Drug Development and Industrial Pharmacy, 34:781–788, 2008

ISSN: 0363-9045 print / 1520-5762 online
DOI: 10.1080/03639040801925735

informa
healthcare

Preparation of a Solid Dispersion by a Dropping Method to Improve the Rate of Dissolution of Meloxicam

Amir Bashiri-Shahroodi, Parya Reisi Nassab, and Piroska Szabó-Révész
Department of Pharmaceutical Technology, University of Szeged, Szeged, Hungary

Róbert Rajkó
Department of Unit Operations and Environmental Engineering, University of Szeged, Szeged, Hungary

Application of a solid dispersion system is one of the methods used to increase the bioavailability of poorly water-soluble drugs. Adaptation of the dropping method from the chemical industry as a formulation procedure may help the scaling-up process and simplify the formulation of poorly water-soluble compounds. Meloxicam (ME), a nonsteroidal anti-inflammatory drug that is poorly soluble in water, and polyethylene glycol (PEG) 4000, a water-soluble carrier, were formulated by using a dropping method in an attempt to improve the dissolution of ME. Pure ME and physical mixtures and tablets of ME–PEG 4000 (1:3 ratio) were compared as regards their dissolution with samples formulated by the dropping method. The results revealed that the round particles (solid drops) exhibited a higher dissolution rate than those of the physical mixtures, tablets, and pure ME. Self-modeling curve resolution (SMCR) as a chemometric method was used to evaluate X-ray powder diffractometry (XRPD) data. The results demonstrated the presence of a new crystalline phase in the solid dispersion, which can help the fast and quantitative dissolution from the solid drops. The round particles can be adapted to individual therapy by using a distributor.

Keywords dropping method; solid dispersion; meloxicam; PEG 4000; dissolution; poorly water-soluble drug; chemometrics

INTRODUCTION

Improvement of the oral bioavailability and solubility behavior of poorly water-soluble drugs is still one of the most challenging aspects of drug development. Various methods have been introduced to enhance the bioavailability of poorly water-soluble drugs, which can be summarized as the methods used in physical and chemical modifications. Decrease of the particle size, modification of the crystal habit, and the use of surfactants and drug dispersions in carriers (eutectic mixtures, solid dispersions, and solid solutions) are among the methods used in physical modification. The application of soluble prodrugs and salt formation are the most frequently used methods in chemical modification.

Among the physical modifications, the preparation of solid dispersions has become one of the most active areas of research in the pharmaceutical field with a view to improve the bioavailability of poorly soluble drugs. Sekiguchi and Obi (1961) developed a method to enhance the bioavailability of poorly water-soluble drugs, which was later termed solid dispersion. This method involved the formation of eutectic mixtures of drugs with water-soluble carriers through the melting of their physical mixtures, which resulted in solubility enhancement. Numerous articles have been published on various aspects of solid dispersions, but despite promising early results on a laboratory scale, the commercial application of solid dispersion in dosage form design has been very limited and few products have been marketed. The method of preparation, the formulation into dosage forms, and the scaling-up processing of solid dispersion system all involve limitations. Chiou and Riegelman (1971) defined solid dispersion as a dispersion of one or more active ingredients in an inert carrier or matrix in the solid state prepared by a melting (fusion), solvent, or melting–solvent method. Dispersions obtained through a fusion process are often called melts, and those obtained by the solvent method are frequently referred to as coprecipitates or coevaporates. On the basis of their fast-release mechanisms, Chiou and Riegelman (1971) classified solid dispersions into the following six representative types: (a) simple eutectic mixtures, (b) solid solutions, (c) glass suspensions, (d) amorphous precipitates in crystalline carriers, (e) compounds or complexes, and (f) combinations of some of the previous five types.

Some methods frequently used for the preparation of solid dispersions are as follows:

- conventional melting or fusion (Chiou & Riegelman, 1969; Goldberg, Gibaldi, & Kanig, 1966; Sekiguchi & Obi, 1961; Sekiguchi, Obi, & Ueda, 1964),

Address correspondence to Piroska Szabó-Révész, Department of Pharmaceutical Technology, University of Szeged, Eötvös u. 6, H-6720 Szeged, Hungary. E-mail: revesz@pharm.u-szeged.hu

- solvent evaporation (Bloch, Elegakey, & Speiser, 1983; Chiou & Riegelman, 1969; Cirri et al., 2004; Kim & Jarowski, 1977; Malone et al., 1966; Sekikawa et al., 1983; Tachibana & Nakamura, 1965; Takayama, Nambu, & Nagai, 1982),
- melt extrusion (Flament, Dupont, Leterme, Farah, & Gayot, 2004; Rauwendaal, 1986),
- direct capsule filling with melt material (Chatman, 1987; Francois & Jones, 1978; Serajuddin, Sheen, Mufson, Bernstein, & Augustine, 1988).

The aim of this research was to devise a dropping method for the preparation of solid dispersions that not only increases the dissolution of poorly water-soluble drugs but also simplifies the formulation process, which may help in the overcoming of the scaling-up difficulties. The most frequently used methods of preparation are introduced below, and the results of experimental work carried out to prepare a solid dispersion of meloxicam (ME) as a poorly water-soluble drug by the dropping method are presented.

Preparation of a Solid Dispersion by a Dropping Method

Solidification in Drops

The dropping method, developed by Bülau and Ulrich (1977) to facilitate the crystallization of different chemicals, is a new procedure for producing round particles from melted solid dispersions.

Laboratory-Scale Preparation. A solid dispersion of a melted drug–carrier mixture is dropped onto a cooling plate, where it solidifies into round particles (Figure 1). The size and shape of the particles can be influenced by factors such as the viscosity of the melt and the size of the pipette. As viscosity is highly temperature dependent, it is very important to adjust the temperature so that, when the melt is dropped onto the plate, it solidifies into a spherical shape. The dropping method does not use organic solvents and therefore has none of the problems associated with solvent evaporation. The method also avoids the pulverization, sifting, and compressibility difficulties encountered with other melt methods, and the plug formation mentioned in connection with the direct capsule-filling method does not occur. The disadvantage is that only thermostable drugs can be used, and the physical instability of solid dispersions is a further challenge.

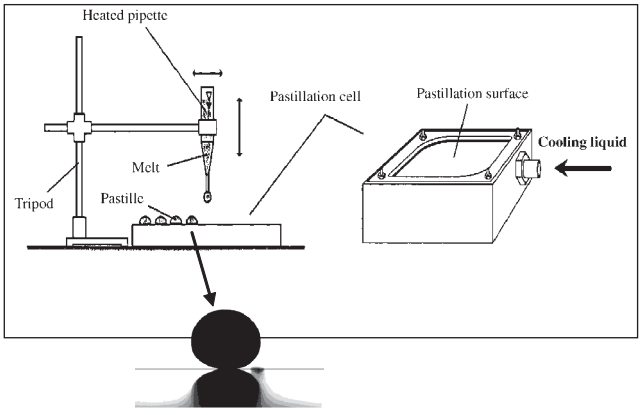

FIGURE 1. Equipment used in the dropping method with solid drops (Bülau & Ulrich, 1977) (contact angle of the drop: 174 ± 0.1°).

MATERIALS

The ME sample was supplied by EGIS Ltd. (Budapest, Hungary). Polyethylene glycol (PEG) 4000 was from Hungaropharma Ltd. (Budapest, Hungary). All other reagents and solvents were of analytical grade.

METHODS

Preparation of Physical Mixture

For the preparation of a ME–PEG 4000 physical mixture, ME and PEG 4000 were weighed and mixed for 5 min using a pestle and mortar and sieved through a 400-μm mesh. About 60 mg of ME–PEG 4000 powder mixture (containing 15 mg of ME and 45 mg of PEG 4000) was filled into a hard gelatin capsule (size no. 2) for further investigations.

Tablet-Making

ME–PEG 4000 tablets were prepared with a Korsch EKO eccentric tablet machine (Emil Korsch Maschinenfabrik, Berlin, Germany). The compression tools were single, flat punches 10 mm in diameter, furnished with strain gauges. The physical mixture of ME–PEG 4000 was compressed at a pressure of 10 ± 1 kN, an air temperature of 24°C, and an air relative humidity of 45%. The crushing strength of the tablets was investigated with a Heberlein apparatus (Flisa, Le Locle, Switzerland). The geometrical parameters were measured with a screw micrometer (Mitutoyo, Tokyo, Japan). The weight of the tablets was calibrated to 60 mg. Each tablet contained 15 mg of ME and 45 mg of PEG 4000.

Preparation of Solid Dispersion by Dropping Method

For the preparation of the ME–PEG 4000 solid dispersion by the dropping method, PEG 4000 was weighed and melted in a double-layered beaker at 58°C (±1°C) and a measured amount of ME was added and stirred. The measured amounts of ME and PEG 4000 corresponded to a drug–carrier ratio of 1:3 (each solid drop contained 5 mg of ME and 15 mg of PEG 4000). The melted drug–carrier mixture was pipetted and placed into an adjustable heating device to keep the temperature constant. The melted drug–carrier mixture was dropped onto a stainless steel plate, where it solidified into round particles. The temperature of the stainless steel plate was 20°C (±1°C). Three round particles (60 mg) were placed into hard gelatin capsules (size no. 2) for further investigations.

Investigation of Particle Size

The particle size distribution of the ME sample was measured by laser diffraction (Malvern Mastersizer 2000, Malvern Ltd., Worcestershire, UK). For the measurements, the samples were dispersed in air and deagglomerated at an air pressure of 1 bar. The particle size was determined to be in the range of 0.02–2,000 μm, and the measurements were repeated three times.

The particle size of the product obtained with the dropping method (S3) was determined with a screw micrometer (Mitutoyo).

Dissolution Studies

Samples of tablets, physical mixture, pure ME, and round particles were prepared for dissolution studies. The physical mixture, round particles, and pure ME as reference sample were filled into hard gelatin capsules (size no. 2). Each capsule contained 15 mg of ME and 45 mg of PEG 4000. Dissolution tests were performed with a Pharmatest (Hainburg, Germany) dissolution tester, set with a paddle speed of 100 rpm. Artificial enteric juice (900 mL) with a pH of 7.5 (± 0.1) at 37°C (± 0.5°C) was used. Samples were withdrawn at 5, 10, 20, 30, 60, and 90 min and were assayed spectrophotometrically at 361 nm (Helios α; Spectronic Unicam, Cambridge, UK) after filtering.

Kinetic Calculation by Langenbucher

The dissolution profiles of samples and pure ME can be described by modified Langenbucher model (Langenbucher, 1972).

$$\sqrt[3]{1-\frac{m_t}{m_0}} = \ln t$$

where m_0 is the mass of the drug at time $t = 0$ and m_t at time t. The linear transformation resulted in the rate constant (k value) and the intercept value (n).

Differential Scanning Calorimetry

Thermal analysis was carried out with a differential scanning calorimetry (DSC) instrument (Mettler-Toledo GmbH, Schwerzenbach, Switzerland). About 10 mg of samples and 2.5 mg of pure ME were weighed into a nonhermetically sealed aluminum pan. The samples were heated from 25 to 300°C at a heating rate of 30°C/min. The instrument was calibrated by using indium.

X-Ray Powder Diffractometry

X-ray powder diffractometry (XRPD) was performed with a Philips X-ray diffractometer (PW 1050/70 PW 1710). The measurement conditions were radiation source, CuKα; scan speed (2θ/s), 0.035; step size (2θ/s), 0.035; and time per step, 1.0 s.

Chemometric Method

Fiala (1980) developed a procedure, correlation analysis, for the XRPD analysis of mixtures of components. Nassab, Rajkó, and Szabó-Révész (2006) introduced a multivariate curve resolution method for the same purpose, but without reference to the Joint Committee on Powder Diffraction Standards (JCPDS). The chemometric method of multivariate curve resolution with alternative least squares (MCR-ALS) (Tauler, 1995; Tauler, Casassas, & Izquierdo-Ridorsa, 1991) can break the data matrix into profiles (composition profiles and pure diffractogram profiles) with the use of certain constraints (De Juan & Tauler, 2003; De Juan, Vander Heyden, Tauler, & Massart, 1997; Tauler, 2001). Unfortunately, this decomposition is very often not unique because of the rotational and intensity (scaling) ambiguities (Tauler, Smilde, & Kowalski, 1995; Van Benthem, Keenan, & Haaland, 2002). The rotational ambiguities can be moderated or even eliminated if convenient constraints can be used (De Juan & Tauler, 2003; De Juan et al., 1997; Tauler, 2001). Tauler et al. (1995) developed a Matlab code for MCR-ALS with some constraints.

The self-modeling curve resolution (SMCR) method, one of the oldest chemometric procedures, was introduced for two-component systems by Lawton and Sylvestre (1971) to deconvolve raw spectroscopic data into the product of two physically interpretable profile matrices provided that both concentrations and absorbances are nonnegative, accepting both as minimal constraints. Unfortunately, the solution is not unique: the method can give feasible regions only for the pure component profiles without further restrictions. Borgen and Kowalski (1985) and Borgen, Davidsen, Mingyang, and Øyen (1986) generalized the LS method for three-component systems with the same minimal constraints. Rajkó and István (2005) recently revisited Borgen's method, gave a clearer interpretation, and used computational geometry tools to find inner and outer polygons.

We now introduce the SMCR method to evaluate XRPD data.

RESULTS AND DISCUSSION

The particle size distribution of ME is important as regards the wettability properties and dissolution: the relatively small particle size of ME promotes its dissolution rate when it is blended with PEG 4000. For the development of the product, micronized ME was chosen because of its ideal particle size and specific surface. The particle size distribution of ME at D 90% was 5.97 μm (SD ± 0.31) and at D 10% was 0.73 μm (SD ± 0.01).

Preformulation studies were carried out to determine the most suitable ratio of the drug–carrier mixture. The sample involving a drug–carrier ratio of 1:3 with PEG 4000 as carrier exhibited the best drug release properties (Bashiri-Shahroodi, Szabó-Révész, & Erős, 2003).

In the dropping method, the temperature of the melted drug–carrier mixture was 58°C, which is determined by the

melting point of PEG 4000. The surface energy of the plate onto which the melt is dropped is the most important factor in the production of round particles of the ME–PEG 4000 solid dispersion. The reason for the choice of a stainless steel plate was its moderate surface energy (30.17 mN/m). Higher (e.g., enamel, 51.12 mN/m) and lower (e.g., teflon, 18.75 mN/m) surface energies did not result in spherical particles (Hassner, Ulrich, Pallagi, & Szabó-Révész, 2001). Figure 1 illustrates the equipment used in the dropping method with solid drops developed by Bülau and Ulrich (1977).

Tablets (as the most frequently used dosage form), physical mixtures, and round particles (solid drops) were compared with the pure drug to determine and compare the drug release properties. The components and the parameters of the investigated samples are summarized in Table 1.

The rates of dissolution of the above-mentioned three samples and pure drug were measured and are shown in Figure 2, which demonstrates that all three samples dissolved faster than the pure drug and there was a significant increase in the rate of dissolution of the sample formulated by the dropping method (S3). The sequence of the rates of dissolution of the samples was round particle (S3) → physical mixture (S1) → tablet (S2) → pure ME. The effect of the high specific surface area of ME was not manifested because of the tendency of the small (~6 μm) crystals to agglomerate. After dissolution of the capsule, the particles that were very hydrophobic formed clusters in the artificial enteric juice. This was demonstrated by the rate constant (k = 0.1795) of the dissolution of ME, which was calculated for modified Langenbucher function (Table 2). The

TABLE 1
Parameters of Investigated Samples and Pure ME

Sample	Composition	Dosage Form	Characteristic Parameters
S1 (physical mixture)	15 mg ME and 45 mg PEG 4000	Capsule, no. 2	–
S2 (tablet)	15 mg ME and 45 mg PEG 4000	Tablet (pressed from physical mixture)	Height: 1.83 mm ($SD \pm 0.05$ mm) Crushing strength: 35.7 N ($SD \pm 5$ N) Diameter of tablet: 10 mm
S3 (round particle)	5 mg ME and 15 mg PEG 4000 For one solid drop	Capsule, no. 2. with 3 round particles	Diameter of particles: 2.75 mm ($SD \pm 0.12$ mm)
ME (pure)	15 mg ME	Capsule, no. 2.	–

ME, meloxicam; PEG, polyethylene glycol.

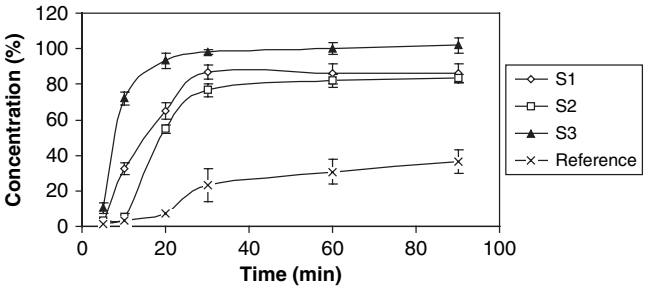

FIGURE 2. Rates of dissolution of different samples. Ref std, pure ME; S1, physical mixture; S2, tablet; S3, round particles developed by dropping method.

three samples (round particles, physical mixture, and tablet) dissolved faster, and the differences between these curves can be characterized by the rate constants (k) according to the modified Langenbucher function.

Further examinations (DSC, XRPD, and chemometric analyses) were carried out to find out why samples formulated by the dropping method had better dissolution properties than other samples.

The DSC method was used to determine the physical–chemical properties of ME and the binary systems (physical mixture and round particles). The thermogram of ME exhibited a sharp endothermic peak at 270, corresponding to the melting point of ME. The samples (S1 and S3) in which PEG 4000 was present, the peak was about 64°C for PEG 4000 and 230°C for ME due to the partly dissolving of ME in the melted PEG 4000. This phenomenon appeared in the dropping method too, where ME was added to melted PEG 4000 (S3). It resulted in smaller normalized enthalpy value (–19.24 J/g) as opposed to the physical mixture (S1), in which this value is higher (–32.04 J/g). In the cases of the tablets and physical mixture, no heat was applied, so there was no possibility for ME to dissolve in PEG 4000. This might be one of the reasons why the samples formulated by the dropping method exhibited better dissolution than the tablets and physical mixtures. Figure 3 shows the DSC investigation results.

TABLE 2
Characteristic Langenbucher Function Values of the Investigated Samples

Sample	k (Rate Constant)	n (Intercept)	R^2
S1 (physical mixture)	0.1818	0.2604	.8822
S2 (tablet)	0.1776	0.3041	.9128
S3 (round particle)	0.3868	0.5700	.9961
ME (pure)	0.1795	0.0693	.9519

ME, meloxicam.

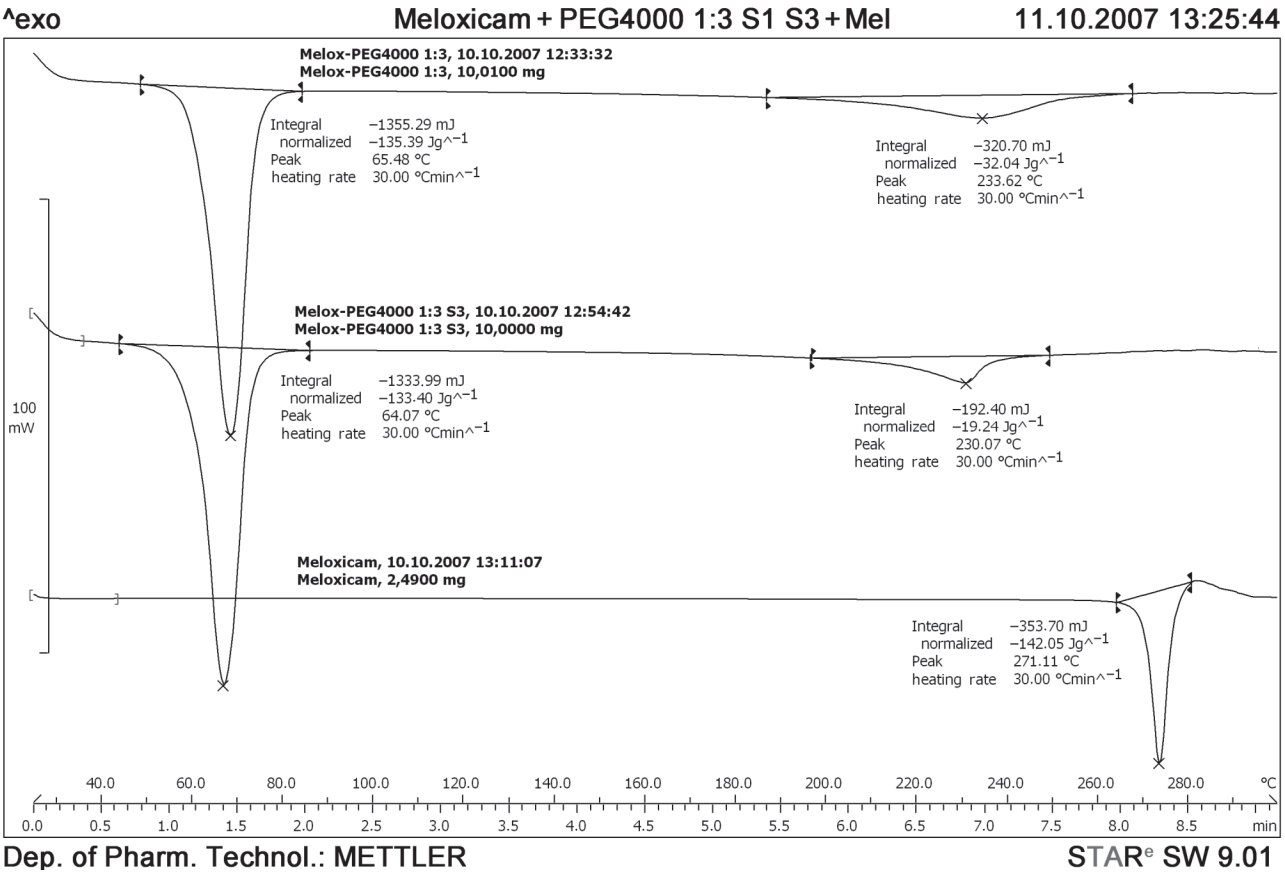

FIGURE 3. Differential scanning calorimetry (DSC) curves of pure meloxicam (ME) (bottom curve), physical mixture (S1, upper curve), and round particles formulated by the dropping method (S3, middle curve).

XRPD was used to investigate the starting materials ME, PEG 4000a (untreated and commercial), and PEG 4000b (melted and solidified) and also the sample formulated by the dropping method (S3) and the physical mixture (S1) (Figure 4). Visual inspection did not reveal any significant difference in crystal structure, that is, the diffractograms of the physical mixture and the particles formulated by the dropping method seemed to be very similar. The diffractograms of S1 and S3 displayed the characteristic values of the starting materials. It is clear that, in the case of S3, the crystals of ME that dissolved in the melted PEG 4000 recrystallized during cooling. The round particles contained the recrystallized ME in suspended form. Consequently, the XRPD studies demonstrated the stable crystalline form of ME in S3 and the absence of any well-defined ME–PEG 4000 interaction.

The question arose of whether the fast and quantitative dissolution of ME from S3 can be explained only in terms of the melt technology and/or the homogeneous distribution of ME in the solid dispersion. To investigate this we used a chemometric method, SMCR, to evaluate XRPD data. The Borgen plot (Figure 5) of the transformed diffractograms revealed that points 1 and 2 of the inner polygon are very close to each other because they are the transformed parallel diffractograms of PEG 4000a and PEG 4000b. Points 3 (S1) and 4 (S3) are farther from each other, which means that the dissimilarity is larger than that for the two kinds of PEG 4000.

In Figure 6, based on the three components given by the SMCR method, the bands of the diffractograms indicate PEG 4000, ME, and a new crystalline phase in the solid dispersion. The estimated bands for the components of the samples were first calculated via the unconstrained SMCR method. Constraints can be applied to make bands as narrow as possible. The ME content in the PEG 4000 sample is zero or near zero, the PEG 4000 content in the ME sample is zero, and the new crystalline phase content in the ME and PEG 4000 samples is zero or as little as possible. Figure 7 depicts the estimated bands given by using these constraints. It can be concluded that the content of the new crystalline phase is smaller in the physical mixture, whereas both the PEG 4000 and the ME contents are decreased in the round particles formulated by the dropping method, and additionally the content of the new crystalline phase in the solid dispersion is increased. The explanation may be as follows. The SMCR calculation indicated a small amount of the new crystalline phase in the physical mixture (S1). This

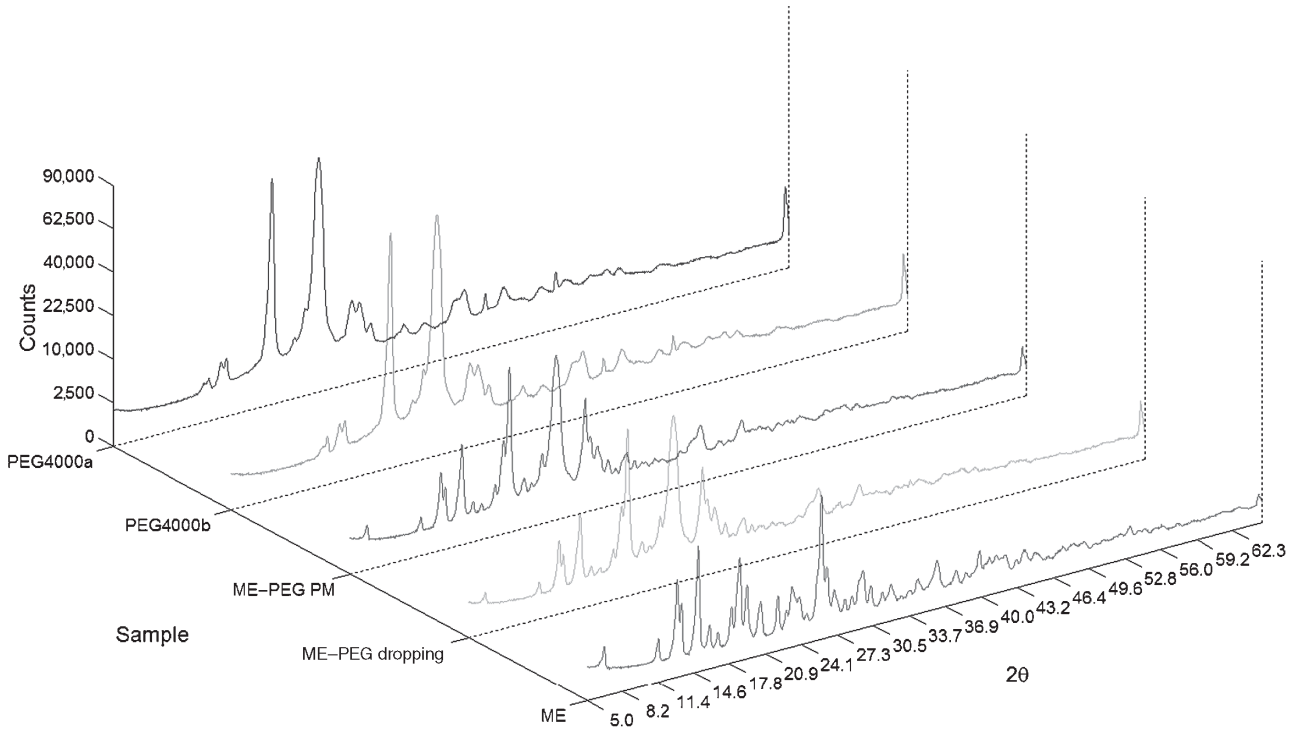

FIGURE 4. X-ray powder diffraction. Starting materials, ME (pure), PEG 4000a (untreated and commercial), and PEG 4000b (melted and solidified). Samples, S1—physical mixture (ME–PEG PM), S3—round particle (ME–PEG dropping).

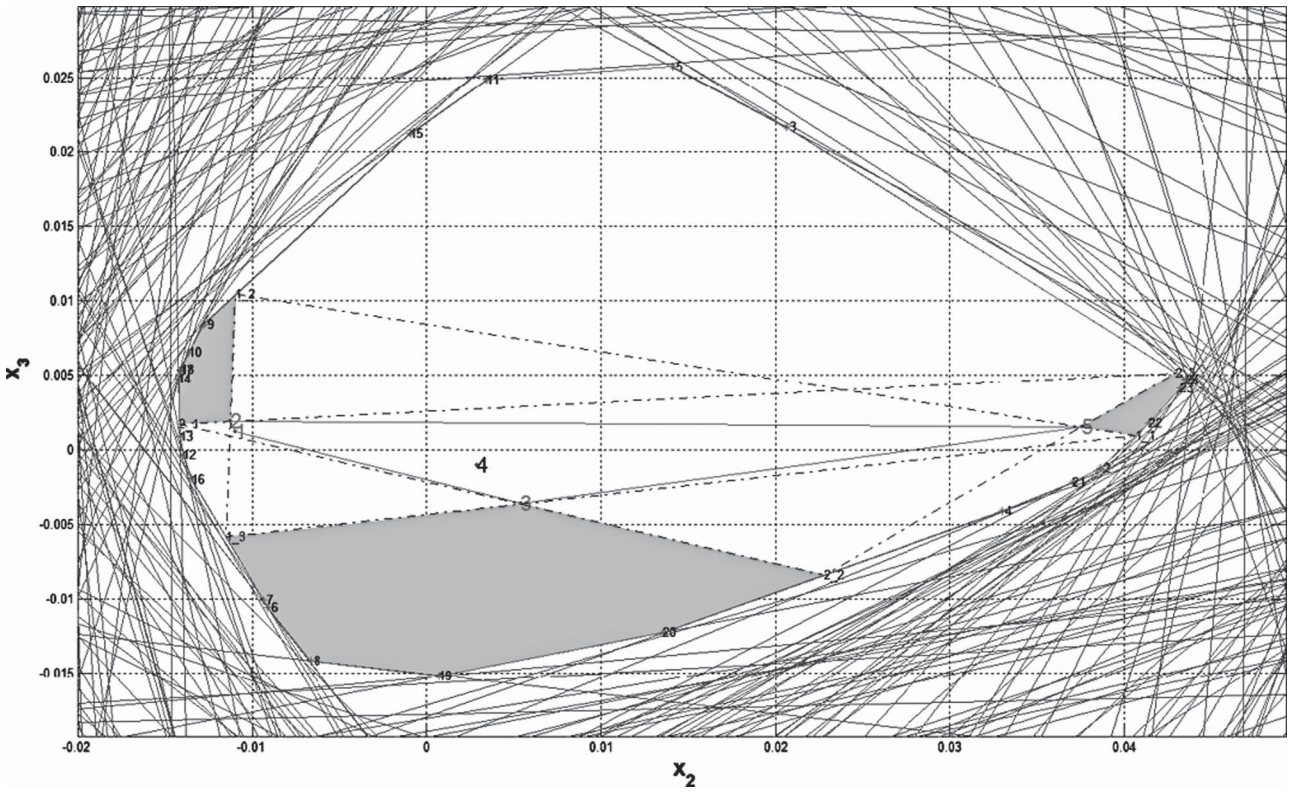

FIGURE 5. Borgen plot of the transformed diffractograms. There are five points in or on the inner polygon according to the five samples shown in Figure 4.

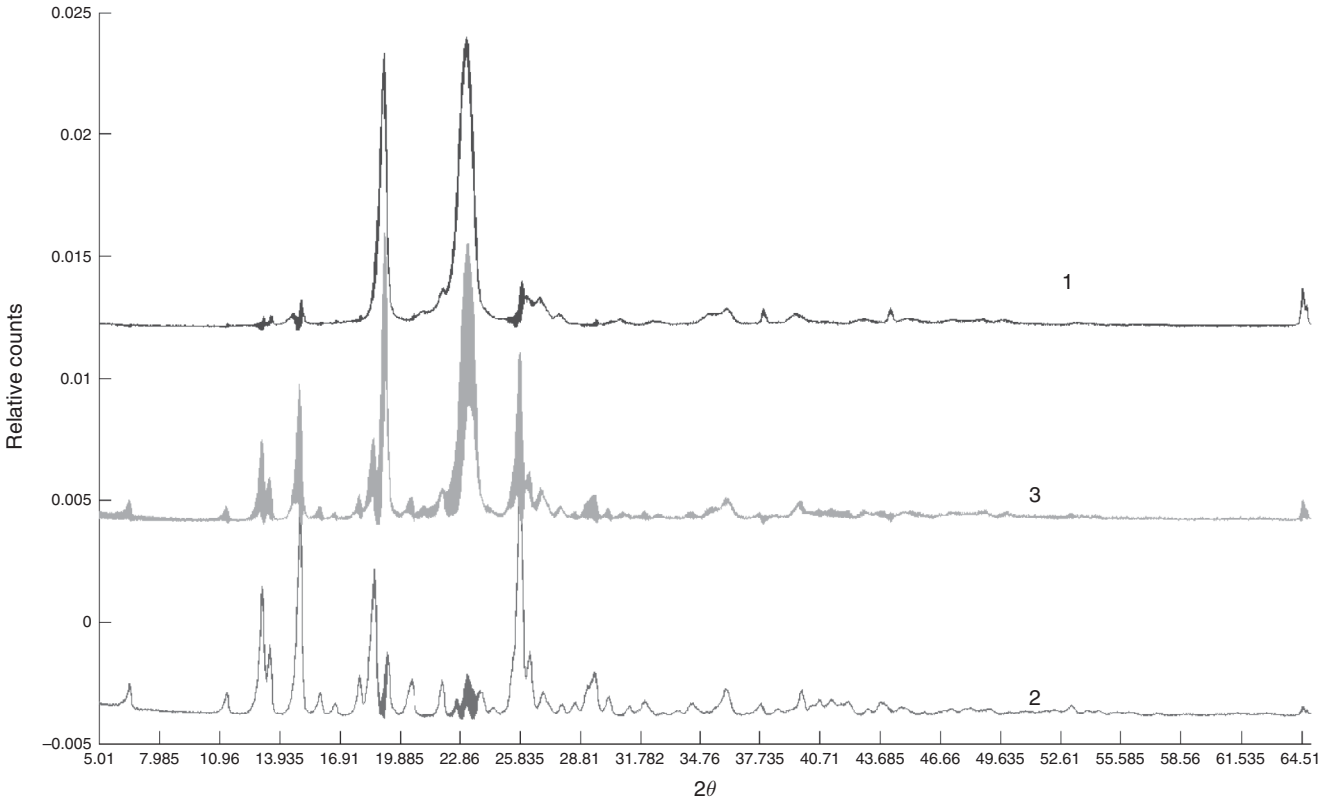

FIGURE 6. Diffractograms of the three components given by the self-modeling curve resolution (SMCR) method. Blue band (1), PEG 4000; red band (2), ME; green band (3), new crystalline phase.

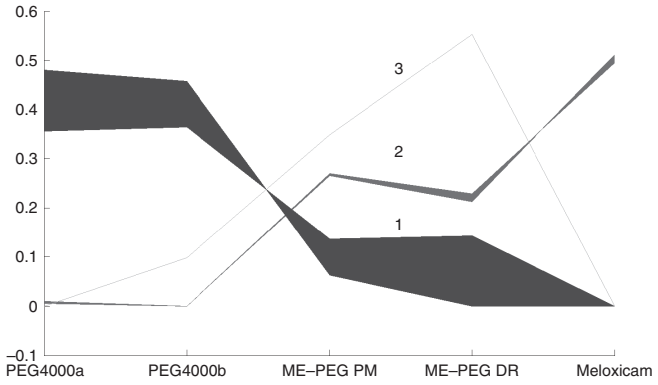

FIGURE 7. Compositions of the samples given by using the self-modeling curve resolution (SMCR) method and the constraints detailed in the text. Blue band (1), PEG 4000; red band (2), ME; green band (3), new crystalline phase.

suggests rearrangement of ME and PEG 4000 in the binary system because of the mechanical effects (mixing, friction, and heat). The melt technology naturally results in a greater change in the structure of the binary system, with the interaction between ME and PEG 4000. This is connected with the partial dissolution of the ME sample in the melted PEG 4000 (Figure 3, DSC scan) and the fast solidification of the drops. Some of the dissolved ME returns to the original state after solidification (solid dispersion), whereas the remainder of the ME sample, in the form of molecule or molecule-clusters, is incorporated in the macromolecules of PEG 4000. This interaction between ME and PEG 4000 does not give a different appearance to the X-ray diffractogram because of the overlapping of the characteristic values, but the chemometric method demonstrated the presence of the new crystalline phase, which can contain the ME sample in molecularly dispersed form or in molecule-cluster form, which can help in the fast and quantitative dissolution from the solid dispersion of S3.

CONCLUSIONS

It can be concluded that the dropping method is a viable technology that is used to produce solid dispersions of ME in a single step by dropping the melted drug–carrier (PEG 4000) mixture so as to form spherical particles. These round particles can be filled into hard gelatin capsules or used as final dosage form. The dropping method does not involve the use of organic solvents and therefore has none of the problems associated with solvent evaporation. The method also avoids the pulverization, sifting, and compressibility difficulties encountered with other melt methods. Although there is still much work to do in this field (uniformity and stability), the dropping method appears to be a promising procedure for the formulation of

solid dispersion. Simplification of the formulation process may overcome the manufacturing difficulties.

ACKNOWLEDGMENTS

This study was supported by the German Academic Exchange Service and the Hungarian Scholarship Committee (DAAD-MÖB). The authors are grateful to Professor Joachim Ulrich (Martin-Luther-University, Halle-Wittenberg, Germany) for providing facilities.

REFERENCES

Bashiri-Shahroodi, A., Szabó-Révész, P., & Erős, I. (2003). Dropping method solution for formulating solid dispersions. *Pharm. Technol. Eur., 15*, 27–32.

Bloch, D. W., Elegakey, M. A., & Speiser, P. (1983). Spray-dried solid dispersions of hydrochlorothiazide and chlorthalidone in pentaerythritol. *Pharm. Acta Helv., 58*, 14–22.

Borgen, O. S., Davidsen, N., Mingyang, Z., & Øyen, Ø. (1986). The multivariate N-component resolution problem with minimum assumptions. *Microchim. Acta, 2*, 63–73.

Borgen, O. S., & Kowalski, B. R. (1985). An extension of the multivariate component-resolution method to three components. *Anal. Chim. Acta, 174*, 1–26.

Bülau, H. C., & Ulrich, J. (1977). Parameters influencing the properties of drop-formed pastilles. In J. Ulrich (Ed.), *CGOM4* (pp. 123–130). Aachen, Germany: Shaker Verlag.

Chatman, S. M. (1987). The use of bases in SSM formulations. *S.T.P. Pharm., 3*, 575–582.

Chiou, W. L., & Riegelman, S. (1969). Preparation and dissolution characteristics of several fast-release solid dispersions of griseofulvin. *J. Pharm. Sci., 58*, 1505–1509.

Chiou, W. L., & Riegelman, S. (1971). Pharmaceutical applications of solid dispersion systems. *J. Pharm. Sci., 60*, 1281–1302.

Cirri, M., Mura, P., Rabasco, A. M., Ginés, J. M., Moyano, J. R., & Gonzales-Rodriguez, M. L. (2004). Characterization of ibuproxan binary and ternary dispersions with hydrophilic carriers. *Drug Dev. Ind. Pharm., 30*, 65–74.

De Juan, A., & Tauler, R. (2003). Chemometrics applied to unravel multicomponent processes and mixtures—revisiting latest trends in multivariate resolution. *Anal. Chim. Acta, 500*, 195–210.

De Juan, A., Vander Heyden, Y., Tauler, R., & Massart, D. L. (1997). Assessment of new constraints applied to the alternating least squares method. *Anal. Chim. Acta, 346*, 307–318.

Fiala, J. (1980). Powder diffraction analysis of a three-component sample. *Anal. Chem., 52*, 1300–1304.

Flament, M. P., Dupont, G., Leterme, P., Farah, N., & Gayot, A. (2004). Development of 400 μm pellets by extrusion-spheronization: Application with Gelucire 50/02 to produce a "Sprinkle" form. *Drug Dev. Ind. Pharm., 30*, 43–51.

Francois, D., & Jones, B. E. (1978, October). The hard capsule with the soft center (pp. 55–61). *European Capsule Technology Symposium*, Constance.

Goldberg, A. H., Gibaldi, M., & Kanig, J. L. (1966). Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures II. Experimental evaluation of eutectic mixture: Urea-acetaminophen system. *J. Pharm. Sci., 55*, 482–487.

Hassner, T., Ulrich, J., Pallagi, E., & Szabó-Révész, P. (2001). Kugeln ohne Kanten. Einfluss der Oberflaecheneigenschaften auf die Tropfenerstarrung von Schmelzen auf festen Oberflaechen. *Verfahrenstechnik, 35*, 34–39.

Kim, K. H., & Jarowski, C. I. (1977). Surface-tension lowering and dissolution rate of hydrocortisone from solid-solutions of selected normal-acyl esters of cholesterol. *J. Pharm. Sci., 66*, 1536–1540.

Langenbucher, F. (1972). Linearization of dissolution rate curves by Weibull distribution. *J. Pharm. Pharmacol., 24*, 979–981.

Lawton, W. H., & Sylvestre, E. A. (1971). Self modeling curve resolution. *Technometrics, 13*, 617–633.

Malone, M. H., Hochman, H. I., & Nieforth, K. A. (1966). Desoxycholic acid enhancement of orally administered reserpine. *J. Pharm. Sci., 55*, 972–974.

Nassab, P. R., Rajkó, R., & Szabó-Révész, P. (2006). Physicochemical characterization of meloxicam-mannitol binary systems. *J. Pharm. Biomed. Anal., 41*, 1191–1197.

Rajkó, R., & István, K. (2005). Analytical solution for determining feasible regions of self-modeling curve resolution (smcr) method based on computational geometry. *J. Chemom., 19*, 1–16.

Rauwendaal, C. (1986). *Polymer extrusion* (pp. 20–55). New York: Hanser Publishers, München, Wien.

Sekiguchi, K., & Obi, N. (1961). Studies on absorption of eutectic mixture. I. A comparison of the behavior of eutectic mixture of sulfathiazole and that of ordinary sulfathiazole in man. *Chem. Pharm. Bull., 9*, 866–872.

Sekiguchi, K., Obi, N., & Ueda, Y. (1964). Studies on absorption of eutectic mixtures. *Chem. Pharm. Bull., 12*, 134–144.

Sekikawa, H., Fukyda, W., Takada, M., Ohtani, K., Arita, T., & Nakano, M. (1983). Dissolution behavior and gastrointestinal absorption of dicumarol from solid dispersion-systems of dicmarol-polyvinylpyrrolidone and dicumarol-beta-cyclodextrin. *Chem. Pharm. Bull., 31*, 1350–1356.

Serajuddin, A. T. M., Sheen, P. C., Mufson, D., Bernstein, D. F., & Augustine, M. A. (1988). Effect of vehicle amphiphilicity on the dissolution and bioavailability of a poorly water-soluble drug from solid dispersions. *J. Pharm. Sci., 77*, 414–417.

Tachibana, T., & Nakamura, A. (1965). A method for preparing an aqueous colloidal dispersion of organic materials by using water-soluble polymers–dispersion of beta-carotene by polyvinylpyrrolidone. *Kolloid-Z Polym., 203*, 130–133.

Takayama, K., Nambu, N., & Nagai, T. (1982). Pharmaceutical interactions in dosage forms and processing. 28. Factors affecting the dissolution of ketoprofen from solid dispersions in various water-soluble polymers. *Chem. Pharm. Bull., 30*, 3013–3016.

Tauler, R. (1995). Multivariate curve resolution applied to second order data. *Chemom. Intell. Lab. Syst., 30*, 133–146.

Tauler, R. (2001). Calculation of maximum and minimum band boundaries of feasible solutions for species profiles obtained by multivariate curve resolution. *J. Chemom., 15*, 627–646.

Tauler, R., Casassas, E., & Izquierdo-Ridorsa, A. (1991). Self-modeling curve resolution in studies of spectrometric titrations of multi-equilibria systems by factor-analysis. *Anal. Chim. Acta, 248*, 447–458.

Tauler, R., Smilde, A., & Kowalski, B. R. (1995). Selectivity, local rank, 3-way data-analysis and ambiguity in multivariate curve resolution. *J. Chemom., 9*, 31–58.

Van Benthem, M. H., Keenan, M. R., & Haaland, D. M. (2002). Application of equality constraints on variables during alternating least squares procedures. *J. Chemom, 16*, 613–622.