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Sodium-Carboxymethylcellulose/Polyphenol-Gossypol-Carboxymethylcellulose Copolymer Films for Ocular Drug Delivery: Preparation and Physico-Chemical Properties

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In present work, the formation of nanostructured antiviral biosoluble ophthalmic drug films composed of sodium carboxymethylcellulose/polyphenol-gossypol-carboxymethylcellulose copolymer is described. The biorelease time and physico-chemical parameters of the ophthalmic drug films were regulated by changes in the degree of substitution and polymerization of sodium carboxymethylcellulose and the pH value of its aqueous solutions. The morphology and size of the antiviral agent embedded in sodium carboxymethylcellulose films were determined by using atomic force microscopy and dynamic light scattering. The UV spectroscopy was used to observe drug release from the polymeric matrix and it was determined that the maximum drug release occurred after 24 h. By regulating the concentration of polyphenol-gossypol-carboxymethylcellulose copolymer antiviral substance in the polymer, the spherical nanoparticles with sizes of 5-24 nm and cubic nanoparticles with sizes of 46-95 nm were formed.

Keywords: Drug delivery, Antiviral eye films, Sodium carboxymethylcellulose, Polymer drug mixture film, Release kinetics.

INTRODUCTION

In ophthalmology, drugs are delivered to the eye tissue in various ways for preventing and treating diseases with different aetiologies [1,2]. Most ophthalmologists follow the traditional method of instilling drugs for treating the eye diseases [3]. However, this method has several disadvantages; for example, approximately 80% of drug is lost with tear fluid and because of rapid absorption by the mucous membrane of the eye. To make up for the wasted drug and to ensure efficacy of the treatment, the frequency of instillation has to be increased to ensure a therapeutic concentration in the eye tissues [4,5].

Ophthalmic drugs can be more effective when their therapeutic concentrations are maintained in the eye tissue for long durations [6,7]. However, when the drug is administered as eye drops, its action is not long-lasting; as a result, the required therapeutic concentration of the drug is not obtained in the anterior chamber of eye to effectively inhibit the growth and development of viruses. Thus, liquid drug instillation does not facilitate the effective prevention and treatment of infections in ophthalmic treatment [8,9].

Several studies have investigated the pharmacodynamics of drugs and the principles of antiviral therapy, showing that the choice of a drug and it's optimal dosage form are equally crucial for effective prevention and treatment and for ensuring the long-term maintenance of the therapeutic concentration of drug [10,11]. In contemporary to the ophthalmic practice, the polymeric forms of biosoluble antiviral ophthalmic drug films (ODFs) with prolonged effects are used, which allow for less frequent instilling of the active substance while maintaining its therapeutic concentration [12]. Using these films, lower dosage of the drug is required and the negative effects of frequent instillation of eye drops can be avoided. Previously, the changes in the therapeutic concentrations of eyedrop drugs with low molecular weights and in different polymeric forms of ODFs were also investigated [13,14].

As shown in Fig. 1, the therapeutic concentrations of eye drops remain limited to the upper and lower critical concentrations for treatments of any form, including ophthalmologic use. When a drug is delivered into the eye, it's therapeutic concentration corresponds to the upper limit-1 (Fig. 1a), which results in the enhanced toxicity and therefore adversely affects both healthy and unhealthy ocular tissue. If the therapeutic concentration of the medicine falls below the minimum limit, the therapy impact on the sick organ diminishes until it is lost entirely.

In comparison to using low molecular weight ophthalmic eyedrops, using ODFs in their polymeric form over an extended period of time can dramatically reduce the frequency of medication. This reduced medication frequency is directly proportional to the length of time as ODFs retained in the eye tissue [15]. Thus, the prolonged use of the polymeric form of the drug, areas with high upper and lower critical concentrations become significantly smaller than when a low molecular weight analogue of the drug is used. As a result of the slow, gradual dissolution of the film in the tear fluid, ODFs allow the administration of accurate and controlled drug dosages and ensure longer active durations [16]. Additionally, it reduces the number of drug injections, increases the therapeutic concentration of curative substances in the eye tissue, reduces the time for overall treatment by 2-3 times and facilitates the treatment where the use of other drug forms is difficult or impossible, particularly in the conjunctival sac.

Recent studies [17,18] have focused on improving the topical ocular delivery of antiviral agents using advanced drug delivery polymeric systems. Sodium carboxymethyl cellulose (Na-CMC) is a water soluble film of biodegradable polymer and widely used for preparing oral pharmaceuticals, particularly for increasing the viscosities of ointments and for producing hydrogel based pastes and as drug carriers [19,20]. It is one of the key components for developing adhesive absorption systems for treating eye infections and for regulating the kinetics of the release of active substances in systems that come in contact with the eye tissue.

Compounds based on carboxymethylcellulose copolymer and gossypol salt with antiviral activity for the treatment of herpes infection have been extensively researched [21]. Low molecular weight of polyphenol-gossypol stimulates the synthesis of interferon drug, which possesses high antiviral activity. However, due to it's high toxicity and water solubility through pores, polyphenol-gossypol has limited utility in the ophthalmology. The aim of this research is to study the physicochemical properties of ODFs based on Na-CMC containing the nanostructured antiviral agent of polyphenol-gossypol-carboxymethylcellulose copolymer (PGC-CMC).

EXPERIMENTAL

Purified samples of sodium carboxymethylcellulose (Na-CMC) with various degrees of substitution of (0.70-0.85) and a degree of polymerization of (420-810) were experimentally obtained from cotton cellulose [22] and used as polymer matrices [23]. The PGC-CMC was purchased from Radiks Ltd., Uzbekistan whereas glycerol ($C_3H_8O_3$) with 99.5% purity was purchased from Aslkimyo Ltd., Uzbekistan. Other chemicals were of analytical grade and used without further purification.

Preparation of polymeric forms of biosoluble nanostructured ophthalmic drug films (ODFs): Nanostructured antiviral biosoluble ODFs based on Na-CMC and PGC-CMC were prepared by solvent casting method [24,25]. To obtain the polymeric forms of the biosoluble nanostructured ODFs, a water soluble Na-CMC with a degree of substitution (DS) = 0.70-0.85 and a degree of polymerization (DP) = 420-810 was used.

The Na-CMC solution was prepared by first dissolving 2.0 g Na-CMC in 98 mL deionized water. The Na-CMC solution (Na-CMC 2%, pH 7.1) was stirred magnetically for 50 min at 30 ºC until thoroughly dissolved. Antiviral PGC-CMC solutions (0.4%) were prepared by dissolving 0.4 g of polymer powder in 99.6 mL deionized water for 20 min at 25 ºC under continuous stirring. The film-forming solutions were obtained by mixing Na-CMC and PGC-CMC solutions at different volume

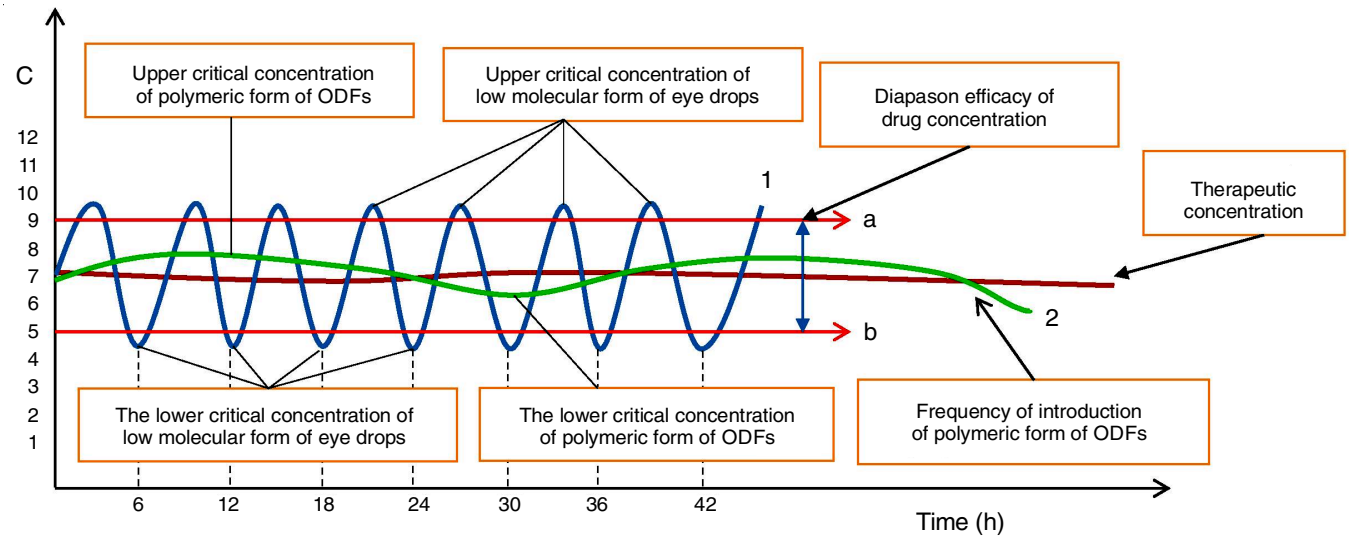

Fig. 1. Changes in the therapeutic concentrations of eye drops with low molecular weight (1) and the polymeric forms of ODFs (2) an over time

ratios, where part of Na-CMC was gradually replaced with PGC-CMC by up to 80%. The formulations were named according to the Na-CMC/PGC-CMC volume ratios of (100:0), (90:10), (80:20), (70:30) and (0:100). Then, calculated amount of 0.1 wt.% glycerol, acted as plasticizer, was added under stirring. The pH values of the combined solutions were in the range of 7.4-7.6. The film-forming solutions were sonicated for 1 h until a fully homogeneous mixtures formed. Then, 20 mL of each solution was poured into a 90 mm diameter Petri dish and dried at 25 ºC for 48 h.

Characterization: The FTIR spectra of the prepared ophthalmic drug films (ODFs) were recorded with an INVENTIO-S FTIR spectrometer (Bruker, Germany) using an attenuated total reflectance (ATR) accessory equipped with a diamond crystal. The morphologies of ODF surface layers were analyzed using an AFM-5500 atomic force microscope (Agilent 5500 AFM, Austria). The sizes and shapes of the PGC-CMC in the ODF films were examined by using DLS with a ZETASIZER Nano ZS (Russia). The average size of PGC-CMC, replaced on the film surface, was determined by processing the corresponding micrographs with Mathcad software.

Drug release study: The residence time of the administered drug in the body is one of the crucial factors in drug delivery systems. Systems for delivering drugs are frequently utilized to extend drug retention. In this work, *in vitro* drug release assays were carried out by placing rectangular ODFs (2 cm × 2 cm) in glass vials containing 20 mL of phosphate buffer solution (pH = 7.4) at 25 ºC and shaking the vials until the maximum amount of medication was released. The absorbance at a fixed wavelength (356 nm) was measured using a UV-VIS spectrophotometer (Specord 210) at predetermined intervals in accordance with a calibration curve for the PGC-CMC reference solution. The cumulative release of PGC-CMC was calculated using the following equation [26,27]:

$$\text{Cumulative release} = \frac{M_t}{M_\infty} \times 100$$

where M_t is the amount of PGC-CMC substance released at time t and M_∞ is the amount of PGC-CMC released at an infinite time (namely, at equilibrium). Release studies were performed in triplicate and the average values are reported as the final result.

The UV spectrum of 1% aqueous PGC-CMC solution exhibited the absorption at 356 nm. The optical density of the as-obtained solution was determined at the indicated wavelength. Then, the concentration of PGC-CMC released from the ODFs into the phosphate buffer solution was determined using a calibration plot. The concentration of PGC-CMC was measured at regular intervals in 100 mL ODF solutions at 37 ºC. The measurements were continued until the optical density of the solution ceased to change.

Percent swelling: After the determination of weight and diameter of original film, the samples were allowed to swell on the surface of a physiological solution plate kept in an incubator at 37 ± 0.2 ºC. An increase in the weight of each film (n = 3) was determined at preset time intervals (1-2 h). The percent swelling, %S, was calculated using the following equation:

$$\text{Swelling (\%)} = \frac{X_t - X_o}{X_o} \times 100$$

where X_t is the weight of the swollen film after time t, and X_o is the initial film weight at time zero.

RESULTS AND DISCUSSION

The prepared biosoluble antiviral ophthalmic drug films (ODFs) were transparent, elastic and oval-shaped with smooth surfaces, smooth edges and light-yellow in colour. The PGC-CMC antiviral polymeric material does not form films with the desired physico-chemical and physico-mechanical properties, since the obtained films were fragile and not suitable for ophthalmic purposes. The ODFs that were made quickly broke down in the eyeball membrane and taken out without assuring that the needed therapeutic concentration of the drug was retained for a sufficient period of time. By adjusting the ratio of the carboxymethyl and carboxymethylate-anionic functional groups in the Na-CMC macromolecules, films were obtained with different periods of swelling and complete dissolution, as shown in Table-1.

As shown in Table-1, the pH of initial Na-CMC solution is a crucial parameter for regulating the degree of swelling and the time for dissolution. By changing the pH of 2 wt.% Na-CMC solution, the ratio of carboxymethyl (p) and carboxymethylate (m) to ionic functional groups (Fig. 2) in Na-CMC macromolecule was changed. When the pH of 2 wt.% Na-CMC solution was decreased from 9.2 to 3.2, the ratio of the carboxyl and carboxymethylate groups changed from 0:100 to 94:6 (%). Simulaneously, when the pH of 2 wt.% solution of Na-CMC decreased, the tensile strength of the films increased from 33.4

TABLE-1
SWELLING AND COMPLETE DISSOLUTION OF Na-CMC FILMS WITH DIFFERENT RATIOS OF CARBOXYMETHYL AND CARBOXYMETHYLATE-ANIONIC GROUPS (DP-630, DS-0.83, CONCENTRATION OF Na-CMC SOLUTION AND CONCENTRATION OF GLYCEROL WERE 2 wt.% AND 0.1 wt.%, RESPECTIVELY). THE FILMS WERE PRODUCED ON GLASS SUBSTRATES AT 37 °C

pH values of 2 wt.% solutions of Na-CMC	Ratio of carboxymethyl and anionic carboxymethylate groups (%)	Film thickness (μ)	Tensile strength (Mpa)	Relative elongation at break (%)	Degree of swelling of the films in physiological solution during 60 min (%)	Term of complete dissolution of the films (min)
9.2	0:100	45	33.4	8.5	205.0	380
8.1	11:89	40	34.3	8.2	185.0	420
7.4	38:62	43	34.3	8.0	175.0	450
6.0	60:40	45	35.3	7.8	170.0	520
4.5	78:22	43	36.3	6.1	142.0	The gel doesn't dissolve
3.2	94:6	45	37.3	4.3	110.0	

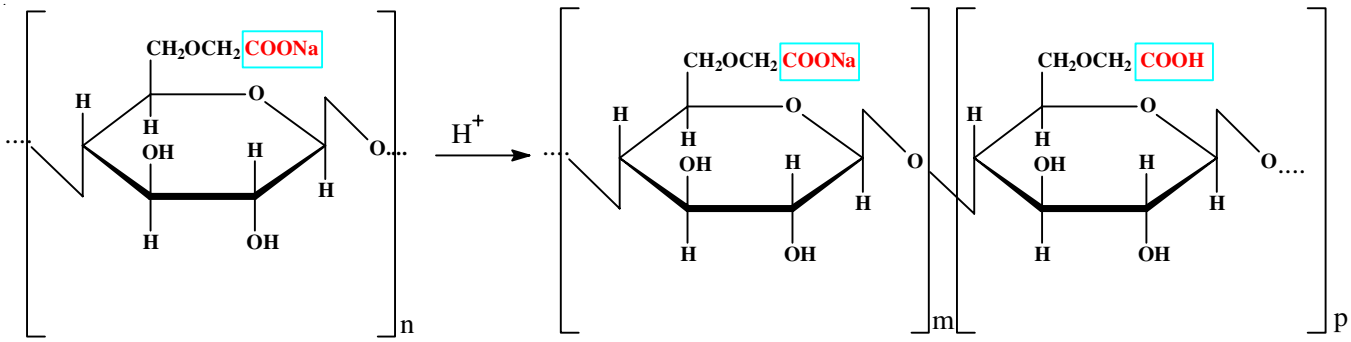

Fig. 2. Structure of Na-CMC containing carboxymethyl (p) and carboxymethylate anionic (m) functional groups

MPa to 37.3 MPa. This improvement in tensile strength can be attributed to the formation of intermolecular ester bonds during the interaction between carboxymethyl and the free hydroxyl groups of the glucose linkages.

With increase in the number of the carboxymethyl groups (p) in Na-CMC macromolecules to up to 60% of the content, the samples became more soluble in water. However, the molecules became insoluble in water when the content of carboxymethyl groups was >60%; because the formation of intermolecular ester bonds during the interaction between carboxymethyl and the free hydroxyl groups of the glucose linkages took place, according to eqn 1:

$$R_1—O—CH_2—COOH + R_2—OH \longrightarrow R_1—O—CH_2—CO—R_2 + H_2O \quad (1)$$

where R_1 and R_2 is a glucose unit of carboxymethylcellulose and a hydroxyl group of a glucose unit, respectively. This reaction was accompanied by the formation of ester bonds which are stable in aqueous media.

For Na-CMC, the degree of swelling and solubility are directly dependent on the ratio and distribution of the carboxymethyl and carboxymethylate-anionic functional groups in the macromolecules and the DP of Na-CMC. Fig. 3 shows that the process of crosslinking of Na-CMC depends on the ratio of hydroxymethyl and carboxymethylate groups in Na-CMC.

Controlling the degree of swelling, solubility, and physicomechanical characteristics of the film-forming matrix during the formation of ODFs. This allowed for regulated drug release from the Na-CMC polymer matrix.

Spectal analysis: The FTIR spectral analysis was perfo-rmed to confirm the changes in the chemical compositions of the Na-CMC macromolecules. The films were formed as the pH of the solutions increased (Fig. 4). In the FTIR spectra of the Na-CMC films, the absorption bands were observed at 1740 cm^{-1} and 1600 cm^{-1}, which confirmed the formation of carbonyl groups in the carboxymethylate-anionic complexes (Fig. 4, curve a), and the appearance of carboxymethyl and carboxymethylate anionic groups (Fig. 4, curve b) and carboxylmethyl links (Fig. 4, curve c). These absorption peaks were observed in the FTIR spectra of films produced from Na-CMC solutions at pH of 8.6 and 4.2. The spectra of films with different concentrations produced in solutions at different pH values (7.4-7.6) exhibited the absorption peaks at 1610 and 1710 cm^{-1}, which confirmed the presence of both carboxymethyl and carboxymethylate anionic groups [28].

In addition, the release of the PGC-CMC antiviral agent from the polymer matrix and its transition kinetics into the solution were also investigated. Fig. 5 illustrates the rapid transformation of the material into a solution, which occurs in ~1 h [29]. The obtained ophthalmic drug films (ODFs) from Na-CMC:

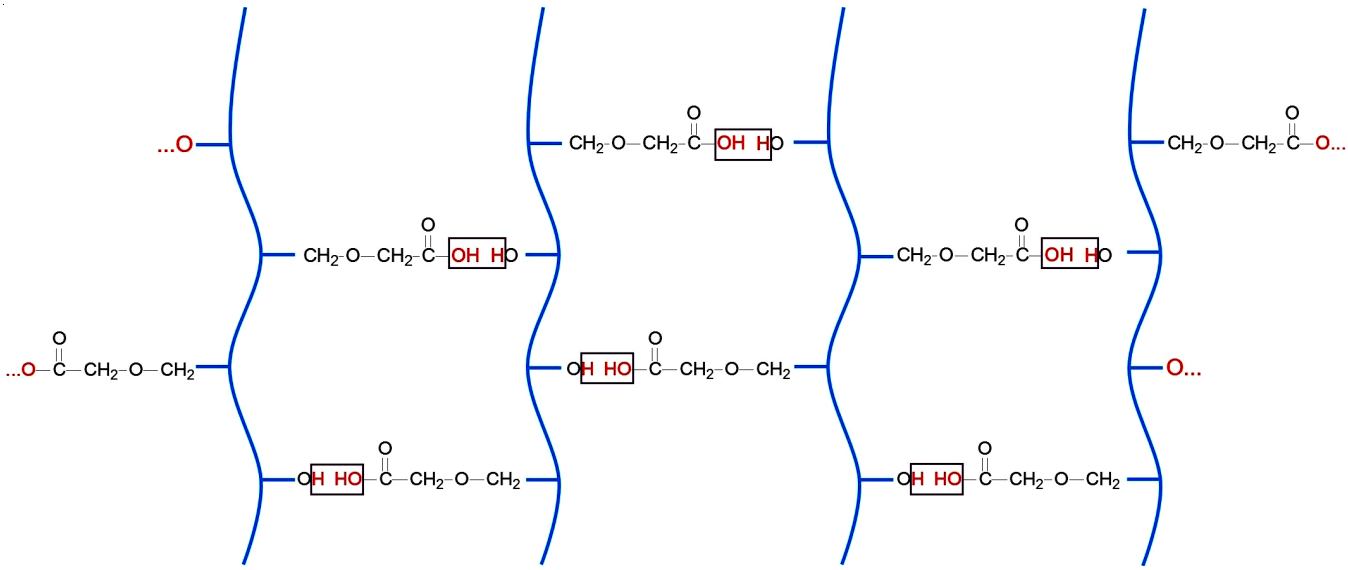

Fig. 3. Structure of cross-linked Na-CMC

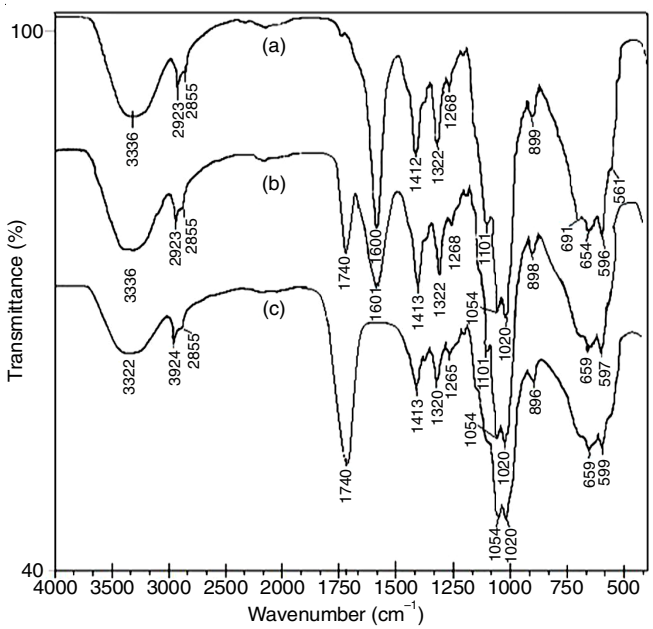

Fig. 4. FTIR spectra of film samples [(a) Purified Na-CMC (carboxyl: carboxymethylate-0:100%); (b) Copolymer Na-H-CMC (carboxyl: carboxymethylate-60:40%); (c) H-CMC (carboxyl:carboxymethylate-94:4%)]

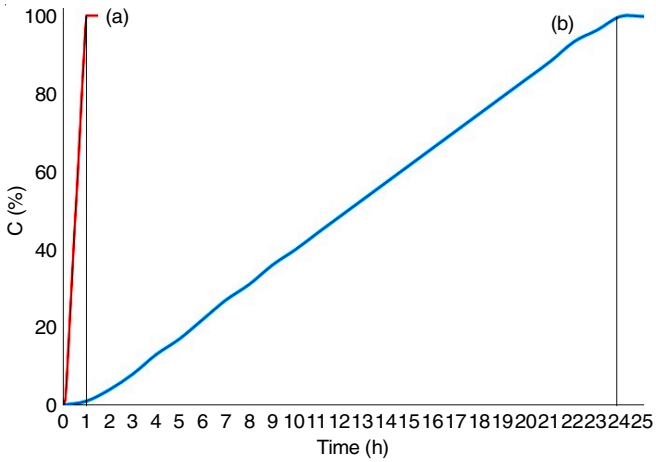

Fig. 5. Kinetics of the transition of a substance from ODFs to a physiological solution over time, (a) PGC-CMC antiviral substance (b) ODFs

PGC-CMC at 80:20 (curve B), the migration of the substance from the film progressed slowly and was completed after 24 h, confirming the prolonged effect. Further, the dynamics of material release from the ODF structures in solutions at different pH values were investigated. The initial phase of film dissolution consisted of ODF swelling. It was a natural physical process that preceded the film's dissolution and determined the rate of drug release. Due to their increased mobility, solvent molecules penetrated the matrix during swelling, displacing the macromolecules and increasing their volume.

The transport of solvent molecules in the matrix was possible due to the inequality, $\mu_o > \mu_n$, where μ_o is the chemical potential of the solvent (solution) and μ_n is the chemical potential of the solvent (solution) in the polymer matrix. The difference between the chemical potentials of the solvent itself and in the polymer matrix was the decisive factor during the swelling [30].

The substance and composite solutions containing the polymeric matrix and the drug were prepared at a ratio of Na-CMC:PGC-CMC of 80:20 wt.% to investigate the release kinetics of the material from the prepared ophthalmic drug films (ODFs). The concentration of the substance solution, ODFs and the content of the substance was 1.4%, 7% and 20%, respectively. In both solutions, the concentration of the substance was 1.4%. The obtained solutions were subjected to ultrasonic dispersion, and then, 30 mL of each solution was cast on glass substrates and heated to 65 ± 5 ºC. The resulting ODFs were placed in 100 mL of the phosphate buffer solution. Due to the slow mixing of the medium, which decreased the thickness of the diffuse layer and the diffusion coefficient, the effect of diffusion on the kinetics of the process was excluded. The UV-spectroscopy was used to measure the optical density over time at a wavelength of 356 nm to achieve the constant values for the two solutions.

The films dissolved in two stages; in the first, the films reacted with phosphate buffer solution, resulting in the formation of a saturated solution around the film; and in the second stage, the saturated solution dissolved into the water volume *via* diffusion (Fig. 5).

Morphology studies: AFM was used to study the samples of the polymer Na-CMC matrix and ODFs with different PGC-CMC contents. As shown in Fig. 6a, no nanostructures or nanoparticles were observed in the films of pure polymer matrix of Na-CMC, which can be attributed to the homogeneous structure of the films during formation. The process of film formation proceeded uniformly and without the release of nanoparticles in the film structure. Nanoparticles with a size of 25-75 nm were observed on films obtained from the polymer-polymer compositions formed from the Na-CMC polymer matrix (80%) and PGC-CMC (20%) (Fig. 6b). This was attributed due to the differences in their solubilities. Despite the relatively high DP values (630 ± 20) and the high DS (0.85 ± 2.0) of Na-CMC, these substances were soluble in water over the whole range of concentrations considered in this study.

In contrast to the matrix, in the substance macromolecule with relatively low DP values, there were bulky hydrophobic fragments of gossypol that decreased the solubility of the substance compared to that of the polymer matrix. Consequently, during the formation of the films from polymer-polymer composite solutions, with increase in the concentrations of the solutions, nanoparticles were formed during the drying process. These nanoparticles were surrounded by a matrix of macromolecules, which prevented the agglomeration of the formed nanoparticles.

The antiviral ODFs were cast on the glass substrates from the produced polymer-polymer mixtures of solutions with different contents of the PGC-CMC antiviral substance. Then, AFM was carried out and the results are shown in Fig. 7. The spherical nanoparticles of the PGC-CMC antiviral substance with a size of 5-24 nm were observed on the film surface after the introduction of 10% PGC-CMC antiviral substance into the matrix of the Na-CMC films. The nanoparticle size distribution showed high uniformity. When the content of the substance in the films was increased up to 20%, the size of the nanoparticles

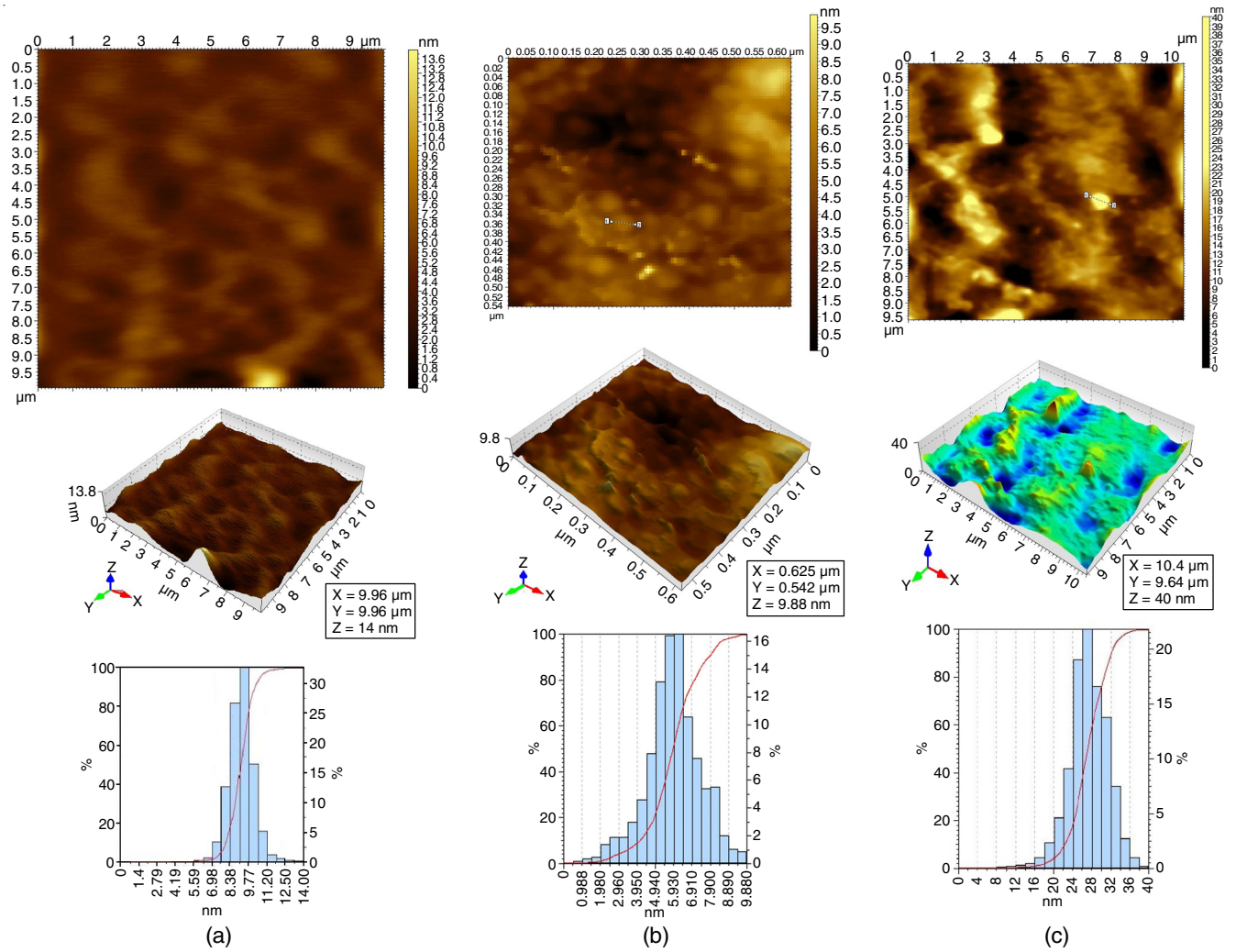

Fig. 6. AFM images of ODFs [(a) Na-CMC (100%), (b) PGC-CMC substance (100%), (c) ODF (80% Na-CMC and 20% PGC-CMC substance)]

increased to 14-52 nm, and the number of nanoparticles on the surface of the films increased.

Further increase in the content of PGC-CMC to 30% in the films transformed the shape of the nanoparticles from spherical to cubic, and their sizes increased to 46-95 nm. The cubic shape of the PGC-CMC substance can be attributed to the partial orientation of the macromolecules during the process of casting films from the Na-CMC and PGC-CMC solutions. This was because of the loss of compatibility of the substance with Na-CMC during the process of solvent removal, resulting in the formation of PGC-CMC and nanocapsules in the Na-CMC films [31,32].

Conclusion

The antiviral ophthalmic drug films (ODFs) based on the composite of sodium carboxymethylcellulose (Na-CMC) solutions and a polyphenol-gossypol-carboxymethylcellulose (PGC-CMC) antiviral substance with the requisted the physico-mechanical and drug prolongation properties were obtained. Drug prolongation was achieved by changing the ratio of carboxymethyl and carboxymethylated anionic macromolecules in the polymer matrix. The prolonging effect of ODFs was determined by the kinetics release of PGC-CMC substance from the structure of the polymeric matrix during the swelling and dissolution of ODFs. The formation of PGC-CMC nanoparticles in the ODF structures was attributed to the differences in the solubilities of the substance and the polymer matrix. Thus, the findings of this study provide insights for developing new ODFs for applications in various domains such as chemistry, biology and pharmacology for developing high molecular weight compounds. The methods presented herein for the formation of new ODFs can be applied for the molecular design of the polymer forms of biologically active compounds.

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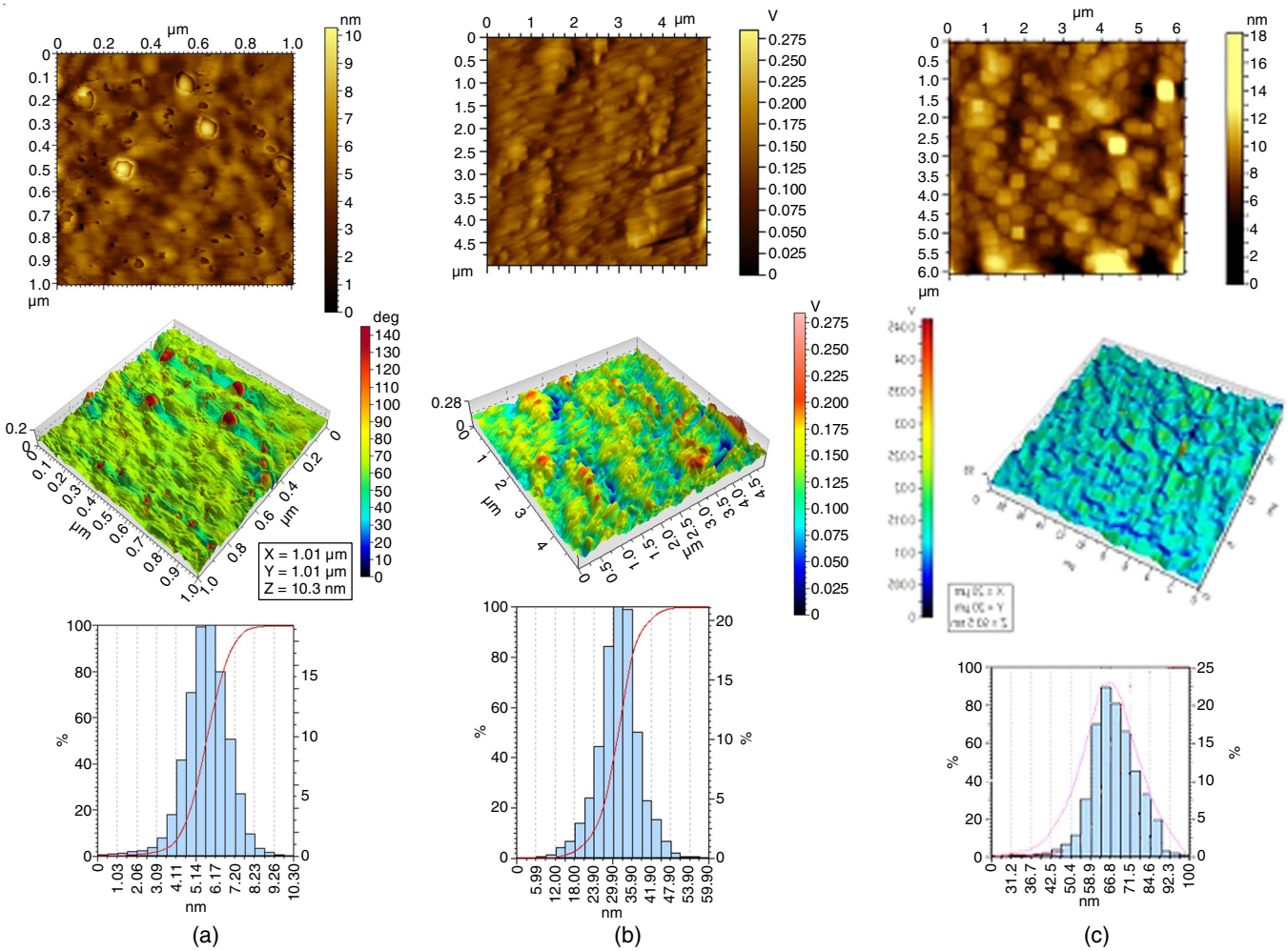

Fig. 7. AFM images of ODFs and the uniform distribution of nanoparticles in the film structure, (a) 10%, (b) 20% and (c) 30% of the PGC-CMC substance [(a) Spherical nanoparticles of PGC-CMC substance that are 5-24 nm in size; (b) Spherical nanoparticles of PGC-CMC substance with a size of 14-52 nm; (c) Cubic forms of nanoparticles of PGC-CMC substance with a size of 46-95 nm]

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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