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Research paper

Comparative evaluation of interpolyelectrolyte complexes of chitosan with Eudragit® L100 and Eudragit® L100-55 as potential carriers for oral controlled drug delivery

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Abstract

With a view to the application in oral controlled drug delivery systems, the formation of interpolyelectrolyte complexes (IPEC) between chitosan (CS) and Eudragit® L100 (L100) or Eudragit® L100-55 (L100-55) was investigated at pH 6.0, using elementary analysis. The interaction or binding ratio of a unit molecule of CS with Eudragit® L copolymers depends on the molecular weight of CS, and changes from 1:0.85 to 1:1.22 ($1.17 < \varphi < 0.82$) for L100 and from 1:1.69 to 1:1.26 ($0.60 < \varphi < 0.79$) for L100-55, respectively. Based on the results of FT-IR, the structure of the IPECs can change substantially as a function of pH (from 5.8 till 7.4). Swelling behavior of physical mixtures (PM) is definitely different, and potential interactions between the two polyelectrolytes were not observed. The release of the model drug diclofenac sodium (DS) was significantly delayed from tablets made up of the IPEC and can be modified by two ways: choosing Eudragit® L copolymer types and/or changing the molecular weight of CS in the IPECs composition.

Keywords: Interpolyelectrolyte complex; Eudragit® L100; Eudragit® L100-55; Chitosan; Infrared spectroscopy; Elementary analysis; Diclofenac sodium; Oral controlled drug delivery

1. Introduction

Modification of the properties of a polymer can be obtained by copolymerisation or derivatisation, 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 also in human clinical trials, a lot of time and resources must be spent to 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 (IPEC) may provide a valuable tool to design drug delivery systems with specific physicochemical properties.

IPEC with polysaccharides, obtained as precipitates on mixing cationic with anionic polymers in aqueous solutions, have been reported previously, mostly with participation of chitosan (CS) as polycation. The advantages

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Abbreviations: IPEC, interpolyelectrolyte complex; CS, chitosan; CS_{LW}, low molecular weight chitosan; CS_{MW}, medium molecular weight chitosan; CS_{HW}, high molecular weight chitosan; MW, molecular weight; L100, Eudragit® L100; L100-55, Eudragit® L100-55; PM, physical mixture of the polymers; DS, diclofenac sodium; SIT, simulated the intestinal tract; GIT, gastro-intestinal tract.

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of using IPEC as a polymeric carrier in controlled systems for drug release were already investigated [1]. Different polyanions of natural and synthetic origin were used as oppositely charged polyelectrolytes in interpolyelectrolyte complexation with CS [2–16] and well reviewed [17–18].

One of the approaches of preparing oral controlled release formulations is to combine the properties of biodegradable polysaccharides with those of enteric coatings [19]. This idea was also used in preparation of CS multicore microspheres, coated by Eudragit® types S or L. According to the results obtained, Eudragit will slowly and continuously dissolve over time, due to CS–Eudragit® complexation, thus leaving the CS microcores increasingly exposed to the release medium. To the best of our knowledge, this is the only scientific report dealing with ionic interactions of the polysaccharide CS with Eudragit® S, although the authors observed it only by IR analysis in a pellet film coating during the release measurements [20]. Unfortunately, the physicochemical characteristics of the system were not investigated.

The first systematic investigations of polycomplexes made up from different types of Eudragit® were done by our group [21–26].

In previous studies, we found that the composition of IPEC between low molecular weight CS (CS_{LW}) and Eudragit L100-55 is nearly equimolar, according to turbidimetry and apparent viscosity measurements. The structure of the solid IPEC, obtained by precipitation at pH 6.0, was investigated by means of FT-IR spectroscopy, and clearly proved that the synthesized products actually can be considered as IPEC [27]. The swelling properties of CS_{LW}/L100-55 system were also investigated [28].

The purpose of the present study is to characterize the physicochemical properties of IPECs made up of chitosan and two types of Eudragit® L – L100 and L100-55 with respect to their possible application as new pharmaceutical carriers for oral controlled drug delivery. Fig. 1 shows the molecular structures of the polymers. Diclofenac sodium (DS) was used as a model drug.

2. Materials and methods

2.1. Materials

Low-CS_{LW} (MW 160 kDa, viscosity of 1% acetic acid solution: 20–200 mPa s), medium-CS_{MW} (MW 400 kDa, viscosity of 1% acetic acid solution: 200–400 mPa s), high-CS_{HW} (MW 600 kDa, viscosity of 1% acetic acid solution: 400–800 mPa s) molecular weights CS were purchased from Fluka (Buchs, Switzerland). Eudragit® copolymers (L100–MW 135 kDa, L100-55–MW 250 kDa) were generously donated by Degussa® (Darmstadt, Germany). The polymers were used after vacuum drying at 40 °C during 2 days. DS, which was used as a model drug, was purchased from Sigma (Bornem, Belgium).

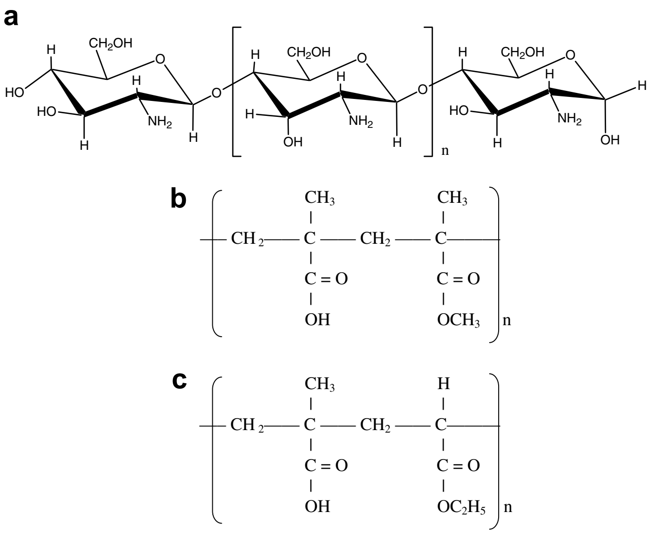


Fig. 1. Molecular structures of chitosan (a) Eudragit L100 (b) and Eudragit L100-55 (c).

2.2. Synthesis of solid IPEC

CS solutions (5 mM, pH 6.0) were mixed with L100 or L100-55 solutions (5 mM, pH 6.0) at constant temperature. After isolation of the precipitate from the solution, it was washed with demineralized water, and the solid IPECs were subsequently dried under vacuum for 2 days at 40 °C. The dried complex was ground with a grinder and ball milled. The powder was passed through a 200 μm sieve and used for further study.

2.3. Elementary analyses

The composition of the solid IPECs was investigated by elementary analyses using a model CHN-3 elementary analyzer (Dzerginsk, Russia) and calculated as $\varphi = [CS]/[L100]$ or [CS]/[L100-55].

2.4. Infrared spectroscopy

FT-IR spectra of the solid IPEC CS/L100 and CS/L100-55 systems, pure polymers, PM and samples during or after swellability testing were measured using a Bruker FT-IR model Vector 22 spectrophotometer (Bruker, Germany) using the KBr disk method.

2.5. Preparation of tablets

For swellability testing, unless otherwise stated, flat-faced tablets of 100 mg weight (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 weight (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, Sittard, The Netherlands).

2.6. Degree of swelling of tablets

The degree of swelling was investigated in conditions, which simulated the intestinal tract (SIT) [20]: the first 2 h in buffer solution of pH 5.8, the next 2 h in a buffer solution of pH 6.8, and finally 2 h in a buffer solution of pH 7.4. The compositions of the media used were those described in BP 98. The polymeric matrix was placed in a tared 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. The degree of swelling was determined after every 15 min: the basket was removed from the medium, dried by filter paper and weighed. 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 is the weight of the swollen sample.

2.7. Release testing of diclofenac sodium

The release of diclofenac sodium from matrix tablets was performed at 37 ± 0.1 °C using a standard dissolution tester DT 600 (Erweka, 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: pH 5.8 during the first 2 h, then 6.8 during the second and third hours, and finally pH 7.4 was maintained until the end of the experiment. Aliquots (3 ml) of 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, Germany). 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

According to the specifications of Degussa®, L100-55, ethyl acrylate–methacrylic acid copolymer with ratio 1:1 and L100, methyl methacrylate–methacrylic acid copolymer with ratio 1:1, are soluble from pH 5.5 and 6.0, respectively. On the other hand, the pK_a value of CS was reported to be 6.3 [5], hence the CS macromolecules are partially ionized at pH 6.0 and the charge density will be relatively low. The possibility of interaction between these two polyelectrolytes was investigated at pH 6.0, in which all polymers are soluble and partially ionized.

3.1. Composition studies

In order to confirm the binding ratio of each component in the solid IPEC, element analysis was performed. The results are given in Table 1 and clearly prove that the binding molar ratio of CS to L100 in the case of CS_{MW} and CS_{HW} is close to each other ($0.89 < \varphi < 0.82$) and consists of an excess of L100, but in case of CS_{LW} it contained some higher amount of CS ($\varphi = 1.17$). In case of CS/L100-55 (Table 2), all of the samples contain an excess amount of polyanion ($0.60 < \varphi < 0.79$); the binding ratio depends on the molecular weight of CS: an increase in MW leads to a decrease of the amount of polyanion included into the IPEC. If the compositions of the IPEC are compared it is obvious that the samples with CS_{HW} are probably the same, but the others are different. Such differences could be explained from the differences in physicochemical properties of the copolymers. According to the chemical structure, both Eudragit® L types have the same ratio between charged and non-charged fragments in the copolymer (1:1), but differences in pH-sensitive solubility depend on the nature of the non-ionized – ether groups. In case of L100-55 it contains more hydrophilic ethyl acrylate units,

Table 1
Characteristic composition of IPEC CS/L100, detecting by elementary analysis

Type of CS	Experimental value (mean, $n = 2$) (%)		Calculated value (%)		IPEC composition	
	C	N	C	N	φ	Molar ratio [CS]/[L100]
CS_{LW}	49.21	4.37	49.25	4.36	1.17	1/0.85
CS_{MW}	43.64	3.68	43.64	3.64	0.89	1/1.13
CS_{HW}	44.26	3.60	44.25	3.59	0.82	1/1.22

Table 2
Characteristic composition of IPEC CS/L100-55, detecting by elementary analysis

Type of CS	Experimental value (mean, $n = 2$) (%)		Calculated value (%)		IPEC composition	
	C	N	C	N	φ	Molar ratio [CS]/[L100-55]
CS_{LW}	47.14	2.95	47.12	2.96	0.60	1/1.69
CS_{MW}	45.12	3.35	45.11	3.34	0.72	1/1.38
CS_{HW}	45.34	3.54	45.36	3.53	0.79	1/1.26

while L100 consists of the more hydrophobic methyl methacrylate monomer units. This means that at the same pH they have the same charge density (same equal amount of carboxyl groups are able to interact with oppositely charged polycation sequences), but a different capability to react. This can be illustrated by the interpolyelectrolyte reaction between CS_{LW} and the polyacid copolymers: hydrophobic L100 is included in the polycomplex in a lower amount ($\varphi = 1.17$) compared with the more hydrophilic L100-55, which interacts with CS_{LW} so that the amount of copolymer is approximately twice as high ($\varphi = 0.6$).

Moreover, CS chains at pH 6.0 include ionized amino groups ($–NH_3^+$), which can form ionic bonds with L100 and L100-55, and also undissociated ($–NH_2$) and non-ionized amide groups (–NH), which cannot interact with the polyacid copolymers. Thus, CS chains that consist of uncomplexable groups can be considered in a way that this homopolymer acts as a copolymer at this pH value. So, interaction between oppositely charged macromolecules could be explained as an interpolymer reaction of two “copolymers” and the influence of inactive groups (structural defects) on IPEC formation must be significant. Let us discuss this phenomenon in more detail.

Formation of the stoeichiometric IPEC CS_{MW}/L100 ($\varphi = 0.89$) can be explained as follows: due to structural non-complementarity of CS and the polyacid copolymers, approximately 50% of the ionogenic groups of both polyelectrolytes are placed so that they do not have the possibility to form intermacromolecular ionic bonds. This is schematically presented in Fig. 2a. According to this scheme, interaction of an amino group of one unit of CS with a carboxyl group of the polyanion excludes binding of an amino group of a following unit of CS with a neighbouring carboxyl group of L100. In this case, the stoichiometric IPEC can form a relatively well organized macromolecular network due to available non-compensated positively charged amino groups of CS and carboxyl groups of L100. It is known that formation of such network increases the stability of stoichiometric polycomplexes [29]. On the contrary, in IPEC, which contains approximately a two times higher amount of polyacid copolymers (CS_{LW}/L100-55, $\varphi = 0.60$), every amino group of CS can form ionic bonds with the carboxyl groups of L100-55. Nevertheless, in this case the regular structure of CS is completely destroyed, which could be accompanied by partial breakage of intermolecular hydrogen bonds in its chains and loss of the well-oriented structure of the polysaccharide. Double-formed chains of IPEC twist and roll up to a compact conformation. These structures are schematically presented in Fig. 2b. The results obtained concurred with previous observations of interpolyelectrolyte complex formation between polyacrylates and CS [30–34].

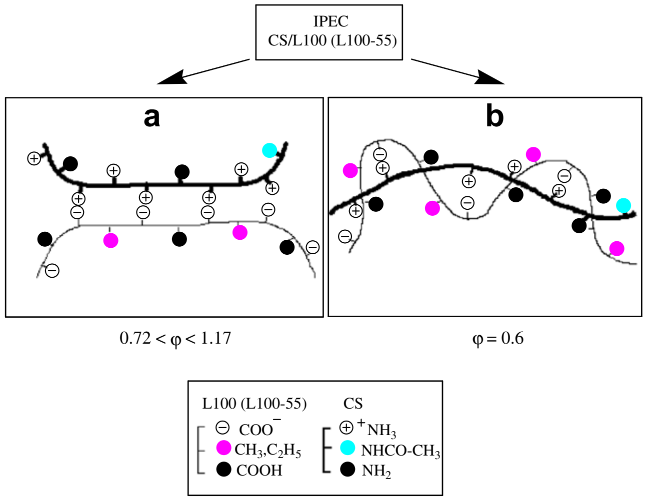


Fig. 2. Schematic representation of the ionic interactions between CS and L100 or L100-55.

3.2. Structural studies

Fig. 3 shows FT-IR spectra of the CS-L100-55 solid interpolymer complexes obtained by precipitation at pH 6.0. The IR spectra of the solid complexes showed some remarkable differences as compared to the pure polymers L100-55, CS and its PM. CS has the characteristic bands of the undissociated primary amino groups ($–NH_2$) at 3445 cm^{-1} and amide groups (–NH) at 1640 cm^{-1}. L100-55 has the characteristic band of the carboxylic groups at 1740 cm^{-1}. In the case of IPECs the peaks corresponding to the amino groups of CS and those of the carboxylic groups of L100-55 remained at 3445, 1640 and 1730 cm^{-1}, respectively. In addition, a significant new band appeared at 1560 cm^{-1}. This peak can be attributed to the ionic interaction between the ionized carboxylic groups of L100-55 and the protonated amino groups ($–NH_3^+$) of CS. These results concur with previous observations between carboxymethylcellulose, polyacrylate or carrageenan with CS [2,4,13]. Together with the fact that the binding ratio of the complex was stoichiometric, this finding seems to point to ionic bonding as a primary binding force in the complex formation between CS and L100-55. An increase in peak intensity at 1730 and 1560 cm^{-1} can be observed when the molecular weight of CS increased. Therefore, the structure of the CS/L100-55 polycomplex changed with varying MW of CS close to the observations in elementary analysis: an increase in CS (from a minimum in CS_{LW} to a maximum in CS_{HW}) content led to an increase in peak intensity at 1560 cm^{-1}. Similar results were observed in polyion complex formation between CS (MW 440 kDa) and sodium polyacrylate (MW 1510 kDa), but the estimated differences occurred due to differences in pH value of the reaction medium [4]. IPEC CS/L100 prepared with different types of molecular weight of CS resulted in comparable IR spectra as those for CS/L 100-55 (data not shown).

3.3. Swellability studies

It is well known that the potential of polymeric carriers to be used as controlled release materials can be predicted by determination of their swelling characteristics.

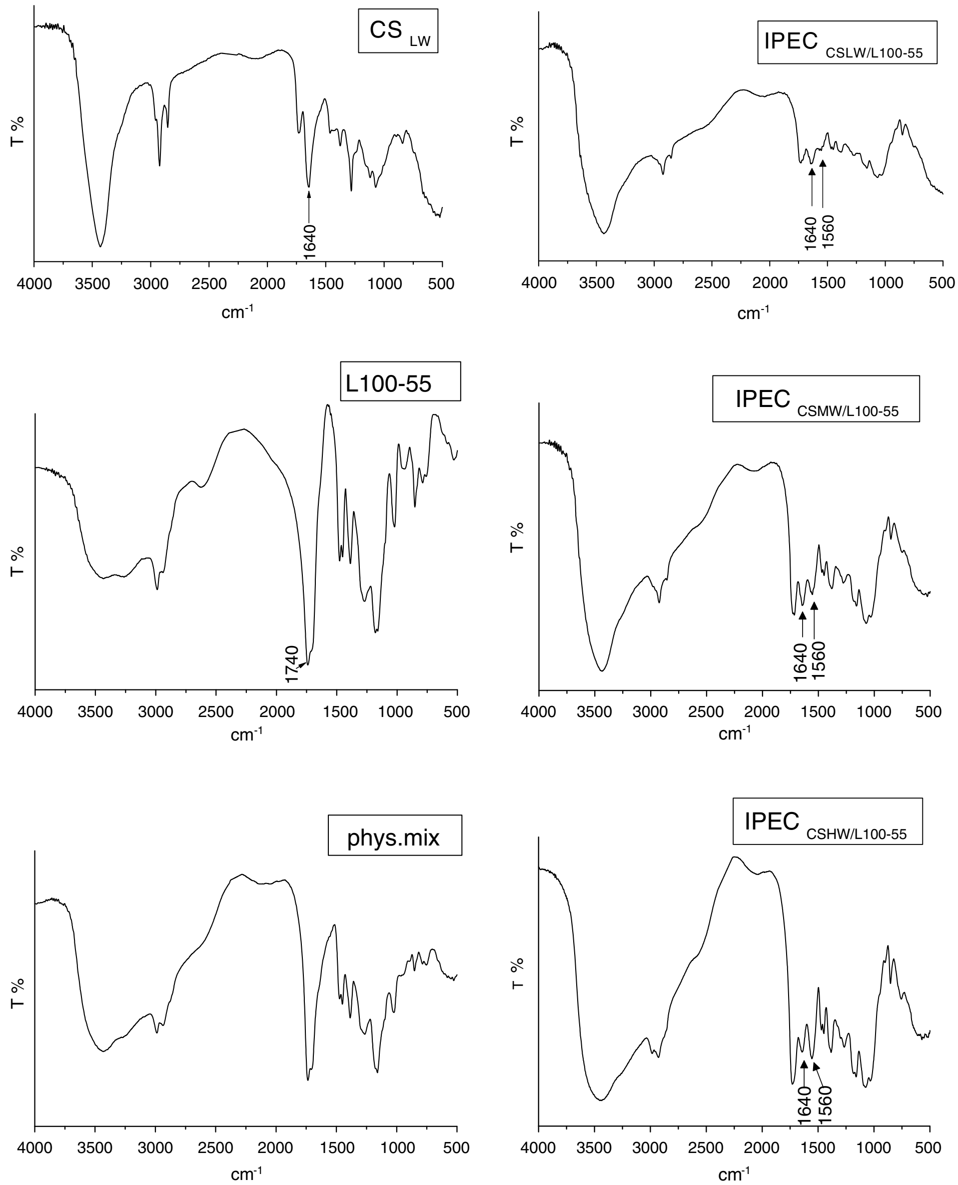
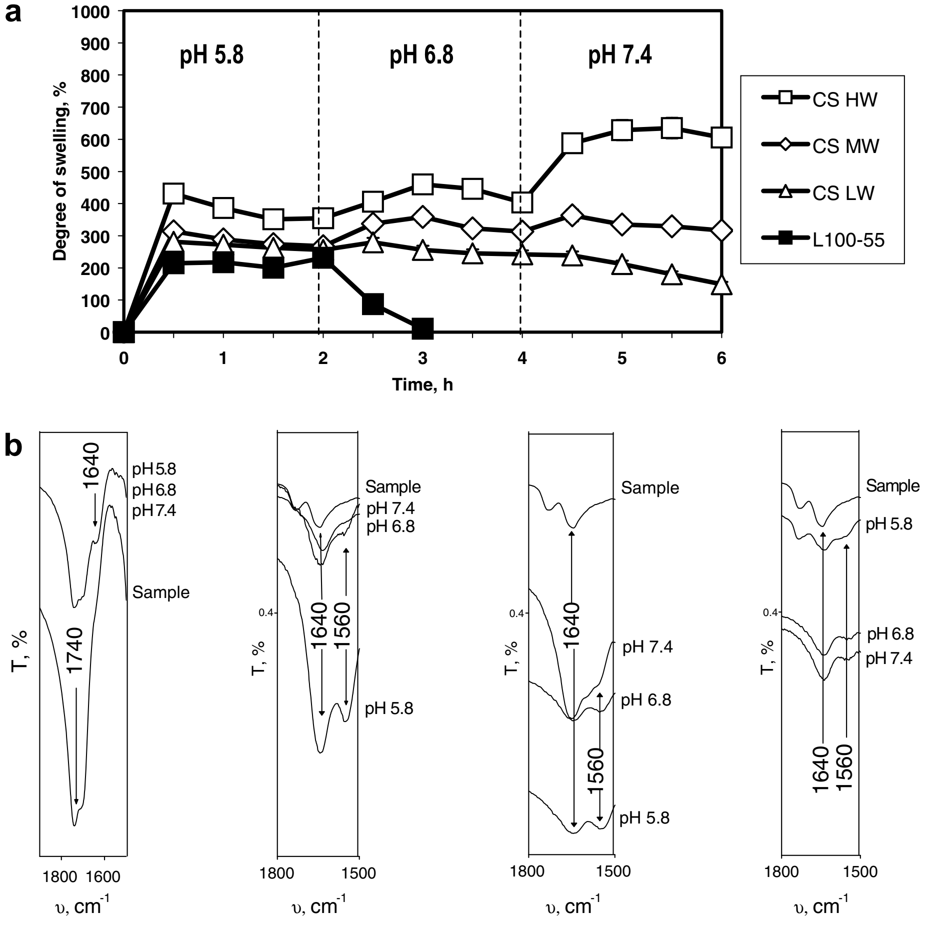


Fig. 3. FT-IR spectra of CS_{LW}; L100-55; physical mixture of CS_{LW} and L100-55; IPEC CS_{LW}/L100-55; IPEC CS_{MW}/L100-55; IPEC CS_{HW}/L100-55.

In the previous study, we already checked the swelling behavior of polycomplex matrices made up from CS and L100 in simulated gastro-intestinal tract (GIT) mediums [35]. Independently from MW of CS used, all systems are stable in pH 1.2 (1 h) and pH 6.8 (2 h). In the present study, we used only simulated intestinal mediums with gradually increased pH (from 5.8 to 7.4) in order to make detailed evaluation of the durational part of GIT.

At first, we attempted to measure the swelling characteristics of individual polymers in SIT conditions (Fig. 4a). According to the specifications of Degussa®, the dissolution of L100-55 and L100 depend on the copolymer structure and is well regulated by the ratio between methyl methacrylate or ethyl acrylate and methacrylic acid. At pH 5.8, tablets of L100 completely disintegrated rapidly (data not shown). This is expected according to the dissolution properties of L100, which start from pH 6.0. As for L100-55 matrices they start to swell and dissolve simultaneously while passing through the first buffer solution (pH 5.8) and completely disintegrate during the next hour. CS matrices, which are soluble in the first medium, show high swellability properties. In the following buffer solutions the degree of swelling only increased in case of CS_{HW}, in spite of deprotonation of the amino groups. Nevertheless, after 24 h all CS matrices were completely disintegrated. FT-IR was used to further explain the swelling behavior. The results are shown in Fig. 4b. According to Fig. 3, the main differences between polymers, its physical mixtures and IPECs can be observed in a narrow region from 1500 till 1800 cm^{-1}. This region was used for demonstration of structural changes. A decrease of the intensity of the carbonyl stretching vibration at 1740 cm^{-1} as compared to the commercial product as well as the appearance of a band due to carboxylate groups at 1640 cm^{-1} while

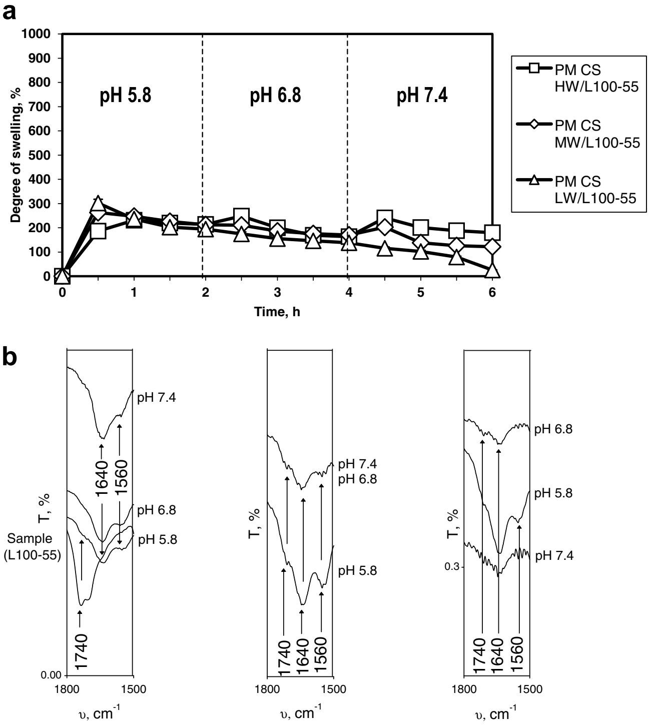


L100-55 CS_{LW} CS_{MW} CS_{HW}

Fig. 4. (a) Degree of swelling of CS with different MW and L100-55 in SIT conditions ($n = 3$; ±SD); (b) FT-IR spectra of matrices consisting of individual polymers during swellability testing.

passing through all three mediums was observed in the FT-IR spectra of L100-55. Changes in case of CS with different MW are also evident. The FT-IR spectrum of CS shows the absorption band of the carbonyl stretching vibration of the secondary amide at 1640 cm^{-1} in the commercial products while the bending vibration band of the protonated $-NH_3^+$ of non-acylated 2-aminoglucose primary amines groups at 1560 cm^{-1} [16] only appeared in buffer solutions. In spite of some differences in samples of CS with different MW, it seems that they exist probably due to different swelling rate while immersing the matrices in the three media. That is why the peak of ionized amino groups in CS_{LW} disappeared at pH 7.4, but still exists in other samples: as a shoulder in CS_{MW} and as a band in CS_{HW} due to continuously losing the charges in chains after the pH reached a value higher than the pK_a of CS.

Tablets prepared from the physical mixtures showed a very low swelling behavior, and comparable whether L100 or L100-55 is included in the matrix (Figs. 5a and 6a). The swelling profiles are similar: increasing degree of swelling in acidic medium due to a progressively increasing the number of ionized $-NH_3^+$ groups of CS and decreasing of swellability for systems containing L100, probably due to leaching of undissolved particles of L100 in case of low and medium MW CS. Anyway, all compositions are stable during 6 h. Physical mixtures with L100-55 contain systems that show a significant increase in swelling behavior in the last medium in case of medium and high MW CS and also with complete dissolution when the matrix is made up of CS_{LW}. Nevertheless, all matrices of PM disintegrated after 24 h. Analysis of FT-IR spectra of these systems indicated the origin of our previously discussed interpretation of swelling behavior. Comparison of the PM of CS and L100-55 or L100 (Figs. 5b and 6b) with individual polymers shows that there occurred no interactions in the systems although this could be possible in the two first media (pH 5.8–6.8). All peaks are the superposition of those of the groups of the individual polymers. For example, the spectra of CS–L100-55 systems at pH 5.8 are similar: they include a weak band of the remaining amount of L100-55 (carbonyl stretching at 1740 cm^{-1}) and both bands of $-NH_3^+$ and NH– groups of CS at 1560 and 1640 cm^{-1}, respectively. At pH 7.4 only the band at 1640 cm^{-1} is still present indicating the absence of L100-55 at the end of the experiment. So, only non-protonated CS is the main matrix-forming material, which preserves

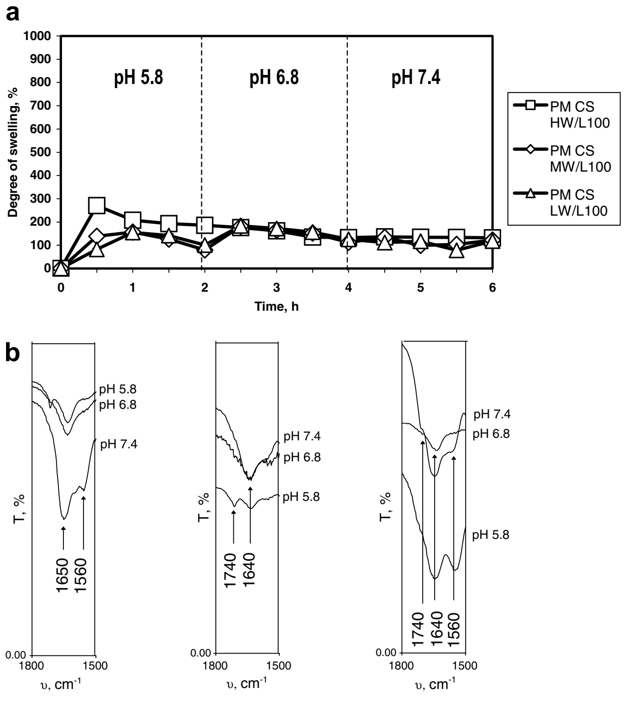


PM $_{\text{CS LW/L100-55}}$ PM $_{\text{CS MW/L100-55}}$ PM $_{\text{CS HW/L100-55}}$

Fig. 5. (a) Degree of swelling of physical mixtures of CS with different MW and L100-55 in SIT conditions ($n = 3$; ±SD); (b) FT-IR spectra of matrices consisting of physical mixtures of polymers during swellability testing.

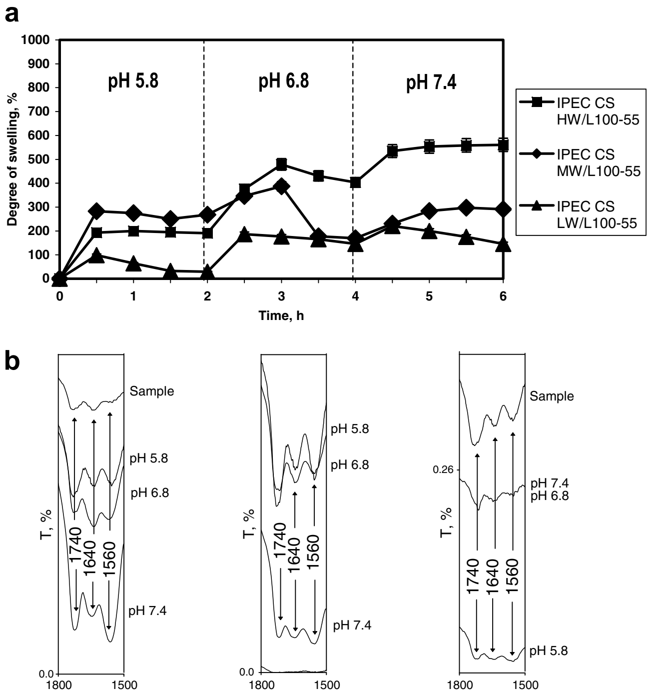
the shape of the tablet. As for CS–L100 systems the differences in FT-IR spectra are comparable.

The swelling behavior of IPECs is completely different from that of the PM (Figs. 7a and 8a). First of all we will try to discuss the swellability of L100-55 containing polycomplexes. IPECs based on medium and high MW CS behave similarly as individual CS of the same MW, especially for polycomplexes containing CS_{HW}. Indeed, changes during swelling testing in the IPEC structure for systems made up of high MW CS were observed. These systems contain a lot of 'defects' and behave similar to CS_{HW} due to electrostatic repulsion of free ionized amino groups that are responsible for swelling. In case of IPEC made up of CS_{MW}, in the first medium the degree of swelling is 200% (this is less as compared to CS_{MW} (H = 300%)), but afterwards a twofold increase in swelling at pH 6.8 can be observed. This can be explained by a change in the IPEC structure. According to the structure of the original IPEC, and the low charge density at pH 6.0, it has a lot of 'defects'. Such fields contain protonated amino groups, which are not able to interact due to steric hindrance and rigidity of the polysaccharide chains, non-ionized amino groups of CS and ether groups of the methacrylic copolymer. While immersing the polycomplex matrix into the acidic medium (pH 5.8), free amino groups are protonated and their hydration increases the degree of swelling at the first part of the experiment. Later, full ionization of all amino groups turns it into a polyelectrolyte with a rela-



PM $_{\text{CS LW/L100}}$ PM $_{\text{CS MW/L100}}$ PM $_{\text{CS HW/L100}}$

Fig. 6. (a) Degree of swelling of physical mixtures of CS with different MW and L100 in SIT conditions ($n = 3$; ±SD); (b) FT-IR spectra of matrices consisting of physical mixtures of polymers during swellability testing.



IPEC $_{\text{CS LW/L100-55}}$ IPEC $_{\text{CS MW/L100-55}}$ IPEC $_{\text{CS HW/L100-55}}$

Fig. 7. (a) Degree of swelling of IPECs made up of CS with different MW/L100-55 in SIT conditions ($n = 3$; ±SD), (b) FT-IR spectra of polycomplex matrices during swellability testing.

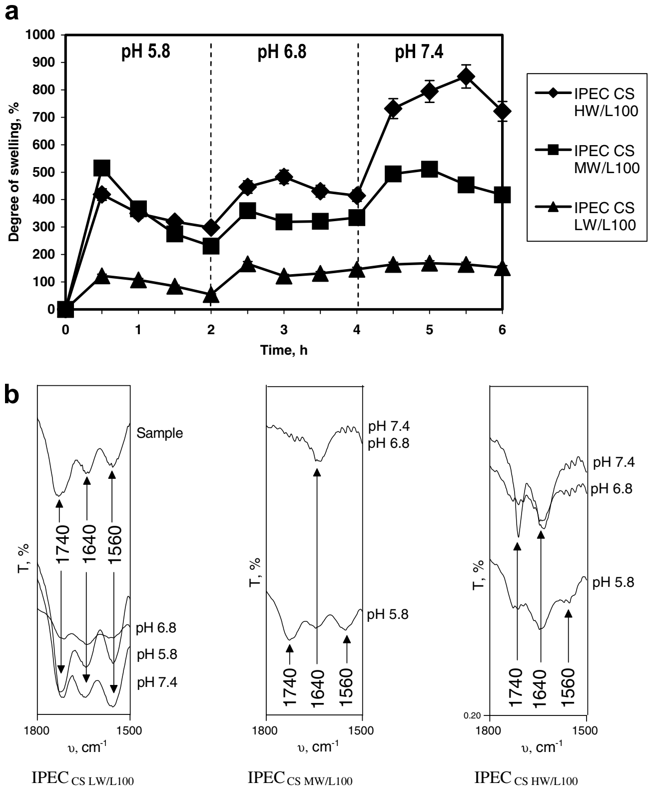


Fig. 8. (a) Degree of swelling of IPECs made up of CS with different MW/L100 in SIT conditions ($n = 3$; ±SD); (b) FT-IR spectra of polycomplex matrices during swellability testing.

tively high charge density. As a 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 [36–37]. Ionized amino groups of CS are charging the protonated carboxylic acid groups of L100-55 (weak polyacid) and can form new interpolymer contacts. Hence, the number of 'loops' is decreased and goes to a minimum value. Comparable observations were made with IPEC prepared from two types of Eudragit® [21,23] and Eudragit® E 100 and alginate sodium [22]. However, the degree of swelling is much higher for the current IPECs.

After moving the matrix to the second medium with pH 6.8, carboxylic groups of L100-55 present in 'loops' are now becoming more ionized and an increase of the degree of swelling results. However, previously protonated amino groups localized in 'defect' fields are losing their charge and become responsible for the increase of the hydrophobic units in the IPEC structure. As a result the swelling slightly decreases at the end of the second medium but starts to increase in the third buffer (pH 7.4) due to a progressive increase in the number of carboxylate group, in spite of the solubility of CS which decreases at higher pH values. The lowest swelling profile was observed for the polycomplex with low MW CS. According to previously discussed differences in IPECs composition, this sample was completely different as compared to others, because it contains the largest amount of L100-55 ($\varphi = 0.60$). So it can be concluded that IPECs prepared from different molecular weight grades of CS showed comparable swelling behavior, but the degree of swelling was proportional to the molecular weight (Fig. 7a). Moreover, all systems did not disintegrate until 24 h. The synthesized IPECs, as many of the investigated stoichiometric polycomplexes, will have a more or less homogenic network structure in the swollen state consisting of interacting and 'defect' fields, which could be changed during swelling. This structure is clearly sensitive to the pH value. Let us try to discuss the existence of possible structural changes in CS/L100-55 systems thoroughly. FT-IR spectra (Fig. 7b), which were obtained in all media, proved that all three polycomplexes are stable during the experiment. In all the cases, a significant absorbance band at 1570 cm^{-1} belonging to the ionic bonds (interaction between carboxylate groups of L100-55 and ionized amino groups) remains during swellability testing for all polycomplexes in all pH values. It is most interesting that the intensity of the characteristic peaks changed. CS_{HW}/L100-55, which has the largest amount of interacting fields (high degree of complexation) at the start, transforms to the lowest degree of complexation at the end with a weak peak intensity at 1570 cm^{-1}. The swelling profile of this sample can be explained by a decrease of the amount of interacting fields leading to an increase of 'defect' sequences in the polycomplex structure which are responsible for swelling, especially in the two last media. The CS_{MW}/L100-55 system is characterized by an increase of peak intensity in acidic medium: polycomplex matrices are structurally changed; the degree of complexation showed a twofold increase. In the next media, the intensity of the characteristic peak became weaker, but it is still more pronounced as compared to the sample of start IPEC CS_{MW}/L100-55 before swelling. Finally, the CS_{LW}/L100-55 system, which has the lowest intensity of the peak at 1570 cm^{-1}, due to a low degree of complexation, transformed during swelling to an IPEC with the highest amount of interacting fields. Moreover, the degree of complexation increases proportionally with increasing pH. Completely different changes were observed in the second system, CS/L100. The swelling profiles are depicted in Fig. 8a. According to the results, two of the polycomplexes with medium and high MW CS showed the highest degree of swelling (more than pure CS matrices); increasing the MW of CS leads to an increase in the swellability of the IPECs. FT-IR spectra of these two systems (Fig. 8b) showed that they are stable in the first acidic medium, but with a relatively low degree of complexation, more clearable for the high MW CS sample (according to the weak peak intensity at 1570 cm^{-1}) and completely destroyed to individual polymers afterwards. We can conclude that these two samples are very sensitive to pH and are not stable in SIT conditions. The reason is that polycomplexes with participation of L100 (consisting of more hydrophobic methacrylate chains) are simply destroyed in neutral media due to the existence of a large amount of 'defect' fields and low degree of complexity. Similar results of high pH-sensitivity were observed in polycomplex systems made up of CS–pectin [38] and CS–dextran sulfate [39].

In the case of CS_{LW}/L100, although it contains an excess amount of CS ($\varphi = 1.17$), its swelling profile was the lowest. Compared to the previously discussed CS_{LW}/L100-55 sample it has a very similar swelling profile, but in case of the IPEC made up of L100 it has more stable profile, especially in the last two media. According to the FT-IR spectra we observed the same increase in peak intensity at the characteristic band as in the CS_{LW}/L100-55 sample. This means that in case of complexation of CS_{LW}, the swelling behavior is probably the same and not depending on the type and physicochemical properties of the two types of Eudragit®.

3.4. Drug release studies

In order to assess the potential of the IPECs to be used in matrix DDS, we evaluated the release of the model drug diclofenac sodium from all investigated matrix systems. Meanwhile, according to opposite charges of DS and CS we consider that the possible interaction is too weak in order to influence on the release of the drug used [40,41]. According to our previously published results about dissolution behavior of ibuprofen, as a model drug, from the polycomplex matrix systems based on CS and L100 in gastro-intestinal simulated conditions [35], in the present study, we used only intestinal mediums with gradually increased mediums. The first reason is that all polycomplexed matrices are stable in gastric simulated environment, the second one is that both model drugs (ibuprofen, DS) are insoluble at pH 1.2 and there release checking is impossible.

Release of DS from matrices made up of CS with different MW revealed that, CS_{LW} led to a smaller drug release as compared to those with the medium and high MW grade of CS (Fig. 9a). However, the release of the drug from the matrices made up of CS_{LW} and CS_{MW} was close to each other. These results are in good agreement with the swelling properties of the polysaccharide matrices. As expected, very low (in case L100) and low (in case L100-55) DS release occurred in a pH-gradient (from 5.8 to 7.4) medium

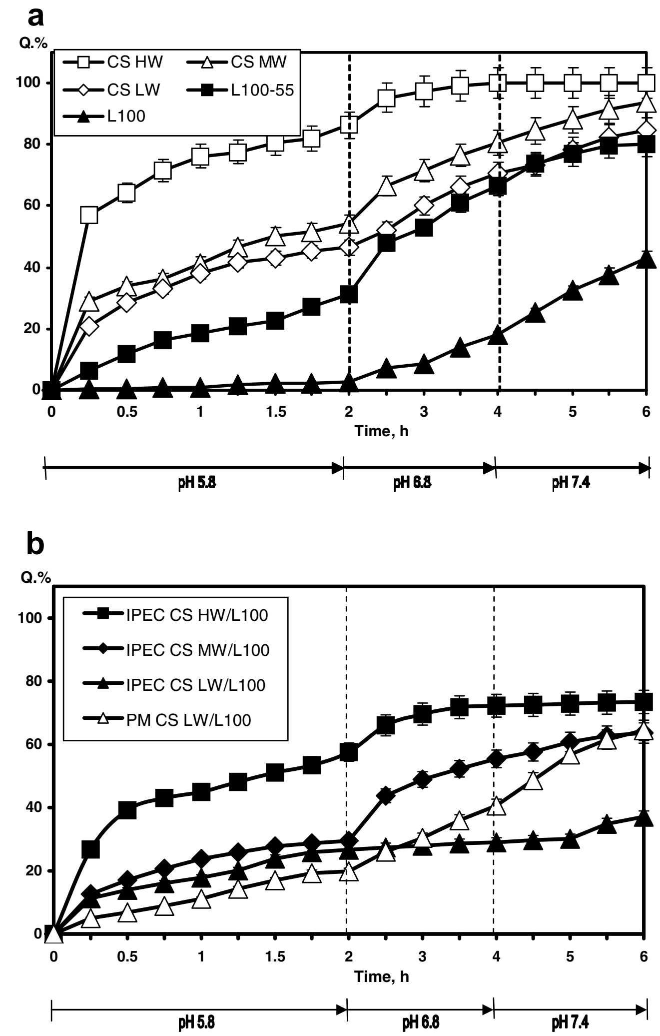


Fig. 9. DS release from matrices made up of (a) pure polymers (CS with different MW, L100 and L100-55); (b) IPECs made up of CS with different MW/L100 and physical mixture of CS_{LW} and L100 in the same molar ratio as in the polycomplex in SIT conditions ($n = 3$; ±SD).

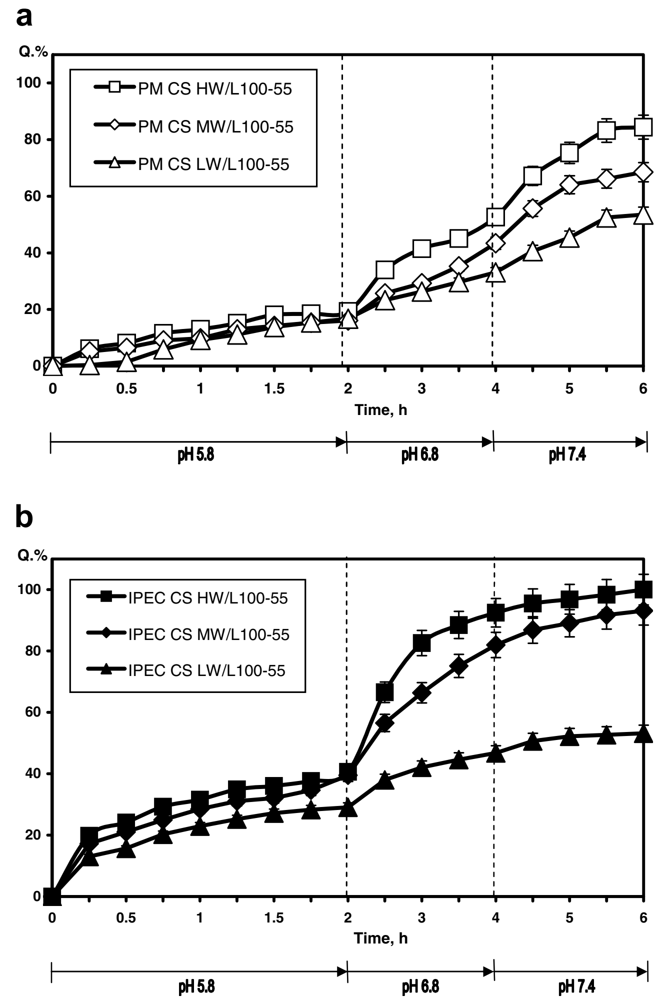
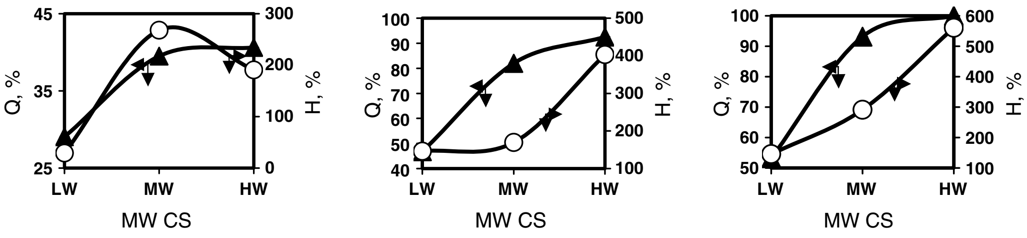
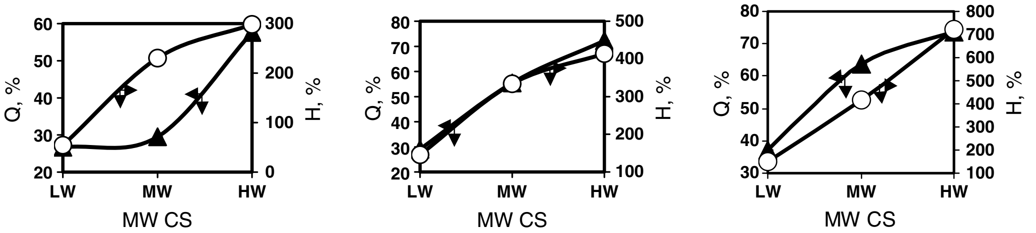


Fig. 10. DS release from matrices made up of (a) physical mixtures of CS with different MW and L100-55 in the same molar ratio as in the polycomplex; (b) IPECs made up of CS with different MW/L100-55 in SIT conditions ($n = 3$; ±SD).

(a) IPECs CS/L100-55



(b) IPECs CS/L100



pH 5.8 pH 6.8 pH 7.4

Fig. 11. Degree of swelling (H, %) and DS release (Q, %) from polycomplex matrices made up of IPECs made up of CS/L100-55 (a) or CS/L100 (b) in SIT conditions as a function of the CS molecular weight (CS MW).

showing that, below solubility of the enteric copolymers, no drug release occurred (L100). After this lag time, which was more evident in case of L100, the drug release occurred continuously.

Drug release from the physical mixtures was much slower. However, this is not due to interpolymer interaction since the results of FT-IR studies clearly indicated the absence of it. As shown in Figs. 9b and 10a, DS release was slowed down when decreasing the MW of CS in both types of PM. In addition, the slowest release was observed for CS_{LW}–L100-55 instead of CS_{LW}–L100. These results are in a good agreement with swellability testing.

As shown in Fig. 9b, polycomplex matrices made up of CS/L100 show a release behavior that is somehow slower than that of the pure polymers. The reason is that due to high swelling properties at all pH values, these polycomplexes form gel-like matrices, which can sustain DS release. In case of CS_{LW}/L100 polycomplex the release profile is the slowest, with the most constant drug release rate as well as swelling properties as compared to all the other systems. That means, that an excess of CS_{LW} in the IPEC structure ($\varphi = 1.17$) led to formation of a well-equilibrated polycomplex (with a high degree of complexation) which is not so pH-sensitive and stable in SIT conditions.

Fig. 10b shows the release profiles from IPECs based on L100-55 and all three CS grades. All of them had a similar release rate in acidic medium with high drug release in case of medium and high CS grades and slow DS release for the CS_{LW}/L100-55 system. From the comparison of the profiles with polycomplex matrices made up of two different enteric copolymers but with the same CS_{LW}, we can conclude that the IPEC with L100-55 ($\varphi = 0.6$) with excess amount of methacrylic copolymer has a higher degree of swelling and has a DS release which is two times higher. However, these two profiles are characterized by a constant and slow release behavior (sustained-release systems).

It must be noted that all release results are in agreement with the swelling properties of the synthesized IPECs. Fig. 11 summarizes the dependence of the degree of swelling and the amount of DS release for different pH values as function of the MW of CS, included in the IPECs.

4. Conclusion

The results of the present investigation confirm the formation of IPECs between CS and L100 or L100-55. The molar ratio of a unit molecule of CS with Eudragit® L copolymers depends on the molecular weight of CS, showing a change from 1:0.85 to 1:1.22 ($1.17 < \varphi < 0.82$) for L100 and from 1:1.69 to 1:1.26 ($0.60 < \varphi < 0.79$) for L100-55, respectively. The differences between the different IPECs that were observed during the swelling experiments as well as during the drug release studies show that drug release can be tuned based not only on the composition of the IPEC, but also mainly on the type of methacrylic copolymer included. This changed the structure of the polycomplexes and could regulate their properties. The results of physicochemical and release properties evaluation showed the potential of these interpolymer complexes to be used in oral controlled drug delivery.

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