Sodium alginate and carbopol microcapsules: preparation, polyphenol encapsulation and release efficiency

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An approach for the preparation of a polymer delivery system consisting of sodium alginate (SA) and carbopol was developed. The efficiency of the inclusion of medicinal compounds in these systems was investigated using the polyphenols curcumin and resveratrol as examples. Curcumin and resveratrol possess anti-inflammatory, antitumor, and antibacterial effects, which makes them promising compounds for use in clinical practice. The main disadvantage of these polyphenols is their low bioavailability. The formation of microcapsules occurs due to the precipitation of a mixture of SA and carbopol (carbopol 940 or ETD 2020), containing a model object, in a calcium chloride solution. The dependence of the inclusion of drugs in microcapsules and their release into gastrointestinal environment imitators on the viscosity characteristics of carbopol, which is part of the microcapsule shell, was investigated.

Key words: hydrogels, polymeric microcapsules, delivery system, carbopol 940, carbopol ETD 2020, sodium alginate.

Hydrogels are delivery systems composed of a cross-linked polymer network and a large quantity of water, which ensures their physical resemblance to many tissues of an organism.[1] These systems have many useful properties, including low toxicity and good biocompatibility, because their chemical structure is similar to that of biologically active molecules of glycosaminoglycans, for example, heparin sulfate, chondroitin sulfate, and hyaluronan, present in the native extracellular matrix.[2] They are widely used in cardiology, oncology, immunology, and burn treatment.[3—5] The hydrogels currently available include spherical micro- and nanoparticles for oral use, transdermal dressings, implants, suspensions, ointments, and suppositories.[6] They can be divided into two groups depending on their origin: natural and synthetic. Natural hydrogels, as a rule, include collagen, gelatin, alginate, *etc*. Hydrogels based on sodium alginate (SA) are well known in chemical technology.[7,8] They are used as independent carriers for various drugs and as carriers for smaller delivery systems. In the work,[9] the authors included nanoemulsions with curcumin in SA microcapsules (size of 460 μm) for oral delivery.[9] Calcium carbonate microparticles were introduced into alginate hydrogels for oral delivery of superoxide dismutase.[10] The inclusion of nanostructured lipid carriers (NLCs) in alginate hydrogel microcapsules made it possible to increase their stability compared to a NLC dispersion and a NLC—alginate sol.[11]

Sodium alginate is a smart polymer with thermo-reversible, pH-dependent properties, capable of reversible gelation under certain conditions. Alginate hydrogels exhibit pH-dependent properties due to carboxyl groups in the main chain.[7] Typically, gels are formed by electrostatic cross-linking between a multivalent cation (*e.g.*, Ca^{2+}, Mg^{2+}, Fe^{2+}, Ba^{2+}, or Sr^{2+}) and anionic carboxyl groups (COO^-).[12,13] This method of cross-linking of natural polymers is the simplest to implement in comparison with other possible methods of hydrogel formation (for example, chemical methods based on the polymerization of free radicals).[6] Cross-linking can occur at room temperature and physiological pH. However, these systems have limited stability. The stability of hydrogels can be ensured using chemical cross-linking. For this purpose, polysaccharides are modified with organic solvents, which can lead to the manifestation of gel toxicity. Therefore, other polymers are introduced into the system in order to improve the properties of alginate hydrogels (to increase the release time of the encapsulated objects, to increase the stability, *etc*.), namely chitosan, poloxamer,[14—16] *etc*. In the work,[17] alginate hydrogels were modified with tannic acid and polyvinyl alcohol, which made it possible to increase the inclusion of the dye. A similar work was

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carried out by another group of researchers, replacing polyvinyl alcohol with polyethyleneimine.[18] Alginate hydrogels modified with chitosan are actively used for oral delivery of doxorubicin.[19] The obtained particles were non-degradable in the intestinal environment imitator (large intestine, small intestine), as well as in the stomach environment imitator.

Carbopol is also one of the smart polymers capable of gelation under the influence of pH in human mucosa.[7] Carbopol is a mucoadhesive polymer derived from acrylic acid.[7,20,21] When dissolved in water, carbopol forms gels with a low pH due to its large quantity of carboxyl groups (more than 50%). It exhibits a considerable thickening ability in various polar media (aqueous, alcohol, aqueous alcohol, *etc.*) in a wide range of pH values. To obtain a specific pH value, carbopol must be neutralized. Various amines can be used as neutralizers, for example, triethanolamine (TEA), ethanolamine, diisopropylamine, *etc.*[7,20]

Earlier, a number of works reported on the effect of carbopol on some characteristics of calcium alginate microcapsules. For example, the effect of carbopol 940 on the rate of release of methylene blue from modified alginate microcapsules has been studied.[21] Other groups of researchers have worked on the development of microcapsules containing various brands of carbopols.[22—24] The work[22] investigated capsules obtained by liquid granulation and containing carbopol 974P and Avicel PH101, with or without 5% chlorphenamine maleate. It was shown that the rate of release of the drug is dependent on carbopol concentration within the capsule, the stirring rate of the blades during liquid granulation, as well as pH and ionic strength of the solvent. In the work[23] it was proposed to use carbopol 974P for oral delivery of sustained release carbamazepine granules.

The goal of this work is to develop a polymer delivery system for biologically active compounds with low bioavailability based on natural biodegradable smart polymers and to study their physicochemical properties. The objectives include an analysis of the effectiveness of including curcumin and resveratrol depending on the changes of the technological parameters of microcapsule preparation and the viscosity characteristics of carbopol (carbopol 940 and ETD 2020), as well as a comparison of the release of these polyphenols from microcapsules having various compositions into a stomach environment imitator.

Curcumin is a hydrophobic polyphenol derived from the *Curcuma longa* rhizome. According to published results, curcumin has antitumor, anti-inflammatory, antioxidant, antibacterial, antidiabetic, and antirheumatic effects.[25—29] However, in addition to all the positive properties, curcumin is not devoid of considerable pharmacological disadvantages. These include poor solubility in water, instability, low bioavailability, low penetrating ability.[26] Therefore, the use of curcumin as a therapeutic molecule remains a serious problem. The development of various systems for improving the bioavailability of curcumin and its targeted delivery is an urgent task.[26—33]

Resveratrol is a non-flavonoid polyphenolic compound found in grape seed and peanuts in great quantities. Resveratrol has a wide range of effects on the body: neuroprotective, anti-inflammatory, antidiabetic, antiviral, antibacterial, antitumor.[34,35] The main problem with using resveratrol in clinical practice is related to its low bioavailability (no more than 1% when administered orally).[36]

Experimental

In this work we used SA from brown algae (Sigma Aldrich, USA, molecular weight 120—190 kg mol^{-1}), carbopol 940 (Acros Organics, Belgium), carbopol ETD 2020 (Lubrizol, Belgium), resveratrol (WIRUD, Germany), TEA (LenReaktiv, Russia), anhydrous calcium chloride (Vekton, Russia), curcumin extract (97% content; Vidya Herbs P.Ltd, India).

Preparation of polymer microcapsules with polyphenol. Polymer mixtures with biologically active substances were prepared according to the following procedure. A dry weighed portion of polyphenol (2 mg) was dissolved in 95% ethanol (10 mL) at room temperature (20 °C). Then polyphenol solution (1 mL) was added to a 1% aqueous solution of SA with constant stirring. The obtained mixture was stirred for 10 min for better distribution of polyphenol in the polymer solution. After that, an aqueous solution of carbopol of one of the brands (carbopol 940 or ETD 2020) was added to the resulting solution of polymer with polyphenol, followed by stirring for 10 min. In experiments investigating the effect of TEA on the inclusion of polyphenol, a 10% aqueous solution of TEA (1 or 5 mL) was added dropwise to the obtained mixture.

Hydrogel microcapsules were formed by adding the obtained mixture of polymers containing polyphenol to a 0.5 *M* calcium chloride solution. An aqueous alcohol solution of polymers was added dropwise using a 5 mL syringe with an internal needle size of 0.6×25 mm with constant stirring of the calcium chloride solution at different stirring rates. After 10—30 min, the obtained microcapsules were filtered through a membrane filter (0.45 μm, Millipore), then washed three times with water to remove the unreacted compounds. The microcapsules were dried to constant weight at 60 °C in a drying oven.

Determination of the inclusion of polyphenols in microcapsules. Pre-weighed dry microcapsules were mixed at 300 rpm in 0.5 *M* phosphate buffer (100 mL, pH 7.9) for 3 h at 20 °C until they were completely dissolved. Then the solution was filtered (0.45 μm, Millipore), and the polyphenol content in the filtrate was determined by UV spectrophotometry at a wavelength of 430 nm (for curcumin) and 307 nm (for resveratrol).

The quantity of polyphenol included in hydrogel was calculated using the formula

$$I = [(P_{tot} - P_{free})/P_{tot}] \cdot 100\%,$$

where P_{tot} is the starting quantity of polyphenol, P_{free} is the quantity of polyphenol in the supernatant after reaching equilibrium.

Determination of the release of polyphenols from microcapsules in 0.1 *M* HCl. The stomach environment was imitated using a 0.1 *M* HCl solution. A dry weighed portion of microcapsules

(20 mg) was added to a 0.1 *M* HCl solution (30 mL) at 37 °C. Aliquots of the suspension (2 mL) were collected at regular intervals. The aliquots were centrifuged at 5000 rpm for 5 min, and the concentration of the included substance in the supernatant was determined spectrophotometrically. An equivalent volume of 0.1 *M* HCl was added to the system. The efficiency of the release of the encapsulated object was evaluated as the ratio of the quantity of polyphenol in the supernatant to its starting content in the microcapsules.

Spectrophotometry. The study of optical properties was carried out on an Agilent Cary 100 spectrophotometer (Agilent Technologies). Concentrations of curcumin and resveratrol were calculated using calibration curves at λ_{max} = 430 nm (absorption maximum in the UV region of curcumin, $\varepsilon = 8675$ L mol^{-1} cm^{-1}), λ_{max} = 307 nm (absorption maximum in the UV region of resveratrol, $\varepsilon = 2093$ L mol^{-1} cm^{-1}).

Viscometric studies. The dynamic viscosity of polymer mixtures consisting of SA and carbopol was measured at room temperature (20 °C) using a Brookfield DV2T rotational viscometer (shear rate 50 rpm, a set of six spindles).

Results and Discussion

Selection of technological parameters based on the analysis of the inclusion of polyphenols in microcapsules. In this study, the solution stirring duration and rate were varied when forming microcapsules with curcumin, and the effect of these parameters on the morphology and encapsulation of the object was assessed. Determined using an OPTIKA microscopy B-193 optical microscope, the size of the microcapsules in the swollen form averaged 4 mm and was less than 1 mm after drying in a drying oven at 60 °C. The stirring rate had a considerable effect on parameters such as microcapsule shape and size. When droplets of the SA—carbopol 940 mixture come into contact with the precipitant solution (0.5 *M* $CaCl_2$ aqueous solution), stirring creates flows that affect the formation of microcapsules. As the stirring rate increases, the microcapsules lose their spherical shape, and their morphology becomes less regular.

The size of microcapsules can be changed by altering the composition of the mixtures involved in the reaction and by varying the needle diameter.[21] When varying technological parameters, such as the solution stirring rate (Table 1) and duration (Table 2), the inclusion of curcumin in microcapsules changes little.

Based on the obtained results, the optimal conditions for the formation of microcapsules were selected from the point of view of morphology and inclusion, namely: stirring rate 500 rpm, stirring duration 20 min, a pair of solutions: 1% SA solution + 2% carbopol 940 solution.

Study of the degree of swelling of microcapsules. Complexation between polymers (carbopol and SA) occurs due to the electrostatic interaction between the carboxyl groups of polymers and the positively charged calcium ions. Due to their sparsely cross-linked structure, carbopols show limited swelling, which, in turn, makes it possible to use them for the development of prolonged hydrogel forms of drugs.[21] The viscosity characteristics of carbopol ETD 2020 and carbopol 940 differ. Studies have shown that a 2% carbopol 940 solution in water (dynamic viscosity 3085 cP, shear rate 50 rpm) is more viscous compared to a similar solution of carbopol ETD 2020 (dynamic viscosity 1125 cP, shear rate 50 rpm).

Table 1. Influence of stirring rate on the inclusion of curcumin in microcapsules (stirring duration 20 min)

System	Stirring rate /rpm	Encapsulation (%)
SA (1%) +	300	94.7
+ carbopol 940 (2%)	500	93.0
	800	86.1
SA (1%) +	300	73.4
+ carbopol 940 (1%)	500	74.1
	800	73.9
SA (2%) +	300	68.5
+ carbopol 940 (1%)	500	70.9
	800	68.8

Water absorption by microparticles with different carbopol contents is given in Table 3. The quantity of water W_{up} included in the system was calculated using the formula

$$W_{up} = [(W_t - W_d)/W_d] \cdot 100\%,$$

where W_t is the mass of wet particles (mg), W_d is the mass of dry particles (mg).

We note that the absorption of water after 60 min tended to decrease, which is related to the beginning of the process of disintegration of the capsules.

Continuous heating at 37 °C in phosphate buffer (pH 7.8) led to the microcapsules being completely dissolved within 60 min. This is the expected result because SA is soluble in an alkaline medium.

Influence of the carbopol brand on the inclusion of polyphenols in microcapsules. The quantity of polyphenol

Table 2. Influence of stirring duration on the inclusion of curcumin in microcapsules (stirring rate 500 rpm)

System	Stirring duration /min	Encapsulation (%)
SA (1%) +	10	92.5
+ carbopol 940 (2%)	20	93.6
	30	93.1
SA (1%) +	10	72.8
+ carbopol 940 (1%)	20	72.3
	30	73.3
SA (2%) +	10	69.1
+ carbopol 940 (1%)	20	72.1
	30	69.5

Table 3. Swelling of microparticles in water at a temperature of 37 °C

System	W_{up} (%)	
	30 min	60 min
SA (1%) + + carbopol ETD 2020 (1%)	62.9	58.9
SA (1%) + + carbopol ETD 2020 (2%)	90.4	85.2
SA (1%) + + carbopol 940 (1%)	94.8	82.1
SA (1%) + + carbopol 940 (2%)	99.6	88.9

included in microcapsules for different ratios of polymers in the shell is given in Table 4.

It was shown that the encapsulation of polyphenols in the system increases with the concentration of both brands of carbopol.

Effect of the introduction of TEA on the inclusion of polyphenols in microcapsules. The regulation of pH plays an important role when working with mixtures containing carbopol. The thickening of carbopols takes place after their neutralization using a base. When working with this polymer, it is important to remember that its maximum viscosity is achieved in a neutral medium (pH 6—7). Figure 1, using the example of mixtures of a 1% solution of SA and a 2% solution of carbopol (carbopol 940 and ETD 2020), shows the dependence of their dynamic viscosity (at a temperature of 20 °C) on the change in pH caused by neutralization using a 10% aqueous solution of TEA. In the case of a polymer mixture, maximum viscosity is

Table 4. Encapsulation of polyphenols in systems of SA and carbopol (stirring rate 500 rpm, stirring duration 20 min)

Polyphenol	System	Encapsulation (%)
Resveratrol	SA (1%) + + carbopol ETD 2020 (1%)	40.2
	SA (1%) + + carbopol ETD 2020 (2%)	48.8
	SA (1%) + + carbopol 940 (1%)	46.4
	SA (1%) + + carbopol 940 (2%)	59.8
Curcumin	SA (1%) + + carbopol ETD 2020 (1%)	75.9
	SA (1%) + + carbopol ETD 2020 (2%)	89.6
	SA (1%) + + carbopol 940 (1%)	71.7
	SA (1%) + + carbopol 940 (2%)	93.5

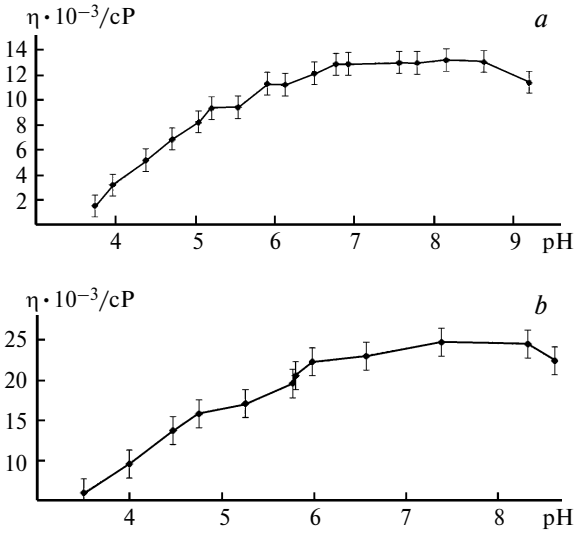

Fig. 1. Dependence of dynamic viscosity (η) of a mixture of a 1% SA solution and a 2% carbopol, namely, carbopol 940 (*a*) or ETD 2020 (*b*), solution on the quantity of a 10% TEA solution added to it (the number of repeated measurements at a single point is equal to 10).

achieved at more alkaline pH values (pH 7—8). Most likely, this is due to the tendency of SA to fold into a globule in an acidic medium and to swell in an alkaline medium. Similar results were also obtained for mixtures of a 1% solution of SA and a 1% solution of carbopol of both brands.

The introduction of TEA into a mixture of the starting polymers can affect the efficiency of inclusion in the polymer microcapsules. Triethanolamine is a weak base which is able to ionize the carboxyl groups in carbopol.

As a result of ionization of the carboxyl groups, the gel changes its spatial structure, thereby increasing the viscosity. From Table 5 it follows that an increase in the viscosity of the polymer leads to an increase in the inclusion of both curcumin and resveratrol in the microcapsules.

The introduction of TEA into the starting polymer mixture leads to the formation of hydrogels with a highly dense polymer network. Since the introduction of TEA increases the number of negatively charged groups, this can lead to an increase in the electrostatic interaction between the drug and the polymer. Thus, an increase in the efficiency of capture of target objects by microcapsules can occur. However, when including resveratrol and curcumin, electrostatic interaction does not occur due to the possibility of formation of negatively charged groups in both polyphenols. This effect can explain the small difference in the inclusion of these polyphenols in hydrogels when neutralizing the mixture with TEA (5 mL, the ratio of the TEA solution volume to the polymer mixture solution volume is 1 : 6) (Table 6).

Influence of carbopol brand on the release of polyphenols from microcapsules. As part of this work, we investigated

Table 5. Influence of the introduction of a 10% TEA solution (1 mL, the ratio of the volumes of TEA solution and polymer mixture solution is 1 : 30) on the encapsulation of polyphenols (stirring rate 500 rpm, stirring duration 20 min)

Polyphenol	System	Viscosity/cP	pH	Encapsulation (%)
Resveratrol	SA (1%) + carbopol ETD 2020 (1%)	1040	4.98	51.5
	SA (1%) + carbopol ETD 2020 (2%)	4536	4.0	69.5
	SA (1%) + carbopol 940 (1%)	742	4.43	56.7
	SA (1%) + carbopol 940 (2%)	3192	3.90	65.6
Curcumin	SA (1%) + carbopol ETD 2020 (1%)	1040	4.98	84.9
	SA (1%) + carbopol ETD 2020 (2%)	4536	4.0	88.2
	SA (1%) + carbopol 940 (1%)	742	4.43	72.9
	SA (1%) + carbopol 940 (2%)	3192	3.90	78.6

Table 6. Influence of the introduction of a 10% TEA solution (5 mL, the ratio of the volumes of TEA solution and polymer mixture solution is 1 : 6) on the encapsulation of polyphenols (stirring rate 500 rpm, stirring duration 20 min)

Polyphenol	System	Viscosity/cP	pH	Encapsulation (%)
Resveratrol	SA (1%) + carbopol ETD 2020 (1%)	3364	8.17	62.6
	SA (1%) + carbopol ETD 2020 (2%)	14540	5.77	69.9
	SA (1%) + carbopol 940 (1%)	2644	5.80	66.6
	SA (1%) + carbopol 940 (2%)	6480	4.85	63.1
Curcumin	SA (1%) + carbopol ETD 2020 (1%)	3364	8.17	68.9
	SA (1%) + carbopol ETD 2020 (2%)	14540	5.77	62.8
	SA (1%) + carbopol 940 (1%)	2644	5.80	68.3
	SA (1%) + carbopol 940 (2%)	6480	4.85	66.2

the kinetics of the release of polyphenols (curcumin and resveratrol) from microcapsules due to the dissolution of their shells by the stomach environment imitator medium. The release mechanism in this delivery system consists of the dissolution of the shell and the subsequent diffusion of polyphenols from it. In this study, 0.1 *M* HCl was used as the stomach environment imitator. The results are given in Table 7.

The influence of the content of various brands of carbopol on the release profile of polyphenols into the 0.1 *M* HCl stomach imitator is related to the influence of this polymer on the granule structure.[21] The density of the granules should increase both with the concentration of this polymer and with viscosity. Consequently, granules formed at higher concentrations should have a denser structure, as demonstrated in many published works.[21] However, in this work, no considerable dependence of the release of polyphenols on the concentration of polymers or the viscosity of their solutions was observed.

Polymer combinations (as compared to single carriers) are increasingly attracting attention for the development of drug delivery systems with controlled release. In this work, we used a pair of polymers, namely, SA and two types of carbopol, for the formation of microcapsules. Carbopol 940 was found to be more effective compared to ETD 2020, both in terms of the inclusion of model drugs in microcapsules and in terms of their release.

Table 7. Release of polyphenols from microcapsules of sodium alginate and carbopol into 0.1 *M* HCl (pH 2) after 3 h at a temperature of 37 °C

Polyphenol	System	Yield (%)
Curcumin	SA (1%) + carbopol ETD 2020 (1%)	2.2
	SA (1%) + carbopol ETD 2020 (2%)	2.8
	SA (1%) + carbopol 940 (1%)	1.3
	SA (1%) + carbopol 940 (2%)	1.6
Resveratrol	SA (1%) + carbopol ETD 2020 (1%)	3.5
	SA (1%) + carbopol ETD 2020 (2%)	2.9
	SA (1%) + carbopol 940 (1%)	2.8
	SA (1%) + carbopol 940 (2%)	1.9

It was shown that the addition of TEA does not always have a positive effect on the inclusion of the drug in the delivery system.

The release of polyphenols included in microcapsules into 0.1 *M* HCl after 3 h of incubation did not considerably differ and did not depend on viscosity and concentration of polymers in the system.

This paper does not contain descriptions of studies on animals or humans.

The authors declare no competing interests.

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