DRUG SYNTHESIS METHODS AND MANUFACTURING TECHNOLOGY

DIFFUSION-TRANSPORT PROPERTIES OF A POLYCOMPLEX MATRIX SYSTEM BASED ON EUDRAGIT® EPO AND CARBOMER 940

R. I. Mustafin,[1] T. V. Kabanova,[1] E. R. Zhdanova,[1] A. V. Bukhovets,[1] V. R. Garipova,[1] Sh. F. Nasibullin,[1] and V. A. Kemenova[2]

Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 44, No. 3, pp. 38 – 41, March, 2010.

Original article submitted November 5, 2009.

New interpolyelectrolyte complexes (IPEC) between Eudragit® EPO (EPO) and Carbomer 940 (C940) were synthesized for assessment as controlled-release delivery carriers for oral systems. Depending on the structural properties, the resulting IPEC were distinct from the individual (co)polymers and their physical mixtures in terms of their swelling profiles in media simulating the gastrointestinal tract. Changes in structure and composition occurring within the polycomplex matrix on swelling were studied by IR spectroscopy, MT-DSC (modulated temperature differential scanning calorimetry), and elemental analysis. The mechanism underlying the transport of the model drug ibuprofen from the polycomplex matrix was identified.

Key words: Polycomplex, controlled release, ibuprofen, Eudragit®, Carbomer 940.

Studies creating oral carriers for the controlled transport of drugs to the site optimal for their absorption in the gastrointestinal tract (GIT) have current relevance. However, the introduction of new synthetic polymer compounds is associated with a risk of unpredictable toxicity, which is generally due to residual monomers, organic solvents, and oligomeric fragments of polymer chains formed by metabolic processes [1 – 3]. In this regard, modification of the structures of polymer excipients which have been widely used for decades, without using physiologically unsafe chemical reagents, is one of the most promising approaches to generating controlled changes in the properties of polymers. One such possibility consists of preparing interpolyelectrolyte complexes (IPEC) consisting of oppositely charged macromolecules. This type of physical modification of polymer structures resulting from the formation of intermolecular ionic bonds is frequently additionally stabilized by proton-acceptor and hydrophobic interactions and produces new compounds with controlled changes in their properties [4, 5]. It is evident that the products of this type of interaction between two polymers can only result in decreases in toxicity, because of screening of chemically active ionogenic groups.

We have reported the first studies and characterization of a new IPEC based on Carbomer 940 and the intestinally soluble copolymer Eudragit® EPO [6, 7].

The aim of the present work was to assess the possibility of using this polycomplex based on Carbomer 940 and Eudragit® EPO as a carrier for oral, controlled-release transport of a model drug, i.e., ibuprofen.

EXPERIMENTAL SECTION

Studies were performed using Eudragit® EPO (EPO) from Evonik Röhm GmbH (Germany) with a mean molecular weight of 150,000 and Carbomer 940 (C940) from Federa (Belgium) with a mean molecular weight of 1,500,000. Preparation of polyelectrolyte solutions was based on the mean molecular weights of the copolymer units. The polycomplex was synthesized and purified as described previously [6, 7]. The model drug was ibuprofen (Sigma, USA).

[1] Medical University, Kazan', Russia.
[2] Science Research Center of Biomedical Technology, All-Russian Science Research Institute of Medicinal and Aromatic Plants, Moscow, Russia.

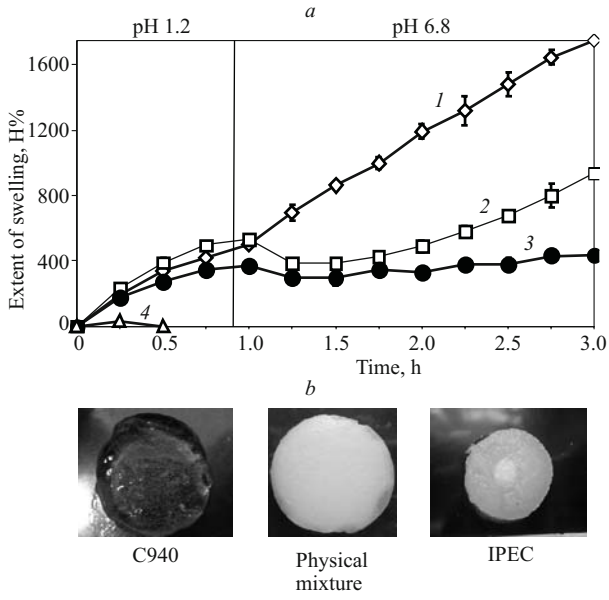

Fig. 1. Comparative characteristics of the swelling kinetics of individual polymers and the IPEC (*a*); external appearance of the matrix at the end of the experiment (*b*): *1*) C940; *2*) physical mixture; *3*) IPEC; *4*) EPO.

Preparation of polymer matrixes, evaluation of their swelling kinetics, and assessment of ibuprofen release were performed as described previously [8, 9]. IR spectra were recorded using samples pressed into KBr tablets on a Bruker FT-IR Vector 22 instrument (Germany). IPEC compositions were determined by elemental analysis for C and N using a CHN-3 analyzer (Russia). Samples were analyzed by modulated temperature differential scanning calorimetry (MT-DSC) using a model 2930 calorimeter from TA Instruments (England) over a temperature range from –20°C to 160°C at a rate of 2°C/min. The apparatus was calibrated using indium.

RESULTS AND DISCUSSION

The transport properties of matrix carriers are known to depend on their swelling characteristics in physiological media [3]. Thus, we determined the extent of swelling of polycomplex matrixes in conditions simulating passage through the GIT. Comparison of the characteristics of individual polymers, their physical mixtures, and the C940/EPO polycomplex demonstrated significant differences in their behavior (Fig. 1). One of the components of the IPEC, C940 (polyacrylic acid with a low level of cross-linking), has high swelling capacity. C940 showed a greater level of swelling than the physical mixture of polymers and the polycomplex.

The other component of the polycomplex, EPO, dissolves in acidic conditions simulating the stomach in 30 min, such that its swelling could not be assessed. The physical mixture of (co)polymers swelled uniformly over 6 h in phosphate buffer simulating the intestinal medium, which was due to the presence of C940, though the extent of swelling was smaller, perhaps because of interaction between the (co)polymers and the formation of a three-dimensional network structure of the IPEC throughout the volume of the tablet. Figure 1 shows visual differences between the matrixes consisting of these polymers, their mixture, and the IPEC. The photograph of the polycomplex matrix shows its layered structure consisting of an inner opaque nucleus and a highly swollen opalescent hydrogel layer. Given that the composition of the initial C940/EPO IPEC was, on the basis of elemental analysis [7], 1.75:1, we assessed possible compositional changes in the matrix during the period it was held in media simulating the GIT.

Thus, elemental analysis was performed at the end of experiments to determine the composition of the polycomplex in the outer gel layer of the matrix, where there was found to be a seven-fold molecular excess of C940 over EPO. At the same time, the inner layer of the tablet was a dense but fully hydrated gel with a composition of 3:1, i.e., a three-fold excess of the linked component (Fig. 2*a*). Thus, the process of swelling of the polycomplex matrix was accompanied by clear compositional differences. The question of possible structural changes was addressed using IR spectroscopy and MT-DSC.

The results showed that that the polycomplex was degraded in the outer gel layer (Fig. 2*b*) as evidenced by the fact that the IR spectra lacked the characteristic band at 1560 cm^{-1} corresponding to valent oscillation of ionized carboxyl groups in C940 linked by intermolecular ionic bonds with protonated dimethylamino groups in EPO [7]. At the same time, the polycomplex in the inner layer of the matrix did not degrade despite the changes detected in its composition. This is associated with the characteristic disproportionation of the linear copolymer with a radial distribution of EPO macromolecules from the center to the periphery throughout the volume of the matrix. Diffusion of the dissolution medium front was accompanied by degradation of the IPEC. The nucleus of the matrix, despite changes in its composition, retained its polycomplex structure. It is thus clear that the opalescence of the outer layer was due to the presence of unionized EPO macromolecules, which had lost solubility at neutral pH, on the surface of the swollen C940 microgel.

These structural and compositional changes in the polycomplex matrix during passage through media simulating the GIT were supported by MT-DSC data. Our previous studies established that the polycomplex composition of 1.75:1 has a glass transition temperature of 154°C [7]. Thermal analysis of the outer layer of the gel with a seven-fold excess of C940 showed it to have a marked endothermic effect at 50°C, i.e., close to the T_g of EPO, which is 54.06°C; the absence of the characteristic T_g of C940 at 130°C [10] had the result that the thermal change in the mobility of the network polymer was also not seen (Fig. 3*a*, curve *2*). The inner layer of the tablet, consisting of IPEC with a composition of 3:1, conversely,

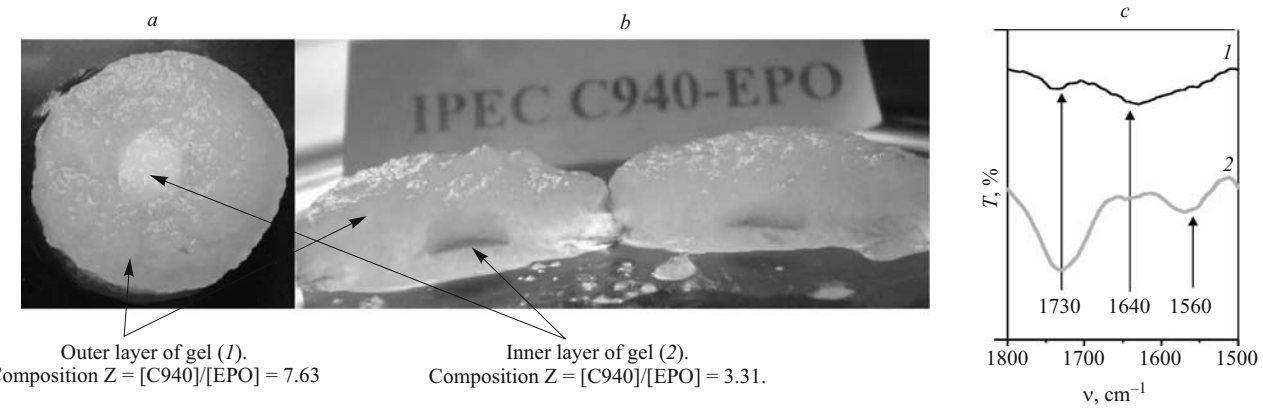

Fig. 2. Elemental analysis (*a*, *b*) and IR spectra (*c*) of the outer (*1*) and inner (*2*) layers of the polycomplex matrix after treatment with media simulating passage through the GIT.

had a marked and unique T_g at 163.52°C (Fig. 3*b*, curve *2*), which supports the polycomplex nature of its structure. The increase in T_g as compared with the initial IPEC resulted from the decrease in the proportion of the polycomplex component with the lower glass transition temperature (EPO), which is consistent with published data [11].

The contributions of the structural and compositional changes occurring in the polycomplex matrix in conditions simulating passage through the GIT were addressed by studying the kinetics of ibuprofen release from the matrix using individual polymers and the C940/EPO composition (Fig. 4). Given the acidification of the Carbomer-based matrix and the physicochemical properties of ibuprofen, drug release was slowest with this material. The profile of ibuprofen release from the EPO matrix resulted from the drug-copolymer interaction due to opposite charges as described in one of our previous reports [8]. The characteristics of drug release from the polycomplex matrix were due to possible binding of ionized ibuprofen molecules with EPO macromolecules freely oriented in the outer layer and located in so-called "defective" areas of the IPEC in the inner layer of the matrix.

Thus, physicochemical studies of structural and compositional changes occurring within the pH-sensitive polycomplex matrix revealed a putative mechanism for the transport of a model drug in conditions simulating passage through the GIT. Studies of the properties of the Carbomer 940/Eudragit® EPO IPEC indicated that it may have value in further biopharmaceutical studies addressing its possible use as a potential polymer carrier for drugs.

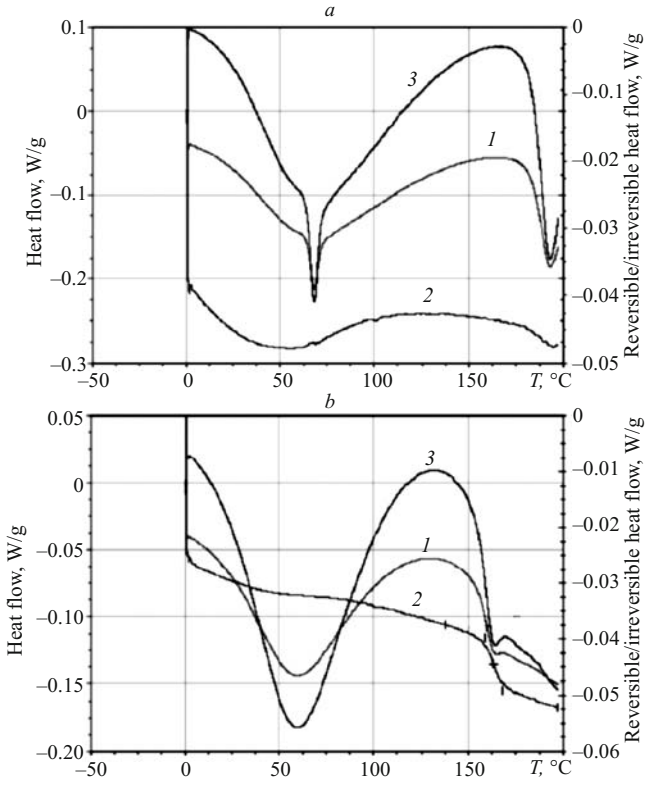

Fig. 3. DSC thermograms of the outer (*a*) and inner (*b*) layers of the polycomplex matrix after 24 h in conditions simulating passage through the GIT: heat flow curves (*1*), reversible heat flow (*2*), irreversible heat flow (*3*).

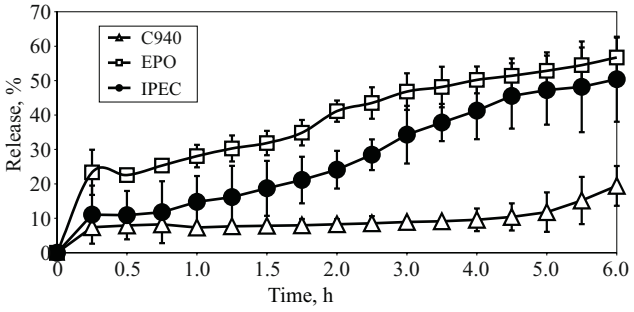

Fig. 4. Profiles of ibuprofen release from the polycomplex matrix as compared with individual polymers in conditions simulating passage through the GIT.

REFERENCES

1. A. K. Bajpai, S. K. Shukla, S. Bhanu, S. Kankane, *Progr. Polym. Sci.*, **33**(11), 1088 – 1118 (2008).
2. T. R. Hoare, D. S. Kohane, *Polymer*, **49**, 1993 – 2007 (2008).
3. C.-C. Lin, A. T. Metters, *Adv. Drug Deliv. Rev.*, **58**, 1379 – 1408 (2006).
4. A. B. Zezi and V. B. Rogacheva, *Advances in Polymer Chemistry and Physics* [in Russian], Khimiya, Moscow (1973), pp. 3 – 30.
5. V. A. Kemenova, R. I. Mustafin, K. V. Alekseev, et al., *Farmatsiya*, **60**(1), 67 – 71 (1991).
6. T. V. Kabanova, E. R. Zdanova, R. I. Moustafine, *J. Control. Rel.*, **116**(2), e33-e35 (2006).
7. E. R. Zdanova, T. V. Kabanova, G. G. Chisameeva, R. I. Moustafine, *Proc. 5th World Meeting on Pharm. Biopharm. & Pharm. Technol.*, Geneva (2006), Abstr. 19.
8. R. I. Mustafin and T. V. Kemenova, *Khim.-Farm. Zh.*, **39**(2), 34 – 38 (2005).
9. R. I. Moustafine, T. V. Kabanova, V. A. Kemenova, G. Van den Mooter, *J. Control. Rel.*, **103**, 191 – 198 (2005).
10. A. Gómez-Carracedo, C. Alvarez-Lorenzo, J. L. Gómez-Amoza, A. Concheiro, *Int. J. Pharm.*, **274**, 233 – 243 (2004).
11. R. I. Moustafine, I. M. Zaharov, V. A. Kemenova, *Eur. J. Pharm. Biopharm.*, **63**, 26 – 36 (2006).