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Editorial

Peptide and Protein Delivery at a Glance

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Peptide and protein drugs have found an important position in therapeutics. Recent advances in pharmaceutical biotechnology have led to an increase in the number of protein products in the market. As these therapeutic proteins and peptides are made available, it will be essential to formulate these drugs into safe and effective delivery systems.

The twenty different naturally occurring amino acids join with each other by peptide bonds and build polymers referred to peptides and proteins. Although the distinction between peptides and proteins is arbitrary, a peptide contains less than 20 amino acids, having a molecular weight less than 5000, while a protein possesses 50 or more amino acids and its molecular weight lies above this value.

The most important challenge to the formulation of peptides and proteins into effective dosage forms is to ensure their stability over their shelf lives. Physical instability (including denaturation, aggregation, precipitation and adsorption onto surfaces) and chemical instability (including oxidation, hydrolysis, deamidation, beta-elimination, racemization and disulfide exchange) may occur for a given peptide or protein, due to the presence of multiple susceptible sites. It should be noted that in most cases, more than one pathway of physical and/or chemical instability may be responsible for the degradation of peptides and proteins. Therefore, compared to the formulation of traditional dosage forms, formulation of peptide and protein drugs is very difficult and, regardless of the route of administration, product development should start with preformulation studies including physicochemical characterization, solubility determination, stability determination under various conditions, isoelectric point determination, optical pH determination and characterization of impurities. Also, choice of buffer system, pH of the vehicle, selection of an appropriate solvent system and preservation of the formulation, as well as selection of appropriate pharmaceutical excipients, are among the factors that should be considered in the formulation development of peptides and proteins, in order to prevent or minimize the various physical and chemical degradation pathways.

Although most protein pharmaceuticals are usually formulated as a solution or suspension and delivered by invasive routes such as subcutaneous injections, major efforts in both academic and industrial laboratories have been directed toward developing effective oral formulations and increasing the oral absorption of intact protein through the use of formulations that protect the macromolecule and/or enhance it's uptake into the intestinal mucosa. However, in spite of these major attempts, relatively little progress has been made. For the efficient delivery of peptides and proteins by non-parenteral route, in particular via the gastrointestinal tract, novel concepts are needed to overcome significant enzymatic and diffusion barriers. In general, the difficulties associated with developing effective oral peptides and proteins formulations are normally ascribed to a) poor intrinsic permeability across biological membranes due to the hydrophobic nature and large molecular size, b) susceptibility to enzymatic attack, c) rapid post-absorptive clearance, and d) chemical instability.

It is quite appreciated that not all peptides and proteins with therapeutic applications will need to be absorbed from the gastrointestinal tract. Those substances used exclusively in life threatening situations for a short period of time and those with rapid renal clearance or metabolism can be administered by injection, while for substances that are required prophylactically or for the control of nonvital functions, gastrointestinal absorption is most desirable. On the other hand, it is also evident that macromolecules such as proteins are absorbed from the GI tract, but only in small

quantities. To overcome this problem, a variety of permeation enhancers, including salicylates, mixed bile salts fatty acid micelles, chelators, fatty acids, surfactants and medium chain glycerides have received considerable attention in an attempt to increase the absorption of peptides. These enhancers are capable of modifying the basic barrier properties of the intestinal epithelial cell membrane. However, it has been shown that manipulation of formulation variables in order to enhance the absorption of these compounds has varying degrees of success so that the bioavailability of these products is still fairly low and unpredictable.

Two approaches for providing protection against proteolytic attacks are a) chemical modification of small peptides and b) protecting peptides or proteins in physical environment of formulation itself, prior to absorption, using microemulsions, nanoparticles and bioadhesive particles.

Due to the complex nature of peptides and proteins, self aggregation is a major concern in formulation efforts. It has been shown that the use of surfactants could maximize monomer concentration during peptide and protein release and minimize the size of complex for permeation through epithelial cell layer.

Peptides and proteins play a key role in physiological activities (e.g. reproduction, growth, etc.) and have been used for the treatment of various pathologic conditions such as diabetes mellitus, endocrine disorders, autoimmune disorders and specific metabolic abnormalities. Recent developments in the field of biotechnology, recombinant DNA technology and analytical methods for peptides and proteins are resulting in a greater availability of peptides and proteins for therapeutic use. It seems that the enzymatic degradation and poor administration of macromolecules from the gastrointestinal tract have limited the administration of peptides and proteins to the parenteral route. However, in the past few years, new advances have been achieved in the delivery of peptides and proteins via mucosal (nasal, pulmonary, rectal and ocular), transdermal and topical routes, as well as oral administration. Regardless of the route of administration, the aims of a formulator are to maintain the stability of peptides and proteins prior to their absorption and localization at or near the target site, decrease their antigenicity properties, prolong their half-life and increase their absorption through biological membranes.

The scientific community has reached a new stage in the understanding of the properties of peptides and proteins and in the manufacturing of these therapeutic agents. In the past, administration of peptides and proteins was believed to be impossible, while nowadays it is expected that the obstacles for effective delivery of therapeutic peptides and proteins will be overcome and more products would be made available to the patients.

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