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Development of Orodispersible Ibuprofen Tablets Based on a Polymer-drug Complex

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Abstract

Introduction. Orodispersible dosage forms are a very promising direction in the development of dosage forms. Such dosage forms are designed for both systemic and local action of the active pharmaceutical ingredients that make up their composition. Active pharmaceutical ingredients from orodispersible forms enter directly into the systemic circulation, bypassing the "first pass effect".

Aim. Development of orodispersible tablets based on the Eudragit® EPO/ibuprofen polymer-drug complex and evaluation of ibuprofen release from the resulting system.

Materials and methods. Samples of the polymer-drug complex (PDC) were obtained with different ratios of EPO and ibuprofen, as well as with different mixing orders. Turbidimetric studies to find the stoichiometry of the resulting EPO/IB PLC were performed spectrophotometrically (Lambda 25, PerkinElmer, U.S.A.) at a wavelength of 600 nm. Thermal analysis was performed by modulation differential scanning calorimetry (mDSC) on a Discovery™ DSC instrument (TA Instruments, U.S.A.). Samples sealed in Tzero aluminum pans (TA Instruments, U.S.A.) were scanned in the temperature range from 0 to 250 °C at a speed of 2 °C/min. IR spectra were recorded on a Nicolet iS5 FT-IR spectrometer (Thermo Fisher Scientific, U.S.A.) with an ATR nozzle, in the range from 500 to 4000 cm^{-1}. Drying of samples of complexes and dispersible tablets was carried out in a FreeZone 1L laboratory freeze dryer (Labconco, U.S.A.) for a 24 hours at a temperature of –49 °C and at a pressure of 0.350 mbar. The drug release was evaluated on a dissolution tester DT 828 (ERWEKA GmbH, Germany) in a volume of 900 ml, at 37 ± 0.5 °C and a blade rotation speed of 50 rpm.

Results and discussion. Studies on the formation of PDC Eudragit® EPO/ibuprofen (EPO/IB) were carried out at various molar ratios. On samples of PDC and individual components, bands are observed that are characteristic both for EPO – at 2770 and 2820 cm^{-1}, confirming the presence of non-ionized dimethylamino groups, and at 1725 cm^{-1}, corresponding to the stretching vibrations of carboxyl groups. A new band is appeared at 1573 cm^{-1}, which confirm the formation of ionic bonds between carboxylate groups of IB and ionized dimethylamino groups of EPO. The mDSC thermograms of the samples are characterized by a single glass transition temperature (T_g) at 27,3 ± 0,3 °C (for molar ratio 1:2) and 44,9 ± 0,4 °C. (for molar ratio 1:1), which confirm the formation of polymer-drug complexes. Received PDC Eudragit® EPO/ibuprofen in a molar ratio of 1:2 and 1:1 and oral dispersible tablets based on them by lyophilization. The resulting systems are characterized by immediate release of IB with maximum rates at 30 min for a 1:1 composition and 60 min for a 1:2 composition.

Conclusion. Eudragit® EPO/ibuprofen polymer drug complex can be used to develop orodispersible tablets providing immediate release of IB.

Keywords: orodispersible tablets, Eudragit® EPO, ibuprofen

Conflict of interest. The authors declare that they have no obvious and potential conflicts of interest related to the publication of this article.

Contribution of the authors. Ramil R. Khusnutdinov, Regina R. Musina and Radmir R. Alsynbaev were carried out the synthesis of a polymer-drug complex and turbidimetric studies. Ramil R. Khusnutdinov conducted FT-IR spectroscopy of samples. Shamil F. Nasibullin performed DSC analysis of samples. Elizaveta S. Elizarova received samples of orodispersible tablets. Regina R. Musina, Radmir R. Alsynbaev and Venera R. Timergalieva were carried out the drug release experiments evaluation. Venera R. Timergalieva wrote and corrected the article. Rouslan I. Moustafine was responsible for conceptualization and research methodology, as well as reviewed and corrected the article. The article was written with the participation of all co-authors. All co-authors agreed on the final version of the article.

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Разработка диспергируемых в полости рта таблеток ибупрофена на основе полимер-лекарственного комплекса

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Резюме

Введение. Диспергируемые в ротовой полости системы доставки лекарств являются весьма перспективным направлением в разработке современных лекарственных форм (ЛФ). Они предназначены как для системного, так и для местного действия активных фармацевтических ингредиентов (АФИ), входящих в их состав. АФИ из диспергируемых форм попадают непосредственно в системный кровоток, минуя «эффект первого прохождения через печень».

Цель. Разработка диспергируемых в ротовой полости таблеток на основе полимер-лекарственного комплекса (ПЛК) Eudragit® EPO/ибупрофена и оценка высвобождения АФИ из полученной системы.

Материалы и методы. Получены образцы ПЛК при различном соотношении Eudragit® EPO (EPO) и ибупрофена (ИБ), а также при разном порядке смешивания. Турбидиметрические исследования по поиску стехиометрии образующегося ПЛК EPO/ИБ проводили спектрофотометрически (Lambda 25, PerkinElmer, США) при длине волны 600 нм. Термический анализ проводился методом модулированной дифференциальной сканирующей калориметрии (мДСК) на приборе Discovery™ DSC (TA Instruments, США). Образцы, завальцованные в алюминиевые тигли Tzero (TA Instruments, США), сканировали в диапазоне температур от 0 до 250 °C при скорости 2 °C/мин. ИК-спектры регистрировали на ИК-Фурье-спектрометре Nicolet iS5 (Thermo Fisher Scientific, США) с ATR насадкой, в диапазоне от 500 до 4000 $см^{-1}$. Сушка образцов комплексов и диспергируемых таблеток проводилась в лабораторной лиофильной сушилке FreeZone 1L (Labconco, США) в течение суток при температуре –49 °C и при давлении 0,350 мбар. Оценку высвобождения проводили на тестере растворения DT 828 (ERWEKA GmbH, Германия) в объеме 900 мл, при 37 ± 0,5 °C и скорости вращения лопастей 50 об/мин.

Результаты и обсуждение. Исследования по образованию полимер-лекарственных комплексов Eudragit® EPO/ибупрофен (EPO/ИБ) проводили при различном мольном соотношении. На образцах ПЛК и индивидуальных компонентов наблюдаются полосы, характерные как для EPO – при 2770 и 2820 $см^{-1}$, подтверждающие наличие неионизированных диметиламино-групп, так и при 1725 $см^{-1}$, соответствующую валентным колебаниям карбоксильных групп. Появление новой полосы при 1573 $см^{-1}$ подтверждает образование ионной связи между карбоксилатными группами ИБ и ионизированными диметиламино-группами EPO. мДСК-термограммы образцов характеризуются единственной температурой стеклования (T_c) при 27,3 ± 0,3 °C (для соотношения 1:2) и 44,9 ± 0,4 °C (для соотношения 1:1), что подтверждает образование полимер-лекарственных комплексов. Получены ПЛК Eudragit® EPO/ибупрофен в мольном соотношении 1:2 и 1:1 и диспергируемые в полости рта таблетки на их основе методом лиофилизации. Полученные системы характеризуются немедленным высвобождением ИБ с максимальными показателями при 30 мин – для состава 1:1 и 60 мин для состава 1:2.

Заключение. Полимер-лекарственный комплекс Eudragit® EPO/ибупрофен может быть использован для разработки диспергируемых в ротовой полости таблеток, обеспечивая немедленное высвобождение ИБ.

Ключевые слова: диспергируемые в полости рта таблетки, Eudragit® EPO, ибупрофен

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Вклад авторов. Р. Р. Хуснутдинов, Р. Р. Мусина, Р. Р. Алсынбаев проводили синтез полимер-лекарственного комплекса, турбидиметрические исследования. Р. Р. Хуснутдинов проводил ИК-спектроскопию образцов. Ш. Ф. Насибуллин проводил мДСК-анализ образцов. Е. С. Елизарова получала образцы диспергируемых таблеток. Р. Р. Мусина, Р. Р. Алсынбаев, В. Р. Тимергалиева проводили оценку высвобождения. В. Р. Тимергалиева проводила написание и корректировку статьи. Р. И. Мустафин проводил концептуализацию и методологию исследования, а также корректировку статьи. Статья была написана при участии всех соавторов. Все соавторы согласовывали итоговую версию статьи.

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INTRODUCTION

Orally dispersible drug delivery systems are a very promising direction in the development of modern dosage forms (DF) [1–6]. They are intended for both systemic and local action of active pharmaceutical ingredients (API) included in their composition [5, 7]. According to pharmacopoeial requirements, oral dispersible DFs should be dispersed within three minutes [2]. The

advantages of these DFs are ease of administration for patients with swallowing disorders, dysphagia, as well as in geriatrics and pediatrics [2–4, 8–9]. As well, compared to the oral forms, APIs from dispersible forms enter directly into the systemic circulation, bypassing the "first pass effect through the liver", which is achieved due to the high blood supply to the oral cavity, as well as the mucoadhesive properties of the components that make up these dosage forms, which ensure the retention of particles on the surface of the oral mucosa [7, 10–20].

For the development of dispersible tablets, we have selected a polymer-drug complex based on Eudragit® EPO and ibuprofen. Eudragit® EPO is a pharmaceutical terpolymer used in modified release oral dosage forms [21–23]. Previously, our research group studied the mucoadhesive properties of Eudragit® EPO, as well as polycomplexes obtained with ourr participation, and obtained systems for transbuccal delivery of metronidazole and metformin [10, 11].

The aim of this work is to develop dispersible tablets based on the Eudragit® EPO/ibuprofen polymer drug complex and evaluate the release of APIs from the resulting systems.

MATERIALS AND METHODS

We used Eudragit® EPO (EPO), a terpolymer of N,N-dimethylaminoethyl methacrylate (DMAEMA) with methyl methacrylate (MMA) and butyl methacrylate (BuMA), (PDMAEMA-co-MMA-co-BuMA at a molar ratio of 2:1:1, MM 150 kDa) as a cationic copolymer (Evonik Industries AG, Germany). The polymer was used after drying at 40 °C in a VD 23 vacuum oven (Binder, Germany) for 2 days. Ibuprofen (SigmaAldrich, USA) was used as an anion and API. Maltodextrin (DE 16.5–19.5) and Span® 80 (TM 80, 1000–2000 MPa) manufactured by Merck (Sigma-Aldrich, USA) were used as auxiliary substances necessary for the formation of tablets dispersible in the oral cavity. Artificial saliva was prepared from the following components: calcium chloride (chemically pure) 0.444 g, potassium chloride (chemically pure) 0.745 g, sodium chloride (chemically pure) 0.4096 g, sodium bicarbonate (chemically pure) 0.168 g, potassium dihydrogen phosphate (chemically pure) 0.9112 g (NPF TatKhimProdukt LLC, Russia), deionized water up to 1 l.

Obtaining samples of polymer-drug complex EPO-ibuprofen. When preparing polymer solutions, we proceeded from the molecular weight of its unit. PLC samples were obtained at different molar ratios of EPO and IB, as well as at different mixing orders for their solutions. To do this, aqueous solutions of EPO were prepared at concentrations from 0.002 to 0.05 M, preliminarily dissolving weighed portions of the polymer in an acidic medium with the addition of a 1 M solution of acetic acid (pH = 2), and then bringing the interaction pH to 6.5 with 1 M NaOH solution. The IB solution was used at a concentration of 0.005 M, preliminarily dissolving the API in an alkaline medium with the addition of 1 M NaOH solution (pH = 9), and then adjusting the reaction pH to 6.5 with 1 M acetic acid solution. Then the same amount of ibuprofen solution was added to the polymer samples (direct mixing order). The samples were kept for three days to complete the reaction. To obtain PLC in the reverse order of mixing, aqueous solutions of IB were prepared in concentrations from 0.001 to 0.025 M, previously dissolved in an alkaline medium with the addition of 1 M NaOH solution (pH = 9), and then brought to an interaction pH of 6.5 with 1 M solution of acetic acid. The EPO solution in this case was prepared at a concentration of 0.005 M, preliminarily dissolving a sample of EPO in an acidic medium with the addition of a 1 M solution of acetic acid (pH = 2), followed by bringing the reaction pH to 6.5 with a 1 M NaOH solution. Then, the same amount of EPO solution was added to the IB solutions (reverse mixing order). The samples were also kept for three days. The degree of turbidity of mixed solutions was assessed turbidimetrically on a Lambda 25 UV Vis spectrophotometer (PerkinElmer, USA) at a wavelength of 600 nm.

Thermal analysis was performed by simulated temperature DSC (mDSC) on a Discovery™ DSC instrument (TA Instruments, USA). Samples in amounts from 5 to 7 mg in Tzero aluminum crucibles hermetically sealed using a special press (TA Instruments, USA) were placed in the thermocell of the device, preliminarily calibrated using reference standards (benzoic acid, octadecane, and metallic indium), and scanned in the range temperatures from 0 to 250 °C at a speed of 2 °C/min.

PLC IR spectra compared to individual polymer (EPO) and API (IB), as well as their physical mixture in an equal ratio (1 : 1), were recorded on a Nicolet iS5 IR-Fourier spectrometer (Thermo Fisher Scientific, USA) with an ATR nozzle using a zinc selenium crystal in the range from 500 up to 4000 cm^{-1}. The assignment of absorption bands in the IR spectra was carried out in accordance with the literature data [24][1, 2].

[1] Spectrophotometry and light-scattering. Available at: http://www.pharmacopeia.cn/v29240/usp29nf24s0_c851.html#usp29nf24s0_c851. Accessed: 03.06.2022.

[2] EVONIC. Available at: https://corporate.evonik.com/en. Accessed: 03.06.2022.

The synthesis of PLC in amounts required for further pharmaceutical studies was carried out by mixing solutions of EPO and IB (with preliminary dissolution and bringing to the interaction pH, as described above) in the ratios of EPO/IB (1:1) and 1:2 (by moles). The resulting PLA precipitates were separated from the supernatant, washed three times with purified water and freeze-dried (FreeZone 1L, Labconco, USA) for a day at –49 °C; the main drying was carried out at a pressure of 0.350 mbar.

To prepare oral dispersible tablets, 100 mg, PLC was dispersed in 50 % maltodextrin syrup, span-80 was added – 1.42 % of the total mass of the mixture. Then the mixture was poured into blisters for tablets, frozen in a FreeZone 1L laboratory freeze dryer (Labconco, USA) for a day at a temperature of –49 °C; the main drying was also carried out at a pressure of 0.350 mbar. The yield of the preparation process for dispersible tablets in the oral cavity was 95 % (the production scheme is shown in figure 1).

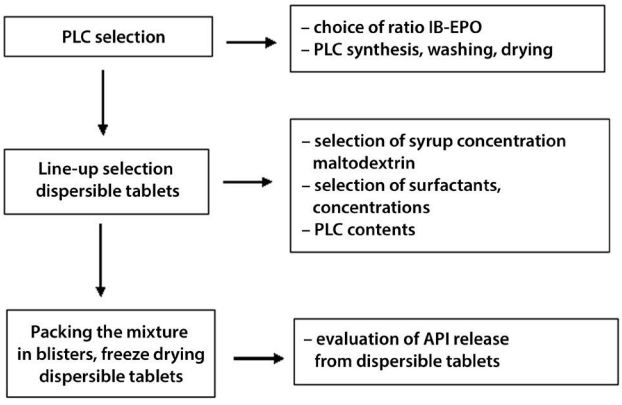

Figure 1. Scheme of preparing orodispersible tablets

The release was evaluated on a dissolution tester DT 828 (ERWEKA GmbH, Germany) at 37 ± 0.5 °C and at a blade rotation speed of 50 rpm. Artificial saliva with a volume of 900 ml was used as a dissolution medium. The orodispersible tablets were placed in the bottom of a beaker, covered with a perforated disc using the USP 5 paddle-over-disc dissolution method, a highly specialized method that allows evaluation of release from transdermal and sublingual DF[1]. Every 30 min, the medium was sampled in a volume of 5 ml for analysis with the replenishment of the corresponding volume with pure medium. The release test was carried out for 5 hours. The amount of released IB was determined by UV spectrophotometry (Lambda 25, PerkinElmer, USA) at a wavelength of 221 nm.

RESULTS AND DISCUSSION

Eudragit® EPO is a pharmaceutical grade terpolymer used to produce mainly oral modified release DFs [21–23]. Due to the presence of positively charged dimethylamino groups in the EPO structure, its interaction with the negatively charged carboxyl groups of ibuprofen becomes apparent (figure 2). Therefore, in order to evaluate the possible interaction of the components, PLC Eudragit® EPO/ibuprofen (EPO/IB) were obtained at various molar ratios. The results of the turbidimetric study of supernatants are shown in figure 3.

Based on the obtained results, it should be noted that with the direct mixing order, an increase in the proportion of IB in the system leads to an increase in the turbidity of the supernatant [in Z (EPO/IB) compositions from 0.2 to 1] (figures 3–5). With the reverse mixing order, the formation of a PLC precipitate is observed in samples of compositions Z (EPO/IB) from 0.3 to 2. For further studies, we selected two PLC EPO/IB compositions: at an equimolar ratio of components (1:1) and with a two-fold molar excess ibuprofen (1:2).

The IR spectra of PLC samples in an equimolar ratio, EPO, ibuprofen and their physical mixture (PS) in the same ratio are shown in figure 6. It should be noted that the IR spectra of PS and IB are, in fact, their superposition, which proves the absence of a chemical bond between the polymer and API during mechanical mixing of substances. On PLC samples (1:1), in comparison with the individual components, bands appear that are characteristic both for EPO – at 2770 and 2820 cm^{-1}, confirming the presence of dimethylamino groups, and at 1725 cm^{-1}, corresponding to the stretching vibrations of carboxyl groups, as well as 1573 cm^{-1}, confirming formation of an ionic bond between the carboxylate groups of IB and ionized dimethylamino groups of EPO [24].

mDSC analysis was also performed to confirm the formation of a polymer-drug complex. Based on the results obtained, the samples are characterized by a single glass transition temperature, which confirms their formation as a new chemically individual compound. For the EPO/IB sample (at a ratio of 1:2), T_c was 27.3 ± 0.3 °C (figure 7), and in the case of EPO/IB (at a ratio of 1:1), the glass transition temperature was 44.9 ± 0 .4 °C.

To obtain DF, Eudragit® EPO PLC/ibuprofen was previously prepared in molar ratios of 1:2 and 1:1. The

[1] USP dissolution testers. Available at: https://www.usp.org/chemicalmedicines/dissolution. Accessed: 06.03.2022.

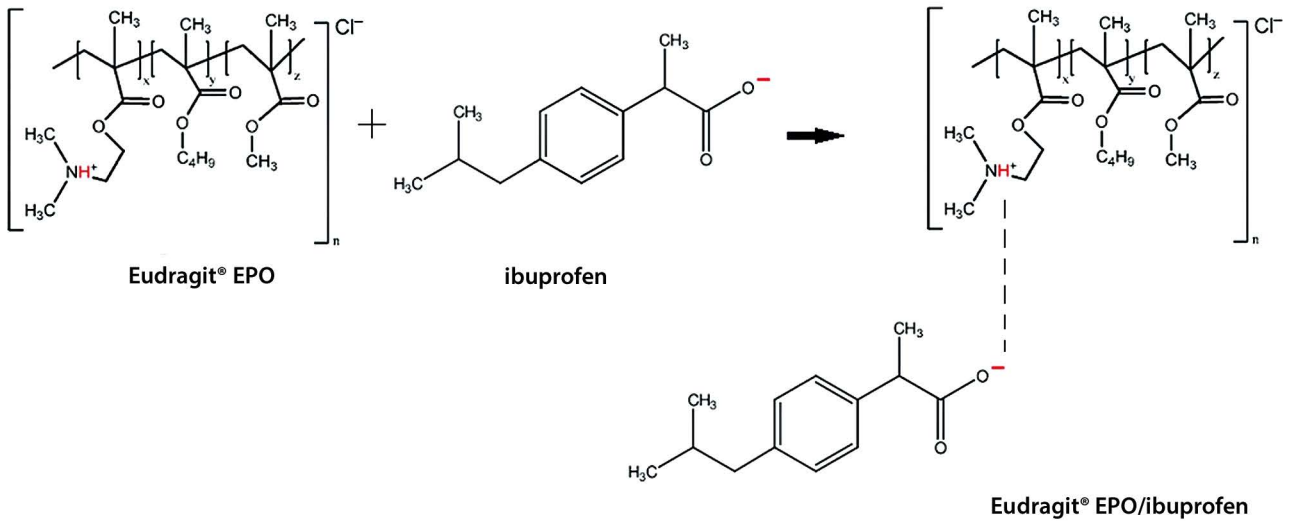

Figure 2. **Scheme of the interaction of the structural monomeric fragment of Eudragit® EPO and ibuprofen**

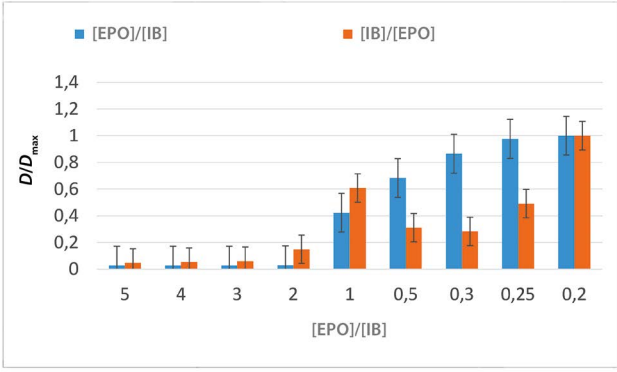

Figure 3. **Dependence of the relative optical density (*D*) of the Eudragit® EPO/ibuprofen system on the composition of the polymer-drug complex (*Z* = [EPO]/[IB]) with the forward (blue color) and reverse (orange color) order of mixing solutions at pH = 6.5; D_{max} – the maximum value of the optical density in the system**

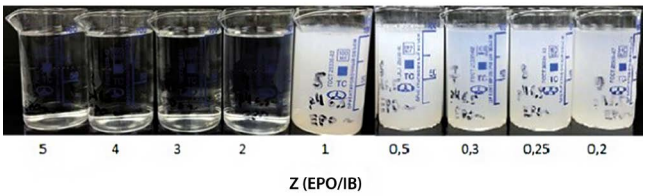

Figure 4. **Photo of PDC solutions of the samples of Eudragit® EPO/ibuprofen in the direct order of mixing (pH = 6.5)**

orally dispersible tablets obtained after freeze drying were hard, even tablets that were easily removed from the blister.

The release was evaluated in an artificial saliva environment due to the fact that the obtained tablets are intended for dispersion in the oral cavity, followed by

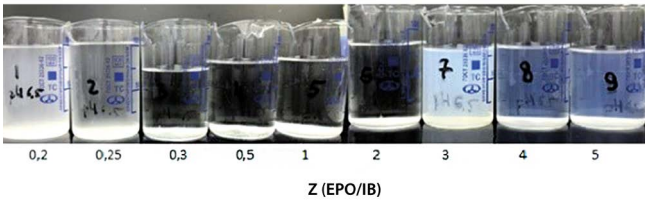

Figure 5. **Photo of PDC samples of Eudragit® EPO/ibuprofen in the reverse order of mixing solutions (pH = 6.5)**

immediate release of the API. The peculiarity of the study was to modify the dissolution method USP 2 – "paddle stirrer" by placing a tablet under a perforated disk intended for analysis by the pharmacopoeial dissolution method USP 5 – "blade over disk" in order to best simulate the release process through the mucous membrane of the oral cavity (cheeks).

The results of ibuprofen release from orodispersible tablets are shown in figure 8. It is should be noted that samples containing the equimolar composition of PLC EPO/IB show maximum release rates after 30 minutes, then by 60 minutes, the level of released API decreases to 50 % and remains at this level for the next 4 hours of the experiment. As for EPO/IB 1:2 sample, the maximum release is reached after 60 min, however, the level of released API is significantly lower than with the equimolar composition. It is possible that in the case of an equimolar composition, the tablets are easier to disperse and, accordingly, release IB more quickly. Photos of tablet samples during the release process are shown in figure 9, they give opportunity to trace the change in the

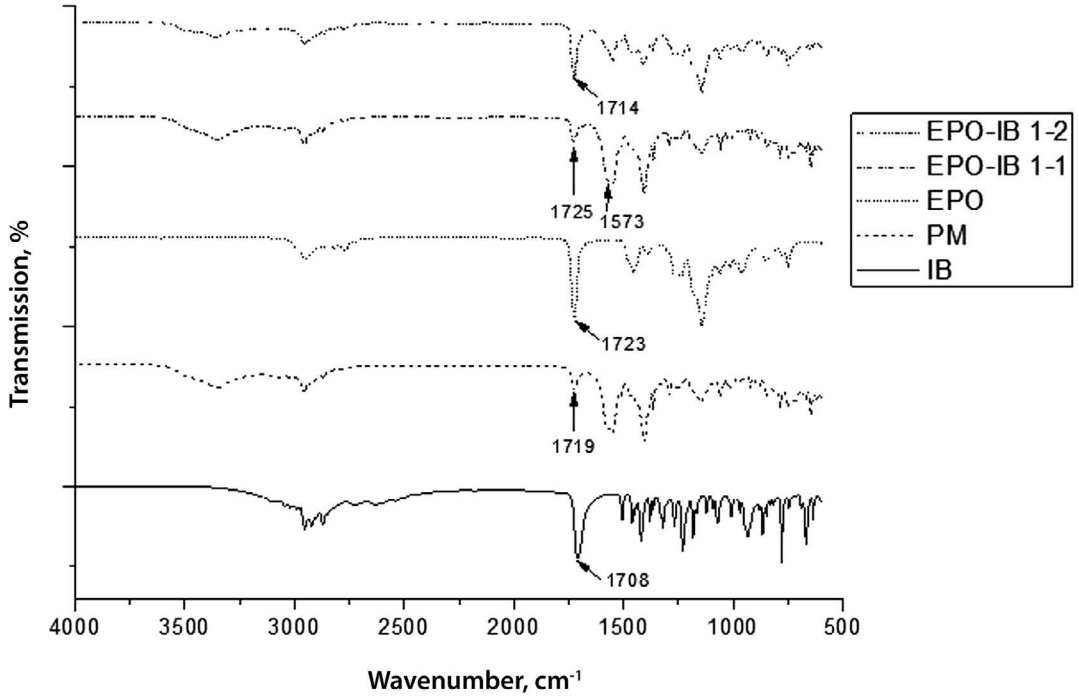

Figure 6. **FTIR spectra of Eudragit® EPO/ibuprofen (IB-EPO 1-2; 1-1) PDC samples, Eudragit® EPO (EPO), physical mixture of Eudragit® EPO and ibuprofen (PM), ibuprofen (IB) (along the ordinate axis – transmission, %; along the abscissa axis – wavenumber, cm^{-1})**

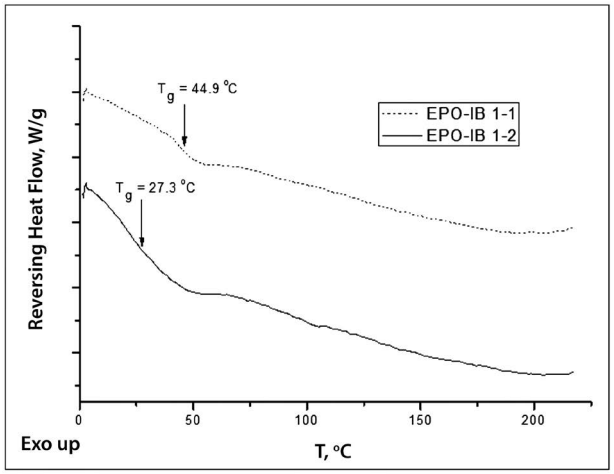

Figure 7. **DSC-MT thermograms of Eudragit® EPO/ibuprofen PDC samples in molar ratios of 1:2 and 1:1 (ordinate – reversing heat flow, W/g; abscissa – temperature, °C)**

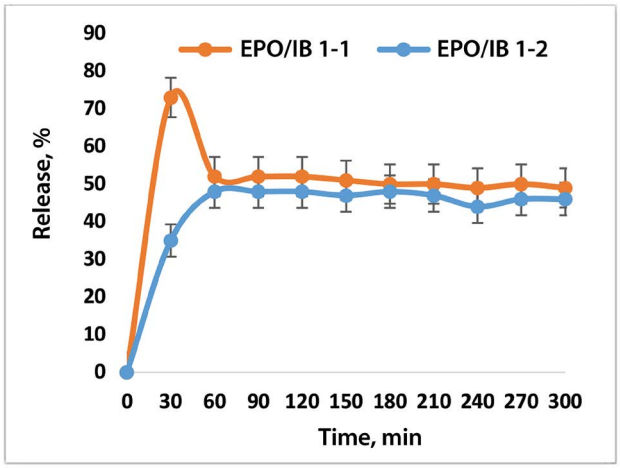

Figure 8. **Ibuprofen release profiles from tablets based on Eudragit® EPO/ibuprofen PDC at a ratio of components 1:1 and 1:2**

appearance of the matrices from its wetting to the formation of dispersed particles, ending by 3–5 minutes, followed by the release of the API from the tablets.

CONCLUSION

Based on the structural features of pharmaceutical polymer Eudragit® EPO used to obtain dosage forms with a modified release, we have obtained its polymer-

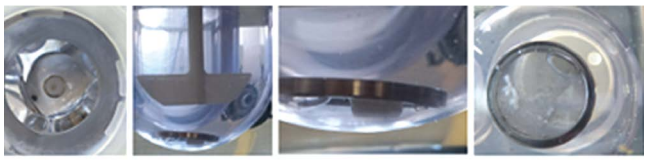

Figure 9. **Changes of external appearance of orodispersible tablets during API release**

drug complexes with ibuprofen. The use of such a design as a transmucosal delivery system is a very promising direction in the development of orodispersible tablets. In this regard, polymer-drug complexes Eudragit® EPO/ibuprofen (EPO/IB) were obtained in the work at various molar ratios and, depending on the mixing order of their solutions, the optimal composition was selected. As a result of the study, we selected two compositions: with an equimolar ratio of components (1:1) and with a twofold excess of ibuprofen (1:2). In accordance with IR spectroscopic and thermal analysis, it was revealed that the obtained systems of polymer-drug complexes are individual chemical compounds with characteristic absorption bands for Eudragit® EPO and ibuprofen. The presence of a new characteristic band at 1573 cm and a single glass transition temperature in the obtained EPO/IB samples confirms the formation of a polymer-drug complex. On their basis, oral dispersible tablets were obtained, and the release of ibuprofen from them was evaluated according to the USP 5 method. The obtained tablets are characterized by an immediate release of API with a maximum release (about 75–80 % IB), which is observed by 30 minutes for composition 1:1. As for 1:2 composition, the maximum release (at the level of 40–50 %) is achieved only by 60 minutes, followed by a uniform release within 4 hours for both compared systems. Thus, the resulting polymer-drug complex Eudragit® EPO/ibuprofen of equimolar composition can be recommended for further studies in order to develop oral-dispersible tablets, since it provides an immediate release of the API included in the polymer-drug complex.

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