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Interpolymer Complexes Based on Carbopol® and Poly(2-ethyl-2-oxazoline) as Carriers for Buccal Delivery of Metformin

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Abstract

Introduction. Buccal drug delivery has a number of advantages over oral administration: ease of application, good blood supply to the buccal mucosa, drug can enter the systemic circulation directly, avoiding the "first pass effect through the liver", and are not exposed to the acidic environment of the gastric juice and the destructive action of digestive enzymes. The use of interpolymer complexes (IPCs) makes it possible not only to ensure adhesion to the mucosal membranes of the oral cavity, but also to achieve a prolonged release of drugs.

Aim. Development of carriers based on interpolymer complexes using Carbopol® 971 NF (C971) and poly(2-ethyl-2-oxazoline) (POZ) of different molecular weights for buccal delivery of metformin (MF).

Materials and methods. The study of IPC adhesion was carried out using a TA.XTplus texture analyzer (Stable Micro Systems, UK); mucin compacts with a diameter of 13 mm were used as a substrate; these were prepared by compressing porcine gastric mucin powder using a manual hydraulic press for IR spectroscopy (PerkinElmer, USA) at a pressure of 2.45 MPa. The study of the swelling capacity was carried out by placing polymer matrices in an artificial saliva medium, with constant thermostating at a temperature of 37.0 ± 0.5 °C for 5 hours. The study of the release of MF from the matrices based on IPC was carried out using a DFZ II apparatus (Erweka, Germany) according to the Flow Through Cell method (USP IV) with cells for tablets (22.6 mm) and adaptors for ointments, creams and gels in a medium simulating saliva. The concentration of MF in the samples from the dissolution tests was determined with UV-spectrophotometry (Lambda, PerkinElmer, USA) at 232.8 nm.

Results and discussion. In a comparative study of the mucoadhesive properties of polymer samples, IPC compacts showed a mucoadhesion capacity comparable to that of poly(2-ethyl-2-oxazoline); at the same time, compacts from physical mixtures (PM) and C971 are inferior in terms of the separation force to IPC samples, however, POZes dissolve in an artificial saliva medium, that is, they are not suitable as dosage forms for buccal delivery. For 5 hours of the experiment to assess the swelling capacity, the IPC matrices did not change significantly, which can ensure their comfortable use as carriers for buccal delivery. When evaluating the release of metformin from polymer matrices (with weight ratio MF/IPC 1: 0.5), the most complete release (more than 90 %) is observed from both IPC matrices compared to matrices of PM and individual polymers.

Conclusion. Polycomplex matrix systems based on C971-POZ (50 kDa) and C971-POZ (500 kDa) are suitable for buccal delivery of metformin.

Keywords: interpolymer complexes, metformin, buccal delivery, polyoxazoline, adhesion.

Conflict of interest: no conflict of interest.

Contribution of the authors. Anastasia S. Viktorova, Elizaveta S. Elizarova and Regina S. Romanova have carried out the preparation of samples, evaluation of swelling and bioadhesive properties as well as experiments on drug release. Venera R. Timergalieva prepared and corrected the article. Vitaliy V. Khutoryanskiy and Rouslan I. Moustafine were responsible for conceptualization and research methodology, as well as reviewed and corrected the article. The article was written with the participation of all coauthors. All of the above authors agreed on the final version of the article.

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Интерполимерные комплексы на основе Carbopol® и поли(2-этил-2-оксазолина) как носители для трансбуккальной доставки метформина

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Резюме

Введение. Трансбуккальная доставка лекарственных веществ (ЛВ) имеет ряд преимуществ по сравнению с пероральным введением: удобство применения для пациента, хорошее кровоснабжение буккальной слизистой, ЛВ попадают непосредственно в системный кровоток, минуя «эффект первого прохождения через печень», а также не подвергаются воздействию кислой среды желудочного сока и разрушающего действия пищеварительных ферментов. Применение интерполимерных комплексов (ИПК) позволяет не только обеспечить адгезию к слизистым оболочкам ротовой полости, но и получить пролонгированное высвобождение ЛВ.

Цель. Разработка носителей на основе интерполимерных комплексов с участием Carbopol® 971 NF и поли(2-этил-2-оксазолина) разных молекулярных масс для трансбуккальной доставки метформина (МФ).

Материалы и методы. Исследование адгезии ИПК проводилось на анализаторе текстуры TA.XTplus (Stable Micro Systems, Великобритания), в качестве субстрата использовали компакты муцина диаметром 13 мм, полученные путем прессования на ручном гидравлическом прессе для ИК-спектроскопии (PerkinElmer, США) при давлении 2,45 МПа. Исследование набухающей способности проводили помещением полимерных матриц в среду искуственной слюны при постоянном термостатировании при температуре 37,0 ± 0,5 °С в течение 5 часов. Исследование высвобождения метформина из матриц на основе соответствующих ИПК производилось на приборе DFZ II (ERWEKA, Германия) по методу USP IV «Проточная ячейка» с использованием ячеек для таблеток (22,6 мм) и адаптеров для изучения высвобождения мягких лекарственных форм – ЛФ (мазей, кремов, гелей) в среде, имитирующей слюнную жидкость. Оценка количества высвободившегося МФ проводилась УФ-спектрофотометрически на приборе Lambda 25 (PerkinElmer, США) при длине волны 232,8 нм.

Результаты и обсуждение. При сравнительном исследовании мукоадгезивных свойств образцов полимеров компакты из ИПК показали сопоставимую с поли(2-этил-2-оксазолином (ПО) разных молекулярных масс (50 и 500 кДа) способность к мукоадгезии; в то же время компакты из физических смесей (ФС) полимеров и Carbopol® 971 NF (С971) уступают по показателю силы отрыва образцам ИПК, при этом ПО растворяются в среде искусственный слюны, то есть непригодны для трансбуккальных систем. За 5 часов эксперимента, по оценке набухающей способности, матрицы ИПК изменились незначительно, что может обеспечить их комфортное для пациента использование в качестве носителей для буккальной доставки. При оценке высвобождения ЛВ из матриц (при соотношении МФ/ИПК 1:0,5) наиболее полное высвобождение (более 90 %) происходит из обеих матриц ИПК по сравнению с матрицами ФС и индивидуальных полимеров.

Заключение. Поликомплексные матричные системы на основе С971-ПО 50 кДа, С971-ПО 500 кДа являются подходящими для трансбуккальной доставки метформина.

Ключевые слова: интерполимерные комплексы, метформин, трансбуккальная доставка, Carbopol® 971 NF, полиоксазолины, адгезия.

Конфликт интересов: конфликта интересов нет.

Вклад авторов. А. С. Викторова, Е. С. Елизарова и Р. С. Романова проводили приготовление образцов, оценку набухающих, биоадгезивных свойств, высвобождения. В. Р. Тимергалиева написала и проводила корректировку статьи. В. В. Хуторянский и Р. И. Мустафин осуществляли концептуализацию и методологию исследования, а также рецензирование и корректировку статьи. Статья была написана при участии всех соавторов. Все вышеуказанные авторы согласовали итоговую версию статьи.

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INTRODUCTION

Buccal drug delivery has a number of advantages over oral administration: convenient use, a dosage form fixes not only painlessly but also does not cause discomfort in the event of adverse reaction. Moreover, the buccal mucosa is characterized with a good blood supply, and any drug substance can enter the systemic circulation directly avoiding the "first pass effect in the liver", and is not exposed to the acidic environment of the gastric juice and the destructive action of digestive enzymes. [1, 2].

For many decades, the mucoadhesive properties of polymers of synthetic and natural origin have been investigated. One of the variants for enhancing adhesion properties of dosage forms was the combination of chemically complementary types of macromolecules with the formation of interpolymer complexes (IPC), which have been also successfully proven as carriers in bioadhesive drug delivery systems [3, 4]. The group of Japanese investigators led by Nagai [5, 6] was the first to prove the prospectiveness of the field, they showed the prospectiveness of IPCs derived with combination of rare crosslinked polyacrylic acid (carboxyvinyl polymer, carbomer, Carbopol®) with hydroxypropylcellulose [5] or polyvinylpyrrolidone [6] by formation of macromolecular hydrogen chains between them.

Earlier, our research team had investigated the mucoadhesive properties of interpolyelectrolyte complexes (IPEC) formed by polyanions (Carbopol ® (71g NF, 2020 NF, 10 Ultrez), Noveon® AA-1) and oppositely charged polycations (Eudragit® EPO, chitosan – CTT A system for gast-

roretentive delivery of metronidazole based on Eudragit ® copolymers was developed [11].

We also offered the system for transbuccal metronidazole delivery based on Noveon AA-1 and Eudragit® EPO [12]. As well, we had earlier produced and characterized IPCs based on S971/PO, and well, diffusive and transport properties were examined on the example of generation of a polycomplex matrix system of mesalazin delivery to the large intestine [13].

The flow chart of the interpolymer reaction between the tested polymers was shown in figure 1.

The aim of the work was to investigate the applicability of IPCs with Carbopol® 971 NF (proton-donor polymer) and poly(2-ethyl-2-oxazolin) (proton-acceptor polymer) of different molecular weights as new mucoadhesive carriers for transbuccal delivery of hypoglycemic drug substance – metformin.

MATERIALS AND METHODS

Poly(2-ethyl-2-oxazolin) of various molecular weights (PO 50 kDa and PO 500 kDa) was purchased from company Sigma-Aldrich (Great Britain). Carbopol® 971 NF (rare crosslinked, 4000–11000 cP, 3000 kDa) (C971) was kindly provided by the Lubrizol Advanced Materials, Inc. (USA).

Polymers were used after being dried under a vacuum at temperature 40 °C for 2 days. As a simulator, metformin (Sigma-Aldrich, Belgium) was used. For an investigation of bioadhesive properties mucin isolated from pig stomachs (type II) was used (Sigma-Aldrich, USA).

IPCs based on S971iPO50kDaiPO 500 kDA were produced with ratio 1.25:1 (by molls), predominant carbopol at pH 4.5 and 4.3 for poly(2-ethyl-2-oxazolin) with a molecular weight of 50 and 500 kDa, respectively, using the method described earlier [13].

Mucoadhesion of polycomplex matrixes was investigated on texture analyzer TA.XTplus (Stable Micro Systems, Great Britain); as a substrate, we used mucin compacts produced by compression on a manual hydraulic press for IR-spectroscopy (PerkinElmer, USA), using the compressor 13 mm in diameter (PIKE Technologies, USA) with pressure of 2.45 MPas for 10 seconds.

For an investigation of mucoadhesion and determination of swelling degree, plano-cylindrical tablets were prepared from a polymeric carrier 100 mg by compression of the assigned amount of powders (S971, PO 50 kDa, PO 500 kDa, their PSs and polycomplexes based on C971-PO 50 kDa, C971-PO 500 kDa) on a manual hydraulic press, similarly to the description given above. Swelling ability was investigated by placing polymeric matrixes to baskets (from device USP I) which were immersed to thermostate IC control eco 18c (IKA® Werke GmbH, Germany) at 37.0 ± 0.5 °C. The volume of the artificial saliva medium with pH = 7.0 prepared by the method [14], was 40 ml. The baskets were withdrawn from the medium every 15 minutes within the first hour, and then every 30 minutes; baskets with tablets were dried carefully with filter paper and weighed. Swelling degree (%H) was calculated by the following equation:

$$\%H = (m_2 - m_1/m_1) \times 100,$$

where m_1 is the weight of a dry sample; m_2 is the weight of a swelled sample.

The study of MF release from matrixes based on corresponding IPCs was performed on device DFZ II device (ERWEKA, Germany) with the USP 4 method ("a flow cell") in the closed cycle using special testing adapters for soft dosage forms (ointments, creams, gels) in the medium imitating salivary liquid. MF concentration in test fractions withdrawn by the collector was determined within

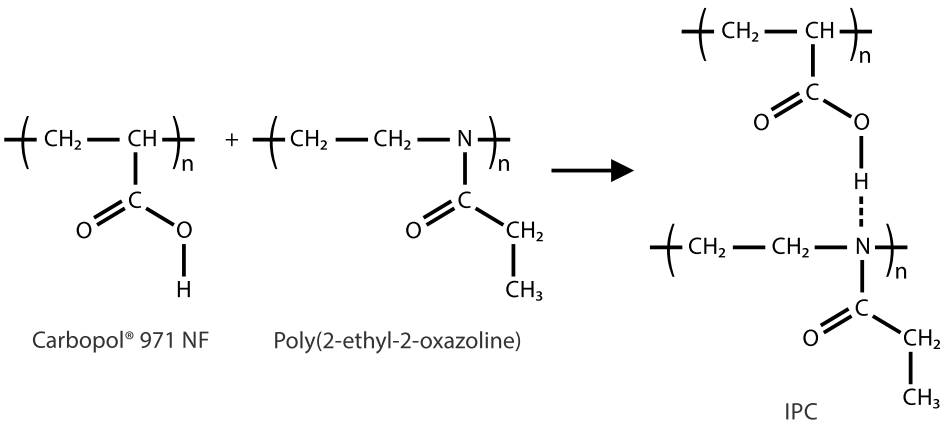

Figure 1. Scheme of formation of interpolymer complexes based on Carbopol® 971 NF and poly(2-ethyl-2-oxazoline)

5 hours at laminar stream rate generated with addition of glass beads 1 mm in dimension in a cell, 4 ml/min., close to the rate of salivary fluid delivered in a human's mouth [1, 15]. The matrixes containing mixture of polymeric the carrier and MF in the ratio 0.5:1 (by weight), with a diameter of 13 mm were tabletted on a manual hydraulic press for IR-spectroscopy (PerkinElmer, the USA) under the same conditions as for determination of mucoadhesion and investigation of swelling process. The quantity of the released drug substance was evaluated with UV-spectroscopy on device Lambda 25e (PerkinElmer, USA) at the wavelength of 232.8 nm.

RESULTS AND DISCUSSION

Despite the fact that group of polymers of poly (2-ethyl-2-oxazoline) type was first described in 1960, their intensive investigations have been performed in the current decade [16]. As it turned out, PO have appeared be non-toxic, biocompatible and bio-inert nonionic polymers which made them very promising materials for biomedical use, qualified as an alternative to polyethylene glycols which are widely used for this purpose [17]. Despite the PO efficacy, so far there are only few investigations on their possible use in pharmaceutical technology, and in particular in drug delivery systems [18–20].

Perhaps, the recent publication by Ruiz-Rubioidr was the closest to the purpose of our investigation [14], in which the authors studied the interaction of two carbopol types (Carbopol® 971 and 974) with PO and showed the prospectiveness of IPCs used as carriers for buccal hydrocortisone delivery. As a model for mucoadhesion investigation studying, the authors used the isolated pig buccal tissues and also the standard dissolution method "Rotating paddle" (USP II) used in most cases in studies of drug substance release from the buccal systems [21–26].

The systemic analysis of publications on the selection of the method as close as possible to the actual conditions for application of transbuccal dosage forms showed that four main variants with pharmacopoeial devices are used in the DS release test: the method already mentioned above with "Rotating paddle" (USP II) with a tablet placed to the surface of the dissolution medium [27]; the modified USP II method differing by the fact that buccal system has one surface limited to an impenetrable membrane, and another one is fixed by cianoacrylate glue to the glass of 2 x 2 cm in size transferred in the dissolution medium; the third – the modified USP I method according to the Italian Pharmacopeia, Farmacopea Ufficiale XI Ed. (F.U.XI)] using a core (a basket holder) on which lower platform instead of a basket the tablet is fixed, which surface which has been moistened with 50 µl of the artificial salivary fluid, and after 2 minutes, after a vessel is filled with the dissolution medium, a release process begins [28]; and the fourth – "Flow cell" method (USP IV) in "open cycle" configuration with large cells used for tablets (22.6 mm) and the minimum flow rate providing the artificial salivary liquid with minimum possible rate of 2–4 ml/min. [29]. In addition, the Chinese researchers have described and patented the system developed especially for investigation of release process from the buccal DF underlying the device which scheme and the principle of work are very similar to the vertical Franz cell with the only difference that it is a flow cell, and a DF is fixed on the top cover opening thus only one of the system surfaces for DS release [30].

Analyzing the variants described in the literature, we have considered it appropriate to combine the principle underlying the device of the Chinese scientists, and one of the adapters which is presented in a wide variety by producers of "Flow cell" devices (ERWEKA, Germany; Sotax AG, Switzerland) and recommended by American, European, British and other pharmacopeias in investigations of corresponding DFs. For this reason, we were interested in the adapter for release investigations from soft DFs (ointments, creams, gels) which use allows, on the one hand, to provide predominant involvement of one of the surfaces of the delivery system in the release process but, on the other hand – constancy of laminar inflow of the dissolution medium with a low speed from the bottom DF side that, in our opinion, brings closer these conditions to natural conditions of salivary liquid inflow in the mouth to a buccal tablet. In this regard, it seemed interesting to us to estimate the variant offered in the study as the additional method allowing to evaluate DS release from the transbuccal delivery system.

As it is known that one of important properties of the polymeric carrier for transbuccal delivery is swelling ability and the marked mucoadhesive properties to get a prolonged release of DS when the system is used [1, 2].

For evaluation of mucoadhesion of test polymers to the mucosa, we used the method based on the detachment force measurement [31]. For mucoadhesion evaluation, we had previously moistened a mucin compact with the solution simulating the salivary fluid for formation of a superficial gel layer. Then the test sample was smoothly pressed with force of 0.1 N for 60 seconds, then the matrix was detached from the mucin compact to the assigned distance, and the matrix detachment force was recorded [9, 10].

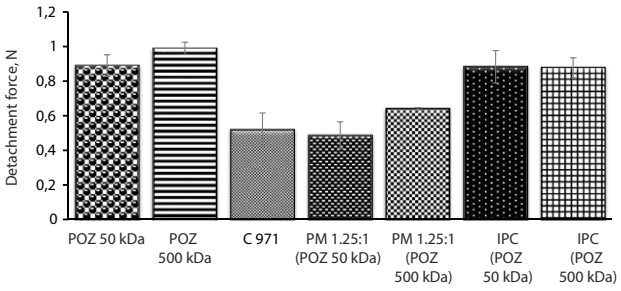

Figure 2. Results of measuring the detachment force F (N – Newton) of individual polymers (C971, POZ 50 kDa, 500 kDa), their physical mixtures and polycomplexes (C971-POZ 50 kDa, C971-POZ 500 kDa) from mucin compacts

Figure 2 presented the results of detachment force measurements of the test samples. During the comparative study of mucoadhesive properties of polymer samples, IPC compacts showed mucoadhesion ability comparable to the one of poly (2-ethyl-2-oxazoline) samples; meanwhile, compacts from physical mixtures and C971 are inferior to IPC samples in detachment force value. It was shown that detachment force of IPC C971-PO sample 50 kDa exceeded a value of a pharmaceutical substance with the similar composition almost twice that indicated better mucoadhesive ability of a polycomplex. The linear correlation was shown not in all samples, however despite the highest detachment force values of compacts based on poly(2-ethyl-2-oxazoline), this compact type was not suitable for the transbuccal prolonged delivery as POs of both molecular weights rapidly dissolved in the medium simulating the salivary fluid.

It should be noted that our study results on the detachment of individual polymers from the surface of mucin compacts contradicted the working data presented in [14], as well as conventional concepts of polymer charge effect on mucoadhesive properties. Polyelectrolytes generally exhibit more pronounced mucoadhesive properties than non-ionic polymers [2]. In our case, samples based on non-ionic poly(2-ethyl-2-oxazolines) have shown a more pronounced adhesion ability compared to samples based on anionic S971. This difference is likely due to the use of mucin compacts rather than the actual buccal tissue of animals as a model substrate. The compacts being swelled may form a highly porous gel that promotes the penetration of macromolecules of linear poly(2-ethyl-2-oxazolines) to a greater extent than the rare crosslinked C971, the diffusion ability of which is strongly suppressed.

Diffusion transport properties of the matrices were evaluated in the medium simulating the salivary fluid. Figure 3 presents photos of matrix swelling in the medium of artificial salivary fluid. Over 5 hours, polycomplex matrices changed slightly compared to PS and S971 which can provide their patient-friendly use as carriers for buccal delivery.

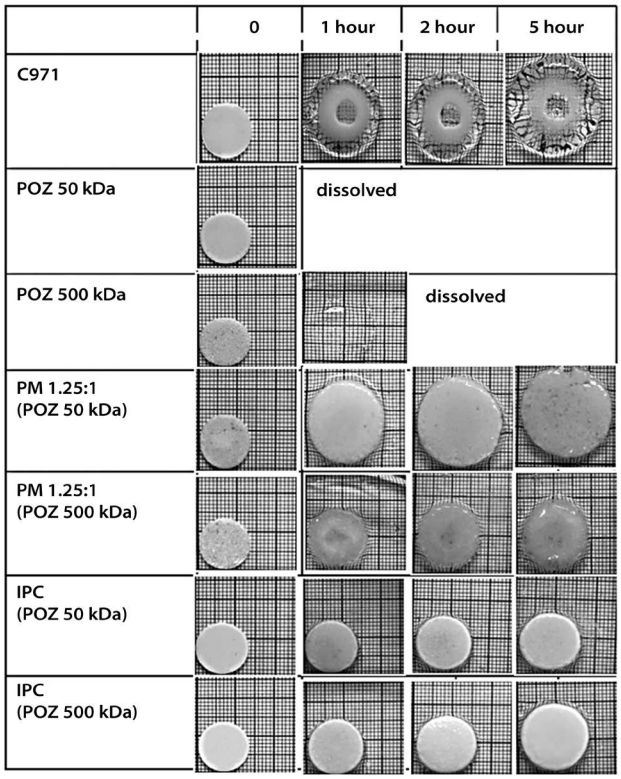

Figure 3. Comparative characteristics of individual polymers, their physical mixtures and IPC in the process of swelling in an environment simulating salivary fluid

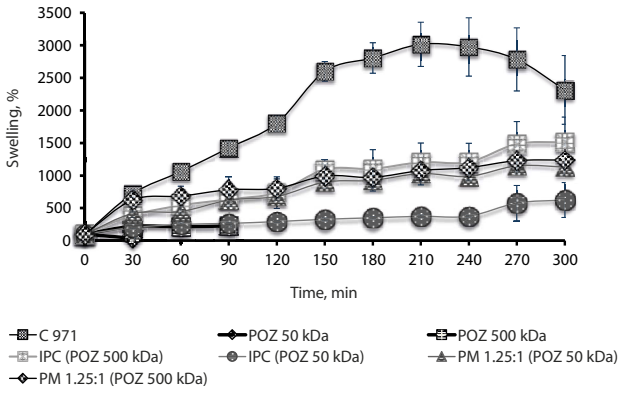

Figure 4. Comparative characteristics of swelling profiles in a medium simulating salivary fluid

Based on the swelling profiles of the matrices (figure 4), we may state that the matrices based on the PO 50 kDa, 500 kDa dissolve during the first hour of the experiment. All other samples of the test matrices passed the tests and did not break down within 5 hours of the study. IPC and PS samples swell uniformly, C971

has a higher swelling ability exceeding IPC and PS samples in 3 times. In contrast, carbopol matrices are characterized with the presence of a pronounced core and a transparent hydrogel layer around due to hydration of the ionized carboxyl groups of the rare crosslinked polymer [9, 10].

The next stage of the evaluation of diffusion transport properties was to investigate the release rate of hydrophilic drug substance – metformin from matrices based on individual polymers, their pharmaceutical substances and polycomplexes in the medium simulating the salivary fluid with USP IV method ("Flow cell") using special test adapters for soft DFs (ointments, creams, gels). When selecting them as a model of buccal application, we relied not only on formation of hydrogel structures in the swelling process of the tested matrices (figure 3), but also on the obvious proximity to the actual application conditions simulating the continuous flow of artificial salivary fluid to the buccal tablet located on top of the adapter (figure 5).

Figure 5. Flow-through cell made by ERWEKA (Germany) for oral dosage forms with adaptor for release evaluation of ointments, creams and gels

As shown in figures 6 and 7, the drug substance release begins from the immersion of the samples to the medium, is increased throughout the test time and reaches the maximum by the end of the experiment. It can be stated that the greatest release (more than 90 %) with the maximum MF release value reached at 2 hours followed by the achieved concentration maintained at a constant level for additional 3 test hours, occurs from both IPC matrices, regardless of their molecular weights compared to PS matrices and individual polymers.

The tested diffusion transport properties of tableted matrices in the medium simulating the saliva show the prospectiveness of S971-based PKI and PO used as carriers for buccal delivery. However, despite the comparable swelling ability and the pronounced mucoadhesive

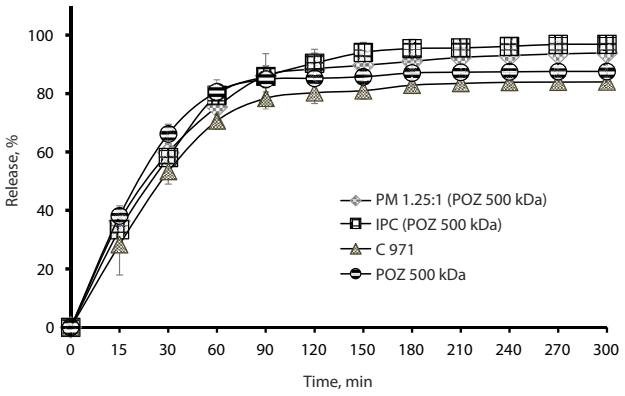

Figure 6. Comparative characteristics of the release profiles of metformin from matrices based on C971, POZ 500 kDa, IPC C971-POZ 500 kDa and their physical mixture in a medium simulating salivary fluid

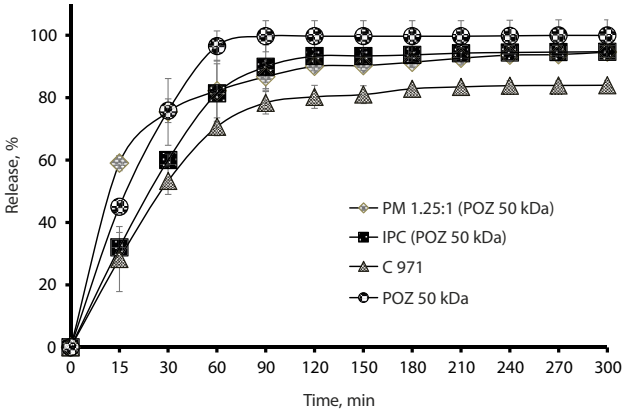

Figure 7. Comparative characteristics of the release profiles of metformin from matrices based on C971, POZ 50 kDa, IPC C971-POZ 50 kDa and their physical mixture in a medium simulating salivary fluid

properties of the polycomplex matrices being compared, only IPC compacts 50 kDa PKI do not almost increase in size, which, given the cost-effective availability of PO 50 kDa, makes the carrier more preferable for the use in metformin transbuccal delivery systems.

CONCLUSION

During the comparative study of mucoadhesive properties of polymers samples, compacts of IPC C971-PO 50 kDa, S971-PO 500 kDa have shown mucoadhesive ability comparable to the one of poly(2-ethyl-2-oxazoline). When evaluating the swelling capacity, the polycomplex matrices have changed slightly compared to physical mixtures of individual polymers and carbopol which can provide their patient-friendly use as buccal delivery carriers. When evaluating metformin release with the proposed "flow cell" method using special

test adapters for soft DFs (ointments, creams, gels), the greatest release (more than 90 %) is found in both polycomplex matrices compared to the matrices of physical mixtures and individual polymers. The proposed version allows to evaluate the release of drug substances in the conditions adequately close to natural functioning conditions of transbuccal delivery systems. Based on the combination of the tested properties, IPC C971-PO 50 kDA is recommended as perspective for further studies as a carrier for buccal tablets.

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