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White Paper

Overcoming Challenges in Ophthalmic Formulations through Polymer Selection – A Closer Look at Polyvinyl Alcohol

Smita Rajput, Hemgir Gosavi

Ophthalmic drug formulations are growing in importance due to the increased prevalence of eye-related disorders such as diabetic retinopathy and macular degeneration.[1] However, ocular drug delivery is challenging due to unique anatomical and physiological barriers such as pre-corneal loss factors including tear turnover, nasolacrimal drainage with potential systemic absorption via the conjunctiva or nasal mucosa, transient residence time, and the relative impermeability of the corneal epithelial membrane.[2] The low ocular bioavailability (<10%) of conventional ophthalmic formulations is driving the need for novel approaches to improve delivery of the desired concentration, at the site of action, at a controlled rate.[3]

The formulation of ophthalmic drugs must address a unique combination of requirements. In addition to ensuring quality, drug tolerability and fostering patient compliance, formulators must also consider tonicity, viscosity, pH, stability, sterility and microbiological purity. Further, pharmacopoeias state that ophthalmic solutions must be essentially free from particles that can be observed on visual inspection.

Polymers are an important part of the formulation toolbox and offer several benefits for ophthalmic dosage forms (Figure 1). They can increase contact time with the target tissue and reduce drainage of the solution, helping to enhance efficacy of the drug. If viscosity is initially too low, polymers can help increase it to sustain release of the active pharmaceutical ingredient (API). They can act as solubilizers, inhibit crystallization, stabilize the formulation, and serve as a lubricant.

This white paper provides an overview of polymers that can be used in ophthalmic formulations and highlights advantages offered using polyvinyl alcohol (PVA) through case studies.

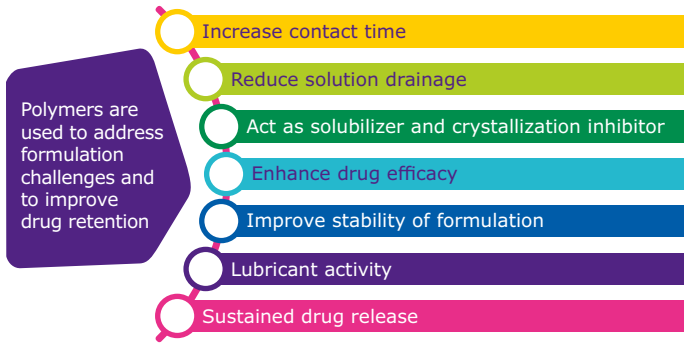

Figure 1.

Overview of how polymers can be used to address the unique formulation challenges presented by ophthalmics.

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Considerations for Polymer Selection

In addition to selecting the right polymer for the formulation, aspects related to preparing the polymer solution, sterilization and interaction with other excipients in the final formulation must be considered.

A variety of polymers can be used in ophthalmic formulations including those of natural, synthetic and semi-synthetic origins. Natural polymers such as gellan, xanthan, and guar gum, and hyaluronic acid are relatively inconsistent in terms of viscosity and have the potential for a higher microbial load as compared to semi-synthetic and synthetic polymers. Control over the microbial load can be challenging and for an ophthalmic formulation, there is a stringent limit to what is allowed. Semi-synthetic polymers have a higher probability of batch-to-batch variation and broader range of viscosity which can impact performance. Examples include hydroxypropyl methylcellulose (HPMC), carboxymethyl cellulose (CMC), and hydroxyethyl cellulose (HEC). The advantages of synthetic polymers include high batch-to-batch consistency and a narrow range of viscosity which helps to deliver a reproducible performance. Examples of synthetic polymers are polyvinyl alcohol (PVA), carbomer and polyvinyl pyrrolidone (PVP).

Following selection of the polymer, the next step is preparation of the solution. Preparation of bulk-quantity polymer solutions for scale-up or commercial manufacturing can be time-consuming. For some polymers, heating is required for dissolution, and this necessitates use of jacketed vessels as well as additional time needed for heat-up of the solvent and cool-down of the polymer solution. If the polymer is not properly dissolved, the final concentration will be impacted. Also, in this process step the polymer choice is very important: if a polymer of insufficient quality and purity is used, insoluble impurities may be encountered in the polymer solution. Removal of these undissolved particles is mandatory to meet the quality expectations for ophthalmic preparations such as the pharmacopeial requirement for particle-free eye drops.

After preparing the polymer solution, it must be sterilized. Selection of the sterilization method, which can include steam or filtration, is critical as it must be compatible with the polymer solution. The method should not have an impact on the critical quality attributes of the polymer such as viscosity or the molecular weight. Preparation of the final formulation can also present challenges. The potential for interaction of the polymers with other excipients throughout the shelf life and any impact on stability must be understood.

PVA: A Versatile Excipient for Ophthalmics

PVA (sometimes referred to as PVOH) is a biocompatible synthetic polymer produced by the polymerization of vinyl acetate and partial hydrolysis of the resulting esterified polymer. PVA has been used in approved drug products for decades and has a long history of use in the food and cosmetic industries. It is generally recognized as safe (GRAS) by the US Food and Drug Administration (FDA),[4] does not have any immunogenic effects, and its long-term use has been demonstrated in many different formulations including oral, topical and ophthalmic.

PVA was first used in ophthalmics in the 1960s to increase solution viscosity and prolong precorneal residence time.[5] Incorporation of PVA in ophthalmic preparations significantly delays precorneal drainage of locally applied formulations, leading to an improved therapeutic effect.

PVA offers many advantages for ophthalmic formulations (Figure 2). It is water soluble, has a narrow range of viscosity, and a high degree of swelling, offering the precise viscosity needed for formulations to remain in the eye cavity. This polymer also forms a transparent solution which is important for medications administered to the eye, as is high adhesion and high correlation properties, which are also important for retention in the eye cavity. With excellent lubricant activity, this polymer is well-suited for lubricating eye drops. Finally, PVA acts an inhibitor of crystallization which means it helps retain solubility of the API throughout storage of the dosage form.

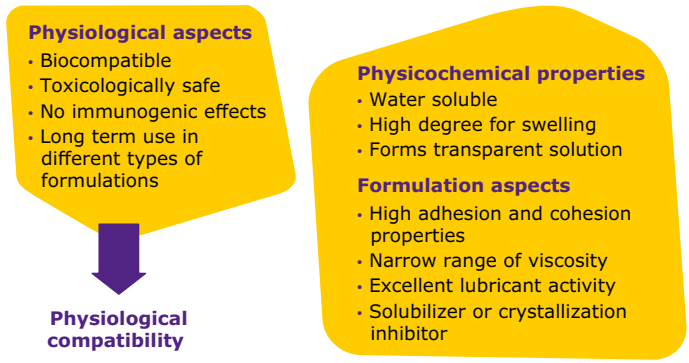

Figure 2.

Characteristics of PVA that make it well-suited for ophthalmic formulations.

PVA Selection

PVAs are available in different grades based on viscosity, hydrolysis and the microbial load (total aerobic bacteria, total yeast and total mold count), which should be specified by the manufacturer. Another important consideration when using PVA is the possible presence of crotonaldehyde, which is a process impurity generated during synthesis. While there is no information in the pharmacopeia regarding the limit of this impurity, given its toxic nature, it is important that this impurity content is known and controlled. Due to stringent regulatory requirements in this segment, a multi-compendial product and regulatory and documentation support by the manufacturer is desirable to facilitate regulatory submission. Again, the selection of the right polymer is critical: with PVA, there are different grades available on the market and the choice will affect the final product performance.

Different grades come with different physicochemical properties, making them suitable for different applications. Lower viscosity grades of PVA can be used for lubricant activity, to enhance API solubility and as inhibitors of crystallization. If the formulation is a suspension or gel, a high viscosity grade PVA is more suitable and can be used as a thickener or viscosity enhancer. Different hydrolysis grades of PVA, which refers to the amount of residual, unhydrolyzed acetate groups within the polymer chain, also affect the polymer performance. Higher hydrolysis grades improve tensile strength of the hydrogel and provide a stronger gel scaffold through H-bonds while lower hydrolysis grades might be a better choice for drug delivery of poorly water-soluble APIs. However, since some pharmacopoeias restrict the hydrolysis grade variation, there is limited flexibility in this aspect.

PVA grade	Average molecular mass [g/mol]*	Liquid				Semi-solid
		Lubricant	Thickener/ viscosity enhancer	Solubilizer/ solubility enhancement	Suspension	Hydrogel forming (gel)
PVA 4-88	32,000	X	X	X		
PVA 5-88	40,000	X	X	X		
PVA 8-88	64,000	X	X			
PVA 18-88	96,000		X		X	
PVA 26-88	135,000		X		X	
PVA 40-88	164,000		X		X	X
PVA 28-99	94,000		X		X	X

* Approximate values, determined using GPC method

Table 1.

PVA suitability for different applications based on the respective viscosity and molecular weight. The PVA grade naming convention (e.g. 4-88) specifies the apparent viscosity in mPa•s of a 4% aqueous solution at 20 °C (first number) and the hydrolysis grade (second number).

PVA Solution Preparation

Table 2 compares the preparation, appearance, and presence of foam and particles in solutions of three different polymers: PVA, HPMC, and CMC. The selected concentrations reflect those commonly used in ophthalmic preparations. While the temperature requirement for solubilization of PVA was relatively high, the solution was clear with no foaming or particles (visually observed). In PVA handling, a higher temperature must be applied for dissolution processes. Having considered this aspect, it is easy to obtain a clear, particle free solution without foam. While HPMC and CMC can be dissolved at room temperature, it may be challenging to obtain particle-free solutions.

Parameters	1.4% PVA solution	1.0% HPMC solution	0.5% CMC solution
Preparation time	20–35 min	30–45 min	25–30 min
Temperature	90–95 °C	Room temperature	Room temperature
Appearance	Clear	Clear	A little hazy
Foaming	No	Yes	No
Particles	No	Yes	Yes

Table 2.

Comparison of solubilization parameters for three polymers.

PVA solutions were subjected to a viscosity analysis at concentrations ranging from 0.5% to 2.0% (Figure 3). This type of analysis aids in the selection of the best PVA for a particular ophthalmic formulation, whether it is a lubricant eye drop, a suspension or gel.

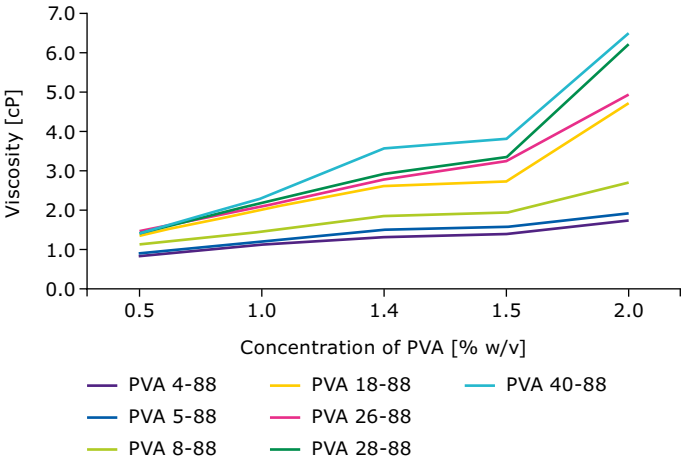

Figure 3.

Viscosity profiles of different grades of PVA.

Figure 4 shows the results of an experiment in which lower viscosity PVAs were combined with a higher viscosity PVA (40-88) to achieve different viscosities.

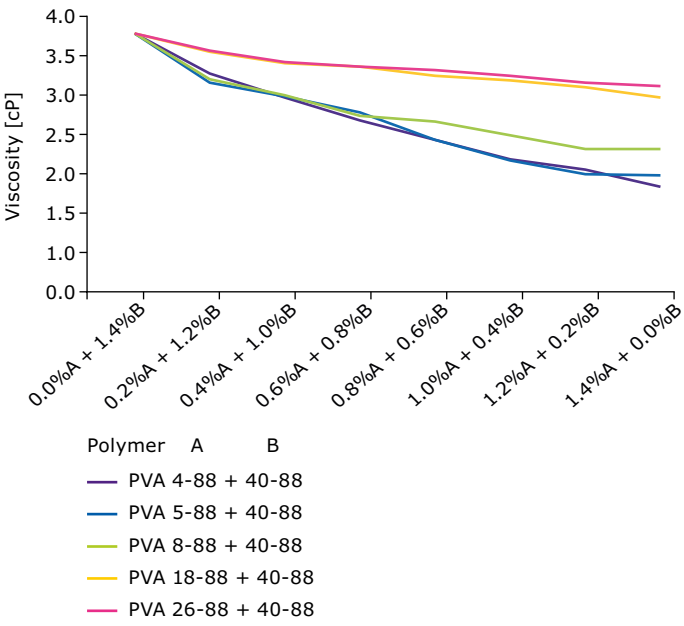

Figure 4.

Use of different PVA grades in combination to achieve a target viscosity.

PVA Solution Sterilization

A critical aspect of polymer handling especially relevant for ophthalmic formulations is sterilization. Different sterilization methods can be used with polymer solutions including steam and filtration and each can affect attributes of the polymer in different ways.

To demonstrate this, solutions of PVA, HPMC, and CMC were subjected to steam sterilization at 121 °C for 15 minutes at 15 psi. The PVA solution remained clear and transparent while the CMC solution took on a cloudy appearance and the HPMC solution turned to a white colloidal nature and then became transparent when cooled to room temperature.

Viscosity of the polymeric solutions was evaluated following sterilization times of 15, 20, and 25 minutes (Figure 5). The viscosity of the PVA and HPMC solutions remained similar across all time periods while the viscosity of CMC decreased significantly after the first 15 minutes of steam sterilization, indicating that some degradation might be occurring.

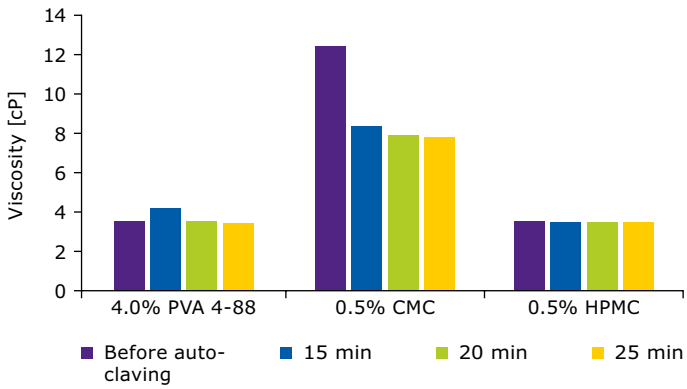

Figure 5.

Viscosity of polymeric solutions before autoclaving and after 15, 20 and 25 min sterilization.

Sterile filtration is another option for sterilization. Successful sterile filtration relies on several factors including filtration surface area, cost of the filter, filtration hold volume and hold time and the exposed area of the filter as this can contribute to extractables and leachables. The goal when selecting the best conditions is to minimize filter surface area which minimizes costs and have a low hold volume and time which reduces the exposure to extractables and the leachables.

Polymer / Filter type	V_{max} [L/m²]	Filter size [inch]	V_{max} [L/m²]	Filter size [inch]	V_{max} [L/m²]	Filter size [inch]	V_{max} [L/m²]	Filter size [inch]
	1.4% PVA 4-88		1.4% PVA 40-88		1.0% HPMC		0.5% CMC	
Millipore Express® SHF 0.2 µm (PES)	**28,361**	**3**	1,989	5	1,037	10	not feasible	
Durapore® 0.22 µm (PVDF)	**10,753**	**2**	539	10	735	10	not feasible	

Table 3.

Filterability comparison of PVA, HPMC and CMC solutions with regard to V_{max} and filter size using PES and PVDF filters.

0.2 µm polyvinylidene fluoride (PVDF) and polyethersulfone (PES) membranes were evaluated for the sterile filtration of a PVA solution in terms of the filter capacity V_{max} and mean flux (Figure 6). Filtration of the PVA 4-88 solution was possible through both the PVDF and PES membranes. Out of these two options, the PES membrane is deemed favorable as it provides better process economics with a higher V_{max} and mean flux.

Table 3 compares the sterile filtration of 100 L of PVA, HPMC and CMC solutions using Millipore Express® SHF (PES) and Durapore® filters (PVDF) with a limit of 30 minutes. Filtration was performed at room temperature using one filter unit at 1.5 bar of pressure.

V_{max} represents the volume which can be filtered before a filter is plugged and as such, the higher the value, the better. The V_{max} was relatively high for the SHF membrane for both the low (4-88) and high (40-88) viscosity PVA grade as compared to the PVDF membrane. The CMC solution could not be filtered using this method due to high viscosity. In the case of HPMC, filtration is feasible, but the filter size required to process this batch is much larger than for the PVA. Results of this study demonstrate that scale up and commercial production are more viable with PVA, without any challenge to sterile filtration, as compared to HPMC or CMC.

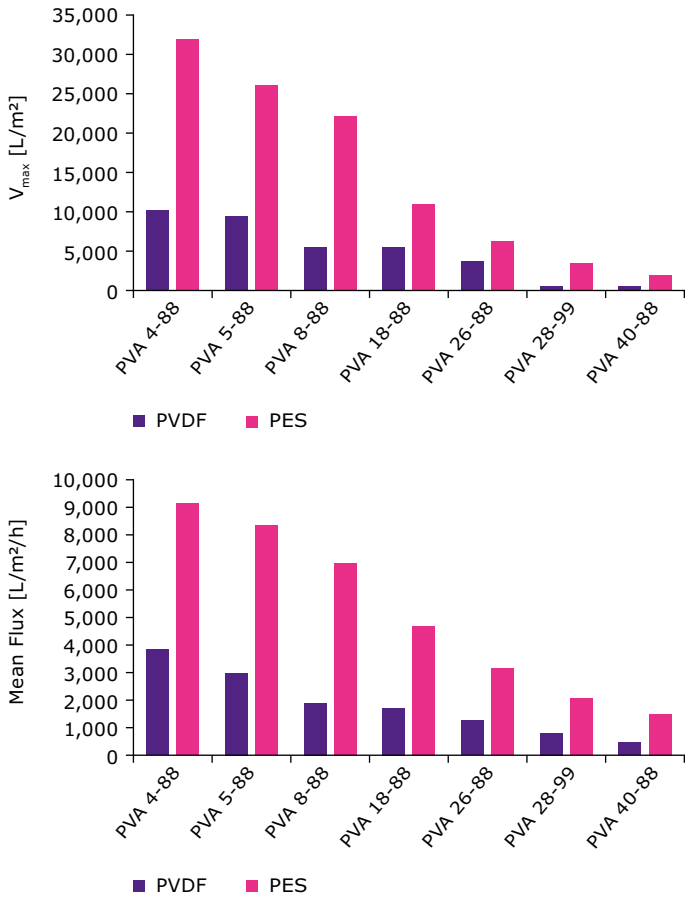

Figure 6.

V_{max} and mean flux of PVDF and PES filters used for sterile filtration of solutions of different PVA grades.

Excipient Compatibility

A final consideration when selecting a polymer is the compatibility with other excipients and the API contained within the final ophthalmic formulation; other excipients may include preservatives, inorganic salts to maintain osmolarity, and buffers.

Figure 7 provides a comparison of how inorganic salts influence the viscosity of PVA, HPMC and CMC polymers. Viscosity of the PVA was not altered, indicating compatibility. In contrast, when the CMC came into contact with the inorganic salts, viscosity was drastically changed.

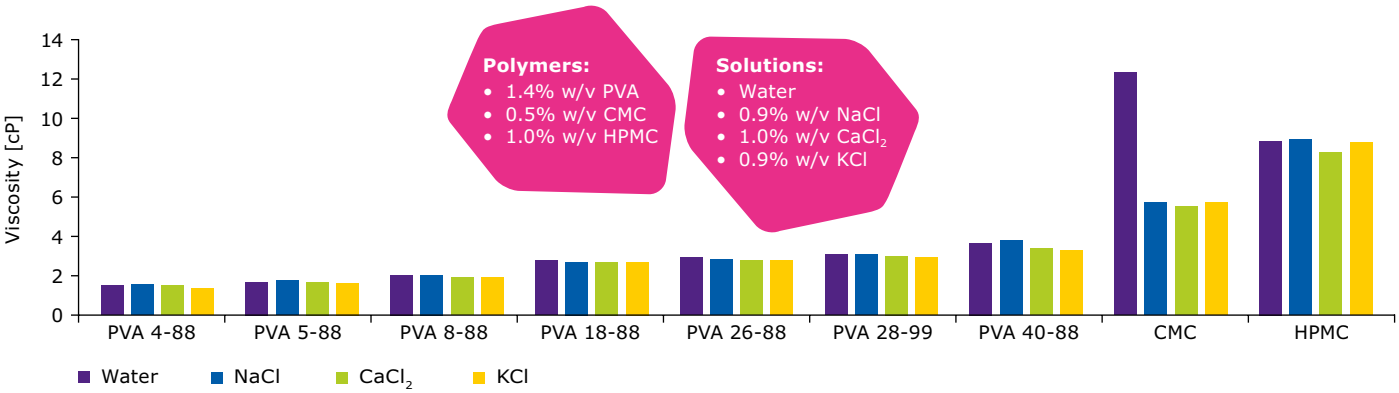

Figure 7.

Compatibility of PVA, HPMC and CMC solutions with commonly used inorganic salts.

The effect of pH on viscosity of the polymer solutions must also be considered. Figure 8 shows the changes in polymer viscosity when the pH was shifted from 5.5 to 8.5, which is the typical range of ophthalmic solutions. There was no change in viscosity of the PVA solution across the pH range.

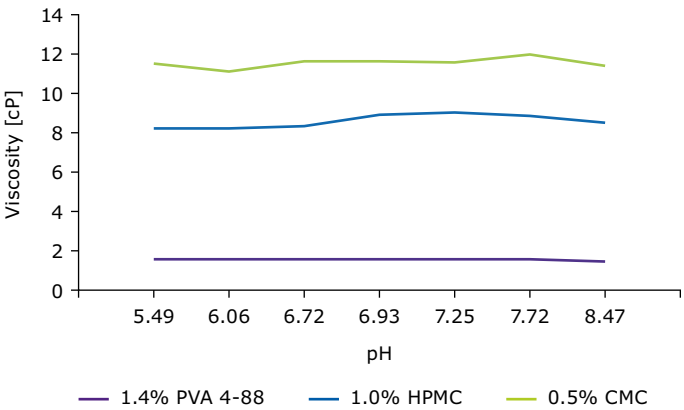

Figure 8.

Effect of pH on solution viscosity: Comparison of PVA, HPMC and CMC solutions.

Marketed formulations of PVA were also reviewed to confirm compatibility with other excipients. The compositions of the investigated formulations suggest compatibility of PVA with citric acid, phosphate, and sodium acetate buffers, the preservatives benzalkonium chloride, EDTA and thimerosal, sodium chloride and potassium chloride, miscellaneous excipients including antioxidants like sodium metabisulfite, sodium thiosulfate pentahydrate, surfactants including polysorbate 80 and finally, polyols such as sorbitol, glycerol and polyethylene glycol.

Examining excipient compatibility with PVA, we observed that the PVA precipitated completely when mixed with boric acid and thus cannot be used in combination in ophthalmic formulations containing boric acid. This is one of the few limitations of the use of PVA in these formulations.

Parameter	PVA	HPMC	CMC
Origin of source	Synthetic	Semi-synthetic	Semi-synthetic
Viscosity range/variation	85–115%	80–120% (low visc) 70–130% (high visc)	>50% variation
Microbial load	Minimal	High	High
Solution preparation	Heating at 90–95 °C	Room temperature but foam formation	Room temperature
Ease of sterile filtration	Yes	Yes	No
Change in CQA after filtration	No	No	Not applicable
Steam sterilization	Yes	Yes	Yes (change in viscosity)
Impact of pH	No	No	No
Impact of ions	No	No	Yes

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Table 4.

Comparison of polymers used in ophthalmic formulations shows the clear advantage of PVA.

The Advantages of PVA

The data presented in this white paper confirm that PVA meets all the essential requirements to be used in ophthalmic preparations and offers important benefits compared to HPMC and CMC (Table 4).

As they are semi-synthetic in nature, HPMC and CMC have a relatively large range in viscosity compared to PVA and can be expected to have a higher microbial load. While PVA requires a higher temperature for solution preparation, foam and particles have been observed in HPMC and CMC solutions.

PVA and HPMC can be sterile filtered while CMC cannot. PVA has a high throughput, and the filter surface area required is relatively low compared to that needed to process an HPMC solution. No changes were observed in the viscosity of PVA and HPMC following sterile filtration; the viscosity of both was also stable following steam sterilization while changes were observed in the viscosity of CMC. Changes in pH did not affect the PVA solution and this polymer was shown to be compatible with a variety of inorganic salts.

Ophthalmic medications play a critical role in the treatment of many diseases and conditions and their use continues to expand. The unique route of administration imposes stringent requirements for the final formulation to ensure a success drug product. While several polymers are available for use in ophthalmic formulations, PVA offers important advantages, is best suited to overcome many formulation challenges, and should be considered as an alternative to HPMC and CMC.

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Lit. No. MS_WP8594EN
01/2022