Patent Publication 2: JP-H10-324634-A

Patent Publication 3: JP-H07-166154-A

Patent Publication 4: JP-2010-106015-A

Patent Publication 5: JP-2008-88174-A

Non-patent Publication 1: Supervised by Yoshihisa Oguchi, Edited by Kazuo Tsubota, Ocular Surface *no Shindan to Chiryo* (Diagnosis and Treatment of Ocular Surface), Medical-Aoi Publications, Inc., pp83-87, 1993

Non-patent Publication 2: Charles H. Powell et al., Lipophilic versus hydrodynamic modes of uptake and release by contact lenses of active entities used in multipurpose solutions, Contact Lens & Anterior Eye, 33, 9-18, 2010

Non-patent Publication 3: Takashi Sakimoto, *Chiryo-you Kontakuto Renzu heno Boufuzai no Kyuchaku* (Adsorption of Preservatives on Therapeutic Soft Contact Lenses), Journal of Japan Contact Lens Society, 35, pp177-182, 1993

Non-patent Publication 4: Edited by Yuichi Ohashi, *Ganka* (Ophthalmology) New Insight 2, *Tengan-yaku - Joshiki to Hijoshiki* (Ophthalmic Solution - Common Sense and Preposterousness), Medical View Co., Ltd., pp36-43, 1994

Non-patent Publication 5: Yuichi Ohashi, *Ganka* (Ophthalmology) New Insight 2, *Tengan-yaku - Joshiki to Hijoshiki* (Ophthalmic Solution - Common Sense and Preposterousness), Medical View Co., Ltd., pp56-65, 1994

## SUMMARY OF THE INVENTION

No effective ophthalmic solution has ever been obtained in which preservatives are inhibited from being adsorbed

of sodium chloride, 0.1 g of potassium chloride, 0.4 g of boric acid, 0.0076 g of sodium hydroxide, (C) 0.0004 g of Cosmocil CQ (registered trademark) (20% aqueous solution, containing 0.00008 g of hexamethylene biguanide (weight average molecular weight of 2806, from which the number of the repeating units k in formula (1) is 14 in average)), and (D) 0.1 g of 2-methacryloyloxyethyl phosphorylcholine/butyl methacrylate copolymer (80 : 20) were added one after another, and stirred. Then, purified water was added to make the total volume to 100 mL. Then, the resulting mixture was subjected to filter sterilization to obtain a sterile ophthalmic solution. The osmotic pressure of this ophthalmic solution was 290 mOsm/kg, the pH was 7.4, and the appearance was colorless and transparent. The details are shown in Table 2.

Examples 1-2 to 1-10

A sterile ophthalmic solution was prepared in the same way as in Example 1-1, except that the components of the kinds and amounts shown in Table 2 were used. The appearance, pH, and the osmotic pressure of the obtained solution are shown in Table 2.

Table 2

| | | | Example 1-1 | Example 1-2 | Example 1-3 | Example 1-4 | Example 1-5 | Example 1-6 | Example 1-7 | Example 1-8 | Example 1-9 | Example 1-10 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Amount (g) | Component A | Hydroxypropyl methylcellulose (1) | 0.1 | | 0.1 | 0.1 | | | 0.1 | | | 0.1 |
| | | Hydroxypropyl methylcellulose (2) | | 0.2 | | | 0.2 | 0.2 | | 0.2 | 0.2 | |
| | | Hydroxypropyl methylcellulose (3) | | | | | | | | | | |
| | | Hydroxypropyl methylcellulose (4) | | | | | | | | | | |
| | Component B | Sodium chloride | 0.63 | 0.74 | 0.63 | 0.63 | 0.74 | 0.74 | 0.63 | 0.74 | 0.70 | |
| | | Potassium chloride | 0.10 | 0.13 | 0.10 | 0.10 | 0.13 | 0.13 | 0.10 | 0.13 | | 0.85 |
| | Component C | | 0.0004 (net: 0.00008) | 0.0004 (net: 0.00008) | 0.0004 (net: 0.00008) | 0.0004 (net: 0.00008) | 0.0004 (net: 0.00008) | 0.0004 (net: 0.00008) | 0.0004 (net: 0.00008) | 0.0004 (net: 0.00008) | 0.0004 (net: 0.00008) | 0.0004 (net: 0.00008) |
| | Component D | | 2.0 (net: 0.1) | 2.0 (net: 0.1) | 1.0 (net: 0.05) | 3.0 (net: 0.15) | 1.0 (net: 0.05) | 3.0 (net: 0.15) | 2.0 (net: 0.1) | 2.0 (net: 0.1) | 2.0 (net: 0.1) | 2.0 (net: 0.1) |
| | Others | Boric acid | 0.4 | | 0.4 | 0.4 | | | | | 0.4 | 0.4 |
| | | Borax | | | | | | | | | | |
| | | Disodium edetate dihydrate | | 0.05 | | | 0.05 | 0.05 | | 0.05 | | |
| | | Sodium hydrogenphosphate hydrate | | | | | | | 0.43 | 0.43 | | |
| | | Sodium dihydrogen phosphate anhydrous | | | | | | | 0.032 | 0.032 | | |
| | | Sodium hydroxide | 0.0076 | 0.0058 | 0.0076 | 0.0076 | 0.0058 | 0.0058 | | | 0.0076 | 0.0076 |
| | Purified water | | Make total to 100 mL | Make total to 100 mL | Make total to 100 mL | Make total to 100 mL | Make total to 100 mL | Make total to 100 mL | Make total to 100 mL | Make total to 100 mL | Make total to 100 mL | Make total to 100 mL |
| Properties | | Appearance | Colorless and transparent | Colorless and transparent | Colorless and transparent | Colorless and transparent | Colorless and transparent | Colorless and transparent | Colorless and transparent | Colorless and transparent | Colorless and transparent | Colorless and transparent |
| | | pH | 7.4 | 7.2 | 7.4 | 7.4 | 7.2 | 7.2 | 7.4 | 7.2 | 7.4 | 7.4 |
| | | Osmotic pressure (mOsm/kg) | 290 | 278 | 288 | 289 | 281 | 279 | 287 | 278 | 287 | 276 |

Component C: Cosmocil CQ (registered trademark, ARCH CHEMICALS), 20% aqueous solution of hexamethylene biguanide hydrochloride

Component D: 2-methacryloyloxyethyl phosphorylcholine/butyl methacrylate copolymer solution, 5 % aqueous solution (NOF CORPORATION)

Table 3

| | | | Comparative Example 1 | Comparative Example 2 | Comparative Example 3 | Comparative Example 4 | Comparative Example 5 | Comparative Example 6 | Comparative Example 7 |
|---|---|---|---|---|---|---|---|---|---|
| Amount (g) | Component A | Hydroxypropyl methylcellulose (1) | | | 0.1 | 0.1 | 0.1 | 0.1 | |
| | | Hydroxypropyl methylcellulose (2) | | | | | | | 0.2 |
| | | Hydroxypropyl methylcellulose (3) | | 0.2 | | | | | |
| | | Hydroxypropyl methylcellulose (4) | 0.1 | | | | | | |
| | Component B | Sodium chloride | 0.63 | 0.74 | 0.63 | 0.63 | 0.63 | 0.005 | 1.0 |
| | | Potassium chloride | 0.1 | 0.13 | 0.1 | 0.1 | 0.1 | | 1.0 |
| | Component C | | 0.0004 (net: :0.00008) | 0.0004 (net: 0.00008) | 0.00015 (net: 0.00003) | 0.0004 (net: 0.00008) | 0.001 (net: 0.0002) | 0.0004 (net: 0.00008) | 0.0004 (net: 0.00008) |
| | Component D | | 2.0 (net: 0.1) | 2.0 (net: 0.1) | 1.0 (net: 0.05) | | 3.0 (net: 0.15) | 2.0 (net: 0.1) | 2.0 (net: 0.1) |
| | Others | Boric acid | 0.4 | | 0.4 | 0.4 | 0.4 | | |
| | | Borax | | | | | | | |
| | | Disodium edetate dihydrate | | 0.05 | | | | | 0.05 |
| | | Sodium hydrogenphosphate hydrate | | | | | | 6.1 | 0.43 |
| | | Sodium dihydrogen phosphate anhydrous | | | | | | 0.73 | 0.032 |
| | | Sodium hydroxide | 0.0076 | 0.0058 | 0.0076 | 0.0076 | 0.0076 | | |
| | Purified water | | Make total to 100 mL | Make total to 100 mL | Make total to 100 mL | Make total to 100 mL | Make total to 100 mL | Make total to 100 mL | Make total to 100 mL |
| Properties | | Appearance | Colorless and transparent | Colorless and transparent | Colorless and transparent | Colorless and transparent | Colorless and transparent | Colorless and transparent | Colorless and transparent |
| | | pH | 7.4 | 7.4 | 7.4 | 7.4 | 7.4 | 7.4 | 7.4 |
| | | Osmotic pressure (mOsm/kg) | 289 | 287 | 286 | 287 | 288 | 283 | 630 |

Component C: Cosmocil CQ (registered trademark, ARCH CHEMICALS), 20% aqueous solution of hexamethylene biguanide hydrochloride

Component D: 2-methacryloyloxyethyl phosphorylcholine/butyl methacrylate copolymer solution, 5 % aqueous solution (NOF CORPORATION)

0.0004 g of Cosmocil CQ (registered trademark) (20 % aqueous solution, containing 0.00008 g of hexamethylene biguanide), (D) 0.1 g of 2-methacryloyloxyethyl phosphorylcholine/butyl methacrylate copolymer (80 : 20) were added one after another, and stirred. The resulting solution, while maintained at 50 °C, was stirred for 1 hour. Then, purified water was added to make the total volume to 100 mL. The light transmittance at 500 nm of the resulting solution at 30 °C was 100.0 %. This solution was subjected to filter sterilization to obtain a sterile ophthalmic solution. The osmotic pressure of this ophthalmic solution was 290 mOsm/kg, the pH was 7.4, and the appearance was colorless and transparent. The details are shown in Table 6.

Examples 2-2

To 80 g of purified water heated to 80 °C, (A) 0.2 g of hydroxypropyl methylcellulose (2) (METOLOSE (registered trademark) 60SH-4000; 29.0 % methoxy groups, 9.3 % hydroxypropoxy groups, methoxy group/hydroxypropoxy group ratio of 3.1, viscosity of 2% aqueous solution at 20 °C of 4000 mPa·s) was introduced in small portions, and vigorously stirred with a magnetic stirrer for 30 minutes to obtain a dispersion. The light transmittance at 500 nm of this dispersion at 80 °C was 1.2 %. This dispersion was cooled down to 50 °C to obtain a uniform solution. The light transmittance at 500 nm of this solution at 50 °C

was 98.3 %. To this solution, (B) 0.74 g of sodium chloride, 0.13 g of potassium chloride, and 0.0058 g of sodium hydroxide, 0.05 g of disodium edetate dihydrate, (C) 0.0004 g of Cosmocil CQ (registered trademark) (20% aqueous solution, containing 0.00008 g of hexamethylene biguanide), and (D) 0.1 g of 2-methacryloyloxyethyl phosphorylcholine/butyl methacrylate copolymer (80 : 20) were added one after another, and stirred. The resulting solution, while maintained at 50 °C, was stirred for 1 hour. Then, purified water was added to make the total volume to 100 mL. The light transmittance at 500 nm of the resulting solution at 30 °C was 98.4 %. This solution was subjected to filter sterilization to obtain a sterile ophthalmic solution. The osmotic pressure of this ophthalmic solution was 278 mOsm/kg, the pH was 7.2, and the appearance was colorless and transparent. The results are shown in Table 6.

The results of the cytotoxicity test on the soft contact lens extract using V79 cells with respect to the ophthalmic solutions of Examples 2-1 and 2-2 are shown in Table 7. Table 7 shows that the ophthalmic solutions of Examples 2-1 and 2-2 were demonstrated to have little cytotoxicity and high safety.

Table 6

| | | | Example 2-1 | Example 2-2 |
|---|---|---|---|---|
| Amount (g) | Component A | Hydroxypropyl methylcellulose (1) | 0.1 | |
| | | Hydroxypropyl methylcellulose (2) | | 0.2 |
| | | Hydroxypropyl methylcellulose (3) | | |
| | | Hydroxypropyl methylcellulose (4) | | |
| | Component B | Sodium chloride | 0.63 | 0.74 |
| | | Potassium chloride | 0.1 | 0.13 |
| | Component C | | 0.0004 (net: 0.00008) | 0.0004 (net: 0.00008) |
| | Component D | | 2.0 (net: 0.1) | 2.0 (net: 0.1) |
| | Others | Boric acid | 0.4 | |
| | | Borax | | |
| | | Disodium edetate dihydrate | | 0.05 |
| | | Sodium hydrogenphosphate hydrate | | |
| | | Sodium dihydrogen phosphate anhydrous | | |
| | | Sodium hydroxide | 0.0076 | 0.0058 |
| | Purified water | | Make total to 100 mL | Make total to 100 mL |
| Properties | | Light transmittance (@80°C) | 53.0 | 1.2 |
| | | Light transmittance (@50°C) | 99.4 | 98.3 |
| | | Light transmittance (ophthalmic solution, @30°C) | 100.0 | 98.4 |
| | | Appearance | Colorless and transparent | Colorless and transparent |
| | | pH | 7.4 | 7.2 |
| | | Osmotic pressure (mOsm/kg) | 290 | 278 |

Component C: Cosmocil CQ (registered trademark, ARCH CHEMICALS), 20% aqueous solution of hexamethylene biguanide hydrochloride

Component D: 2-methacryloyloxyethyl phosphorylcholine/butyl methacrylate copolymer solution, 5 % aqueous solution (NOF CORPORATION)