The Short-term Effects of Artificial Tears on the Tear Film Assessed by a Novel High-Resolution Tear Film Imager: A Pilot Study

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Purpose: The purpose of this study was to investigate the effects of artificial tears (AT) on the sublayers of the tear film assessed by a novel tear film imaging (TFI) device.

Methods: The mucoaqueous layer thickness (MALT) and lipid layer thickness (LLT) of 198 images from 11 healthy participants, 9 of whom had meibomian gland disease, were prospectively measured before and after exposure to 3 different AT preparations (Refresh Plus; Retaine [RTA]; Systane Complete PF [SYS]), using a novel nanometer resolution TFI device (AdOM, Israel). Participants were assessed at baseline and at 1, 5, 10, 30, and 60 minutes after instilling 1 drop of AT during 3 sessions on separate days. Repeated-measures analysis of variances were used for comparisons with $P < 0.05$ considered significant.

Results: For all ATs, the mean MALT was greatest 1 minute after drop instillation, with an increase of 67%, 55%, and 11% above the baseline for SYS, Refresh Plus, and RTA, respectively. The SYS formulation demonstrated the highest percentage increases in mean MALT and LLT at most postdrop time points. The MALT differences were significantly higher in the SYS than in the RTA ($P = 0.014$). After 60 minutes, no AT group demonstrated statistically significant changes in MALT or LLT compared with baseline.

Conclusions: We report, for the first time, the effects of AT on MALT and LLT using a high-resolution TFI. A substantial acute mean MALT increase occurs 1 minute after AT instillation with all agents tested, but there were clear differences in response and durability, suggesting the benefits of choosing specific AT according to the needs of each patient.

Key Words: tear film, tear film imager, AdOM, artificial tears

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Artificial tears (AT) are typically prescribed by clinicians for symptomatic relief of ocular surface pathologies, with early stage dry eye disease (DED) being one of the most common indication.[1] Owing to DED's high prevalence, there is a large variety of AT brands sold over the counter (OTC) within the US market.[1] These AT solutions encompass groups with differing wetting features and active and inactive ingredients, including viscosity-enhancing agents (VEAs), preservatives, surfactants, lipids, osmoprotectants, and electrolytes, as summarized in Table 1.[1–3]

For clinicians and patients alike, the abundance of AT options often creates confusion regarding the most suitable formulation for a particular individual. Because most AT are available OTC, patients self-treat before seeking subspecialty care.[4] In addition, difficulties in diagnosis and the discrepancy between the objective signs and reported symptoms of DED[5] often lead clinicians to use a 'trial and error' approach when choosing a specific preparation to recommend for specific DED subtypes.[6]

DED has been defined by the Tear Film and Ocular Surface Society as "a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film (TF) and accompanied by ocular symptoms, in which TF instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles."[7] Clinically, DED is typically divided into aqueous tear deficient (ATD) and evaporative categories. In ATD, tear production is diminished, while in evaporative DED, tear production is sufficient, yet the TF is unstable. Inflammation

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TABLE 1. Common AT in the US Market

Brand	Preservative	VEA	Surfactant	Lipid	Osmo-Protectant	Electrolyte/Buffers	Manufacturer	Cost*
Systane Original®	PQ (or none†)	*PEG*, *PG*, HPG	None	None	None	BA, CC, MG, PC, ZC	Alcon	$18.26 (or $19.19†)
Systane Complete®	PQ, EDTA (or none†)	PG, HPG	Polyoxyl-40 stearate, STS	DPTG, mineral oil	Sorbitol	BA	Alcon	$29.81 (or $35.49†)
Systane Ultra®	PQ (or none†)	*PEG*, *PG* HPG	None	None	Sorbitol	BA, PC, SC, aminomethyl propanol	Alcon	$28.10 (or $19.01†)
Systane Balance®	PQ, EDTA	*PG*, HPG	Polyoxyl-40 stearate, STS	DPTG, mineral oil	Sorbitol	BA	Alcon	$29.82
Bion Tears®	None	*Dextran 70*, *HPMC*	None	None	None	CC, MG, PC, sodium bicarbonate, SC, ZC	Alcon	$43.99
Refresh Tears®	Sodium chlorite	CMC	None	None	None	BA, CC, MG, PC, SB, SC	Allergan	$13.40
Refresh Classic®	None	Povidone, PVA	None	None	None	SC	Allergan	$26.62
Refresh Plus®	None	CMC	None	None	None	CC, MG, PC, sodium lactate, SC	Allergan	$15.90
Refresh Relieva®	Sodium chlorite (or none†)	*CMC*, SH	None	None	*Glycerin*, erythritol, (and L-carnitine†)	BA, CC, MG, PC, SB, sodium citrate	Allergan	$40.00 (or $45.64†)
Refresh Optive Mega 3 with flaxseed oil®	None	*CMC*, carbomer	*PS80*, Polyoxyl-40 stearate	Castor oil, flaxseed oil	*Glycerin*, erythritol, L-carnitine, trehalose	BA, BHT‡	Allergan	$59.96
Refresh Optive Advanced®	Sodium chlorite (or none†)	*CMC*, carbomer	Polysorbate-80	Castor oil	*Glycerin*, erythritol, L-carnitine	BA	Allergan	$22.18 (or $40.23†)
Refresh Digital®	Sodium chlorite (or none†)	*CMC*, carbomer	Polysorbate-80	Castor oil	*Glycerin*, erythritol, L-carnitine	BA	Allergan	$32.38 (or $33.12†)
Retaine MGD®	None	None	Tyloxapol, Poloxamer-188	*Mineral oils*, CKC	Glycerin	Tris HCl, tromethamine	Ocusoft	$55.45
Soothe XP ®	PQ, EDTA (or EDTA only†)§	N/A	Octoxynol-40, Polysorbate-80	*Mineral oils*	N/A	BA, SB	Bausch & Lomb	$19.32 (or $55.80†)
BioTrue Hydration Boost ®	None	SH	None	None	*Glycerin*, erythritol	BA, PC, SB, SC	Bausch & Lomb	$22.23
Blink Tears®	Sodium chlorite (or none†)	*PEG*, SH	None	None	None	CC, MG, PC, SC, BA, SB	Johnson & Johnson Vision	$16.09 (or $36.97†)
iVizia Sterile Lubriciant Eye Drops®	None	*Povidone*, SH	None	None	Trehalose	Tromethamine, SC	Similasan	$35.40
TheraTears®	Sodium perborate (or none†)	*CMC*	None	None	None	Borate buffers, CC, MG, PC, sodium bicarbonate, SC, sodium phosphate	Prestige Consumer Healthcare	$12.38 (or $16.63†)
GenTeal Tears® Moderate	PQ	*Dextran 70*, *HPMC*	Polysorbate-80	None	*Glycerin*	BA, CC, MG, PC SC, zinc chloride, glycine‖	Alcon	$32.51
GenTeal Tears® Moderate-PF	None	*Dextran 70*, *HPMC*	None	None	None	PC, SB, SC	Alcon	$14.29

Italics ingredients are the designated active ingredients.
Composition list excludes water, hydrochloric acid, sodium hydroxide.
*Cost is based on lowest price seen for 1 fluid ounce of product on Amazon.com.
†Information on PF formulation of this product is in parentheses.
‡BHT is an antioxidant.
§This product is labeled as PF formulation but there is EDTA in the PF version.
‖Glycine is an amino acid.
BA, boric acid; BHT, butylated hydroxyl toluene; Carbomer, Carbomer copolymer type A; CC, calcium chloride; CKC, cetalkonium chloride; CMC, carboxymethylcellulose sodium; DPTG, dimyristoyl phosphatidylglycerol; EDTA, Edetate Sodium; HPG, Hydroxylpropyl-guar; HPMC, hydropxpropyl methylcellulose; MG, magnesium chloride; PC, potassium chloride; PEG, Polyethylene glycol 400; PG, propylene glycol; PQ, Polyquaternium-1; PVA, polyvinyl alcohol; SB, sodium borat; SC, sodium chloride; SH, sodium hyaluronate; STS, sorbitan tristearate; XP, Xtra protection; ZC, zinc chloride.

has been more closely linked with ATD, although it can manifest as a variable component of all DED subtypes, along with eyelid issues (eg, anterior blepharitis) and meibomian gland abnormalities (eg, plugging, atrophy, abnormal meibum quality).[7] Risk factors for DED include demographics (eg, female sex, older age), comorbidities (eg, autoimmune diseases, pain conditions), and environmental factors (eg, air pollution, computer use). However, each of these risk factors likely contributes to a different DED phenotype necessitating further data to establish optimal treatment approaches for DED subtypes.

The diagnosis, monitoring, and treatment of ocular surface disorders are complex, creating a need for novel, noninvasive approaches for the diagnosis of such conditions.[8] Currently, there are several new TF imaging devices on the market, each with different features and capabilities. There are those capable of measuring the mucoaqueous layer, lipid layer, and other dynamic parameters (Tear Film Imager, AdOM),[9] those that measure the lipid layer alone (Keratography, Oculus),[10] and those that image meibomian glands using near-infrared light (Lipiview, Johnson & Johnson).[11] The Ocular Surface Analyzer (SBM System R, Orbassano, Torino, Italy) measures tear break-up time, lipid layer thickness (LLT), tear meniscus height, and meibomian gland morphology.[12] These devices use different technologies to measure various biomarkers with different levels of repeatability and reproducibility, making it challenging to compare their outcomes interchangeably.[10]

Limited access to these technologies poses another challenge for the management of DED. Most clinics are not equipped with objective, high-resolution, and noninvasive tools to monitor the effectiveness of OTC AT preparations. Current tools used to monitor the effects of OTC AT include patient symptoms, Schirmer testing, slitlamp examination, tear osmolarity testing, fluorescein staining, TF break-up time, tear meniscus height,[13] rose bengal, and lissamine green dyes. In addition, various patient questionnaires, such as the ocular surface disease index (OSDI), Standardized Patient Evaluation of Eye Dryness, Dry Eye Questionnaire, and National Eye Institute Visual Function Questionnaire-25, can be used to screen and monitor patient symptoms.[14] The current difficulty in objective DED assessment and OTC AT effectiveness is a significant impediment in assessing the effectiveness of treatment regimens.

The pervasive nature of DED has created a global OTC AT market that reached 4.9 Billion USD in 2022 and is expected to reach 6.4 billion USD by 2028, according to market research reports.[15] This high market value has facilitated continued investments in AT manufacturing, marketing, and distribution worldwide. Awareness of DED has also recently been boosted by governmental agencies, such as the National Institutes of Health, as indicated by their support of the "National Dry Eye Awareness Month" initiative.[16] Despite the growth in awareness of DED, a void in clinical trials comparing different brands of AT remains.[17,18] Furthermore, the lack of quantitative data to monitor therapeutic responses to treatment makes tailoring dry eye treatment difficult for each patient. The lack of evidence-based decision making in the selection of DED therapy may explain the limited success and poor patient adherence to OTC AT treatment.[19,20]

In this pilot investigation, we used tear film imaging (TFI) (Fig. 1) to assess changes in the mucoaqueous layer thickness (MALT) and LLT of the TF over time following the administration of 3 common brands of AT: Refresh Plus (REF), Retaine (RTA), and Systane Complete PF (SYS). We selected PF AT to minimize the potential influence of preservatives on the TF.[26] SYS contains VEA, lipids, and surfactants; REF composed primarily of VEA and retain primarily of lipids and surfactants. Specifically, VEAs are believed to act as moisturizing water-retaining agents that are added to increase TF thickness and retention of AT on the ocular surface.[23,24] By contrast, lipids and surfactants are used to replenish the lipid layer in patients with deficiencies.

METHODS

Eleven healthy participants, including 9 with meibomian gland disease (MGD), were evaluated in a prospective pilot study conducted between August 2022 and March 2023 at the New York Eye and Ear Infirmary of Mount Sinai, New York, NY. All participants signed a written informed consent form before the initiation of this study. The study was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by the Institutional Review Board of the Icahn School of Medicine at Mount Sinai, New York, NY.

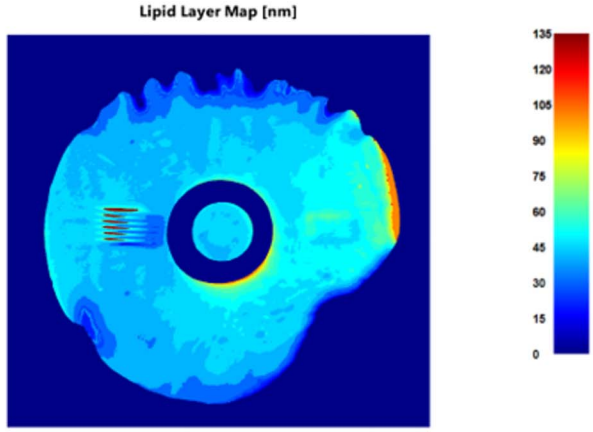
Inclusion criteria included age 18 years or older, absence of eye disease, and willingness to be assessed on 3 separate days. Exclusion criteria included any ocular surface pathology requiring treatment with ocular medications, past ocular surgery, refractive laser procedures, or the use of any eye drops, gels, or ointments. Nine (82%) of the 11 patients recruited had previously been diagnosed with MGD but were not receiving treatment at the time of study entry. All participants underwent thorough anterior segment examination, including fluorescein staining and tear break-up time, by 1 examiner (M.C.) and completed an OSDI questionnaire.

The participants were evaluated following the administration of 3 common commercially available brands of PF OTC Ats: REF (Allergan), RTA (MSD), and SYS (Alcon).

The TFI device assesses the MALT and LLT using spectral interference technology to image the precorneal surface with a large field of view (6.5-mm diameter) and high lateral resolution,[21] which measures static and dynamic parameters of the TF during a single measurement.[9,21] A combined thermometer and hygrometer device (model H5075, Govee) was used to detect temperature and humidity changes in the room where TFI was performed.

A total of 198 images from 11 participants were obtained before and after the installation of the different ATs. Each patient participated in 3 sessions on separate days, and the same eye was imaged before and after instilling a different AT brand. Each session consisted of a baseline TF measurement in OU before administering 1 drop of AT to the study eye, followed by the measurements of the TF of the study eye at 1, 5, 10, 30, and 60 minutes after AT administration. The study eyes were randomly chosen from each patient, and the patients were instructed to blink

Patient Name / ID	_ /	Eye	
Age / Gender	/	Date / Time	/
TFI operator			
MALT	Mucus-Aqueous Layer Thickness	**3366**	nm
MALTR	Mucus-Aqueous Thinning Rate	**-30**	nm/sec
LLT	Lipid Layer Thickness	**42.5**	nm
LBUT	Lipid Break-Up Time		sec
IBI	Inter-Blink Interval	**> 20.00**	sec
LMU	Lipid Map Uniformity	**6**	nm^2



Adopted with permission from AdoM, Advanced Optical Technologies Ltd. Table includes an anonymized example of a healthy subject captured parameters. The thickness map on the right represents a variability map of the lipid layer in nanometer resolution.

FIGURE 1. Sample result of a healthy patient from the Tear Film Imager. Adopted with permission from AdOM, Advanced Optical Technologies Ltd.

normally before and at the beginning of the examination. For accuracy purposes, we used 0.01 fluid ounce each, held at 90 degrees above the eye, dispersing only 1 drop per patient. All installations were acquired by 1 of 3 trained device operators. To avoid time and ambient parameter bias, all participants completed their 3 sessions within a 14-day period in the same temperature-controlled room. Two separate rooms were used in the study. Each patient had all their tests performed in the same room, and all images were acquired by 1 of 3 trained device operators. The AT regimen was randomized to avoid any effect of order.

A repeated-measures analysis of variance (ANOVA) was performed using the LLT and MALT measured at each time point, with time as a repeated factor within drop type, allowing each time to have a different variance and correlations between times, and a random subject effect to account for the correlation of the data from the 3 drop types within each subject. The area under the curve (AUC) across all the time points was calculated using the trapezoidal rule. AUC analyses were also performed using repeated-measures ANOVA, with drop type as the only repeated factor, allowing each drop type to have a different variance and different correlations between drop types. A 5% significance level was used for all the tests.

RESULTS

Participant Characteristics

Table 2 lists the participant demographics. None of the participants reported using any prescribed or OTC eye drops. The mean OSDI score of participants was 5.32. One participant reported symptoms of dry eyes. Ophthalmic examination revealed mild MGD in all subjects except for 2 participants who were free of MGD. No other major pathology was noted. The combined thermometer and hygrometer displayed only small temperature and humidity changes of 2.7°C and 11%, respectively, throughout all imaging sessions.

TABLE 2. Participant Characteristics and Anterior Segment Examination

				BCVA		L/L		Conj		Cornea		TBUT	
ID	Gender	Age	OSDI	OD	OS	OD	OS	OD	OS	OD	OS	OD	OS
1	F	25	2.08	20/50	20/20	N	N	N	N	N	N	≥10	≥10
2	M	36	16.67	20/15	20/20	MGD	MGD	N	N	N	N	3	3
3	M	26	0	20/20	20/25	MGD	BLPH, MGD	N	N	N	N	9	9
4	M	25	8.3	20/40	20/20	BLPH, MGD	BLPH, MGD	N	N	N	N	≥10	≥10
5	M	39	0	20/15	20/15	BLPH, MGD	BLPH, MGD	N	N	N	N	≥10	≥10
6	M	24	2.27	20/15	20/15	Trace MGD	Trace MGD	N	N	N	N	≥10	≥10
7	M	25	2.08	20/15	20/15	BLPH, MGD	BLPH, MGD	N	N	N	N	n/a	n/a
8	M	32	0	20/20	20/20	MGD	MGD	N	N	N	N	≥10	≥10
9	M	21	6.25	20/20	20/20	BLPH, MGD	BLPH, MGD	N	N	Trace PEE	Trace PEE	≥10	≥10
10	F	34	14.58	20/20	20/20	BLPH, MGD	BLPH, MGD	N	N	N	PEE	5	6
11	M	24	6.25	20/15	20/15	Greasy tear film	Greasy tear film	N	N	N	N	n/a	n/a

BCVA, best corrected visual acuity; BLPH, blepharitis; L/L, Slit lamp examination findings for Lids/Lacrimation; MGD, meibomian gland dysfunction; N, unremarkable; PEE, punctate epithelial erosions; TBUT, tear break-up time.

Descriptive Statistics

Tables 3 and 4 present the mean MALT and LLT, respectively, for the 11 participants at the measured time points from baseline through 60 minutes after drop instillation for the 3 AT used. For all AT, the mean MALT was highest 1 minute after drop instillation, with an increase of 67%, 55%, and 11% from baseline for SYS, REF, and RTA, respectively (Fig. 2A). Notably, the SYS formulation demonstrated the highest percent increase in mean MALT and LLT at most time points after drop instillation (Fig. 2A, B).

Analysis of Each Time Point

No statistical differences were found in the baseline MALT and LLT measurements between the AT groups. Figures 3A, B show box and whisker plots that illustrate the MALT and LLT measurements, respectively, for the 11 participants at the measured time points from baseline through 60 minutes after drop instillation for the 3 AT used.

Statistically significant differences in the MALT and LLT measurements for different ATs at each time point are presented in these figures. When comparing the overall differences between the ATs, we found that MALT and LLT values were higher for SYS than for RTA ($P = 0.001$ and $P = 0.043$, respectively) and REF ($P = 0.04$, $P = 0.027$, respectively).

Furthermore, the box and whisker plots show a narrower distribution of MALT and LLT measurements at the 60-minute time point compared with baseline for all AT groups.

Analysis of Each AT Group

The difference in mean MALT measurement compared with baseline was significantly higher for REF at 1 minute ($P < 0.0001$), SYS at 1 ($P < 0.0001$) and 5 ($P = 0.0003$) min, and lower for RTA at 30 minutes ($P = 0.01$; Table 3). The mean LLT measurements were significantly higher than baseline for SYS at 1 minute ($P = 0.029$), 5 minutes ($P < 0.0001$), 10 minutes ($P = 0.001$), and 30 minutes ($P = 0.019$, Table 4). No significant difference relative to baseline was found for either MALT or LLT for any of the AT at the 60-minute time point.

For the calculated AUC, the overall test for any differences among the drops was significant only for delta MALT ($P = 0.04$), with SYS > RTA ($P = 0.014$). Although the overall tests for a significant drop effect were not significant in the ANOVA, examination of the pair-wise comparisons between drops revealed statistically significant differences between absolute LLT SYS > REF ($P = 0.014$) and relative MALT SYS > RTA ($P = 0.022$).

DISCUSSION

The increasing incidence of DED and abundance of OTC AT therapies have resulted in diverse approaches to AT usage and a lack of consensus on the best approach for optimal patient care. The use of new technologies to provide an objective assessment of the TF enables the use of specific biomarkers to guide the management of DED. To the best of our knowledge, this is the first study to report the short-term

TABLE 3. Mean MALT in Nanometers (n = 11)

AT	Baseline	1 min	5 min	10 min	30 min	60 min
REF	4194	6491*	4514	3876	3544	3413
SYS	3211	5348*	4609*	3623	3450	3432
RTA	4056	4505	3675	3406	3163*	3540

*Statistically significant difference compared with baseline measurement using repeated-measures ANOVA

TABLE 4. Mean LLT in Nanometers (n = 11)

AT	Baseline	1 min	5 min	10 min	30 min	60 min
REF	41	46	50	52	44	42
SYS	43	56*	68*	69*	60*	38
RTA	42	45	54	52	48	45

*Statistically significant difference compared with baseline measurements using repeated-measures ANOVA.

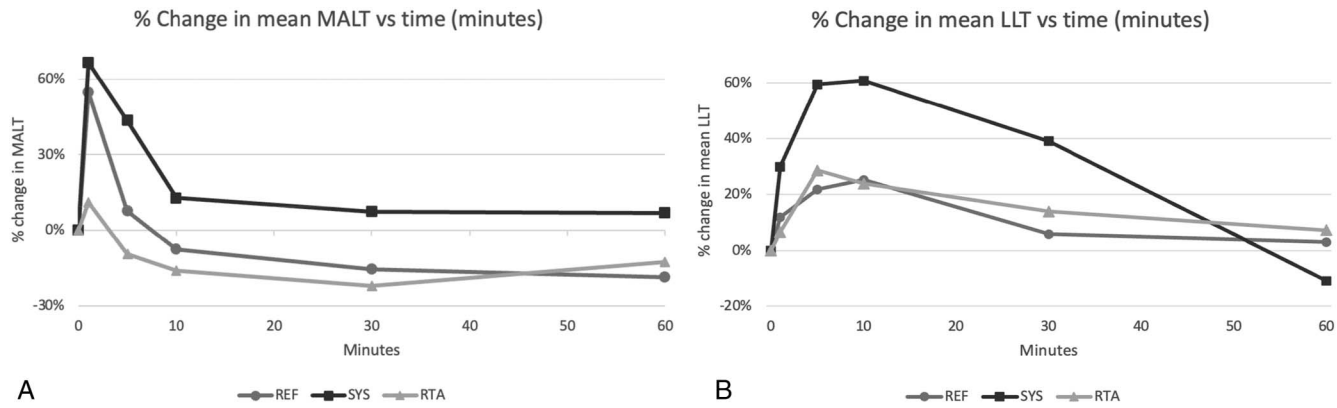


FIGURE 2. A, MALT percent change over time. B, LLT percent change over time.

effects of different OTC AT on the MALT and LLT of TF, assessed at the nanometer level with a high-resolution TFI in humans. Previous reproducibility testing of the TFI[9] suggests that the observed differences in the effects of different AT preparations likely indicate differential effects of these ATs on specific components of the TF.

Among the studied OTC ATs, SYS had the largest impact on MALT and LLT, with a 67% increase in MALT observed after 1 minute. Previous studies have indicated that differences in the physical qualities and tip configuration of eye drop dispensers may affect the quantity of solution administered and the ultimate effect of the drop.[22] To control for any effect of the physical differences in the eye drop dispensers and drop handling for the 3 AT studied, we chose PF, single-use containers, 0.01 fluid ounce each, held at 90 degrees above the eye, dispersing only 1 drop per patient by the same operator. The tests were conducted in the same indoor location under the same climate conditions in a span of 14 days. Despite controlling for these factors, small variances in the volume contained per drop may affect the measured MALT and LLT. Imaging the patients at consistent time points allowed us to partially control for this variability within each patient. The different components of the 3 AT formulations used in this study may also be associated with the changes in MALT (Table 5). Specifically, VEAs are believed to act as moisturizing water-retaining agents that are added to increase TF thickness and retention of AT on the ocular surface.[23,24] By contrast, lipids and surfactants are used to replenish the lipid layer in patients with deficiencies. SYS contains VEA, lipids, and surfactants. In this study, SYS demonstrated significant changes to LLT, while AT composed primarily of VEA (REF) or primarily of lipids and

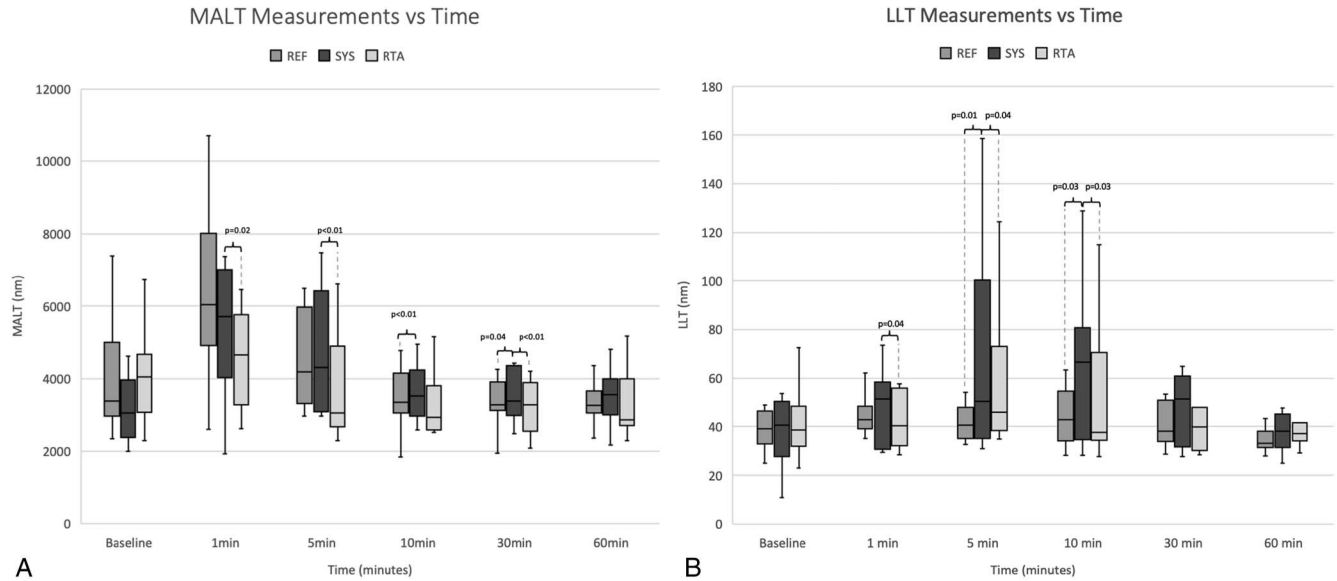


FIGURE 3. A, Box and whisker plot of MALT measurements for all participants versus time. Statistically significant difference in relative MALT values between AT groups using repeated-measures ANOVA. B, Box and whisker plot of LLT measurements for all participants versus time. Statistically significant difference in relative LLT values between AT groups using repeated-measures ANOVA. This plot excludes outlier points (defined as data points that are more than 1.5 times the interquartile range above the third quartile or below the first quartile of the data).

TABLE 5. Active and Nonactive Ingredients of the AT That Were Used in the Study

Brand	Preservative	VEA	Surfactant	Lipid	Osmo-Protectant	Electrolyte/Buffers	Manufacturer	Cost*
Refresh Plus®	None	CMC	None	None	None	CC, MG, PC, sodium lactate, SC	Allergan	$15.90
Systane Complete® PF	None	PG, HPG	Polyoxyl-40 stearate, STS	DPTG, mineral oil	Sorbitol	BA	Alcon	$35.49
Retaine MGD®	None	None	Tyloxapol, Poloxamer-188	*Mineral oils*, CKC	Glycerin	Tris HCl, tromethamine	Ocusoft	$55.45

Italics ingredients are the designated active ingredients.
The composition list excludes water, hydrochloric acid, and sodium hydroxide.
Information was retrieved from user manual and safety data sheet.
*Cost is based on lowest price seen for 1 fluid ounce of product on Amazon.com.
BA, boric acid; CC, calcium chloride; MG, magnesium chloride; PC, potassium chloride; SC, sodium chloride; HPG, Hydroxylpropyl-guar; PG, propylene glycol; STS, sorbitan tristearate.

surfactants (RTA) demonstrated milder changes to LLT, as shown in Figure 1B. This suggests that AT formulations composed primarily of lipids and surfactants do not have a substantial impact on LLT, unless in combination with VEAs, which are added to increase the AT retention time.[25] Notably, many AT components, designated as active ingredients or inactive excipients, may have significant biological activity. In this study, we specifically selected PF AT to minimize the potential influence of preservatives on the TF.[26]

In this pilot study, we also found intragroup variability in addition to intergroup differences in MALT and LLT. This variability should be further studied in larger cohorts across a span of ages, as this variability may be attributed to each participant's unique cornea and precorneal TF characteristics. These characteristics include corneal roughness,[27] epithelial irregularity,[28] corneal curvature, upward drift of the TF after a blink,[29] precorneal TF thickness,[29] time after the blink is measured, and meibomian gland function.[30] It is also possible that differences in the refractive index of the different AT preparations accounted for some of the differences in the TFI measurements obtained. Therefore, we conducted a laboratory examination using different AT at different temperatures to determine whether refractive index might contribute to the intergroup and intragroup variability of TF characteristics, but no clinical significance was noted between drops at different temperatures (see Appendix, Supplemental Digital Content 1, http://links.lww.com/ICO/B642).

This study has several limitations. First, the number of patients included in this pilot study was small. The different operators of the device may have also introduced measurement variability, although all operators underwent standardized training by AdOM LTD, and most of the imaging sessions were conducted by a single operator (G.A.).

In conclusion, our pilot analysis demonstrated significantly different short-term effects of 3 common OTC AT products on the thickness of the mucoaqueous and lipid layers of the TF at nanometer resolution. Among the ATs, SYS had the largest impact on MALT and LLT. These results suggest the need for larger, long-term AT studies using TFI to better understand DED and assess the effect of various treatments on TF. The correlation of these objective measures with clinical findings and symptoms will assist in designing algorithms to tailor the most effective AT regimen to individual patients.

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REFERENCES

1. Labetoulle M, Benitez-Del-castillo JM, Barabino S, et al. Artificial tears: biological role of their ingredients in the management of dry eye disease. *Int J Mol Sci*. 2022;23:2434.
2. *Artificial Tears: A Primer*. Available at: http://webeye.ophth.uiowa.edu/eyeforum/tutorials/artificial-tears.htm. Accessed May 11, 2023.
3. Kathuria A, Shamloo K, Jhanji V, et al. Categorization of marketed artificial tear formulations based on their ingredients: a rational approach for their use. *J Clin Med*. 2021;10:1289–1311.
4. Bilkhu P, Sivardeen Z, Chen C, et al. Patient-reported experience of dry eye management: an international multicentre survey. *Contact Lens Anterior Eye*. 2022;45:101450.
5. Hua R, Yao K, Hu Y, et al. Discrepancy between subjectively reported symptoms and objectively measured clinical findings in dry eye: a population based analysis. *BMJ Open*. 2014;4:e005296.
6. Wu KY, Chen WT, Chu-Bédard YK, et al. Management of Sjogren's dry eye disease—advances in ocular drug delivery offering a new hope. *Pharmaceutics*. 2022;15:147.
7. Wolffsohn JS, Travé Huarte S, Jones L, et al. Clinical practice patterns in the management of dry eye disease: a TFOS international survey. *Ocul Surf*. 2021;21:78–86.
8. Alvarez OP, Galor A, AlBayyat G, et al. Update on imaging modalities for ocular surface pathologies. *Curr Ophthalmol Rep*. 2021;9:39–47.
9. Segev F, Geffen N, Galor A, et al. Dynamic assessment of the tear film muco-aqueous and lipid layers using a novel tear film imager (TFI). *Br J Ophthalmol*. 2020;104:136–141.
10. Sutphin JE, Ying GS, Bunya VY, et al. Correlation of measures from the OCULUS keratograph and clinical assessments of dry eye disease in the dry eye assessment and management study. *Cornea*. 2022;41:845–851.
11. Kim WJ, Ahn YJ, Kim MH, et al. Lipid layer thickness decrease due to meibomian gland dysfunction leads to tear film instability and reflex tear secretion. *Ann Med*. 2022;54:893–899.
12. Sánchez-González MC, Capote-Puente R, García-Romera MC, et al. Dry eye disease and tear film assessment through a novel non-invasive ocular surface analyzer: the OSA protocol. *Front Med (Lausanne)*. 2022;9:938484.
13. Szczesna-Iskander DH, Muzyka-Wozniak M, Llorens Quintana C. The efficacy of ocular surface assessment approaches in evaluating dry eye treatment with artificial tears. *Sci Rep*. 2022;12:21835.
14. *Dry Eye Syndrome Questionnaires - EyeWiki*. Available at: https://eyewiki.aao.org/Dry_Eye_Syndrome_questionnaires. Accessed March 16, 2023.

15. *OTC Artificial Tears Market Size, Share, Growth, Trends 2023-2028*. Available at: https://www.imarcgroup.com/otc-artificial-tears-market. Accessed March 16, 2023.
16. Janine A. *Clayton. July Is National Dry Eye Awareness Month | Office of Research on Women's Health*. Available at: https://orwh.od.nih.gov/about/director/messages/dry-eye-month-2019. Accessed March 16, 2023.
17. Semp DA, Beeson D, Sheppard AL, et al. Artificial tears: a systematic review. *Clin Optom (Auckl)*. 2023;15:9–27.
18. Pucker AD, Ng SM, Nichols JJ. Over the counter (OTC) artificial tear drops for dry eye syndrome. *Cochrane Database Syst Rev*. 2016;2:CD009729.
19. Swanson M. Compliance with and typical usage of artificial tears in dry eye conditions. *J Am Optom Assoc*. 1998;69:649–655.
20. Uchino M, Yokoi N, Shimazaki J, et al. Adherence to eye drops usage in dry eye patients and reasons for non-compliance: a web-based survey. *J Clin Med*. 2022;11:367.
21. Cohen Y, Trokel S, Arieli Y, et al. Mapping the lipid layer of the human tear film. *Cornea*. 2020;39:132–135.
22. Van Santvliet L, Ludwig A. Determinants of eye drop size. *Surv Ophthalmol*. 2004;49:197–213.
23. Braun RJ, Fitt AD. Modelling drainage of the pre-corneal tear film after a blink. *Math Med Biol*. 2003;20:1–28.
24. Wong H, Fatt I, Radke CJ. Deposition and thinning of the human tear film. *J Colloid Interf Sci*. 1996;184:44–51.
25. Paugh JR, Nguyen AL, Ketelson HA, et al. Pre-corneal residence time of artificial tears measured in dry eye subjects. *Optom Vis Sci*. 2008;85:725–731.
26. Ribeiro MVMR, Barbosa FT, Ribeiro LEF, et al. Effectiveness of using preservative-free artificial tears versus preserved lubricants for the treatment of dry eyes: a systematic review. *Arq Bras Oftalmol*. 2019;82:436–445.
27. King-Smith PE, Kimball SH, Nichols JJ. Tear film interferometry and corneal surface roughness. *Invest Ophthalmol Vis Sci*. 2014;55:2614–2618.
28. Betancurt C, Perez VL, Shousha MA, et al. Epithelial irregularity index (EIF) as an objective measure of dry eye: a pilot study. *Invest Ophthalmol Vis Sci*. 2012;53:1850.
29. King-Smith PE, Fink BA, Hill RM, et al. The thickness of the tear film. *Curr Eye Res*. 2004;29:357–368.
30. Benedetto DA, Clinch TE, Laibson PR. In vivo observation of tear dynamics using fluorophotometry. *Arch Ophthalmol*. 1984;102:410–412.