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Enhancement of the Dissolution and Permeation Rates of Meloxicam by Formation of Its Freeze-dried Solid Dispersions in Polyvinylpyrrolidone K-30

M. El-Badry and M. Fathy
Department of Pharmaceutics, Faculty of Pharmacy, Assiut University, 71526, Assiut, Egypt

ABSTRACT Freeze-drying (FD) and solvent evaporation (SE) were used to prepare solid dispersions (SDs) of meloxicam (MX) in polyvinylpyrrolidone K-30 (PVP). The SDs were prepared at different ratios, namely 1:1, 1:3, and 1:5 MX:PVP weight ratio. Differential scanning calorimetry (DSC), infrared absorption spectroscopy (IR), and x-ray powder diffractometry (XPD) were utilized to characterize the physicochemical properties of the SDs. Meloxicam (MX) in the solid dispersions appeared with less crystallinity form and was present in a complete amorphous form at higher PVP ratio. Dissolution rates of MX as a pure drug, physical mixtures (PMs), and SDs indicated a marked increase of the dissolution rate of MX in presence of PVP. The increase in the dissolution rate was dependent on the ratio of PVP and the method of preparation. In addition, the permeability of the drug through standard cellophane membrane and hairless mouse skin was also evaluated. The permeation rate of MX was significantly increased in the case of SDs and was dependent on the ratio of PVP. The results were primarily due to increase wettability, the solubilization of the drug by the carrier, and formation of MX amorphous form.

KEYWORDS Meloxicam, Polyvinylpyrrolidone, Solid dispersion, Freeze-drying, Solubility, Permeability

INTRODUCTION

Meloxicam (MX) is a relatively new oral non-steroidal anti-inflammatory drug (NSAID). It is reported to be a selective inhibitor of cyclo-oxygenase-2 (COX-2) and used in the management of rheumatoid arthritis, for the short-term symptomatic treatment of acute exacerbations of osteoarthritis, and for the symptomatic treatment of ankylosing spondylitis (Fleischmann et al., 2002).

The rate and extent of dissolution of the active ingredient from any dosage form often determines the rate and extent of absorption of the drug (Betageri & Makarla, 1995). In the case of a drug that is poorly water soluble, dissolution

Address correspondence to M. Fathy, Department of Pharmaceutics, Faculty of Pharmacy, Assiut University 71526, Assuit, Egypt; E-mail: Fathy@mailcity.com

may be the rate-limiting step in the process of drug absorption. Drugs with poor water solubility, such as piroxicam, have been shown to be unpredictably and slowly absorbed compared with drugs of higher solubility (Hajratwala, 1974). Therefore, a better oral, parenteral, or topical formulation can be developed by increasing the water solubility of the drugs.

The formation of SDs is an effective method for increasing the dissolution rate of poorly soluble drugs, hence, improving their bioavailability (El-Gazayerly, 2000). Some proposed mechanisms of action of SDs formulations include the solubilizing effect of the carrier, decreased agglomeration and aggregation of drug particles, particle size reduction to molecular size and increased drug solubility via complex formation or solubilization, and improved wetting (Chiou & Riegelman, 1971; Hajratwala & Ho, 1984; Serajuddin, 1999; El-Badry & Fathy, 2004).

Polyvinylpyrrolidone (PVP) is well tolerated physiologically, readily soluble in water, and has been used for increasing the dissolution and oral absorption of many water insoluble drugs (Akbuga et al., 1988; Kondo et al., 1994; Yagi et al., 1996; Margarit et al., 2001). In addition, the stability of aged PVP SDs was reported to be high (Ingkatawornwong et al., 2001).

Very limited reports are available for enhancing the solubility of MX (Chowdary & Hymavathi, 2001; Baboota & Agarwal, 2002, 2003; Seedher & Bhatia, 2003). Therefore, this study was carried out to modify the solubility and dissolution characteristics of the drug using PVP as a carrier. Solvent evaporation involves dissolving the drug and carrier in a common organic solvent, and then removing the solvent by evaporation. Freeze-drying has been used to remove organic solvent from SDs and was compared with the removal of the solvent by evaporation at room temperature.

In addition, the solid state properties of different systems were investigated using powder x-ray diffractometry (XRD), differential scanning calorimetry (DSC), and infrared (IR) spectroscopy. As the transdermal route has been recognized as one of the highly potential routes of systemic drug delivery and provides the advantage of avoidance of the first-pass effect, ease of use and withdrawal (in case of side effect) and better patient compliance (Sinha & Kaur, 2000), the permeation of MX through standard cellophane membrane and hairless mouse skin was examined for evaluating its percutaneous absorption.

EXPERIMENTALS

Materials

Meloxicam (MX) was kindly provided by Medical Union Pharmaceuticals (MUP) Co., Abu-Sultan, Ismailia, Egypt and PVP (Average MW 44000) was obtained from BDH Chemicals Ltd., Poole, England. All other chemicals and solvents were of analytical reagent grade.

Preparation of SDs of MX and PVP

Solid dispersions (SDs) were prepared at different MX and PVP weight ratios, namely 1:1, 1:3, and 1:5, using solvent evaporation method and freeze-drying method as following.

Solvent Evaporation Method

The accurately weighed amounts of the drug and PVP were dissolved in the least quantities of methylene chloride. Then the solvent was evaporated under continuous stirring at room temperature. The dried mass was crushed, dried in an oven at 50°C, ground gently with a mortar and pestle, sieved, and the 100–250 μm particle size fractions were used throughout the study. The samples were kept in a desiccator until the next experiments.

Freeze-drying Method

The accurately weighed amount of the drug (150 mg) was dispersed in 5 mL methanol. A 30% ammonium hydroxide solution of 2.5 mL was added drop wise with stirring followed by dissolving different amounts of PVP (150, 450, or 750 mg). The clear solution was completed to 50 mL with water, and then filtered using a millipore filter (0.45 μm). The filtrate was lyophilized in Labconco, Freeze Dry/Shell Freeze System, Freezone-6 (Labconco Corporation, Kansas City, MO, USA). The dried mass was crushed, ground gently with a mortar and pestle, sieved, and the 100–250 μm particle size fractions were used in this study. The samples were kept in a desiccator until the next experiments. The content of MX in each sample was determined by dissolving amounts of sample equivalent to 10 mg of MX in 100 mL of 0.1 N NaOH and measuring the absorbance at 362 nm (Solidad Garcia et al., 2000) after filtration and proper dilution. The experiments were repeated two times and the average was taken.

Physical mixtures (PMs) of MX and PVP, at the same ratios as in SDs, were prepared by gentle mixing of the components using spatula.

Determination of Solubility

Excess amounts of samples (pure MX, PMs, or SDs) were added to 5 mL of phosphate buffer of pH 7.4 (USP 25 and NF 20, 2002), sonicated for one hour, and agitated in a thermostatically controlled shaker with a temperature maintained at 37°C for 72 h. The suspension was filtered (0.45 μm Millipore filter), diluted with 0.1 NaOH, and analyzed spectrophotometrically (Double beam spectrophotometer, Shimadzu-50–02, Kyoto, Japan) at 362 nm. The average of two experiments was taken.

Infrared Absorption Spectroscopy (IR)

Infrared absorption spectroscopy (IR) measurements were performed using a Hitachi 295 spectrophotometer (Hitachi, Tokyo, Japan) using the KBr disc method. The samples were scanned over the range of 4000 to 400 cm^{-1}.

Differential Scanning Calorimetry (DSC)

Thermal analysis data were recorded using a TA 50I PC system with Shimadzu software programs. Differential scanning calorimetry (DSC-50, Shimadzu, Japan) was used under the following conditions: sample weight 3–5 mg, scanning rate 10°C/min, and N_2 as purging gas at rate of 30 mL/min. The instrument was calibrated with pure indium. The samples were heated in hermetically sealed aluminum pans in the temperature range 25–300°C.

X-ray Powder Diffractometry (XRD)

X-ray powder diffractometry was carried out using an automated x-ray diffractometer (Model FW 1700 series, Philips, Eindhoven, Netherlands) with a filter Ni C_uK (α) radiation detector, voltage 40 kV, current 30 mA, and at a scanning rate of 10 mm/sec.

Dissolution Study

The dissolution study was accomplished using USP type II (paddle) method using an Erweka equipment, model DT-06, Düsseldorf, Germany. The dissolution medium was 500 mL of 0.1 N HCl or phosphate buffer pH 7.4 (USP 25 and NF 20, 2002) maintained at 37 ± 0.5°C temperature and 50 rpm stirring rate. A weighed amount of the sample (equivalent to 10 mg MX) was dispersed onto the surface of the dissolution medium. At appropriate intervals, 5 mL samples were withdrawn, filtered (0.45 μm Millipore filter), and the concentration of MX was determined spectrophotometrically at 332 and 362 nm for 0.1 N HCl and phosphate buffer pH 7.4, respectively (Solidad Garcia et al., 2000). The average of two experiments was calculated.

Permeation Study

The permeation study was conducted using standard cellophane membrane or hairless mouse skin as following.

Using Cellophane Membrane

A piece of cellophane membrane (semipermeable cellophane membrane No 30/32, Fischer Sci. Co., London, England) was stretched over the end of an open-ended glass tube. The tube was immersed in a 400 mL beaker containing 100 mL of phosphate buffer pH 7.4 and kept in vertical position so that the membrane was just below the surface of the buffer solution. The surface area available for diffusion was 2.51 cm^2. The tube (donor) and beaker (receptor) were maintained at 37°C under shaken in a thermostatically controlled shaker. A 3 mL aliquot of saturated buffer solution (pH 7.4) of MX as a pure drug or SDs prepared by FD (Table 1) was inserted into the tube. At time intervals (up to 6 h), samples (5 mL) were removed from the receptor and analyzed spectrophotometrically at 362 nm. The experiment was repeated three times and the average of readings was calculated. The steady-state flux was calculated from the individual cumulative amounts versus time plots (Loftsson, 1982).

Using Hairless Mouse Skin

Female hairless mice (8–10 weeks old) were killed by cervical dislocation and their full-thickness skins removed. The adhering fat and other visceral tissue were removed. To remove extraneous debris and leachable enzymes, the dermal side of the skin was in contact with a saline solution for 2 h. Then, 6 h treatment of the dermal side with a 1 mL phosphate buffer, to equilibrate the membrane, was done before starting

TABLE 1 **Solubility and R.D.R. in Phosphate Buffer pH 7.4 of Pure MX, PM, SDs Prepared by SE and FD Method at Different MX:PVP ratios.**

System	MX:PVP ratio	Solubility ($MX10^{-3}$)	R.D.R. at different times (min)			
			5	10	15	20
MX	1:0	1.736	—	—	—	—
PM	1:1	2.186	1.74	2.37	3.05	3.45
SE	1:1	2.283	3.16	4.92	4.7	4.49
FD	1:1	3.846	12.49	12.61	10.72	9.34
PM	1:3	2.583	7.26	7.83	7.09	6.11
SE	1:3	2.477	8.40	8.98	7.31	6.20
FD	1:3	4.349	22.48	20.8	16.26	13.24
PM	1:5	2.866	9.77	10.37	8.74	7.50
SE	1:5	4.287	21.75	19.05	14.58	12.91
FD	1:5	6.785	25.13	21.95	17.08	13.51

R.D.R. represents the ratio between the amounts of drug released from MX/PVP combination to that from drug alone at the same time.

the diffusion experiment. As previously mentioned in permeation study through cellophane membrane, mouse skin was used instead of the standard cellophane membrane and the same procedures were applied

RESULTS AND DISCUSSION

Infrared Absorption Spectroscopy (IR)

Infrared absorption spectroscopy (IR) spectra of MX, PVP, PMs, and SDs are shown in Fig. 1. Infrared absorption spectroscopy (IR) spectra of MX showed sharp bands at 3550, 3285, 1615, 1546, and 1523 cm^{-1} due to stretching vibration bands of OH, NH, C=O, and two S=O, respectively. C=O stretching band of PVP appeared at 1650 cm^{-1} and C–N band at 1287 cm^{-1}. Infrared absorption spectroscopy (IR) spectra of PMs showed bands similar to that of both drug and PVP. Solid dispersions (SDs) prepared using SE or FD method at 1:1 ratio or that prepared at 1:3 ratio using SE method displayed similar spectra as that of PMs at the corresponding ratios indicating absence of the interaction between MX and PVP. Solid dispersions (SDs) prepared using SE method at 1:5 or that prepared using FD method at 1:3 or 1:5 ratio showed decrease in intensity and shift to higher wave number for the bands appeared at 1546 and 1523 cm^{-1}. This finding suggested that there may be a sort of molecular interaction of the drug and PVP in SDs and seemed to occur at higher ratio of PVP. Tantishaiyakul et al. (1999) found that the interaction of piroxicam with PVP was dependent on the piroxicam:PVP ratio. At 1:4 piroxicam:PVP weight ratio, they suggested intermolecular hydrogen bonding was stronger than that of other ratios, therefore the N–H or O–H stretching of piroxicam might be weakened, resulting in a weak and broad peak that was completely covered by bond stretches from PVP.

Differential Scanning Calorimetry (DSC)

Differential scanning calorimetry (DSC) thermograms of MX, PVP, PMs, and SDs are shown in Fig. 2. Meloxican (MX) showed an endothermic peak at 262°C corresponding to its melting point. No peak melting point was seen in the thermogram of PVP because of the amorphous structure of the polymer. At various ratios of MX:PVP, PMs always showed the drug endothermic peak. The weakness of the peak in case of PM might be attributed to the dilution effect of PVP. Solid dispersions (SDs) prepared by SE showed broad peak at lower ratios (1:1 and 1:3 ratio) indicating that some crystals of pure MX kept their crystalline nature. At the same time, the peak disappeared completely at 1:5 MX:PVP ratio suggesting that MX was changed to an amorphous state. Solid dispersions (SDs) prepared at 1:1 ratio using FD method showed endothermic of pure MX indicating presence of MX in crystalline state. However, the melting peak of MX was not observed in SDs prepared by FD method at 1:3 or 1:5 ratio. These observations indicated that MX was converted completely to an amorphous form by FD and with the presence of a lower amount of PVP than that required by SE.

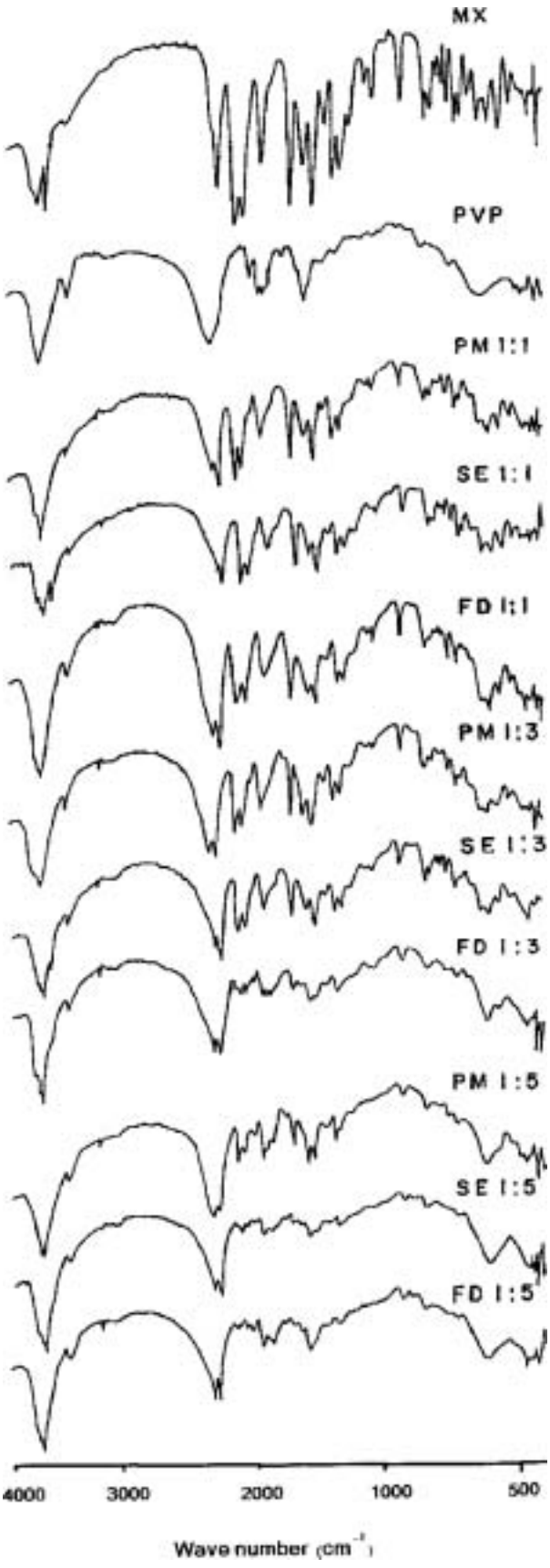

FIGURE 1 **Infrared Spectra of MX, PVP, PM, and SDs Prepared by SE or FD at Different Ratios of MX:PVP.**

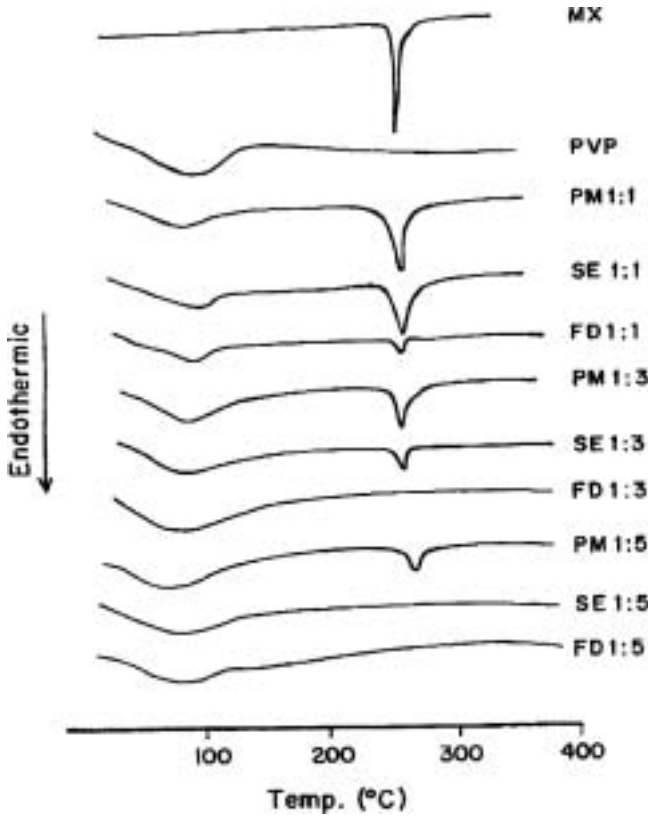

FIGURE 2 **DSC Thermograms of MX, PVP, PM, and SDs Prepared by SE or FD at Different Ratios of MX:PVP.**

X-ray Powder Diffractometry (XRD)

Figure 3 displays x-ray powder diffraction of the MX, PVP, PMs, and SDs. Meloxican (MX) is a highly crystalline powder and has characteristic sharp peaks appearing at diffraction angles of 2θ at 13.79, 15.65, 19.31, 19.98, 26.58, and 27.08°. Because of amorphousness of PVP, it appeared as a halo structure. The characteristic MX diffraction peaks remained constant in physical mixtures in spite of a higher ratio of PVP (1:5 MX:PVP) indicating that MX was in the crystalline state. The crystalline structures of MX in solid dispersions, prepared by FD or SE method, at 1:1 MX to PVP weight ratio, displayed the same patterns. Also, in case of 1:3 ratio prepared using SE method, the characteristic peaks of pure MX did not change. While in case of 1:3 ratio prepared using FD method, the SD possessed much lower crystallinity degree. No peaks were displayed for SDs prepared at 1:5 MX to PVP weight ratio regardless the method of preparation. The absence of diffraction peaks indicated the presence of MX in amorphous form. The results of DSC and XRD

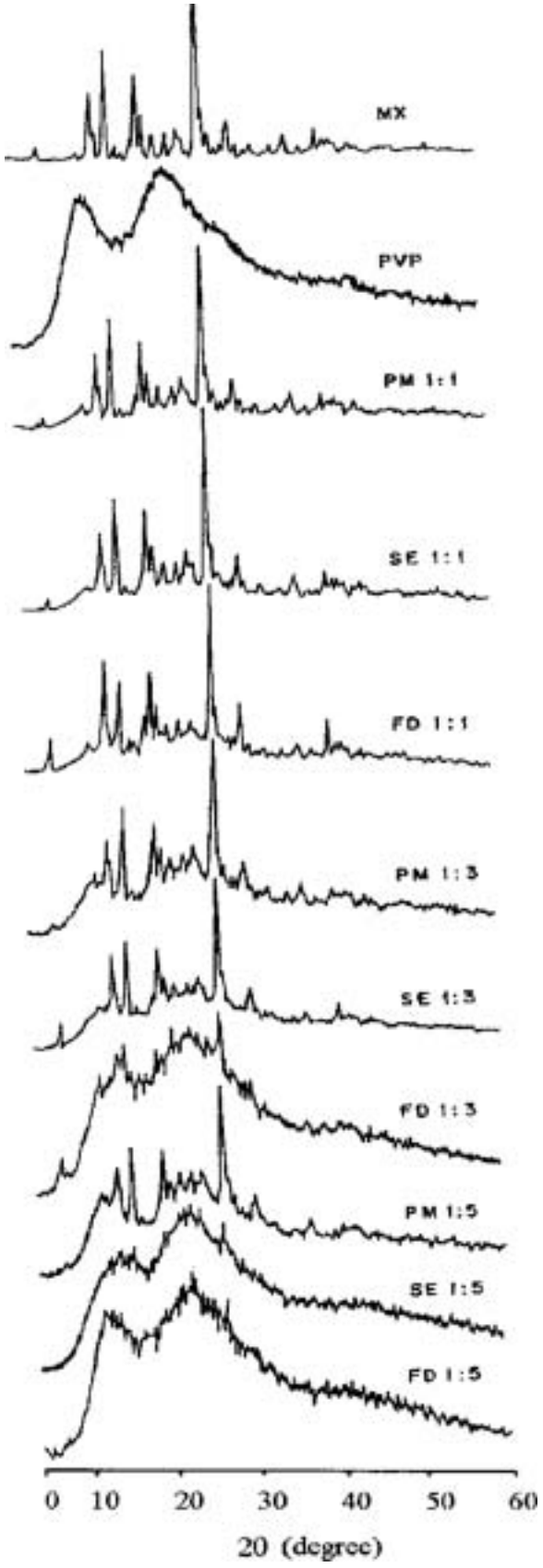

FIGURE 3 X-Ray Powder Diffraction (XPD) pattern of MX, PVP, PM, and SDs Prepared by SE or FD at Different Ratios of MX:PVP.

revealed that the formation of amorphous form was dependent on the fraction of PVP and method of preparation. Sekikawa et al., 1987, pointed out that PVP might inhibit the association of the drug molecules to form the crystal nucleus and inhibit the crystal growth and this inhibitory effect was associated with molecular weight and proportion of PVP.

Solubility Study

The solubility of MX was measured in phosphate buffer pH 7.4 at 37°C (Table 1). In general, the presence of PVP increased the solubility of MX. With the increase in the ratio of PVP, the solubility increased. Physical mixtures (PM) and SDs prepared by SE at 1:1 and 1:3 MX:PVP ratio gave the same enhancement in the MX solubility (about 1.5 fold increase) while SDs prepared by SE at 1:5 gave 2.5 fold increase in the solubility. Solid dispersions (SDs) prepared by FD at 1:1, 1:3, and 1:5 MX:PVP ratio gave 2.2, 2.5, and 3.9 fold increase in the solubility, respectively. The data were consistent with that displayed by DSC and XRD whereas with the decrease in the crystallinity the solubility increased.

Dissolution Study

The dissolution rate of MX in the form of powder, PMs, and SDs was examined in both of 0.1 N HCl (Figs. 4–6) and phosphate buffer (pH 7.4) (Figs. 7–9).

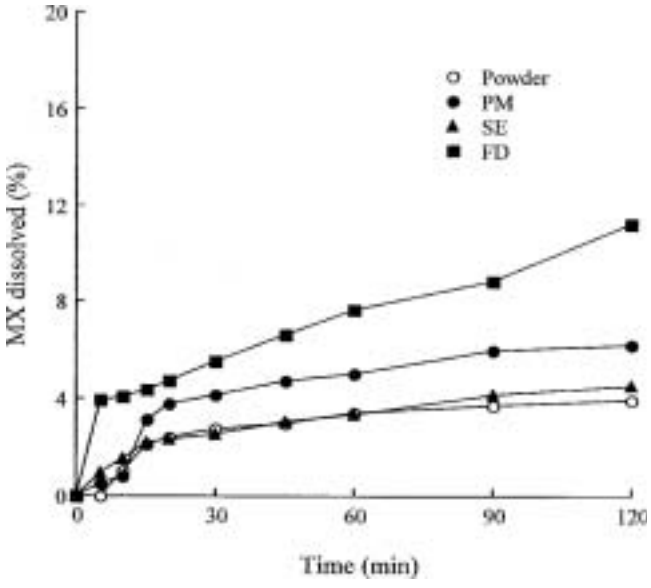

FIGURE 4 Dissolution Profiles, in 0.1 N HCl, of MX from Its Powder, PM and SDs Prepared by SE or FD Method at 1:1 MX:PVP Ratio.

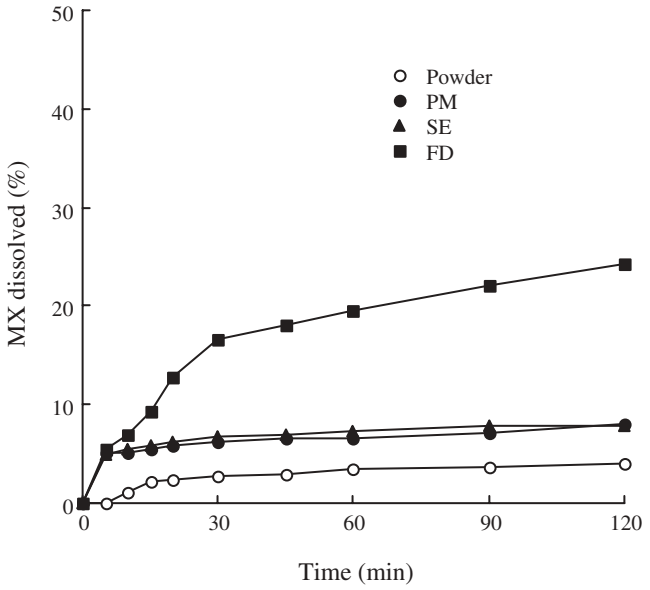

FIGURE 5 **Dissolution Profiles of MX, in 0.1 N HCl, from Its Powder, PM and SDs Prepared by SE or FD Method at 1:3 MX:PVP Ratio.**

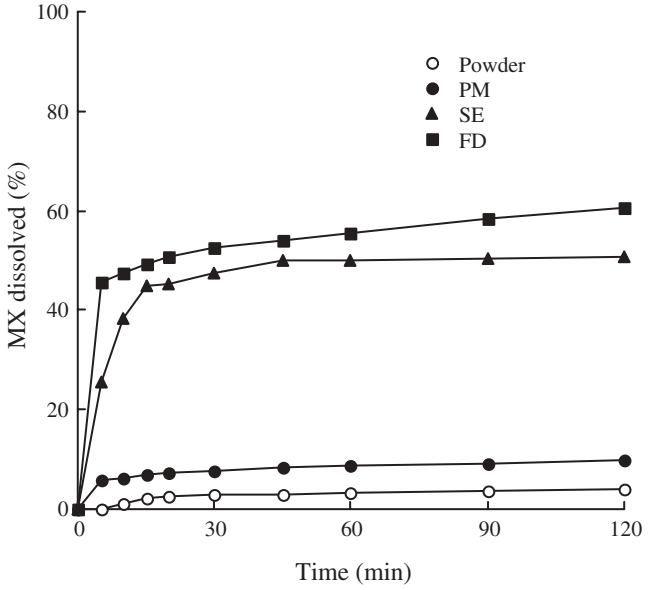

FIGURE 6 **Dissolution Profiles of MX, in 0.1 N HCl, from Its Powder, PM and SDs Prepared by SE or FD Method at 1:5 of MX:PVP Ratio.**

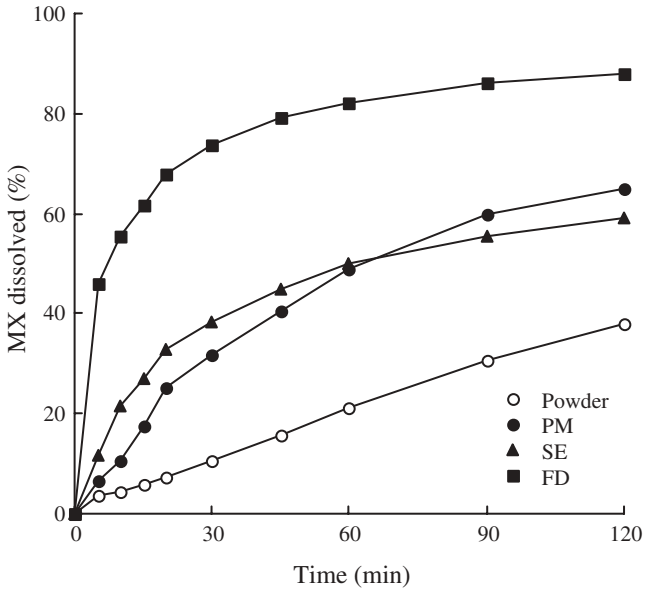

FIGURE 7 **Dissolution Profiles of MX, in Phosphate Buffer (pH 7.4), from Its Powder, PM and SDs Prepared by SE or FD Method at 1:1 of MX and PVP.**

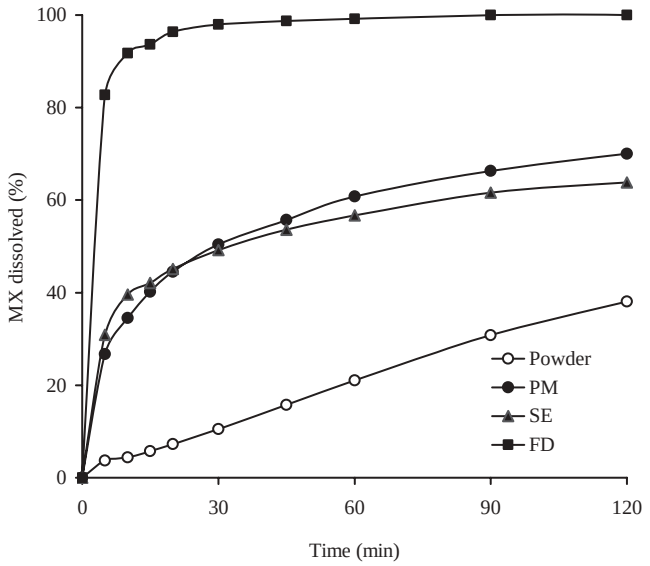

FIGURE 8 **Dissolution Profiles of MX, in Phosphate Buffer (pH 7.4), from Its Powder, PM and SDs Prepared by SE and FD Method at 1:3 of MX and PVP.**

The dissolution rate of pure MX was extremely low, with only about 4% and 38% of drug released during 120 min of the dissolution run in 0.1 N HCl and phosphate buffer (pH 7.4), respectively. This might be attributed to poor wettability and particle agglomeration during the run that caused the powder to float on the surface of dissolution medium. The observation is clearer with 0.1 N HCl when used as dissolution medium than in phosphate buffer (pH 7.4). The dissolution rate of MX from all systems (PMs or SDs) was markedly increased than that of pure MX. Figures 4 and 5 showed slight increase (less than 2%) in dissolution rate of PMs than that of SDs prepared, using SE method, at 1:1 or 1:3 ratio in 0.1 N HCl. This increase

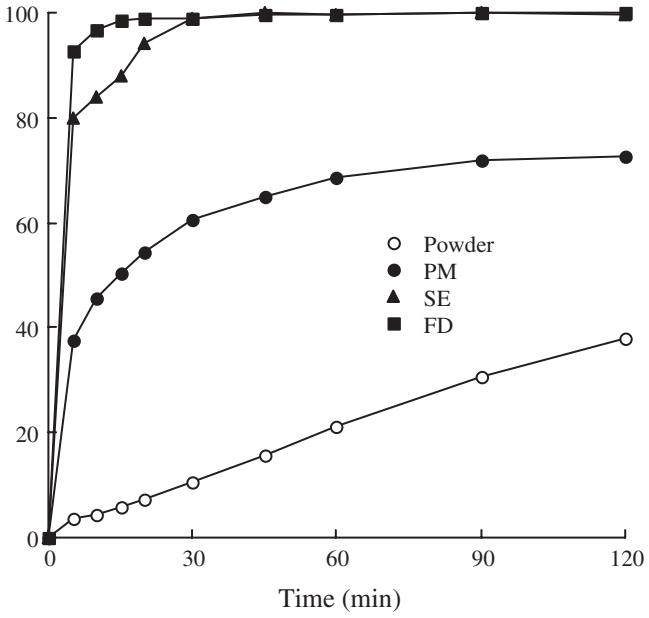

FIGURE 9 **Dissolution Profiles of MX, in Phosphate Buffer (pH 7.4), from Its Powder, PM and SDs Prepared by SE or FD Method at 1:5 of MX and PVP.**

in dissolution rates of drug in presence of PVP in form of PM could be attributed to an increasingly effective solubilization process by the carrier in the diffusion layer immediately surrounding the drug particle (Prabhu et al., 2001). In addition, Sekikawa et al. (1987) proposed that PVP in the medium may lower the surface tension and facilitated the wetting, thus, the dissolution of drug. With the increase in the ratio of PVP, the dissolution rate increased where the decrease in the surface tension of the medium also was found to be changed as the weight ratio of PVP increased (Akbuga et al., 1988). The SDs prepared by SE gave comparable release rate with that of PM at 1:1 or 1:3 ratio of MX:PVP, particularly after 30 min in phosphate buffer (pH 7.4) (Figs. 7, 8). For more clarification, relative dissolution rate (R.D.R.) values were calculated as the ratio between the amount of the drug released in the form of different systems (PMs or SDs) to that released from the pure MX powder at the same time and are depicted in Table 1. However, the ratio prepared by SE at 1:5 MX:PVP displayed a higher release rate than that of PM in both media of dissolution (Figs. 6 and 9). The dissolution rate of MX from SDs prepared by FD is higher than from PMs or pure drug. The SDs prepared by FD showed higher release rate than from that prepared by SE, particularly at low weight fraction of PVP (Figs. 4, 5 and Figs. 7, 8). The higher dissolution rate from SDs may be attributed to the formation of a high energy amorphous phase of drug. Inhibition of growth of the drug crystal structure by PVP in SDs has been linked to improve dissolution behavior and the formation of highly supersaturated drug solutions (Doherty & York, 1987). Moreover, the faster dissolution rate of MX from SDs may be due to lower contact angle, improved wetting, deaggregation, decreased particle size, and therefore, increased surface area. In addition to PVP, interaction with MX might initiate the solubilization of the drug. These results were in consistent with that obtained from DSC, XRD, and solubility.

Permeation Study

The total amount of the drug permeated (μg/cm^2) through the standard cellophane membrane or hairless mice skin as a function of time during the course of 6 h is shown in Figs. 10 and 11. The permeation profiles for individual data were linear with *r* ranged from 0.97–0.999. The results indicated that both cellophane membrane and hairless mouse skin was permeable to MX and that the percutaneous absorption might be described by zero-order kinetics during the time of study. The permeation rate of the drug from its saturated solution, in phosphate

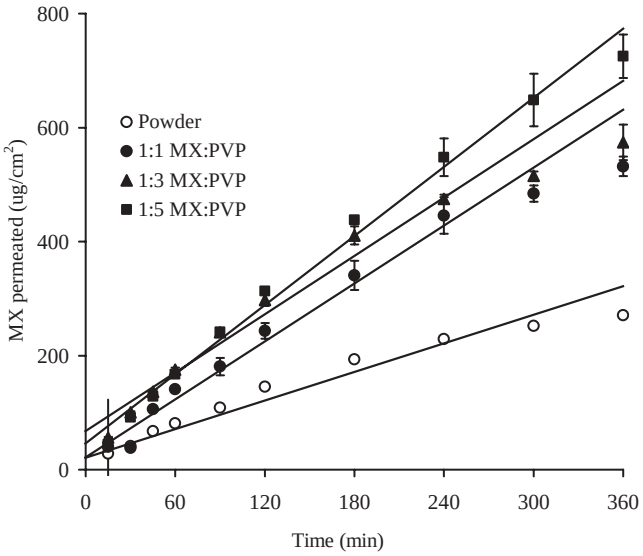

FIGURE 10 **Permeation Profiles of MX Through Standard Cellophane Membrane from Saturated Solutions of MX Powder or Its SDs in PVP Prepared by FD Method at Different MX:PVP Ratios. Error Bars Represent SD (*n* = 3).**

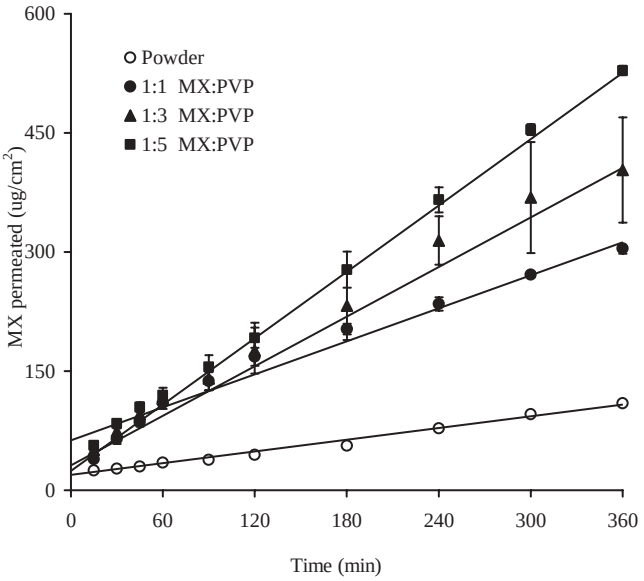

FIGURE 11 **Permeation Profiles of MX Through Hairless Mouse Skin from Saturated Solution of MX Powder or Its SDs in PVP Prepared by FD Method at Different MX:PVP ratios. Error Bars Represent SD (n = 3).**

buffer pH 7.4, across the two membranes was calculated from the slope of the graph as μg cm^{-2} h^{-1} (Table 2). As the fraction of PVP increase, the permeation rate increased which could be attributed to the increased in the amount of MX dissolved, and hence, drug availability at the surface of the membranes increased resulting in high concentration gradient. To clarify the differences in the permeation coefficients (Table 2) with different ratio of PVP, analysis of variance (ANOVA: single factor) was performed. It was noted that the permeability coefficient decreased in case of cellophane membrane (F = 23.81 and P = 0.0002) with enhancement factor (EF) <1 as the fraction of PVP increased. While in the case of mouse skin, the permeability coefficient increased along the ratio of 1:1 and 1:3 MX:PVP and then declined at 1:5 ratio (F = 9.72 and P = 0.005) with EF > 1. The decrease in permeability coefficient at 1:5 ratio might be a result of increase in the viscosity of solution in the donor phase. The EF for permeation rate was higher in the case of hairless mouse skin than that of cellophane membrane (Table 2) suggesting that PVP might possess a role as penetration enhancer that appeared on using viable membranes. Although the exact mechanism for this increase needs to be fully elucidated, the results prevailed that the percutaneous absorption of MX improved by PVP.

CONCLUSION

Infrared absorption spectroscopy (IR), DSC, and x-ray diffraction studies determined that there was a significant loss in crystallinity of MX in form of SDs Polyvinylpyrrolidone K-30 (PVP) has an improving effect on the properties of MX as the solubility, dissolution rate, and permeation through cellophane membrane or hairless mouse skin. This improving effect was dependent on the fraction of PVP and the method of preparation. Solid dispersions (SDs) prepared by FD were superior in dissolving MX than that prepared by solvent evaporation. With the increase in PVP fraction, the solubility, dissolution rate, and permeability of MX increased. The usefulness and the mechanism of PVP in enhancing the percutaneous absorption need more exploration.

TABLE 2 **Permeation Rate and Permeation Coefficient of MX Through Cellophane Membrane and Hairless Mouse Skin***

		Cellophane membrane			Hairless mouse skin		
System	MX:PVP ratio	Permeation rate (μg cm^{-2} h^{-1})	Permeability coefficient (cm/h)	EF**	Permeation rate (μg cm^{-2} h^{-1})	Permeability coefficient (cm/h)	EF
Drug	1:0	42.70 ± 1.32	0.070 ± 0.002	—	15.02 ± 0.28	0.024 ± 0.005	—
FD	1:1	88.60 ± 4.12	0.066 ± 0.003	0.87	44.11 ± 1.10	0.033 ± 0.001	1.38
FD	1:3	90.40 ± 3.42	0.059 ± 0.002	0.84	59.98 ± 6.05	0.039 ± 0.007	1.83
FD	1:5	120.32 ± 8.42	0.050 ± 0.004	0.71	82.04 ± 3.47	0.034 ± 0.005	1.46

*Results are presented as mean ± SD (n = 3).

**EF = Enhancement factor was calculated as the ratio of mean permeation coefficients for the drug in form of FD dispersions to that of pure drug.

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