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POLYMER SOLID DISPERSION SYSTEM OF NIMESULIDE: *IN VITRO* DISSOLUTION ASSESSMENT, THERMODYNAMIC AND PHYSICOCHEMICAL CHARACTERISTICS

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Nimesulide is a well-known non-steroidal anti-inflammatory active pharmaceutical ingredient (API), but it is poorly soluble in water, which makes its bioavailability relatively low.

The aim of the work *was to investigate the effect of polyvinylpyrrolidone (PVP) of different molecular weights on the phase solubility of nimesulide and to evaluate the thermodynamic parameters of the obtained complexes in order to determine the optimal polymer for further development of a solid dispersed system (SDS) of nimesulide and to study its physicochemical properties, which lead to an improvement in the solubility of API in the composition of the obtained composite material.*

Materials and methods. *The dependence of the nimesulide dissolution profile in water on the concentration of PVP of different molecular weights was studied by the Higuchi and Connors method. SDS was prepared by the «green» method of solvent evaporation and were characterised by Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC) and powder X-ray diffraction (PXRD) and were evaluated for dissolution profiles.*

Research results. *The influence of PVP of different molecular weights on the phase solubility of nimesulide was studied, and it was found that the best increase in solubility in water was observed in the system with PVP K-25 – 5.27 times. Thermodynamic parameters of this composition were also investigated. The FTIR results indicate that the formation of complexes between the API and the polymer is predominantly due to hydrogen bonds. DSC and PXRD showed that nimesulide is present in SDS in an amorphous form. The results of the in vitro release kinetics study showed that the release rate of nimesulide from the formed SDS was higher than the dissolution rate of the comparison drug.*

Conclusions. *A solid dispersed system prepared by the «green» method of solvent evaporation using PVP K-25 as a carrier can be used as a good strategy for formulating effective anti-inflammatory drugs of nimesulide with increased bioavailability*

Keywords: *nimesulide, phase solubility, thermodynamic characteristics, polyvinylpyrrolidone, solid dispersed system, increase in solubility*

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1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely used medicinal products worldwide [1, 2]. Since the discovery of aspirin by Felix Hoffmann from Bayer Industrial (Germany) in 1897, non-steroidal anti-inflammatory drugs have gained the status of "best sellers" in the pharmaceutical industry. They hold leading positions in the pharmaceutical market because they are the first-choice drugs for treating various inflammatory conditions, pain, and fever [3, 4].

Medicines based on nimesulide have unique properties among a wide range of NSAIDs. It is the only representative of non-steroidal anti-inflammatory active pharmaceutical ingredients (APIs) in the class of arylsulfonamides [4]. Nimesulide is a potent and selective inhibitor of cyclooxygenase-2 (COX-2), highly effective in suppressing various forms of pain and inflammatory conditions with minimal adverse effects on the gastrointestinal tract, rapid onset of analgesic action, and relatively low toxicity [5, 6]. Medicines based on nimesulide are widely used to treat inflammatory processes, acute pain, symptomatic treatment of osteoarthritis, and primary dysmenorrhea [5, 6]. However, with frequent use, one should always consider the API's toxicological profile, which is associated with the risk of liver damage. This is why nimesulide drugs have been banned in some European countries [7, 8].

The analysis of literary sources established that nimesulide's efficacy and powerful anti-inflammatory and analgesic activity is not limited to COX-2 inhibition only [6, 9, 10]. Thus, the mechanisms of action of nimesulide include inhibition of histamine release from mast cells and basophils [11], the release of tumour necrosis alpha-factor (TNF-α) [12], formation of reactive oxygen species (ROS) [13], as well as lowering the level of metalloproteinases that can destroy proteoglycans, collagens

and other components of the connective tissue matrix in the joints [14]. The multifactorial mechanism of action of nimesulide has opened potential opportunities for using nimesulide for new therapeutic purposes, some of which have already been tested experimentally [15–17].

According to the biopharmaceutical classification system (BCS), nimesulide, like most non-steroidal anti-inflammatory APIs, belongs to class II. It has high permeability to lipophilic biological membranes but low solubility in water (~0.01 g/l) [18, 19]. Due to low water solubility, the release of this API from solid oral dosage forms slows down, and its bioavailability decreases. It creates prerequisites for the use in medical practice of excessive doses of nimesulide and the occurrence of undesirable adverse effects [20]. That is why studies aimed at increasing the solubility of nimesulide are critical. After all, increasing the solubility in water will improve the API's bioavailability and the possibility of reducing the dose while maintaining a high pharmacological effect.

Scientists have already tried to solve the problem of the low solubility of nimesulide using various pharmaceutical technologies. The methods that have been applied to increase the solubility of nimesulide include the technique of using cosolvents [21, 22], complex formation with cyclodextrins [22–24] and phospholipids [25], the formation of nanoemulsion systems [26], as well as the method of formation of solid dispersed systems (SDSs) [22, 27–29]. Each method has advantages and disadvantages, which can somewhat limit its use in the pharmaceutical field. That is why, even now, there is a need for research into methods of increasing the solubility of nimesulide.

Among all the methods mentioned above, one of the most interesting and practical approaches for increasing solubility is represented by solid dispersed systems [30]. A solid dispersed system is defined as the dispersion of one or more active components in a suitable inert carrier or matrix in a solid state. It can be prepared by solvent evaporation, solvent melting, and melt evaporation methods [31]. The popularity of SDS is evident because, in recent years, the number of studies and patents on the methods and use of SDS has increased significantly [31, 32]. The SDS formation method was effectively used to significantly improve the dissolution rate and oral absorption of many sparingly soluble APIs [33, 34]. Particles in solid dispersions have a reduced size, mostly amorphous state, and a higher degree of porosity and wettability, significantly increasing the solubility of sparingly soluble APIs. Also, a significant advantage of this method is the possibility of preparing solid dispersed systems in different ways [33, 34].

Literature data indicate that solid dispersed systems of nimesulide were quite successfully produced by melting [27], hot extrusion [28], and solvent evaporation methods [22, 27, 29]. It is worth noting that preparing solid dispersed systems by solvent evaporation is one of the easiest and most popular methods of SDS formation [35]. Its basic principle is that a sparingly soluble API and a carrier are mixed and dissolved in a common solvent, which evaporates. After that, the obtained SDS is crushed and sieved. Typical solvents used in this method are water, alcohols (methanol, ethanol, or isopropanol), or other organic solvents, such as dichloromethane, acetone, ethyl acetate, etc. [35, 36].

According to literature sources, researchers used an organic solvent, methanol, to obtain the SDS of nimesulide by solvent evaporation [27, 29]. However, it is worth noting that the complete removal of this solvent, like many other organic solvents, poses a particular problem, and its residual content in SDS, in turn, can cause certain toxicity [31, 34].

The aim of the work was to investigate the effect of polyvinylpyrrolidone (PVP) of different molecular weights on the phase solubility of nimesulide and to evaluate the thermodynamic parameters of the obtained complexes in order to determine the optimal polymer for further development of a solid dispersed system of nimesulide following the "green chemistry" principles and to study its physicochemical properties, responsible for improving the solubility of API in the composition of the obtained composite material.

Polyvinylpyrrolidone was chosen as a polymer carrier for forming nimesulide SDS in this work; it is a universal and popular polymer that has been used in the pharmaceutical industry for a long time, particularly for developing new API delivery systems. This polymer has many advantages: it is non-toxic, non-ionic, inert, heat-resistant, pH-stable, and biocompatible [37].

2. Research planning (methodology)

The methodology of the research includes:

1. Analysis of the scientific literature.

2. Investigation of the effect of the concentration of pharmaceutically acceptable polyvinylpyrrolidone polymer of different molecular weights (PVP K-12, PVP K-17, PVP K-25) on the phase solubility of nimesulide to determine the type of polymer that most effectively improves the solubility of API in aqueous medium.

3. Calculation of the thermodynamic parameters of the best composition of nimesulide with PVP to understand the forces controlling the formation of complexes between the API and the polymer, as well as the potential mechanisms responsible for improving the solubility of nimesulide in the presence of the PVP.

4. Samples of a solid dispersed system of nimesulide based on polyvinylpyrrolidone were prepared using the «green» method of solvent evaporation.

5. Investigation using Fourier transform infrared (FTIR) spectroscopy to determine the interaction between nimesulide and the polymer that occurs during the formation of SDS, in particular, to establish potential interactions through the formation of hydrogen bonds, which can improve the solubility of the API and ensure better physical stability of the amorphous form of the resulting SDS.

6. Investigation using differential scanning calorimetry (DSC) and powder X-ray diffraction (PXRD) to determine the change in the degree of crystallinity of the API in SDS due to dispersion in an amorphous polymer carrier. The transition of nimesulide from the crystalline to the amorphous state during the formation of SDS may

be one of the mechanisms responsible for its improved dissolution in the obtained polymer composites.

7. The release profile of nimesulide from SDS was investigated using the *in vitro* method using the «Dissolution» test and a comparison with the reference drug.

3. Materials and methods

The research was conducted in February–September 2024.

3. 1. Materials

The following materials were used during the experimental studies: nimesulide (Mangalam Drugs and Organics Ltd., India); polyvinylpyrrolidone of three different types: PVP K-12 (average molecular weight 2,500 Da), PVP K-17 (average molecular weight 10,000 Da) and PVP K-25 (average molecular weight 30,000 Da) from JRS PHARMA GmbH & Co. KG (Germany); Aulin granules for oral suspension, 100 mg/2 g (Angelini Francesco, Italy); potassium bromide (Sigma-Aldrich, USA); 1-substituted potassium phosphate (Merck, Germany); finely granular sodium hydroxide (Merck, Germany).

3. 2. Methods

Phase solubility study.

The study of nimesulide phase solubility at appropriate concentrations of pharmaceutically acceptable polymer carriers was conducted according to the method described by Higuchi and Connors [38].

Excess nimesulide (0.5 mg) was placed into 2 ml Eppendorf microtubes. Polyvinylpyrrolidone solutions of different types (PVP K-12, PVP K-17, and PVP K-25) were added to the API; their concentrations increased according to the Fibonacci sequence (1.33–12.00 mM). At least three samples of each molar ratio were prepared.

Subsequently, these solutions were mixed using a TS-100C thermal shaker with an SC-24C block (Biosan, Latvia) for 30 minutes at 37.0±0.5 °C. Next, the mixture was centrifuged on a CM-3 centrifuge (Micromed, China) for 20 minutes at 6,000 rpm to separate solid and aqueous phases.

After the end of the centrifugation process, nimesulide assay in the supernatant liquid was measured by the spectrophotometric method on the OPTIZEN POP UV spectrophotometer (Mecasys, South Korea) at a wavelength of λ=400 nm with the addition of 0.1 M NaOH [39] according to a previously plotted calibration graph of the relation between nimesulide concentration and the optical solution density (R^2=0.9999).

The nimesulide-polymer system, which showed the best indicator of improvement of nimesulide solubility during the study of phase solubility profiles, was exposed to four different temperatures: 25.0±0.5 °C; 30.0±0.5 °C; 37.0±0.5 °C; 40.0±0.5 °C [40]. During the experiment, the temperature values did not exceed 40.0 °C since the goal was to study the nimesulide dissolution profile in the SDS composition in environments close to physiological conditions.

The stability constants, SC, were calculated from the linear part of the phase solubility diagram according to the Higuchi-Connors equation (eq. (1)) [38, 40]:

$$K_s = \frac{Slope}{S_o\left(1-Slope\right)}, \quad (1)$$

where *Slope* is the angular slope factor obtained by linear regression on the straight part of the solubility diagram; S_0 – API solubility in the absence of polymer.

The dissociation constant is inversely proportional to the complex formation constant and can be calculated according to eq. (2) [41]:

$$K_D = \frac{1}{K_S}. \quad (2)$$

Study of thermodynamic characteristics.

Based on the obtained phase solubility data, we also calculated the thermodynamic characteristics of the API system with the polymer, in particular, such as the Gibbs free energy index, free energy change, enthalpy, and entropy change [42]. These indicators are necessary to understand the thermodynamic forces that control the formation of complexes between the API and the polymer and that are crucial for predicting the system's behavior [43].

The change in Gibbs free energy was calculated according to eq. (3):

$$\Delta G_{tr}^0 = -RT \log\frac{S}{S_0}, \quad (3)$$

where R is the gas constant; T is the reaction's absolute temperature; S/S_0 is the ratio between the API solubility values in the polymer's presence and the pure API's solubility value [44].

Calculations of Gibbs free energy were carried out according to eq. (4):

$$\Delta G^0 = -2.303\ RT \ln K_s, \quad (4)$$

where K_s is the stability constant of the complex [44].

The enthalpy change (ΔH^0) was determined from eq. (5) [44]:

$$Spole = \frac{\Delta H^0}{2.303R}, \quad (5)$$

where *slope* is the tangent of the angle of inclination of the straight line formed using the values of $\ln K_s$ and $1/T$ of the integrated form of the Van't-Hoff equation (eq. (6)) [45]:

$$\ln K_s = -\frac{\Delta H^0}{RT} + \frac{\Delta S^0}{R}. \quad (6)$$

Entropy changes (ΔS^0) were calculated according to eq. (7) [45, 46]:

$$\Delta G^0 = \Delta H^0 - T\Delta S^0. \quad (7)$$

Preparation of a solid dispersed system of nimesulide with a polymer carrier.

The required amount of nimesulide (1.0 g) and polyvinylpyrrolidone polymer carrier (19.0 g) was weighed on an AS 60/220 R2 analytical balance (Radwag, Poland). They were successively poured into a flask, and then water obtained using a laboratory RO-4 water treatment plant (Werner, Germany) was added to this mixture. The resulting solution was heated using a Brookfield TC-200 water thermostat with a Brookfield TC-350 cooling system (Brookfield, UK) at 37.0±0.5 °C and intensively stirred for 60 min. The aqueous phase was decanted and dried in an SP-50C oven (Riva-Stal, Ukraine) for 24 h at a temperature of 50.0±0.5 °C to the constant weight.

The obtained solid dispersed system of nimesulide was crushed, sieved through a sieve with a mesh size of approximately 150 μm, and used for further studies.

Fourier transform infrared spectroscopy method.

FTIR spectra of pure nimesulide, the polymer, and the formed solid dispersed system were obtained using a Spectrum 1000 FTIR spectrometer (Perkin Elmer, USA). FTIR spectra of SDS and components were recorded in KBr tablets in the range of wave numbers from 4,000 to 400 cm^{-1} during 16 scans with a resolution of 2 cm^{-1}.

Differential scanning calorimetry method.

Thermal analysis of the samples was performed using the DSC Q2000 (TA Instruments, USA). Samples of pure nimesulide, polymer and solid dispersed system (approximately 5 mg) were weighed, placed in aluminium pans that were sealed with a lid and heated in the instrument at 10 °C/min from 20 to 300 °C under a dry nitrogen gas purge. An empty pan sealed with its lid was used as the reference. Data analysis was performed using TA Universal Analysis software.

Powder X-ray diffraction method.

Crystalline and amorphous phases of the samples under study were identified through powder X-ray diffraction analysis. X-ray powder diffractograms of all samples were obtained by using an apparatus named Siemens D500 X-ray Diffractometer (Siemens, Germany), using CuKα radiator (λ=1.54184 Å) with a Ni filter. The scanning rate was in the 2θ range of 5–60° with a scan step size of 0.02° (2θ) and a scan step time of 10 s.

Study of the nimesulide release kinetics in vitro.

The study of dissolution profiles was carried out on a VK7000 paddle dissolution device with a VK750D water heater (Vankel, USA) according to the EP method 2.9.3 [47] in buffer media pH 6.8; 7.5 and 7.8. When studying the dissolution profiles of nimesulide, it was taken into account that the active pharmaceutical ingredient is a weak acid with low solubility in water. Therefore, using standard media with low pH values (1.2–6.8) for comparing dissolution profiles is impractical [39].

The volume of the dissolution medium was 900 ml, the paddle rotation speed was 50 rpm, and the temperature was 37.0±0.5 °C.

Sampling was conducted in 5, 10, 15, 20, 30, 45, 60, and 90 minutes after the start of the test. The amount of solution sampled for testing (5.0 ml) was compensated with the same volume of buffer solution heated to a temperature of 37.0±0.5 °C.

The degree of nimesulide release from SDS was determined by the spectrophotometric method in the ultraviolet region on an OPTIZEN POP UV spectrophotometer (Mesasys, South Korea) at a wavelength of 400 nm with the addition of NaOH solution according to a previously plotted calibration graph of the dependence of nimesulide concentration on the absorbance of the solution (R^2=0.9999) [39].

Aulin, granules for oral suspension, 100 mg/2 g (Angelini Francesco, Italy), was used as the reference drug.

Statistical data analysis.

Results were expressed as mean±standard deviation evaluated in three independent replicates. Data were analysed for statistical significance using one-way ANOVA with Tukey HSD post-hoc test. Values of $p \leq 0.05$ were considered reliable.

4. Results

4. 1. Effect of polyvinylpyrrolidone of different molecular weights on the phase solubility of nimesulide in water

The phase solubility of nimesulide in the complex with polymer-carriers – PVP of different molecular weights was studied. The obtained data are presented in the form of curves – profiles of the phase solubility of nimesulide at the corresponding concentrations of polymers PVP K-12, PVP K-17, and PVP K-25 at a temperature of 37.0±0.5 °C (Fig. 1).

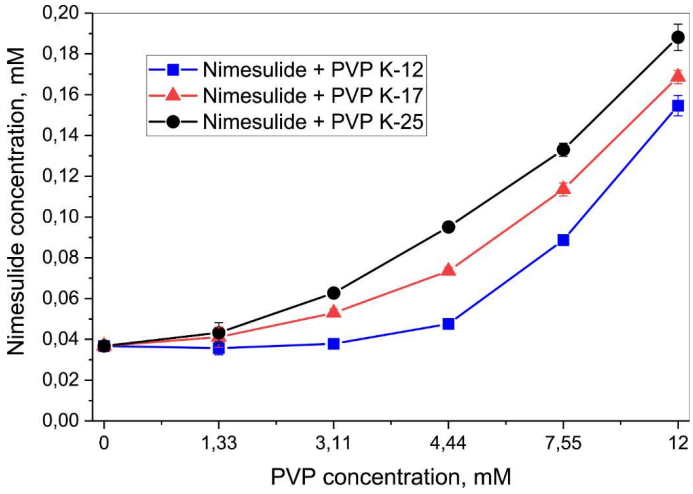

Fig. 1. Profile of the phase solubility of nimesulide at a corresponding concentration of polyvinylpyrrolidone of different molecular weights at a temperature of 37.0±0.5 °C

The obtained data indicate that the increase in solubility of nimesulide depends on the formulation of the investigated compositions. The solubility of nimesulide increases as the amount of polyvinylpyrrolidone in the system increases.

The figure also shows that the solubility increases to a greater extent with an increase in the PVP molecular

weight. Thus, according to the graphic data, PVP K-17 increases the solubility of nimesulide by 4.75 times, which is a better indicator compared to PVP K-12, the presence of which improves the API solubility only by 4.36 times. However, the maximum value of nimesulide solubility increase is observed in the system with PVP K-25 – 5.27 times.

Considering the best indicator of the improvement of API solubility in the system based on PVP K-25, it was chosen to study the influence of variable temperature on phase solubility.

The study results of the influence of four different temperatures on the phase solubility of nimesulide in a complex with PVP K-25 are presented in Fig. 2, *a–d*.

The experiment results indicate a linear increase in the solubility of nimesulide in the aqueous medium with increasing temperature and the concentration of the water-soluble polymer PVP K-25. The maximum value of the improvement in nimesulide solubility in the presence of the polymer was recorded at the test temperature of 40.0±0.5 °C – 5.73 times.

The slope angle, stability and dissociation constants of intermolecular complexes of nimesulide system with PVP K-25 were also calculated at temperature values of 25.0±0.5 °C; 30.0±0.5 °C; 37.0±0.5 °C; 40.0±0.5 °C. The results are shown in Table 1.

According to the results in Table 1, it is the nimesulide system with PVP K-25 that has the highest value of the stability constant.

Table 1

Slope angle, stability, and dissociation constants of nimesulide in the polymer composition based on PVP K-25 in water at different temperatures

Temperature	*Slope*	K_S	K_D
25.0±0.5 °C	0.0219	627.5628	0.00159
30.0±0.5 °C	0.0242	695.1058	0.00144
37.0±0.5 °C	0.0302	872.8128	0.00115
40.0±0.5 °C	0.0344	998.5217	0.00100

4. 2. Thermodynamic characteristics

According to the results of the phase solubility of nimesulide in the presence of the polymer at different temperature values, the thermodynamic parameters characteristic for the formation of the complex were calculated [48, 49].

The results of calculations of the values of change in Gibbs free energy are shown in Table 2.

Values of enthalpy and entropy changes were calculated according to equations (5)–(7) and according to the Van't Hoff plot – a plot of the dependence between ln K_s and 1/*T*. This plot is shown in Fig. 3.

Table 2

The value of the Gibbs free energy change (ΔG^0_{tr}, kJ×M^{-1}) for the nimesulide system with PVP K-25 at different temperatures

PVP K-25 concentration, mM	Temperature			
	25 °C (298 K)	30 °C (303 K)	37 °C (310 K)	40 °C (313 K)
1.33	–0.062±0.054	–0.064±0.055	–0.211±0.056	–0.636±0.081
3.11	–0.444±0.010	–0.518±0.036	–0.631±0.033	–1.029±0.024
4.44	–0.939±0.023	–0.926±0.049	–1.098±0.022	–1.391±0.034
7.55	–1.137±0.052	–1.223±0.050	–1.473±0.027	–1.798±0.021
12.00	–1.466±0.067	–1.604±0.026	–1.861±0.039	–1.972±0.018

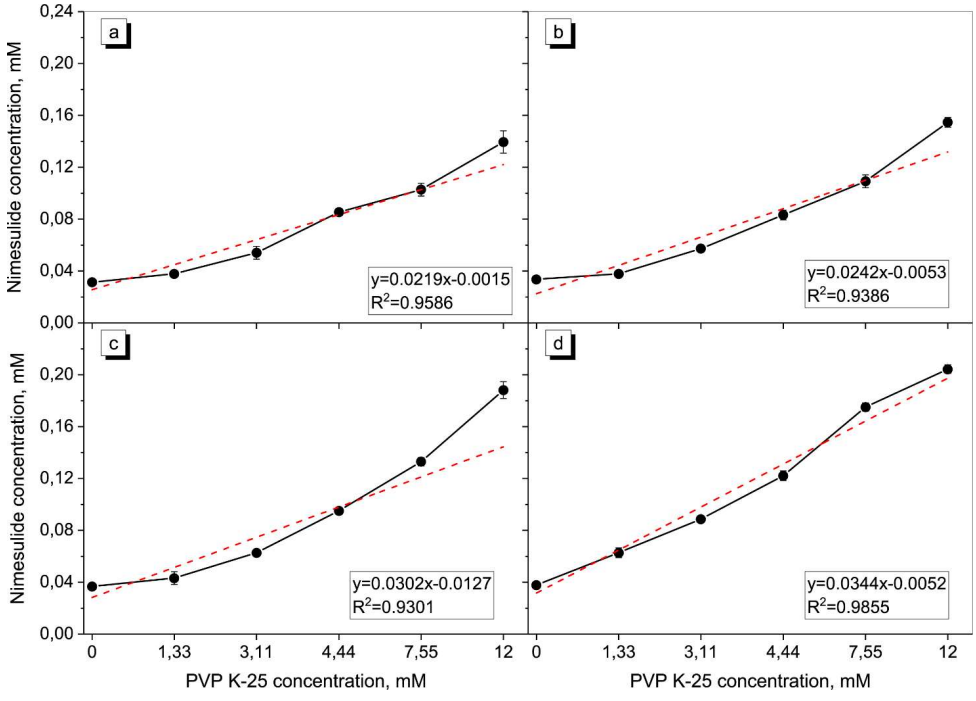

Fig. 2. Phase solubility profile of nimesulide polymer composition based on PVP K-25 in water at different temperatures: *a* – 25.0±0.5 °C; *b* – 30.0±0.5 °C; *c* – 37.0±0.5 °C; *d* – 40.0±0.5 °C

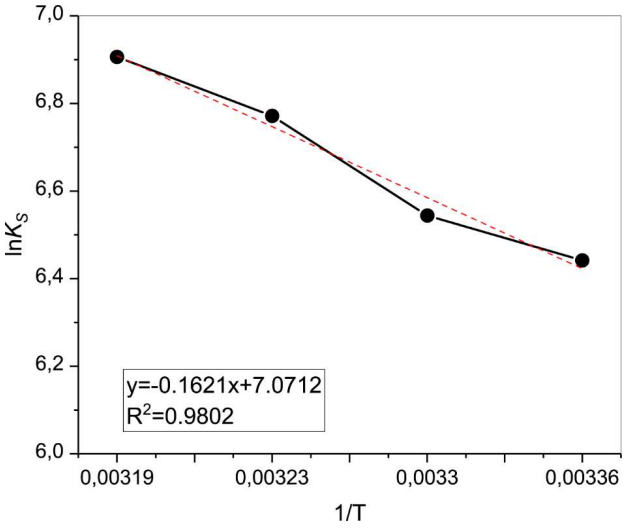

Fig. 3. Van't-Hoff plot of the process of complex formation between nimesulide and PVP K-25 polymer

Thermodynamic characteristics of the polymer composition of nimesulide with PVP K-25 are presented in Table 3.

All these calculated thermodynamic parameters of the system are crucial for predicting the behaviour of the system.

Table 3

Thermodynamic characteristics of the polymer composition of nimesulide with PVP K-25

Temperature	ΔH^0, kJ×M^{-1}	ΔG^0, kJ×M^{-1}	ΔS^0, J×M^{-1}×K^{-1}
25.0 °C (298 K)	–3.117	–15.964	43.109
30.0 °C (303 K)	–3.117	–16.489	44.132
37.0 °C (310 K)	–3.117	–17.457	46.258
40.0 °C (313 K)	–3.117	–17.976	47.473

4. 3. Infrared spectroscopy with Fourier transform

The solid dispersed system of nimesulide with PVP K-25, obtained by solvent evaporation, and its components were analyzed by infrared spectroscopy with Fourier transform.

The obtained FTIR spectrum meet all the acceptance criteria, providing the required resolution (2 cm^{-1}), frequency measurement accuracy with an error of no more than ±1 cm^{-1}, and high peak sharpness without noise i.e., the spectra are stable and repeatable.

Fig. 4 shows the FTIR spectrum of nimesulide (a), polyvinylpyrrolidone K-25 (b), and the solid dispersed system of API with the polymer (c).

The graphic data shows pure nimesulide's FTIR spectrum contains this API's absorption maxima characteristic. The first peak characteristic of nimesulide is observed at 3285 cm^{-1}, which confirms the presence of the –N–H group in the compound. At the frequency of 3100–3000 cm^{-1}, there are absorption bands of valence bonds of aromatic groups –C–H, with maxima at 3086 and 3010 cm^{-1}. Absorption bands of aliphatic groups –C–H lie in the 3000–2750 cm^{-1} range, with absorption maxima at 2931 and 2846 cm^{-1}. The absorption band of –C=C bonds has a maximum at a frequency of 1589 cm^{-1}. Absorption bands within the 1560–1350 cm^{-1} interval with an absorption maximum at 1521 cm^{-1} indicate the presence nitro – NO_2 functional group. An absorption peak of the –S=O group is observed at 1153 cm^{-1}. In addition, a characteristic vibrational band of the –S–N bond in the sulfonamide group at 952 cm^{-1} is noted. This observation is consistent with data obtained by researchers earlier [50, 51].

In the FTIR spectrum of PVP K-25, the absorption band of –O–H bonds valence vibrations has an absorption maximum at 3430 cm^{-1}. In the 3820–2840 cm^{-1} region, there are absorption bands of valence bonds of aliphatic groups –C–H, with maxima at 2959 and 2925 cm^{-1}. The absorption band of –C=O bonds has a maximum at a frequency of 1654 cm^{-1}. Deformational fluctuations of –C–H bonds are observed at a frequency of 1500–1340 cm^{-1} with maxima at 1438 and 1374 cm^{-1} – bands of medium and medium-high intensity. Fluctuations of –C–N bonds in the pyrrolidone ring are reflected by a band of medium intensity with a maximum of 1290 cm^{-1}. The same results were obtained earlier in other studies [52–54].

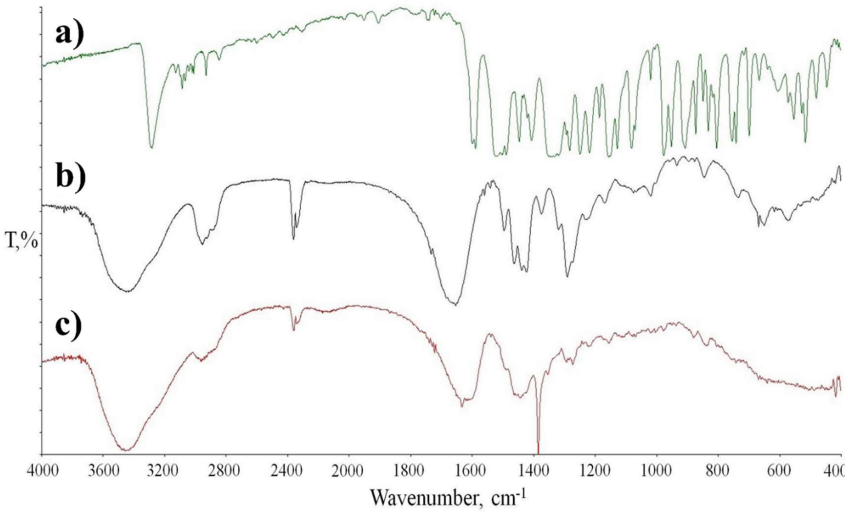

Fig. 4. FTIR spectra of: *a* – nimesulide; *b* – polyvinylpyrrolidone K-25; *c* – SDS of nimesulide with PVP K-25

In the FTIR spectrum of the solid dispersed system, no valence vibrations of the –N–H group, characteristic of nimesulide, were detected. Instead, there is one broad absorption band between 3600 cm^{-1} and 3000 cm^{-1}, and other absorption maxima are shifted towards lower wavenumbers and have a reduced intensity.

4. 4. Differential scanning calorimetry analysis

DSC was used to probe the melting of pristine nimesulide powder, polymer, and SDS of nimesulide samples.

The DSC thermograms obtained meet all the necessary acceptance criteria, namely: temperature measurement accuracy with an error of no more than ±0.1°C, high sensitivity (0.5 μW) and repeatability of the results of three measurements of one sample with a deviation of no more than 2 %.

DSC thermograms of pure nimesulide, PVP K-25 and solid dispersed system are shown in Fig. 5.

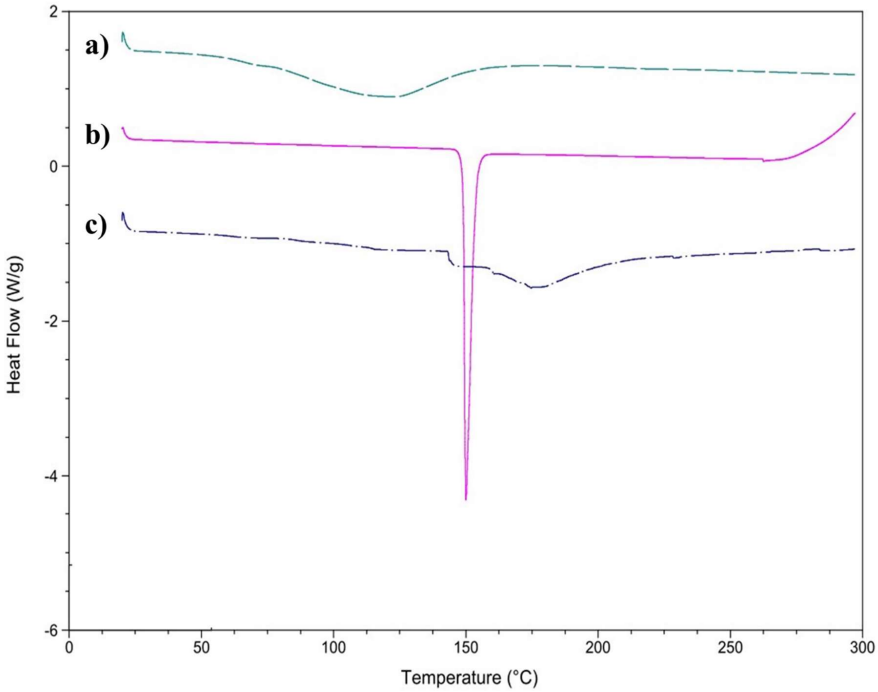

Fig. 5. DSC thermograms of: *a* – PVP K-25; *b* – nimesulide; *c* – SDS of nimesulide with PVP K-25

The DSC thermogram of nimesulide showed a sharp endothermic peak at 150 °C corresponding to its melting point at the crystalline state [55]. The DSC thermogram curve of PVP K-25 has a characteristic broad endotherm from 60 to 150 °C, which corresponds to the process of dehydration of the hygroscopic polymer and indicates its amorphous nature, as reported earlier [56]. However, the thermogram of the solid dispersion system of nimesulide did not show a sharp melting peak of the active ingredient but instead a broad endotherm.

4. 5. Powder *X*-ray diffraction analysis

Powder X-ray diffraction was used to further confirm the change in the physical state of nimesulide after incorporation into the polyvinylpyrrolidone matrix and to identify the crystallisation properties.

The obtained powder X-ray diffraction spectra meet all the necessary acceptance criteria, as they are characterised by high resolution with well-defined and intense peaks, which allows for accurate positioning and interpretation of the material structure. The peak positions are determined with high accuracy (±0.02°), which ensures correct phase identification and correlation. The results are reproduced with minimal variation (±1.0 %), which ensures the reliability of the data obtained.

The X-ray diffraction patterns for pure nimesulide, PVP K-25 and solid dispersed system are shown in Fig. 6.

The resulting diffractogram for nimesulide showed sharp diffraction peaks with high intensity at approximately 2θ=5.41°, 10.65°, 12.02°, 17.17°, 18.14°, 19.33°, 21.64° and 23.10°, which indicates its crystalline nature. The results are in agreement with those obtained earlier [25]. The PXRD pattern of PVP K-25 exhibited no significant diffraction peaks, which is in line with the amorphous nature of that polymer, as previously reported [57]. The diffractogram of the solid dispersed system of nimesulide based on PVP K-25 showed a marked decrease in the intensity of the corresponding peaks of API.

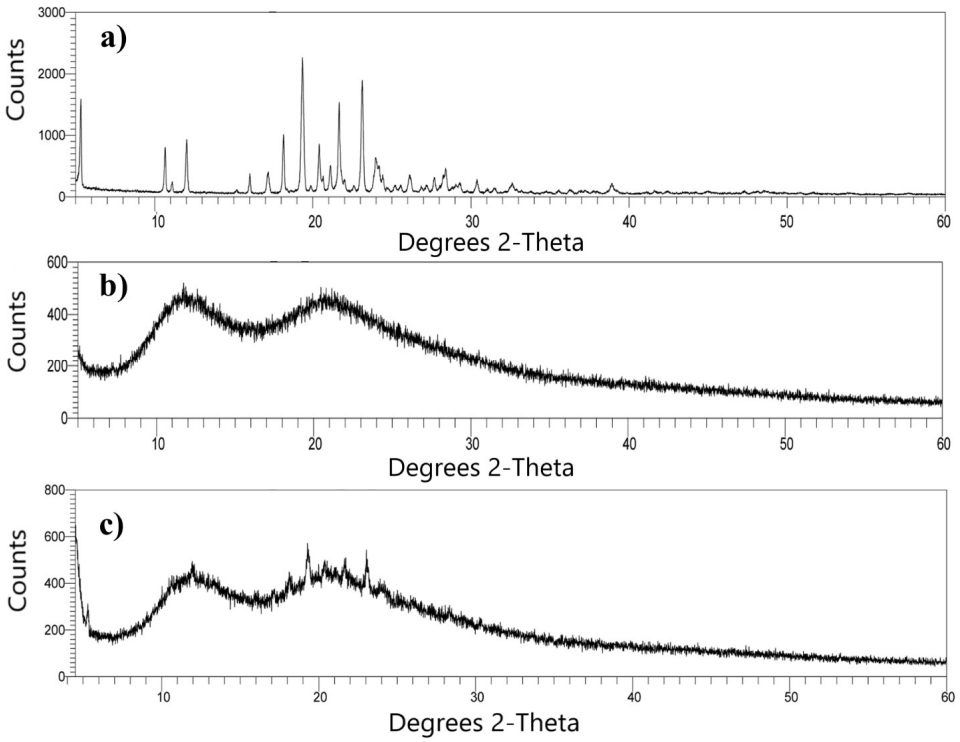

Fig. 6. Powder X-ray diffraction spectra of: *a* – nimesulide; *b* – PVP K-25; *c* – SDS of nimesulide with PVP K-25

4. 6. Kinetics of *in vitro* nimesulide release from SDS

Results of the study of nimesulide release kinetics from a solid dispersed system with PVP K-25 and the original medicinal product Aulin in the form of granules for oral suspension in buffer media pH 6.8, 7.5, and 7.8 are presented in Fig. 7. The formed polymeric SDS of nimesulide contains the same amount of active pharmaceutical ingredient as the comparator drug. The deviation between the results of three independent measurements does not exceed 2 % for each point of the dissolution curve, which guarantees the accuracy and reliability of the data obtained on the release of the active ingredient from the developed SDS and the comparison drug.

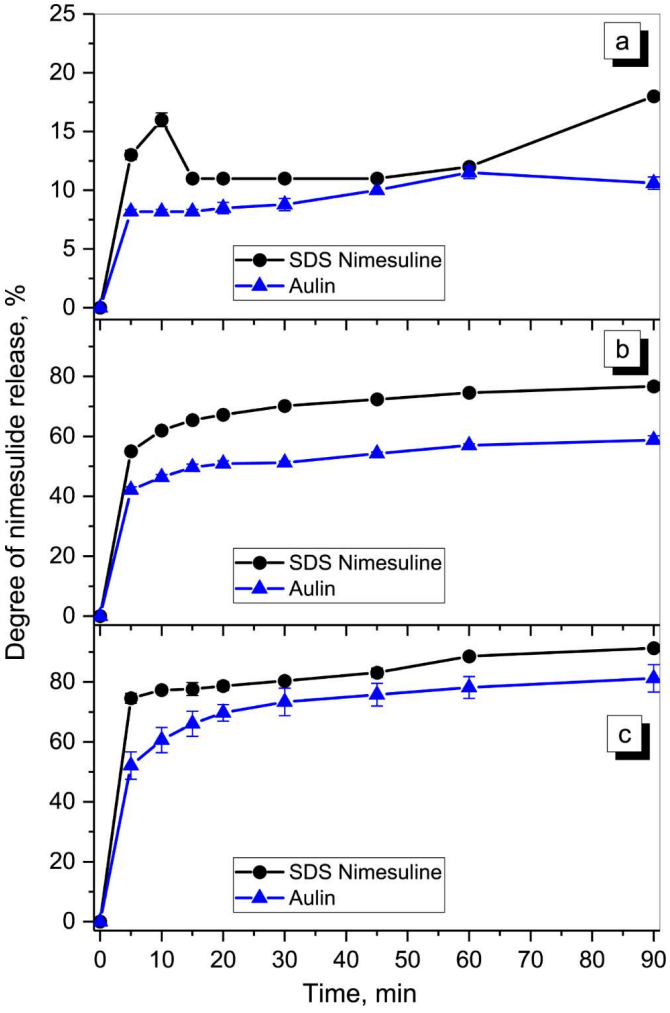

Fig. 7. The release profile of nimesulide from SDS and of the original drug Aulin in buffer media pH 6.8 (a), pH 7.5 (b), and pH (7.8) (c)

Graphical data show that, during the study of nimesulide release kinetics in a pH 6.8 buffer medium (Fig. 7, *a*), a more intense release of nimesulide from SDS in the first minutes than the original drug was observed. The degree of nimesulide release from SDS in the first 5 min was about 14 %, while the comparator showed only 8 % API release. At minute 10 of the test, the degree of nimesulide release from SDS increased to 16 %, and the dissolution rate of Aulin remained at the same level. At the end of the experiment, the dissolution degree of nimesulide released from the polymer SDS was 18 %, while that of Aulin was only 11 %.

Results of the study of nimesulide dissolution from SDS in buffer medium pH 7.5 (Fig. 7, *b*) showed that the SDS formation by the solvent evaporation technology significantly improved the dissolution of nimesulide. It was established that nimesulide release from polymeric SDS in the first 5 minutes was 55 %, which is 1.3 times more compared to the original drug Aulin. After 90 minutes after the start of the study, the degree of nimesulide release from the SDS composition was more than 77 %, while Aulin showed a result of only 59 %.

According to the results of the "Dissolution" test in buffer medium pH 7.8 (Fig. 7, *c*), it was established that the degree of nimesulide release from SDS is also higher than that of Aulin. At the beginning of the experiment (5 min), the degree of nimesulide release from SDS was 1.44 times higher than the original drug. At the end of the study, the degree of nimesulide release from the SDS composition was more than 90%, while Aulin showed a result of 80 %.

5. Discussion

The results of our studies showed that the increase in nimesulide solubility depends on the molecular weight of polyvinylpyrrolidone: the higher the molecular weight of polymer, the higher the phase solubility of the investigated API. This observation could be accounted by the higher hydrophilicity and water solubility of the high molecular weight PVP. Our results obtained correlate with those of other researchers [58, 59]. In particular, it was also shown that the dissolution behaviour of amorphous solid dispersions of celecoxib-PVP depends on the molecular weight of the polymer: the solubility of API in different SDS increased with increasing molecular weight of PVP (except for the sample based on PVP K60, which showed a lower solubility than the system based on PVP K30) [58]. Another study indicates an increase in the phase solubility of glycyrrhetinic acid in water with an increase in the molecular weight of PVP [59]. This confirms that the degree of increase in the solubility of APIs in the SDS composition can be controlled by the molecular weight of PVP.

When checking the effect of temperature on the phase solubility profile and stability of nimesulide systems with PVP K-25, it was found that at all studied temperatures, the obtained stability constants of the polymer composition complexes are in the range from 627.5628 M^{-1} to 998.5217 M^{-1} (Table 1). According to the literature [48], ideally, the optimal values of the stability constant are in the range from 100 to 1000 M^{-1}. Thus, we can confirm the favourable conditions for the formation of strong nimesulide complexes with K-25 PVP at all studied temperatures.

The value of the Gibbs free energy change is an important characteristic that provides information on whether the reaction conditions are favourable for the solubilization of the API in the aqueous carrier solution. In

our case, according to Table 2, the negative values of the Gibbs free energy change indicate favourable conditions for nimesulide solubilization in the presence of a pharmaceutically acceptable polymer [44]. In addition, the values of free energy changes decrease with increasing temperature and PVP K-25 concentration. Therefore, an increase in the polymer concentration and the reaction temperature will contribute to a better course of the reaction of the formation of intermolecular complexes [44, 60].

According to the obtained data (Table 3), it can be concluded that the formation process of intermolecular complexes is exothermic. That is, it occurs with the release of energy. Negative enthalpy values ΔH^0 demonstrate it [49, 61]. The intermolecular complex formation process has a spontaneous nature at studied temperatures. It is shown by the negative values of the Gibbs free energy change ΔG^0 [45, 61, 62]. Positive entropy values ΔS^0 prove that the formation of a complex between nimesulide and the polymer carrier probably occurs during the destruction of the aqueous solvate shell of the molecules [63]. Similar conclusions were made by researchers who developed solid dispersion systems of metoclopramide with PVP K-30 and studied their thermodynamic characteristics [62].

The FTIR method (Fig. 4) showed that the formation of a complex between the API and the polymer occurs due to the interaction between the N–H group of nimesulide and the –O–H groups in the pyrrolidone fragment of the polymer. The area of the absorption band of –O–H groups is larger in the FTIR spectrum of SDS than in the FTIR spectrum of the pure polymer, and the absorption peak characteristic of nimesulide at 3285 cm^{-1} has disappeared. A noticeable difference in the area of the absorption band of the –O–H group indicates a change in the number of hydrogen bonds. This fact confirms that the intermolecular interaction between the API and the polymer carrier occurs through a hydrogen bond. Also, in the FTIR spectra of SDS of nimesulide, we can observe a decrease in the intensity of the characteristic peaks of the studied substances, which further confirms the inclusion of API in the polymer matrix of polyvinylpyrrolidone and the interaction between the components of the system. The interaction between nimesulide and PVP 40000 due to hydrogen bonds in the composition of solid dispersed systems is also evidenced by the results of studies cited in the work of other scientists [22].

Analyzing the DSC thermogram of the solid dispersion system of nimesulide (Fig. 5, *c*), it can be seen that PVP K-25 affected the position and sharpness of the endothermic peak of API. We can confirm that there was an interaction between the API and the polymer carrier since there is no sharp melting endotherm of the active pharmaceutical ingredient on the SDS thermogram of nimesulide, and instead, a broad endotherm is observed. This indicates that the crystalline transition of nimesulide to the amorphous state occurred during the formation of a solid dispersion. These conclusions were made in accordance with the literature [64].

The results of the X-ray structural analysis (Fig. 6) indicate that, in the composition of a solid dispersed system, nimesulide was molecularly dispersed in the polymeric matrix of polyvinylpyrrolidone and changed from a crystalline to an amorphous state. This is indicated by the halo (or broad) diffraction pattern of the polymeric SDS of nimesulide. Similar results of PXRD on the change of the crystalline state of nimesulide to amorphous in polymer-based solid dispersed systems were obtained by other researchers [22, 29].

According to the presented results of the study of the release kinetics of nimesulide from SDS (Fig. 7), it was established that the introduction of nimesulide into a solid dispersed system based on a water-soluble polymer carrier by the method of solvent evaporation accelerates the degree of API release in all studied buffer media in comparison with the original drug Aulin in the form of granules for oral suspension.

Practical relevance. The results of this study are extremely important, as obtained on the basis of a pharmaceutically acceptable polymeric carrier and an environmentally friendly SDS solvent overcomes the disadvantage of the poor dissolution of nimesulide and opens the way for the development of oral forms of nimesulide with improved solubility.

Study limitations. A long drying time can be considered as one of the limitations when using the proposed method of solvent evaporation to obtain solid dispersion systems of nimesulide.

The prospects for further research consist in the developed and studied pharmaco-technological characteristics of dosage forms based on highly soluble dispersed systems of nimesulide, obtained by the "green" method of solvent evaporation.

6. Conclusions

This study investigated the effect of a pharmaceutically acceptable polyvinylpyrrolidone polymer of different molecular weights (PVP K-12, PVP K-17, PVP K-25) on the phase solubility of nimesulide in water. It was established that the maximum value of nimesulide solubility increase is observed in the system with PVP K-25 – 5.27 times, therefore it was used for the preparation of solid dispersions of nimesulide by the solvent evaporation method.

For the first time, the thermodynamic parameters of forming a solid dispersed system of nimesulide with PVP K-25 were also investigated. It has been found that the negative values of the Gibbs free energy change indicate favourable conditions for nimesulide solubilization in the presence of this polymer. At the same time, increasing the concentration of the polymer and the temperature of the experiment contribute to a better course of the reaction with the formation of intermolecular solid complexes. The obtained enthalpy values indicate that the complex formation process is exothermic. Positive entropy values confirm that the formation of complexes between nimesulide and the polymer carrier probably occurs during the destruction of the aqueous solvate shell of the molecules.

Using the method of FTIR spectroscopy, it was proved that the formation of complexes between API and polymer in a solid dispersion occurs mainly due to hydro-

gen bonds. The results of both DSC and XRD analyses confirm that nimesulide has transitioned to an amorphous state in the obtained SDS based on PVP K-25.

According to the results of the study of release kinetics of nimesulide from SDS using the "Dissolution" test, it was established that the introduction of nimesulide into a solid dispersed system based on a water-soluble polymer carrier by the method of solvent evaporation improves the degree of API release in all studied buffer media, pH 6.8, 7.5 and 7.8, in comparison with the original drug Aulin in the form of granules for oral suspension.

A solid dispersed system prepared by the «green» method of solvent evaporation using PVP K-25 as a carrier can be used as a good strategy for formulating effective anti-inflammatory drugs of nimesulide with increased bioavailability.

Conflict of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

All data generated or analysed during the study are included in this article.

Use of artificial intelligence

The authors confirm that they did not use artificial intelligence technologies when creating the current work.

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