NVT Application Note 06-CR

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Investigation of crystal polymorphism using sulfathiazole

Experiment

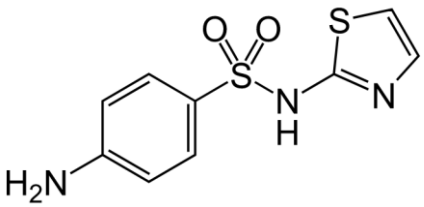
The CrystalBreeder was evaluated using Sulfathiazole as a sample compound known to have five crystal polymorphs. Sulfathiazole and 16 different organic solvents were placed in each vial of CrystalBreeder, suspended, and heated to dissolve the compound completely. After the crystals then precipitated by gradual cooling, the structural polymorphs were analyzed by XPRD.*

*XRPD: X-ray powder diffraction

*Information on sample compounds

Sulfathiazole

CAS No.: 72-14-0
Chemical formula: C9H9N3O2S2
Molecular weight: 255.31
Solubility: 373 μg/mL (25°C)
LogP : 0.05 (DRUGBANK data)



Crystallization: Cooling method (complete dissolution by heating, followed by cooling to crystallize)

Suspend the compound in 16 different organic solvents
↓
Heat to 65°C and dissolve the compound completely
↓
The solution is cooled to 0°C at **-1°C/min** and **-10°C/min** , and the precipitated units are evaluated by XRPD*.

Result 1

In the first time, the product was heated to 65°C with a 30 mg/mL feed concentration and did not dissolve in any of the solvents.
We therefore lowered the feed concentration to 10mg/mL whereupon it dissolved in 6 solvents.

Feed concentration 30 mg/mL
(3 mg/100 μL)
→Insoluble in all solvents at 65°C

Methanol
Ethanol
2-Propanol
1-Butanol
Benzyl alcohol
Acetonitrile
Ethyl acetate
1-Propyl acetate
1-Butyl acetate
Methyl ethyl ketone
Methyl isobutyl ketone
Tetrahydrofuran
1,4-Dioxane
Anisole
Toluene
Chlorobenzene

Feed concentration 10 mg/mL
(1 mg/100 μL)
→Dissolved in 6 solvents at 65°C

Methanol
Ethanol
2-Propanol
1-Butanol
Benzyl alcohol
Acetonitrile
Ethyl acetate
1-Propyl acetate
1-Butyl acetate
Methyl ethyl ketone
Methyl isobutyl ketone
Tetrahydrofuran
1,4-Dioxane
Anisole
Toluene
Chlorobenzene

Result 2

We observed polymorphic precipitation in the 6 solvents at different cooling rates (-1℃/min and -10℃/min) and observed different polymorphs (forms in the table below) and precipitation temperatures in each solvent.

	10mg/mL Dissolution temperature	Precipitation temperature after dissolution (-1℃/min Temperature)	form	Precipitation temperature after dissolution (-10℃/min)	form
Benzyl alcohol	24.8℃	(Still supersaturated at 0℃)	-	(Still supersaturated at 0℃)	-
Methyl ethyl ketone	45.8℃	(Still supersaturated at 0℃)	-	(Still supersaturated at 0℃)	-
Ethanol	55.8℃	26.2℃	II+IV	10.2℃	II+IV
Acetonitrile	40.9℃	24.3℃	II	9.2℃	II
Methanol	29.4℃	9.2℃	III	(Still supersaturated at 0℃)	-
Tetrahydrofuran	42.8℃	31.1℃	V	29.3℃	I?+V
1,4-Dioxane	-	-	IV+V	-	IV+V
2-Propanol	-	-	III+IV		
Ethyl acetate	-	-	III+IV		
Chlorobenzene	-	-	III+IV		
1-Butanol	-	-	III+IV		
1-Propyl acetate	-	-	III+IV		
1-Butyl acetate	-	-	III+IV		
Methyl isobutyl ketone	-	-	III+IV		
Anisole	-	-	III+IV		
Toluene	-	-	III+IV		

Same as results obtained by conventional measurement method

Conclusion

Using CrystalBreeder, we prepared several crystal forms of Sulfathiazole as a sample compound. We confirmed that we achieved four different crystal forms depending on the solvent used.
According to the density rule, form IV is the most stable polymorph at room temperature.
Form IV > III > II > V > I

Bakar et al, int. J. Pharm. 414 (2011), 86 - 103.

Crystallization method	Form
Conventional measurement methods	III+IV
CrystalBreeder (cooling method)	I? II III IV V

Crystal16

CrystalBreeder

CrystallineRR
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