

Claims

1. A method for improving the solubility of a physiologically active protein or peptide in an aqueous solution having a pH from 5.0 to 7.0 compared to that of the physiologically active protein or peptide which is not conjugated to an immunoglobulin Fc fragment,
wherein the method comprises conjugating the physiologically active protein or peptide to the N-terminus of an immunoglobulin Fc fragment via a non-peptidyl polymer having two ends; wherein each end of the non-peptidyl polymer is linked to the immunoglobulin Fc fragment or the physiologically active protein or peptide; and
wherein the physiologically active protein or peptide is exendin-4, glucagon, glucagon-like peptide-1 (GLP-1), glucagon-like peptide-2 (GLP-2), insulin, or oxyntomodulin.
2. The method of claim 1, wherein the immunoglobulin Fc fragment is an Fc fragment derived from IgG, IgA, IgD, IgE, or IgM.
3. The method of claim 2, wherein the immunoglobulin Fc fragment is a hybrid of domains in which each domain has a different origin derived from immunoglobulin selected from the group consisting of IgG, IgA, IgD, IgE, and IgM.
4. The method of claim 2, wherein the immunoglobulin Fc fragment is a dimer or a multimer consisting of single chain immunoglobulins of the same origin.
5. The method of claim 4, wherein the immunoglobulin Fc fragment is a human aglycosylated IgG4 Fc fragment.
6. The method of claim 1, wherein the non-peptidyl polymer is polyethylene glycol.
7. The method of claim 1, wherein the non-peptidyl polymer is selected from the group consisting of polypropylene glycol, copolymer of ethylene glycol and propylene glycol, polyoxyethylated polyol, polyvinyl alcohol, polysaccharide, dextran, polyvinyl ethyl ether, a biodegradable polymer such as polylactic acid (PLA) and polylactic-glycolic acid (PLGA), a lipid polymer, chitin, hyaluronic acid, and a combination thereof.
8. The method of claim 1, wherein the aqueous solution comprises a citric acid or acetic acid buffer solution, polysorbate as a non-ionic surfactant, mannitol as a sugar alcohol, and sodium chloride or methionine as an isotonic agent.
9. A composition for improving the solubility of a physiologically active protein or peptide in an aqueous solution having a pH from 5.0 to 7.0, wherein the composition comprises a conjugate of the physiologically active protein or peptide and an immunoglobulin Fc fragment in which the physiologically active protein or peptide is linked to the N-terminus of the immunoglobulin Fc fragment via a non-peptidyl linker having two ends as an active ingredient,

wherein the physiologically active protein or peptide is exendin-4, glucagon, glucagon-like peptide-1 (GLP-1), glucagon-like peptide-2 (GLP-2), insulin, or oxyntomodulin.

10. Use of a pegylated Fc fragment in the manufacture of a conjugate in which a physiologically active protein or peptide is conjugated to the N-terminus of an immunoglobulin Fc fragment via a non-peptidyl polymer having two ends, wherein the solubility of the physiologically active protein in an aqueous solution having a pH from 5.0 to 7.0 is improved compared to that of the physiologically active protein or peptide which is not conjugated to an immunoglobulin Fc fragment, wherein the physiologically active protein or peptide is exendin-4, glucagon, glucagon-like peptide-1 (GLP-1), glucagon-like peptide-2 (GLP-2), insulin, or oxyntomodulin.