Protein or Peptide drugs: Applications, Problems and Solutions

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It has always been an aspiration for a pharmaceutical company to create a drug that would be ideal with high specificity, high affinity, solubility and safety. These attributes backed up by low cost in manufacture, easy to formulate, simplicity to deliver and proper pharmacokinetic profile seems to be unattainable characteristic in most of the drugs because of the variety of their biophysical property (Tomlinson, 2004). Apart from these idealistic properties, there are diseases such as cancer, enzyme deficiency disorders, protein-dysfunction disorders, genetic and degenerative diseases or even in case of infectious diseases, where direct introduction of therapeutic proteins or peptides are desirable. Not all the ideal qualities required for a drug are possessed by protein drugs, but properties such as high specificity, affinity and ability to stay in target areas longer due to their size and sometimes their ability of being easily degraded are very beneficial for many ailments. These properties are some, to name a few, to make peptide/protein drugs to become popular.

If the history of use of the protein drugs is observed, first peptide drugs used were porcine or bovine insulin for diabetes since 1920. Similar applications of thyroid hormones and factor VII have been reported to be used in thyroid disorder and blood clotting factor disorders. There can be no alternative to protein drugs till date in cases such as diabetes and haemophilia where chemical drugs cannot reach into action. Supplying a proper dose of normal protein is the only option in cases where they are aberrantly produced or not produced at all. With the advancement of molecular biology since 1970s much therapeutic proteins have been developed. Haemophiliac globulins, growth hormones, erythropoietin, colony stimulating factors, interferon, natural proteins or ‘first generation recombinant proteins’, viral or bacterial proteins (as vaccines) and monoclonal antibodies have been produced (Tomlinson, 2004). There are several advantages of protein or peptide as drugs. They can directly act against any abnormality as in the case of diabetes. They have been used to elicit the immune response in the form of peptide vaccine to boost up body defence mechanism against infection. These synthetic vaccines can also be used to confer protection against carcinogens and toxicants (Greiner, 1987). When recombinant interferon αA and monoclonal antibody were used, the combination was able to overcome the antigenic heterogeneity of carcinoma cell populations and enhancing the efficacy of monoclonal antibodies to detect and treat the carcinoma lesions (Kobilka et al., 1988). Due to differences in permeability of membrane and endothelial cells, the biodistribution of peptides is different in different tissues of the body. This leads to difference in accumulation of drug delivery.
systems and this property can be exploited in site specific treatment of diseases (e.g. antibody targeting). Therefore, importances of protein drugs appear more prominently where conventional chemical therapy or any other therapies fail to work. This justifies the popularity of this family of drugs.

The use of this promising aspect of recombinant biotechnology is not out of challenges. As the proteins are normally bigger in size than normal chemical drugs, this disables them from crossing the capillaries and to distribute in extracellular fluids and also from crossing the cell membrane and distributing in intracellular fluids. The process of extravasation of macromolecules from endothelial cells into tissues, transcytosis, decreases with molecular weight to the extent that it entirely ceases at the size of 350,000Da. These poor delivery characteristics are worsen by their metabolic instability, high hydrophilicity and non-lipophilic character causing poor biomembrane passage. These properties highly influence pharmacokinetic and pharmacodynamic behaviour leading to decreased bioavailability, the fraction of drug reaching the bloodstream in an active form, less than 1-2%. (Humphrey and Ringrose, 1986). Even after they are in systemic circulation, they have short biological half-lives because of rapid metabolism and clearance from the body owing to glomerular filtration in kidneys, enzyme degradation, immune system processing, and endocytosis (Humphrey and Ringrose, 1986, Lee, 1991). Xeno-proteins used can be intrinsically immunogenic and antigenic. Mostly smaller proteins are mainly excreted by the kidneys, whereas large proteins are degraded by enzymes. Selective endocytosis or phagocytosis of lipoproteins and glycosylated proteins is performed by reticuloendothelial system (RES) (Hashida et al., 2001). Likewise, hormones and cytokines are eliminated from circulation by receptor-mediated endocytosis and intracellular processing (Kotto-Kome et al., 2004).

The increased circulatory half-life of protein drug can be achieved by PEGylating which is conjugating the protein or peptide with poly ethylene glycol (PEG) (Harris, 2003). This increases the hydrophilicity of the molecule so that it is not recognized by macrophages because of prevention of opsonisation. This method causing steric stabilization results in circulation of particles for longer time. PEGylation also reduces the immunogenicity that the protein might possess. Some PEGylated drugs commercially available are asparaginase, interferon α, tumour necrosis factor and granulocyte-colony stimulating factor (Mehwar, 2000). Steric stabilization from PEGylation has been used to create both nano particle and liposomes of peptide drugs. Example of this method is a non protein-drug named Caelyx which is a sterically stabilised liposome formulation containing Doxorubicin for the treatment of Kapsosi’s sarcoma in HIV infected patients (Judson et al., 2001). The result of phase II trial of Judson et al group’s research shows that there has been significant response of anti tumour property of the formulation.

Other general measures to bypass the degradation or decrease in bioavailability have been taken and they are presented as follows

A. Using non-parenteral route of administration: Administering the drug locally to the area without much involvement of the systemic circulation
can highly decrease the immune response from the compound and prevent it from being degraded by immune system and proteases. Non-parenteral routs are more preferable due to patient compliancy as well because, peptide drugs need to be injected in high volume for concentration to meet the active concentration. High frequency of injection of drugs cannot be preferable to the patients. Alternative routes like oral, rectal, buccal, nasal, transdermal, pulmonary, vaginal and ocular are followed to bypass the direct delivery bypassing hepatic first-pass metabolism, utilize sufficient absorption areas, and a reduced presence of proteolytic enzymes.

B. Use of stabilization techniques: These techniques involve a protein drug stabilized in a carrier material whether in entrapped form within the matrix, encapsulated in a semipermeable membrane, covalently bonded to a carrier or adsorbed to the career. Most frequently used technique for delivery via non-parenteral peptide is entrapment, encapsulation and covalent binding.

**Entrapment and Encapsulation:** This method has been extensively utilized for drug delivery. It follows two different techniques such as hydrogels and nanocapsules/microspheres, and lipid drug delivery systems like liposomes and microemulsions (Ingemann, 1986). This technique is expected to have protective effect on the enzymatic and overcome the adsorption barrier. An example of successful delivery of drugs using microencapsulated systems is nafarelin (D-[Na] (2) LHRH) which has been prepared by microencapsulation in poly (d, lactic-co-glycolic) acid (PLGA) (Kent et al., 1986). This system showed increase in half-life by seven times than that of native compound and was applicable both in parenteral as well as nasal spray with desired efficacy in animal models. Few more examples of this system are gonaderelin analogues which are leuprolide acetate in microparticles for advanced prostate cancer/breast cancer, Triptrorelin pamoate, Octreotide acetate and Lanreotide acetate.

Liposomes which are vesicles of amphiphillic material prepared in micro or nano scales are potential drug delivery system for peptide drugs. Their versatility of sizes, surface charge and lipid composition and their ability of incorporating almost any drug regardless of solubility in water make this system useful. Encapsulated insulin into liposomal carriers for pulmonary delivery (in dried powder inhalation form) showed promising effect in glycemic level in blood for long-lasting effect and with a relatively high pharmacological bioavailability (Senior, 1987).

Another method in drug delivery is the use solid lipid nanoparticles which have been successfully explored as they combine advantages of liquid lipid-based colloidal system and solid systems (Joshi et al., 2008). Solid lipid nanoparticles have been proven that they can be used in delivery of anticancer drug tamoxifen citrate (Caliceti et al., 2004). This system of drug delivery can be useful because of their slow and prolonged release capability. Different polymers, especially polysachharides such as chitosan and alginate or combination of both can be used for the preparation of nanoparticle carrier of the protein drugs.
Evaluation of N-trimethylchitosan nanoparticles for the delivery of fluorescein isothiocyanate labelled bovine serum albumin and vaccine (urease) has shown the suitability of the system as protein/vaccine carriers for oral delivery (Chen et al., (2008). This can withstand the low pH condition which has been a major hurdle of oral protein drug delivery. A remarkable achievement of this system has been made in oral delivery of insulin loaded in alginate/chitosan nanoparticles which has been shown to reduce blood glucose level to 40% in rats (Sermento et al., 2007). Method of using nanoparticles keeps potential of being used widely in oral delivery method of drugs.

Protein drugs remain a kind of attainable panacea to all the known diseases with the help of advanced recombinant technology. Difficulties of bypassing the immune response and body defence walls remains difficult but not unattainable aspect for this method to be widely applied. Several methods are in research and some of them like nanoparticle drug delivery have already shown some hints of being greatly useful. Conjugated forms of protein and chemicals have also been a huge field of research which increases the fold of efficacy of drugs that macromolecules can offer. With advancement in proper delivery system and understanding of diseases, it can be hoped that protein drugs are going to be the next generation of therapeutics.

References