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Role of Additives like Polymers and Surfactants in the Crystallization of Mebendazole

Smiti KUMAR, Garima CHAWLA, and Arvind K. BANSAL*

Department of Pharmaceutical Technology (Formulations), National Institute of Pharmaceutical Education and Research (NIPER), Sector 67, Phase X, S.A.S. Nagar, Punjab–160062, India

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Crystallization in the presence of additives like surfactants and polymers is a relatively less explored area but is important for polymorphic screening of a compound during its developmental stage. Surfactants and polymers act by various mechanisms to influence either the growth or the nucleation phase, resulting in modification of either the polymorphic form or the crystal habit. The present study was aimed at understanding the crystallization behavior of the model drug mebendazole (MBZ) in the presence of an inert polymer polyvinyl pyrrolidone (PVP) and an anionic surfactant sodium lauryl sulphate (SLS). Crystals were generated by the antisolvent approach using the surfactant and polymer solutions in water as the antisolvents. Change in habit from needles to plates took place as a result of modification of the crystallization process in the presence of additive molecules. This was confirmed by quantification of these additives using specific analytical methods, which revealed their presence in small amounts in the final product (0.02, 0.15, and 0.24% w/w SLS in crystals generated using 0.5, 1.0, and 2.0% SLS, respectively, and 0.94, and 1.24% w/w PVP K30 and PVP K90, respectively). Their presence in the crystals led to modification in the dissolution of the drug. SLS improved the extent of dissolution while PVP had a negative impact and led to reduction in the amount of MBZ released even below that of the pure drug. The study highlights the influence of polymeric and surfactant additives on the crystallization process leading to modified performance.

Key words——crystallization; polymer; surfactant; crystal habit; mebendazole; dissolution

INTRODUCTION

Crystallization is one of the most difficult unit operations and involves a complex process of molecular aggregation, which has been described as ''stochastic''. The generation of a final crystal involves a delicate balance between the various thermodynamic, kinetic, and process parameters. Crystals could be generated employing any of the available techniques, sublimation, solvent evaporation, vapor diffusion, thermal treatment, crystallization from the melt, precipitation by change in pH, growth in the presence of additives, or grinding.[1] A number of factors influence the crystallization process, like the nature of solvent, rate and extent of supersaturation, heating/cooling rates, stirring rate, and presence of additives.[2] The use of tailor-made additives to influence crystallization is relatively recent and less explored. Additives suitable for controlling crystal shapes do so by virtue of their structural relationships with the crystal surfaces in question and are of different types: low molecular-weight inorganic compounds, low molecular-weight organic compounds, or substances similar in structure to crystallizing solute. In addition, polymeric materials and surface-active agents, which are not similar in structure to the crystal surface, can also influence molecular aggregation during crystallization.[3] Nucleation has been reported to be significantly affected by the viscosity of the medium provided by the polymers, surface tension reduced by surfactants, and supersaturation created by the replacing solvent.[4] Crystallization in the presence of such additives has been carried out to modulate processability and bioavailability (BA) (Table 1).

The present study was aimed at understanding the crystallization behavior of mebendazole (MBZ), a water-insoluble antihelminthic drug, in the presence of an inert polymer polyvinyl pyrrolidone (PVP) and an anionic surfactant sodium lauryl sulphate (SLS). The solvent-change or anti-solvent approach was used, and the role of concentration and grade of additives was studied in the recrystallized product. The generated crystals were characterized for polymorphic or habit modification using a multitude of analytical techniques. Limited studies have discussed the effects of such additives on the crystallization process; however none of them quantified the amount of sur-

*e-mail: akbansal@niper.ac.in

Table 1. List of Drugs for Which Crystallization Has Been Carried Out in the Presence of Polymers and/or Surfactants

Drug	Polymer	Surfactant	Effect on solid form generated	Reference
Celecoxib	HPMC	Polysorbate 80	Form IV formed with improved dissolution, and BA	10
Chlorpropamide	PEG, PVP	Polysorbate 80	Size reduction	21
			Enhanced dissolution	
Hydrocortisone acetate	HPMC, PVP, MC, PEG400	—	Habit change in presence of cellulosic polymers, Nucleation delayed	11
RS-8359, MAO inhibitor	HPMC, HPC, PVP	—	Inhibitory effect on crystallization	22
Carbamazepine	PEG 6000	—	Physical, solid dispersed, and eutectic mixtures	23
Diflunisal	PEG 4000	—	Solid dispersions Drug : polymer : 2 : 1=form I	24
			1 : 1=form III	
Ibuprofen	Eudragit (methacrylate polymer)	—	Spherical crystal agglomeration	25
			Particle size reduction	
			Increase in sphericity, surface roughness, interparticle porosity	
Ibuprofen	—	Surfactants (with PEG chain)	Well-formed plates with triangular tops	26
		Surfactants (without PEG chain)	Agglomerated plates	
		Hydrophilic additives	Inc. flowability, improved handling and dissolution	
Sulfathiazole	—	Aqueous surfactant solutions (Polysorbate 80)	Enhanced dissolution	27
Prednisone				
Chloramphenicol				
Ethyl p-hydroxy benzoate	—	Poloxamer 188	Habit change	28
			Size reduction	
β-Sitosterol	—	Polysorbate 80	Flaky, small-sized crystals	29

BA, bioavailability; Inc., Increased.

factant (s) or polymer (s) remaining on the generated crystals. Therefore a key focus of this study was to study the effects of these additives on the crystallization process and additionally the amount of additive (s) present in the generated crystals was quantified to understand their role in the modulation of dissolution behavior.

MATERIALS AND METHODS

Materials Crystalline MBZ (form C) was a gift from Supharma Chem (Gujarat, India). PVP K30 and K90 were gifts from ISP Technologies (Wayne, NJ, USA) and SLS was procured from Qualigens Fine Chemicals (Mumbai, India). Stains-all dye was purchased from Sigma Aldrich (Steinheim, Germany). All other reagents used were either HPLC or AR grade.

Solubility Determination of Drug in Solvents The saturation solubility of MBZ in different solvents (Table 2) was determined using the synthetic method. A known volume of solvent was placed in 5-ml screw-capped glass vials to which incremental addition of solute was carried out until the solution remained clear. The approximate visual solubility of the drug in solvents was determined by noting the weight of drug added to the solvent until complete dissolution.

Crystallization Using the Antisolvent Method Good solvents and antisolvents were identified on the basis of solubility studies (Table 2). A crystallization protocol was developed wherein the drug was dissolved in the good solvent [*N*,*N*-dimethyl acetamide (DMA) and *N*,*N*-dimethyl formamide (DMF)] and stirred at approximately 500 rpm for 10 min. The antisolvent (solution of PVP or SLS in water) was then poured into the drug solution with stirring. The stirring was continued for about 10 min until crystals started precipitating out. The generated crystals were filtered and dried at room temperature. Three different concentrations of SLS, 0.5, 1, and 2% w/v were employed to study the effect of surfactant concentration on crystallization. In case of PVP, the concentra-

Table 2. Solubility Values of MBZ in Different Solvents

Solvent	Approximate solubility values of MBZ (mg/ml)
N,*N*-Dimethyl acetamide (DMA)	20
N,*N*-Dimethyl formamide (DMF)	20
Dimethyl sulpfoxide (DMSO)	25
Ethyl acetate	5
Acetic acid : methanol	5
Methanol	5
Formic acid	35
Formic acid : methanol	10
Formic acid : butanol	10
Formic acid : isopropyl alcohol	10
Water	Practically insoluble
Chloroform	<1
Ether	<1
Ethanol	<1
Carbontetrachloride	<1
Octanol	<5
Toluene	<5
Hexane	<5
Dichloromethane	<5

tion was maintained constant at 5% w/v while two different grades, PVP K30 and PVP K90, were used.

Characterization of Generated Crystals

Microscopy Crystal habit was observed at different magnifications both with and without silicone oil under optical and polarized light using a Leica DMLP polarized light microscope (Leica, Wetzlar, Germany) equipped with IM 50 V1.20 Twain module imaging software (Leica, Germany).

Powder X-ray Diffraction (PXRD) PXRD patterns of the solid forms were recorded at room temperature on a Bruker D8 Advance diffractometer (Karlsruhe, Germany) with Cu Kα radiation (1.54 Å) at 40 kV 40 mA passing through a nickel filter with a divergence slit (0.5°), antiscattering slit (0.5 °), and receiving slit (1 mm). The diffractometer was equipped with a 2θ compensating slit and was calibrated for accuracy of peak positions with silicon pellets. Samples were subjected to PXRD analysis in continuous mode with a step size of 0.01° and step time of 0.5 sec over an angular range of 3 to 40° 2θ. The crystals generated were loaded in a polymethyl methacrylate (PMMA) holder and pressed with a clean glass slide to ensure coplanarity of the powder surface with the surface of the holder. Obtained diffractograms were analyzed with DIFFRAC plus EVA (ver. 9.0) diffraction software.

Quantification of Polymer and Surfactant in Crystals

SLS Quantification The quantification method for SLS with colorimetry using Stains-all dye was adopted from a previously reported study[5] and validated for linearity, precision, accuracy, and inter-and intraday variation as per the ICH guidelines.[6] ''Stains-all'' stock solution (1.8 mM) was prepared and further diluted with formamide and deionized water to prepare Stains-all intermediate solution (this solution is stable for 3 days when stored in the dark at 4℃), which was used for standard curve preparation and sample analysis.

Preparation of Calibration Curve Different concentrations of SLS (0.01–0.2% w/v) were prepared from the stock solution of SLS using water as the diluent. One hundred microliters of these solutions was placed in different test tubes and 20 ml of Stains-all intermediate solution was added to each. The color of Stains-all dye changes from fuschia to yellow in the presence of SLS. The absorbance scan was taken in the range of 400–750 nm and readings were measured at 438 nm.

Analysis of SLS in Crystals An accurately weighed amount (5 mg) of crystals was dispersed in 5 ml of water and filtered. One hundred microliters of the filtrate was mixed with 20 ml of Stains-all intermediate solution and the absorbance of the solution measured at 438 nm. The concentration of SLS was determined using the calibration curve.

PVP Quantification For the determination of PVP, the HPLC method previously developed by the authors[7] was adopted using an Ultrahydrogel column and UV detector. The method was validated as per the ICH guidelines[6] by determining linearity, range accuracy, and precision.

***In vitro* Dissolution Studies** Dissolution studies were carried out using the USP type II paddle apparatus at 75 rpm. The dissolution media used was 0.1 N HCl, without SLS, to improve the discriminatory power of the test.[8] The powder dissolution for 2 h at 37 ℃ was carried out for pure MBZ, crystals generated using different concentrations of SLS, different grades of PVP, and the physical mixtures of drug and additives (concentration ratio used as quantified). The samples withdrawn at regular intervals were analyzed after appropriate dilution using a UV spectrophotometer (Beckman DU 6401, USA) at 245 nm.

The differences between the amount of drug released in the case of pure MBZ and that of generated crystals were analyzed statistically.

Statistical Analysis Statistical analysis was performed to assess the difference in the amount of drug released from pure MBZ and generated crystals. The percentage of drug released with time was the quantitative parameter used for comparison between different crystals in Kruskal-Wallis one-way analysis of variance on ranks (SigmaStat version 2.03; Systat Software Inc., CA, USA). A significance level of $p < 0.05$ denoted significance in all cases.

RESULTS AND DISCUSSION

Solubility Determination of Drug in Solvents The solubility of an active pharmaceutical ingredient in solvents and solvent mixtures has a considerable influence on the choice of solvents and the course of operation in solvent-based processes such as crystallization.[9] Therefore solubility studies were performed to determine the saturation solubility of MBZ in different solvents to be selected for recrystallization. For a solvent to be used for recrystallization purposes, the solubility of the solute should be on the order of 5–200 mg/ml at room temperature.[1] It was found that MBZ was practically insoluble in most of the commonly used solvents, and thus the choice of crystallizing solvents was very limited. As can be seen from Table 3, the drug showed a solubility of 20 mg/ml in DMA, DMF, and dimethyl sulphoxide (DMSO) at 25 ℃, while in mixtures of formic acid with butanol or isopropyl alcohol (IPA), it showed a solubility of 10 mg/ml. In other solvents like methanol, ethyl acetate, and acetic acid, the values were less than or equal to 5 mg/ml. It was almost insoluble in water, ethanol, ether, chloroform, and mineral acids. Therefore, for crystallization in presence of additives using the antisolvent approach, DMA and DMF were mainly used as good solvents while aqueous solutions of SLS and PVP were used as antisolvents.

Table 3. Average Particle Size Range (microns) for Crystals Generated in the Presence of SLS

Sample	Maximum number of particles in size range (μm)
MBZ	5–10
MBZ DMA SLS 0.5%	5–10
MBZ DMA SLS 1.0%	2.5–6.0
MBZ DMA SLS 2.0%	0.2–2.0

Characterization

Microscopy The morphologic features of various crystals generated in the presence of additives were visually examined using light microscopy. Stable, pharmaceutically useful MBZ occurs as fine micronized needles, while the recrystallized product using different additives had different external appearances (Fig. 1).

Particle size of pure MBZ was in the range of 1.5–13.0 μm when observed under the microscope in presence of silicone oil and the maximum number of particles were in the range of 5–10 μm. Birefringence was observed under polarized light. Crystallization in the presence of SLS led to a change in habit from needles to plates and rods. Also an increase in the concentration of the surfactant led to a reduction in crystal size. Table 3 shows the average range of particle size for crystals generated using various concentrations of surfactants.

The crystals generated in the presence of PVP were very fine and in the range of 1–2 μm. This may be because polymers create or prolong supersaturation and increase the viscosity of the medium for controlling crystallization.[10] Reported studies have suggested that adsorption of polymers on the surface of nuclei leads to the formation of a diffusional boundary layer, which inhibits nucleation and growth, resulting in finer crystal yield.[11]

Crystal morphology plays a valuable role in pharmaceutical processing and product development of solid dosage forms.[12] Differences in crystal habit may strongly influence the particle orientation and modify the flowability, packing, compaction, compressibility, and dissolution characteristics of a drug powder.[13]

Powder X-Ray Diffraction PXRD is an authentic and fool-proof method for determining the crystallinity and identification of a polymorphic form of a substance. The X-ray diffraction pattern of a solid form is characteristic and gives direct information about the molecular arrangement within the crystal.[14] Form C of MBZ is characterized by distinct 2θ values at 5, 12, 16, 20, 22, 25, and 29° 2θ.[8] As can be seen in Fig. 2, crystals generated in the presence of both SLS and PVP retained the same polymorphic form, thus suggesting that additives led to only a change in crystal habit rather than polymorphic trans-

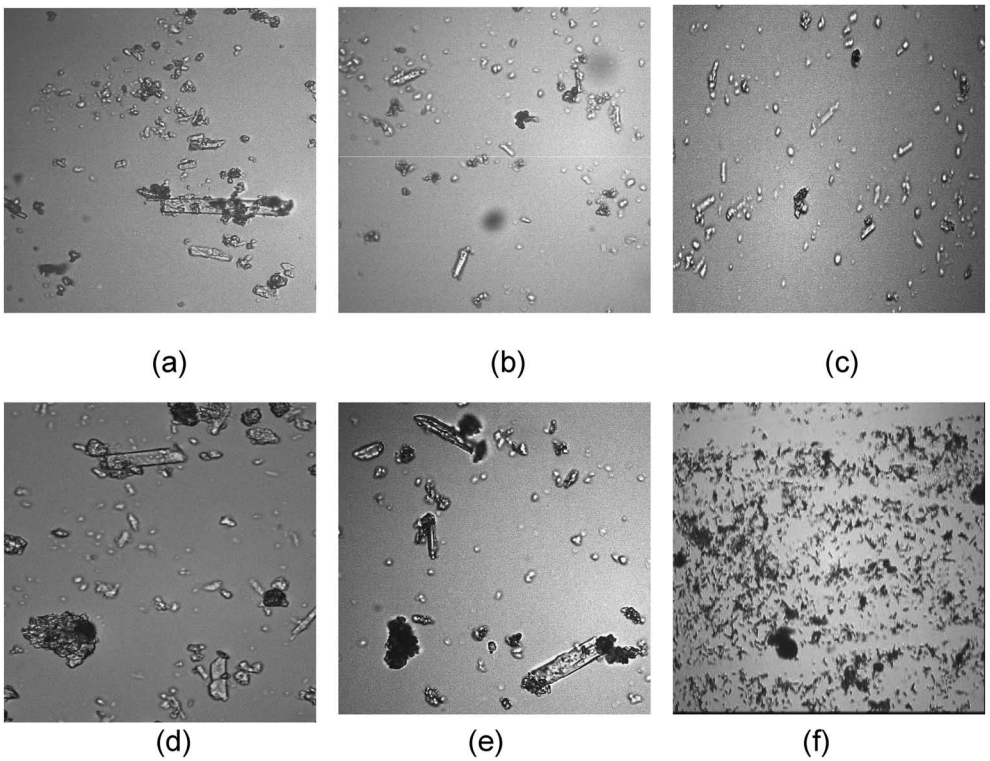

Fig. 1. Photomicrographs (×630) of Crystals

Generated in the presence of (a) 0.5% SLS, (b) 1.0% SLS, (c) 2.0% SLS, (d) 5% PVP K30, (e) 5% PVP K90, (f) untreated MBZ (a, d, and e are zoomed photomicrographs to depict the habit clearly).

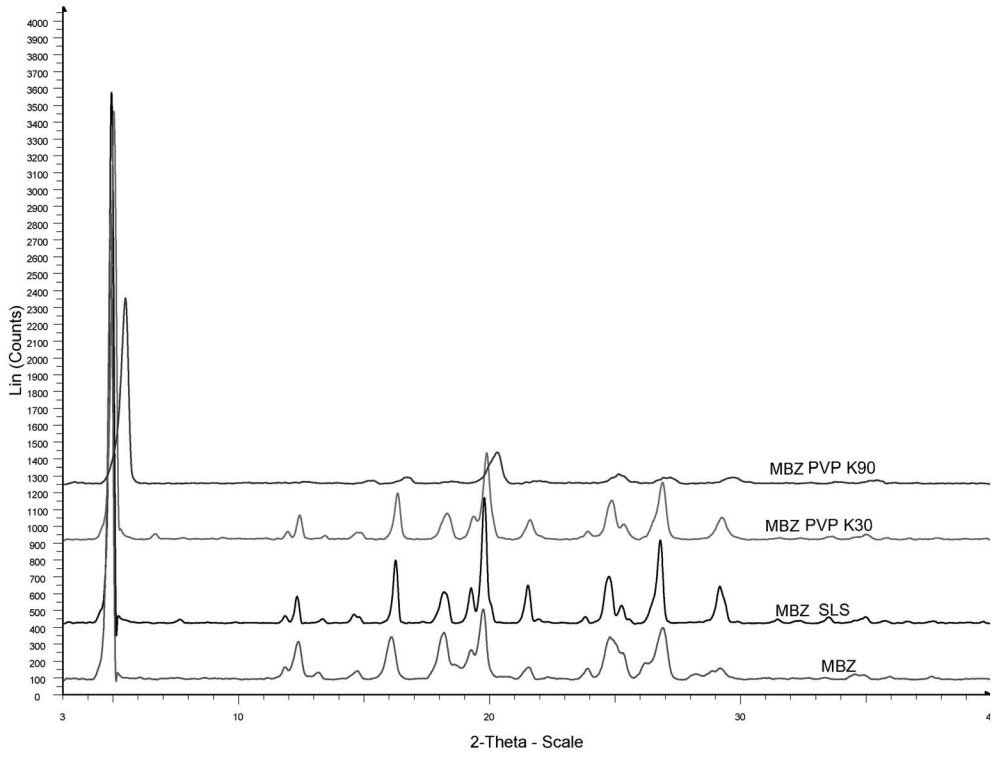

Fig. 2. PXRD Patterns of Crystals Generated Using SLS and PVP

formation.

A shift in peaks was observed in the case of crystals generated in the presence of PVP K90. It was previously reported that lattice distortions brought about by deformation of the crystals (crystal defects) affect peak positions in the powder diffraction pattern.[15] Hence the presence of PVP in the crystals might have led to either changes in the d_{hkl}-spacing or the loss in periodicity in the crystals, resulting in the observed shifts.

Quantification of Additives

Quantification of PVP A calibration curve was generated using standard solutions of PVP K30 and K90. In the case of PVP K30, linearity was found in the range of 10–80 μg/ml with $R^2=0.9728$, while for PVP K90, $R^2=0.9993$ was obtained in the range of 25–250 μg/ml. The HPLC method used was validated and the precision was found to be $<2\%$ RSD. It was assumed that some of the additive used during crystallization would be retained in the recrystallized product. PXRD patterns identical to MBZ for crystals generated using SLS and PVP K30 suggested that these additives are not within the crystal lattice but only adsorbed on the surface. However, in the case of product recrystallized from PVP K90, a shift in diffraction peaks was observed, indicative of lattice distortions brought about by the additive. It is expected that even a small concentration of additive whether within or on the crystal surface can influence the *in vitro* dissolution. The concentration of PVP present in the crystals was determined from the calibration curves. Polymer grade (different molecular weight and viscosity) did not have any effect on the residual amount in the crystals. The presence of polymer during crystallization might have altered the crystal growth and nucleation process, thereby modifying the habit. This residual amount in the final crystals may also have an influence on the dissolution of the drug.

Quantification of SLS A colorimetric method using Stains-all dye was employed for the determination of SLS present in the crystals. The method was validated and was found to be precise with RSD$<2\%$. The calibration curve depicted linearity ($R^2=0.9965$) within a range of 0.01–0.2% w/v SLS. The method was selective for SLS, without any interference from the drug. The amount of SLS retained on the crystals generated using different initial concentrations of the surfactant, *i.e.* 0.5, 1, and 2% was found to be 0.02, 0.15, and 0.24%, respectively. Although the amount of SLS remaining in the crystals increased with the use of increasing initial concentration of the surfactant during crystallization, the increase was not linear. To understand the effects of this residual amount of surfactant in the crystals, dissolution studies were performed.

***In vitro* Dissolution Studies** To assess the differences (in terms of dissolution) between pure MBZ and the generated crystals, 0.1 N HCl was chosen as a discriminatory dissolution medium. USP 24 describes 0.1 N hydrochloric acid containing 1% SLS as the dissolution medium for MBZ. Reports have shown that high concentration of SLS in the USP dissolution medium does not allow the use of this test to distinguish between the solubility differences of the three MBZ polymorphs.[8] The most discriminating medium, therefore, was 0.1 N HCl, containing no SLS. The untreated drug showed a release of 67.32% in 2 h. When crystallized in the presence of SLS, the crystals showed an increase in the amount of drug released at the end of 2 h (Fig. 3). The increased extent of dissolution was not proportional to the increase in concentration of the surfactant, although in all cases the values were significantly better than that of pure MBZ. On statistical treatment of data, the values of drug released from crystals prepared with DMA and different concentrations of SLS failed in the normality test; hence Kruskal-Wallis one way analysis of variance on ranks was applied. There was a statistically significant difference ($p<0.05$) between the amount released from crystals prepared in the presence of 0.5 and 2% SLS and between 1 and 2% SLS, as the differences in the median values among the treatment groups were greater than would be ex-

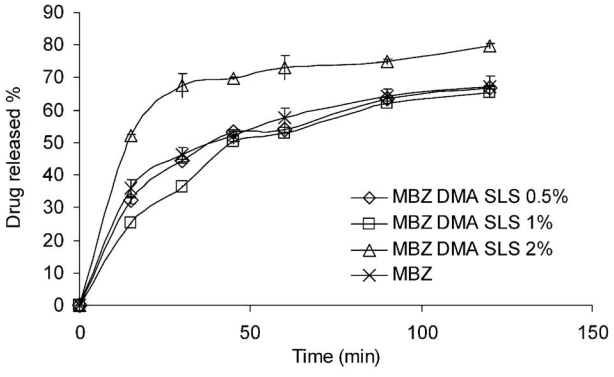

Fig. 3. Dissolution Profiles of Crystals
Generated in the presence of SLS 0.5, 1.0, and 2.0% compared with untreated MBZ.

pected by chance.

To assess the role of surfactant in the modification of the crystallization process, the dissolution of a control, *i.e.*, physical mixture of the drug with the quantified amount of SLS in the crystals, was carried out. Mathematical comparisons between the drug release profiles were made using the concept of similarity factor (f_2) calculated as below.[16]

$$f_2 = 50 \times \log \left\{ \left[1 + \left(\frac{1}{n} \right) \sum_{t=1}^{n} |R_t - T_t|^2 \right]^{-0.5} \times 100 \right\}$$

where n is the sample number and R_t and T_t are the percentages of the reference (crystallized product) and test (physical mixture) drug release, respectively, at different time intervals t. This similarity factor (f_2) is a logarithmic reciprocal square root transformation of the sum of the squared error and is a measurement of the similarity in the percent dissolution between the two curves. f_2 values greater than 50 (50–100) ensure the sameness or equivalence of the two curves. This factor is endorsed by the FDA as the acceptable and preferred method for dissolution profile comparison. The main advantages of the f_2 equation are that it is easy to compute and provides a single number to describe the comparison of dissolution profile data.[17]

The f_2 values of the crystals produced using SLS 0.5 % (f_2=47.4), SLS 1% (f_2=50.7), and SLS 2% (f_2 =41.1) confirmed the difference in the dissolution profiles of these crystals compared to their physical mixtures with MBZ. In all the three cases (different ratios of SLS and MBZ), the dissolution was less compared with the crystallized product (Fig. 4), but higher than that of untreated MBZ.

This may be attributed to the tendency of the surfactants to be adsorbed and slow the growth of hydrophobic surfaces of crystals, thus making the final crystals less hydrophobic.[4] Other probable factors for enhanced dissolution of the crystals generated in the presence of surfactants may be an increase in the crystal defect density within the crystal lattice, leading to thermodynamic instability and therefore faster dissolution. The presence of surfactant might also lead to ease of wetting of crystals by the dissolving solvent. Another possibility could be the formation of a solid solution of water-soluble surfactant in the drug crystal which might also enhance dissolution.[10,18] In comparison, in the case of a physical mixture of MBZ and SLS, the improvement in the amount of drug released is only due to the physically adsorbed surfactant, which promotes wetting of the

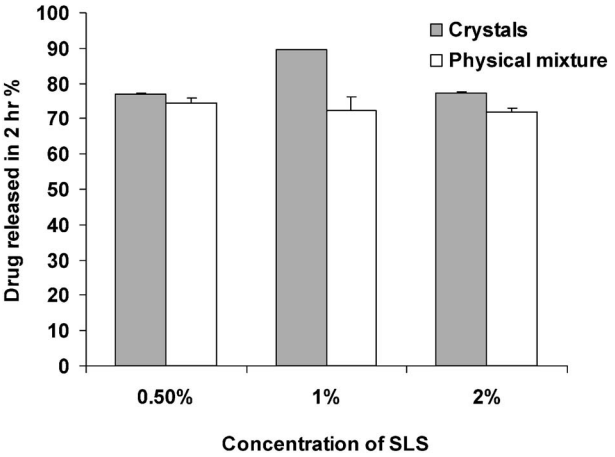

Fig. 4. Effect of Different Concentrations of SLS on Amount of Drug Released from Crystallized Product and Physical Mixtures
error bars show S.D.

poorly water-soluble drug. In this case, the surfactant had no role to play in the habit modification or generation of finer crystals to aid in dissolution.

Dissolution of the crystals generated in the presence of PVP (both K30 and K90) was retarded and values even lower than those of pure MBZ were obtained (Fig. 5). Fig. 6 shows a comparison of the amount of drug released from products crystallized in the presence of PVP K30, K90, and their physical mixtures with MBZ. The f_2 values of the crystals produced using PVP K 30 (f_2=35.7) and PVP K90 (f_2=44.7) confirmed the difference in the dissolution profiles of these crystals compared with their physical mixtures with MBZ.

The decrease in dissolution may be attributed to the increase in the thickness of the diffusion layer (as per Higuchi's model) due to the high viscosity of the polymer.[19] These water-soluble polymers do not show saturation solubility as such, but rather swell and sorb water to produce a continuum of concentration between the solid surface and the bulk medium.[20] Once in solution in the diffusion layer, the viscosity is sufficiently high to render diffusion through the concentrated layer slow, thereby impeding dissolution. When mixed physically, the contact of the polymer with the drug is not as strong compared with the prolonged and closer contact during crystallization, thereby retarding dissolution to slightly lower levels. A similar effect was seen with the use of two different grades of the polymer. These findings are in contrast to those in previously reported

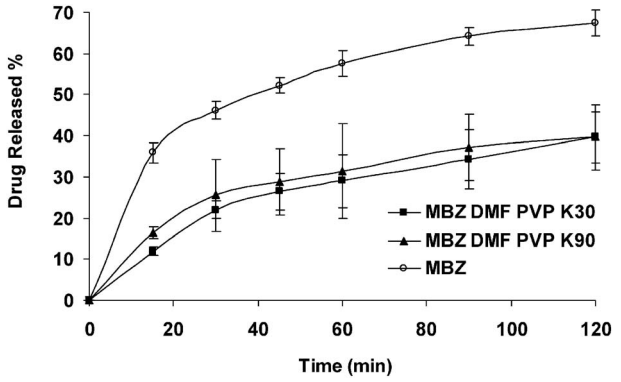

Fig. 5. Dissolution Profile of Crystals
Generated in the presence of PVP K30 and K90 compared with untreated MBZ.

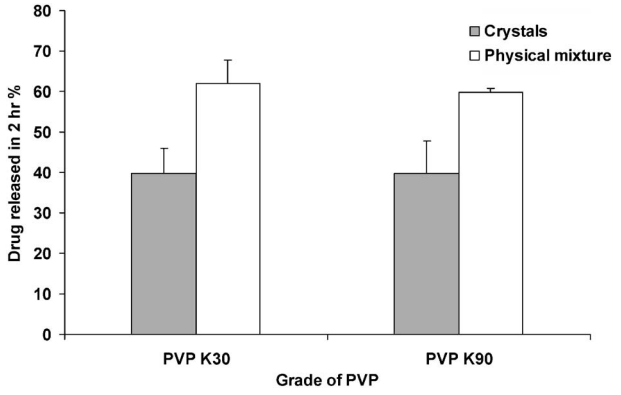

Fig. 6. Effect of Different Grades of PVP on Amount of Drug Released from Crystallized Product and Physical Mixtures
error bars show S.D.

studies,[21] wherein PVP was found to improve dissolution and the effect was more pronounced with the use of a higher viscosity grade. However, there have been reports regarding the inhibitory effect of this polymer on crystallization.[18] The reasons for such an effect are attributed to the structural interaction of PVP with the drug molecule, thereby influencing the crystallization process.

CONCLUSION

Crystals generated using the antisolvent approach in the presence of SLS and PVP were isomorphic with form C of MBZ, although they exhibited variable crystal habit and smaller mean particle size. Quantification of the residual amount of additives in the generated crystals led to the conclusion that small amounts of these additives are incorporated in the final crystals that are responsible for the difference in dissolution of the drug. Both categories of additives had a different influence on the crystals generated; SLS improved dissolution while PVP retarded it when compared with the untreated drug. The increase in the concentration of SLS used improved dissolution but did not have a linear effect. Variation in the grade of PVP did not have a significantly different effect on the crystals produced. Therefore no generalizations can be made regarding the influence of such additives on the final product.

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REFERENCES

1) Guillory J. K., ''Polymorphism in Pharmaceutical Solids,'' Marcel Dekker, New York, 1999, pp. 183–226.
2) Brittan H. G., Vippagunta S. R., Grant D. J. W., *Adv. Drug Delev. Rev.*, **48**, 3–26 (2001).
3) Hornedo N. R., ''Encyclopedia of Pharmaceutical Technology,'' Marcel Dekker, New York, 1990, pp. 399–434.
4) Hornedo N. R., *J. Pharm. Sci.*, **88**, 651–660 (1999).
5) Rusconi F., Valton E., Nguyen R., Dufourc E., *Anal. Biochem.*, **295**, 31–37 (2001).
6) ICH ''International Conference on Harmonisation on Technical Requirements for Registration of pharmaceuticals for Human Use. Guideline on Validation of Analytical Procedure: Methodology. Q2B. Step 4 draft.'' International Conference on Harmonisation, Geneva 1997.
7) Dilawar, M. M. N., ''Reverse Engineering of Pharmaceutical Formulations,'' Department of Pharmaceutical Technology (Formulations), M. Pharm, NIPER, Mohali, Punjab, 2005, pp. 30, 46.
8) Swanepoel E., Liebenberg W., Devarakonda B., DE. Villiers M. M., *Pharmazie*, **58**, 117–121 (2003).
9) Lee T., Kuo C. S., Chen Y. H., *Pharm. Tech.*, **30**, 72–90 (2006).

10) Lu G. W., Smith M., Geiger B. M., Pfund W., *J. Pharm. Sci.*, **95**, 305–317 (2006).
11) Raghavan L., Davis A. F., Hadgraft J., *Int. J. Pharm.*, **212**, 213–221 (2001).
12) Chawla G., Gupta P., Thilagavathi R., Chakraborti A. K., Bansal A. K., *Eur. J. Pharm. Sci.*, **20**, 305–317 (2003).
13) Tiwary A. K., *Drug Dev. Ind. Pharm.*, **27**, 699–709 (2001).
14) Chao R. S., Vail K. C., *Pharm. Res.*, **4**, 429–432 (1987).
15) Bandyopadhyay R., Selbo J., Amidon G. E., Hawley M., *J. Pharm Sci.*, **94**, 2520–2530 (2005).
16) US Food and Drug Administration, Guidance for Industry, Dissolution Testing of Immediate Release Solid Oral Dosage Forms, Rockville, MD, USA, 1997.
17) Hara T. O., Dunne A., Butler J., Devane J., *J. Pharm. Sci. Tech. Today*, **1**, 214–223 (1998).
18) Sekikawa H., Arita T., *Chem. Pharm. Bull.*, **26**, 118–126 (1978).
19) Corrigan O. I., *Drug Dev. Ind. Pharm.*, **11**, 697–724 (1985).
20) Craig D. Q. M., *Int. J. Pharm.*, **231**, 131–144 (2002).
21) Abd E. B. A., Foda N., Tayel S., Badawi S. S., *Drug Dev. Ind. Pharm.*, **16**, 1649–1660 (1990).
22) Usui F., Kusai A., Nishimura K., Yamamoto K., *Int. J. Pharm.*, **154**, 59–66 (1997).
23) Naima Z., Siro T., Juan-Manuel G. D., Chantal C., René C., Jerome D., *Eur. J. Pharm. Sci.*, **12**, 395–404 (2001).
24) Oharriz M., Goni M. M., Espinosa C. R., Ilarduya M. C. T., Zornoza A., *Eur. J. Pharm. Sci.*, **8**, 127–132 (1999).
25) Rasenack N., *Int. J. Pharm.*, **245**, 9–24 (2002).
26) Lee T., Kuo C. S., Chen Y. H., *Pharm. Tech.*, **30**, 72–90 (2006).
27) Chiou W. L., Athanikar N., *J. Pharm. Sci.*, **65**, 1702–1704 (1976).
28) Mackellar A. J., Newton J. M., Chowdhary B. Z., Orr C. A., *Int. J. Pharm.*, **112**, 65–78 (1994).
29) Nikander A. B., Christiansen L., Yliruusi J., *AAPS Pharm. Sci. Tech.*, **4**, E44 (2003).