*Thermochimica Acta*, 199 (1991) 165–171
Elsevier Science Publishers B.V., Amsterdam



# Thermal behaviour and physicochemical properties of naproxen in mixtures with polyvinylpyrrolidone [1]

G.P. Bettinetti [a], P. Mura [a], F. Giordano [b] and M. Setti [c]

[a] *Dipartimento di Scienze Farmaceutiche, Università di Firenze, Via G. Capponi 9, 50121 Florence (Italy)*
[b] *Dipartimento di Chimica Farmaceutica, Università di Pavia, Viale Taramelli 12, 27100 Pavia (Italy)*
[c] *Dipartimento di Scienze della Terra, Università di Pavia, Via A. Bassi 4, 27100 Pavia (Italy)*

(Received in final form 30 September 1991)

**Abstract**

The thermal behaviour (DSC, TGA) of naproxen (NAP) and various grades of polyvinylpyrrolidone (PVP; $Mr \approx 10000$, 25000, 40000 and 360000), and their mixtures was investigated. A profound modification of the NAP melting peak, observed in the DSC curves of simply blended systems (physical mixtures) with PVP, was attributed to a solid-state interaction. This interaction proved to be influenced by the composition of the mixture, the PVP average molecular weight and the type of manipulation of the sample (grinding, compaction, heating). The high dispersion of NAP within the PVP matrix probably gives rise to the formation of crystalline drug microaggregates (molecular clusters) responsible for the thermal behaviour. The chemical and physical stability (dissolution rate, crystallinity) of NAP was not significantly affected in the mixtures with PVP.

## INTRODUCTION

Differential scanning calorimetry (DSC) is particularly useful for the rapid screening of interactions in drug-carrier solid mixtures. DSC curves recorded under the same experimental conditions are compared for both individual components and their combinations. Our work in improvement of the dissolution properties of naproxen (NAP) by means of solid dispersions in a hydrophilic amorphous polymer, polyvinylpyrrolidone (PVP), has disclosed profound changes in the DSC profile in the melting range of the crystalline drug in a simply blended NAP–PVP mixture of $Mr \approx 25000$ [1]. Because analogous changes observed in cross-linked PVP–drug systems are dependent on both the mixture composition and the sample manipulation

*Correspondence to:* G.P. Bettinetti, Dipartimento di Scienze Farmaceutiche, Università di Firenze, Via G. Capponi 9, 50121 Firenze, Italy.

[1] Presented at the 12th National Conference on Calorimetry and Thermal Analysis, Bari, Italy, 11–13 December 1990.

(simple mixing, grinding, compaction) [2], we thought it worthwhile to consider these factors in binary systems of NAP with both previously tested PVP [1] and with PVP of different average molecular weights. In the present paper, the thermal behaviour (DSC, TGA) of NAP, PVP ($Mr \approx$ 10000, 25000, 40000 and 360000) and of some drug–polymer mixtures is reported. X-ray powder diffractometry and dissolution studies using the constant surface-area disc method were employed to check the nature of the NAP/PVP interaction and the chemical and physical stability of NAP in the mixtures.

## EXPERIMENTAL

NAP (Sigma), PVP of $Mr \approx 25000$ (Merck) [1] and PVP of $Mr \approx 10000$ (K15), 40000 (K30) and 360000 (K90) (Fluka) of commercial grade were used. Each material was sieved and the respective 75–150 $\mu$m granulometric fraction was collected. NAP and each grade of PVP were gently mixed at different ratios in an agata mortar with a spatula, and combinations ranging from 10% to 90% by weight of NAP (physical mixtures) were obtained. A portion of each mixture was then ground by hand with a pestle until no further changes in the thermal traces could be detected (approximately 10 min).

Temperature and enthalpy measurements were performed with a Mettler TA4000 apparatus equipped with a 20 or 25 mod. DSC cell (5 or 10 K $min^{-1}$, 35–175°C) on 5–15 mg samples in pierced Al pans (Mettler M3 microbalance).

Thermogravimetric analysis was conducted on a Mettler TG50 apparatus (10 K $min^{-1}$, 30–140°C) on 15–25 mg samples in alumina crucibles under a nitrogen atmosphere (10 ml $min^{-1}$).

X-ray diffraction patterns were collected with a computer-controlled Philips PW1800 apparatus in the 2–40° $2\theta$ interval (scan rate 1°($2\theta$) $min^{-1}$) using Cu K$\alpha$ radiation monochromatized with a graphite crystal.

Dissolution tests were carried out in water at 37 ± 0.5°C according to the rotating disc method. About 300 mg of NAP/PVP 1:1 (by weight) physical mixture of each grade of PVP were compressed, using a 0.85 cm diameter die in a hydraulic press, giving discs that do not disintegrate under the test conditions (about 1.5 t). Discs were also prepared using physical mixtures previously heated at 100°C for 20 min. The disc was inserted into a stainless steel holder so as to expose only one surface of about 1.33 $cm^2$ to the dissolution medium (150 ml). The holder was connected by a shaft to the speed motor, centred at the bottom of a 200 ml beaker and rotated ($f = 100$ $min^{-1}$); 3 ml samples were removed at appropriate intervals and assayed spectrophotometrically at 274 nm for NAP content [1]. Each test was repeated at least three times.

## RESULTS AND DISCUSSION

### *Individual components*

The results of thermal analysis recorded at 5 K $min^{-1}$ on NAP, PVP K15 and PVP K30 are presented in Fig. 1. Curve a (m.p. 156.1 ± 0.3°C and $\Delta_{fus}H = 134 \pm 5$ J $g^{-1}$, 16 runs) is characteristic of NAP samples obtained by recrystallization from ethanol, methanol, isopropanol, ethyl acetate and chloroform, or by spontaneous evaporation of solutions in organic solvents or acidification of alkaline aqueous solutions. Neither polymorphs nor solvated forms of NAP (see the broken line TGA curve over the DSC curve a in Fig. 1) were isolated. As shown by curve b in Fig. 1, during the cooling of the NAP melt an exothermal effect occurs ($T_{cryst} = 112 \pm 10$°C and $\Delta_{cryst}H = 107 \pm 8$ J $g^{-1}$, 5 runs) due to crystallization of NAP. The same sample in the second heating run (not shown here) melts at 155.5 ± 0.2°C, with an enthalpy change $\Delta_{fus}H = 136 \pm 1$ J $g^{-1}$ (5 runs).

The thermal behaviour of all the PVPs is that expected for hygroscopic, amorphous substances (see, for example, curve d in Fig. 1), with a large endothermal effect in the 95–110°C range due to polymer dehydration. The water content determined by TGA varies from 8% to 12% by weight.

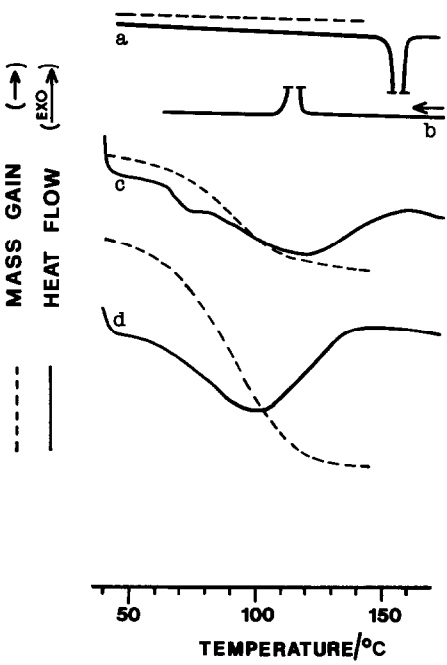


Fig. 1. DSC (solid line) and TGA (broken line) curves of the individual components: curve a, NAP (recrystallized from methanol); curve b, crystallization of NAP from the curve a melt; curve c, PVP of $Mr \approx 10000$ (PVP K15); curve d, PVP of $Mr \approx 40000$ (PVP K30).

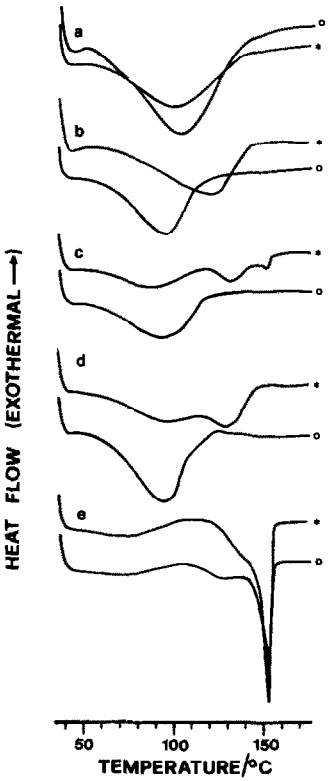


Fig. 2. DSC curves of physical mixtures of NAP with PVP of $Mr \approx 25000$ containing different drug to polymer weight ratios: curve a, 1:1.5; curve b, 1:1.2; curve c, 1:1; curve d, 1.2:1; curve e, 1.5:1. Asterisks (*) indicate simply-blended mixtures, circles (○) ground mixtures.

A glass transition at about 60°C (curve c in Fig. 1) is observed for PVP K15 [3].

*NAP and PVP mixtures*

The weight loss recorded with TGA (not shown) is in all cases proportional to the amount of PVP in the mixture. DSC curves of physical mixtures recorded at 10 K $min^{-1}$ on NAP and PVP of $Mr \approx 25000$ in different weight ratios, are shown in Fig. 2. A flat DSC profile can be observed in the melting range of NAP, even for simply blended mixtures with drug contents below 50% by weight (Fig. 2). This behaviour constitutes a common feature of the combinations of NAP with the other grades of PVP tested here. It resembles that already described for other drugs such as nifedipine [4], prednisolone [5], ibuprofen [6], aspirin [7], bromazepam [8], ketoprofen [9] and oxprenolol hydrochloride [10], and has often been quoted as evidence of pharmaceutical incompatibility between

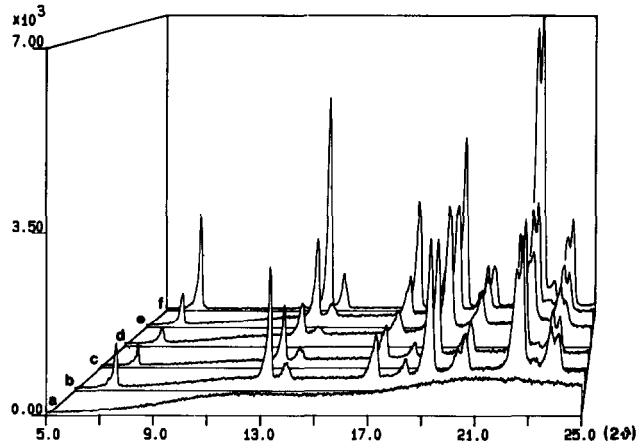


Fig. 3. X-ray diffraction powder patterns of NAP, PVP of $Mr \approx 10000$ (PVP K15) and the 1:1 (by weight) physical mixture. Curve a, PVP K15 alone; curve b, simply blended mixture; curve c, as curve b, stored for 3 days; curve d, ground for 10 min; curve e, heated at 100°C for 10 min; curve f, NAP alone.

the drug and PVP. Grinding influences the DSC profile of mixtures with compositions ranging between 40% and 60% by weight of NAP (Fig. 2, curves b, c and d). For both blended and ground mixtures containing 60% or more of NAP, in the 100–160°C range, there is a thermal effect similar to that observed in mixtures of trimethoprim with cross-linked PVP [2,11,12]. The apparent failure of NAP to melt when mixed with both the PVPs tested here and with cross-linked PVP [1] may be explained by the formation of crystalline microaggregates of the drug and their high dispersion within the polymer matrix [12]. A kind of saturation is reached when the NAP content is about 67% by weight. NAP in excess of this composition does not interact and undergoes normal melting (Fig. 2, curve e), as is also revealed by second heating runs (recrystallization from the melt and remelting).

X-ray analyses of all the physical mixtures of NAP with different PVPs were the weighted averages of the single-component spectra, i.e. two broad bands centred at about 12° and 21° $2\theta$ for amorphous PVP and sharp peaks corresponding to the NAP reference pattern no. 34-1751 (1988) of JCPDS (Joint Committee on Powder Diffraction Standards). As shown in Fig. 3 for the NAP/PVP K15 system only, in all mixtures containing PVP up to $Mr \approx 40000$, the drug maintained its crystallinity and chemical stability on ageing, as well as on grinding, compaction and heating, whereas NAP crystallinity in the combination with the highest molecular weight PVP (K90) was reduced. This is in agreement with the dissolution-rate enhancement of NAP observed for the NAP/PVP of $Mr \approx 360000$ 1:1 (by weight) system, as shown by the dissolution rates in Table 1. However, heating the NAP/PVP of $Mr \approx 360000$ mixture to 100°C cancels the positive influence

TABLE 1

Dissolution rate constants of NAP and its 1:1 (by weight) physical mixtures with PVP (rotating disc method)

| Sample | $k$ (mg cm$^{-2}$ h$^{-1}$) [a] |
|---|---|
| NAP | 0.33(3) |
| NAP/PVP $Mr \approx 10000$ | 0.41(7) [b] |
| | 0.37(5) [c] |
| NAP/PVP $Mr \approx 25000$ | 0.45(8) [b] |
| | 0.39(7) [c] |
| NAP/PVP $Mr \approx 40000$ | 0.62(9) [b] |
| | 0.55(4) [c] |
| NAP/PVP $Mr \approx 360000$ | 2.3 (3) [b] |
| | 0.43(6) [c] |

[a] Standard deviation in parentheses (3 runs).
[b] Discs from mixtures blended at room temperature.
[c] Discs from mixtures kept at 100°C for 20 min.

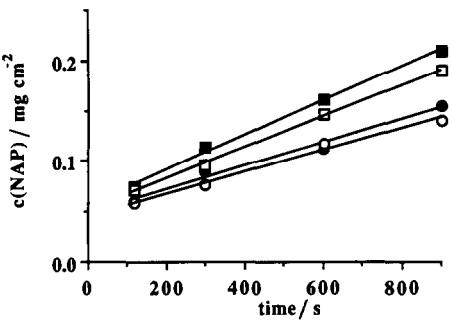


Fig. 4. Dissolution tests (rotating disc method in water at 37°C) of 1:1 (by weight) physical mixtures of NAP with PVP: amount of drug released per unit surface area vs. time: ○, PVP of $Mr \approx 10000$ and $Mr \approx 25000$; □, PVP of $Mr \approx 40000$. Solid symbols refer to discs from mixtures blended at room temperature, open ones to those from the same mixtures kept at 100°C for 20 min. The coefficient of variation at each time point (3 runs) was about 10%.

of this polymer on the NAP dissolution rate. The values in Table 1 were calculated according to ref. 13 by plotting the amount of drug released per unit surface area versus time (Fig. 4). It is evident that NAP always displays enhanced dissolution rates when mixed with PVP, even in discs prepared from pre-heated powders.

## CONCLUSIONS

NAP exists as a single, stable crystalline modification. In mixtures with PVP of different grades, a flat DSC profile can be observed in the melting range of NAP, even for simply blended mixtures with drug contents below

50% by weight. This behaviour is probably due to a solid-state interaction analogous to that observed in other systems [12]. The high dispersion of NAP within the PVP matrix probably gives rise to the formation of crystalline drug microaggregates (molecular clusters) responsible for the thermal behaviour. NAP/PVP interaction capability is reached when the NAP content is about 60% by weight. This interaction improves the dissolution characteristics of NAP, which maintains its crystallinity and chemical stability on ageing, as well as on grinding and compaction. The modification of the melting peak of the drug constitutes the phenomenology of the interaction between the drug and the polymer and does not represent a pharmaceutical incompatibility; in other words, it does not necessarily debar PVP as a partner in NAP formulations.

ACKNOWLEDGEMENT

This work was partly subsidised by a C.N.R. grant to G.P.B.

REFERENCES

1 G.P. Bettinetti, P. Mura, A. Liguori, G. Bramanti and F. Giordano, Farmaco Ed. Prat., 43 (1988) 331.
2 F. Giordano, G.P. Bettinetti, A. La Manna and G. Giuseppetti, J. Calorim. Anal. Therm., 16 (1985) 220.
3 D.T. Turner and A. Schwartz, Polymer, 26 (1985) 757.
4 I. Sugimoto, A. Kuchiki, H. Nakagawa, K. Tohgo, S. Kondo, I. Iwane and K. Takahashi, Drug Dev. Ind. Pharm., 6 (1980) 137.
5 N. Fukuda, N. Higuchi, M. Ohno, H. Kenmochi, H. Sekikawa and M. Takada, Chem. Pharm. Bull., 34 (1986) 1366.
6 N.M. Najib, M. Suleiman and A. Malakh, Int. J. Pharm., 32 (1986) 229.
7 J.A. Plaizier-Vercammen, in G.A. Digenis, B.J. Agha, J. Ansell and L. Blecher (Eds.), Proc. 2nd Int. Symp. Povidone, Univ. of Kentucky, College of Pharmacy, Lexington, Kentucky, 1987, p. 181.
8 A.R. Fassihi and P.H.R. Persicaner, Int. J. Pharm., 37 (1987) 167.
9 S.A. Botha and A.P. Lotter, Drug Dev. Ind. Pharm., 15 (1989) 415.
10 S.A. Botha and A.P. Lotter, Drug Dev. Ind. Pharm., 15 (1989) 1843.
11 F. Giordano, G.P. Bettinetti and A. Marini, J. Calorim. Anal. Therm., 17 (1986) 493.
12 T. Zerlia, A. Marini, V. Berbenni, V. Massarotti, F. Giordano, A. La Manna, G.P. Bettinetti and C. Margheritis, Solid State Ionics, 32/33 (1989) 613.
13 J.G. Wagner, Drug Intell. Clin. Pharm., 4 (1970) 77.