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Comparison of polyethylene glycol, polyvinylpyrrolidone and urea as excipients for solid dispersion systems of miconazole nitrate

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Summary

The objective of this investigation was to examine the feasibility of preparing fast-release solid dispersions of miconazole nitrate (MN), using 3 different water-soluble excipients: polyethylene glycol (PEG-6000), polyvinylpyrrolidone (PVP-10,000) and urea. Solid dispersions of miconazole were prepared by fusion or coprecipitation from ethanol. The phase diagrams of the MN-PEG dispersions were characteristic of a monotectic system, the MN-urea dispersions of a simple eutectic system with a eutectic composition of 80% MN and 20% urea, and the MN-PVP dispersions of a continuous solid solution. Solubilization and wetting of the drug both favored PEG and urea over PVP in promoting the dissolution of MN. Accordingly, a 7-fold increase in the dissolution rate of MN was achieved with both PEG and urea, while the dispersion of MN in PVP resulted in only a two-fold enhancement. The coprecipitated dispersion of MN in 80% w/w PEG and fused dispersions of MN in 80% w/w urea gave comparable results, and the highest initial dissolution rates among samples studied. Based on the results of this investigation solubilization and wetting were found to be more important than particle size reduction as a means of increasing the dissolution rate of MN.

Introduction

Solid dispersion represents a useful pharmaceutical technique for increasing the dissolution, absorption, and therapeutic efficacy of drugs in dosage forms (Mayersohn and Gibaldi, 1966; Chiou and Riegelman, 1969). The properties, performance, and practical applications of solid dispersions depends on factors such as: (a) the method of preparation, (b) composition, (c) selection of a suitable carrier, and (d) physicochemical properties of the drug (Chiou and Riegelman, 1971; Hajratwala, 1974). Therefore, a thorough understanding of these factors are necessary to formulate an effective solid dispersion dosage form for a particular drug.

The primary purpose of this study was to examine the feasibility of preparing fast-release solid dispersions for the antifungal drug, miconazole nitrate (MN), using 3 different water-soluble carriers: polyethylene glycol (PEG)-6000, polyvinylpyrrolidone (PVP)-10,000 and urea. The effect of method of preparation was studied specifically in the case of the MN–PEG 6000 systems.

MN (1-[2,(4,dichlorophenyl)-2-(2,4-dichlorobenzyloxy)ethyl] imidazole mononitrate is a

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broad-spectrum antifungal agent (Godefroi et al., 1969). It is a relatively non-toxic agent and has been used experimentally in the treatment of various systemic mycoses, including candidiasis, coccidiodomycosis, cryptococcosis and histoplasmosis (Brugans et al., 1972). It is presently available in both topical and i.v. dosage forms (Stranz, 1980).

In clinical studies it has been found that the oral bioavailability of MN is only 27% when administered as a microsuspension (Boelaert et al., 1976). Its poor bioavailability, attributed partly to its very low aqueous solubility, precludes the effectiveness of the drug when administered orally. It was felt that a strategy aimed at enhancing the dissolution rate of miconazole nitrate by preparing solid dispersions of the drug in a suitable carrier may improve the oral bioavailability of the drug.

Materials and Methods

Materials

The following materials and drugs were of food or pharmaceutical grade and used as supplied: PEG-6000 (Wyandotte Chemical Co., Wyandotte, MI); urea (Fisher Scientific Co., Fair Lawn, NJ); miconazole nitrate (Sigma Chemical Co., St. Louis, MO).; spectroscopic grade ethanol 95%, HPLC grade methanol, ammonium hydroxide, monobasic sodium phosphate, hydrochloric acid, and sodium hydroxide (Fisher Scientific Co., Fair Lawn, NJ); monobasic potassium phosphate (Mallinckrodt Inc., Paris, KY); dibasic sodium phosphate (Sigma Chemical Co., St. Louis, MO). Deionized, double-distilled water was used in all studies.

Preparation of solid dispersion systems

Physical mixtures. The physical mixtures were prepared by thoroughly grinding together accurately weighed quantities of MN and the excipients (PEG, PVP or urea) for 5 min using a mortar and pestle. The relative proportions of drug and excipients were varied to yield the following compositions in terms of percent weight of drug: 20%, 40%, 60% and 80%. The blends were passed through a no. 60 screen (U.S. Standard), and the total weight of each blend was varied from 4 to 6 g. Similarly, pure MN and each of the excipients were separately ground to represent pure drug (100%) and pure excipients (0%).

Fused dispersions. Fused dispersions of MN and urea were obtained by heating 1–2 g of the corresponding ground physical mixtures in a heating dish on a hot-plate until a homogeneous liquid melt was obtained. The melted mixture was cooled and solidified rapidly by placing the dish on a ice-water bath and rapidly stirring with a glass rod. The fused dispersions were crushed, pulverized and placed in a vacuum desiccator until further use.

A classical fusion method wherein a mixture of drug and excipient are directly heated to form a comelt could not be applied to MN–PEG systems. This was primarily due to the large discrepancy between the melting points of PEG (60–65 °C) and MN (180–185 °C) and that PEG degrades at the higher temperature. A lower eutectic temperature was also not found. In order to maximize the chance of inducing favorable solid-state interaction between the drug and the excipient, a solvent-melt technique was employed. It has been shown that 5–10% (w/w) of liquid compounds can be directly incorporated into PEG without significant loss of its solid property (Chiou and Riegelman, 1971). Hence, weighed portions of MN were dissolved in warm ethanol and the solution was incorporated directly into the melt of PEG, obtainable below 70 °C without removing the liquid solvent.

Coprecipitated dispersions. Coprecipitated dispersions of MN and PEG were prepared by dissolving 1–2 g of the corresponding physical mixtures in ethanol and evaporating the solvent under vacuum at ~ 40 °C. The resulting semisolid mass was dried under vacuum in a desiccator, and milled as described above. Coprecipitated dispersions of MN–PVP were prepared similarly.

Thermal analysis

The physical nature, solid–solid interactions, and homogeneity of solid dispersion systems were tested by subjecting the samples to thermal analysis. The information was compiled to construct phase diagrams to rationalize and predict the optimum solid dispersion systems.

Thaw-melt method. This was accomplished using both a capillary melting point apparatus (Thomas Co., Philadelphia, PA), and a digital melting point analyzer (Fisher Scientific Co., Fair Lawn, NJ) which enabled accurate heating rates, better visualization and improved temperature hold capabilities. Each apparatus was pre-calibrated using a benzoic acid standard (m.p. 195 °C, Fisher Scientific Co., Fair Lawn, NJ). There was excellent agreement between observations in both cases. When using the melting point apparatus, a sample was placed in a glass capillary tube and heated at a rate of 5 °C/min. When using the digital melting point analyzer the sample was placed between a microscope slide and a cover slip, and sealed with silicone grease. The sample was heated at a constant rate by means of a heating stage interfaced with a digital temperature display. Visualization was possible using a high-powered magnifying glass fixed on a mount over the sample and heating stage. The apparatus thus resembled a hot-stage microscope but lacked the polarizing lenses of the latter. This precluded the determination of intricate crystallographic events, although it was visually possible to differentiate between crystals of the drug and excipient due to their distinctive crystal habits. All determinations were made in triplicate. For the purpose of constructing phase diagrams, observations were made during heating as previously elaborated (Goldberg et al., 1966). These included noting the temperature at which melting started (thaw point) and the temperature at which complete melting was affected (melting point). These two temperatures were used to define the melting point range.

Differential scanning calorimetry. The DSC thermograms were recorded using a Model DSC-1B differential scanning calorimeter (Perkin Elmer Co., Norwalk, CT). Scans were recorded at a scan rate of 10 °C/min and a range of 8 mcal/deg. The chart speed was 20–40 mm/min with a 50 mV input. The instrument was calibrated with benzoic acid and indium. Triplicate DSC scans were obtained for known amount of MN (10–15 mg). Single determinations were made for the physical mixtures and solid dispersions at the various compositions, and of pure PEG, PVP and urea. The temperature and location of every peak on the thermogram was recorded and the melting point range was assigned as described previously (Feldman and Gibaldi, 1967).

Solubility studies

Solubility studies were performed to determine the extent of interaction between the drug and the excipients in aqueous solution. Excess amounts of MN (50 mg) were placed in 20 ml glass vials with Teflon-lined screw caps prefilled with 10 ml of the dissolution containing varying concentrations (0.01%, 0.1%, 1%, 5% w/v) of the excipients. Samples were equilibrated at 37 °C for 48 h in a water bath. Filtered 1 ml samples were diluted and analyzed for MN by HPLC.

Dissolution studies

The in vitro dissolution rate of MN from untreated samples (i.e. no added excipients), solid dispersions of MN and drug-excipient physical mixtures were measured according to the U.S.P. Method II (U.S.P. XXI, 1985). The dissolution samples were passed through a no. 60 (U.S. Standard) sieve and contained an equivalent of 50 mg of MN. Dissolution studies were run in duplicate in 0.2 M phosphate buffer (pH 7.4) prepared as described in the U.S.P monograph (U.S.P XXI, 1985). The dissolution fluid (500 ml) was placed in 1-liter round-bottom dissolution vessel and pre-equilibrated at 37 ± 0.5 °C in a water-bath. The samples were sprinkled on the surface of the dissolution medium and stirred at 100 rpm. Five-ml samples were withdrawn at 1, 5, 15, 30, 45, 60, 90 and 120 min intervals with volume replacement. Drug content was analyzed by HPLC and a cumulative correction was made for the removed samples in determining the total amount of drug dissolved.

Wettability index

The change in wettability of MN upon incorporation of the drug in PEG, urea and PVP at various compositions was evaluated. For this purpose, a technique previously employed to screen suspending agents (Hiestand, 1964) was modified, wherein the end of a glass pipet was plugged with glass wool, and the pipet filled with the powdered

formulations to a height of 5 cm. One ml of distilled water was then placed on top of the powder bed and the time required for water to soak through a distance of 3 cm was noted. This value was termed the wettability index.

Analytical procedure

A published high-performance liquid chromatographic method and employed to assay for miconazole (Cavrinii et al., 1982). The chromatographic system consisted of an isocratic pump (Waters Model 6000A, Waters Associates, Milford, MA), a fixed wavelength U.V. detector, a fixed loop (50 μl) manual injector (Waters Model U6K), and a strip-chart recorder (Omniscribe, Houston, TX). The system was run at a flow rate of 1 ml/min ($\sim$ 2000 p.s.i), and the detection wavelength was 254 nm. The chromatography was performed at ambient temperature using a reversed phase octadecasilane column (Fisher Scientific Co., Fair Lawn, NJ). The mobile phase consisted of methanol and 0.05M ammonium dihydrogen phosphate buffer (85 : 15).

Calibration curves for miconazole were prepared using econazole nitrate as the internal standard and plotting the observed peak height ratio of miconazole to econazole versus miconazole concentration.

Results and Discussion

Phase diagrams

The phase diagrams obtained by the thaw-melt method and the DSC thermograms were in agreement (5–10 °C difference) for all systems studied. Miconazole nitrate and the excipients when subjected to DSC each gave a single peak corresponding to their fusion temperature. Furthermore, when heated slowly each substance melted over the same temperature range as defined by the beginning and the summit of the corresponding peak in the DSC thermogram. The binary phase diagrams were qualitatively and quantitatively independent of the method of preparation for the solid dipsersions.

MN-PEG systems. Typical phase diagrams for the MN-PEG dispersions are shown in Figs. 1–3. Melting point analysis showed a constant melting point (solidus point) of PEG at 60–65 °C at all

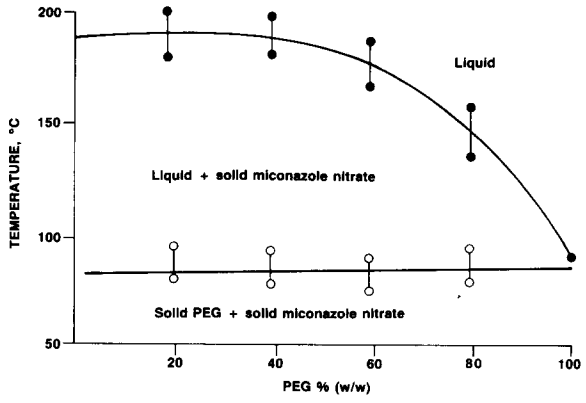

Fig. 1. Phase diagram of physical mixtures of MN and PEG; (●) liquidus point, (○) solidus point. The bars represent the range of triplicate temperature readings.

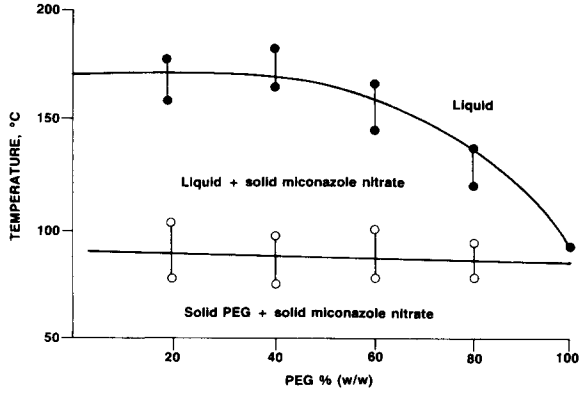

Fig. 2. Phase diagrams of fused dispersions of miconazole nitrate and PEG; (●) liquidus point (○) solidus point. The bars represent the range of triplicate determinations.

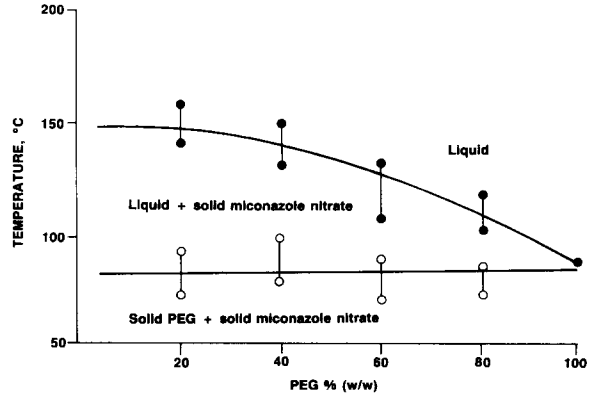

Fig. 3. Phase diagrams of coprecipitates of miconazole nitrate and PEG; (●) liquidus point, (○) solidus point. The bars represent the range of triplicate determinations.

compositions, corresponding to the endothermic peak in the DSC thermogram. The liquidus point, defined as the temperature above which no more crystals were visible (Kaur et al., 1980) increased as the proportion of drug increased. This increase was highest for the physical mixtures of MN and PEG, lower for the fused dispersions and lowest for the coprecipitated dispersions.

Each of the 3 phase diagrams of the MN-PEG exhibited monotectic behavior, characterized by the absence of complete dissolution of MN in the molten PEG at the melting point of the excipient. The rising liquidus curve on the monotectic diagrams correspond to the solubility of the drug in the excipient at a specified temperature (Kaur et al., 1980). For example, if MN is added to a sample of PEG at 125 °C line from the pure PEG limit at the right of each figure, the added MN will dissolve until the solid MN-solution equilibrium line (liquidus curve) is reached. At that point, the solution is saturated with MN. If the solution behaves ideally, the equilibrium solubility curve can be expressed in terms of the drug can be expressed in terms of the freezing point depression and heat of fusion (Moore, 1962). There was no evidence of formation of a solid solution or solid complex between PEG and MN. The lowering of the liquidus temperature indicated favorable solid–solid interactions in the dispersion systems of MN-PEG, which may result in dissolution enhancement of MN.

MN-urea systems. The phase diagram presented in Fig. 4 shows that the MN-urea dispersion represents a simple eutectic binary mixture. Eutectic systems usually form upon rapid solidification of fused liquids of two components which show complete liquid miscibility and negligible solid–solid solubility (Chiou and Riegelman, 1971). The eutectic composition of the MN-urea solid dispersion was found to be 80% MN and 20% urea. At 90% MN the sample started to melt at a temperature higher that the eutectic temperature (~ 110 °C) which indicates, together with the DSC results, the existence of solid solute dissolved in a solid solvent. This phenomenon is often called a mixed crystal because the two components crystallize together in a homogeneous one-phase system. Both eutectic mixtures and solid solutions

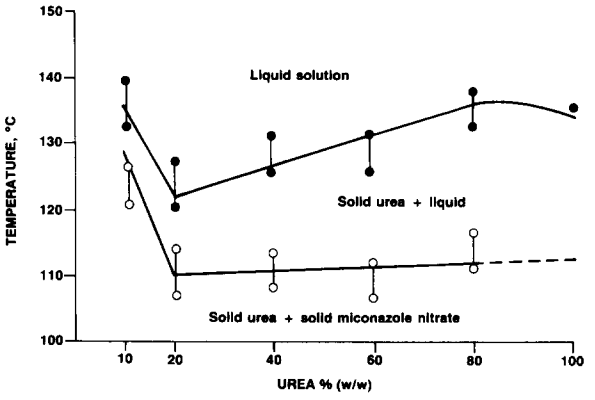

Fig. 4. Phase diagrams of fused dispersions of miconazole nitrate and urea; (●) liquidus point, (○) solidus point. The bars represent the range of triplicate determinations.

have been known to cause an increase in the dissolution rate in selected case (Chiou and Riegelman, 1971).

MN-PVP systems. The phase diagram for the solid dispersion system consisting of MN and PVP (Fig. 5) may be best described as a continuous solid solution. These systems usually imply that the drug and excipient are miscible at solid state in all proportions (Chiou and Riegelman, 1971). These systems may theoretically increase drug dissolution rate.

Equilibrium solubility

Equilibrium solubility studies were conducted to determine the solubilization effect of the three

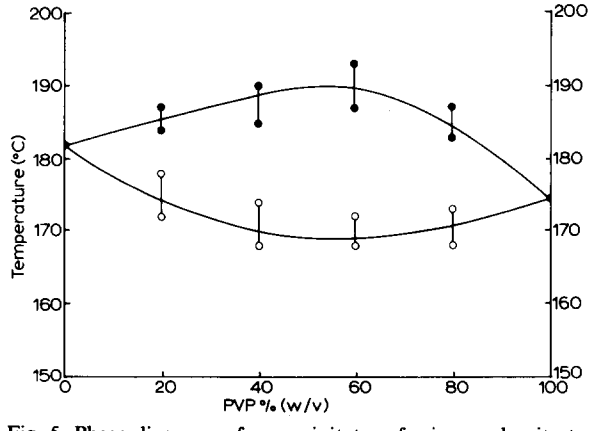

Fig. 5. Phase diagrams of coprecipitates of miconazole nitrate and PVP; (●) liquidus point, (○) solidus point. The bars represent the range of triplicate determinations.

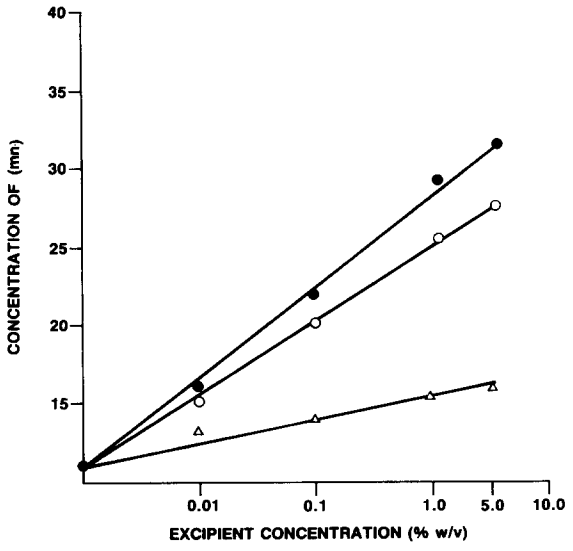

Fig. 6. The effect of urea (●), PEG (○) and PVP (△) on the aqueous solubility of miconazole nitrate at 37 °C.

excipients on MN. As illustrated in Fig. 6, urea and PEG were found to interact strongly with MN in aqueous solution. This interaction was manifested in a linear increase in the solubility of MN to the extent of 0.58 mg/g of PEG and 0.87 mg/g of urea. On the contrary, the extent of increase in the solubility of MN with PVP was minimal, merely 0.09 mg/g of PVP added. The equilibrium solubility of MN in water at 37 °C was 1.2 mg/100 ml. An increase in MN solubility as a function of PEG and urea concentration may be attributed to the breaking of water structure of these excipients, and thereby creating a more energetically favorable environment (Roger and Anderson, 1982). Therefore, it may be expected that PEG and urea are more likely to result in an increase in the drug dissolution rate compared to PVP.

Wettability index

The change in wettability of MN upon incorporation of the drug with PEG, PVP and urea was evaluated and the wettability index data are presented in Table 1. As can be noted, the wettability index was markedly decreased with increasing excipient concentrations. However, the decrease was much greater for the powder mixtures containing PEG and urea than those containing PVP. Thus,

TABLE 1

Wettability indices of MN–excipient mixtures

Excipient composition (%w/v)	Wettability index		
	PEG	Urea	PVP
0	97 ± 1.42	97 ± 1.42	97 ± 1.42
20	45 ± 1.5	42 ± 1.1	51 ± 0.87
40	30 ± 1.2	28 ± 0.9	40 ± 0.92
60	16 ± 1.5	15 ± 1.3	23 ± 1.2
80	5 ± 1.4	4 ± 1.1	18 ± 0.98

Values in mean time (s) ± S.D.; time for water to soak through a distance of 3 cm.

rank-order was consistent with the observed equilibrium solubility results. It may be expected that better the wettability and dispersibility of a drug in a solid dispersion system, the better the chances of achieving an increase in drug dissolution rate. This is due to the fact that each single crystallite of the drug is intimately encircled by the soluble excipient which can readily dissolve and cause water to contact and wet the drug particle (Sekiguchi and Obi, 1961).

Dissolution rate

MN–PEG system. The dissolution rate profiles for the MN-PEG systems are shown in Fig. 7. For clarity of presentation the standard error bars are not shown, but the coefficient of variation between duplicate determinations at each time point was always less than 5%. The relative dissolution rate data (Table 2) of the different samples were calculated by determining the amount of MN dissolved from a particular sample and normalizing for the amount of drug dissolved from the untreated sample (control) over the same time interval. At 30 min, the ratio of the coprecipitated dispersion (80% PEG) to that of the control was ~ 7, while for the corresponding fused dispersion this value was only ~ 2. Therefore, the coprecipitation method was superior to the fusion method in enhancing the dissolution rate of MN. This observation was consistent with the phase solubility behavior of the two systems, as the coprecipitate demonstrated a lower liquidus curve compared to the fused dispersion.

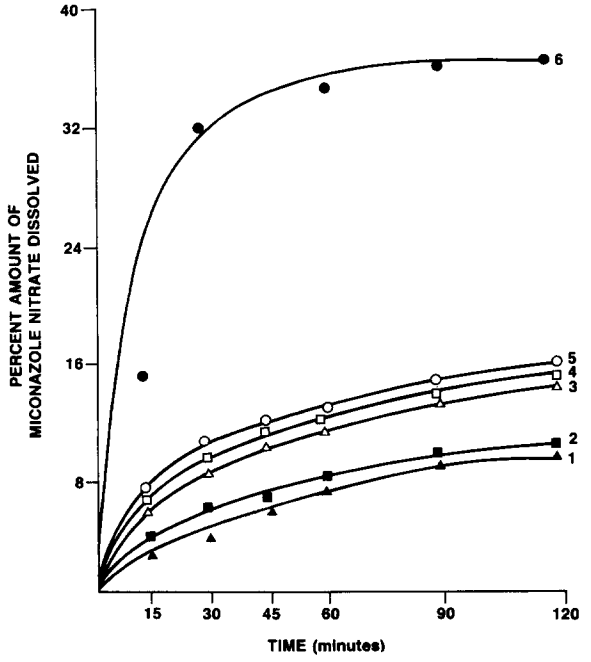

Fig. 7. Dissolution of miconazole nitrate from its solid dispersions with PEG. 1, MN alone, 2, 20/80 MN–PEG physical mixture; 3, 80/20 MN–PEG fused dispersion; 4, 20/80 MN–PEG fused dispersion; 5, 80/20 MN–PEG coprecipitate; 6, 20/80 MN–PEG coprecipitate.

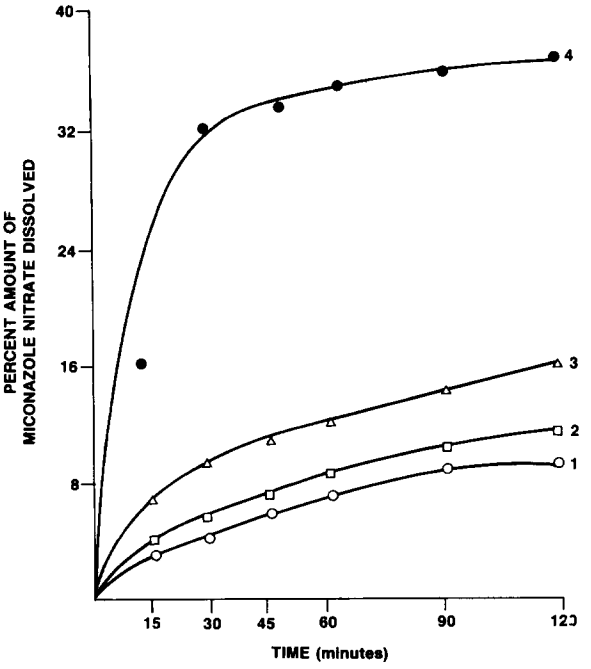

Fig. 8. Dissolution of miconazole nitrate from its solid dispersion with urea. 1, MN alone; 2, 20/80 MN : urea physical mixture; 3, 80/20 MN : urea fused dispersion; 4, 20/80 MN : urea fused dispersion.

MN–urea system. The dissolution results for the MN-urea systems are presented in Table 3 and Fig. 8. In general, the observations were similar to those for the MN-PEG systems in that increasing the excipient concentration in the dispersion resulted in an increase in drug dissolution rate. No such enhancement was apparent in the physical mixture. It is also noted that forming a eutectic mixture was a less effective means of increasing the dissolution rate of MN compared to increasing the proportion of urea in the dispersion. Therefore, reduction in drug particle size by forming a eutectic (Sekiguchi and Obi, 1961) does not appear to be as important as solubilization and wetting in contributing to faster dissolution of MN. Furthermore, the 2–7-fold enhancement in dissolution rate observed for both the PEG and urea dispersions are consistent in terms of order of magnitude to the latter rationale. For molecularly

TABLE 2

Relative dissolution rate of MN–PEG systems

Sample no.	Composition (%w/v)		Form	Relative dissolution rate		
	MN	PEG		15 (min)	30 (min)	60 (min)
1	100	0	powder	1.0	1.0	1.0
2	20	80	physical mix	1.0	1.1	1.1
3	80	20	fused	1.7	1.9	1.6
4	20	80	fused	2.0	2.0	1.8
5	80	20	coprecipitate	2.2	2.1	1.7
6	20	80	coprecipitate	3.6	6.9	5.0

TABLE 3

Relative dissolution rates of MN–urea systems

Sample No.	Composition (%w/v)		Form	Relative dissolution rate		
	MN	Urea		15 (min)	30 (min)	60 (min)
1	100	0	Powder	1.0	1.0	1.0
2	20	80	Physical mix	1.3	1.2	1.4
3	80	20	fused [a]	2.2	2.1	1.7
4	20	80	fused	4.0	7.2	5.1

[a] Eutectic composition

dispersed drug particles dissolution enhancement would be expected to be considerably greater.

MN–PVP systems. The dissolution data for the MN-PVP systems are presented in Table 4 and Fig. 9. The maximum enhancement in the dissolution rate of MN achieved using PVP dispersion was less than two-fold. Solid dispersion systems characterized by a continuous solid solution as in the case for MN-PVP seldom exhibit fast-release dissolution properties (Chiou and Riegelman, 1971). It may be speculated that in this case the amount of MN solubilized by PVP was so small that it was not sufficient to effectively inhibit the crystallization of MN during the solvent removal process (Sekikawa et al., 1978). This, along with minimal solubilization and wetting of MN afforded by MN, diminish the ability of MN-PVP dispersion to increase the drug dissolution rate.

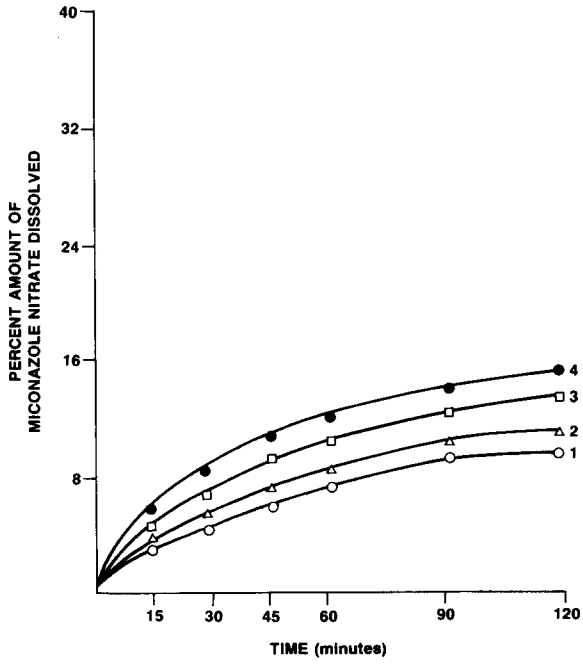

Fig. 9. Dissolution of miconazole nitrate from its solid dispersions with PVP. 1, MN alone; 2, 20/80 MN : PVP physical mixture; 3, 80/20 MN : PVP coprecipitate; 4, 20/80 MN : PVP coprecipitate.

Conclusion

Solid dispersions of MN containing high concentrations of PEG and urea concentrations were most effective in increasing the drug dissolution

TABLE 4

Relative dissolution rate of MN–PVP systems

Sample no.	Composition (%w/v)		Form	Relative dissolution rate		
	MN	PVP		15 (min)	30 (min)	60 (min)
1	100	0	powder	1.0	1.0	1.0
2	20	80	physical mix	1.0	1.1	1.2
3	80	20	coprecipitate	1.4	1.5	1.5
4	20	80	coprecipitate	1.7	1.8	1.8

rate. In comparison, MN-PVP dispersions were marginally effective. A 7-fold advantage in dissolution of MN may be realized by using solid dispersions containing PEG or urea. For the solid dispersion systems evaluated, the contribution of wetting and solubilization were more important than particle size reduction in causing an increase in the dissolution rate.

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