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Characteristics of interpolyelectrolyte complexes of Eudragit E 100 with sodium alginate

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Abstract

With a view to the application in oral drug delivery formulations, the possibility to form interpolyelectrolyte complexes (IPEC) of Eudragit E 100 (EE) with sodium alginate (AL) was investigated, employing turbidimetry, apparent viscosity measurements, FT-IR and elementary analysis. The interaction or binding ratio of a unit molecule of AL with EE was largely affected by the pH value of the media, showing a change from 1.5:1 to 1:1.25 ($0.66 < Z < 1.25$) with increase in pH value from 2.5 to 6.0. Based on the results of elementary analysis and FT-IR, the interaction ratio of each component in the solid complexes was very close to that observed in turbidity and apparent viscosity measurements thus proving that the synthesized products actually can be considered as IPEC.

Keywords: Interpolyelectrolyte complex; Eudragit E 100; Sodium alginate; Solution apparent viscosimetry; Infrared spectroscopy; Turbidimetry; Elementary analysis

1. Introduction

The use of different types of Eudragits for controlled drug delivery has been well known for several years. Since Eudragits can act as polyelectrolytes, they can be used for many purposes such as enteric drug formulation, or swelling controlled drug release regulated by the percentage of charged and non-ionized (ether) groups in the molecular structure of methyl-(ethyl)-methacrylate copolymers. Some of them can be considered as polycations (Eudragit types E, RL, RS, NE) and others as polyanions (Eudragit types L, S). The first ones have positively charged groups: dimethylamino groups in Eudragit type E, or quaternary amino groups in Eudragit types RL, RS and NE. The second ones have

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negatively charged groups: carboxyl groups in Eudragit types L and S.

Interpolyelectrolyte complexes (IPEC), obtained as precipitates by mixing cationic and anionic polymers in aqueous solutions, have often been reported. It is known that the stoichiometry of both components in binary IPEC depends on the pH values of the media, ionic strength, concentration and sometimes on the order of mixing (Kabanov, 1972; Fukuda, 1979). Although, the advantages of using IPEC as a polymer carrier in controlled release systems are well known (Kawashima et al., 1985; Lorenzo-Lamoza et al., 1998; Takahashi et al., 1990; Majeti and Kumar, 2000; Takayama et al., 1990; Miyazaki et al., 1994, 1995; Sezer and Akbuğa, 1999a,b; Takka and Acartürk, 1999; Sezer and Akbuğa, 1999b; Mitrevej et al., 2001), the possibility of using Eudragits in IPEC is not well investigated. To the best of our knowledge, the only scientific report dealing with the use of Eudragit in IPEC is that in which ionic interactions of Eudragit S with chitosan are described, although the authors observed only the ionic interaction by IR analysis in a pellet film coating during the release measurements. Unfortunately they did not make a complete investigation of the system (Lorenzo-Lamoza et al., 1998).

The purpose of the present study was to investigate the basic physicochemical properties of IPEC composed of Eudragit type E100 (EE) with sodium alginate (AL). Fig. 1 shows the molecular structures of the polymers. EE was selected as a polycation because of its solubility in acidic conditions. The use of other cationic types of Eudragit is not possible because they are pH independent and not soluble in aqueous solutions. On the other hand, AL was used as the anionic polymer.

2. Materials and methods

2.1. Materials

EE and AL were generously donated by Rohm Pharma (Darmstadt, Germany), and Federa (Brussels, Belgium), respectively. The polymers were used after vacuum drying at 40 °C during 2 days.

2.2. Turbidity measurements

Solutions of EE (0.0001–0.001 M) in acetate buffer (0.05 M; pH 2.5–6.0) were mixed with solutions of AL (0.0001–0.001 M) in acetate buffer (0.05 M; pH 2.5–6.0) at constant temperature. The turbidity of each sample solution was determined at 600 nm (a wavelength where no absorption due to the polymers occurred), using a UVIKON 810P spectrophotometer (Kontron Instruments, Van Hopplynus, Brussels, Belgium).

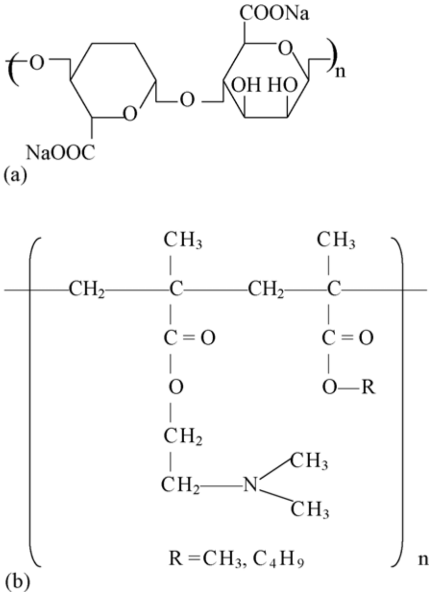

Fig. 1. Molecular structures of alginic acid (a) and Eudragit E 100 (b).

2.3. Apparent viscosity measurements

Solutions of EE (0.0001–0.001 M) in acetate buffer (0.05 M; pH 2.5, 4.0 and 5.5) were mixed for 10 min with solutions of AL (0.0001–0.001 M) in acetate buffer (0.05 M; pH 2.5, 4.0 and 5.5) at constant temperature using the vibromixter Hellma CUV-MIX 342. After centrifugation for 1 h at 5000 rpm with rotor cooling at 5 °C in a MLW K23D centrifuge, the specific viscosity of the supernatant solution was determined at 25.0 ± 0.1 °C using a Ubbelohde viscometer.

2.4. Synthesis of solid IPEC

A solution of EE (0.01 M) in acetate buffer (0.05 M; pH 2.5–6.0) was mixed with a solution of AL (0.01 M) in acetate buffer (0.05 M; pH 2.5–6.0) 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 at least 2 days at 40 °C.

2.5. *Elementary analyses*

The composition of the solid IPEC was investigated by elementary analyses using a Perkin-Elmer model 240B elementary analyzer (Perkin-Elmer, Norwalk, CT, USA). Tests were performed in duplicate.

2.6. *Infrared spectroscopy*

FT-IR spectra of the solid IPEC systems were measured using a Perkin-Elmer model FT-IR 2000 spectrophotometer (Perkin-Elmer, Norwalk, CT, USA) using KBr disks. Analysis of the spectra was performed using the Spectrum v2.00 software (Perkin-Elmer, Norwalk, CT, USA).

3. Results and discussion

According to the specifications of Rohm Pharma, EE (a copolymer of 2-dimethylaminoethyl methacrylate, methyl methacrylate and *n*-butyl methacrylate) is soluble in acidic medium up to pH 6.0, due to hydratation of protonated dimethylamino groups. Alginic acid is a carboxylic acid containing polysaccharide (copolymer of D-mannuronic acid and L-guluronic acid), which is soluble from pH > 2.5, due to ionization of carboxylic acid groups. Investigation of interaction between these two polymers were investigated in the pH range between 2.5 and 6.0.

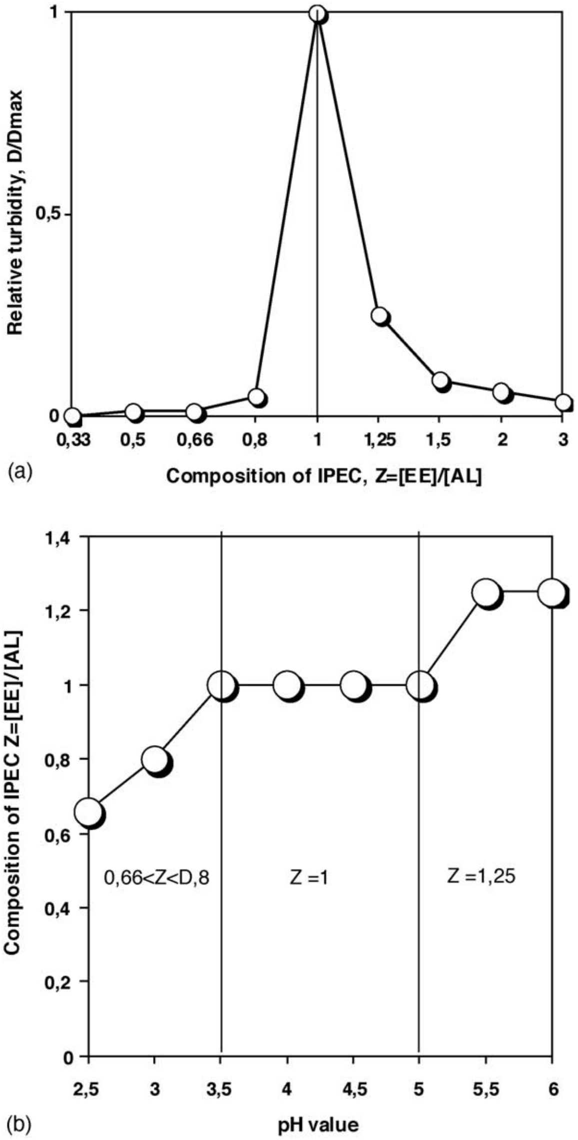

Fig. 2. (a) Turbidity of EE–AL system as a function of polymer mixing ratio at pH 4.0 and (b) relationship between the composition of IPEC and the pH.

The formation of IPEC was first studied by turbidity and viscosity measurements. Fig. 2a shows a typical curve of a turbidimetric titration of a solution of AL by a solution of EE at pH 4.0. The relative turbidity is plotted as a function of the EE:AL molar ratio in fixed mixtures. Maximum turbidity was found at the unit molecular weight ratio of 1:1. The addition of an excess amount of EE led to a decrease of the turbidity due to precipitation and subsequent segregation of the formed IPEC. The observed molar ratio of interaction corresponded to the stoichiometry of the obtained product. Fig. 2b shows the molar ratio of IPEC compositions as a function of the pH value of the reaction mixture. The curve can clearly be divided into three zones. In strong acidic medium (pH 2.5–3.0) maximum turbidity is observed in a molar ratio of the components $Z = 0.66–0.8$. So in this case the formed IPEC is made up of different amounts of AL molecules. Most of the EE molecules are ionized in the solutions. On the contrary, the degrees of ionization of AL molecules would

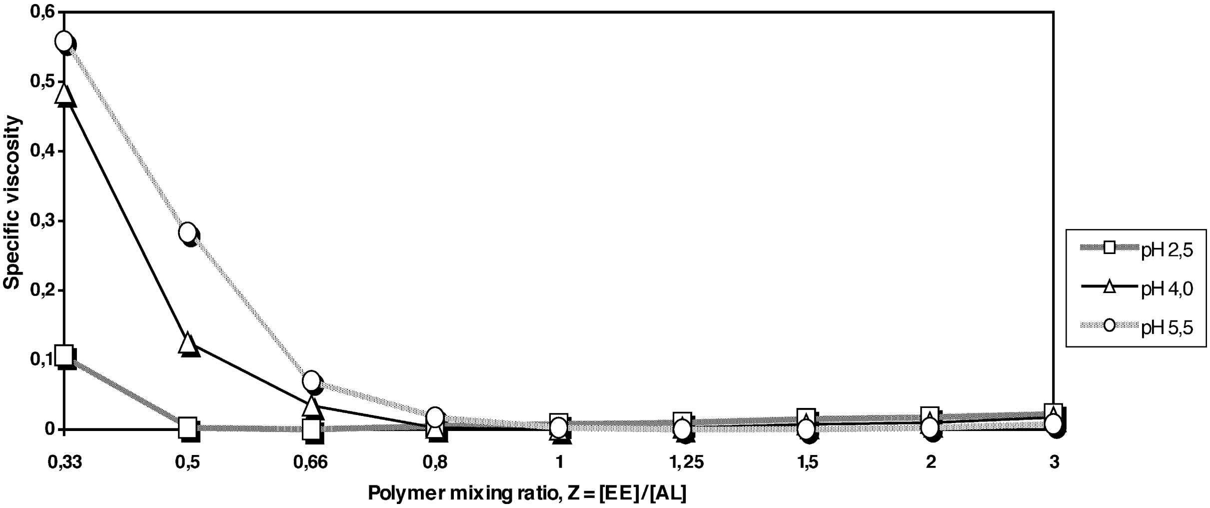

Fig. 3. Specific viscosity of the supernatant solution in EE–AL systems of different polymer mixing ratios.

decrease with decreasing pH values in the media. As a result, much larger amounts of AL macromolecules were required to interact with EE macromolecules in the media of low pH values. When the pH is increased, ionization of the carboxylic acid groups is increased and the charge density on AL molecules is also increased and a higher amount of AL will be able to interact with EE. That is why in the pH region from 3.5 to 5.0 *Z* is a constant and corresponds to an interaction molar ratio of 1:1. In the third part of the curve (the range between pH 5.5 and 6.0) the situation is changed now to the opposite as compared to the first zone. Due to a decrease of protonated dimethylamino groups of EE a decrease in the reactive capacity of the polycation occurred and thus the formed IPEC contains an excess amount of EE ($Z = 1.25$). In these pH regions, AL molecules are mostly ionized. Accordingly, if the active sites of the polymer molecules for the complexation are not affected by steric hindrance, the binding ratio should be altered with a change of pH values in the media. Similar phenomena have been observed in the complex formation between chitosan and polyacrylate sodium and AL (Takahashi et al., 1990; Majeti and Kumar, 2000).

Although experiments were performed with solutions of EE and AL in a concentration range from 0.0001 to 0.001 M, no influence of the concentration could be observed, which can be attributed to the low polymer concentration used (Kabanov, 1972).

Fig. 3 shows the apparent viscosity of the supernatant of EE–AL mixture solutions at three values of pH, from one of the three above mentioned zones. The effect of pH in the media on the interaction ratio of the complex was again similar to the result obtained in the turbidity experiments. In the case of pure EE or pure AL, the apparent viscosity of these solutions increased continuously with an increase of polymer concentration. Therefore, the decrease of apparent viscosity observed in the EE–AL mixtures system showed that the IPEC was formed in all investigated media and was removed by the centrifugation procedure. The low values of the apparent viscosity in samples with an excess amount of EE (right part of the curve) corresponded to low apparent viscosity of EE as compared with AL solutions and also by selective binding to the poorly flexible polymer chains of AL necessary to form a precipitate of the IPEC with a characteristic composition EE:AL. The influence of rigidity or flexibility of the polymer chains to the structure and composition of formed IPEC is very close to the results obtained for the interaction between chitosan with AL, polyacrylate sodium and hyaluronate sodium (Takahashi et al., 1990; Takayama et al., 1990).

In a next set of experiments, we calculated the binding or interaction ratio of each component in the solid IPEC based on the results obtained by elementary analysis. The results (mean; $n = 2$) are shown in Table 1. The data obtained show that the binding ratios of AL and EE

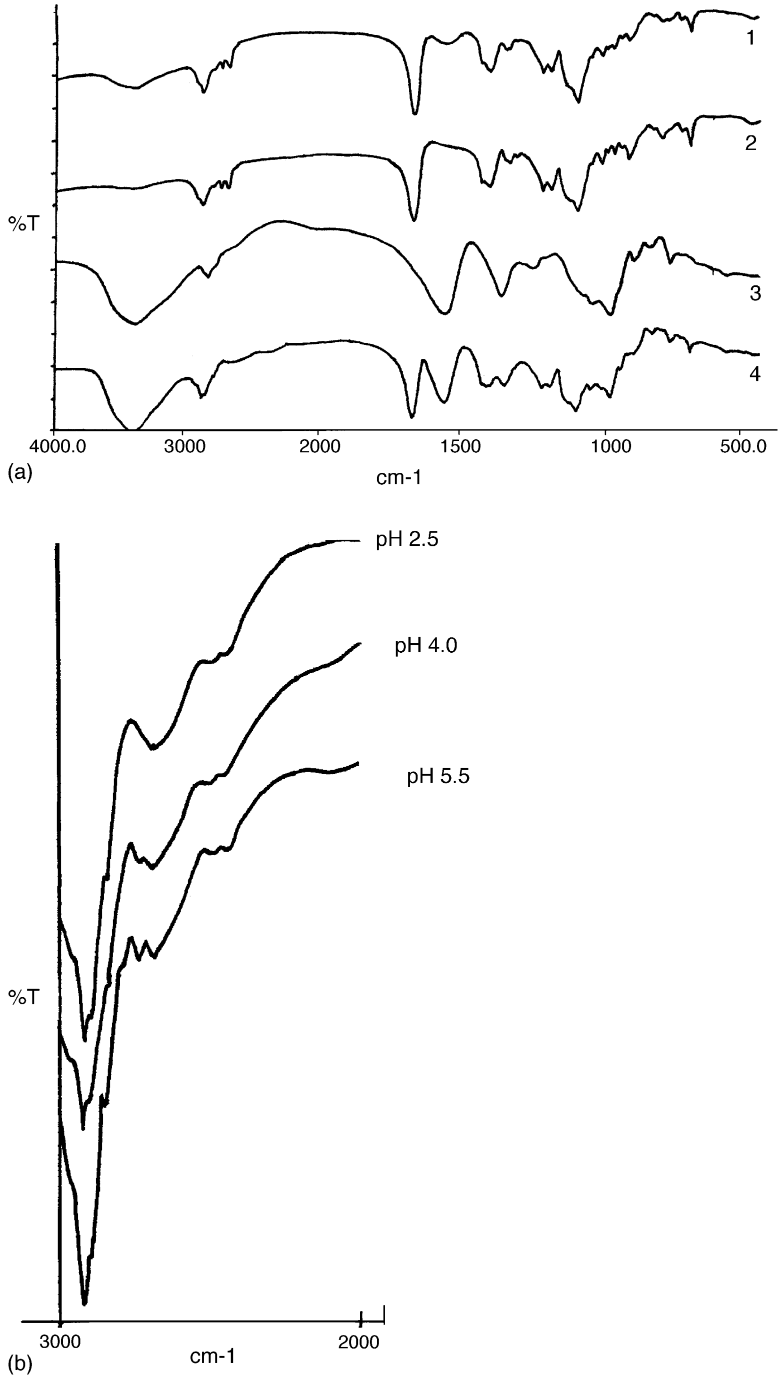

Fig. 4. (a) FT-IR spectra of (1) physical mixture of EE and AL in a ratio 1:1.5; (2) pure EE; (3) pure AL; (4) IPEC, $Z = 0.66$. (b) FT-IR spectra of IPEC prepared at different pHs.

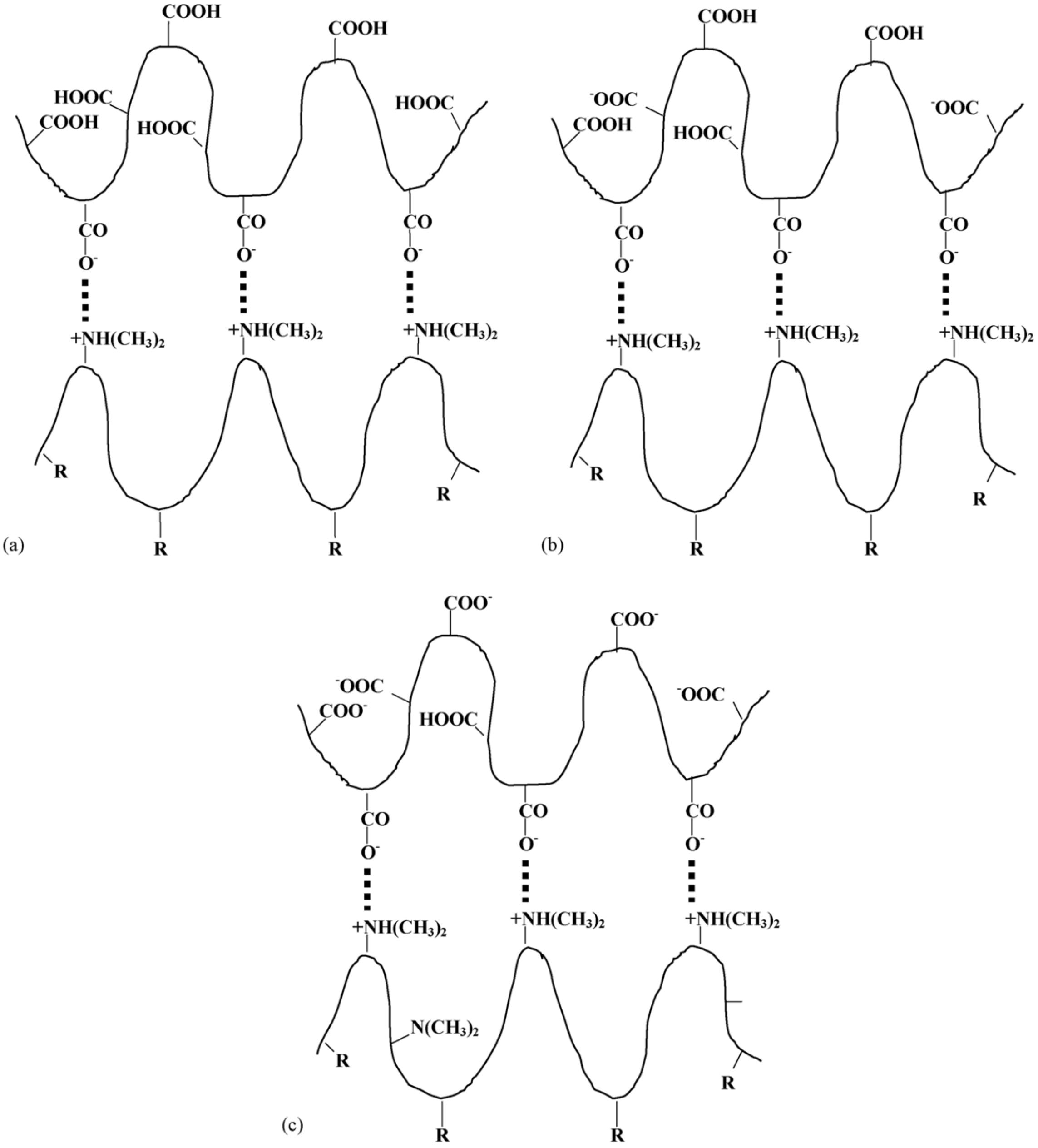

Fig. 5. Schematic representation of the ionic interactions between AL and EE at pH 2.5 (a); pH 4.0 (b) and pH 5.5 (c). R represents non-ionized monomer units of EE.

changed from 1.5:1 to 1:1.25 with increasing pH values, and concur with the results from the turbidimetric analysis. A change in pH leads to a change in polymer charge density, hence a different composition of the IPEC results. These phenomena were close to those observed in chitosan–polyacrylate and chitosan–AL systems (Takahashi et al., 1990; Majeti and Kumar, 2000).

Table 1
Element analysis of different IPEC

	pH = 2.5 (Z = 0.66)			pH = 4.0 (Z = 1)			pH = 5.5 (Z = 1.25)		
	C	H	N	C	H	N	C	H	N
Calculated value	50.77	7.93	2.45	51.07	8.12	2.68	51.13	8.31	2.75
Experimental value (mean, n = 2)	50.02	7.86	2.47	51.02	8.04	2.64	51.04	8.20	2.77

Fig. 4a shows FT-IR spectra of the EE–AL solid complexes (label 4) obtained as precipitates in the medium of pH 2.5. IR spectra of the solid complex were greatly different from those of EE alone (label 2), AL alone (label 3) or a physical mixture of AL and EE at a molar weight ratio of 1.5:1 (label 1). The characteristic peak that becomes more pronounced at $1580\,\mathrm{cm}^{-1}$, might be assigned to the absorption band of the carboxylate groups of AL that forms the ionic bonds with protonated dimethylamino groups of EE. On the other hand, a broad peak, appearing at approximately $2720\,\mathrm{cm}^{-1}$ and two weak bands at 2510 and $2480\,\mathrm{cm}^{-1}$, might be assigned to the polymers salts absorption band which was brought about by the interaction of the dimethylamino groups of EE with the carboxyl groups of AL. Fig. 4b shows FT-IR spectra of the EE–AL solid complex obtained as precipitates in the medium with different pH value (2.5, 4.0 and 5.5). Although all of them have a band at $2720\,\mathrm{cm}^{-1}$, compositions where $1 < Z < 1.25$ are characterized by two new peaks at 2770 (in the case $Z = 1$ and 1.25) and $2820\,\mathrm{cm}^{-1}$ (only for $Z = 1.25$). This means that these samples of IPEC have also non-ionized dimethylamino groups in their structure. Indeed, while the pH of the medium is increased, the number of protonated groups of EE is dramatically decreased, but they are still able to form IPEC with AL molecules. Together with the fact that the binding ratio of the complex was affected by the change of pH values in the media (Figs. 2 and 3), the ionic bonding seems to be a primary binding force for the complex formation between EE and AL.

Analysis of different samples of IPEC shows that all of them are structurally complementary compounds independent from the pH of the medium in which the solid complex was obtained. Existence of non-ionized dimethylamino groups were observed by IR spectroscopy, and this means that they are localized in ‘defects’ fields, which are also called ‘loops’. Polymer chains in this case are not be able to interact with each other due to steric problems and low charge density of the macromolecules. Formation of electrostatic contacts in such polymer–polymer fields is not possible. That phenomenon is well known for the structure of stoichiometric IPEC (Kabanov, 1972).

According to the results obtained we can propose that the structure of IPEC that we synthesized depends from the pH value and could be presented as depicted in Fig. 5. The number of protonated amino groups (positively charged) decreases with increasing pH, while the number of deprotonated carboxylic acid groups (negatively charged) increases with increasing pH.

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