

1 **ABSTRACT**

2 **Purpose:** The physical properties of contact lens care solutions and Eye Drops (ED)
3 may affect initial comfort and dry eye symptomatology in contact lens wearers, although
4 these properties are not always provided by manufacturers. The present study aimed to
5 measure and compare the osmolality and pH of commercially available contact lens care
6 solutions and ED.

7 **Methods:** Forty-four solutions were tested (17 lens care solutions and 27 ED) and
8 classified by the presence and/or combination of the viscosity/lubrication-enhancing
9 ingredients. Solution osmolality was obtained with the Fiske 110 osmometer and pH was
10 measured with a micro-pH 2000. Each measurement was taken ten times, following the
11 manufacturer's instructions, while controlling for room temperature and humidity.
12 Differences between the values of the physical properties of the solutions were analysed
13 by type and viscosity/lubrication-enhancing agent subclassification.

14 **Results:** Osmolality ranged from 192.6 ± 2.17 to 364.6 ± 2.88 mOsm/Kg, while pH ranged
15 from 6.35 [6.35-6.26] to 7.99 [7.99-8.00]. A significant difference in the osmolality and
16 pH values of contact lens care solutions and ED was found when classified by type or
17 viscosity/lubrication-enhancing agent (ANOVA and Kruskal-Wallis respectively, both $p <$
18 0.001).

19 **Conclusions:** The physical properties of some contact lens care solutions and ED are
20 not readily available. The osmolality and pH values of various commercially available
21 lens care solutions and ED vary significantly both by type and viscosity/lubrication-
22 enhancing ingredients.

23

24 **Keywords:** lens care solutions, eye drops, osmolality, pH, viscosity/lubrication-
25 enhancing principles

26 1. INTRODUCTION

27 There are approximately 140 million contact lens wearers globally [1]. While overall, rigid
28 gas permeable lens fitting is decreasing compared to soft contact lenses [2-4], speciality
29 rigid lens prescribing is increasing [5, 6]. Despite the introduction of new contact lens
30 care solutions and materials, 25-50% of contact lens wearers report discomfort,
31 particularly at the end of the day, which is a key factor in contact lens drop out [1, 7-14].
32 Contact Lens Discomfort (CLD) frequently affects contact lens users, reducing the overall
33 and comfortable wearing time. A consensus on the definition and causes of CLD was
34 recently established by the International Tear Film Ocular Surface (TFOS) in the CLD
35 Workshop [1, 8, 15, 16].

36 The TFOS workshop advised that avoiding contact lens care systems with high
37 osmolarity or low pH may reduce stinging and contact lens discomfort [17]; high
38 osmolarity is presumed to trigger a cascade of signalling events within surface epithelial
39 cells which leads to the release of inflammatory mediators and proteases [18, 19],
40 whereas pH acidification induces a decrease the lens hydration and could contribute to
41 a tight fitting lens [17, 20, 21]. Although switching to daily disposable contact lenses
42 eliminates ocular surface exposure to lens care solutions [16, 22], contact lens wearers
43 are still exposed to lens packaging solutions or Eye Drops (ED) used to improve comfort
44 [16, 23]. Therefore, the physicochemical properties of these solutions should be
45 evaluated in order to study the interrelation between lens care system and comfort,
46 ultimately aiming at minimising solution related CLD [17].

47 The Dry Eye Workshop (DEWS) and DEWS II reports [24, 25] recommend artificial tears
48 as the most adequate medication for patients with dry eye disease (DED). The
49 prevalence and incidence of DED have increased exponentially, mainly motivated by the
50 current lifestyle and the increased life expectancy that trigger the tear film destabilisation
51 [26, 27]. Additionally, recent studies estimated that this disease implies high annual costs
52 to the health care systems of the different countries [28]. Patients with DED experience
53 a range of ocular symptoms, including discomfort, pain, burning, foreign body sensation,

54 and visual disturbances which negatively impact their quality of life [26, 29]. The use of
55 ED (such as artificial tears and/or supplements), is the main palliative treatment for DED,
56 but does not treat the underlying cause of elevated tear film osmolarity and instability
57 leading to inflammation of the ocular surface and underlying tissues.

58 Previous studies have analysed saline solutions (SS), multi-purpose solutions (MPS),
59 gas permeable solutions (GPS), neutralised and un-neutralised hydrogen peroxide-
60 based solutions (HPS) and ED [9-12, 30-32], reporting great variation in both
61 measurement techniques and results. Moreover, there are many commonly used or new
62 commercially available solutions whose physical properties have not yet been
63 documented. The purpose of this study was to use high precision instrumentation to
64 measure and compare the osmolality and pH of commercially available solutions based
65 on their composition (SS, MPS, GPS, neutralised and un-neutralised HPS and ED) in
66 order to provide the clinician with useful information for the management of CLD and
67 DED.

68

69 **2. MATERIAL AND METHODS**

70 **2.1 Solutions**

71 Forty-four solutions were tested: 1) 17 contact lens care solutions including SS, MPS,
72 GPS, and HPS; and 2) 27 ED. The composition of the solutions is reported in **Table 1**
73 and 2, where ingredients are stratified by their function. Solutions were grouped by the
74 main active and inactive viscosity and lubrication-enhancing ingredients. Groups were
75 created based on the FDA classifications (Title 21/Chapter I/Subchapter D/ Part 349) as
76 follows: 1) Cellulose Derived (hydroxypropyl methylcellulose, carboxymethylcellulose
77 sodium, etc.), 2) Hyaluronic Acid (HA) and/or derivatives, 3) Polyvinylpyrrolidone (PVP),
78 4) Polyvinyl Alcohol (PVA), 5) Liquid Polyols (polyethylene glycol, propylene glycol, etc.),
79 6) Hydroxypropyl-Guar (HP-GUAR), and 7) Solutions containing other ingredients not
80 included in the previous groups. **Each solution were assigned to a group based on their**

81 **composition.** The order of testing of the solutions was randomised; however, once a
82 solution was chosen, it was serially measured.

83 Table 1 - Main components of the lens care solutions tested. Care solutions were classified by the presence and/or combination of the
84 main active and inactive viscosity and lubrication-enhancing ingredients studied. CHG: Chlorhexidine Gluconate. EDTA:
85 Ethylenediaminetetraacetic Acid. GPS: Gas Permeable solutions. HA: Hyaluronic Acid. HPMC: Hydroxypropyl Methylcellulose. HPS:
86 Hydrogen Peroxide Solution. MAPD: Myristamidopropyl Dimethylamine. MPS: Multipurpose solution. PAPB: Polyaminopropyl
87 Biguanide. PEG: Polyethylene Glycol. PHMB: Polyhexanide. Polyquad: Polyquaternium-1. PVA: Polyvinyl Alcohol. PVP:
88 Polyvinylpyrrolidone. SH: Sodium Hyaluronate. SS: Saline Solution

Classification	Solution	Manufacturer	Class	Surfactant/ Wetting agents/ Cleaners	Preservative/ Chelating agents	Other reported agents (e.g., buffers)
Cellulose Derived	Boston Simplus	B&L	GPS	HPMC, Glucam, Poloxamine 1107, Hydranate, (Hydroxyalkylphosphonate)	0.003% CHG 0.0005% PAPB	Boric acid, Sodium borate, Sodium chloride
HA/SH	Biotrue	B&L	MPS	HA, Poloxamine	0.00013% PAPB 0.0001% Polyquad EDTA	Sulfobetaine, Boric acid, Sodium borate, Sodium chloride
	Avizor Sensitive Unique	AVIZOR	MPS	HA, Poloxamer	0.0001% PHMB EDTA	Buffered
PVP	All Clean	AVIZOR	MPS	PVP, 0.25% Poloxamer	0.0002% PHMB 0.1% EDTA	Borax, Boric acid
Liquid Polyols	SoloCare Aqua	MENICON	MPS	Sorbitol, 0.05% Poloxamer 407	0.0001% PHMB EDTA	Dexpanthenol (provitamine B5), Thromethamine, Sodium dihydrogen phosphate
	Opti-Free Express	ALCON	MPS	Sorbitol, Poloxamine (Tetronic 1304)	0.001% Polyquad 0.0006% MAPD 0.05% EDTA, Citrate	Sodium chloride, Boric acid, Aminomethylpropanol
	Opti-Free Pure Moist	ALCON	MPS	HydraGlyde (Polyoxyethylene-polyoxybutylene), Poloxamine (Tetronic 1304)	0.001% Polyquad 0.0006% MAPD EDTA, Citrate	Boric acid, Sodium chloride

	GP Conditioner Avizor	AVIZOR	GPS	0.1% Viscosifying agent	0.0002% PHMB 0.1% EDTA	Aqueous, isotonic, buffered solution
Cellulose Derived + PVP	GP Multi Avizor	AVIZOR	GPS	PVP, HPMC, 0.25% Poloxamer	0.0002% PHMB 0.1% EDTA	Buffered
Cellulose Derived + PVP + Liquid Polyols	Boston Advance Comfort	B&L	GPS	Cellulosic viscosizer, PVA, PEG	0.003% CHG 0.0005% PAPB 0.05% EDTA	Buffered
Others	Avizor Saline	AVIZOR	SS	No	0.00005% PHMB	Buffered, isotonic and sterile solution
	Avizor Saline Unidose	AVIZOR	SS	No	No	Buffered, aqueous, isotonic, and sterile solution
	Alvera	AVIZOR	MPS	Poloxamer	0.0002% PHMB 0.1% EDTA	Aloe Vera, Borax, Boric acid, Sodium tetraborate decahydrate, Sodium chloride
	ReNu Multiplus	B&L	MPS	1 % Poloxamine (Tetronic 1107), 0.03 % Hydranate, (Hydroxyalkylphosphonate)	0.0001% PHMB 0.1% EDTA	Boric acid, Sodium borate
	ReNu Sensitive Eyes MPS	B&L	MPS	1% Poloxamine	0.00005% PHMB EDTA	Boric acid, Sodium chloride, Sodium borate
Hydrogen Peroxide Solution	AOsept	ALCON	HPS	-	3% Hydrogen peroxide	Phosphates
	Easysept	B&L	HPS	-	3% Hydrogen peroxide	Sodium phosphonate

90 Table 2 -Main components of eye drops tested. Eye drops were classified by the presence and/or combination of the main active and
 91 inactive viscosity and lubrication-enhancing ingredients studied. CMC: Carboxymethylcellulose. EDTA: Ethylenediaminetetraacetic
 92 Acid. HA: Hyaluronic acid. HP-GUAR: Hydroxypropyl-guar. HPMC: Hydroxypropyl methylcellulose. NIG: N-hydroxy-methyl-glycinate.
 93 PEG: Polyethylene Glycol. PG: Propylene Glycol. PHMB: Polyhexanide. Polyquad: Polyquaternium-1. PVP: Polyvinylpyrrolidone. PVP:
 94 Polyvinylpyrrolidone. SH: Sodium Hyaluronate. UD: Unidose

Classification	Solution	Manufacturer	Class	Surfactant/ Wetting agents/ Cleaners	Preservative/ Chelating agents	Other reported agents (e.g., buffers)
Cellulose Derived	Lens lubricant Sensitive Eyes	B&L	MULTI-TEAR	HPMC	Sorbic Acid EDTA	Sodium chloride, buffered isotonic solution,
	Opto Idro + A	OPTOX	MULTI-TEAR	0.30% HPMC	NIG EDTA	Glycine, Proline, Lysine, Leucine, Buffered solution,
	Opto Idro + A UD	OPTOX	UD-TEAR	0.30% HPMC	No	Glycine, Proline, Lysine, Leucine, Buffered solution
	Opto Prolens	OPTOX	MULTI-TEAR	HPMC, Phospholipids	No	Lipids
	Refresh Contacts	ALLERGAN	MULTI-TEAR	CMC	PURITE	Sodium chloride, Boric acid, Sodium borate decahydrate, Potassium chloride, Calcium chloride, Magnesium chloride, Hydrochloric, Sodium hydroxide
	Refresh Contacts UD	ALLERGAN	UD-TEAR	CMC	PURITE	Sodium chloride, Boric acid, Sodium borate decahydrate, Potassium chloride, Calcium chloride, Magnesium chloride, Hydrochloric, Sodium hydroxide
HA/SH	Biotrue Multidose	B&L	MULTI-TEAR	0.24% HA	No	Sodium chloride, Potassium chloride, Sodium phosphates
	Biotrue Unidose	B&L	UD-TEAR	0.20% HA	No	Sodium chloride, Potassium chloride, Sodium phosphates
	Moisture Drops	AVIZOR	MULTI-TEAR	0.10% HA	PHMB EDTA	Borax, Sodium chloride

	Moisture Drops UD	AVIZOR	UD-TEAR	0.10% HA	EDTA	Borax, Sodium chloride
	Opto Gel A	OPTOX	MULTI-TEAR	0.30% HA	NIG EDTA	Glycine, Proline, Lysine, Leucine, Buffer solution
	Opto Gel A UD	OPTOX	UD-TEAR	0.30% HA	No	Glycine, Proline, Lysine, Leucine, Buffer solution
	Opto Red	OPTOX	MULTI-TEAR	0.15% HA	NIG EDTA	Glycine, Proline, Lysine, Leucine, Echinacea Extract
	Opto Yal A	OPTOX	MULTI-TEAR	0.15% HA	NIG EDTA	Glycine, Proline, Lysine, Leucine, Buffer solution
	Opto Yal A UD	OPTOX	UD-TEAR	0.15% HA	No	Glycine, Proline, Lysine, Leucine, Buffer solution
	Opto Sol	OPTOX	MULTI-TEAR	0.15% HA	NIG EDTA	0.5% Ginkgo biloba extract
	Opto Sol UV	OPTOX	UD-TEAR	0.15% HA	No	0.5% Ginkgo biloba extract
PVP	Comfort Drop Avizor	AVIZOR	MULTI-TEAR	1% PVP	EDTA	-
	Comfort Drop Avizor UD	AVIZOR	UD-TEAR	1% PVP	EDTA	-
Cellulose Derived + PVP	Hidro Health DD	DISOP	MULTI-TEAR	0.1% PVP, 0.1% Hydroxyethyl Cellulose	0.0001% PHMB 0.1% EDTA	Sodium chloride, Boric acid, Sodium, Tetraborate
Cellulose Derived + HA/SH	Acuaiss	DISOP	MULTI-TEAR	HA, Hydroxyethyl Cellulose	0.0001% PHMB 0.02% EDTA	Sodium chloride, Boric acid, Sodium, Tetraborate
	Acuaiss UD	DISOP	UD-TEAR	HA, Hydroxyethyl Cellulose	0.0001% PHMB 0.02% EDTA	Sodium chloride, Boric acid, Sodium, Tetraborate
Liquid Polyols + HP-GUAR	Systane Ultra	ALCON	MULTI-TEAR	0.4% PEG 400, 0.3% PG, HP-guar, Sorbitol	Polyquad	Aminomethylpropanol, Boric acid, Potassium chloride, Sodium chloride
Liquid Polyols + HA/SH + PVP	Ocudry 0.2 Avizor UD	AVIZOR	UD-TEAR	0.20% HA, PVP, Glycerin	No	Chlorine, Sodium, Calcium, Potassium and Magnesium electrolytes
	Ocudry 0.3 Avizor UD	AVIZOR	UD-TEAR	0.30% HA, PVP, Glycerin	No	Chlorine, Sodium, Calcium, Potassium and Magnesium electrolytes

Liquid Polyols +HA/SH + HP- Guar	Systane Ultra Plus Hydration	ALCON	MULTI-TEAR	HA, 0.4% PEG 400, 0.3% PG, HP-guar, Sorbitol	Polyquad EDTA	Aminomethylpropanol, Boric acid, Borax, Sodium citrate, Potassium chloride, Sodium chloride
Others	Opto Idro UD	OPTOX	UD-TEAR	Mineral solution	No	Buffered saline solution

95

96 **2.2 Measurement protocols**

97 During the measurement protocols outlined below, all instruments and solutions were kept under
98 controlled temperature and humidity conditions (23-25°C, and 50-60% humidity) [33]. All samples
99 were collected from the same original packaging and both osmolality and pH measurements were
100 repeated 10 times for each tested solution.

101

102 **2.2.1 Osmolality**

103 Osmolality was measured using the Fiske 110 (Advanced Instruments Inc., Norwood, MA, USA),
104 an osmometer based on the freezing point depression principle, considered the gold standard in
105 osmolality assessment [34-38]. The Fiske 110 osmometer measurement ranges from 0 to 2000
106 mOsm/kg H₂O with a resolution of 1 mOsm/kg H₂O. Prior to the measurement protocol, calibration
107 was performed according to the manufacturers' instructions.

108 From each solution, 20 µl were collected by a masked observer and measured in the osmometer,
109 following the manufacturer's instructions. SS, MPS, non-neutralised HPS and ED were directly
110 vortexed in the original solution packaging prior to collection, while HPS solutions were first
111 neutralised following the manufacturers' instructions.

112

113 **2.2.2 pH**

114 The pH was measured using the micro-pH 2000 (Crison Instruments, S.A., Barcelona), a pH
115 meter whose measurement ranges from 0 to 14 (resolution of 0.01 pH), with maximum variations
116 of 0.1 mV in 5 seconds (thermal deviation of 0.002 pH/°C). The pH meter was calibrated prior to
117 the measurements following **manufacturer's instructions** (4.00 and 7.02 pH buffer solutions). From
118 each solution, 8 ml were collected by a masked observed and measured in the pH meter following
119 the manufacturer's instructions. SS, MPS, non-neutralised HPS and ED were vortexed in the
120 original solution packaging prior to collection to a beaker, while HPS solutions were first
121 neutralised following the manufacturers' instructions.

122

123 **2.2.3 Statistical analysis**

124 Statistical analyses were performed using SPSS software v.23.0 (SPSS Inc., Chicago, IL), with a
125 significance value of $p < 0.05$ used for all statistical tests. The normality of the data was assessed
126 using the Shapiro-Wilk test [39]: osmolality values were a normally distributed while pH values
127 were not normally distributed.

128 Osmolality and pH values were calculated as the mean of the 10 measurements obtained for
129 each solution and then the differences between each solution were calculated. Between group
130 differences in osmolality and pH were also calculated based on the classification described above
131 in the solutions section (presence and/or of the main active/inactive viscosity and lubrication-
132 enhancing ingredients).

133 For osmolality data, differences between solutions and groups were assessed using a one-way
134 analysis of variance (ANOVA), while unpaired t-tests and Tukey's post-hoc comparisons were
135 used to detect significant pairwise differences [39]. For pH data, differences between solutions
136 and groups were assessed using the Kruskal-Wallis test, while the Mann-Whitney U test was used
137 to detect significant pairwise comparisons [39].

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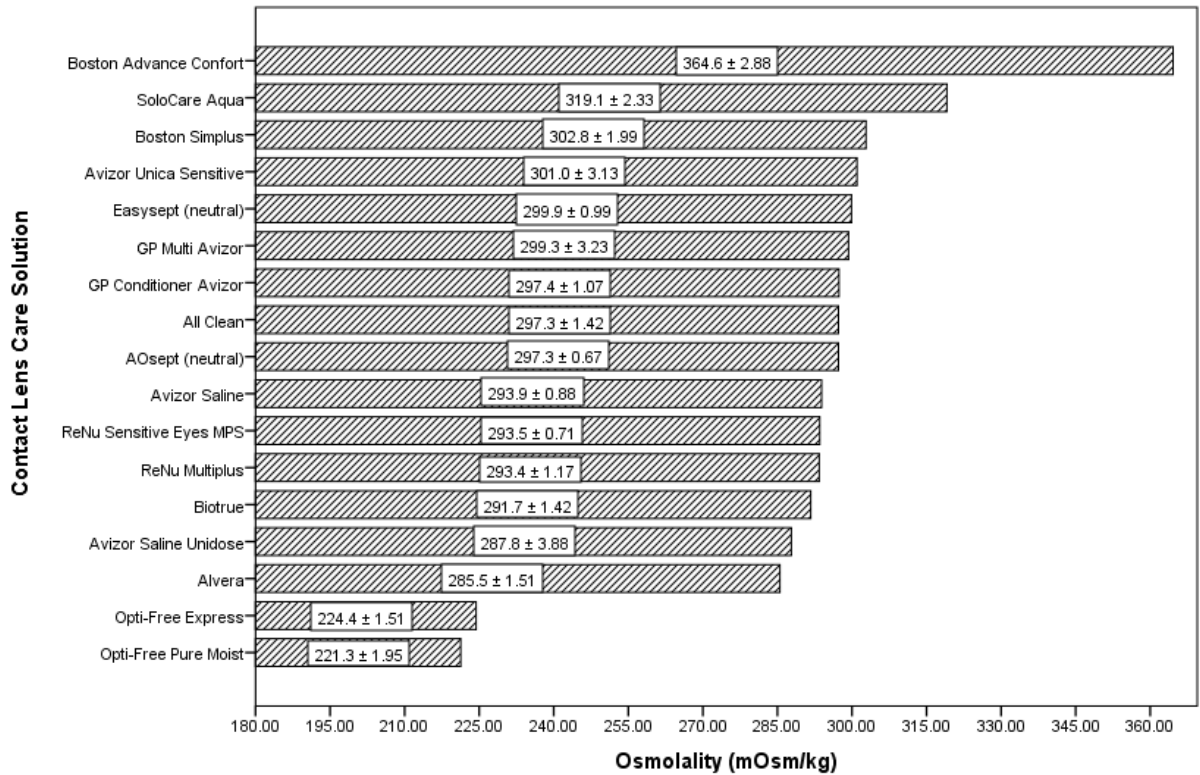
139 **3. RESULTS**

140 **3.1 Osmolality**

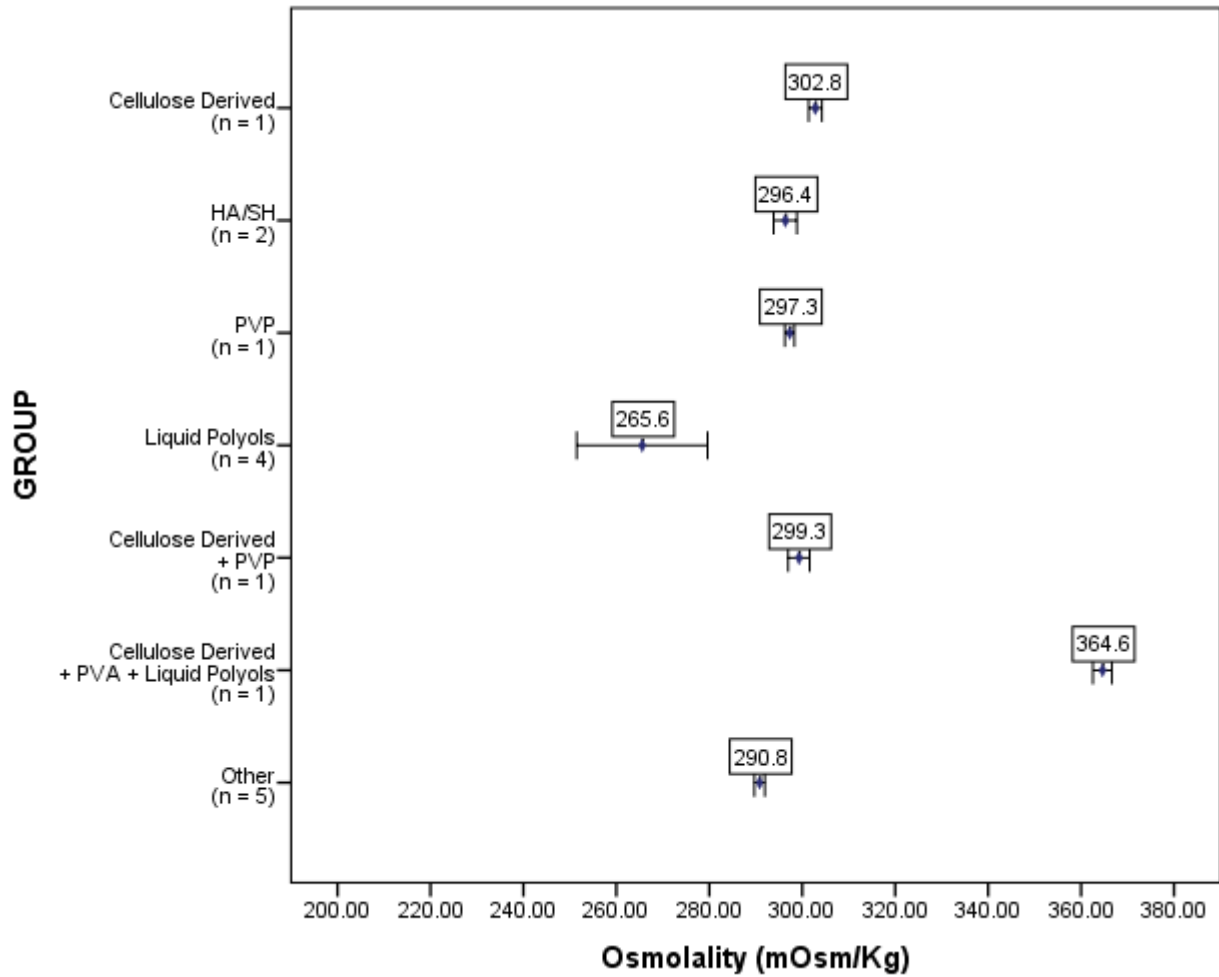
141 **3.1.1 Contact lens care solutions**

142 SS, MPS and GPS osmolality ranged from 221.3 ± 1.95 to 364.6 ± 2.88 mOsm/Kg (neutralised and
143 non-neutralised HPS were excluded from the reported range, Figure 1). Statistically significant
144 differences in osmolality were found between contact lens care solutions (ANOVA, $p < 0.001$).
145 Contact lens care solutions were grouped by the presence of the main active/inactive viscosity
146 and lubrication-enhancing ingredients to assess for any differences in osmolality (Figure 2);
147 statistically significant differences in osmolality were also found between subgroups (ANOVA, p

148 < 0.001). Tukey's post-hoc test showed that osmolality differences between the Liquid Polyols
 149 and the combination of Cellulose Derived + PVA + Liquid Polyols were statistically significant
 150 (analysed by pairs) (Table 3).



151
 152 Figure 1 - Osmolality of the lens care solutions studied. Values are shown as mOsm/Kg
 153 (mean±SD). SD: Standard Deviation



154

155 Figure 2 - Osmolality of the lens care solutions studied grouped by the composition of the main
 156 active/inactive viscosity and lubrication-enhancing ingredients. Values are shown as mOsm/Kg.
 157 Error bars indicate 95% CI. Values are represented as mean. CI: Confidence Interval. HA:
 158 Hyaluronic Acid. PVA: Polyvinyl Alcohol. PVP: Polyvinylpyrrolidone. SH: Sodium Hyaluronate

159 Table 3 - Tukey post-hoc tests (mean differences represented as columns minus rows) for the osmolality values obtained on the lens
 160 care solutions tested grouped by the main composition agent/s. Values are shown as mOsm/Kg. HA: Hyaluronic Acid. PVA: Polyvinyl
 161 Alcohol. PVP: Polyvinylpyrrolidone. SH: Sodium Hyaluronate. *p ≤ 0.05, **p ≤ 0.001

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	Cellulose Derived (n = 1)	HA/SH (n = 2)	PVP (n = 1)	Liquid Polyols (n = 4)	Cellulose Derived + PVP (n = 1)	Cellulose Derived + PVA + Liquid Polyols (n = 1)
HA/SH (n = 2)	6.45					
PVP (n = 1)	5.50	-0.95				
Liquid Polyols (n = 4)	37.25**	30.80**	31.75*			
Cellulose Derived + PVP (n = 1)	3.50	- 2.95	- 2.00	- 33.75**		
Cellulose Derived + PVA + Liquid Polyols (n = 1)	- 61.80**	- 68.25**	- 67.30**	- 99.05**	- 65.30**	
Others (n = 5)	11.98	5.53	6.48	- 25.27**	8.48	73.78**

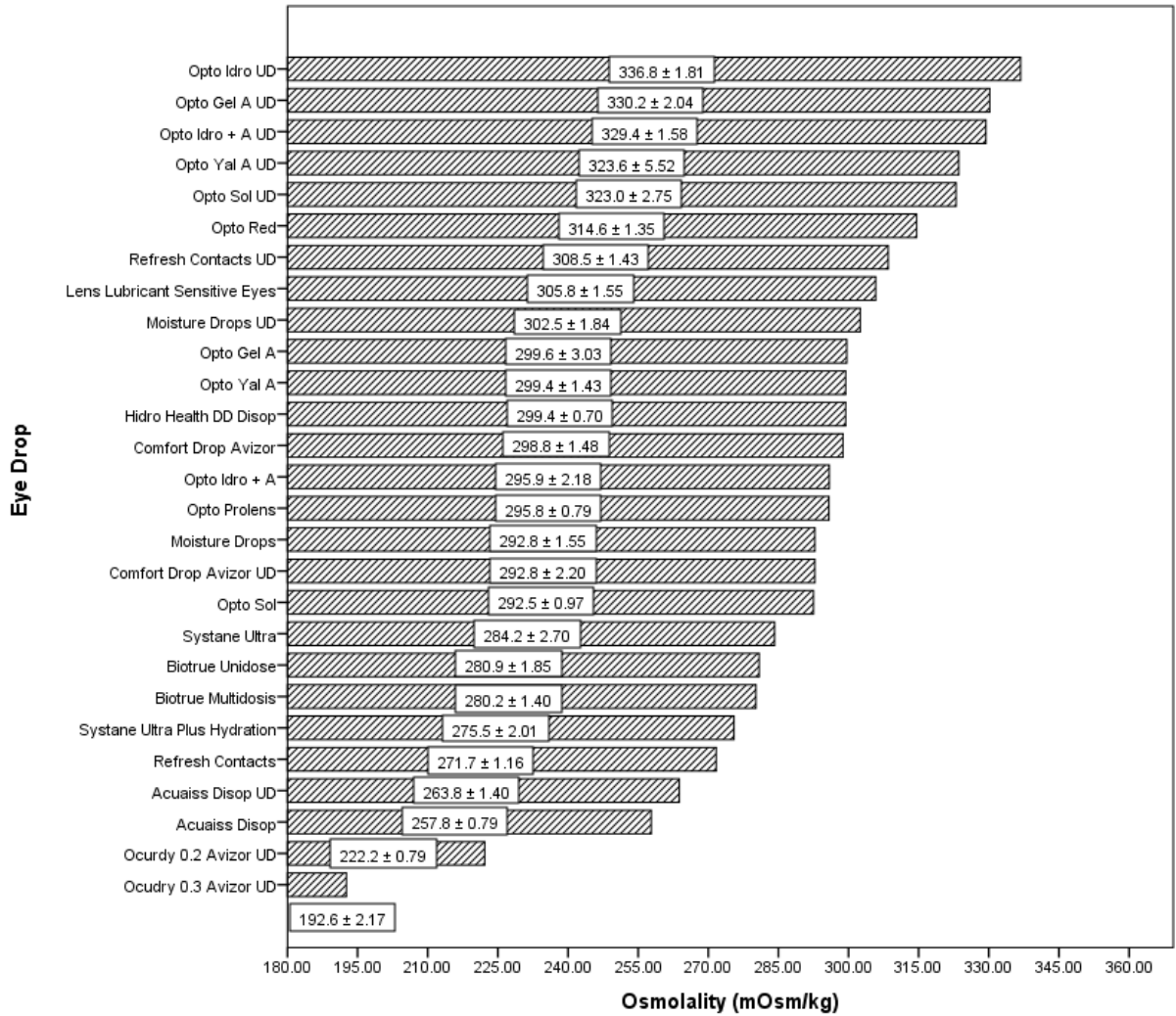
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164 The osmolality measurements were 297.3 ± 0.67 mOsm/kg (mean \pm SD) and 1320.8 ± 2.35
165 mOsm/kg for the neutralised and un-neutralised A0sept solution respectively, while for the
166 Easysept solution these values were 299.9 ± 0.99 and 1283.5 ± 6.15 mOsm/kg. Statistically
167 significant differences were found in the osmolality value between the two HPS (both neutralised
168 and un-neutralised, unpaired t-test, both $p < 0.001$).

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170 **3.1.2 Eye drops**

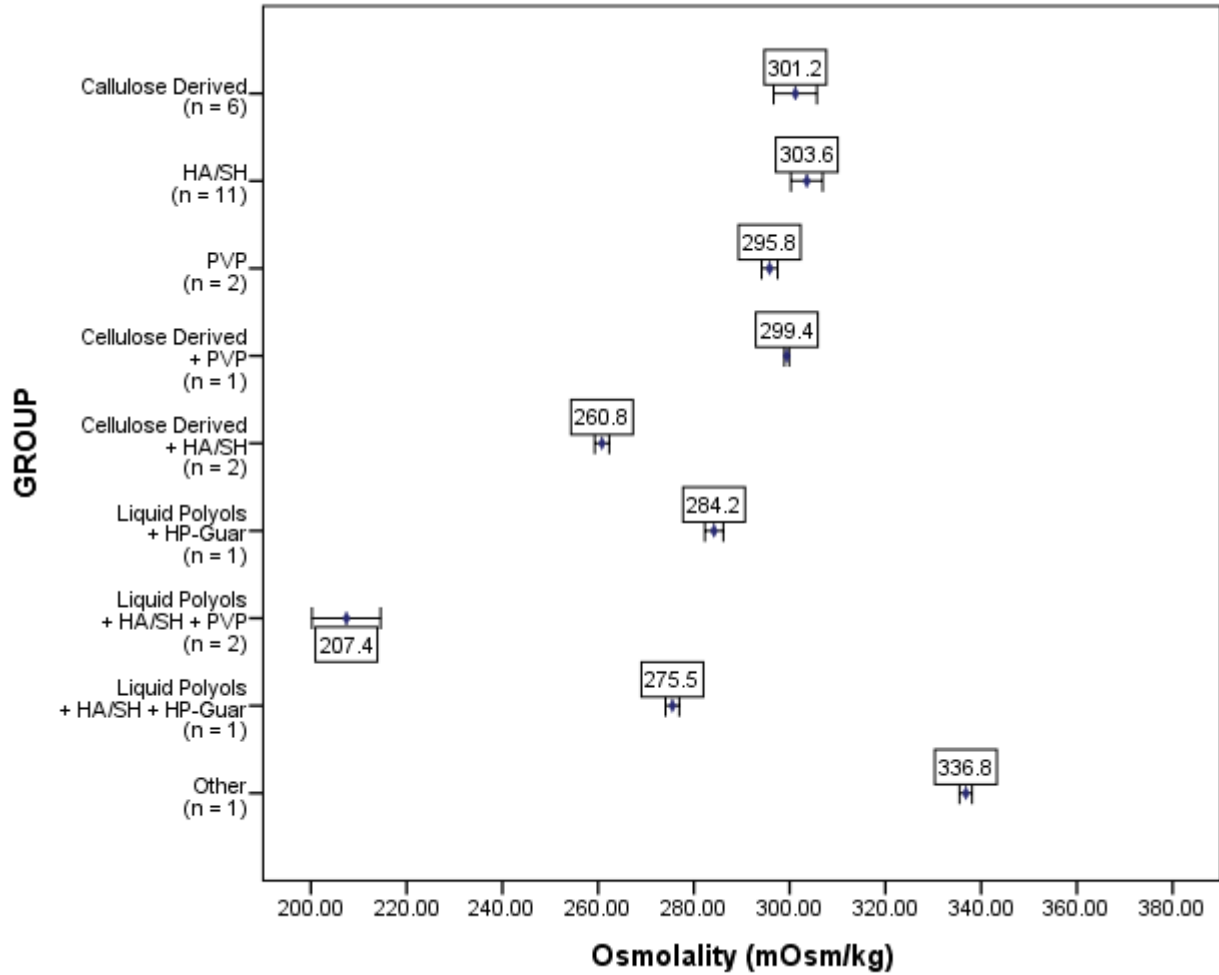
171 The ED osmolality ranged from 192.6 ± 2.17 to 336.8 ± 1.81 mOsm/Kg (Figure 3). Statistically
172 significant differences in osmolality were found between the selected ED (ANOVA, $p < 0.001$).
173 ED were grouped by the presence of the main active/inactive viscosity or lubrication-enhancing
174 ingredients to assess for any differences in osmolality (Figure 4); statistically significant
175 differences in osmolality were also found between ED subgroups (ANOVA, $p < 0.001$). Tukey's
176 post-hoc test showed that differences in osmolality were statistically significant between some
177 subgroups analysed by pairs (Table 4): the combination of Liquid Polyols + HA/SH + PVP and
178 the Others against all the other subgroups (all $p < 0.001$), Cellulose Derived + HA/SH vs. Cellulose
179 Derived, HA/SH, PVP, Cellulose Derived + PVP and Liquid Polyols + HP-Guar (all $p \leq 0.002$),
180 Liquid Polyols + HP-GUAR vs. Cellulose Derived and HA/SH (both $p \leq 0.023$), and finally, Liquid
181 Polyols + HA/SH + HP-GUAR vs. Cellulose Derived, HA/SH, PVP and Cellulose Derived + PVP
182 (all $p \leq 0.013$) (Table 4).



183

184 Figure 3 - Osmolality of the ED studied. Values are shown as mOsm/Kg (mean±SD). SD:

185 Standard Deviation. ED: Eye Drops



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187 Figure 4 - Osmolality of the ED studied grouped by the composition of the main active/inactive
 188 viscosity and lubrication-enhancing ingredients. Values are shown as mOsm/Kg. Error bars
 189 indicated 95% CI. Values plotted as the mean. CI: Confidence Interval. ED: Eye Drops. HA:
 190 Hyaluronic Acid. HP-GUAR: Hydroxypropyl-Guar. PVP: Polyvinylpyrrolidone. SH: Sodium
 191 Hyaluronate

192 Table 4 - Tukey post-hoc tests (mean differences represented as columns minus rows) for the osmolality values obtained on eye drops
 193 tested grouped by the main composition agent/s. Values are shown as mOsm/Kg. HA: Hyaluronic Acid. HP-GUAR: Hydroxypropyl-
 194 guar. PVP: Polyvinylpyrrolidone. SH: Sodium Hyaluronate. *p ≤ 0.05, **p ≤ 0.001

	Cellulose Derived (n = 6)	HA/SH (n = 11)	PVP (n = 2)	Cellulose Derived + PVP (n = 1)	Cellulose Derived + HA/SH (n = 2)	Liquid Polyols + HP-Guar (n = 1)	Liquid Polyols + HA/SH + PVP (n = 2)	Liquid Polyols + HA/SH + HP- Guar (n = 1)
HA/SH (n = 11)	- 2.39							
PVP (n = 2)	5.38	7.77						
Cellulose Derived + PVP (n = 1)	1.78	4.17	-3.60					
Cellulose Derived + HA/SH (n = 2)	40.38**	42.77**	35.00**	38.60**				
Liquid Polyols + HP-Guar (n = 1)	16.98*	19.37*	11.60	15.20	-23.40*			
Liquid Polyols + HA/SH + PVP (n = 2)	93.78**	96.17**	88.40**	92.00**	53.40**	76.80**		
Liquid Polyols + HA/SH + HP-Guar (n = 1)	25.68**	28.07**	20.30*	23.90*	- 14.70	8.70	- 68.10**	
Others (n = 1)	- 35.62**	- 33.23**	- 41.00**	- 37.40**	- 76.00**	- 52.60**	- 129.40**	- 61.30**

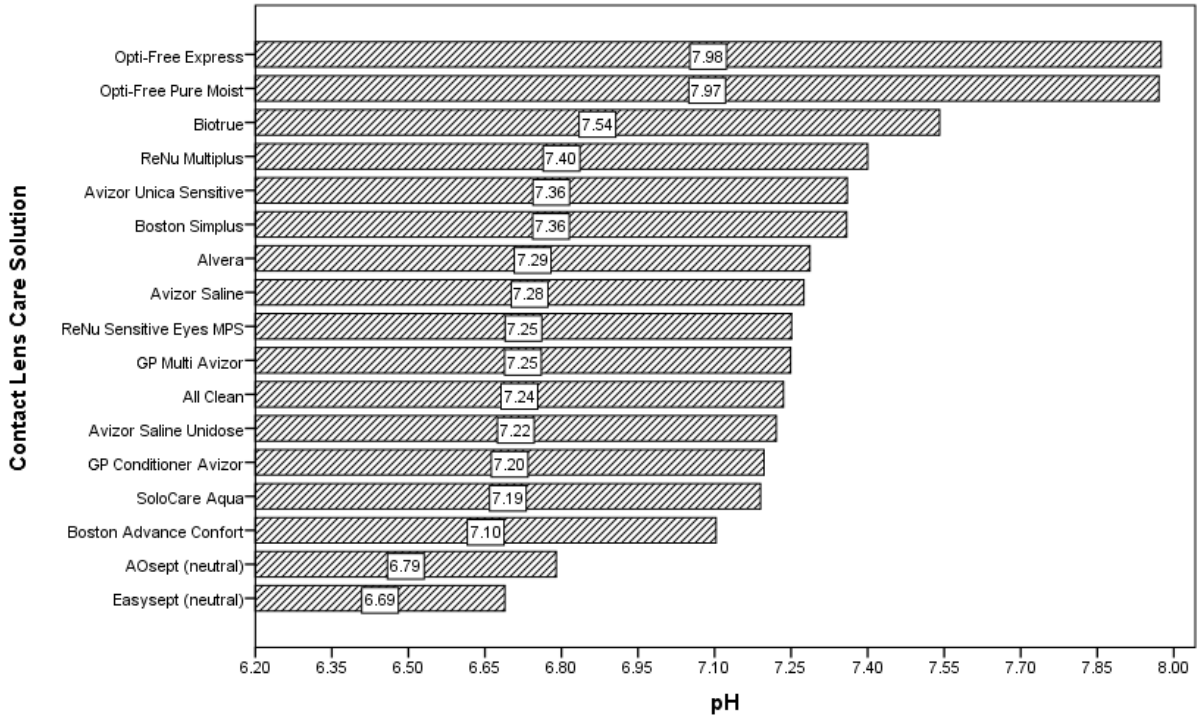
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3.2 pH

3.2.1 Contact lens care solutions

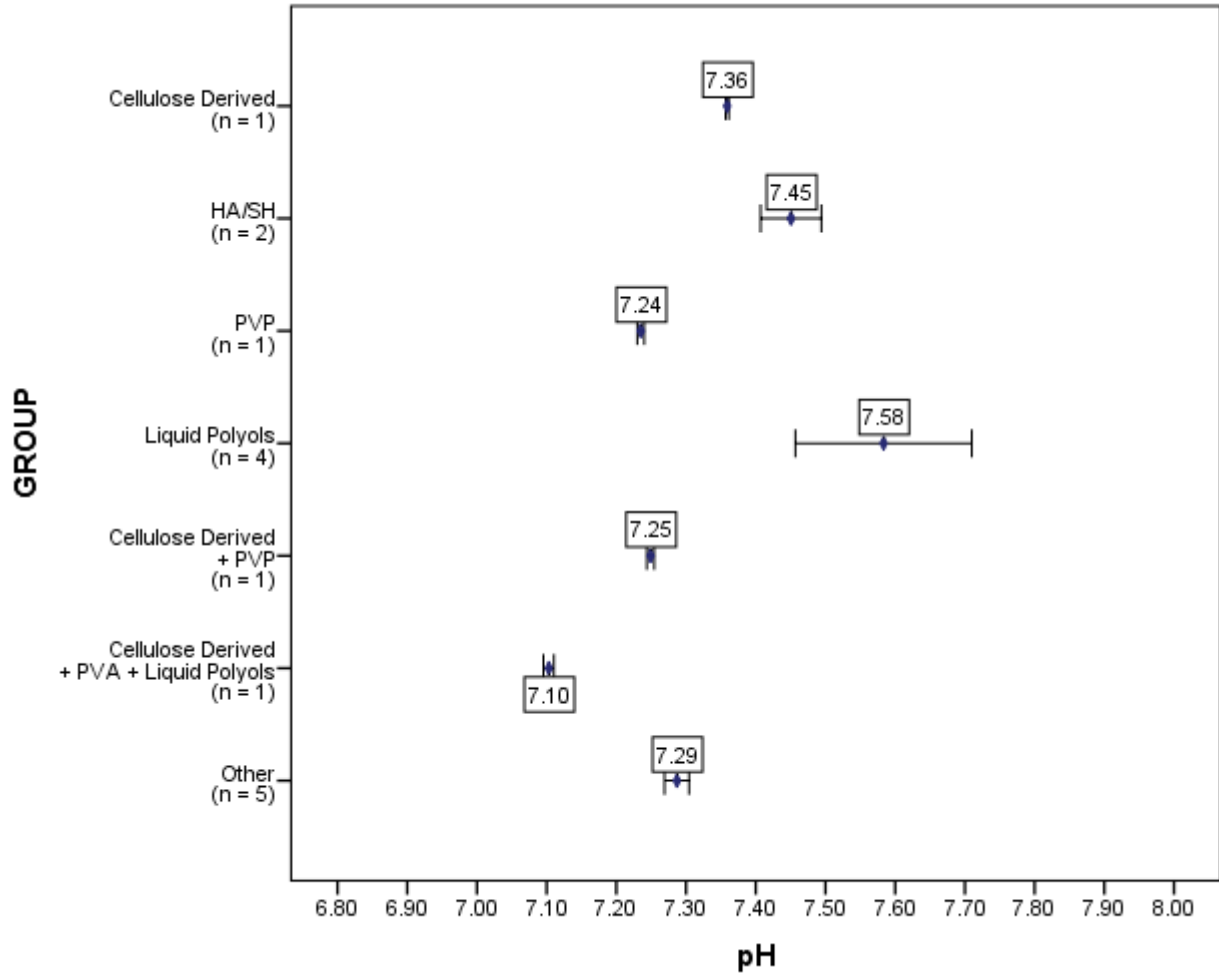
The pH value of SS, MPS and GPS ranged from 6.69 [IQR 6.68-6.69] to 7.98 [IQR 7.92-8.01] (neutralised and non-neutralised HPS were excluded from the reported range, Figure 5). Statistically significant differences in pH were found between contact lens care solutions (Kruskal-Wallis, $p < 0.001$). Contact lens care solutions were grouped by the main active/inactive viscosity and lubrication-enhancing ingredients to assess for any differences in pH (Figure 6); statistically significant differences in pH were also found between subgroups (Kruskal-Wallis, $p < 0.001$). A statistically significant pH difference was found between the combination of Cellulose Derived + PVA + Liquid Polyols against all the other subgroups (Mann-Whitney U test, all $p < 0.001$), PVP vs. Cellulose Derived and HA/SH (both $p < 0.001$), and the Cellulose Derived + PVP vs. Cellulose Derived, HA/SH and PVP (all $p \leq 0.001$), and finally, the Others against all the other subgroups vs. Cellulose Derived, HA/SH, PVP and Cellulose Derived + PVP (all $p \leq 0.027$) (Table 5).



211

212 Figure 5 - pH of the lens care solutions studied. Values are shown as median. pH is a non-

213 dimensional parameter



214

215 Figure 6 - pH of the lens care solutions studied grouped by the composition of the main
 216 active/inactive viscosity and lubrication-enhancing ingredients. pH is a non-dimensional
 217 parameter. Error bars indicate 95% CI. Values are shown as median. CI: Confidence Interval. HA:
 218 Hyaluronic Acid. PVA: Polyvinyl Alcohol. PVP: Polyvinylpyrrolidone. SH: Sodium Hyaluronate

219 Table 5 - Mann Whitney-U tests (mean differences represented as columns minus rows) between pairs of pH values obtained on the
 220 lens care solutions tested grouped by the main composition agent/s. pH is a non-dimensional parameter. HA: Hyaluronic Acid. PVA:
 221 Polyvinyl Alcohol. PVP: Polyvinylpyrrolidone. SH: Sodium Hyaluronate. *p ≤ 0.05, **p ≤ 0.001

	Cellulose Derived (n = 1)	HA/SH (n = 2)	PVP (n = 1)	Liquid Polyols (n = 4)	Cellulose Derived + PVP (n = 1)	Cellulose Derived + PVA + Liquid Polyols (n = 1)
HA/SH (n = 2)	- 0.09*					
PVP (n = 1)	0.12**	0.22**				
Liquid Polyols (n = 4)	- 0.22	- 0.13	- 0.35			
Cellulose Derived + PVP (n = 1)	0.11**	0.20**	- 0.01**	0.33		
Cellulose Derived + PVA + Liquid Polyols (n = 1)	0.26**	0.35**	0.13**	0.48**	0.15**	
Others (n = 5)	0.07*	0.16**	- 0.05*	0.30	- 0.04*	- 0.18**

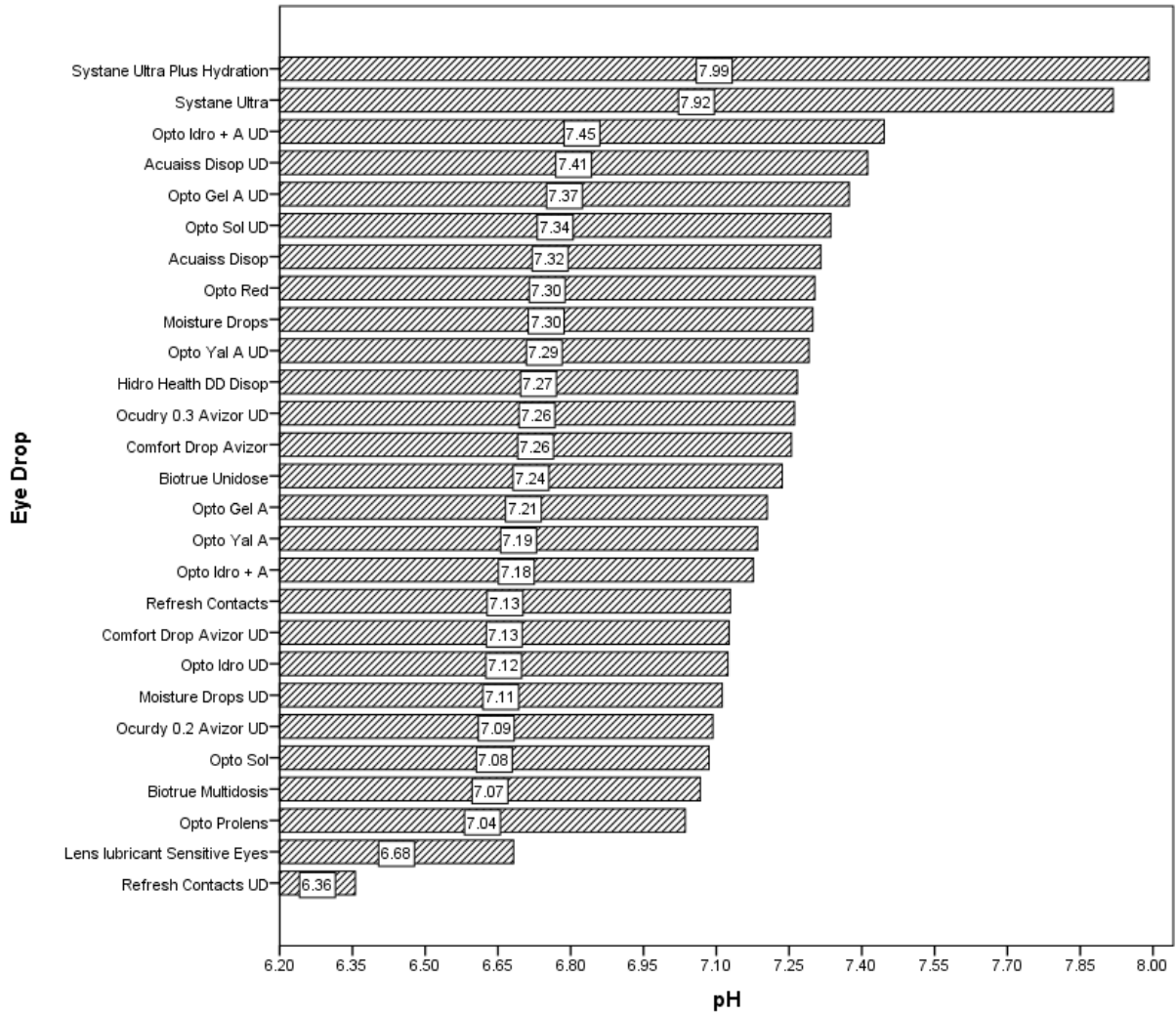
222

223 The pH median value measurements were 6.79 [IQR 6.79-6.79] and 6.57 [IQR 6.57-6.57] for the
224 neutralised and un-neutralised A0sept solution respectively, while for the Easysept solution these
225 values were 6.69 [IQR 6.68-6.70] and 6.46 [IQR 6.46-6.47]. Statistically significant differences
226 were found in the pH value between the two HPS (both neutralised and un-neutralised, Mann-
227 Whitney U test, both $p < 0.001$).

228

229 **3.2.2 Eye drops**

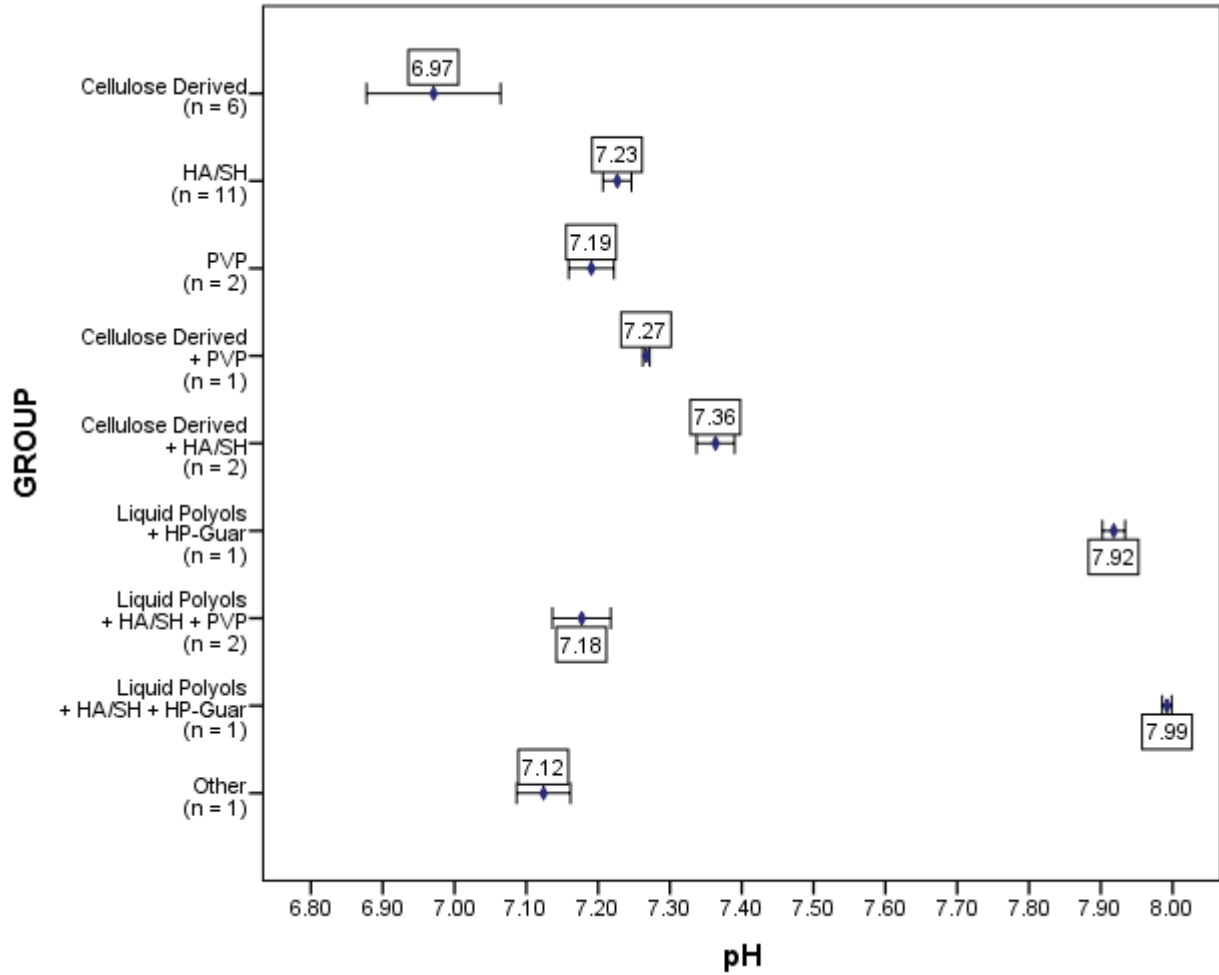
230 The ED pH ranged from 6.35 [IQR 6.35-6.26] to 7.99 [IQR 7.99-8.00] (Figure 7). Statistically
231 significant differences in pH were found between the ED solutions in the subgroups (Kruskal-
232 Wallis, $p < 0.001$). ED were grouped by the presence of the main active/inactive viscosity and
233 lubrication-enhancing ingredients to assess for any differences in pH (Figure 8); statistically
234 significant differences in pH were also found between ED subgroups (Kruskal-Wallis, $p < 0.001$.
235 A significant difference of the pH was found between the combination of Cellulose Derived +
236 HA/SH, Liquid Polyols + HP-GUAR, Liquid Polyols + HA/SH + PVP, Liquid Polyols + HA/SH +
237 HP-GUAR, the other components against all the other subgroups vs. all the other subgroup (Mann
238 Whitney U test, all $p \leq 0.001$), and also the PVP vs. Cellulose Derived or Cellulose Derived + PVP
239 (both $p \leq 0.033$) (Table 6).



240

241 Figure 7 - pH of the ED studied. Values are shown as median. pH is a non-dimensional parameter.

242 ED: Eye Drops



243

244 Figure 8 - pH of the ED studied grouped by the composition of the main active/inactive viscosity
 245 and lubrication-enhancing ingredients. pH is a non-dimensional parameter. Error bars indicate
 246 95% CI. Values are shown as median. CI: Confidence Interval. ED: Eye Drops. HA: Hyaluronic
 247 Acid. HP-GUAR: Hydroxypropyl-Guar. PVP: Polyvinylpyrrolidone. SH: Sodium Hyaluronate

248 Table 6 - Mann Whitney-U tests (mean differences represented as columns minus rows) between pairs of pH values obtained on eye
 249 drops tested grouped by the main composition agent/s. pH is a non-dimensional parameter. HA: Hyaluronic Acid. HP-GUAR:
 250 Hydroxypropyl-guar. PVP: Polyvinylpyrrolidone. SH: Sodium Hyaluronate. *p ≤ 0.05, **p ≤ 0.001

	Cellulose Derived (n = 6)	HA/SH (n = 11)	PVP (n = 2)	Cellulose Derived + PVP (n = 1)	Cellulose Derived + HA/SH (n = 2)	Liquid Polyols + HP-Guar (n = 1)	Liquid Polyols + HA/SH + PVP (n = 2)	Liquid Polyols + HA/SH + HP-Guar (n = 1)
HA/SH (n = 11)	- 0.26							
PVP (n = 2)	- 0.22*	0.04						
Cellulose Derived + PVP (n = 1)	- 0.30	- 0.04	- 0.08*					
Cellulose Derived + HA/SH (n = 2)	- 0.40**	- 0.14**	- 0.17**	- 0.10**				
Liquid Polyols + HP-Guar (n = 1)	- 0.95**	- 0.69**	- 0.73**	- 0.65**	- 0.55**			
Liquid Polyols + HA/SH + PVP (n = 2)	- 0.21**	0.05**	0.01**	0.09**	0.19**	0.74**		
Liquid Polyols + HA/SH + HP-Guar (n = 1)	- 1.02**	- 0.77**	- 0.81**	- 0.73**	- 0.63**	- 0.07**	- 0.82**	
Others (n = 1)	- 0.15**	0.10**	0.07**	0.14**	0.24**	0.79**	0.05**	0.87**

251

252 4. DISCUSSION

253 In this study, the osmolality and pH of commercially available contact lens care solutions and ED
254 displayed significant variability between individual products. Differences in both parameters were
255 also observed when solutions were grouped by the presence and/or combination in their
256 composition of the main active, inactive viscosity, and lubrication-enhancing ingredients. Despite
257 their potential impact on CLD and dry eye symptomatology, these physical properties are not
258 always provided by manufacturers.

259 “Osmolality” and “osmolarity” are two terms that are often used interchangeably when referring to
260 dilute solutions, such as biological solutions that are **primarily water; for tears, the difference**
261 **between these terms** is less than 1-5% [36, 40]. Previous studies proposed that tear film
262 osmolarity is around 302 ± 6.3 mOsm/L in healthy eyes [36, 41-43]. While in the present study most
263 of the lens care solutions were in a range close to these values (from 285.5 ± 1.51 to 302.8 ± 1.99
264 mOsm/Kg), some showed a hypoosmolar value (Opti-Free Pure Moist, 221.3 ± 1.95 mOsm/Kg), or
265 a high hyperosmolar value (Boston Advance Comfort, 364.6 ± 2.88 mOsm/Kg) (Figure 1). It is
266 important to note that some contact lens care solutions, such as peroxides (neutralised and un-
267 neutralised) or Boston Advance Comfort, do not contact the ocular surface and are only used for
268 disinfection. The same trend was found for the ED, with the observed range close to the
269 considered “normal” values (from 275.5 ± 2.01 to 305.8 ± 1.55 mOsm/Kg), but some showed a
270 hypoosmolar value (OcuDry 0.3 Avizor UD, 192.6 ± 2.17 mOsm/Kg) or a hyperosmolar value (Opto
271 Gel A UD, 330.2 ± 2.04 mOsm/Kg) (Figure 2). Tear hyperosmolarity is considered the central
272 mechanism in high-prevalence diseases such as dry eye [36, 41, 44], where the tear film
273 osmolarity easily reaches values close to 325-340 mOsm/L [36, 41-43, 45, 46]. High osmolarity
274 is assumed to be the trigger for a cascade of signalling events within surface epithelial cells,
275 leading to the release of inflammatory mediators and proteases [18, 19]. Therefore, high
276 osmolarity contact lens care solutions could cause discomfort or ocular surface damage; however,
277 even though some of them showed non-physiological osmolality values, those products are

278 commercially successful. Therefore, it could be hypothesised that either the tear film or the ocular
279 surface has the capacity to withstand osmolality variations within the values obtained in this study
280 for the duration that the solution is in contact with the eye; additional clinical work on this topic
281 would be of interest. On the other hand, it has been proposed that hypoosmolar products can
282 cause the opposite effect, decreasing or also heating the levels of damage generated by a
283 hyperosmolar tear film physiopathology. Yang et al. [47] found that Opti-Free resulted in lower
284 blink rates and significantly lower ocular symptoms than ReNu and ClearCare; both solutions
285 showed differences in the osmolality values, where Opti-Free was hypoosmolar compared to the
286 normal tear film range, while the other two solutions were within this normal range [9, 10, 36, 41-
287 43]. Furthermore, contact lens wearers have reported a preference for hypoosmotic saline drops
288 while wearing contact lenses [23]. Montani [30] also concluded that hypoosmotic ED could reduce
289 tear osmolality shortly after drop instillation (two hours) and after a longer time frame (three
290 weeks). The impact of the contact lens solution and ED osmolality on ocular comfort and ocular
291 surface signs requires further investigation.

292 Most of the lens care solutions were in a pH range close to neutral or low basic value (7.11-7.36),
293 or high basic values (Opti-Free Express, 7.98 [IQR 7.96-8.00]) (Figure 5), whereas HPS solution
294 (even neutralised) showed acid values (Easysept neutral, 6.69 [6.68 - 6.70]). The same was
295 observed for ED, while most were close to neutral or basic values (7.03-7.43), some showed a
296 high basic value (Systane Ultra Plus Hydration, 7.99 [IQR 7.99-8.00]), or an acid value (Refresh
297 Contacts UD, 6.35 [IQR 6.35 - 6.36]) (Figure 7). Human tears have been reported to have a
298 relatively neutral pH that falls in the 6.6-7.8 range [48], being able to tolerate a much wider pH
299 range (6.2-9.0 at 0.2M strength) [49]. The influence of pH on ocular surface health has not been
300 established; Khurana et al. [50] found no significant differences in tear film pH between healthy
301 and dry eye patients. It seems that the tears can compensate the pH variations through a buffering
302 mechanisms [51], but lens comfort can be negatively affected during contact lens insertion,
303 probably secondary to a decrease in lens hydration induced by acidification which leads to a tight

304 fitting lens [17, 20, 21, 52, 53]. While lens care solutions can impact wearers comfort, it is unclear
305 how pH affects the ocular surface physiology [52, 54]. For example, previous studies [13, 55, 56]
306 reported that ReNu Multiplus showed a clinically relevant increase of corneal staining ratio and
307 dry eye symptomatology compared with Opti-Free. Both solutions have shown high statistical
308 differences in pH compared to each other [9, 10], which suggests that the influence of the pH on
309 ocular comfort or damage is still unclear and requires further clinical investigation.

310 Contact lens care solutions and ED are complex formulations containing common or specific
311 viscosity or lubrication-enhancing agents. The combination of these components impacts the
312 physical properties of the final solution, which could potentially influence patient comfort. In the
313 present study, the tested solutions were grouped according to the main component or the
314 combination of the most common ingredients used in the market. The tight confidence intervals
315 may suggest that these agents have a relevant impact on osmolarity and pH; although it is
316 important to note that some of those groups are composed of a small number of solutions. When
317 comparing measurements across categories, most of the comparisons showed statistically
318 significant differences in the osmolality and pH values, both in contact lens care solutions and ED
319 grouped by the main viscosity/lubrication-enhancing agent (both $p < 0.001$), and only a few of the
320 comparisons showed no osmolality and pH differences. Eye care practitioners should be aware
321 of the physical properties of commercially available ophthalmic solutions, as they play a key role
322 in recommending a solution that is best suited for CLD and dry eye management, and patient
323 education [13, 55, 56].

324 The main strength of this study is that all solutions were tested using the same instrumentation;
325 previous studies have reported pH and osmolarity/osmolality differences between solutions [9-
326 12, 30-32], likely as a result of discrepancies in the devices used (e.g. osmolality by vapor
327 pressure or freezing point depression techniques) [33-35, 45, 57-59]. **Although all measurement**
328 **principles used in osmolarity/osmolality assessment showed reliability**, it is important to note that
329 freezing point depression techniques are considered the gold standard on osmolality

330 measurement [34-38]. Additionally, room temperature and humidity were controlled during the
331 measurement protocols (an important factor for physicochemical assessment), and all
332 measurements were performed on the same day, reducing any potential variation. On the other
333 hand, the main limitation was focusing only on the viscosity or lubrication-enhancing agents, since
334 solutions may contain other agents not considered in the analyses; those complex formulations
335 may influence the pH and osmolality. While the stratification by ingredients used here showed
336 tight CIs, other components such as preservatives, buffers, surfactants, chelating agents, or other
337 viscosity or lubrication-enhancing agents may have an impact in the final pH or the osmolality of
338 the solutions.

339

340 **5. CONCLUSION**

341 In summary, the present study detailed two physicochemical properties, osmolality and pH, of
342 commercially available contact lens care solutions and ED that are not always provided by
343 manufacturers. Although information on the individual components of solutions is relatively easy
344 to find, there is very little information on the physical properties of these solutions. These two
345 properties were highly variable among the tested solutions, a result that should be considered
346 when prescribing contact lens solutions and ED, due to their impact on the tear film physiology
347 and homeostasis. However, whether the observed differences are clinically significant is unclear
348 and needs further investigation.

349

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353

354 **CONFLICT OF INTEREST STATEMENT**

355 The authors declare that they have no conflict of interest in the present work and received no
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357

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