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Interpolymer complexes of Carbopol® 971 and poly(2-ethyl-2-oxazoline): physicochemical studies of complexation and formulations for oral drug delivery

Rouslan I. Moustafine,[1*] Anastasiya S. Viktorova,[1] Vitaliy V. Khutoryanskiy[1,2*]

[1] Institute of Pharmacy, Kazan State Medical University, 16 Fatykh Amirkhan Street, 420126 Kazan, Russian Federation

[2] Reading School of Pharmacy, University of Reading, Whiteknights, PO box 224, Reading RG66AD, United Kingdom

Abstract

Carbopol® 971 and poly(2-ethyl-2-oxazoline) form hydrogen-bonded interpolymer complexes in aqueous solutions and their complexation is strongly dependent on solution pH. This work investigated the complexation between these polymers in aqueous solutions. The compositions of interpolymer complexes as well as the critical pH values of complexation were determined. The structure of these complexes was studied in solutions using transmission electron microscopy and in solid state using elemental analysis, FTIR spectroscopy and differential scanning calorimetry. Solid compacts were prepared based on interpolymer complexes and physical blends of these polymers and their swelling behaviour was studied in aqueous solutions mimicking the fluids present in the gastrointestinal tract. These materials were used to prepare oral formulations of mesalazine and its release from solid matrices was studied in vitro. It was demonstrated that the complexation between Carbopol® 971 and poly(2-ethyl-2-oxazoline) has a profound effect on the drug release from matrix tablets.

Keywords: interpolymer complexes, Carbopol®, polyoxazoline, hydrogen bonding, nanoparticles, critical pH, mesalazine, oral drug delivery

***Correspondence**: Dr Rouslan I. Moustafine rouslan.moustafine@gmail.com and Prof Vitaliy V. Khutoryanskiy v.khutoryanskiy@reading.ac.uk

1. Introduction

Hydrophilic polymers and their combinations are often used to formulate dosage forms as they provide a number of unique features required for successful drug delivery. When polymer combinations are used for this purpose the performance of the resulting material is often affected by specific attractive interactions occurring between them. The most common types of specific interactions are electrostatic attraction and hydrogen bonding. Electrostatic attraction may occur in combinations of oppositely charged polyelectrolytes and typically results in formation of interpolyelectrolyte complexes (Mustafin, 2011). Hydrogen-bonded interpolymer complexes (IPC) are commonly formed as a result of interactions between polycarboxylic acids, acting as proton donors, and non-ionic water-soluble polymers, exhibiting proton-accepting properties (Bekturov and Bimendina, 1981; Kemenova et al, 1991; Khutoryanskiy, 2007; Kharlampieva et al, 2009).

Poly(2-oxazolines) is an interesting class of functional materials, which is represented by several polymers soluble in water (e.g. poly(2-methyl-2-oxazoline), poly(2-ethyl-2-oxazoline), poly(n-propyl-2-oxazoline, etc). The synthesis of these polymers was first described in the 1960s; however, they received recognition as highly promising biomedical materials only in the last decade (Hoogenboom, 2009; Viegas et al, 2011; Luxenhofer et al, 2012; de la Rosa, 2014; Hoogenboom and Schlaad, 2017; Lorson et al, 2018). Numerous recent studies reported the use of poly(2-oxazolines) in the design of micellar structures for drug delivery (Hruby et al, 2010), vectors for gene therapy (Lehner et al, 2017), hydrogels (Farrugia et al, 2013), polymer-drug/protein conjugates (Mero et al, 2008), and mucus-penetrating nanoparticles (Mansfield et al, 2015; Mansfield et al, 2016). Polyoxazolines are generally non-toxic, biocompatible, and bioinert, which makes them highly promising for various biomedical applications. These polymers are often viewed as an alternative to polyethylene glycols (Bludau et al 2017; Khutoryanskiy, 2018).

Water-soluble poly(2-oxazolines) exhibit a number of interesting physicochemical properties such as temperature-responsive behaviour (Christova et al, 2003; Diehl and Schlaad, 2009; Ambreen and Siddiq, 2014) and proton-accepting ability that facilitates their interactions with proton-donating polymers (Kim et al, 2002). These properties have been successfully utilised in the development of self-assembled materials such as micelles (Filippov et al, 2017), interpolymer complexes and polymeric blends (Dai et al, 1994; Isasi et al, 1996; Kim et al, 2002), and multi-layered constructs (Su et al, 2017; Su et al, 2018).

The application of poly(2-oxazolines) in the design of solid dosage forms for drug delivery has also received recent interest, but it is still studied insufficiently (Claeys et al, 2012; Policianova et al, 2014; Fael et al, 2018). Recently, interpolymer complexes and physical blends of poly(2-ethyl-2-oxazoline)s and two Carbopol® grades (Carbopol® 974 and Carbopol® 971) were reported for the development of mucoadhesive tablets for buccal delivery of hydrocortisone (Ruiz-Rubio et al, 2018). It was demonstrated that the interaction between these polymers is pH-dependent and the behaviour of tablets is strongly affected by the interactions between the polymers. Taking the pH-responsive nature of these complexes they could also be of interest as materials for oral drug delivery, where a dosage form will experience different pH environments during its transit through gastrointestinal tract.

In the present study the complexation between Carbopol® 971 and poly(2-ethyl-2-oxazoline) of different molecular weights was explored both in solutions and in solid state. The effect of solution pH on the complexation between polymers was explored and the critical pHs of complexation were determined. The structure of interpolymer complexes in solid state was studied by elemental analysis, FTIR spectroscopy and differential scanning calorimetry. Solid compacts composed of either IPCs or physical mixtures (PMs) were studied in the media mimicking different parts of gastrointestinal tract. These solid materials were used to formulate a model drug mesalazine relevant for gastrointestinal drug delivery and its release from the dosage forms was studied in vitro.

2. Materials and Methods

2.1. Materials

Poly(2-ethyl-oxazoline)s (5000, 50000, 500000 g mol^{-1}; named as POZ 5 kDa, POZ 50 kDa and POZ 500 kDa in the text, respectively) were purchased from Sigma-Aldrich (Irvine, UK) and Carbopol® 971 (weakly cross-linked, 4000-11000 cP, 3000 kDa) (named as C971 in the text), was generously donated by Lubrizol Advanced Materials (Wickliffe, OH, U.S.A.). Potassium dihydrogen phosphate, hydrochloric acid and sodium hydroxide were provided by Sigma-Aldrich (Irvine, UK) and used for preparing the media mimicking conditions of gastro-intestinal tract. Mesalazine (5-aminosalicylic acid, 5-ASA) was purchased from Sigma-Aldrich (Irvine, UK). A Milli-Q water purification system from Millipore (Bedford, MA, U.S.A.) was used for preparation of all solutions.

2.2. Methods

2.2.1 IPC formation

Aqueous mixtures were prepared by mixing 0.002 unit-mol/L individual polymer solutions in deionized water. Solutions were mixed to give different unit molar ratios of the polymer components. The obtained interpolymer complexes (IPCs) were left for 1 hour in the media, and then turbidity of all solutions was measured spectrophotometrically (Lambda 25, Perkin Elmer, Norwalk, CT, U.S.A.) at 400 nm. The complexation between C971 and POZ was initially evaluated in water without adjusting the pH.

For pH_{crit} determination, samples were typically analyzed in solutions, whose pH ranged from 3.0 to 8.0, which was adjusted by adding small portions of 0.1 M NaOH or 0.1 M HCl. The pH measurements were performed using a portable pH meter Orion Star A 325 (Thermo Scientific, U.S.A.) with Orion™ ROSS Ultra™ low maintenance pH/ATC Triode™ (Thermo Scientific, U.S.A.). The turbidity of these solutions was measured at 400 nm using a UV/Vis-spectrophotometer (Lambda 25, Perkin Elmer, Norwalk, CT, U.S.A.). Turbidity readings were taken immediately after adjusting pH. All experiments were repeated in triplicate, and the turbidity values are reported as mean ± standard deviation.

The composition with the maximal turbidity was selected for the tablet formulation. IPCs were prepared by mixing 0.1 M POZ and 0.125 M C971 solutions in acetate buffer (pH=3.5) and at constant temperature. After isolation of the precipitates from the solutions, they were washed twice with demineralized water and the IPCs were subsequently freeze-dried for 2 days at -27 °C (Labconco® Freeze Dry System, FreeZone 1 L, MO, U.S.A.). The dried IPCs were ground with A 11 basic grinder (IKA® Werke GmbH, Staufen, Germany) and used for further study. The samples were stored in tightly sealed containers at room temperature.

2.2.2. Transmission electron microscopy (TEM)

TEM images of IPC were acquired using a JEM 2100 plus TEM (Jeol Ltd., Watchmead England) at 200 kV. For sample preparation, the copper grids were brought in contact with dispersions of IPC for 30 s and then dried off with a filter paper. The pH of polymer mixtures in aqueous solutions prior to TEM examination was adjusted by adding small amounts of 0.2 mol/L HCl or NaOH and was measured using a digital pH-meter (Metrohm, Herisau, Switzerland).

2.2.3. Elemental analysis

The composition of freeze-dried IPC (C971/POZ 50 kDa and C971/POZ 500 kDa) samples and physical mixture (PM) samples before, during, and after swelling testing were investigated by elemental analysis using a Thermo Flash 2000 CHNS/O elemental analyzer (Thermo Fisher Scientific, Paisley, UK). PMs were prepared by mixing C971 and POZ powders at 1.25:1 molar ratio.

2.2.4. Fourier transform infrared spectroscopy (ATR-FTIR)

ATR-FTIR-spectra were recorded using a Nicolet iS5 FTIR spectrometer (Thermo Scientific, Waltham, MA, U.S.A.). The untreated freeze-dried samples of solid IPC (C971/POZ 50 kDa and C971/POZ 500 kDa) and PM samples before, during, and after swelling testing were directly mounted over the iD5 smart single bounce ZnSe ATR crystal. The spectra were analyzed using OMNIC spectra software.

2.2.5. Thermal analysis

Modulated DSC (mDSC) measurements were carried out using a Discovery DSC™ (TA Instruments, New Castle, DE, U.S.A.), equipped with a refrigerated cooling system (RCS90). TRIOSTM software (version 3.1.5.3696) was used to analyze the results (TA Instruments, New Castle, DE, U.S.A.). Tzero aluminum pans (TA Instruments, New Castle, DE, U.S.A.) 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 at 50 mL/min was used as a purge gas through the DSC cell. Indium and n-octadecane standards were used to calibrate the DSC temperature scale; enthalpic response was calibrated with indium. The modulation parameters used were: 2 °C/min heating rate, 40 s period and 1 °C amplitude. Calibration of heat capacity was done using sapphire. Samples were analyzed from 0 to 200 °C.

2.2.6. Preparation of Tablets

To determine the degree of swelling, flat-faced tablets of 100 mg polymer carrier were prepared by compressing the given amount of powders (C971, POZ 50 kDa, POZ 500 kDa, PMs, and IPCs) in a hydraulic press (Perkin Elmer, Waltham, MA, U.S.A.), equipped with flat-faced punches with 13 mm diameter (Pike Technologies, Madison, WI, U.S.A.) with a compression pressure of 6.24 MPa. For dissolution testing, 150 mg biconvex tablets (100 mg 5-ASA and 50

mg polymer carrier) with 6 mm diameter were prepared by compressing the given amount of the polymer carriers at 6.24 MPa using a hydraulic press (Perkin Elmer, Waltham, MA, U.S.A.).

2.2.7. Determination of the Degree of Swelling of Matrices

Swelling was investigated under conditions, mimicking the gastro-intestinal tract (GIT): the first two hours in simulated gastric medium (0.1 M HCl; pH 1.2), then four hours in simulated intestinal medium (phosphate buffer; pH 6.8).

2.2.7.1. Gravimetric measurements

The polymer matrices (d=13 mm) were placed in a tarred basket (from USP I apparatus), which was immersed into a thermostatted bath at 37.0 ± 0.5 °C on IC control eco 18c (IKA® Werke GmbH, Staufen, Germany). The volume of the medium was 100 mL. The basket was removed from the medium every 15 min within the first hour and then every 30 min; the tablets were carefully dried using a filter paper and weighed. The degree of swelling (H, %) was calculated using the following equation:

$$H_{\%} = (m_2 - m_1 / m_1) \times 100,$$

where m_1 is the weight of the dry sample and m_2 is the weight of the swollen sample.

2.2.7.2. Image analysis

The polymer matrices (d=13 mm) were placed into petri dishes with 40 mL of the medium preheated to 37.0 ± 0.5°C. The petri dishes with matrices were removed from thermostatted bath every 1 hour, placed on a graph paper and changes in the sizes of the matrices were measured.

2.2.8. Release of mesalazine (5-ASA) from the polymer matrices in GIT mimicking conditions

The release of 5-ASA from the matrix tablets was performed under sink conditions at 37.0 ± 0.1 °C using the USP I Apparatus (the off-line dissolution tester DT 828 with an auto sampler ASS-8, a fraction collector FRL 824 and a peristaltic pump ICP-8 (Erweka, Heusenstamm, Germany)). The basket rotation speed was 100 rpm and the volume of the medium was 900 mL. The release was investigated for 6 h under GIT mimicking conditions, where the pH of the release medium was gradually increased: 2 h in 0.1 M hydrochloric acid (pH = 1.2) and then in phosphate buffer solution (pH = 6.8) until the end of experiment. Aliquots (5 mL) of solution were automatically taken at specific time intervals, and the volume of medium was

made up to the original value by adding fresh dissolution medium. The amounts of 5-ASA released in the dissolution medium were determined by UV/Vis-spectrophotometry at 302 nm (at pH=1.2) and 330 nm (at pH=6.8), respectively (Lambda 25; Perkin-Elmer, Waltham, MA, U.S.A.). Results are given as the mean values of three determinations ± standard deviations. Release rates (RR) were determined by calculating the slopes of the released 5-ASA (%) vs time profiles in the first 120 min of experiment.

Results and Discussion

3. Formation of interpolymer complexes in aqueous solutions

Simple mixing of 0.002 unit-mol/L aqueous solutions of C971 and POZ (without adjustment of pH) at room temperature results in immediate appearance of turbidity, which was used to estimate the compositions of IPCs formed. **Figure 1** presents the turbidity data for the polymers mixed at different molar ratios. It is widely recognised that the maximal values of turbidity generally correspond to the compositions of IPC (Satoh et al, 1989; Takayama et al, 1990; Moustafine et al, 2006). POZ 50 kDa exhibited greater ability to increase the turbidity of solution mixtures with the maximal values observed at [C971]:[POZ]=1.25:1 mol/mol. Similar trend is observed for POZ 500 kDa; however, its turbidity is significantly lower ($p<0.005$). POZ 5 kDa exhibited much lower ability to increase the solution turbidity in mixtures with C971.

(Figure 1 is here).

It could be anticipated that these polymers should form 1:1 complexes, i.e. one unionised carboxylic group of C971 forms hydrogen bond with one proton-accepting nitrogen according to the proposed scheme (**Figure 2**). A deviation from 1:1 ratio observed in our experiments could be related to two factors: (1) a weakly cross-linked nature of C971, which results in steric hindrances and not complete availability of carboxylic groups of polyacid to interact with POZ; (2) under the pH conditions of this experiment not all carboxylic groups of C971 are non-ionised and capable of forming hydrogen bonds with POZ. This result agrees with the previous studies of C971 – POZ complexes using gravimetric analysis (Ruiz-Rubio et al, 2018).

(Figure 2 is here)

Previously, Khutoryanskiy and co-workers (Mun et al, 2000; Nurkeeva et al, 2003; Khutoryanskiy et al, 2004a; Khutoryanskiy et al, 2004b; Nurkeeva et al, 2005; Zhunuspayev

et al, 2008) have demonstrated that the complexation between poly(carboxylic acids) and non-ionic polymers is facilitated under acidic conditions and formation of colloidal IPCs is typically observed below a certain critical pH of complexation (pH_{crit}). pH_{crit} values were proposed as a criterion for the ability of a given pair of polymers to form hydrogen-bonded IPCs: greater pH_{crit} indicated a stronger ability of polymers to form complexes. To the best of our knowledge, the data on pH_{crit} of complexation involving poly(2-oxazolines) is still very limited in the literature. Su et al (2017) recently reported that the thickness of miltilayered films, formed using layer-by-layer deposition of poly(acrylic acid) (PAA) and POZ onto a solid substrate, showed a pH dependence, typical for hydrogen-bonded IPCs: a rapid increase in the film thickness is observed upon decrease in pH in the 3.5-4.0; above pH 4.0 the films did not form. The authors assigned the pH 3.5-4.0 to the critical pH of complexation between these polymers. In the present work the critical pHs were determined for Carbopol® 971 – POZ complexes using turbidimetric technique. **Figure 3** shows the dependence of solution turbidity of 1:1 polymer mixtures as a function of pH. It is clearly seen that a decrease in solution pH results in a rapid increase in turbidity at pH 4.8±0.2, when POZ 50 kDa was used to form IPC. This is slightly larger than the pH_{crit} reported by Su et al (2017) for complexes of POZ 50 kDa with PAA, but the discrepancy may be related to the difference in the methods used to determine pH_{crit} (film formation vs turbidimetric studies) and also the weakly cross-linked nature of Carbopol® 971 compared to PAA.

(Figure 3 is here)

POZ with lower (5 kDa) and larger (500 kDa) molecular weights show their pH_{crit} around 4.2-4.5 (no significant difference between pH_{crit} for 5 kDa and 500 kDa ($p>0.05$), but significantly lower than pH_{crit} for 50 kDa ($p<0.05$)). It is well known from the literature (Mun et al, 2000; Nurkeeva et al, 2003; Khutoryanskiy et al, 2004a; Khutoryanskiy et al, 2004b; Nurkeeva et al, 2005) that increase in molecular weight of the polymers typically leads to increase in pH_{crit}. An anomalous lower complexation ability of POZ 500 kDa observed in experiments presented in Figure 1 (lower turbidity values) and also lower pH_{crit} values compared to POZ 50 kDa (Figure 2) is possibly related to extremely large length of POZ 500 kDa macromolecules that approach so-called upper limit in molecular weights of polymers, previously reported by Bekturov and Bimendina (1981).

A comparison of pH_{crit} values, previously reported for complexes of PAA and poly(N-vinyl pyrrolidone) pH_{crit}=4.85±0.05, poly(methyl vinyl ether) pH_{crit}=4.85±0.05, polyacrylamide

258 pH_{crit}=3.00 ± 0.05, poly(ethylene oxide) pH_{crit}=2.88 ± 0.05, poly(vinyl alcohol) pH_{crit}=2.67 ±
259 0.05 and some other polymers (Khutoryanskiy et al, 2004a), with the values determined for
260 POZ in the present work allows to conclude that poly(2-ethyl-2-oxazoline) exhibits strong
261 complexation ability. This ability to form IPCs is comparable with poly(N-vinyl pyrrolidone)
262 and poly(methyl vinyl ether). It should be noted that in the current study we used polymer
263 concentrations of 0.01 unit-mol/L similar to the measurements reported by Khutoryanskiy et
264 al (2004a); however, the difference in the two studies is in the use of Carbopol® 971 (weakly
265 cross-linked PAA, 3000 kDa) and linear PAA 450 kDa.

266 In order to get an insight into the changes in the structure of IPCs at different pHs
267 transmission electron microscopy (TEM) was used (**Figure 4a**). This experiment provides an
268 excellent opportunity to see the evolution of IPC structure upon gradual decrease in solution
269 pH. At pH 4.79, which is very close to pH_{crit} the structure of IPC looks like a network of fibrous
270 material with the presence of some very small particles (18±6 nm). Upon decrease in pH to
271 4.54 these particles become larger and denser (41±4 nm), but still are surrounded and connected
272 to each other by fibrous material, which is possibly made of not fully complexed
273 macromolecules. Under strongly acidic conditions the dense particles of IPC are fully formed;
274 they are not stabilised by uncomplexed macromolecules and their size reaches 649±185 nm
275 (pH 2.14) and 513±92 nm (pH 2.50). Very similar structural changes at different pHs were
276 reported previously for the IPC formed by PAA and methylcellulose (Khutoryanskaya et al,
277 2007). The proposed mechanism of IPC formation at different pHs is shown in **Figure 4b**.

278 **(Figure 4 is here)**

279 *4. Physicochemical studies in solid state*

280 *4.1.Fourier transform infrared spectroscopy (ATR-FTIR)*

281 ATR-FTIR spectrum of pure POZ independently from its molecular weight is characterized
282 by the presence of a stretching band of amide I at 1635 cm^{-1}. For C971, the band corresponding
283 to the self-associated carboxylic group (COOH) is located at 1703 cm^{-1} (Nguyen et al., 2016;
284 Ruiz-Rubio et al., 2018; Garipova et al, 2018). Clearly, the presence of POZ and C971 in the
285 spectrum of the polymer mixture (PM) is indicated by their characteristic peaks with high
286 intensities, such as the peak of the carboxyl stretching band of C971 (1705 cm^{-1}) and a
287 "shoulder" of amide I of POZ (1635 cm^{-1}). In the IPC, a shift of the C=O bands could be
288 observed to 1720 cm^{-1}, while the amide I band shifts to 1600 cm^{-1}. These bands are related to
289 hydrogen bond formation between carboxyl groups of C971 and amide groups of POZ.

(Figure 5 is here)

4.2. Thermal analysis

Figure 6(a, b) shows the DSC thermograms of C974, POZ 50 kDa (a), POZ 500 kDa (b), their PMs and IPCs. Carbopol 974 presents a *Tg* at 132.6 ^{o}C, whereas the *Tg* of POZ 50 and POZ 500 kDa are detected at 51.7 and 56.2^{o}C, respectively. The presence of two unchanged *Tg* values in the PM prepared from C971 and both POZ samples (50 and 500 kDa) is indicating a phase separation of the polymers, i.e., confirmed that they were not molecularly miscible (Moustafine et al., 2011, 2013). The IPCs of these polymers present an intermediate glass transition of 128.3-128.9 ^{o}C, similar to the changes observed in other IPCs and IPECs formed via hydrogen and ionic bonding, respectively (Khutoryanskiy et al, 2004b; Khutoryanskiy et al, 2004c; Ruiz-Rubio et al., 2018; Mustafin, 2011; Mustafin et al., 2011, 2015; Moustafine et al., 2011, 2013).

(Figure 6 is here).

5. Swelling properties

Swelling of the matrices in the media mimicking the gastrointestinal tract indicate that the compacts based on POZ 50 kDa and POZ 500 kDa completely dissolved at the end of the first hour (**Figure 7**). Matrices from C971 showed the highest values in swelling estimated by both methods (**Figure 8a, b**). During swelling, the matrices separated into two clearly visible layers, transparent external gel and non-hydrated white core. We believe that the external layer is formed due to the hydration of macromolecules with ionized carboxyl groups, while the core is still containing the chains with protonated COOH groups. Physical mixtures with POZ 50 kDa (PM-1) and POZ 500 kDa (denoted as PM-2) show the values of matrix size similar to C971, but characterized by gradual release of POZ, localized in the external layer of the matrices in buffer medium. On the contrary, the swelling profiles of PM-1 and PM-2 are similar to each other only in acidic medium and have different character in the buffer at pH 6.8. The PM matrices based on POZ 50 kDa have two times lower swelling index in the buffer medium, compared to the swelling profile of PM with POZ 500 kDa. Moreover, in the case of two PM samples containing POZ with different molecular weight a stable swelling profile was observed only in the case of PM-1, relatively independent of the medium. PM-2 had a swelling profile similar to the matrices composed of pure C971, but with three times lower swelling degree as compared to the pure Carbopol®. These observations are believed to be resulting from hydrogen bonding effect between these polymers, which was probably happened within PM matrices under acidic conditions.

(Figure 7 is here)

Upon swelling, the polycomplex matrices showed the smaller dimensions, which means lower swelling ability. Additionally, the swelling profiles of IPC matrices showed similar character, but different swelling ability: in case of IPC formed with POZ 500 kDa the maximal swelling was approximately two times greater compared to the IPC with POZ 50 kDa. So, only PMs and IPCs with POZ 50 kDa show the most stable profiles with the lowest swelling degree, but in case of PM it has three times lower degree of swelling. The formulations consisting of proton-accepting non-ionic polymers (PVP, PEO, HPMC, HPC, MC, etc.) and proton-donating polycarboxylic acids – (polyacrylic / polymethacrylic acids, Carbopol® grades) could form IPCs under acidic pH and their swelling and drug release properties are controlled by three-dimensional network structure, which was formed as a result of complex formation between the polymers following water penetration into the matrix (Takayama and Nagai, 1987; Satoh et al., 1989; Ozeki et al., 1998a, 1998b, 1999, 2000, 2005; Tan et all., 2001).

(Figure 8 is here)

For further analysis the matrices with gel layers and non-hydrated cores were taken out from the dissolution baskets in GIT- mimicking media at different time intervals (0, 2 and 6 h); their gel layers and non-hydrated cores were physically separated and freeze-dried. The algorithm of their physicochemical analysis is schematically illustrated in **Figure 9**.

(**Figure 9 is here)**

ATR-FTIR spectra (**Figure 10**) were recorded to gain a deeper insight into the spatial distribution of the macromolecules and their interactions in the matrix tablets containing PM based on POZ and C971 following their hydration. In the intact interpolymer complex, a shift of the C=O bands is observed to 1720 cm^{-1}, while the amide I band shifts to 1600 cm^{-1}. These bands are related to hydrogen bonding between carboxyl groups of C971 and amide groups of POZ.

(Figure 10 is here)

During the first 2 h in pH 1.2, the monolith polycomplex matrix has the composition similar to IPC without any differences in FTIR spectra and *Tg* values; however, there is a slight change in the composition of IPC from C971/POZ 1.4:1 into 1.5:1. During the swelling for 4 h in the buffer solution (pH 6.8), the gel layer is formed that is composed of mainly C971 in its ionized hydrated form (appearance of a new band at 1557 cm^{-1}). In contrast, the amount of

POZ (according to the elemental analysis results, presented in **Table 1**) in the gel layer within 4 h (pH 6.8) is decreased and reached 2.7:1 C971/POZ molar ratio. This is also evidenced by the presence of amide I stretching at 1633 cm^{-1} and the individual *Tg* value assigned to the pure POZ at 45.1±0.8 ºC. Moreover, an increase in the *Tg* values from 125.2±0.3 to 127.9±0.7 ºC and observed shifts of the characteristic bands at 1600 to 1606 cm^{-1} are related to the presence of hydrogen bonds between amide groups of POZ and carboxyl groups of C971; however, some segments of the IPC contain partly ionized COO^- groups leading to dissociation of some interpolymer bonds. On the contrary, the non-hydrated core of IPC matrices still consists of the polycomplex structure, whose composition is close to the original IPC and IPC monolith matrix taken after its exposure to the acidic medium (pH 1.2). This result agrees with our studies using TEM technique.

(Table 1 is here).

The swelling behavior of PMs was found to be completely different from the tablets based on IPCs. Clearly, POZ and C971 dispersed uniformly in the intact tablet prior to hydration, as reflected by the presence of their characteristic peaks with high intensities in the spectrum of PM, such as the peak of the carboxyl stretching band of C971 (1704 cm^{-1}) and a "shoulder" of amide I of POZ (1633 cm^{-1}). According to above discussed mechanism of IPCs formation and also the literature data (Takayama and Nagai, 1987; Satoh et al., 1989; Ozeki et al., 1998a, 1998b; Tan et al., 2001; Zhang et al., 2016a, 2016b; Yusif et al., 2016; Szakonyi and Zelko, 2016, Nguyen et al., 2016), the passage of the tablets through pH 1.2 media facilitates strong interaction between the polymers. However, the spectral and thermal analysis results did not provide any evidence for the complexation under these conditions: the band corresponding to the self-associated carboxylic groups (COOH) located at 1704 cm^{-1} showed a very minor shift to 1707 cm^{-1} and the presence of amide I stretching was observed at 1622 cm^{-1}; *Tg* values at 51.7±0.9 ºC and 131.9±0.8 ºC observed are assigned to the pure POZ 50 kDa and C971, respectively. Moreover, some amount of pure POZ 50 kDa is leaching from the matrices, so the composition of mixture is changed from C971/POZ 1.4:1 to 2.2:1.

During 4 h swelling of PM-1 in pH 6.8, the matrix composition becomes different to the composition of IPC. As it is seen from the data presented in **Fig. 10** and **Table 1**, PM-1 with POZ 50 kDa tablets completely transformed to the transparent gel with maximal gel-forming capacity, which is clearly visible compared to pure C971 matrix. Additionally, in the ATR-FTIR spectrum of the freeze-dried gel layer (formed during 4 h swelling) the peak at

1704 cm^{-1}, corresponding to the carboxylic groups of C971, disappeared and was replaced by a new band at 1556 cm^{-1} assigned to the carboxylate ion (COO^-). These findings indicated that the carboxylic groups in C971 were ionized when it came to contact with pH 6.8 buffer. This is also confirmed by higher *Tg* value (145.7±0.7 ºC) assigned to the ionized C971 that is in good agreement with literature (Gomez-Carracedo et al., 2004). POZ was also present in the gel layer: the peak at 1630 cm^{-1} corresponding to the amide I stretching and somehow higher *Tg* value (59.4±0.9 ºC) were assigned to POZ. At 4 h in pH 6.8 (with a total swelling time of 6 h), the gel layer lost substantial amount of POZ, as confirmed by remarkable change in C971/POZ composition from 1.4:1 to 5.8:1. So, the leaching of pure POZ from the gel layer is evident. The diffusion of POZ from the gel layer led to increase in the diffusional path length of the matrix, by which the drug release rate could be sustained (Ruiz-Rubio et al., 2018).

POZ was predominantly present in the non-hydrated core at 4 h of swelling, evidenced by a strong band at 1627 cm^{-1}. In particular, the peak at 1704 cm^{-1} assigned to the self-associated carboxylic groups of C971 exhibited a gradual increase in the intensity with time and shifted to 1715 cm^{-1} corresponding to the carbonyl C=O stretching vibrations bands (Takayama and Nagai, 1987; Satoh et al., 1989; Ozeki et al., 1998a, 1998b, 1999, 2000, 2005). At 6 h of swelling, the non-hydrated core was completely transformed into hydrated form: *Tg* value assigned to POZ at 45.2±0.7 ºC and slightly ionized C971 at 140.4±0.9 ºC. Composition of the material after complete hydration also changed from C971/POZ 1.4:1 to 2.4:1.

In addition, a frequency shift in the peak assigned to the amide I stretching group of POZ in the gel layer and non-hydrated core at 6 h of swelling changed from 1633 cm^{-1} to 1600 cm^{-1} and appearance of characteristic *Tg* value at 125.2±0.3 ºC, typical for strong hydrogen bonding between POZ and C971 were not observed.

6. Drug release studies

Mesalazine (5-ASA) is an anti-inflammatory drug that is used to treat some conditions of gastrointestinal tract, for example, inflammatory bowel disease (Quinteros et al, 2010). 5-ASA was used in this work as a model drug. The release of 5-ASA from the matrices was evaluated under GIT mimicking conditions. **Figure 11** shows the dissolution profiles from the matrices based on C971 as well as their IPCs and PMs with POZ. Drug released faster from the matrices composed of pure POZ (RR=0.8513 %/min and 0.6665 %/min for 50 and 500 kDa POZ, respectively) and IPCs (RR=0.3676 %/min and 0.9016 %/min for 50 and 500 kDa POZ, respectively) compared to pure C971 (RR=0.1644 %/min) and PMs (0.1017 %/min and 0.1610

%/min for 50 and 500 kDa POZ, respectively). Moreover, IPCs with POZ 500 kDa show faster release in acidic medium compared to all other samples. Additionally, the whole release process for this IPC is finished during the first 2 h in acidic medium. Understanding of this observation could come from our TEM results and evaluation of the swelling data. According to TEM data, under strongly acidic conditions the dense IPC particles with POZ 500 kDa are formed and their size reaches 649±185 nm (pH 2.14). Thus, in our release media (pH 1.2) the IPC particles became bigger that leads to formation of greater pores in the system compared to the IPC formed with POZ 50 kDa. Further evidence comes from the swelling properties of polycomplex matrices. The swelling index, estimated by two methods shows that IPC with POZ 500 kDa matrices exhibits greater swelling at pH 1.2 compared to IPC with POZ 50 kDa due to the formation of compact monolith structure with much lower porosity. Moreover, the observed phenomena also indicate that POZ is predominantly present on the surface of microgels formed from weakly cross-linked C971.

Despite that diffusion of POZ 500 kDa from non-hydrated core to the gel layer may be slower due to its high molecular weight, compared to PM made from POZ 50 kDa, drug release process may proceed differently. It is known that hydrogen bonds in IPC matrices help increasing the gel strength to improve the release-retarding capacity of polymer matrix (Tan et al., 2001; Zhang et al., 2015, 2016; Yusif et al., 2016; Szakonyi and Zelko, 2016, Nguyen et al., 2016). Thus, in case of some proton-accepting non-ionic polymers (e.g. hydroxypropyl cellulose, HPC) and polycarboxylic acids (PAA or Carbopols), which could form IPC in acidic pH region and of course, in typical dissolution media, the release of drugs is controlled by the three-dimensional network structure, which is affected by complex formation between these polymers following water penetration into the matrix (Satoh et al, 1989). If it can happen we will see a significant retardation of drug release, but mostly in the case of PM matrices and not for IPCs.

The release rate of 5-ASA greatly decreases when the matrix was composed of PM. According to the abovementioned explanation of the swelling results, the decrease in the release rate in this case could be due to the complexation between the polymers, which has happened inside the matrix during penetration of dissolution media, resulting in the formation of three-dimensional network. This leads to the formation of insoluble fibers in the matrix structure, which significantly retard the drug release process.

(Figure 11 is here)

Based on these results, the following explanation of drug release from IPC system could be proposed: in acidic medium, macromolecules of IPC swell significantly and 5-ASA partially dissolves from the surface of the matrix. The remaining amount of the undissolved drug after its transfer to another medium could continuously dissolve and diffuse from the swollen gel layer, that acts as a driving force for 5-ASA molecules. On the contrary, at pH 6.8, hydrogen bonds between POZ and C917 are dissociated due to gradual ionization of COOH groups of C971 and 5-ASA, leading to destruction of interpolymer contacts (according to FTIR and mDSC data). Together with release of free POZ macromolecules (according to elemental analysis data) this facilitates dissolution of 5-ASA. Hence, C971 was responsible for sustaining drug release during the first 2 h to prevent the initial burst release. POZ then diffused gradually from the non-hydrated core to the gel layer, decreasing the gel strength and resulting in the gradual destruction of hydrogen bonding interaction between POZ and C971. For this reason, the rate of 5-ASA release in this polymer system (mixture-loaded matrix) progressively increased at latter stages.

Additionally, drug release from different matrices could also be affected by specific interactions of mesalazine with C971 and POZ. As 5-ASA contains both proton-donating and proton-accepting groups in its structure, its interaction with Carbopols via ionic contacts (Quinteros et al, 2011) and with POZ via hydrogen bonding could not be ruled out completely. pH of dissolution medium is also expected to have effect on these interactions.

Conclusions

Formation of interpolymer complexes between Carbopol® 971 and poly(2-ethyl-2-oxazoline) of different molecular weights has been studied in aqueous solutions at different pHs. It was established that interpolymer hydrogen bonding is responsible for this complex formation; these interactions are possible only under acidic conditions. The evolution in the structure of the products of interpolymer interaction was studied in solutions with different pH. Upon a gradual decrease in solution pH the polymer mixtures evolved from completely non-interacting macromolecules to initial interpolymer associates, which then converted into primary compact IPC particles that were eventually transformed into spherical aggregates. Tablets were then prepared from interpolymer complexes and physical mixtures of Carbopol® 971 and poly(2-ethyl-2-oxazoline) with and without a model drug (mesalazine). The structure of these materials was evaluated using FTIR and differential scanning calorimetry methods as well as swelling studies in the media mimicking conditions of gastrointestinal tract. It was established

that the state of the polymers in the mixture and their swelling behavior is affected by the possibility of the complexation between them. The release of mesalazine from these tablets is also strongly influenced by the presence of interpolymer complexation. To the best of our knowledge, this is the first time when interpolymer complexes between Carbopol® 971 and poly(2-ethyl-2-oxazoline) were used to prepare solid dosage forms for gastrointestinal drug delivery. Potentially future research could compare poly(2-ethyl-2-oxazoline) with other non-ionic polymers capable of forming interpolymer complexes with Carbopol® 971 (e.g. polyvinylpyrrolidone and polyethylene oxide) to establish if it could offer any advantages as a novel pharmaceutical excipient.

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688

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695 **Figure 2.** Proposed scheme of complexation between Carbopol® 971 and POZ via hydrogen
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Figures

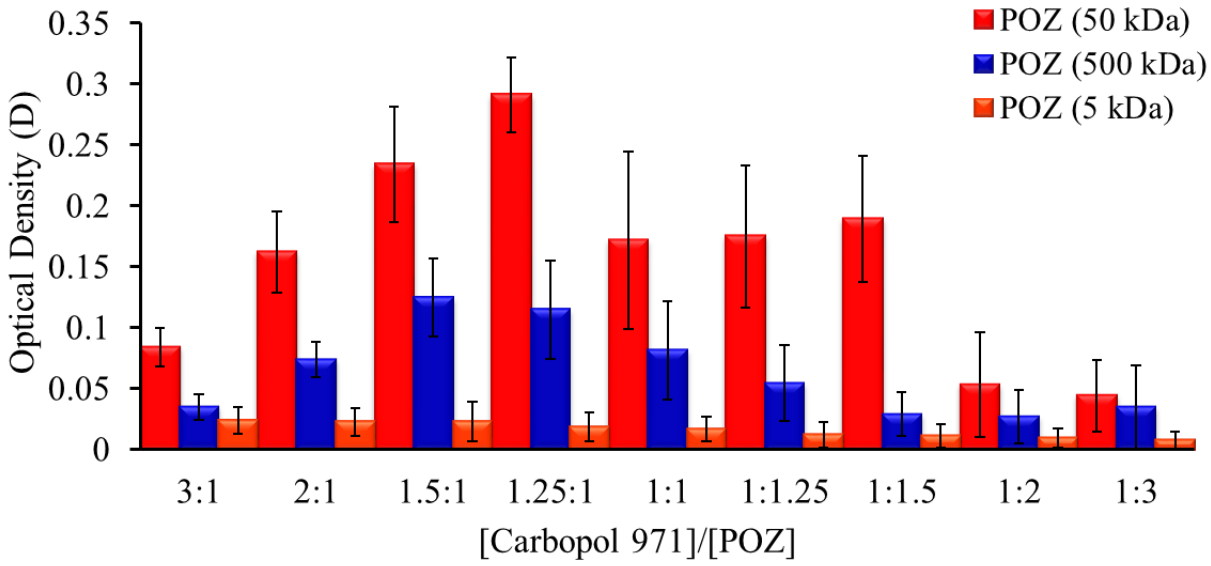


Figure 1. Turbidity of solution mixtures of Carbopol® 971 and POZ at different unit-molar ratios. Concentrations of Carbopol® 971 and POZ are 0.002 unit-mol/L.

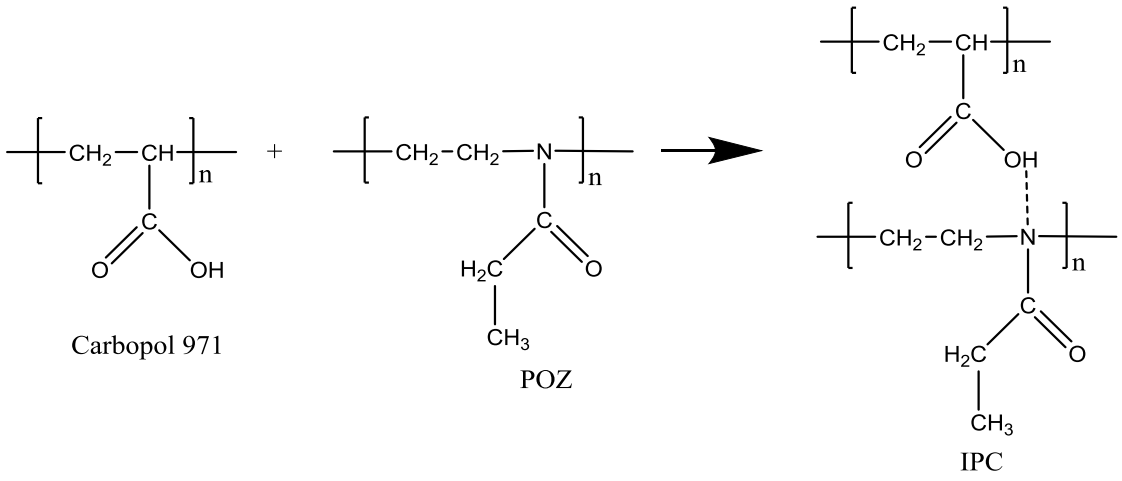
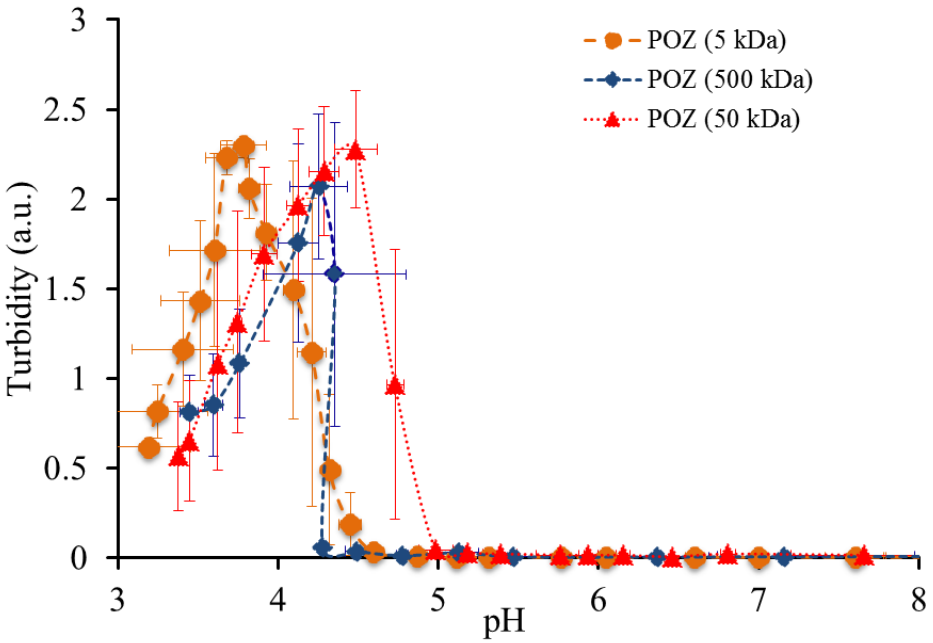


Figure 2. Proposed scheme of complexation between Carbopol® 971 and POZ via hydrogen bonding.



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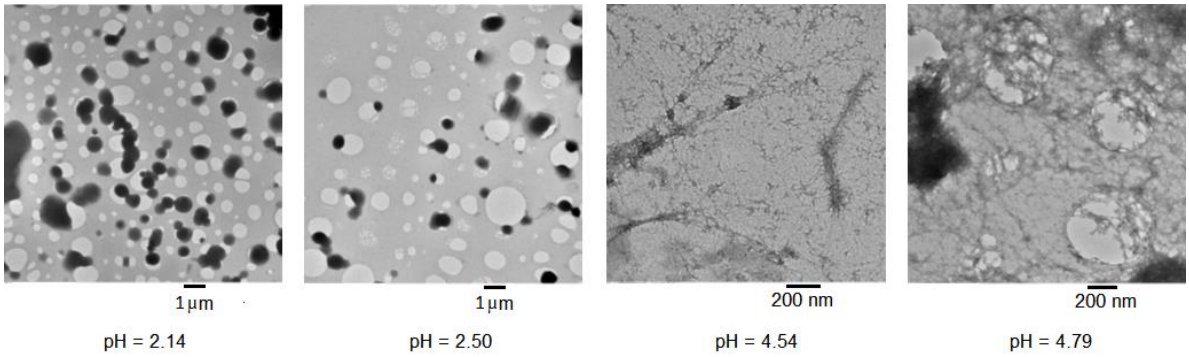
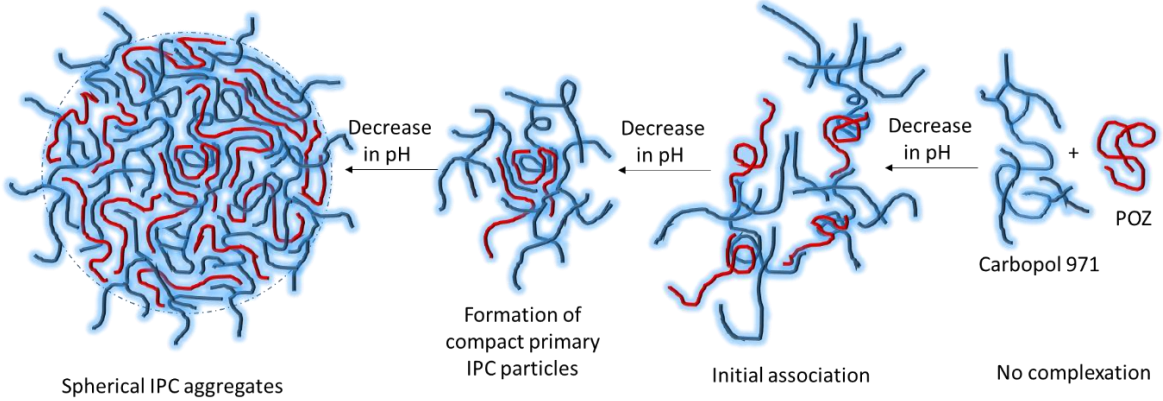
728 **Figure 3.** Turbidity of 1:1 unit-mol solution mixtures of Carbopol® 971 and POZ as a function
729 of pH. Concentrations of Carbopol® 971 and POZ are 0.01 unit-mol/L.

730



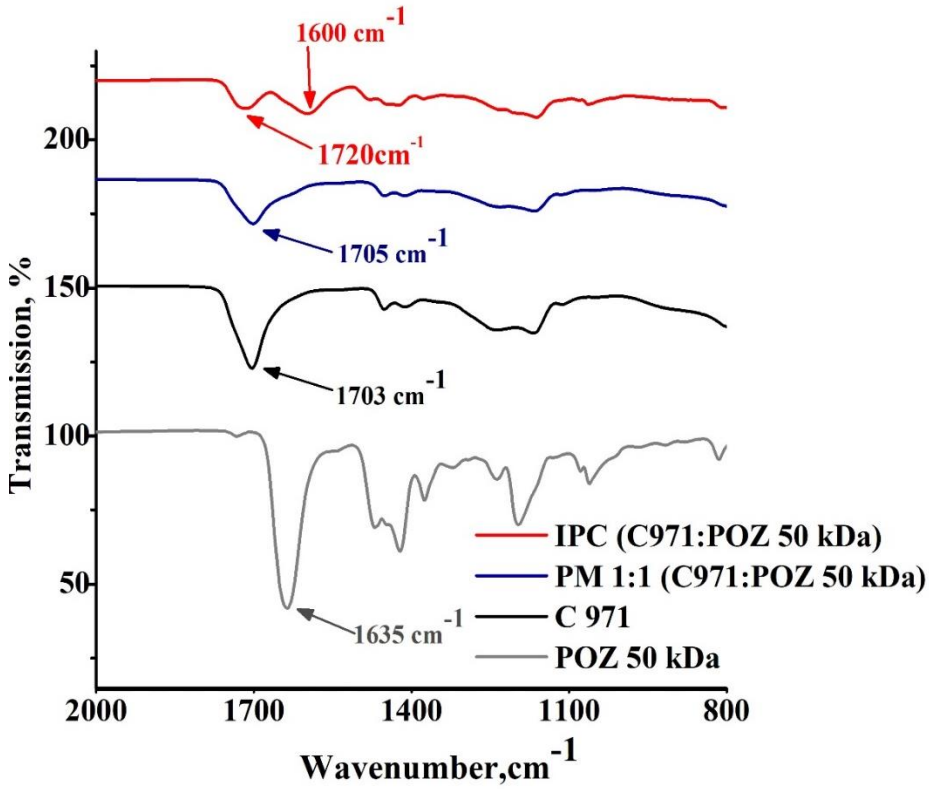
731
732 (a)



733
734 (b)

735 **Figure 4.** TEM images of IPCs prepared by mixing 0.01 unit-base mol/L solutions of
736 Carbopol® 971 and POZ (500 kDa) in 1:1 unit-base molar ratio and adjusting pH by addition
737 of HCl (a); Proposed mechanism of IPC formation at different pHs (b).

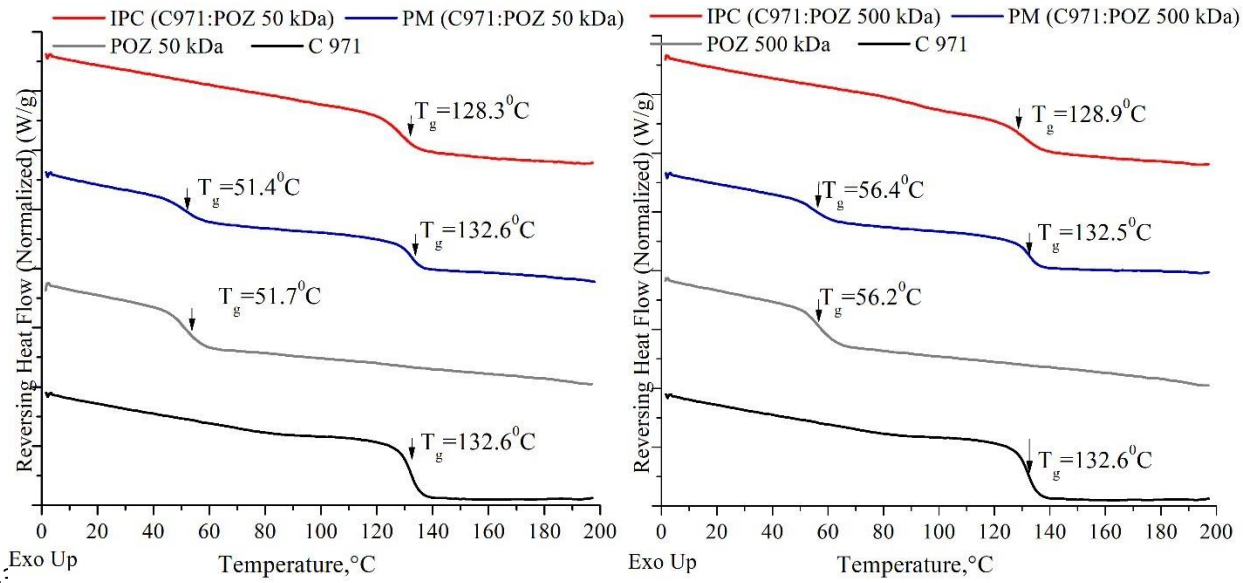
738



739

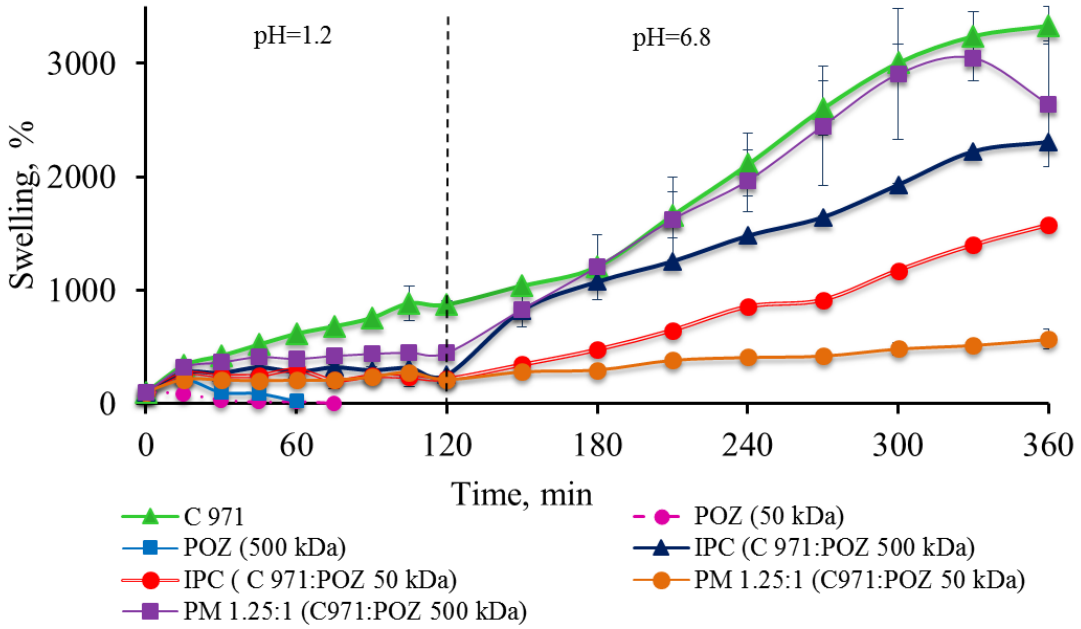
740 **Figure 5.** FTIR spectra of IPC (C971:POZ 50 kDa), physical mixture (C971:POZ 50 kDa),
741 and individual C971 and POZ 50 kDa.

742



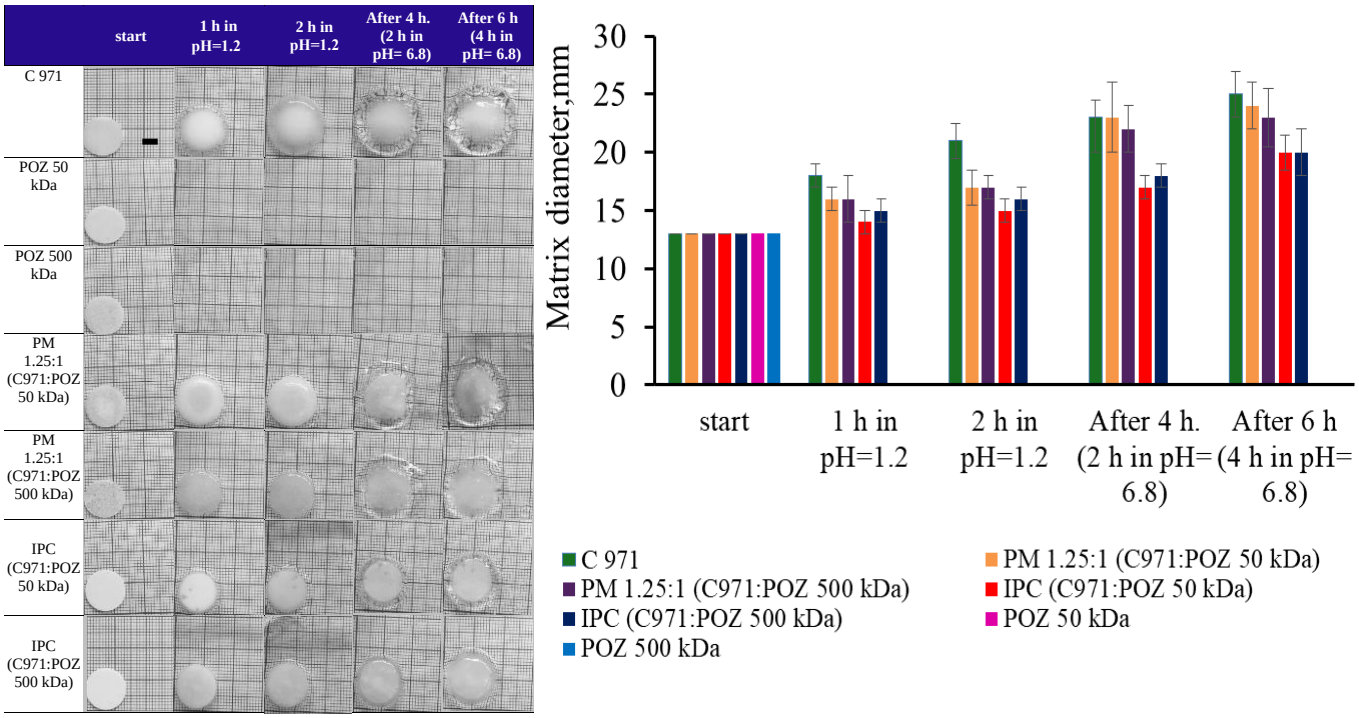
(a) (b)

Figure 6. DSC thermograms of: (a) IPC (C971:POZ 50 kDa); physical mixture (C971:POZ 50 kDa); C971; POZ 50 kDa, (b) IPC (C971:POZ 500 kDa); physical mixture (C971:POZ 500 kDa); C971; POZ 500 kDa.



754 **Figure 7.** Comparison of swelling profiles of different matrices in the media mimicking gastro-
755 intestinal tract conditions.

756



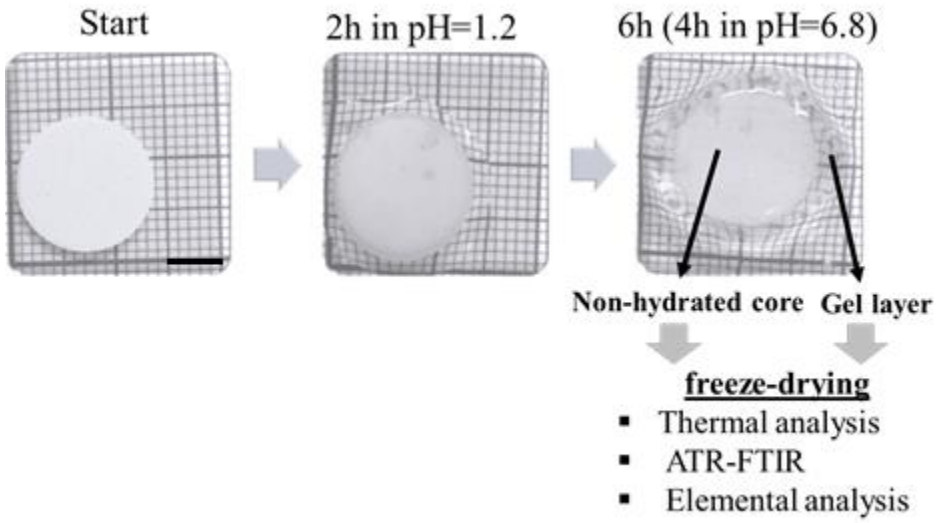
757

758 (a) (b)

759 **Figure 8.** Changes in the external appearance of different matrices during swelling test (a):
760 images and resulting matrix diameters generated through the image analysis (b). Scale bar is 5
761 mm

762

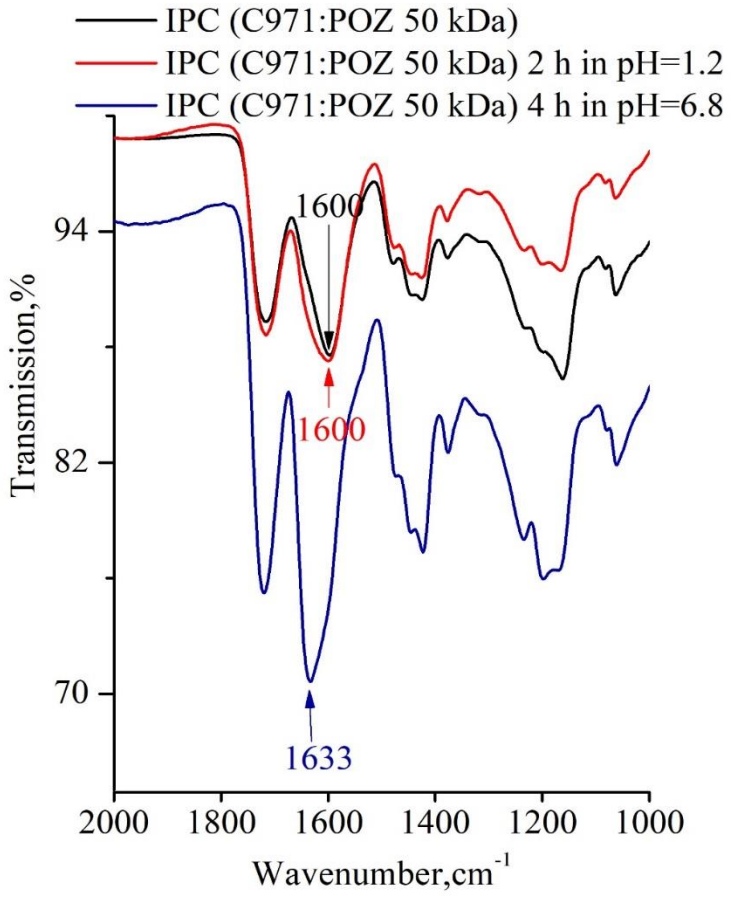
763



764

765 **Figure 9.** Schematic representation of the physicochemical analysis of samples after swelling
766 in the media mimicking gastro-intestinal tract conditions. Scale bar is 5 mm

767



768

769 **Figure 10.** FTIR spectra of IPC based on POZ 50 kDa and C 971 after swelling in the media
770 mimicking gastro-intestinal tract conditions.

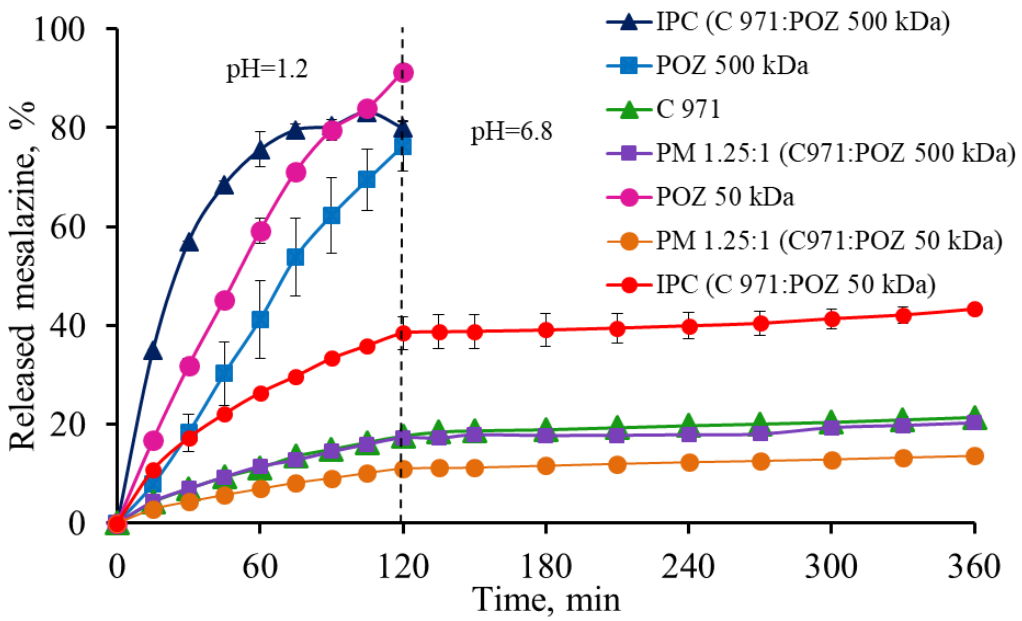


Figure 11. Release profiles of mesalazine from matrix systems under the conditions mimicking the gastro-intestinal tract.