Characteristics of Interpolyelectrolyte Complexes Based on Different Types of Pectin with Eudragit® E PO as Novel Carriers for Colon-Specific Drug Delivery

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Article

Characteristics of Interpolyelectrolyte Complexes Based on Different Types of Pectin with Eudragit® E PO as Novel Carriers for Colon-Specific Drug Delivery

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Abstract: Many studies have been conducted using pectin for modified drug delivery. In this regard, the goal of the work was to obtain interpolyelectrolyte complexes based on citrus or apple pectin and the Eudragit® EPO and study properties from the standpoint of using these carriers for oral drug delivery. Turbidity, gravimetry, viscosity, elementary analysis and FTIR spectroscopy, DSC analysis were used for physicochemical characterization. Diffusion-transport characteristics were studied to assess the swelling ability of the matrices and the release of diclofenac sodium. Mathematical modeling of the release parameters was carried out using the Krosmayer-Peppas equation. During the turbidity study, stoichiometry compositions were selected for the studied IPECs EPO/PecA and EPO/PecC at pH values = 4.0, 5.0, 6.0, 7.0. FTIR spectra of the complexes are characterized by an increase in the intensity of the bands at 1610 cm^{-1} and 1400 cm^{-1}. According to the DSC analysis IPEC has a certain Tg = 57.3°C. The highest release rates are shown by IPEC EPO/PecC_1 and EPO/PecC_4. The mechanism of drug transport from the matrices IPEC EPO/PecC, IPEC EPO/PecA_3 and EPO/PecA_4 can be characterized as Super Case II. Anomalous (non-Fickian release) is typical for IPEC EPO/PecA_1 and EPO/PecA_2. Thus, the resulting systems are suitable for colon-specific drug delivery systems.

Keywords: Eudragit® E PO; citrus pectin; apple pectin; diclofenac sodium; interpolyelectrolyte complex

1. Introduction

To date, one of the promising ways to improve the safety of drug carriers is the use of biopolymers. The most widespread are biopolymers of a polysaccharide nature: pectin, sodium alginate, starch, chitosan, inulin [1-11]. Many studies have been conducted on the use of natural polysaccharides in drug delivery systems. Such studies include research of IPEC based on the biodegradable polymer starch and kappa carreginan [12]. In other studies IPECs between naturally sulfated polysaccharides of the seaweed Polysiphonia nigrescens and cationized agaroses and Eudragit E were prepared, characterized, and explored for controlled drug release [13]. Often in works, polyelectrolyte complexes are obtained by the interaction of oppositely charged polymers. So, polyelectrolyte complex film between pectin and chitosan was prepared by blending two polymer solutions and then solvent casting method [14]. In addition, numerous studies have been conducted on the interaction of pectin and chitosan as drug delivery systems [15-19]. There have also been studies on the interaction of cellulose derivatives - sodium carboxymethylcellulose [20,21].

Due to the fact that the present work studied systems based on pectin and a copolymer of acrylic and methacrylic acid, it is necessary to mention previously conducted studies involving these polymers.

Pectin is one of the most widespread and available polysaccharides in the plant world. In pharmaceutical technology, it is used as a binder [1]. It should be noted that pectin belongs to

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biodegradable polymers. It is stable in the upper gastrointestinal tract (GIT) but is degraded by the microflora of the large intestine, mainly anaerobic bacteria such as Bifidobacterium, Bacteroides and lactobacilli of the genus Lactobacillus [22].

Moreover, there are many oral drug delivery systems (DDS) containing pectin and calcium pectinate, such as tablets, particles, microparticles, pellets and beads, such forms are discussed and systematized in detail in a review on pectin-based delivery systems for the treatment of colon cancer [4].

By the research group of Semde et.al. films based on pectin or calcium pectinate with cellulosic (Aquacoat® ESD 30, Surelase®) or acrylic (Eudragit® NE30D, RS30D) polymer dispersions were obtained and studied [23]. The leaching of pectin from the obtained films was studied, a slowdown in the dissolution of pectin from films containing Eudragit® RS30D was noted, which is explained by the interaction of ionized carboxyl groups of pectin with quarter amino groups of Eudragit® RS30D [23].

In addition, the same team of authors studied the effect of pectinolytic enzymes on the release of theophylline from dispersions containing pectin or calcium pectinate coated with cellulosic (Aquacoat® ESD 30, Surelase®) or acrylic (Eudragit® NE30D, RS30D) dispersions. The release of theophylline was found to be lower in the presence of pectinolytic enzymes. The authors attribute this to the ability of pectin to hydrate, swell, and form channels through which the hydrophilic drug substance easily diffuses into the environment. In the presence of pectinolytic enzymes, the hydration of pectin decreases, as a result of which the release level decreases. The release of the drug substance from the dosage form occurs due to the degradation of pectin [24].

In the work of other authors (Ofori-Kwakye and Fell) films based on pectin, HPMC, chitosan were developed by the solvent cast method using 0.1 M hydrochloric acid or 0.1 M acetic acid [25]. The leaching of pectin in a medium simulating the upper GIT was studied in the presence and absence of pectinolytic enzymes. In contrast to the previous work of the other authors (Semde et al.), the addition of enzymes led to an increase in the dissolution of pectin, which they explain as degradation of pectin from the obtained films [24]. Attention is also drawn to the complex formation between the ionized carboxyl groups of pectin and the amino groups of chitosan, which is part of the dosage form [25].

Biodegradable gels based on pectin and chitosan were obtained by a group of Khutoryansky, rheological properties, swelling ability of gels, degradation under the action of the enzyme and release of cisplatin were studied [26].

Copolymers of methacrylic and acrylic acids are widely used as bases for matrices [27-28]. Among them, a special place is occupied by polymers under the common trade name "Eudragit", produced by the company "Evonik Ind.", Germany. They are organic solutions or aqueous dispersions of synthetic copolymers of methacrylic acid and its esters. Depending on the ratio of carboxyl and ether groups, these copolymers dissolve at different pH values and may differ in dissolution rate. They are used to obtain tablet coatings that allow you to control the release of the drug in desirable GIT. For example, Eudragit® E is a weak base used to develop coatings that are soluble in the stomach region [18-20]. Many studies have been carried out on the production of systems based on polymethacrylates and oppositely charged ions [31-35].

Taking into account the ability of the studied polymers to interact, it becomes possible to obtain chemically new compounds as interpolyelectrolyte complexes (IPECs) in order to modify the properties of individual polymers [39].

Earlier, the research group of Moustafine obtained and studied IPECs based on Eudragit® EPO and polysaccharide alginate [29,30]. In the research both physicochemical and swelling ability properties, the processes occurring during the swelling of matrices in the GIT environments were studied, and the drug release model of the diclofenac sodium was assessed [30]. Several researches on the production of IPEC and encapsulation of such substances as fluorouracil, indomethacin has been conducted [36-38].

The interaction of high and low viscosity alginate with Eudragit® EPO was also studied by researchers, where a comparative evaluation of the obtained IPECs with physical mixtures of these

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polymers was carried out, the interaction of these polymers and the slowing down of the release of diltiazem hydrochloride from tablets was proved [40].

Another group of scientists conducted studies on the interaction of sodium alginate with quaternary polymethacrylates, obtained gel bids, and noted a slowdown in the release of the drug propranolol hydrochloride [41].

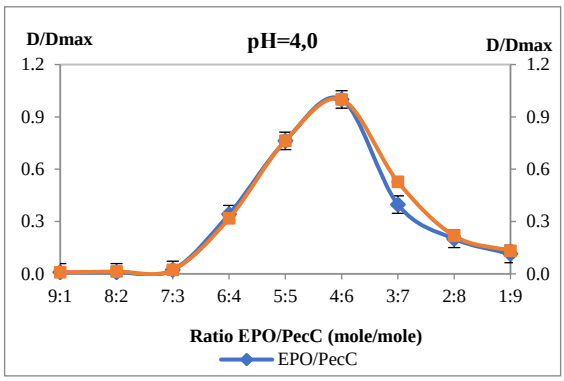
IPECs obtained on the basis of pectin and Eudragit® E PO synthetic copolymer opens up the possibility of developing a drug delivery system for colon-targeting. Given that Eudragit® EPO and pectin are oppositely charged polyelectrolytes (PEs), one of the possible ways to modify their structure is to include them in an IPEC. Thus, taking into account the huge number of studies of DDS using pectin, well-known properties of pectin as the ability to hydrate, the aim of our research was to obtain and study IPECs based on pectin and Eudragit® E PO copolymer for developing modified oral DDS.

2. Results

2.1. Turbidity measurements

Dependence of the degree of turbidity on the composition of the reaction medium shown in the pictures (Figures 1 a-h).

Based on the results of turbidimetry, graphs representing a typical turbidimetric titration curve were constructed, which have a maximum at certain ratios of polymers; when an excess amount of pectin or EPO macromolecules is added, turbidimetry decreases and IPECs precipitates.



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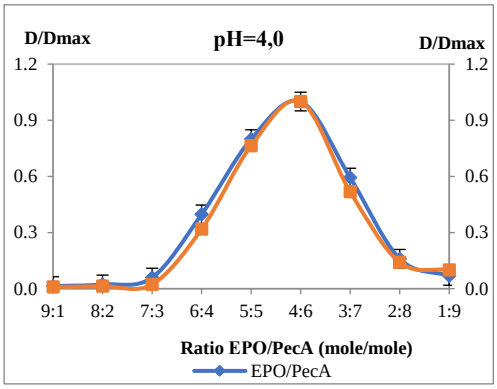

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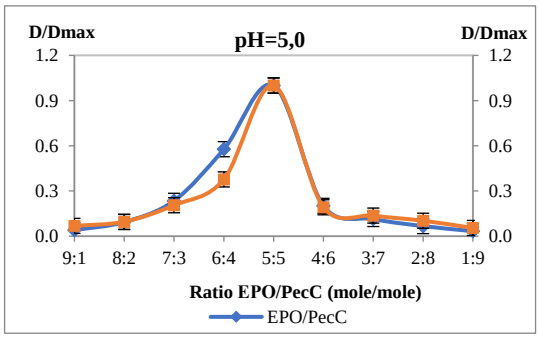

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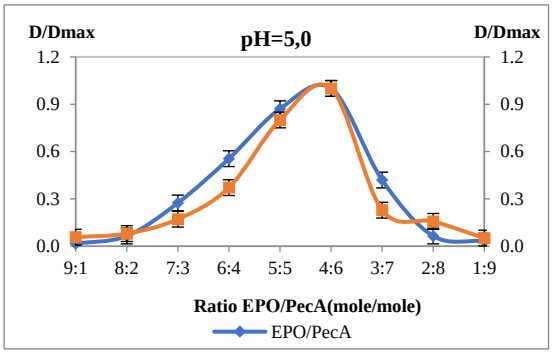

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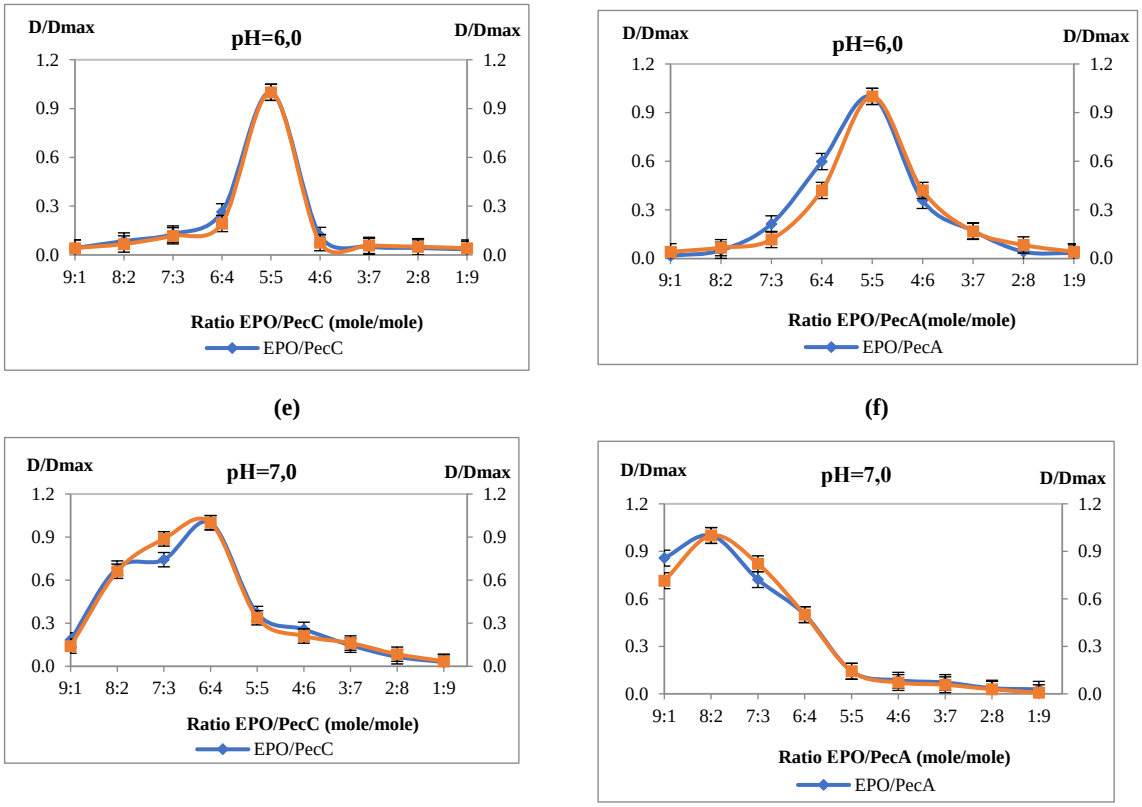
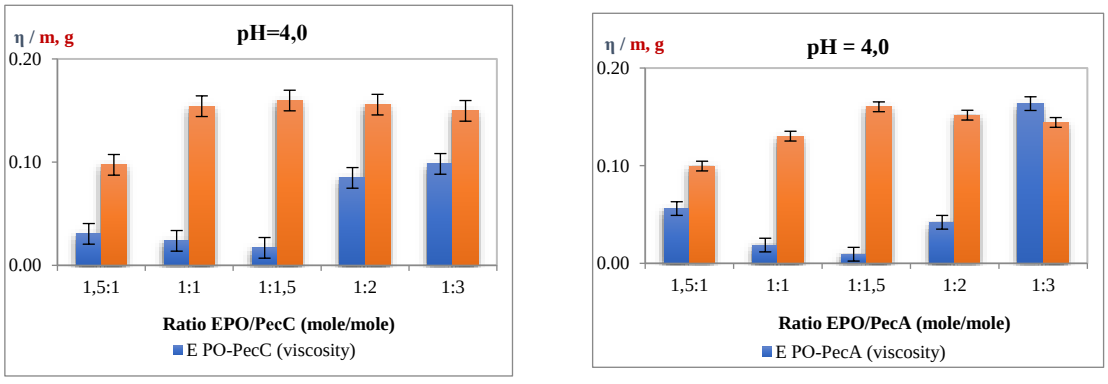


Figure 1. Dependence of the degree of turbidity on the composition of the reaction medium. **(a)** – at pH=4.0 EPO/PecC, PecC/EPO, **(b)** - at pH=4.0 EPO/PecA, PecA/EPO, **(c)** - at pH=5.0 EPO/PecC, PecC/EPO, **(d)** - at pH=5.0 EPO/PecA, PecA/EPO , **(e)** - at pH=6.0 EPO/PecC, PecC/EPO, **(f)** - at pH=6.0 EPO/PecA, PecA/EPO, **(g)** - at pH=7.0 EPO/PecC, PecC/EPO, **(h)** - at pH=7.0 EPO/PecA, PecA/EPO.

2.2. Apparent viscosity measurements and gravimetry

In the frame of our work, we synthesized IPECs with different compositions at the differ pH values of used medium. The minimum viscosity value and the maximum yields of IPEC precipitates at these points indicate that the interpolyelectrolyte reaction was most complete; these points are correspond to stoichiometry compositions. In the figures with histograms of viscosity and gravimetry EPO - Pec, the following relationships can be noted as stoichiometry compositions: for pH = 4.0 - 1:1.5 for both type of pectine, for pH = 5.0 - 1:1 for PecC, 1:1.5 for PecA, for pH = 6.0 - 1:1 for both type of pectine, for pH = 7.0 – 1.5:1 for PecC, 4:1 for PecA (Figures 2 a - h).



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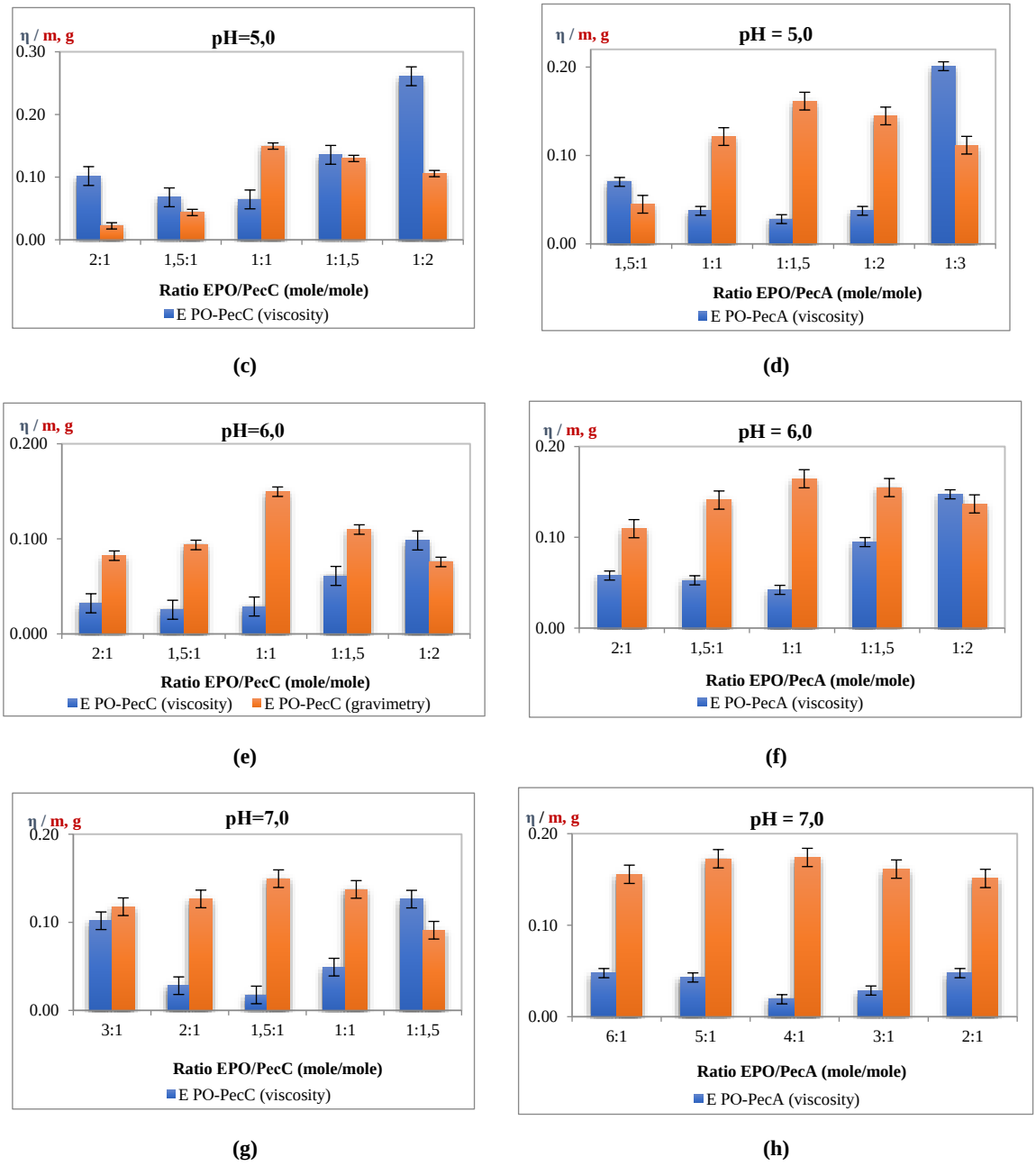

Figure 2. Dependence of the viscosity and gravimetry on the composition of the reaction medium. **(a)** – at pH=4.0 EPO/PecC, PecC/EPO, **(b)** - at pH=4.0 EPO/PecA, PecA/EPO, **(c)** - at pH=5.0 EPO/PecC, PecC/EPO, **(d)** - at pH=5.0 EPO/PecA, PecA/EPO , **(e)** - at pH=6.0 EPO/PecC, PecC/EPO, **(f)** - at pH=6.0 EPO/PecA, PecA/EPO, **(g)** - at pH=7.0 EPO/PecC, PecC/EPO, **(h)** - at pH=7.0 EPO/PecA, PecA/EPO.

2.3. Elementary analyses

From the results of elemental analysis (Table 1) , it can be assumed that the higher the degree of esterification of pectin, the less reactive it is and more of it is required to neutralize the oppositely charged polymer. In our case, apple pectin has a high degree of esterification (73.0 ± 1.1).

Table 1. Elementary analysis results

pH	EPO/PecC (mole/mole)	EPO/PecA (mole/mole)

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4,0	1 : 1,74	1 : 1,8
5,0	1 : 1,41	1 : 1,67
6,0	1 : 1,35	1 : 1,38
7,0	1,4: 1	1,78 : 1

2.4. FT-IR spectroscopy

The FTIR spectrum of the EPO/PecC complex, shown in Figure 3a, is characterized by an increase in the intensity of the bands at 1610 cm^{-1} and 1400 cm^{-1} in comparison with the FTIR spectrum of the physical mixture (Figure 3b), while in the FTIR spectrum of the EPO/PecA complex (Figure 4 a) a band appears at 1610 cm^{-1}.

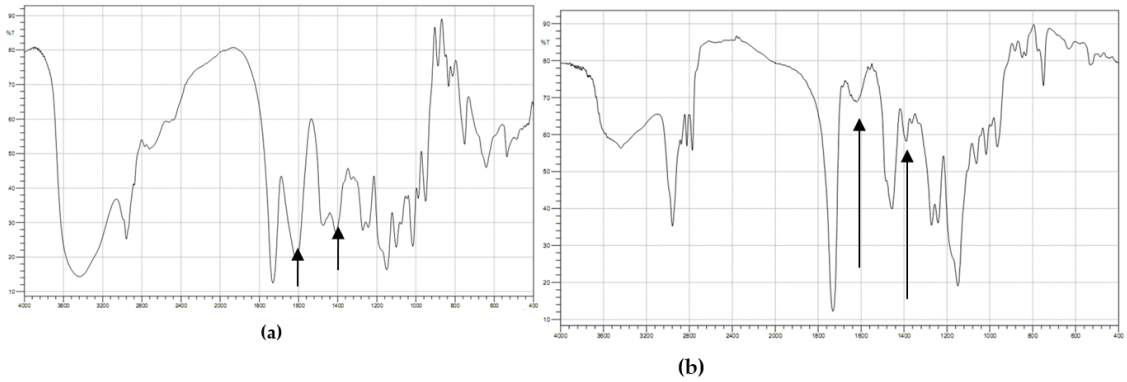

Figure 3. The FTIR spectrum of the IPECs and of the physical mixtures: **(a)** IPEC EPO/PecC, **(b)** Physical mixture EPO/PecC.

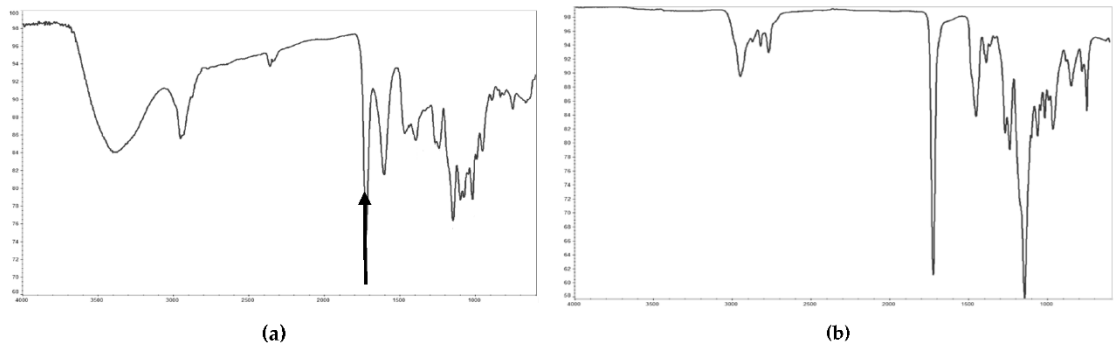

Figure 4. The FTIR spectrum of the IPECs and of the physical mixtures: **(a)** IPEC EPO/PecA, **(b)** Physical mixture EPO/PecA.

2.5. Thermal analysis

DSC analysis was carried out on samples of IPEC, a physical mixture of the same composition, and individual polymers used to obtain this IPEC (Figure 5). DSC thermograms show the presence of a glass transition temperature for all samples except citrus pectin. That is, pectin does not vitrify. The remaining samples have only but different glass transition temperatures (Tg), which shows that these are chemically individual compounds.

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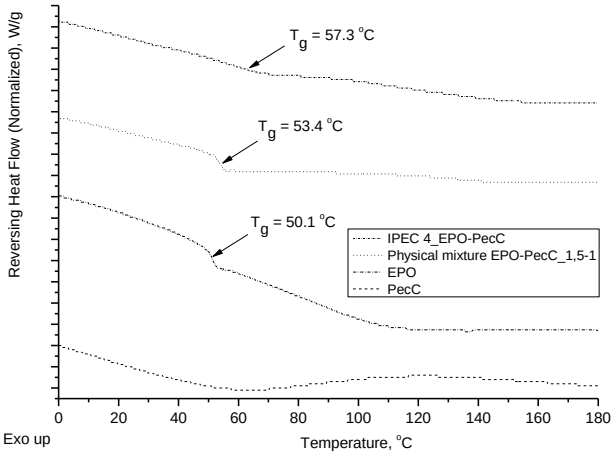

Figure 5. Results of DSC analysis of the IPEC EPO/PecC_4 sample, physical mixture IPEC EPO/PecC_1.5:1 and individual polymers.

2.6. Determination of the degree of swelling of matrices

Taking into account the pharmaceutical focus of our research, the next stage of our work was to study the diffusion-transport properties of the resulting polycomplexes, in comparison with physical mixtures of similar composition and individual polymers.

One of the most important characteristics of polymers is their ability to swell, which determines their physicochemical properties and the feasibility of using them as a polymer carrier of drugs.

In our work, we studied the swelling kinetics of IPEC obtained at the identified EPO/Pec ratios in media mimicking the GIT conditions (7 hours), in comparison with individual polymers and physical mixtures of a composition similar to the composition of IPEC EPO/Pec.

Figure 6 a, b show the swelling curves of polycomplexes (symbols are presented in the Table 2), figure - 6 c, d of a physical mixture and an individual polymer (pectin). There is no swelling profile for Eudragit® E PO. This is due to the fact that this copolymer, which has a basic character, dissolves in an acidic environment. Therefore, tablets prepared from this copolymer dissolved in mimicking the stomach fluid medium (pH = 1.2).

Table 2. Sample symbols.

Sample symbol	**Molar ration of polymers EPO/Pec**	**pH at which IPEC was obtained**
IPEC EPO/PecC_1	1:1.5	4.0
IPEC EPO/PecC_2	1:1	5.0
IPEC EPO/PecC_3	1:1	6.0
IPEC EPO/PecC_4	1.5:1	7.0
IPEC EPO/PecA_1	1:1.5	4.0
IPEC EPO/PecA_2	1:1.5	5.0
IPEC EPO/PecA_3	1:1	6.0
IPEC EPO/PecA_4	4:1	7.0

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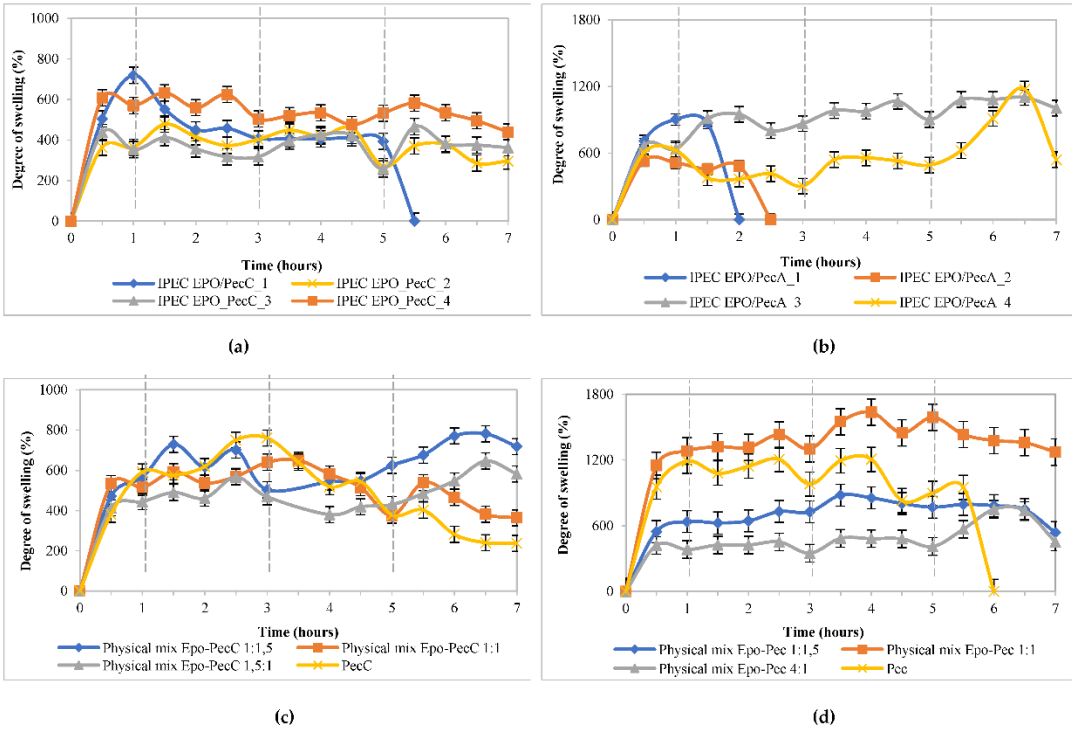
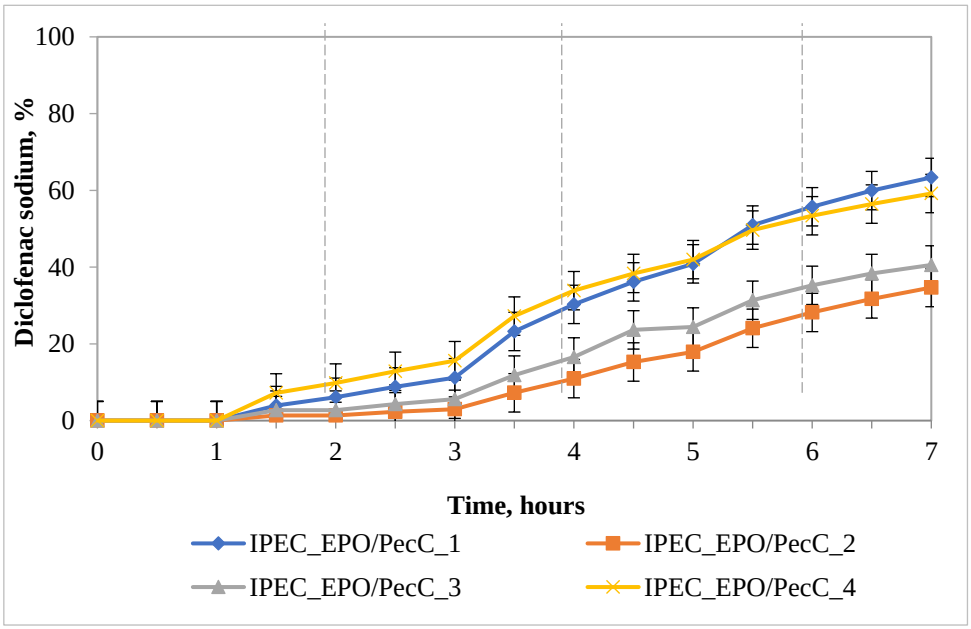


Figure 6. Kinetics of swelling of the studied samples. **(a), (b)** – IPEC samples, **(c),(d)** – Physical mixtures and pectine.

2.7. In Vitro Drug Release Test

An oral system based on polycomplexes, upon entering the body, is exposed to environments with different pH values (from 1.2 to 7.5), which affects the rate of drug release in various parts of the GIT therefore, we determined the rate of release of a model drug diclofenac sodium (DS) from polymer matrices based on IPECs in mimicking the GIT conditions.

Figure 7 shows the release profiles of DS from matrices based on IPEC EPO/Pec. The release of DS from tablets can be characterized as delayed type. For a more detailed analysis of the transport mechanisms of DS from IPEC matrices, mathematical modeling of the drug release processes was carried out according to the Krosmeyer-Peppas equation [43] (Table 3).



(a)

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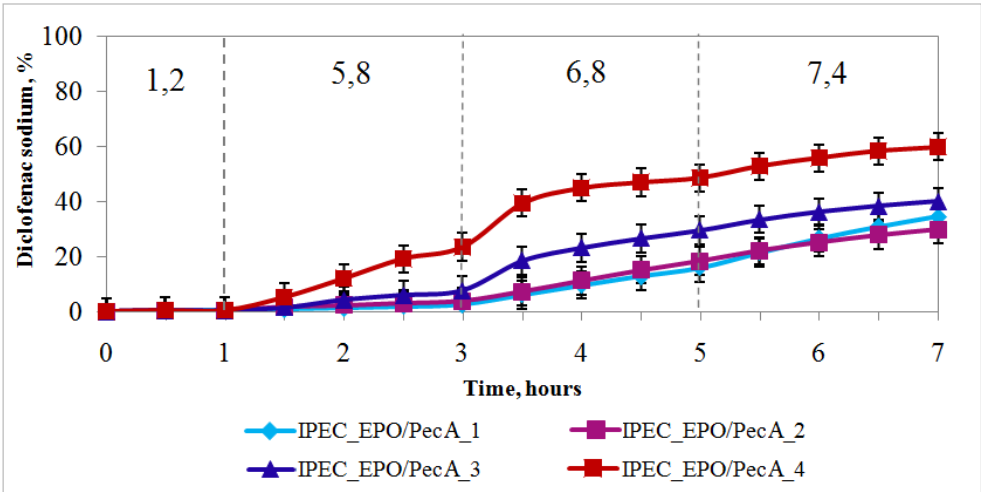

(b)

Figure 7. Kinetics of drug release of a model drug substance from IPEC matrices: **(a)** - based on EPO/PecC, **(b)** - based on EPO/PecA.

Table 3. Results of mathematical modeling of drug release from IPEC matrices according to the Korsemeyer-Peppas equation.

Parameters	IPEC_EPO/PecC_1	IPEC_EPO/PecC_2	IPEC_EPO/PecC_3	IPEC_EPO/PecC_4
Exponential release (*n*)	14.032±1.849	4.762±0.751	8.415±0.908	16.366±1.637
Constant release (*k*)	0.766±0.064	1.032±0.074	0.818±0.052	0.658±0.049
Correlation coefficient (R^2)	0.93828	0.95789	0.96337	0.94553
Transport mechanism	Super Case II	Super Case II	Super Case II	Super Case II
	IPEC_EPO/PecA_1	**IPEC_EPO/PecA_2**	**IPEC_EPO/PecA_3**	**IPEC_EPO/PecA_4**
Exponential release (*n*)	0.526±0.123	0.819±0.178	2.612±0.632	5.149±0.808
Constant release (*k*)	2.186±0.129	1.884±0.122	1.453±0.139	1.287±0.091
Correlation coefficient (R^2)	0.98515	0.98119	0.9588	0.97361
Transport mechanism	Anomalous transport	Anomalous transport	Super Case II	Super Case II

3. Discussion

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Presented figures shows typical curves of turbidimetric titration of EPO and pectin solutions and conversely (pectin-EPO) in a medium of estimate pH values: 4.0, 5.0, 6.0, 7.0.

It should be noted that at pH=4, turbidity maximum is observed at a ratio of EPO/Pec polymers of 4:6, regardless of the mixing order during synthesis, both for apple and citrus pectins (Figures 1a, b). At pH=5, in the case of PecC, the maximum is observed at a polymer ratio of 5:5, and for PecA, 4:6 (Figures 1c, d). At pH = 6, the maxima are in both cases at a polymer ratio of 5:5 (Figures 1 e,f). And at pH = 7 - 6:4 is typical for PecC, and 8:2 for PecA (Figures 1 g,h). Therefore, most turbidity of system corresponds to maximum interaction between copolymers.

The results of the viscosity and gravimetric analysis from the copolymers combinations are shown in Figures. The decrease in viscosity of the supernatant of EPO-pectin mixture solutions observed in the system showed that the IPEC was formed in the investigated medium and was removed by centrifugation. According to the turbidimetry, viscosity, and gravimetry measurements optimal molar ratio of copolymers mixtures (EPO/pectin) were observed at pH=4.0 (1:1.5), pH 5.0 and 6.0 (1:1), pH 7.0 (1.5:1).

To assess the interaction of PEs, FTIR spectra of IPEC samples (Figures 3a, 4a) and physical mixtures (Figures 3b, 4b) of the same composition were recorded. FTIR spectra of the IPECs are characterized by increasing the intensity of the bands at 1610 cm^{-1} and 1400 cm^{-1}, which can be assigned to the absorption band of the carboxylate groups that form the ionic bonds with the protonated dimethylamino groups of EPO. Furthermore, the presence in the complexes of the band at 2450 cm-1 corresponds to the absorption of ionized dimethylamino groups EPO relation to the polycomplex with the carboxylate groups of pectin. This band is absent in the FTIR spectra of the physical mixture. The polycomplexes are stabilized my macromolecular ionic bonds according to the presented scheme (Figure 8).

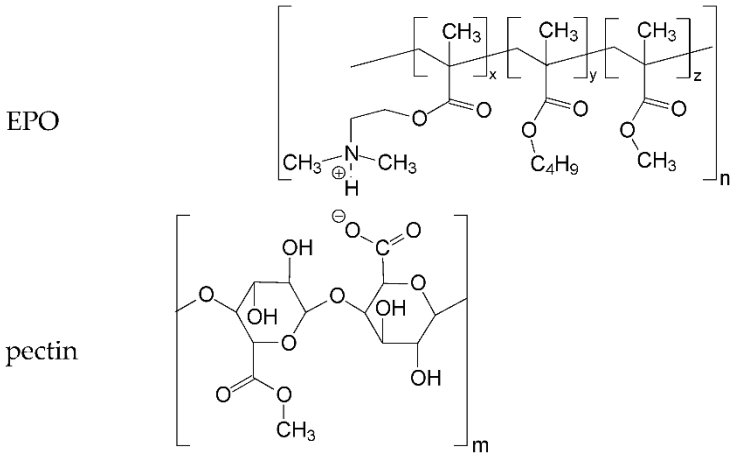

Figure 8. Scheme of interaction between EPO and pectin.

According to the elemental analysis (Table 1), the ratios obtained from the analysis are very close to the molar ratios at which the samples were synthesized. But it should be noted that in compare to citrus pectin IPECs a little more amount of apple pectin macromolecules is required due to its higher esterification values (73.0 ± 1.1).

Thus, the results of physicochemical characterization confirm the formation of IPECs between oppositely charged PEs at pH values from 4.0 till 7.0. The structure of synthesized Eudragit EPO/pectin IPECs due to differences in starting change density of interacted macromolecules depends from the molar ratio of each component in the polyion mixture and correlate with their estimated stoichiometric compositions, showing change from 1:1.5 to 1.5:1.

According to the DSC analysis (Figure 5), DSC thermograms were obtained with different Tg's temperatures: for EPO Tg = 50.1°C, for the physical mixture EPO/PecC Tg = 53.4 °C, and for IPEC Tg = 57.3°C. Thus, with the addition of pectin in polycomplex structures, resulting Tg of the samples increases. It is interesting to note that in the thermogram of the physical mixture we do not see two glass transition temperatures, despite the fact that this is a mechanical mixture of two polymers:

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pectin and EPO, most likely due to the fact that pectin itself does not vitrify. However, the difference in Tg between the physical mixture and IPEC is observed due to the fact that the pectin macromolecules in IPEC structure is ionically bounded to EPO, unlike the physical mixture which were proved that IPEC was successfully synthesized (single Tg at 57.3°C higher that EPO with Tg at 50.1°C).

The next stage of research was an assessment of diffusion-transport properties, namely the kinetics of swelling of polymer matrices in mimicking the GIT conditions. According to the results, IPEC samples obtained at pH = 4.0 in a ratio of 1:1.5 based on citrus pectin (Figure 6a) and at pH = 4.0 and pH = 5.0 in a ratio of 1:1.5 based on apple pectin (Figure 6 b) are disintegrated: by the sixth hour (pH = 7.4) based on PecC and by the second hour (pH = 5.8) based on PecA. Possibly, due to the composition of these IPECs, which has contained excess amount of pectin in polycomplex structure. Since pectin is a hydrophilic polymer, it is easily hydrated in aqueous salt medium, and the tablet matrix is easily disintegrated. A similar result was described in a theophylline release studies [24]. Perhaps apple pectin is more hydrophilic, since IPEC based on it is desintegrated faster - after 2-2.5 hours at pH = 5.8 (Figure 6 b). In the physical mixture, the dimethylamino groups of Eudragit® E PO and the carboxyl group of pectin are in a free state, therefore they are easily ionized in the analyzed medium (pH = 5.8), contributing to the swelling of the hydrated matrix (Figure 6 c, d). The subsequent decrease in swelling rates (at pH = 6.8) is due to the gradual dissolution of the polymers. At pH = 7.4, a slowdown in the dissolution of the physical mixture matrix is observed compared to pectin, which is apparently due to the formation of ionic bonds between two oppositely charged polymers. The profile of the pectin matrix is of a similar nature, but due to the intensity of dissolution of the polymer itself at pH = 7.4, it has lower values by the end of the experiment. It is interesting to note that the swelling ability of IPEC and physical mixtures based on apple pectin is significantly higher than that based on citrus pectin (Figure 6 a, b, c, d). It should conclude, that all IPEC samples are suitable for further evaluation as carriers for oral drug release.

According to drug delivery results DS show 'intestinal' type of release profiles (Figure 7 a, b). IPECs in this study belongs to 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 corresponding to the colon region [42]. Swelling ability 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 sequences in the structure of IPECs. Similar studies based on sodium alginate and Eudragit® E have been reported in our research group previously [30].

The highest release rates are shown by IPEC based on citrus pectin IPEC_EPO/PecC_1 and IPEC_EPO/PecC_4 (Figure 7 a), which is also consistent with the swelling properties of these matrices, although the matrix based on IPEC_EPO/PecC_1 is destroyed at pH = 7.4, which may be due to the fact that the sample was obtained at a more acidic value pH=4.0. The mechanism of drug transport from the matrix can be characterized as Super Case II, since the release exponential is greater than 1. (Table 3).

If we compare the data on swelling and release of IPEC on PecA (Figure 7 b), we can note that matrices based on samples IPEC_EPO/PecA_1 and IPEC_EPO/PecA_2 swell and collapse in a slightly acidic environment pH = 5.8, and when assessing the release, they show a low level of DS release. IPEC_EPO/PecA_3 and IPEC_EPO/PecA_4 swell well, IPEC_EPO/PecA_4 especially when transferred to pH = 7.4, and also surpasses other samples based on apple pectin in terms of release level. This IPEC was obtained at pH=7.0, which may be why swelling and release are higher than other samples. According to the mathematical calculation (Table 3), IPEC_EPO/PecA_3 and IPEC_EPO/PecA_4 have a release exponent greater than 1 (n>1), so the mechanism of drug transport from the matrix is Super Case II [43]. Super Case-II release is the drug transport mechanism associated with stresses and state transition in hydrophilic polymers which swell in GIT mimicking fluids. Anomalous (non-Fickian release) is typical for IPEC_EPO/PecA_1 and IPEC_EPO/PecA_2 ($0.5<n<1$) [43].

Thus, the resulting systems are suitable for colon-specific drug delivery; since they show a characteristic lag phase in the first hours of release in stomach mimicking fluids, followed by an

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increase in the amount of DS release after moving to the intestinal mimicking conditions with pH of 6.8 and 7.4 values.

4. Materials and Methods

4.1. Materials

Pectin from citrus peel (Poly-D-galacturonic acid methyl ester, Galacturonic acid ≥74.0 %, PC) and pectin from apple (Poly-D-galacturonic acid methyl ester, degree of esterification 70-75 %, PA) were used as polyanions (Merck group, Sigma-Aldrich, U.S.A.). Eudragit® E PO (EPO), a terpolymer of *N,N*-dimethylaminoethyl methacrylate (DMAEMA) with methylmethacrylate (MMA) and butylmethacrylate (BuMA) (PDMAEMA–co–MMA–co–BuMA) (molar ratio 2:1:1, MW 150 kDa), was used as a cationic copolymer (Evonik Industries AG, Germany). As a model drug substances, diclofenac sodium (DS), Merck (Sigma-Aldrich, U.S.A.) was used.

4.2. Methods

4.2.1. Turbidity measurements

Polymer solutions were prepared at various ratios at a concentration of 0.0002 M. Mixing was carried out in two orders. Using a magnetic stirrer, the systems were brought into equilibrium and the degree of turbidity of the solutions was determined by the value of the optical density. Both the influence of the mixing order and the ratio of PE solutions were studied (Table 4). The turbidity of each sample solution was determined at 600 nm (a wavelength where no absorption due to the polymers occurred), using a Lambda 25 spectrophotometer (Perkin Elmer, USA).

Table 4. Order and mixing ratios of polymers for turbidity measurements

Mixing order	**Polymer ratio**								
EPO/PecC(or PecA)*	9:1	8:2	7:3	6:4	5:5	4:6	3:7	2:8	1:9
PecC(or PecA)/EPO*	9:1	8:2	7:3	6:4	5:5	4:6	3:7	2:8	1:9

4.2.2. Apparent viscosity measurements

Were prepared solutions of Pec and EPO in various atios (Table 5). After the polymers were dissolved, the resulting solutions were adjusted to the required pH values (4.0; 5.0; 6.0; 7.0). The systems were brought to a state of equilibrium by prolonged stirring on a magnetic stirrer at 700 rpm. within 3 minutes. The resulting systems were centrifuged at 5000 rpm for 30 min, then the precipitate was separated by filtration through a glass filter (POR-100), an aliquot of 10.0 ml was taken, and the solution outflow time was measured at least 3 times using a stopwatch with an accuracy of 0 .1 second. The relative viscosity of the solution was determined by the formula:

$$\eta = \frac{\tau}{\tau_0} - 1,$$

where:

η – relative viscosity of the solution;

τ – solution outflow time, sec;

τ_0 – solvent flow time, sec.

Table 5. Molar ratio of polymers for viscosity measurements

Molar ratio EPO/ PecC(or PecA)												
6:1	5:1	4:1	3:1	2:1	1,5:1	1:1	1:1,5	1:2	1:3	1:4	1:5	1:6

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4.2.3. Gravimetry

Aqueous solutions of Eudragit® EPO and pectin were prepared at different concentrations (Table 5) and mixed in two orders. The resulting systems were kept for 7 days, then the supernatant liquid was drained off and the precipitate was dried at room temperature for 2 days, followed by drying in a vacuum oven at a temperature of 40 ℃ to constant weight and weighed on an analytical balance with an accuracy of 0. 0001.

4.2.4. Synthesis of solid IPEC

Synthesis of a new IPECs between countercharged type of a cationic (meth)acrylate terpolymer (Eudragit EPO) and anionic polysaccharide (pectin) were determined at different pH values from 4.0 to 7.0, depending on copolymers solubility. The PE solutions were mixed in different orders and in different molar ratios, from 5:1 to 1:5 to a constant final concentration of 0.0032 g/ml. Eudragit®E PO was dissolved in 0.005 M acetic acid and pectin in 0.005 M NaOH. Then the pH was adjusted to the required value (4.0; 5.0; 6.0; 7.0) by adding 0.005 M NaOH or 0.005 M acetic acid, respectively. Next, a pectin solution (50 drops/min) was gradually (dropwise) added to the Eudragit® EPO solution through a separating funnel. After complete precipitation of the IPEC precipitate, the supernatant liquid was decanted, and the complex itself was repeatedly washed with distilled water. The resulting polycomplex was dried for 3-4 days at room temperature, followed by drying to constant weight at 40°C under vacuum. Then, IPEC was crushed and sifted through a sieve with a hole diameter of 0.25 mm.

4.2.5. Elementary analyses

The compositions of the dried IPC samples were investigated by elemental analysis using a CHNS/O Elemental analyzer Thermo Flash 2000 (Thermo Fisher Scientific, Paisley, UK) and calculated as Z = [EPO]/[PecC](or[PecA]) (mol/mol). The vacuum dried samples (at 40 ◦C for 2 days) were weighed into a crucible on a XP6 Excellence Plus XP micro balance (Mettler Toledo, Greifensee, Switzerland). The crucibles with samples were packed and placed into the combustion reactor via autosampler. Temperature in the oven was 900 ◦C, and a gas flow rate was 10 mL/min. Calibration of the instrument was performed with atropine standard (Thermo Fisher Scientific, Paisley, UK). Eager Xperience Data Handling Software was used to analyze the results. Tests were performed in triplicate.

4.2.6. FT-IR spectroscopy

ATR-FTIR spectra were recorded by a Nicolet iS5 FTIR spectrometer (Thermo Scientific, Waltham, MA, USA) using the iD5 smart single bounce ZnSe ATR crystal. The spectra were analyzed using OMNIC spectra software.

4.2.7. Thermal analysis

Modulated DSC (mDSC) measurements were carried out using a Discovery DSC™ (TA Instruments, New Castle, DE, USA), equipped with a refrigerated cooling system (RCS90). TRIOS™ software (version 3.1.5.3696) was used to analyze the DSC data (TA Instruments, New Castle, DE, USA). Tzero aluminum pans (TA Instruments, New Castle, DE, USA) were used in all calorimetric studies. The empty pan was used as a reference and the mass of the reference pan and of the sample pans were taken into account. Dry nitrogen was used as a purge gas through the DSC cell at 50 mL/min. Indium and n-octadecane standards were used to calibrate the DSC temperature scale; enthalpic response was calibrated with indium. Calibration of heat capacity was done using sapphire. Initially the samples were cooled from room temperature to 0 ◦C, then kept at 0 ◦C for 5 min and analyzed from 0 to 250 ◦C. The modulation parameters used were: 2 ◦C/min heating rate, 40 s period and 1 ◦C amplitude. Glass transition temperatures were determined using the reversing heat flow signals. All measurements were performed in triplicate.

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4.2.8. Preparation of tablets

In order to determine the degree of swelling, flat-faced 100 mg IPEC compacts with 8 mm diameter were prepared by compressing the given amount of powder powders (EPO, PecC, PecA, PMs and IPECs) at 2.45 MPa using a hydraulic press (PerkinElmer, Waltham, MA, USA). For dissolution testing, flat-faced 150 mg compacts (100 mg of DS and 50 mg polymer carrier) and 8 mm diameter were prepared by powder compression at 2.45 MPa using a hydraulic press (PerkinElmer, Waltham, MA, USA)

4.2.9. Determination of the degree of swelling of matrices

As model media mimicking the gastrointestinal tract (GIT) a 0.1 M hydrochloric acid solution (pH = 1.2 for 1 hour) and phosphate buffers (pH = 5.8 for 2 hours, pH = 6.8 for 2 hours; pH = 7.4 for 2 hours) were chosen. The polymeric matrix is placed in a tarred basket (from the dissolution test equipment), which was immersed into a thermostated bath (37°C ± 0.5°C). The volume of the swelling medium was 40 mL. The degree of swelling was determined every 30 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.

4.2.10. In Vitro Drug Release Test

The release of DS from the matrix tablets in GIT mimicking conditions was carried out in a dissolution tester, the DT-828 (Erweka, Langen, Germany), at 37 ± 0.5°C, by using the USP I Apparatus (Basket Method). The basket rotation speed was 100 rpm and the volume of the medium was 900 mL. The release was investigated for 7 h under GIT mimicking conditions, where the pH of the release medium was gradually increased: 1 hour in 0.1M hydrochloric acid (pH = 1.2), then 2 hours in phosphate buffer solution with pH = 5.8, then 2 hours in phosphate buffer solution with pH = 6.8 and finally 2 hours in phosphate buffer solution with pH = 7.4. Aliquots (5 mL) of solution were taken every 30 minutes, and the volume of medium was made up to the original value by adding fresh dissolution medium. The amounts of DS released in the dissolution medium were determined by UV/Vis-spectrophotometry at 276 nm (Lambda 25; PerkinElmer, Waltham, MA, USA). Results are given as the mean values of three determinations ± standard deviations.

5. Conclusions

During the turbidity study, stoichiometry points were selected for the studied pairs of polymers EPO/PecA and EPO/PecC at pH values = 4.0, 5.0, 6.0, 7.0. These results were reproduced and confirmed in viscosity and gravimetry studies at higher concentrations. According to FTIR spectroscopy, DSC analysis data, the synthesized IPECs represent individual chemical compounds. The ratios obtained from the elementary analysis are very close to the molar ratios at which the samples were synthesized. The swelling ability of IPEC and physical mixtures based on apple pectin is significantly higher than that based on citrus pectin. All test samples are suitable for further evaluation of model drug release. According to drug delivery results DS show 'intestinal' type of release profiles. IPECs in this study belongs to 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. The highest release rates are shown by IPEC EPO/PecC_1 and EPO/PecC_4, which is also consistent with the swelling properties of these matrices. The mechanism of drug transport from the matrices IPEC EPO/PecC can be characterized as Super Case II. IPEC EPO/PecA_3 and EPO/PecA_4 have a release exponent greater than 1 (n>1), so the mechanism of drug transport from the matrix is Super Case II. Anomalous (non-Fickian release) is typical for IPEC EPO/PecA_1 and EPO/PecA_2. Thus, the resulting systems are suitable for drug delivery to the intestinal region.

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