



(12) **United States Patent**  
**Brittain et al.**

(10) **Patent No.:** **US 8,791,270 B2**  
(45) **Date of Patent:** **Jul. 29, 2014**

(54) **BENDAMUSTINE PHARMACEUTICAL COMPOSITIONS**

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(\* ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **13/969,724**

(22) Filed: **Aug. 19, 2013**

(65) **Prior Publication Data**

US 2013/0338205 A1 Dec. 19, 2013

**Related U.S. Application Data**

(63) Continuation of application No. 13/719,409, filed on Dec. 19, 2012, which is a continuation of application No. 13/654,898, filed on Oct. 18, 2012, now Pat. No. 8,461,350, which is a continuation of application No. 11/330,868, filed on Jan. 12, 2006, now Pat. No. 8,436,190.

(60) Provisional application No. 60/644,354, filed on Jan. 14, 2005.

(51) **Int. Cl.**  
**C07D 235/04** (2006.01)  
**A61K 47/10** (2006.01)  
**A61K 31/4184** (2006.01)  
**A61K 9/19** (2006.01)  
**A61K 9/00** (2006.01)

(52) **U.S. Cl.**  
CPC . **A61K 9/19** (2013.01); **A61K 47/10** (2013.01);  
**A61K 31/4184** (2013.01); **A61K 9/0019**  
(2013.01)

USPC ..... **548/304.7**; 34/284

(58) **Field of Classification Search**  
USPC ..... 34/284  
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,590,028 A 6/1971 Report et al.  
4,012,448 A 3/1977 Smith et al.  
4,537,883 A 8/1985 Alexander et al.  
4,659,699 A 4/1987 Francis  
4,670,262 A 6/1987 Battelli et al.  
4,959,215 A 9/1990 Sauerbier et al.  
5,036,060 A 7/1991 Alam et al.  
5,066,647 A 11/1991 Palepu et al.  
5,130,305 A 7/1992 Palepu et al.  
5,183,746 A 2/1993 Shaked et al.  
5,192,743 A 3/1993 Hsu et al.  
5,204,335 A 4/1993 Sauerbier et al.  
5,227,373 A 7/1993 Alexander et al.  
5,227,374 A 7/1993 Alexander et al.

5,268,368 A 12/1993 Palepu  
5,413,995 A 5/1995 Alexander et al.  
5,418,223 A 5/1995 Palepu et al.  
5,750,131 A 5/1998 Wichert et al.  
5,770,230 A 6/1998 Teagarden et al.  
5,776,456 A 7/1998 Anderson et al.  
5,955,504 A 9/1999 Wechter et al.  
5,972,912 A 10/1999 Marek et al.  
6,034,256 A 3/2000 Carter et al.  
6,077,850 A 6/2000 Carter et al.  
6,090,365 A 7/2000 Kaminski et al.  
6,271,253 B1 8/2001 Carter et al.  
6,380,210 B1 4/2002 DeSimone et al.  
6,492,390 B2 12/2002 Carter et al.  
6,545,034 B1 4/2003 Carson et al.  
6,569,402 B1 5/2003 Cheesman et al.  
6,573,292 B1 6/2003 Nardella  
6,613,927 B1 9/2003 Kwok  
6,780,324 B2 8/2004 Le Garrec et al.  
8,420,130 B1 4/2013 Nuijen et al.  
8,436,190 B2 5/2013 Brittain et al.  
2002/0031527 A1 3/2002 Wu et al.  
2002/0102215 A1 8/2002 Klaveness et al.  
2003/0232874 A1 12/2003 Nardella  
2004/0053972 A1 3/2004 Nara  
2004/0058956 A1 3/2004 Akiyama et al.  
2004/0072889 A1 4/2004 Masferrer  
2004/0096436 A1 5/2004 Carson et al.  
2004/0152672 A1 8/2004 Carson et al.  
2004/0247600 A1 12/2004 Leoni  
2005/0020615 A1 1/2005 Rubino  
2005/0060028 A1 3/2005 Horres et al.  
2005/0176678 A1 8/2005 Horres et al.  
2006/0051412 A1 3/2006 Petereit et al.  
2006/0128777 A1 6/2006 Bendall et al.

(Continued)

FOREIGN PATENT DOCUMENTS

DE 34727 A1 12/1964  
DE 80967 C 6/1970  
DE 159289 A1 3/1983  
DE 159877 A1 4/1983  
DE 3907079 9/1989  
DE 293808 A5 9/1991  
DE 10016077 A1 12/2001  
DE 10306724 A1 9/2003  
DE 10304403 A1 8/2004  
EP 334083 A1 9/1989

(Continued)

OTHER PUBLICATIONS

Avis et al., "Pharmaceutical Dosage Forms: Parenteral Medications vol. 1" Marcel Dekker Inc, 1992, pp. 217-227.

(Continued)

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(57) **ABSTRACT**

The present invention provides pharmaceutical formulations of lyophilized bendamustine suitable for pharmaceutical use. The present invention further provides methods of producing lyophilized bendamustine. The pharmaceutical formulations can be used for any disease that is sensitive to treatment with bendamustine, such as neoplastic diseases.

**23 Claims, 6 Drawing Sheets**

(56)

## References Cited

## U.S. PATENT DOCUMENTS

2009/0264488 A1 10/2009 Cooper et al.  
 2011/0190363 A1 8/2011 Drager et al.  
 2012/0071532 A1 3/2012 Cooper et al.  
 2013/0041003 A1 2/2013 Brittain et al.  
 2013/0123316 A1 5/2013 Brittain

## FOREIGN PATENT DOCUMENTS

EP 0656211 A1 6/1995  
 EP 0780386 A1 6/1997  
 EP 1354952 A1 10/2003  
 EP 1444989 A1 8/2004  
 WO WO 96/28148 A2 9/1996  
 WO WO 97/08174 A1 3/1997  
 WO WO 03/066027 A1 8/2003  
 WO WO 03/077882 A2 9/2003  
 WO WO 03/081238 A2 10/2003  
 WO WO 03/086470 A2 10/2003  
 WO WO 03/094990 A1 11/2003  
 WO WO 2004/041118 A2 5/2004  
 WO WO 2006/076620 A2 7/2006  
 WO WO 2009/120386 A2 10/2009

## OTHER PUBLICATIONS

Excerpt from Rote Liste 2003, Arzneimittelverzeichnis für Deutschland, 2 pages.

Flamberg, et al., "Low Temperature Vacuum Drying of Sterile Parenterals from Ethanol" Bulletin of the Parenteral Drug Association, Sep.-Oct. 1970, 24(5), 209-217.

Fürst et al., "The hydrolytic degradation of IMET 3393", Pharmazeutische Zentralhalle für Deutschland 1969, 108(9), 608-614.

Gandhi et al., "Bendamustine in B Cell Malignancies: The New, 46-year old kid on the Block" Clinical Cancer Research, Dec. 2009, 15(24), 7456-7461.

Jennings, Thomas A., "Extracts from Lyophilization. Introduction and Basic Principles". 2002, by CRC Press LLC, Boca Raton, Florida, 33431.

Jonkmann-de Vries et al., "Pharmaceutical Development of (Investigational) Anticancer Agents for Parenteral Use-A Review Drug Development and Industrial Pharmacy", 1996, 22(6), 475-494.

Kasraian et al., "The Effect of Tertiary Butyl Alcohol on the Resistance of the Dry Product Layer During Primary Drying", 1995, Pharm. Res, 12(4), 491-495, hier: Zusammenfassung.

Kasraian et al., "Thermal Analysis of the Tertiary Butyl Alcohol-Water System and its Implications on Freeze-Drying", 1995, Pharm. Res, 12(4), 484-90, hier: Zusammenfassung.

Kibbe, Arthur, H., Handbook Pharmaceutical Excipients, 3rd Edition, 2000, Mannitol, American Pharmaceutical Association and Pharmaceutical Press.

Kim, et al., "The Physical State of Mannitol after Freeze-Drying: Effects of Mannitol Concentration, Freezing Rate, and a Noncrystallizing Cosolute" Journal of Pharmaceutical Sciences, 87(8), Aug. 1998, 931-935.

Nuijen, B., "Pharmaceutical Development of a Parenteral Lyophilized Formulation of the Novel Antitumor Agent Aplidine", PDA Journal of Pharmaceutical Science and Technology, May/Jun. 2000, 54(3), 193-208.

Oesterle, et al., "The Influence of Tertiary Butyl Alcohol and Volatile Salts on the Sublimation of Ice From Frozen Sucrose Solutions: Implications for Freeze-Drying" Pharmaceutical Development and Technology, 1998, 3(2), 175-183.

Rey et al., "Freeze-Drying/Lyophilization of Pharmaceutical and Biological Products", Second Edition, revised and expanded, New York, Taylor and Francis Group, 2004, Seiten 239-243.

Rowe et al., "Handbook of Pharmaceutical Excipients" Fourth Edition, The Royal Pharmaceutical Society of Great Britain, 2003, pp. 373-377.

Rowe, et al, Handbook of Pharmaceutical Excipients, Sixth Edition, Pharmaceutical Press and the American Pharmacists Association, Royal Pharmaceutical Society of Great Britain, 2009, 16 pages.

Seager et al., Structure of Products Prepared by Freeze-Drying Solutions Containing Organic Solvents, PDA Journal of Pharmaceutical Science and Technology, Jul.-Aug. 1985, 39(4), 161-179, hier: Zusammenfassung.

Tang, X. and Pikal, M. J., "Design of Freeze-Drying Processes for Pharmaceuticals: Practical Advice" Pharmaceutical Research, 21(2), Feb. 2004, 191-200.

Telang, C. and Suryanarayanan, R., "Crystallization of Cephalothin Sodium During Lyophilization from Tert-Butyl Alcohol-Water Cosolvent System" Pharmaceutical Research, Jan. 2005, 22(1), 153-160.

Van Drooge et al., "Incorporation of Lipophilic Drugs in Sugar Glasses by Lyophilization using a Mixture of Water and Tertiary Butyl Alcohol as Solvent" Journal of Pharmaceutical Sciences, Mar. 2004, 93(3), 713-725.

Wade, A. and Weller, Paul J., Handbook of Pharmaceutical Excipients, Second Edition, American Pharmaceutical Association, Washington and The Pharmaceutical Press, London, 1994, pp. 294-298.

Wittaya-Areekul, Sakchai et al., Freeze-Drying of tert-Butanol/Water Cosolvent Systems: A Case Report on Formation of a Friable Freeze-Dried Powder of Tobramycin Sulfate Journal of Pharmaceutical Sciences, 91(4), Apr. 2002, 1147-1155.

Aivado et al., "Bendamustine in the Treatment of Chronic Lymphocytic Leukemia: Results and Future Perspectives", Seminars in Oncology, Aug. 2002, 29(4), 19-22, Suppl. 13.

Barman Balfour et al., "Bendamustine", Drugs, 2001, 61(5), 631-638, Auckland, New Zealand.

Berge et al., "Pharmaceutical Salts", Journal of pharmaceutical sciences, Jan. 1977, 66(1), 1-19.

Bremer, Karl, "High Rates of Long-Lasting Remissions After 5-Day Bendamustine Chemotherapy Cycles in Pre-Treated Low-Grade Non-Hodgkin's-Lymphomas", Journal of Cancer Research and Clinical Oncology, Nov. 2002, 128(11), 603-609.

Byrn et al., "Pharmaceutical Solids: A Strategic Approach to Regulatory Consideration", Pharmaceutical Research, Jul. 1995, 12(7), 945-954.

Chow et al., "Anti-Cd20 Antibody (Idoc-C2b8, Rituximab) Enhances Efficacy of Cytotoxic Drugs on Neoplastic Lymphocytes In Vitro: Role of Cytokines Complement, and Caspases", Haematologica, Jan. 2002, 87(1), 33-43.

Chow et al., "In AML Cell Lines Ara-C Combined with Purine Analogues is Able to Exert Synergistic as Well as Antagonistic Effects on Proliferation, Apoptosis and Disruption of Mitochondrial Membrane Potential", Leukemia & Lymphoma, 2003, 44(1), 165-173.

Chow et al., "Synergistic Effects of Chemotherapeutic Drugs in Lymphoma Cells Are Associated With Down-Regulation of Inhibitor of Apoptosis Proteins (Iap), Prostate- Apoptosis-Response-Gene 4(Par-4), Death-Associated Protein (Dazz) and With Enforced Caspase Activation", Biochemical Pharmacology, Jan. 2003, 66(5), 711-724.

Department of Health and Human Services, Food and Drug Administration, "International Conference on Harmonisation; Guidance on Impurities: Residual Solvents," Federal Register, Dec. 24, 1997, 62(247), 67377-67388.

Diehl et al., "Bendamustine in the Treatment of Hematologic Malignancies", Semin. Oncol., Aug. 2002, 29(4), 1-3, Suppl. 13, Saunders, Philadelphia, PA.

Fichtner et al., "Antineoplastic Activity and Toxicity of Some Alkylating Cytostatics (Cyclophosphamide, Ccnu, Cytostasan) Encapsulated in Liposomes in Different Murine Tumor Models", Journal of Microencapsulation, Jan. 1986, 3(2), 77-87.

Gandhi, Varsha, "Metabolism and Mechanisms of Action of Bendamustine: Rationales for Combination Therapies", Seminars in Oncology, Aug. 2002, 29(4), 4-11, Suppl. 13.

Goodman et al., The Pharmacological Basis of Therapeutics, 1985, 7th edition, Macmillan publishing company, New York.

(56)

## References Cited

## OTHER PUBLICATIONS

- Heider et al., "Efficacy and Toxicity of Bendamustine in Patients With Relapsed Low-Grade Non-Hodgkin's Lymphomas", *Anti-Cancer Drugs*, Oct. 2001, 12(9), 725-729.
- Kath et al., "Bendamustine Monotherapy in Advanced and Refractory Chronic Lymphocytic Leukemia", *Journal of Cancer Research and Clinical Oncology*, Jan. 2001, 127(1), 48-54.
- Koenigsman et al., "Fludarabine and Bendamustine in Refractory and Relapsed Indolent Lymphoma a Multicenter Phase 1111 Trial of the East German Society of Hematology and Oncology (OSHO)", *Leukemia & Lymphoma*, Sep. 2004, 45(9), 1821-1827.
- Kollmannsberger et al., "Phase II Study of Bendamustine in Patients With Relapsed or Cisplatin-Refractory Germ Cell Cancer", *Anti-Cancer Drugs*, Aug. 2000, 11(17), 535-539.
- Konstantinov et al., "Cytotoxic Efficacy of Bendamustine in Human Leukemia and Breast Cancer Cell Lines", *Journal of Cancer Research and Clinical Oncology*, May 2002, 128(5), 271-278.
- Leoni et al., "SDX-105 (Trenda), Active in Non-Hodgkins Lymphoma Cells, Induces the Mitotic Catastrophe Death Pathway", *Blood*, 104(11), 2004, Abs 4593, p. 232b.
- Maas, "Stabilität von Benamustinhydrochlorid in Infusionslösungen", *Pharmazie*, 1994, 49(10), 775-777 (Translation Included).
- McKim et al., "Dimethyl Sulfoxide USP, PhEur in Approved Pharmaceutical Products and Medical Devices," *Pharmaceutical Technology*, May 2, 2008, 1-7.
- Mottu et al., "Organic Solvents for Pharmaceutical Parenterals and Emboic Liquids: A Review of Toxicity Data," *PDA J. Pharma. Sci. & Tech.* 54(6) Nov.- Dec. 2000, 456-469.
- Ni et al., "Use of Pure T-Butanol as a Solvent for Freeze-Drying: A Case Study", *International Journal of Pharmaceutics*, Sep. 2001, 226(1-2), 39-46.
- Niemeyer et al., "SDX-105 (bendamustine) is a Clinically Active Chemotherapeutic Agent With a Distinct Mechanism of Action", *Proc Annu Meet Am Assoc Cancer Res*, Mar. 2004, 45, 1st ed., 2 pages.
- Nowak et al., "Upon Drug-Induced Apoptosis in Lymphoma Cells X-linked Inhibitor of Apoptosis (XIAP) Translocates from the Cytosol to the Nucleus", *Leukemia & Lymphoma*, Jul. 2004, 45(7), 1429-1436.
- Ozegowski et al., "IMET 3393, gamma-(1-methyl-5-bis-(chloro-ethyl)-amino-benzimidazolyl(2)-buttersäure-hydrochlorid, ein neues Zytostatikum aus der Reihe der Benzimidazol-Loste", *Zbl Pharm.*, 1971;110, Heft 10, 1013-1019 (Translation Included).
- Remington: *Pharmaceutical Sciences*, 1990, Mack Publishing company, Easton, Pennsylvania.
- Ribomustin: Bendamustine Product Monograph, Jan. 2002, 3-58, Ribosepharm GMBH, Munchen, Germany.
- Ribomustin: Bendamustine Product Monograph, Mar. 2005, 3-73, Ribosepharm MBH, Munchen, Germany.
- Rummel et al., "In Vitro Studies With Bendaustine: Enhanced Activity in Combination With Rituximab", *Seminars in Oncology*, Aug. 2002, 29(4), 12-14, Suppl. 13.
- Scasnar et al., "Stability Studies of <sup>14</sup>C-Cytostasan Solutions and Its Extraction Using Dicarbolide of Cobalt", *Die Pharmazie*, Mar. 1988, 43(3), 176-179.
- Schmidt-Hieber et al., "A Phase II Study of Bendamustine Chemotherapy As Second-Line Treatment in Metastatic Uveal Melanoma", *Melanoma Research*, Dec. 2004, 14(6), 439-442.
- Schoffski et al., "Repeated Administration of Short Infusions of Bendamustine: A Phase I Study in Patients With Advanced Progressive Solid Tumors", *Journal of Cancer Research and Clinical Oncology*, Jan. 2000, 126(1), 41-47.
- Schrijvers et al., "Phase I Studies with Bendamustine: An update", *Seminars in Oncology*, Aug. 2002, 29(4), 15-18, Suppl. 13.
- Schwanen et al., "In Vitro Evaluation of Bendamustine Induced Apoptosis in B-Chronic Lymphocytic Leukemia", *Leukemia*, Oct. 2002, 16(10), 2096-2105.
- Strumberg et al., "Bendamustine Hydrochloride Activity Against Doxorubicin-Resistant Human Breast Carcinoma Cell Lines", *Anti-Cancer Drugs*, Jun. 1996, 7(4), 415-421.
- Weide et al., "Bendamustine Mitoxantrone and Rituximab (BMR): A New Effective Regimen for Refractory or Relapsed Indolent Lymphomas", *Leukemia & Lymphoma*, Feb. 2002, 43(2), 327-331.
- Weide et al., "Bendamustine/Mitoxantrone/Rituximab (BMR): A Very Effective, Well Tolerated Outpatient Chemoimmunotherapy for Relapsed and Refractory CD20-positive Indolent Malignancies. Final Results of a Pilot Study", *Leukemia & Lymphoma*, Dec. 2004, 45(12), 2445-2449.
- Weidmann et al., "Bendamustine is Effective in Relapsed or Refractory Aggressive non-Hodgkin's Lymphoma", *Annals of Oncology*, Aug. 2002, 13(8), 1285-1289.
- Werner et al., "Hydrolyseprodukte des Cancerostaticums Cytostasan (Bendamustin)", *Pharmazie*, Apr. 1987, 42, 272-273.
- Zulkowski, et al., "Regression of Brain Metastases From Breast Carcinoma After Chemotherapy With Bendamustine", *Journal of Cancer Research and Clinical Oncology*, Feb. 2002, 128(2), 111-113.
- Chow et al., "In Vitro Induction of Apoptosis of Neoplastic Cells in Low-Grade Non-Hodkin's Lymphomas by Combinations of Established Cytotoxic Drugs With Bendamustine", *Haematologica*, May 2001, 86(5), 485-493.
- EC Safety Data Sheet: Ribomustin® in <http://www.docstoc.com/docs/22323231/EC-Safety-Data-Sheet-Bendamustin> (published: Jul. 3, 1998; updated Mar. 1, 2007), 8 pages.
- Gust et al., "Investigations on the Stability of Bendamustin, a Cytostatic Agent of the Nitrogen Mustard Type. I. Synthesis, Isolation, and Characterization of Reference Substances", *Monatshefte für Chemie*, 1997, 128(3), 291-299.
- Kanekal et al., "SDX-105(TREANDA) Enhances the Tumor Growth Inhibitory Effect of Rituximab in Daudi Lymphoma Xenografts", 2004, *Blood*, ASH Annual Meeting Abstracts, 104, Abstract 4580.
- Koster et al., "Carboplatin in Combination With Bendamustine in Previously Untreated Patients With Extensive-Stage Small Lung Cancer (SCLC)", *Clinical Drug Investigation*, 2004, 24(10), 611-618.
- Ponisch et al., "Bendamustine in the Treatment of Multiple Myeloma: Results and Future Perspectives", *Seminars in Oncology*, Aug. 2002, 29(4), 23-26, Suppl. 13.
- Preiss et al., "Pharmacokinetics of Bendamustin (Cytostasan) in Patients", *Pharmazie*, Mar. 1985, 40(11), 782-784.
- Rummel et al., "Bendamustine in the Treatment of Non-Hodgkin's Lymphoma: Results and Future Perspectives", *Seminars in Oncology*, Aug. 2002, 29(4), 27-32, Suppl. 13.
- Rxlist, *The Internet Drug Index*, Treanda®, 2013, pp. 1-2, <http://www.rxlist.com/script/main/rxlist.asp?articlekey=88624&pf=3&page=1>.
- Scasnar et al., "Radiochemical Assay of Stability of <sup>14</sup>C-Cytostasan Solutions During Preparation and Storage", *Journal of Radioanalytical and Nuclear Chemistry*, 1998, 121(2), 489-497.
- Teagarden et al., "Practical Aspects of Lyophilization Using Non-Aqueous Co-Solvent Systems," *European Journal of Pharmaceutical Sciences*, Mar. 2002, 15(2), 115-133.
- Wittaya-Areekul et al., "Freeze-Drying of Tert-Butyl Alcohol/Water Cosolvent Systems: Effects of Formulation and Process Variables on Residual Solvents," *Journal of Pharmaceutical Sciences*, Apr. 1998, 87(4), 491-495.

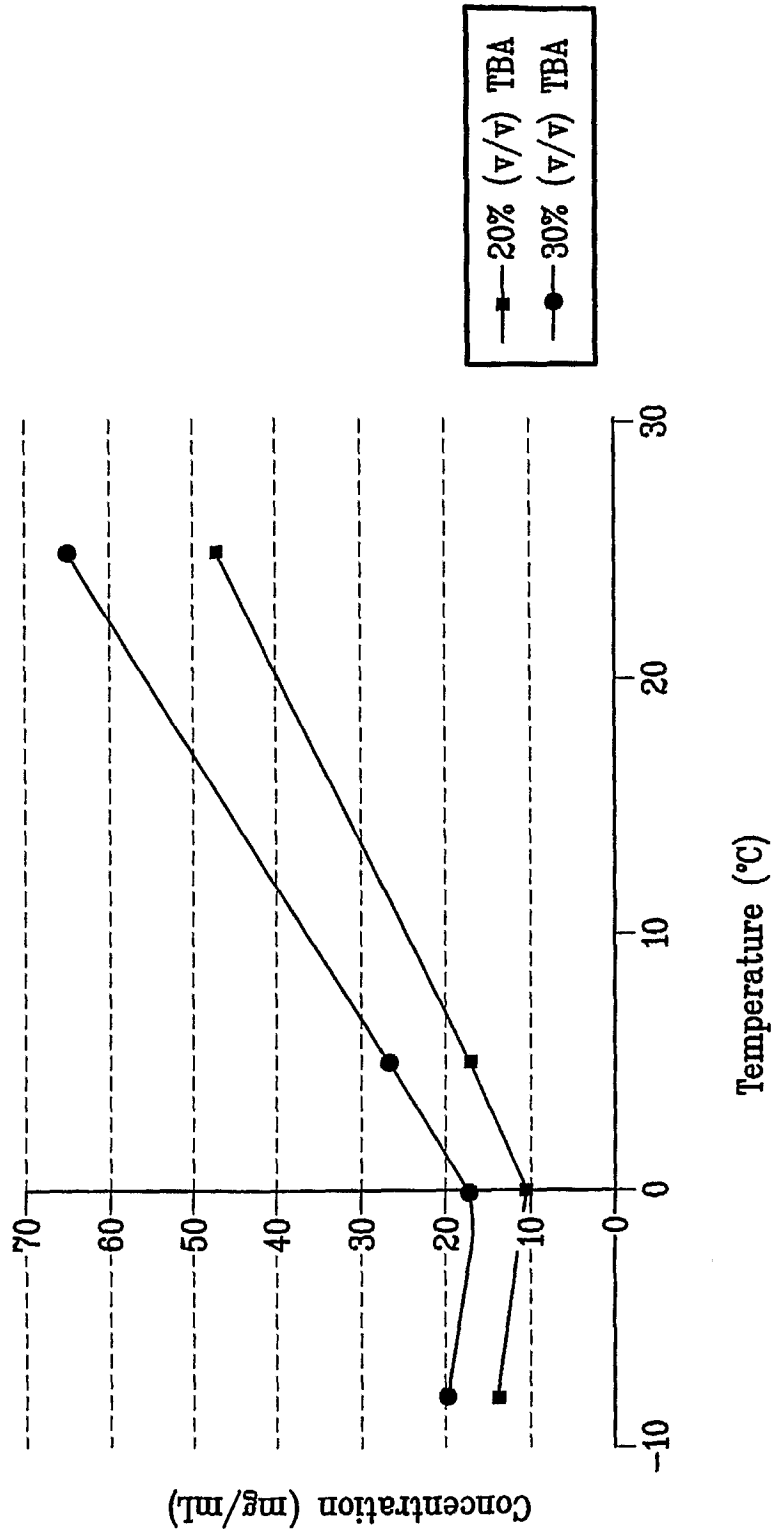


FIG. 1

Bendamustine Purity after 24 hours at 5°C in Various Alcohol/Water Co-Solvents

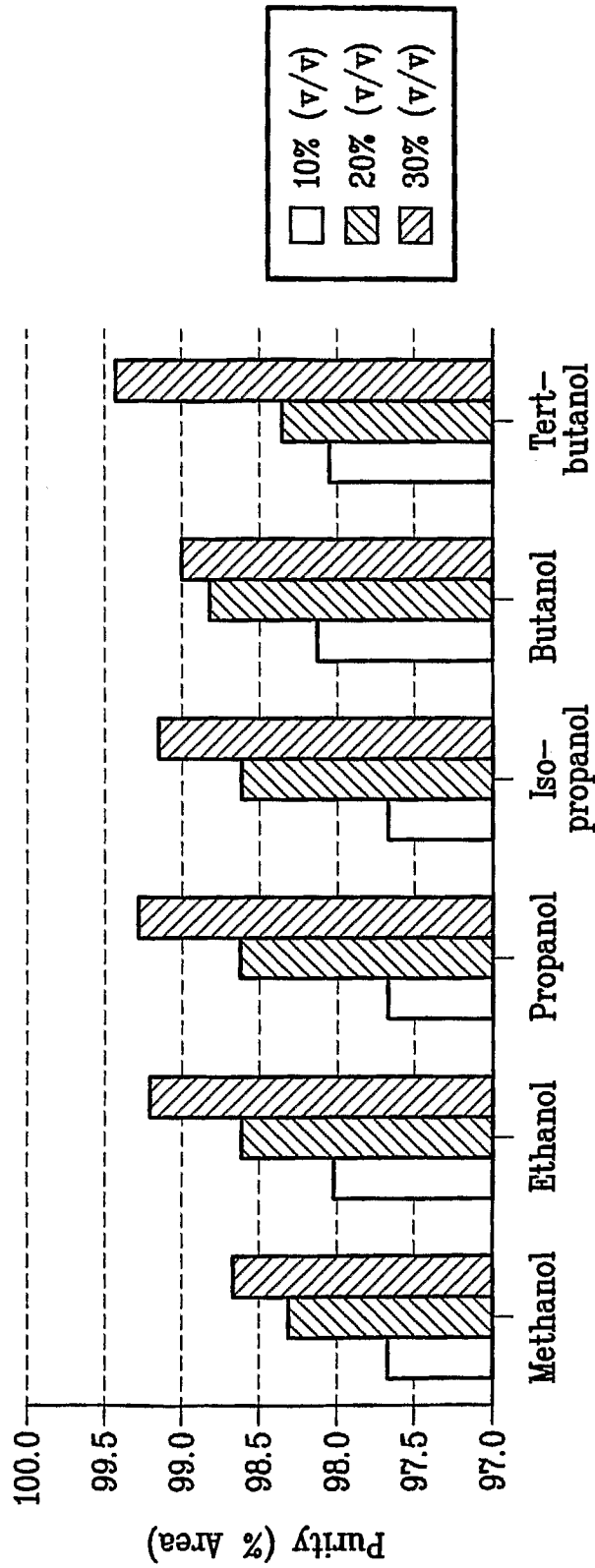


FIG. 2

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