Interpolyelectrolyte complexes based on Carbopol® and oppositely charged polymers as new carriers for oral controlled diclofenac delivery

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ABSTRACT

Carbopol® are polymers of acrylic acid and crosslinking agents; there is the prospect of penetration of linear macromolecules between mesh size of crosslinked Carbopol® microgels for a certain period of time. Interpolyelectrolyte complexes (IPEC) samples between Carbopol® and linear polycations (Eudragit® EPO – EPO, chitosan – CS) were obtained at different interpolyelectrolyte reaction (IPER) times (1, 3 and 7 days). Confirmation of the IPEC structures were proved by FTIR and mDSC. Moreover, according to the results of elemental analysis and mDSC, an increase in the duration of IPER time did not lead to a significant increase in the fraction of the incorporated EPO (CS), since its amount in polycomplex samples remains almost unchanged and the *Tg*s varies slightly and it depends from the Carbopol® grade used. Analysis of the particle size and zeta potential of polycomplex gels showed that the obtained IPEC samples are nanosized, the particle charge depends on the presence of free ionized carboxyl groups Carbopol® (Noveon®) or positively charged dimethylamino groups of EPO on their surfaces. Increasing the duration of IPER up to 3 days a decrease in zeta potential values was observed. In case of 7 days, an increase in particle size was observed due to their aggregation (C2020/EPO, C10/EPO, NAA-1/EPO). Mathematical modeling of diclofenac sodium release according to the Korsmeyer-Peppas equation showed that all IPEC samples were characterized by the Super Case II transport mechanism, except for C10/EPO sample, which was characterized by abnormal transport.

This paper is dedicated to 70th Anniversary of Prof Sarkyt Kudaibergenov.

KEYWORDS

Interpolyelectrolyte complexes, Carbopol®, Eudragit®, chitosan, intestinal type of release, diclofenac

INTRODUCTION

For many decades, Carbopol® brand polymers have been one of the most popular in pharmaceutical industries and they are used in the preparation of various dosage forms, including oral formulations.[1,2,3,4,5] Along with polymers, a large number of studies are conducted in the world science to develop interpolyelectrolyte complexes (IPEC) based on Carbopol® brand polymers.[6,7] Systems based on Carbopol® and Eudragit® were studied as systems for the controlled release of paracetamol.[8] Systems based on IPEC Carbopol® / Chitosan [9,10] were also investigated. In addition, the mechanisms of drug release from chitosan-anionic polycomplex systems were also investigated.[11]

Other widespread polymers in the production of oral dosage forms and in the field of research of oral modified release systems are the Eudragit® brand polymers. Eudragit® (meth) acrylic copolymers manufactured by the German concern Evonik Röhm GmbH are used to develop various dosage forms: tablets,[12,13] granules, micro- and nanoparticles, as well as coatings and at various stages of the technological process (as a binder, for granulation, to obtain matrix tablets).[15,16,18]

Eudragit® polymers are used in various stages of dosage forms production and coating methods: in the technology of matrix tablets — in direct compression, in the preparation of solid disperse systems by co-evaporation, in the preparation of microparticles by the coprecipitation method, in wet granulation, by thermal extrusion granulation, in the preparation of microparticles (microspheres, micro granules); in the technology of reservoir systems: for producing film coatings from non-aqueous polymer solutions, using aqueous latex dispersions of polymers, by the method of "dry spraying" in order to obtain dosage forms with a modified or controlled release.[14]

In addition, due to the presence of oppositely charged functional groups in the structure of individual copolymers, IPECs based on the above Eudragit® grades in aqueous and non-aqueous media were obtained and studied, and the prospect of using them as drug delivery systems was proved. [14,16,17,18]

IPEC is the product of the interaction of two or more oppositely charged polyelectrolytes (PE) stabilized by ionic bonds.[19,20]

The aim of our work was to study the interaction of two PE: Carbopol® of various grades: 71G NF, 2020 NF, 10 Ultrez, Noveon® AA-1 and Eudragit® EPO, or chitosan.

Previously, our research group obtained and studied IPEC samples based on Carbopol® 940, 971, 974, Pemulen® and Eudragit® EPO.[12,21,22] As a result of research, several methods for obtaining IPEC have been developed, one of which is used in this work (preparation at a neutral pH value).[23]

Carbopol® are polymers of acrylic acid and crosslinking agents.[24] Due to their network structure, there is the prospect of penetration of linear macromolecules between mesh size of crosslinked

Carbopol® microgels for a certain period of time. For the complete course of the interpolymer reaction, a certain time is required. Therefore, in this work, samples were obtained at different interpolyelectrolyte reaction (IPER) times (1, 3 and 7 days). It was interesting to consider, using the IPEC example, the "relay mechanism" theory, according to which a linear polyelectrolyte is able to penetrate deep into the crosslinked polymer micelles after a certain period of time.[25] The interactions of the crosslinked polyacrylic acid and the poly-L-lysine polymer were investigated by H. Bysell to study the penetration of poly-L-lysine deep into Carbopol® micelles.[26,27]

Earlier, we consecrated the production of complexes based on Carbopol®/Eudragit® EPO, studied the diffusion-transport and their mucoadhesion properties. In this paper, the interaction of polymers and their physical and chemical parameters were also evaluated.[28]

EXPERIMENTAL

Materials

IPEC samples, based on the various grades of Carbopol® polymers 71G NF, 2020 ETD, 10 Ultrez NF (C71G, C2020, C10), Noveon® AA-1 (NAA-1) (Lubrizol Advanced Materials (USA)) and oppositely charged polyelectrolytes - Eudragit® EPO (EPO) (Evonik Industries (Germany)), chitosan (CS) (Sigma Aldrich (USA)) were studied. Carbopol® are polymers of acrylic acid and crosslinking agents, which are different in such parameters as the type of polymer, dispersion viscosity, molecular weight, and the distance between cross-links (Table 1). Eudragit® EPO is cationic copolymer based on dimethylaminoethyl methacrylate and neutral methacrylic acid esters, chitosan is cationic natural polymer. As model drug substances was used diclofenac sodium (DS), Sigma Aldrich (USA). As a comparison dosage form, Voltaren® retard (VR), Novartis International AG (USA) was used.

Methods

Synthesis of IPEC samples

Aqueous dispersions of various grades of Carbopol® (0.005 M) were prepared, letting the polymer swell for 24 hours in purified water, and then adjusting the pH of Carbopol® gel to a value of 7.0. EPO solutions (0.005 M) were prepared by dissolving the polymer powder in purified water with the addition of 1N acetic acid solution, followed by adjustment to pH 7.0. Then EPO solutions were added to swollen Carbopol® gel. The resulting systems were kept for different periods of time: 1 day, 3 days, 7 days, then the supernatant was drained and the IPEC precipitate was dried at room temperature for 2 days, followed by drying in a vacuum oven (Binder, Germany) at a temperature of 60 ° C, at a pressure of 4 atm up to constant weight.

Elemental analysis

Elemental analysis was performed on a CHNS/O Elemental analyzer Thermo Flash 2000 (Thermo Scientific, USA). (Nitrogen (*N*, %) was determined by burning a sample in a quartz tube using an electric furnace due to oxygen of solid oxidizers of copper oxide in a carbon dioxide atmosphere: its content in the test substance is determined by the volume of nitrogen released.

Elemental organic analysis is used to determine the proportion of elements such as carbon, hydrogen, nitrogen, sulfur and others. In order to study the composition of the samples, we were interested in determining the nitrogen content in the final product of IPER – IPEC. Since one of the EPO polymers (or CS, in the case of the C71G / CS pair) contains nitrogen, it becomes possible to find out the fraction of the polycation included in IPEC.

FT-IR spectroscopy

Compared to individual polymers, the FT-IR spectra of the IPEC Carbopol® / EPO and Carbopol® / CS were recorded on a Nicolet iS5 FTIR spectrometer (Thermo Scientific, USA) with an ATR attachment, in the frequency range 500-4000 cm^{-1}. An exact amount of a sample weighing 0.7-0.8 mg, previously ground to a powder, was applied onto the surface of a zinc selenium crystal, and the IR spectrum was recorded. The assignment of absorption bands in the IR spectra was carried out in accordance with literature.[29,30]

mDSC analysis

The measurements were carried out on a DSC with modulated temperature (mDSC) on the Discovery™ (TA Instruments, USA). Samples in the amount of 5-7 mg in a closed aluminum capsule were placed in a thermo-cell of a device pre-calibrated using standard samples (benzoic acid, octadecane and indium metal) and scanned in the temperature range from 25 ° C to 250 ° C at a speed of 2 ° C / min.

Measurement of particle size and z-potential

A suspension was prepared from IPEC samples at a concentration of 0.01% w/v, and then the zeta potential and particle size were measured on a Zetasizer Nano ZS instrument (Malvern, England) by dynamic light scattering.

Preparation of tablets for evaluating drug release from matrices of interpolyelectrolyte complexes

Drug loaded tablets (diclofenac sodium/IPEC 0.1/0.05 ratio), with total weight 0.15 g and diameter 8 mm, were prepared by direct pressing on a manual hydraulic press (PerkinElmer, USA) from synthesized IPECs C71G / EPO, C2020 / EPO, C10 / EPO, NAA-1 / EPO, C71G / CS and diclofenac sodium at a pressure of 25 kgs/ cm^2.

Drug release

The study of the kinetics of drug release was carried out on the dissolution tester DT-828 (Erweka, Germany). As model media imitating the gastrointestinal tract, a 0.1 M hydrochloric acid solution

(pH = 1.2 for1 hour) and phosphate buffers (pH = 5.8 for 2 hours, pH = 6.8 for 2 hours; pH = 7.4 for 2 hours) were chosen.[31]. The volume of the dissolution medium was 900 ml, the basket rotation speed was 100 rpm and the medium temperature 37 ° C ± 0.5 ° C. Sampling was carried out in all media every 30 minutes and an equal amount of buffer solution was replaced. Quantitatively released active substance was determined UV/Vis -spectrophotometrically on a Lambda 25 (PerkinElmer, USA) at a wavelength of 276 nm.[29]

RESULTS

The starting polyelectrolytes (PEs) were taken in a 1:1 molar ratio. Carbopol® is a rare crosslinked PAA, that is, has cross-linking between the polymer chains. IPEC is formed in the form of a precipitate, which is then studied as a new carrier for the oral controlled delivery of drugs.

According to the elemental analysis, we can conclude that the studied PEs at a ratio of 1:1 in the reaction mixture form a product with an excess of the rare-cross-linked Carbopol® polymer.

A new absorption band, absent in individual polymers, appears in the IPECs FT-IR spectra at 1560 cm^{-1}, due to the formation of ionic bonds between Carbopol® carboxylate groups and EPO protonated dimethylamino groups, or CS amino groups. Synthesis of IPEC samples was performed at different reaction times: 1 day, 3 days, 7 days. The IR spectra of the corresponding polycomplexes were also recorded (Figure 1a,b,c,d). According to the obtained results, it can be seen that the absorption bands of 2820, 2770, 1730, 1560 cm^{-1} are maintained regardless of the time during which the samples were held throughout the synthesis.

According to the mDSC, complexes have a single glass transition temperature (in range 127 ° - 138 ° C), different from that of individual polymers (49.5 ° - 131 ° C). Firstly, samples of individual polymers were investigated: Carbopol® of various grades and EPO. Then, IPEC samples were studied at different IPER times in order to detect the effect of the reaction time between oppositely charged PEs. It can be noted that for the IPEC samples C71g / EPO, C2020 / EPO there is a tendency to a decrease in the glass transition temperature, other IPEC samples are characterized by the lack of correlation between *Tg* and the synthesis time.

The C71g-EPO samples with an IPER time of 1 day and 3 days have the largest particle size (Figure 2). Then, as the synthesis time increases to 7 days, the particle size decreases, as the particles become denser, the zeta potential slightly increases (Figure 3).

To assess the release of the drug substance, diclofenac sodium (DS), which is poorly soluble, was chosen as model drug. The starting components (IPEC: drug) were selected in a ratio of 0.5:1. The pH was pregressively increased to mimic the gastrointestinal transit.

As depicted in Figure 4, all the formulations showed gastro-resistance since diclofenac was not detected in the acidic environment. Then, a different pattern was noticed depending on the IPEC

composition. In particular, the increase of pH to 5.8 determined a modest burst effect in the case of IPEC prepared by Carbomer homopolymer Type A (IPEC C71g/EPO and IPEC C10/EPO) followed by a slow drug release comparable to that obtained by formulation prepared by polycarbophyl (IPEC NAA-1/EPO) or using chitosan as cationic polyelectrolyte instead of EPO (IPEC C71G/CS). The selection of Carbomer homopolymer Type B (C2020/EPO IPEC) determined an intermediate pattern since the drug release constant was higher than Polycarbophyl, but the burst effect was negiglible. In all cases the diclofencac release after 3 hours was less than 10% of the initil drug content. The further changes of pH to 6.8 determined an increase of the drug release constant only in the cases of Carbomer homopolymers Type A or Type B (table 1). The slower release obtained by IPEC C10/EPO was attributed to the high Mw of C10 with respect to the other carbomers. The further increase of the pH to 7.4 determined a slight increase of diclofenac release from IPEC made f Polycarbophyl. Finally drug release profile of IPEC C71G/CS appeared independent of pH and overlapped with that obtained by Voltaren® retard.

DISCUSSION

To obtain IPEC, a rare crosslinked polyacrylic acid (PAA) sold under the trademark Carbopol® was chosen, namely 71G, 2020, Ultrez 10, Noveon AA-1, as the polyanion and linear polyelectrolyte Eudragit® EPO was used as the polycation. Each of the aforementioned Carbopol® grades was selected as counterion. Since the C71G polymer has the largest cell size, it was interesting to study the possibility of its interaction with the linear rigid-chain polymer CS with the prospect of the penetration of the linear polymer between the cell sizes of the cross-linked Carbopol® microgels.

The main condition for the synthesis of IPEC samples is the preliminary exposure of the polymer in solution, since this is necessary for wetting and swelling of the polymer powder. Further, after the polymer has been kept in water for 24 hours and the dispersion was adjusted to the desired pH suitable for the polymer interaction, a linear PE solution was added dropwise to it. This is precisely the order in which the components were added due to the high viscosity of the Carbopol® dispersion. PE solutions were dissolved or dispersed in an aqueous solution with the addition of a 1N acetic acid solution, and then adjusted to the pH necessary for the reaction. As far as the pH of the interaction is concerned, the value closest to neutrality was chosen, such that both interacting polymers are in a dissolved and ionized state and are capable of interaction. Then, as the polycation solution is added to the polyanion, IPEC is formed in the form of a precipitate, which is then studied as a new carrier for the oral controlled delivery of drugs.

Elemental organic analysis. The main aim of research was to study the effect of different durations of the interpolyelectrolyte reaction (IPER) on the composition of the sample, namely, to obtain a

complex with an increased content of the EPO polycation. Thus, according to the elemental analysis, we can conclude that the studied PEs at a ratio of 1:1 in the reaction mixture form a product with an excess of the rare-cross-linked Carbopol® polymer. Moreover, an increase in the duration of IPER time does not lead to a significant increase in the fraction of the incorporated EPO, since its amount in polycomplex samples remains almost unchanged. For a more detailed study of the obtained samples, mDSC was performed (Table 2).

IR spectroscopy is one of the methods used to prove the formation of a new compound, as a result of the interactions between the original polymer samples. A new absorption band, absent in individual polymers, appears in the IPECs FT-IR spectra at 1560 cm^{-1}, due to the formation of ionic bonds between Carbopol® carboxylate groups and EPO protonated dimethylamino groups, or CS amino groups. The appearance of new absorption bands, previously absent in the starting polymers, proves the formation of IPECs.[32]

In addition, it was interesting to study duration of IPER time on the composition of the obtained IPEC sample. For this, synthesis of IPEC samples was performed at different reaction times: 1 day, 3 days, 7 days. The IR spectra of the corresponding polycomplexes were also recorded (Figure 1a,b,c,d). According to the obtained results, it can be seen that the absorption bands of 2820, 2770, 1730, 1560 cm^{-1} are maintained regardless of the time during which the samples were held throughout the preparation: in other words, IPER time slightly affects the composition of the obtained sample.

According to the mDSC, the formation of complexes as chemically individual compounds having a single glass transition temperature (in range 127 ° - 138 ° C), different from that of individual polymers (49.5 ° - 131 ° C), has been proven. It can be noted that the glass transition temperature (*Tg*) of various grades of Carbopol® ranges from 125-132º C, and for EPO it is 49.5 º C. Then, IPEC samples were studied at different IPER times in order to detect the effect of the reaction time between oppositely charged PEs. It can be noted that for the IPEC samples C71G / EPO, C2020 / EPO there is a tendency to a decrease in the glass transition temperature, which may be caused by a slight increase in the content of EPO, as polymer with a lower *Tg* value. A possible reason for the increase in the EPO content in IPEC may be the structural features of C71G, namely, the large mesh size of crosslinked Carbopol® microgels, which ensures the penetration of EPO molecules deep into the microgels of the crosslinked polymer. A slight decrease in *Tg* is also characteristic of C2020 / EPO, which may be caused by an increase in the percentage of EPO on the surface, since a significantly smaller distance between crosslinks compared to C71G does not allow EPO molecules to penetrate deep into the micelles. Other IPEC samples are characterized by the lack of correlation between *Tg* and the preparation time, i.e., an increase in the reaction time between polymers does not lead to an increase in the amount of EPO in the complex.

According to the studies, IPEC samples C2020 / EPO, C71G / EPO tend to decrease *Tg*. However, these changes in *Tg* values are small, which is consistent with the results of elemental analysis, where slightly variations in composition between the obtained samples were observed. In other words, an increase in IPER time does not lead to an increase in the fraction of polycation in IPEC.

Thus, synthesis and physicochemical study of the formed IPEC as new chemical compounds were carried out. Their properties were compared with individual polymers: according to FT-IR spectroscopy, IPEC samples have a new absorption band at 1560 cm^{-1}, absent in individual polymers, mDSC analysis proved the formation of complexes as chemically individual compounds, having a single glass transition temperature that differs from those of individual polymers, thus providing a prerequisite for further studies of the samples as carriers for drug delivery.

Measurement of particle size and z-potential

The C71G-EPO samples with an IPER time of 1 day and 3 days have the largest particle size (Figure 2), which can be explained by the aggregation of IPEC particles. Then, as the preparation time increases to 7 days, the particle size decreases, as the particles become denser, the zeta potential slightly increases (Figure 3), which is associated with an increase in the EPO content in IPEC. With an increase in the preparation time, the particles become more compact, due to the large distance between the cross-links, and most of the EPO molecules can penetrate deeply into the Carbopol® microgels.

According to the results, the particle size of IPECs C2020-EPO, C10-EPO, NAA-1-EPO increases due to an increase in their aggregation. EPO polymer have a positive surface charge (+ 44.2), which is associated with the presence of positively charged dimethylamino groups in the polymer structure.

Thus, the analysis of the particle size and surface zeta potential showed that the obtained IPEC samples are nanosized, the particle zeta potential depends on the presence of free ionized carboxyl groups of Carbopol® (Noveon®) or positively charged dimethylamino groups of EPO on the surface.

The next step of the work was to study the release of a model drug substance from IPEC matrices.

As reported above the amount of diclofenac released in the first 3 hours could be considered negligible indepently of the IPEC composition. Aftwerwards increasing the pH the IPEC showed a different pattern evidencing that these composite materials behave differently depending on their composition and can be subdivided in two groups the former formed by the complexation of EPO with carbomer homopolymer showed a dependence of drug release from the pH. This sensitivity

cannot be explained by their dry physico-chemical features but to a different swelling behavior which also justify the fitting results performed according to Korsmeier-Peppas model reported in Table 3.

The different effect of the change of diclofenac release from IPEC cannot be related to the Tg of the IPEC or to different interaction among the two polymer. Thus, we attributed the different patterns obtained to the chemical features of the materials which determined a different swelling of the IPEC and influenced the diffusion of diclofenac from the nanostructure The further increase of pH to 6.8 and then to 7.4 caused an increase of diclofenac release rate constant pattern only in the case of IPEC C2020/EPO, C71/EPO and in a lower extent C10/EPO. Therefore, on the bases of the drug release data it is reasonable to hypothesize the following classification. The IPEC C71g/CS appears insensitive to pH changing, The IPEC C71g/EPO, C2020/EPO and C10/EPO swell at pH 6.8 while NAA-1/EPO swells at pH 7.4. Based on these different behaviors, we behave that IPEC C71g/CS is suitable design of prolonged release dosage forms. Indeed, the diclofenac release pattern obtained with this formulation overlapped with that obtained by Voltaren® retard.

The other formulations are characterized by a lag time of about three hours, after which the drug release gradually increases as the pH changes. Drug delivery systems with a such behaviour (a dissolution threshold of pH 6.0–7.0) are expected to delay the drug release preventing premature drug release in the upper GI tract before reaching colonic sites. Afterward the diclofenac release can be tuned according to Carbomer features used for the IPEC synthesis.

Conclusion

Interpolyelectrolyte complexes (IPEC) samples between Carbopol® and Eudragit® EPO (EPO) were obtained at different interpolyelectrolyte reaction (IPER) times (1, 3 and 7 days). A new absorption bands on the FT-IR spectra of IPEC samples appears at 1560 cm^{-1}, previously absent in individual polymers, due to the formation of ionic bonds between carboxylate groups of Carbopol® and protonated dimethylamino groups of EPO or chitosan amino groups. Confirmation of the IPEC structures are also proved by mDSC results by the appearance of a new single glass transition temperatures (*Tg*) which values are included between *Tg*s of individual polymers. Moreover, according to the results of elemental analysis and mDSC, an increase in the IPER time does not lead to a significant increase in the fraction of the incorporated EPO, since its amount in polycomplex samples remains almost unchanged and the *Tg*s varies slightly. Analysis of the particle size and zeta potential of polycomplex gels showed that the obtained IPEC samples are nanosized, the particle charge depends on the presence of free ionized carboxyl groups Carbopol® (Noveon®) or positively charged dimethylamino groups of EPO on their surfaces. Increasing the

IPER time up to 3 days led to a decrease of zeta potential values. In case of 7 days, an increase in particle size is observed due to samples aggregation (C2020/EPO, C10/EPO, NAA-1/EPO). The release profiles of diclofenac sodium (DS) from all IPEC matrices can be divided into 2 groups: systems providing a gradual release of DS (C2020/EPO, C71G/EPO) and systems exhibiting a sustained release with a pronounced lag phase ($t_{lag} \approx 3$ hours; C71G/CS, NAA-1/EPO, C10/EPO and commercial tablets of Voltaren® retard). Mathematical modeling of drug release according to the Korsmeyer-Peppas equation showed that all samples are characterized by the Super Case II transport mechanism, except for C10/EPO sample, which is characterized by abnormal transport.

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Table 1. Physico-chemical characteristics of the used Carbopol® and Noveon grades

Grades	Type of	Viscosity (0.5%, pH 7.5), Pa · s	Molecular weight, kD	Mesh size, kD
C2020	Carbomer interpolymer Type B (copolymer of acrylic acid and ethylene glycol crosslinked with pentaerythritol allyl ether)	4 700 – 7 700[1]	4 500	11,4
C71G	Carbomer homopolymer Type A (polyacrylic acid, crosslinked ethylene glycol crosslinked with pentaerythritol allyl ether)	400 – 1 100	3 000	237,6
N AA-1	Polycarbophil (polyacrylic acid, crosslinked by divinyl glycol)	200 – 1 200	3 000	_[2]
C 10	Carbomer Interpolymer Type A (polyacrylic acid, crosslinked by pentaerythritol allyl ether))	45 000-65 000	_[2]	_[2]

1 - issued partially neutralized; 2 - no data.

Table 2. The results of elemental analysis and mDSC of IPEC samples obtained at different preparation times

№	Composition of the reaction mixture Z=[Carbopol®] or [Noveon] / [EPO] (mole/mole)	The duration of the IPER (days)	Composition of IPEC Z=[Carbopol®] or [Noveon] / [EPO] (mole/mole)	Glass transition temperatures (*Tg*)
1.	C2020/EPO 1:1	1	3.0/1	134.5±0.3
2.	C2020/EPO 1:1	3	2.8/1	134.1±0.4
3.	C2020/EPO 1:1	7	2.4/1	133.5±0.2
4.	C71G/EPO 1:1	1	2.6/1	138.4±0.1
5.	C71G/EPO 1:1	3	2.4/1	133.1±0.5
6.	C71G/EPO 1:1	7	2.1/1	132.8±0.6
7.	C10/EPO 1:1	1	3.1/1	123.6±0.4
8.	C10/EPO 1:1	3	2.5/1	125.8±0.2
9.	C10/EPO 1:1	7	2.2/1	134.8±0.3
10	N AA-1/EPO 1:1	1	2.3/1	127.7±0.4
11	N AA-1/EPO 1:1	3	2.1/1	137.8±0.2
12	N AA-1/EPO 1:1	7	2.3/1	138.4±0.5

Table 3. The results of mathematical modeling of the processes of release of diclofenac sodium from the studied multicomplex matrices according to the *Korsmeyer-Peppas* equation.

Parameters	NAA-1/ EPO	C2020/EPO	C71G/ EPO	C71G/ CS	C10/EPO
Exponential release (*n*)	1.58±0.076	1.33±0,05	1.16±0.06	1.17±0.09	0.80±0.03
Constant release *(k)*	1.57±0.19	5.02±0.40	6.76±0.69	1.64±0.23	7.74±0.37
Correlation coefficient (R^2)	0.98981	0.99369	0.98445	0.97017	0.99123
Transport mechanism	Super Case-II transport	Super Case-II transport	Super Case-II transport	Super Case-II transport	Abnormal transport
1st Order Kinetics (R^2)	0.99363	0.99124	0.98630	0.98022	0.99308