US006071904A

United States Patent [19]

Ali et al.

[11] **Patent Number: 6,071,904**

[45] **Date of Patent: Jun. 6, 2000**

[54] **PROCESS FOR MANUFACTURING OPHTHALMIC SUSPENSIONS**

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[21] Appl. No.: **08/886,933**

[22] Filed: **Jul. 2, 1997**

Related U.S. Application Data

[60] Provisional application No. 60/032,820, Dec. 11, 1996.

[51] **Int. Cl.**[7] **A61K 31/54**

[52] **U.S. Cl.** **514/222.8**; 514/912

[58] **Field of Search** 514/222.8, 912

[56] **References Cited**

U.S. PATENT DOCUMENTS

5,362,758	11/1994	Ahmed	514/777
5,378,703	1/1995	Dean et al.	514/222.8

FOREIGN PATENT DOCUMENTS

0601619A2	5/1993	European Pat. Off. .
0602702A1	6/1994	European Pat. Off. .
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WO 93/16701	8/1993	WIPO .

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Martin, F. et al. "Sterilisation par la Chaleur des Solutions de Sulfamides", Journal de Pharmacie de Belgique, vol. 25, No. 4, pp. 317–329, Jul.–Aug. 1970.

Primary Examiner—Zohreh Fay
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[57] **ABSTRACT**

Ophthalmic suspensions containing brinzolamide or brinzolamide and a beta-blocker and processes for manufacturing the suspensions are disclosed.

12 Claims, 3 Drawing Sheets

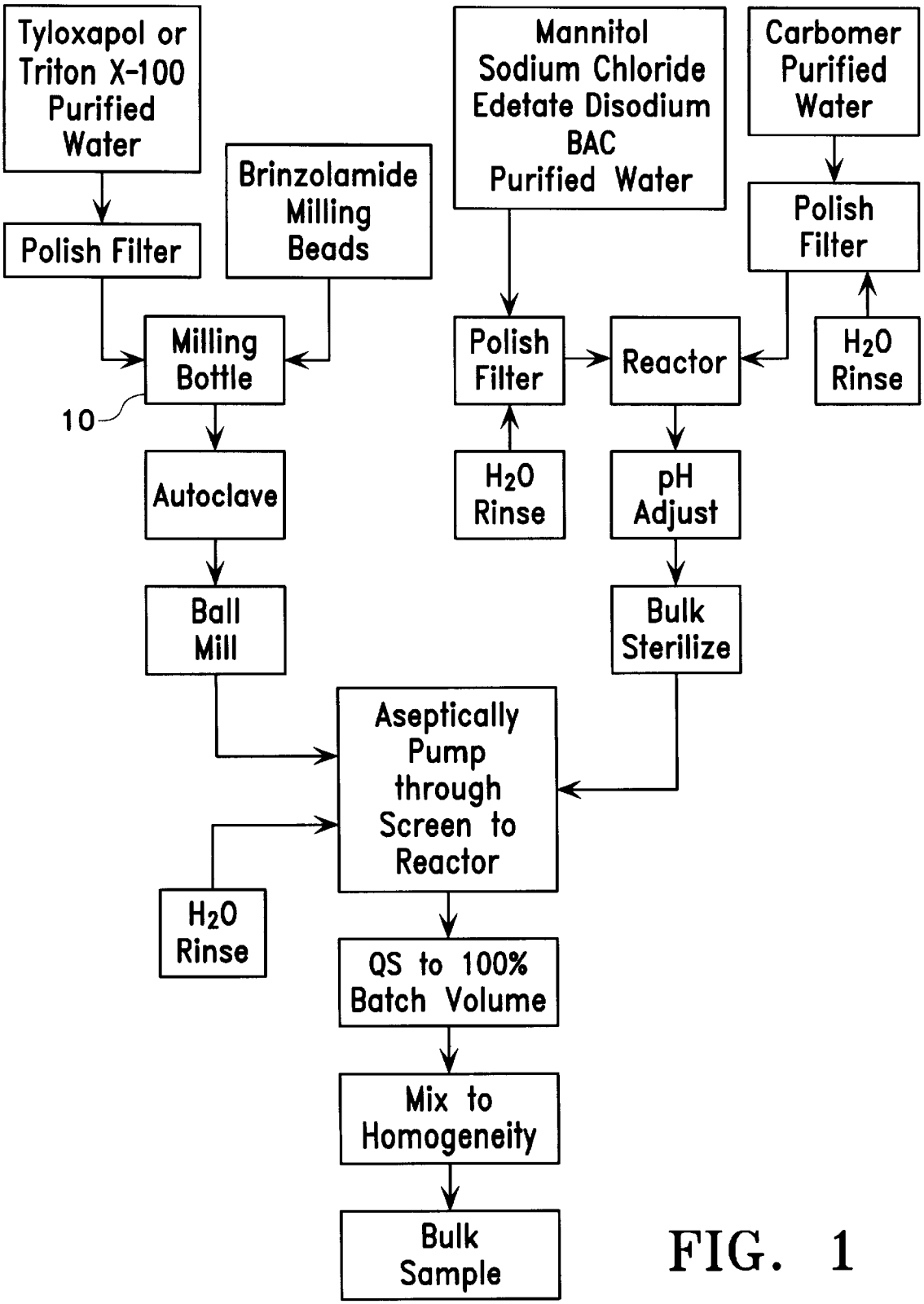

FIG. 1

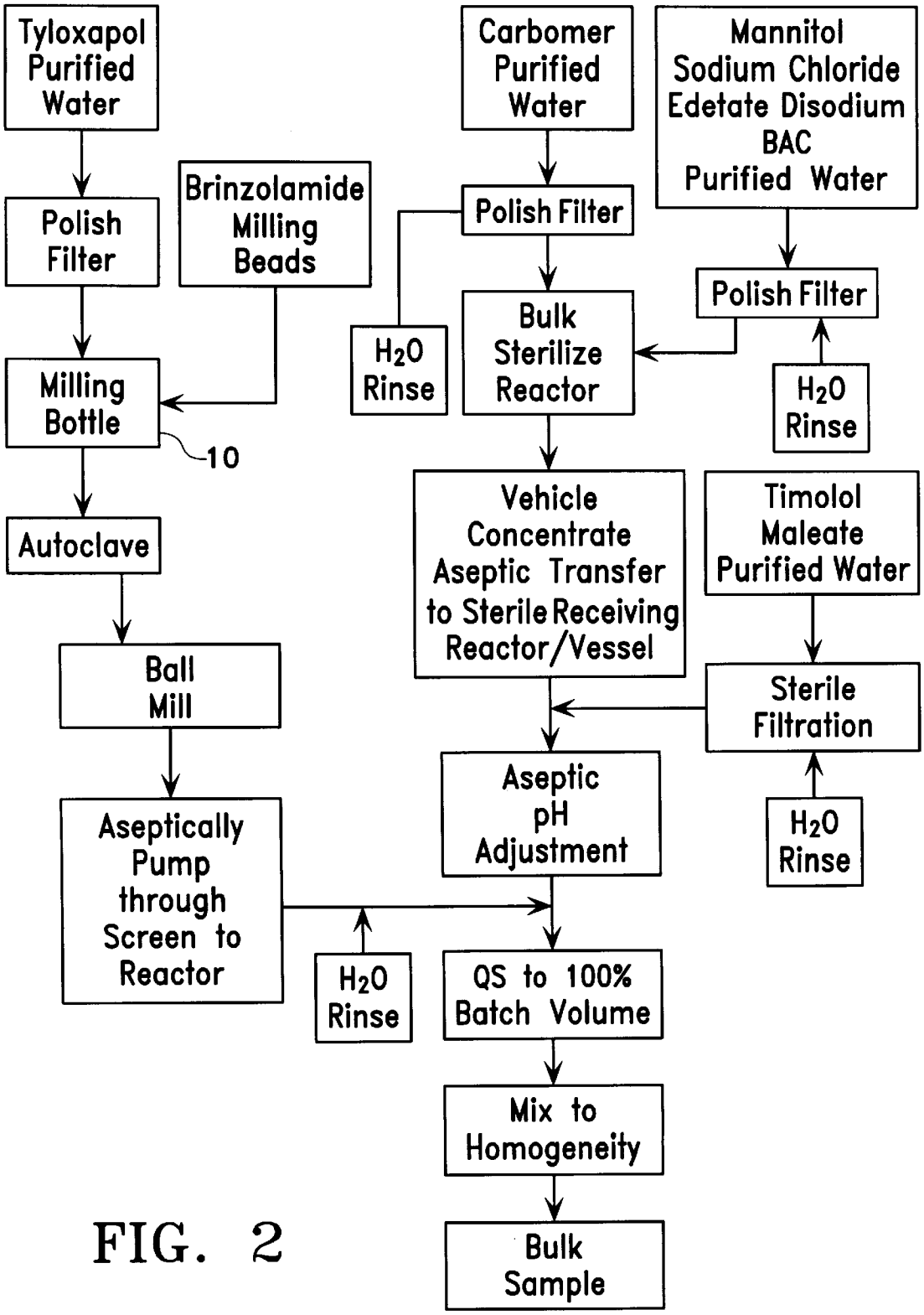

FIG. 2

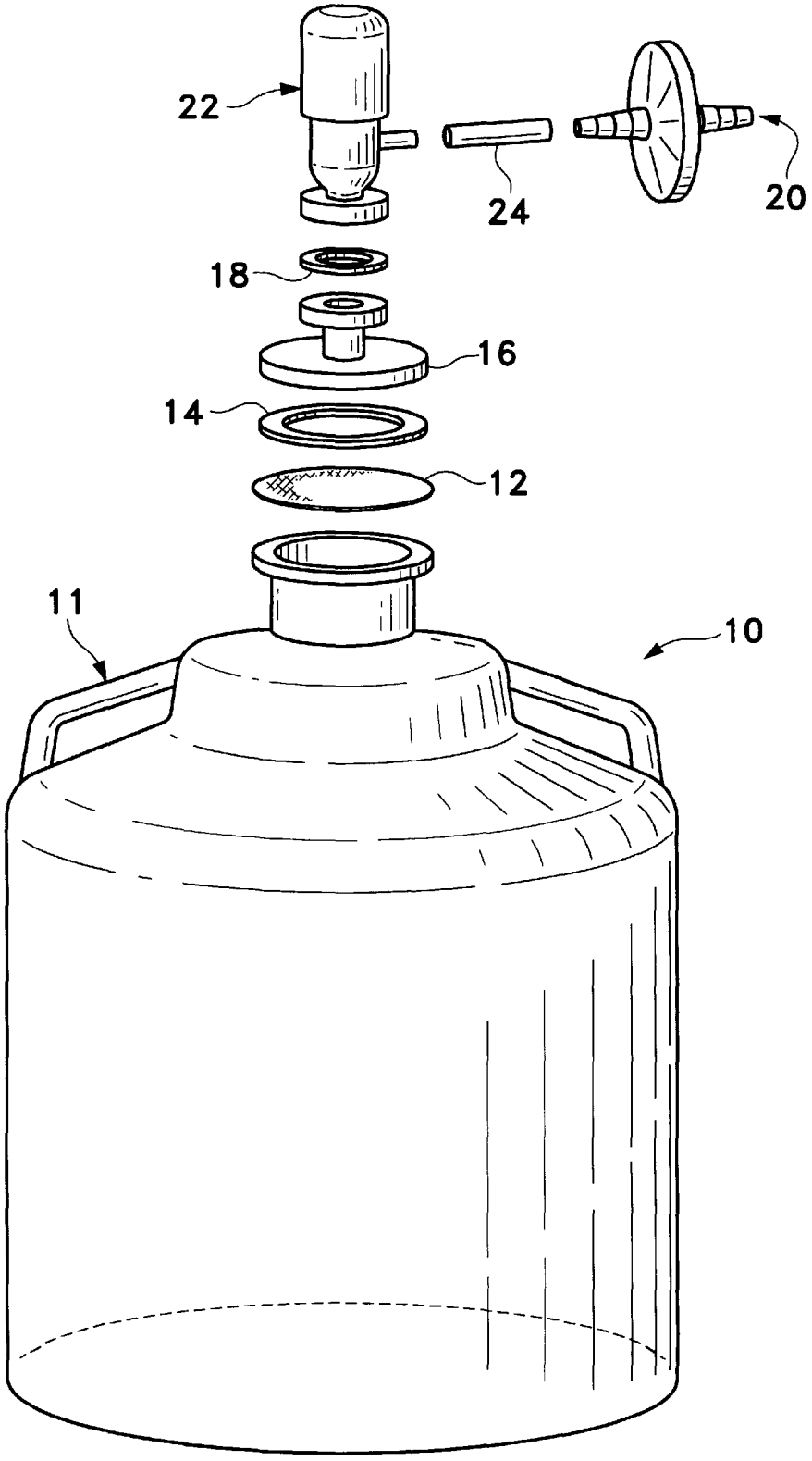

FIG. 3

PROCESS FOR MANUFACTURING OPHTHALMIC SUSPENSIONS

Priority is claimed from the provisional application, U.S. patent application Ser. No. 60/032820, filed Dec. 11, 1996.

This invention relates to sterile topical ophthalmic suspensions containing a carbonic anhydrase inhibitor or a carbonic anhydrase inhibitor and a beta-blocker and processes for making the suspensions. The suspensions are useful in controlling the elevated intraocular pressure in persons suffering from ocular hypertension or primary open angle glaucoma.

BACKGROUND OF THE INVENTION

Sterile, topical, ophthalmic suspensions have typically been manufactured in the past in one of three ways: by bulk sterilization of a milled suspension, by aseptic addition of sterile micronized raw material into a sterile vehicle, or by aseptic addition of a sterile raw material to a sterile menstruum followed by ball milling and aseptic addition of the sterile concentrate into a sterile vehicle.

The present suspensions, containing a carbonic anhydrase inhibitor (CAI) or a CAI and a beta-blocker, can not be made via these routes. Due to the solubility of the CAI at autoclaving temperatures, large needle-like crystals form on cool down of the final formulation. Aseptic ball milling of this final formulation is not practical. Aseptic addition of the CAI to a sterile vehicle is also not practical as the CAI cannot be sterilized by conventional means. Dry heat sterilization causes melting of the material. Sterilization of the CAI by ethylene oxide introduces unacceptable degradation products and residues, and sterilization by gamma irradiation of micronized material produces degradation products unacceptable for regulatory filing.

The present process provides a procedure for making a CAI or a CAI/beta-blocker suspension on a manufacturing scale without the problems described above.

BRIEF DESCRIPTION OF THE DRAWING

FIG. **1** is a flow diagram showing the process for making brinzolamide ophthalmic suspension.

FIG. **2** is a flow diagram showing the process for making brinzolamide/timolol ophthalmic suspension.

FIG. **3** is an expanded side view of one milling bottle that may be used in the present invention.

SUMMARY OF THE INVENTION

The present invention is directed to a CAI and a CAI/beta-blocker suspension, processes for making them, and a "bottle" for use in the processes.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The present CAI suspension contains the pharmaceutically active CAI, R 4-ethylamino-3,4-dihydro-2-(3-methoxy)propyl-2H-thieno [3,2-e]-1,2-thiazine-6-sulfonamide 1,1 dioxide, which is known as brinzolamide. This compound is disclosed in commonly assigned U.S. Pat. No. 5,378,703 (Dean, et al.). The present suspension and the process for making it are not disclosed in Dean, et al.

The process for making the brinzolamide suspension uses autoclaving of a concentrated slurry of brinzolamide in milling bottle **10**, ball milling of the hot slurry, and then adding the slurry to the rest of the ingredients as shown in FIG. **1**.

Referring now to FIG. **1**, first the milling menstruum containing either Tyloxapol, (4-(1,1,3,3-tetramethylbutyl) phenol polymer with formaldehyde and oxirane), available from Sterling Co. or Triton X-100, (α-[4-(1,1,3,3-tetramethylbutyl)phenyl]-ω-hydroxypolyoxy-1,2-ethane diyl), available from Rohm and Haas Corp. is prepared. The milling menstruum is critical to the manufacture of this suspension. Use of menstrua containing surfactants other than Tyloxapol or Triton X-100, such as Polysorbate 80, (sorbitan mono-9-octadecenoate poly (oxy-1,2-ethanediyl) derivatives), a common wetting agent for use in ophthalmic suspensions, results in inadequate milling of large crystals of brinzolamide which form during cool down following autoclaving. Use of Tyloxapol or Triton X-100 at concentrations of about 0.001 to 5 weight percent (wt. %) in the milling menstruum unexpectedly minimizes foaming and allows for adequate milling of the crystals. Although use of either Tyloxapol or Triton X-100 in the milling menstruum is acceptable, Tyloxapol at concentrations of 0.01 to 0.10 wt. % in the final suspension is the preferred agent as Triton X-100 is not commonly used in ophthalmic preparations.

Once the milling vehicle is prepared it is filtered and then mixed with milling beads, such as, alumina, glass, or zirconia, preferably 3mm zirconia-Y beads and added to milling bottle **10**. The mixture is then autoclaved in milling bottle **10** at normal temperatures and pressures known to those skilled in the art, e.g., 121–129° C., preferably 123–127° C., for 30–45 minutes. After autoclaving and while the slurry is above 80° C., the mixture is ball milled under conditions to achieve an average particle size of 0.2–10 μm, preferably 1–5 μm, preferably 18–19 hours at 50–55 RPM.

After milling, the milled slurry is aseptically added through a screen with smaller openings than the milling bead size to the rest of the ingredients including, water, one or more tonicity agents, such as, but not limited to, mannitol or sodium chloride; one or more preservatives, including, but not limited to, benzalkonium chloride or one of its derivatives, polyquaternium 1, thimerosol or EDTA; and at least one polymer, including, but not limited to carbomer, hydroxypropylmethylcellulose (HPMC), hydroxyethylcellulose (HEC), or polyvinylalcohol (PVA) which are mixed, filtered, pH adjusted, and sterilized prior to their combination with the milled mixture. Preferable ingredients are mannitol, NaCl, EDTA, BAC, carbomer, such as Carbopol 934P or 974P.

Sterile, purified water used to rinse the beads is then added to the mixture and the batch is brought to final volume. The ingredients are mixed until homogeneous.

The CAIlbeta-blocker suspension contains brinzolamide, but also includes a beta-blocker, such as, (S)-1-[(1,1-dimethylethyl)amino]-3-[[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy]-2-propanol (Z) 2-butenedioate (1:1) salt, which is known as timolol maleate or (±) 1-[p-[2-(cyclopropylmethoxy)ethyl]phenoxy]-3-(isopropylamino)-Z-propanol hydrochloride, which is known as betaxolol hydrochloride. Different isomers, for example, S-betaxolol, and salts can be used. A sterile ophthalmic solution containing timolol maleate (Timoptic®) is available from Merck and Co., Inc. It is useful for the treatment of elevated intraocular pressure in persons with ocular hypertension or open angle glaucoma. A sterile ophthalmic solution containing betaxolol hydrochloride (Betoptic®) is available from Alcon Laboratories, Inc. It is also useful for the treatment of ocular hypertension and open angle glaucoma.

The process for making the CAI/beta-blocker suspension is similar to that for making the brinzolamide suspension

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