Claims

1. An oral pharmaceutical composition comprising a therapeutic peptide or therapeutic protein of up to 100 kilodalton, a chelator of divalent cations, and an isolated recombinantly expressed Bowman-Birk inhibitor (BBI)wherein

said recombinantly expressed BBI has a nucleotide sequence sharing at least 95% identity with that set forth in SEQ ID NO: 1, or wherein said recombinantly expressed BBI has a nucleotide sequence sharing at least 97% identity with that set forth in SEQ ID NO: 1, or wherein said recombinantly expressed BBI has a nucleotide sequence sharing at least 99% identity with that set forth in SEQ ID NO: 1.

2. The oral pharmaceutical composition of claim 1, wherein said recombinantly expressed BBI has a nucleotide sequence of that set forth in SEQ ID NO: 1.

3. The oral pharmaceutical composition of claim 1, wherein said recombinantly expressed BBI is expressed in a yeast expression system, wherein said yeast expression system is *Pichia pastoris*.

4. The oral pharmaceutical composition of claim 1, wherein said formulation further comprises a trypsin inhibitor other than said BBI, wherein said trypsin inhibitor is KTI3, wherein said KTI3 has been chemically isolated and purified to at least 85% purity as measured by SDS-PAGE, or wherein said KTI3 has been purified to a protein content of greater than 95% as measured by BCA assay, or wherein said KTI3 has been recombinantly expressed.

5. The oral pharmaceutical composition of any one of claims 1-4, wherein said therapeutic protein is useful in treating a subject with a metabolic disease or disorder.

6. The oral pharmaceutical composition of any one of claims 1-4, wherein said therapeutic peptide or therapeutic protein is selected from the group consisting of insulin, influenza hemagglutinin, influenza neuraminidase, a glucagon, interferon gamma, interferon beta, interferon alpha, growth hormone, erythropoietin, GLP-1, a GLP-1 analogue, leptin, granulocyte colony stimulating factor (G-CSF), renin, growth hormone releasing factor, parathyroid hormone, thyroid stimulating hormone, follicle stimulating hormone, calcitonin, luteinizing hormone, glucagon, a clotting factor, an anti-clotting

factor, atrial natriuretic factor, surfactant protein A (SP-A), surfactant protein B (SP-B), surfactant protein C (SP-C), surfactant protein D (SP-D), a plasminogen activator, bombesin, hemopoietic growth factor (colony-stimulating factor, multiple), a tumor necrosis factor (TNF) protein, enkephalinase, RANTES (regulated on activation normally T-cell expressed and secreted), human macrophage inflammatory protein (MIP-1-alpha), serum albumin, Mullerian-inhibiting substance, relaxin, mouse gonadotropin- releasing hormone, DNase, inhibin, activin, vascular endothelial growth factor (VEGF), a neurotrophic factor, neurotrophin-3,-4,-5, or -6 (NT-3, NT-4, NT-5, or NT-6), nerve growth factor, platelet-derived growth factor (PDGF), a fibroblast growth factor, a nerve growth factor, a transforming growth factor (TGF), insulin-like growth factor-I and-II (IGF-I and IGF-II), des (1-3)-IGF-I (brain IGF-I), insulin-like growth factor binding protein 1 (IGFBP-1), IGFBP-2, IGFBP-3, IGFBP-4, IGFBP-5, IGFBP-6, a keratinocyte growth factor, an osteoinductive factor, bone morphogenetic protein (BMP)-2, BMP-4, BMP-7, a colony stimulating factor (CSF), an interleukin (IL), superoxide dismutase, decay accelerating factor, a chemokine family member, and a complement factor.

7. The oral pharmaceutical composition of claim 6, wherein said therapeutic peptide or therapeutic protein is an immunomodulatory, such as Glatiramer acetate.

8. The oral pharmaceutical composition of any one of claims 1-7, wherein said chelator is EDTA.

9. The oral pharmaceutical composition of any one of claims 1-,8 wherein said formulation is an oil-based liquid formulation.

10. The oral pharmaceutical composition of claim 9, further comprising a polyethylene glycol (PEG) ester of a monoglyceride, a diglyceride, a triglyceride, or a mixture thereof.

11. The oral pharmaceutical composition of claim 10, wherein said PEG ester is provided as a mixture of (a) a monoacylglycerol, a diacylglycerol, a triacylglycerol, or a mixture thereof; and (b) a polyethylene glycol (PEG) ester of a fatty acid.

12. The oral pharmaceutical composition of claim 11, wherein part (a) of said mixture comprises C_8-C_{18} monoacylglycerols, diacylglycerols, and triacylglycerols.

13. The oral pharmaceutical composition of claim 11, wherein part (b) of said mixture comprises PEG monoesters and diesters of a mixture of C_8-C_{18} fatty acids genetically attached polypeptide tags or a combination thereof.

14. The oral pharmaceutical composition of claim 11, wherein part (a) of said mixture comprises C_8-C_{18} monoacylglycerols, diacylglycerols, and triacylglycerols; part (b) of said mixture comprises PEG-32 monoesters and diesters of a mixture of C_8-C_{18} fatty acids; said oil-based liquid formulation further comprises (c) free PEG-32; and the weight/weight ratio of part (a) of said mixture to the sum of part (b) of said mixture and (c) is between 10:90 and 30:70 inclusive.

15. The oral pharmaceutical composition of claim 14, wherein (a), (b), and (c) together constitute 8-16% weight/weight inclusive of said oil-based liquid formulation.

16. The oral pharmaceutical composition of claim 9, wherein said oil-based liquid formulation further comprises a free PEG.

17. The oral pharmaceutical composition of any one of claims 9-16, wherein said formulation comprises gelatin and glycerol.

18. The oral pharmaceutical composition of any one of claims 9-17, further comprising a non-ionic detergent.

19. The oral pharmaceutical composition of claim 18, wherein said non-ionic detergent is a polysorbate-based detergent.

20. The oral pharmaceutical composition of claim 19, wherein said polysorbate-based detergent is polysorbate 80.

21. The oral pharmaceutical composition of claim 20, wherein said polysorbate 80 constitutes 3-10% weight/weight inclusive of said oil-based liquid formulation.

22. The oral pharmaceutical composition of any one of claims 9-21, wherein said oil is fish oil.

23. The oral pharmaceutical composition of any one of claims 9-22, wherein said oil-based liquid formulation is water-free.

24. The oral pharmaceutical composition of any one of claims 9-23, further comprising a coating that resists degradation in the stomach.

25. The oral pharmaceutical composition of claim 24, wherein said coating is a pH-sensitive capsule.

26. The oral pharmaceutical composition of claim 24, wherein said coating is a soft gelatin capsule.

27. The oral pharmaceutical composition of any one of claims 1-26 for use in orally administering a therapeutic protein to a subject.

28. The oral pharmaceutical composition for the use of claim 27, wherein said oral pharmaceutical composition prevents rapid degradation of said therapeutic peptide or therapeutic protein in said subject.

29. The oral pharmaceutical composition for the use of claim 27, wherein said oral pharmaceutical composition promotes sustained activity of orally administered therapeutic peptides or therapeutic proteins in said subject, or wherein said oral pharmaceutical composition promotes sustained bioavailability of orally administered therapeutic peptides or therapeutic proteins in said subject.

30. The oral pharmaceutical composition for the use of claim 29, wherein said sustained activity or said sustained bioavailability of orally administered therapeutic peptides or therapeutic proteins exceeds that obtained following the use of an otherwise identical oral formulation comprising a chemically purified BBI instead of said isolated recombinantly expressed BBI.

31. The oral pharmaceutical composition for the use of claim 27, wherein said use provides a therapeutically effective amount of said peptide or protein and wherein said BBI, or said therapeutic peptide or therapeutic protein of up to 100 kilodalton, or a combination thereof is provided in said formulation at a lower concentration than would be therapeutically effective in an otherwise identical oral formulation comprising a chemically purified BBI instead of said isolated recombinantly expressed BBI and said use achieves a comparable therapeutic effect in said subject.