

# SYNTHESIS AND PHYSICOCHEMICAL EVALUATION OF A NEW CARRIER BASED ON AN INTERPOLYELECTROLYTE COMPLEX FORMED BY EUDRAGIT® EPO AND CARBOMER 940

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The formation of interpolyelectrolyte complexes (IPEC) between Eudragit® EPO (EPO) and Carbomer 940 (C940) was investigated with a view to their use in peroral controlled-release drug delivery systems. The structure of the synthesized products was investigated using FTIR spectroscopy and MT—DSC methods, which indicated that the synthesized product can be considered to be an IPEC stabilized by a cooperative system of ionic bonds. Based on results of capillary viscosimetry and elemental analysis, the IPEC prepared at pH 4.0 has a characteristic composition with a C940:EPO mole ratio of 1.75:1.

**Key words:** interpolyelectrolyte complexes, Eudragit® EPO, Carbomer 940, physicochemical properties.

Matrix peroral delivery systems of interpolymer complexes are currently highly interesting to scientists around the world. These are one of the most promising classes of drug carriers and include nanoparticles [1 – 4]. Interpolyelectrolyte complexes (IPEC) result from the reaction of chemically complementary oppositely charged macromolecules. Thus, the study of the possibility of forming polycomplexes with the well-known and widely used (co)polymers of (meth)acrylic acid is definitely interesting. Among such polymers, copolymers produced by the German company Evonik Rohm GmbH under the name Eudragit® deserve special mention [5]. The potential of using IPEC incorporating various types of oppositely charged Eudragit® as polymeric drug carriers has not yet been demonstrated [6 – 9]. However, interpolyelectrolyte coupling of cationic types of Eudragit® to slightly cross-linked acrylic copolymers, which also are broadly used to prepare various drug excipients, seems highly interesting to us. The most well-known brands offered on the world pharmaceutical market are Carbomers, which are included in many of the world's pharmacopoeias. A feature of these polymers is the loss of solubility with a small number of covalent bridging bonds between the macromolecules and the ability to swell

greatly in a solvent [10]. Considering that the monomeric structural fragment is acrylic acid, these polymers have carboxylic acids that are responsible for their polyanionic properties in certain media.

Our goal was to study the preparation, structure, and composition of an IPEC involving slightly cross-linked polyacrylic acid produced under the name Carbomer 940 and the linear polycationic copolymer Eudragit® type E, which is intended mainly for preparing gastric-soluble coatings. The IPEC based on the studied copolymers has not yet been studied.

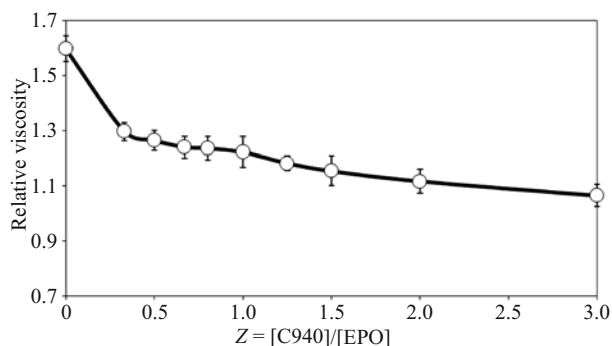
## EXPERIMENTAL PART

We used Eudragit® grade EPO (EPO) (Evonik Rohm GmbH, Germany) of average molecular weight 150,000 and Carbomer 940 (C940) (Federa, Belgium) with average molecular weight 1,500,000. The molecular weight of the (co)polymer unit was used to prepare solutions and dispersions of the polyelectrolytes (PE).

The viscosity of the supernatant solution was measured by preparing samples of the cross-linked polymer by swelling the PE (0.075 – 0.0083 M) for 24 h in acetate buffer at pH 4.0. Then, the samples of the swelled gel with various concentrations of the polyanion were treated with an identical amount of EPO solution (0.025 M) prepared in acetate buffer at the same pH value. The viscosity was determined in

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**Fig. 1.** Relative viscosity as a function of reaction mixture composition  $Z = [\text{C940}]/[\text{EPO}]$ . Along the abscissa, IPEC composition ( $Z$ ), where  $Z = 3$  corresponds to a three-fold excess of C940;  $Z = 0.33$ , its three-fold deficiency at constant EPO concentration in the mixture (0.025 M);  $Z = 0$ , viscosity of starting EPO solution

a Ubbelohde viscosimeter with capillary diameter 0.56 at  $20 \pm 0.1^\circ\text{C}$  using a LORTS water thermostat (Russia).

The IPEC composition was determined using elemental analysis for C:N content on a CHN-3 analyzer (Russia).

IR spectra were recorded in KBr disks on a Bruker FT-IR Vector 22 instrument (Germany).

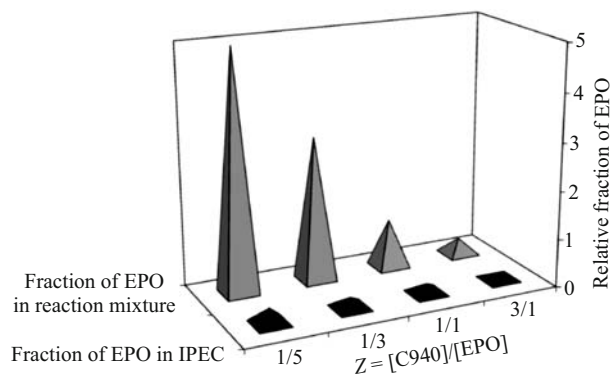
Samples were analyzed using a modeled-temperature differential scanning calorimetry (MT-DSC) on a TA Instruments model 2930 instrument (England). The temperature range was from  $-20$  to  $160^\circ\text{C}$  at heating rate  $2^\circ\text{C}/\text{min}$ . Indium was used to calibrate the instrument.

**IPEC synthesis.** Gel C940 (0.05 M, pH 4.0) was stirred and treated with EPO solution (0.05 M, pH 4.0) at constant temperature. The resulting system was left for 7 d. The supernatant solution was poured off. The precipitate was washed and dried to constant weight in vacuo for 2 d at  $40^\circ\text{C}$ .

## RESULTS AND DISCUSSION

A combination of several methods such as viscosimetry, elemental analysis, IR spectroscopy, and MT-DSC was used to evaluate the effects of different factors on the composition of the produced IPEC. This enabled us to answer clearly the questions of how the ratio of components in the reaction mixture, the solution pH, and the degree of ionization of the polymers affect the final composition of the produced IPEC.

Capillary viscosimetry (Fig. 1) showed that the presence of an excess of C940 in the mixture (right part of the curve) caused a smooth slight decrease of the relative viscosity that was due to binding of the EPO that was present in smaller quantities. In those samples where the EPO concentration corresponded to a 1.5–3-fold excess over the cross-linked polymer (left part of the curve), the additional amount of the linear polyelectrolyte was practically not incorporated as its concentration in the reaction mixture increased (plateau in the range  $0.33 < Z < 1$ ). Elemental analysis found that the ratio of components in the reaction mixture did not have a sig-



**Fig. 2.** Comparison of Eudragit® EPO fraction in reaction mixture to Eudragit® EPO fraction in IPEC (according to elemental analysis).

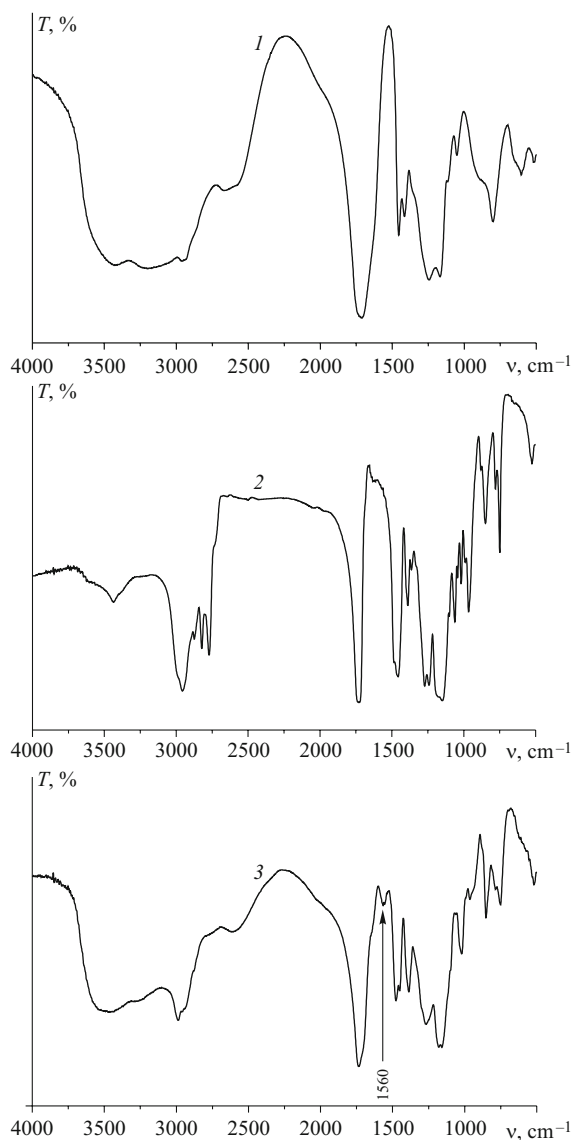
nificant influence on the composition of the produced IPEC (Fig. 2). A rather small amount of the linear copolymer was incorporated into the resulting IPEC when the IPEC was prepared at the same pH value but with a different ratio of reactants in the mixture. Even a five-fold excess of EPO in the mixture did not substantially increase its fraction in the IPEC. This agreed with the capillary viscosimetry data. The resulting IPEC had a characteristic composition corresponding to a C940/EPO mole ratio of 1.75:1.

IR spectroscopy was used to confirm that the IPEC formed. Figure 3 shows that the absorption band at  $1728\text{ cm}^{-1}$  was weaker for the IPEC sample than for the pure (co)polymers. This provided evidence that number of protonated carboxylic acids in the C940 decreased.

A new band at  $1560\text{ cm}^{-1}$  corresponding to stretching vibrations of ionized carboxylates of the polyanion appeared in the IR spectrum of the IPEC. This proved that the resulting IPEC was stabilized by a cooperative system of ionic bonds.

The IR spectrum of the isolated IPEC lacked characteristic bands at  $2820$  and  $2770\text{ cm}^{-1}$  for stretching vibrations of non-ionized aliphatic dimethylamino groups. However, two new bands of medium intensity at  $2720$  and of weak intensity at  $2510$  appeared. According to the literature, these correspond to absorption of salts formed by tertiary amines, the characteristic bands of which are shifted to low-wavelength and appear in the range  $2750 - 2250$ . The results agreed fully with data reported in the literature for polycomplexes formed by oppositely charged types of Eudragit® E/L [6–9].

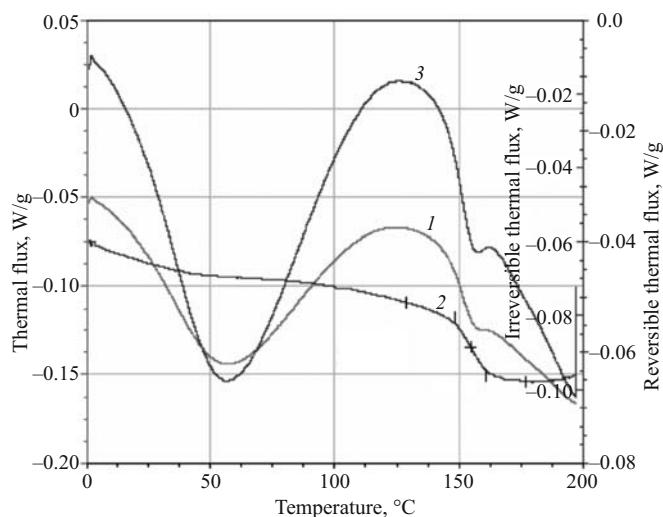
The IPEC was characterized by a single glassification temperature according to the DSC thermogram (Fig. 4, curve 2). The pure (co)polymers, according to our own research and that reported in the literature, had different and very distinct glassification temperatures: EPO,  $54.06^\circ\text{C}$ ; C940,  $130^\circ\text{C}$  [9, 11]. The synthesized IPEC not only contained inclusions of microdomains of the free linear copolymer but also had a glassification temperature that was higher than that of the starting components ( $T_g$ ,  $154.81 \pm 0.2^\circ\text{C}$ ). This indicated that a cooperative system of ionic bonds contributed



**Fig. 3.** IR spectra of Carbomer 940 (1), Eudragit<sup>®</sup> EPO (2), and IPEC,  $Z = 1.75$  (3).

perceptibly to the stability and strength of the produced IPEC.

Thus, the C940/EPO IPEC that we produced was according to the results a pure chemical compound consisting of a polycomplex stabilized by a cooperative system of ionic bonds between the slightly cross-linked polyacid (C940) and the linear polyamine (EPO). Keeping in mind the studied structural and compositional features of the synthesized



**Fig. 4.** MT—DSC thermogram of IPEC Carbomer 940/Eudragit<sup>®</sup> EPO ( $Z = 1.75$ ); along the abscissa, temperature ( $^{\circ}\text{C}$ ); along the ordinate, thermal flux (1), reversible thermal flux (2), irreversible thermal flux (3) (W/g).

IPEC, further physicochemical and biopharmaceutical studies must be performed in order to evaluate the possibility of using it as a drug carrier.

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