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[54] **POLYMER-BOUND NITRIC OXIDE/NUCLEOPHILE ADDUCT COMPOSITIONS, PHARMACEUTICAL COMPOSITIONS INCORPORATING SAME AND METHODS OF TREATING BIOLOGICAL DISORDERS USING SAME**

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Related U.S. Application Data

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[52] **U.S. Cl.** **424/486**; 424/78.08; 514/772.3; 514/611

[58] **Field of Search** 424/78.08, 486

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,153,094	10/1964	Reilly	564/112
4,265,714	5/1991	Nolan et al.	204/153.13
4,482,533	11/1984	Keith	514/652
4,638,079	1/1987	Inskip et al.	560/4
4,708,854	11/1987	Grinstead	423/235
4,921,683	5/1990	Bedell	423/235
4,952,289	8/1990	Ciccone et al.	431/309
4,954,526	9/1990	Keefer	514/611
4,985,471	1/1991	Ohta et al.	522/27
5,039,705	8/1992	Keefer et al.	514/611
5,087,631	2/1992	Shaffer et al.	514/342
5,087,671	2/1992	Loeppky et al.	525/328.2
5,094,815	3/1992	Conboy et al.	422/52

FOREIGN PATENT DOCUMENTS

425154-A1	10/1990	European Pat. Off. .
0469520	5/1992	European Pat. Off. .
211789	7/1984	Germany .
WO89/12627	6/1989	WIPO .

OTHER PUBLICATIONS

Artysbasheva et al., "Synthesis of 1–Alkoxy–3,3–Dialkyltriazene 2–Oxides from Alkoxyamines and Nitrosoamines," translated from *Zhurnal Organicheskoi Khimii* (Journal of Organic Chemistry–U.S.S.R.), 28, (6) 1168–1173 (1987).

Bonakdar et al., "Continuous–Flow Performance of Carbon Electrodes Modified With Immobilized Fe(II)/Fe(III) Centers," *Calanta,* 36, 219–225 (1989).

DeFeudis, "Endothelium–Dependent Vasorelaxation—A New Basis for Developing Cardiovascular Drugs," *Drugs of Today,* 24 (2), 103–115 (1988).

DeLuca et al., "Parenteral Drug–Delivery Systems, " in *Pharmaceutica and Pharmacy Practice,* Banker et al., eds., 238–250 (J. B. Lippincott Co., Philadelphia, PA) (1982).

Drago, "Reactions of Nitrogen(II) Oxide," in *Free Radicals in Organic Chemistry,* Advances in Chemistry Series No. 36, 143–149 (American Chemical Society, Washington, DC) (1962).

Drago et al., "The Reaction of Nitrogen(II) Oxide with Various Primary and Secondary Amines," *J. Am. Chem. Soc.,* 83, 1819–1822 (1961).

(List continued on next page.)

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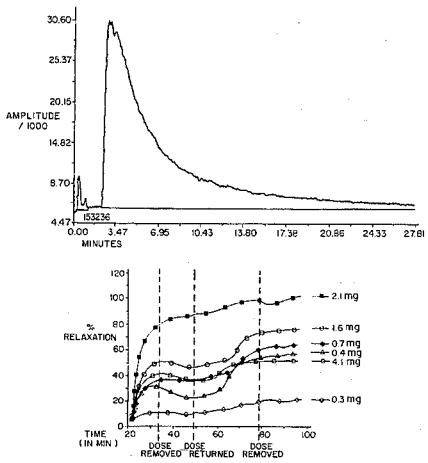
[57] **ABSTRACT**

A polymeric composition capable of releasing nitric oxide including a polymer and 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.

27 Claims, 2 Drawing Sheets