



# Solid Solution of a Poorly Soluble Model Drug in a Phase-Separated Polymer Matrix: Melt-Prepared Dispersions Based on POLYOX™ WSR

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# ***Solid Solution of a Poorly Soluble Model Drug in a Phase-Separated Polymer Matrix: Melt-Prepared Dispersions Based on POLYOX™ WSR***

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## **Introduction**

Solid dispersion technologies hold the promise of enhancing bioavailability of poorly water-soluble drugs, yet intrinsically pose significant challenges that can hinder their commercial success. Specifically these include poor stability of blend morphology, difficulty achieving reproducibility of physico-chemical properties upon scale-up, and the necessity for high processing temperatures when melt processing.<sup>1</sup> In general, the source of these multiple challenges is the poor solubility of the drug in the polymer matrix. Therefore, a complete understanding of drug-polymer miscibility in a proposed system is essential to ensuring its success. Here, we report the results of a fundamental study on the capacity for POLYOX™ WSR, polyethylene oxide, a nonionic hydrophilic polymer, to solvate hydrophobic molecules, and a characterization of the resulting stable solid solutions.

## **Experimental Procedures**

### ***Preparation of POLYOX physical blends***

POLYOX WSR N-10 (approximate molecular weight of 100,000 daltons) was obtained from Dow and ketoprofen from Sigma-Aldrich. POLYOX powder (40 g) and ketoprofen powder (10 g) were mixed in a planetary mixer at 30 rpm for 90 seconds. Melt-processed samples were prepared by wet granulating the dry blend with 10% (w/w) distilled water, mixing the blend in a Brabender Plasticorder for 3 minutes at 100°C, and melt pressing in a die. The mixture was pressed at 100°C for 1 minute without pressure, 1 minute at 2000 psi, and was allowed to cool to room temperature under 1500 psi. Tablets were punched out of the resulting plaque.

### ***Transmission Electron Microscopy (TEM)***

Melt-processed samples were cryo-microtomed (faced) at -75°C (Reichert, Leica, Ultracut E with FC4 cryo-station) and protected from moist air. When samples returned to room temperature, they were stained with RuO<sub>4</sub> vapor (from 0.5% aqueous solution) for 25 minutes. Samples were viewed with

transmission electron microscopy (TEM) (Hitachi 500) at 100 kV.

### ***X-Ray Analysis***

Variable temperature x-ray diffraction (XRD) patterns of blends were obtained using a custom-built DSC-XRD (40 kV and 30 mA), utilizing a copper tube source (d=1.540599Å) primary beam germanium monochromator, and linear position sensitive detector with an angular resolution of 0.02°. Range of 2 theta is as indicated in text. Data were analyzed with JADE 6.0 software (MDI, Livermore, CA).

### ***Differential Scanning Calorimetry (DSC)***

Ten milligram samples were weighed into aluminum pans with lids and crimped. A differential scanning calorimeter (DSC) (TA Instruments) was used with liquid nitrogen accessory. Flow rate of He was 25 cm<sup>3</sup>/min.

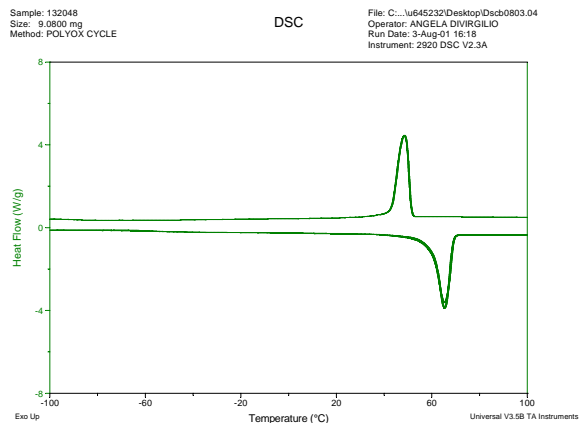
## **Results and Discussion**

Figure 1 shows the DSC for pure POLYOX. Physical blends of POLYOX and ketoprofen (a model poorly water-soluble drug) were analyzed with DSC (Figure 2). Surprisingly, although thermograms of neat ketoprofen are characterized by a strong melting transition at 94°C, the transition was absent in the powder blend. Moreover, a shoulder that precedes the melt transition of POLYOX appeared in thermograms of the physical blends.

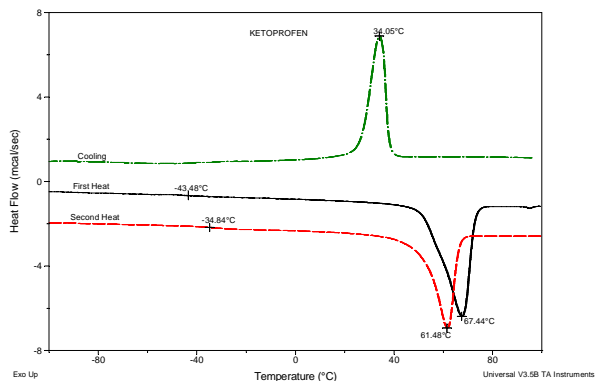
In parallel studies using variable temperature XRD (Figure 3), the ketoprofen peaks (indicated by arrows) lost definition at about 51°C, below the melting point of POLYOX (68°C) and significantly lower than the melting point of neat ketoprofen. This illustrates the dissolution of ketoprofen in the amorphous phase of POLYOX. Moreover, during cooling at a rate of 1°C/min, only POLYOX recrystallized (Figure 4); ketoprofen remained dispersed within the POLYOX. This result indicates the high solubility of ketoprofen in the amorphous fraction of POLYOX and that this high compatibility facilitates the preparation of solid

solutions at low temperatures without requiring surfactants or plasticizers.

**Figure 1. DSC thermogram (first heat) of pure POLYOX powder. Heating rate was 10°C/min.**



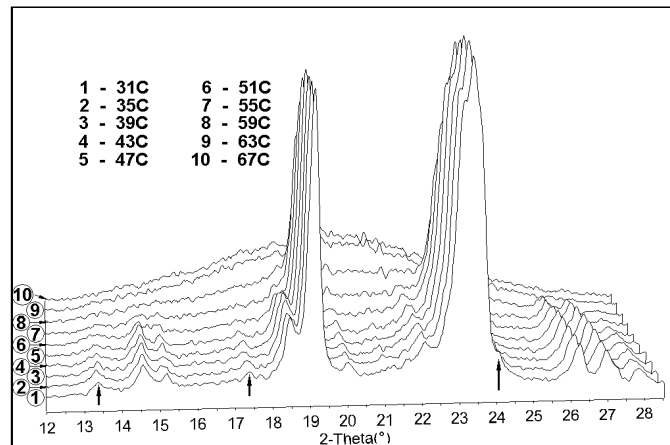
**Figure 2. DSC thermogram of ketoprofen/POLYOX physical powder blends. Heating and cooling rates were 10°C/min.**



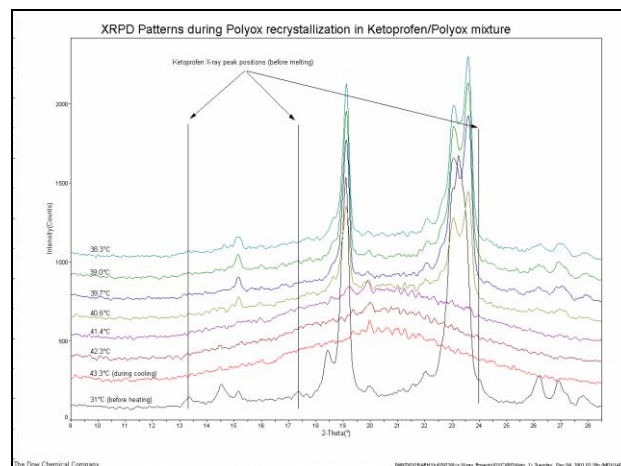
The effect of cooling rate on the morphology of the dispersion was investigated by heating three respective ketoprofen/POLYOX physical blend samples to 100°C and cooling one sample with liquid nitrogen, another in 15°C water, and a third at a controlled rate of 1°C/min. The resulting XRD data indicated that regardless of the cooling rate, the ketoprofen remained dispersed in the POLYOX (Figure 5). This signifies that the thermodynamic drive to form the dispersion is sufficiently strong that rigid process parameters are not required to achieve uniformity of morphology throughout, thus facilitating scale-up.

In addition, the XRD data (Figure 4) indicate that the morphology of the final blend is an amorphous blend of the drug and POLYOX in co-existence with a crystalline phase of POLYOX. TEM micrographs illustrate this phase-separated nature of the POLYOX-based matrix (Figure 6).

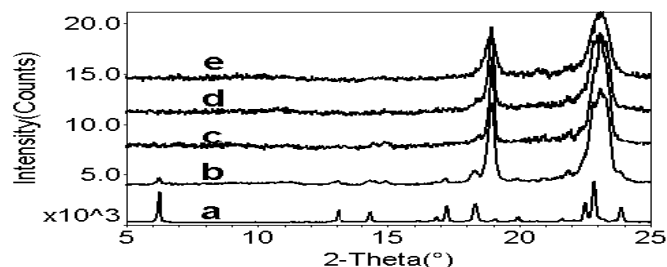
**Figure 3. Variable-temperature XRD (2 theta range from 10°–28°) of ketoprofen/POLYOX physical blends. Arrows identify unique ketoprofen peaks.**



**Figure 4. XRD of physical mixtures at decreasing temperature (1°C/min).**



**Figure 5. XRD of ketoprofen and blends heated, then cooled at different rates. Range of 2 theta is 5°–25°. Note ketoprofen peak at 6°.**

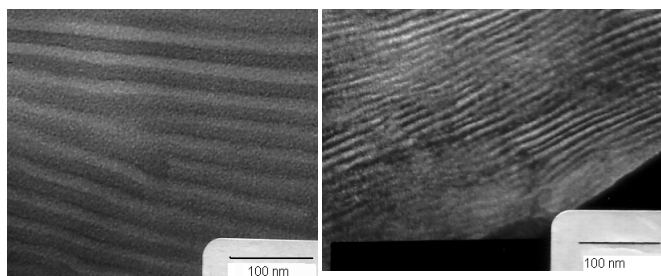


- (a) pure ketoprofen
- (b) ketoprofen/POLYOX physical blend before heating
- (c) physical blend heated and cooled at 1°C/min
- (d) physical blend heated and cooled in 15°C water
- (e) physical blend heated and quenched in liquid N<sub>2</sub>.

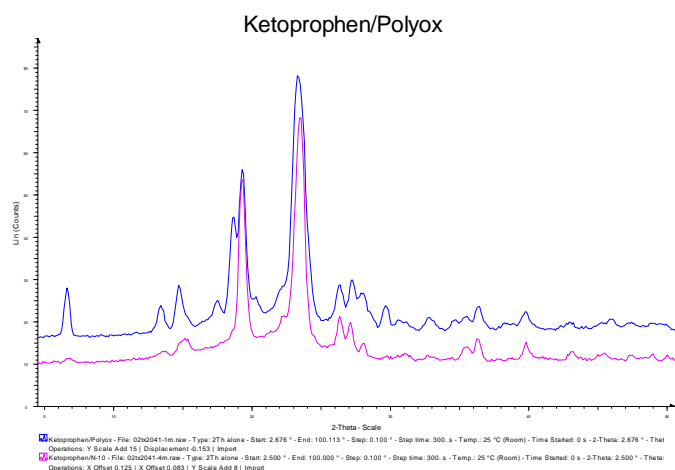
Micrographs of melt blends display a widening of the regions between the crystalline lamellae relative to neat POLYOX, indicating that ketoprofen is dispersed in the amorphous regions of POLYOX that lie between the lamellae. In contrast with solid solutions that are completely glassy in nature and therefore thermodynamically meta-stable, the presence of the crystalline phase of POLYOX serves to stabilize and therefore maintain the morphology of the solid solution.

In fact, POLYOX/ketoprofen melt blends stored for one month at 40°C/75% RH indicated little change in morphology when investigated by XRD (Figure 7). Preliminary DSC studies testing POLYOX for miscibility with other chemical structures were undertaken. Actives included ibuprofen (m.p.=72°C), tolbutamide (m.p.=130°C), sulfathiazole (m.p.=200°C), and hydroflumethazide (m.p.=274°C). Consistently, the strong melting transition of the respective active evident on thermograms of the neat compounds was absent in blend thermograms. This phenomenon suggests that the solvating property of POLYOX is not limited to ketoprofen or ketoprofen-like structures but can be extended to a range of chemical structures (Figure 8).

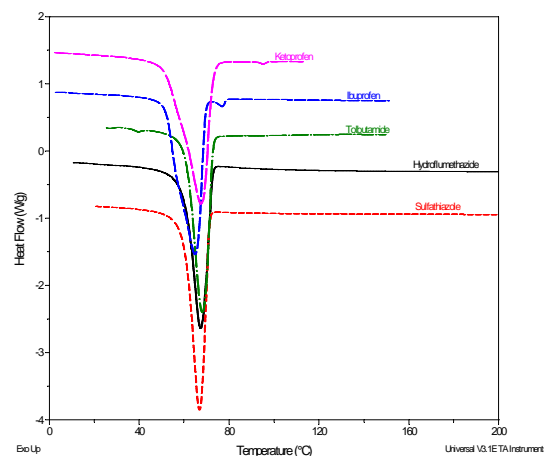
**Figure 6. TEM of neat melt-processed POLYOX (right) and melt-processed blend of ketoprofen and POLYOX (left).**



**Figure 7. XRD data for: (top) ketoprofen physical blend; (bottom) ketoprofen melt blend stored at 40°C/75% RH for one month.**



**Figure 8. DSC of physical mixtures based on POLYOX (10°C/min).**



Active Compound	Melting point (°C)	Active compound chemical structure
Ketoprofen	94	<chem>CC(O)C(=O)c1ccc(cc1)C(=O)c2ccccc2</chem>
Ibuprofen	72	<chem>CC(O)C(=O)c1ccc(cc1)C(C)C</chem>
Tolbutamide	130	<chem>CCCCNC(=O)c1ccc(cc1)C(=O)N</chem>
Sulfathiazole	200	<chem>C1=NC=SC=C1S(=O)(=O)c2ccc(N)cc2</chem>
Hydroflumethazide	273	<chem>C1=NC(=O)N(C1)C(=O)Nc2cc(F)c(S(=O)(=O)N)cc2</chem>

## Conclusions

POLYOX demonstrates a strong capacity to solvate small molecules, easily forming reproducible solid solutions without requiring surfactants, plasticizers, or high processing temperatures. The final morphology of the melt blend includes a crystalline lamellar structure of POLYOX that thermodynamically locks the morphology in place, inhibiting coalescence of drug dispersion during storage.

## References

1. Jachowitz, R., et al., Solid dispersions of ketoprofen in pellets. *Int. J. Pharm.*, 206, 13–21 (2000).

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