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Pedersen et al.

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(54) **PROPYLENE GLYCOL-CONTAINING
PEPTIDE FORMULATIONS WHICH ARE
OPTIMAL FOR PRODUCTION AND FOR USE
IN INJECTION DEVICES**

(75) Inventors: **Tina Bjeldskov Pedersen**, Smørum
(DK); **Claude Bonde**, Lyngby (DK);
Dorthe Kot Engelund, Holte (DK)

(73) Assignee: **Novo Nordisk A/S**, Bagsvaerd (DK)

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patent is extended or adjusted under 35
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This patent is subject to a terminal dis-
claimer.

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(58) **Field of Classification Search** None
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,468,346 A 8/1984 Paul et al.
5,206,219 A 4/1993 Desai
5,272,135 A 12/1993 Takruri
5,455,331 A 10/1995 Pearce
5,652,216 A 7/1997 Kornfelt et al.
5,705,483 A 1/1998 Galloway
6,133,229 A 10/2000 Gibson et al.
6,184,201 B1 2/2001 Drucker et al.
6,268,343 B1 7/2001 Knudsen et al.
6,274,553 B1 8/2001 Furuya
6,284,727 B1 9/2001 Kim et al.
6,380,357 B2 4/2002 Hermeling
6,384,016 B1 5/2002 Kaarsholm
6,444,788 B1 9/2002 Staby
6,586,399 B1 7/2003 Drucker et al.
6,844,321 B2 1/2005 Arentsen

7,022,674 B2 4/2006 DeFelippis et al.
7,049,284 B2 5/2006 Drucker et al.
7,056,886 B2 6/2006 Isaacs
7,238,663 B2 7/2007 DeFelippis et al.
2001/0014666 A1 8/2001 Hermeling et al.
2001/0027180 A1 10/2001 Isaacs
2002/0151467 A1 10/2002 Leung
2003/0060412 A1 3/2003 Prouty, et al.
2003/0069182 A1 4/2003 Rinella
2003/0119734 A1 6/2003 Flink et al.
2003/0158101 A1 8/2003 Drucker
2003/0207802 A1 11/2003 DeFelippis
2003/0220243 A1 11/2003 Glaesner et al.
2003/0220255 A1 11/2003 Knudsen et al.
2004/0156835 A1 8/2004 Imoto et al.
2004/0248782 A1 12/2004 Bridon et al.
2006/0084605 A1* 4/2006 Engelund et al. 514/12
2006/0287221 A1* 12/2006 Knudsen et al. 514/3

FOREIGN PATENT DOCUMENTS

CA 2306024 4/1999
CA 2527743 12/2004
EP 0431679 11/1990
EP 0438767 12/1990
EP 699687 8/1995
EP 708179 4/1996
EP 747390 12/1996
EP 0926159 6/1999
EP 1329462 10/2001
EP 1424077 5/2002
EP 1344533 9/2003
EP 1396499 3/2004
EP 722492 3/2005
JP 10101696 4/1998
JP 2000-510813 8/2000
JP 2001-525371 12/2001
JP 2002-504908 2/2002
JP 2002-508332 3/2002
JP 2002-524514 8/2002
JP 2002-532557 10/2002
JP 2003-519195 6/2003
JP 2003519195 6/2003

(Continued)

OTHER PUBLICATIONS

Singh, S et al—Aaps Pharmscitech—2003—vol. 4—Part 3—pp. 334-
342.

(Continued)

Primary Examiner — Christina Bradley
(74) *Attorney, Agent, or Firm* — Michael J. Brignati

(57) **ABSTRACT**

The present invention relates to pharmaceutical formulations comprising a peptide and propylene glycol, to methods of preparing such formulations, and to uses of such formulations in the treatment of diseases and conditions for which use of the peptide contained in such formulations is indicated. The present invention further relates to methods for reducing the clogging of injection devices by a peptide formulation and for reducing deposits on production equipment during production of a peptide formulation.

31 Claims, 7 Drawing Sheets

FOREIGN PATENT DOCUMENTS

PA	200101010	6/2001
RU	2180218	3/2002
WO	WO 9000200	1/1990
WO	92/19260	11/1992
WO	9318785	9/1993
WO	WO 93/18785	9/1993
WO	93/23010	11/1993
WO	95/22560	2/1995
WO	95/05848	3/1995
WO	WO 9510605	4/1995
WO	95/13825	5/1995
WO	WO 96/20005	7/1996
WO	9624369	8/1996
WO	WO 9638469	12/1996
WO	WO 98/08871	3/1998
WO	WO 98/31386	7/1998
WO	9856406	12/1998
WO	99/16417	4/1999
WO	WO 9921889	5/1999
WO	WO 99/29336	6/1999
WO	WO 99/30731	6/1999
WO	WO 99/43341	9/1999
WO	WO 99/43708	9/1999
WO	WO 9943707	9/1999
WO	WO 00/15224	3/2000
WO	WO 00/37098	6/2000
WO	WO 00/41546	7/2000
WO	WO 00/55119	9/2000
WO	0100223	1/2001
WO	WO 01/43762	6/2001
WO	0151071	7/2001
WO	WO 01/49314	7/2001
WO	WO 01/51071	7/2001
WO	WO 0152937	7/2001
WO	WO 0155213	8/2001
WO	WO 01/77141	10/2001
WO	02/67989	1/2002
WO	0247716	6/2002
WO	WO 02/47715	6/2002
WO	WO 02/48183	6/2002
WO	WO 0248183	6/2002
WO	02098445	12/2002
WO	03/013589	2/2003
WO	WO 03/020201	3/2003
WO	WO 03/002136	4/2003
WO	WO 03/035099	5/2003
WO	WO 2004/029076	4/2004
WO	WO 2004105781	12/2004
WO	WO 2005/000222	1/2005
WO	2005/046716	5/2005
WO	WO 2006/025882	3/2006

OTHER PUBLICATIONS

Non-Final Office Action mailed Dec. 9, 2009 in U.S. Appl. No. 12/184,531 filed Aug. 1, 2008 by Mortensen et al.

Sigma, Custom Peptide Synthesis, 2004, pp. 1-2, http://www.SIGMA-GENOSYS.COM/PEPTIDE_DESIGN.ASP.

Bailey et al. The Kinetics of Enzyme-Catalysed Reactions Biochemical Engineering Fundamentals, 2nd Ed., pp. 129-148 (1986).

Entry for Glycerin in Drugs.Com (www.Drugs.Com/PPA/glycerin-glycerol.html), Printed Aug. 04, 2009.

European Pharmacopoeia, 2007, vol. 1, p. 730, Council of Europe-Strasbourg.

S.E. Bondos & A. Bicknell, Detection and Prevention of Protein Aggregation Before During and After Purification, Analytical Biochemistry, 2003, 223-231, vol. 316, Academic Press.

Shinotesuto, Patent Abstracts of Japan, of JP10101696.

Skovgaard et al., "Using Evolutionary Information and Ancestral Sequences to Understand the Sequence-Function Relationship in GLP-1 Agonists," J. Mol. Bio., 2006, vol. 363, p. 977-988.

Tsoka et al, Selective Flocculation Ands Precipitation for the Improvement of Virus-Like Particle Recovery From Yeast Homogenate, Biotechnol Prog. vol. 16(4), pp. 661-7 (2000).

Non-Final Office Action in U.S. Appl. No. 10/185,923, Filed Jun. 27, 2002, Inventors: Flink et al. Sent Oct. 9, 2007.

Non-Final Office Action in U.S. Appl. No. 11/786,095, Filed Apr. 11, 2007, Inventors: Funk et al. Sent Feb. 24, 2009.

Non-Final Office Action in U.S. Appl. No. 12/343,722, Filed Dec. 24, 2008, Inventors: Funk et al. Sent May 22, 2009.

Non-Final Office Action in U.S. Appl. No. 10/719,601, Filed Nov. 21, 2003, Inventors: Markussen et al. Sent Mar. 4, 2005.

Non-Final Office Action in U.S. Appl. No. 11/220,266, Filed Sep. 6, 2005, Inventors: Markussen et al. Sent Sep. 14, 2006.

Non-Final Office Action in U.S. Appl. No. 11/220,266, Filed Sep. 6, 2005, Inventors: Markussen et al. Sent Feb. 11, 2008.

Non-Final Office Action in U.S. Appl. No. 11/220,266, Filed Sep. 6, 2005, Inventors: Markussen et al. Sent Oct. 1, 2007.

Non-Final Office Action in U.S. Appl. No. 11/290,634, Filed Nov. 30, 2005, Inventors: Juul-Mortensen et al. Sent Jun. 30, 2008.

Non-Final Office Action in U.S. Appl. No. 11/290,634, Filed Nov. 30, 2005, Inventors: Juul-Mortensen et al. Sent Nov. 9, 2007.

Non-Final Office Action in U.S. Appl. No. 11/290,635, Filed Nov. 30, 2005, Inventors: Juul-Mortensen et al. Sent Feb. 2, 2007.

Non-Final Office Action in U.S. Appl. No. 11/290,635, Filed Nov. 30, 2005, Inventors: Juul-Mortensen et al. Sent Feb. 2, 2007.

Non-Final Office Action in U.S. Appl. No. 11/365,274, Filed Mar. 1, 2006, Inventors: Schlein et al. Sent Aug. 20, 2007.

Non-Final Office Action in U.S. Appl. No. 11/365,274, Filed Mar. 1, 2006, Inventors: Schlein et al. Sent Feb. 5, 2007.

Non-Final Office Action in U.S. Appl. No. 11/365,274, Filed Mar. 1, 2006, Inventors: Schlein et al. Sent Jan. 28, 2009.

Final Office Action in U.S. Appl. No. 10/185,923, Filed Jun. 27, 2002, Inventors: Funk et al. Sent Dec. 12, 2006.

Final Office Action in U.S. Appl. No. 10/185,923, Filed Jun. 27, 2002, Inventors: Funk et al. Sent Jun. 14, 2005.

Final Office Action in U.S. Appl. No. 10/185,923, Filed Jun. 27, 2002, Inventors: Hank et al. Sent Jun. 30, 2008.

Final Office Action in U.S. Appl. No. 11/290,635, Filed , Inventors: Juulmortensen et al. Sent Sep. 5, 2007.

Final Office Action in U.S. Appl. No. 11/290,635, Filed Nov. 30, 2005, Inventors: Juul-Mortensen et al. Sent Sep. 5, 2007.

Final Office Action in U.S. Appl. No. 11/365,274, Filed Mar. 1, 2006, Inventors: Schlein et al. Sent Apr. 4, 2008.

Final Office Action in U.S. Appl. No. 11/365,274, Filed Mar. 1, 2006, Inventors: Schlein et al. Sent Aug. 12, 2009.

Final Office Action in U.S. Appl. No. 11/786,095, Filed Apr. 11, 2007, Inventors: Funk et al. Sent Nov. 24, 2009.

Final Office Action in U.S. Appl. No. 12/343,722, Filed Dec. 24, 2008, Inventors: Funk et al. Sent Feb. 18, 2009.

Brittain, Harry G., Buffers, Buffering Agents, and Ionic Equilibria, Encyclopedia of Pharmaceutical Technology, p. 385, 2007.

Remington's Pharmaceutical Sciences, Mack Publishing Company, 16th Edition, 1980, Chapter 79, p. 1406.

Plumer's Principles & Practice of Intravenous Therapy, 2006, Edition 8, pp. 124-128.

European Pharmacopoeia, 3rd Edition, 1997, pp. 17-18.

United States Pharmacopoeia, 24th Edition, 1999, pp. 1977-1978.

Further Experimental Data Jun. 22, 2009.

Frokjaer et al., Pharmaceutical Formulation Development of Peptides and Proteins, 2000, pp. 145-148 and 150-151.

Martin et al., Physical Pharmacy: Physical Chemical Principles in the Pharmaceutical Sciences, 1983, pp. 222-225.

Remington's Pharmaceutical Sciences, Mack Publishing Company, 18th Edition, 1990, Chapter 84, pp. 1545-1550.

Knudsen et al., J. Med. Chem., vol. 43, pp. 1664-1669, 2000.

Stenesh, J. Biochemistry, 1998, pp. 67-69.

Wang et al., J. Parenteral Science and Technology, vol. 42, pp. S4-S26, 1988.

Sigma Production Information on Gly Gly Buffer, Mar. 2010.

Martin et al., Physical Pharmacy, 1983, p. 232.

Declaration of Johnny C. Gonzalez, November 2010, pp. 1-7.

Eli Lilly and Company Product Information on Humalog Insulin Lispro Injection, 2009, pp. 1-12.

- European Pharmacopoeia, 3rd Edition, 2.2.3, 1997, pp. 17-8, Council of Europe-Strasbourg.
- Frokjaer & Hovgaard, Pharmaceutical Formulation Development of, 2000, pp. 145-148 & 150-151.
- Further Experimental Data Dated Jun. 22, 2009.
- Gonzales, Johnny C., Declaration of (Including Curriculum Vita) Dated Nov. 1, 2010 from Patent EP1412384.
- Knudsen, L.B. et al., Potent Derivatives of Glucagon-Like Peptide-1, Journal of Medicinal Chemistry, 2000, vol. 43, pp. 1664-9.
- Kristensen, H.G., Almen Farmaci, 2000, pp. 273-274, 281.
- Mack Publishing Co., Remington's Pharmaceutical Sciences, 16th Edition, 1980, PT. 79, p. 1406.
- Mack Publishing Co., Remington's Pharmaceutical Sciences, 18th Edition, 1990, Chapter 84, pp. 1545-50.
- Martin A. et al., Physical Pharmacy; Physical Chemical Principles in the Pharmaceutical Sciences, 1983, 3rd Edition, p. 232.
- Martin A. et al., Physical Pharmacy; Physical Chemical Principles in the Pharmaceutical Sciences, 1983, 3rd Edition, p. 323.
- Sigma Product Information on Gly-Gly Buffer Dated Mar. 16, 2010.
- Stenesh, J. Biochemistry, 1998, pp. 67-9.
- United States Pharmacopoeia, 24th Edition, 1999, pp. 1977-8.
- Villanueva Penacarril M.L. Potent Glycogenic Effect of Glp-1(7-36) Amide in Rat Skeletal Muscle, Diabetologia, 1994, vol. 37, pp. 1163-6.
- Wang & Hansen, Journal of Parenteral Science & Technology, 1988, vol. 42, pp. 4-26.
- Weinstein, Sharon, Plumer's Principles & Practice of Intravenous, 2006, vol. 8 (8), pp. 124-8.
- Duma et al., Pharmaceutical Dosage Forms: Parenteral Medications, vol. 1, 2nd Edition, p. 20.

* cited by examiner

FIGURE 1

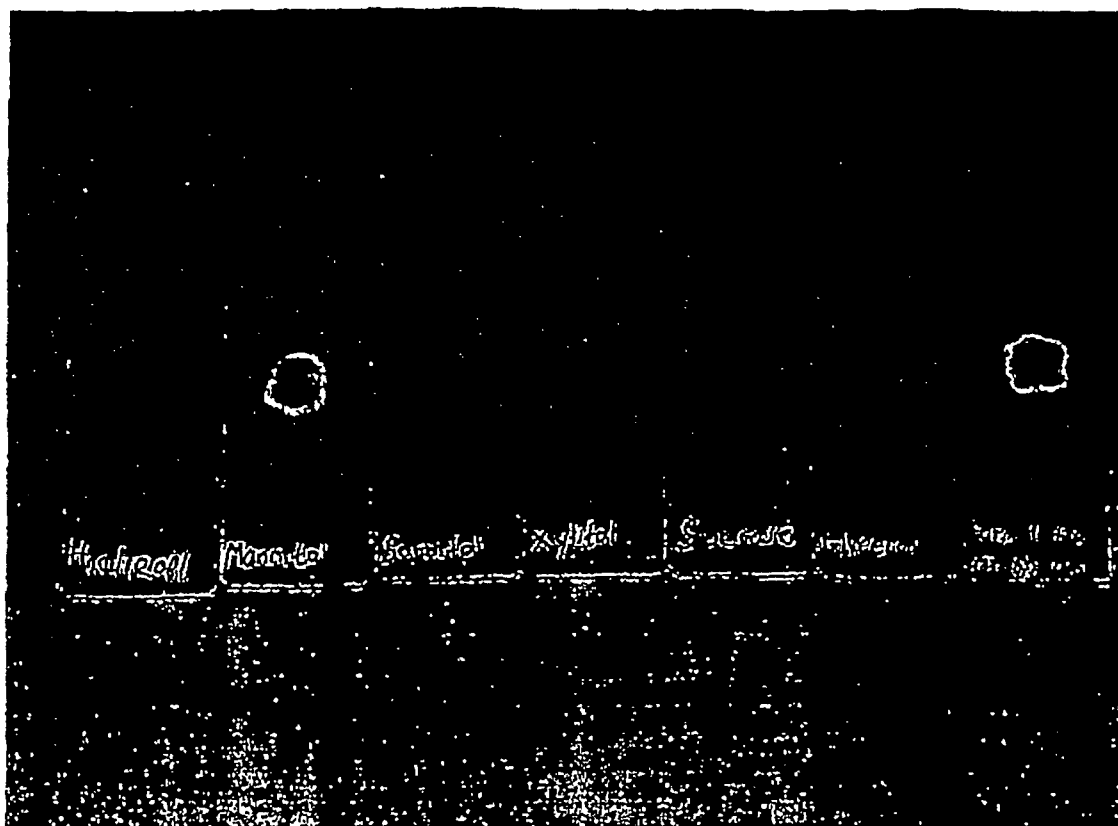


FIGURE 2



Mannitol



Argi-



Inosi-



Glyce-

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