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Phosphate concentration in artificial tears

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Abstract *Background:* Irrigating solutions and eye drops may contain phosphates as part of their buffer system. In the presence of epithelial keratopathy, a high concentration of phosphate favours corneal calcification. Knowledge of the phosphate concentration in artificial tear products helps to prevent this sight-threatening complication. This study gives an overview on the amount of phosphate contained in artificial tears. *Methods:* Fifty-nine samples of commercially available artificial tear preparations were tested. The quantification of phosphate was performed using the molybdate method on a Modular P autoanalyzer. *Results:* Twenty-six of 59 (44%) artificial tear products had a phosphate concentration above physiological levels (>1.45 mmol/l). A phosphate concentration above 25 mmol/l was found in nine products (15%), a concentration higher than 50 mmol/l in three (5%). *Conclusions:* Many artificial tear formulations contain unphysiological levels of phosphate, but very high concentrations are found only in a few products. These preparations have the potential to favour the formation of insoluble crystalline calcium phosphate deposits when used on a damaged corneal surface, and should therefore be used cautiously.

Keywords Cornea · Sodium hyaluronate · Phosphate concentration · Artificial tears · Corneal calcification

Introduction

Eye drop preparations typically consist of a pharmaceutically active drug, a preservative and a vehicle [2]. Potential side effects of the active drug have been studied systematically [4]. The toxic effects of preservatives have also been recognised [3]. Little attention has been given so far to the role of vehicles in the development of ocular adverse effects.

An ophthalmic vehicle is an agent other than the active drug or preservative that is added to a formulation to provide proper tonicity, buffering, and viscosity to complement drug action. The buffering system may consist of acetic, boric and hydrochloric acid, and of potassium or sodium bicarbonate, borate, phosphate and citrate [2]. In many eye drops, the buffering system consists of phosphates. The phosphate is typically introduced in the form of disodium hydrogen phosphate dodecahydrate or sodium dihydrogen phosphate dihydrate. Recent studies have shown that a high concentration of phosphate buffer may cause irreversible corneal calcification with visual loss. Daly et al. reported rapid corneal calcification after

Table 1 Phosphate concentration in commercially available artificial tear preparations, German and Swiss market

	Market	Phosphate, PO^{4-}
	Germany (GER) Switzerland (CH)	mmol/l
Hydroxypropyl methylcellulose (HPMC)		
Artelac–EDO, Gerhard Mann Gmbh	GER	18.2
Berberil Drye Eye–EDO, Gerhard Mann Gmbh	GER	3.3
GenTeal, Novartis Opthalmics	GER	<0.1
Isopto Tears, Alcon	CH	60.6
Lacrigel sine, Winzer	GER	0.4
Sicca–Stulln, Pharma Stulln	GER	<0.1
Sic–Ophtal sine, Winzer	GER	18.5
Tears Naturale, Alcon	CH	<0.1
Carboxyl methylcellulose (CMC)		
Cellufluid, Allergan	CH	<0.1
Cellufresh, Pharm–Allergan	GER	<0.1
Cellumed, Pharm–Allergan	GER	<0.1
Celluvisc UD, Allergan	GER, CH	<0.1
Polyvinyl alcohol (PVA)		
Collylarm, Vifor	CH	<0.1
Hypo Tears, Novartis Ophthalmics	CH	<0.1
Lacrimal OK, Pharm–Allergan	GER	<0.1
Liquifilm N, Pharm–Allergan	GER	28.8
Liquitears, Allergan	CH	29.7
Vistil, Santen	GER	11.2
Polyvidone		
Arufil uno, Chauvin ankerpharm	GER	<0.1
Lacopthal sine, Winzer	GER	<0.1
Lacri–Stulln DU, Pharma Stulln	GER	68.8
Oculac, Novartis Ophthalmics	GER, CH	<0.1
Protagent SE, Alcon	GER, CH	<0.1
Vidirakt S mit PVP, Gerhard Mann Gmbh	GER	<0.1
Vidisept EDO, Gerhard Mann Gmbh	GER	<0.1
Vidisic EDO, Gerhard Mann Gmbh	GER	<0.1
Yxin Tears ED, Pfizer	GER	<0.1
Wet–Comod, Ursapharm	GER	5.7
Glycerine		
Systane, Alcon	GER, CH	<0.1
Dextran		
Dialens, Bausch & Lomb	CH	<0.1
Carbomer980		
Lacrinorm UD, Bausch & Lomb	CH	11.8
Liposic EDO, Gerhard Mann Gmbh	GER	<0.1
Vidisic EDO, Gerhard Mann Gmbh	GER	<0.1
Viscotears SDU, Novartis Ophthalmics	CH	<0.1
Carbomer 974		
Lacryvisc SE, Alcon	CH	<0.1
Siccafluid, Thea Pharma	CH	<0.1
Sodium hyaluronate		
Biolan, Santen	GER	2.1
Comfort Shield UD, i.com medical GmbH	GER, CH	2.3
Fermavisc UD, Novartis Ophthalmics	CH	1.7
Hyabak, Laboratoires Théa, France	CH	10.9

Table1 (continued)

	Market	Phosphate, PO^{4-}
	Germany (GER) Switzerland (CH)	mmol/l
Hyal–drop, Bausch & Lomb	CH	2
HycoSan5, Pharma Medica	CH	48.7
Hylan, Pharma Stulln	GER	<0.1
Hylo–Comod, Ursapharm	GER, CH	50.9
Hylo–Vision, OmniVision	GER	1.9
Oxyal, Santen	GER	<0.1
Vislube, TRB chemedica	GER, CH	9.9
Vismed Gel UD, TRB chemedica	GER, CH	10.8
Vismed UD, TRB chemedica	GER, CH	10.5
Vismed light, TRB chemedica	GER, CH	1.9
Xidan EDO, Gerhard Mann Gmbh	GER	<0.1
Combinations		
Dispatenol, Novartis Ophthalmics (dexapanthnol, polyvinylacohol)	GER	44.3
Hylo–Care, Ursapharm (sodium hyaluronate, dexapanthenol)	GER	25.6
Isopto–Naturale, Alcon (hypromellose, dextran)	GER	<0.1
Lacrimal O.K., Pharm–Allergan (polyvinylalcohol, polyvidone)	GER	<0.1
Lacrisic, Alcon (hypromellose, polyvidone, glycerol)	GER	15.1
Lacrycon UD, Thea Pharma (sodium hyaluronate, glycerine, Carbomer 981)	CH	<0.1
Oculotect sine, Novartis Ophthalmics (retinolpalmitate, hypromellose)	GER	0.1
Siccaprotect, Ursapharm (dexapanthenol, polyvinylalcohol)	GER	44.3

irrigation with phosphate-buffered saline [5]. Similar deposits were described after ocular surface disease and frequent use of phospate-buffered hyaluronic acid artificial tears [1].

Information on phosphate concentrations in artificial tear preparations will help clinicians caring for patients at risk for corneal calcification. This study examines the artificial tear preparations that are currently available in Germany and/or Switzerland.

Materials and methods

All the artificial tear preparations that are listed as drop preparations in the "Rote Liste 2005" (Rote Liste Service GmbH, Frankfurt/Main, Editio Cantor Verlag, Aulendorf, Germany) and the "Arzneimittelkompendium der Schweiz 2005" (Documed AG, Basel, Switzerland) were included in this study. When the preparations were available in multidose and unit dose containers, the samples were taken from the preservative-free formulation. For technical reasons, gel preparations were not included. The quantification of the phosphate was performed with the molybdate method on a Modular P autoanalyzer (Roche Diagnostics, Basel, Switzerland) [7]. The results were compared to the physiological concentrations published elsewhere [7, 8].

Results

The phosphate concentrations of the ocular therapeutics that were studied are listed in Table 1. Table 2 gives an overview of the artificial tears that showed concentrations above physiological levels.

Twenty-six of 59 (44%) of the tested artificial tear products showed a phosphate concentration above physiological levels (>1.45 mmol/l). Concentrations above 25 mmol/l were found in nine products (15%), and high levels above 50 mmol/l in three (5%). There was no correlation between the type of product and the phosphate concentration. The three products with high phosphate concentrations included lubricants based on polyvidone (Lacri-Stulln DU, Pharma Stulln, Germany), hydroxylpropyl methylcellulose (Isopto Tears, Alcon) and sodium hyaluronate (Hylo-Comod, Ursapharm, Germany). Twelve of 15 hyaluronate preparations were buffered with phosphate.

Table 2 Artificial tear products with phosphate concentrations above physiological levels (>1.45 mmol/l)

	Market	Phosphate, PO^{4-}
	Germany (GER) Switzerland (CH)	mmol/l
Lacri–Stulln DU, Pharma Stulln (polyvidone)	GER	68.8
Isopto Tears, Alcon (hypromellose)	CH	60.6
Hylo–Comod, Ursapharm (sodium hyaluronate)	GER, CH	50.9
HycoSan5, Pharma Medica (sodium hyaluronate)	CH	48.7
Siccaprotect, Ursapharm (dexapanthenol, polyvinyl alcohol)	GER	44.3
Dispatenol, Novartis Opthalmics (dexapanthnol, polyvinyl alcohol)	GER	44.3
Liquitears, Allergan (polyvinyl alcohol)	CH	29.7
Liquifilm N, Pharm–Allergan (polyvinyl alcohol)	GER	28.8
Hylo–Care, Ursapharm (sodium hyaluronate, dexapanthenol)	GER	25.6
Sic–Ophtal sine, Winzer (hypromellose)	GER	18.5
Artelac–EDO, Gerhard Mann Gmbh (hypromellose)	GER	18.2
Lacrisic, Alcon (hypromellose, polyvidone, glycerol)	GER	15.1
Lacinorm UD, Bausch & Lomb (carbomer 980)	CH	11.8
Vistil, Santen (polyvinyl alcohol)	GER	11.2
Hyabak, Laboratoires Théa, France (sodium hyaluronate)	CH	10.9
Vismed Gel UD, TRB chemedica (0.3% sodium hyaluronate)	GER, CH	10.8
Vismed UD, TRB chemedica (0.18% sodium hyaluronate)	GER, CH	10.5
Vislube, TRB chemedica (sodium hyaluronate)	GER, CH	9.9
Wet–Comod, Ursapharm (polyvidone)	GER	5.7
Berberil Drye Eye–EDO, Gerhard Mann Gmbh (polyvidone)	GER	3.3
Comfort Shield UD, i.com medical GmbH (sodium hyaluronate)	GER, CH	2.3
Biolan, Santen (sodium hyaluronate)	GER	2.1
Hyal–drop, Bausch & Lomb (sodium hyaluronate)	CH	2
Vismed light, TRB chemedica (0.1% sodium hyaluronate)	GER, CH	1.9
Hylo–Vision, OmniVision (sodium hyaluronate)	GER	1.9
Fermavisc UD, Novartis (sodium hyaluronate)	CH	1.7

Discussion

The constituents of topical medications change the composition of the precorneal tear film. The phosphate concentration may be increased by the vehicle of ophthalmic preparations. Phosphates are widely used as part of buffering systems and were found in many of the artificial tear products in this series.

Recent studies have shown that phosphate buffers play a role in the process of corneal calcification [1, 5, 6, 8, 10]. Calcification occurs when calcium cations and phosphate anions form insoluble crystals within the tissue. In the cornea, deposition typically occurs as hydroxyapatite $Ca_5(PO_4)_3OH$ [1, 5, 9]. (Fig. 1). Deposition of calcium can be observed as a spectrum of clinical findings, ranging from subtle age-related superficial changes to full-thickness calcification of the entire cornea with visual loss.

Forty-five percent of the tested artificial tear products had a phosphate concentration above physiological levels (>1.45 mmol/l). High concentrations (above 25 mmol/l) were only found in nine products. To date, it is not clear which is the critical concentration of phosphate with regard to the onset of corneal calcification. In the animal model, rapid corneal calcification developed after alkali eye burns with large epithelial defects when the eyes were irrigated with Isogutt (Dr. Winzer Pharma GmbH, Germany) [10]. In

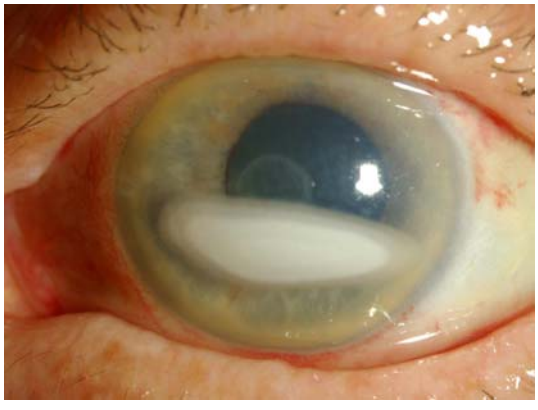

Fig. 1 Formation of a calcified plaque on intensified treatment with phosphate-buffered hyaluronate artificial tears. A chemical burn had led to a complete corneal erosion that was treated with a therapeutic contact lens and hyaluronate eye drops containing 50.9 mmol/l phosphate. The large area of calcification developed within 3 days

this solution, a phosphate concentration of 148 mol/l was measured.

The use of artificial tears for the treatment of epithelial keratopathy or erosions may lead to similar conditions to those in the animal model: With epithelial defects, the drops are typically applied very frequently, and the phosphate-rich lubricants may push the ion product towards precipitation. In addition, the viscous character of many artificial tears may prolong exposure time to the phosphates.

It is beyond doubt that very high topical phosphate concentrations have an impact on the process of corneal calcification. Corneal calcification, however, is dependent on many variables. These include pH, tonicity, size of epithelial defect, and amount of barrier dysfunction [8, 10]. Therefore, the definition of a critical phosphate concentration is difficult. Further studies are required to allow rational recommendations. In the series with calcification following ocular surface disease and intensified use of hyaluronic acid artificial tears [1], the concentration in the lubricant was 50.9 mmol/l, which may serve as a first idea.

When artificial tears are used for the treatment of epithelial defects, phosphate-free or preparations with low phosphate concentrations are preferable. This overview helps the clinician in the selection. The pharmaceutical industry is encouraged to develop phosphate-free preparations for this indication.

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