



[54] PHARMACEUTICAL COMPOSITIONS
CONTAINING ALKYLARYL POLYETHER
ALCOHOL POLYMER

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[*] Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

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Related U.S. Application Data

[60] Division of application No. 08/638,893, Apr. 25, 1996, Pat. No. 5,849,263, which is a continuation-in-part of application No. 08/299,316, Aug. 31, 1994, Pat. No. 5,512,270, which is a continuation-in-part of application No. 08/039,732, Mar. 30, 1993, abandoned.

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[52] U.S. Cl. 424/45

[58] Field of Search 424/45, 78.05,
424/78.06, 78.08, 78.37; 514/179, 885,
887

[56] References Cited

U.S. PATENT DOCUMENTS

2,454,541	11/1948	Bock et al. .	
3,272,700	9/1966	Shupe	514/535
3,663,230	5/1972	Sato et al. .	

(List continued on next page.)

FOREIGN PATENT DOCUMENTS

0571670	12/1993	European Pat. Off. .
0780127	6/1997	European Pat. Off. .
WO9422425	10/1994	WIPO .
WO9511669	5/1995	WIPO .
WO9630028	10/1996	WIPO .

OTHER PUBLICATIONS

Harold N. Glassman, Hemolytic Activity Of Some Nonionic Surface-Active Agents, *Science*, vol. III, Jun. 23, 1950, pp. 688-689.

Oliver H. Lowry, Nira J. Rosebaugh, A Lewis Farr and Rose J. Randall, Protein Measurement With The Folin Phenol Reagent, *Journal Of Biological Chemistry*, vol. 193, 1951, pp. 265-275.

M. V. Pimm and R.W. Baldwin, Influence Of ICRF 159 and Triton WR 1339 On Metastases Of A Rat Epithelioma, *The British Journal Of Cancer*, vol. 31, No. 1, Jan. 1975, pp. 62-67.

Kunihisa Hashimoto, Senji Miura and Chigashi Suzuki, Antimetastatic Effect Of Triton WR 1339, a Nonionic Detergent, On Rat Ascites Tumors, *The Tohoku Journal Of Experimental Medicine*, vol. 128, No. 3, Jul. 1979, pp. 259-265.

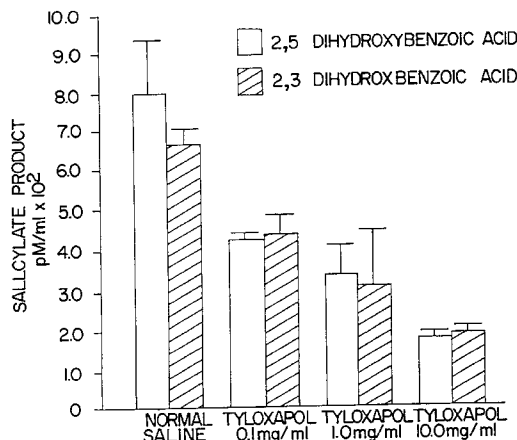
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[57] ABSTRACT

There is provided novel pharmaceutical compositions containing tyloxapol as the active ingredient. These formulations comprise tyloxapol at concentrations above 0.125%, preferably from about 0.25% to about 5.0%. In addition, the invention encompasses pharmaceutical compositions having reduced hypertonicity which compositions comprise tyloxapol in pharmaceutically acceptable solutions without significant concentrations of hypertonic agents or other active ingredients NaHCO₃, or active phospholipids, such as DPPC. The less hypertonic formulations allow one to derive all the benefits of the active ingredient tyloxapol, such as its reduced toxicity and enhanced half-life, while avoiding or reducing side effects, such as bronchospasms, associated with the various hypertonic agents or other active ingredient agents.

9 Claims, 8 Drawing Sheets



Petitioner InnoPharma EX 1092
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IPR2015-00903

U.S. PATENT DOCUMENTS

4,039,669	8/1977	Beyler et al. .	
4,826,821	5/1989	Clements	514/78
4,944,941	7/1990	Ammann .	
5,110,806	5/1992	Clements .	
5,134,129	7/1992	Lichtenberger .	
5,145,684	9/1992	Liversidge et al. .	
5,259,963	11/1993	Wiedemann .	
5,362,758	11/1994	Ahmed	514/777
5,399,363	3/1995	Liversidge et al. .	
5,474,760	12/1995	Ghio et al. .	
5,512,270	4/1996	Ghio et al. .	
5,576,311	11/1996	Guy .	
5,747,001	5/1998	Wiedmann et al. .	
5,770,585	6/1998	Kaufman et al. .	
5,830,436	11/1998	Ghio et al.	424/45
5,840,277	11/1998	Ghio et al.	424/45
5,849,263	12/1998	Kennedy	424/45
6,024,940	2/2000	Ghio et al.	424/45
6,037,328	3/2000	Hu et al.	514/23

OTHER PUBLICATIONS

- Robert A. Floyd, Julia J. Watson and Peter K. Wong, Sensitive Assay Of Hydroxyl Free Radical Formation Utilizing High Pressure Liquid Chromatography With Electrochemical Detection Of Phenol And Salicylate Hydroxylation Products, *Journal Of Biochemical And Biophysical Methods*, vol. 10, 1984, pp. 221–235.
- Julio F. Turrens, James D. Crapo and Bruce A. Freeman, Protection Against Oxygen Toxicity By Intravenous Injection Of Liposome–Entrapped Catalase And Superoxide Dismutase, *Journal Of Clinical Investigation*, vol. 73, Jan. 1984, pp. 87–95.
- Robert A. Floyd, Julia J. Watson and Peter K. Wong, Use Of Salicylate With High Pressure Liquid Chromatography And Electrochemical Detection (LCED) As A Sensitive Measurement Of Hydroxyl Free Radicals In Adriamycin Treated Rats, *Journal Of Free Radicals In Biology & Medicine*, vol. 2, 1986, pp. 13–18.
- M.F. McCarty, An Antithrombotic Role For Nutritional Antioxidants: Implications For Tumor Metastasis And Other Pathologies, *Med–Hypotheses*, Apr. 1986, pp. 345–357.
- Eiko Kondo and Koomi Kanai, Triton WR–1339 As A Biological–Response Modifier In Mycobacterial Infection, *Japan Journal Medical Science Biology*, vol. 39, 1986, pp. 35–47.
- Sadis Matalon, Bruce A. Holm and Robert H. Notter, Mitigation Of Pulmonary Hyperoxic Injury By Administration Of Exogenous Surfactant, *American Physiological Society*, 1987, pp. 756–761.
- Robert A. Greenwald, Determination Of HOC1 Production By Micloperoxidase, *CRC Handbook Of Methods For Oxygen Radical Research*, 1987, p. 300.
- W.H. Tooley, J.A. Clements, K. Muramatsu, C.L. Brown and M.A. Schlueter, Lung Function In Prematurely Delivered Rabbits Treated With A Synthetic Surfactant, *Am Rev Respir Dis*, Sep. 1987, pp. 651–656.
- Robert H. Notter, Biophysical Behavior Of Lung Surfactant: Implications For Respiratory Physiology And Pathophysiology, *Seminars In Perinatology*, vol. 12, No. 3, Jul. 1988, pp. 180–212.
- R. Randall Baker, Bruce A. Hom, Peter C. Panus and Sadis Matalon, Development Of O₂ Tolerance In Rabbits With No Increase In Antioxidant Enzymes, *American Physiological Society*, 1989, pp. 1679–1684.
- Barry Halliwell and John M.C. Gutteridge, Role Of Free Radicals And Catalytic Metal Ions In Human Disease: An Overview, *Methods In Enzymology*, vol. 186, 1990, pp. 1–83.
- Michael I. Lethem, Stuart L. James and Christopher Marriott, The Role Of Mucous Glycoproteins In The Rheologic Properties Of Cystic Fibrosis Sputum, *Am Rev Respir Dis*, 1990, pp. 1053–1058.
- H. Wiseman, M. Cannon, H.R. Arnstein and D.J. Barlow, The Structural Mimicry Of Membrane Sterols By Tamoxifen: Evidence From Cholesterol Coefficients And Molecular–Modelling For Its Action As A Membrane Anti–Oxidant And An Anti–Cancer Agent, *Biochim–Biophys–Acta.*, Mar. 20, 1992, pp. 197–202.
- Andrew J. Ghio, Thomas P. Kennedy, A. Richard Whorton, Alvin L. Crumbliss, Gary E. Hatch and John R. Hoidal, Role Of Surface Complexed Iron In Oxidant Generation And Lung Inflammation Induced By Silicates, *American Journal Of Physiology, Lung Cellular And Molecular Physiology* 7, vol. 263, Jun. 29, 1992, pp. L511–L518.
- H. Wiseman, C. Smith, B. Halliwell, M. Cannon, H.R. Arnstein and M.S. Lennard, Droloxifene (3–Hydroxytamoxifen) Has Membrane Antioxidant Ability: Potential Relevance To Its Mechanism Of Therapeutic Actions In Breast Cancer, *Cancer–Lett.*, Sep. 14, 1992, pp. 61–68.
- Hong–Suk Kim, Soon–Kyu Chung and Jin Jung, Reevaluation Of The Effect Of Triton X–100 On The Assay Of Superoxide Radical By The Nitrobluetertazolium Reduction Method, *Hanguk Nonghwahak Hoechi (J. Korean Agric. Chem. Soc.)*, 1993, pp. 364–369.
- Correspondence from Carolann W. Hootan, Department Of Health & Human Services, regarding Alevaire, dated May 27, 1994, including brochure of Alevaire® dated Nov. 1965.
- André Cantin and Donald E. Woods, Protection By Antibiotics Against Myeloperoxidase–Dependent Cytotoxicity To Lung Epithelial Cells In Vitro, *J. Clin. Invest.*, vol. 91, Jan. 1993, pp. 38–45.
- Okezie I. Aruoma, Deoxyribose Assay For Detecting Hydroxyl Radicals, *Methods In Enzymology*, vol. 233, 1994, pp. 57–82.
- Andrew J. Ghio, Philip J. Fracica, Stephen L. Young and Claude A. Piantadosi, Synthetic Surfactant Scavenges Oxidants And Protects Against Hyperoxic Lung Injury, *Journal Of Applied Physiology*, vol. 77, 1994, pp. 1217–1223.
- Carol A. Vasconcellos, Phillip G. Allen, Mary Ellen Wohl, Jeffrey M. Drazen, Paul A. Janney and Thomas P. Stoessel, Reduction In Viscosity Of Cystic Fibrosis Sputum In Vitro By Gelsolin, *Science*, vol. 263, Feb. 16, 1994, pp. 969–971.
- Henry J. Fuchs, M.D., Drucy S. Borowitz, M.D., David H. Christiansen, Dr. P.H., Edward M. Morris, Pharm.D., Martha L. Nash, R.N., Boonie W. Ramsey, M.D., Beryl J. Rosenstein, M.D., Arnold I. Smith, M.D. and Mary Ellen Wohl, M.D., Effect Of Aerosolized Recombinant Human DNase On Exacerbations Of Respiratory Symptoms And On Pulmonary Function In Patients With Cystic Fibrosis, *The New England Journal Of Medicine*, vol. 331, No. 10, Sep. 1994, pp. 637–642.
- Bonnie W. Ramsey, M.D., Henry L. Dorris, M.D., Jay D. Eisenberg, M.D., Ronald L. Gibson, M.D., Ph.D., Evan R. Harwood, M.D., Richard M. Kravitz, M.D., Daniel V. Scridlow, M.D., Robert W. Wilmott, M.D., Susan J. Astley, Ph.D., Mary Ann McBurne, M.S., Kim Wentz, M.D., M.P.H., and Arnold I. Smith, M.D., Efficacy Of Aerosolized Tobramycin In Patients With Cystic Fibrosis, *The New England Journal Of Medicine*, vol. 328, No. 24, pp. 1740–1746.

“Pharmazeutische Stoffliste”, 1995, Abdata Pharma-Daten-Service, Eschborn/Taunus XP00203775 “Tyloxapol”—pp. 87–88.

Internal Search Report Application No. PCT/US 97/ 06862.

Rossi, Die Moderne Behandlung Der Mucoviscidose (Zystische Pankreasfibrose), *Deutsche Med. Wochenschr.*, vol. 95, No. 42, pp. 2133–2135, (1970).

Rudnik, Behandlungsergebnisse Von Mucoviszidosekranken Kindern In Einem Sanatorium, *Z. Erkrank. Atm. Org.*, vol. 139, No. 2–3, pp. 117–120, (1974).

Thomassen, Regulation Of Human Alveolar Macrophage Inflammatory Cytokines By Tyloxapol: A Component Of The Synthetic Surfactant Exosurf, *Clin. Immunol. Immunopathol.*, vol. 77, No. 2, pp. 201–205, (Nov. 1995).

Dr. J.W. Cornforth, Dr. P. D’Arcy Hart, R.J.W. Rees and J.A. Stock, Antituberculous effect Of Certain Surface-Active Polyoxyethylene Ethers In Mice, *Nature*, vol. 168, Jul. 28, 1951, pp. 150–153.

Maurice L. Tainter, M.D., Frederick C. Nachod, Ph.D. and Joseph G. Bird, M.D., Alevaire As A Mucolytic Agent, *The New England Journal Of Medicine*, vol. 253, Nov. 3, 1995, pp. 764–767.

K.N.V. Palmer, M.A., M.D. Camb., M.R.C.P., The Effect Of An Aerosol Detergent In Chronic Bronchitis, *The Lancet*, Mar. 23, 1957, pp. 611–613.

John W. Polk, M.D. and Marcelino Medina, M.D., A Comparative Study Of Alevaire And A New Mucolytic Agent, Acumist In Postoperative Patients, *The Eye, Ear, Nose and Throat Monthly*, vol. 49, Jul. 1970, pp. 321–324.

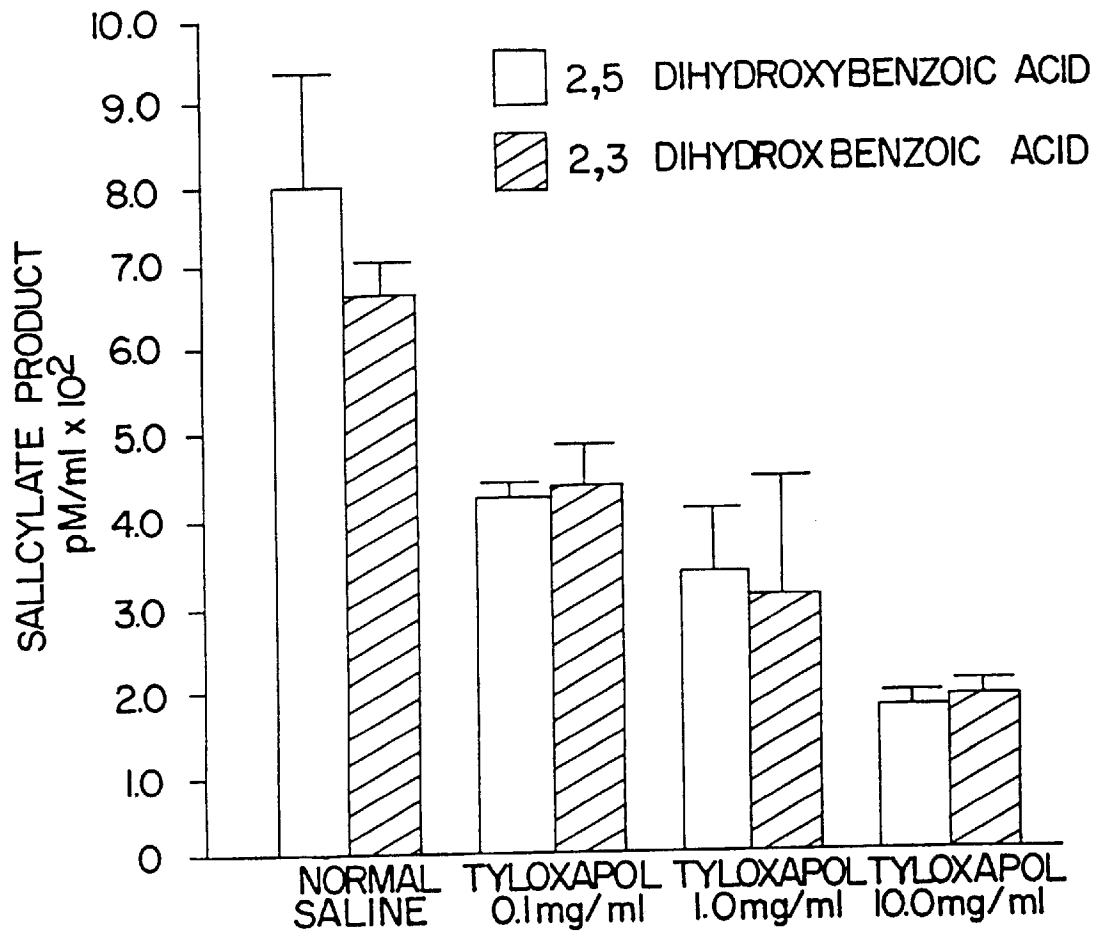


FIG. 1.

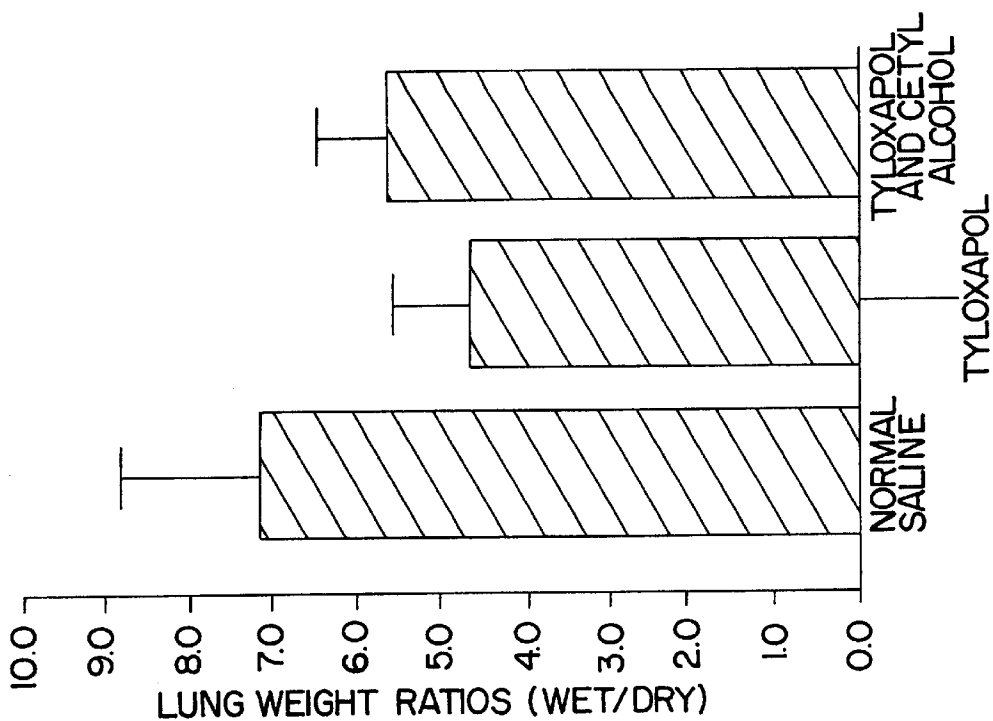


FIG. 3.

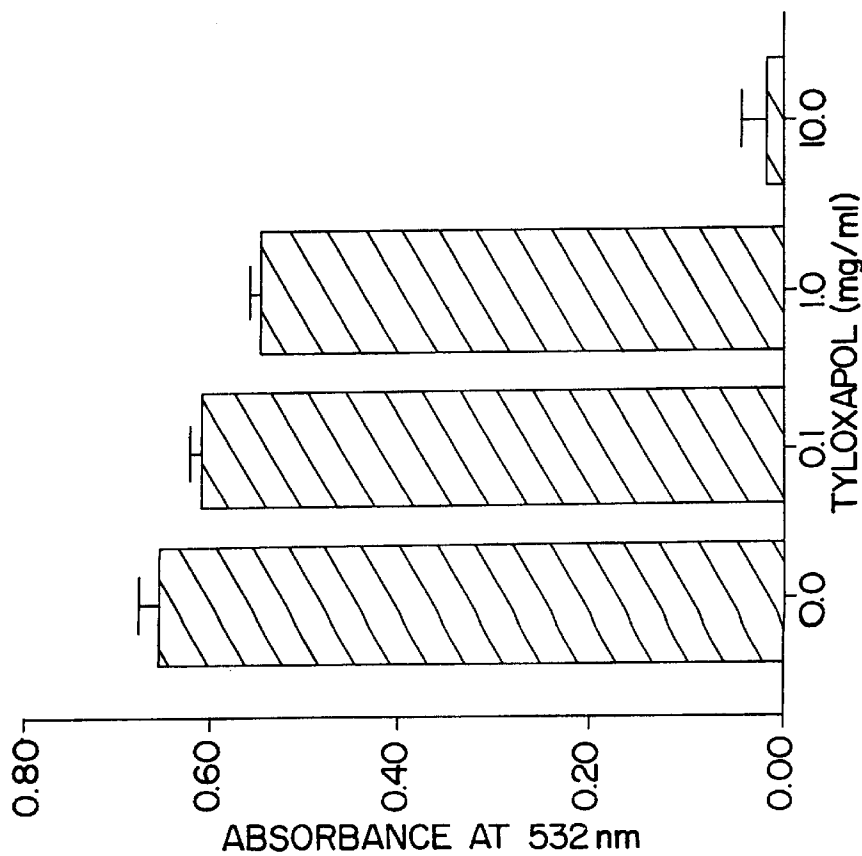


FIG. 2.

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