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Polypeptide Drug Delivery System

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Abstract:

Polypeptide drug delivery system is one of the most important novel drug delivery techniques. Development of this novel system is approached in various way.
At present Polypepide drug delivery system is broadly used, because to reduce the adverse effect , to reduce cost of the treatment, and to achieve better therapeutic effect. There are many peptides that have been used broadly .for e.g. Syntocinon is a peptide administered by I.M./ I.V. route used for labour induction, Pitressin is used for post operative abdominal distension. Polypeptide drugs are administered by oral route, transdermal route, nasal, pulmonary and rectal.
But polypeptide drugs having some disadvantages i.e. low PH, enzymatic degradation, lower bioavailability. Peptide bonds (RNH-CO-R) are susceptible to hydrolysis and degradation of peptides associated with covalent bond. (polypeptide and drugs are conjugates with covalent bond) . Various approaches have been developed to overcome these problem regarding polypeptide drugs. And to improve therapeutic efficacy i.e. co administration of enzyme inhibitors and administration of prodrug that is converted to therapeutic active agents.
In modern study various drug delivery system has been developed for e.g. mucoadhesive delivery of peptide.In addition peptide mediated nano drug delivery systems for tumor targeting will play more important role in cancer therapy.

1. Introduction :

In modern days Polypeptide drug delivery system is broadly applied. Polypeptide drug is composed of the conjugation of polypeptide and drug by covalent bond, and it binds with polymeric receptor, then drug is delivered to the target site. Polypeptide drug delivery system is highly used in case of drug resistant, in substituted of chemotherapeutic agents, control release drug delivery (sustained release) . It is also suitable for elucidating the activity of unknown polypeptides with in cell. It provides medicaments and methods for delivery of biologically active polypeptides. Polypeptide also includes peptdomimetics such as polypeptoids and semi polypeptoids which are peptide analogs, which having more stability under physiological conditions. The Polypeptide drug delivery system based on polymer because the conjugation of polymer-peptide enhances the permeability of drug through tissue and other organs. Most useful Polymer is HPMA co polymer.

Polypeptide

Peptide is short polymer formed the linking in a defined order of a alpha amino acids. The link between one amino acid residue and the next is known as amide bond or a peptide bond.

Classifications of Peptides

♣ **Ribosomal Peptide :** Ribosomal Peptide synthesized of mRNA, they are often subjected to proteolysis to generate the mature form. These function typically in higher organism as hormones, some organism produce peptide as antibiotics, such as microcins.

♣ **Non Ribosomal Peptides :** These peptides are assembled by enzymes that are specific to each peptide, rather than the most common peptide is gluthione. Which is component of the antioxidant defences of more aerobic organism. This peptide in plant & fungi are synthesized by modular enzyme complex called non ribosomal peptide synthesis.

Peptide in Molecular Biology

Most important is that peptide allow the creation of peptide antibodies in animals without the need of purify the protein . This involves synthesizing antigenic peptide of sections of the protein. Peptides are recently used in the study of protein structure and function. Synthetic peptides used as probes to see where protein peptide interaction occurs. Inhibitory peptides are also used in clinical research to examine the effects of the inhibition of cancer proteins and other cases.

Peptide families in Humans

All Of the human peptides are synthesized by cells as longer proppeptides or Proproteins . They are release in to the blood stream, where they performs their signaling functions. Various humans peptides are discussed below-

♠ Opioid peptides : For e.g. a) POMC peptide. b) enkephalin
♠ Cacitonin peptides : For e.g. a) Calcitonin b) Amylin
♠ Pancreatic Polypeptide Related Peptide For e.g. a) NPY peptide b) PYY peptide c) HPP peptide
♠ Vasoactive Intestinal Peptide For e.g. a) Secretin b) glucagons

Various Types of Peptides

- Polypeptide – This peptides are consists ingle linear chain of amino acids
- Oligopeptide – It Consists of 30-50 amino acids
- Nona peptide - The peptide that is active in association with neural tissue.

Primary Structure of Polypeptide

The Primary structure is equivalent to specifying the sequence of its monomeric subunits, e.g.- the nucleotide or peptide sequence.

Peptide Bond	Average length	Single Bond	Average length	Hydrogen Bond	Average (± 30)
Cα – C	153 pm	C – C	154 pm	O-H---O-H	280 pm
C – N	133 pm	C – N	148 pm	N-H---O=C	290 pm
N – Cα	146 pm	C – O	143 pm	O-H---O=C	280 pm

Polypeptides are unbranched polymer so, their primary structure can be composed of sequence of amino acids along their backbone. Proteins can become cross linked in most commonly disulfide bonds. The chiral centre of a polypeptide chain can undergo racemization. In particular the L – amino acids normally found in protein , can spontaneously isomerizes at the C – alpha atom to form D – amino acids which can not be cleaved by proteases.

N – Terminal amino group of the polypeptide can be modified co valently. For e.g

1.1 **Acetylation :** -C(=O)-CH3 ⇒ N Terminal group changing to acetyl group.

1.2 **Formylation** : -C(=O)H ⇒ N Terminal group blocked by formyl group.

1.3 **Pyroglutamate** : N- Terminal group changing to form cyclic pyroglutamate group.

1.4 **Myristoylation :** -C(=O)-(CH2)-CH3 ⇒ It is similar to acetylation.

1.5 Amidation : Most important example of this glycosyl phosphatidylatinositol.

Development of Primary Polypeptide Structure

Most important development of primary structure is peptide cleavage. Proteins are often synthesized in an inactive precursor from typically from an N-Terminal or C- Terminal segment blocks the active site of the protein inhibiting its function. The protein is activated by cleaving of the inhibitory peptide.

Secondary Polypeptide Structure

Amino acids are arranged in this structure and structure contains H – bonds. Primary & crucial function of H – bonds are to stabilze the folding pattern of the structure. There are multiple secondary structure but α- helix and β- pleated sheets are most stable structure. The α- helix is clockwise directional structure and β- pleated sheets are anti parallel structure.

Tertiary Polypeptide Structure

It is the three primary dimensional structures. This structure contains disulfide bonds. Disulfide bonds are created between the chains of cysteine. Two thiol (-SH) groups oxidizes to form disulfide bonds (S- S). But the disulfide bonds are rare in cytosine

Quaternary Polypeptide Structure

This structure consists of multiple monomer subunits. The polypeptide having quaternary structure is higher molecular weight. The Hemoglobin consists of quaternary structure. When this structure is arranged by similar type's monomer subunits, it is called Homotetramer. And when it is arranged by different types of monomer subunit, then it is referred to Heterotetramer (For e.g. Hemoglobin).

Polymer

The polypeptide drug delivery system based on polymer, polymer- polypeptide conjugation enhances the permeability of drug through tissue..

A Polymer is large molecular composed of repeating structural units connected by bonds. Well known example of polymer is Polyethylene, DNA and Protein. The structure of polymer has a strong influence on the properties of polymer. For e.g. a linear chain polymer may be soluble or insoluble in water depending on whether it composed of polar monomers (e.g. ethylene oxide) or non polar monomer (e.g. styrene).The branching of polymer chains affects the bulk properties of polymers. Long chain branches may increase polymer strength, toughness due to an enlargement and attachment. Short chains on other hand may reduce polymer strength due to disruption.

Classes of Polymer

Polymer are classified into four groups

- ♠Natural Polymer: For e.g. Shellac and amber
- ♠Biopolymer: For e.g. Protein and nucleic acid. These play an important role in biological processes.
- ♠Synthetic Polymer: Bakelite, neoprene, PVC etc.
- ♠Miscellaneous Polymer: For e.g. Cellulose.

Drug Delivery

Drug delivery is the method or process of administered a pharmaceutical compound to achieve a therapeutic effect in humans or animals. Drug delivery technology is parent protected formulation technologies that modify drug release profile , absorption, distribution, metabolism and excretion for the benefit of improving product efficacy and safety.

Most important common methods of delivery include the preferred non invasive oral, topical, transmucosal, (nasal, buccal, vaginal, ocular, and rectal) and inhalation routes. Many medication i.e. peptide, protein, vaccine in generally may not be delivered using these routes. Because they might be susceptible to enzymatic degradation or can not be absorbed into the systemic circulation efficiently, due to molecular size and changes tissue to be therapeutically effective. For this reason many protein peptide drugs to be delivered by injection. For e.g. immunization are based on the delivery of protein drugs. Current efforts in the area of drug delivery include the development target delivery, in which the drug is only active in the target area of the body (for e.g. cancerous tissue).

Amylin

Amylin is an islet amyloid polypeptide, binds with calcitonic receptor and posses effects. Amylin is 37 residue peptide hormone secreted by pancreatic β- cell. It is found in pancreatic islets of patient suffering diabetes mellitus. It carries an important role as part of the endocrine pancreas and contributes to glycemic control. Amylin is an inhibitor of appearance of nutrient (especially glucose)

It posses synergistic action with insulin. Other important roles are slowing of gastric emptying and inhibition of digestive secretion (gastric acid, pancreatic enzymes, and bile ejection).Rodent. One important thing is rodent amylin is believed for anorectic action.

The structure of amylin is a amino acid sequence of with disulfide bonds between cystenine residue two and seven.

m-RNA Display

In ribosomal display, the translated proteins remains conjugated to the ribosome. In mRNA display, mRNA first translated and then covalently bonded to the protein that associated with their mRNA via puromycin linkage. Puromycin is an adaptor molecule. The mRNA protein fusions that binds well then reverse transcribed to cDNA.

The main concept is to translate a library of mRNA molecules with stoichometric quantity of ribosome. The release of the polypeptide from the ribosome is catalyzed by the release factor, the mRNA can only released from the ribosome after newly synthesized protein and the tRNA have already dissociated and this is caused by the ribosome recycling factor.

mRNA display technology provides accessible coding information for each peptide/protein display .It occurs by combining a pool of mRNA linked to their translated polypeptide products, through a puromycin DNA linker

Application of mRNA display

Artificial evolution of high affinity diagnostic mRNA display has potential for rapid artificial evolution of high affinity diagnostic and therapeutic antibodies. They increase proteolytic stability of peptide and improved pharmacokinetics properties. So, mRNA display technology has the potential for selecting drug like peptides for therapeutic usage resistant to proteolysis.

mRNA and ribosome display have been applied to single chain antibodies. mRNA display is used to select linear peptides that bind to protein targets.

Purpose of Polypeptide Drug delivery system

Polypeptide drug delivery systems are applied in therapeutic and diagnostic purposes. It is suitable for elucidating the activity of unknown polypeptides within the cell. These methods are utilizes for delivery of biologically active polypeptides and medicaments. By this process delivery of polypeptides intracellular is possible. These polypeptides are delivered to correct compartment of the cell. After intracellular delivery, these polypeptides are surprisingly immediately degraded intracellularly (e.g. in the lysosomes) but retain biological activity. The polypeptide may be a therapeutic antibody, an intrabody, a toxin or an enzyme.

The combination of active targeting (to specific receptor) with passive targeting that is achieved by conjugation.

HPMA copolymer

The most useful co polymer which forms conjugation with polypeptide is HPMA co polymer. This polymer is composed of two repeat units, one is N-alkyl acryl amine and other is oligopeptideside chains. HPMA---Polypeptide conjugation that achieve intracellular delivery of polypeptide. But it is well known that HPMA co polymer does not bind with bioactive polypeptide, and hence bioactive polypeptides are used as a therapeutic agent.

Intracellular delivery of protein phosphates and other polypeptides

Polymer based intracellular delivery system for protein phosphates and other polypeptides, useful for delivery of polypeptides for antitumour, anti inflammatory or immuno suppressive therapy, for treatment of genetic disorder or disease, for therapy of any conditions which requires intracellular delivery of polypeptides, and for the elucidation of the activity of unknown proteins or polypeptides.

Allergic reaction & cancer therapy most important antitumor agents used clinically acts upon metabolic pathways related to cell growth and mitotic activity.

HPMA copolymer & immunosuppressive agents' conjugation:

There are several immunosuppressive agents, and these formed polypeptide-immunosuppressive agent conjugates. In case of obtaining antibody, monoclonal antibody, these conjugations are used. In this case a dye such as FITC (which liberates fluorescein) and it is used to visualize the immunosuppressive agents.. Immunosuppressive therapy is used particularly in transplantation procedures.

Homologs Polypeptide

Homologs polypeptide consists of substantially the same amino acid sequence and biological activity as the polypeptide itself. Example of homologs is (1) deletion homologs containing less than the residues of the polypeptide, (2) substitution homologs: where one or more amino acid residues are replaced by other residues, (3) addition homologs: one or more amino acid residues are added to the polypeptide. All such homologs share the biological activity of the polypeptide. Addition or deletion of amino acids may occur at the N-terminus of the polypeptide, at the C-terminal of the polypeptide or within the sequence. Substitutions may occur any where in the sequence.

Polypeptide into polymer matrix:

Now a day's biodegradable polymer for the controlled release of biologically active agents are used. In this process hydrophobic biodegradable polymer of controlled size is a physically interacted with the protein or polypeptide. Such an interaction promotes incorporation.

Thiomer

Thiomers contain thiol group. Thiomers are mucoadhesive polymer.. These are synthesized by immunomobilization of sulfhydryl bearing ligands on a polymeric backbone. It has been recently studied about finding of polymeric excipients for macromolecular drug delivery as well as their synthesis.

Thiomer technology highly interesting for non-invasive route including oral, nasal, and vaginal route. The efficacy of thiomers has been shown in various studies. For e.g. the increased nasal uptake of human growth hormone by using a drug delivery system containing a thiomer.

Limitation of Chemotherapeutic agents, where drug delivery system used.

Chemotherapeutic treatment of neoplastic disease is often restricted due to adverse systemic toxicity and drug resistance. Resistance to cytostatic or cytotoxic agent can be based on various factors such as premature inactivation to insufficient concentration at

the target site, formation of inactivating antibodies, increase the level of p-glycoprotein that can pump the drug out of the tumor cell. So it is clear that there are various difficulties appears to achieve the anti tumor effects. But there is great demand for innovative drug delivery system that can overcome resistance in its many forms.

2. Inference

Incorporation of polypeptide and proteins into a hydrophobic biodegradable polymer to provide a stable formulation and to achieve protection and controlled release of the polypeptide or protein from the polymer.

Control release of this system achieved due to the physical interaction between the polypeptide or protein and the hydrophobic biodegradable polymer. it provides a micro spherical drug delivery systems which allows targeting of drugs or other agents to specific host tissues or cells via injection or inhalation providing high localized concentrations, sustained activity, systemic administration and treatment , thereby minimizing undesirable systemic effects of toxic drugs administered in native form. Although it enhances the permeability but it has very lower absorption in blood stream and lower bioavailability when it is applied by oral and percutaneous routes, it does not posses rapid therapeutic action.

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