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Interpolyelectrolyte complexes of Eudragit® E PO with sodium alginate as potential carriers for colonic drug delivery: monitoring of structural transformation and composition changes during swellability and release evaluating

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Abstract

Background: With a view to the application in oral colon drug delivery systems, swelling and release behavior of synthesized interpolyelectrolyte complexes (IPEC) between sodium alginate and Eudragit® EPO were investigated. *Method*: The microenvironmental changes in IPECs structure as a function of pH during swellability testing were investigated using FT-IR spectroscopy and elementary analysis. *Results*: All samples of IPECs (Z = 0.66–1.25) during swelling were transformed to a similar structure with approximately the same composition. The release of the model drug diclofenac sodium was significantly delayed from matrices made up of the IPECs and independent from the composition of polycomplexes. *Conclusion*: According to the obtained results, these IPECs can be considered to have potential in colonic drug delivery as combined pH- and time-dependent systems.

Key words: *Alginate; colon drug delivery; diclofenac sodium; Eudragit® E PO; interpolyelectrolyte complex*

Introduction

Nowadays, there are a lot of strategies for specific drug delivery to well-defined sites of the gastrointestinal (GI) tract, the colon being the most important one[1–5]. Enteric polymers are used for this purpose, as they are able to release the drug at a particular pH. The pH-sensitive copolymers, such as methacrylic acid/methyl methacrylate copolymers and Eudragit® types L and S, dissolve in aqueous media at pH 6 and 7, respectively, which may be equivalent to drug release in the distal ileum[6]. Combinations of Eudragit® types L and S also provide a suitable system for colon-specific drug release[7,8]. Recently, a new copolymer has been described to be used in colon delivery, Eudragit® P-4135F, exhibiting a dissolution threshold pH slightly above 7.2[9]. It contains relatively large amounts of methyl acrylate (around 65%) turning it more hydrophobic. However, Eudragit® P-4135F was observed to be very limited in the delivery of hydrophilic compounds because of repulsion with the copolymer[10].

A second approach is the use of polymers of natural origin, polysaccharides, which are hydrolyzed in the colon by means of polysaccharidases. Examples are chitosan, pectin, inulin, guar-gum, amylose, dextrans, and chondroitin sulfate[11–17]. However, because of

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their solubility in the GI fluids, they do not reach the colonic region. To solve this problem, these polymers were chemically derivatized. Although the results obtained with these materials were encouraging, the large intra- and interindividual differences in GI pH make these polymers less suitable with respect to reproducible drug release. To overcome this problem and to increase the site-specificity of drug release, new polymers, containing biodegradable bonds, were synthesized. Given the abundance of bacterial azo reductase in the large intestine, copolymers of hydroxyethyl methacrylate, methyl methacrylate, and methacrylic acid and different bifunctional azo-aromatic agents were synthesized[18]. Although the validity of the biodegradation concept of these polymers was clearly demonstrated both during in vitro and in vivo tests, the time required for biodegradation was approximately 10–12 hours, thus limiting significant drug absorption.

Modification of the properties of a polymer can be obtained by copolymerization or derivatization, a strategy that was successfully applied in the past. However, the major drawback of this approach is that new chemical entities are introduced with an unknown toxicological profile. Before these products can be evaluated in animals and in human clinical trials, a lot of time and resources must be spent on safety evaluation. A sound approach to overcome this problem is the physical modification of the polymer rather than the chemical. In this respect, interpolyelectrolyte complexes (IPECs) may provide a valuable tool to design drug delivery systems (DDS) with specific physicochemical properties.

The advantages of using IPEC as a polymeric carrier in controlled drug release were already reported[19,20]. IPEC made up of cationic and anionic polysaccharides have been reported previously, for example, chitosan and sodium alginate (AL)[21–27]. Recently, a novel approach is used in the preparation of composite IPECs containing microparticles that were formed by tripolyphosphate cross-linking of chitosan, electrostatic complexation by alginate and/or pectin, as well as ionotropic gelation with calcium ions, characterized by improved pH-sensitive drug release properties[28].

Analyzing the above-mentioned results, one of the ways of preparing the colon-specific drug formulations is to combine the properties of biodegradable polysaccharides with those of enteric coatings[29]. This idea is also used in the preparation of chitosan multicore microspheres, coated by Eudragit® types S or L[14]. Polycomplex formation between chitosan and Eudragit® S in the external layer of pellets during release testing, checked by scanning electron microscopy and Fourier transform infrared (FTIR) techniques, provides a suitable approach for colon-specific release. The same result was obtained in the evaluation of a film-coating composite made of pectin and Eudragit® RL, resulting in an extremely slow leaching of pectin and subsequent slower drug release with respect to colon-specific drug delivery. Pectin as an anionic biopolymer bonded with oppositely charged quaternary ammonium groups of Eudragit® RL forms a pectin–Eudragit® RL complex, which prevents the release of incorporated drugs[30]. Furthermore, the similar principle was successfully used in chitosan/succinic acid/Eudragit® RS/RL-coated system via electrostatic interaction between the amine groups of chitosan/quaternary ammonium groups of Eudragit® RS/RL and the carboxyl groups of succinic acid, taking place during release process in colon-simulated medium[31].

It is well known that combining differently charged (meth)acrylate copolymers appears to be an interesting field of investigation, providing advantages in the processing and modulation of release profiles[32]. The systematic investigations of involving Eudragit® Sin IPECs as a new class of drug carriers for the first time were done by our group[33–37]. Polycomplexes based on basic butylated methacrylic terpolymer (Eudragit® E) and countercharged (co)polymers of synthetic (Eudragit® L100-55, L100, S100)[35,36,38] and natural origin (AL[33,34,39], kappa-carrageenan[40], and casein[41]) made up in aqueous solutions have been extensively investigated in recent years. However, a more limited research has been directed toward colon-delivered applications of polycomplex-containing systems. Few papers were devoted to the possibility of involving IPECs as a matrix system for colon-specific delivery[42,43].

Recently, the formation, characterization, and pharmaceutical evaluation of Eudragit® E PO (EE)/sodium AL IPECs have been done by our group with recommendation about these polycomplexes as suitable candidates for controlled release matrix systems.[33,34].

The aim of this study was to monitor the possible structural transformation and composition changes of polycomplex matrices made up of AL and EE during swellability testing in simulated intestinal tract conditions with respect to their potential application as a new system for colon delivery, using diclofenac sodium (DS) as a model drug.

Materials and methods

Materials

AL (MW 365 kD) was purchased from Federa (Brussels, Belgium). EE terpolymer (MW 150 kD) was generously donated by Evonik Röhm GmbH (Darmstadt, Germany). The polymers were used after vacuum drying at 40°C during 2 days. DS was used as a model drug and was purchased from Sigma (Bornem, Belgium).

Synthesis of solid IPECs

A solution of EE (0.01 M) in acetate buffer (0.05 M; pH 2.5, 4.0, and 5.5) was mixed with a solution of AL (0.01 M) in acetate buffer (0.05 M; pH 2.5, 4.0, and 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 at least 2 days at 40°C. Each material was sieved and the respective sieve fraction (≤0.25 mm) was selected.

Elementary analyses

The composition of the formed IPECs (denoted as Z) and their vacuum-dried samples (at 40°C during 2 days) during swellability testing was investigated by elementary analysis using a Perkin-Elmer model 240B elementary analyzer (Perkin-Elmer, Norwalk, CT, USA) and calculated as Z = [EE]/[AL].

Infrared spectroscopy

FT-IR spectra of the solid IPEC EE/AL systems, pure polymers its physical mixtures and the vacuum-dried samples (at 40°C during 2 days) during and after swellability testing were measured using a Bruker FT-IR model Vector 22 spectrophotometer (Bruker, Karlsruhe, Germany) using the KBr disk method. The dried matrices were ground with a grinder and ball milled. The powder was passed through a 200-μm sieve and used for further FT-IR study.

Preparation of tablets

For swellability testing, unless otherwise stated, flat-faced tablets of 100 mg (polymer carrier) and 8 mm diameter were prepared by compressing the given amount of powder at 25 kg/cm^2 using a hydraulic press (Rodac, Sittard, the Netherlands).

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

Swelling studies

The degree of swelling was investigated under conditions that simulated the intestinal tract (SIT)[14]: the first 2 hours in a buffer solution of pH 5.8, the next 2 hours in a buffer solution of pH 6.8, and finally 2 hours in a buffer solution of pH 7.4. The compositions of the release media used were those described in British Pharmacopeia 98. The polymeric matrix is placed in a tarred basket (from the dissolution test equipment), which was immersed into a thermostated bath (37 ± 0.5°C). The volume of the swelling medium was 40 mL. The degree of swelling was determined every 15 minutes: the basket was removed from the medium, dried by filter paper, and weighed. The degree of swelling (H, %) was calculated as

$$H(\%) = \frac{m_2 - m_1}{m_1} \times 100,$$

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

Release testing of DS

The release of DS from matrix tablets was performed at 37 ± 0.1°C using a standard dissolution tester DT 600 (Erweka, Heusenstamm, Germany) (basket method). The rotation speed was 100 rpm, and the volume of the dissolution medium was 900 mL. The pH of the release medium was gradually increased by changing the appropriative buffer solution: pH 5.8 during the first 2 hours, then 6.8 during the second and third hour, and finally the pH was maintained at 7.4 until the end of the experiment. Aliquots (3 mL) of the solution were taken at specific time intervals and the volume was made up to the original value by adding fresh dissolution medium. The amounts of DS released in the dissolution medium were determined spectrophotometrically at 276 nm using a SPEKOL 1300 spectrophotometer (Analytik Jena, Jena, Germany). Results are given as the mean of three determinations. Preliminary experiments had shown that the polymers did not interfere with the quantitation of the model drug.

Results and discussion

At first glance, the usage of gastric-soluble terpolymer—EE in colon drug delivery—is unreal, which probably explains the minor published data on the applications of this polymer in such field[44–46]. But, according to terpolymer structure and comparatively low content of dimethylamino groups (between 20.8% and 25.5%), responsible for dissolution in acidic medium and simultaneously taking place in possible IPEC formation with carboxyl contains AL, lead to screening of ionized positively charged groups of EE by oppositely charged carboxylate AL moieties in intermacromolecular reaction between two countercharged polyelectrolytes. So, which means that the solubility of EE at low pH is reduced by AL network shrinking as this polysaccharide is insoluble under low pH conditions, and the possible dissolution of polyanion at high pH values is reduced by EE that is stable at high pH ranges.

The first attempt and rather positive results in particles/microspheres preparation were previously discussed for countercharged polyions with similar structure–Eudragit® RS/RL–alginate sodium[47–49].

In the previous study, we found that the composition of the prepared IPEC EE/AL depends on the pH 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[34].

In this study, we attempted to evaluate the possible structural and compositional changes that could arise inside matrices (IPEC samples, its physical mixtures with the same compositions, and individual polymers) during swelling and compare them with release characteristics of the model drug, DS.

Structural evaluation of investigated IPEC samples

Structure differences of investigated IPECs were studied by FTIR spectroscopy. Figure 1 shows FTIR spectra of the EE–AL solid complexes with different compositions (Z = 0.66, 1, and 1.25), obtained as precipitates in the medium with different pH value (2.5, 4.0, and 5.5). It is interesting to note that the peak normally present at 1635 cm^{-1} in the AL spectrum, attributed to the asymmetric C=O stretching of the carboxylate groups, is shifted to a lower value (1609 cm^{-1}) in the IPEC spectra and might be assigned to the absorption band of the carboxylate groups of AL that forms the ionic bonds with protonated dimethylamino groups of EE. This corresponds to our previously published results[34] as well as those reported by others[50,51]. Moreover, all spectra show a band at 2720 cm^{-1}; compositions where $1 < Z < 1.25$ are characterized by two new peaks at 2770 (in the case Z = 1 and Z = 1.25) and 2820 cm^{-1} (only for Z = 1.25), respectively. This means that these samples of IPEC have also contained nonionized dimethylamino groups in their structure[52,53].

According to Figure 1, the main differences between all IPECs could be observed in two narrow regions of FTIR spectra from 2500 to 2900 cm^{-1} and 1600 to 1800 cm^{-1}. These regions were selected for possible structural changes estimation. According to Ali Said[42] and our own results[37], applying this technique during swellability testing is very useful for this purpose.

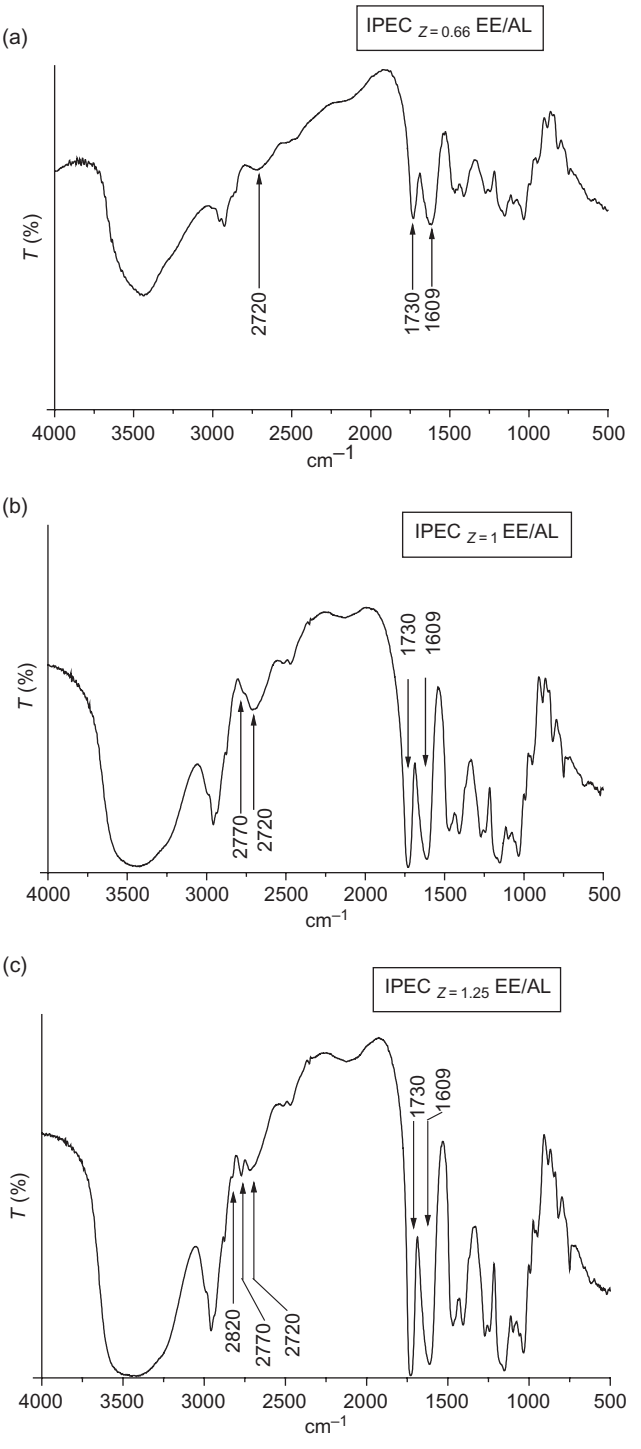

Figure 1. FTIR spectra of IPECs with different compositions: (a) Z = 0.66, (b) Z = 1, and (c) Z = 1.25.

Monitoring of structural microenvironmental transformations inside matrices during pH-dependent swellability testing

To know what happens with polycomplex matrices during swellability testing, we investigated possible changes of individual copolymers and its physical mixtures as well. As expected, the individual copolymers are clearly not suitable to be used in oral DDS. EE is dissolved within 2 hours, and AL having the highest swelling degree formed a gelling matrix that completely dissolved within 4.5 hours (Figure 2a). Figure 2b shows FTIR spectra of matrices made up of individual copolymers during swellability testing. The characteristic peaks of both copolymers are not changed in the region observed. The two peaks at 2770 and 2820 cm^{-1} might

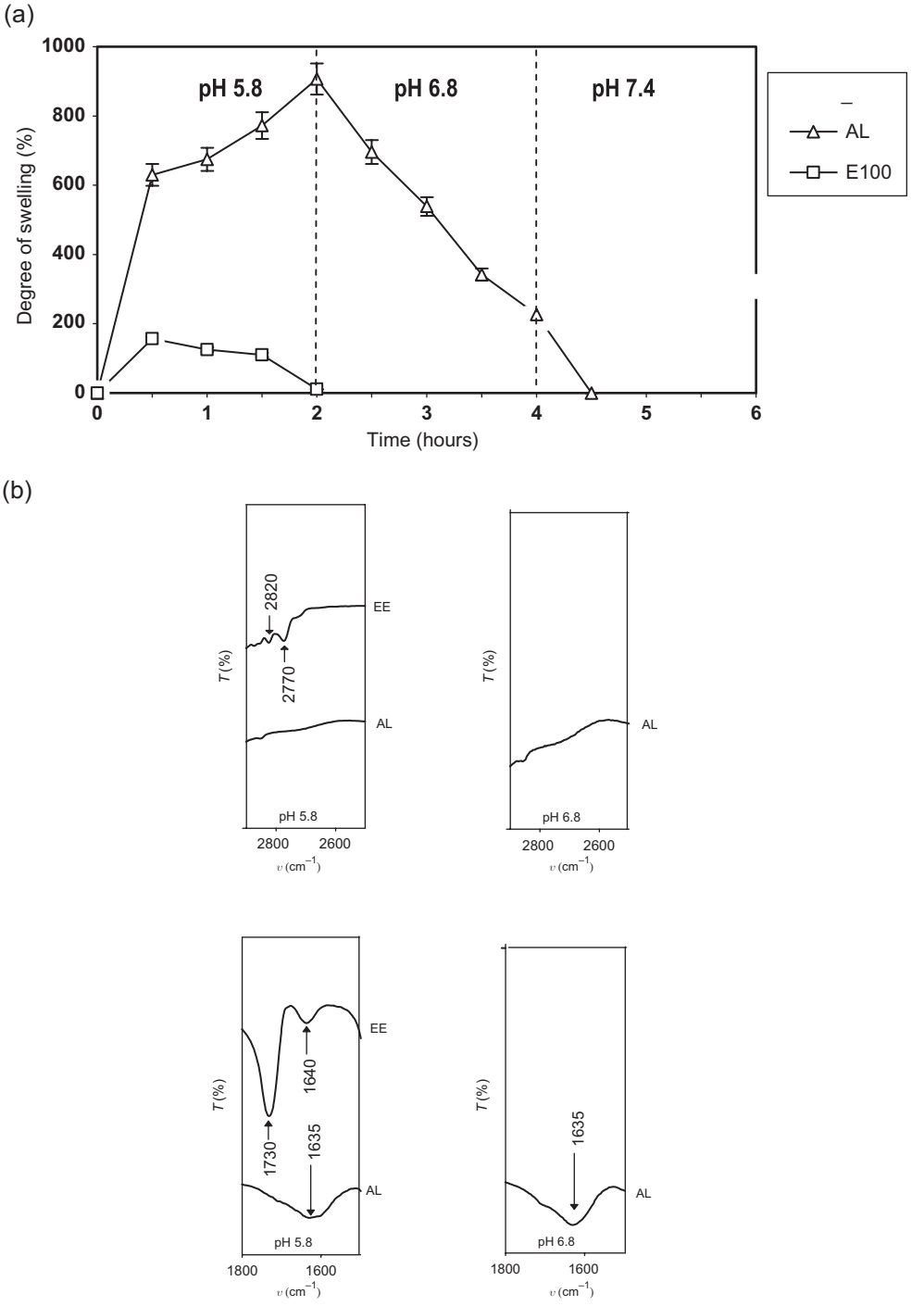

Figure 2. (a) Degree of swelling of EE and AL in SIT conditions (n = 3; ±SD); (b) FTIR spectra of matrices of individual copolymers during swellability testing.

be assigned to the absorption band of the nonionized dimethylamino groups in the structure of EE; the characteristic peak of AL becomes more pronounced at 1635 cm^{-1} and might be assigned to the absorption band of the carboxylate groups of the polysaccharide.

Physical mixtures have different swelling parameters. Samples with an excess amount of AL (Z = 0.66) are characterized by a relative rapid increase in swellability followed by a decrease; it was completely dissolved at the end of the testing period (Figure 3a). In case of two other samples of physical mixtures (Z = 1 and Z = 1.25), more stable swelling profiles can be observed, relatively independent of the medium (Figure 3a). Figure 3b shows FTIR spectra of matrices from physical mixtures.

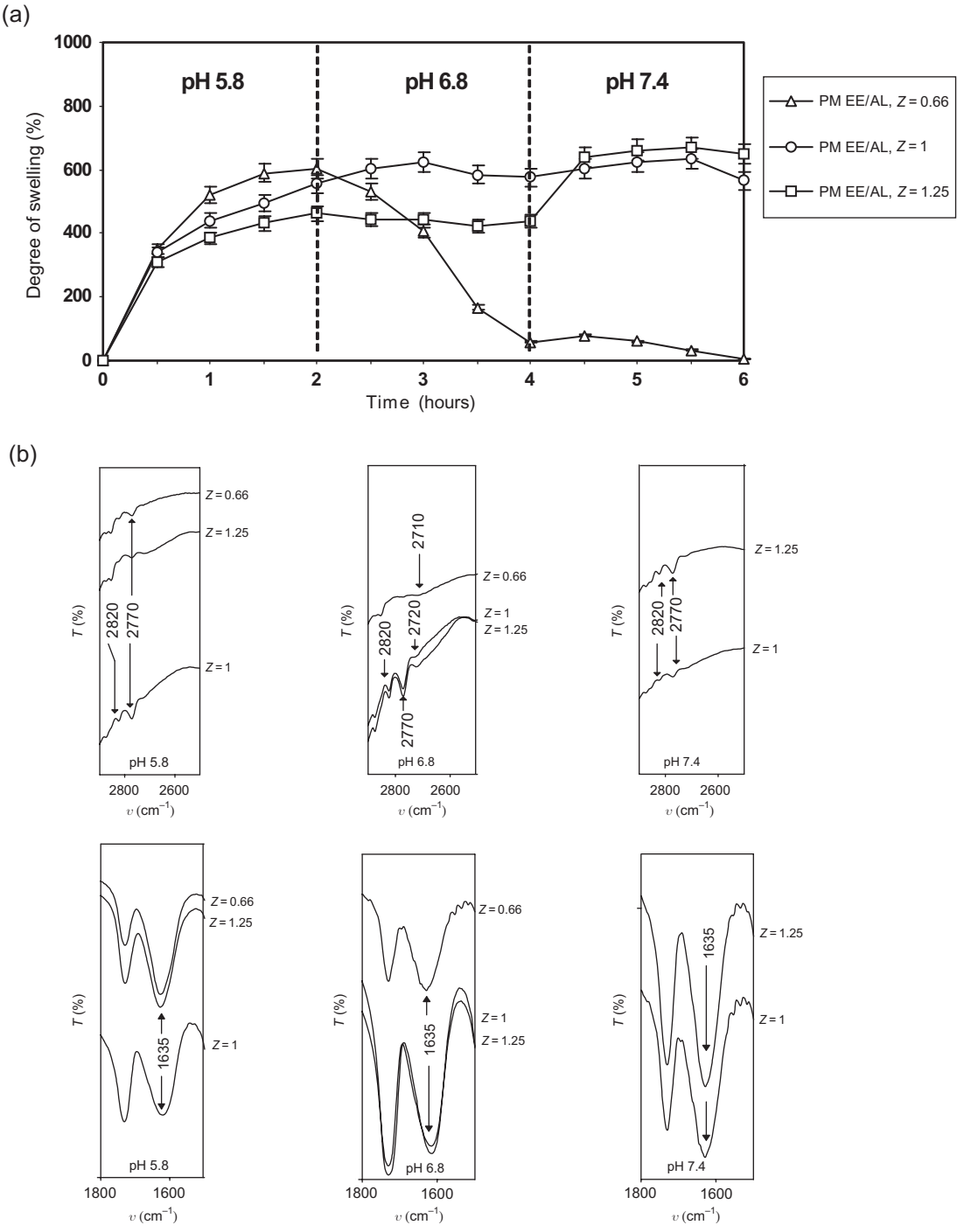

Figure 3. (a) Degree of swelling of physical mixture of EE and AL with different compositions in SIT conditions (n = 3; ±SD); (b) FTIR spectra of matrices consisting of physical mixtures of copolymers during swellability testing.

The characteristic peaks of both copolymers are characterized by minor changes in the observed region because of continuous leaching of EE, localized in external layers of the matrices in acidic medium and swelling/dissolving of AL in neutral region because of the ionization of carboxyl groups of the polyacid. Therefore, the interaction between chains of two oppositely charged copolymers that could be possible as a result of immersing into weak acidic medium (pH 5.8) in which macromolecules could react is not observed (shifting from 1635 cm^{-1} to a lower value 1609 cm^{-1} was not seen). This is very important, because it was supposed by other groups that matrices made up from physical mixtures of oppositely charged (co)polymers that were

immersed in the medium with the optimal pH could lead to IPEC formation in the external layer or in the whole matrix[54,55]. Let us discuss this phenomenon in more detail.

As EE and AL have different pK_a values, their protonation/deprotonation degrees are different at various pHs. The mechanism of pH-sensitive swellings involves the protonation of dimethylamino groups of EE under comparatively lower pHs and deprotonation of carboxylic groups of AL at higher pHs. It is known that the pK_a of AL is 3.2 and 4.0 for glucuronic and mannuronic acids, respectively. Therefore, in investigated pH range (5.8–7.4), all carboxylic acid groups become ionized and the resulting electrostatic repulsion causes the matrices to swell. According to pK_a of 7.0–7.3, poly(dimethylamino) ethylmethacrylate can be protonated and ionized in acidic medium, whereas deprotonation above pH 8.0 can render homopolymer hydrophobic[53]. EE, due to a terpolymer structure, could be losing its solubility from the pH above 5.0 and becomes completely insoluble at pH around 7.0. Consequently, at the pH range from 5.8 to 7.4, ionization of dimethylamino groups takes place, but it smoothly decreases with increasing pH values. Therefore, the interaction between countercharged polymers during swelling could be limited.

The swelling properties of IPEC AL/EE, due to polycomplex structure, definitely have other characteristics as compared to individual copolymers and its physical mixtures in SIT conditions (Figure 4a). The sample of IPEC (Z = 0.66), which contains an excess amount of AL, is characterized by a higher degree of swelling. Indeed, the existence of AL chains, localized in 'defect' fields of the polycomplex, could form a more hydrophilic structure with comparatively high degrees of swelling. These chains consist of free noninteracted carboxyl groups that are completely ionized after removal from the acidic medium (pH 5.8) and being placed in the neutral medium (pH 6.8–7.4). These free AL sequences in IPEC structure lead to the stronger electrostatic repulsion among ionized carboxylic groups, which is not so evident at pH 5.8 and becomes more pronounced at higher pH values (obvious from Figure 4a). At the same time, in two other IPECs (Z = 1 and 1.25), existing ionic bonds consequently decreased the swelling degree, because most of the functional groups responsible for swelling are involved in polycomplex formation despite carboxyl groups in AL macromolecules becoming progressively ionized by further increasing the pH.

As a result, the compositions Z = 1 and Z = 1.25 have a relatively stable, pH-independent profile. However, after 6 hours, all three polycomplexes have an equal degree of swelling. It is known that the structure of the IPECs is changed because the ionic bonds are not fixed and they can move from one electrostatic site to another[56]. Hence, new interpolymer contacts can form without considerably changing the composition of IPEC, and the arrangement of 'defect' fields in the whole IPEC structure is also transformed. These phenomena can be explained by FTIR spectra of the polycomplex matrices during passage through the SIT medium (Figure 4b). All IPECs that are different in the beginning have similar changes with probably the same FTIR spectra in acidic medium (pH 5.8), a different one in the pH 6.8 (according to 2900–2600 cm^{-1} field), and a similar one in the final testing medium, because of similar structure changes that occurred during swelling in this pH region. The results obtained confirmed the above-discussed explanation of swellability profiles. The observed differences in FTIR spectra of polycomplexes with Z = 1–1.25 from Z = 0.66 in pH 6.8 can be explained by a reorganization (transformation), which starts from pH 6.8 and ends at pH 7.4 (obvious from swelling profile and FTIR spectra).

On the basis of the results of FTIR, we can conclude that during 6 hours residence time in SIT media, all polycomplexes have completely changed their structure. Peaks, attributed to intermolecular-interacting ionized dimethylamino groups of EE, that are characterized by the wide absorption band at 2720 cm^{-1} disappeared (because of complete deprotonation of dimethylamino groups, localized in 'defect' fields), but the absorption band at 1609 cm^{-1} still exists, which confirms the safety of polycomplex structure.

Monitoring of microenvironmental changes in polycomplex matrix compositions during swellability testing

To know whether observed structural transformation leads to possible microenvironmental changes in the composition of IPECs, we used elementary analysis. According to Figure 5, compositions of the polycomplex sample (Z = 1) during passage through all three buffer solutions were relatively constant and the unit molar ratio was found to be approximately 1:1 (Z = 1). On the other hand, the composition of IPEC, which contains an excess amount of AL (Z = 0.66), was transformed to a composition with an even lower amount of EE (Z = 0.53 ± 0.02). In case of IPEC, which contains an excess amount of EE (Z = 1.25), reorganization that changes the composition of the polycomplex also happened but finally it reached an equimolar composition. Hence, for two mediums (pH 5.8 and 6.8), good agreements of swellability with elementary analysis results for all IPECs could be observed. Differences in polycomplex composition, estimated by element analysis, for the sample (Z = 0.66) after the final medium (pH 7.4) could be due to IPEC transformation, which led to the formation of characteristic stoichiometric composition of the same

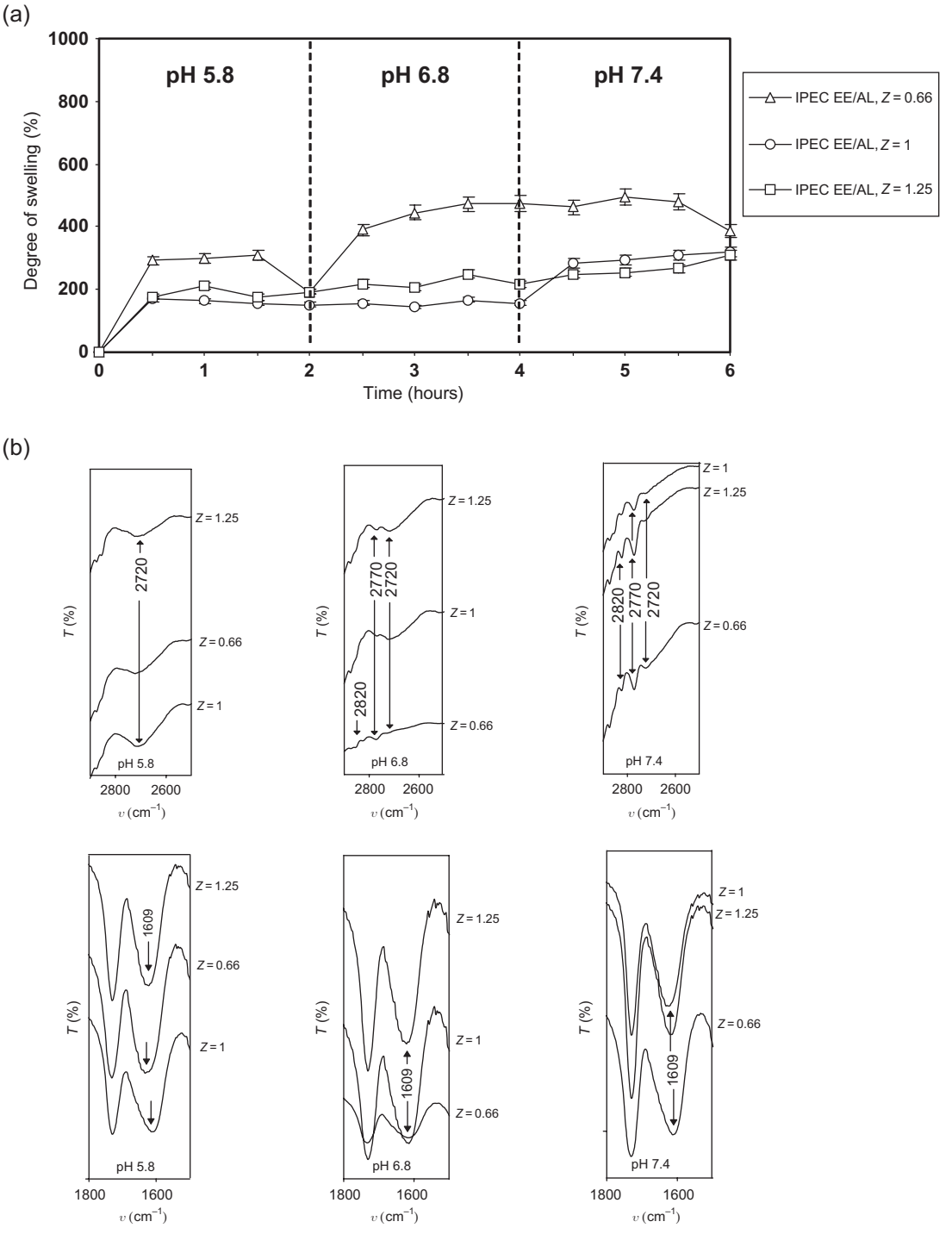

Figure 4. (a) Degree of swelling of IPECs EE/AL with different compositions in SIT conditions (n = 3; ±SD); (b) FTIR spectra of polycomplex matrices during swellability testing.

structure (ratio and reaction capability included to IPEC sequences), which was confirmed by swelling profiles of all tested samples. The three types of synthesized products have relatively constant swelling properties, but only the equimolar composition actually has a pH-independent profile with minimal changes in structure.

The differences in microenvironmental structure of synthesized polycomplexes and their changes during the 6 hours of swelling testing (pH 5.8–7.4), that were confirmed by two methods (FTIR and elementary analysis), could be presented as depicted in Figure 6. Therefore, polycomplexes reorganization over time

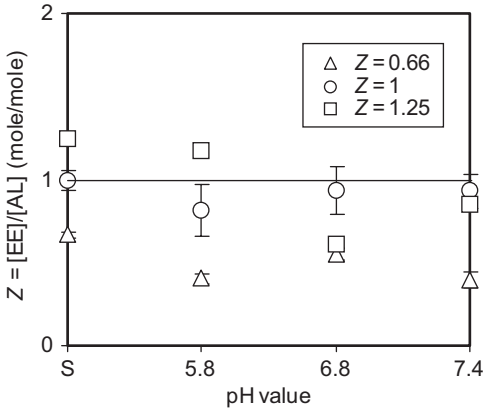

Figure 5. Compositions of polycomplex matrices according to elementary analysis during swellability testing in SIT conditions ($n = 3$; ±SD).

results in IPEC formation of similar composition for all initially different *Z*-ratios.

Release of DS from all evaluated EE/AL systems

Release of DS from the tablets consisting of individual polymers, physical mixture of EE and AL, and IPECs was investigated with respect to the effect of interpolymer complex. According to our previously published results about dissolution behavior of ibuprofen as a model drug from the same polycomplex matrix system based on EE and AL in gastrointestinal-simulated conditions[33], in this study, we used only intestinal mediums with gradually increased pH. The first reason is that all tested polycomplexed matrices are stable in gastric-simulated environment; the second one is that both model drugs (ibuprofen, DS) are less soluble at pH 1.2 and their release checking is not possible.

Figure 7 shows the release curves of DS from the tablets consisting of EE alone, AL alone, and the physical mixtures of EE and AL at molar weight ratios according to IPEC compositions. In case of the alginate matrix, the release process is relatively continuous and can be explained by the ionization of the carboxylic groups, which leads to a fast dissolution of AL up to 6 hours and correlates with its swellability. EE dissolved partially in acidic medium because of hydration of protonated dimethylamino groups. After immersing in a buffer solution with pH 6.8, it becomes insoluble. The release rate is higher in the beginning (pH 5.8–6.8) and decreases at the end (pH 7.4). Taking into consideration the swelling profile of EE and the chemical structure of DS, we could also assume the possibility of drug—polymer interactions, which could have happened during release process. Recently, explanation about the ionic interaction between protonated dimethylamino groups EE macroion and DS as carboxylic group containing drug with evaluation the potentialities of EE–DS system was provided[57]. Additionally, detailed studies on the interaction of the quaternary ammonium polycations—Eudragit® RL[58] and RS[59] copolymers by means of ionic bond formation with DS were reported. We suppose that similar interactions have happened in our case too, which dramatically sustained DS release from EE matrix.

The release process from the matrices of physical mixtures is slower than that observed in the systems with individual copolymers. The reason is that increasing swelling force of AL due to electrostatic repulsion of polysaccharide chains at high pH values is reduced by EE that is insoluble at this pH range. However, to accept the polymer as carrier for colon-specific drug delivery system, it should not release the drug and protect it in acidic medium and start to release at colon and small intestine[42]. Therefore, matrices on the base of individual copolymers and its physical mixture with tested compositions ($Z = 0.66$–1.25) are not suitable for colon DDS.

It is well known that site-specific drug delivery to the colon may be achieved by different approaches. Ideally, the approach based on the combination of pH-dependent and time-controlled release mechanism seems encouraging[2,4,45]. According to this and special structure of IPECs, it could be supposed that polycomplex matrices could combine pH and time-controlled DDS: resist the release of majority of drug from the formulation for an additional 3 ± 1 hours (i.e., the usual small intestinal transit time) and deliver drug primarily to the colon[45].

In our case, DS release from the polycomplex matrices has 'intestinal' type of release profiles, which were close to each other up to 6 hours. These results correlate with the microenvironmental structure transferring, which we checked during swellability testing by FTIR spectroscopy. Polycomplex matrices have the same structural changes while passing from one medium to another. Thus, the main part of the profiles of all IPEC types is mostly the same during the first 6 hours of observation. After 6 hours, the release rate increased and reached that of the physical mixtures. The reason is that the carboxylate groups localized in 'defects' have an increased swellability, which leads to a more hydrophilic structure of two types of IPECs ($Z = 0.66$–1). Existence of excess amount of unbounded and nonionized dimethylamino groups in polycomplex composition ($Z = 1.25$), localized in 'defects' regions of IPEC structure, while staying in the last medium, sustained continuous drug release as compared to other IPECs. The reason is that carboxylic groups of DS supposedly could interact with dimethylamino groups of EE chains in 'defects' fields. Similar findings were reported by Omari et al.[58] about the effect of DS–Eudragit® RL interaction on drug release behavior from matrix tablets.

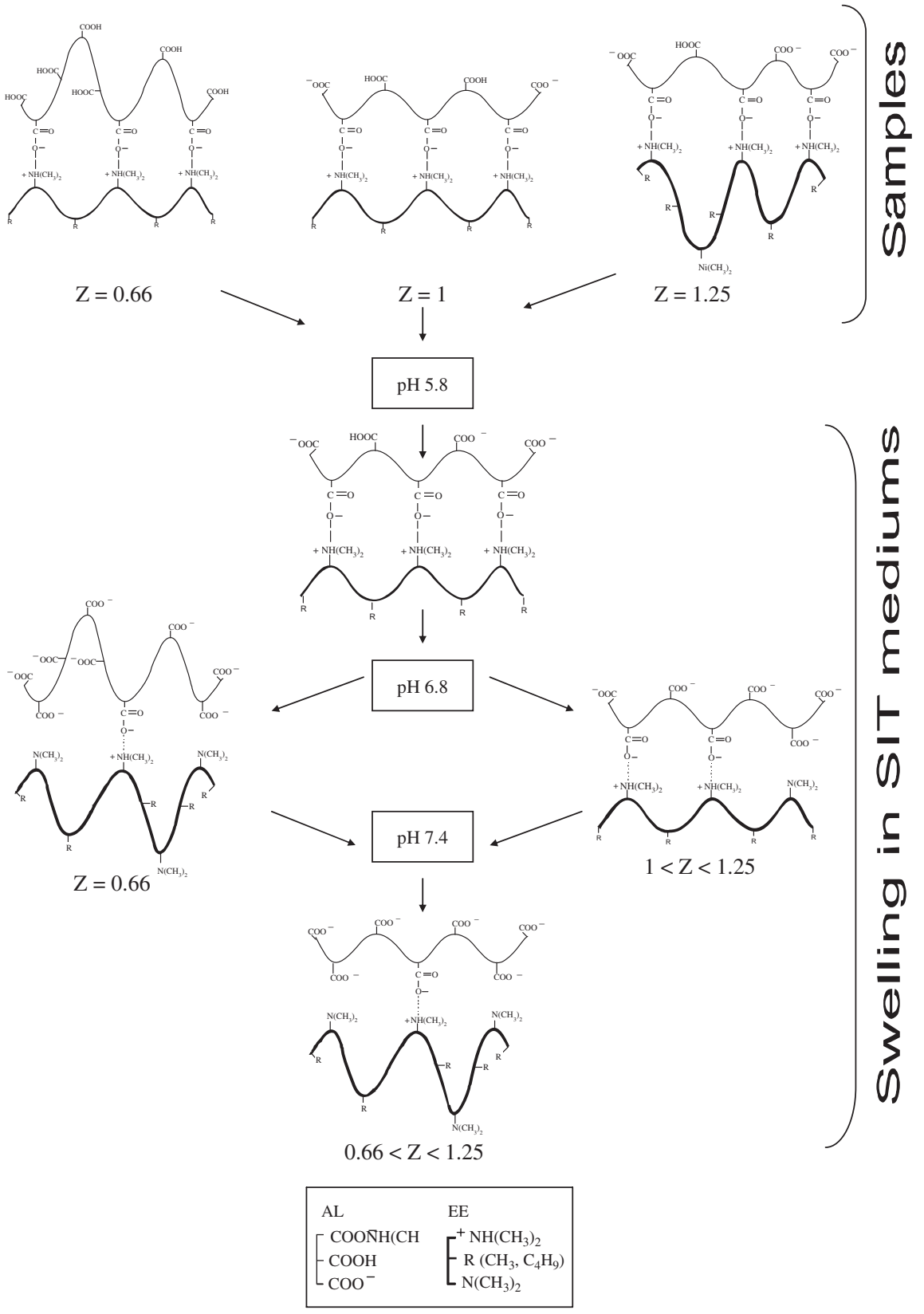

Figure 6. Schematic representation of the IPEC structures that were formed by ionic interactions between EE and AL at different pH values of tested mediums.

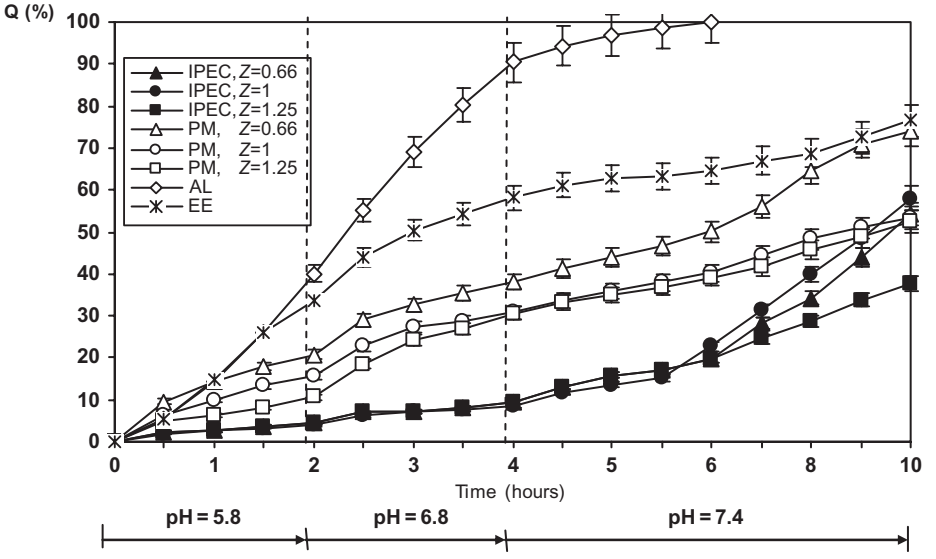

Figure 7. DS release from matrices made up of IPECs with different compositions, physical mixtures of EE and AL in the same molar ratio as in the polycomplexes, and individual copolymers in SIT conditions ($n = 3$; ±SD).

The differences between polycomplex matrices and physical mixtures suggest that all investigated IPECs due to proved pH-sensitivity are suitable for combined pH- and time-dependent colon-specific DDS because the release rate is minimal for a period of time, followed by comparatively rapid release of the drug at a site in the colon region, which corresponds to the 'intestinal' type of release profiles[5]. Swellability of matrixes, which were prepared from IPEC, can be tuned by their composition. This gives the possibility to tune the ratio of hydrophilic and hydrophobic parts in the structure of IPEC[56]. Matrices were made from physical mixtures more suitable to be used in sustained release formulations.

In our systems, we observe that independently from the composition, all polycomplex matrices gave a positive result—they did not show any critical structural changes that could be influenced during the release process. Therefore, some differences in the composition of the synthesized IPEC cannot seriously change its swelling and release properties.

Conclusion

The results observed clearly indicate that all the investigated IPECs ($0.66 < Z < 1.25$) have stable and universal swelling and release properties because of probably the same structural changes inside the polycomplex matrices during passage through the SIT media. These IPECs have characteristics that may be suitable for colon-specific drug delivery as combined pH- and time-dependent systems.

Declaration of interest: The authors report no conflicts of interest.

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