Review Article

An Over View: Protien and Peptide Based Drug Delivery

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ABSTRACT

In the last three decades therapeutic peptides and proteins have 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 up to a few dozen amino acids proteins are rapidly degraded by digestive enzymes. Till recently, injections (i.e. intravenous, intramuscular or subcutaneous route) remain the most common means for administering these protein and peptide drugs. The alternate routes that have been tried with varying degrees of success are the oral, buccal, intranasal, pulmonary, transdermal, ocular and rectal. In this review, the aim is to focus on the various routes and approaches for delivery of Peptide and protein drugs.

Keywords: Proteins, Peptides, Approaches, delivery.

INTRODUCTION

Proteins are chains of amino acids, each joined to it neighbor by a specific type of covalent bond. The polymerization of L-α-amino acids by peptide bonds forms the structural framework 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[1].

The chemical and structural complexities involved demand an effective delivery system in which the physicochemical and biologic 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[2].

Peptide and Protein Structure

It is essential to have an idea about structure of protein and peptide in order to deal with various problems encountered while developing drug delivery system.

The proteins are relatively 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[3].

All peptides and proteins are polymers of amino acids connected via amide linkages referred to as peptide bonds.

- **Primary structure:** It 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

Barriers to Peptide and Protein Delivery [4, 5]

The successful delivery of peptide and protein based pharmaceuticals is primarily determined by its ability to cross the various barriers presented to it in the biological milieu. Various barriers encountered are-

- Enzymatic Barriers
- Intestinal Epithelial Barriers
- Capillary Endothelial Barrier
- Blood Brain barrier (BBB)

DELIVERY OF PEPTIDE AND PROTEIN DRUGS

Different routes include

1. Oral route
2. Buccal route
3. Nasal route
4. Transdermal route
5. Pulmonary route
6. Rectal route
7. Parenteral route

ORAL ROUTE[6-13]

Oral route is the most popular route of delivery from the patient's point of view. Main advantages of this route are convenience, acceptability and high patient compliance. The main barriers to successful oral delivery of protein and peptides are similar to that of traditional drug candidates, but these are more pronounced in the case of peptide/protein moieties.

The main barriers to effective oral delivery are-

- Poor intrinsic permeability of peptides/proteins across biological membranes.

- Susceptibility to enzymatic attack by intestinal proteases and peptidases.
- Rapid post-absorptive clearance.
- Physical instability like aggregation and adsorption.

Various approaches that are developed for oral delivery of proteins and peptide drugs: Modification by chemical synthesis of prodrugs and analogues

Preparation of prodrugs and analogues of natural peptides/proteins is a rational approach toward achieving their improved delivery. This strategy of altering the peptide/protein structure by reversible (prodrug) or irreversible (analogue) chemical modification is aimed to transiently modify physicochemical properties of drugs. This modification assists in manipulating the pharmacokinetic parameters; improve the therapeutic value of the parent drug by facilitating membrane permeation and providing stability against degradation**.**

Enzyme inhibitor

Various enzyme inhibitors have been employed to achieve successful delivery of peptide and protein based drugs.

Examples: Metalloprotease inhibited by EDTA, Enzyme aminopeptidases are inhibited by Bestain & Bacitracin, Enzyme metalloendoproteases inhibited by Phosphoramidon.

This approach has been used successfully for the delivery of insulin and vasopressin.

Insulin with enzyme inhibitor (Aprotinin, bacitracin, betatin) which result in significance reduction in insulin digestion and improve in its intestinal absorption profile

Use of Penetration Enhancers

Peptide/protein drug moieties, due to their molecular size, often require penetration enhancers to achieve therapeutically significant levels of luminal absorption.

Mechanism of absorption of protein and peptide drug is via Trans cellular & Para cellular route.

Carrier system

This strategy is particularly applicable in the case of poorly absorbed peptides/proteins, which are unstable in the Gastro intestinal (GI) lumen and their targeting to a specific tissue or organ is to be affected. The proper designing of the delivery system not only protects the drug from gastrointestinal degrading components in the physical environment of the formulation prior to absorption, but also localized the drug at or near the cellular membrane to maximize the driving force for passive permeation.

Various strategies employed are

Lipid carriers and emulsions

The most common type of lipid vesicles is liposomes. Since liposomes comprises of bilayers with an aqueous core, both lipid soluble and water soluble drugs can be encapsulated. Drug denaturation during encapsulation is minimized as they are formed under mild conditions. Solid lipid nanospheres and fat emulsions can also be used.

- Lipid molecules can form other type of particulates like immune stimulating complexes (ISCOM) and cochleates. ISCOMs are three dimensional cages with a diameter of 30nm to 70nm and can be formed by mixing lipids, cholesterol and saponin (Quil A). The potent immuno adjuvant properties of Quil A render ISCOMs suitable for oral delivery of antigens.

- Cochleates are phospholipids-calicum precipitates and have a typical structure of a large continuous solid lipid bilayer sheet rolled up into a spiral. The calcium ions keep the cochleates in their rolled up forms. On removing calcium ions with chelating agents the cochleates unroll and form large liposomes.

Emulsomes

Emulsomes are colloidal drug carrier units. It is typically a lipoidal drug delivery vehicle and could be prepared using relatively higher concentration of lecithin (5-10%). The interesting feature of the system is that unlike oil phase of an emulsion (o/w), the internal phase in the case of emulsomes remains to be in solid or quasi-solid state at ambient temperatures.

- Insulin (w/o/w oil being palmitic acid in octyl-Decyl triglyceride) and the internal phase contain macromolecule (protein /peptide drug) for oral administration. This system holds promise for its effective utilization in oral administration of protein /peptide.

Particulate Carriers

The particulates employed as delivery vehicles can be replicating and non-replicating in nature. The replicating systems comprise of attenuated or genetically modified strains of viruses and bacteria, which continue to propagate in vivo after administration, e.g. genetically engineered Vaccine virus and attenuated strains of Salmonella. The non-replicating particulate systems are polymeric particles and lipid containing particles. They encapsulate the drugs within the particles and thereby lend a protective cover to them in the hostile GI environment.

Bioadhesive Systems

Carbopol and carbophil are reported to interact nonspecifically with the mucus layer over the intestinal epithelial cells. Bioadhesive systems, by virtue of their mucoadheisve properties, intensify the contact between dosage form and the intestinal mucosa and thereby assist the drug to exert its effects at locally high concentrations within a restricted area. Due to increased contact to the

absorbing mucosa a steep concentration is maintained and this lead to decrease in the diffusional path length and increase in the absorption and local delivery of drug. This technique used to target the drug action in colon.

Ex: Vasopressin Hydroxy propyl methacrylate nanoparticle cross linked by divinyl glycol *in vivo* absorption through rat intestine is increased.

Combination strategies

Combining two or more strategies that can act together to counter the barriers can be beneficial. *Eudragit L 100* insulin microspheres containing protease inhibitors (aprotinin), Bowman-Birk inhibitors (BBI), chymostatin (CS), and trypsin inhibitor (TI) were designed. The enteric polymer coating protected insulin from trypsinic and/or chymotrypsinic degradation.

Competitive Oral delivery Technology

Peptide transport system

Aspecific carrier system, the intestinal peptide transporter or Dipeptide transporter, is reported to exit for the uptake of dipeptide from intestine.

This isa sodium independent mechanism and is responsible for acquiring nutrient. Transport of antibiotic like amino cephalosporin is known to occur through this transport.

Vitamin B_{12} Coated Nanoparticles

Vitamin B_{12} transport system has limited capacity. VB_{12} linkage is itself does not offer protection against proteolysis in the stomach and small intestine.

An approach to counter these problems is to employ nanoparticle as carrier for drug this could amplify the uptake system 10,000 to 100000000 fold and the drug moiety is protected in gastrointestinal milieus. Another benefit could be that the peptide/protein moiety to be delivered need not be linked to the VB_{12} directly. This would potential benefit in case of peptidal molecule like hirudine and vasopressin.

Uptake and transport of VB_{12}-coated nanoparticle performed by Caco-2 cell have demonstrated a 2-4 fold enhancement in uptake and transcytosis of nanoparticle across the cells.

BUCCAL ROUTE [14-17]

Buccal membrane has numerous elastic fibers in the dermis, which is another barrier for diffusion of drug across the buccal membrane.

The barriers for efficient drug absorption are:

- Mucus layer covering the oral epithelium.
- Epithelial barriers.
- Peptidases in the saliva and the mucus layer and microbial flora.

The buccal peptide absorption is assumed to be via passive absorption mechanism. The various parameters that influence the extent of buccal peptide absorption are molecular weight, polarity, conformation, dissociation and enzymatic and chemical stability.

The conventional means include aqueous solutions, buccal or sublingual tablets and capsules. However, the inherent problem with these dosage forms is the risk of drug loss by accidental swallowing or by the salivary washout. They do not allow drinking and patient at times is even a handicap for speaking. Administration time is limited with these formulations and thus controlled release cannot be achieved. To overcome these drawbacks self-adhesive systems have been designed which are capable of being in intimate contact with the mucosa, viz. buccal, sublingual or gingival. The various adhesive polymers include water soluble and insoluble hydrocolloid polymers from both the ionic and the nonionic types. Some of the polymers are sodium carboxy methyl cellulose, hydroxyl propylmethyl cellulose, polyvinyl pyrrolidone, acacia, calcium carbophil, gelatin, and polyethylene glycol.

The various strategies employed for Buccal Delivery are

- Adhesive tablets
- Adhesive gels
- Adhesive patches
- Absorption promoters

Adhesive Tablets

Adhesive tablets for buccal administration were designed as eroding hydrocolloid/filler tablets. Adhesive tablets of nitroglycerine based on hydroxypropylcellulose were designed. In stark contrast to conventional tablets, these adhesive tablets allow speaking and drinking without any major discomfort.

Adhesive Gels

Viscous adhesive gels have been designed for local therapy using polyacrylic acid and polymethacrylate as gel forming polymers. Gels are reported to prolong residence time on the oral mucosa to a significant level. This not only improves absorption but also allows for sustained release of the active principle.

Adhesive Patches

In adhesive patches, the adhesive polymer may act as the drug carrier itself, and as an adhesive link between a drug loaded layer and the mucosa. Alternatively, a drug containing disk may be fixed to the mucosa by using a self-adhesive shield. In this approach drug loss to the saliva is decreased and the drug action and the drug effect of additives are confined to the site of application by creating a local microenvironment.

Absorption promoters

To augment the efficiency of buccal peptide administration some absorption promoters have been tried. These include sodium lauryl sulphate, sodium

myristate, bile acids, sodium glycocholate, sodium 5-methoxysalicylate and citric acid.

NASAL ROUTE [18-22]

Generally, the intranasal route is suited for the intermittent delivery of highly potent peptide/protein drugs having low molecular weight. Peptidal drug moieties like calcitonin, ACTH, insulin and interferon are reported to have appreciable absorption through nasal mucosa. Nasal route is chiefly use to delivery of protein drug. For achieving a systemic effect, the nasal route is the most efficient one after the parenteral route.

Barriers to systemic absorption through nasal route

- Extent of absorption varies with the mucus secretion and mucus turnover.
- Peptidases and proteases present in the mucus or associated with nasal membrane serve as enzymatic barrier in protein/peptide absorption.
- Alteration in absorption profile in diseased conditions like allergic condition and chronic rhinitis and upper respiratory tract infections.
- Penetration enhancers and preservatives may damage mucosal cell membrane and may even be ciliotoxic.

Types of dosage form

- Nasal spray
- Nasal drops
- Aerosol

Various approaches for Nasal Delivery of peptide/protein drugs are

Viscosity modification

The clearance time from the nasal cavity can be delayed by using solutions with higher viscosity. For example the half time of clearance could be increased significantly with 0.6 % of hydroxypropyl methylcellulose.

pH Modification

Peptides and proteins usually exhibit the lowest solubility at their isoelectric point. Thus, by adjusting the pH farther away from the isoelectric point of a particular peptide, its solubility can be increased. However satisfactory nasal absorption of insulin was observed with sodium deoxycholate, that insulin is capable of crossing the nasal membrane in an acidic medium.

Dissociation of Aggregation

Proteins are likely to form higher-order aggregates in solution. For instance, at pH 7.0, insulin exists in solution chiefly as hexameric aggregates. Insulin fails to cross the nasal membrane. Sodium deoxylcholate disrupts the formation of insulin hexamers and with sodium deoxycholate disrupts of the formation of insulin hexamer or dissociation of insulin hexamer to dimer or monomer. It has been demonstrated higher order aggregates and dissociation of insulin hexamers to dimers and monomers is responsible for better transport of insulin across the nasal epithelium. Dissociation of insulin hexamer responsible for better transport of insulin across nasal epithelium.

Reverse Micelle Formation

Bile salts are known to promote the Trans membrane movement of endogenous and exogenous lipids, and other polar substances within the G.I tract by the virtue of their ability to affect the micellar properties of bio membranes.

Permeation enhancer and enzyme inhibitor

Penetration enhancers like bile salts, surface active agents and chelating agents are reported to increase nasal absorption of peptides/proteins. They increase the fluidity of the lipid bilayer membrane and open up aqueous pores as a result of calcium ion chelation. Peptidase inhibitors enhance the absorption by suppressing peptidase activity in both the mucus and mucosal cells.

Bile salt act as both by surfactant (permeation enhancer) and by inhibiting proteolytic enzyme and thereby enhancing the nasal absorption of insulin. Problem with permeation enhancer is that damages the nasal mucosa.

Ex: sodium taurodihydrofusidate serve excellent nasal absorption enhancer of insulin and nontoxic to systemic circulation and locally.

Increase nasal blood flow

With an increase in local nasal blood flow an enhancement in nasal peptide absorption has been reported. This occurs due to concentration gradient of peptide passive diffusion. Vasoactive agents, which are known to enhance nasal blood flow, include histamine, prostaglandin E1 and beta-adrenergic agonist.

Drug Delivery Design

Different nasal delivery systems like drops, sprays and inhalers have variable results in terms of intensity, duration of effect. Nasal drops produce far greater pathologic changes and faster clearance than the nasal sprays and inhalers. Metered dose aerosol and metered dose pump can achieve accurate dose dispensation and good distribution in the nasal cavity.

TRANSDERMAL ROUTE [23]

Advantages of Transdermal Route for peptide/protein Delivery are:

- Better and improved patient compliance
- Elimination of hepatic first pass phenomenon
- Controlled administration is possible and thereby avoidance of toxic effects. Also drugs with shorter half-life can be administered

- Administration of drugs with low therapeutic index is possible.

Limitations of Transdermal Route for peptide/protein Delivery are:

- A low rate of permeation for most protein drugs due to their large molecular weight and hydrophilicity and lipophilic nature of the stratum corneum
- High intra and inter patient variability

Various approaches for Transdermal delivery Route of peptidal drugs are:

- Iontophoresis
- Phonophoresis
- Penetration enhancers
- Prodrugs

Iontophoresis

Iontophoresis is a method that induces migration of ions or charged molecules when an electric current is allowed to flow through an electrolyte medium. To undergo Iontophoresis protein/and peptide molecules must carry charge. To achieve this pH and ionic strength of solution are controlled. Protein/and peptide (charged molecules) are repelled by the same charge on electrode and penetrate through the skin under the influence of electric current. The two electrodes are placed on the stratum corneum, one of the electrode drug is loaded (reservoir electrode) and current is applied which increased the permeability of skin and drug molecule flow through epidermis →→→ dermis→ papillary layer →→ subdermal tissue→→blood circulation.

Example: Insulin, TRH, Vasopressin, Leuprolide are successfully delivered by this technique.

Phonophoresis

In this method, ultrasound is applied via a coupling contact agent to the skin. The drug absorption is enhanced via thermal effect of ultrasonic waves and subsequent temporary alterations in the physical structure of the skin. It may be presumably due to fluidization of bio membrane.

Example: Insulin and Erythropoietin.

Penetration enhancers

The impervious nature of the stratum corneum is a major barrier to achieve good drug flux through the skin. A popular solution to this problem is incorporation of penetration enhancers into transdermal products. Penetration enhancers have the properties of reversibly reducing the barrier resistance of the horny layer and thereby increasing the amount of drug reaching the living tissue. Oleic acid, dimethylsulphoxide, surfactants and azone have been used as Penetration enhancers. These agents fluidize the intracellular lipid lamellae of stratum corneum and increase the pore which helps in penetration of drug molecule.

Prodrugs

Another strategy that ensures some promising results especially with small peptides is based on prodrugs/analogues. The enzymes present in the skin selectively regenerate the active drug. Prodrug with modeled physico-chemical characteristics permeated well across the skin than drug.

Trans ferosomes

Trans ferosomes are phosphatidylcholine based supramolecular aggregates designed to be sufficiently deformable so that they can cross the intact skin barrier. These carriers contain at least one polar amphiphilic component (e.g. cholate) and thus the resultant vesicle membranes are extremely flexible in their disposition.

PULMONARY ROUTE [24-26]

Particles that reach the alveoli can be absorbed into the systemic circulation, avoiding first pass metabolism and the harsh conditions of the gut. Particle characteristics such as aerodynamic diameter can be engineered to deliver particles to different areas of the lung (Figure 1). The aerodynamic diameter d_a is derived from Stoke's Law and is defined by:

$$d_a=(\rho_p/\rho_0)^{0.5}d_g$$

Where ρ_p is the particle density, ρ_0 is standard particle density (1 g/cm^3) and d_g is the geometric diameter of the particle. The deposition of particles according to their aerodynamic diameter is presented below.

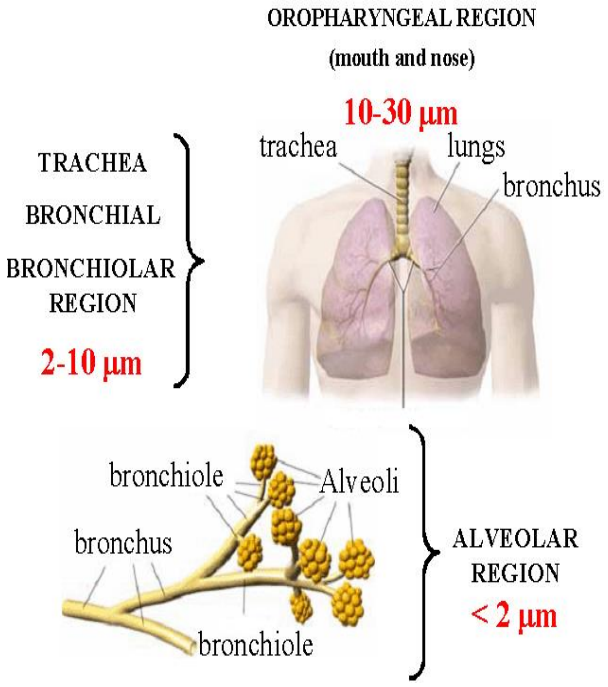

Figure 1: Deposition of drug based on particle size

Advantages of Pulmonary Route for peptide/protein Delivery are:

- Provides a direct route to the circulation.
- Reduction in dose requirement up to 50 fold and thus a cost effective option.
- Fast absorption.
- Safe route for drug entry even in patients with lung diseases.
- No triggering of immune function.
- Increased patient compliance with a minimum of discomfort and pain.

Aerosol with or without penetration enhancers, dry powders are used for Pulmonary delivery of peptide/protein drugs. Example insulin is delivered by aerosol while calcitonin is administered as dry powder.

However there are few disadvantages associated with current delivery devices for pulmonary delivery. They are:

- Most of the drugs are delivered to the upper lung, an area with low systemic absorption.
- Only a small amount of drug delivered.

Similar to intestine both simple diffusion and carrier mediated transport mechanisms operate in lungs.

The lung is, by necessity, a durable organ. An average person daily inhales air along with all the dust and all the particles floating in it. The safety issue pertaining to the pulmonary route for peptide/protein administration should be considered with regard to immunogenicity

RECTAL ROUTE [27-29]

Advantages of Rectal route are:

- It is highly vascularized.
- It avoids to a large extent the first pass or presystemic metabolism.
- It is suitable for drugs that can cause nausea/vomiting and irritate the gi mucosa on oral administration.
- In case of adverse reaction or drug overdose, the drug absorption can be interrupted.
- A large dose of drug can be administered.
- Drug can be targeted to the lymphatic system.

Various factors affecting absorption from the rectal route are:

- Amount of liquid present in the rectum.
- pH and buffer capacity of the rectal fluid.
- Surface tension and viscosity of the rectal fluid.
- Luminal pressure exerted by the rectal wall which enhances rectal absorption.
- Solubility, partition coefficient, pKa of the drug.
- Particle size and surface properties of the drug.

The conventional dosage forms including gels, solutions and suppositories have been used for peptidal delivery. Among these, gels were found to offer an optimal balance between retention at the site of administration and rate of peptide release. Most of the peptide/protein drugs require absorption enhancers to attain a reasonable level of absorption.

PARENTERAL ROUTE [5]

Parenteral mode of drug delivery has been the major route of choice for protein/peptide, owing to their poor absorption and metabolic instability when given by other alternative routes. Potent nature of these moieties demands their targeting to specific receptors to improve therapeutic index of a drug. If peptides are presented at high dosage levels, there stands the possibility of generation of immune responses and other undesirable deleterious side effects and interactions. Targeting thus protects both the drug and body from these contraindicative manifestations.

The parenteral drug delivery system includes Intravenous, intramuscular, subcutaneous, intraperitoneal, intrathecal use.

The drug carrier systems employed for defined and controlled delivery of drug through this route are particulates, soluble carriers and miscellaneous systems as discussed below:

PARTICULATES

Microspheres

These are solid spherical particles in the particle size range
of few tenths of a micrometer to several hundred micrometer, containing dispersed drug in either solution or microcrystalline from.

Advantages:

- They can be administered subcutaneously, intramuscularly or intraperitoneally and thus implantation of the delivery system is not obligatory.
- Using an appropriate technique and subsequent optimization they can be prepared economically.

Disadvantages:

- Drug release may be poorly defined.
- They may interact or form complexes with the blood components.

Nanoparticles

They are similar to microspheres but their particle size is in the nanometer range (*10-100nm*). They can be employed for the targeted delivery of peptide/protein. Owing to their small size they can even pass through the sinusoidal spaces in the bone marrow and spleen. To enhance their specificity, moieties with targeting potential like monoclonal antibodies can be attached to the nanoparticles. The typical constitutive polymers include polybutylcyano-acrylate, polymethacrylate, albumin, acrylic resins, chitosan etc.

Liposomes

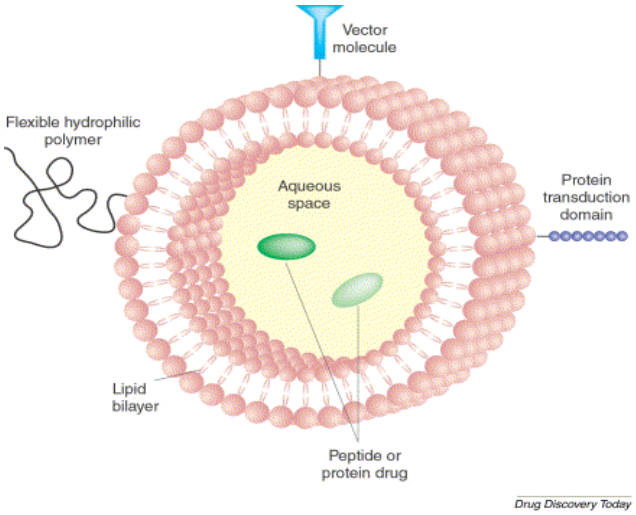

Figure 2: Structure of Liposome

- These serve as a "depot", releasing the drug slowly following enzymatic degradation
- Liposomes protect the entrapped peptides from enzymatic degradation on intravenous administration (Figure 2).
- Phosphatidylcholines (lecithin) are the main components used for the preparation of liposomes
- Liposome membranes are semi-permeable and can thus be used as controlled release systems
- Liposomes form an important means of targeting drugs directly to the liver
- Disadvantage is Phosphatidylcholines are easily susceptible to oxidation. So, surfactant vesicles called as "niosomes" are developed.

Advantages:

- Flexibility in size, shape and structure.
- Relatively non-toxic disposition.
- Ability to encapsulate both hydrophilic and lipophilic peptides/protein.

Disadvantages:

- The constituent phospholipids have an inherent tendency to interact with peptides/proteins. This can adversely affect their release kinetics and shelf life of liposomal preparation.
- Poor viability to commercial scale production of liposomes.

Emulsions

Colloid sized emulsion droplets can be utilized for parenteral delivery of peptides. This delivery system can be of great significance and utility in protecting hydrophilic or lipophilic drugs from direct contact with body fluids and also in delivering the drug over a prolonged period of time. Multiple emulsions can further prolong the release of drug.

Ex: delivery of influenza vaccine and diphtheria toxoid in emulsion.

Cellular carriers

Peptide/protein pharmaceuticals can be encapsulated in erythrocytes to achieve their prolonged release or targeting.

Advantages:

- Biodegradability
- Non immunogenic profile.
- Large circulation life (up to 4 months)
- Easy availability.
- Offers enzymatic and immunological protection to the entrapped drug.

Limitations:

- Their permeability to a large number of drugs.
- Long term storage is problematic.

SOLUBLE CARRIERS (MACROMOLECULES)

The soluble carrier systems include conjugates, chemically modified drugs and hybrid proteins. The peptide/proteins drug can be conjugated with a polymer/macromolecule. This helps to improve the stability, non-immunogenicity and achieve selective or targeted drug delivery. Generally the protein-polymer conjugates retain the pharmacologic activity of the protein, although to a lesser extent than the native protein. In most cases, the plasma half-life of the protein is increased significantly and this compensates for more than the reduction in the pharmacologic activity of the protein polymer conjugate. PEG is one of the most widely employed polymers for protein conjugation.

Macromolecule Derivative of peptide /protein drug molecule

1. Bovine serum with PEG - Reduce immunological properties

2. Asparaginase with PEG - prolong plasma half life

3. Asparaginase with DL-alanine-N-carboxyanhydride- better protease stability

MISCELLANEOUS

Various sophisticated systems have been designed and devised for controlled and Targeted delivery of peptide/proteins. It includes-

On demand systems

Externally augmented demand delivery systems are particularly beneficial in the delivery of polypeptides like insulin. The device consists of an ethylene-vinyl acetate matrix with magnetic beads or cylinders. The magnetic beads alternately compress and expand the matrix in the presence of magnetic field. On exposure to external oscillating magnetic field the drug release was increased

up to 30 times. On removal of the magnetic field, the drug release rates returned to normal.

Another approach for external modulation of release is the application of ultra sound (20 KHz for 20min) after implantation of drug in bioerodible polymer matrix. The ultrasound enhances the water penetration into the polymer matrix and thereby exposes more linkages of hydrolysis with higher degradation and release rates.

Self-regulated systems

The self-regulated systems hold distinctive potential to deliver insulin to diabetics in response to blood glucose concentration. One of the polymer based systems utilizes a cationic hydrogel polymeric membrane with immobilized glucose oxidase. As glucose diffuses into the polymer, the immobilized glucose oxidase catalyses its biochemical conversion in to gluconic acid. The pH of the microenvironment within the membrane is lowered and the amine groups in the membrane get protonated. As a result, the membranes swells and its permeability to the insulin held in the adjacent reservoir increases.

Temperature-sensitive system

Some polymers like polyacrylamide derivatives inherently have a thermo sensitive swelling behavior. This leads to temperature dependent release pattern for delivery of peptide/proteins. The temperature sensitivity of insulin permeation through a poly-N-iso propyl acrylamidebutyl-methacrylate copolymer membrane varies with the hydrophobic component of the copolymer.

Pumps

Pumps differ from other diffusion based system in that primary driving force for delivery is the pressure difference and not the concentration difference of the drug between the formulation and the surroundings. Pressurizing the drug reservoir, by osmotic action or by direct mechanical actuation, can generate this pressure difference to affect drug release. The pump can either be implantable or externally portable.

Mechanical pumps

Mechanical pumps are technically simple, rugged and can be easily manipulated to deliver peptidal drugs in several different wave form. But the prime concerns are in terms of its susceptibility to mechanical failure, high power requirement and relatively large size.

Osmotic pump

Osmotic pumps have been used extensively for delivery of a large number of peptide/proteins drugs in animals. These pumps can be implanted subcutaneously. Some of the representative examples of drugs that have been delivered in osmotic pumps include insulin, ACTH, calcitonin, LHRH, growth hormone, neurotensin and vasopressin.

Advantages

- Better flexibility and freedom for the patient.
- The desired physiological levels of the drug can be easily attained.

Disadvantages:

- Possibility of mechanical or electrical failure.
- Prohibitive cost of the device.

Now a days, controlled release micro pumps are used for delivery of insulin.

OCULAR ROUTE [30-34]

Mechanism of Drug Absorption By Ocular Route

Barrier to ocular route is;

- Tear dilution
- Lachrymal drainage
- Protein binding

The systemic delivery of peptide/protein drugs has been attempted through the ocular route. The concept behind ocular drug delivery to the systemic circulation exploits the stable dynamics of the lachrymal system that exports the drug to the nasal cavity from where considerable systemic absorption results.

Attempts have been made through this route for administering insulin. However, palpable movements and tears swiftly wash the insulin solution away. To address this problem, viscosity of the insulin solution has been increased by sodium hyaluronic acid.

The feasibility of ocular peptide/protein delivery using eye drops as a delivery system is limited. The eye drops exhibit low bioavailability, low therapeutic efficacy and short duration of activity. To address these limitations eye inserts can be employed.

Another device based on absorbable gelatin sponge has been successfully used to improve upon the above mentioned limitations. The device is fabricated by punching a disc of gelatin. The drug solution is sorbed into the disc and the wet matrices dried under vacuum. This device has been employed for insulin delivery.

The benefits of this device are-

- Relatively simple and cheap manufacturing procedure.
- On hydration the device becomes soft and pliable and hence comfortable.
- The treatment can be terminated simply by removal of the device from the eye.
- Have been tried to deliver the drug in retinopathy due to diabetic

The first approach in ocular drug delivery system is that to prolong the contact time by incorporating various polymers

Ex; PVA (polyvinyl alcohol), PVP (polyvinyl pyrrolidone), MC, CMC, HPMC.

Table 1: Marketed products (Proteins & peptides)

Drug	Brand	Route	Use
Insulin	Humulin R, NOVOLIN R	Parental	Diabetes mellitus
Captopril	Capoten	Oral	Antihypertensive
Enfurvitide	Fuzeon	Parental	Antiviral
Streptokinase	Streptase	Parental	Thromboembolism
Oxytocin	Pitocin	Parental	Induction of labour

CONCLUSION

The peptide and protein drugs are the main stay in the therapy and diagnosis of a number of diseases. The peptide and protein nature places several constraints in selecting a delivery system and the route of administration that can facilitate their safe and effective delivery. Various drug delivery systems that can protect them from proteolytic degradation, enhance permeation through the absorptive epithelia, prolong the dose retention at the site of administration are developed. The additional challenge for the pharmaceutical scientists is designing and developing of drug delivery systems that can achieve three major objectives, viz. pulsatile or multi-rate delivery, self-regulated mechanism and site-specific or targeted delivery.

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