US005691423A

United States Patent [19]

Smith et al.

[11] Patent Number: 5,691,423

[45] Date of Patent: Nov. 25, 1997

[54] **POLYSACCHARIDE-BOUND NITRIC OXIDE-NUCLEOPHILE ADDUCTS**

[75] Inventors: **Daniel J. Smith**, Stow; **Debashish Chakravarthy**, Garrettsville, both of Ohio; **Larry K. Keefer**, Bethesda, Md.

[73] Assignee: **The United States of America as represented by the Department of Health and Human Services**, Washington, D.C.

[21] Appl. No.: **419,424**

[22] Filed: **Apr. 10, 1995**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 935,565, Aug. 24, 1992, Pat. No. 5,405,919.

[51] **Int. Cl.**[6] **A61K 31/785**; C08B 15/06; C08B 37/00

[52] **U.S. Cl.** **525/377**; 424/78.17; 424/499; 536/18.7

[58] **Field of Search** 525/377; 424/78.17

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,153,094	10/1964	Reilly .	
3,826,832	7/1974	Anderson et al. .	
4,265,714	5/1981	Nolan et al. .	
4,482,533	11/1984	Keith .	
4,638,079	1/1987	Inskip et al. .	
4,708,854	11/1987	Grinstead .	
4,921,683	5/1990	Bedell .	
4,952,289	8/1990	Ciccone et al. .	
4,954,526	9/1990	Keefer .	
4,985,471	1/1991	Ohta et al. .	
5,039,705	8/1991	Keefer et al. .	
5,087,631	2/1992	Shaffer et al. .	
5,087,671	2/1992	Loeppky et al. .	
5,094,815	3/1992	Conboy et al. .	
5,155,137	10/1992	Keefer et al.	514/611
5,212,204	5/1993	Keefer et al. .	
5,234,956	8/1993	Lipton .	
5,366,997	11/1994	Keefer et al. .	
5,389,675	2/1995	Christodoulou et al. .	
5,405,919	4/1995	Keefer et al.	525/377
5,482,925	1/1996	Hutsell	514/11

FOREIGN PATENT DOCUMENTS

425154	10/1990	European Pat. Off. .
211789	7/1984	German Dem. Rep. .
2126035	12/1971	Germany .
211789	8/1982	Germany .
WO 89/12627	6/1989	WIPO .
WO 90/09785	9/1990	WIPO .
WO 91/04022	4/1991	WIPO .
WO 91/05551	5/1991	WIPO .
WO 92/05149	4/1992	WIPO .
WO 93/07114	4/1993	WIPO .
WO 93/20088	10/1993	WIPO .
WO 93/20806	10/1993	WIPO .
WO 95/10267	4/1995	WIPO .
96/13164	5/1996	WIPO .

OTHER PUBLICATIONS

Chakravarthy, Debashish, "Fabrication and Evaluation of Novel Wound Dressings and Related Biomaterials (dextran, microspheres)," *Chemical Abstracts,* 122, No. 26, (1995) Abstract No. 322432.

Mascarenhas, Oscar Carlton, "Epoxy–Based Medical Grade Adhesive Hydrogels and Nitric Oxide Releasing Polymers," *Chemical Abstracts, 121,* No. 18, (1994) Abstract No. 206664.

Smith et al., "Nitric Oxide–Releasing Polymers Containing the [N(o)NO] Group," *Journal of Medical Chemistry, 39,* No. 5, 1148–1156 (1996).

Stamler et al., "S–Nitrosylation of proteins with nitric oxide: Synthesis and characterization of biologically active compounds," *Proc. Natl. Acad. Sci. USA,* 89, 444–448 (1992).

Stamler et al., "Nitric Oxide Circulates in Mammalian Plasma Primarily as an S–Nitroso Adduct of Serum Albumin," *Proc. Natl. Acad. Sci. USA,* 89, 7674–7677 (1992).

Stuehr et al., "Nitric Oxide: A Macrophage Product Responsible for Cytostasis and Respiratory Inhibition in Tumor Target Cells," *J. Exp. Med.,* 169, 1543–1555 (1989).

Thomlinson et al., "The Histological Structure of Some Human Lung Cancers and the Possible Implications for Radiotherapy," *Br. J. Cancer, IX,* 539–549 (1955).

Trissel, "Intravenous Infusion Solutions," *Handbook on Injectable Drugs* (4th ed.), 622–629 (American Society of Hospital Pharmacists, Bethesda, MD) (1986).

von Sonntag, *The Chemical Basis of Radiation Biology,* pp. 31–56 and 295–352 (Taylor & Francis, London) (1987).

Weitz et al., "Zur Kenntnis der stickoxyd–schwefligen Säure (II.Mitteil)," *Berichte d. D. Chem. Gesellschaft, LXVI,* 1718–1727 (1933). (Nitrosylsulfuric acid, *Chemical Abstracts,* 28, 2636.).

WHO Task Group on Environmental Health Criteria for Oxides of Nitrogen, *Environmental Health Criteria 4: Oxides of Nitrogen,* (World Health Organization, Geneva) (1977).

Wiersdorff et al., "N–aryl–N–nitrosohydroxylamine salts," *Chem. Abstracts,* 77, 48034f (1972).

Wilcox et al., "Effect of Cyanide on the Reaction of Nitroprusside with Hemoglobin: Relevance to Cyanide Interference With the Biological Activity of Nitroprusside," *Chem. Res. Toxicol.,* 3, 71–76 (1990).

Wink et al., "DNA Deaminating Ability and Genotoxicity of Nitric Oxide and Its Progenitors," *Science,* 254, 1001–1003 (1991).

(List continued on next page.)

Primary Examiner—Peter F. Kulkosky

Attorney, Agent, or Firm—Leydig, Voit & Mayer, Ltd.

[57] **ABSTRACT**

A polymeric composition capable of releasing nitric oxide comprises a polysaccharide including a nitric oxide-releasing $N_2O_2^-$ functional group bound to the polymer; pharmaceutical compositions including the polymeric composition; and methods for treating biological disorders in which dosage with nitric oxide is beneficial. The compositions can be used as and/or incorporated into implants, injectables, condoms, prosthesis coatings, patches, and the like for use in a wide variety of medical applications.

4 Claims, No Drawings