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Research paper

Physicochemical characterization and drug release properties of Eudragit® E PO/Eudragit® L 100-55 interpolyelectrolyte complexes

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Abstract

The formation of interpolyelectrolyte complexes (IPEC) between Eudragit® E PO (EE) and Eudragit® L 100-55 (EL) was investigated, using turbidimetry, apparent viscosity measurements, elementary analysis and MT-DSC. The structure of the synthesized IPEC was investigated using FT-IR spectroscopy. The binding ratio of a unit molecule of EL with EE was found to be approximately 1:1 at pH 5.5. Based on the results of elementary analysis and FT-IR, the binding ratio of each component in the solid complexes was very close to that observed in turbidity and apparent viscosity measurements and indicate that the synthesized products can be considered as IPEC. As a result of electrostatic interaction between the polymer chains, the glass transition temperature of the IPEC increased significantly. Due to the structure of the IPEC, two maxima were observed in the swelling behavior as a function of pH. The release of the model drug ibuprofen (IBF) was significantly retarded from tablets made up of the IPEC as compared with individual copolymers, its physical mixture and Eudragit® RL PO (RL), RS PO (RS).

Keywords: Interpolyelectrolyte complex; Eudragit® E PO; Eudragit® L 100-55; Eudragit® RL PO; Eudragit® RS PO; Glass transition temperature; pH-dependent swelling behavior; Ibuprofen; Controlled release

1. Introduction

The formation of interpolyelectrolyte complexes (IPEC) by the cooperative reactions involving oppositely charged polyions is well known. Two main classes of interpolymer complexes are distinguished: stoichiometric IPEC, which include the polymers in equimolar ratio and non-stoichiometric IPEC that have an excess amount of one polyelectrolyte. The last one is also called as soluble IPEC because of its hydrophilic properties. Moreover, in the structure of interpolymer complexes, two types of chains can be distinguished: the interacting chains, which belong to both interacting polymers and the loops, which are also called 'defects' of non-interacting chains, that have no reaction capability. A variety of IPEC can be obtained by changing the chemical structure of component polymers, such as molecular weight, flexibility, functional group structure, charge density, hydrophilicity and hydrophobicity balance, stereoregularity and compatibility, as well as reaction conditions: pH, ionic strength, concentration, mixing ratio and temperature [1–5].

According to the theoretical model, a very naïve picture of the 'polycondensation' could be considered as: polyanion sequence effectively complexed by the same polycation macromolecules (intramolecular complexation) or by another polycation macromolecule (intermolecular complexation). The balance intramolecular/intermolecular complexation depends on the relative concentration in polycation sequence in the vicinity of the considered polyanion sequences.

The process of IPEC formation may be divided into three main classes: (1) primary complex formation; (2) formation process within intracomplexes; (3) intercomplex aggregation process. The first step is realized through secondary binding sources such as Coulomb forces (very rapid). The second step involves the formation of new bonds and/or the correction of the distortions of the polymer chains. The third step involves the aggregation of secondary complexes, mainly through hydrophobic interactions [5,6].

The preparation of three types of IPEC has been reported to poly(vinylbenzyltrimethylammonium chloride)–poly(methacrylic acid) systems [7].

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Despite the large number of studies devoted to polymer complex formation and properties, only a few of them attempt the investigation of copolymers interaction. The reason is the complexity of such systems. Most of the systems completely changed as compared to homopolymers of the similar structure, due to the involvement of non-ionized monomer units, which could unify into non-complexable sequences. Furthermore, the polydispersity, pH-dependent solubility (due to the chemical structure) and the structural irregularity of synthetic copolymers largely influence the properties of copolymer complexes, which can be basically different from those of the initial components.

The most developed copolymers that could be widely used for controlled drug delivery are different types of Eudragit®, which are produced by Röhm GmbH & Co. KG. Depending on the pH, these copolymers act as polyelectrolytes which make them suitable for different purposes, from gastric or intestinal soluble drug formulations to insoluble but swellable delivery forms, regulated by the number of charged and non-ionized (ether) groups in the structure of these copolymer. Some of them, which are soluble in aqueous mediums with different pH values, can be considered as polycations (Eudragit® type E) and the others as polyanions (Eudragit® types L and S). The first one can have positively charged groups: dimethylamino groups in Eudragit® type E. The second one can have negatively charged groups: carboxylate groups in both types L and S [8].

The possibility of involving Eudragits® in IPEC in order to modify their structure is not so well investigated [9–11], despite of the advantages of using IPEC as a polymeric carrier in controlled systems for drug release are already well known [12–15].

The selection of the components forming the IPEC can be made on the basis of their properties, which are very important due to its pharmaceutical application, such as biocompatibility, pH-dependent solubility and swellability characteristics, physicochemical stability, etc.

The aim of this study was to investigate some fundamental physicochemical and release properties of IPEC made up of Eudragit® type E PO (EE) and Eudragit® L 100-55 (EL) with respect to their application in drug delivery. Fig. 1 shows the molecular structures of both polymers. Gastric soluble EE was selected as the polycationic polymer. On the other hand, EL, which is usually used as an enteric coating, was used as the anionic polymer.

2. Materials and methods

2.1. Materials

The different types of Eudragit® (E PO, L 100-55, RL PO, RS PO) were generously donated by Röhm GmbH & Co. KG (Darmstadt, Germany). The polymers were used after vacuum drying at 40 °C during 2 days. Ibuprofen (IBF), which was used as a model drug, was purchased from Sigma (Bornem, Belgium).

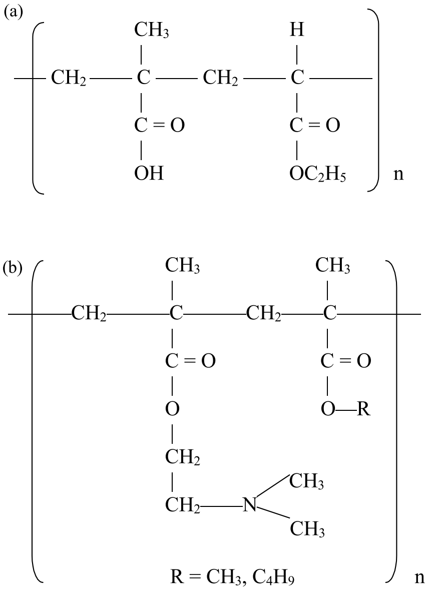

Fig. 1. Molecular structures of Eudragit L100-55 (a) and Eudragit E PO (b).

2.2. Methods

2.2.1. Turbidity measurements

All concentrations in prepared polymer solutions were calculated according to the monomer unit of used polyelectrolyte. EE solutions (0.1–0.25 mM) were prepared by dissolving the polymer in 0.1 M CH_3COOH; subsequently, this solution was diluted with demineralized water to the desirable volume and titrated by 0.1 M NaOH to the final pH of 5.5. EL solutions (0.1–0.25 mM) were prepared by dissolving the polymer in 0.1 M NaOH; subsequently, this solution was diluted with demineralized water to the desirable volume and titrated by 0.1 M CH_3COOH to the final pH of 5.5. EE solutions were subsequently mixed with EL solutions at room temperature at pH 5.5 for 2 h to prepare the sample solution for turbidity measurements. In all samples the final value of the pH was monitored (744 pH meter, Metrohm, Switzerland). The turbidity of each sample solution was determined at 600 nm (a wavelength where no absorption due to the polymers occurred), using a Shimadzu UV–VIS 160A spectrophotometer (Duisburg, Germany).

2.2.2. Viscosity measurements

EE solutions (0.05 M) were prepared by dissolving the polymer in 1 M CH_3COOH followed by diluting this solution with demineralized water to the desirable volume and titrated by 1 M NaOH to the final pH of 5.5. EL solutions (0.05 M) were prepared by dissolving the polymer in 1 M NaOH followed by diluting this solution with demineralized water to the desirable volume and titrated by 1 M CH_3COOH to the final pH value of 5.5. EE solutions were then mixed with EL solutions at room temperature for 10 min and subsequently centrifuged for 1 h at 5000 rpm at 5 °C in a MLW model K23D centrifuge (VEB MLW, Germany). The specific viscosity of the supernatant solution was determined at 25.0 (±0.1)°C using an Ubbelohde viscometer (Schott, Germany).

2.2.3. Synthesis of solid IPEC

EE solutions (0.05 M, pH 5.5) were mixed with EL solutions (0.05 M, pH 5.5) at constant temperature. After isolation of the precipitate from the solution, it was washed with demineralized water and the solid IPEC was subsequently dried under vacuum for 2 days at 40 °C.

2.2.4. Elementary analysis

The composition of the solid IPEC was investigated by element analysis using a Perkin Elmer model 240B elementary analyzer (Perkin Elmer, Norwalk, CT).

2.2.5. Fourier transform-infrared (FT-IR) spectroscopy

FT-IR spectra of the solid IPEC EE–EL systems, physical mixtures and pure polymers were measured using a Bruker FT-IR model Vector 22 spectrophotometer (Bruker, Germany) using the KBr disk method.

2.2.6. MT-DSC-measurements (modulated temperature DSC)

MTDSC measurements were carried out using a 2920 Modulated DSC (TA Instruments, Leatherhead, UK), equipped with a refrigerated cooling system (RCS). Data were treated mathematically using the Thermal Solutions software (TA Instruments, Leatherhead, UK). Dry helium at a flow rate of 40 ml/min was used as the purge gas through the DSC cell and 150 ml/min of nitrogen was used through the RCS unit. TA Instruments (Leatherhead, UK) pans with pierced lid were used for all calorimetric studies; the mass of each empty sample pan was matched to the mass of the empty reference pan within ±0.1 mg. The amplitude used was 0.212 °C, the period 40 s and the underlying heating rate 2 °C/min. Octadecane, benzoic acid, cyclohexane and indium standards were used to calibrate the DSC temperature scale; enthalpic response was calibrated with indium. The heat capacity signal was calibrated using dry, powdered aluminum oxide. Validation of temperature, enthalpy and heat capacity measurement using the same standard materials showed that deviation of the experimental from the reference value was less than 0.5 °C for temperature measurement, less than 0.1% for enthalpy measurement and less than 0.9% for measurement of the heat capacity in the range between 50 and 150 °C.

Measurements were performed in duplo.

2.2.7. Preparation of tablets

In order to determine the degree of swelling, flat-faced tablets of 100 mg weight (polymer carrier) and 8 mm diameter were prepared by compressing the given amount of the IPEC powder at 25 kg/cm^2 using a hydraulic press (Rodac, Sittard, The Netherlands).

For dissolution testing, flat-faced tablets of 150 mg weight (100 mg of IBF, 50 mg polymer carrier) and 8 mm diameter were prepared by compressing the given amount of the IPEC powder at 25 kg/cm^2 using a hydraulic press (Rodac, Sittard, The Netherlands).

2.2.8. Degree of swelling of tablets

The degree of swelling was investigated in conditions, which simulated the gastro-intestinal tract: the first hour in acidic medium (pH 1.2), and the next 2 h in a buffer solution (pH 6.8). The compositions of the media used were those described in USPXXV as dissolution media No. 1 (pH 1.2) and No. 2 (pH 6.8). The polymeric matrix is placed in a tarred basket (from the dissolution test equipment), which was immersed into a thermostated bath (37.0±0.5 °C). The volume of the swelling medium was 40 ml. After every 15 min, the basket was removed from the medium, accurately dried by filter paper and weighed. For determination of equilibrium degree of swelling, a final weighting was performed after 24 h.

The degree of swelling (H, %) was calculated as:

$$H(\%) = (m_2 - m_1/m_1)100$$

in which m_1 is the weight of the dry sample and m_2 the weight of the swollen sample.

2.2.9. Release testing of ibuprofen

The release of IBF from matrix tablets was performed at 37 °C using a standard dissolution tester LORTS (St Petersburg, Russia) (basket method). The rotation speed was 100 rpm and the volume of the dissolution medium was 500 ml. The dissolution media used were those described in USPXXV as dissolution media No. 1 (pH 1.2) and No. 2 (pH 6.8). Aliquots (3 ml) of solution were taken at specific time intervals and the volume was made up of the original value by adding fresh dissolution medium. The amounts of IBF released in the dissolution medium were determined spectrophotometrically at 264 nm. Results are given as the mean values of three determinations. Preliminary experiments had shown that the polymers did not interfere with the quantitation of the model drug.

3. Results and discussion

3.1. Conformation of IPEC formation

3.1.1. Composition study

EE, [(poly-(*n*-butyl methacrylate-(2-dimethylaminoethyl)-methacrylate-methyl methacrylate) copolymer with ratio 1:2:1], is soluble in acidic conditions up to pH 6.0, due to hydratation of protonated dimethylamino groups. On the other hand EL, ethyl acrylate–methacrylic acid copolymer with ratio 1:1, which is soluble from pH 5.5 due to hydratation of ionized carboxyl groups. The possibility of interaction between these two polyelectrolytes was investigated at pH 5.5, in which both polymers are soluble and partially ionized.

IPEC formation was first investigated using turbidimetry and viscosity measurements. Fig. 2 shows a typical curve of a turbidimetric titration of EL solution by EE solution in a medium of pH 5.5. At this pH the degree of ionization of both polyelectrolytes and their charge density is very small. The relative turbidity is plotted as a function of the EL:EE molar ratio ($Z = [\mathrm{EL}]/[\mathrm{EE}]$). The maximum turbidity was found at the

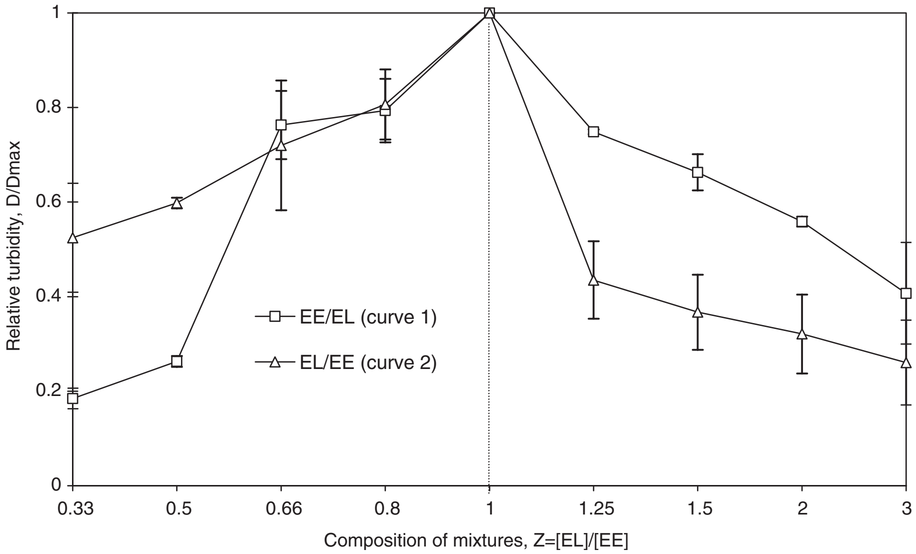

Fig. 2. Turbidity of the EE–EL system as a function of the composition of the mixture and the order of mixing; *curve 1:* addition of EL solution to EE solution; *curve 2:* addition of EE solution to EL solution ($n=3$; ±SD).

unit molecular weight ratio of 1:1. The results also show that the order of mixing of the two polymer solutions did not influence the point of maximum turbidity. The addition of an excess amount of EE again led to a drop in the turbidity value due to segregation of the formed IPEC. The observed binding molar ratio corresponds to the stoichiometry of the obtained product.

Fig. 3 shows the apparent viscosity of the supernatant of EL–EE mixture solutions at pH 5.5. In the case of EL alone or EE alone, the specific viscosity of these solutions increased continuously with an increase of the polymer concentration. Therefore, the decrease of viscosity observed in the EL–EE mixture system showed that the IPEC was formed in the investigated medium and was removed by centrifugation. At the same time, the pH of the supernatant solution decreased if the amount of EL that was added to the EE solution was increased. A minimum in the curve is observed when the mixture of two polymers became equimolar.

In order to confirm the interaction or binding ratio of each component in the solid IPEC, elementary analysis was performed. The results are given in Table 1 and clearly prove that the molar ratio of interaction between EL and EE is 1:1.

Although experiments were performed with solutions of EE and EL in a concentration range from 0.1 mM to 0.05 M, no influence of the concentration could be observed, which can be attributed to the well equilibrated IPEC systems formation due to comparatively low polyelectrolyte concentrations used. Moreover, in concentrated polymer solutions not equilibrated, disproportional polycomplexes are formed [1,2,5].

It is known that ionic strength could have influence on IPEC formation only in very high concentration of low molecular salts (more than 0.5 M). In such cases, salts ions

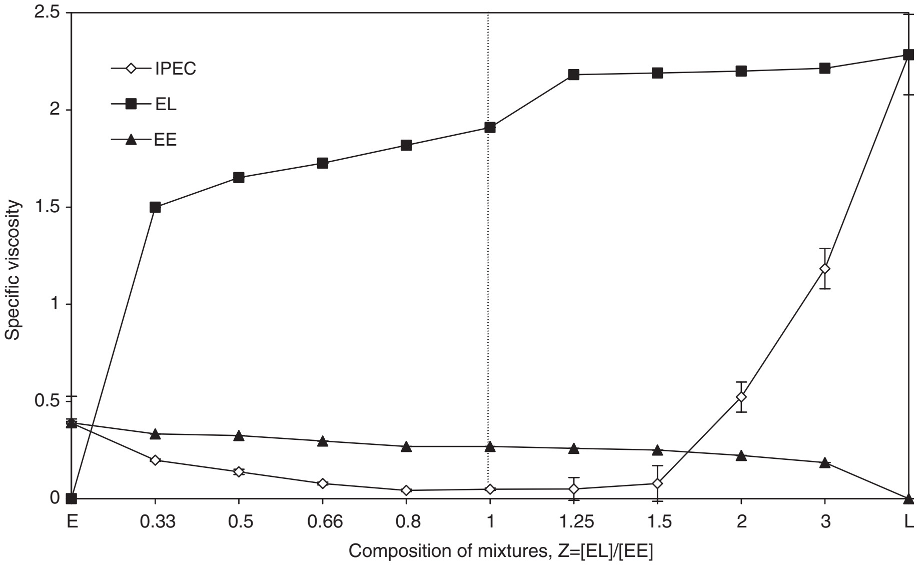

Fig. 3. Specific viscosity of solutions of the individual polymers (EE, EL) and supernatant solutions of EE–EL systems as a function of the polymer ratio ($n=3$; ±SD).

Table 1
Elementary analysis of the IPEC composed of EE and EL at pH 5.5

Values	Element			Molar ratio, $\varphi=[EE]/[EL]$
	C	H	N	
Calculated, %	61.53	8.71	2.39	1/1
Experimental, % (mean, $n=2$)	58.96	8.59	2.40	

could be compete in interpolyelectrolyte reaction. Moreover, ionic strength about 2–3 M may destroy IPEC to individual polymers [2]. According to this, our experiments also show no influence of low molecular salts that are formed during polymers solutions preparing and mixing on IPEC formation.

3.1.2. Structures study

3.1.2.1. Infrared spectroscopy. Fig. 4a shows FT-IR spectra of the EL–EE solid interpolymer complex obtained by precipitation at pH 5.5. The IR spectra of the equimolar complex showed some remarkable differences as compared to those of a physical mixture of EL and EE at a molar weight ratio of 1:1. A strong band appears at 1560 cm^{-1}, which might be assigned to the absorption band of carboxylate groups that form the ionic

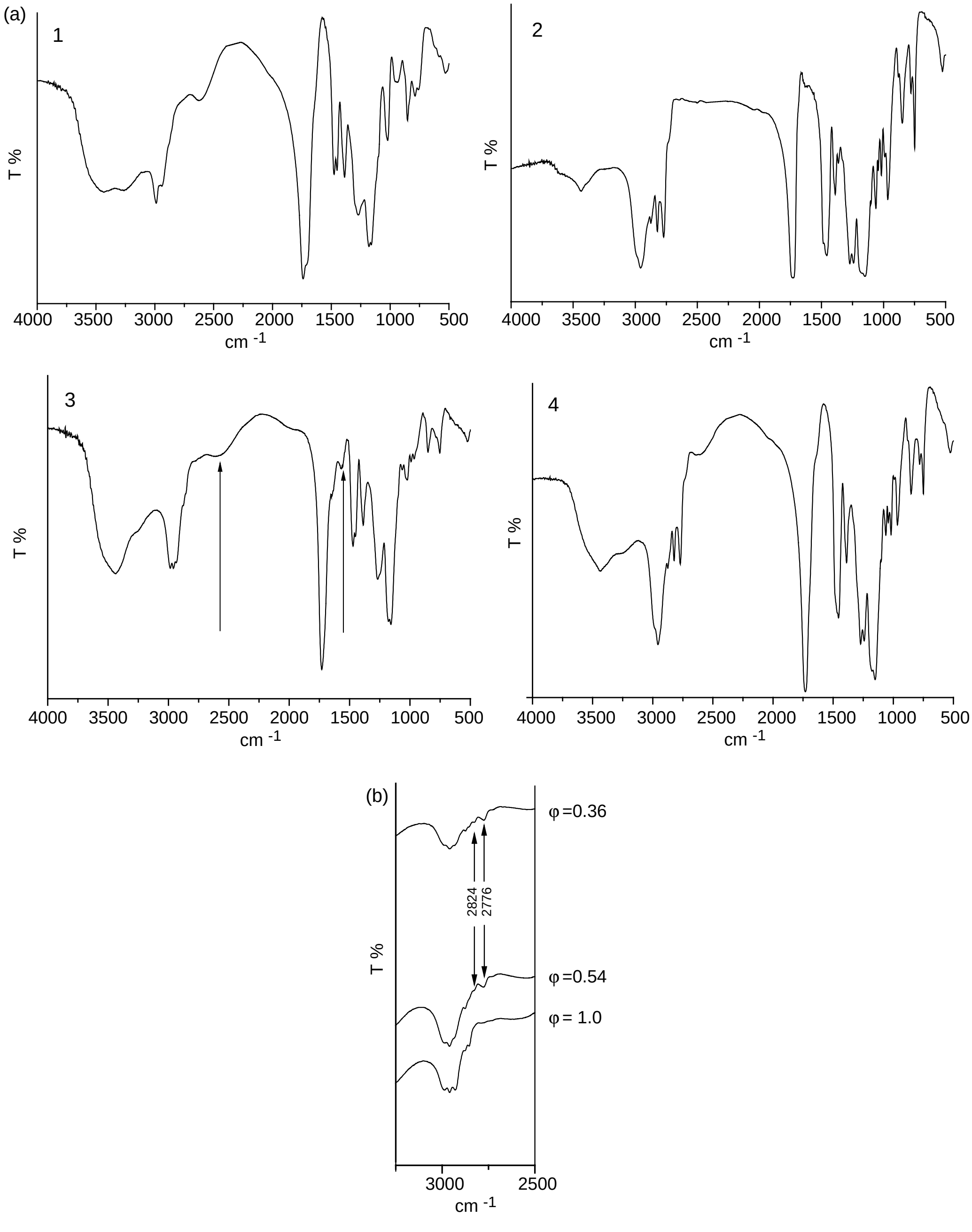

Fig. 4. (a) FT-IR spectra of (1) pure EL; (2) pure EE; (3) IPEC, $\varphi=1$; (4) physical mixture of EE and EL in a molar ratio 1:1. (b) FT-IR spectra of IPEC with different compositions.

bonds with protonated dimethylamino groups of EE. On the other hand, a broad band at 2540 cm^{-1}, might be assigned to the polymer salts absorption band which was brought about by the interaction of the ionized dimethylamino groups of EE with the carboxyl groups of EL. Indeed, at this pH the amount of ionized groups of EE is dramatically reduced, although the polymer is still able to form IPEC with EL molecules. These phenomena were close to those observed in Eudragit® E 100–Eudragit® L 100 system [10].

Together with the fact that the binding ratio of the complex was stoichiometric, the ionic bonding seems to be a primary binding force for the complex formation between EE and EL.

Fig. 4b shows FT-IR spectra of the EL–EE solid complexes obtained as precipitates in the same conditions, but with different molar ratio in reaction mixture—*Z*. According to the results of elementary analysis, they have different compositions ($0.36 < \varphi = [EL]/[EE] < 1$). Although all of them have a bands at 1560 and 2540 cm^{-1}, composition, where $\varphi = 0.36$, which contain significant excess amount of EE, is characterized by two peaks at 2776 and 2824 cm^{-1}, which is corresponded to non-ionized dimethylamino groups of EE. In the case, $\varphi = 0.39$–0.54 a band at 2830 cm^{-1} was significantly reduced and only a small shoulder could be observed in polycomplex with $\varphi = 0.77$. This indicates a difference in the amount of protonated and non-protonated dimethylamino groups of EE in the structure of IPEC. All these peaks are completely disappeared if $\varphi = 0.91$–1. This means that only equimolar IPEC did not have non-ionized dimethylamino groups in its structure. Indeed, while the content of EE in IPEC is increased, the amount of protonated groups of EE is also increased. Analysis of different samples of IPEC shows that all of them are structurally complementary compounds independent from the composition of solid complex was obtained. Existences of non-ionized dimethylamino groups which can localize mainly in ‘defects’ fields, means that the structure of formatted IPEC is changed and was greatly dependent from the composition of polycomplex. Similar results were observed in our previous investigations about IPEC formation between EE and alginate sodium, but estimated differences has happened due to differences in pH value of reaction medium [11].

3.1.2.2. Thermal analysis. In order to confirm that observed by FT-IR appearance of non-ionized dimethylamino groups are not due to existence a microdomains of free EE in the structure of IPEC and for further proven that the formation of IPEC between EE and EL is the result of an electrostatic interaction between these polymers, MT-DSC experiments were performed. Applying heat to a system with decreased mobility, due to interpolymer interaction must lead to a glass transition temperature, which is higher than in the absence of such interactions (ideal behavior). These theoretical values were calculated by the Gordon–Taylor equation [16]

$$T_{gx} = \frac{T_{g1}w_1 + T_{g2}Kw_2}{w_1 + Kw_2} \tag{1}$$

in which T_{g1} and T_{g2} are the glass transition temperature of EE (52.1 ± 1.3 °C) and EL (124.4 ± 1.6 °C), respectively, w_1 and w_2 are the number of moles of EE and EL in the dispersions, respectively, and K is a constant which was estimated using the Simha–Boyer rule [17]

$$K \cong \frac{\rho_1 T_{g1}}{\rho_2 T_{g2}} \tag{2}$$

where ρ is the density of the polymers; the densities are 0.810 and 0.830 for EE and EL, respectively, and K is calculated to be 0.803.

Fig. 5 shows the variation of the T_g as a function of the IPEC composition, moreover all investigated compositions (samples are the same as estimated by FT-IR) have only one T_g, above the T_g of EE, thus prove that synthesized products have homogenic structure and actually not include microdomains of free macromolecules EE. Two samples of IPEC ($\varphi = 0.91$–1) have the T_g value more than T_g’s of individual copolymers. It is well known, that these phenomena could only if IPEC have a high degree of complexation θ, which is equal to the ratio of the concentration of complexed groups to the total concentration of all capable to react groups of anyone of polyelectrolytes [2].

Other IPECs ($\varphi = 0.36$–0.77), according to FT-IR data, which contains non-complexable sequences of non-ionized dimethylamino groups in ‘defects’ fields, have T_g values less than T_g of EL. T_g increases with increasing amount of EL in the

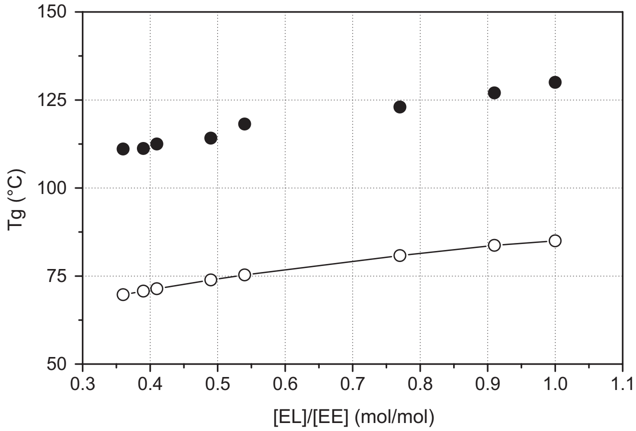

Fig. 5. Theoretical (open symbol) and experimental (closed symbol) values of the glass transition temperature of the IPEC with different compositions.

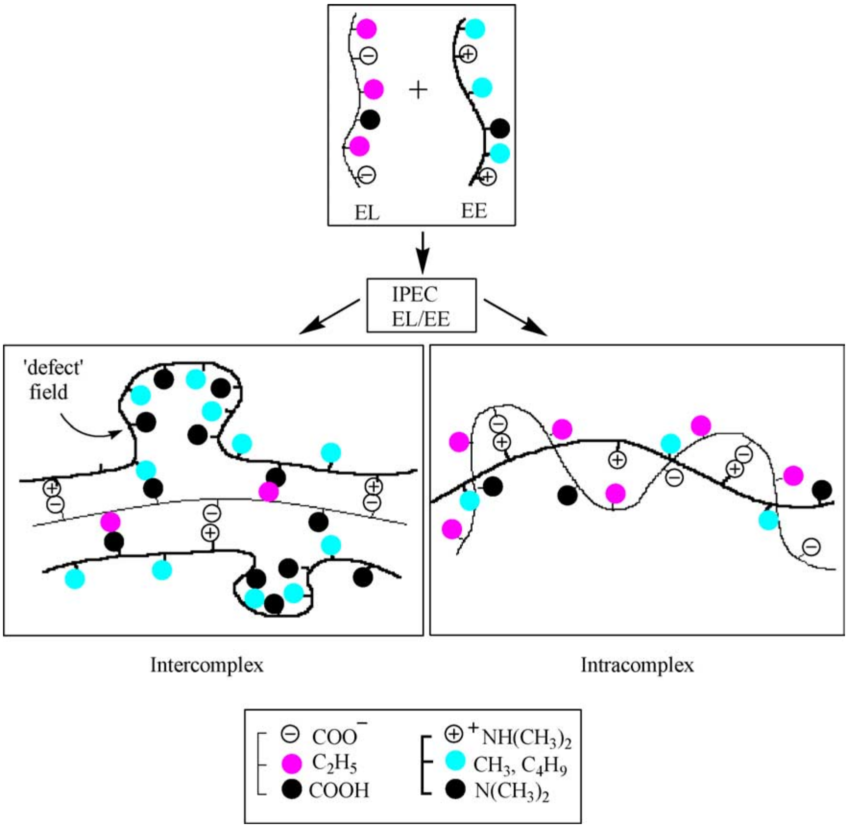

Fig. 6. Schematic representation of the ionic interactions between EL and EE.

IPEC, but more striking is the large deviation between the experimentally obtained values and the calculated ones (Eqs. (1) and (2)). The latter assumes volume additivity during mixing and the absence of orienting interactions. It is clear that the IPEC do not behave as an ideal system. Indeed, more heat needs to be added before these systems gain the necessary mobility to enter the glass transition region, thus confirming the existence of strong electrostatic interactions between the polymer chains. According to the results achieved, we propose that formulated IPEC's can belong to two main types: (1) intramolecular complexes ($0.91<\varphi<1$); (2) intermolecular complexes ($0.36<\varphi<0.77$). The differences in structure of synthesized polycomplexes that were confirmed by two methods (FT-IR, MT-DSC) could be presented as depicted in Fig. 6. Nevertheless, the above-mentioned types of IPEC could be changed while changes of pH or ionic strength could occur, that leads to form stoichiometric IPEC's with different degree of complexation.

The influence of T_g on the structure and composition of the resulting IPEC is very close to the results obtained for the interaction between some other polyions and also for hydrogen bonded polycomplexes [18–22].

3.2. Pharmaceutical evaluation of EE–EL systems

3.2.1. Swelling behavior of acrylic matrices

A comparative analysis of the swelling behavior of a physical mixture (molar ratio of polyelectrolytes is 1:1) and individual polymers is shown in Fig. 7a. Tablets prepared from the physical mixture showed a slight increase in weight after 15 min, but disintegrated rapidly afterwards during the first hour in acidic medium. The explanation can be found in the fact, that the polymers are acting individually and no interpolymer interaction occurs. Indeed, EE which is used as a gastric soluble film coating, was already dissolved after 30 min in acidic medium and although EL is not soluble in this medium, tablets prepared from this polymer are not disintegrated and swell in acidic medium up 200% and after immersing it to the medium of pH 6.8 swell initially up to 400% but completely dissolved later (after 3 h). According to the specification of Röhm GmbH & Co. KG, it should dissolve fast in pH 6.8, but it still has values up to the end of experiment. The investigated polymers or their physical mixture are therefore clearly not suitable to be used in oral sustained release systems. The swelling properties of IPEC ($\varphi=1$) definitely have other characteristics (Fig. 7b). In acidic medium the degree of swelling increased to approximately 200% after the first 30 min, followed by an almost twofold decrease, which can be explained by a change in the interpolymer complex structure. Indeed, according to the structure of the original IPEC, and the low charge density at pH 5.5, it has lot of 'defects' (Fig. 6). Such fields contain non-ionized dimethylamino groups of EE and ether groups of both copolymers. While immersing the polycomplex matrix into the acidic medium, free dimethylamino groups are protonated and their hydratation increases the degree of swelling at the beginning of

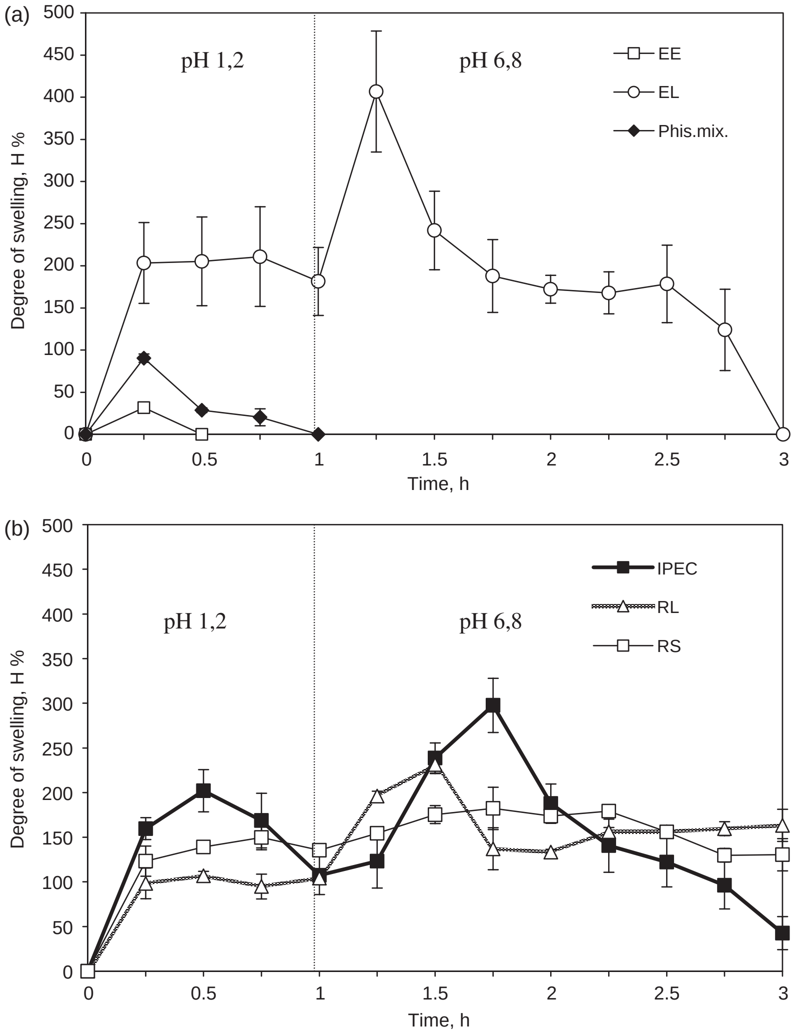

Fig. 7. (a) Degree of swelling of pure EL, EE and a physical mixture EE–EL (1:1). (b) Degree of swelling of RL, RS and IPEC, φ = 1 (*n* = 3; ±SD).

experiment. Later, full ionization of all dimethylamino groups turns it to a polyelectrolyte with a relatively high charge density. As the result, the structure of the IPEC is changed because the ionic bonds are not fixed and they can move from one electrostatic site to another. Completely ionized dimethylamino groups are charging the protonated carboxylic acid groups of EL (weak polyacid) and can form new interpolymer contacts, which are dramatically increased and reach a maximum value ($\theta \rightarrow 1$). Hence, the number of 'defects' is decreased and goes to a minimum value.

After moving the matrix to the medium at pH 6.8 the degree of swelling again increases for 1.5 h (300%) and reaches the equilibrium value of only 50% after 3 h. The carboxylic acid groups of EL that is present in such 'defects' are becoming ionized at pH 6.8 and consequently the degree of ionization increases. Oppositely, the previously protonated dimethylamino groups present in loops are losing their charge and lead to an increase of the hydrophobic units in the total IPEC structure, and this contributes to the observed decrease in swelling. Aggregation of interacting chains and non-charged fragments in 'defects' leads to the formation of hydrophobic entities, especially in intercomplex type of IPEC (Fig. 6), and hence some kind of monolith structure is formed, which did not disintegrate during 24 h. Taking into consideration that both polyelectrolytes have on average one charged unit for every two-monomer units, the IPEC contains non-interacting parts each having a length of approximately the length of the non-ionized monomer. We can consider it, as non-charged fields between electrostatic chains, creating small loops, which increases the hydrophobic properties of the IPEC. These phenomena were also discussed in our previous investigations about IPEC formation with participation of Eudragit® L 100 [10]. Nevertheless, such distribution of ionic 'cross-linked' fields is characteristic for IPEC's, which are synthesized in diluted solutions, is well known [1,2]. As a result, the IPEC is not well equilibrated and the percentage of interacting fields is not so large ($\theta_{\min}$). The synthesized IPEC, as many of the investigated stoichiometric polycomplexes in a swollen form has a pH-sensitive network structure, which consists of interacted and 'defect' fields.

In order to check the influence of polymer matrix structure on swellability properties we compare our IPEC (φ = 1) with Eudragit® type RL PO (RL) and RS PO (RS), which are traditionally apply in controlled release systems and, as we

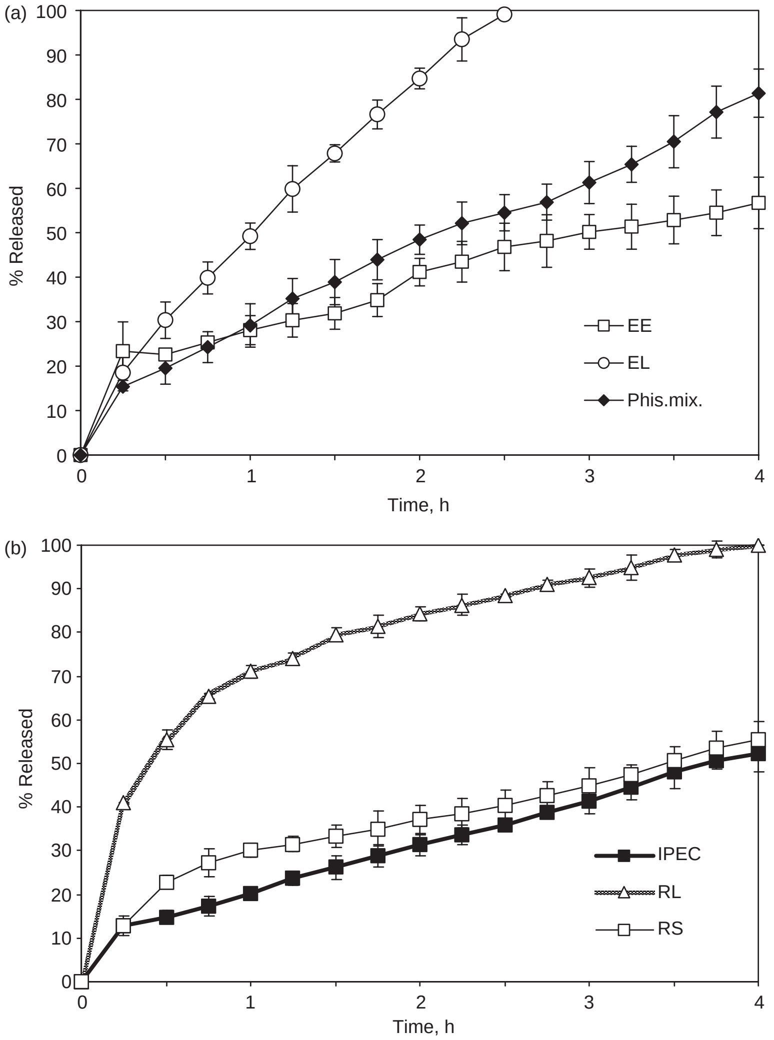

Fig. 8. (a) Release of ibuprofen from matrix tablets made up of EE, EL and a physical mixture EE–EL (1:1). (b) Release of ibuprofen from matrix tablets made up of RL, RS and IPEC, φ = 1 (*n* = 3; ±SD).

think, the most interesting for comparative evaluation. As it can be clearly seen from Fig. 7b, the swellability profiles had similar characters, especially in pH 6.8 region, however, the end value of degree of swelling after 3 h are approximately three times higher for both Eudragit® samples (150%), but as for RS, it has more stable profile, without any peaks. It means that, in spite of its hydrophobic structure, RL has more hydrophilic properties, unlike RS, which is definitely hydrophobic. According to the specifications of Röhm GmbH & Co. KG, these copolymers containing a 10% (RL) or 5% (RS) of quaternary amino groups, which are responsible for its swellability properties, are recommended as pH-independent carriers. On contrary, the swelling of the polycomplex pH-sensitive matrix is easily regulated by changing the hydrophobic (interacted chains) and hydrophilic (defects) sequences in IPEC structure, which are changeable after its emplace into the mediums with different pH and/or ionic strength.

3.2.2. Drug release from acrylic matrices

In a next set of experiments, we tested the potential of the IPEC to be used in matrix drug delivery systems to retard and control the release of the model drug IBF. Although acrylic polymers have already been used in preparing prolonged release matrix systems of IBF [23], we also try to apply our acrylic IPEC systems for this purpose. According to the chemical structure of IBF, we could also take into consideration the possibility of drug–polymers interactions, which could have happened during release process. Well-known examples of IBF as carboxylic group containing drug which interact with vinyl polymers such as polyvinylpyrrolidone (PVP), and polyvinylacetate by means of hydrogen bonds formation [24–26]. Ionic interactions of some non-steroidal anti-inflammatory drugs with acrylic polymers are also known [27–29].

Matrix tablets containing 100 mg of IBF and 50 mg of the polymer carrier were therefore prepared and the release of the drug was investigated at pH 1.2 for 2 h, after which the tablets were transferred to the dissolution medium of pH 6.8. The results of the drug release from different types of matrices are shown in Fig. 8. Mainly, due to the fact that IBF is not soluble in the acidic medium (pK_a 5.2), the release was less than 1% (data not shown).

Dissolution profiles of IBF from EL, EL and physical mixture ($Z=1$) matrices are shown in Fig. 8a. The most slow release profile can be observed for EE matrix. A theoretical interaction could be possible between IBF and oppositely charged polycation—EE during release experiments. In the previous study, we already checked the possibility of IBF–EE complex formation by FT-IR method in gastro-intestinal simulated conditions [30]. Drug–polycation complex in matrix tablet is formed in acidic medium (pH 1.2) after 1 h and in phosphate buffer solution (pH 6.8) during two more hours' observation. But, the formation of drug–polymer complex did not make the release profile so slow, that we could expect. The reason is, that the complex formation makes the systems more hydrosoluble. The similar results were achieved for IBF–PVP complex [24,25]. Taking into account that macromolecules of IPEC contains non-interacting sequences with free dimethylamino groups, they could also be able to interact with IBF. Unexpectedly, we did not see any interaction with Eudragit® E 100–Eudragit® L 100 IPEC system, in spite of retarding IBF release rate from polycomplexed matrix in the same conditions [10,30].

Comparative analysis of IPEC ($\varphi=1$) with RL and RS samples (Fig. 8b) show that IBF release at pH 6.8 from the IPEC matrix is the slowest. Approximately, 40% is released after 4 h. The release profile does not show any initial burst effect (as compare to RL), but is nearly linear from the start. Moreover, the release process for EL and RL matrices are completely finished up to the end of experiment (2.5 and 4 h, respectively). As for EL matrix, high solubility of this copolymer from $\text{pH}>5.5$ leads to fast dissolution of matrix together with IBF molecules in the medium with pH 6.8. According to swellability properties of RL matrix, the extensive release of IBF is observed due to pH-independent structure of RL matrix. Drug molecules could simply diffuse through swelled matrix. The achieved results are in agreement with the swelling properties of EL and RL. Differences in swellability and release properties of polycomplexed matrices (physical mixture and IPEC) could be explained by structure modification, which has happened during continuous penetration of the dissolution medium into the matrix. In case of physical mixture, as compared to IPEC, comparatively low retardant capacity of IBF release is observed. The reason is, interpolymer complex formation could not be possible at these conditions and differences in drug release are mainly explained by the anionic properties of IBF and EL. Thus, in case of some polyanions (sodium polyacrylate, alginate or hyaluronate) and homopolymeric acids (polyacrylic acid), which could form interpolymer complexes in wide pH region and of course, in usually estimated dissolution medias, the release of drugs was controlled by the three-dimensional network structure, which was produced by complex formation following water penetration into the tablet [15,31]. If it can happen we will see a significant retardation of drug release, but we did not observe it. Based on these results, the explanation of drug release from this system could be understood as follows. In acidic medium, macromolecules of EE swell and partially dissolve. The remaining amount of completely ionized EE after removal to another medium could continuously lose charges on dimethylamino groups of polycation chains, that has led to the formation of an insoluble fibers in matrix structure. On contrary, at pH 6.8, most of carboxyl groups in EL and IBF are in the ionized forms. Therefore, the repulsive force between negative charges of both components results in the increasing of drug release.

The releasing rate of IBF greatly decreases when the matrix was prepared by the IPEC. According to the above-mentioned explanation of swellability results, the decreasing of release rate in this case could be due to the modification process, which has happened inside the polycomplexed matrix during penetration of dissolution mediums into the tablet. Moreover, molecules of IBF, which could not compete in interpolyelectrolyte reaction, could not find free sequences of charged dimethylamino groups in formatted monolith structure of IPEC matrix, which could definitely sustain drug release. According to FT-IR results achieved for IPEC based on Eudragit® E 100–Eudragit® L 100 copolymers [30] we think that the same processes could be possible in present EE–EL system.

Based on the results obtained, we can conclude that universal properties of the EL–EE interpolyelectrolyte complexes, which could be easy regulated by changing of macromolecular parameters (composition of IPEC, degree of complexation), should be applicable to the design of more precisely controlled oral drug delivery systems.

4. Conclusion

The results of the present investigation confirm the formation of an interpolyelectrolyte complex between EE and EL at pH 5.5. Two types of polycomplexes are formed: inter- or intra-IPEC. The structure of synthesized IPEC is dependent on molar ratio of each component in polyion mixture and correlate with their glass transition temperatures. Equimolar composition of IPEC ($\varphi=1$) has the highest T_g and does not contain sequences of non-ionized dimethylamino groups due to the well-equilibrated structure. In-vitro swelling and release experiments showed the potential of this interpolymer complex to be used in controlled drug delivery systems.

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