



# Improvement of ferning patterns of lubricant eye drops mixed with various electrolytes and carboxymethylcellulose

Ali M. Masmali

Cornea Research Chair, Optometry Department, College of Applied Medical Sciences, King Saud University, P.O. Box 10219, Riyadh, 11433, Saudi Arabia

## ARTICLE INFO

### Keywords:

Tear ferning patterns  
Five-point tear ferning grading scale  
Electrolyte  
Artificial tears  
Sodium carboxymethylcellulose  
Basic tear solution

## ABSTRACT

**Purpose:** To investigate the effect of the addition of electrolytes, basic tear solution (BTS), and sodium carboxymethylcellulose (SCMS) on the tear ferning (TF) patterns of Blink Contact Soothing Eye Drops® and Refresh Plus Tears®.

**Method:** Samples of Blink Contact Soothing Eye Drops® and Refresh Plus Tears® (10 µL) were mixed with different volumes (3–30 µL) of several electrolytes, namely sodium chloride, potassium chloride, calcium chloride, magnesium chloride hexahydrate, sodium hydrogen carbonate, and sodium dihydrogen phosphate, BTS, and SCMS. Samples (1 µL) of the mixtures were dried on a glass slide at room temperature and the TF patterns were inspected using a light microscope, graded using the Masmali five-point grading scale and compared to the corresponding TF grades of the artificial tears.

**Results:** The TF grades of Blink Contact Soothing Eye Drops® and Refresh Plus Tears® improved from 1.2 and 1.5, respectively to 0.2 when calcium chloride was used as the electrolyte. Improvements in TF grades were also observed when other electrolytes (*e.g.*, sodium dihydrogen phosphate), BTS, and SCMS were used.

**Conclusion:** The tear ferning test can be used to evaluate the effect of the addition of electrolytes to an artificial tear *in-vitro*. The TF patterns of artificial tear solutions such as Blink Contact Soothing Eye Drops® and Refresh Plus Tears® can be improved with the addition of various concentrations of electrolytes, BTS, and SCMS, however further research is still needed to understand the clinical relevance of TF patterns with respect to the management of dry eye symptoms and their potential role in the development of new artificial tears.

## 1. Introduction

The integrity of the ocular surface is influenced by the status of the tear film [1–4], which protects the eye against infections caused by different microorganisms, provides the cornea with nutrients and oxygen, and establishes a smooth optical surface [5–7]. Tear instability may be due to increased tear evaporation or a decrease in tear quantity, causing dry eye [1–4]. Dry eye symptoms include discomfort, inflammation, itching, burning, and reduced vision quality [1–4], and severe dry eye, if not treated, can lead to conjunctival and corneal damage [9].

Approximately 10–20% of the global population suffers from dry eye symptoms [10–13], which are more common in the elderly and women [14]. Various factors can contribute to dry eye, such as aging, hormonal changes, long-term computer use, contact lens wear, alcohol consumption, diabetes, and environmental conditions [15–18]. Various diagnostic techniques can be used to detect dry eye, the most common being the phenol red thread test (PRT), the Schirmer test, tear-break-up time (TBUT), and osmolarity tests [18–20]. The tear ferning (TF) test is

a simple technique to assess tear quality *in-vitro* by observing the ferns of a dried tear sample under a microscope [21–23]. Tear ferning patterns can be classified according to the Masmali five-point grading scale, with grades  $\geq 2$  typically observed in tear samples from patients with dry eye [23]. The TF test is a reliable test that gives consistent ferning grades at any time of the day. In young patients without dry eye, the average coefficient of variation was approximately 0.3% (range 0.05–1.6%) and the mean difference for repeated subjective TF grading was approximately 0.1 (95% limits of agreement  $\sim \pm 0.40$ ) [22]. In addition, this test can be used in association with other *in-vivo* tests to diagnose dry eye [22].

Mild and moderate dry eye symptoms are often managed with the use of various types of artificial tears [24–27]. Artificial tears containing sodium hyaluronate and sodium carboxymethylcellulose (SCMC) can increase tear film stability by virtue of their viscoelastic and anionic properties, respectively [28,29]. Some artificial tears reduce dry eye symptoms associated with excessive evaporation of the tears (lipid based), while others target aqueous tear deficiency [30–32]. Both Optive Advanced Lubricant Eye Drops® and Optive Eye Drops®

E-mail address: [amasmali@ksu.edu.sa](mailto:amasmali@ksu.edu.sa).

<https://doi.org/10.1016/j.clae.2019.04.010>

Received 8 January 2019; Received in revised form 7 April 2019; Accepted 8 April 2019

1367-0484/ © 2019 British Contact Lens Association. Published by Elsevier Ltd. All rights reserved.

**Table 1**  
Concentrations (mg/100 mL) of electrolytes used for lubricant eye drops [33].

| Electrolytes  | Concentration (mg/100 mL) |
|---|---------------------------|
| Sodium chloride (NaCl)  | 680                       |
| Potassium chloride (KCl)  | 140                       |
| Calcium chloride (CaCl <sub>2</sub> )                           | 5                         |
| Magnesium chloride (MgCl <sub>2</sub> ·6H <sub>2</sub> O)       | 12                        |
| Sodium hydrogen carbonate (NaHCO <sub>3</sub> )                 | 218                       |
| Sodium dihydrogen phosphate (NaH <sub>2</sub> PO <sub>4</sub> ) | 9.4                       |

(Allergan) contain polysorbate-80 (0.5%) in lipid media and can be used to reduce the evaporation of tears [30].

The aim of this study was to investigate the effect of the addition of various monovalent electrolytes such as sodium chloride (NaCl) and potassium chloride (KCl), divalent electrolytes such as calcium chloride (CaCl<sub>2</sub>) and magnesium chloride hexahydrate (MgCl<sub>2</sub>·6H<sub>2</sub>O) and hydrogenated electrolytes such as sodium hydrogen carbonate (NaHCO<sub>3</sub>) and sodium dihydrogen phosphate (NaH<sub>2</sub>PO<sub>4</sub>), basic tear solution (BTS), and SCMC, on the TF patterns of different artificial tear solutions such as Blink Contact Soothing Eye Drops<sup>®</sup>, Refresh Plus Tears<sup>®</sup>, Bausch & Lomb Advance Eye Relief<sup>®</sup>, Refresh Optive Advanced<sup>®</sup>, and Tears Natural<sup>®</sup>. A mixture of equal volumes of these particular electrolytes (Table 1) leads to the production of BTS [33]. It was hypothesized that the addition of electrolytes and SCMC would improve TF patterns since the addition of electrolyte solutions to the chosen artificial tears would more closely match the chemistry of natural tears.

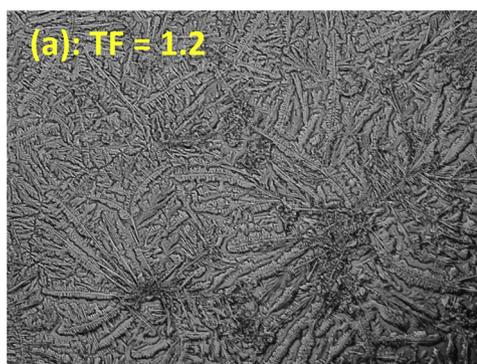
## 2. Materials and methods

### 2.1. Electrolyte solutions

Salts were purchased from Avonchem Limited (Wellington House, Macclesfield, UK) and used without further purification. Each electrolyte was weighed (mg) using an FA2004 N analytical balance (Sum Yau Instruments, Japan) and a solution of each electrolyte was prepared in double distilled water (100 mL) [33]. The mixture of each salt in water was stirred for 5 min using a Stuart CB161 magnetic stirrer (Stuart, Cole-Parmer, UK) to ensure complete solubility. Table 1 shows the concentration of each electrolyte used. A 1:1 mixture of NaCl and KCl (monovalent electrolytes), CaCl<sub>2</sub> and MgCl<sub>2</sub>·6H<sub>2</sub>O (divalent electrolytes), and NaHCO<sub>3</sub> and NaH<sub>2</sub>PO<sub>4</sub> (hydrogenated electrolytes) were prepared.

### 2.2. Basic tear solution

A basic tear solution (BTS) was prepared by mixing equal volumes of the six electrolytes presented in Table 1 [33].



**Fig. 1.** Tear ferning patterns: (a) Blink Contact Soothing Eye Drops<sup>®</sup> and (b) Refresh Plus Tears<sup>®</sup>. The images were 10× magnification.

### 2.3. Sodium carboxymethylcellulose

Sodium carboxymethylcellulose (average molecular weight of 250,000) was purchased from Sigma-Aldrich Chemical Company, UK. A solution of SCMC (250 mg) in double distilled water (100 mL) was prepared. The effect of the addition of SCMC solution (0.25%) on the TF grades of the two artificial tears was tested. A mixture of each artificial tear drop (10 μL) and SCMC solution (0.25%; 3, 6, 9, 12, 15, 18, 21, 24, 27, or 30 μL) was mixed well and the TF patterns were recorded.

### 2.4. Artificial tears

Blink Contact Soothing Eye Drops<sup>®</sup> (10 mL; Abbott Medical Optics Santa Ana, CA, USA), Refresh Plus Tears<sup>®</sup> (4 × 0.6 mL unit doses; Allergan), Bausch & Lomb Advance Eye Relief<sup>®</sup> (15 mL; Bausch & Lomb Inc.), Refresh Optive Advanced<sup>®</sup> (30 × 0.4 mL unit doses; Allergan), and Tears Natural<sup>®</sup> (15 mL; Alcon) were used.

### 2.5. Tear ferning test

A sample (1 μL) of each artificial tear was dried on a glass microscope slide (Sigma-Aldrich Chemical Company, Gillingham, UK) for 10 min at 23 °C and humidity less than 40% [34–36]. The slide was observed using Olympus DP72 light microscope (Olympus Key Med Ltd., UK) and the ferns were subjectively graded using 0.1 increments of the Masmali five-point grading scale [34]. A mixture of electrolyte, BTS or SCMC (3–30 μL) and artificial tears (10 μL) was prepared. A sample (1 μL) of each mixture was dried on a glass slide and the TF patterns for each mixture were graded. The TF grade for each mixture was compared to those obtained for the artificial tears [34]. One sample of each artificial tear was tested and the grading was completed two examiners. The grading scores of both examiners were identical in most cases and the average was used in cases when different grades were assigned. The second examiner was masked to avoid potential bias.

## 3. Results

### 3.1. Artificial tears

The TF patterns for Blink Contact Soothing Eye Drops<sup>®</sup> and Refresh Plus Tears<sup>®</sup> are shown in Fig. 1. The other artificial tears, Bausch & Lomb Advance Eye Relief<sup>®</sup>, Refresh Optive Advanced<sup>®</sup>, and Tears Natural<sup>®</sup> did not produce distinctive TF patterns and, therefore, no attempts were made to examine the change in TF patterns with the addition of electrolyte, BTS, or SCMC solution. The compositions of the artificial tears examined and their uses are shown in Table 2.

### 3.2. Electrolytes

Electrolyte solutions (3–9 μL), namely NaCl, KCl, CaCl<sub>2</sub>, MgCl<sub>2</sub>·6H<sub>2</sub>O,

**Table 2**  
Ingredients and the uses of artificial tears used [24–29].

| Artificial tear   | Ingredients  | Use   |
|---|--|---|
| Blink Contact Soothing Eye Drops <sup>®</sup> (10 mL; Abbott)             | Sodium hyaluronate (0.15%) and OcuPure preservative (0.0005%)  | Replenishes tear film and improves tear film stability                |
| Refresh Plus Tears <sup>®</sup> (4 × 0.6 mL; Allergan)                    | SCMC (0.5%), sodium chloride, potassium chloride, calcium chloride dehydrate, magnesium chloride hexahydrate, boric acid and sodium borate decahydrate                       | Lubricates and decreases symptoms of eye dryness                      |
| Bausch & Lomb Advance Eye Relief <sup>®</sup> (15 mL; Bausch & Lomb Inc.) | Glycerin (0.3%), propylene glycol (1.0%), benzalkonium chloride (0.01%), boric acid, edetate disodium, potassium chloride, purified water, sodium borate and sodium chloride | Reliefs burning and irritation due to dry eye                         |
| Refresh Optive Advanced <sup>®</sup> (30 × 0.4 mL; Allergan)              | SCMC (0.5%), glycerin (1%) and polysorbate 80 (0.5%)   | Reliefs burning, irritation, and discomfort due to dryness of the eye |
| Tears Naturale <sup>®</sup> (15 mL; Alcon)                                | Dextran 70 and hypromellose  | Lubricates and decrease ocular irritation due to deficient tear       |

**Table 3**  
Tear ferning grades of Blink Contact Soothing Eye Drops<sup>®</sup> and Refresh Plus Tears<sup>®</sup> and their mixtures with electrolyte solutions.

| Electrolyte                          | Ratio <sup>a</sup> | TF grade                                      |                                 |
|--------------------------------------|--------------------|---|---------------------------------|
|                                      |                    | Blink Contact Soothing Eye Drops <sup>®</sup> | Refresh Plus Tears <sup>®</sup> |
| —                                    | —                  | 1.2   | 1.5                             |
| NaCl                                 | 10:3               | 1.4   | 1.7                             |
|                                      | 10:6               | 1.4   | 1.7                             |
|                                      | 10:9               | 1.5   | 1.9                             |
| KCl                                  | 10:3               | 0.8   | 1.5                             |
|                                      | 10:6               | 0.9   | 1.5                             |
|                                      | 10:9               | 0.9   | 1.4                             |
| CaCl <sub>2</sub>                    | 10:3               | 0.5   | 1.4                             |
|                                      | 10:6               | 0.4   | 1.0                             |
|                                      | 10:9               | 0.2   | 0.2                             |
| MgCl <sub>2</sub> ·6H <sub>2</sub> O | 10:3               | 0.9   | 1.4                             |
|                                      | 10:6               | 0.5   | 1.3                             |
|                                      | 10:9               | 0.7   | 1.3                             |
| NaHCO <sub>3</sub>                   | 10:3               | 0.9   | 1.0                             |
|                                      | 10:6               | 1.0   | 0.9                             |
|                                      | 10:9               | 1.0   | 0.5                             |
| NaH <sub>2</sub> PO <sub>4</sub>     | 10:3               | 0.9   | 0.8                             |
|                                      | 10:6               | 0.5   | 1.0                             |
|                                      | 10:9               | 1.4   | 0.5                             |

<sup>a</sup> Ratio by volume (μL) of artificial tears to electrolyte solution prepared in Table 1.

NaHCO<sub>3</sub>, or NaH<sub>2</sub>PO<sub>4</sub>, were mixed with artificial tears (10 μL). The tear ferns for each mixture were observed under a light microscope and the TF patterns were graded (Table 3). Examples of the TF images of Blink Contact Soothing Eye Drops<sup>®</sup> and Refresh Plus Tears<sup>®</sup>, after the addition of electrolyte solutions, are shown in Figs. 2 and 3, respectively.

Table 3 and Figs. 2 and 3 shows that the TF grades of the artificial tears used decreased after the addition of electrolyte solutions. Many of the electrolytes used lead to an improvement in the TF grades of both artificial tears. Calcium chloride was found to be the most efficient electrolyte to improve the TF grades of artificial tears. For example, the TF grade of Blink Contact Soothing Eye Drops<sup>®</sup> improved from 1.2 to 0.2–0.5 when CaCl<sub>2</sub> was added regardless of the volumes ratio between CaCl<sub>2</sub> and the artificial tear. For Refresh Plus Tears<sup>®</sup>, the TF grade was improved from 1.5 to 0.2 when CaCl<sub>2</sub> (10:9) was used. A high proportion of (10:9) hydrogenated electrolytes (NaHCO<sub>3</sub> and NaH<sub>2</sub>PO<sub>4</sub>) also improved the TF grade of Refresh Plus Tears<sup>®</sup> to 0.5.

### 3.3. BTS and electrolytes

The grade for various concentrations of electrolyte solutions added to the artificial tears, are displayed in Table 4 and example images for the two artificial tears after the addition of the basic tear and electrolyte solution, are shown in Figs. 4 and 5.

The TF grade for Blink Contact Soothing Eye Drops<sup>®</sup> improved when BTS, mono, and divalent electrolytes were used. For example, the TF

grade improved from 1.2 to 0.7 when mono and divalent electrolytes were used. No improvement was observed when hydrogenated electrolytes were used. For Refresh Plus Tears<sup>®</sup>, the TF grade improved in all cases. The TF grade was 0.2 when hydrogenated electrolyte (10:6) was used, unlike the Blink Contract Soothing Eye Drops<sup>®</sup>.

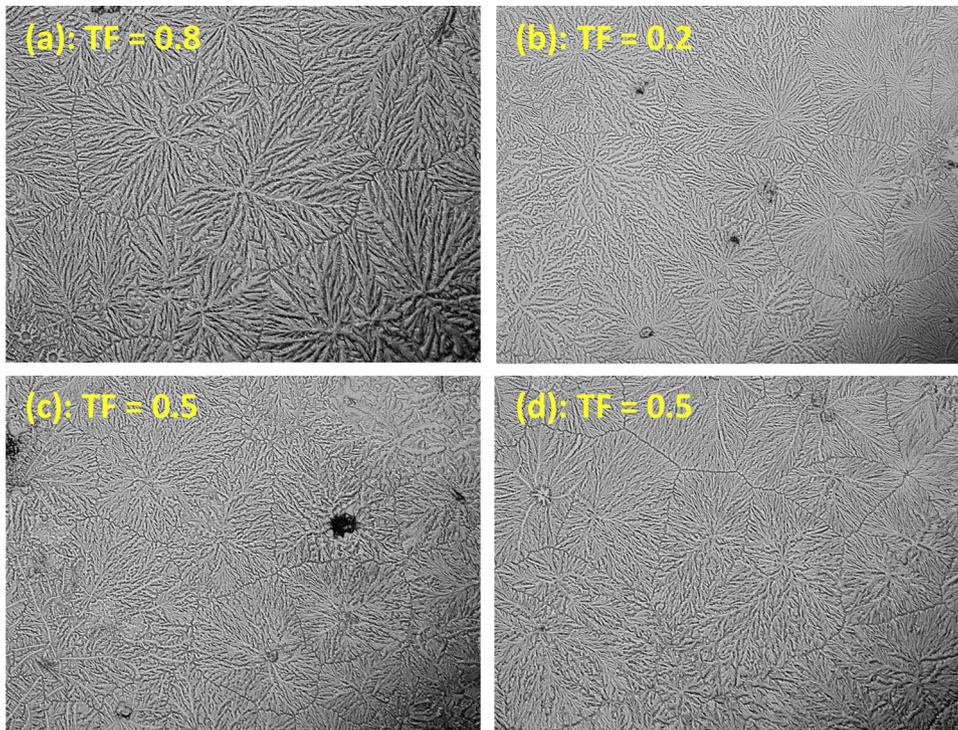
### 3.4. SCMC solution

For Blink Contact Soothing Eye Drops<sup>®</sup>, an improvement in TF grade (0.7–0.9) was observed when the ratio between artificial tears and SCMC was 10:12–30. Some examples of the TF patterns for the Blink Contact Soothing Eye Drops<sup>®</sup> after the addition of SCMC are represented in Fig. 6. No significant improvement was observed in the TF grade of Refresh Plus Tears<sup>®</sup> when SCMC was added. Clearly, Figs. 1–6 show that the TF grades have been reduced (better ferns) after the addition of electrolyte solutions compared with those obtained for the artificial tears.

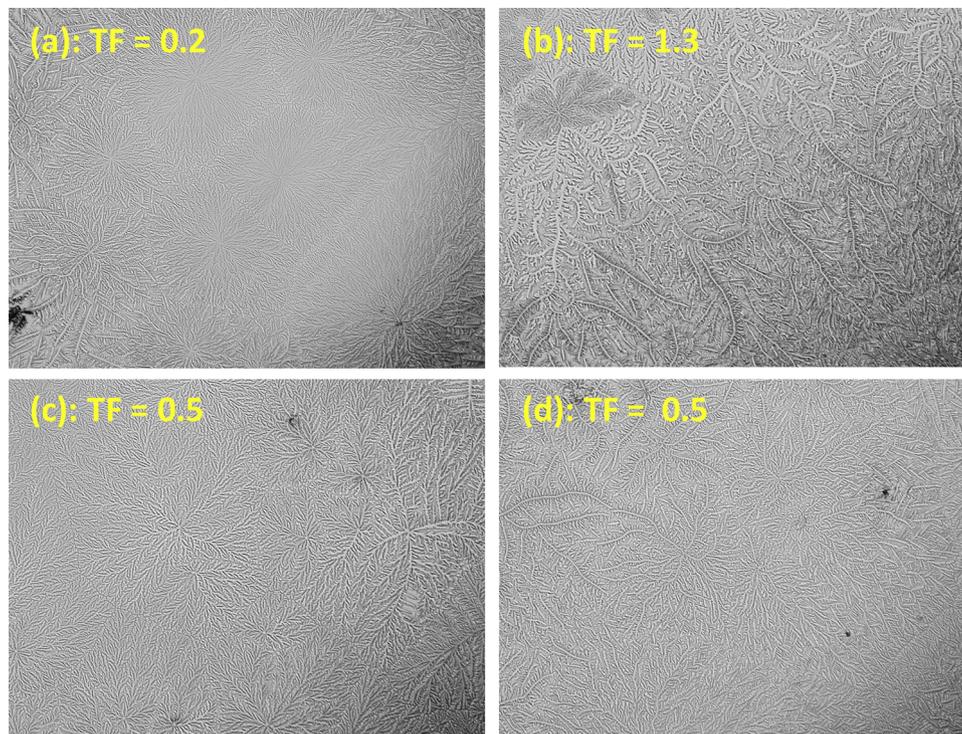
## 4. Discussion

Dried tears produce specific crystalline patterns (fern). Such ferns are characteristic for various biochemical processes that are dependent on the type and concentration of electrolyte ions, large molecules, and proteins present in the tear film [21]. Normal ferns can be produced when enough electrolyte ions and large molecules such SCMC are present, and this study demonstrates that electrolytes and SCMC solution can be used to improve the tear ferning grades of artificial tears. The TF grades for both Blink Contact Soothing Eye Drops<sup>®</sup> and Refresh Plus Tears<sup>®</sup> were improved by the addition of many of the electrolyte solutions used. Calcium and magnesium chlorides caused the most significant improvement in the TF grade of Blink Contact Soothing Eye Drops<sup>®</sup>. Sodium hydrogen carbonate and sodium dihydrogen phosphate led to a significant improvement in the TF grade of Refresh Plus Tears<sup>®</sup>. In addition, BTS, mono, and divalent electrolytes led to a noticeable improvement in the TF grade of Blink Contact Soothing Eye Drops<sup>®</sup>. A mixture of hydrogenated electrolytes was found to be very effective for improving the TF grade of Refresh Plus Tears<sup>®</sup>. In addition, the TF grade of Blink Contact Soothing Eye Drops<sup>®</sup> was improved when SCMC was used. Tear ferning grades of the artificial tears used in this study were improved with the addition of electrolyte and SCMC solutions. This method can be used to assess changes in TF patterns, which may be a useful *in-vitro* test to use in conjunction with *in-vivo* assessments of new formulations.

Artificial tears containing SCMC are efficient in reducing the symptoms and signs of dry eye; resulting in improvements in Schirmer and tear-break-up time test scores and a reduction in corneal sodium fluorescein staining [37]. In addition, eye drops, especially, those containing SCMC and sodium hyaluronate, contribute to the healing of corneal epithelial wounds [38–41]. In the current study, the TF grade for Blink Contact Soothing Eye Drops<sup>®</sup> improved with the addition of SCMC. A number of previous studies have examined the correlations



**Fig. 2.** Tear ferning patterns of Blink Contact Soothing Eye Drops<sup>®</sup> and electrolyte mixtures. The images were 10× magnification. (a) Blink Contact Soothing Eye Drops<sup>®</sup> and KCl (10:3), (b) Blink Contact Soothing Eye Drops<sup>®</sup> and CaCl<sub>2</sub> (10:9), (c) Blink Contact Soothing Eye Drops<sup>®</sup> and MgCl<sub>2</sub>·6H<sub>2</sub>O (10:6), (d) Blink Contact Soothing Eye Drops<sup>®</sup> and NaH<sub>2</sub>PO<sub>4</sub> (10:6).



**Fig. 3.** Tear ferning patterns of Refresh Plus Tears<sup>®</sup> and electrolyte mixtures. The images were 10× magnification. (a) Refresh Plus Tears<sup>®</sup> and CaCl<sub>2</sub> (10:9), (b) Refresh Plus Tears<sup>®</sup> and MgCl<sub>2</sub>·6H<sub>2</sub>O (10:9), (c) Refresh Plus Tears<sup>®</sup> and NaHCO<sub>3</sub> (10:9), (d) Refresh Plus Tears<sup>®</sup> and NaH<sub>2</sub>PO<sub>4</sub> (10:9).

between TF grades, assessed *in-vitro*, and various metrics derived from other diagnostic dry eye tests, with variable results. For example, in healthy subjects, the correlations between the TF grades and the scores from McMonnies questionnaire ( $r = 0.130$ ;  $p = 0.553$ ), TBUT ( $r = 0.248$ ;  $p = 0.254$ ), and Schirmer test ( $r = -0.046$ ;  $p = 0.834$ ) were weak and not statistically significant [22]. In subjects with controlled diabetes, the correlations between TF grades and PRT ( $r = -0.349$ ;  $p = 0.005$ ), McMonnies questionnaire score ( $r = 0.228$ ;

$p = 0.075$ ), and TBUT ( $r = -0.374$ ;  $p = 0.003$ ) were often statistically significant, but again weak associations. In subjects with uncontrolled diabetes, moderate negative correlations were observed between TF grades and TBUT ( $r = -0.539$ ;  $p < 0.001$ ) and PRT ( $r = -0.410$ ;  $p = 0.001$ ) [42]. In smokers, the correlations between TF grades and the scores from McMonnies questionnaire, TBUT, and PRT tests were small and insignificant [18]. Such insignificant or small correlations between the TF grades and the scores from other clinical measures

**Table 4**  
Tear ferning grades of Blink Contact Soothing Eye Drops<sup>®</sup> and Refresh Plus Tears<sup>®</sup> and their mixtures with basic tear and electrolyte solutions.

| Electrolyte  | Ratio <sup>a</sup> | TF grade                                      |                                 |
|--------------|--------------------|---|---------------------------------|
|              |                    | Blink Contact Soothing Eye Drops <sup>®</sup> | Refresh Plus Tears <sup>®</sup> |
| —            | —                  | 1.2   | 1.5                             |
| BTS          | 10:3               | 0.9   | 1.2                             |
|              | 10:6               | 0.9   | 1.0                             |
|              | 10:9               | 1.0   | 1.0                             |
| Monovalent   | 10:3               | 0.8   | 1.4                             |
|              | 10:6               | 0.9   | 1.5                             |
|              | 10:9               | 0.7   | 0.8                             |
| Divalent     | 10:3               | 1.0   | 1.0                             |
|              | 10:6               | 0.7   | 1.4                             |
|              | 10:9               | 0.8   | 0.8                             |
| Hydrogenated | 10:3               | 1.2   | 1.0                             |
|              | 10:6               | 1.4   | 0.2                             |
|              | 10:9               | 1.4   | 0.9                             |

<sup>a</sup> Ratio by volume (µL) between artificial tears and electrolyte solution prepared in Table 1. BTS: basic tear solution. Monovalent: monovalent electrolyte, which is a 1:1 mixture of NaCl and KCl. Divalent: divalent electrolyte, which is a 1:1 mixture of CaCl<sub>2</sub> and MgCl<sub>2</sub>. Hydrogenated: hydrogenated electrolyte, which is a 1:1 mixture of NaHCO<sub>3</sub> and NaH<sub>2</sub>PO<sub>4</sub>.

could be due the fact that each test assesses a different parameter associated with signs or symptoms of ocular surface disease.

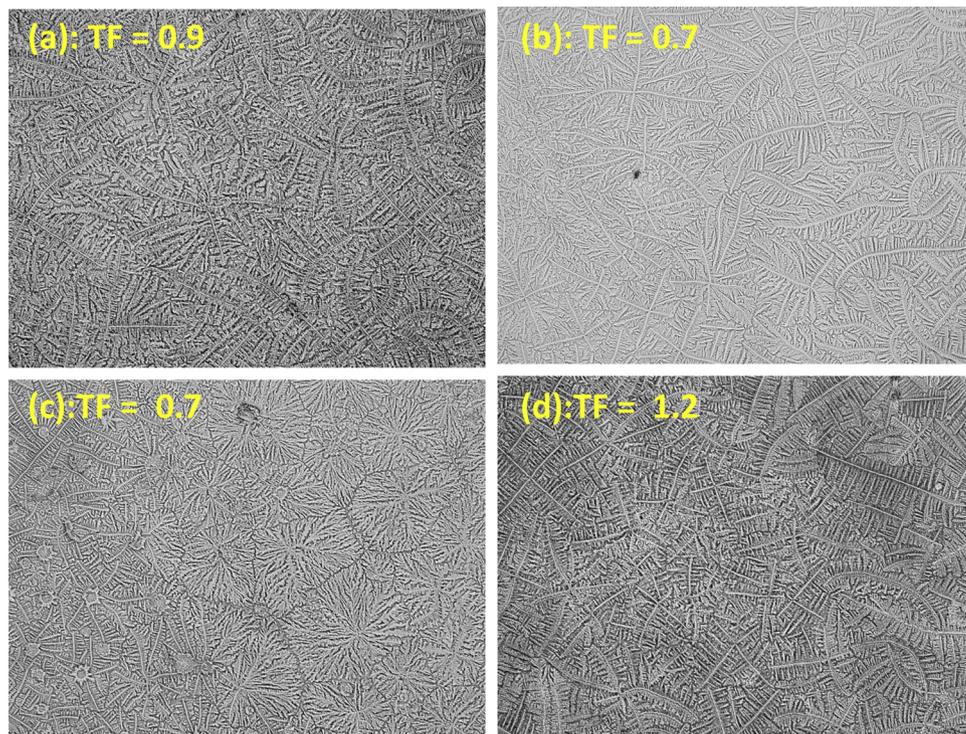
Previous reports suggest that the TF test is a valid and repeatable *in-vitro* test and can be used in combination with other common clinical tests to detect dry eye [21–23]. The mean difference and 95% limits of agreement for TF grades of repeated measures obtained from different tear samples collected from the same individual at different period of the day was found to be approximately 0.1 ± 0.4 on a five-point

grading scale [22]. In the current study, many of the changes in the tear ferning grades were relatively small (the absolute average change across all measurements was 0.4 with a range from 0 to 1.3) and within the 95% limits of agreement for repeatability of subjectively graded TF patterns of human tears. However, the tear ferns obtained from an artificial tear samples in the current study (not human tears as used in previous repeatability analyses) were graded as almost identical between two independent observers (mean difference less than ± 0.1).

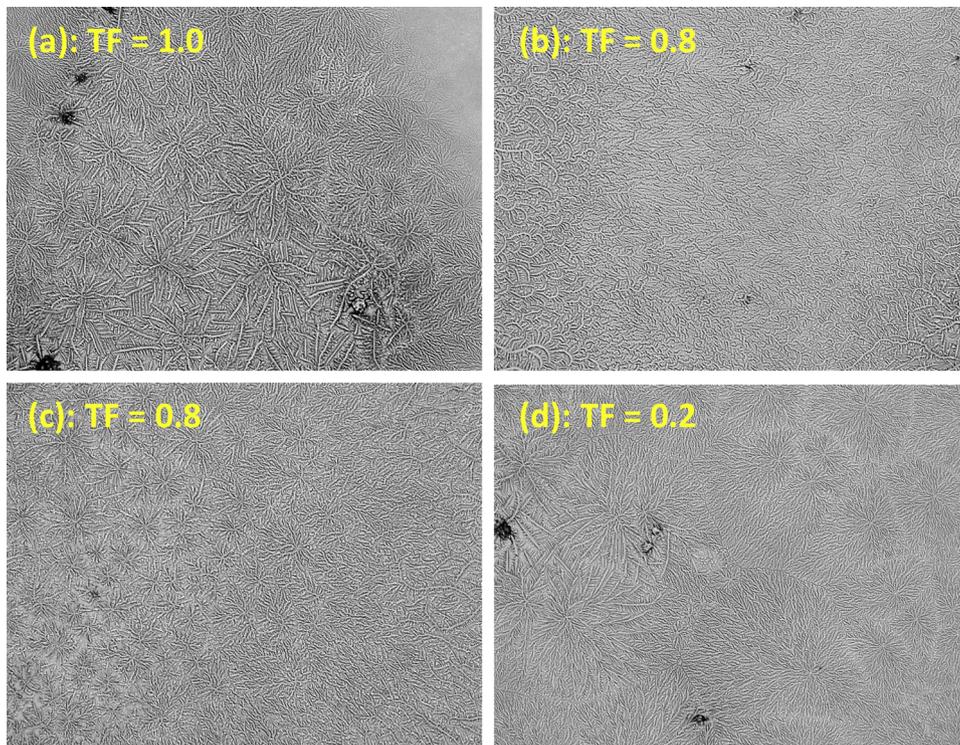
This study has a limitation that it has been performed only using few electrolytes, but further studies should investigate the use of different electrolytes and proteins to improve the TF grades of artificial tears. In addition, different combinations of salts and various ratios of monovalent, divalent and hydrogenated electrolyte solutions should be tested. Moreover, only artificial tears that have clear tear ferning can be used where the tear ferning test is applicable. Further research is still needed to understand the clinical relevance of the current work to allow the translation of the *in-vitro* TF data to *in-vivo* performance.

### 5. Conclusion

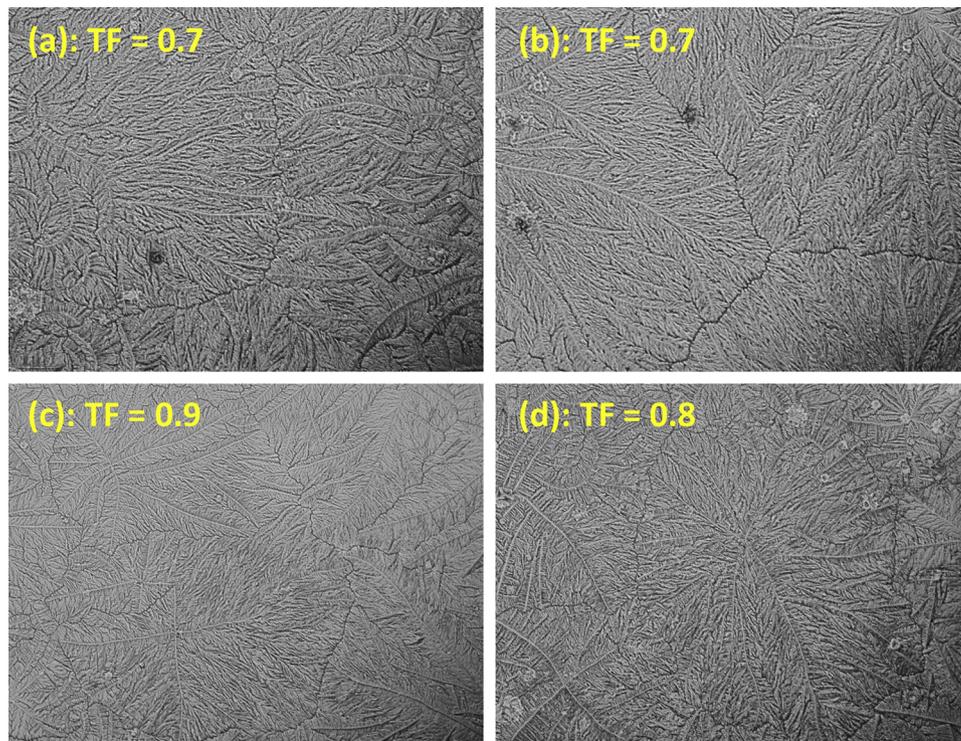
The tear ferning test can be used to evaluate the effect of addition of electrolytes to an artificial tear *in-vitro*. The TF patterns for artificial tears such as Blink Contact Soothing Eye Drops<sup>®</sup> and Refresh Plus Tears<sup>®</sup> were improved by the addition of various electrolytes, basic tear solution, and large organic molecules such as sodium carboxymethylcellulose. Further research is still needed to understand the clinical relevance of TF patterns with respect to the management of dry eye symptoms and their potential role in the development of new artificial tears.



**Fig. 4.** Tear ferning patterns of Blink Contact Soothing Eye Drops<sup>®</sup> with BTS and electrolyte mixtures. The images were 10 × magnification. (a) Blink Contact Soothing Eye Drops<sup>®</sup> and BTS (10:3), (b) Blink Contact Soothing Eye Drops<sup>®</sup> and monovalent electrolyte (10:9), (c) Blink Contact Soothing Eye Drops<sup>®</sup> and divalent electrolyte (10:6), (d) Blink Contact Soothing Eye Drops<sup>®</sup> and hydrogenated electrolyte (10:3).



**Fig. 5.** Tear ferning patterns of Refresh Plus Tears<sup>®</sup> with BTS and electrolyte mixtures. The images were 10× magnification. (a) Refresh Plus Tears<sup>®</sup> and BTS (10:6), (b) Refresh Plus Tears<sup>®</sup> and monovalent electrolyte (10:9), (c) Refresh Plus Tears<sup>®</sup> and divalent electrolyte (10:9), (d) Refresh Plus Tears<sup>®</sup> and NaH<sub>2</sub>PO<sub>4</sub> (10:6).



**Fig. 6.** Tear ferning patterns of Blink Contact Soothing Eye Drops<sup>®</sup> and SCMC mixtures. The images were 10× magnification. (a) Blink Contact Soothing Eye Drops<sup>®</sup> and SCMC (10:12), (b) Blink Contact Soothing Eye Drops<sup>®</sup> and SCMC (10:18), (c) Blink Contact Soothing Eye Drops<sup>®</sup> and SCMC (10:27), (d) Blink Contact Soothing Eye Drops<sup>®</sup> and SCMC (10:30).

## Competing interests

The author declares no conflict of interest regarding the publication of this paper.

## Acknowledgements

The author is grateful to the Deanship of Scientific Research, King Saud University for funding through the Vice Deanship of Scientific Research Chairs.

## References

- [1] A.J. Bron, et al., Functional aspects of the tear film lipid layer, *Exp Eye Res* 78 (3) (2004) 347–360.
- [2] M. Evangelista, et al., Comparison of three lubricant eye drop solutions in dry eye patients, *Optom Vis Sci* 88 (12) (2011) 1439–1444.
- [3] D. Dursun, et al., The effects of experimental tear film removal on corneal surface regularity and barrier function, *Ophthalmology* 107 (9) (2000) 1754–1760.
- [4] The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye Workshop (2007), *Ocul Surf* 5 (2) (2007) 75–92.
- [5] E. Goto, et al., Impaired functional visual acuity of dry eye patients, *Am J Ophthalmol* 133 (2) (2002) 181–186.
- [6] I.K. Gipson, Distribution of mucins at the ocular surface, *Exp Eye Res* 78 (3) (2004) 379–388.
- [7] T. Sakimoto, et al., Upregulation of matrix metalloproteinase in tear fluid of patients with recurrent corneal erosion, *Jpn J Ophthalmol* 51 (5) (2007) 343–346.
- [8] E.M. Messmer, The pathophysiology, diagnosis, and treatment of dry eye disease, *Dtsch Arztebl Int* 5 (2015) 71–81 quiz 82.
- [9] J.L. Gayton, Etiology, prevalence, and treatment of dry eye disease, *Clin Ophthalmol* 3 (2009) 405–412.
- [10] P.A. Asbell, Increasing importance of dry eye syndrome and the ideal artificial tear: consensus views from a roundtable discussion, *Curr Med Res Opin* 22 (11) (2006) 2149–2157.
- [11] S. Hitoe, J. Tanaka, H. Shimoda, MaquiBright standardized maqui berry extract significantly increases tear fluid production and ameliorates dry eye-related symptoms in a clinical pilot trial, *Panminerva Med* 56 (3 Suppl. 1) (2014) 1–6.
- [12] A. Galor, et al., Dry eye medication use and expenditures: data from the medical expenditure panel survey 2001 to 2006, *Cornea* 31 (12) (2012) 1403–1407.
- [13] J.E. Lee, et al., A randomised controlled trial comparing a thermal massager with artificial teardrops for the treatment of dry eye, *Br J Ophthalmol* 98 (1) (2014) 46–51.
- [14] R. Latkany, Dry eyes: etiology and management, *Curr Opin Ophthalmol* 19 (4) (2008) 287–291.
- [15] J. Wong, et al., Non-hormonal systemic medications and dry eye, *Ocul Surf* 9 (4) (2011) 212–226.
- [16] M.A. Javadi, S. Feizi, Dry eye syndrome, *J Ophthalmic Vis Res* 6 (3) (2011) 192–198.
- [17] E.K. Akpek, et al., Treatment of Sjogren's syndrome-associated dry eye an evidence-based review, *Ophthalmology* 118 (7) (2011) 1242–1252.
- [18] A.M. Masmali, et al., Assessment of tear film quality among smokers using tear ferning patterns, *J Ophthalmol* 2016 (2016) p. 8154315.
- [19] A. Masmali, et al., Comparative study of repeatability of phenol red thread test versus Schirmer test in normal adults in Saudi Arabia, *Eye Contact Lens* 40 (3) (2014) 127–131.
- [20] A. Masmali, et al., Investigation of tear osmolarity using the TearLab Osmolarity System in normal adults in Saudi Arabia, *Eye Contact Lens* 40 (2) (2014) 74–78.
- [21] A.M. Masmali, C. Purslow, P.J. Murphy, The tear ferning test: a simple clinical technique to evaluate the ocular tear film, *Clin Exp Optom* 97 (5) (2014) 399–406.
- [22] A.M. Masmali, et al., Repeatability and diurnal variation of tear ferning test, *Eye Contact Lens* 41 (5) (2015) 262–267.
- [23] A.M. Masmali, et al., Application of a new grading scale for tear ferning in non-dry eye and dry eye subjects, *Cont Lens Anterior Eye* 38 (1) (2015) 39–43.
- [24] M. Markoulli, et al., The effect of Optive and Optive Advanced Artificial Tears on the healthy tear film, *Curr Eye Res* 43 (5) (2018) 588–594.
- [25] L. Essa, D. Laughton, J.S. Wolffsohn, Can the optimum artificial tear treatment for dry eye disease be predicted from presenting signs and symptoms? *Cont Lens Anterior Eye* 41 (1) (2018) 60–68.
- [26] B.C.H. Ang, et al., Sodium hyaluronate in the treatment of dry eye syndrome: a systematic review and meta-analysis, *Sci Rep* 7 (1) (2017) 9013.
- [27] A.D. Pucker, S.M. Ng, J.J. Nichols, Over the counter (OTC) artificial tear drops for dry eye syndrome, *Cochrane Database Syst Rev* 2 (2016) p. CD009729.
- [28] J.H. Lee, et al., Efficacy of sodium hyaluronate and carboxymethylcellulose in treating mild to moderate dry eye disease, *Cornea* 30 (2) (2011) 175–179.
- [29] M.E. Johnson, P.J. Murphy, M. Boulton, Effectiveness of sodium hyaluronate eye-drops in the treatment of dry eye, *Graefes Arch Clin Exp Ophthalmol* 244 (1) (2006) 109–112.
- [30] T. Kaercher, et al., A prospective, multicenter, noninterventional study of Optive Plus(R) in the treatment of patients with dry eye: the prolipid study, *Clin Ophthalmol* 8 (2014) 1147–1155.
- [31] J.C. Wojtowicz, et al., Effect of systane and optive on aqueous tear evaporation in patients with dry eye disease, *Eye Contact Lens* 36 (6) (2010) 358–360.
- [32] D.R. Korb, et al., The effect of two novel lubricant eye drops on tear film lipid layer thickness in subjects with dry eye symptoms, *Optom Vis Sci* 82 (7) (2005) 594–601.
- [33] W.G. Bachman, G. Wilson, Essential ions for maintenance of the corneal epithelial surface, *Invest Ophthalmol Vis Sci* 26 (11) (1985) 1484–1488.
- [34] A.M. Masmali, P.J. Murphy, C. Purslow, Development of a new grading scale for tear ferning, *Cont Lens Anterior Eye* 37 (3) (2014) 178–184.
- [35] M. Rolando, F. Baldi, M. Zingirian, The effect of hyperosmolarity on tear mucus ferning, *Fortschr Ophthalmol* 83 (6) (1986) 644–646.
- [36] V. Peponis, et al., Protective role of oral antioxidant supplementation in ocular surface of diabetic patients, *Br J Ophthalmol* 86 (12) (2002) 1369–1373.
- [37] A. Okanobo, et al., Efficacy of topical blockade of interleukin-1 in experimental dry eye disease, *Am J Ophthalmol* 154 (1) (2012) 63–71.
- [38] J.S. Lee, et al., Comparison of cytotoxicity and wound healing effect of carboxymethylcellulose and hyaluronic acid on human corneal epithelial cells, *Int J Ophthalmol* 8 (2) (2015) 215–221.
- [39] Y. Diebold, et al., Carbomer- versus cellulose-based artificial-tear formulations: morphologic and toxicologic effects on a corneal cell line, *Cornea* 17 (4) (1998) 433–440.
- [40] M. Ayaki, A. Iwasawa, Y. Niwano, Comparative assessment of the cytotoxicity of six anti-inflammatory eyedrops in four cultured ocular surface cell lines, as determined by cell viability scores, *Clin Ophthalmol* 6 (2012) 1879–1884.
- [41] M.A. Masmali, et al., Investigation of ocular tear ferning in controlled and uncontrolled diabetic subjects, *Eye Contact Lens* 44 (2018) S70–S75.