HOW SOLVENTS AFFECT THE RATE OF POLYMORPHIC TRANSFORMATION IN POLYMORPH SCREENING

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Abstract:

The most stable polymorph may be efficiently obtained via solvent-mediated polymorphic transformation. Form II's nucleation rate controls the rate of solvent-mediated polymorphic transformation of sulfamerazine at 24°C in different solvents and solvent combinations. In general, a greater solubility is caused by a faster transformation rate in a solvent, and a low solubility by a slower rate (8 mmol/L). Nucleation is prevented in these solvents due to a high interfacial energy, which causes the metastable zone to be broader than the solubility difference between two polymorphs. The solubility is only one factor in deciding the transformation rate; the intensity of the solvent-solute interactions is equally crucial. Sulfamerazine undergoes a slower transition in solvents that are more likely to accept hydrogen bonds. Because a solvent's solubility is proportional to its hydrogen bond acceptor propensity, the rate of polymorphic transformation is a function of both the solute's and the solvent's solubility and the strength of their hydrogen bonding interactions. Temperature and agitation level affect the crystallization kinetics of the stable polymorph, which in turn affects the pace of polymorphic transition. The American Pharmaceutical Association and Wiley-Liss, Inc. published this work in 2001. "Journal of Pharmaceutical Science" 90:1878–1890, 2001

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Introduction:

A chemical may exhibit polymorphism if it can exist in many crystalline forms with various molecular groupings and/or conformations in the crystal lattice.1 Preformulation in pharmaceutical R&D requires the identification, synthesis, and characterization of polymorphs due to the fact that various polymorphs display

substantially varied pharmaceutically important characteristics.2 Since other polymorphs are metastable and might undergo transformation to the more stable form during storage, the more stable polymorphic form is often used in a commercial formulation. Bioavailability alterations, solid dosage form physical instability, precipitation from solutions, and other formulation issues might result from such a phase transition. Products like ritonavir, which undergo phase transition during storage, might fail if the most stable polymorph is overlooked.S

In the field of polymorph screening, recrystallization from various solvents is now among the most used procedures.4 Nevertheless, a metastable polymorph is often acquired initially along this process, as per Ost-wald's rule of stages 5. A streamlined process for identifying the most reliable

Methods of polymorphic transformation mediated by solvents (Scheme 1):

The process of polymorphic transformation mediated by solvents is known as polymorph. Suspending the less stable form in a saturated solution is the method used in this procedure. Because this metastable form has a greater apparent solubility than the more stable form, it will crystallize while the less stable form dissolves (Scheme 1). Not only may solvent-mediated transformation be used to create the more stable polymorph, but it can also be used to compare the relative stability of polymorphs and remove the less stable polymorph from a mixture of polymorphs to guarantee phase purity. Solvents that allow for rapid polymorphic transformation are ideal for these applications. Conversely, solvents that facilitate delayed polymorphic transition are ideal for recrystallization from solutions in order to produce the metastable polymorph. Because the pace of change in various solvents ranges from minutes to years, it is important to choose a solvent that will either speed up or slow down the transformation accordingly. At this time, the solvent Grade for HPLC. The organic solvent was made as dry as possible by including molecular sieves or anhydrous calcium sulfate (Drierite; Hammond, Xenia, OH) into the mixture. Two solvents with known volumes were combined to make the solvent mixes.

Y-Ray Powder Diffractometry (PXRD):

The polymorphs and their polymorphic compositions were identified using a PXRD diffractometer (D5005; Siemens, Ker- many). The samples underwent scanning from 14.5° to 16.5° 2θ with a step size of 0.01° and 2 s per step while

being subjected to Cu K¤ radiation (45 kV and 40 mA). The powder's very tiny particle size (less than 50 µm) made the preferred orientation highly improbable. In order to ascertain the polymorphic composition, the peaks at 16.1° and 15.6° 2θ, which correspond to SMK Form I and Form II, respectively, were selected by a comparison of the integrated peak areas (Figure 1), as mentioned before.7 For a 1:1 blend of Polymorphs I and II, the peak areas of these two distinctive peaks were determined to be equal. Polymorph II could be easily and reliably identified in the presence of Polymorph I since the detection limit was found to be less than 1%. To determine the polymorphic composition,greatest point on thestill requires a lot of time-consuming trial and error. In order to help researchers pick the right solvent to speed up or slow down solvent-mediated polymorphic transformation, this work aims to show what variables control the transformation rate. In

Data and Procedure:

The following materials were sourced from Sigma Co.: SMK (4-amino-N-[4-methyl-2-pyrimidinyl]benze-nesulfonamide) (Lot # 47H0114, purity >99.9%). Recrystallization from isopropyl alcohol (IPA; 2-propanol) was used to produce polymorph I. Form I was suspended in acetonitrile for 20 days to prepare Polymorph II.7,8 The results of the suspension test showed that all of the resulting forms had a perfect phase purity.8 Water, like all other solvents

Transformation Mediated by Solvents in Polymorphism:

51–54°C is the transition temperature for SMK. Although it becomes more stable at higher temperatures, polymorph I is metastable at 24°C. At a temperature of 24°C, Polymorph I was suspended in a presaturated solution. There were 20 milligrams per milliliter of suspended solid in the solvent. At a rate of around S00 strokes per minute, a wrist-action shaker (Model 75; Burrell, Pittsburgh, PA) was used to agitate the suspension. A shaking water bath (BT-47; Yamato Scientific Co., Ltd., Tokyo, Japan) was used to regulate the temperature and agitation level in order to investigate the polymorph I to polymorph II transition at various temperatures and with varying degrees of agitation. At certain intervals, we filtered off a little amount of the liquid and used powder X-ray diffraction to identify the solid phase's polymorphic composition.

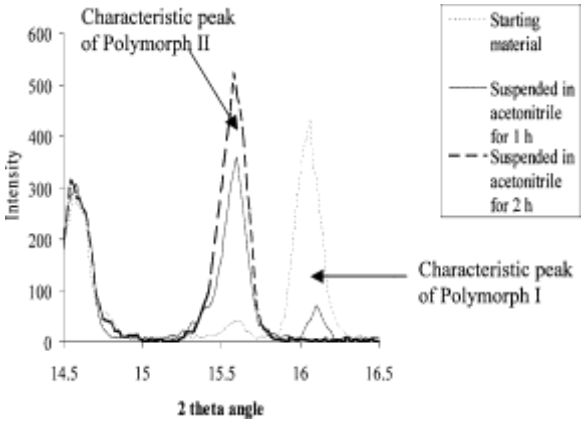

Figure 1.Powder X-ray diffraction patterns of mixtures of sulfamerazine PolyorphsI and II, suspended in acetonitrile after various times. The diffraction peaks used for quantification are shown by arrows

The amount of SMK in the solution was measured at λ = S07 nm using a spectrophotometer (DU 7400; Beckman, Irvine, CA) throughout the transformation process. Using the same method as before to get the polymorphic transformation rate, we geometrically combined 90% Form I and 10% Form II (by geometric dilution) and suspended them in solutions to find the crystal growth rate of Form II. The main nucleation phase of the transition was skipped when 10% Form II seeds were present. Form II, which is more stable in solution, grows at a rate that is proportional to the polymorphic transformation rate.

How Dissolves:

At 24°C, the solubility of SMK Form II was tested in a variety of solvents and solvent combinations. A shaking water bath (BT-47; Yamato Scientific Co., Ltd.) was used to equilibrate a suspension of particles in 10 mL of solvent, which had been previously suspended. The suspension was shaken at 100 strokes/min. Parts of the solution were removed after 7 days, and the solvent was vacuum-evaporated. Aqueous hydrochloric acid solution with a concentration of 0.1 M was used to dissolve the solid residues in a quantitative manner. Following the procedures outlined in "Solvent-Mediated Polymorphic Transformation," the amount of SMK in the solution was ascertained by the use of ultraviolet spectrophotometry.

Rock crystal formation:

The following solvents were used for recrystallization of SMK: water, methanol, 2-propanol (IPA), acetonitrile, a water-acetonitrile combination (1:4, v/v), a water-methanol mixture (1:4, v/v), and tetrohydrofuran (19). The saturated solutions were cooled at a rate of 0.1°C/min after being created at two different temperatures: 62°C and 50°C. We filtered the solution as soon as it got murky, and then we used powder X-ray diffraction (PXRD) to identify the polymorphic form of the crystallized solid.

Visual Analysis via SEM:

An SEM (S-800; Hitachi, Tokyo, Japan) operating at an accelerating voltage of 10 kV was used to examine the shape and size of the particles. A layer of 50 A˚ of platinum was sputter-coated onto the samples.

Computer Programs:

To view the crystal structure of the SMK polymorphs, the program Cerius2 (version S.0; Molecular Simulations Inc., San Diego, CA) was used, which was obtained from the Cambridge Structural Tech Database. Analytical Software Co., Tallahassee, FL's Statistix (version 7), was used for statistical assessments.

Summaries and Analyzes:

Transformation Mediated by Solvents in Polymorphism

Schema 1 shows the three stages of the solvent-mediated transformation: crystal development, dissolution, and nucleation of the more stable polymorph. The pace may be limited at each stage. Figure 2 shows the concentration-time profile of SMK in solution during transformation; this profile can tell us whether the transformation rate is dictated by the dissolution rate or the crystallization rate (which includes nucleation and crystal growth). Until almost 90% of the suspended Form I had converted to Form II, the concentration stayed constant at a value near to its solubility, according to the concentration-time profile. The fact that the dissolving rate of Form I more than made up for the solute loss caused by crystallization of Form II suggests that the crystallization rate of Form II is much slower.10 Similar concentration-time patterns were seen in all of the solvents utilized in this investigation. Soluble form II nucleation and crystal growth rates govern transformation rates in different solvents. The nucleation rate often lags behind the crystal growth rate while crystallization is underway.11 The nucleation rate is lower than the crystal growth rate in all solvents except acetic acid during the polymorphic transition of SMK, as indicated in Table 1.

Rate of Polymorphic Transformation as a Function of Temperature and Agitation Level

Form I to Form II SMK transformations in acetonitrile were used to study the effect of temperature and agitation on the polymorphic transition rate. In Table 2 we can see the findings summarized. Increasing the agitation level from 100 to S00 strokes/min has no effect on the crystal development rate. This finding contradicts the hypothesis that the

	24°C, S00 Stroke /Min	24°C ,100 Stroke /Min	S0°C ,100 Stroke /Min	50° C,10 0 Strok e/Mi n
Relativenucle ationrate	1	0.5	0.0625	0
Relativecrysta lgrowthrate	1	1	0.62	0.17

diffusion rate of solute molecules in acetonitrile regulates crystal growth rate and instead points to the rate of solute molecule integration into developing crystals as the controlling factor.

Table1.Relative Rates of Nucleation and Crystal Krowth for Sulfamerazine Polymorph II in Acetonitrile at Different Temperatures and Degrees of Agitation

solution in bulk.11.4 SS On the other hand, increasing the agitation level speeds up the nucleation rate. An increase in the nucleation rate, as predicted by equation 2, together with an increase in the rate of solute molecule transfer at greater degrees of agitation, would account for this finding. The free energy disparity between two polymorphs changes at various temperatures. A reduction in the modulus of the free energy difference between Polymorph I and II is seen when the temperature rises for SMK below the transition temperature, which is 51–54°C. Consequently, supersaturation is less at 50°C or S0°C compared to 24°C. Nucleation and crystal growth speeds are determined by the degree of supersaturation, even if molecular mobility is greater and interfacial energy is lower at higher temperatures, which may aid in these processes. Consequently, at a higher temperature, S0°C, nucleation and crystal formation are both slowed down compared to below, at 24°C. At 50°C, there isn't enough of a difference in solubility between the two polymorphs to trigger nucleation.

In the End:

When it comes to solvent-mediated polymorphic trans-formation of SMK, the nucleation rate dictates the pace. A combination of solubility and the strength of the solvent-solute contacts, particularly the hydrogen bonding interactions, dictates the pace of transformation. A solvent with high solubility and moderate solvent-solute interactions may be used to suspend the metastable polymorph in order to induce polymorphic transformation and crystallization of the more stable polymorph. To delay polymorphic

transition in solution, a solvent with poor solubility should be used for crystallization of the metastable polymorphs. Polymorph screening might benefit from the qualities offered by solvent combinations. The agitation level and temperature cause changes in the rate of polymorphic transformation in chemicals. Increasing the nucleation rate and making the transition easier can be the result of a change in agitation level. Because of its effect on the free energy difference between polymorphs, temperature mostly determines the degree of supersaturation. A reduction in the degree of super-saturation as a result of a temperature shift slows down crystal growth and nucleation, which in turn slows down the pace of polymorphic transition.

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Conflict of Interest

The Author declares that there is no conflict of interest.

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