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Original article

Evaluation of 18 artificial tears based on viscosity and pH

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Abstract

Introduction: Different polymers used in artificial tear formulations influence their physical properties, such as viscosity and pH, hence affecting their bioavailability. There is limited data available from manufacturers specifying the physical properties of artificial tears, even though these data can contribute to their efficacy and effectiveness.
Purpose: The aim of this study was to evaluate 18 artificial tears available in the Malaysian market based on their physical properties.
Methodology: Viscosity and pH of 18 artificial tears were evaluated using rheometer and compact pH-meter, respectively, at standard room temperature (25°C). The amount of fluid used for both tests of each artificial tear was standardised using micropipette. The Kruskal-Wallis test was employed to compare the viscosity median between the three groups (low, medium, and high viscosity) of artificial tears, while the independent t-test was used to compare the pH between preservative and non-preservative artificial tears. A p-value of 0.05 was set as the level of significance.
Results: The mean viscosity for all 18 artificial tears was 12.05 cP ± 10.21 within a range of 0.55 cP to 34.49 cP. There was a significant difference observed in viscosity between low- ($n = 7$), median- ($n = 8$), and high- ($n = 3$) viscosity groups, $\chi^2(2) = 14.474$, $p = 0.001$. The mean pH for all 18 artificial tears was 7.21 ± 0.43, with a range of 6.19 to 7.85. pH for preservative artificial tears was slightly alkaline compared to non-pre-

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servative artificial tears (7.26 ± 0.47 *vs* 7.14 ± 0.38, respectively).
Conclusion: Rheological findings indicated that different formulations of artificial tears have different viscosities, with most artificial tears falling within the recommended values. There was no difference in terms of pH between preservative and non-preservative artificial tears.

Keywords: artificial tears, pH, physical properties, viscosity

Penilaian terhadap 18 jenis air mata tiruan berdasarkan kelikatan dan pH

Abstrak

Pendahuluan: Polimer yang berlainan yang digunakan dalam formulasi air mata tiruan mempengaruhi sifat fizikalnya, seperti kelikatan dan pH, sehingga mempengaruhi ketersediaan bio mereka. Terdapat data terhad dari syarikat pengeluaran yang menyatakan sifat fizikal air mata tiruan, sedangkan data ini dapat menyumbang kepada keberkesanan dan keberkesanannya.
Tujuan: Bagimenilai 18 jenis air mata tiruan yang terdapat di pasaran Malaysia berdasarkan sifat fizikalnya.
Metodologi: Kelikatan dan pH 18 jenis air mata tiruan dinilai masing-masing menggunakan rheometer dan pH-meter padat, pada suhu bilik standard (25° C). Jumlah cecair yang digunakan untuk kedua-dua ujian setiap air mata tiruan itu diseragamkan menggunakan mikropipet. Ujian Kruskal-Wallis digunakan untuk membandingkan median kelikatan antara tiga kumpulan (kelikatan rendah, sederhana, dan tinggi) air mata buatan. Sementara ujian independent t digunakan untuk membandingkan pH antara air mata tiruan mengandungi pengawet dan tanpa pengawet. Nilai p 0.05 ditetapkan sebagai tahap perbezaan signifikan.
Hasil: Min kelikatan untuk kesemua 18 jenis air mata tiruan adalah 12.05 cP ± 10.21 dalam julat 0.55 cP hingga 34.49 cP. Terdapat perbezaan yang signifikan dalam kelikatan antara kumpulan kelikatan rendah (n = 7), median (n = 8), dan tinggi (n = 3), $\chi 2$ (2) = 14.474, p = 0.001. Min pH untuk semua 18 jenis air mata tiruan adalah 7.21 ± 0.43, dengan julat 6.19 hingga 7.85. pH untuk air mata tiruan mengandungi pengawet adalah sedikit alkali berbanding air mata tiruan tanpa pengawet (masing-masing 7.26 ± 0.47 *vs* 7.14 ± 0.38).
Kesimpulan: Penemuan reologi menunjukkan bahawa formulasi air mata tiruan yang berbeza mempunyai kelikatan yang berbeza, namun begitu kebanyakan air mata tiruan berada dalam nilai yang disyorkan. Tiada perbezaan dari segi pH antara air mata tiruan mengandungi pengawet dan tanpa pengawet.

Kata kunci: air mata tiruan, kelikatan, pH, sifat fizikal

Introduction

Artificial tears, also known as ocular lubricants, are commonly the first-line therapy among eye care providers in managing dry eye disease. Currently, artificial tears are the preferred choice for both patients and practitioners in managing ocular surface disorders due to their simplicity of use, minimal side effects, and affordability. Previous work[1-3] has suggested that long-term use of artificial tears was proven to revitalise ocular surface integrity; however, short-term effects remain debatable.[4-6] Commercially available artificial tear products are unique as their mechanism of action depends on the formulation used by the respective manufacturers. These formulations are not only limited to types of lubrication agents, demulcents, and emollients, but also the addition and selection of preservatives.[7,8]

It is an established fact that topical administration of artificial tears will increase the tear volume in the cul-de-sac, which in turn will drain through the *puncta*. The cul-de-sac has the anatomical limitation of being able to hold only approximately 30 µl under normal conditions when in upright position and unblinking state. Hence, overflow of tears from the cul-de-sac to the *puncta* occurs when this capacity is reached.[9,10] As a result, overflow leads to reduced bioavailability due to shorter ocular residence time between the ocular surface and the artificial tears. Artificial tears with higher viscosity are more effective due to prolonged residence time caused by slower drainage rate of tears from the ocular surface, while also increasing the adhesive capacity of macromolecules within the mucin layer.[11]

Despite increased residence time, high-viscosity artificial tears may cause other issues, such as ocular discomfort or irritation, and in the worst case, damage to the ocular epithelium due to an increased friction rate between the artificial tears and ocular surface during blinking.[12] Besides viscosity, another critical factor that can induce undesirable ocular symptoms is pH. It is crucial for manufacturers to ensure that artificial tear formulations fall within the normal ocular comfort range (pH range of 6.6 to 7.8).[13,14] Previous work[15] has commented that pH levels that lie outside the normal ocular comfort range could lead to epiphora as well as burning and stinging sensation, which can indirectly compromise patient compliance.

Hence, understanding the physical properties of artificial tears is crucial for eye care practitioners for better management of ocular surface-related diseases such as dry eye and pterygium. However, it is worth noting that information regarding these physical properties are not readily available on the leaflet packaging or pamphlets, thus leading to a lack of awareness among eye care practitioners. To the best of the authors' knowledge, there is no study or review that addresses the physical properties (viscosity and pH) of artificial tears in Malaysia. Thus, this study aimed to determine the clinical physical properties, focusing on viscosity and pH, of 18 established artificial tears available in the Malaysian market.

Materials and methods

Eighteen commercially available artificial tears were selected at the International Islamic University Malaysia Eye Specialist Clinic (IESC) and International Islamic University Malaysia Optometry Clinic. The list was compiled based on the artificial tears available in the local market. The product profiles are listed in Table 1.

Viscosity was measured using Thermo Scientific Rheometer (Model HAAKE RheoWin, Version 3.61.0004, Thermo Fisher Scientific Inc, Massachusetts, USA) (Fig. 1). Viscosity was measured for each artificial tear. Each sample of artificial tear (1 ml) was collected using micropipette and applied on the lower measuring plate of the rheometer. The temperature of all samples was standardized to 25° C.[18] The measurement started as the upper plate of the rheometer started to move into rotation due to the torque applied, while the lower plate was fixed throughout the measurement.[18] The settings for torque and rotational speed were done manually, while shear stress was automatically set by the rheometer. The viscosity of each artificial tear was calculated by the built-in software,[18] based on the equation below:

$$\text{Viscosity } (\eta) = \frac{\text{Shearstress}(\tau)}{\text{Shearrate}\,(\gamma)}$$ Equation 1. Viscosity equation

For pH assessment, a compact pH-meter (LAQUAtwin pH-meter pH33, Horiba Advanced Techno Co., Ltd., Shiga, Japan) (Fig. 2) was used. Prior to measurement, two-point calibration was performed using a standard solution (pH 4.01 and pH 7.00).

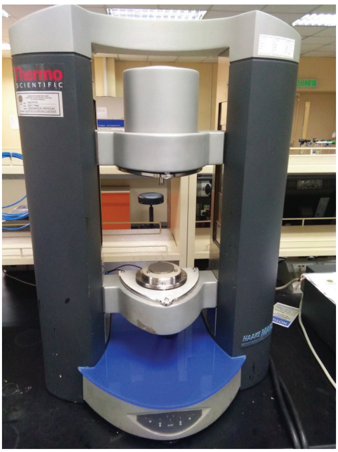

Fig. 1. Rheometer to measure the viscosity. *Fig. 2.* Compact pH-meter for pH measurement.

A sample of each artificial tear (0.2 ml) obtained using micropipette was dropped on the flat sensor until it covered the entire flat sensor surface. The instrument then automatically measured the pH of the sample. The measurement was completed in approximately one minute. Three measurements were obtained for each sample and an average value was taken for analysis. Prior to the next artificial tear sample, the sensor was cleaned using distilled water to avoid sample cross-contamination.

IBM SPSS Statistics for Windows version 20 (IBM Corp., Armonk, N., USA) was used to execute the statistical calculations. The normality of the data was analysed using the Shapiro-Wilk normality test. The viscosity level was evaluated using the Kruskal-Wallis test[19] and grouped into low-, medium-, and high-viscosity, while the independent t-test was employed to compare the mean pH between preservative and non-preservative artificial tears.

Results

Viscosity

The viscosity of 18 artificial tears was evaluated at maximum shear rate (100 s^{-1}). Based on the findings, Vismed gel was found to have the highest viscosity (34.39 cP), while Cationorm had the lowest viscosity (0.55 cP). A graphic illustration of viscosity levels for all artificial tears tested is shown in Figure 3.

Based on single-sweep rheological analysis (Fig. 4), we found shear-thinning behaviour for all the artificial tears tested, meaning higher viscosity was observed at low shear stress and viscosity decreased under high shear stress. Thus, based on the findings, artificial tears can be further classified into three groups; low, medium and high viscosity. A previous study conducted by Meadows *et al.*[20] classified artificial tears with a viscosity of 2.7-7.7 cP as low viscosity, while Källmark and Pettersson[21] defined artificial tears in the range of 21-305 cP as high viscosity and artificial tears

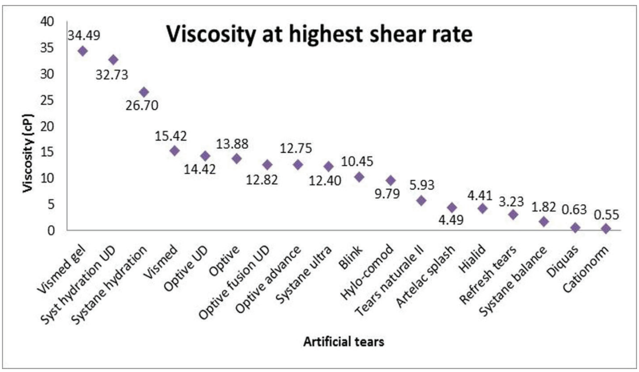

Fig. 3. Evaluation of different viscosity levels for 18 artificial tears tested in the study.

Table 1. Artificial tears profiles

Artificial tear brand	Manufacturer	Lubricant	Ingredients	Preservative	Discard after
Tears Naturale II	Alcon Laboratories Inc, Fort Worth, TX, USA	Dextran 0.1% Hypromellose 0.3%	Potassium chloride, purified water, sodium borate and sodium chloride. May contain hydrochloric acid and/or sodium hydroxide to adjust pH.	Polyquaternium 10.0011%	1 month
Systane Hydration unit dose (UD)	Alcon Laboratories Inc, Fort Worth, TX, USA	Sodium hyaluronate 0.1% Hydroxypropyl guar	Polyethylene glycol 400, propylene glycol, sorbitol, aminomethyl propanol, boric acid, sodium borate, potassium chloride and sodium chloride.	None	N/a
Systane Hydration	Alcon Laboratories Inc, Fort Worth, TX, USA	Sodium hyaluronate Hydroxypropyl guar	Polyethylene glycol 400, propylene glycol, sorbitol, aminomethyl propanol, boric acid, sodium borate, disodium EDTA, sodium citrate, potassium chloride, sodium chloride	Polyquaternium 10.0011%	3 months
Systane Balance	Alcon Laboratories Inc, Fort Worth, TX, USA	Propylene glycol 0.6%	Boric acid, dimyristoyl phosphatidylglycerol, edatate disodium, hydroxypropyl guar, mineral oil, polyoxyl 40 stearate, sorbitan tristearate, sorbitol, purified water, hydrochloric acid, sodium hydroxide	Polyquaternium 10.0011%	6 months

Artificial tear brand	Manufacturer	Lubricant	Ingredients	Preservative	Discard after
Systane Ultra	Alcon Laboratories Inc, Fort Worth, TX, USA	Polyethylene glycol 400 0.4% Propylene glycol 0.3%	Aminomethylpropanol, boric acid, hydroxypropyl guar, potassium chloride, purified water, sodium chloride, sorbitol, hydrochloric acid, sodium hydroxide	Polyquaternium 10.0011%	6 months
Hialid	Santen Pharmaceutical Co., Ltd., Japan	Sodium hyaluronate 0.1%	ε-aminocaproic acid, disodium edetate hydrate, propylene glycol, and benzalkonium chloride as additives	Benzalkonium chloride	1 month
Refresh Tears	Allergan Inc., Irvine, California, USA	Carboxymethylcellulose sodium 0.5%	Boric acid, calcium chloride, magnesium chloride, potassium chloride, purified water, sodium borate, sodium chloride. May contain hydrochloric acid and/or sodium hydroxide.	Purite	3 months
Optive Fusion unit dose (UD)	Allergan Inc., Irvine, California, USA	Sodium hyaluronic 0.1% Carboxymethylcellulose 0.5%	Boric acid, calcium chloride dehydrate, erythritol, levocarnitine, magnesium chloride hexahydrate, potassium chloride, purified water, sodium borate decahydrate, sodium citrate dihydrate	None	N/a
Optive Advanced	Allergan Inc., Irvine, California, USA	Carboximethylcellulose sodium 0.5% Glycerin 1% Polysorbate 80 0.5%	Boric acid, castor oil, erythritol, levocarnitine, carbomer copolymer type A, purified water, sodium hydroxide	Purite	6 months

Artificial tear brand	Manufacturer	Lubricant	Ingredients	Preservative	Discard after
Optive	Allergan Inc., Irvine, California, USA	Carboxymethylcellulose sodium 0.5% Glycerin 0.9%	Boric acid, calcium chloride dehydrate, erythritol, levocarnitine, magnesium chloride hexahydrate, potassium chloride, purified water, sodium borate decahydrate, sodium citrate dihydrate	Purite	6 months
Optive unit dose (UD)	Allergan Inc., Irvine, California, USA	Carboxymethylcellulose sodium 0.5% Glycerin 0.9%	Boric acid, calcium chloride dehydrate, erythritol, levocarnitine, magnesium chloride hexahydrate, potassium chloride, purified water, sodium borate decahydrate, sodium citrate dihydrate	None	N/a
Artelac Splash	Bausch & Lomb, Berlin, Germany	Sodium hyaluronate 0.2%	Potassium chloride, sodium chloride, disodium phosphate dodecahydrate, sodium dihydrophosphate dehydrate, purified water	None	N/a
Vismed Gel	TRB Chemedica, Germany	Sodium hyaluronate 0.3%	Sodium chloride, potassium chloride, disodium phosphate, sodium citrate, magnesium chloride, calcium chloride and water	None	N/a

Artificial tear brand	Manufacturer	Lubricant	Ingredients	Preservative	Discard after
Blink Intensive Tears	Abbott Medical Optics	Polyethylene glycol 400 0.25% Sodium hyaluronate 0.2%	Boric acid, sodium borate (decahydrate), sodium chloride, potassium chloride, calcium chloride (dihydrate), magnesium chloride, purified water	OcuPure	1 month
Cationorm Ophthalmic Emulsion	Santen Pharmaceutical Co., Ltd., Japan	Mineral oil	Cetalkonium chloride, tyloxapol, poloxamer 188, tris hydrochloride, tromethamine, mineral oils, glycerol, purified water	None	N/a
Hylo Comod	Ursapharm Arzneimittel GmbH, Germany	Sodium hyaluronate 0.1%	Citrate buffer, sorbitol, water	None	6 months
Vismed	TRB Chemedica, Germany	Sodium hyaluronate 0.18%	Sodium chloride, potassium chloride, disodium phosphate, sodium citrate, magnesium chloride, calcium chloride, and water for injections	None	N/a
Diquas*	Santen Pharmaceutical Co., Ltd., Japan	Diquafosol sodium 3%	Sodium phosphate hydrate, disodium edetate hydrate, sodium chloride, potassium chloride, dilute hydrochloric acid, sodium hydroxide	Chlorhexidine gluconate solution	1 month

*Diquas is a secretagogue agent that stimulates the secretion of tear fluid from conjunctival epithelial cells and mucin secretion from conjunctival goblet cells.[16,17]

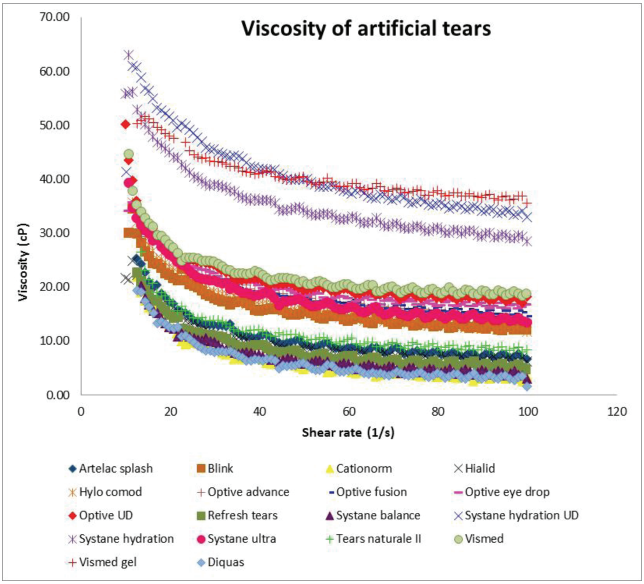

Fig. 4. Flow curves of dynamic viscosity as a function of shear rate.

in the range of 1.3-20 cP as low viscosity. However, neither study considered the range for medium-viscosity artificial tears. For this study, the viscosity groups of artificial tears were defined as follows: low viscosity, 0.55-7.7 cP; medium viscosity, 7.8-20 cP; and high viscosity, 21-305 cP.

The Kruskal-Wallis test was employed to compare the median between the three groups (low, medium, and high viscosity) of artificial tears. The result revealed that there was a significant difference in viscosity between the low (n = 7), median (n = 8), and high (n = 3) viscosity group, $\chi^2(2) = 14.474$, $p = 0.001$, with a mean rank viscosity of 4.00 for the low group, 11.50 for the medium group, and 17.00 for the high group, as summarised in Table 2.

pH

The majority (83.3%; 15 out of 18) of the selected artificial tears were weak bases, while the remaining four artificial tears were acidic (Fig. 5). Descriptive analysis revealed that mean pH for all artificial tears was slightly alkaline with a pH of 7.21 ± 0.43. A similar trend was noted between preservative and non-preservative artificial tears, in which mean pH was 7.26 ± 0.47 for preservative artificial tears and 7.14 ± 0.38 for non-preservative artificial tears. No significant difference ($p = 0.579$) in pH between these two groups was noted. The pH profiles for all selected artificial tears and comparison of pH between the preservative and non-preservative artificial tears are summarised in Figure 5 and Table 3, respectively.

Table 2. Comparison of variation in viscosity groups for 18 artificial tears

Artificial tear	Viscosity (cP)	Group	Viscosity mean rank	Chi-square (df)	*p*-value
Cationorm	0.55	Low-viscosity artificial tears ($n = 7$)	4.00	14.474 (2)	0.001
Diquas	0.63				
Systane Balance	1.82				
Refresh Tears	3.23				
Hialid	4.41				
Artelac splash	4.49				
Tears Naturale II	5.93				
Hylo Comod	9.79	Medium-viscosity artificial tears ($n = 8$)	11.40		
Blink	10.45				
Systane Ultra	12.40				
Optive Advance	12.75				
Optive Fusion UD	12.82				
Optive	13.88				
Optive UD	14.42				
Vismed	15.42				
Systane Hydration	26.70	High-viscosity artificial tears ($n = 3$)	17.00		
Systane Hydration UD	32.73				
Vismed Gel	34.49				

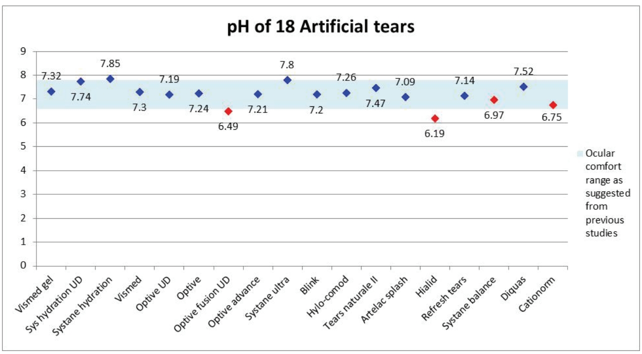

Fig. 5. pH of preservative and non-preservative artificial tears.

Table 3. Comparison of pH between preservative and non-preservative artificial tears

Artificial tears	Preservative artificial tears Mean (SD) (n = 10)	Non-preservative artificial tears Mean (SD) (n = 8)	p-value*
pH	7.26 (0.47)	7.14 (0.38)	0.579

*Based on independent t-test findings, with level of significance set at 0.05.

Discussion

Rheological analysis of artificial tears and its relation to ocular residence time

Rheology evaluates fluid flow and its deformation due to mechanical force, and one type of rheological analysis is evaluating viscosity under shear rate dynamics.[22] Related to artificial tears, rheological analysis can be used to characterise their behaviour on the ocular surface.[23] Previous studies have suggested that the cut-off viscosity of < 30 cP for artificial tears was crucial in order to avoid ocular discomfort, blurred vision, and ocular irritation that could indirectly lead to faster drainage of tears due to reflex tears and blinking.[24,25] However, the shear rate were not specified in these studies.[24,25] Therefore, the exact viscosity could be different depending on the shear rate applied by the rheometer. In this study, 16 out of 18 artificial tears (88.89%) had a viscosity < 30 cP (at shear rate of 100/s^{-1}), except for Vismed Gel (34.49 cP) and Systane Hydration UD (32.73 cP).

Generally, the rheology of natural tears can be categorised as that of a non-Newtonian fluid, as its viscosity is dependent on shear rate.[23,26] Specifically, the effects of viscosity on the ocular surface can be related to two phenomena, which are the blinking and inter-blinking state. A previous study estimated the shear rate in the open eye to be 10s^{-1}, rising to 10 000s^{-1} in the blinking eye, with zero shear rate in the closed eye.[27] Hence, it is important for manufacturers to ensure that the formulation of artificial tears has high viscosity at low shear rate (open eye) in order to increase ocular retention time, as maximises the bioavailability of artificial tears. Meanwhile, at high shear rate (blinking), low-viscosity formulations are able to provide comfort and prevent excessive stress to the ocular surface during blinking. With regards to this study, it was found that all selected artificial tears showed pseudo-plastic (shear-thinning) behaviour, whereby viscosity is inversely proportional to shear rate.

Previous literature has indicated that viscosity plays a significant role in increasing the residence time and enhancing the efficacy of artificial tears. A study by Paugh *et al.*[28] showed that higher-viscosity, pseudo-plastic artificial tears increased the precorneal residence time by more than two-fold compared to control solution (saline). The authors also commented that, apart from viscosity, the residence time of artificial tears could also be influenced by factors such as the degree of mucoadhesion of viscous polymers, spreading of the drop upon instillation, and relative comfort after drop. A recent study[29] compared precorneal retention time between two different artificial tears (eye drops and eye gel) over 120 minutes, finding that the artificial tear with higher viscosity (eye gel) was retained on the ocular surface longer than the eye drop-based artificial tear. The eye gel-based artificial tear was found at maximum value after one minute of instillation and returned to baseline after 60 minutes of observation. This indicates that gel-based artificial tears with higher viscosity can prolong ocular residence time. However, they can also induce undesirable symptoms, such as blurred vision, due to its viscosity.

Effect of pH on ocular comfort

It has been previously reported that normal tear pH ranges from 6.5 to 8.0,[30-34] while a study conducted by Khurana *et al.*[35] indicated that the mean pH of tears among dry eye patients was 7.46 ± 0.24. Previous studies have suggested that the pH of artificial tears should be in the range of 6.6 to 7.8 pH in order to avoid any discomfort after instillation.[13,14,30,34] In our study, 14 artificial tears (77.78%) had a pH within the ocular comfort range of 6.19 to 7.85. It was found that Optive Fusion UD (6.49) and Hialid (6.19) had pH values < 6.6, while Systane Hydration had a pH beyond the maximum value of recommended ocular comfort rate (7.85) (Fig. 5).

In our study, comparison of pH between preservative and non-preservative artificial tears showed that preservative artificial tears were slightly alkaline (7.26 ± 0.47) compared to non-preservative artificial tears (7.14 ± 0.38). However, the difference between these two groups was insignificant ($p = 0.579$). This result suggested that preservatives added in artificial tears did not influence the pH. On the other hand, previous studies have suggested that the pH of artificial tears was closely related to buffering agents, as these agents act as pH stabilizers to ensure the formulations are soluble, active, and tolerable.[36] Common buffer agents used in artificial tears formulations are citrate, acetate, phosphate, borate, and Tris-HCl (tris hydroxymethyl aminomethane and hydrochloric acid); all of these agents are non-toxic to the eye.[36,37]

Generally, the results of this study showed that commercially available artificial tears have a wide range of pH levels. The pH levels of artificial tears that fall beyond the ocular comfort range can cause ocular irritation, stinging sensation, or ocular discomfort.[38,39] This not only compromises patient compliance, but also reduces bioavailability and efficacy due to excessive tearing, which results in rapid flushing of the instilled artificial tears.[40] Tong *et al.*[15] recommended patients to try several artificial tears in order to find the most comfortable formulation, with a suitable pH for their tear film. However, it is highly desirable that eye care practitioners themselves, *i.e.* the physicians who prescribe the artificial tears, guide patients in selecting the most suitable formulation on a case-by-case basis and along with the clinical evidence so that treatment is ultimately beneficial.

It is worth noting that, although this study evaluated 18 artificial tears, it only covers two factors of the physical properties, namely, viscosity and pH. Thus, further improvements need to be done. We suggest that future studies should include more brands of artificial tears (both preservative and non-preservative artificial tears) available in Malaysia in order to provide more comprehensive data regarding their physical properties. Other physicochemical properties, such as osmolarity, surface tension, density, and molecular weight, should also be included in future analysie in order to provide inclusive data in determining the effectiveness of artificial tear formulations.[41] Our study had a significant technical limitation, as the rheometer we employed could only measure viscosity at a shear rate of $10s^{-1}$ to $100s^{-1}$. Given that the blinking process involves high shear rates (up to $10{,}000s^{-1}$),[27] we suggest that future studies use more advanced rheometers, as they are able to characterise the viscosity of artificial tears at this shear rate during blinking. Future studies could also determine whether basic or acidic artificial tear formulations offer better ocular sensation after instillation.

Conclusion

Viscosity and pH are important factors that determine patient compliance with treatment. Artificial tears with high viscosity and close to normal pH provide better tear distribution and ocular comfort, respectively. Our results suggested that certain properties vary significantly between the brands of artificial tears tested.

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