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Study on the Solubility of Ketoprofen From Solid Dispersions with Polyvinylpyrrolidone

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Abstract—The solubility of ketoprofen (nonsteroidal anti-inflammatory drug) from solid dispersions based on polyvinylpyrrolidone (PVP-10000, PVP-12600 and PVP-24000) is studied. The use of solid dispersions (SDs) increases the solubility and dissolution rate. The solubility of ketoprofen from SD increases by 1.5–2.6 times. The rate of dissolution from SDs increases by 1.5–3.2 times. The studies conducted by a complex of physical and chemical methods suggest that an improved release of ketoprofen from SDs is due to the generation of solid solution of the active substance in the polymer, the formation of intermolecular hydrogen bonds of the active substance with polyvinylpyrrolidone and the solubilizing effect of the polymer during the dissolution of ketoprofen. The results obtained can be used in the development of fast-dissolving solid dosage forms of ketoprofen with enhanced bioavailability.

Keywords: solid dispersions, solubility, ketoprofen, polyvinylpyrrolidone
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INTRODUCTION

Ketoprofen is a representative of the group of nonsteroidal anti-inflammatory drugs (NSAID). This drug is widely used in the treatment of inflammatory and degenerative diseases of the musculoskeletal system, ischialgia, renal colic, sciatica, and relief of pain in the postoperative and post-traumatic period, often used in gynecological, dental and oncological practice [1, 2].

Ketoprofen is a white or almost white odorless powder (Fig. 1). It is not hygroscopic, easily soluble in alcohol, chloroform, acetone, ether, benzene and strong alkalis, but practically insoluble in water, which limits the possibilities of its use, in particular in the form of fast-dissolving dosage forms (DFs) such as granules and tablets [2, 3].

For water-insoluble active substances (ASs), the rate of absorption is often determined by the rate of their dissolution. Theoretically, the dissolution rate of the active substance can be increased by reducing the size of its particles, which does not always lead to an increase in the rate of its dissolution and absorption. During micronization, there is a sharp increase in the specific surface of the particles and the van der Waals attraction between non-polar molecules is enhanced, which contributes to the aggregation and agglomeration processes. A marked dispersity can lead to a decrease in the pharmacological activity as a result of the sorption of AS on the equipment walls (production losses), as well as adsorption from the air on the surface of particles of gases, moisture, dust, etc. [4, 5].

Obtaining salt forms of poorly soluble ASs only partially solves the problem of their solubility. When the salt form of an AS is dissolved, its ionized form transfers into a solution. However, it is known that the molecules of a substance in the body are absorbed predominantly in a non-ionized form. In this regard, the improvement of the bioavailability of such drugs is still an open question. In addition, obtaining salt forms of AS imposes a number of additional requirements for the manufacture and storage of drugs; for example, it is necessary to maintain a certain pH level. At the same time, difficulties may arise regarding the pharmaceutical incompatibility of the ingredients of the

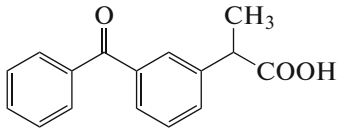

Fig. 1. Ketoprofen, $C_{16}H_{14}O_3$, (2RS)-2-(3-benzoylphenyl)propanoic acid (254.28 g/mol).

manufactured drugs associated with the physicochemical and chemical processes of the drugs' interaction with each other, as well as with excipients or biological fluids during the manufacture, storage, or reception of drugs—for example, the formation of precipitates of the original low-soluble form of drugs, etc. [4, 5].

To increase the solubility and bioavailability of ASs, a method for producing solid dispersions (SDs) is used. SDs are a bi- or multicomponent systems consisting of an AS and carrier. They represent a highly dispersed solid phase of ASs or molecular dispersed solid solutions with the partial formation of complexes with a carrier material of variable composition [6, 7]. Various polymers are used as a carrier for the preparation of SDs.

Currently, there are an increasing number of studies on the increase in the solubility of ketoprofen, and hence its bioavailability. Thus, in patent no. 2353352 of the Russian Federation, the authors describe the preparation of a solid dosage form of ketoprofen for rapid release in the gastrointestinal tract (GIT). Tablets are obtained by directly compressing a mixture of ASs and a lactose mixture with soluble and insoluble polyvinylpyrrolidone (PVP) (kollidon 30 and kollidon CL). However, the mixture of AS and polymer powders is capable of ensuring the dissolution of ketoprofen only in the gastrointestinal tract within 1–8 h [8]. The introduction of ketoprofen in SDs allows us to dissolve ASs in less than 5 min and obtain fast-dissolving drugs used by patients in a dissolved form based on SDs.

The development of composite materials for medical purposes based on PVP K-15 modified with ketoprofen and silver nanoparticles in supercritical carbon dioxide is described in the literature. According to the results of this study, it was established that the material impregnated into supercritical carbon dioxide is characterized by a faster release of ASs [9]. However, the method described in this paper requires the development of a special installation for the impregnation of PVP with ketoprofen in supercritical carbon dioxide, while obtaining SDs by solvent removal is simpler from a technological point of view and cheaper since it allows combining the preparation of SDs with the phase of wet granulation prior to tabletting the fast-dissolving tablets and can be carried out on the available equipment.

At the moment, there are no drug developments on the pharmaceutical market that combine the method of SDs and fast-dissolving DFs. In the literature, there are no examples of obtaining and studying ketoprofen SDs with PVP with increased solubility for further introduction into fast-dissolving DFs of effervescent granules and tablets. Thus, increasing the solubility of ketoprofen by the SD method is an urgent task in pharmaceutical technology.

The aim of the work is to study the solubility of ketoprofen SDs obtained based on polyvinylpyrrolidone.

MATERIALS AND METHODS

Ketoprofen produced by Siwei Development Group LTD (China), which meets the requirements of regulatory documents (USP 38), was used in the study. Polyvinylpyrrolidone with different molecular weights was used as the polymer carrier for SD production: 10000 ± 2000 and 24000 ± 2000 (Sigma-Aldrich, United States), 12600 ± 2700 (AK Sintvita, Russia).

Technology for preparation of solid dispersion. The choice of the technology for manufacturing SDs is based on the physicochemical properties of ASs and polymers. The melting method cannot be used due to the fact that heating leads to the destruction of PVP; therefore, samples of SDs with PVP were prepared by removing the solvent at a temperature that does not cause destruction of the polymer. Ethyl alcohol was used as the common solvent. The calculated amount of AS and the polymer were dissolved in ethanol, then the solvent was evaporated under vacuum in a water bath at a temperature of 40 ± 2°C.

Technology of mixture preparation. Mixtures of ketoprofen and PVP were prepared by co-grinding the components in a mortar for 1 min in the same proportion as in their respective SDs.

Study of ketoprofen dissolution. The obtained SDs are amorphous yellowish powders, prone to sticking. The main problem of the experiment was the impossibility of using the dissolution test according to the general pharmacopoeia monograph OFS.1.4.2.0014.15. In this respect, a modified procedure was developed. Preliminary tests showed that the results of the dissolution test, performed according to the procedure on a rotating basket device, are similar to the results obtained using a modified procedure. The solubility and dissolution rate of the ASs and SDs were studied according to the developed modified procedure. A conical flask with the sample was placed on an MSH Basic magnetic stirrer (200 rpm; IKA, Germany) with thermostatting (37 ± 1°C), and 150 mL of purified water was added. After 5, 10, 15, 20, 30, 40, 50, and 60 min, 5 mL of the solution was taken out and the taken volume was compensated with purified water. The solutions were filtered through Minisart syringe nozzles with a pore size of 0.45 μm (the filter material was nylon). If necessary, the sample was diluted with purified water.

The absorbance of the solution was measured on a UNICO 2800 recording UV spectrophotometer (United States) at the maximum absorption length of ketoprofen (260 ± 2 nm) in quartz cuvettes with a layer thickness of 10.0 mm. Purified water was used as the reference solution. Under the experimental conditions, it was established that the absorbance of PVP solutions

Table 1. Results of study on dissolution of ketoprofen ($n = 5$)

Composition of sample	Weight of AS : polymer sample (g)	Average value of ketoprofen concentration in solution of sample (g/L) after certain period of time from start of dissolution, min							
		5	10	15	20	30	40	50	60
Ketoprofen (AS)	0.6	0.1251	0.1395	0.1459	0.1523	0.1547	0.1593	0.1670	0.1722
AS (recrystallized)	0.6	0.0550	0.1087	0.1304	0.1438	0.1477	0.1560	0.1595	0.1600
Mixture of AS : PVP-12600 (1 : 2)	0.9 : 1.8	0.1610	0.1666	0.1688	0.1631	0.1637	0.1706	0.1744	0.1770
SD AS : PVP-12600 (1 : 1)	0.6 : 0.6	0.0470	0.1001	0.1469	0.1764	0.2091	0.2291	0.2499	0.2611
SD AS : PVP-12600 (1 : 2)	0.6 : 1.2	0.0770	0.1334	0.1959	0.2401	0.2856	0.3179	0.3450	0.3736
SD AS : PVP-12600 (1 : 3)	0.6 : 1.8	0.1251	0.2225	0.2872	0.3343	0.3826	0.4166	0.4315	0.4423
SD AS : PVP-12600 (1 : 4)	0.6 : 2.4	0.1768	0.3122	0.3922	0.4314	0.4217	0.4196	0.4164	0.4143
SD AS : PVP-12600 (1 : 1)	0.9 : 0.9	0.1268	0.2088	0.2470	0.2866	0.3023	0.3245	0.3449	0.3430
SD AS : PVP-12600 (1 : 2)	0.9 : 1.8	0.2262	0.3581	0.4096	0.4270	0.4270	0.4270	0.4270	0.4270
SD AS : PVP-12600 (1 : 3)	0.9 : 2.7	0.0406	0.1274	0.2116	0.2745	0.3162	0.3888	0.4273	0.4555
SD AS : PVP-12600 (1 : 4)	0.9 : 3.6	0.4063	0.4207	0.4350	0.4394	0.4482	0.4535	0.4535	0.4535
SD AS : PVP-12600 (1 : 2)	1.2 : 2.4	0.0763	0.1517	0.2285	0.2786	0.3356	0.3736	0.4086	0.4177
SD AS : PVP-12600 (1 : 3)	1.2 : 3.6	0.1467	0.2190	0.2813	0.3194	0.3709	0.4007	0.4015	0.4045
SD AS : PVP-10000 (1 : 2)	0.9 : 1.8	0.0771	0.1332	0.1880	0.2297	0.2692	0.3278	0.3520	0.3528
SD AS : PVP-24000 (1 : 2)	0.9 : 1.8	0.2471	0.2559	0.2595	0.2673	0.3039	0.3328	0.3427	0.3638

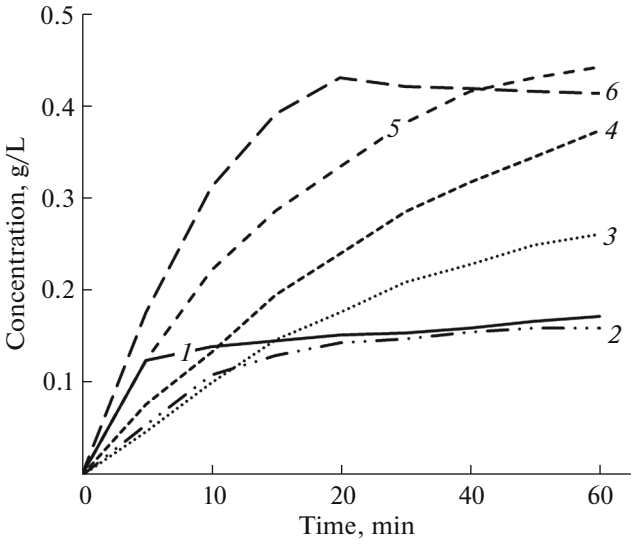

Fig. 2. Dissolution of ketoprofen: (*1*) original powder; (*2*) recrystallized AS (after removal of solvent); (*3*) SD (AS with PVP-12600) (0.6 : 0.6 by weight); (*4*) SD (AS with PVP-12600) (0.6 : 1.2 by weight); (*5*) SD (AS with PVP-12600) (0.6 : 1.8 by weight); (*6*) SD (AS with PVP-12600) (0.6 : 2.4 by weight).

at the selected wavelength was zero. The results of measurements of the ketoprofen concentration in the studied solutions are presented in Table 1 and Figs. 2–4.

IR absorption spectra were recorded from samples in the form of disks with potassium bromide relative to air (background spectrum) on an FSM 1201 FTIR spectrophotometer (Russia).

Sample preparation. Samples of AS, SD, and PVP (~0.5 mg) containing the same amount of ketoprofen and/or the polymer were weighed on an analytical balance, then potassium bromide powder was added bringing the total weight of the sample to ~300 mg. The obtained sample was crushed in a mortar for 2 min and pressed in a mold (PF 13, Infraspek) with a diameter of 13 mm with preliminary air evacuation for 5 min at a force of 8 Tf.

Microcrystalloscopic analysis was performed using a Levenhuk D50LNG digital microscope (China). Ketoprofen was studied in the form of the original substance, as well as after recrystallization from ethanolic solution (in order to compare the results obtained using SD). The sample of ketoprofen substance for microscopy was prepared as follows: a small amount of the studied powder was applied to the surface of a microscope slide, mixed with a drop of vaseline oil, and microscoped under a cover glass. In the case of ketoprofen SD, a drop of the solution of AS and the polymer (in appropriate proportions) in a common solvent (ethyl alcohol) was applied to a microscope slide and microscoped after the solvent was removed. In the case of recrystallized ketoprofen, a drop of ethanol solution of the AS was applied on a microscope slide and microscoped after removal of the solvent. Similarly, the SD carriers were studied. The investigated microcrystalline samples are presented in Fig. 5. All pictures were taken at a magnification of ×4.

RESULTS AND DISCUSSION

Solid dispersions of ketoprofen with PVP are yellowish amorphous powders that are prone to sticking. The results of measurements of the ketoprofen concentration in solutions in the study of its solubility in the form of a powder (a mixture of AS with PVP) and SD are presented in Table 1 and Figs. 2–4. Samples for the dissolution study were taken so as to obtain saturated AS solutions. The relative error of the mean values of the ketoprofen concentration given in the table ranged from 3.6 to 4.3%.

The increase in the solubility was calculated as the ratio of the concentration of the saturated solution obtained by dissolving the SDs to the concentration of the saturated solution obtained by dissolving the ketoprofen substance after 60 min after the start of the dissolution.

As follows from the data presented in Table 1 and Figs. 2–4, the use of SDs in all cases increases the solubility and dissolution rate of the ASs.

The effect of the ratio of the AS and the polymer, as well as the ketoprofen content in the SDs was studied using PVP-12600 as an example. The ratio of the AS and the polymer most strongly affects the dissolution rate and solubility. Under the ketoprofen content in SDs of 0.6 g and at a ratio with polymer of 1 : 1, the solubility of the AS increases by 1.5 times. The concentration of the AS 60 min after the start of the dissolution from the substance was 0.1722 g/L, and the concentration of the AS in the SD solution with PVP-12600 (1 : 1 or 0.6 : 0.6 by weight) at the same time point was 0.2611 g/L. The solubility of ketoprofen increases with an increasing PVP content in the SD (Fig. 2). With the ratio between the AS and the polymer increasing from 0.6 : 0.6 to 0.6 : 1.2, the solubility increased by 2.2 times (the concentration of ketoprofen after 60 min from the start of the AS dissolution was 0.3736 g/L). With the tripling in the PVP content to a ratio with AS of 0.6 : 1.8, the solubility increased by 2.5 times (up to 0.4423 g/L). A further increase in the PVP content to the ratio of 1 : 4 (0.6 : 2.4 by weight) does not lead to a more intensive increase in the solubility, which grows by 2.4 times (to 0.4143 g/L).

A similar dependence was obtained in the study of SDs with an AS content of 0.9 g (Fig. 3). Thus, the solubility of ketoprofen from an SD of 1 : 1 (0.9 : 0.9 by weight) doubled. The maximum concentration of the AS (0.3449 g/L) is reached 50 min after the start of the dissolution and after 60 min remains almost unchanged (0.3430 g/L). In an SD of 1 : 2 (0.9 : 1.8 by weight), the solubility increased by 2.5 times (the ketoprofen concentration after 60 min from the start of

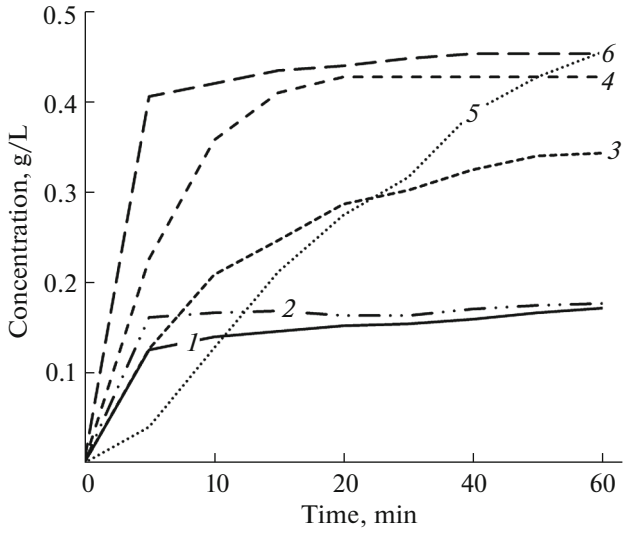

Fig. 3. Dissolution of ketoprofen: (*1*) original powder; (*2*) mixture of AS with PVP-12600 (0.9 : 1.8 by weight); (*3*) SD (AS with PVP-12600) (0.9 : 0.9 by weight); (*4*) SD (AS with PVP-12600) (0.9 : 1.8 by weight); (*5*) SD (AS with PVP-12600) (0.9 : 2.7 by weight); (*6*) SD (AS with PVP-12600) (0.9 : 3.6 by weight).

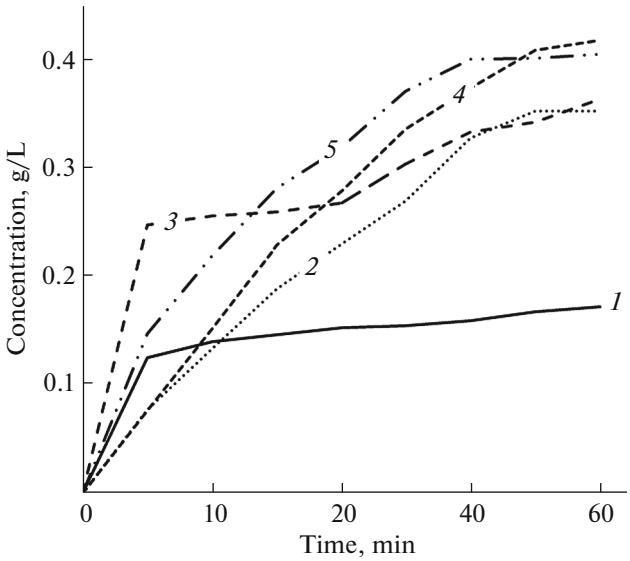

Fig. 4. Dissolution of ketoprofen: (*1*) original powder; (*2*) SD (AS with PVP-10000) (0.9 : 1.8 by weight); (*3*) SD (AS with PVP-24000) (0.9 : 1.8 by weight); (*4*) SD (AS with PVP-12600) (1.2 : 2.4 by weight); (*5*) SD (AS with PVP-12600) (1.2 : 3.6 by weight).

the dissolution was 0.4270 g/L). In an SD of 1 : 3 (0.9 : 2.7 by weight) and an SD of 1 : 4 (0.9 : 3.6 by weight), the solubility increased by 2.6 times (the concentration of ketoprofen after 60 min from the start of the dissolution was 0.4555 and 0.4535 g/L, respectively). As confirmation, Fig. 3 shows the kinetic curves of the dissolution from an SD with the AS content of 0.9 g.

As can be seen from Fig. 4, an increase in the ketoprofen content in SD to 1.2 g did not lead to a statistically significant increase in solubility compared with the SD in which the content of the AS was 0.9 g. Thus, with an increase in the content from 1 : 2 (1.2 : 2.4 by weight) to 1 : 3 (1.2 : 3.6 by weight) the solubility increases by 2.4 times (0.4177 g/L) and by 2.3 times (0.4045 g/L), respectively.

With the ratio between the AS and the polymer increasing from 1 : 1 to 1 : 2, the solubility increases on average by 1.34 times; with the ratio increasing from 1 : 2 to 1 : 3, the solubility increases on average by 1.12 times; and with an increase from 1 : 3 to 1 : 4, the solubility increases on average by 0.97 times. Consequently, 1 : 2 and 1 : 3 can be considered as the optimal ratios. However, due to the fact that an increase in the PVP content can often have a negative effect on the quality indicators of solid DFs (compressibility, strength) the ratio of AS : PVP-12600 of 1 : 2 is chosen as the best one.

When studying SDs with PVP having other molecular weights, under the ratio of the AS equal to 2 : 1, in the case of PVP-10000, the solubility doubled (0.3528 g/L), and in the case of PVP-24000, it increased by 2.1 times (0.3638 g/L). Thus, it is most expedient to use PVP-12600 as the polymer carrier, since its use leads to an increase in the solubility of the AS from the SD on average by 2.4 times.

It was established that the effect of an SD on the rate of ketoprofen dissolution is also significant. For example, in comparison with the substance when dissolving SD AS : PVP-12600 (1 : 2 or 0.9 : 1.8 by weight and 1 : 4 or 0.6 : 2.4 by weight) in the first 15–30 min, the AS dissolution accelerates by 2.8 times from the average value of 0.1510 g/L (AS) to 0.4151 g/L (SD).

In order to prove the advantages of using the technological approach of the SD, the dissolution kinetics of the AS from its mixture with PVP-12600 was studied in the ratio of 0.9 : 1.8 by weight. Mixing the AS and PVP barely increases the solubility of ketoprofen (statistically insignificant increase by 1.07 times), and only slightly accelerates the dissolution process in the first 15 min. However, within 20 min, the AS concentration in the mixture with PVP is 0.1631 g/L, whereas in the solution of the substance it is 0.1523 g/L.

It was found that the recrystallization of the AS does not affect the rate of dissolution and the solubility. For this, the dissolution kinetics of ketoprofen, previously recrystallized from ethyl alcohol, was studied. As follows from the data presented in Table 1 and Fig. 2, the maximum concentration in the solution of the recrystallized AS was reached 60 min after the start of the dissolution and was 0.1600 g/L, which is almost identical to the concentration of the solution of the initial AS after the same period of time (0.1722 g/L).

According to the results of the study, it can be concluded that the increase in the rate of dissolution and

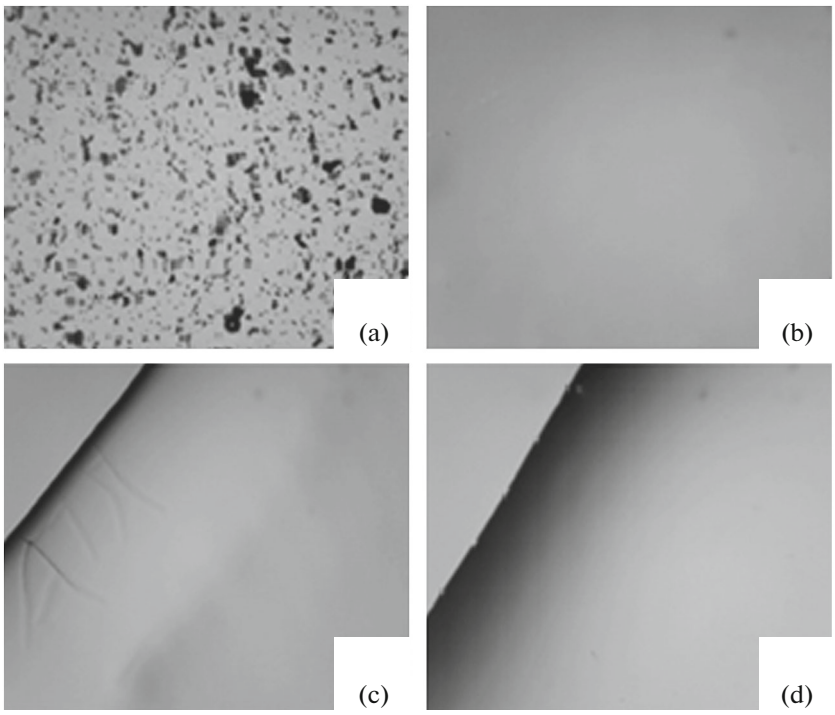

Fig. 5. Results of microcrystalloscopy: (a) original powder, (b) recrystallized AS, (c) PVP-12600, (d) SD (AS : PVP-12600 = 0.9 : 1.8 by weight).

the solubility of ketoprofen is due to the technology for producing the SD by the method of solvent removal rather than by the presence of the polymer (in the mixture) or recrystallization process.

To identify the mechanisms underlying the increase in the solubility of ketoprofen from SDs, methods of analysis such as microcrystalloscopy and IR spectroscopy were used.

According to the data of microcrystalloscopy in a light background of the microscope field, we have listed the studied objects:

—the powder of the original substance of ketoprofen is represented by a large number of small formless transparent crystals (it can be assumed that the AS was previously crushed, since debris is not characteristic and difficult to measure, Fig. 5a);

—recrystallized ketoprofen: after removing the solvent, ketoprofen loses its crystalline structure and an amorphous transparent film is formed (Fig. 5b);

—PVP-12600: after removing the solvent, PVP-12600 is represented by a wavy layer of transparent film, bursting along the edges, without any crystals (Fig. 5c);

—SD with PVP: there are no visible signs of ketoprofen as a separate solid phase; the SD is a transparent homogeneous film representing a 33% solution of the AS in the polymer (Fig. 5d).

Thus, based on the results of the microcrystalloscopic analysis, we can conclude that the cause for the observed increase in the solubility of ketoprofen from SDs with PVP-12600 is not the loss of the crystalline structure (which probably did not occur, since the original ketoprofen is more similar to amorphous solid) but the solubilizing action of PVP and the disintegration of the AS molecules into PVP—the preparation of a solid solution of ketoprofen in PVP even before the stage of dissolution in water.

Analysis of the changes in the microstructure of the studied AS-PVP systems at different concentrations of components for describing the processes of the AS release from the SDs is undoubtedly a separate topic for future research.

To confirm the assumption of the formation of the AS-PVP hydrogen bond, IR spectra of PVP-12600, ketoprofen and its SDs with PVP-12600 were obtained and analyzed in a ratio of 1 : 2 (0.9 : 1.8 by weight). Preliminarily, the effect of solvents on PVP in the process of preparing SDs was studied by IR spectroscopy. Significant differences in the characteristic frequencies between the IR spectra of the polymer before and after removal of the solvent were not found.

A characteristic feature of the IR spectra of SDs with PVP is a reduction in the intensity of a significant number of characteristic bands of the AS as a part of the SD. This phenomenon was repeatedly noted in a number of other works [7, 10] and is probably associated with a significant shielding effect of the polymer. Due to the potent shielding effect of the polymer, the infrared spectrum of solid dispersion of ketoprofen

and PVP, which represents a 33% solid solution of the AS in PVP, is almost identical in appearance to the IR spectrum of PVP, which suggests that no significant covalent chemical interactions between components of SDs leading to a change in the chemical structure of the AS in the process of obtaining SDs occur. Any interactions are of a non-covalent nature, which allows us to eliminate the chemical modification of ketoprofen and to guarantee the safety of the therapeutic effect of the AS under the conditions of SDs.

When dissolving SDs, the following mechanism is possible: when released from the matrix of the polymer as it is dissolved, the molecules of poorly soluble hydrophobic ketoprofen are solubilized by PVP and a stable system such as a colloidal solution of AS in water is formed. Therefore, when an SD is dissolved, a significant increase in the solubility and dissolution rate of ketoprofen in the water is observed, due to which it becomes possible to obtain its saturated solutions with a consistently high level of concentration exceeding the concentration of the solution of the initial AS.

CONCLUSIONS

The studies were carried out within a promising scientific and practical direction developed in Russia—SDs in medicine and pharmacy. SDs of ketoprofen with PVP, obtained by solvent removal, were first investigated. The results of the study indicate an increase in the solubility and dissolution rate in water of ketoprofen from solid dispersions with PVP, obtained by the method of solvent removal. PVP-12600 was chosen as the optimal carrier for producing SDs of ketoprofen under a ratio with AS of 2 : 1 (1.8 : 0.9 by weight). This ratio provides the greatest increase in the solubility and dissolution rate of the AS. From the standpoint of the conducted complex of studies, it can be assumed that the increase in the solubility of ketoprofen from SDs with PVP is associated with obtaining a solid solution of the AS in the polymer, the formation of intermolecular hydrogen bonds of the AS with PVP, and with the solubilizing effect of the polymer under the dissolution of ketoprofen.

The results obtained in the course of this study can be applied to the development of rapidly dissolving (effervescent) solid DFs of ketoprofen with enhanced bioavailability.

REFERENCES

1. Mudit Dixit, Parthasarthi K. Kulkarni, and Panner Selvam, *Indian J. Pharm. Educ. Res.*, 2012, vol. 46, no. 4, p. 296.
2. Belyatskaya, A.V., Krasnyuk, I.I., Krasnyuk, I.I., Machikina, T.E., Korosteleva, Yu.A., Stepanova, O.I., Skovpen', Yu.V., and Vorob'ev, A.N., *Razrab. Registr. Lek. Sredstv*, 2017, no. 2, p. 102.
3. *European Pharmacopoeia*, Strasbourg, 8th ed.
4. Krasnyuk, I.I., Jr., *Pharm. Chem. J.*, 2009, vol. 43, no. 4, p. 226.
5. Khabriev, R.U., Popkov, V.A., Reshetnyak, V.Yu., Krasnyuk, I.I., and Lapshova, A.S., *Ross. Med. Zh.*, 2009, no. 2, p. 42.
6. Krasnyuk, I.I., Belyatskaya, A.V., Krasnyuk, I.I., Stepanova, O.I., Ovsyannikova, L.V., Grikh, V.V., Allenova, T.M., and Odintsova, E.B., *Farmatsiya*, 2016, no. 6, p. 7.
7. Krasnyuk, I.I., Jr., Beliatskaya, A.V., Krasnyuk, I.I., Stepanova, O.I., Korol', L.A., Valeeva, A.M., Grikh, V.V., Ovsyannikova, L.V., and Kosheleva, T.M., *BioNanoScience*, 2017, vol. 7, no. 2, p. 340. doi 10.1007/s12668-016-0342-6
8. RF Patent 2353352, *Byull. Izobret.*, 2007, no. 12.
9. Nikitin, L.N., Vasil'kov, A.Yu., Banchero, M., Manna, L., Naumkin, A.V., Podshibikhin, V.L., Abramchuk, S.S., Buzin, M.I., Korlyukov, A.A., and Khokhlov, A.R., *Russ. J. Phys. Chem. A*, 2011, vol. 85, no. 7, p. 1190.
10. Krasnyuk, I.I., *Doctoral (Pharm.) Dissertaion*, Moscow: Sechenov First Moscow State Med. Univ., 2010.

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