# pH Stability of ophthalmic solutions

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**Background:** In this study, we evaluated the pH value of 17 ophthalmic solutions, and we investigated whether the pH of these solutions changed over time after the bottle was opened.

**Methods:** Fifteen bottles of each type of solution were chosen at random from different production lots. A 0.05-ml increment was taken from each bottle and was measured daily using a micropH 2002 Crison pH-meter over a period of 30 days.

**Results:** The results revealed differences between the pH values of the solutions; nine solutions presented pH values within ocular comfort range and eight solutions presented pH values between 3.5 and 6.4. Ten solutions presented nonstatistically significant variations over time ($p > 0.01$) and seven solutions presented isolated but statistically significant variations.

**Conclusions:** We may assume that the nine solutions with pH values within the ocular comfort range will not produce initial discomfort. The solutions with acid pH values will produce initial discomfort. The solutions with nonstatistically significant pH variations over 30 days in relation to their initial pH values presented great stability.

**Key Words:** Aqueous solution, cornea, eyedrops, ophthalmic solutions, pH variation, topical dosage

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Except for the skin, the eye is the most easily accessible site for topical administration of medication. The most commonly used dosage form is an aqueous solution of a drug delivered as an eyedrop, which is applied topically to act on the ocular surface or in the interior of the eye.

An aqueous solution instilled onto the eye is subject to the influences exerted by the normal protective physiological mechanisms present in the eye. Assuming normal tear drainage, the instilled solution is eliminated completely from the eye within 5 or 6 minutes of its application. This results in a very short period during which the drug has access to the ocular tissues.

The cornea is relatively impermeable to most drugs due to its trilaminate structure, which consists of a hydrophilic stroma located between the outermost highly lipophilic epithelial layer and the endothelial layer, which is less lipophilic. The intact corneal epithelium contributes to the resistance to hydrophilic drugs, whereas the stroma limits permeability to lipophilic drugs. Although a damaged epithelium does not offer great resistance to the permeability of hydrophilic drugs, in the case of a healthy corneal epithelium, the permeability to hydrophilic drugs is achieved by varying the physicochemical properties of the drug, either by derivation chemistry or by altering the pH and so manipulating its ionization.[1] In spite of the fact that the corneal epithelium is relatively impermeable to most ocular drugs, transcorneal penetration is believed to be the best pathway for drug absorption into the eye.[1-3]

The paracellular and transcellular pathways are the two mechanisms for drug transport across the cornea. In the paracellular mechanism, the drug penetrates through inter-

## Table 1. Ophthalmic solutions evaluated, their trade names, manufacturing laboratory, composition and action, remarks

| Name (manufacturer/ country of manufacture): indication for use/remarks | Active ingredients (each ml) | Inactive ingredients (excipients) | Action |
|---|---|---|---|
| **Oftalmotrim Dexa® (Cusi S.A./Spain): anti-inflammatory; protect from light, discard a month after opening bottle** | 1 mg dexamethasone sodium phosphate; 1 mg trimethoprim 10,000 IU polymyxin B sulphate | Benzalkonium chloride, sulfuric acid, CINa, sodium hydroxide, trisodium citrate, polysorbate 80, citric acid, water for injection | Association of cortico-steroid (dexamethasone) and antimicrobial agents (trimethoprim and polymyxin B). Reduces the inflammation and eliminates the infection |
| **Cortoftal® (Cusi S.A./ Spain): anti-inflammatory; protect from light, discard a month after opening bottle** | 1 mg clobetasone butyrate | Benzalkonium chloride, CINa, monosodium phosphate, edetate disodium, polysorbate 80, hipromelose, water for injection | Anti-inflammatory steroid |
| **Oftalar® (Cusi S.A./ Spain): anti-inflammatory; protect from light, discard at end of treatment; discard a month after opening bottle** | 1 mg pranoprophen (DCI) | Benzalkonium chloride, boric acid, polysorbate 80, sodium tetraborate, edetate sodium, water for injection | Nonsteroidal anti-inflammatory |
| **Poly-Pred Liquifilm® (Allergan/Ireland): anti-inflammatory; discard at end of treatment** | 5 mg/ml prednisolone acetate 5 mg/ml neomycin sulfate 10,000 µ/ml polymyxin sulfate B | 14 mg/ml Liquifilm (polyvinyl alcohol), polysorbate 80, propilene glycol, sodium acetate, thimerosal, water for injection | Anti-inflammatory steroid and antibiotic |
| **Colircusi Gentamicina® (Cusi S.A./Spain): ocular infec-tions; discard a month after opening bottle** | 3 mg gentamicin (sulfate) | Benzalkonium chloride, monosodium phosphate, disodium phosphate, CINa, water for injection | Antibiotic of the aminoglycoside group |
| **Oftalmotrim Colirio® (Cusi S.A./Spain): ocular infections; protect from light, discard a month after opening bottle** | 1 mg trimethoprim 10,000 IU polymyxin sulfate B | Methylhydroxybenzoate sodium, sulfuric acid, CINa, water for injection | Antimicrobial agents association |
| **Alomide® (Alcon Iberhis S.A./Belgium): allergic ocular disorders; discard a month after opening bottle** | Lodoxamide (DCI) 1 mg/ml tromethamine | Benzalkonium chloride, 0.007 mg/ml mannitol, hydroxypropyl methylcell-ulose, sodium citrate, citric acid, edetate disodium, tyloxapol, sodium hydroxide, and/or hydro-chloric acid, purified water | Antihistaminic and anti-inflammatory activity |
| **Colircusi Ciclopléjico® (Cusi S.A./Spain): mydriatric and cycloplegic action; discard a month after opening bottle** | 10 mg cyclopentolate hydrochloride | Methyl parahydroxybenzoate, propyl parahydroxybenzoate, CINa, water for injection | Parasympathicolitic action with mydriatic and cycloplegic action |
| **Colircusi Atropina® (4:1) (Cusi S.A./Spain): myd-riatic and cycloplegic action; discard a month after opening bottle** | 5 mg atropine sulfate | Parahydroxybenzoate of methyl, parahydroxyben-zoate of propyl, CINa, disodium phosphate, monopotassium phosphate, water for injection | Parasympathicolitic action with mydriatic and cycloplegic action |

cellular space; in the transcellular mechanism, the drug penetrates through the intracellular space. The principal drug properties that influence drug absorption via the transcellular pathway are the lipophilicity, the pKa, which determines the percentage of the absorbed un-ionized form of the drug present at a given pH, the solubility, and the molecular size.[4-8]

The adjustment of an ophthalmic solution's pH by the appropriate choice of a buffer is one of the most important considerations in its formulation. Buffers may be used in ophthalmic solutions for one or more of the following reasons: to maintain the physiological pH of tears upon administration in order to minimize epiphora and patient discomfort; to optimize the therapeutic activity of the

## Table 2. Ophthalmic solutions evaluated, their trade names, manufacturing laboratory, composition and action, remarks

| Name (manufacturer/ country of manufacture): indication for use/remarks | Active ingredients (each ml) | Inactive ingredients (excipients) | Action |
|---|---|---|---|
| **Colircusi Anestésico® (4:1) (Cusi S.A./Spain): local anesthetics: discard a month after opening bottle** | 5 mg tetracaine hydrochloride 0.5 mg naphazoline hydrochloride | Chlorobutanol, monosodium phosphate, disodium phosphate, CINa, water for injection | High anesthetic action |
| **Cusimolol® (4:1) (Cusi S.A./ Spain): reduces intraocular pressure: protect from light** | 5 mg timolol (maleate) | Benzalkonium chloride, monosodium phosphate, disodium phosphate, CINa, water for injection | Reduces the intraocular pressure, beta-adrenergic blocking agent |
| **Xalatan® (Pharmacia& Upihn/Sweden): reduces intraocular pressure: protect from light, discard a month after opening bottle** | 50 micrograms Latanoprost | Benzalkonium chloride, CINa, disodium hydrogen phosphate anhydrous, water for injection | Reduces intraocular pressure in acute glaucoma |
| **Elebloc® (Cusi S.A./Spain): reduces intraocular pressure: discard at end of treatment, discard a month after opening bottle** | 20 mg arteolol hydrochloride | Benzalkonium chloride, CINa, monobasic sodium phosphate, dibasic sodium phosphate, water for injection | Reduces intraocular pressure, nonselective beta-adrenoceptor blocking agent |
| **Colircusi Philocarpina® 2 (Cusi S.A./Spain): reduces intraocular pressure: discard a month after opening bottle** | 20 mg pilocarpine chloride | Benzalkonium chloride, polividone, CINa, sodium tetraborate, water for injection | Parasympathomimetic action, produces miosis and reduces intraocular pressure |
| **Liquifilm Lágrimas® (Allergan/Ireland): lubricant: discard a month after opening bottle** | 14 mg/ml polyvinyl alcohol (DCI) | 0.05 Benzalkonium chloride, dibasic sodium phosphate, CINa, monosodium phosphate, edetate disodium, hydrochloric acid, and sodium hydroxide (para pH), water for injection | Ocular lubricant |
| **Vistafrin Liquifilm® (Allergan/Ireland): lubricant** | 1.2 mg/ml phenylephrine hydrochloride, with 14 mg/ml liquifilm (polyvinyl alcohol) | Benzalkonium chloride, acetate sodium, dibasic sodium phosphate, monosodium phosphate, antipirine, sodium tiosulfate, edetate disodium, hydrochloric acid, and sodium hydroxide, purified water | To relieve ocular congestion |
| **Celluvisc® (Allergan/Ireland): lubricant** | 4 mg sodium carmelosa (DCI) | CINa, sodium lactate, CLK, calcium chloride, water for injection | Ocular lubricant |

active ingredient by altering corneal penetration through changes in the degree of ionization; and, finally, to optimize product stability.

According to Carney and Hill,[9] the physiological pH is 7.45, and the ocular range is between 6.6 and 7.80 pH units. For maximum comfort, an ophthalmic solution should have the same pH as the lacrimal fluid, or the pH of the solutions should lie within the ocular comfort range. Several studies show that the pH of contact lens solutions is maintained within ocular comfort range; therefore, these solutions are well-tolerated.[10-15]

The most common active ingredients found in ophthalmic solutions are salts formed from weak bases, which are most stable at an acidic pH. Thus, the formulator is often faced with the need to choose a pH that does not compromise the stability of the product, but is still compatible with

**Table 3. Mean, standard deviation (SD), range, and p values for the ophthalmic solutions evaluated**

| Ophthalmic solution | Mean | SD | Range | | *p* value |
|---|---|---|---|---|---|
| Gentamicina® | 6.61 | 0.02 | 6.58 | 6.62 | <0.001 |
| Oftalar® | 7.64 | 0.03 | 7.58 | 7.69 | 0.055 |
| Cusimolol® | 6.92 | 0.02 | 6.88 | 6.96 | <0.001 |
| Elebloc® | 6.69 | 0.02 | 6.64 | 6.73 | <0.001 |
| Oftalmotrim Dexa® | 7.33 | 0.03 | 7.28 | 7.39 | <0.001 |
| Liquifilm® | 7.24 | 0.04 | 7.17 | 7.29 | 0.718 |
| Celluvisc® | 7.20 | 0.05 | 7.11 | 7.28 | 0.370 |
| Vistafrim® | 6.89 | 0.02 | 6.86 | 6.91 | 0.002 |
| Xalatan® | 6.77 | 0.02 | 6.73 | 6.79 | <0.001 |
| Atropina® | 5.18 | 0.03 | 5.13 | 5.24 | 0.168 |
| Oftalmotrim® | 5.79 | 0.04 | 5.73 | 5.85 | 0.011 |
| Alomide® | 5.09 | 0.11 | 5.00 | 5.44 | 0.045 |
| Cortoftal® | 5.25 | 0.05 | 5.13 | 5.30 | 0.255 |
| Poly-Pred® | 6.44 | 0.03 | 6.38 | 6.50 | <0.001 |
| Ciclopléjico® | 3.55 | 0.03 | 3.51 | 3.59 | 0.117 |
| Anestésico® | 4.70 | 0.11 | 4.53 | 4.84 | 0.904 |
| Pilocarpina® | 3.72 | 0.03 | 3.66 | 3.76 | <0.001 |

the ocular surface. The solution to this dilemma is usually to maintain the product at an acid pH with a low-capacity buffer. Provided the drug itself has a weak buffering effect and the volume instilled is small, the tears should be able to adjust the pH rapidly to a value near 7.45, thereby minimizing any discomfort. However, occasionally the drug itself may exert a significant buffering effect and thus a different salt form may be necessary.[16]

The purpose of this article is to evaluate the pH value of 17 ophthalmic solutions frequently used in ophthalmic practice in Spain—some of these in worldwide distribution—and to investigate their variation over time. For this, measurements were taken over a test period of 30 days, which is the recommended period of use after the bottles have been opened. The pH values will determine the solutions that are most compatible with ocular physiology and are more stable during the time (30 days) of the study.

## Materials and Methods

Seventeen ophthalmic drugs were selected for pH measurement and comparison in this study. Tables 1 and 2 show the solutions evaluated, their trade names, manufacturing laboratory, composition and action, observations, indication for use, and recommended time of use once the bottle is opened.

For statistical purposes, we used 15 bottles of each solution, chosen at random from different production lots, in order to obtain a general mean pH value for that particular solution, not the pH of one specific lot.

Using a micropH 2002 Crison pH-meter,[17] the pH values of the solutions were measured over a 30-day period after the bottles were opened, as this was the maximum length of use recommended by the manufacturer. The pH-meter, which uses an Ingold electrode sensor, measures electric potential differences with a high-entry impedance ($10^{14}$ Ohms) and high resolution (0.1 mv), giving precise readings. The accuracy and repeatability of the pH-meter are $\pm$ 0.001 and $\pm$ 0.002 pH units, respectively.

Measurements were randomized. A 0.005-ml increment was taken from each bottle and was measured daily. The pH value was measured five times for each sample. The electrode sensor was rinsed with distilled water between measurements. The pH-meter was calibrated using two standard buffered solutions of 7.02 and 4.00 pH units before the first measurement, after 10 measurements, and after the final measurement.

All solutions were tested at room temperature, ranging from 19° to 21° C, and the humidity was maintained at 65% (by air conditioner) during the testing period. The Xalatan® and the Oftalmotrim Dexa® were kept in a refrigerator for 30 days; the rest of the solutions were kept at room temperature.

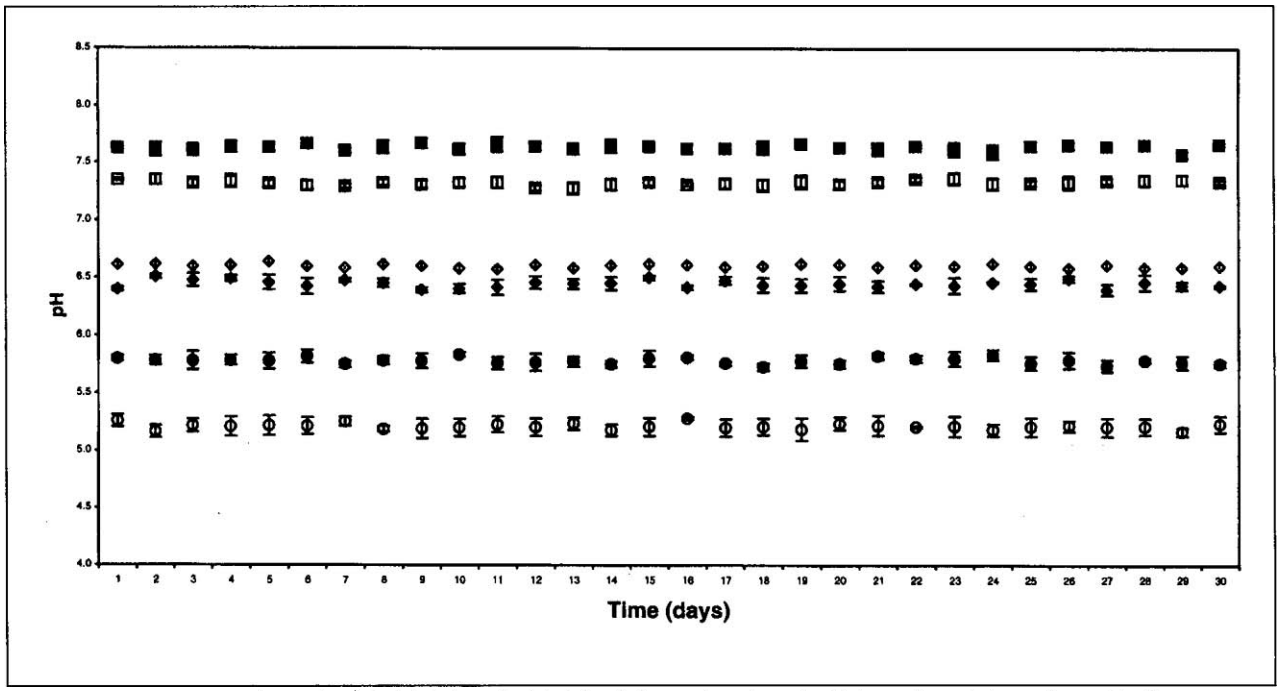


**Figure 1** The mean pH values and standard deviations of ophthalmic solutions evaluated over the 30-day testing period. ◇ = Gentamicina®; ■ = Oftalar; □ = Oftalmotrim Dexa®; ● = Oftalmotrim®; ○ = Cortoftal®; and ◆ = Poly–Pred®.

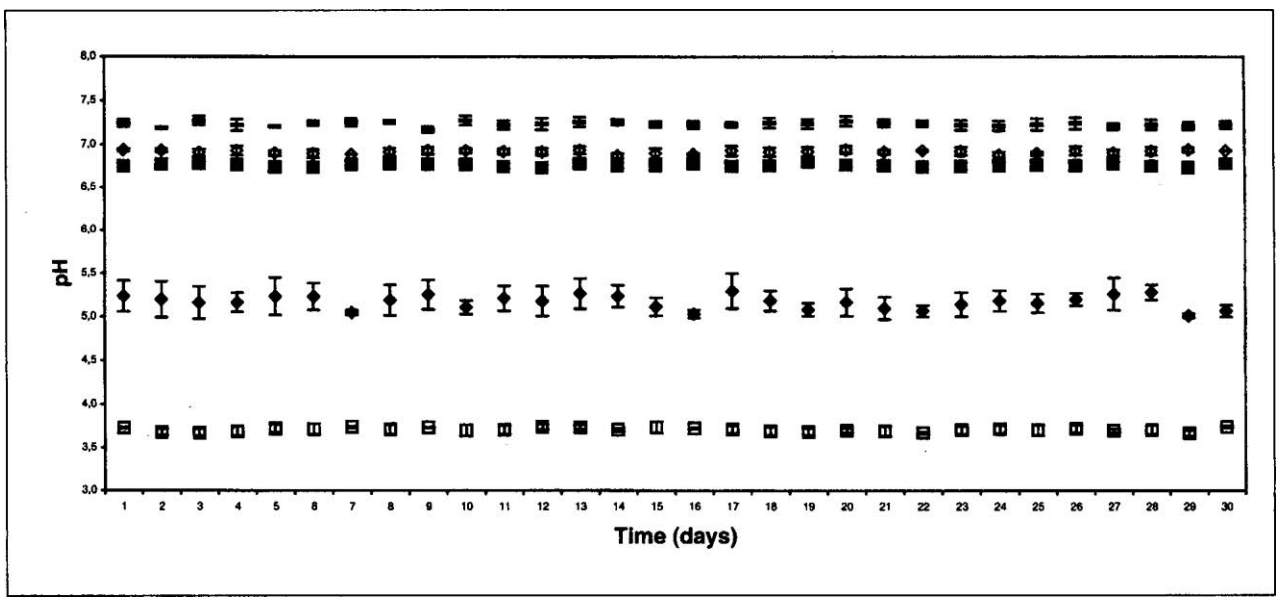


**Figure 2** The mean pH values and standard deviations of ophthalmic solutions evaluated over the 30-day testing period. ◇ = Cusimolol®; — = Liquifilm®; ■ = Xalatan®; ◆ = Alomide®; and □ = Pilocarpina®.

## Results

Figures 1, 2, and 3 show the pH values obtained over 30 days for all the solutions. The pH of each solution changed over time. However, using the one-way analysis of variance (ANOVA) test[18] with the criterion of $p > 0.01$, we did not find statistically significant differences in pH over time for 10 of the 17 solutions analyzed: Cortoftal®, Oftalar®, Oftalmotrim®, Alomide®, Colircusi Ciclopéjico®, Colircusi Atropina®, Colircusi Anestésico® (4:1), Liquifilm Lagrimas®, Vistafrin Liquifilm®, and Celluvisc®.

The rest of the solutions—seven of the 17 solutions studied—presented statistically significant variations on isolated days, as follows:

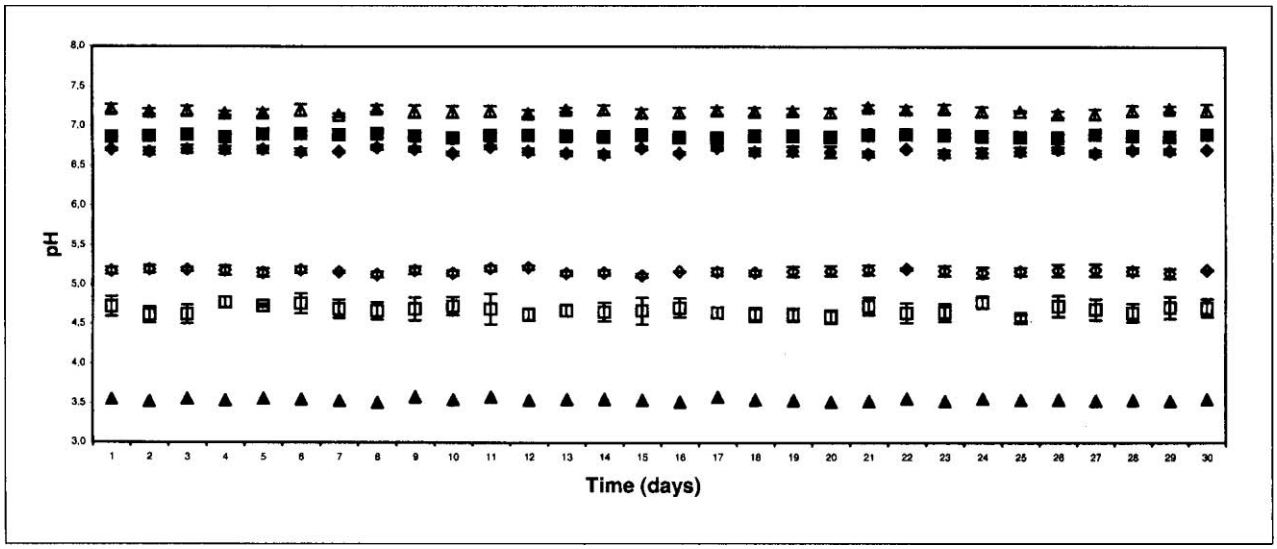


**Figure 3** The mean pH values and standard deviations of ophthalmic solutions evaluated over the 30-day testing period. ◆ = Elebloc®; ■ = Vistafrin®; Δ = Celluvisc®; ◇ = Atropina®; ▲ = Ciclopléjico®; and □ = Anestésico®.

Colircusi Gentamicina® (4:1) presented a significant variation on Day 22 in relation to Day 7;
Elebloc® 2 presented a variation on Day 16 in relation to Day 2, Day 22, and Day 30;
Oftalmotrim Dexa® presented variation on Day 7 in relation to Day 2 and Day 22;
Colircusi Pilocarpina® 2 presented significant variation on Day 22 in relation to all other Days;
Poly-Pred® presented variation on Day 7 in relation to Day 2, on Day 16 in relation to Day 7, on Day 22 in relation to Day 2, and on Day 30 in relation to Day 7; and
Xalatan® presented variation on Day 7 in relation to Day 2, on Day 16 in relation to Day 2, on Day 22 in relation to Day 7 and Day 16, and on Day 30 in relation to Day 2 and Day 16.

It should be noted that Cusimolol® (4:1) presented a significant variation from Day 22 after the opening of the bottle to the thirtieth day.

The mean average standard deviations (SDs) and range of the pH values of the ophthalmic solutions measured are shown in Table 3. All the solutions had mean pH values that ranged from 7.69 and 3.51 pH units. The pH values for nine solutions lie well within the ocular comfort range:[13] Colircusi Gentamicina® (4:1), Oftalar®, Cusimolol®, Elebloc®, Oftalmotrim Dexa®, Liquifilm®, Celluvisc®, Vistafrin Liquifilm®, and Xalatan®. The remaining eight solutions—Colircusi Atropina® (4:1), Oftalmotrim®, Alomide®, Cortoftal®, Poly-Pred®, Colircusi Ciclopléjico®, Colircusi Anestésico® (4:1), and Colircusi Pilocarpina® 2—presented pH values below the minimum value of the ocular comfort range. The standard deviation values over time ranged from 0.02 to 0.11, depending on the solution tested.

## Discussion

Figures 1, 2, and 3 indicate that the pH values of all the solutions evaluated fluctuated over time. These low variations in pH over time are secondary to the action of the buffer agent, which functions to maintain the pH. The differences obtained may be due to the different buffer agents used in the specific solutions.

The buffer agents present in the studies of ophthalmic solutions are phosphate, citrate, citrate-phosphate, bicarbonate, acetate, and borate.[19,20] The buffering agents found in the ophthalmic solutions studied without statistically significant pH variations over time are phosphate, borate, and citrate. The most-used buffer agent is phosphate. The buffer agents present in the solutions with statistically significant pH variations are phosphate, acetate, citrate, and borate. We do not find a relation between ph variation and buffer agents. These solutions contained isotonic agents and preservatives that also react with air, modifying the solution pH value.

The solutions that do not present statistically significant pH variations over time are Cortoftal®,

Oftalar®, Oftalmotrim®, Alomide®, Colircusi Ciclopéjico®, Colircusi Atropina® (4:1), Colircusi Anestésico® (4:1), Liquifilm Lagrimas®, Vistafrin Liquifilm®, and Celluvisc®.

The solutions that presented isolated variations and maintained the original pH value on most of the 30 Days studied are: Colircusi Pilocarpina® 2%, Elebloc® 2, Colircusi Gentamicina® (4:1), Oftalmotrim Dexa®, Poly-Pred®, and Xalatan®. The isolated variations could be due to insufficient buffer agent, but the cause of the isolated pH variations is not clear.

We need to draw attention to Cusimolol® (4:1), since it presented statistically significant pH variations from Day 22 through Day 30. In this case the pH change could be due to insufficient buffer. The mean pH values from Day 22 to Day 30 ranged from 6.931 to 8.930 pH units. These variations are indeed minimal. Therefore, a clinical study of Cusimolol® (4:1) to verify that these pH variations do not affect the therapeutic action of the ophthalmic solution should be performed.

In spite of the variations, the pH values of all the evaluated solutions are at a tolerable level for the ocular surface.

In this study, we obtained a group of nine solutions—Elebloc®, Cusimolol® (4:1), Colircusi Gentamicina® (4:1), Oftalmotrim Dexa®, Liquifilm®, Vistafrin®, Celluvisc®, Xalatan®, and Oftalar®—that present a pH value within the ocular comfort range and do not affect ocular physiology. Within this group of solutions, the artificial tear solutions may be highlighted: Liquifilm® and Celluvisc® and the vasoconstrictor-ocular decongestant, Vistafrin Liquifilm®. The pH value of these solutions must be close to the physiological pH for maximum ocular comfort,[21,22] since these solutions are prescribed to return the tears to a normal pH.

The other eight solutions—Oftalmotrim®, Colircusi Atropina® (4:1), Colircusi Ciclopéjico®, Colircusi Anestésico® (4:1), Colircusi Pilocarpina® 2, Alomide®, Cortoftal®, and Poly-Pred®—have a slightly acid pH. The difference between the lacrimal pH and ophthalmic solution pH will initially produce discomfort and lacrimation.

Consequently, in these cases, an initial decrease of ocular comfort is necessary to increase absorption and improve the therapeutic effect of the ophthalmic solution; in the case of frequent use of the solution, we must take into account the question of whether the benefit is greater than the discomfort produced. It is the task of the dispensing doctor to decide whether extended use is appropriate.

## Conclusions

The solutions with a more-stable pH during the test period were Cortoftal®, Oftalar®, Oftalmotrim®, Alomide®, Colircusi Ciclopéjico, Colircusi Atropina® (4:1), Colircusi Anestésico® (4:1), Liquifilm Lagrimas®, Vistafrin Liquifilm®, and Celluvisc®, and the solutions with a pH closer to physiologic pH were Elebloc®, Cusimolol® (4:1), Colircusi Gentamicina® (4:1), Oftalmotrim Dexa®, Liquifilm®, Vistafrin®, Celluvisc®, Xalatan®, and Oftalar®.

In conclusion, in this study we evaluated the pH of 17 ophthalmic solutions and their evolution over a period of 30 days, obtaining a fluctuation in pH, which for most of the solutions is not statistically significant.

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