RESEARCH ARTICLE

The Use of Several Polymers in the Composition of Eye Drops to Improve their Rheological Properties

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ABSTRACT

The physical and chemical properties (viscosity, pH measurement, calculation of osmolarity values) of polymeric solutions were studied. Such solutions are proposed to be included in the composition of eye drops to improve their rheological properties: as a solution of polyethylene glycol 6000 (PEG-6000), polyethylene glycol 4000 (PEG-4000), methylcellulose (MC), carboxymethyl cellulose (Na-CMC), Hydroxybromoyl methylcellulose (HPMC), hydroxyethylcellulose (HEC), collidone-25, dextrin, and microcrystalline cellulose). It was found that all polymers have different biological, physical, and chemical properties at different concentrations. Depending on the requirements for specific eye drops, polymeric solutions such as HPMC D 4000 H 2208 (0.4%) solution (pH 7.02; viscosity 12.74 mm^2/s), HEC 250 HX (0.3%) (pH 7.0; viscosity 14.03 mm^2/s), HEC 250 HX (0.3%) (pH 7.0; viscosity 14.03 mm^2/s) and PEG-6000 PLURACARE (15%) (pH 7.03; viscosity 1488 mm^2/s) can be used as adjuvants to increase and prolong the effect of the efficacy of eye drops, since their pH value is closest to the human eye.

Keywords: Eye drop, pH measurement, Osmolarity, Polymeric solutions, Viscosity.

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INTRODUCTION

It is known that there is an apparent increase in the number of eye diseases, as well as the number of infected people all over the world. In addition to the emergence of new diseases of the organs of vision, and an increase in the average age of the population, which is usually characterized by poor vision. On the other hand, there is continuous development in formulations and techniques for treating eye diseases, as there is still the production of different ophthalmic dosage forms related to those diseases. As it is known, the most common dosage form in the world of ophthalmology is eye drops.[1-5]

Eye drops are doses of a highly sterile aqueous or oily solution, which are also considered to be pure of foreign particles, and contain one or more active substances intended for instillation into the conjunctival sac or the conjunctival eye or into the eyeball—packaged according to the required workmanship method.[3,6,7] In addition, as it is known, modern eye drops possess a number of disadvantages: represented by inconvenience in use, low bioavailability, and washing the drug from the eye during instillation (without long-term effect).[8,9]

Allergic eye diseases are one of the most common eye diseases, which is an inflammation of the eye's mucous membrane caused by contact with allergens. Damage to the conjunctiva ranges from slight redness and itching during the flowering season to severe clinical manifestations of atopy to progressive vision loss with atopic keratoconjunctivitis.[10] In addition, allergic eye diseases can occur in association with or isolated from other forms of atopy.[11-13]

The most common clinical forms of allergic conjunctivitis are the following, which have their characteristics that must be considered when choosing a treatment: pollen conjunctivitis, vernal keratoconjunctivitis, drug allergy, chronic allergic conjunctivitis, allergic conjunctivitis when wearing contact lenses, conjunctivitis The great papillary.[14,15]

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Accordingly, the process of developing the formulation and technology of eye drops to treat allergic conjunctivitis is promising and important, through the production of long-acting and more effective drops, and this may be done by introducing new generations of antihistamines in eye solutions, Which will have a lower frequency of side effects and a long time of presence on the surface of the eye tissue.

Therefore, our work aimed to study some of the physical and chemical properties of some polymer solutions that can be added to eye drops in the context of developing new long-acting eye drops for the treatment of various eye diseases.

MATERIALS AND METHODS

The first step of the research was to test the polymer solutions separately by knowing the speed and density of bacterial and fungal growth on the polymeric solution added to the agar in Petri dishes. In the chemo-physical tests, solutions on which the growth of microbes was observed in a density were excluded.

Prepare HEC Solutions: The Hydroxyethylcellulosum solution was prepared by weighing an exact sample of the substance 0.1; 0.2; 0.3; 0.4, and 0.5 according to the solution concentration, then measuring 50 mL of water for injection into a heat-resistant beaker. The water beaker was heated on the heating platform of the magnetic stirrer. Heating is stopped when the water temperature reaches 90°C, and the stirrer is on. The necessarily weighted fraction of HEC was then gradually introduced into the water beaker. The beaker of water with polymer was placed on the magnetic stirrer and stirred for an additional 15 minutes. The solution was then transferred to a volumetric flask, the bottom of the flask was rinsed with water for injection to avoid loss of HEC concentration, and then the volume of solution was raised to 100 mL with water. The solution is considered ready if there are no gel particles in the solution.

Prepare HPMC Solutions: A hydroxypropyl methyl ether cellulose solution was prepared by weighing an exact sample of the substance in a ratio of 0.1, 0.2, 0.3, 0.4, and 0.5 according to the concentration of the solution, then measuring 50 mL of water for injection into a heat-resistant beaker. The water of the injection flask was placed on the heating pad of the heated magnetic stirrer and heated to 90°C, after which the stirring was run, then the necessarily weighted fraction of HPMC was gradually introduced into the flask. Stirring was then performed for 40 minutes, after which the polymer solution was closed, transferred to a refrigerator (8 ± 2 °C), and left for 40 minutes. The polymer solution was placed on the magnetic stirrer and stirred for 15 minutes. The solution was then transferred to a volumetric flask, the bottom of the flask was rinsed with water for injection to avoid loss of HPMC concentration, and the volume of solution was raised to 100 mL with water. The solution is then considered ready.

Preparation of Na-CMC Solution: A solution (the sodium salt of carboxymethyl cellulose) was prepared by weighing an exact amount of substances 1, 2, 3, 4, and 5 according to the concentration of the solution and measuring 50 ml of water for injection in a beaker heat. The injection flask water was heated on the heating platform of the magnetic stirrer. The heating was stopped and the stirring was turned on at 90°C. Then the required weighted portion of Na-CMC is gradually introduced into another flask in small portions. Then the beaker with polymer was placed on the magnetic stirrer and stirred for an additional 10 minutes. Then the solution was transferred to a volumetric flask, the bottom of the flask was rinsed with water to avoid Na-CMC loss, and then the volume of the solution was raised to 100 mL with water. The solution is then ready.

Prepare PEG-6000 Solutions: A solution of polyethylene glycol was prepared by weighing an exact fraction of the substance 10, 11, 12, 13, 14, and 15% according to the concentration of the solution, then measuring 50 mL of water. The water of the injection flask was heated on the heating platform of the magnetic stirrer. Heating was stopped when the water reached 90°C and stirring was turned on, then the weighted fraction of PEG was gradually introduced into a beaker. Then the beaker with polymer was placed back on the magnetic stirrer and stirred for an additional 10 minutes. The solution was then transferred to a volumetric flask, the bottom of the flask was rinsed with water to avoid loss of PEG-6000 concentration, and the volume of solution was then increased to 100 mL with water. Then the solution is ready.

Preparation of MC Solution: Prepare a solution of cellulose methyl ether by weighing an exact sample of 0.1 substance; 0.2; 0.3; 0.4, and 0.5 according to the concentration of the solution, then measure 50 ml of water for injection into a heat-resistant beaker. Then the water is heated on the heating platform of the magnetic motor. The heating is stopped, and the stirring is turned on when the water temperature reaches 90 degrees Celsius. Then the weighted portion of the MC corresponding to the concentration of the solution is gradually introduced into another beaker. Then the beaker with polymer was placed on the magnetic stirrer and stirred for an additional 15 minutes. The solution was transferred to a volumetric flask. The bottom of the flask was rinsed with water for injection to avoid loss of MC concentration. The volume of solution was then increased to 100 mL with water. The solution is ready if it is free of gel particles.

The chemo-physical properties of the following substances were studied: hydroxyl-ethyl cellulose (HEC) 250 HX, hydroxyl-propyl methylcellulose (HPMC) D 4000 H 2208 and polyethylene glycol 6000 (PEG-6000) PLURACARE, Methyl-cellulose (MC) Meilose GMC-5220, Sodium carboxy-methyl-cellulose (Na-CMC) A500.[16]

To study the chemo-physical properties, solutions of HEC, HPMC, PEG-6000, MC, Na-CMC polymers were prepared in the following concentrations: HEC 0.1-0.5 %; HPMC: 0.1-0.5 %; PEG-6000: 10-15 %; MC: 0.1-0.5 %; Na-CMC: 1-5 %.[17,18]

Viscosity Measurement of Polymer Solutions

At the first stage of studying the physicochemical properties after preparing the polymeric solutions, the dynamic viscosity of these solutions was measured by using a set of viscometers of the VPZh brand at an ambient temperature of 25°C.[19]

PH measurement of Polymer Solutions

Further, a study of the pH of the polymer solutions was carried out. The hydrogen index was determined in accordance with the requirements of the General Pharmacopoeia Monograph.1.2.1.0004.15 "Ionometry". We used an ATON-101MP microprocessor pH meter at an ambient temperature of 25°C.

The device was calibrated in accordance with the operating instructions for two standard buffer solutions given in the general pharmacopoeial monograph "Buffer solutions". In each case, three measurements of the pH value were carried out.

Calculating the Values of Osmolarity of Polymer Solutions

At the next stage of the study, the values of osmolarity of solutions of the proposed compositions were calculated according to the following formula.

$$C_{OCM} = \sum \frac{m_i \times n_i \times 100}{Mi}$$

C_{ocm}= osmolarity of the solution, mOsm/l;

m_i= the substance contained in the solution, g/l;

n_i = the total number of ions formed from one molecule of a solute as a result of dissociation;

M_i= the molar mass of the substance, g/mol.

RESULT AND DISCUSSION

Some polymeric solutions were excluded in the chemical tests, which included the following solutions (polyethylene glycol 4000 (PEG-4000), Kollidon-25, Dextrin, and Microcrystalline Cellulose (MCC), due to the dense growth of microbes on the surfaces of the agar dishes to which these solutions were added. Which in turn, it will lead to the growth of microbes on the surface of human eye tissues when used with eye drops (Fexofenadine hydrochloride).[20]

Measurement of Viscosity and pH Values.

By studying some of the physical and chemical properties of polymer solutions that can be added to eye drops in order to obtain more and longer effective drops, the results of the viscosity measurement showed that the polymer solutions had great variation or difference in the viscosity values as shown in Table 1, where the range of Those values range from 1.11 for the solution (Na-CMC) A500 at the concentration (1 %) up to the highest viscosity value of 31.13 for the solution (HEC) 250 HX at the concentration (0,5 %) (Table 1).

As for the pH of all-polymer solutions, the results did not show that significant difference in the pH factor, as happened when measuring the viscosity, where the lowest pH factor of the (PEG) 6000 PLURACARE solutions at the concentration (14 %), which was 6.84, while the highest measurement was pH of the solution (HEC) 250 HX at the concentration (0.4 %), which reached 7.23, and as shown in Table 1. All pH measurements were close, and they fall within the acceptable range for the human eye, which ranges between 6.6-7.8 (Table 1).[21]

In this regard, the choice of optimal prolongation was carried out in terms of viscosity, based on the requirements of the General Pharmacopoeia Monograph.1.4.1.0003.15 "Ophthalmic dosage forms." Additionally, it was found that changes in the concentration of the hydrophilic polymer did not reveal any regularity in the change in the pH of the solution.

According to the recommendations of the State Pharmacopoeia of the Russian Federation XIV edition (OFS.1.4.1.0003.15 Ophthalmic dosage forms), the viscosity of ophthalmic solutions should be in the range of 5-15 mm^2/s. Samples numbered 3, 9, and 16 are close to the recommended values, the viscosity of which is 14.03 mm^2/s. (HEC 0.3 %), 12.74 mm^2/s. (HPMC 0.4 %) and 14.88 mm^2/s (PEG-6000 15 %), respectively. For the rest of the samples of these polymers, the recommended viscosity index is exceeded.[22]

However, Na-CMC was excluded from the polymer solutions from further participation in developing an ophthalmic dosage form since a relatively large amount of substance is required to achieve optimal values of the viscosity index. This, firstly, may be potentially disadvantageous in terms of minimizing costs in the production of eye drops and, secondly, does not satisfy one of the key principles of

Table 1: Results of the physicochemical properties of solutions (viscosity, pH)

No	*Name and concentration of polymer solution*	*Viscosity, mm^2/s*	*pH*
1	HEC 250 HX (0,1 %)	2,28	7,11
2	HEC 250 HX (0,2 %)	5,69	7,19
3	HEC 250 HX (0,3 %)	14,03	7,00
4	HEC 250 HX (0,4 %)	26,50	7,23
5	HEC 250 HX (0,5 %)	31,13	7,10
6	HPMC D 4000 H 2208 (0,1 %)	2,15	6,90
7	HPMC D 4000 H 2208 (0,2 %)	4,08	6,98
8	HPMC D 4000 H 2208 (0,3 %)	7,02	7,14
9	HPMC D 4000 H 2208 (0,4 %)	12,74	7,02
10	HPMC D 4000 H 2208 (0,5 %)	22,35	6,99
11	PEG -6000 PLURACARE (10 %)	1,90	7,08
12	PEG -6000 PLURACARE (11 %)	3,23	7,12
13	PEG -6000 PLURACARE (12 %)	5,11	6,95
14	PEG -6000 PLURACARE (13 %)	7,34	7,11
15	PEG -6000 PLURACARE (14 %)	10,15	6,84
16	PEG -6000 PLURACARE (15 %)	14,88	7,03
17	MC Meilose GMC-5220 (0,1 %)	4,23	7,17
18	MC Meilose GMC-5220 (0,2 %)	6,50	7,00
19	MC Meilose GMC-5220 (0,3 %)	9,11	7,21
20	MC Meilose GMC-5220 (0,4 %)	17,32	7,10
21	MC Meilose GMC-5220 (0,5 %)	24,01	7,06
22	Na-CMC A500 (1 %)	1,11	7,07
23	Na-CMC A500 (2 %)	3,20	6,99
24	Na-CMC A500 (3 %)	5,09	6,90
25	Na-CMC A500 (4 %)	7,14	7,15
26	Na-CMC A500 (5 %)	9,33	7,02

Table 2: Calculation of the osmolarity of the individual components of the model solutions

No.	*Component*	$C_{осм} \times 1000$, *mOsm/L*
1	Fexofenadine hydrochloride	3,99
2	Twin-20	10,81
3	HPMC D 4000 H 2208 (0,4%)	0,047
4	HEC 250 HX (0,3%)	0,038
5	PEG -6000 PLURACARE (15%)	0,051

pharmaceutical development, the essence of which is to strive for a minimum content of excipients in the dosage form.

In turn, MC was also excluded from further studies since the optimal value of the viscosity at the concentrations at which satisfactory viscous solutions of other polymers were obtained was not achieved.

Thus, the following polymers, HEC 250 HX 0.3%, HPMC D 4000 H 2208 0.4%, and PEG-6000 PLURACARE 15%, were selected as hydrophilic bases for the further development of the eye drops for the treatment of allergic conjunctivitis.

Results of Osmolarity of Polymer Solutions

The osmolarity values of Fexofenadine hydrochloride, Twin-20, and the selected polymer solutions with appropriate pH and viscosity factor (HEC 250 HX 0.3%, HPMC D 4000 H 2208 0.4%, and PEG-6000 PLURACARE 15%) were calculated according to the mathematical formula shown in the working methods.

The results of the theoretical calculation of the osmolarity of the components included in the study and the proposed solutions are presented in Table 2.

According to the recommendations of the State Pharmacopoeia of the Russian Federation XIV edition (OFS.1.4.1.0003.15 Ophthalmic dosage forms), the osmolarity of eye drops should be within 0.6–2.0% sodium chloride solution. In addition, in accordance with the General Pharmacopoeia Monograph.1.2.1.0003.15 Osmolarity solutions are considered isotonic if their osmolarity is 239–376 mOsm/L. In this regard, at the next stage of the study, the values of the osmolarity of the solutions of the proposed compositions were calculated according to formula 3.[23]

The osmolarity results of the three polymeric solutions selected in terms of the appropriate pH and viscosity factor showed that the osmolarity values of these solutions are somewhat close to the acceptable osmotic ratio.

CONCLUSION

The polymer solutions added to the agar, on which the microbes grew rapidly and intensively in Petri dishes, could not be used with eye drops because they help microbial growth on the eye tissues, so these solutions were excluded.

Based on the results of the study of the physicochemical properties of polymers intended for introduction into the composition of Alfex eye drops in order to ensure their prolonged effect, the choice of HPMC D 4000 H 2208 (0,4%) solution (pH 7.02; viscosity 12.74 mm2/s), HEC 250 HX (0,3%) (pH 7.0; viscosity 14.03 mm2/s) and PEG -6000 PLURACARE (15%) (pH 7.03; viscosity 14,88 mm2/s). In addition, these solutions have acceptable osmolality values close to those suitable for the human eye.

Therefore, these solutions, or one of them, can be added to the composition of the eye drops and some protective materials against microbes. In the end, a better model of eye drops can be obtained in terms of the effectiveness and longevity of the effect.

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