

**AMPHIPHILIC DRUG-OLIGOMER
CONJUGATES WITH HYDROLYZABLE
LIPOPHILE COMPONENTS AND METHODS
FOR MAKING AND USING THE SAME**

1. INTRODUCTION

The present invention relates generally to hydrolyzable drug-oligomer conjugates, pharmaceutical compositions comprising such conjugates, and to methods for making and using such conjugates and pharmaceutical compositions.

2. BACKGROUND OF THE INVENTION

Many peptides and proteins (collectively referred to herein as "polypeptides") are potentially useful as therapeutic agents but lack an adequate method of administration.

The usefulness of polypeptides as therapeutic agents is limited by the biological barriers that must be traversed before a polypeptide can reach its specific *in vivo* target. Parenterally administered polypeptides are readily metabolized by plasma proteases. Oral administration, which is perhaps the most attractive route of administration, is even more problematic. In the stomach, orally administered polypeptides risk enzymatic proteolysis and acidic degradation. Survival in the intestine is even more unlikely due to excessive proteolysis. In the lumen, polypeptides are continuously barraged by a variety of enzymes, including gastric and pancreatic enzymes, exo- and endopeptidases, and brush border peptidases. As a result, passage of polypeptides from the lumen into the bloodstream is severely limited.

There is therefore a need in the art for means which enable parenteral and oral administration of therapeutic polypeptides.

2.1 Routes of Administration of Polypeptide Drugs

The problems associated with oral and parenteral administration of polypeptides are well known in the pharmaceutical industry. Various strategies have been used in attempts to improve oral and parenteral delivery of polypeptides.

Penetration enhancers (e.g., salicylates, lipid-bile salt-mixed micelles, glycerides, and acylcarnitines) has been investigated for improving oral administration. However, penetration enhancers frequently cause serious local toxicity problems, such as local irritation and toxicity, partial or complete abrasion of the epithelial layer, as well as tissue inflammation. Furthermore, penetration enhancers are usually co-administered with the polypeptide drug, and leakages from the dosage form are common.

Another common strategy for enhancing oral delivery is co-administration of the polypeptide drug with a protease inhibitor (e.g., aprotinin, soybean trypsin inhibitor, and amastatin). Unfortunately, protease inhibitors also inhibit the desirable effects of proteases. Accordingly, methods and compositions are needed for effectively delivering polypeptide drugs in the absence of protease inhibitors.

Attempts have also been undertaken to modify the physiochemical properties of polypeptide drugs to enhance penetration of such drugs across mucosal membranes. One such approach has been to conjugate polypeptide drugs to lipophilic molecules; however, results have suggested that simply raising lipophilicity is not sufficient to increase paracellular transport.

Other methods for stabilizing polypeptides have been described. Thus, for example, Abuchowski and Davis have disclosed various methods for derivatizing enzymes to provide water-soluble, non-immunogenic, *in vivo* stabilized products ("Soluble polymers-Enzyme adducts", *Enzymes as Drugs*, Eds. Holcenberg and Roberts, J. Wiley and Sons,

New York, N.Y., (1981)). Abuchowski and Davis disclose various ways of conjugating enzymes with polymeric materials, such as dextrans, polyvinyl pyrrolidones, glycopeptides, polyethylene glycol and polyamino acids.

The resulting conjugated polypeptides are reported to retain their biological activities and solubility in water for parenteral applications. Furthermore, U.S. Pat. No. 4,179,337 discloses that polyethylene glycol renders proteins soluble and non-immunogenic. However, these polymeric materials do not contain components which improve intestinal mucosa binding or which facilitate or enhance membrane penetration. Thus, these conjugates are not intended for oral administration.

Meisner et al., U.S. Pat. No. 4,585,754, teaches that proteins may be stabilized by conjugating them with chondroitin sulfates. Products of this combination are usually polyanionic, very hydrophilic, and lack cell penetration capability; they are usually not intended for oral administration.

Mill et al., U.S. Pat. 4,003,792, teaches that certain acidic polysaccharides, such as pectin, alginate, hyaluronic acid and carrageenan, can be coupled to proteins to produce both soluble and insoluble products. Such polysaccharides lack the capacity to improve cell penetration characteristics and are not intended for oral administration.

Other researchers have shown that polyethylene glycol linked to a protein improves stability against denaturation and enzymatic digestion. (Boccu et al. *Pharmacological Research Communication* 14, 11-120 (1982)). However, these polymers do not contain components for enhancing membrane interaction. Thus, the resulting conjugates suffer from the same problems as noted above and are not suitable for oral administration.

Conjugation of polypeptides to low molecular weight compounds (e.g., aminoethic acid, fatty acids, vitamin B12, and glycosides) has also been described (R. Igarishi et al., "Proceed. Intern. Symp. Control. Rel. Bioact. Materials, 17, 366, (1990); T. Taniguchi et al. *Ibid* 19, 104, (1992); G. J. Russel-Jones, *Ibid*, 19, 102, (1992); M. Baudys et al., *Ibid*, 19, 210, (1992)). The resulting polymers do not contain components necessary to impart both solubility and membrane affinity necessary for bioavailability following oral administration.

Encapsulation of proteinaceous drugs in an azopolymer film has also been employed as a means for enabling oral administration of polypeptide drugs (M. Saffan et al., in *Science*, 223, 1081, (1986)). The film is reported to survive digestion in the stomach but is degraded by microflora in the large intestine where the encapsulated protein is released. This approach is also known to lengthen the *in vivo* duration of action of polypeptide drug. However, the technique utilizes a physical mixture and does not facilitate the absorption of released protein across the membrane.

Similarly, liposomes have been used to stabilize polypeptide drug for oral as well as parenteral administration. A review of the use of liposomes is found in Y. W. Chien, "New Drug Delivery Systems", Marcel Dekker, New York, N.Y., 1992. Liposome-protein complexes are physical mixtures. Results of liposome-based administration are often erratic and unpredictable. Furthermore, use of liposomes can result in undesirable accumulation of the polypeptide drug in certain organs. Other disadvantages of liposome-based formulations include high cost, complex manufacturing processes requiring complex lypophilization cycles, and solvent incompatibilities.

Another approach for facilitating the oral delivery of polypeptide drugs is the use of "proteinoids" (Santiago, N.