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Oxycellulose as mucoadhesive polymer in buccal tablets

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Abstract
Background: Oxycellulose (OC) is biodegradable and bioabsorbable cellulose derivative used in medicine to support hemostasis and tissue healing. Recently, its antimicrobial and immunomodulating properties, as well as its potential in modern therapeutic systems as release modifying excipient, drug carrier, and/or mucoadhesive polymer, are widely discussed. *Method*: To study its last-mentioned characteristics, directly compressed tablets containing 5 mg of cetylpyridinium chloride (CPC) as a model drug and 90 mg of mucoadhesive polymer [oxycellulose sodium (NaOC) alone or in a combination with one of five widely used mucoadhesive polymers] were prepared to ensure 8 hours prolonged release of CPC. Physicochemical and mucoadhesive properties of prepared tablets were evaluated. *Results*: Based on obtained results, tablets containing OC in combination with hydroxypropylmethylcellulose (Methocel® K100LV) or carboxymethylcellulose sodium showed the best quality parameters (friability < 0.04%, tablet thickness < 2.17 mm, tablet hardness > 85 N, residence time > 256 minutes, mucoadhesive strength > 3.45 mN/mm^2) and dissolution profiles (more than 81% of CPC released within 8 hours). *Conclusion*: NaOC embodies excellent compressing, mechanical, and mucoadhesive properties; however, formulation with higher content of NaOC only showed shorter adhesion time (107 ± 7 minutes) and faster drug release (93.66% of CPC released within 2 hours), because of its good solubility in aqueous media.

Key words: *buccal mucoadhesive tablets; cetylpyridinium chloride; in vitro tablet characterization; oxycellulose sodium; prolonged drug release*

Introduction

Oral cavity is complex and dynamic environment containing a diversity of microorganisms. Bacterial infections are caused mainly by the normal endogenous flora; they are rarely of exogenous origin. Local antibacterial agents can play two roles in controlling oral diseases: a preventive role as common part of oral hygiene products and therapeutic one for the treatment of inadequate plaque growth, gingivitis, and other local oral infections that affect more than 75% of adults[1,2]. The control of dental plaque, which is closely associated with gingivitis and dental caries, may be achieved by topical applications of antimicrobial agents. For the adequate effectiveness of antiseptic agents, it is necessary to achieve the minimum inhibitory concentration for a sufficiently long period[3].

Cationic detergents have been known for a number of years to possess bactericidal and fungicidal properties, because of a strong tendency to interact with the negatively charged bacterial cell surfaces, causing disruption of their membrane function[4]. Cetylpyridinium chloride (CPC), a quaternary ammonium salt, has been found effective in controlling the accumulation of bacterial plaque on teeth, with subsequent improvement of gingivitis[5]. It acts primarily by penetrating the cell membrane, which causes a leakage of components from inside of the cell, bacterial metabolism disruption, cell growth inhibition, and finally bacterial or fungal death[1]. CPC has bactericidal activity against gram-positive and, at higher concentrations, against gram-negative microorganisms. It has also a good activity against some fungal species, for example, *Candida albicans*[6]. The minimum inhibition concentration of the drug was

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determined in 5 μg/mL of saliva for four essential oral species of microorganisms: *C. albicans, Staphylococcus aureus, Escherichia coli,* and *Streptococcus mutans*[5].

Topical drugs delivered into the oral cavity tend to be rapidly dislodged, diluted, or removed and for some antibacterial agents the duration of activity is only slightly longer than the retention time of the delivery vehicle. More frequent use of the antimicrobial preparation may improve activity but has patient compliance complication; therefore, the development of prolonged release oral delivery device would be advantageous[2,3]. Oral mucoadhesive tablets belong to modern dosage forms that allow controlled drug release after buccal application[7]. Mucoadhesive polymers, the basic part of mucoadhesive dosage forms, are generally identified as macromolecular organic hydrocolloids that contain numerous hydrogen bond-forming groups, notably carboxyl, hydroxyl, amide, and amine groups. High molecular weight, sufficient degree of polarity, and flexibility of polymer chain are considered vital to provide optimal driving force for polymer-mucus adsorption and interpenetration[8]. Mucus is viscoelastic hydrogel. It primarily consists of 1–5% of water-insoluble highly glycosylated glycoproteins with large peptide backbone and oligosaccharides as side chains, often terminated in either sialic acid, sulfonic acid, or L-fructose; 95–99% of water; and several other components in small quantities, for example, proteins, enzymes, electrolytes, and nucleic acids. As a result, mucus is negatively charged at physiological pH[9,10].

The term mucoadhesion can be defined as the attachment of synthetic or natural macromolecules to mucus and/or an epithelial surface. Five theories have been suggested to play a major role in mucoadhesion: adsorption, diffusion, electronic, fracture, and wetting theories[11,12]. They are defined by many polymer-related factors that affect the quality of mucoadhesion, such as molecular weight, flexibility, hydrogen-bonding capacity, cross-linking density, charge, concentration, hydration (swelling), and also environmental factors—salivation, quality of mucus, ionic strength, and so on[13,14].

So far many polymers have been used to ensure the best properties of mucoadhesive solid dosage forms. The main groups of these excipients are poly(acrylic acid)-based polymers (e.g., carbomer and polycarbophil)[15], various gums (e.g., guar, hakea, and xanthan), lectins, polyoxyethylenes, pectins[16], chitosan,[17] and cellulose derivates, such as hydroxypropylmethylcellulose[18], methylcellulose, hydroxyethylcellulose, and carboxymethylcellulose sodium[11,14]. The majority of above-mentioned polymers embody, in addition to mucoadhesion, also the ability of hydration and gel-forming barrier, one of the basic properties of drug release-controlling agents[19].

Oxycellulose (oxidized cellulose, OC) is another excipient of the wide range of pharmaceutically and medically used cellulose derivatives. Oxidation of one primary (C_6) and two secondary (C_2, C_3) hydroxyl groups of each anhydroglucose unit in cellulose chain results in formation of a product important for its unique properties of biodegradability and bioabsorbability under physiological conditions to nontoxic products through both chemical and enzymatic processes[20–23]. OC has been used in medicine for many years as material supporting hemostasis; it avoids tissue adhesion after surgical operation and is a material improving tissue healing in chronic wound care[24]. For pharmaceutical and medical needs, OC with presence of 16–24% of carboxylic groups in its structure as well as some of its salts, sodium, calcium, aluminium, and so on, is most suitable[20,25]. Recent studies disclose OC antimicrobial[26] and immunomodulating activity[27], as well as potential usage in modern therapeutic systems as release modifying excipient[28–30], drug carrier[26,31,32], analytical exchanger, enterosorbent[33], and/or mucoadhesive polymer,[34] and so on.

The objective of this work was the formulation of buccal mucoadhesive tablets, based on oxidized cellulose, in this term new pharmaceutical excipient, and evaluation of OC influence on physicochemical properties of prepared tablets and their dissolution profiles. Besides usual excipients, formulations contained 5 mg of model drug—CPC and 90 mg of mucoadhesive polymer—OC sodium (NaOC) alone, or in a combination with one of five widely used mucoadhesives, that is, polyethylenoxide, carboxymethylcellulose sodium, two types of hydroxypropylmethylcellulose, and hydroxyethylcellulose in different ratios. The aim of this experiment was to ensure 8 hours prolonged release of CPC and its salivary concentration higher than its minimum inhibition concentration (5 μg/mL), without the necessity of residual tablet fragments elimination from oral cavity.

Materials and methods

Materials

To prolong the model drug release, that is, CPC monohydrate (Sigma-Aldrich, Prague, Czech Republic), different mucoadhesive polymers were used: NaOC (VUOS a.s., Rybitvi, Czech Republic); carboxymethylcellulose sodium (Jan Kulich, Hradec Kralove, Czech Republic); hydroxylpropylmethycelluloses—Methocel® E4M, Methocel® K100LV, and poly(ethylenoxide) polymer—Polyox® WSR301 (Colorcon Lmt., Dartford, UK); hydroxyethylcellulose—Cellosize WP-40 (Sigma-Aldrich) either alone or in a combination. Magnesium stearate, colloidal silica dioxide (Zentiva a.s., Prague, Czech Republic), and lactose monohydrate—Tablettose® 80

(Meggle Pharma, Wasserburg, Germany) were included to improve the powder flow properties. Mucin (type II), as the basis of artificial mucous membrane, was supplied by Sigma-Aldrich. Isotonic phosphate buffer (IPB) of pH 6.8 was prepared according to Ph.Eur. 6. All other chemicals used in this experiment were of analytical grade.

Characterization of used materials and tableting mixtures

Important polymer particle characteristics

All the powder materials used in this experiment were screened through a 125-µm sieve to obtain particle size <125 µm. Mucoadhesive polymers were then analyzed by an optical analysis using optical microscope (DN 45; Lambda, Prague, Czech Republic) connected to the CCD camera (Alphaphot; Nikon, Tokyo, Japan) and operated by Ia32 software. Two hundred randomly chosen particles of each polymer were used as representative samples. Particle size distributions were determined; particles mean diameters and surfaces were calculated automatically. Stereomicroscopic photographs of polymer particles were taken to characterize the particle shape.

Viscosity studies

The 6% (w/w) of polymeric dispersion of each polymer and their mixtures, corresponding to Table 1, were prepared separately by dispersing 3 g of polymer or polymer mixture in distilled water in a conical flask; then the water was added up to 50 g. The dispersions were kept for 48 hours at 20°C to complete swelling of polymers (no solid particles were observed in the mixtures), and then the dynamic viscosities of 6% (w/w) gels or solutions were determined using Brookfield viscometer (LVTVD-II; Brookfield Engineering Laboratories, Inc., Middleboro, MA, USA) for samples showing viscosities between 10 and 2000 Pa·s and Stabinger viscometer (Stabinger SVM 3000; Anton Paar Ltd., Hertford, UK) for low-viscose samples. The presented values are the means of three determinations.

Preparation of mucoadhesive tablets

Tablets were prepared from different mucoadhesive polymers and their combinations, other excipients, and CPC as shown in Table 1. Drug and excipients were mixed in laboratory three-axial homogenizer (Turbula C2; Willy A. Bachofen AG: Maschinenfabrik, Basel, Switzerland) for 15 minutes. Each mixture was then directly compressed using the eccentric tablet press (EK0; Korsch Pressen, Berlin, Germany) with a 7-mm diameter flat-faced punches, using a constant compression force of 65 ± 5 kN and compression speed of 20 tablets per minute to produce batches of 200 tablets.

Table 1. Mucoadhesive polymers and their mixtures.

	Content of mucoadhesive polymer (%)					
Sample	NaOC	Polyox	K100LV	E4M	HEC	NaCMC
Polyox-1	–	90	–	–	–	–
NaOC:Polyox (1:2)	30	60	–	–	–	–
NaOC:Polyox (1:1)	45	45	–	–	–	–
NaOC:Polyox (2:1)	60	30	–	–	–	–
K100LV-1	–	–	90	–	–	–
NaOC:K100LV (1:2)	30	–	60	–	–	–
NaOC:K100LV (1:1)	45	–	45	–	–	–
NaOC:K100LV (2:1)	60	–	30	–	–	–
E4M-1	–	–	–	90	–	–
NaOC:E4M (1:2)	30	–	–	60	–	–
NaOC:E4M (1:1)	45	–	–	45	–	–
NaOC:E4M (2:1)	60	–	–	30	–	–
HEC-1	–	–	–	–	90	–
NaOC:HEC (1:2)	30	–	–	–	60	–
NaOC:HEC (1:1)	45	–	–	–	45	–
NaOC:HEC (2:1)	60	–	–	–	30	–
NaCMC-1	–	–	–	–	–	90
NaOC:NaCMC (1:2)	30	–	–	–	–	60
NaOC:NaCMC (1:1)	45	–	–	–	–	45
NaOC:NaCMC (2:1)	60	–	–	–	–	30
NaOC-1	90	–	–	–	–	–

All samples intended for tabletting contained 5% of cetylpyridinium chloride, 2% of colloidal silicon dioxide, 2% of magnesium stearate, and 1% of lactose monohydrate.

Average weight of tablets was about 100 ± 5 mg. Prepared tablets were manually dedusted and kept for 48 hours in polyethylene bag before next testing.

Evaluation of physicochemical properties of mucoadhesive tablets

Thickness of tablets

The thickness of five tablets was measured using digital slide calliper; the thickness of one tablet and SD of measurement were calculated. The presented values are the means and SDs of five determinations.

Friability of tablets

Approximately 6.5 g of dedusted tablets, precisely weighed, were placed into a plastic drum of the abrasion tester (TAR10; Erweka GmbH, Heusenstamm, Germany) and rotated for 4 minutes at 25 rpm, corresponding to Ph. Eur. 6. The dust was thereafter removed and tablets were reweighed. Their friability, that is, the weight loss after agitation, was expressed as a percentage. The presented values are the means and SDs of three determinations.

Tablet hardness and tensile strength

Tablet hardness and compression tester (C50; Engineering System, Notthingham, UK) were used for the determination of tablet hardness. Tablet tensile strength (T) was calculated from measured values, using the following equation:

$$T = \frac{2F}{\pi d t}, \tag{1}$$

where F, d, and t denote the diametral crushing force, tablet diameter, and tablet thickness, respectively[35]. Ten randomly selected tablets of each formulation were tested; hardness and tensile strength mean values and SDs were calculated.

Surface pH of mucoadhesive tablets

Tablet surface pH was determined to investigate its possible side effects in oral cavity (i.e., inadequate salivary, irritation, etc.)[8]. Tablets were put in glass beaker filled with 40 mL of IPB (pH 6.8). The surface pH was noted by bringing a combine glass electrode immediate to the tablet surface at the times of 30, 60, and 120 minutes after insertion of the tablet in the buffer[36,37]. The pH meter was stabilized for 1 minute before each measurement. All experiments were performed in triplicate for each sample, and the mean values and SDs were calculated.

Measurement of tablet mucoadhesive strength

Mucoadhesive strength was measured as the force needed to pull out a tablet from a layer covered with mucin, simulating oral mucosa. The apparatus consisted of a modified two-arm physical balance[6] where the right pan was replaced by a tablet holder, to fix examined tablet by cyanoacrylate glue. The material to simulate human oral mucosa is often discussed. In general, animal mucosa membranes, from various animal species and different locations, either uncovered or covered with a mucin layer are used[38]. In this experiment, a piece of microporous semipermeable cellophane membrane uniformly covered by the 5% (w/w) dispersion of porcine stomach mucin in IPB (1 mL/cm^2) was used as oral mucosa substitution[39]. This artificial membrane was glued to the right part of balance platform. Each tablet was wetted by 15 µL of IPB for initial hydration and swelling, firmly fixed to the tablet holder as described above, and attached to prepared artificial mucosa by applying a pressure of 5-g weight on the tablet surface for 3 minutes. Thereafter, the weight was removed and 5-g weights were added slowly one by one to the left pan, until the tablet was separated from the mucosal surface. This gave the weight in grams for the calculation of the mucoadhesive force per unit surface area, according to the formula:

$$F = \frac{m \cdot g}{A}, \tag{2}$$

where F is the mucoadhesive force (kg/m/s^2), m is the weight applied (kg), g is the acceleration due to the gravity (m/s^2), and A is the surface area of the tablet (m^2). Each experiment was performed five times for each sample of tablets and the mean values and SDs were calculated.

Water uptake studies

Six tablets of each formulation were separately placed in a series of dissolution baskets made of stainless steel mesh. Each set (tablet and basket) was accurately weighed before being placed in a beaker containing 40 mL IPB at 37 ± 0.5°C. The set containing the swollen tablet in the basket was weighed at fixed time intervals (15, 30, 60, 120, 240, and 480 minutes) after drying the basket with a filter paper[6,40]. The increase in tablet weight was calculated as percent water uptake using the following relation:

$$\Delta m = \frac{(m_t - m_0) \cdot 100}{m_0}, \tag{3}$$

where Δm is a change of tablet weight in percent, m_t is the weight of swollen tablet at each time interval t, and m_0 is the tablet initial weight. The experiment was carried out in triplicate.

Determination of the in vitro residence time

In vitro residence time was determined using modified disintegration apparatus[8] (ZT 4; Erweka GmbH). A piece of artificial mucosa (cellophane membrane covered with mucin layer) was glued to the surface of plastic slab. The mucoadhesive tablet, wetted on one surface with 15 µL of IPB, was attached to prepared membrane by applying a pressure of 5-g weight on the tablet surface for 30 seconds. The plastic slab was vertically fixed to the apparatus and allowed to move up and down to ensure complete immersion of the tablet in IPB (1000 mL at 37 ± 0.5°C) at the lowest point and removal at the highest point. The time necessary for complete erosion or detachment of the tablet from artificial mucosa was recorded as the mean value and SD of three determinations.

Content uniformity

Ten randomly selected representative tablets from each batch were crushed. Aliquots of the crushed tablets were weighed and the required amount of distilled water was added to dissolve the drug. The dispersion was kept at laboratory temperature (20°C) for 48 hours. Samples were filtered and then analyzed spectrophotometrically (Lambda 25; Perkin Elmer, Wellesley, MA, USA) at 259 nm. The CPC content was calculated from standard calibration equation with linearity range $r^2 = 0.999$ for absorbances of CPC concentrations between 0.1 and 1.0 mg/100 mL in distilled water. All experiments were performed five times for each batch and the mean values and SDs were calculated.

In vitro release studies

In vitro release of CPC was determined using standard paddle dissolution apparatus (Erweka DT-D6) with paddle speed of 50 rpm in 500 mL of IPB at 37 ± 0.5°C. One surface of the tested tablet was fixed to a cellophane membrane with cyanoacrylate glue; thus only the remaining surface of the tablet was exposed to the dissolution medium. Samples of 3 mL were withdrawn at 15, 30, 60, 120, 240, 360, and 480 minutes of the experiment, and the drug concentration in dissolution medium was analyzed spectrophotometrically at 259 nm. The volume of withdrawn medium was replaced by an equal amount of IPB kept at 37°C. Six randomly selected tablets of each formulation were tested; results are presented as mean values and SDs.

Results and discussion

Powders characteristics

Particle size and shape

Mean particle diameter of mucoadhesive polymers was calculated from microscopic analyses data (Table 2). As can be seen from the measured values the mean particle diameter decreases in rank order K100LV (79.6 µm) > E4M (69.2 µm) ≈ HEC (68.6 µm) > Polyox (61.7 µm) ≈ NaCMC (59.3 µm) > NaOC (35.7 µm). Small size of NaOC particles could improve physical properties (e.g., increase the hardness and reduce the thickness) of tablets containing higher proportion of this polymer in the formulation. Together with increasing mean particle diameter also the particle surface decreased more or less. Figure 1 demonstrates the anisometric structure of all used cellulose derivates.

Viscosity studies

Viscosities of the 6% (w/w) aqueous dispersions of polymers alone and their mixtures in the same ratios as used in tablets are summarized in Table 3. It is generally known that polymer dispersion viscosity is related to the quality of gel barrier formed on the surface of hydrophilic matrices, when wetted. It can significantly influence the drug release profile[41]. The highest viscosities, that is, >2000 Pa·s, were measured in Polyox (Polyox-1), NaCMC (NaCMC-1) dispersions, and their mixtures with lower amount of NaOC [NaOC:Polyox (1:2),

Table 2. Particle size and surface of mucoadhesive polymers.

Polymer	Particle size distribution (%) Size class 0.0–50.0 µm	 50.1–100.0 µm	 100.1–150.0 µm	Mean particle diameter (µm)	Mean particle surface (µm^2)
Polyox	58.5	24.5	17.0	61.7	76.2
K100LV	37.0	35.5	27.5	79.6	94.3
E4M	29.5	50.5	20.0	69.2	78.1
HEC	22.0	66.5	11.5	68.6	73.6
NaCMC	36.0	57.0	7.0	59.3	63.2
NaOC	81.0	15.5	3.5	35.7	41.7

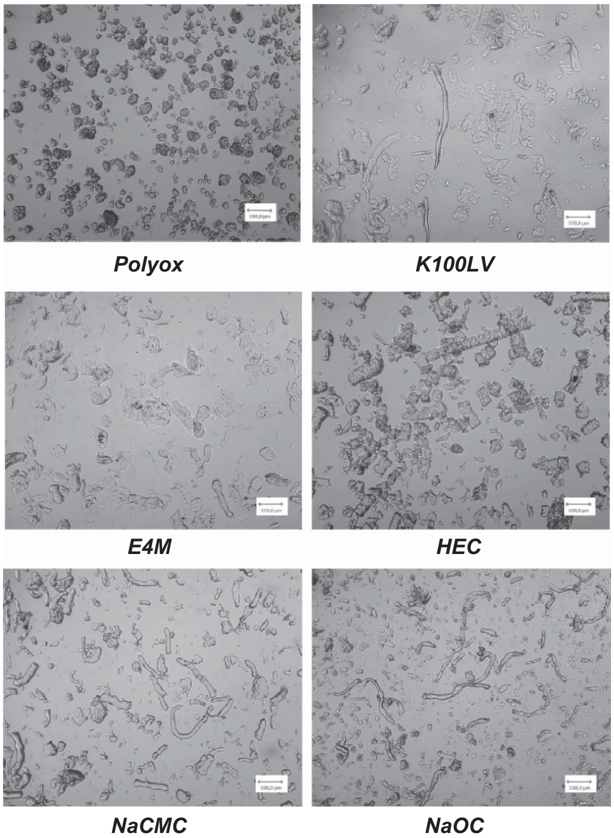

Figure 1. Stereomicroscopic photographs of mucoadhesive polymers (the length bar conforms to 100 μm).

NaOC: NaCMC (1:2)]. It was determined that NaOC dispersion (sample NaOC-1) had the lowest viscosity (27.848 Pa·s) of all used mucoadhesive polymers. This property resulted in viscosity reduction of all samples with higher content of NaOC. Aqueous dispersions of NaOC:K100LV (1:2), NaOC:K100LV (1:1), NaOC: K100LV (2:1), NaOC:HEC (1:1), and NaOC:HEC (2:1) showed lower viscosity values than the viscosities of initial polymers. This could be explained by electrostatic repulsion of remote polymer chains in diluted polymeric dispersions, where the distances of interacting chains are too large for attractive interactions (e.g., hydrogen bonds), prevailing in close contact of polymers[42].

Tablet evaluation

Thickness of tablets

The thickness of measured tablets ranged between the values of 1.86 and 2.76 mm (Figure 2). NaOC-1 tablets containing only NaOC as a polymeric carrier showed the smallest thickness. This result pointed to good compressing properties of NaOC, also noticeable from the same figure, showing the tendency of decreasing tablet thickness in each sample group with increasing content of oxidized cellulose in the formulation.

Table 3. Groups of samples, mucoadhesive polymer ratios, their aqueous dispersion (6% w/w) viscosities.

Group	Sample	Mucoadhesive polymer type and ratio	Dynamic viscosity (Pa·s)
I		**NaOC:Polyox**	
	Polyox-1	0:1	>2000.000^{a}
	NaOC:Polyox	1:2	>2000.000^{a}
	NaOC:Polyox	1:1	1320.000
	NaOC:Polyox	2:1	57
II		**NaOC:K100LV**	
	K100LV-1	0:1	55.300
	NaOC:K100LV	1:2	2.899
	NaOC:K100LV	1:1	1.121
	NaOC:K100LV	2:1	0.406
III		**NaOC/E4M**	
	E4M-1	0:1	750.000
	NaOC:E4M	1:2	570.000
	NaOC:E4M	1:1	140.000
	NaOC:E4M	2:1	33.000
IV		**NaOC/HEC**	
	HEC-1	0:1	112.000
	NaOC:HEC	1:2	35.000
	NaOC:HEC	1:1	1.116
	NaOC:HEC	2:1	0.559
V		**NaOC/NaCMC**	
	NaCMC-1	0:1	>2000.000^{a}
	NaOC:NaCMC	1:2	>2000. 000^{a}
	NaOC:NaCMC	1:1	237.000
	NaOC:NaCMC	2:1	46.000
VI		**NaOC**	
	NaOC-1	1:0	27.848

^{a}Viscosities higher than 2000 Pa·s were not measurable.

Friability of tablets

All tested tablet samples showed friability values lower than Ph. Eur. 6. limit, that is, 1%, with the exception of HEC-1 tablets, where the friability value was 3.44% (Table 4). This finding can be related to the lowest tablet hardness of this sample, as discussed further.

Tablet hardness and tensile strength

The resistance of tablets against radial crushing force entirely depends on tablet shape, size, and its composition, for example, the particle size and shape of the original powders, their deformation properties, melting temperature, and moisture content of tabletting mixtures, when all the process variables are kept constant[43]. Tablet hardness is the measure of their quality, in terms of their porosity, dissolution profile, disintegration time, swellability, and so on. The highest hardness of all tested tablets, prepared by equal compression force

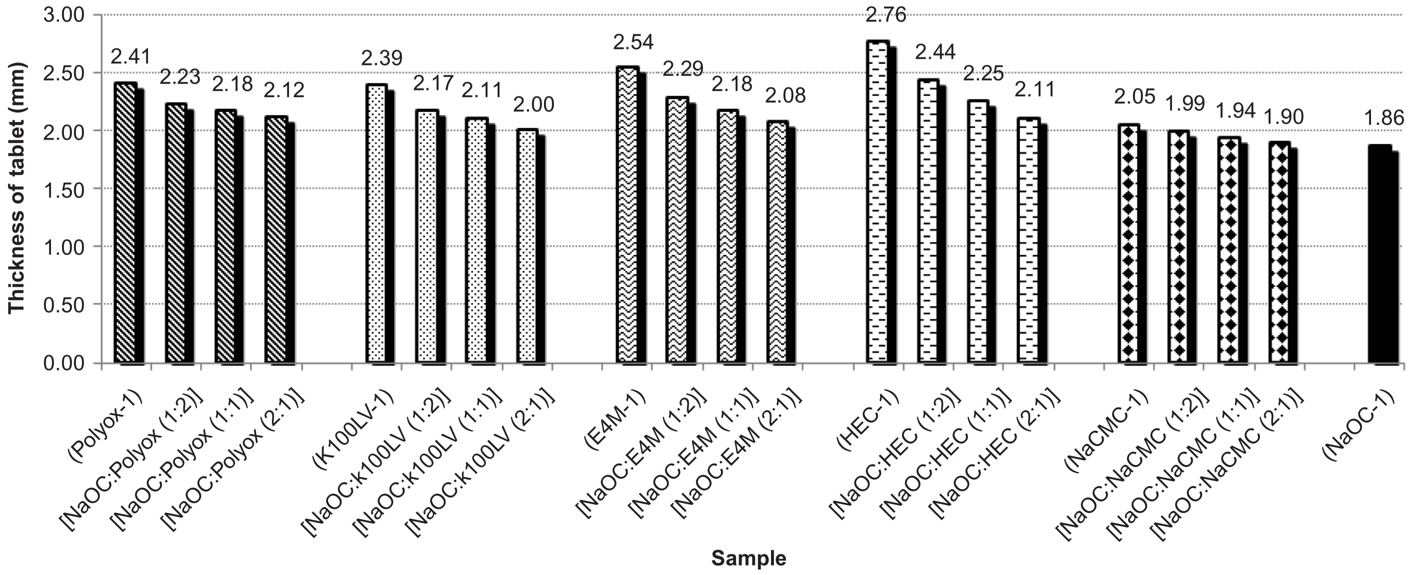

Figure 2. Tablet thickness. SDs of tablet thickness are not mentioned as their values were very small (<0.02).

Table 4. Tablet characteristics.

		Physicomechanical properties of tablets									
		Friability* (%)	Tablet surface pH*				Tablet average weight		In vitro residence time		Content uniformity (mg)
Group	Sample		t = 0 hour	t = 0.5 hour	t = 1 hour	t = 2 hours	mg	SD	Minutes	SD	
I	Polyox-1	0.02	6.80	6.91	6.98	7.02	99.7	0.7	>480	N.D.	4.68 ± 0.12
	NaOC:Polyox (1:2)	0.01	6.80	6.92	6.98	7.02	100.1	0.8	>480	N.D.	4.66 ± 0.14
	NaOC:Polyox (1:1)	0.01	6.80	6.94	6.99	7.06	102.8	0.6	> 480	N.D.	4.99 ± 0.31
	NaOC:Polyox (2:1)	0.02	6.80	6.92	6.97	7.03	103.2	1.4	384	5	5.21 ± 0.22
II	K100LV-1	0.01	6.80	6.94	6.98	7.04	102.9	1.1	422	17	5.18 ± 0.24
	NaOC:K100LV (1:2)	0.03	6.80	6.94	6.99	7.05	99.8	0.6	256	42	5.11 ± 0.18
	NaOC:K100LV (1:1)	0.03	6.80	6.94	6.99	7.04	100.9	0.9	63	15	5.03 ± 0.19
	NaOC:K100LV (2:1)	0.01	6.80	6.94	6.98	7.06	100.3	1.6	58	2	4.78 ± 0.16
III	E4M-1	0.01	6.80	6.94	6.98	7.05	100.8	0.3	>480	N.D.	4.62 ± 0.11
	NaOC:E4M (1:2)	0.10	6.80	6.95	7.01	7.06	100.1	0.5	240	22	4.84 ± 0.14
	NaOC:E4M (1:1)	0.04	6.80	6.95	6.99	7.05	99.9	0.8	174	12	5.12 ± 0.27
	NaOC:E4M (2:1)	0.03	6.80	6.95	6.99	7.06	100.2	0.7	119	7	5.11 ± 0.22
IV	HEC-1	3.44	6.80	6.94	6.99	7.05	101.9	1.2	1	N.D.	4.89 ± 0.15
	NaOC:HEC (1:2)	0.33	6.80	6.97	6.99	7.09	102.1	1.3	278	15	5.19 ± 0.09
	NaOC:HEC (1:1)	0.12	6.80	6.95	7.00	7.06	100.9	0.5	283	21	5.02 ± 0.07
	NaOC:HEC (2:1)	0.08	6.80	6.94	6.98	7.05	102.6	0.9	204	14	4.88 ± 0.12
V	NaCMC-1	0.79	6.80	6.95	6.99	7.07	100.3	1.1	360	31	4.78 ± 0.14
	NaOC:NaCMC (1:2)	0.04	6.80	6.97	7.02	7.07	102.1	0.8	262	28	4.71 ± 0.17
	NaOC:NaCMC (1:1)	0.03	6.80	6.97	7.02	7.08	100.3	0.6	268	15	4.69 ± 0.04
	NaOC:NaCMC (2:1)	0.01	6.80	6.96	7.01	7.06	100.4	0.9	233	16	4.73 ± 0.15
VI	NaOC-1	0.02	6.80	6.96	7.00	7.08	101.8	1.2	107	7	4.96 ± 0.26

*SDs are not mentioned, as their values were very small (<0.05).

(65 ± 5 kN), was determined in sample NaOC-1 (246.5 ± 6.4 N; Figure 3). Samples HEC-1, E4M-1, and NaCMC-1 showed the lowest hardness (i.e., 14.3; 22.6; 25.2 N), some of them (HEC-1) also connected with high friability. In all tested samples increasing hardness values were observed together with increased content of OC in a formulation (Figure 3). The same tendency was observed in graphical expression of tensile strength values.

Surface pH of mucoadhesive tablets

Surface pH of tablets was measured in isotonic phosphate buffer of pH 6.8. Within 2 hours lasting test, slowly increasing pH of IPB to neutral values (7.02–7.09, Table 4) was observed. These results correspond to chemical composition of most used polymers (Figure 4) that have no free carboxylic groups in the structure or the acidity of these groups is relatively weak, so the buffering capacity of IPB is strong enough to ensure neutral surface pH of tablets. This could be advantageous compared with mucoadhesive formulations using polyacrylic acid derivates with acidic surface reaction (pH 3.5), as acidic reaction may induce mucosal irritation, inadequate salivary, and/or unpleasant feelings in patients oral cavity[8].

Measurement of mucoadhesive strength

Mucoadhesive properties of polymers are influenced by several factors, such as molecular weight, polymer surface microstructure, polymer chain flexibility, cross-linking density, polymer concentration, and polar groups' concentration, influencing polymer hydrogen-bonding capacity, hydration speed, and capacity[44]. It was observed that the mucoadhesive properties of polymer sodium salts are higher than those of their analogous parent molecules[45]. This phenomenon may be attributed to the water uptake increase because of the presence of sodium ions in polymer molecule. Ionic concentration inside the polymeric network creates osmotic pressure resulting in facilitating entrance of water inside the network, swelling of the polymer, and interpenetrating of polymer chains and mucus structures, one of the primary determinations of mucoadhesive potential.

Sample of NaOC-1 tablets showed the highest mucoadhesive strength (Figure 5). The addition of NaOC to most of the other polymers (HEC, NaCMC, and E4M) caused the improvement in tablet mucoadhesive strength. Thus considerable improvement (more than three times) was reached in NaOC:NaCMC (2:1) tablets

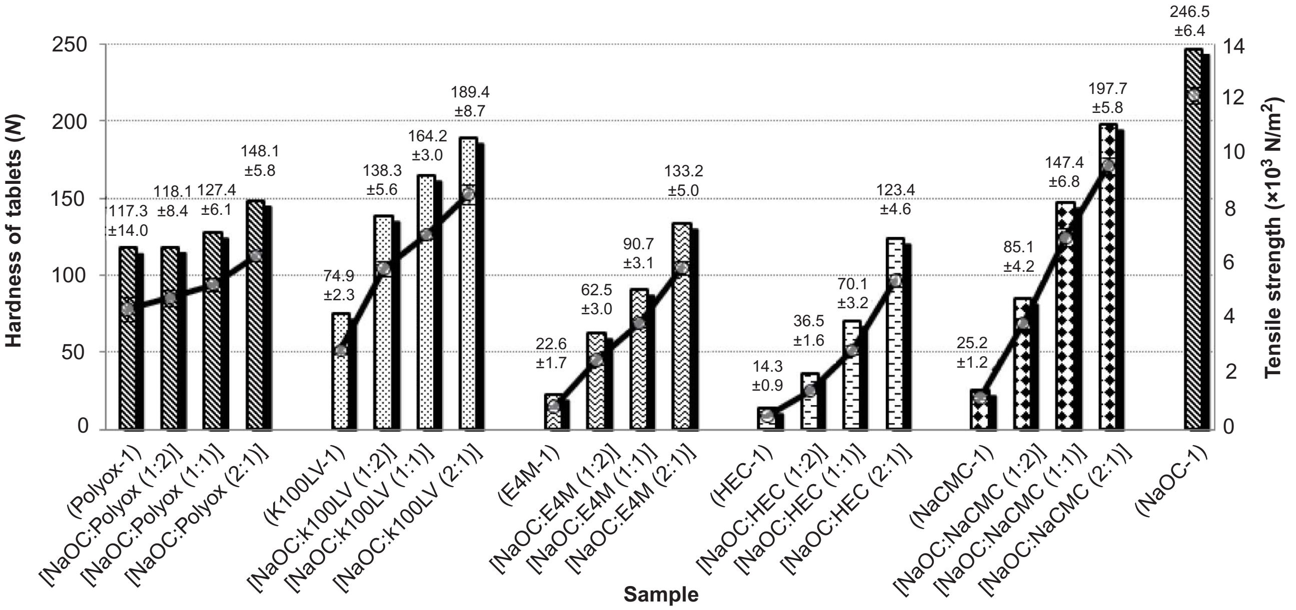

Figure 3. Tablet hardness and tensile strength.

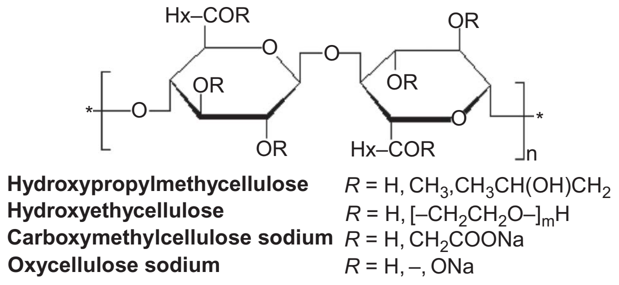

Figure 4. Chemical structures of used cellulose derivatives.

(8.30 ± 0.45 vs. 2.43 ± 0.29 mN/mm^2). The increase in mucoadhesive strength was also significant in tablets containing HEC with the lowest mucoadhesivity at all. In this case, the addition of NaOC enhanced the force from 0.32 mN/mm^2 (HEC-1) to 3.32 ± 0.53 mN/mm^2 [NaOC:HEC (2:1)]. The lowest mucoadhesive strength of HEC-1 tablets could be explained by low viscosity of HEC and its low water uptake capacity leading to the formation of unstable gel layer, which is concerned in the creation of mucoadhesive bonds. The improvement of mucoadhesive strength of tablets from this group containing higher amount of NaOC could be caused by interpolymer synergistic interactions between non-ionic (HEC) and ionic (NaOC) polymer, resulting in the stabilization of mucoadhesive gel barrier[46]. The mucoadhesive strength of tablets containing only one mucoadhesive polymer as a carrier decreased in rank order:NaOC-1 > Polyox-1 > K100LV-1 > NaCMC-1 > E4M-1 > HEC-1. In comparison, mucoadhesive strengths of samples having mucoadhesive polymer ratio with NaOC 1:1 decreased in a sequence: NaOC: NaCMC (1:1), NaOC:Polyox (1:1), NaOC:K100LV (1:1), NaOC:E4M (1:1), and NaOC:HEC (1:1). This may be attributed to a different way of formation of mucoadhesive bonds between polymer and mucus components. NaOC and NaCMC as the representatives of sodium salts of anionic polymers with a great occurrence of carboxyl groups in polymer chains interact with mucin at the base of relatively strong hydrogen and electrostatic bonds with mucus glycoproteins[44]. Strong mucoadhesive properties of Polyox are based on another binding mechanism to the mucosal surface. This interaction, as presented in the literature[47], comes from rapid swelling of this polymer, interpenetrating of polymer chains into the mucin network and creating secondary chemical (van der Waals) bonds. Stronger mucoadhesivity of HPMC-type K100LV compared with E4M could be caused by lower viscosity and molecular weight of type K100LV and presence of only about 19–24% of hydrophobic methoxyl groups in the polymer versus 28–30% of methoxyl groups in E4M, which enables faster hydration, that is, the basic presumption of mucoadhesion and incorporation of K100LV polymer chains into the mucus network[48].

Water uptake studies

Figure 6 demonstrates swelling profiles of all tested samples of mucoadhesive tablets measured as a change

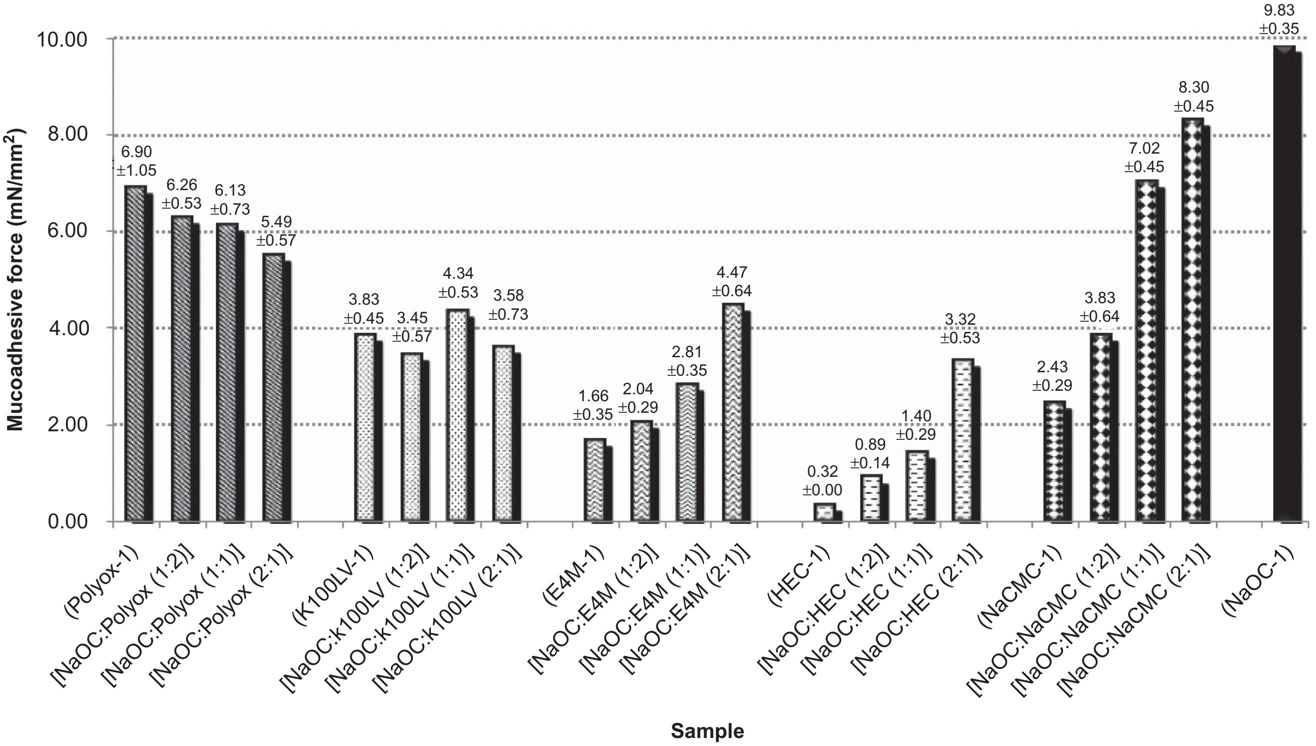

Figure 5. Comparison of mucoadhesive strength of tablets.

in tablet weight (%) during 8 hours testing period (Table 5 presents SD values of this experiment). NaOC-1 tablets showed moderate weight growth only in the first half an hour and then the tablet weight started to decrease slowly, because of fast dissolution of tablet matrix. Similar tendency, explainable with low mechanical durability (hardness 14.3 ± 0.9 N, friability 3.44%), was observed in HEC-1 tablets.

Within Group I, the hydrating profiles of all samples were quite similar, with maximum water uptake after 6 hours, when all samples reached minimally eightfold of their initial weight. Exceptional behavior showed sample Polyox-1, whose hydrating capacity was not exhausted and the weights of tablets were slowly increasing during the whole testing period indicating that Polyox® WSR301 has high potential for water uptake within long time period (Figure 6). Concerning the other samples from Group I, the weight of tablets decreased during last 2 hours of the test because of slow erosion of the matrix, related to NaOC dissolution.

Tablets from Group II (Figure 6) had moderate hydrating profiles. The maximum water uptake embodied sample NaOC:K100LV (2:1) and NaOC:K100LV (1:1) (maximum weight of tablet 614.1 and 595.4 mg after 4 hours). Swelling maximum of samples K100LV-1 and NaOC:K100LV (1:2) was reached after 6 hours in IPB when matrix erosion started to predominate. All three samples composed from mucoadhesive polymeric mixtures embodied higher hydrating capacities than samples containing NaOC or K100LV only. This phenomenon could be explained by creating of physicochemical bonds between carboxylic groups of NaOC and free hydroxyl groups of K100LV, because this interaction matrix swelling could increase[49].

Similar tendency in swelling and water uptake was observed also in tablets of Group III containing HPMC E4M. Main difference between Groups II and III was in the swelling capacity. Higher viscosity (Table 3) and the formation of stronger gel barrier by HPMC E4M caused, that samples from Group III showed, almost two times higher water uptake capacity than samples from Group II.

Samples from Group IV containing HEC and NaOC as mucoadhesive polymers demonstrated the lowest water uptake probably because of a combination of two polymers with rapid solubility in water (NaOC-1 and HEC-1), resulting in fast matrix dissolution. The weight of tablets in sample HEC-1 increased within first 30 minutes from 101.9 to 380.9 mg and then decreased rapidly to 158.0 mg after 1 hour. This fact was supported by insufficient mechanical properties of these tablets (very low hardness 14.3 N and great friability 3.34%), which enabled fast entrance of water into this polymeric matrix. Rapid dissolution of matrices is partially moderated in

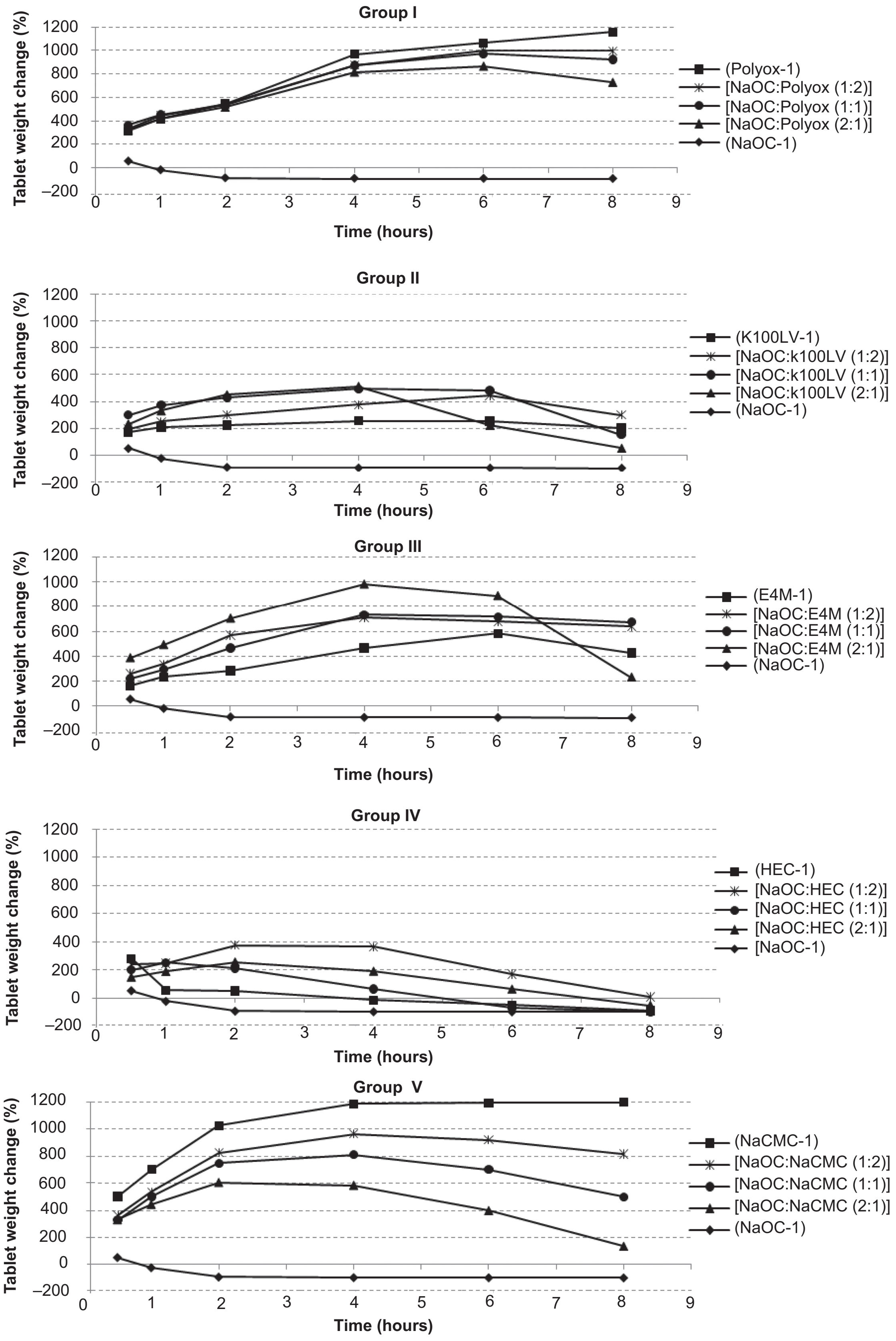

Figure 6. Water uptake studies.

Table 5. SD values of water uptake and dissolution studies.

	Water uptake						Dissolution studies						
	SD (%)						SD (%)						
	Time (hours)						Time (hours)						
Sample	**0.5**	**1**	**2**	**4**	**6**	**8**	**0.25**	**0.5**	**1**	**2**	**4**	**6**	**8**
Polyox-1	19.2	20.1	64.0	50.3	17.1	33.8	2.4	1.6	1.3	1.6	1.8	1.0	5.7
NaOC:Polyox (1:2)	58.7	41.5	38.6	33.8	54.4	41.1	2.9	0.6	2.5	1.5	3.0	1.6	5.1
NaOC:Polyox (1:1)	48.8	36.7	7.4	37.3	21.3	24.5	2.0	2.3	4.7	1.9	4.3	1.0	2.7
NaOC:Polyox (2:1)	40.3	49.5	53.1	45.2	64.3	55.3	1.1	1.7	2.3	0.1	6.3	1.5	2.5
K100LV-1	27.2	7.8	21.1	36.5	34.1	45.8	1.4	0.5	1.5	1.5	2.5	3.6	2.8
NaOC:K100LV (1:2)	31.4	35.8	36.5	43.1	19.1	47.9	0.9	3.1	0.8	2.0	4.4	6.0	3.2
NaOC:K100LV (1:1)	48.6	52.1	45.1	10.4	32.1	31.7	1.4	1.1	1.0	1.6	3.4	3.2	2.4
NaOC:K100LV (2:1)	47.2	13.2	48.1	48.2	22.1	53.9	0.2	1.4	4.2	5.2	3.3	3.4	3.2
E4M-1	26.4	25.9	47.7	43.8	52.3	41.3	2.1	3.0	4.1	3.4	1.0	5.7	5.5
NaOC:E4M (1:2)	12.7	26.2	40.9	13.1	2.5	4.5	0.5	0.8	0.6	3.2	4.6	1.1	1.2
NaOC:E4M (1:1)	52.3	57.0	52.4	57.7	59.8	43.4	0.1	1.3	1.3	1.3	3.2	3.7	2.8
NaOC:E4M (2:1)	40.7	42.6	47.5	54.0	63.3	59.1	0.7	0.8	1.1	1.5	1.4	5.0	1.4
HEC-1	47.8	21.6	43.7	10.1	16.3	12.2	2.3	2.7	3.9	3.5	3.3	3.2	3.3
NaOC:HEC (1:2)	51.3	56.2	44.0	37.0	21.2	32.7	1.7	1.7	4.7	4.1	6.1	5.0	4.8
NaOC:HEC (1:1)	23.5	25.7	35.1	20.6	18.1	2.6	0.7	3.0	4.2	3.6	3.7	3.2	4.1
NaOC:HEC (2:1)	13.5	20.2	22.0	48.5	35.5	27.8	1.8	3.8	4.0	3.5	3.8	1.5	2.4
NaCMC-1	15.3	25.6	33.7	28.1	38.5	45.2	1.5	1.4	3.1	5.7	1.8	0.7	0.7
NaOC:NaCMC (1:2)	34.9	35.9	19.8	19.0	45.8	38.4	0.6	1.0	3.8	3.4	4.0	4.1	3.2
NaOC:NaCMC (1:1)	6.6	13.4	21.8	30.6	30.7	35.9	1.1	2.4	3.2	3.6	1.6	1.4	1.1
NaOC:NaCMC (2:1)	49.4	56.4	40.2	28.6	33.4	52.5	1.2	1.4	2.7	3.2	2.8	3.3	1.3
NaOC-1	1.5	14.5	4.7	3.7	3.2	3.6	0.9	2.7	0.9	3.1	2.8	2.3	2.4

samples NaOC:HEC (1:2), NaOC:HEC (1:1), NaOC: HEC (2:1) because of mucoadhesive polymers cross-linking interaction and more stable hydrogel barrier formation, reducing hydration of polymeric core and fast dissolution of the matrix. These cross-linking interactions between ionic and nonionic polymers depend on the substitution characteristics of polymers that provide the same number of interacting groups[50].

Swelling properties of tablets belonging to Group V are directly depending on the ratio of NaOC in a formulation (Figure 6). Samples of tablets NaCMC-1 increased their weight more than 12-fold (from 100.3 to 1285.6 mg) within first 4 hours of the test. Water uptake capacity of other samples was gradually decreasing with increasing NaOC concentration in the formulation. In following 4 hours of the experiment, a decrease in swollen tablet weights was measured. This phenomenon was as significant as the amount of NaOC in formulation increased and could be explained by the solubility of tablets with higher content of NaOC.

In vitro residence time

A modified disintegration apparatus was used to determine in vitro residence time of wetted tablets attached to artificial mucosa as described above. The longest in vitro residence time (>8 hours) was determined in samples containing Polyox alone (Polyox-1), NaOC-Polyox mixtures [NaOC:Polyox (1:2), NaOC:Polyox (1:1)], and HPMC E4M alone (E4M-1) (Table 4). No correlation was found between mucoadhesive strength and in vitro residence time of the tablets. On the contrary, it could be observed that all four mentioned samples exhibited high viscosity values of water dispersions of used polymer mixtures (>750 Pa·s). It seems that tablets formed from polymers exhibiting high values of mucoadhesive strength do not necessarily reside longer on the artificial mucosal surface. Surface charge density and chain flexibility are considered to be prerequisites for mucoadhesion, whereas the residence time is dependent also on the dissolution rate of the polymer and the stability of gel barrier formed on the surface of mucoadhesive tablet[6]. It was determined that despite the highest mucoadhesive strength of sample NaOC-1 (9.83 ± 0.35 mN/mm^2), its in vitro residence time was only 107 ± 7 minutes. This could be caused by higher solubility of OC matrices, low viscosity of NaOC dispersions in water, and because of the unstable surface gel barrier formation. Fast dissolution and lowest water uptake of NaOC-1 tablets could also contribute to their short time of residence despite NaOC mucoadhesive properties. This tendency was observed for all samples containing higher amount of NaOC, and it was accompanied with increasing tablet dissolution and a decrease in aqueous dispersions viscosities. Thus in Group II, in vitro residence time decreased from 422 ± 17 minutes (sample K100LV-1) to 58 ± 2 minutes [sample NaOC:K100LV (2:1)], in Group III from more than 480 minutes (E4M-1) to 119 ± 7 minutes [NaOC:E4M (2:1)], because of its slower hydration in first half an hour of the experiment (similarly as K100LV-1) (Figure 6) and, however, much higher viscosity (more than 14 times) of its aqueous dispersion than K100LV-1 sample (Table 3).

HEC-1 tablets exhibited in vitro residence time of only 1 minute as they completely dissolved. The shortest time of mucoadhesion was influenced by the weakest mucoadhesive bonds (0.32 N), fast dissolution, and insufficient mechanical properties of hydroxyethylcellulose tablets, which implicate their rapid disintegration. Samples NaOC:HEC (1:2), NaOC:HEC (1:1), and NaOC:HEC (2:1) embodied considerable prolongation of residence time (278 ± 15 minutes, 283 ± 21 minutes, and 204 ± 14 minutes, respectively). Residence time of the last sample decreased because of high NaOC content and its fast solubility. All samples from Group V, containing NaCMC, had relatively long residence times between 360 ± 31 minutes (NaCMC-1) and 233 ± 16 minutes [NaOC:NaCMC (2:1)], caused by high content of carboxylic groups together with sodium ions of these polymers, forming hydrogen and electrostatic force bonds with mucin components. All tested tablets remained attached to the mucus surface and did not separate until their complete erosion or dissolution.

Content uniformity

The theoretical content of CPC in tablets should be 5.0 mg. The true mean drug content measured from all samples was 4.91 ± 0.20 mg (calculated from calibration equation for CPC in distilled water with linearity range $r^2 = 0.999$). The lowest drug content was measured in sample E4M-1 (4.62 ± 0.11 mg) and the highest by sample NaOC:Polyox (2:1) (5.21 ± 0.22 mg; Table 4). All the tested samples were within pharmacopoeia limits and indicated good reproducibility.

In vitro dissolution testing

Drug release from hydrophilic matrices is a complex phenomenon including several different physical processes. In particular, the formation and physical properties of the hydrated surface barrier are important determinants of drug release performance. This gel layer formation and its stability, which together with the properties of active pharmaceutical ingredient define the kinetics of drug delivery from matrix systems, are controlled by the concentration, viscosity, and chemical structure of the polymers[51].

NaOC-1 sample, chosen as a reference, showed CPC dissolution profile with strong burst effect (86.44% of the model drug was released in first 60 minutes; Figure 7) and its complete release after 4 hours of dissolution testing. It may be attributed to fast dissolution of matrix tablets connected with rapid solubility of NaOC and low viscosity (27.848 Pa·s) of formed surface gel layer. For tablets composed of individual polymers, similar tendency has been observed in HEC-1 and NaCMC-1 tablets. Dissolution of HEC-1 tablets can be explained by substandard mechanical properties of these tablets (friability 3.44%, hardness 14.3 ± 0.9 N), low viscosity of surface gel layer (112 Pa·s), and fast dissolution of this tablet sample. Drug release from NaCMC-1 was slightly prolonged up to 4 hours. On one hand these tablets showed high viscosity values (>2000 Pa·s); on the other hand high water uptake and fairly good dissolution of this polymer were the reasons of insufficiently prolonged drug release.

All samples from Group I, containing Polyox as the mucoadhesive polymer, showed incomplete drug release lower than 60% after 8 hours of testing (Figure 7). Polyox formed long-lasting stable gel barrier on the tablet surface, retarding drug release. The slowest drug release profile (15.75% after 8 hours) was observed in sample NaOC: Polyox (1:2). This phenomenon could be explained by optimal ratio of participating ionic and nonionic polymer to achieve the maximum synergistic effect of interactions[50]. This explanation could not be supported by experimental data, because viscosity value of NaOC:Polyox (1:2) mixture is higher than measurable 2000 Pa·s, as well as in sample Polyox-1 with 59.11% released CPC in 8 hours. In samples NaOC: Polyox (1:1) and NaOC:Polyox (2:1), the influence of NaOC solubility predominated above the possible interactions and because of this 40.68% and 56.15% of CPC were released from tablets after an 8-hour dissolution test.

In Group II, samples NaOC:K100LV (1:1) and NaOC: K100LV (2:1) released only 55.96% and 45.81% of CPC, respectively, during the dissolution test, because of the possible interaction of HPMC and NaOC mentioned above[50]. From the dissolution profiles (Figure 7), it could be observed that sample K100LV-1 released 79.36% of CPC during dissolution test, probably because of the absence of carrying polymer interaction. Faster drug release (84.99%) has been determined in sample NaOC:K100LV (1:2), which could be explained by mucoadhesive polymer ratio outside of optimum for their interaction and NaOC content causing faster CPC release compared to K100LV-1.

Samples from Group III containing HPMC E4M of high viscosity grade showed incomplete dissolution less than 60% of released CPC in 8 hours (Figure 7). With increasing NaOC concentration drug release increased although the differences between dissolution profiles of NaOC:E4M (1:1) and NaOC:E4M (1:2) were very small.

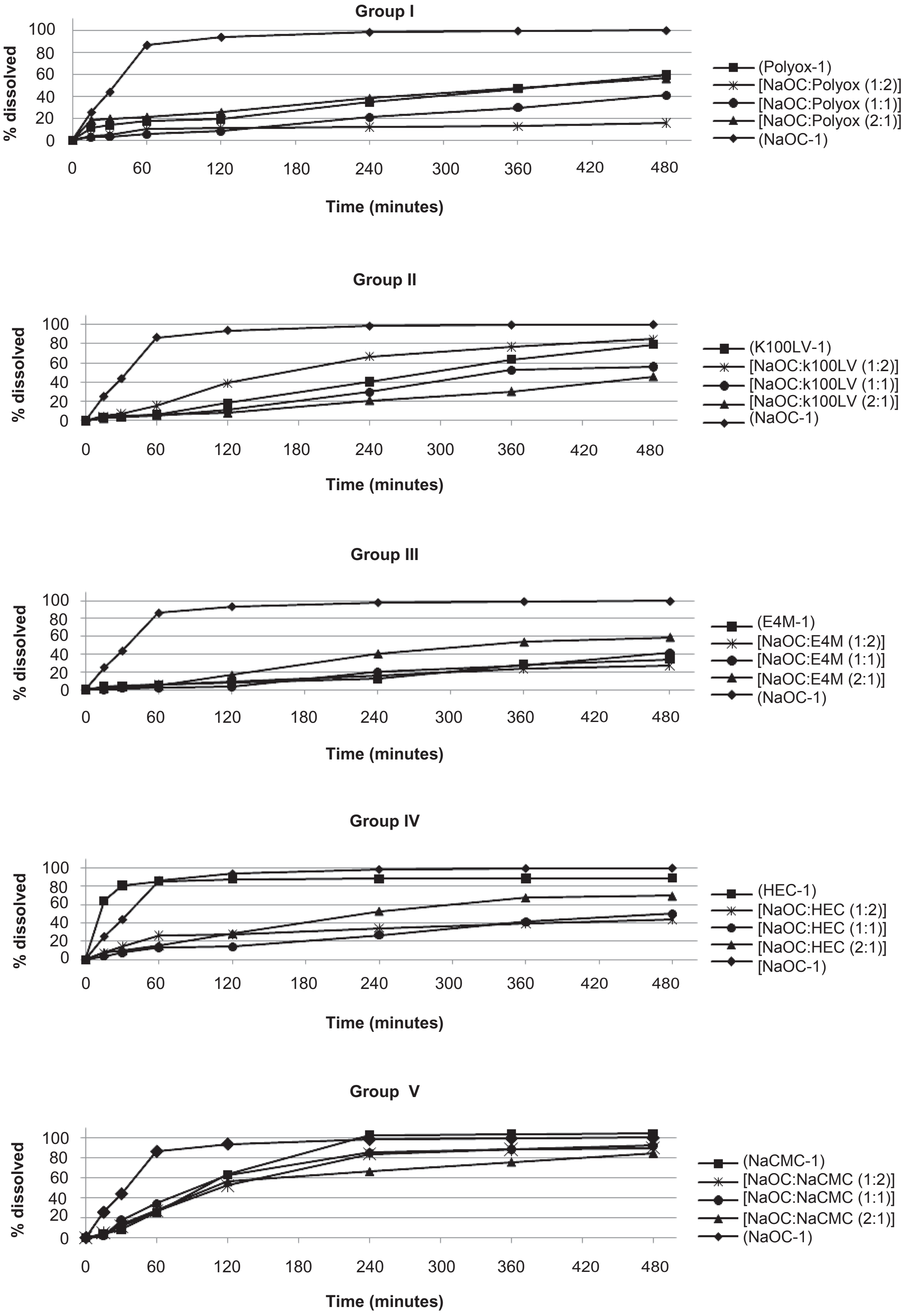

Figure 7. Dissolution profiles.

Similar dissolution profile was noticed also in E4M-1. These results could be ascribed to HPMC E4M slower hydration and dissolution because of higher content of hydrophobic methoxyl groups when compared to K100LV[48]. These characteristics together with significantly higher viscosity of gel layer cause slow CPC dissolution profiles. The influence of higher NaOC solubility was noticed in sample NaOC:E4M (2:1), which released 58.92% of CPC within the dissolution testing.

HEC-1 tablets released 85.60% of CPC during the first hour of dissolution (Figure 7), because of their fast disintegration and dissolution. Despite this strong burst effect, the drug release was incomplete. This phenomenon could be explained by the affinity of positively charged quaternary nitrogen present in CPC molecules to 'anionic centers' (i.e., hydroxyl groups) of used mucoadhesive polymers. These bonds could lead to CPC–HEC complex formation, which could cause incomplete drug release.

Tablets containing only one of anionic mucoadhesive polymers (i.e., NaOC or NaCMC) released CPC relatively fast (Figure 7). Combination of both polymers improved their gel-forming properties that led to prolonged dissolution of CPC from samples NaOC:NaCMC (1:2), NaOC:NaCMC (1:1), and NaOC:NaCMC (2:1) that released 89.80%, 91.89%, and 84.67% of CPC (Figure 7). From the dissolution point of view, their profiles seemed optimal.

Conclusions

This experimental study confirmed that NaOC is an appropriate excipient for mucoadhesive solid dosage forms. Best formulations of buccal tablets were selected on the base of the obtained results, that is, physicochemical parameters, mucoadhesive characteristics, and drug dissolution profiles. Group I tablets, containing Polyox and NaOC as mucoadhesive polymers, showed the best mucoadhesive properties; however, drug release was slow ranging from 15.75% to 59.11% after 8 hours of dissolution testing. Similarly, a combination of NaOC and high-viscous type of HPMC E4M (Group III) also resulted in the formation of tablets of good characteristics but slow dissolution profiles. This problem could be solved by soluble filler addition, for instance mannitol, sucrose, or lactose, improving also the tablets' taste. Sample NaOC:K100LV (1:2) from Group II could be because of its physicochemical properties (friability 0.03%, tablet thickness 2.17 mm, tablet hardness 138.3 ± 5.6 N, low tendency to water uptake), mucoadhesive properties (residence time 256 ± 42 minutes, mucoadhesive strength 3.45 ± 0.57 mN/mm^2), and dissolution profile (84.99 ± 3.17% of CPC released within 8 hours), a good candidate for in vivo testing. Also samples NaOC:NaCMC (1:2) and NaOC:NaCMC (1:1) from Group V reached both good physicochemical and mucoadhesive properties (friability < 0.04%, tablet thickness < 1.99 mm, tablet hardness > 85 N, residence time > 260 minutes, mucoadhesive strength > 3.8 mN/mm^2), and dissolution profiles (more than 81% of CPC released within 8 hours) that make them suitable candidates for further experiments.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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