

PEGylation – Successful Approach for Therapeutic Protein Conjugation

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Protein Therapeutics

Proteins including peptides as therapeutics have been expanded in recent years due to improvements in expression or synthesis of proteins and peptides that closely resemble fully human analogues over the last few decades. However, the main drawbacks associated with protein therapeutics are physicochemical instability, low solubility, proteolytic degradation, relatively short circulating half-life and immunogenicity. Several strategies have emerged as ways to improve the pharmacokinetic and pharmacodynamic properties of protein therapeutics, including manipulation of amino acid sequence to decrease immunogenicity and proteolytic cleavage, fusion or conjugation to immunoglobulins and serum albumin proteins, incorporation into microsize or nanometer delivery carriers for protection and sustained release, and conjugating to natural or synthetic polyethylene glycol (PEG), polysialic acid, and hydroxyethyl starch polymers.

PEGylation

PEGylation can be defined as the conjugation of one or more PEG molecules to proteins, peptides, non-peptide molecules or particle surface. PEGylation technology was first attempted by Davis and Abuchowskyon albumin and catalase modification in the 1970s [1,2]. Since then, PEGylation has been expanded tremendously as one of the most successful modifying strategies and a wide range of PEGylated therapeutics has been approved by the Food and Drug Administration (FDA) for parenteral or topical administration as a component of various foods, cosmetics, and drug delivery systems.

The first FDA-approved PEGylated biopharmaceutical appeared on the market in 1990, which was Adagen[®], a PEGylated form of adenosine deaminase. After that, another seven successful PEGylated proteins have been approved by the FDA, including Oncaspar[®] (Pegaspargase), PEG-Intron[®] (PEGylated IFN- α 2b), Pegasys[®] (PEGylated IFN- α 2a), Neulasta[®] (pegfilgrastm), Somavert[®] (Pegvisomant), Mircera[®] (PEGylatedepoetin- β), and Cimzia[®] (Certolizumabpegol). In addition to these already approved PEGylated biopharmaceuticals, many new products are currently under investigation and in different stages of clinical trials.

PEGylation Process

PEGs are hydrophilic, non-toxic, non-immunogenic, and relatively chemically inert polymers consisting of repetitive units of ethylene oxide. It has been approved by the FDA as “generally recognized as safe” [3]. A large number of potential PEG molecules are available in linear or branched configurations and in different molecular weights.

To couple PEGs to a protein molecule, it is necessary to activate the PEG by preparing a derivative of the PEG having a functional group at one or both termini. PEGylation of proteins can be achieved by a chemical reaction between the amino acid of protein and suitably activated PEGylation reagents. Typical reactive amino acids for proteins include lysine, cysteine, histidine, arginine, aspartic acid, glutamic acid, serine, threonine, tyrosine, N-terminal amino group and the C-terminal carboxylic acid. The most common route for PEG conjugation of proteins has been to activate the PEG with functional groups suitable for reaction with lysine and N-terminal amino acid groups. There is also an array of available chemical and enzymatic

methods for PEGylation conjugation, which offers the possibility to tailor the requirements of different proteins. Various aspects of process in the PEGylation have been considered, including attachment site on the protein, activation type of PEG reagent, and structure of linker [4].

Benefits of PEGylation

PEGylation increases the solubility of proteins because PEG has the unique property of being soluble in many different solvents, ranging from water to many organic solvents. As low solubility is a disadvantage shared by many therapeutic proteins, protein PEGylation benefits for both the formulation and administration of proteins with limited solubility at physiological pH. PEG conjugation can increase apparent size of the proteins and then reduce renal filtration and decrease clearance. Furthermore, the PEGylation, alone or in combination with targeted drug delivery systems, can also be used to alter distribution or even to increase the targeted delivery of therapeutic molecules to specific sites [4]. In addition, PEGylation alters physicochemical properties of the parent molecule in conformation, steric hindrance, electrostatic binding, and hydrophobicity [3]. The clinical use of many protein drugs is limited by the immunological response. After conjugation, PEGs can form a protective ‘shell’ around the protein and shield antigenic epitopes of the proteins from immunogenic recognition and proteolytic enzymes from degradation, which reduce immunogenicity and prolong therapeutic protein body-residence time, allowing less frequent administrations [5-7].

Overall, PEGs provide an excellent combination of properties with a highly flexible hydrophilic chain to act as a protecting polymer and are generally used in modern marketed PEGylated proteins. After PEGylation, therapeutic proteins can alter physicochemical properties, improve the pharmacodynamics, pharmacokinetic, and immunological properties of the protein to extend their potential uses.

Future Perspectives

In the future, the fields of non-protein drug such as small interfering RNA and DNA and diagnostics PEGylation can be further explored with regard to the chemistry of binding as well as the targeting of these molecules. Another area of development will be the PEGylation of cells to create new drug-delivery systems, in-body bioreactors, or nonimmunogenic cells for safer transplantations. As many years of PEGylation development have indicated the theoretical and commercial usefulness of PEGylation technology, there will be many more applications that are still to be explored.

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