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**Brittain et al.**

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(54) **BENDAMUSTINE PHARMACEUTICAL COMPOSITIONS**

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

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

(58) **Field of Classification Search**

USPC ..... 34/284; 548/304.7  
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.
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.
2002/0102215 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.

(Continued)

**FOREIGN PATENT DOCUMENTS**

DE	34727	12/1964
DE	80967	6/1970

(Continued)

**OTHER PUBLICATIONS**

Kanekal et al., Kanekal et al. (SDX-105(Treanda) Enhances the Tumor Growth Inhibitory Effect of Rituximab in Daudi Lymphoma Xenografts, 2004, Blood (ASH Annual Meeting Abstracts), vol. 104.\*

RxList, Treanda, 2013, pp. 1-2.\*

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, 2002, 128(11), 603-609.

(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.

**4 Claims, 6 Drawing Sheets**

(56)

**References Cited**

## U.S. PATENT DOCUMENTS

2005/0176678 A1	8/2005	Horres et al.
2006/0051412 A1	3/2006	Peterreit et al.
2006/0128777 A1	6/2006	Bendall et al.
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.

## FOREIGN PATENT DOCUMENTS

DE	159289	3/1983
DE	159877	4/1983
DE	3907079	9/1989
DE	293808	9/1991
DE	10016077	12/2001
DE	10306724	9/2003
DE	10304403	8/2004
EP	334083 A1	9/1989
EP	0656211	6/1995
EP	0780386	6/1997
EP	1354952	10/2003
EP	1444989	8/2004
WO	WO 96/28148	9/1996
WO	WO 97/08174	3/1997
WO	WO 99/42125	8/1999
WO	WO 03/066027	8/2003
WO	WO 03/077882 A2	9/2003
WO	WO 03/081238	10/2003
WO	WO 03/086470	10/2003
WO	WO 03/094990	11/2003
WO	WO 2004/041118 A2	5/2004
WO	WO 2006/076620	7/2006
WO	WO 2009/120386	10/2009

## OTHER PUBLICATIONS

- 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 (IDE-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., "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.
- Chow et al., "Synergistic effects of chemotherapeutic drugs in lymphoma cells are associated with down-regulation of inhibitor of apoptosis proteins (IAPs), 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.
- 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.
- 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.
- Gust et al., "Investigations on the Stability of Bendamustine, a Cytostatic Agent of the Nitrogen Mustard Type, I. Synthesis, Isolation, and Characterization of Reference Substances", *Monatshefte für Chemie*, 1997, 128(3), 291-299.
- Heider et al., "Efficacy and toxicity of bendamustine in patients with relapsed low-grade non-Hodgkin's lymphomas", *Anti-Cancer Drugs*, 2001, 12(9), 725-729.
- Kath et al., "Bendamustine monotherapy in advanced and refractory chronic lymphocytic leukemia", *Journal of Cancer Research and Clinical Oncology*, 2001, 127(1), 48-54.
- Koenigsman et al., "Fludarabine and Bendamustine in Refractory and Relapsed Indolent Lymphoma a Multicenter Phase III Trial of the East German Society of Hematology and Oncology (OSHO)", *Leukemia & Lymphoma*, 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*, 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*, 2002, 128(5), 271-278.
- Köster 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.
- 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 embolic 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-(β-chloräthyl)-amino-benzimidazolyl(2)-buttersäure-hydrochlorid, ein neues Zytostatikum aus der Reihe der Benzimidazol-Loste", *Zbl Pharm.*, 1971;110, Heft 10, 1013-1019 (Translation Included).
- 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 bendamustine (Cytostasan) in patients", *Pharmazie*, Mar. 1985, 40(11), 782-784.
- Remington: *Pharmaceutical Sciences*, 1990, Mack Publishing company, Easton, Pennsylvania.
- Ribomustine: Bendamustine Product Monograph, Jan. 2002, 3-58, Ribosepharm GmbH, München, Germany.
- Ribomustine: Bendamustine Product Monograph, Mar. 2005, 3-73, Ribosepharm MBH, München, Germany.
- 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.
- 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.

(56)

**References Cited****OTHER PUBLICATIONS**

- 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.
- Scasnar et al., "Stability studies of 14C-Cytostasan solutions and its extraction using dicarbolidic 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, 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, 2000, 126(1), 41-47.
- Schrijvers et al., "Phase I studies with bendamustine: An update", Seminars in Oncology, 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, 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, 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, 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, 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, 2002, 128(2), 111-113.
- 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.
- U.S. Appl. No. 13/719,379, filed Dec. 19, 2012, Cephalon, Inc.
- Mundipharma GmbH, Ribomustin EC Safety Data Sheet in accordance with 91/155/EEC. Eight Pages, Jan. 3, 2007.
- Ribopharm. Fachinformation (Zusammenfassung der Merkmale des Arzneimittels/SPC). Four Pages, Oct. 2005.
- Avis et al., "Pharmaceutical Dosage Forms: Parenteral Medications Volume 1" Marcel Dekker Inc, 1992, pp. 217-227.
- 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.
- 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 Cephalexin 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.

\* cited by examiner

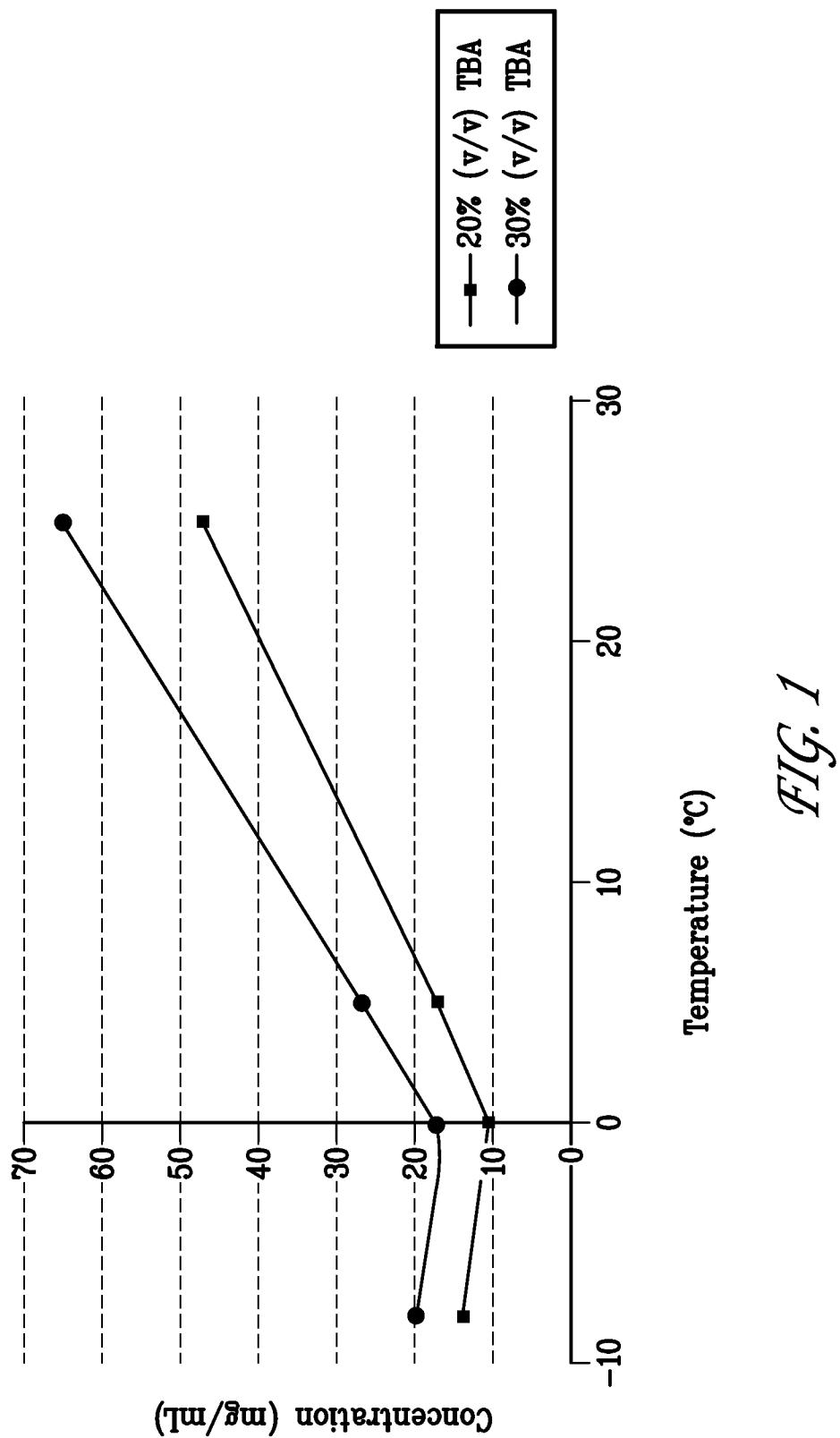
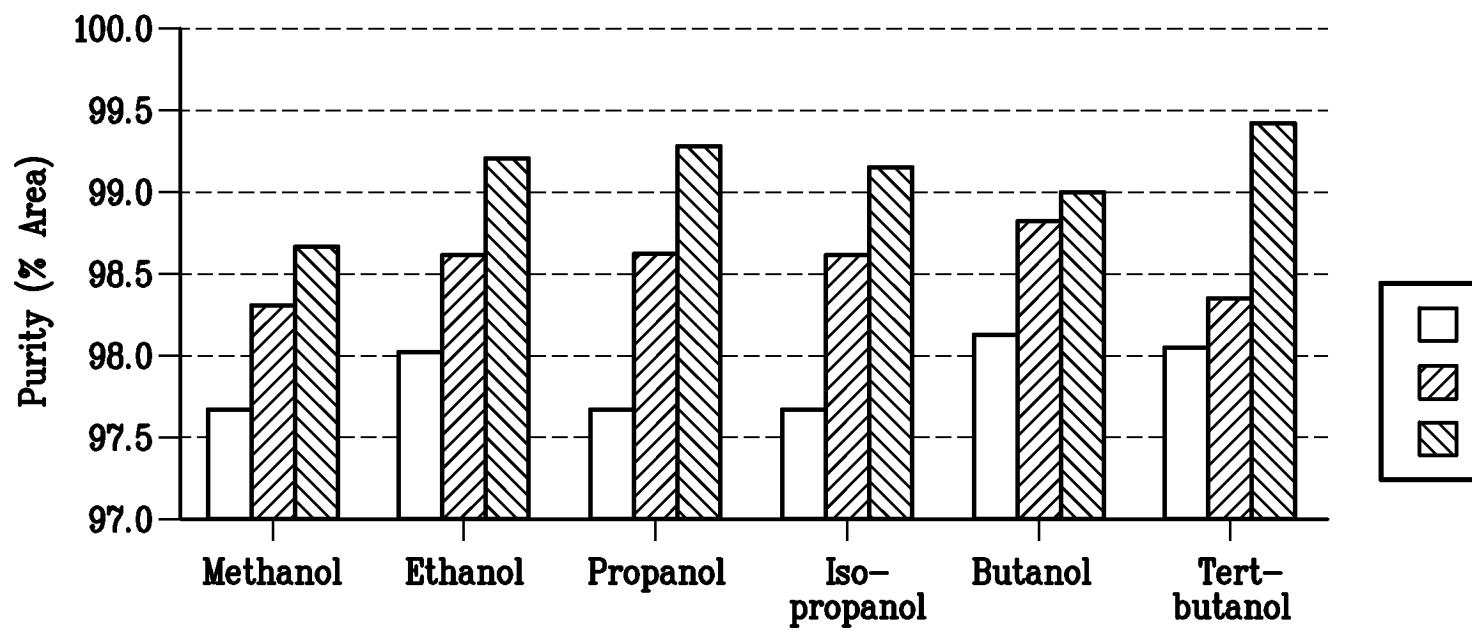


FIG. 1

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



*FIG. 2*

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