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(54) **COPOLYMER-1 IMPROVEMENTS IN COMPOSITIONS OF COPOLYMERS**

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(58) **Field of Search** **514/2**, **12**, **903**; **424/78.37**

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,849,550 A * 11/1974 Teitelbaum et al. 424/78
 4,594,409 A 6/1986 Hayashii et al. 525/420

FOREIGN PATENT DOCUMENTS

DE	39 30733	3/1991
EP	03 78246	7/1990
EP	0 383 620	* 8/1990
EP	9 83020	8/1990
SU	1882051	9/1985
SU	1664845	7/1991

OTHER PUBLICATIONS

D. Teitelbaum et al., "Dose-Response Studies on Experimental Allergic Encephalomyelitis Suppression by COP 1," *Israel Journal of Medical Sciences*, vol. 10, No. 9, Sep. 1974, pp. 1172-1173.

D. Teitelbaum et al., "Suppression of Experimental Allergic Encephalomyelitis by a Synthetic Polypeptide", *Eur. J. Immunol.*, 1971, 1, 242-248.

D. Teitelbaum et al., "Protection Against Experimental Allergic Encephalomyelitis", *Nature*, 1972, 240, pp. 564-566.

C. Webb et al., "Further Studies on the Suppression of Experimental Allergic Encephalomyelitis by Synthetic Copolymer", *Israel J. Med. Sci.*, 1972, 8, pp. 656-657.

R. Arnon et al., "Suppression of Experimental Allergic Encephalomyelitis by a Synthetic Copolymer Immunological Cross Reactive with Basic Encephalitogen", *Israel J. Med. Sci.*, 1972 8, pp. 1759-1760.

D. Teitelbaum et al., "Suppression of Experimental Allergic Encephalomyelitis with Basic Polymers", *Eur. J. Immunol.*, 1973, 3, pp. 273-279.

C. Webb et al., "In vivo and in Vitro Immunological cross-reactions between Basic Encephalitogen and Synthetic Basic Polypeptides Capable of Suppressing Experimental Allergic Encephalomyelitis", *Eur. J. Immunol.*, 3, pp. 279-286 (1973).

D. Teitelbaum et al., "Suppression of Experimental Allergic Encephalomyelitis in Rhesus Monkeys by a Synthetic Basic Copolymer", *Clin. Immunol. Immunopath.*, 1974, 3, pp. 256-262.

D. Teitelbaum et al., "Dose-response Studies on Experimental Allergic Encephalomyelitis Suppression by COP-1", *Israel J. Med. Sci.*, 1974, 10, pp. 1172-1173.

C. Webb et al., "Suppression of Experimental Allergic Encephalomyelitis in Rhesus Monkeys by a Synthetic Basic Copolymer", *Isr. J. Med. Sci.*, 1975, 11, p. 1388 (abstract).

C. Webb et al., "Molecular Requirements Involved in Suppression of EAE by Synthetic Basic Copolymers of Amino Acids", *Immunochemistry*, 1976, 13, pp. 333-337.

O. Abramsky et al., "Effect of a Synthetic Polypeptide (COP-1) on Patients with Multiple Sclerosis and with Acute Disseminated Encephalomyelitis", *J. Neurol. Sci.*, 1977, 31, pp. 433-438.

D. Teitelbaum et al., "Suppression of Experimental Allergic Encephalomyelitis in Baboons by COP-1." *Israel J. Med. Sci.*, 1977, 13, 1038 (abstract).

M. Sela et al., "Experimental Allergic Encephalomyelitis in Menarini Series on Immunopathology, vol. 1, First Symposium of Organ Specific Autoimmunity", Cremona, Italy, Jun. 1977, Miescher P.A. eds., pp. 9-21, Schwabe Co., Basel, (1978).

R. Arnon et al., "Suppression of EAE in Baboons by a Synthetic Polymer of Amino Acids", *Neurology*, 1978, 28, 336 (abstract).

E.C. Alvord et al., "Myelin Basic Protein Treatment of Experimental Allergic Encephalomyelitis in Monkeys", *Ann. Neurol.*, 1979, 6, pp. 469-473.

A.B. Keith et al., "The Effect of COP-1, a Synthetic Polypeptide, on Chronic Relapsing Experimental Allergic Encephalomyelitis in Guinea Pigs", *J. Neurol. Sci.*, 1979, 42, pp. 267-274.

Z. Lando et al., "Effect of Cyclophosphamide on Suppressor Cell Activity in Mice Unresponsive to EAE", *J. Immunol.*, 1979, 123, pp. 2156-2160 (abstract).

(List continued on next page.)

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(57) **ABSTRACT**

The present invention relates to an improved composition of copolymer-1 comprising copolymer-1 substantially free of species having a molecular weight of over 40 kilodaltons.

1 Claim, 2 Drawing Sheets

OTHER PUBLICATIONS

- Z. Lando et al., "Experimental Allergic Encephalomyelitis in Mice—Suppression and Prevention with COP-1", *Israel J. Med. Sci.*, 1979, 15, pp. 868–869 (abstract).
- D. Teitelbaum et al., "Blocking of Sensitization to Encephalitogenic Basic Protein in Vitro by Synthetic Basic Copolymer (COP-1)." in *Cell biology and Immunology of Leukocyte Function*, Academic Press, New York, 1979, pp. 681–685.
- D. Teitelbaum, "Suppression of Experimental Allergic Encephalomyelitis with a Synthetic Copolymer—relevance to Multiple Sclerosis", in *Humoral Immunity in Neurological Diseases*, Karcher D., Lowenthal A. & Strosberg A.D. eds. Plenum Publishing Corp., 1979, pp. 609–613.
- R. Arnon et al., "Desensitization of Experimental Allergic Encephalomyelitis with Synthetic Peptide Analogues" in *The Suppression of Experimental Allergic Encephalomyelitis and Multiple Sclerosis*, Academic Press, New York, 1980 pp. 105–107.
- R. Arnon, "A Synthetic Copolymer of Amino Acids in a Clinical Trail for MS Therapy" in *Progress in Multiple Sclerosis Research*, Bauer, Ritter, eds. Springer Verlag N.Y., 1980 pp. 416–418.
- M. B. Bornstein et al., "Treatment of Multiple Sclerosis with a Synthetic Polypeptide: Preliminary results.", *Trans. Am. Neurol. Assoc.*, 1980, 105, pp. 348–350.
- M. B. Bornstein et al., "Treatment of Multiple Sclerosis with a Synthetic Polypeptide: preliminary results", *Ann. Neuro.*, 1980, 8, pp. 117 (abstract).
- J. R. McDermott et al., "Antigen-induced Suppression of Experimental Allergic Neuritis in the Guinea Pig.", *J. Neurol. Sci.*, 1980, 46, pp. 137–143.
- R. Arnon, "Experimental Allergic Encephalomyelitis—Susceptibility and Suppression", *Immunological Rev.*, 1981, 55, pp. 5–30.
- M. B. Bornstein et al., "Multiple Sclerosis: Trial of a Synthetic Polypeptide", *Ann. Neurol.*, 1982, 11, pp. 317–319.
- C. G. Brosnan et al., "The Response of Normal Human Lymphocytes to Copolymer-1." *J. Neuropath. Exp. Neurol.*, 1983, 42, pp. 356 (abstract).
- R. P. Lisak et al., "Effect of Treatment with Copolymer 1 (COP-1) on the in Vivo and in Vitro Manifestations of Experimental Allergic Encephalomyelitis (EAE)", *J. Neurol. Sci.*, 1983, 62, 281–293.
- M. B. Bornstein et al., "Clinical Trials of Copolymer 1 in Multiple Sclerosis", *Ann. N.Y. Acad. Sci. (USA)*, 1984, pp. 366–372.
- M. B. Bornstein et al., "Clinical Trials of a Synthetic Polypeptide (Copolymer 1) for the Treatment of Multiple Sclerosis" in R.E. Gonsett et al., eds. *Immunological and clinical aspects of multiple sclerosis*, 1984, pp. 144–150.
- C. F. Brosnan et al., "Copolymer 1: Effect on Normal Human Lymphocytes", *Ann. N.Y. Acad. Sci. (USA)*, 1984, 436, pp. 498–499.
- J. Burns et al., "Human Cellular Immune Response in Vitro to Copolymer 1 and Myelin Basic Protein (MBP)", *Neurology*, 1985, 35, (suppl 1), 170 (abstract).
- C. F. Brosnan, et al., "Immunogenic potentials of copolymer 1 in normal lymphocytes" *Neurology*, 1985, 35, pp. 1754–1759.
- M. B. Bornstein et al., "Multiple Sclerosis: Clinical Trials of a Synthetic Polypeptide, Copolymer 1.", *Neurology*, 1985, 35, (suppl 1), p. 103 (abstract).
- D. Teitelbaum et al., "Monoclonal antibodies to Myelin Basic Protein Cross Road with a Synthetic EAE Suppressive Copolymer, COP 1.", *Proc. 7th European Immunology Meeting*, Jerusalem, 1985 (abstract).
- J. Burns et al., "Human Cellular Immune Response to Copolymer 1 and Myelin Basic Protein." *Neurology*, 1986, 36, pp. 92–94.
- M. B. Bornstein, "COP-1 may be Beneficial for Patients with Exacerbating–remitting Form of Multiple Sclerosis", *Adv. Ther. (USA)*, 1987, 4, p. 206 (Abstract).
- H. L. Winer, "COP-1 Therapy for Multiple Sclerosis", *New England Journal of Medicine*, 1987, 317, pp. 442–444.
- R. Arnon et al., "Suppression of Demyelinating Diseases by Synthetic Copolymers", from: *A multidisciplinary approach to myelin disease* G. Serlupi Crescenzi, ed. Plenum Publishing Corporation, 1988, pp. 243–250.
- M. B. Bornstein et al., "Pilot Trial of COP-1 in Chronic Progressive Multiple Sclerosis: Preliminary Report", *Elsevier Science Publisher*, 1989, pp. 225–232; Conference "The International Multiple Sclerosis Conference: an update on Multiple Sclerosis" Roma (Italy), Sep. 15–17, 1988.
- E. Grgacic et al., "Cell-mediated Immune Response to Copolymer 1 in Multiple Sclerosis Measured by the Macrophage Procoagulant Activity Assay", *Int. Immunol.*, 1990, 2, pp. 714–718.
- M. B. Bornstein et al., "Clinical Trials of COP-1 in Multiple Sclerosis", *Handbook of Multiple Sclerosis*, S. D. Cook Marcel Rekker et al., 1990, pp. 469–480.
- M. Wender, Copolymer 1 (COP-1) in the Treatment of Multiple Sclerosis (letter) *Neur. Neurochir. Pol. (Poland)*, 1990, 24, pp. 113.
- Z. Meiner, "COP-1 Multicenter Clinical Trial in Exacerbating–remitting Multiple–Sclerosis: one year follow-up", *J. of Neurol.*, 1991, suppl 1. (abstract).
- D. Teitelbaum et al., "Cross-reactions and Specificities of Monoclonal Antibodies Against Myelin Basic Protein and Against The synthetic, Copolymer 1." *Proc. Natl. Acad. Sci., (USA)* 1991, 88, pp. 9528–9532.
- M Salvetti et al., "Myelin Basic Protein T Cell Epitopes in Patients with Multiple Sclerosis", 72 (Abstract) (1991).
- M. B. Bornstein et al., "Treatment of Multiple Sclerosis: Trial design, results and future Perspectives", Rudick R.K. & Goodkin D.E., eds. Springer Verlag, London, New York, 1992, pp. 173–198.
- D. Teitelbaum et al., "Synthetic Copolymer 1 Inhibits Human T-Cell Lines Specific for Myelin Basic Protein", *Proc. Natl. Acad. Sci., (USA)*, 1992, 89, 137–141.
- K. P. Johnson, "Clinical Studies in Copolymer 1 Therapy for Exacerbating–remitting Multiple Sclerosis", *Comm. presented at the Congress for Advances in the Understanding and Treatment of Multiple Sclerosis*, Boston (USA), Oct. 28–29, 1992.
- R. Milo et al., "Inhibition of Myelin Basic Protein–Specific Human T–Cell Lines by COP-1", *Israel J. Med. Sci.*, 1992, 28, p. 486 (Abstract).
- R. Arnon et al., "On the Existence of Suppressor Cells", *Int. Arch. Allergy Immunol.*, 1993, 100, pp. 2–7.
- M. Sela, "Polymeric Drugs as Immunomodulatory Vaccines Against Multiple Sclerosis", *Makromol. Chem. Macromol. Symp.*, 1993, 70/71, pp. 147–155.

- Z. Meiner et al., "The Israeli COP-1 Multicenter Clinical Trial in Exacerbating-remitting Multiple Sclerosis two-year followup.", 9th Congress of the European Committee for Treatment and Research in Multiple Sclerosis, Florence (Italy), Oct.-Nov., 1993 Abstract.
- R. Milo et al., "Copolymer-1 (COP-1) regulates class II MHC Expression and Cytokine Synthesis in the Monocyte-Macrophage Cell Line", *The IBC Conference on Multiple Sclerosis*, San Diego, Dec. 10, 1993 (Abstract).
- M. Fridkis-Hareli et al., "Specific and Promiscuous Binding of Synthetic Copolymer-1 to Class II Major Histocompatibility Complex Molecules on Living Antigen Presenting Cells", *Israeli Biochemistry Society*, 1994, Mar. pp. 21-22 (Abstract).
- M. Fridkis-Hareli et al., "Synthetic Copolymer-1 and Myelin Basic Protein do not Undergo Processing Prior to the Binding to Class II Major Histocompatibility Complex Molecules on Antigen Presenting Cells", *The Israeli Immunol. Soc.*, May 3-4, 1994 (Abstract).
- R. Arnon et al., "Immunospecific Drug Design-Prospects for Treatment of Autoimmune Diseases", *Therapeutic Immunol.*, 1994, 1, pp. 65-70.
- M. Fridkis-Hareli et al., "Synthetic Copolymer-1 Inhibits the Binding of MBP, PLP and MOG Peptides to Class II Major Histocompatibility Complex Molecules on Antigen Presenting Cells" *Neurochem Meeting*, Aug. 14-19, 1994.
- Masha Fridkis-Hareli et al., "Synthetic Copolymer 1 and Myelin Basic Protein Do Not Require Processing Prior to Binding To Class II Major Histocompatibility Complex Molecules On Living Antigen Presenting Cells", *J. Neurochem.*, 63, Suppl. I, 561, 1994.
- Kenneth P. Johnson, "Experimental Therapy of Relapsing-Remitting Multiple Sclerosis With Copolymer-1", *American Neurological Association*, 1994, 36, pp. 115-117.
- E. Kott et al., "COP-1 Increases Suppressor Cells Number In Multiple Sclerosis", *Israel Neurological Association*, 1994, p. 17.
- The COP-1 Multicenter Clinical and Research Group Study, "COP-1 Multicenter Trial in Relapsing Remitting Multiple Sclerosis: 3 Year Follow Up", *Abstracts of Symposia and Free Communications*, Jun. 25-29, 1994, suppl 1, 241, p. 6.
- Yafit Stark, "Expanded Clinical Trials of Treatments for Multiple Sclerosis: Copolymer 1 Treatment Investigational New Drug Program", *Ann. Neurol.*, 1994, 36, pp. 114-115.
- R. Milo et al., "Additive Effect of Copolymer-1 and Interferon-B on the Immune Response to Myelin Basic Protein", *Assaf Harofeh Medical Center, Sackler School of Medicine, Tel-Aviv University, University of Maryland School of Medicine*, p. 22 (1994).
- R. Milo et al., "Additive Effects of COP-1 and IFN-Beta on Immune Responses to Myelin Basic Protein", *Neurology*, 1994, 44, suppl. 2 A212.
- D. Teitelbaum et al., "Immunological Parameters in a Multicenter Clinical Trial of COP1 in Multiple Sclerosis: A 2-year follow-up", *Neurology*, 1994 44, suppl. 2 A358.
- M. Fridkis-Hareli et al., "Copolymer 1 Displaces MBP, PLP and MOG, but can not be displaced by these antigens from the MHC Class II binding Site"(1994).
- Paul Cotton, "Options for Multiple Sclerosis Therapy", *JAMA Medical News & Perspectives*, 1994, 272, No. 18.
- Lawrence Jacobs, "Advances in specific therapy for multiple sclerosis", *Neurology*, 1994, 7, pp. 250-254.
- L. Durelli, "Immunotherapeutics of Multiple Sclerosis" pp. 467-475 (1994).
- Lawrence Myers et al., "The Peculiar Difficulties of Therapeutic Trials for Multiple Sclerosis", *Neurologic Clinics*, Feb. 1990, 8, pp. 119-141.
- D. A. Francis, "The Current Therapy of Multiple Sclerosis", *Journal of Clinical Pharmacy and Therapeutics*, 1993, 18, pp. 77-84.
- Jonathan L. Carter et al., "Newer Drug Therapies for Multiple Sclerosis", *Drug Therapy*, Mar. 1990, pp. 31-43.
- Brian G. Weinshenker et al., "Natural history and treatment of multiple sclerosis", *Current Opinion in Neurology and Neurosurgery*, 1992, 5, pp. 203-211.
- Stuart Nightingale M.D. et al., "Access to Investigational Drugs for Treatment Purposes", *American Family Physician*, Sep. 15, 1994, pp. 845-847.
- Shalini Bansil, M.D. et al., "Multiple Sclerosis: Pathogenesis and Treatment", *Seminars in Neurology*, 1994, 14, No. 2, pp. 146-153.
- Masha Fridkis-Hareli et al., "Direct binding of myelin basic protein and synthetic copolymer 1 to class II major histocompatibility complex molecules on living antigen-presenting cells-specificity and promiscuity", *Proc. Natl. Acad. Sci. USA*, May 1994, 91, pp. 4872-4876.
- E. Gurevich, "Study of the MHC-competition between BP and Cop 1 using human cytotoxic T-cell clones" *Isr. J. Med. Sci.*, 1993 (Abstract).
- Masha Fridkis-Hareli et al., "Synthetic Copolymer 1 and Myelin Basic Protein do not require Processing prior to binding to class II major Histocompatibility Complex Molecules on Living Antigen Presenting Cells", Department of Chemical Immunology, The Weizmann Institute of Science, Rehovot, 76100, Israel (1993).
- Rolak, "Copolymer-I Therapy for Multiple Sclerosis," Dept. of Neurology, Baylor College of Medicine, Clinical Neuropharmacology, pp. 391-396.* (1993).
- M. Bodanszky, "Principles of Peptide Synthesis," Springer-Verlag, Berlin, Heidelberg, New York, Tokyo, 1984, 118-229.*
- J. Burns et al., "Failure of Copolymer 1 to Inhibit the Human T-cell Response to Myelin Basic Protein", *Neurology*, 41, pp. 1317-1319, 1991.
- Clinical Trial Protocol No. 9001; first patient enrolled Oct. 23, 1991.
- Clinical Trial Protocol No. 9002; first patient enrolled Jun. 17, 1993.

* cited by examiner

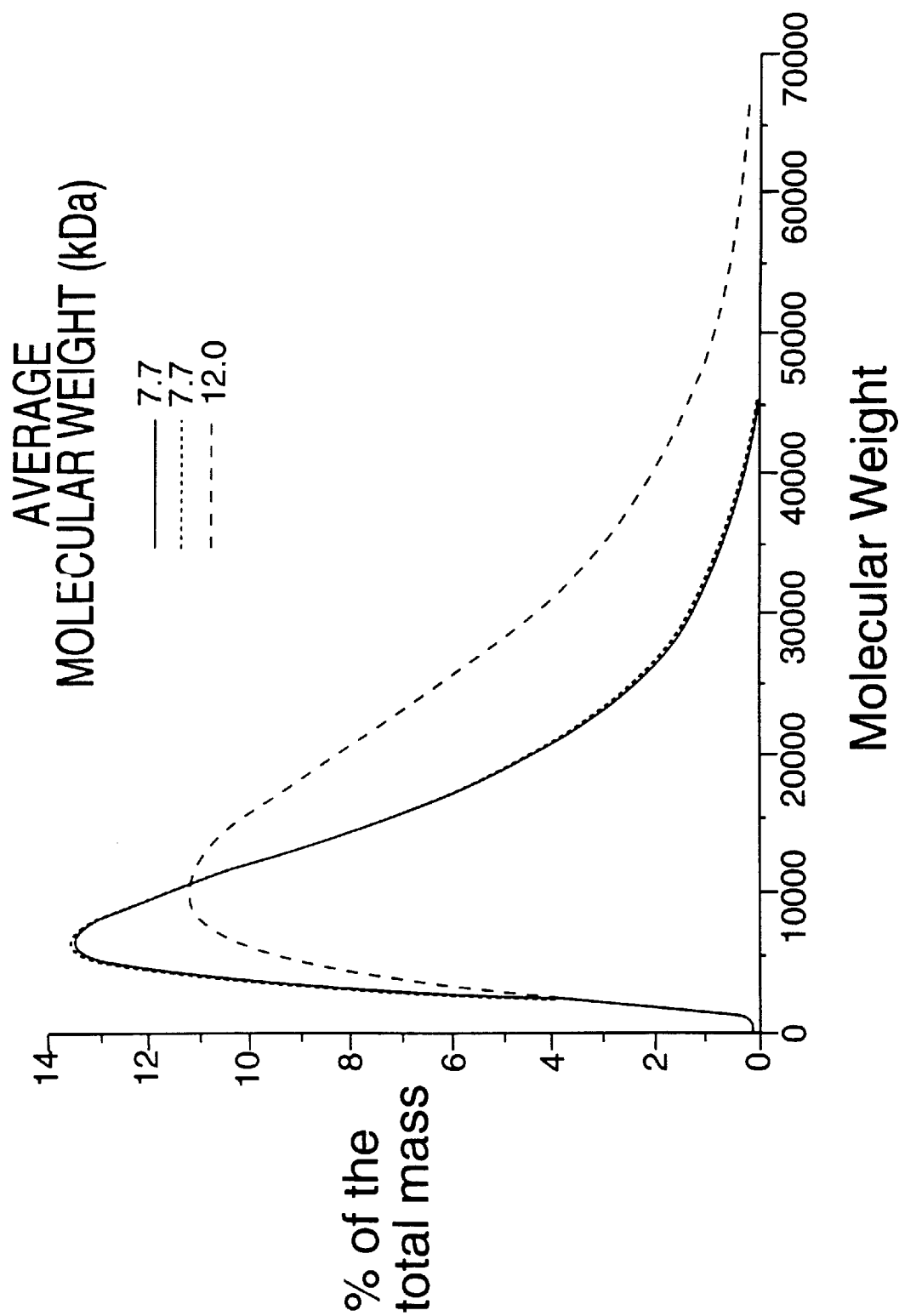


FIG. 1

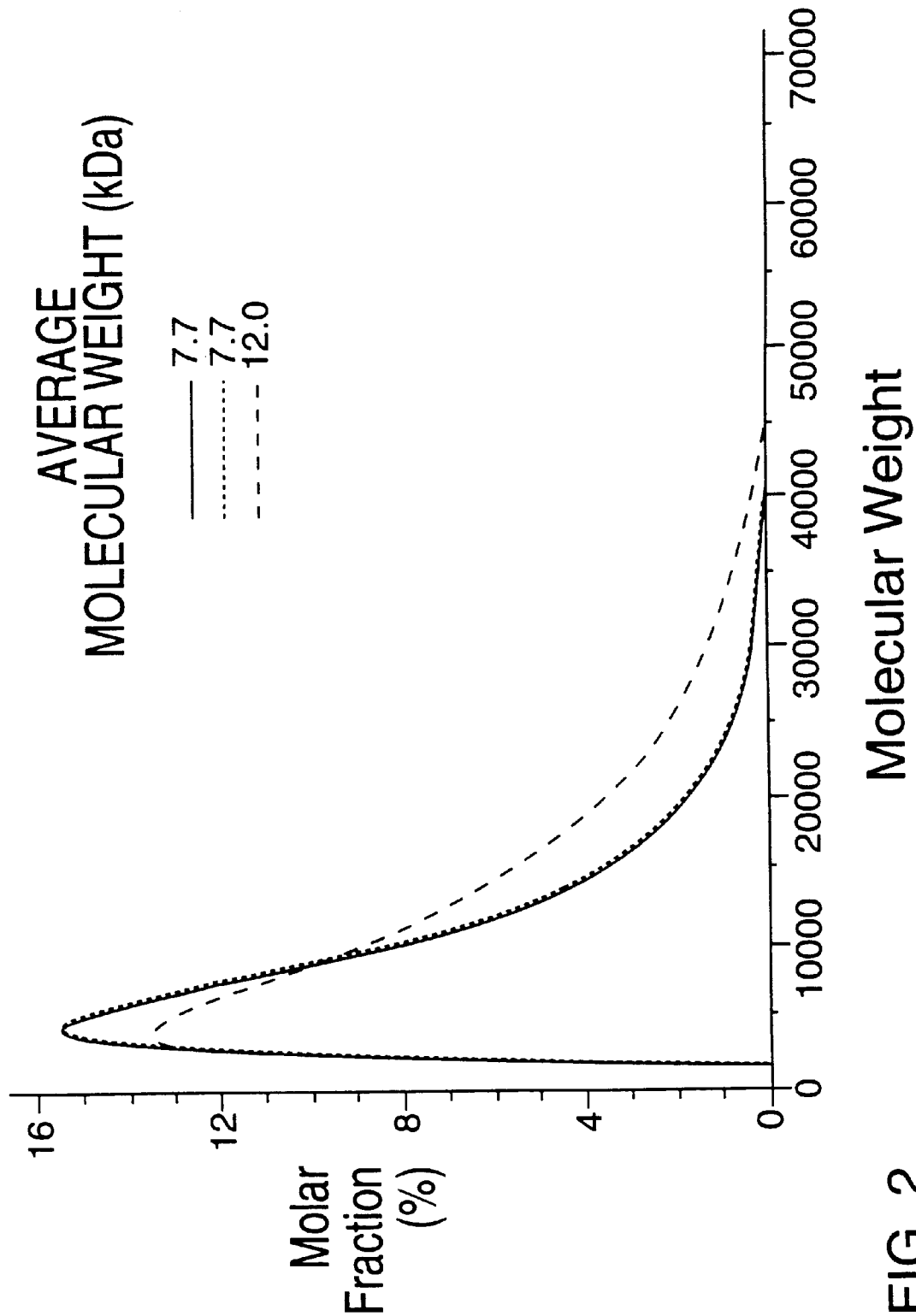


FIG. 2

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