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DISSOLUTION PROPERTIES OF NAPROXEN IN COMBINATIONS WITH POLYVINYLPYRROLIDONE

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ABSTRACT

The effect of the molecular weight of polyvinylpyrrolidone on the solubility and dissolution properties of naproxen using solid dispersions (coevaporates and colyophilized products) and physical mixtures was investigated. Factors such as method of drug incorporation with the polymer and polymer mass fraction influence the dissolution rate of naproxen from both powders and constant surface area discs. The best results were obtained with the colyophilized products at the drug-to-polymer 7:3 weight ratio, in the rank order (most effective to least) K15>K30>K90 (dispersed amount) and K30>K90>K15 (rotating disc). The physical state of naproxen, *i.e.* amorphous or crystalline, in solid combinations with polyvinylpyrrolidone was checked by means of X-ray powder diffraction. Drug-polymer interactions in the liquid state were revealed with solubility experiments. Drug-polymer interactions in solid state were demonstrated by combining the X-ray diffraction data with the results of thermal analysis (DSC, TGA) and microscopic observation.

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INTRODUCTION

In a previous study dealing with the dissolution properties of naproxen (NAP), polyvinylpyrrolidone (PVP) with a molecular weight of about 25,000 was found to be a suitable carrier for improving NAP dissolution rate from solid dispersions [1]. Since the molecular weight of the polymer may play a role in the performance of a solid dispersion [2], it seemed of interest to consider the effect of this parameter on NAP dissolution from various NAP/PVP combinations. Thus PVP with molecular weights of about 10,000, 40,000, and 360,000 was used to prepare coevaporates, colyophilized products and physical mixtures at different drug-to-polymer ratios. Both the dispersed amount and the constant surface area disc methods were chosen to determine NAP dissolution properties. NAP/PVP interactions in both liquid and solid states which might be responsible for the dissolution performance of the drug were also investigated. The results of solubility and dissolution rate studies, X-ray powder diffraction (XRD), differential scanning calorimetry (DSC) and microscopic observation are presented and discussed.

MATERIAL AND METHODS

Materials - NAP (Sigma) and PVP (Fluka) of $M_r \approx$ 10,000 (K15), 40,000 (K30), and 360,000 (K90) of commercial grade were used. Each material was sieved and the respective 75-150 µm granulometric fraction was collected. Other chemicals used were of analytical grade.

Preparation of Samples - Coevaporates were obtained by dissolving NAP (500 mg) and PVP at suitable weight ratios (*i.e.* NAP/PVP 7:3, 5:5 and 3:7) in a minimum volume of absolute methanol at room temperature, removing the solvent under vacuum in a rotatory evaporator at 45 °C, and drying the residue under vacuum at room temperature up to constant weight. The solid was pulverized with a pestle and mortar and sieved collecting the 75-150 µm granulometric sieve fraction. Colyophilized products were prepared by dissolving NAP (1 g) and PVP

at suitable weight ratios in aqueous 0.02% (*gg*) ammonia solution (500 mL) and freeze-drying at -50°C and 1.3×10^{-2} mm Hg (Lyovac GT2, Leybold-Heraeus). Neither residual ammonia nor decomposition products of NAP were detected in the samples [1]. Physical mixtures were prepared by blending in an agata mortar at room temperature.

Solubility Determinations - Excess NAP (30 mg) was added to 30 mL of water or aqueous PVP solution (2 to 10 g of PVP in 100 mL of water, or 0.18 to 0.9 mol L^{-1} as vinylpyrrolidone equivalent) in a 100 mL sealed glass container which was then electromagnetically stirred at 37.0 ± 0.5 °C until equilibrium was achieved (2 d). An aliquot was filtered through a 0.45 μm membrane filter and analyzed for NAP content at 274 nm in the conditions described elsewhere [1]. Each experiment was repeated four times. The apparent 1:1 stability constants (L mol^{-1}) of the soluble complexes were calculated from the slopes of the solubility curves [1].

Dissolution Tests - The dissolution rate of NAP in different samples was determined in water at 37.0 ± 0.5 °C. According to the dispersed amount method, 20 mg of NAP or NAP equivalent were added to 300 mL of water and tested in the conditions described elsewhere [1]. Each test was repeated at least three times. According to the disc method, about 300 mg of powder were compressed using a 1.3 cm diameter die in a KBr press, at a suitable force for obtaining discs which do not disintegrate under the test conditions (about 1.5 t). The disc was inserted into a stainless steel holder so that only one surface of about 1.33 cm^2 was exposed to the dissolution medium (150 mL). The holder was connected with a shaft to the speed motor, centered at the bottom of a 200-mL beaker, and rotated (f = 100 min^{-1}). 3 mL samples were removed at appropriate intervals and spectrophotometrically assayed at 274 nm for NAP content as in the dispersed amount method, adding the same volume of fresh medium to the beaker and calculating the correction for the cumulative dilution [1]. Each test was repeated at least three times.

Thermal Analysis - Temperature and enthalpy measurements were performed with a Mettler TA4000 apparatus equipped with a DSC 20 or

TABLE 1

Apparent Stability Constants ($K_{(1:1)}$) of Naproxen (NAP) and Polyvinylpyrrolidone (PVP) Complexes and Amount of NAP Dissolved by 0.8 M Vinylpyrrolidone Equivalent (c(NAP)*) in Water at 25 and 37 °C.

PVP	$K_{(1:1)}$, L mol^{-1}		c(NAP)*, mmol L^{-1}	
	25 °C	37 °C	25 °C	37 °C
---			0.12	0.18
K15	6.3	6.0	0.77	1.2
K30	6.5	5.4	0.82	1.1
K90	11	7.7	1.4	1.6

25 cell (5 or 10 K min^{-1}, 35...175 °C) on 5...15 mg (Mettler M3 microbalance) samples in pierced Al pans. Thermogravimetric analysis was conducted on a Mettler TG 50 apparatus (10 K min^{-1}, 30...140 °C) on 15...25 mg samples in alumina crucibles under a nitrogen atmosphere (10 mL/min).

X-ray Diffraction - X-ray diffraction patterns were recorded with a computer-controlled Philips PW 1800 apparatus in the 2...40° 2 θ interval (scan rate 1° min^{-1}), using CuKα radiation monochromatized with a graphite crystal.

RESULTS AND DISCUSSION

Solubility and Dissolution Rate Studies - NAP solubility in water at 25 and 37 °C was positively affected by each grade of PVP. The increase in NAP solubility as a function of the PVP concentration in solution was linear, following the A_L type phase-solubility diagram profile [1]. The apparent stability constants of formation of the possible complexes between NAP and PVP, $K_{(1:1)}$ (in liter per moles, taking the PVP repeating unit to be its molecular weight), were calculated at both

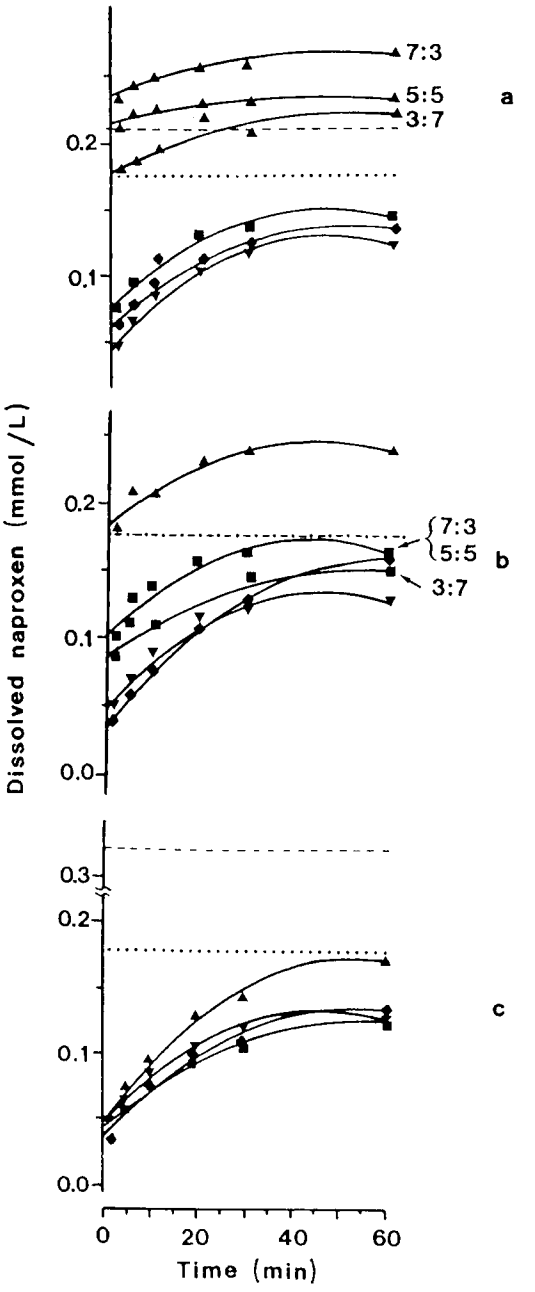

FIGURE 1

Dissolution of naproxen (NAP) alone and from combinations with polyvinylpyrrolidone (PVP) in the 7:3, 5:5 and 3:7 drug-to-polymer weight ratios: (a) PVP K15; (b)PVP K30; (c) PVP K90.

(▼) NAP alone; (■) physical mixture; (◆) coevaporate; (▲) colyophilized product; (....) NAP aqueous solubility; (----) NAP concentration attainable in PVP solution (dispersed amount in water at 37 °C, non-sink conditions, coefficient of variation at each time point (n=3) about 2%).

TABLE 2

Ratios Of the Amount of Naproxen (NAP) Dissolved from NAP/Polyvinylpyrrolidone (PVP) Colyophilized Products to the Amount Dissolved from NAP alone in Water at 37 °C at Three Time Points.

Colyophilized Product	2 min	10 min	30 min
NAP/PVP K15 3:7 (by weight)	3.8	2.2	1.7
5:5 (")	4.4	2.6	1.9
7:3 (")	4.8	2.8	2.2
NAP/PVP K30	3.6	2.3	2.0
NAP/PVP K90	1.2	1.1	1.2

temperatures from the slopes of the curves. The values are given in Table 1, with the amounts of NAP solubilized by 0.8 M vinylpyrrolidone equivalent of PVP. PVP K90 exhibited the greatest solubilizing capacity for NAP, with a 12 and 9 times increase in its water solubility at 25 and 37 °C, respectively. K15 and K30 PVP grades showed a very close solubilizing ability, similar to that of the already-tested intermediate-grade PVP [1]. The rate of dissolution of NAP and its combinations (physical mixtures, coevaporates, colyophilized products) with each grade of PVP in the 7:3, 5:5, and 3:7 drug/polymer ratios as mass fraction, was determined in water at 37 °C. The results of dispersed amount experiments are shown in Figure 1. A positive effect of PVP molecular weight on the drug dissolution properties is particularly evident for the colyophilized products, in the rank order (most effective to least) K15>K30>K90. An effect of NAP mass fraction on the amount of drug released was observed for the NAP/PVP K15 colyophilized products, the drug-to-polymer one 7:3 (by weight) giving the best performance (Table 2).

The dissolution behaviour of the colyophilized products from constant surface area discs was determined only for the NAP/PVP 7:3 (by weight) composition owing to the rapid deaggregation of discs at higher PVP contents under the experimental conditions. Coevaporates

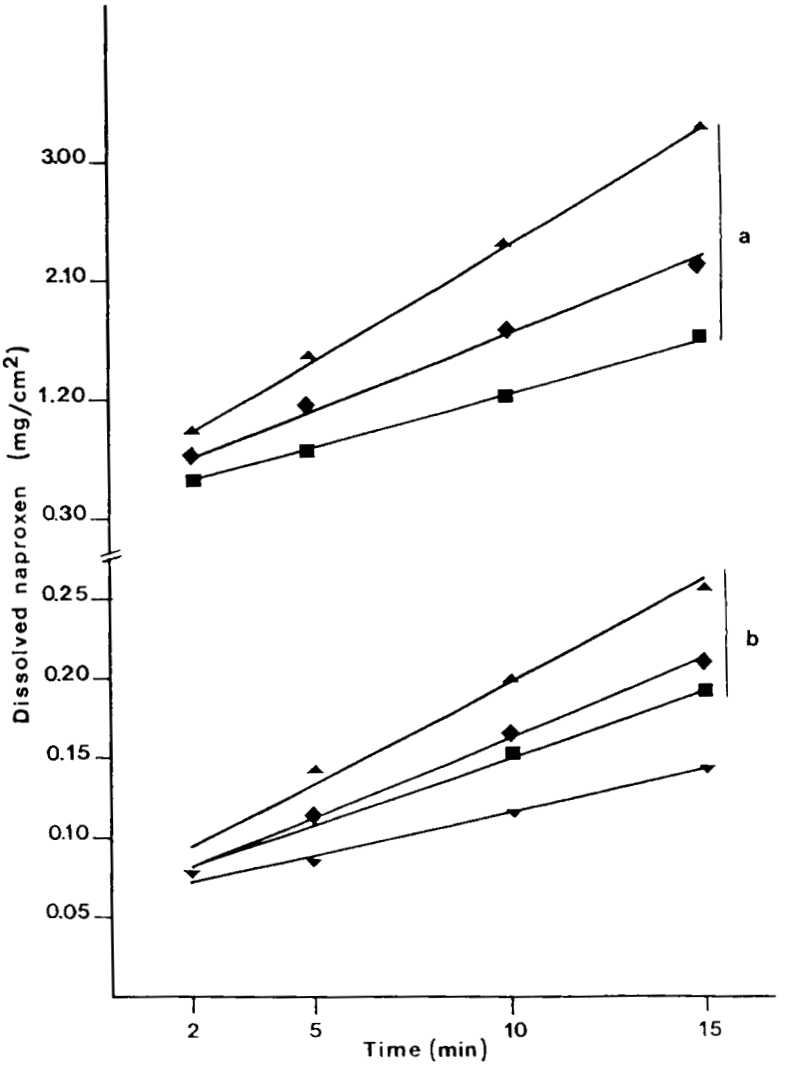

FIGURE 2

Dissolution of naproxen (NAP) alone and from (a) colyophylized products and (b) coevaporated with polyvinylpyrrolidone (PVP K15, K30, and K90) in the 7:3 drug-to-polymer weight ratio.
(▼) NAP alone; (■) PVP K15; (▲) PVP K30; (◆) PVP K90 (rotating disc method in water at 37 °C, coefficient of variation at each time point (n=3) about 10%, rate constants in Table 3).

TABLE 3

Dissolution Rates (mg cm^{-2} h^{-1}) of Naproxen (NAP) and its Systems with Polyvinylpyrrolidone (PVP) of Different Molecular Weight in the 7:3 by Weight Ratio (Rotating Disc Method, Standard Deviation in Parentheses).

		Colyophilized Product	Coevaporate	Physical Mixture
NAP/PVP K15		4.73(7)	0.52(4)	0.43(3)
NAP/PVP K30		10.6(9)	0.79(4)	0.61(4)
NAP/PVP K90		6.60(26)	0.62(6)	0.50(5)
NAP	0.33(3)			

and physical mixtures of the same composition were also tested, and the results are presented in Fig. 2 and Table 3.

The grade of PVP with the lowest molecular weight which was the most effective in improving NAP release from NAP/PVP powders, was the least effective for the corresponding constant surface area discs. In these systems the rank order (most effective to least) was K30>K90>K15, regardless of the method of incorporation of the drug with the polymer. A better dissolution-promoting effect of PVP K30 than of PVP K15 has been reported for indomethacin/PVP coprecipitates [3]. Unlike colyophilized products, physical mixtures containing less than 70% NAP (by weight), i.e. at the 5:5 and 3:7 NAP/PVP weight fractions, could be compressed into constant surface area discs suitable for dissolution rate determination. PVP K30 was still the best carrier for NAP. The best performance was given by the NAP/PVP K30 3:7 physical mixture (by weight), whose dissolution rate (1.23(5) mg cm^{-2} h^{-1}) was twice that of the corresponding 7:3 composition (see Table 3).

Solid State Studies - The XRD peaks of crystalline NAP [4] were present in all the physical mixtures with the amorphous polymer. The intensities of some peaks (*e.g.* those at 18.5°, 20.0°, and 23.5° 2θ) were roughly proportional to the drug content. Crystalline NAP was also present in

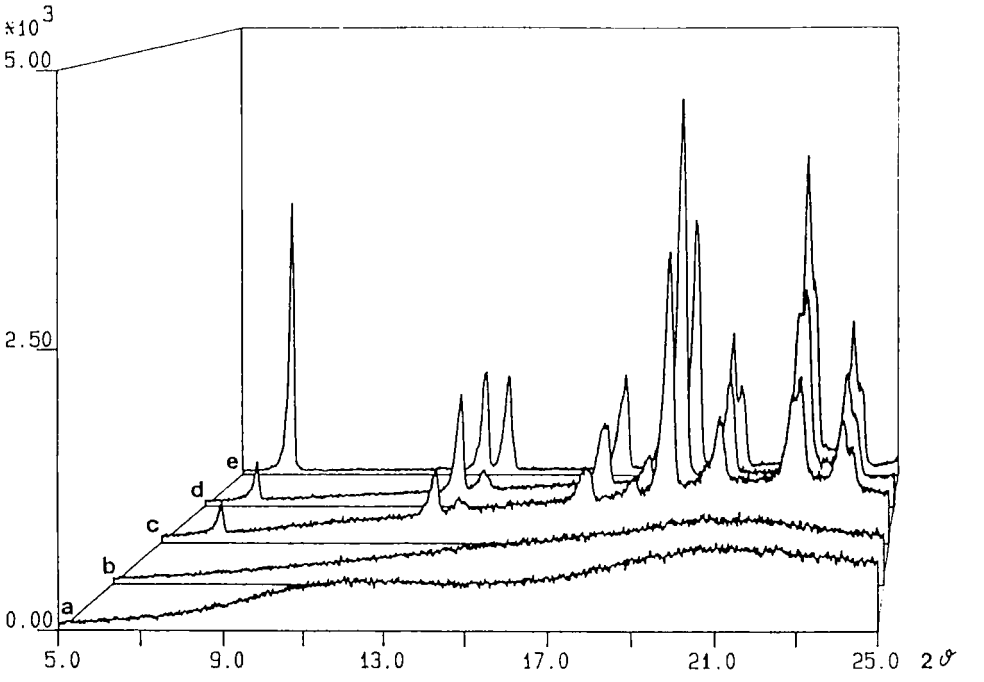

FIGURE 3
X-ray diffraction powder patterns of (e) naproxen (NAP), (a) polyvinylpyrrolidone (PVP) K15, and the respective (b) 3:7, (c) 5:5, (d) 7:3 (by weight) coevaporates.

the NAP/PVP 5:5 and 7:3 (by weight) coevaporates, as shown in Fig. 3 for those with PVP K15 as an example. The colyophilized products, which showed the highest dissolution rates, were totally amorphous. A lack of NAP crystallinity has already been found in co-spray dried products with PVP K15 [5]. Since the X-ray amorphous NAP/PVP K15 3:7 coevaporate powder (by weight) (curve *b* in Fig. 3) dissolved to a much lesser extent than the colyophilized product of the same composition (see Fig. 1), some dissolution-enhancing factors deriving from the freeze-drying process, *e.g.* large specific surface area, good wettability, and/or high-energy amorphous phase, evidently play a role in dissolution of colyophilized products.

Microscopic analysis showed that the NAP/PVP K15 3:7 (by weight) colyophilized product was an aggregate of glassy flakes (glass

dispersion), whilst the coevaporate looked like an amorphous resin of sintered grains. The NAP/PVP K90 3:7 colyophilized product (by weight) appeared as a doughy and waxy solid, so that the poor dissolution properties of colyophilized preparations with PVP K90 could be ascribed to the stickiness imparted to the system by this a grade of PVP.

XRD patterns also showed that no phase changes, *i.e.* amorphous to crystalline NAP, were induced by compacting the colyophilized powders into discs. Likewise, it was shown that the compaction and grinding of physical mixtures, as well as heating at 100 °C for 1 h, did not substantially influence NAP crystallinity and chemical stability. The dissolution rate of colyophilized products from discs, which was one order of magnitude higher than that of the respective coevaporates and physical mixtures (see Table 3), could be ascribed to the presence of amorphous drug. The relatively low effectiveness of PVP K15 in promoting NAP dissolution rate from discs as compared with the grades with higher molecular weights (Table 3) might be related to the strength of the NAP/PVP K15 powder compact due to the better properties of PVP K15 as a binder [6]. The behaviour during crushing tests and microscopic analysis of crushed discs of NAP/PVP 7:3 colyophilized products (by weight) confirmed this view. For samples containing PVP K15, the fracture was actually perfectly clean and the fracture surfaces were indistinguishable from the intact surface of the disc. Schistosity structures were instead evident on the fracture surfaces of discs made up with PVP K30 and K90.

Fig. 4 shows the DSC curves recorded at 10 K min^{-1} on the NAP/PVP K15 samples tested in dissolution rate experiments. The large endothermal effect ending at about 110 °C is due to polymer dehydration [4], as determined by the weight loss recorded with TGA (not shown). A glass transition at about 55 °C [7] was observed for the NAP/PVP K30 and NAP/PVP K90 colyophilized products containing excess polymer (see Fig. 4). As expected, NAP melting at about 156 °C [4] was absent in the X-ray amorphous samples (colyophilized products and NAP/PVP K15 coevaporate containing excess polymer). However NAP failed to melt even in coevaporates and physical mixtures containing crystalline drug.

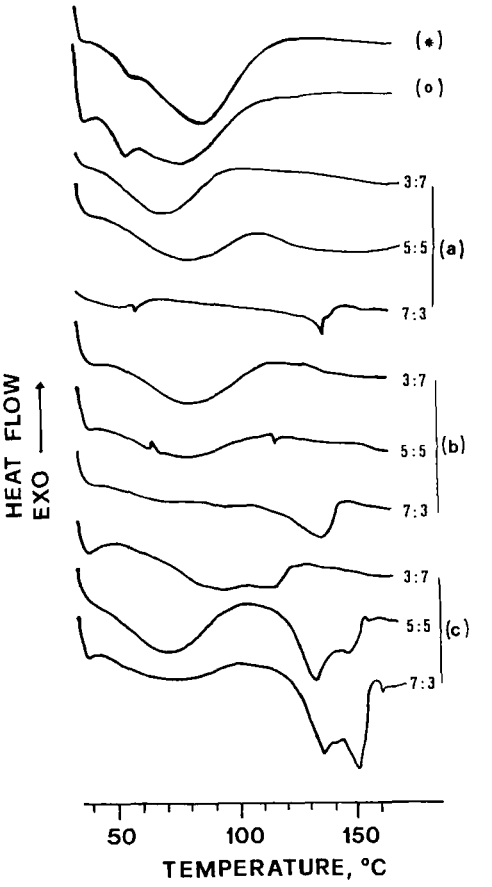

FIGURE 4
DSC curves of naproxen (NAP)/polyvinylpyrrolidone (PVP) K15 preparations ((a) colyophilized products, (b) coevaporates, (c) physical mixtures: NAP to PVP weight ratio on the curve), NAP/PVP K30 3:7 (by weight) colyophilized product (°), and NAP/PVP K90 3:7 (by weight) colyophilized product (*).

The same behaviour was observed for the mixtures of NAP with grades of PVP of higher molecular weight and explained by the formation of crystalline microaggregates of the drug and their high dispersion within the polymer matrix [4]. Thermomicroscopic analysis of the NAP/PVP K15 5:5 physical mixture (by weight) showed that water present in PVP emerged from 70 to 120 °C and then NAP crystals spread out into the softened PVP matrix with concomitant comminution. Fusion occurred in the broad range of 135...150 °C, whose final temperature

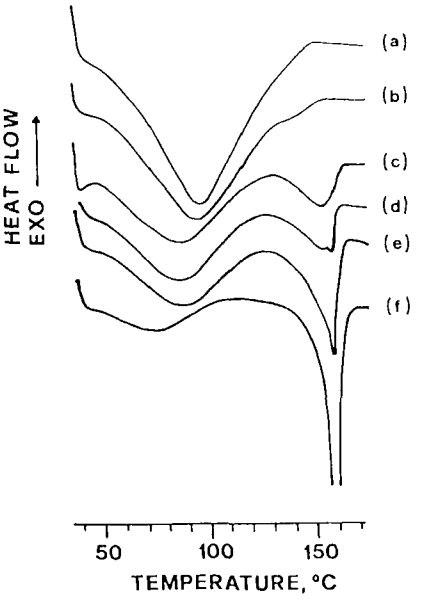

FIGURE 5
DSC curves of naproxen (NAP)/polyvinylpyrrolidone (PVP) K90 physical mixtures in the (a) 3:7, (b) 4:6, (c) 5:5, (d) 6:4, (e) 7:3, (f) 8:2 weight ratios.

was lower than the pure NAP melting point. A kind of saturation was postulated for this a NAP/PVP solid state interaction induced by heating [4]. DSC analysis of some NAP/PVP K90 physical mixtures (Fig. 5) actually showed that NAP in excess of about 70% by weight did not interact and underwent normal melting.

CONCLUSIONS

NAP/PVP K15 and NAP/PVP K30 7:3 colyophilized products (by weight) show the best in vitro NAP dissolution properties, respectively as powders and constant surface area discs. PVP of $M_r \approx 10,000$ (K15) is more effective than the already tested PVP of $M_r \approx 24,000$ [1], with an amount of drug dissolved from powders 50% greater than NAP solubility. Better improvements in NAP dissolution properties, however, were achieved using cyclodextrins [8,9], which gave a 10-15 times increase in the amount of NAP dissolved from powders, and dissolution rates from

discs which were about one order of magnitude higher than the best ones obtainable using PVP. On the other hand the grades with lower molecular weights, PVP K15 in particular, are better binders than cyclodextrins for direct compression NAP formulations. Despite the greatest solubilizing capacity for NAP in aqueous dissolution exhibited by PVP K90, this polymer is not particularly effective in improving the drug dissolution properties, probably owing to its tendency both to impart stickiness to the solid preparations and to increase the viscosity of the diffusion layer around the dissolving particles [10]. Phase changes are induced neither by compacting the colyophilized amorphous powders nor by grinding, heating at 100 °C, or compacting the mixtures containing crystalline NAP. Instead, a tendency to crystallize on ageing was observed for the 5:5 and 7:3 NAP/PVP K15 colyophilized products. The solid state of NAP, *i.e.* amorphous or crystalline, in the combinations with PVP is easily detected by XRD. DSC may give a flat profile in the NAP melting region even for mixtures containing crystalline NAP [4], as a consequence of NAP/PVP solid state interactions induced by heating.

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REFERENCES

[1] G. P. Bettinetti, P. Mura, A. Liguori, G. Bramanti, F. Giordano, *Il Farmaco, Ed.Pr.*, 43, 331 (1988).

[2] J. L. Ford, *Pharm. Acta Helv.*, 61, 69 (1986).

[3] K. Takayama, N. Nambu, T. Nagai, *Chem. Pharm. Bull.*, 29, 2718 (1981).

[4] G. P. Bettinetti, P. Mura, F. Giordano, M. Setti, *Thermochim. Acta*, 00, 00, (1991).

[5] O. I. Corrigan, E. M. Holohan, M. R. Reilly, *Drug Dev. Ind. Pharm.*, 11, 677 (1985).

[6] C. Nystrom, M. Glazer, *Int. J. Pharm.*, 23, 255 (1985).

[7] D. T. Turner, A. Schwartz, *Polymer*, 26, 757 (1985).

[8] G. P. Bettinetti, P. Mura, A. Liguori, G. Bramanti, F. Giordano, *Il Farmaco, Ed.Pr.*, 44, 195 (1989).

[9] G. P. Bettinetti, A. Gazzaniga, P. Mura, F. Giordano, M. Setti, *Drug. Dev. Ind. Pharm.*, 18, 39 (1992).

[10] A. T. Florence, P. H. Elworthy, A. Rahaman, *J. Pharm. Pharmac.*, 25, 779 (1973).