



# United States Patent [19]

[11] Patent Number: **5,498,421**

Grinstaff et al.

[45] Date of Patent: **\*Mar. 12, 1996**

[54] **COMPOSITION USEFUL FOR IN VIVO DELIVERY OF BIOLOGICS AND METHODS EMPLOYING SAME**

5,318,767 6/1994 Liversidge et al. .... 424/4  
5,362,478 11/1994 Desai et al. .... 424/9

### FOREIGN PATENT DOCUMENTS

[75] Inventors: **Mark W. Grinstaff**, Pasadena; **Patrick Soon-Shiong**, Los Angeles, both of Calif.; **Michael Wong**, Champaign, Ill.; **Paul A. Sandford**, Los Angeles, Calif.; **Kenneth S. Suslick**, Champaign, Ill.; **Neil P. Desai**, Los Angeles, Calif.

0129619A1 2/1985 European Pat. Off. .  
0295941A2 12/1988 European Pat. Off. .  
0361677A1 4/1990 European Pat. Off. .  
0391518A2 10/1990 European Pat. Off. .  
0418153A1 3/1991 European Pat. Off. .  
0190050B1 5/1991 European Pat. Off. .  
0213303B1 9/1991 European Pat. Off. .  
85/00011 1/1985 WIPO .  
87/01035 2/1987 WIPO .  
88/01506 3/1988 WIPO .  
88/07365 10/1988 WIPO .  
89/03674 5/1989 WIPO .  
90/13780 11/1990 WIPO .  
90/13285 11/1990 WIPO .  
91/15947 10/1991 WIPO .

[73] Assignee: **Vivorx Pharmaceuticals, Inc.**, Santa Monica, Calif.

[\*] Notice: The term of this patent shall not extend beyond the expiration date of Pat. No. 5,362,478.

[21] Appl. No.: **200,235**

[22] Filed: **Feb. 22, 1994**

### Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 23,698, Feb. 22, 1993, Pat. No. 5,439,686, and a continuation-in-part of Ser. No. 35,150, Mar. 26, 1993, Pat. No. 5,362,478.

[51] Int. Cl.<sup>6</sup> ..... **A61K 37/22**; A61K 9/127

[52] U.S. Cl. .... **424/450**; 424/451; 424/455; 424/9.3; 424/9.34; 424/9.37; 424/9.4; 424/9.5

[58] Field of Search ..... 424/451, 45, 450

### [56] References Cited

#### U.S. PATENT DOCUMENTS

3,959,457 5/1976 Speaker et al. .... 424/19  
4,073,943 2/1978 Wretlind et al. .... 424/358  
4,247,406 1/1981 Widder et al. .... 252/62.53  
4,572,203 2/1986 Feinstein ..... 128/661  
4,671,954 6/1987 Goldberg et al. .... 424/450  
4,718,433 1/1988 Feinstein ..... 128/660  
4,789,550 12/1988 Hommel et al. .... 424/493  
4,844,882 6/1989 Widder et al. .... 424/9  
4,929,446 5/1990 Bartolucci ..... 424/439  
5,059,699 10/1991 Kingston ..... 549/511  
5,110,606 5/1992 Geyer et al. .... 424/489  
5,250,283 10/1993 Barnhart ..... 424/5

### OTHER PUBLICATIONS

Abuchowski et al., "Alteration of Immunological Properties of Bovine Serum Albumin by Covalent Attachment of Polyethylene Glycol" *J. Biol. Chem.* 252:3578 (1977).  
Burgess et al., "Potential use of albumin microspheres as a drug delivery system. I. Preparation and in vitro release of steroids" *International Journal of Pharmaceutics* 39:129-136 (1987).

(List continued on next page.)

*Primary Examiner*—Thurman K. Page

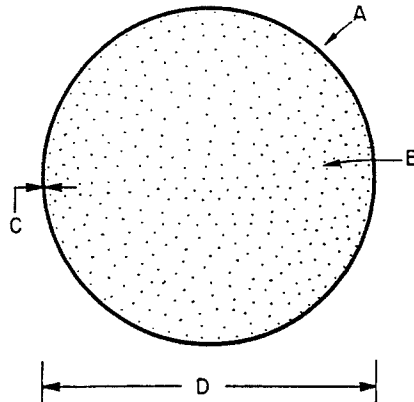
*Assistant Examiner*—William E. Benston, Jr.

*Attorney, Agent, or Firm*—Stephen E. Reiter; Pretty, Schroeder, Brueggemann & Clark

### [57] ABSTRACT

In accordance with the present invention, there are provided compositions useful for the in vivo delivery of a biologic, wherein the biologic is associated with a polymeric shell formulated from a biocompatible material. The biologic can be associated with the polymeric shell itself, and/or the biologic, optionally suspended/dispersed in a biocompatible dispersing agent, can be encased by the polymeric shell. In another aspect, the biologic associated with polymeric shell is administered to a subject, optionally dispersed in a suitable biocompatible liquid.

**30 Claims, 3 Drawing Sheets**



## OTHER PUBLICATIONS

- Chen et al., "Comparison of albumin and casein microspheres as a carrier for doxorubicin" *J. Pharm. Pharmacol.* 39:978-985 (1987).
- Feinstein et al., "Two-Dimensional Contrast Echocardiography. I. In Vitro Development and Quantitative Analysis of Echo Contrast Agents" *JACC* 3(1):14-20 (1984).
- Grinstaff and Suslick, "Nonaqueous Liquid Filled Microcapsules" *Polym. Prepr.* 32:255-256 (1991).
- Gupta et al., "Albumin microspheres. III. Synthesis and characterization of microspheres containing adriamycin and magnetite" *International Journal of Pharmaceutics* 43:167-177 (1988).
- Ishizaka et al., "Preparation of Egg Albumin Microcapsules and Microspheres" *Journal of Pharmaceutical Sciences* 70(4):358-363 (1981).
- Klibanov et al., "Amphipathic polyethyleneglycols effectively prolong the circulation time of liposomes" *FEBS* 268(1):235-237 (1990).
- Koenig and Meltzer, "Effect of Viscosity on the Size of Microbubbles Generated for Use as Echocardiographic Contrast Agents" *Journal of Cardiovascular Ultrasonography* 5(1):3-4 (1986).
- Lee et al., "Serum Albumin Beads: An Injectable, Biodegradable System for the Sustained Release of Drugs" *Science* 213:233-235 (1981).
- Leucuta et al., "Albumin microspheres as a drug delivery system for epirubicin: pharmaceutical, pharmacokinetic and biological aspects," *International Journal of Pharmaceutics* 41:213-217 (1988) (1992).
- Mathew [sic] et al., "Synthesis and Evaluation of some Water-Soluble Prodrugs and Derivatives of Taxol with Antitumor Activity" *J. Med. Chem.* 35:145-151.
- Molecular Biosystems, Inc., "Albunex—Preclinical Investigator's Package".
- Moseley et al., "Microbubbles: A Novel MR Susceptibility Contrast Agent" 10 Annual meeting of Society of Magnetic Resonance in Medicine in San Francisco, Calif. Oct. 1991.
- Suslick and Grinstaff, "Protein Microencapsulation of Nonaqueous Liquids" *J. Am. Chem. Soc.* 112(21):7807-7809 (1990).
- Willmott and Harrison, "Characterization of freeze-dried albumin microspheres containing the anti-cancer drug adriamycin" *International Journal of Pharmaceutics* 43:161-166 (1988).

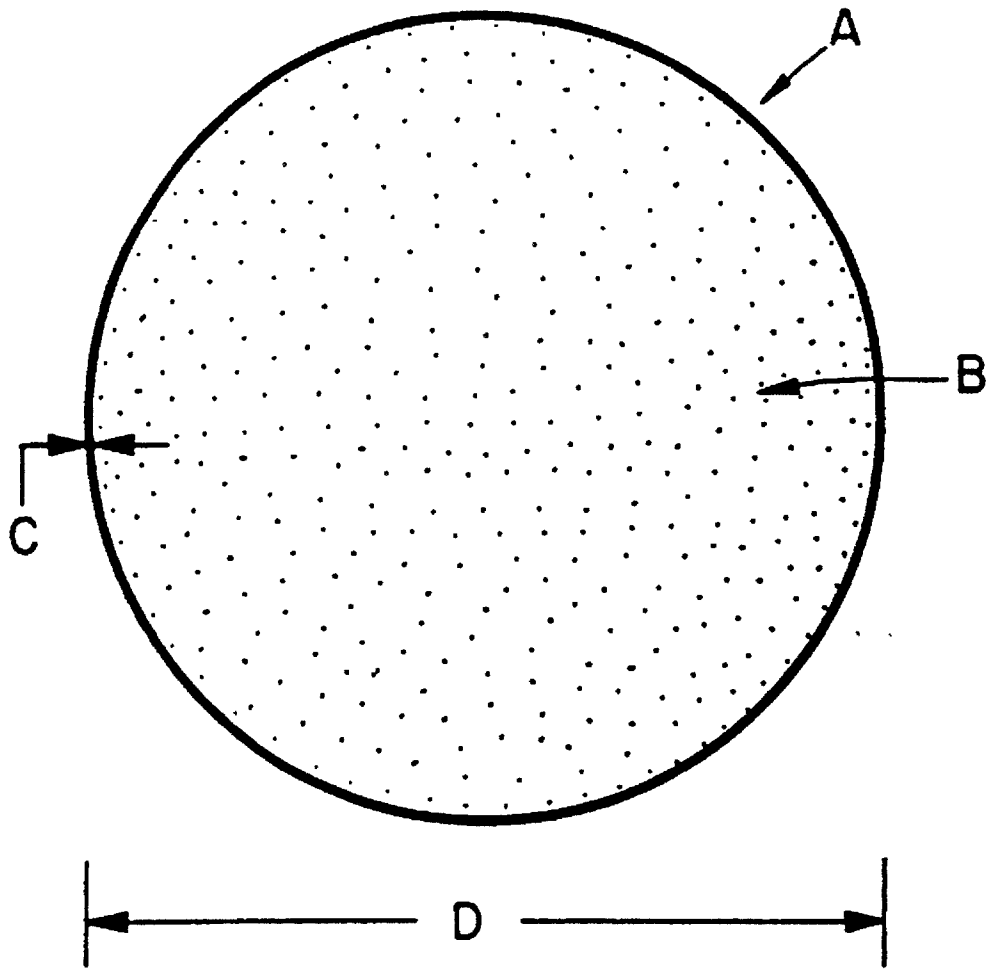


FIG. 1

FIG. 2

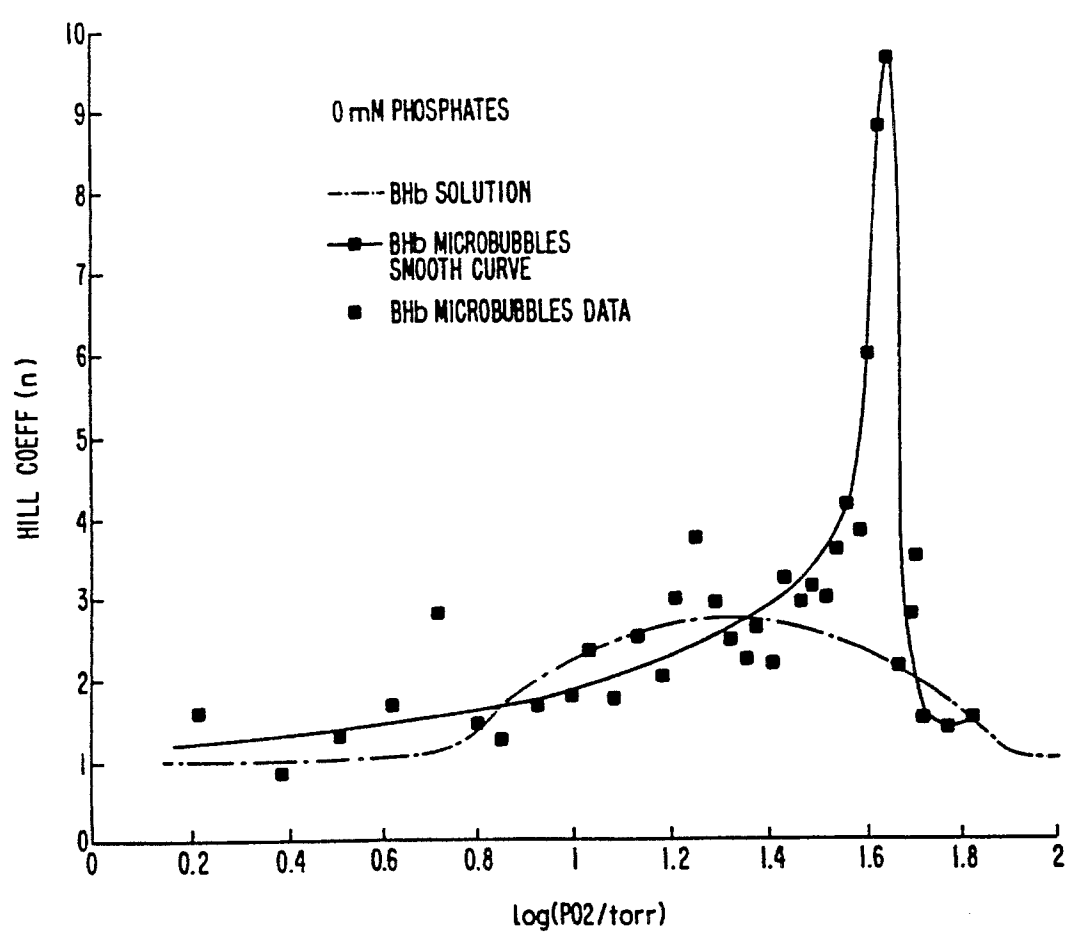
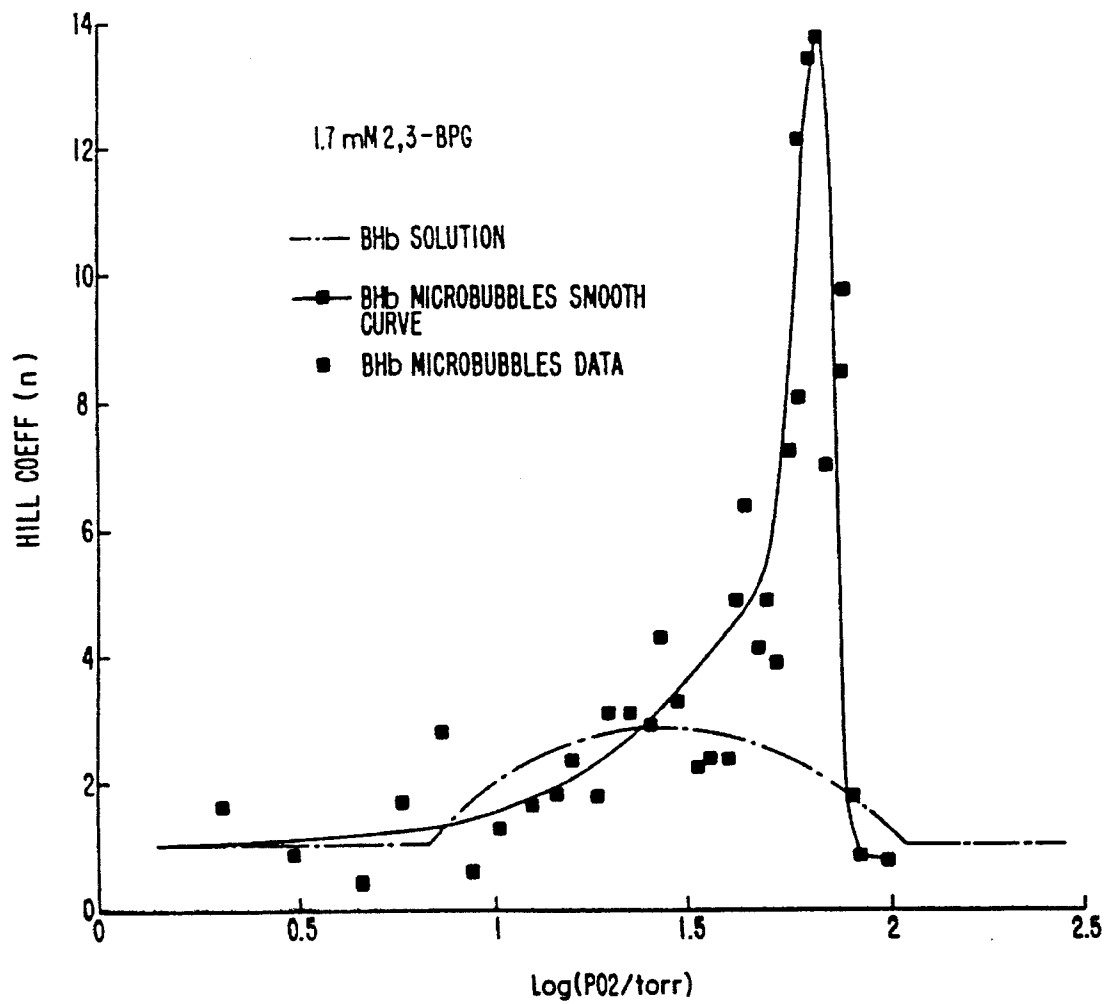


FIG. 3



# Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

## Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

## Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

## Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

## API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

## LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

## FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

## E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.