Preparation, Dissolution and Characterization of Praziquantel Solid Dispersions

Paloma DE LA TORRE, Susana TORRADO, and Santiago TORRADO*

Department of Pharmaceutical Technology, School of Pharmacy, Complutense University, Avda. Complutense n/s. Madrid, Spain. Received March 24, 1999; accepted July 4, 1999

Solid dispersions of praziquantel (PZQ) containing varying concentrations of polyvinylpyrrolidone (PVP) with different molecular weights (3000, 11000 and 34000) were prepared in an attempt to improve the solubility and dissolution rate of PZQ. The physical characteristics of PZQ, physical mixtures and solid dispersions were investigated by a variety of analytical methods including scanning electron microscopy (SEM), differential scanning calorimetry (DSC) and powder X-ray diffraction (XRD). The solubility of PZQ in the coprecipitate was greater when PVP of a smaller molecular weight was used. The dissolution rate of the drug in the coprecipitate was faster when the ratio of the drug to PVP was smaller (1 : 9). SEM was especially useful in the verification of possible PZQ inclusion in the PVP matrix due to the morphological and physical differences between PZQ and PVP. The physical mixture and solid dispersion DSC scans did not present a clear endothermic peak, perhaps due to a low PZQ enthalpy.

The dissolution rate was significantly increased when the PZQ : PVP ratio was at least 1 : 5, which agrees with the inclusion of PZQ in the PVP matrix, as observed by SEM, and the amorphous pattern shown by XRD.

Key words praziquantel; solid dispersions; polyvinylpyrrolidone; scanning electron microscopy; dissolution rate; characterization techniques

Praziquantel (PZQ), 2-(cyclohexylcarbonyl)-1,2,3,6,7,11β-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-one, is an anthelmintic drug effective against a broad range of trematodes and cestodes, and it is the drug of choice for schistosomiasis and other snail-borne human trematodes.[1—4] One of the problems of PZQ is its very low aqueous solubility: 0.04 g/100 ml.[5] A possible way of overcoming this is to alter the physical properties of the drug by preparing a solid dispersion (SD). The solid state forms (*i.e.*, crystalline polymorphs, solvates, amorphous solids) of a drug substance can have a significant impact on the drug's solubility, dissolution rate and bioavailability. Dispersion of the drug within an inert water soluble carrier, such as polyethylene glycol or polyvinylpyrrolidone (PVP) in the solid state,[6,7] known as the solid dispersion system, increases the solubility and the dissolution rate of the drug by simultaneously reducing drug particle size and altering the drug crystal form, usually to an amorphous state.[8—10] Although amorphous solids are often susceptible to changes during storage, the amorphous form of a drug is generally more soluble, which is a useful property, particularly if the drug has low aqueous solubility. Different studies have shown that the most successful carrier to date for promoting amorphous phase formation is PVP, and this appears to be related to the polymer's potent capacity to inhibit crystal growth.[11—13] Solid dispersions of poorly soluble drugs such as anthelmintics, in water soluble carriers, have been previously obtained and have shown an increase in dissolution rate and also in drug bioavailability.[14—16] The present study has been designed to examine the physical properties and dissolution behavior of different PZQ–PVP solid dispersions using a variety of analytical methods.

Experimental

Materials The materials used were as follows: PZQ (Sigma®) and PVP K12PF, PVP K17 and PVP K25 (Basf®) with average molecular weights of 3000, 11000 and 34000, respectively. All other chemicals were of reagent grade or better (Panreac®, Merck®).

Formulations The solid dispersions were prepared using a solvent evaporation method. The required amounts of PZQ and PVP were co-dissolved in a minimal volume of 95% ethanol. The solvent was then evaporated in a vacuum at 50 °C with a rotary evaporator.

Each of the different formulations was ground and sieved to obtain a particle size fraction of 0.42—0.84 mm. After this procedure, and because water can readily plasticize PVP, the residual moisture of the samples obtained by the rotary evaporation method was removed as much as possible by a freeze-drying process. Solid samples (0.5 g) were introduced in 20-ml vials and loaded on a freeze-dryer (Telstar L-3) shelf at *ca.* 5 °C. After thermal equilibration, the shelf temperature was lowered to −40 °C. The product was maintained at this temperature for 2 h. Then, the system was evacuated to a pressure of 0.04 mbar and the shelf temperature was adjusted to −35 °C and held there for 4 h. Afterwards, the shelf temperature was raised successively to −20 °C (8 h), then 0 °C (8 h) and finally 20 °C (2 h). After drying the samples, the vials were capped within 5 min and stored at room temperature (22—24 °C) in a desiccator containing silica gel.

For the present study, physical mixtures were prepared by blending PZQ and PVP in a mortar with spatula immediately before using.

Recrytallized PZQ (R-PZQ) was obtained by the same preparation method used for the solid dispersions but without any carrier.

The different solid dispersions and physical mixtures obtained are listed in Table 1.

Solubility Determination Solubility (w/w) at 37 °C was determined using the shaker method. An excess of the compound was placed in solvent in a screwcapped glass tube, connected to a rotating sample, then immersed in a water bath while being maintained at the required temperature (37 °C), and agitated continuously for 96 h. PZQ samples were withdrawn, filtered through a 0.45 μm Millipore filter and analyzed in a Beckman DU-7 spectrophotometer at 263 nm. The solvent was 0.1 N HCl with a certain amount of sodium lauryl sulfate (SLS) added per ml (0; 0.2; 0.8; 1.25; 1.5; 2; 3; 5, 10 mg). All solubility measurements were performed in triplicate.

These solubility studies allowed us to evaluate the influences on drug solubility of the type of PVP (K12, K17 and K25) employed, the drug:carrier ratio used (1 : 2.4, 1 : 5, 1 : 9) and the different quantities of SLS added to the dissolution medium.

Scanning Electron Microscopy (SEM) Particle morphology, size and shape were analyzed by SEM on a JEOL 6400 electron microscope. All micrographs were the product of secondary electron imaging used for surface morphology identification at different magnifications (×500; ×1000, ×2500).

Powder X-Ray Diffraction (XRD): Structural and Crystal Size Characterization The structural characterization of the material included the conventional θ–2θ powder XRD (Philips X'Pert-MPD) (CAI Difracción rayos X, Farmacia, UCM) of all samples under observation. Measurements were carried out with 2θ 5—40° using a step size of 0.04° (2θ) and 1 s time

* To whom correspondence should be addressed.

Table 1. Formulation of PZQ Solid Dispersions and Physical Mixtures

Formulation	Drug/Carrier ratio (key of formulations)		
	PZQ : PVP 12	PZQ : PVP 17	PZQ : PVP 25
Solid dispersion	1 : 1 (SD-12-1 : 1)	—	—
	1 : 2.4 (SD-12-1 : 2.4)	1 : 2.4 (SD-17-1 : 2.4)	1 : 2.4 (SD-25-1 : 2.4)
	1 : 5 (SD-12-1 : 5)	1 : 5 (SD-17-1 : 5)	1 : 5 (SD-25-1 : 5)
	1 : 9 (SD-12-1 : 9)	1 : 9 (SD-17-1 : 9)	1 : 9 (SD-25-1 : 9)
Physical mixture	1 : 1 (PM-12-1 : 1)		
	1 : 2.4 (PM-12-1 : 2.4)		
	1 : 5 (PM-12-1 : 5)		
	1 : 9 (PM-12-1 : 9)		

per step. This technique allowed us to study the influence of the PVP proportion on solid dispersion physico-chemical characteristics.

Differential Scanning Calorimetry (DSC) For DSC, samples of 2—6 mg in loosely covered aluminium pans were heated from 50 to 250 °C at the rate of 10 °C/min under nitrogen purge, with an empty, loosely covered aluminium pan for reference, in a differential scanning calorimeter, DSC Mettler TA 8000.

***In Vitro* Drug Release** For drug release, testing apparatus 1 of the USP 23 (Van-Kel) with a rotation speed of 50 rpm, was used. In order to avoid small particles of PZQ floating on the dissolution medium, all the samples tested were ground and sieved to obtain a particle size fraction of 0.42—0.84 mm, and an amount of the solid dispersion equivalent to 60 mg of PZQ was introduced into the basket.

The dissolution medium described in the USP 23 (1995) monograph of PZQ tablets consists of 0.1 N hydrochloric acid containing 2.0 mg of SLS per ml with a tolerance of not less than 75% of the labeled amount of PZQ dissolved in 60 min. This great amount of SLS produces such a rapid dissolution of the drug that it is impossible to observe differences in the dissolution profiles of PZQ raw material and solid dispersions. Therefore, and with the aim of obtaining a slower dissolution which allows the observance of differences in dissolution rate between the different formulations, we attempted to carry out a dissolution study without any surfactant. Unfortunately, due to its strong hydrophobic nature, this drug does not wet easily, and it stuck to the wall of the vessel and to the paddle. With a small addition of 0.2 mg/ml of SLS, the wettability of the drug was sufficient to avoid these undesirable facts and to observe differences among the dissolution profiles of the formulations. Therefore, in the present work the dissolution medium was 500 ml of 0.1 N HCl containing only 0.2 mg of SLS per ml. Samples were withdrawn, filtered and analyzed in a Beckman DU 7 spectrophotometer at 263 nm. The studies were repeated three times to obtain the mean value.

Results and Discussion

The solubility coefficient of the PZQ was studied *versus* different concentrations of SLS. As was expected, the solubility magnitude always increased as the surfactant concentration was raised. The different quantities of the surfactant added to the dissolution medium were 0; 0.2; 0.8; 1.25; 1.5; 2; 3; 5 and 10 mg/ml. From the concentration of 0.2 mg/ml good wettability was obtained with a solubility coefficient of 612.01 μg/ml.

As the solid dispersion is a metastable form and tends to transform into the stable form, the drug concentration tended to decrease with the elapse of time during the solubility test. In order to avoid this problem, all the solubility test samples of the different formulations were withdrawn and assayed at an established time (96 h). This allowed us to readily compare the solubility of the different solid dispersions.

With regard to the solubility of the solid dispersions, it was observed that those prepared with PVP K12 presented higher dissolution concentrations as compared with the other formulations obtained with different PVP (K17, K25) but with the same PZQ : PVP proportion (Fig. 1). This increase

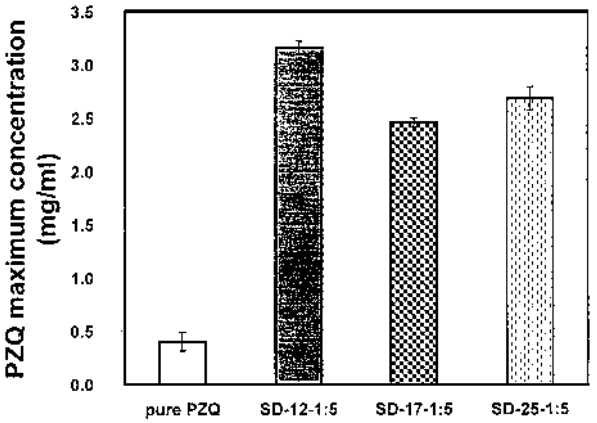

Fig. 1. Solubility Coefficient (mg/ml) of the Pure PZQ and of Three Solid Dispersions with the Same Drug:carrier ratio (1 : 5), but Obtained with Three Different Molecular Weight PVP (K12, K17 and K25)

was also higher as the PZQ : PVP proportion presented a bigger percentage of PVP, becoming almost ten-fold greater in the case of the SD-12-1 : 9 compared with the pure PZQ. Therefore, these PVP K12 solid dispersions were selected for the dissolution rate study.

SEM was used to clarify the surface and shape characteristics of the different samples. The PZQ raw material presented an acicular form (Fig. 2a), while the recrystallized PZQ observed using a higher magnification (×2500) appears as different forms, one of them a more clear filament form of white (Fig. 2b). On the other hand, the physical mixture (PM) and the solid dispersion presented a clearly different appearance (Fig. 3). In the physical mixture we can distinguish between the spherical particles of PVP and the acicular crystallites of PZQ (Fig. 3a). However, in the solid dispersion (Fig. 3b) it is possible to see a big lamellar structure (200—500 μm) attributed to the PVP, and many filament particles (10—20 μm) attributed to PZQ, due to their similar appearances with recrystallized PZQ. In these solid dispersions, the amount of PZQ on the surface of the PVP particles decreased significantly as the PVP ratio was increased (Figs. 3b—d). This reduction in the visible PZQ, observed in the solid dispersions with a PZQ : PVP ratio of at least 1 : 5, was attributed (in large measure) to the inclusion of PZQ in the PVP matrix (see Fig. 3d).

Figure 4 shows the XRD patterns of the PZQ, physical mixture PM-12-1 : 9, solid dispersion SD-12-1 : 9 and PVP K12. PZQ raw material is crystalline, as demonstrated by sharp and intense diffraction peaks. PVP is an amorphous

powder having no crystalline structure. The physical mixture PM-12-1 : 9 presented diffraction peaks consistent with the presence of crystalline PZQ. The lower intensity of the diffraction peaks of the physical mixture PM-12-1 : 9 is the result of a dilution effect. In contrast, the solid dispersion SD-12-1 : 9 showed no PZQ diffraction peaks, indicating that the PZQ present existed in an amorphous state.

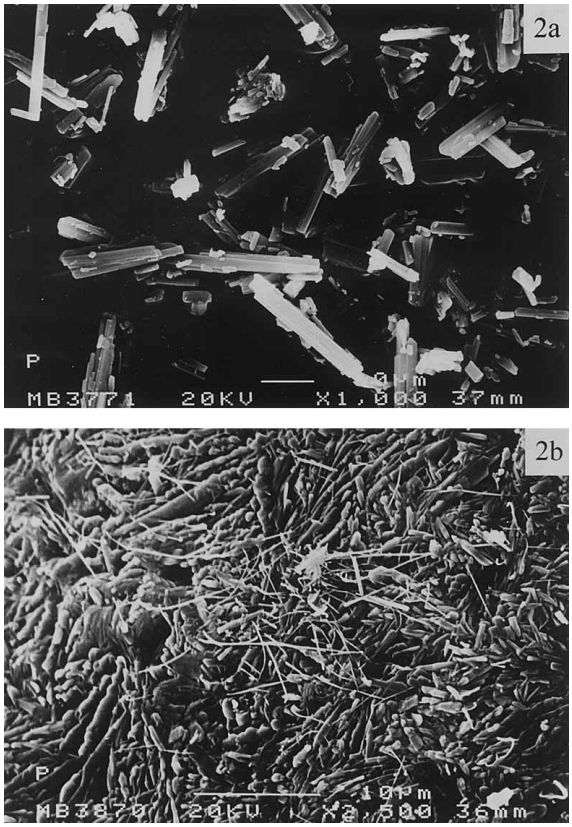

Fig. 2. SEM of PZQ Raw Material (2a) and R-PZQ (2b)

Figure 5 shows the X-ray diffraction patterns of the PVP and the different solid dispersions. The obtained PZQ solid dispersions presented an amorphous form, similar to results obtained previously with other drugs.[14,17,18] Nevertheless, the solid dispersion 1 : 1 presented an amorphous pattern different to the amorphous one of the PVP, which may be attributed to an interaction between the drug and the polymer. On the other hand, as the PVP proportion in the solid dispersion was increased, the XRD pattern was closer to the typical double PVP amorphous one.

Thermal analysis (Fig. 6) shows that PZQ melts at 142.5 °C with no other thermal events. Unfortunately, the physical mixture and solid dispersion 1 : 5 scans do not present a clear endothermic peak at this temperature, probably due to low PZQ raw material enthalpy (ΔH=86.5 J/g), so this technique can not be used for PZQ solid dispersion characterisation.

The dissolution profiles of PZQ, the different solid dispersions and the physical mixture 1 : 9 are illustrated in Fig. 7. The physical mixture 1 : 9 presented a faster dissolution rate than the raw PZQ material.

The initial dissolution rate of the drug in the physical mixture was larger than raw PZQ material. Similar results have been described by other authors with the same or a different carrier.[18—20] Some authors have explained this result in terms of the dispersion effect of additives[21] and by a possible lowering of the surface tension of the medium by PVP resulting in a better wetting of the drug crystal surface.[22] Other authors allude that PVP in solution can form molecular complexes with aromatic acids through electron/donor interactions.[23] On the other hand, Sekizaki *et al*. found that ibuprofen became amorphous when the crystalline powder was merely mixed with PVP and allowed to stand at appropiate

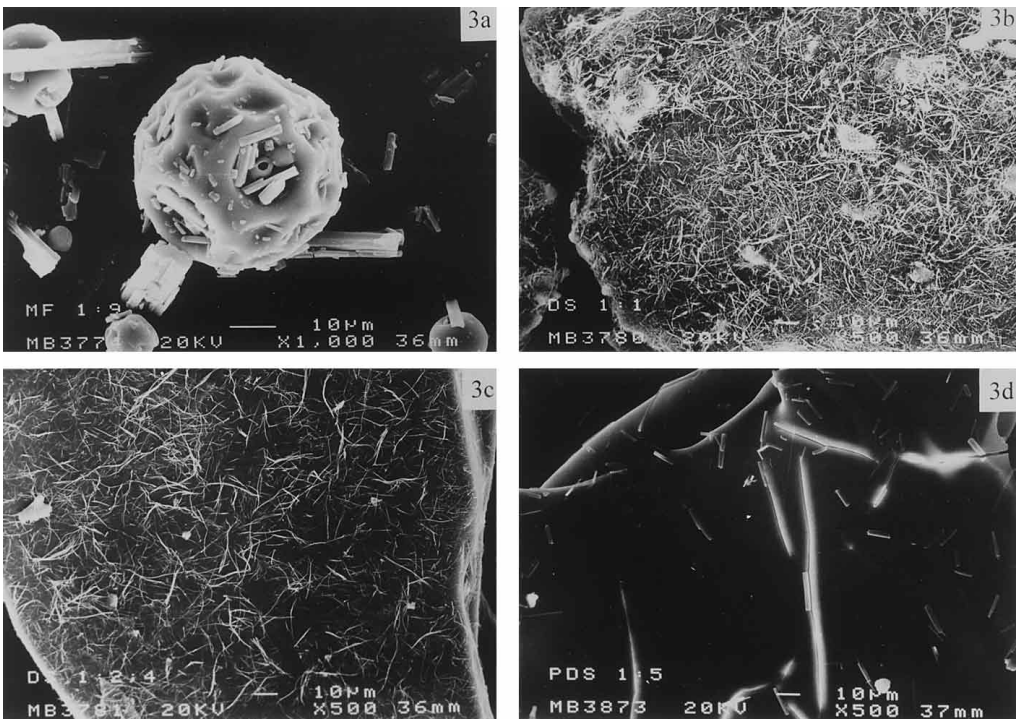

Fig. 3. SEM of PM-12-1 : 9 (3a), SD-12-1 : 1 (3b), SD-12-1 : 2.4 (3c) and SD-12-1 : 9 (3d)

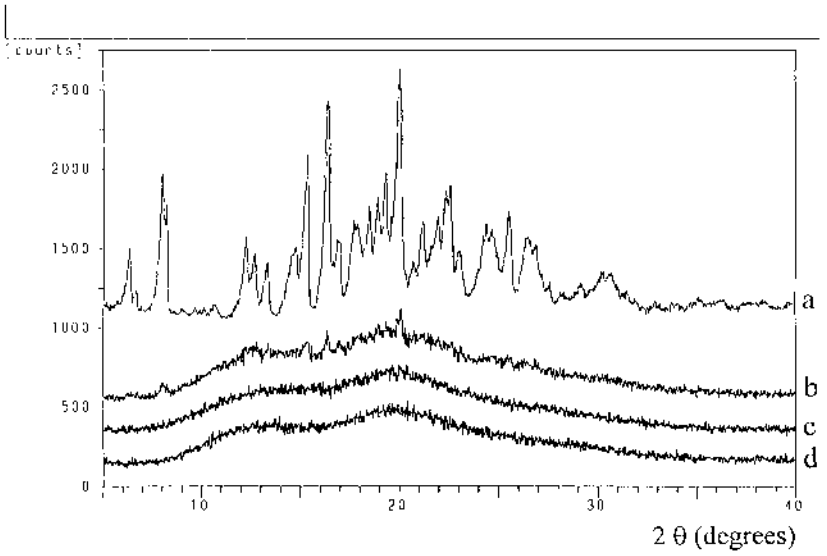

Fig. 4. Powder XRD Scans of Different Products: Pure PZQ (a); PM-12-1 : 9 (b); SD-12-1 : 9 (c) and PVP K12 (d)

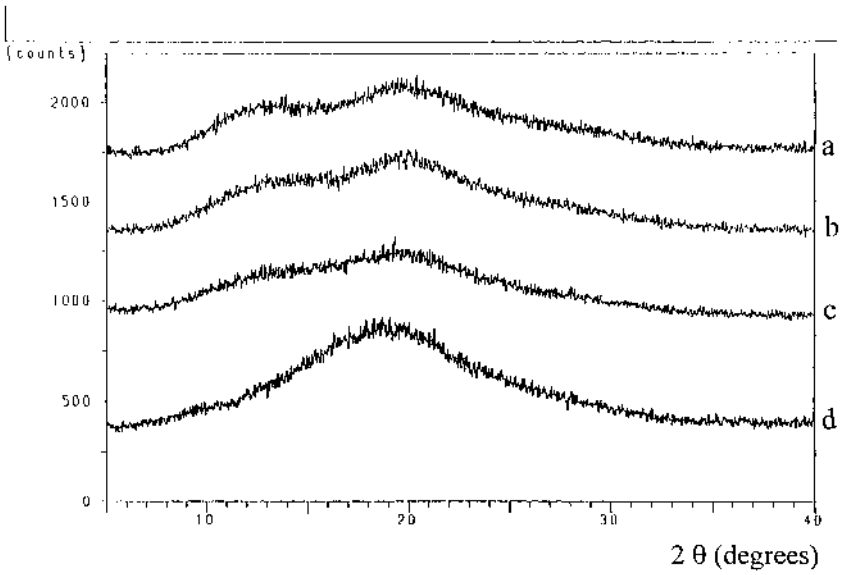

Fig. 5. Powder XRD Scans of Different Products: PVP K12 (a); SD-12-1 : 9 (b); SD-12-1 : 5 (c) and SD-12-1 : 1 (d)

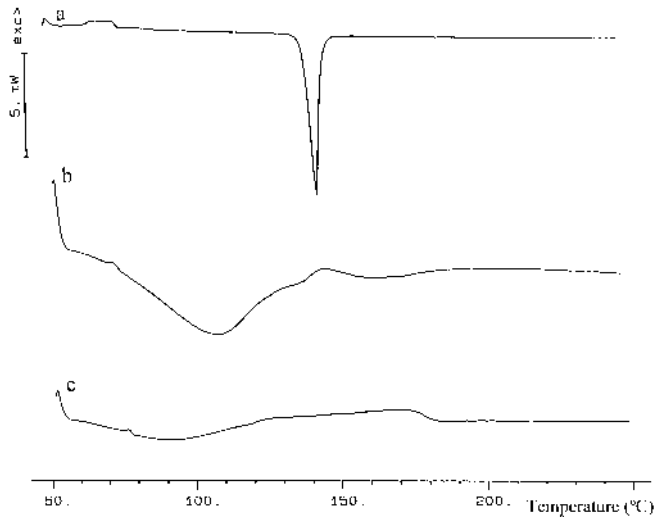

Fig. 6. DSC Scans of Different Products: Pure PZQ (a); PM-12-1 : 5 (b) and SD-12-1 : 5 (c)

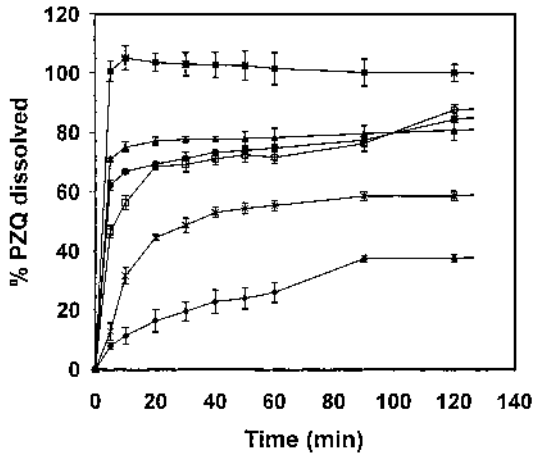

Fig. 7. Dissolution Profiles of Different Products: PZQ Raw Material (–X–); PM-12-1 : 9 (–□–); SD-12-1 : 1 (–◆–); SD-12-1 : 2.4 (–●–); SD-12-1 : 5 (–▲–) and SD-12-1 : 9 (–■–).

temperatures.[24] For the present work, physical mixtures were prepared by blending PZQ and PVP in a mortar with a spatula immediately before use to avoid moisture capture. This immediate use of the physical mixtures would also avoid the possibility of changes in the crystallinity of PZQ due to the presence of PVP. XRD studies showed that the physical mixture presented diffraction peaks consistent with the presence of crystalline PZQ. The lower intensity of the diffraction peaks of the physical mixture PM-12-1 : 9 as compare with the pure drug is the result of a dilution effect.[25]

However, the simple addition of PVP to the drug can not explain the high increase in the dissolution rate of the solid dispersions, which consistently presented a faster PZQ dissolution than the physical mixture, even with a lower PVP proportion. Similar results have been obtained with other drug–PVP coprecipitates.[14]

These studies show that significant increases in the solubility and dissolution rate of PZQ can be achieved with solid dispersions containing PVP. All the PZQ–PVP coprecipitate systems were in an amorphous form, and the majority of them (SD-12-1 : 2.4; SD-12-1 : 5 and SD-12-1 : 9) presented a faster dissolution profile than the drug alone. Nonetheless, the SD-12-1 : 1 presented a slower dissolution rate than the raw PZQ material, probably due to the formation of a drug carrier complex of low solubility. These anomalous reductions in the dissolution rate of a number of drugs in the presence of low concentrations of PVP have been previously observed, as described by Corrigan.[26] However, with a PZQ : PVP ratio of at least 1 : 5, the dissolution rate presented a very significant increase, which agrees with PZQ inclusion in the PVP matrix observed by SEM and the amorphous pattern shown by XRD.

We can thus conclude that only by using a variety of analytical methods (SEM, powder XRD and DSC) can the physical–chemical changes produced during the PZQ : PVP solid dispersion obtention of a new PZQ polymorph method be fully characterized. The mixed use of these techniques lets us know the reasons for an enhancement of the dissolution rate and the solubility coefficient of PZQ. SEM was especially interesting as it allowed us to observe the raw material inclusion into the PVP matrix as the polymer ratio was increased. The XRD was shown to be a suitable technique with which to assess differences between the amorphous PZQ : PVP coprecipitates. Among the different solid dispersions obtained by the coprecipitation method using PVP as a carrier, the SD-12-1 : 5 is recommended. Further investigations dealing with the *in vivo* behavior, including anthelmintic effects of these formulations, are now under way.

Acknowledgments This work has been supported by an FIS Project No. 99/0118.

References

1) Reynolds J. E. F. (ed.), "Martindale. The Extra Pharmacopoeia," 31st Edition, The Royal Pharmaceutical Society, London, 1996, pp. 123—125.
2) Wu M. H., Wei C. C., Xu Z. Y., Yuan L. C., Lian W. N., Yang Q. J., Chen M., *Am. J. Trop. Med. Hyg.*, **45**, 345—349 (1991).
3) Yangco B. G., Lerma C., Lyman G. H., Price D. L., *Antimicrob. Agents Chemother.*, **31**, 135—138 (1987).
4) Silva N., Guyatt H., Bundy D., *Drugs*, **53**, 769—788 (1997).
5) Budavari S. (ed.), "The Merck Index: An Encyclopedia of Chemicals, Drugs and Biologicals," 11th Edition, Merck & Co., Inc., Rahway, N. J., U.S.A., 1989, p. 1222.
6) Sekiguchi K., Obi N., *Chem. Pharm. Bull.*, **9**, 866—872 (1961).
7) Chiou W. L., Riegelman S., *J. Pharm. Sci.*, **60**, 1281—1302 (1971).
8) Yano K., Kajiyama A., Yamazaki S., Matsumura Y., Watanabe K., Yamamoto K., *Chem. Pharm. Bull.*, **44**, 2309—2313 (1996).
9) Suzuki H., Sunada H., *Chem. Pharm. Bull.*, **45**, 1688—1693 (1997).
10) Kai T., Akiyama Y., Nomura S., Sato M., *Chem. Pharm. Bull.*, **44**, 568—571 (1996).
11) Yoshioka M., Hancock B. C., Zografi G., *J. Pharm. Sci.*, **84**, 983—986 (1995).
12) Taylor L. S., Zografi G., *Pharm. Res.*, **14**, 1691—1698 (1997).
13) Tantishaiyakul V., Kaewnopparat N., Ingkatawornwong S., *Int. J. Pharm.*, **143**, 59—66 (1996).
14) Torrado S., Torrado S., Torrado J.J., Cadórniga R., *Int. J. Pharm.*, **140**, 247—250 (1996).
15) Chiba Y., Kohrl N., Iseki K., Miyazaki K., *Chem. Pharm. Bull.*, **39**, 2158—2160 (1991).
16) Lopez-García M. L., Torrado S., Torrado J. J., Martínez-Fernandez A. R., Bolás-Fernández F., *Int. J. Parasitology*, **27**, 781—785 (1997).
17) Yuasa H., Takahshi H., Ozeki T., Kanaya Y., Ueno M., *Chem. Pharm. Bull.*, **41**, 397—399 (1993).
18) Yagi N., Terashima Y., Kenmotsu H., Sekikawa H., Takada M., *Chem. Pharm. Bull.*, **44**, 241—244 (1996).
19) Danjo K., Nakata T., Otsuka A., *Chem. Pharm. Bull.*, **45** 1840—1844 (1997).
20) Kearney A. S., Gabriel D. L., Mehta S. C., Radebaugh G. W., *Int. J. Pharm.*, **104**, 169—174 (1994).
21) Shah N., Pytelwski R., Eisen H., Jarowski I., *J. Pharm. Sci.*, **63**, 339 (1974).
22) Sekikawa H., Nakano M., Arita T., *Chem. Pharm. Bull.*, **27** 1223—1230 (1979).
23) Plaizier-Vercammen J. A., De Neve R. E., *J. Pharm. Sci.*, **70**, 1252—1256, (1981).
24) Sekizaki H., Danjo K., Eguchi H., Yonezawa Y., Sunada H., Otsuka A., *Chem. Pharm. Bull.*, **43**, 988—993 (1995).
25) Hirasawa N., Okamoto H., Danjo K., *Chem. Pharm. Bull.*, **47**, 417—420 (1999).
26) Corrigan O. I., *Drug Dev. and Ind. Pharm.*, **11**, 697—724 (1985).