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The impact of phosphates in eye drops on the ocular surface

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HIGHLIGHTS

There is a need to raise awareness about the impact of excipients contained in ophthalmic preparations on the ocular surface. The choice of preparation should be individually tailored to the patient's clinical condition, with excipients evaluated with the same level of scrutiny as the active pharmaceutical ingredient.

ABSTRACT

The ocular surface plays a key role in maintaining corneal transparency and protecting the visual organ from external factors. One of the threats to its integrity is the use of topical ophthalmic preparations containing phosphates, which – when the epithelium is damaged – can lead to the formation of calcium phosphate deposits and the development of band keratopathy. The aim of this article is to present the role of phosphates as excipients in eye drops, their mechanism of action, potential toxicity, and the risks associated with their long-term use. Special attention is given to the conditions that promote corneal calcification and the negative impact of phosphates on epithelial healing and regeneration processes. The article emphasizes the need to raise awareness among physicians and patients about the potential adverse effects of phosphates and the necessity for caution in their use, particularly in individuals with a compromised ocular surface.

Key words: ocular surface, cornea, phosphate buffer, calcium phosphate deposits

INTRODUCTION

The ocular surface is a remarkable and essential component of the visual system. It comprises the ocular surface tissues as well as their associated adnexal structures, including the cornea, conjunctiva, corneoscleral limbus, eyelids, eyelashes, tear film, the main lacrimal gland and accessory lacrimal glands, and the Meibomian glands. The primary functions of these structures are to maintain corneal transparency and to provide anatomical, physiological, and immunological protection against microorganisms, allergens, toxins, and mechanical trauma. The function and integrity of these structures are closely integrated and influenced by the nervous, immune, endocrine, and vascular systems. The proper structure and quality of the tear film depend on adequate hydration of the ocular surface. A transparent, smooth, and well-hydrated cornea constitutes the principal refractive surface of the visual system.

The cornea is the most anterior structure of the eye and is therefore directly exposed to the external environment, rendering it susceptible to desiccation, infection, and injury. In ocular surface diseases, damage to the epithelium covering the conjunctiva and cornea may result in pain, conjunctival hyperemia, foreign body sensation, discomfort, and – most importantly – visual impairment. In some cases, epithelial injury may become permanent and lead to keratopathy, corneal ulceration, and other ocular surface disorders. Therefore, early diagnosis, prevention, and appropriate treatment are essential.

The European Medicines Agency (EMA) has identified patients with ocular surface disease as the population at highest risk of developing superficial band keratopathy and deeper corneal calcification following exposure to phosphate-containing excipients in topical ophthalmic medications [1]. It is therefore essential to increase awareness among both physicians and patients regarding this potential adverse effect in order to prevent it effectively.

THE ROLE OF PHOSPHATES IN OPHTHALMIC DROPS

Phosphates – most commonly in the form of dihydrogen phosphates and sodium or potassium hydrogen phosphates – are widely used excipients in ophthalmic formulations. They act as buffering agents, maintaining the pH of the solution within the physiological range (pH 6.5–7.5), and contribute to product stability. In addition, they facilitate the dissolution of certain active substances and may improve the tolerability and comfort of eye drops. From a chemical perspective, phosphates are generally well tolerated by a physiologically intact ocular surface. However, concerns arise when phosphate-containing formulations are used in patients with a compromised corneal epithelial barrier, particularly in the presence of inflammation, trauma, or dry eye disease.

PHOSPHATES IN OPHTHALMIC PREPARATIONS

A review of the literature confirms that phosphate buffers are present in numerous ophthalmic preparations, including:

- anti-inflammatory eye drops (e.g., dexamethasone-containing formulations)
- anti-glaucoma medications (e.g., β-adrenergic antagonists, carbonic anhydrase inhibitors, prostaglandin analogues, and α-adrenergic agonists/antagonists)
- antibiotic solutions (e.g., tobramycin)
- lubricants and artificial tears.

In recent years, an increasing number of studies have highlighted the potentially detrimental effects of phosphate-containing formulations on ocular surface health, particularly in patients with epithelial compromise and/or during long-term use.

MECHANISMS OF ACTION AND TOXICITY

The pathogenesis of calcium phosphate deposition in the cornea has not yet been fully elucidated. It is generally accepted that corneal calcification may occur via two principal mechanisms: (1) systemic disturbances of serum calcium and phosphate metabolism, and (2) local deposition secondary to tissue injury – potentially even minor epithelial microtrauma – in the setting of chronic ocular surface inflammation. Under physiological conditions, calcium and phosphate remain in equilibrium within the tear film; however, disruption of this balance may result in the formation of hydroxyapatite and/or calcium phosphate deposits [2, 3]. Factors that promote the formation of calcium phosphate deposits include increased tear film osmolarity due to excessive evaporation, an increase in tear pH (e.g., related to corneal metabolism), elevated calcium and/or phosphate concentrations, and the presence of preservatives such as benzalkonium chloride (BAK), which may enhance phosphate-related toxicity by disrupting the corneal epithelial barrier.

The primary mechanism underlying the adverse effects of phosphates is their ability to bind calcium ions naturally present in the tear film and corneal tissues. When phosphate concentrations are increased and the epithelial barrier is compromised, this may lead to:

- precipitation of insoluble calcium phosphate salts, particularly hydroxyapatite crystals – $Ca_5(PO_4)_3OH$
- deposition of calcium phosphate in various corneal layers, including the epithelium, Bowman's layer, and the corneal stroma.

Band keratopathy – involving Bowman's layer and the anterior corneal stroma – most commonly develops in the interpalpebral zone, where increased tear evaporation creates

a more alkaline microenvironment [4]. In contrast, deeper calcific deposits involving the posterior stroma and Descemet's membrane are typically associated with corneal epithelial damage and disruption or absence of Bowman's layer. Both band keratopathy and deeper corneal calcification have been linked to the use of phosphate-containing eye drops [5]. Calcium phosphate deposition may compromise corneal optical clarity, resulting in reduced visual acuity and, in severe cases, permanent ocular surface damage with subsequent corneal opacity. These lesions are often irreversible and may require surgical intervention, such as superficial keratectomy or corneal transplantation.

In addition, studies have shown that phosphates may interfere with the migration and proliferation of corneal epithelial cells, thereby delaying epithelial wound healing and potentially increasing the risk of secondary infection. Calcium phosphate precipitation appears to occur particularly rapidly in the presence of epithelial injury, such as mechanical trauma, chemical burns, chronic exposure to preservatives (e.g., benzalkonium chloride [BAK]), and corneal inflammation. Moreover, the presence of calcium phosphate deposits may itself adversely affect the ocular surface, frequently causing symptoms such as discomfort, foreign body sensation, tearing (epiphora), burning, and conjunctival hyperemia; these symptoms may exacerbate underlying inflammation and further reduce patient comfort and quality of life.

Studies by Stanley, Leopold, and Caldeira reported that tear calcium concentrations range from 0.0211 to 0.041 mg/mL, with a basal tear secretion rate of approximately 120–240 mL/h. Accordingly, the calcium influx to the corneal surface in a healthy eye is estimated to be 2.53–9.84 mg/h. Given that ocular surface injury is often associated with a marked increase in tear production, corneal exposure to calcium may substantially exceed physiological levels under such conditions [6–9].

Phosphate buffers used in topical ophthalmic formulations are typically present at concentrations substantially exceeding physiological phosphate levels in the tear film. It has been estimated that, under conditions of unrestricted phosphate availability, complete corneal calcification may develop within approximately 20.4 days due to interactions between phosphate ions and calcium naturally present in tears [10].

Ozalp et al. evaluated phosphate concentrations and osmolarity in commercially available topical medications intended for chronic ocular use in Turkey. The highest phosphate concentrations were observed among anti-glaucoma preparations (20.3 ±35.4 mmol/L), followed by antihistamine drops (17.3 ±17.9 mmol/L), corticosteroids (15.2 ±19.1 mmol/L), artificial tears (0.8 ±1.0 mmol/L), and non-steroidal anti-inflammatory drugs (NSAIDs; 0.04 ±0.08 mmol/L) [11].

A similar study conducted in Spain by de Frutos-Lezaun et al. assessed phosphate concentrations and pH values in commercially available artificial tear formulations. Notably, phosphates were detected in 33.8% of the 71 products tested [12]. In contrast, Bernauer et al. reported that a considerable proportion of artificial tears available on the market contained phosphate concentrations above physiological levels (>1.45 mmol/L). Of the 59 products analyzed, 26 (44%) exhibited elevated phosphate concentrations; among these, nine formulations (15%) exceeded 25 mmol/L, and three products (5%) contained more than 50 mmol/L phosphate [13].

In Spain, 37 phosphate-containing anti-glaucoma preparations have been identified [12]. Similarly, in Germany, 47% of anti-glaucoma medications (10 of 21 preparations analyzed) were found to contain phosphates at concentrations exceeding physiological levels [14].

Importantly, not only phosphate-containing eye drops but also ophthalmic irrigation solutions may be harmful when they contain these compounds. In 1982, Reim et al., based on animal studies and clinical observations, reported that although ocular surface irrigation with phosphate-buffered solutions may be beneficial in the management of ocular burns, it can also promote the formation of insoluble calcium phosphate deposits within the cornea [15].

Animal studies have demonstrated that repeated ocular surface irrigation with phosphate-buffered solutions can result in macroscopically visible corneal calcification within as little as 4 days [16]. Similar findings have also been reported in humans [17].

Taravella et al. analyzed cases of band keratopathy associated with topical corticosteroid phosphate formulations and identified several predisposing factors, including epithelial injury, chronic topical therapy, ocular surface inflammation, penetrating keratoplasty, herpes simplex virus (HSV) infection, and dry eye disease. Based on their findings, the authors recommended discontinuing phosphate-containing topical corticosteroid preparations in patients who develop band keratopathy [18].

In a study by Kompa et al. evaluating the incidence of corneal calcification following chemical burns and the use of phosphate-buffered eye drops, corneal calcification was observed in 31 of 63 eyes (49.2%) treated with phosphate-containing preparations during the follow-up period. In contrast, among 89 eyes treated with phosphate-free drops, calcification developed in only 23 cases (25.8%), while the remaining 66 corneas remained clear [19].

Schrage et al. retrospectively analyzed 176 eyes in 98 patients with severe chemical burns. The authors reported that a single initial ocular irrigation with a phosphate solution was not associated with corneal calcification ($p = 0.134$). However, they found a significant association between the incidence of corneal calcification and chronic use of phos-

phate-buffered eye drops ($p < 0.005$). The authors also proposed a mechanism to explain this phenomenon, suggesting that post-burn corneal calcification may result from exposure to corrosive calcium-containing agents or from prolonged treatment with phosphate-containing drops.

One potential contributor to calcium phosphate precipitation is a deficiency of calcium ion-stabilizing proteins, such as hyaluronate or fetuin. Thermal or chemical injury may denature these proteins, leading to a loss of calcium-binding capacity and an increase in the concentration of free (ionized) calcium. Once the solubility product (Ksp) of calcium (Ca^{2+}) and phosphate ions (PO_4^{3-}) is exceeded, insoluble calcium phosphate salts may precipitate and deposit within the corneal tissue.

In addition, collagen fibers lacking a protective glycosaminoglycan layer may serve as an initial scaffold for crystal formation, in a manner reminiscent of bone tissue mineralization. Consequently, calcium phosphate may deposit on exposed collagen fibrils, ultimately leading to corneal calcification [20].

The EMA reviewed 117 case reports in which phosphate-containing ophthalmic medications – used both as buffered formulations and as phosphate-containing active substances – were associated with corneal calcification. The findings confirmed an association between the use of these preparations and corneal calcification, particularly in patients with a compromised ocular surface. Importantly, phosphate-related adverse effects were reported regardless of treatment duration, frequency of administration, phosphate concentration, drug dose, or the type of buffering system used. The EMA emphasized the need to inform both prescribers and patients – especially those undergoing treatment for corneal epithelial damage – about the risks associated with phosphate-containing ophthalmic preparations [1].

CONLUSION

The available evidence from previous studies and clinical reports indicates that phosphates in ophthalmic drops – despite their technological advantages – may pose a clinically relevant risk to the ocular surface, particularly in patients with corneal epithelial compromise or other factors predisposing to disruption of ocular surface homeostasis. Importantly, corneal calcification and subsequent corneal opacity may be irreversible, resulting in persistent visual impairment and a substantial reduction in patients' quality of life.

In conclusion, there is strong scientific and clinical rationale for limiting the use of phosphate-containing eye drops, especially in at-risk populations. Increased awareness among ophthalmologists as well as non-ophthalmic prescribers is warranted regarding the potential impact of excipients on ocular surface integrity. The selection of topical ophthalmic therapy should therefore be individualized and based on the local clinical condition as well as the complete formulation profile, including excipients, rather than solely on the active ingredient, in order to maximize patient safety.

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