

# Physico-chemical Studies on Solid Dispersions of Niflumnic Acid Prepared with PVP

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*Niflumnic acid is an important anti-inflammatory drug with low aqueous solubility. In order to increase the degree of dissolution of niflumnic acid, products were prepared with polyvinylpyrrolidone (PVP) K-25, using physical mixing and solvent evaporation methods. The solubilities of the products were characterized by means of dissolution and in vitro membrane diffusion from simulated media. The wettability properties of the pure ingredient and its products were determined, with registration of their contact angles. In contrast with the very poor solubility of pure niflumnic acid, the dispersion of the drug in the polymers considerably enhanced the dissolution. This can be attributed to the improved wettability and dispersibility, the particle size reduction and the decrease in the crystalline fraction of the drug.*

*Keywords: solid dispersion, niflumnic acid, polyvinylpyrrolidone, dissolution*

Many drugs possess poor water solubility and their bioavailability is limited by their dissolution rates. Niflumnic acid (NIF), an anthranilic acid derivative, is a frequently used anti-inflammatory drug, which also has a weak analgetic effect [1, 2]. It is primarily used to treat different forms of rheumatism, e.g. rheumatoid arthritis and arthrosis, and to decrease other inflammatory phenomena. Three hour after a 250 mg dose administered to 6 male volunteers as the first dose on day 10 of a 14-day 250 mg / 4 times daily dosage regimen, the mean peak plasma concentration of radiolabelled NIF was 123 µg/mL [3,4].

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 drugs having poor water-solubility can provide better bioavailability in the amorphous state. A number of papers have been published on the favourable effects of PVP on the solubility and rate of dissolution of anti-inflammatory non-steroidal drugs (e.g. naproxen and piroxicam), using different pharmaceutical formulation methods [6,7].

The aim of our study was to alter the physico-chemical properties of the NIF in order to increase its solubility and thereby enhance the pharmaceutical potential. In the present study, products were prepared in different weight ratios, using two technological methods.

## Experimental part

Niflumnic acid: 2-[[3-(trifluoromethyl) phenyl]amino]-3-pyridine-carboxylic acid (G. Richter Pharmaceutical Factory, Hungary); polyvinylpyrrolidone: Plasdone K-25 ( $M_w \sim 34.000$ ), (C/o ISP Customer Service GmbH, Germany). Other chemicals: ethanol, methanol and acetone (Reanal Co., Budapest, Hungary).

## Chemical structure of niflumnic acid

### Preparation of the samples

The two-component products were prepared in four

different weight ratios (NIF : PVP weight ratio = 1:1, 1:2, 1:4 and 1:6).

The physical mixtures (PMs K-25) were mixed, pulverized in a mortar and sieved through a 100 µm sieve.

Solid dispersions (SDs K-25) were prepared using the solvent evaporation method with drug : PVP K-25 weight ratios of 1:1, 1:2, 1:4 and 1:6. To a solution of NIF (1 g) in 30 mL of acetone, the appropriate amount of PVP K-25 was added. The minimum amount of methanol was added to dissolve the polymer. The solvents were removed under reduced pressure at 30°C and the residue was dried under vacuum at room temperature for 3 h [8]. The samples were pulverized and sieved through a 100 µm sieve.

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 be neutralized by the diffusion process can be increasing the viscosity of the solution around the particle [8]. The products were stored under normal conditions at room temperature (22°C).

### Particle size distribution

The LEICA Image Processing and Analysis System (LEICA Q500MC, LEICA Cambridge Ltd., England) was used to measure the particle size distribution of SDs. We determined and compared the products with the pure drug, using 350 particles per sample. The characteristics of the particles were described by their length, breadth, surface area, perimeter and roundness. Roundness is a shape factor that provides information about the circularity via the following formula:

$$\text{roundness} = \frac{\text{perimeter}^2}{4\pi \cdot \text{area} \cdot 1.064}$$

### Wettability studies

The OCA Contact Angle System (Dataphysics OCA 20, Dataphysics Inc., GmbH, Germany) was used for studies of the wettability of NIF and its products. 0.15 g of powder was compressed under a pressure of 1 ton by a Specac

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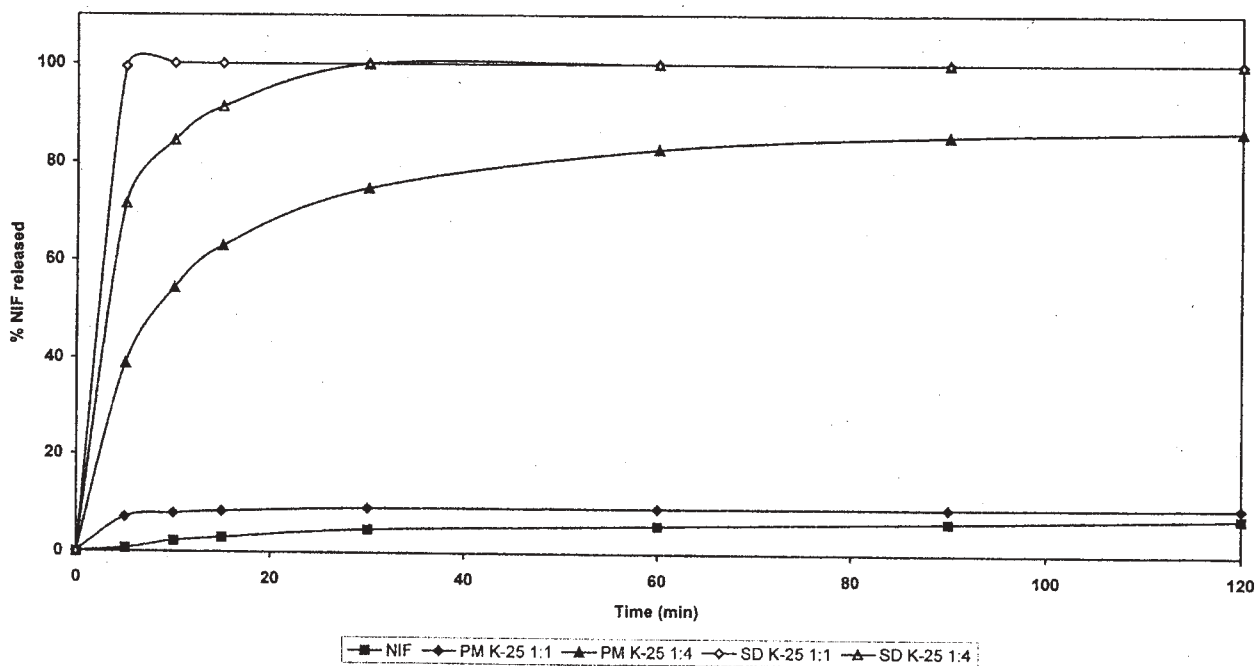


Fig. 1. Chemical structure of niflumnic acid

hydraulic press (Specac Inc., USA). The wetting angles of the pressings were determined after 4.3  $\mu\text{L}$  of distilled water had been dropped into 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.

#### Determination of the saturation concentration

Saturation concentrations were determined at 25  $^{\circ}\text{C}$ . 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 (Unicam UV2/Vis spectrometer, Unicam Ltd., England).

#### 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. Thus, NIF is absorbed from both the stomach and the intestines. Accordingly, it is necessary to investigate the *in vitro* dissolution from both media.

The modified paddle method with the USP dissolution apparatus (USP rotating-basket dissolution apparatus, type DT; kneading mixer, type LK5, Erweka Apparatebau GmbH, Heusenstamm, Germany) 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) ( $\text{pH} = 1.1 \pm 0.1$ ; 94.00 g of 1 N HCl, 0.35 g of NaCl, 0.50 g of glycine in 1000 mL of distilled water), simulated intestinal medium (SIM) ( $\text{pH} = 7.0 \pm 0.1$ ; 14.4 g of  $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$ , 7.1 g of  $\text{KH}_2\text{PO}_4$  in 1000 mL of distilled water). The basket 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 ( $\lambda_{(\text{SGM})} = 256 \text{ nm}$ ,  $\lambda_{(\text{SIM})} = 288 \text{ nm}$ ).

#### Mathematical models of *in vitro* dissolution

*In vitro* dissolution has been recognized as an important element in drug development. The nature of the drug, and its polymorphic form, crystallinity, particle size, solubility and amount in the pharmaceutical dosage form can influence the release kinetics. Several theories/kinetics

models describe drug dissolution from immediate and modified release dosage forms. The following mathematical models were used to evaluate the results of the dissolution as concerns the dissolution profiles of NIF and its products [9].

The Langenbucher equation is very frequently used with modifications depending on the different dissolution profiles. In this equation, the scale parameter,  $a$ , defines the time scale of the process and the shape parameter,  $b$ , characterizes the curves.

Langenbucher model:

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

Modified Langenbucher:

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

(Bt)<sup>a</sup> model:

$$\sqrt[3]{\frac{m_t}{m_0}} = 1 - (bt)^a,$$

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 [10].

The kinetics analyses were carried out with an *in vitro* - *in vivo* kinetic computer program.

#### *In vitro* membrane diffusion

Stricker's Sartorius apparatus (Sartorius-Membran-filter GmbH, Germany) was used [11]. Measurements were performed from 100.0 ml of SGM or SIM to simulated plasma (SPL) ( $\text{pH} = 7.5 \pm 0.1$ ; 20.5 g of  $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$  and 2.8 g of  $\text{KH}_2\text{PO}_4$  in 1000 ml of distilled water). 20 mg samples of drug or products containing 40 mg of NIF were placed in the donor phase in all cases. The artificial membrane was made of cellulose acetate (pore size 3  $\mu\text{m}$ , diffusion surface 40  $\text{cm}^2$ ). The temperature was  $37.5 \pm 1.5 \text{ }^{\circ}\text{C}$ . 5.0 mL samples were taken five times (after 30, 60, 90, and 150 min) and their NIF contents were determined spectrophotometrically after filtration and dilution. The amount of diffused active agent and the diffusion constant  $K_d$  were calculated in the linear part of the diffusion plots:

$$K_d = \frac{c_{II2} - c_{II1}}{T_2 - T_1} \cdot \frac{1}{c_{I0}} \cdot \frac{V_{II0}}{F} \text{ [cm min}^{-1}\text{]}$$

where  $c_{II}$  is the corrected drug concentration in phase II at time  $T_x$  ( $\text{mg mL}^{-1}$ );  $V_{II0}$  is the volume of aqueous phase II at time  $T_x$  (100 mL);  $F$  is the surface area of the membrane ( $\text{cm}^2$ );  $T_x$  is time (min); and  $c_{I0}$  is the theoretical initial drug concentration in phase I ( $\text{mg mL}^{-1}$ ).

## Results and discussion

### Characterization of NIF and its products

According to the particle size distribution, the characteristics (length, width, area, perimeter and roundness) of at least 350 particles were determined in the SDs K-25 at all ratios. Table 1 summarizes the average values, as results. The size of the most frequent NIF particles is between 30-60  $\mu\text{m}$ . About 50 % of the particles had a particle size between 10- 20  $\mu\text{m}$ . Reduction of the length and width of the particles were significant for the 1:2, 1:4 SDs K-25 (from  $\sim 46 \mu\text{m}$  to  $\sim 14 \mu\text{m}$ ). This can result 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

investigated kinetically with the focus on SGM because two-thirds of the dose of the most NIF administered is absorbed from the stomach. On the basis of Table 3, it was concluded that the dissolution of NIF from products into SGM is described most precisely by the Langenbucher equation. The release of NIF (dissolution rate constant, K) was studied kinetically by using precise of the mathematical models presented earlier, as a function of the correlation coefficient of the dissolution process (table 4). The processes of dissolution in SGM were prolonged and saturation was observed after 30 min. For the PMs K-25 involving the use of PVP K-25, the quantity of NIF dissolved increased only gradually. In both media, extensive dissolution did not occur and the degrees of dissolution of the different products were nearly the same. An approximately 1.5-fold solubility increase was measured, independently of the weight ratios. A maximum solubility increase of 3.5-fold was observed for the SDs K-25, in SGM. NIF alone yielded the slowest initial dissolution rate. As shown in table 4, the dissolution rate constants of NIF from all PMs K-25 were almost the same, but in some cases higher than NIF alone. This might cause to the surface tension lowering effect of PVP to the medium, resulting in

**Table 1**  
CHARACTERIZATION OF PARTICLES OF SOLID DISPERSIONS

		Length [ $\mu\text{m}$ ]	Width [ $\mu\text{m}$ ]	Perimeter [ $\mu\text{m}$ ]	Area [ $\mu\text{m}^2$ ]	Roundness
NIF	Average	45.640	26.005	138.863	766.290	1.989
	sd	22.631	81.095	76.847	568.442	1.173
SD K-25 1:1	Average	21.390	13.355	84.088	127.226	2.850
	sd	13.553	8.198	63.623	115.060	1.334
SD K-25 1:2	Average	13.272	10.149	45.731	94.452	1.696
	sd	4.005	3.003	15.896	49.602	0.493
SD K-25 1:4	Average	14.647	8.569	48.034	76.955	2.463
	sd	5.535	3.036	20.128	49.602	0.990
SD K-25 1:6	Average	18.371	10.622	62.336	116.662	2.622
	sd	7.503	3.865	28.269	76.234	1.105

solubility, which at 25 °C is 26.75  $\text{mg mL}^{-1}$ . The concentration of NIF in water could be increased even 10-fold (from 26.75  $\mu\text{g mL}^{-1}$  to 227.1  $\text{mg mL}^{-1}$ ). The water solubility of NIF in the PMs K-25 was improved 2-3-fold and that of the SDs K-25 4-8-fold. The relevant results are shown in table 2. The contact wetting angles after 5 s 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. The investigation of the systems produced by physical mixing revealed that, with increasing PVP content, the contact wetting angles decreased: the 1:6 products were wetted 2-3 times better than NIF itself. The solvent evaporation methods gave the best results except, for the 1:1 SD K-25 (7.5°).

### Dissolution rate studies

NIF has an acidic character, and its *in vitro* dissolution (from 200 mg) was therefore better in SIM (14.33 mg/100 mL at 120 min) than in SGM (9.92 mg/100 mL at 120 min). The dissolution behaviour of the SDs K-25 was better than that of the PMs K-25 in both media.

The processes of drug release from the products were

**Table 2**  
SATURATION CONCENTRATIONS (25°C) AND WETTING ANGLES OF NIF AND PRODUCTS

Products	$C_{\text{water}}$ [ $\mu\text{g mL}^{-1}$ ]	Wetting angles [°] $\pm$ sd
NIF	26.75	71.1 $\pm$ 0.2
PMs K-25	1:1	92.83
	1:2	77.44
	1:4	65.04
	1:6	38.46
SDs K-25	1:1	7.5 $\pm$ 3.4
	1:2	123.10
	1:4	134.62
	1:6	166.10

**Table 3**  
CORRELATION COEFFICIENTS OF DISSOLUTION IN SGM OF NIF AND PRODUCTS

Materials and products	Langenbucher	M. Langenbucher	BTa
NIF	0.960	0.998	0.989
PMs K-25	1:1	0.990	0.971
	1:2	0.990	0.985
	1:4	0.978	0.978
	1:6	0.996	0.988
SDs K-25	1:1	0.979	0.997
	1:2	0.842	0.927
	1:4	0.986	0.989
	1:6	0.997	0.953

wetting of hydrophobic NIF crystalline surface [12]. Dissolution rates for solid dispersions were significantly greater than those for PMs K-25 and NIF. 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.

All of the methods resulted in fast dissolution in SIM: the saturation concentration was reached in 5-15 min. Figure 2 presents the dissolution profiles of NIF and 1:1, 1:4 PMs K-25 and SDs K-25. All of the solid dispersions resulted 100 % drug release in SIM while for the 1:4 and 1:6 PMs K-25 resulted 86 % drug release.

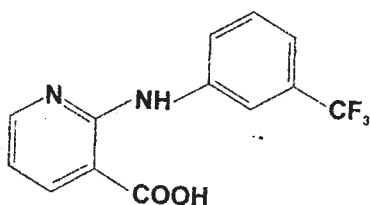


Fig. 2. Dissolution profile in SIM of NIF and products

#### Investigation of *in vitro* membrane diffusion

7.88 mg of NIF was able to diffuse out during 150 min into SGM, and 9.35 mg into SIM. For all the products except the SDs K-25, the diffusion was more advantageous than that of NIF into SGM. The diffusions of the products were also valuable in the case of SGM.

As regards the PMs K-25, the diffusion from the 1:4 compositions exhibited a 2-fold increase after 150 min. A 4.5-fold diffusion increase was measured for the SDs K-25. The last part of the diffusion plots had a saturated character, as a consequence of the increased amount of diffused drug. This is the explanation of the significant differences in the values of the diffusion rate constants. Accordingly, the linear part (between 30 and 90 min) of the plots was used to calculate the diffusion rate constants. Table 5 lists these diffusion rate constants: NIF had a  $K_d$  value of  $6.603 \cdot 10^{-3} \text{ cm min}^{-1}$ , while the  $K_d$  values for the samples were improved. The PM K-25 with a weight ratio of 1:4, and the SD K-25 with a weight ratio of 1:1 displayed the highest  $K_d$  values.

#### Conclusion

**Table 4**  
CHARACTERISTIC PARAMETERS OF LANGENBUCHER MODEL FOR NIF AND PRODUCTS

Materials and products	Correl. coef.	K
NIF	0.976	0.0049
PMs K-25	1:1	0.983
	1:2	0.992
	1:4	0.994
	1:6	0.999
SDs K-25	1:1	0.990
	1:2	0.876
	1:4	0.996
	1:6	0.992

**Table 5**  
DIFFUSION CONSTANS ( $K_d$ ) OF NIF AND PRODUCTS FROM SGM

Products	$K_d (10^{-3})$ [cm min <sup>-1</sup> ]	sd ( $10^{-3}$ ) ±
NIF	6.60	1.70
PMs K-25	1:1	2.99
	1:2	1.66
	1:4	3.33
	1:6	2.73
SDs K-25	1:1	2.91
	1:2	1.28
	1:4	2.39
	1:6	1.49

To investigate the effects of the water-soluble polymer PVP on the physicochemical characteristics of NIF, products were prepared in different ratios using physical mixing and solvent methods. These combinations offered an opportunity to analyse the physicochemical characteristics of SDs in comparison with the respective PMs K-25.

The extents of *in vitro* dissolution of the PMs K-25 were nearly the same in both media, with the exceptions of the 1:4 and 1:6 ratios in SIM, where a 12-fold improvement was found. The maximum solubility increase in SGM was 3.5-fold for a SDs K-25, while a more than 14-fold increase was found in SIM. According to the kinetic analysis, PVP enhanced the rate of dissolution of NIF. The increase in dissolution rate of NIF might be achieved by SDs K-25 (3-5 fold). SDs K-25 exhibited better dissolution rates than PMs K-25, resulted from the increase in drug wettability, reduced drug particle size, or prevent drug aggregation. The wettability and saturation concentration indicated that the products had a hydrophilic character. The membrane diffusion was 2-4.5-times better than that of the pure drug.

Our next study will focus on the characterisation of the structural interaction between NIF and PVP. However, further studies should be performed concerning storage and bioavailability of NIF in solid dispersions, because these

systems are presumably suitable for the formulation of oral- or semisolid dosage forms.

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