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***Research article / Оригинальная статья***

# Composition and Technology Development for Obtaining Amorphous Solid Dispersion of Ebastine by Hot Melt Extrusion to Increase Dissolution Rate

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## Abstract

**Introduction.** Ebastine is a second-generation antihistamine drug available in the form of orally disintegrating tablets and film-coated tablets. Ebastine substance exhibits high bioavailability, but low solubility in water and gastrointestinal tract media. The technology of solid dispersions based on polymer carriers by hot melt extrusion is proposed to solve the problem of ebastine low solubility.

**Aim.** Composition development of extrudate and its production technology to create an amorphous solid dispersion of ebastine in oder to increase the recovery rate and bioavailability.

**Materials and methods.** Ebastin micronized (JSC "Active Component", Russia); ebastin crystalline (Arevipharma GmbH, Germany); VIVAPHARM® PVP/VA 64 (JRS Pharma GMbH & Co. KG, Germany). Extrudates were obtained on a HAAKE™ miniCTW co-rotating twin-screw laboratory extruder (Thermo Fisher Scientific, Germany). Extrudates were studied by differential scanning calorimetry, synchronous thermal analysis, powder X-ray diffraction and FTIR-spectroscopy. The quantitative content of the active ingredient was determined by spectrophotometry. The content of related impurities in the amorphous solid dispersion of ebastine was determined by HPLC.

**Results and discussion.** The technology of amorphous solid dispersion of ebastine by hot melt extrusion was developed. The pharmacokinetic properties of ebastine were significantly improved. The process of obtaining solid dispersion with 20 % of ebastine was optimized in order to reduce the content of impurities in the extrudate.

**Conclusion.** The maximum concentration of ebastine for proper quality amorphous solid dispersion based on PVP/VA64 amounted to 20 %. Obtaining a solid dispersion by hot melt extrusion with ebastine content in PVP/VA64 higher than 30 % is impossible because the melt does not possess the glass transition property.

**Keywords:** orally disintegrating tablet, ebastine, hot melt extrusion, extrudate, amorphous solid dispersion, solubility

**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.** Konstantin A. Gusev and Denis N. Maimistov designed the experiment plan. Andrey R. Aliev, Konstantin A. Gusev and Georgij V. Rechkalov produced extrudates by hot melt extrusion. Yuliya E. Generalova quantified resulting impurities in the extrudate. Nadezhda A. Aksenova carried out simultaneous thermal analysis. Galina M. Alekseeva и Andrey R. Aliev carried out FTIR-spectroscopy. Konstantin A. Gusev and Elena V. Flisyuk processed the data obtained. All authors participated in the discussion of results and wrote the manuscript.

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# Разработка состава и технологии получения аморфной твердой дисперсной системы эбастина методом экструзии горячего расплава для увеличения скорости растворения

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## Резюме

**Введение.** «Эбастин», антигистаминный препарат второго поколения, выпускается в форме орально диспергируемых таблеток и таблеток, покрытых пленочной оболочкой. Субстанция эбастина характеризуется высокой биодоступностью, но низкой растворимостью в воде и средах желудочно-кишечного тракта. Для решения проблемы низкой растворимости эбастина предложена технология создания твердых дисперсий на основе полимерных носителей методом экструзии горячего расплава.

**Цель.** Разработка состава и технологии получения экструдата для создания аморфной твердой дисперсной системы эбастина с целью ускорения процесса высвобождения и повышения биодоступности.

**Материалы и методы.** Эбастин микронизированный (АО «Активный Компонент», Россия); эбастин кристаллический (Arevipharma GmbH, Германия); VIVAPHARM® PVP/VA 64 (JRS Pharma GMbH & Co. KG, Германия). Экструдаты получали на двухшнековом лабораторном экструдере с сонаправленным вращением шнеков HAAKE™ miniCTW (Thermo Fisher Scientific, Германия). Образцы исследовали методами дифференциальной сканирующей калориметрии, синхронного термического анализа, порошковой рентгеновской дифракции и ИК-фурье-спектроскопии. Количественное содержание действующего вещества определяли методом спектрофотометрии, а содержание родственных примесей в аморфной твердой дисперсии эбастина определяли методом ВЭЖХ.

**Результаты и обсуждение.** Разработана технология получения аморфной твердой дисперсии эбастина методом экструзии горячего расплава, значительно улучшены фармакокинетические свойства активного вещества, оптимизирован процесс получения твердой дисперсии, содержащей 20 % эбастина, с целью уменьшения содержания количества примесей в экструдате.

**Заключение.** Максимальная концентрация эбастина для аморфной твердой дисперсии надлежащего качества на основе PVP/VA64 составила 20 %. Получение твердой дисперсии методом экструзии горячего расплава с содержанием эбастина в PVP/VA64 выше 30 % невозможно, так как расплав не стеклуется.

**Ключевые слова:** орально диспергируемые таблетки, эбастин, экструзия горячего расплава, аморфная твердая дисперсия, растворимость

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

**Вклад авторов.** К. А. Гусев и Д. Н. Маймистов разработали план эксперимента. А. Р. Алиев, К. А. Гусев и Г. В. Речкалов реализовали получение экструдатов методом экструзии горячего расплава. Ю. Э. Генералова определяла содержание образующихся примесей в экструдате. Н. А. Аксенова проводила синхронный термический анализ. Г. М. Алексеева и А. Р. Алиев проводили ИК-спектроскопию. К. А. Гусев и Е. В. Флисюк обрабатывали полученные данные. Все авторы участвовали в обсуждении результатов и написании текста статьи.

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**Для цитирования:** Гусев К. А., Алиев А. Р., Генералова Ю. Э., Аксенова Н. А., Речкалов Г. В., Маймистов Д. Н., Алексеева Г. М., Флисюк Е. В. Разработка состава и технологии получения аморфной твердой дисперсной системы эбастина методом экструзии горячего расплава для увеличения скорости растворения. *Разработка и регистрация лекарственных средств*. 2023;12(4):126–135. https://doi.org/10.33380/2305-2066-2023-12-4-1577

## INTRODUCTION

Allergic reactions affect more than a third of the world's population, and the incidence of these diseases is increasing annually, according to the World Health Organization. There are more than 60 % of respondents in Russia who face allergy symptoms every year, as reported by a Rambler&Co survey in 2021. Antihistamines (AHs) are often prescribed to eliminate symptoms of allergic rhinitis, and as an additional therapy for asthma.

Antihistamines remain the first-line therapy for allergic diseases, which significantly relieve allergy symptoms. One of the promising forms of AHs are orally disintegrating tablets, allowing convenient intake and rapid onset of pharmacological effect.

Ebastine, a second-generation antihistamine, is available as orally disintegrating tablets and film-coated tablets. Ebastine substance is characterized by high bioavailability, but low solubility in water and gastrointestinal tract (GIT). To increase bioavailability of the active substance in orally disintegrating tablets freeze-drying technology is used. When the release profile of film-coated tablets is required, a micronized substance is used.

The production technology of freeze-dried tablets is characterized by high costs and the uniqueness of the equipment. In order to increase the solubility and bioavailability of the active ingredient, therefore, other more optimal methods can be used.

There are several approaches that improve the absorption of the substance in the GIT by increasing solubility and/or dissolution rate. Solubility enhancement methods are divided into chemical (salts [1], co-crystals [2] and prodrugs [3]) and physical (complexation [4], creation of self-emulsifying compositions, liposomal technologies [5], micronization [6], transformation to amorphous state and creation of solid dispersion systems (SDS) based on polymeric carriers [7]). Chemical modifications have very limited application due to the characteristics of the active molecules. At the same time, physical methods are more versatile and widely used in finished pharmaceutical products (FPPs).

Particle size reduction is one of the most common technologies to enhance drug solubility, as the solubility of the active pharmaceutical ingredient (API) is inherently related to particle specific surface area. This method is widely used in pharmaceutical technology to increase bioavailability of poorly soluble APIs [6], thereby decreasing the therapeutic dose of the drug substance (DS) and reducing side effects. However, reduction in particle size has a relatively small effect on solubility of the API, because it does not increase the ultimate solubility of the API, but rather its dissolution rate by increasing the area available for solvation. For instance, Xi Han et al. reported that micronization of ibuprofen did not increase its dissolution rate [8].

The API acquires poor technological properties with milling. Lack of flowability, agglomeration, enhanced reactivity and adsorption properties are a consequence of the increasing of free surface energy of particles during milling. At the same time, the system becomes thermodynamically unstable: particles interact with air oxygen, other components of the powder mixture and the environment (gases, fine particles or microorganisms), with the material of the mills, and also adsorb moisture, which leads to a decrease the storage stability. Another significant limitation of this technology is electrostatic charge accumulation by particles and equipment elements during milling, which causes dusting of the API and its adhesion to the equipment surface, which results in increased process losses. As a result the process becomes more complicated and there are increased losses at each stage of production of the finished dosage form based on micronized substance.

The production of solid dispersion systems (SDS) based on polymeric carriers by hot melt extrusion (HME) is proposed as an alternative industrial method to increase solubility and bioavailability of APIs. It allows for a greater enhancement of solubility compared to the micronization method. Thus, Nam Ah Kim et al. reported that the SDS of butein is characterized by an increase in solubility by more than 20-fold relative to the micronized substance [9].

HME is a continuous or a batch process that involves melting, mixing, homogenizing, and pushing the material through a die under heating [7]. As a result of melting, subsequent mixing, extrusion and cooling, a polymer-based SDS containing the API is formed. In such system, the API is incorporated in a carrier, which consists of one or more pharmaceutically acceptable polymers, plasticizers and excipients.

Polymers used for HME in pharmacy may be water-soluble or water-insoluble, or may provide solubility of SDS in certain media. Water-insoluble carriers include polymers such as ethyl cellulose and various waxes: the release of API in such system occurs by diffusion. Water-soluble polymers include hydroxypropyl methylcellulose (HPMC), polyethylene oxides, polyethylene glycols, polyvinylpyrrolidone and its copolymers, and their compositions, from which the API is released by diffusion or erosion during dissolution of the polymer matrix [10, 11]. It is known from the literature that the main parameters for the pharmaceutically suitable polymeric carriers are thermal properties and specific characteristics of the extrusion process.

Physical and chemical properties of the carrier polymer determine the main properties of SDS allowing to modify the release of API from the final dosage form, determining the solubility of APIs in the dosage form and storage stability. Previously, the authors conducted studies on the production of solid dispersions [7] and extrudates [12] with predefined technological properties. Based on literature and experience in technology development, a copolymer of polyvinylpyrrolidone and vinyl acetate (60:40 ratio) was chosen as a polymeric carrier for ebastine substance. This polymeric carrier allows to significantly increase the API solubility and has a low extrusion temperature.

Pharmaceutical substances of ebastine obtained from two manufacturers were used in the study: crystalline ebastine and micronized ebastine. Both samples are practically insoluble in water, and slightly soluble in 0.01 M HCl. Additionally, micronized ebastine has poor technological properties such as low flowability, dusting and static charge accumulation.

**The aim** of this work is the development of the extrudate composition and its production technology for creating an amorphous SDS (ASDS) of ebastine to accelerate the release process and increase bioavailability.

## MATERIALS AND METHODS

**Materials.** Ebastine micronized – (JSC"Active Component", Russia); ebastine crystalline (Arevipharma GmbH, Germany); VIVAPHARM® PVP/VA 64, hereinafter – PVP/VA (JRS Pharma GMbH & Co. KG, Germany).

**Equipment.** Haake™ miniCTW twin-screw laboratory extruder (Thermo Fisher Scientific, Germany) with co-rotating conical screws; ZLJ-125 cone mill calibrator (Shanghai Unique Machinery Technology Co., Ltd., China); DGN-II multifunctional pharmaceutical machinery (Shanghai Unique Machinery Technology Co., Ltd., China); DSC 3+ thermal analysis system (Mettler Toledo GmbH, Switzerland); Simultaneous Thermal Analyzer (STA) 6000 (PerkinElmer, USA); FSM 1201 FTIR spectrometer (JSC "SPB Instruments", Russia); Ultima IV-285 automated X-ray powder diffractometer (Rigaku Corporation, Japan); SF-2000 spectrophotometer (LLC "OKB Spektr", Russia); Flexar HPLC system (PerkinElmer, USA); DT 626/1000 HH dissolution tester (ERWEKA GmbH,, Germany).

**Simultaneous thermal analysis** was performed on a STA 6000 simultaneous thermal analyzer. The analysis was conducted in a ceramic crucible with a volume of 250 µl. The crucible was heated at a rate of 10 K/min in the temperature range of 20 °C to 400 °C in the inert atmosphere of nitrogen gas.

**Differential scanning calorimetry (DSC)** was performed on a DSC 3+ differential scanning calorimeter. The method consisted of three consecutive phases: heating, cooling and heating in the range of 0 and 150°C. The temperature was being changed at a rate of 10 K/min in nitrogen atmosphere with a flow rate of 50 ml/min. Standard 40 µl aluminum pans with perforation were used. Temperature and enthalpy were calibrated against pure metals, indium (ME-119442) and zinc (ME-119441), according to the manufacturer's instructions. Data was processed using Mettler STARe software V16.20c.

The sample **absorption spectra** were measured on FSM 1201 FTIR spectrometer in the wavelength range of 500 $cm^{-1}$ to 4000 $cm^{-1}$. Sample preparation was carried out according to the standard method, the investigated substance was pressed into a tablet with KBr for IR spectrometry. Data were processed using Python3.9 software, matplotlib library 3.7.0 was used for visualization.

The samples were examined by **X-ray powder diffraction** using the Ultima IV-285 automated powder diffractometer with the following parameters: X-ray tube radiation – $Cu_{K\alpha 1+2}$, wavelengths – $\lambda_{CuK\alpha 1} = 1.54059$ Å and $\lambda_{CuK\alpha 2} = 1.54443$ Å, tube mode – 40 кВ / 30 mA, position-sensitive detector, reflection geometry, Bragg – Brentano focusing scheme, sample rotation speed 20 rpm, diffraction angle interval – $2\theta = 3–60°$, scanning interval – 0,02°, scanning speed – 2 °/min, in the air atmosphere. Samples were prepared by dry pressing of the studied compound into a low-background cuvette made of monocrystalline silicon (depth 0.5 mm, diameter of the studied area 20 mm).

**Methodology for obtaining extrudates.** Mixing of ebastine and PVP/VA64 was carried out in the tumbling barrel for 20 minutes at 45 rpm. HME was performed in the HAAKE™ MiniCTW twin-screw laboratory extruder with co-rotating conical screws. The extruder was assembled, a die with a 1 mm bore diameter was installed and the material barrel heating temperature was set. The mixture was loaded in equal portions and the loading consistency was monitored by the screw torque. The operating torque under which the processed compound was consistently extruded through the die was fixed. The extrudate was pulled out manually, its diameter was kept in a range of 1.0 to 1.4 mm to simplify subsequent grinding.

The obtained extrudate was milled on a ZLJ-125 cone mill calibrator through a 1.0 mm round-meshed sieve and a rotary knife speed of 500-600 rpm (knife with a circular profile). The milled extrudate was passed through a 710 µm mesh sieve and the fraction less than 710 µm was packed in a foil ZIP bag to protect from light and moisture during storage.

**Quantitative determination** of ebastine was carried out by UV-spectrophotometry. A solution of ebastine in 96 % ethyl alcohol with a nominal concentration of 1 mg/ml was prepared, and the resulting solution was filtered through the 0.45 µm pore diameter nylon filter. Then, 1.0 ml of the filtrate was placed in a 100 ml volumetric flask, adjusted with 0.01 M HCl and mixed.

The optical density of the tested solution of SDS and the solution of the ebastine standard sample was measured on a spectrophotometer at the maximum absorption wavelength of 258 nm; 0.01 M HCl was used as the reference solution.

**The dissolution kinetics test** was carried out on an ERWEKA DT 626/1000 HH dissolution tester with a paddle stirrer speed of 50 rpm in 0.01 M HCl. The dissolution medium volume was 1000 ml and the medium temperature was 37 ± 0,5 °C. 10 ml samples were taken and strained through the 0.45 µm pore diameter nylon filter at equal time intervals of 15, 30, 45 minutes, followed by medium refilling. UV-spectrophotometry with a monitor sample was used for quantitative determination.

**Impurities were determined** by high-performance liquid chromatography (HPLC). The analysis was performed on the Flexar high-pressure liquid chromatograph equipped with a pump forming a gradient on the low-pressure side, autosampler, column thermostat and UV-detector. A solution with an active ingredient nominal concentration of 2 mg/ml (with water-acetonitrile 8 : 2 as a solvent) was prepared for testing.

Preparation of buffer solution (pH 6.0): 950 ml of water for chromatography, 1.4 ml of triethylamine and 0.3 ml of phosphoric acid were placed in the 1000 ml volumetric flask, then phosphoric acid is added (if necessary) to pH 6,0 ± 0,1, the volume was adjusted to the mark with water for chromatography and mixed. The resulting solution was strained through the 0.45 µm pore diameter nylon filter.

**Mobile phase A.** 300 ml of buffer solution and 100 ml of acetonitrile were taken, mixed and degassed.

**Mobile phase B.** 500 ml of methanol and 100 ml of acetonitrile were taken, mixed and degassed.

The chromatogram recording time should be at least 1.5 times the retention time of ebastine.

Chromatographic parameters are presented in Table 1.

**Table 1. Chromatography conditions**

| | |
|---|---|
| Column | Kromasil 300-5C8, 250 mm × 4.6 mm, 5 µm |
| Eluent | MP A : MP B (55 : 45) |
| Flow rate | 1,5 ml/min |
| Column temperature | 40 °C |
| Detector | UV, 210 nm |
| Sample volume | 20 µl |

## RESULTS AND DISCUSSION

Thermal properties of micronized and non-micronized substances were investigated to determine the applicability of HME in the production of ebastine solid dispersion. According to the obtained DSC results, the melting points of the samples were 86.1 °C and 87.5 °C, respectively. The results of synchronous thermal analysis indicate that the destruction of the ebastine substance started at temperatures above 200 °C. Thus, the initial operating range of the ebastine substance extrusion was established from 80 to 150 °C depending on the final composition of solid dispersion.

Non-micronized ebastine was chosen as a feedstock due to its technological properties optimal for extrusion and production of SDS.

The thermal properties of the obtained PVPVA64 sample were investigated by simultaneous thermal analysis. The results showed that the PVPVA64 sample (VIVAPHARM® PVP/VA 64) contained 1.5 % water by weight with no obvious melting effects. The characteristic endothermic effect from 40 to 100 °C corresponded to mass loss by water evaporation (Figure 3). As it has been previously studied, the extrusion operating temperature range of PVPVA64 lies in the range from 120 to 200 °C.

To clarify the minimum extrusion operating temperature of PVPVA64, the pure polymer was extruded in the temperature range of 110 to 180 °C in increments of 10 °C. The minimum extrusion operating temperature of pure VIVAPHARM® PVP/VA 64 was 140 °C.

Considering that API has a melting point significantly lower in comparison with the carrier, it could perform as a plasticizer and potentially allow the extrusion operating temperature to be reduced to 120 °C at 20 % ebastine content in the mixture.

To determine the optimum extrusion temperature range at the same screw speed (20 rpm), a compound containing 20 % ebastine and 80 % carrier by weight was extruded at temperatures of 120, 130 and 140 °C. During the extrusion process, the screws' torque, the material residence time in the extruder and the exterior of the extrudate were evaluated. Pictures of the obtained extrudates are presented in Figure 1. The quantitative content of ebastine and the sum of impurities were evaluated in the obtained samples. The data are summarized in Table 2.

The extrudates obtained at 120 °C are turbid. As the process temperature increased, the resulting products became transparent and then acquired a yellowish tint. Similarly, as the temperature became higher, the amount of ebastine impurities in the extrudates increased (Table 2).

Based on the obtained data, optimization of extrusion process parameters was carried out in order to reduce the heat effect on the product. Extrudates were obtained at temperatures of 120 and 130 °C at screw speeds of 50 rpm and 100 rpm, thus reducing the time of ebastine residence in the extruder.

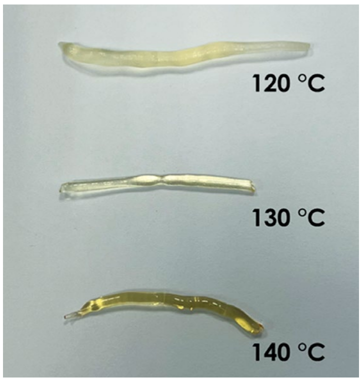

**Figure 1.** **Photograph of ebastine and PVP/VA64 extrudates prepared at various temperatures**

The extrudate parameters were evaluated similarly to the previous experiment, the results are presented in Table 3.

According to the results presented in Table 3, for samples No. 4-7 it was possible to reduce the amount of impurities to the reference range in the final dosage form (less than 0.2 %). Moreover, with decreasing residence time of the component mixture in the extruder, the dynamics of impurity reduction was observed. The extrudate samples No 4–7 are all visually colorless and transparent.

**Table 2.** **Results of extrusion ebastine SDS**

| № | Ebastine content, % | PVPVA64 content, % | $T_{extrusion}$, °C | Screw rotation speed, rpm | Residence time in extruder, sec | Torque, N · m | Amount of impurities, % |
|---|---|---|---|---|---|---|---|
| *Pure ebastine (Arevipharma GmbH, Germany)* | | | | | | | 0,058 ± 0,005 |
| 1 | 20 | 80 | 120 | 20 | 195 | 0,09 | 0,41 ± 0,01 |
| 2 | | | 130 | | | 0,06 | 0,58 ± 0,01 |
| 3 | | | 140 | | | 0,06 | 0,76 ± 0,02 |

**Table 3.** **Results of extrusion ebastine SDS after optimization**

| № | Ebastine content, % | PVPVA64 content, % | $T_{extrusion}$, °C | Screw rotation speed, rpm | Residence time in extruder, sec | Torque, N · m | Amount of impurities, % |
|---|---|---|---|---|---|---|---|
| *Pure ebastine (Arevipharma GmbH, Germany)* | | | | | | | 0,058 ± 0,005 |
| 4 | 20 | 80 | 120 | 50 | 100 | 0,15 | 0,19 ± 0,02 |
| 5 | | | 130 | | | 0,12 | 0,16 ± 0,02 |
| 6 | | | 120 | 100 | 80 | 0,3 | 0,13 ± 0,01 |
| 7 | | | 130 | | | 0,3 | 0,14 ± 0,01 |

The possibility of increasing ebastine concentration in SDS for the subsequent production of a final dosage form was investigated in the scope of this work. Extrudates containing 30 % ebastine by weight were obtained with the following extrusion parameters (Table 3). Additionally, several experiments were carried out to obtain extrudates with 50 % of ebastine by weight. These extrudates did not have the property of glass transition at the normal conditions.

The composition with 30 % ebastine by weight showed a significant increase of impurities up to 0.8 % at 120 °C and 100 rpm. Thus, the maximum concentration of ebastine in the PVPVA64-based binary solid dispersion was 20% by weight.

Quantification of ebastine was carried out to control the quality of extrudates. The content of ebastine in the obtained SDS corresponded to the stated one taking into account the error of the method. The content of ebastine in the obtained SDS matched the reported value, within the procedural error.

Solid dispersion of ebastine (20 %) was characterized by simultaneous thermal analysis. The DSC curves of ebastine SDS (20 %), PVP/VA64 and pure crystalline ebastine are presented in the Figure 2. The DSC curve of the ebastine solid dispersion did not show a separate peak corresponding to the melting of the pure substance, which may indicate the formation of an amorphous solid dispersion of the API as a result of HME processing.

The ebastine SDS (20 %) was analyzed by FTIR spectroscopy. The IR spectra between 2000 and 450 cm$^{-1}$ of pure ebastine, PVPVA64 and SDS of ebastine are shown in Figure 3. The main characteristic peaks of ebastine are present in the spectrum of the solid dispersion, with no new peaks indicating the absence of chemical reactions involving both components. The broadening and insignificant shift of the bands in the IR spectrum of SDS in comparison with the IR spectra of the initial substances can indicate both the transition of the API from the crystalline to amorphous state and the interaction of the polymeric carrier with ebastine (formation of hydrophobic and hydrogen bonds).

The crystallinity of the following samples – pure crystalline ebastine, PVPVA64, mechanical mixture of PVPVA64 and ebastine solid dispersion (20 %) – was evaluated by X-ray powder diffraction. According to the obtained results (Figure 4), ebastine is in the crystalline phase, PVPVA64 – in the amorphous phase, mechanical mixture of ebastine and PVPVA64 – a combination of crystalline and amorphous phases, the solid dispersion is in the amorphous phase.

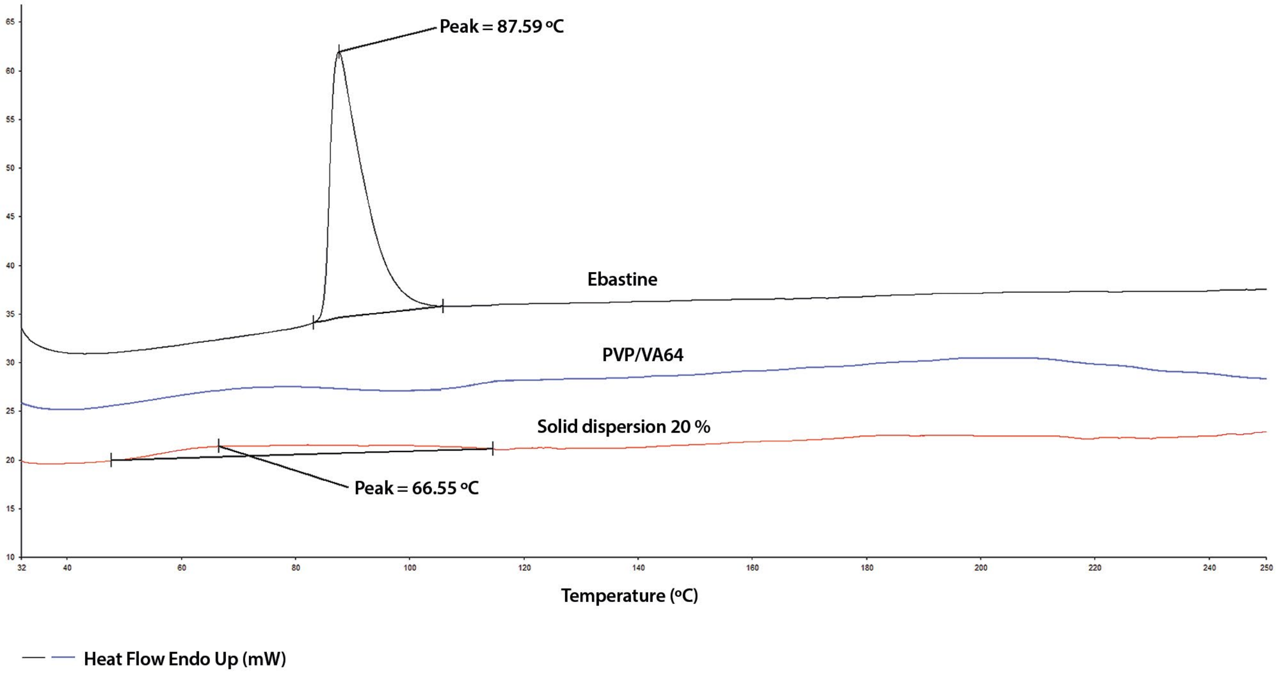

**Figure 2.** **Results of DSC ebastine, PVP/VA64 and SDS (20 %)**

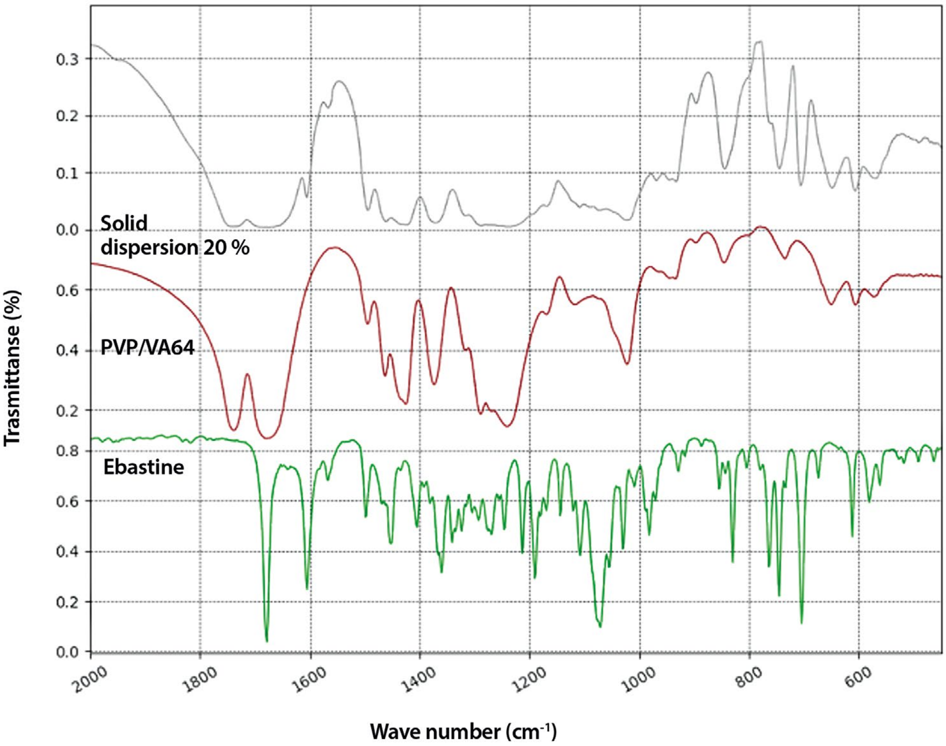

**Figure 3.** **FTIR spectrum of ebastine, PVP/VA64 and SDS (20 %)**

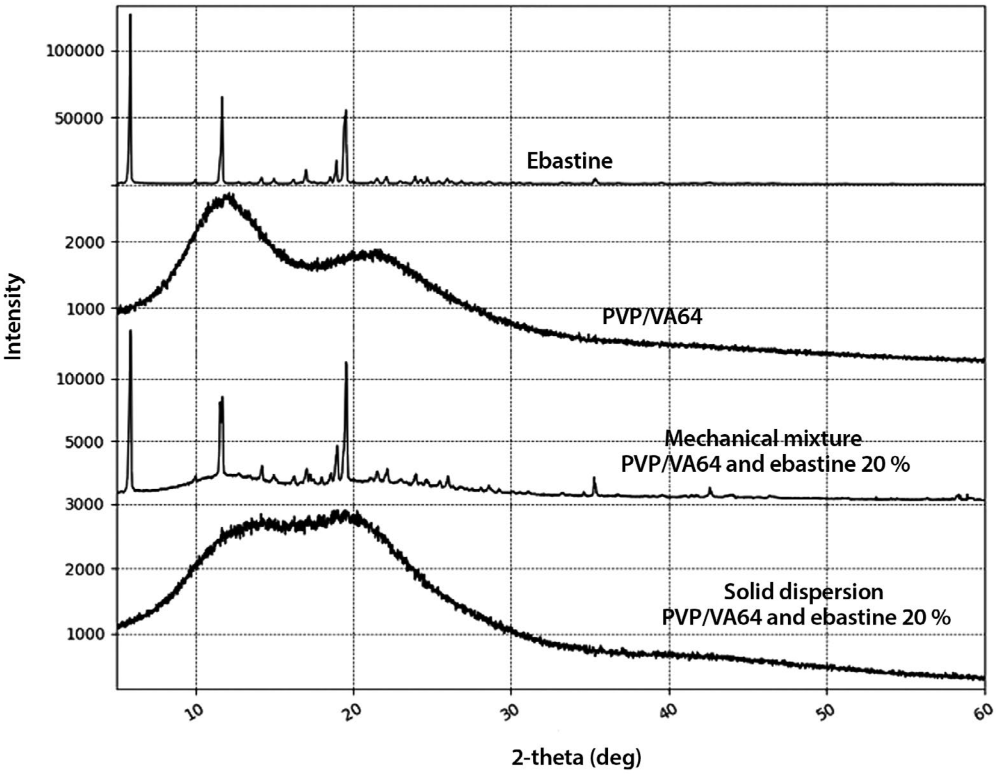

**Figure 4.** **XRPD-results**

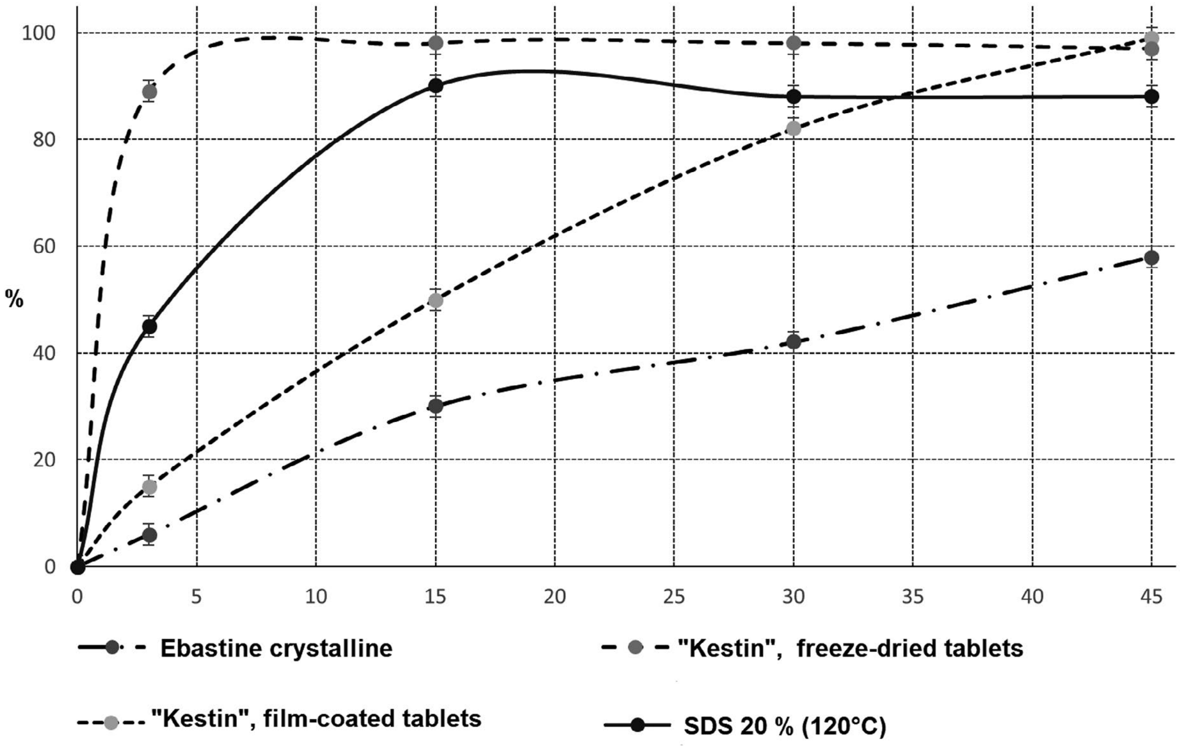

**Figure 5.** **Ebastine release kinetics from various samples**

Thus, ASDS with 20 % ebastine was obtained from PVPVA64.

To evaluate the dissolution rate of the ebastine from solid dispersion, a comparative dissolution kinetics test was performed. The original crystalline substance, Kestine film-coated tablets and Kestine freeze-dried tablets were used for comparison.

According to the obtained results (Figure 5), the crystalline substance showed a low dissolution rate (53.5 % after 45 min). The highest dissolution rate was observed to the Kestine original freeze-dried tablets. At the same time, solid dispersion showed the result exceeding the release rate of API from film-coated tablets and approaching the result of freeze-dried tablets.

Based on the study of ebastine release kinetics, it is possible to produce orally disintegrating tablets by direct pressing method based on ebastine ASDS obtained by HME.

## CONCLUSION

The result of this work is the development of ebastine ASDS containing 20 and 30 % of the API with improved pharmacokinetic properties. The possibility of developing ebastine ASDS using crystalline (non-micronised) pharmaceutical substance was demonstrated. The dissolution and release rate of ebastine from ASDS was increased, in comparison with the micronised substance, by hot melt extrusion technology. The optimisation of extrusion technology was performed to reduce the amount of related ebastine impurities in the target ASDS. The profile of dissolution kinetics of the obtained ASDS was investigated, significant improvement of the rate of ebastine dissolution and release from ASDS was demonstrated. The dissolution kinetics of ASDS appeared to be close to orally disintegrating tablets obtained by freeze-drying method. The perspective of further research provides the possibility of producing orally dispersible tablets with ASDS of ebastine by direct compression.

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