# Amorphisation of Nifluminic Acid with Polyvinylpyrrolidone Prepared Solid Dispersion to Reach Rapid Drug Release

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*This paper describes the enhancement of dissolution rate of nifluminic acid by spray dry process, as a solid dispersion method using polyvinylpyrrolidone (PVP C-15) as a water soluble polymer. Using solid dispersions as a well-known principle on an industrial scale, it has to be combined with low-cost and repetable manufacturing method. Therefore, the aim of the authors was the amorphisation of the drug applying another type of PVP and another sample-preparation method as earlier. The products were characterized by means of solubility and dissolution from simulated media. The wettability properties of the pure ingredient and its products were determined, with registration of their contact angles. The drug-polymer interaction in the solid state was investigated by using differential scanning calorimetry, Fourier transform infrared spectroscopy and X-ray powder diffraction. The results suggested that the drug is found in the amorphous state in the solid dispersion and, using this method, it is possible to reach rapid drug release.*

*Keywords: amorphisation, solid dispersion, thermoanalytical investigations, nifluminic acid, polyvinylpyrrolidone*

Nifluminic acid (NIF), a frequently used anti-inflammatory drug, possesses poor water solubility and its bioavailability is limited by its dissolution rate [1-3]. It is primarily used to treat different forms of rheumatism, e.g. rheumatoid arthritis and arthrosis, and to decrease other inflammatory phenomena. Its usual single dose is 250 mg for adults. It has some side-effects, such as nausea or vomiting. In cases of stomach ulcer, it may be only used under medical control [4]. Among the polymers that are employed for the formulation with slightly water-soluble active ingredients, polyvinylpyrrolidone (PVP) displays marked complexing and solubilizing properties [5]. The aim of the preparation of PVP dispersions is generally to transform the drug into the amorphous form and thus to achieve faster dissolution.

The aim of our study was to alter the physicochemical properties of the NIF to reach its amorphous form, so as to increase its solubility, dissolution rate and thereby enhance the pharmaceutical potential [6]. According to the literatures the amorphisation of NIF was investigated by solid dispersion methods using cyclodextrin [7]. In our previous studies cyclodextrins with and without PVP were used [8,9]. In the present study, products were prepared in two weight ratios, applying a low molecular weight PVP and using spray drying method with ethanol. The solid-state interaction between NIF and PVP were explored by means of differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FT-IR), X-ray powder diffraction (XRPD).

## Experimental part

*Materials*

NIF: 2-[[3-(trifluoromethyl)phenyl]amino]-3-pyridine-carboxylic acid (G. Richter Pharmaceutical Factory, Hungary); polyvinylpyrrolidone: PVP C-15 ($M_w$ ~ 8.000), (C/o ISP Customer Service GmbH, Germany); other chemicals (Reanal Ltd., Budapest, Hungary).

*Products*

Solid dispersions were prepared using the solvent evaporation method with Büchi Mini Dryer B-191 (Switzerland), at 165ºC inlet and 86ºC outlet temperature with a compressed air flow of 600 L $min^{-1}$ and a nozzle diameter of 0.5 mm. The aspirator rate was 80% and the pump rate was 10%. According to some references the molecular weight of the polymer might play a role in the performance of solid dispersion and better results can be obtained with the lower molecular weight. However, at the higher ratio of PVP, the solubilization process can be neutralized by the diffusion process increasing the viscosity of the solution around the particle [10]. For these reasons by the preparation of the spray-dried products (SPD C-15) were prepared in weight ratios of 1:5 and 1:10 with PVP C-15 and were dissolved in 30% ethanol. The products were stored under normal conditions at room temperature (22ºC).

*Particle size analysis*

The LEICA Q500MC Image Processing and Analysis System (LEICA Cambridge Ltd., England) was used to measure the particle size distribution of the samples. We determined and compared the products with the pure drug, using 350 particles per sample. The pure NIF and its products were characterized by average length of particles.

*Determination of the saturation concentration ($C_{water}$)*

The solubility of the sample were determined at 25 °C. NIF and its products were added to distilled water during continuous stirring until the excess drug appeared in suspended form. After filtration, the saturated solution was diluted and the drug concentration was determined spectrophotometrically ($\lambda$ = 284 nm)

## Wettability studies

The Dataphysics OCA 20 Contact Angle System (Dataphysics Inc., GmbH, Germany) was used for studies

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of the wettability of NIF and its products. 0.15 g of powder was compressed under a pressure of 1 ton using 1.3 cm area by a Specac hydraulic press (Specac Inc., USA). The wetting angles of the pressings were determined after 4.3 mL of distilled water had been dropped onto the surface of the pressings. The change in the wetting angle was registered from 1 to 15 s, using the circle fitting method of the OCA System.

*Dissolution studies*

The time to peak concentration of the drug revealed that two-thirds of administered NIF is absorbed from the stomach and one-third from the intestines [11,12]. Accordingly, it is necessary to investigate the *in vitro* dissolution from both media. The modify paddle method with the USP dissolution apparatus was used to examine 200 mg samples of pure NIF or products containing 200 mg of drug in 100 mL of simulated gastric medium (SGM) (*p*H = 1.1 ± 0.1), simulated intestinal medium (SIM) (*p*H= 7.0 ± 0.1). The paddle was rotated at 100 rpm and sampling was performed up to 120 min (sample volume 5.0 mL). After filtration and dilution, the NIF contents of the samples were determined spectrophotometrically ($\lambda_{(SGM)}$ = 256 nm, $\lambda_{(SIM)}$ = 288 nm).

*Kinetic models*

Several theories/kinetics models describe drug dissolution from immediate and modified release dosage forms. The Langenbucher mathematical model was used to evaluate the results of the dissolution as concerns the dissolution profiles of NIF and its products:

$$\sqrt[3]{\frac{m_t}{m_0}} = 1 - \frac{t}{T}$$

where $m_0$ is the mass of drug at time $t$=0 and $m_t$, is that at time $t$, and $T$ is the total time of the dissolution [13,14].

The kinetics analyses were carried out with an *in vitro – in vivo* kinetic computer program according to the dissolution curve's data.

*Differential scanning calorimetry (DSC)*

In DSC (Mettler Toledo DSC 821$^e$ thermal analysis sytem, Mettler Inc., Schwerzenbach, Switzerland) measurements, approximately 2–5 mg of pure drug or product was examined in the temperature range between 25°C and 300°C. The heating rate was 5°C min$^{-1}$. Argon was used as carrier gas, with a flow rate of 10 l h$^{-1}$ during the DSC investigation.

*Infrared spectroscopy*

FT-IR spectra were measured on an AVATAR 330 FT-IR apparatus (Thermo Nicolet, USA), between 4000 – 400 cm$^{-1}$, at 4 cm$^{-1}$ optical resolution. Standard KBr pellet were prepared from 150 mg KBr and calculated amount of the samples containing 0.5 mg of NIF.

*X-ray powder diffraction*

The physical state of the NIF in the different samples was evaluated by X-ray powder diffraction (XRPD). Diffraction patterns were obtained on a Philips PW 1050/ 70 1710 diffractometer, where the tube anode was Cu with Kα = 1.54242 Å. The pattern was collected with a tube voltage of 50 kV and 40 mA of a tube current in step scan mode (step size 0.035, counting time 1 s per step).

## Results and discussion

*Characterization of NIF and its products*

According to the particle size distribution, the size of the most frequent NIF particles is between 30-60 μm. About 50 % of the particles of the SPDs C-15 had a particle size between 10-20 μm. Reduction of the length and width of the particles were significant for the 1:5 SPD C-15 (from ~ 46 μm to ~ 14 μm). This results in an enhanced dissolution rate due to both an increase in the surface area and solubilization.

NIF has a lipophilic character, reflecting its poor water solubility, which at 25°C is 26.75 μg mL$^{-1}$. The concentration of NIF in water could be increased even 15-fold (from 26.75 μg mL$^{-1}$ to 413.33 μg mL$^{-1}$). The results were outstanding in the case of the SPDs C-15, where an 11–15-fold solubility increase was observed. The contact wetting angles after 5s for NIF and its products were determined and compared with the water solubility. The contact wetting angle for NIF was 71.1°, i.e. it is a very hydrophobic drug. The wetting angles of the investigated products were in all cases decreased to 26.3°. The relevant results are shown in table 1.

**Table 1**
SUMMERIZED DATA OF NIF AND PRODUCTS

| Products | Average length (μm) ± SD | $C_{water}$ (μg·mL$^{-1}$) | Contact angles (°) ± SD |
|---|---|---|---|
| NIF | 45.64 ± 22.63 | 26.75 | 71.1 ± 0.2 |
| SPD C-15 1:5 | 14.19 ± 5.178 | 413.33 | 26.3 ± 2.8 |
| SPD C-15 1:10 | 30.23 ± 13.62 | 314.33 | 26.6 ± 2.6 |

*Dissolution rate studies*

NIF has an acidic character, and its *in vitro* dissolution (from 200 mg) was therefore higher in SIM (14.33 mg / 100 mL at 120 min) than in SGM (9.92 mg/100 mL at 120 min).

The release of NIF (dissolution rate constant, K) was studied kinetically by using precisely the mathematical models presented earlier, as a function of the correlation coefficient of the dissolution process. It was concluded that the dissolution of NIF from products into SGM and SIM is described most precisely by the Langenbucher equation. The dissolution rates for solid dispersions were significantly greater than that for NIF. Table 2 presents that the dissolution rate was increased 5 times in SGM and 50 times in SIM using solid dispersons. In the simulated media, the maximum concentration was reached in 5–15 min. PVP may also have an enhancing effect on the wettability and dispersibility of the drug in the dissolution media. This should retard any agglomeration or aggregation of the particles, which can slow the dissolution process. However, according to the product's characterisations the 1:10 ratio resulted lower data.

*Solid state interactions*

DSC thermograms of NIF and its products are shown in figure 1 NIF gave a melting endotherm at 203.81 °C, which can be identified from the literature data as its melting

**Table 2**
DISSOLUTION DATA OF NIF AND PRODUCTS

| Products | SGM | | SIM | |
|---|---|---|---|---|
| | $K^*$ | $R^2$ | $K^*$ | $R^2$ |
| NIF | 0.0049 | 0.976 | 0.0069 | 0.997 |
| SPD C-15 1:5 | 0.0258 | 0.974 | 0.3487 | 0.907 |
| SPD C-15 1:10 | 0.0215 | 0.867 | 0.3439 | 0.909 |

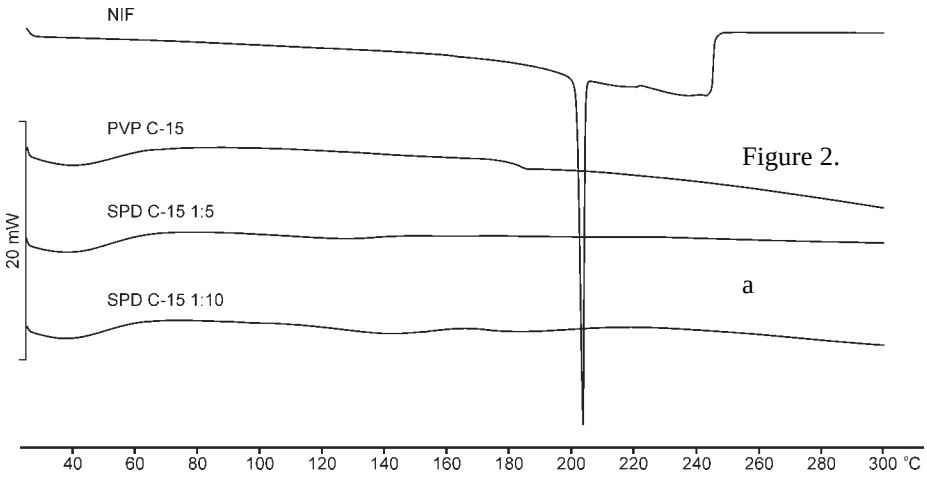


Figure 2.

a

Fig. 1.
DSC thermograms of NIF, PVP C-15 and SPD C-15 1:5 and 1:10

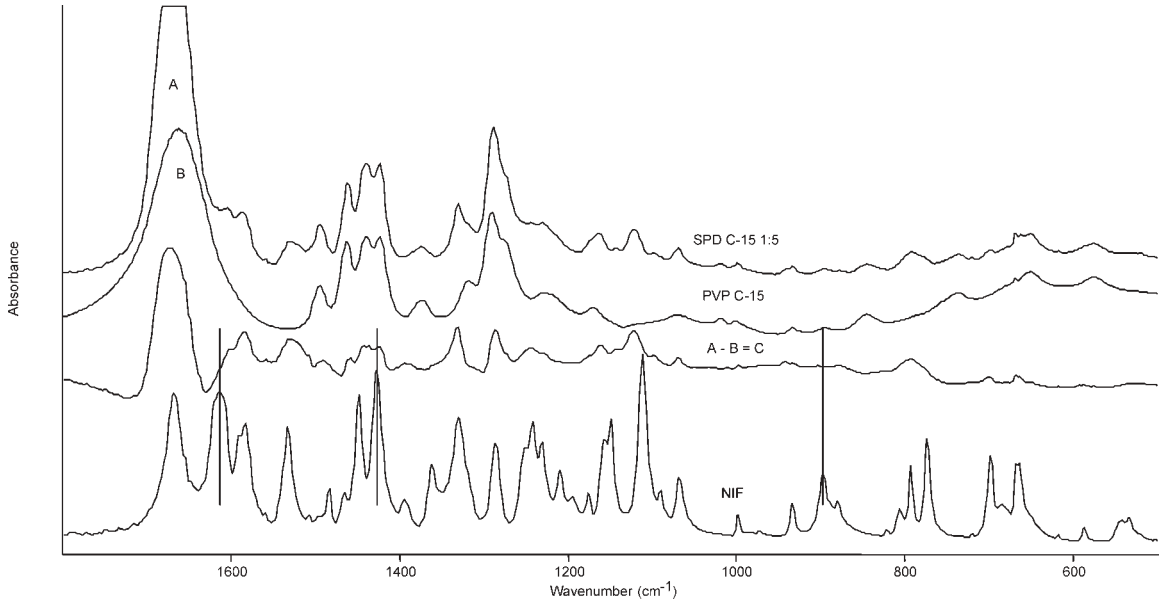


Fig. 2
FT-IR spectra of NIF, PVP C-15, and SPD C-15 1:5

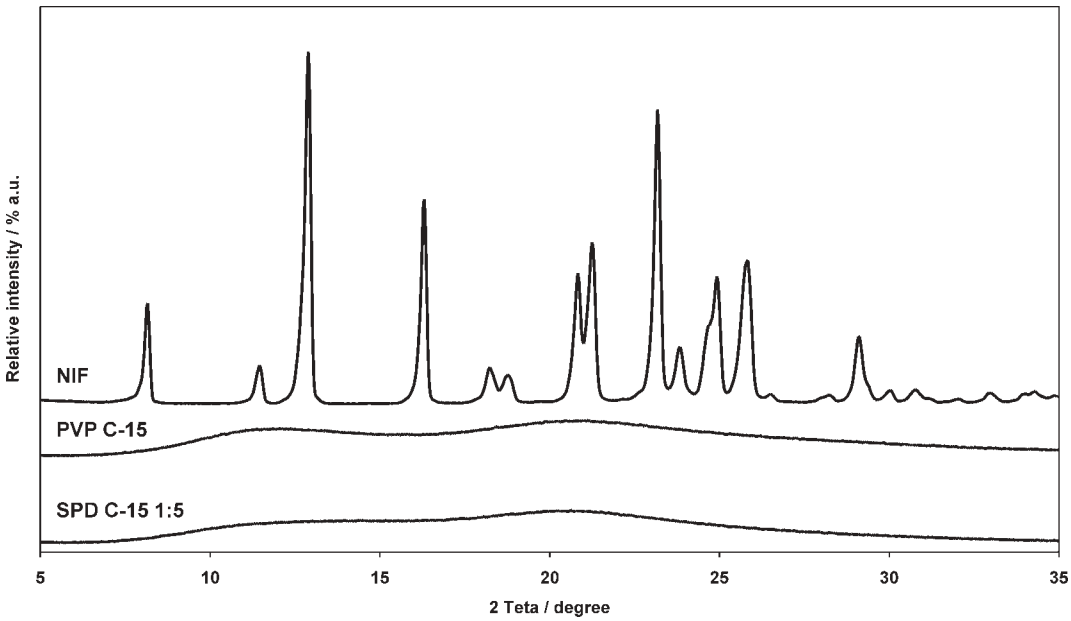


Fig. 3.
X-ray diffraction patterns of NIF, PVP C-15 and SPD 1:5

point. The onset of melting was observed at 201.15 °C and the endset at 203.81 °C; the normalized enthalpy was 127.50 J $g^{-1}$. NIF melting was not observed for any of the X-ray amorphous solid dispersions, as expected. The DSC curves did not reveal a melting peak for NIF in any of the SPDs C-15. This may be due to the interaction between NIF and PVP in these systems.

The interaction between the polymers and NIF was also studied by infrared spectroscopy. Evaluation of spectral changes was performed by subtraction of the polymer

spectrum from the spectra of the samples prepared by various methods.

The solvent evaporation methods resulted in essential changes of the molecular state of NIF. Two strong bands disappeared from the original spectra at 1615 and 1428 $cm^{-1}$, the antisymmetric and symmetric carboxylate stretching modes of the double ion form, which is characteristic for amino acids. A new one developed at 1683 $cm^{-1}$ (fig. 2), the C=O stretching mode of the protonated carboxyl group. Dissolution in alcohols reverses the proton transfer and NIF returns into the neutral, amine-carboxylic form. The preparation of the samples, the interaction between the polymer and the highly dispersed, amorphous, solid phase prevents the proton transfer. This is higher energy state since either the enthalpy difference between the carboxyl O-H and the ammonium $N^+$ -H bond and the lattice energy, originating from the coulonbic interactions of the crystalline state are also missing. Higher energy state for the solid phase, results in higher equilibrium concentration, higher solubility.

The XRPD patterns of NIF, PVP C-15, and SPD 1:5 are shown in figure 3. PVP is an amorphous powder with no crystalline structure. The presence of numerous distinct peaks in the XRPD spectrum indicates that NIF is a crystalline material; its characteristic peaks appear at diffraction angles of 2θ, at 8.18, 12.92, 16.33, 21.30 and 23.21°. The crystalline structures of NIF in all the solid dispersions were different from that of the pure drug, as revealed by the differences in their XRPD patterns. These patterns were similar to those for the PVPs. The absence of diffraction peaks indicated the presence of NIF in amorphous form. Sekikawa et al [15] pointed out that PVP might inhibit the association of the drug molecule to form the crystal nucleus and thereby inhibit crystal growth; the interaction between the drug and the PVP should be the inhibitory and/or retarding factor in the crystallization.

## Conclusions

To investigate the effects of the water-soluble polymer PVP on the physicochemical characteristics of NIF, solid dispersion were prepared in two ratios using spray-drying, as solvent evaporation method.

According to the kinetic analysis, PVP enhanced the rate of dissolution of NIF. The increase in dissolution rate of NIF might be achieved by SPDs C-15 (5-50 fold). SPDs C-15 exhibited higher dissolution rates than NIF, resulted from the increase in drug wettability and decrease of crystalline phase. The wettability and saturation concentration indicated that the products with PVP C-15 had a hydrophilic character.

DSC could not detect the presence of crystalline drug in any of the products. According to the FT-IR spectra, the solvent evaporation methods resulted in essential changes of the molecular state of NIF. The XRPD peaks of the products revealed that the crystallinity of the NIF was changed and the crystalline reflexions of the drug were not detected: the patterns were similar to those of the PVPs. The NIF was found to be amorphous in the solid dispersions prepared by the spray drying. NIF and PVP can be regarded as an interaction.

The goal of this study is the founding of NIF in the amorph form again -as it was earlier published with other type of PVP-, but in this case 30 v/v % of ethanol was used instead of acethone-methanol solvents. However, further studies should be performed regarding bioavailibility of NIF in solid dispersions, because these systems are presumably suitable for the formulation of solid- or semisolid dosage forms with fast drug release. Therefore, the applied drug quantity and the unwanted side-effects can be decreased.

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