and peptides to alter the environment for maximum enzyme stability to suppress proteolytic activity.

It is 4 major types,

Aspartic proteases (pepsin)

Cystinyl proteases (pepsin)

Serenely proteases (thrombin)

Metallo proteases (Carboxypeptidase)

## Penetration enhancers

These are the formulation components that are important to disrupt the mucosal barrier to improve the permeation of large macromolecular substance like protein and peptides. Commonly used components are:

Surfactants –Polysorbate, SLS

Chelating agents –EDTA

Fatty acids –sodium caprate.

Mucoadhesive polymers –thiomers cellular derivatives

Phospholipids-pc.

## Formulation Vehicles

The oral delivery of thermoplastic proteins or peptides can be successfully can be achieved by using various carrier systems like [25,26]

1. Dry emulsions
2. Microspheres
3. Liposome's
4. Nanoparticles

### Dry Emulsions

These are used to prevent the instabilities of the long-term storage of multiple emulsions. The novel approach at which multiple emulsion is replaced by dry emulsions. These are prepared by the spray drying, lyophilization and evaporation techniques.

### Micro spheres

These are for uniform distribution of drug in ODDS in protein peptides drug are known as Microspheres. Used for the protection of the stomach from proteolytic degradations and protection upper portion of small intestine from proteolytic degradations.

### Liposome's

Liposome's are the small microscopic vesicles in which aqueous volume is entirely enclosed but the membrane composed lipid molecules.

### Nanoparticles

These are nano sized colloidal structure having size is 10- 1000nm. The particles in nano metric sized range of the particles are absorbed by the intact by the intestinal epithelium and they are the less prone towards the enzyme degradations. The particle size and surface charges are the influencing the uptake of nano particle system in GI tract.

## MUCO ADHESIVE POLYMERIC SYSTEMS

These systems prevent the pre-systemic metabolism of the therapeutic proteins and peptides and increase the residence time of this drug delivery systems at the site of action.

Eg : Thiomers, polyacrylic acid derivatives and cellulose derivatives.

## INCORPORATION INTO DRUG DELIVERY MATRIX

The drug incorporate in the protein and peptide drug delivery system undergoes three methods [29-34]

- ✓ Emulsification
- ✓ Extrusion and spray drying
- ✓ Polymerization

### Emulsification

In this process water soluble drugs are first dissolved in the aqueous (water solution) and it is soluble in organic solvent. The two solutions are mixed with the appropriate proportion to produce W/O emulsion. This prepared primary emulsion is emulsified into aqueous solution containing emulsifier to produce w/o/w emulsion. Finally, the organic solvent is mainly removed from emulsion by evaporation of solvent under reduced pressure by the filtration and increasing the temperature.

### Extrusion and Spray Drying

The extrusion and spraying are employed to from microspheres and the core material, incorporated as solution and the particulate is mainly ejected from the orifice of fine tubes, syringe to form micro droplets. The size of droplet is mainly depends upon the properties of liquid (melt, solution and suspension) and orifice diameter to jet velocity.

### Polymerization

In this hydro gel having a polymeric drug delivery system preparation by the mixing of monomer with the drug an initiator and a cross linking agents. The intravascular delivery of the protein via hydro system that is photo polymerized in situ on the inner surface of blood vessel. The  $\gamma$ -radiation are producing deleterious effect on integrity of protein molecules one of the drawbacks of protein and peptide drug delivery systems.

## STABILITY ASPECTS

In stability of protein and peptide is determined by the protein degradations pathways in this drug delivery system under two pathways of degradation of protein and peptide molecules:

### They have followed

- Physical degradation pathways
- Chemical degradation pathways

### Physical Degradation Pathways

The native structure of the protein is changed by modifications in to the higher order structures of proteins i.e secondary, tertiary.

### Chemical Degradation Pathways

The native structure of the protein is changed by modifications in to the primary structure.

## APPLICATIONS

- CVS acting drugs protein and peptides (angiotensin 2 antagonist, Bradykinin, Captopril) is important for the lowering blood pressure and improving and improving peripheral circulation for heart failure management [35].
- CNS (cholecystokinin, B- endorphin) is important for the suppressing appetite and relieving pain.
- GI- active protein and peptides (gastrin antagonist, pancreatic enzymes) is important for the reducing the secretion of gastric acid and it is important for digestive supplement [38].
- Immunomodulation of the protein and peptides (brusin, cyclosporine, and interferon) is important for selective B- cell differencing hormone inhibits functions of T- lymphocyte enhancing activity of killer cells.
- Metabolism modulating protein and peptides (insulin vasopressin) is important for treating diabetes mellitus and treating diabetes insipidus.

## RECENT ADVANCES

### PEGylation

- ✓ PEG is a non-toxic hydrophilic FDA approved and changed polymer

- ✓ Increase in vivo half life
- ✓ Increases protease resistance
- ✓ Increases stability

### Depo-foam technology

## CONCLUSION

The scientific community has reached a new stage in the understanding of the properties of peptides and protein and in the manufacturing of these therapeutic agents. The peptide and protein drugs are the main stay in the therapy and diagnosis

of a diseases. Delivering proteins and peptides by the oral route is extremely challenging the very nature of digestive system is desired to break down these polypeptides into amino acids prior to absorption. The low bio ability of drugs remain to be an active area of research. The addition challenge for the pharmaceutical scientists is designing and developing of drug delivery systems they can achieve three major objectives, viz, pulsatile or multiple rate delivery self-regulated mechanism and site specific or targeted delivery.

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