(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
1 October 2015 (01.10.2015)

WIPO | PCT

(10) International Publication Number
WO 2015/147665 A1

(51) International Patent Classification:
*A61K 9/00* (2006.01)

(21) International Application Number:
PCT/PL2015/000052

(22) International Filing Date:
27 March 2015 (27.03.2015)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
P.407710 28 March 2014 (28.03.2014) PL

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

**Published**:

— *with international search report (Art. 21(3))*

WO 2015/147665 A1

(54) Title: PROCESS FOR MANUFACTURING BRINZOLAMIDE OPHTHALMIC SUSPENSION AND EYE DROPS FORMULATION

(57) Abstract: The invention relates to the process for manufacturing brinzolamide ophthalmic suspension and the eye drops formulation comprising brinzolamide as an active pharmaceutical ingredient. The eye drops are useful in controlling the elevated intraocular pressure in persons suffering from ocular hypertension or primary open angle glaucoma.

# Process for manufacturing brinzolamide ophthalmic suspension and eye drops formulation

## Field of the invention

The present invention relates to the process for manufacturing brinzolamide ophthalmic suspension and the eye drops formulation comprising brinzolamide as an active pharmaceutical ingredient. The eye drops are useful in controlling the elevated intraocular pressure in persons suffering from ocular hypertension or primary open angle glaucoma.

## Background of the invention

Brinzolamide, i.e. (4*R*)-4-ethylamino-3,4-dihydro-2-(3-methoxypropyl)-2*H*-thieno[3,2-e][1,2]-thiazine-6 sulfonamide, is a carbonic anhydrase inhibitor used in the treatment of disorders accompanied by the elevated intraocular pressure. The carbonic anhydrase is a systemic enzyme which catalyzes the reversible reaction of carbon dioxide with water to form carbonic acid. Inhibition of this enzyme in ciliary processes leads to lowering the aqueous humor secretion, most probably due to the reduction of hydrocarbonic ($HCO_3^-$) and sodium ions' concentration. This results in lowering the intraocular pressure which is one of the main pathogenic factors leading to optic neuropathy and in consequence to visual field loss in glaucoma. Brinzolamide is indicated for the topical management of primary open-angle glaucoma and ocular hypertension as either monotherapy or adjunctive therapy with topical beta-blockers or prostaglandins.

Azopt®, the medicinal product containing the active pharmaceutical ingredient brinzolamide, is the sterile ophthalmic suspension. According to the Physicians Desk Reference, each milliliter of 1% Azopt® ophthalmic suspension contains 10 mg of brinzolamide, 0.01 mg of benzalkonium chloride as the preservative, as well as the inactive excipients: tonicity agent mannitol, Carbopol 974 P as the viscosity controlling agent, non-ionic polymer Tyloxapol as surfactant, a chelating agent edetate disodium, as well as sodium chloride, sterile water for the eye drops formulation and hydrochloric acid and/or sodium hydroxide to adjust pH.

The patent specification EP 941094 B1 discloses the manufacturing process of the sterile ophthalmic suspension containing brinzolamide or brinzolamide – beta-blocker combination as well as thus obtained ophthalmic suspensions containing as the surfactant Tyloxapol or Triton X-100. The excipients used in the described formulations are consistent with the composition of the registered medicinal product Azopt®. Process for the manufacturing of the ophthalmic suspension includes autoclaving of the brinzolamide suspension in the presence of the surfactant and milling beads, ball milling the hot slurry until brinzolamide particles of the proper size are obtained, and aseptic adding the hot suspension to the vehicle concentrate obtained by mixing the water solution of Carbomer with the slurry of tonicity and preservative agents. The sterile final product is obtained by sterilizing the active substance with saturated steam and autoclaving the mixture of the excipients. Both components are combined in aseptic conditions.

As stated in the specification, the selection of the surfactant's kind and amount, essential for the protection of the substance during milling, is not arbitrary but plays a key role in this process. Use of surfactants other than Tyloxapol or Triton X-100 at concentrations of about 0.001-5.0% results in inaccurate milling of large brinzolamide crystals which form during cooling down following autoclaving.

As it is known from practice, in the synthesis of brinzolamide according to the prior art methods the substance is obtained in the form of quite large crystals. Imaging analysis in diascopic light exhibits high symmetry and sphericity of brinzolamide particles. For example, the circularity parameter, which can take 0-1 values (1 indicates exact roundness), is 0.847, the extension parameter is 0.266, the average length is 37.2 μm and the average width is 25.8 μm. The medium volumetric size of brinzolamide particles D[4,3] assigned by laser diffraction method is about 63 μm and the median d(0.5) is about 61 μm. However, the size of 10% particles is below 30 μm and the size of 90% particles - below 93 μm.

Despite the relatively good repeatability of the shape and size of the brinzolamide particles obtained in different batches of the chemical synthesis, their use in ophthalmic formulations requires substantial size reduction. As it is commonly known, the size and shape of the particles as well as their dispersion in the continuous phase substantially affect the bioavailability and stability of the medicine applied to the eye in the form of an aqueous suspension.

The imaging analysis using an automatic microscope analyzer Morphology G3 f. Malvern in diascopic light and the examination of the particle size distribution of the medical product Azopt® using Malvern Mastersizer 2000 exhibit that the particles in Azopt® are very small, with regular shape, as it is shown in the Table below:

| **Volumetric particle size distribution [μm]** | | | | |
|---|---|---|---|---|
| | d [0.1] | d [0.5] | d [0.9] | D [4,3] |
| Azopt® (serie 1) | 0.78* / 2.94** | 1.94* / 4.38** | 7.44* / 7.59** | 4.53* / 5.06** |
| Azopt® (serie 2) | 0.87* / 2.38** | 2.18 */ 3.67** | 8.29* / 7.79** | 4.16* / 4.86** |

* *measured with Mastersizer 2000*
** *measured with Morphology G3*

The comparison of particle size distribution in two series of the commercially available eye drops formulation Azopt® measured with the microscope analyzer is shown in Fig. 1, while the comparison of the circularity parameter is presented in Fig. 2.

In our research on brinzolamide crystallization we unexpectedly found that it is possible to affect the size of its crystals using a simple chemical operation as the step of the manufacturing process of the finished dosage form. The said operation affords brinzolamide particles with the parameters similar to that in Azopt®, thus eliminating the necessity to reduce the crystals' size by physical methods, prior to formulation, which substantially simplifies the technology of the drug form.

## Disclosure of the invention

The aforementioned process is used in the brinzolamide drug technology wherein the active substance brinzolamide is dissolved and then precipitated in the form of particles with proper size, as a result of changing the pH of the medium. The operation of pH changing is carried out in the solution containing the main components combined in aseptic conditions. The sterile product is obtained by sterile filtration of both brinzolamide and the excipients' solutions, with the exception of the polymeric agent increasing the viscosity of the suspension which is sterilized separately by saturated steam in an autoclave. All other operations, i.e. homogenization of the suspension,

dosing of the final drug product, closing of the containers, labeling and packing are carried out in aseptic conditions, as it is shown on the diagram in Fig. 4.

The present invention provides the process for manufacturing of the ophthalmic suspension containing brinzolamide as an active pharmaceutical ingredient comprising the steps of:

(i) Dissolving brinzolamide in aqueous hydrochloric acid with the addition of mannitol and subjecting thus obtained Solution I to sterilizing filtration;

(ii) Independently, dissolving the excipients, i.e. edetate disodium and benzalkonium chloride, in an aqueous precipitating basic agent, and subjecting thus obtained Solution II to sterilizing filtration;

(iii) Dissolving acrylic acid polymer separately in water, homogenizing, adding sodium hydroxide, and autoclaving to afford Solution III;

(iv) Adding Solution II to Solution I at ambient temperature to adjust pH of the mixture into the range 6.5 – 8.5 and start the precipitation of brinzolamide, and stirring the suspension formed;

(v) Combining Solution III with the suspension of brinzolamide obtained in step (iv);

(vi) Homogenizing the resulting suspension of brinzolamide of step (v);

(vii) Dispensing the homogenized suspension of step (vi) into the sterile containers, closing and sealing.

The amount and type of the excipients in the formulation is selected in order to obtain ophthalmic eye drops suspension which should be characterized by the following parameters: pH within the range 6.5 – 8.5, osmolarity within the range 320 mOsm/kg $H_2O$ and viscosity within the range 1.013-1.020 g/ $cm^3$, which meets the physicochemical characteristics of the Azopt® drug product.

According to the present invention, the pH of the formulation is adjusted by the addition of the basic agent which at the same time plays the role of brinzolamide precipitating agent. Such agents can be selected from the hydroxides approved for use in pharmaceutical products, e.g. hydroxides of sodium, potassium, lithium, calcium or ammonium. Another group of the precipitating agents comprises bicarbonates, e.g. sodium, calcium or ammonium bicarbonates.

In the preferred embodiment of the invention, aqueous sodium bicarbonate ($NaHCO_3$) at the concentration 0.01 – 10 M is used as the precipitating agent. Preferably, the precipitating agent is used at the concentration from 0.1 to 5 M, more preferably 1 M.

The proper osmolarity of the final ophthalmic suspension is achieved by the addition of polyhydroxyl alcohol, i.e. mannitol. This compound is commonly used in ophtalmic formulations as a tonicity agent. The amount of mannitol is found experimentally, to achieve the osmolarity of the final suspension within the range 270 – 320 mOsm/kg $H_2O$. It has to be taken into account that NaCl forming in the process of suspension manufacturing has its own effect on the osmolarity increase.

The viscosity of the suspension is modified with the addition of the aqueous solution of the acrylic acid polymer approved for use in ocular preparations, such as the cross-linked acrylic acid polymers belonging to the Carbomer or Carbopol types, preferably Carbomer 974 P. Such polymers are traditionally used in pharmacy for increasing the viscosity of solutions and for the stabilization of suspensions and emulsions. In ophtalmic formulations the use of the viscosity increasing agent is recommended usually in the amount ranging from 0.45% to 0.5 % w/v. In the case of the present formulation it was found experimentally that the quantity of the agent increasing the viscosity has direct influence on the distribution of particle size in the suspension. The preferred quantity of Carbomer 974 P in the composition of the formulation according to the invention is 4-5 mg/ml. In the case when the concentration of the agent is 5 mg/ml or above, the size of the formed particles is too large; however, the concentration below 4 mg/ml results in a suspension that is too loose and unstable.

According to the invention, the formulation further contains sodium hydroxide, added as a whole to the aqueous solution of the acrylic acid polymer in order to neutralize the acid. The quantity of sodium hydroxide is determined experimentally.

The eye drops formulation additionally contains a preserving and solubilizing agent, traditionally used in ophtalmic medicines, preferably benzalkonium chloride, which is a mixture of alkylbenzyldimethylammonium chlorides with different alkyl substituents.

Due to the technology used for its manufacturing, the suspension obtainable by the process of the invention do not require using of surface tension lowering agents, such as Tyloxapol.

The addition of sodium chloride to the composition is also unnecessary, because this salt forms during the precipitation of brinzolamide from aqueous hydrochloric acid by the solution of the precipitating agent.

Thus, according to the invention, the eye drops formulation in the form of the suspension containing brinzolamide preferably comprises the following excipients: acrylic acid polymer, edetate disodium, benzalkonium chloride, mannitol, sodium hydroxide, hydrochloric acid, sodium bicarbonate and purified water for use in the ophthalmic formulations.

In the preferred embodiment of the invention, in comparison with the qualitative composition of Azopt®, the composition of the eye drops formulation is as follows:

| **AZOPT®** | **Formulation of the invention** |
|---|---|
| Brinzolamide | Brinzolamide |
| Mannitol | Mannitol |
| Benzalconium chloride | Benzalconium chloride |
| Edetate disodium (EDTA) | Edetate disodium (EDTA) |
| Carbomer 974 P | Carbomer 974 P |
| Tyloxapol | - |
| Sodium chloride | - |
| - | Sodium bicarbonate |
| Sodium hydroxide/hydrochloric acid | Sodium hydroxide |
| Purified water | Purified water |

In the more preferred embodiment of the invention, the formulation of the ophthalmic eye drops containing 10 mg/ml of brinzolamide comprises, per 1 mililiter of the suspension:

| | |
|---|---|
| Brinzolamide | 10.0 mg |
| Carbopol 474 P | 0.0042 g |
| Edetate disodium | 0.0001 g |
| Benzalkonium chloride | 0.0001 g |
| Mannitol | 0.035 g |
| Sodium hydroxide | 0.002 g |
| Hydrochloric acid 0.1 M | 0.2774 g |
| Sodium bicarbonate 1 M | 0,0438 g |
| Purified water | q.s. *ad* 100% |

The best mode of carrying out the manufacturing process according to the present invention is illustrated on a flow chart in Fig.4.

Solution I is obtained by dissolving brinzolamide in an aqueous 0.1 M hydrochloric acid in the presence of mannitol as co-solubilizer. Mannitol enhances solubility of brinzolamide in aqueous hydrochloric acid by forming hydrogen bonds with the hydrophilic groups of micelles to prevent their aggregation. Preferably, the operation of dissolving is carried out at ambient temperature, thus avoiding the precipitation of brinzolamide upon cooling. Then, Solution I is subjected to sterilizing filtration through a filter having the pore size 0.2 μm.

Solution II is prepared separately by dissolving the excipients, i.e. edetate disodium and benzalkonium chloride, in the solution of the precipitating agent. Preferably, as the precipitating agent an aqueous 1 M solution of sodium bicarbonate is used. The final Solution II is subjected to sterilizing filtration through a filter having the pore size 0.2 μm.

Solution III, containing Carbomer 974 P and sodium hydroxide, due to its high viscosity, is subjected to autoclaving.

Solution II is combined immediately with Solution I containing brinzolamide in hydrochloric acid, to bring about the precipitation and form a suspension. Preferably, Solution II is added to Solution III.

The obtained suspension is additionally stirred. The stirring time affects the content of brinzolamide in the final suspension, however, its influence on the distribution of particle size was not observed. The optimal time of stirring is 2 hrs. In case of shorter stirring time, the content of brinzolamide in the suspension is too low.

The obtained suspension is then combined with Solution III and homogenized to form uniform particles and further limiting their size.

The homogenization process is well known not only in the pharmaceutical industry. Besides the typical homogenization process, i.e. the homogenization of the product in the form of a liquid, cream or gel, it can be used to obtain suspensions and emulsions as well as to fragment insoluble and firm particles to a very small size. In the homogenization process time and shearing force play a crucial role. The shearing force depends not only on the rotary speed of the stirrer turbine, but also on the stirrer and apparatus geometry and the volume of the homogenizer.

A direct relationship was found in the process of the invention between the size of the batch, homogenization time, rotary speed of the homogenizer, and the particle size distribution of the obtained product. During the homogenization of the suspensions in the laboratory scale, i.e. 50 ml volume, for 5 min with the rotary speed of 8000 rpm, the

size of the obtained particles was similar to that in Azopt®. The extension of the homogenization duration by additional 5 min results in reducing the size of brinzolamide particles in the suspension. Increasing the rotary speed to 20500 rpm for 5 min. affords particles of a smaller size than required. The prolongation of the homogenization time has no impact on the particle size in the suspension.

Experiments performed on a bigger scale using different rotary speeds and times of homogenization reveal that stirring 1000 ml of the suspension with the speed of 8000 rpm does not lead to the formation of a product with the proper particle size distribution. This can be achieved by homogenization at 13500 rpm for 10 min.

The selection of homogenization parameters, which is critical for obtaining a medicinal product suspension with the proper characteristics, is therefore dependent on the scale of the process and apparatus geometry, hence it should not pose any problems for a skilled person.

At the production scale of 1000 ml of the suspension, the advantageous effect can be achieved when the homogenization process is carried out with the homogenizer working on the Rotor-Stator technology, e.g. Ultra-Turrax T 25 digital, at 13500 rpm for 10 min.

The process according to the invention allows significant simplification of the manufacturing process of brinzolamide ophthalmic suspension, by eliminating both the active substance grinding process and the necessity to add the surfactant. The obtained finished dosage form has proper physicochemical characteristics and is stable. The stability of the formulations of the invention was proved by the estimation of the active substance content in the routine stability tests. The product was stored for the scheduled time in strictly definite and monitored conditions of temperature and humidity (25°C/60% of relative humidity and 40°C/75% of relative humidity – accelerated test) according to the directive CPMP/ICH/2736/99 "Stability Testing Guidelines: Stability testing of new drug substances and products".

An example of brinzolamide volumetric particle size distribution in the suspension is shown in Fig. 5 and a microscopic image of the formulation of the invention is presented in Fig. 6.

The invention is illustrated by the following examples which should not be construed as any limitations of its scope.

## Examples

Methodology of particle size distribution and shape measurement

The study was performed with the Malvern Mastersizer 2000 analyzer measuring particle size distribution using laser diffraction method. The microscopic overview of the examined dispersions was performed with the Malvern Morphology G3s microscopy analyzer, following the evaporation of the dispersing agent. The measurements were performed in diascopic light.

**Laser diffraction**

| | |
|---|---|
| Apparatus/dispersion device | Mastersizer 2000 / Hydro 2000S f. Malvern |
| Ultrasounds | 0% |
| Stirring speed | 2,100 rpm |
| Dispersing agent | propan-2-ol |
| Time of a single measurement | 1.5 s |
| Time of the background measurement | 10 s |
| Refraction coefficient of the measured samples | 1.52 |
| Refraction coefficient of the dispersing agent | 1.39 |
| Absorption coefficient | 0.01 |
| Obscuration | 5-10% |

**Microscopy analysis**

| | |
|---|---|
| Apparatus/dispersion device | Morphologi G3S / -, f. Malvern |
| Dispersing agent | propan-2-ol |

Example 1

The ophthalmic suspension containing10 mg/ml of brinzolamide was prepared of the following composition:

| Substance/excipient | g/1 ml | g/1000 g |
|---|---|---|
| Brinzolamide | 0.01 | 10.0 |
| Carbopol 474 P | 0.0042 | 4.2 |
| Edetate disodium (EDTA) | 0.0001 | 0.1 |
| Benzalkonium chloride (BAC) | 0.0001 | 0.1 |
| Mannitol | 0.035 | 35.0 |
| Sodium hydroxide | 0.002 | 2.0 |
| Hydrochloric acid (aq.) 0.1 M | 0.2774 | 277.4 |
| Sodium bicarbonate (aq.) 1 M | 0.0438 | 43.8 |
| Purified water | *q.s. ad* 1 ml | *q.s. ad* 1000 g |

Bottles, droppers and caps were washed, dried and sterilized with radiation. Then the material was protected against secondary contamination with aluminum foil. Work surfaces were wiped with isopropyl alcohol and then sterilized with UV light. Flasks and the filtration set were washed, dried and heated with hot air in a dryer. Then the material was protected against secondary contamination with aluminum foil. The membrane filters made of poly(vinylidene fluoride) (PVDF) were sterilized with steam in an autoclave.

SOLUTION I

The active ingredient was weighed and dissolved in the aqueous 0.1 M solution of hydrochloric acid with the addition of mannitol at ambient temperature while stirring with a magnetic stirrer. The solution was filtered through the PVDF filtration membrane having the pores size 0.2 μm.

SOLUTION II

1M aqueous sodium bicarbonate, EDTA and BAC were weighed and mixed to obtain a solution. The solution was filtered through the PVDE filtration membrane having the pores size 0.2 μm.

SOLUTION III

Carbomer 974 P was weighed, added to water and homogenized. Then sodium hydroxide was added to the mixture with stirring and the whole mixture was sterilized with steam in the autoclave.

Precipitation

SOLUTION II was slowly added to SOLUTION I at ambient temperature. After combining both solutions, the precipitation of brinzolamide occurred accompanied with $CO_2$ evolution.

Stirring

Following the precipitation the slurry was stirred with a magnetic stirrer for 2 hrs at ambient temperature.

Suspension of brinzolamide in the excipients solution

The sterilized SOLUTION III containing Carbomer 974 P was combined with the suspension of brinzolamide solids.

Homogenization

The suspension of brinzolamide (1000 mL) was homogenized for 10 min using the Ultra-Turrax T 25 digital homogenizer (from IKA) at the rotary speed of 13500 rpm. The suspension was dosed with the use of an automatic pipette into 5 ml bottles made of low density polyethylene. The bottles were provided with droppers and sealed with caps.

Contents of the active substance in the final suspension

| Batch No. | Average contents of brinzolamide [mg] *Acceptance criterion: 9,5-10,5 mg/ml* | RSD |
|---|---|---|
| 1 | 9.7 | 0.39 |
| 2 | 10.1 | 0.56 |
| 3 | 10.5 | 0.50 |

Product batches met the acceptance criterion for the active substance in the final suspension.

Particle size distribution

| Prior to homogenization | | | | |
|---|---|---|---|---|
| Batch No. | d (0.1) [µm] | d (0.5) [µm] | d (0.9) [µm] | D (4.3) [µm] |
| 1 | 0.60 | 1.83 | 15.27 | 6.74 |
| 2 | 0.83 | 2.46 | 20.01 | 7.49 |
| 3 | 0.86 | 2.23 | 14.06 | 5.69 |
| After homogenization | | | | |
| | 0.481 | 1.566 | 7.145 | 3.568 |

Example 2

The effect of homogenization parameters on brinzolamide volumetric particle size distribution.

*Distribution of the particle size after homogenization of 50 ml of the suspension at the rotary speed of 8000 rpm*

| Batch No. | Homogenization time [min] | d (0.1) [µm] | d (0.5) [µm] | d (0.9) [µm] | D (4.3) [µm] |
|---|---|---|---|---|---|
| 1-1 | 5 | 1.77 | 3.89 | 14.93 | 7.11 |
| 1-2 | 10 | 1.49 | 2.95 | 7.84 | 4.62 |
| 2-1 | 5 | 1.21 | 2.38 | 6.75 | 3.71 |

| | | | | | |
|---|---|---|---|---|---|
| 2-2 | 10 | 0.09 | 1.08 | 3.42 | 1.71 |

*Distribution of the particle size after homogenization of 50 ml of the suspension at the rotary speed of 20.500 rpm*

| Batch No. | Homogenization time [min] | d (0.1) [µm] | d (0.5) [µm] | d (0.9) [µm] | D(4.3) [µm] |
|---|---|---|---|---|---|
| 1 | 5 | 0.11 | 1.07 | 4.28 | 2.38 |
| 2 | 5 | 0.26 | 0.88 | 2.7 | 1.54 |
| 3 | 15 | 0.11 | 0.87 | 4.1 | 2.06 |

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The effect of homogenization parameters for 1000 ml of the suspension at 8000 rpm and 13500 rpm on brinzolamide volumetric particle size distribution

| Batch No. | Rotary speed of the turbine [rpm] | Homogenization time [min] | Volumetric particle size distribution | | | |
|---|---|---|---|---|---|---|
| | | | d (0.1) µm | d (0.5) µm | d (0.9) µm | D (4.3) µm |
| 1-1 | 8000 | 5 | 1.06 | 3.33 | 20.7 | 7.64 |
| 1-2 | 8000 | 10 | 1.31 | 3.81 | 24.85 | 9.69 |
| 1-3 | 8000 | 15 | 0.84 | 3.41 | 15.41 | 6.91 |
| 1-4 | 8000 | 30 | 0.76 | 3.02 | 20.82 | 7.84 |
| 2-1 | 13500 | 5 | 0.57 | 2.09 | 11.61 | 5.21 |
| 2-2 | 13500 | 10 | 0.12 | 1.22 | 3.53 | 2.38 |
| 2-3 | 13500 | 15 | 0.18 | 1.42 | 6.17 | 2.88 |
| 2-4 | 13500 | 30 | 0.45 | 1.42 | 8.27 | 3.59 |

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**Claims**

1. A process for manufacturing of the ophthalmic suspension containing brinzolamide as an active pharmaceutical ingredient comprising the steps of:
   (i) Dissolving brinzolamide in aqueous hydrochloric acid with the addition of mannitol and subjecting thus obtained Solution I to sterilizing filtration;
   (ii) Independently, dissolving the excipients, i.e. edetate disodium and benzalkonium chloride, in an aqueous precipitating basic agent, and subjecting thus obtained Solution II to sterilizing filtration;
   (iii) Dissolving acrylic acid polymer separately in water, homogenizing, adding sodium hydroxide, and autoclaving to afford Solution III;
   (iv) Adding Solution II to Solution I at ambient temperature to adjust pH of the mixture into the range 6.5 – 8.5 and start the precipitation of brinzolamide, and stirring the suspension formed;
   (v) Combining Solution III with the suspension of brinzolamide obtained in step (iv);
   (vi) Homogenizing the resulting suspension of brinzolamide of step (v);
   (vii) Dispensing the homogenized suspension of step (vi) into the sterile containers, closing and sealing.

2. The process according to claim 1, characterized in that the precipitating agent is hydroxide or bicarbonate of alkali metal, alkaline earth metal, or ammonium is used as the precipitating agent.

3. The process according to claim 2, characterized in that the precipitating agent is sodium bicarbonate.

4. The process according to claim 3, characterized in that the precipitating agent is 0.01 – 10 M aqueous solution of sodium bicarbonate.

5. The process according to claim 1, characterized in that mannitol in the amount of 0.45 – 0.5 % w/v based on the total suspension volume is used.

6. The process according to claim 1, characterized in that the acrylic acid polymer in the amount of 0.4 – 0.5 % w/v based on the total suspension volume is used.

7. The process according to claim 1, characterized in that the suspension from step (iv) is stirred for 2 hrs.

8. A surfactant free formulation of brinzolamide ophthalmic suspension containing brinzolamide obtainable by the process according to claim 1.

9. An eye drops formulation of brinzolamide ophthalmic suspension, characterized in that the said formulation comprises as the carriers and/or excipients acrylic acid polymer, edetate disodium, benzalkonium chloride, mannitol, sodium hydroxide, hydrochloric acid, sodium bicarbonate and purified water.

10. The eye drops formulation according to claim 9, characterized in that 1 ml of suspension contains 10 mg of brinzolamide and 0.0042 g of Carbopol 474 P, 0.0001 g of edetate disodium, 0.0001 g of benzalkonium chloride, 0.035 g of mannitol, 0.002 g of sodium hydroxide, 0.2774 g of 0.1 M hydrochloric acid, 0.0438 g of 1M sodium bicarbonate and purified water up to 1 mL of the total volume.

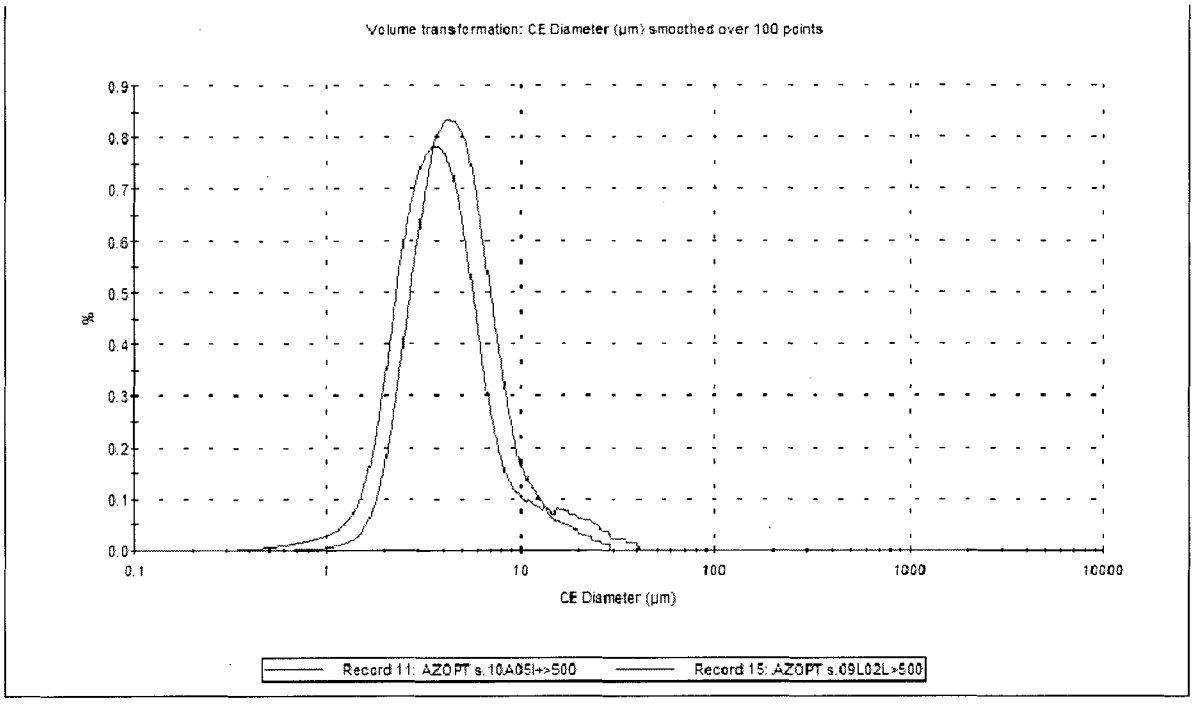


**Fig. 1. Particle size distribution in two series of drug product Azopt®**

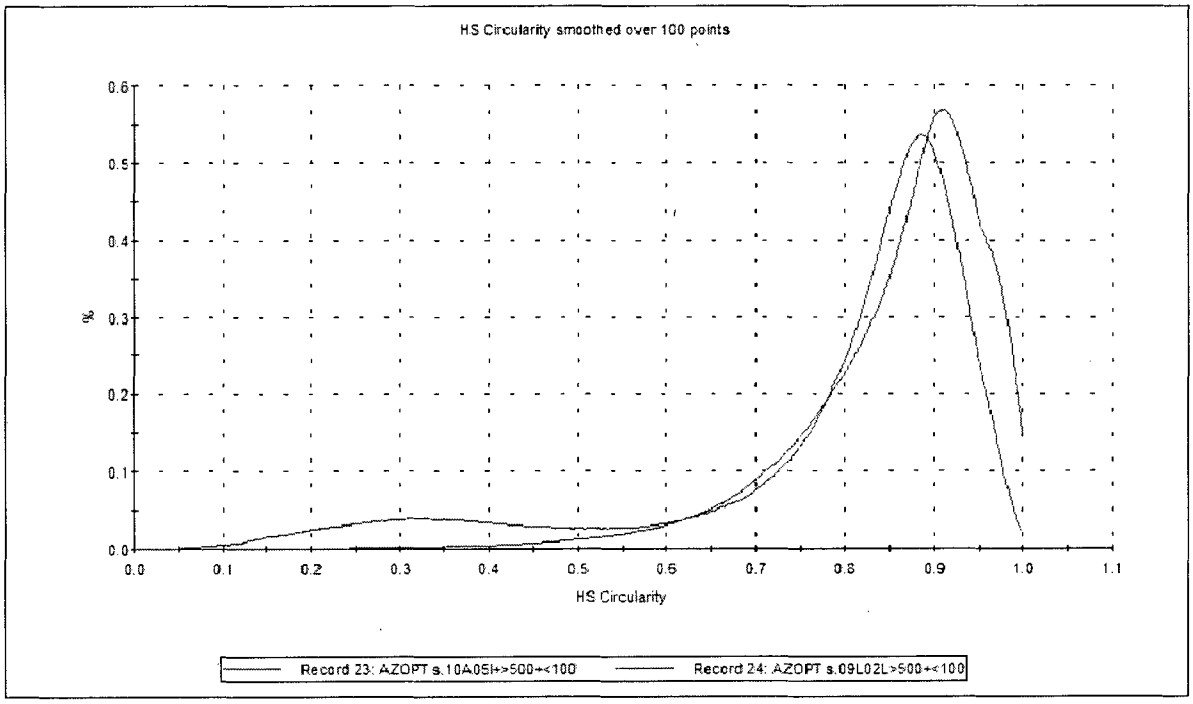


**Fig. 2. Circularity parameter in two series of drug product Azopt®**

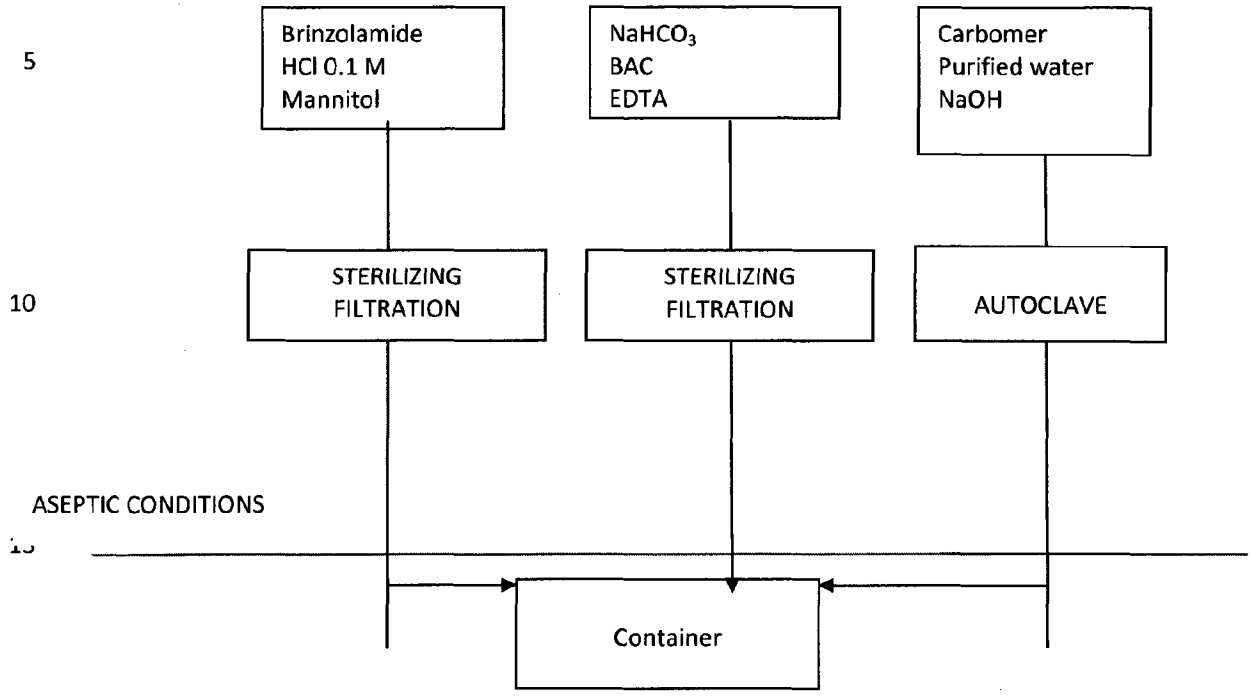


**Fig.3. Flow chart diagram of the process for manufacturing brinzolamide ophthalmic suspension**

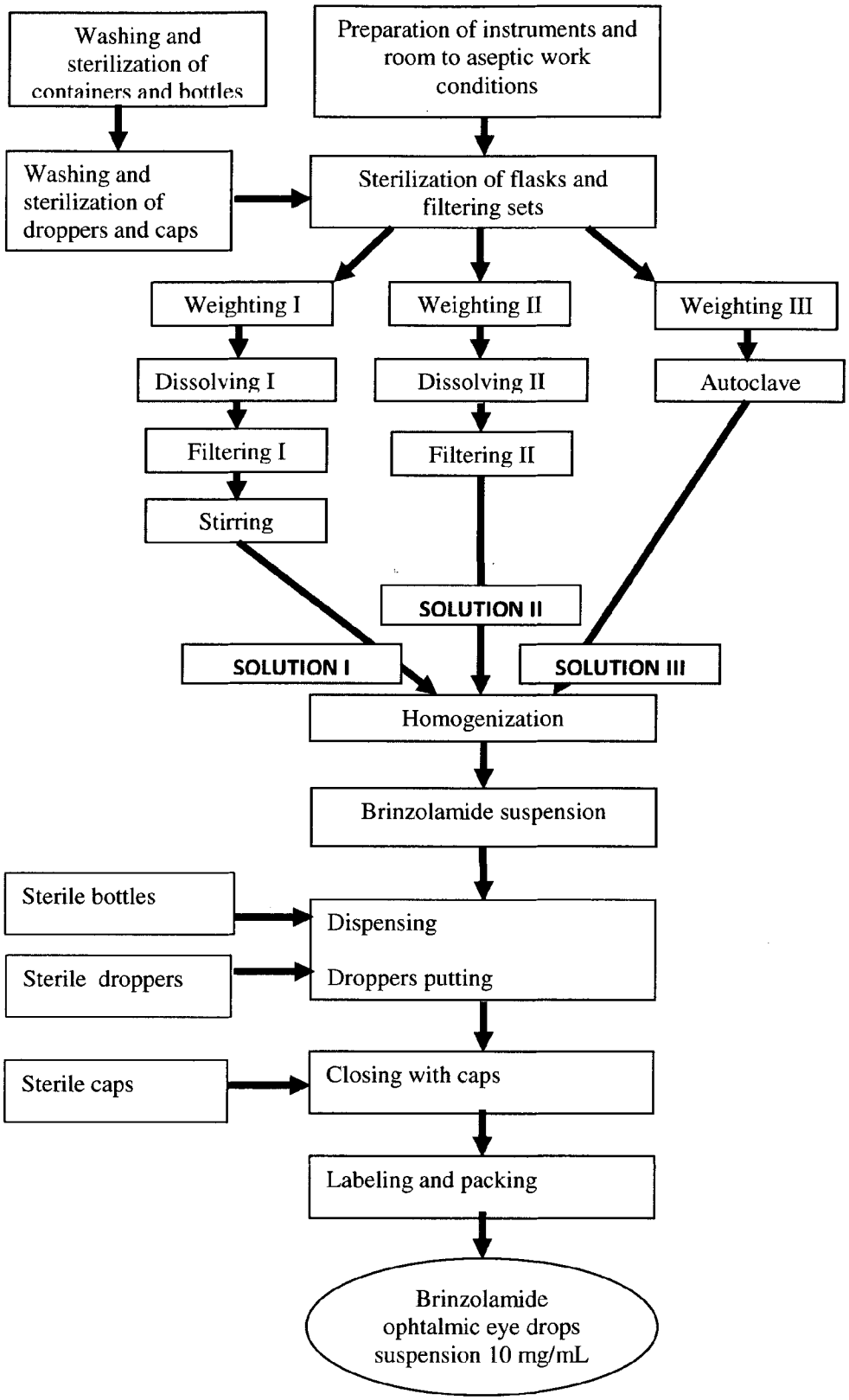


**Fig. 4. Flow chart diagram of the process for manufacturing brinzolamide ophthalmic suspension 10 mg/mL**

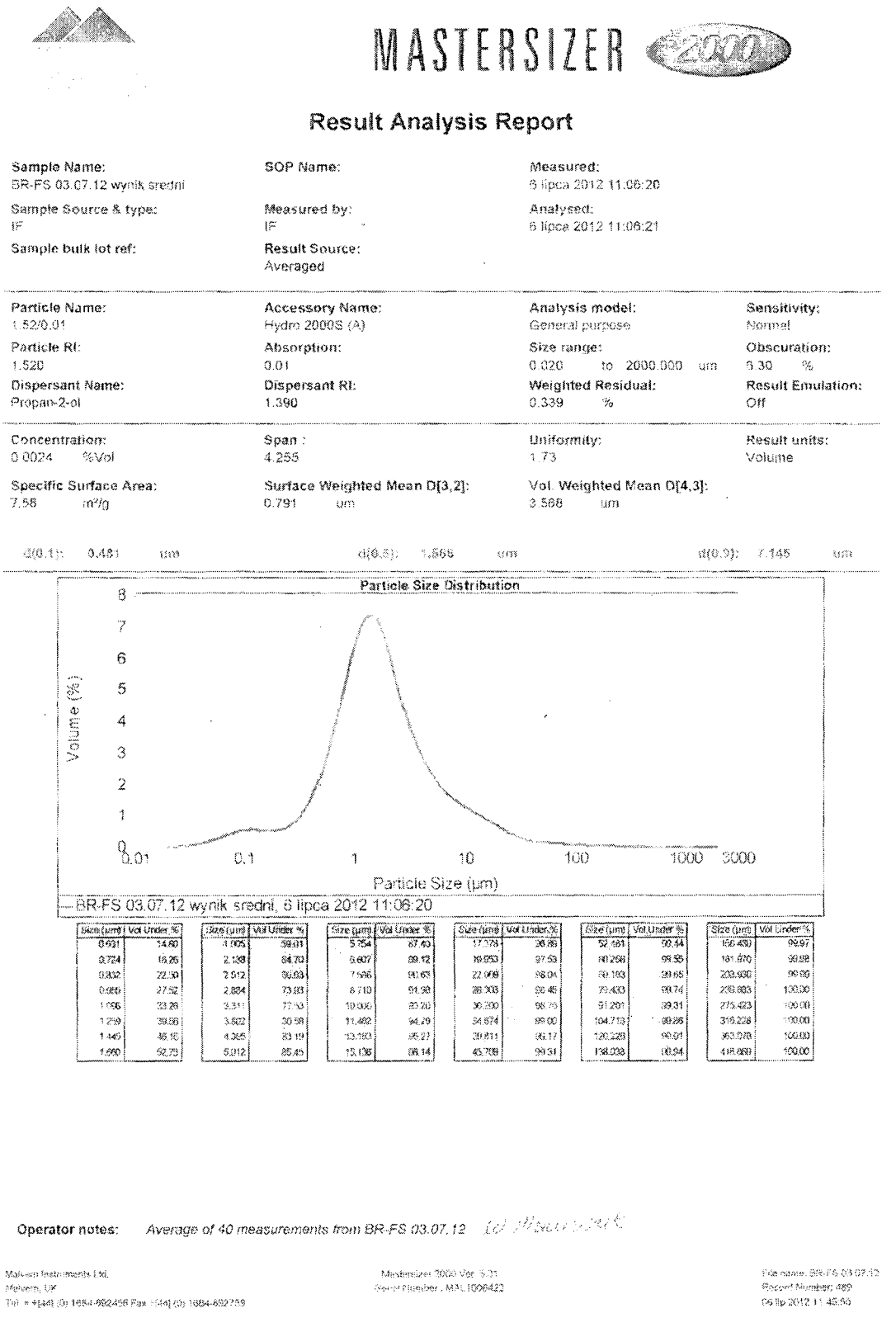


**Fig. 5. Brinzolamide volumetric particie size in the ophthalmic suspension formulation**

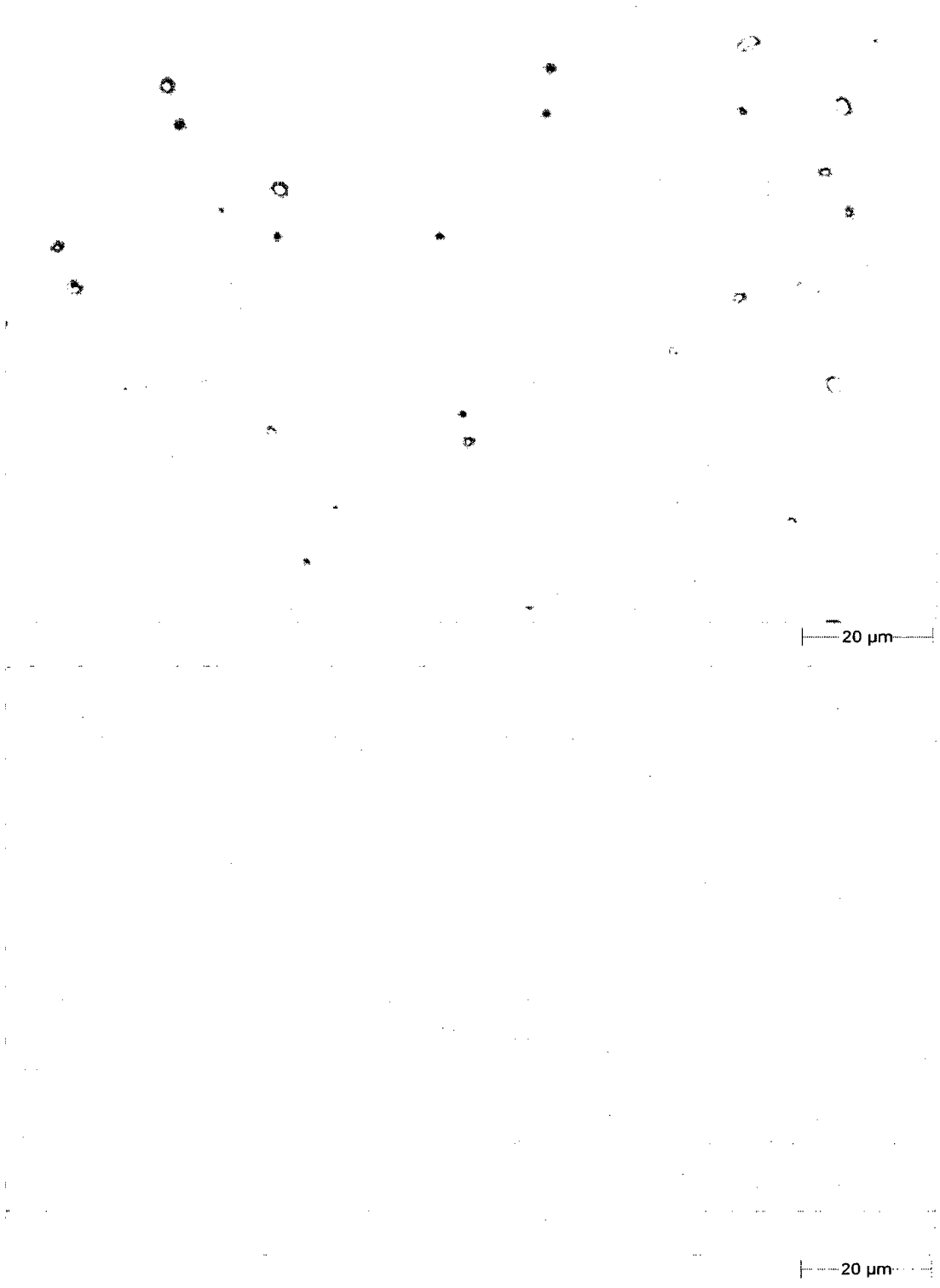


**Fig. 6. Microscopic image of brinzolamide suspension formulation**

# INTERNATIONAL SEARCH REPORT

International application No
PCT/PL2015/000052

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, EMBASE, WPI Data, BIOSIS, FSTA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 28 May 2015 | 10/06/2015 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016 | Schüle, Stefanie |

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