Organic Process Research & Development **2009**, *13*, 1315–1321

A Practical Approach for Using Solubility to Design Cooling Crystallisations

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Abstract:

Crystallisation and recrystallisation are important unit operations in the pharmaceutical industry. In our experience cooling crystallisations are preferred to other ways of generating supersaturation because they are quicker to develop and provide better control of purity and polymorph and particle properties. There is, however, a perception that the yield from cooling crystallisations is low. This work presents an approach to designing cooling crystallisations based on a review of the temperature dependence of solubility for over 100 systems. This methodology is demonstrated with a case study of an in-house development compound. The conclusion is that cooling crystallisations are generally viable.

1. Introduction

Batch crystallisation is a unit operation frequently encountered in the pharmaceutical industry. Both intermediates and final product are often isolated using crystallisation processes. The level of understanding and control of these crystallisations increases during development, as do the justifiable development time and the quantities of materials available, but the product quality is desired to be consistent over time. In this context, quality is typically defined by the levels of various impurities, the polymorphic form and particle properties such as size and shape.

Antisolvent crystallisations are popular as they are generally thought to have high yields as well as being quick to develop and perform. However, these crystallisations can generate high supersaturations and may be mixing dependent. High supersaturation strongly increases the chance of primary nucleation of metastable forms or oiling out[1] and/or may result in the batch "setting solid" due to the formation of networks from primary particles.[2]

Cooling crystallisations on the other hand give good control of the supersaturation and a good, robust definition of the seed point.[3,4] However, in general they are perceived to be low yielding. In the Theory section of this paper this perception is addressed by a brief review of relevant solubility theory and a review of data from the literature.

This leads to a methodology for the rapid design of cooling crystallisations. This methodology was tested for an in-house development compound that was known to exist in several crystal modifications.

2. General Feasibility of Cooling Crystallisations

The perception that cooling crystallisations give low yields is addressed in this section by a brief review of relevant solubility theory and a review of data from the literature. These reviews aim to demonstrate that one can generally identify a solvent, or mixture of solvents, for a cooling crystallisation with a reasonable yield.

2.1. Solubility Curve around a Reference Point. When a solid−liquid system is in equilibrium (Figure 1), the dissolution of a small amount of a solute A (δn_A) does not change the Gibbs energy of the total system ($\Delta G_{sys} = 0$). The driving force for dissolution is an increase in the entropy of the solute transferred from the solid to the liquid phase, which is countered by an increase in Gibbs energy due to a change in environment of solute and solvent molecules:

$$\Delta G_{sys} = (\Delta \mathbf{G}_{S\rightarrow L} + RT\ln(x_i))\delta n_A = 0$$
$$\Delta \mathbf{G}_{S\rightarrow L} = -RT\ln(x_A))$$
$$\ln(x_A) = \frac{\Delta \mathbf{S}_{S\rightarrow L}}{R} - \frac{\Delta \mathbf{H}_{S\rightarrow L}}{RT} \rightarrow \ln(x_A) = a - b/T \quad (1)$$

Here $\Delta \mathbf{G}_{S\rightarrow L}$ is the molar change in free energy on dissolution other than that associated with the ideal entropy of mixing which equals $R\ln(x_A)$, where x_A refers to the mole fraction for which equilibrium between the solid and the solution is reached.[5,6]

Equation 1 justifies a two-parameter model for the design of cooling crystallisations as both $\Delta \mathbf{S}$ and $\Delta \mathbf{H}$ may be assumed constant if the range of temperatures is small. Note that this may not hold for solvates or hydrates.

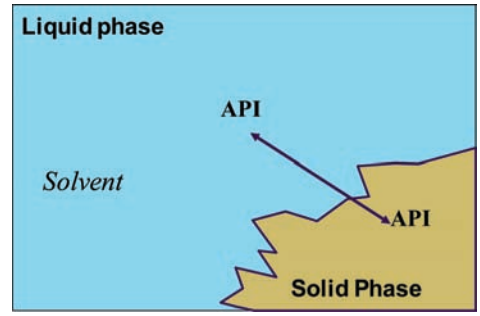

Figure 1. **Solid and liquid in equilibrium.**

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10.1021/op9001438 CCC: $40.75
Published on Web 10/30/2009

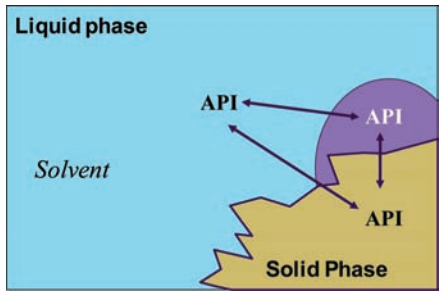

Figure 2. **Ideal solubility.**

2.2. Ideal Solubility. One can describe the dissolution equilibrium as a process in which a small amount of solid is transformed to its subcooled melt, which is subsequently ideally mixed ($\Delta\mathbf{H}_{mix} = 0$, $\Delta\mathbf{S}_{mix} = R \ln(9x_A)$ with the solvent (Figure 2). $\Delta\mathbf{G}_{S\rightarrow L}$ for such an "ideal" process is that associated with the melting of the solid: $\Delta\mathbf{G}_m$

The ideal solubility is defined by the assumption that $\Delta\mathbf{H}_m$ as measured at the melting point remains representative at the temperature at which the solubility is evaluated. At the melting point $\Delta\mathbf{S}_m(T_m) = \Delta\mathbf{H}_m/T_m$ so eq 1 for the ideal dissolution process becomes:

$$\ln(x_A^{id}(T)) = -\frac{\Delta\mathbf{G}_m}{RT} = \frac{\Delta\mathbf{H}_m}{RT_m} - \frac{\Delta\mathbf{G}_m}{RT}$$

$$\ln\left(\frac{x_A^{id}(T)}{x_A^{id}(T_r)}\right) = \frac{\Delta\mathbf{H}_m}{R}\left(\frac{1}{T_r} - \frac{1}{T}\right) \qquad (2)$$

2.3. Non-ideal Solubility. The solubility deviates from ideal behaviour when Gibbs energy associated with the mixing of the melt into the solvent is nonzero. If this is the case, then the Gibbs energy change for the process described by Figure 2 will consist of two terms, one for melting and an additional term for mixing the melt with the solvent ($\Delta\mathbf{G}_{mix} <> 0$). Equation 1 now becomes:

$$\Delta\mathbf{G}_{S\rightarrow L} = \Delta\mathbf{G}_m + \Delta\mathbf{G}_{mix} = -RT\ln(x_A) \qquad (3)$$

If the activity coefficient of the solute, γ_A, is defined by $\gamma_A x_A = x_A^{id}$ then eqs 2 and 3 combine to give the temperature dependence of the activity coefficient:

$$\ln(\gamma(T)) = \frac{\Delta\mathbf{G}_{mix}}{RT} = \frac{\Delta\mathbf{H}_{mix}}{RT} - \frac{\Delta\mathbf{S}_{mix}}{R} \qquad (4)$$

2.4. Non-ideal Temperature Dependence. So far we have not concerned ourselves with the temperature dependence of the molar enthalpy and entropies. The enthalpy and entropy vary with temperature as a function of the heat capacity Cp:[6]

$$\frac{\partial\mathbf{H}}{\partial T} = \mathbf{Cp} \text{ and } \frac{\partial\mathbf{S}}{\partial T} = \frac{\mathbf{Cp}}{T} \text{ if } \mathbf{Cp} \text{ is constant then}$$
$$\mathbf{H}(T) = \mathbf{H}(T_{ref}) + \mathbf{Cp}(T - T_{ref}) \text{ and}$$
$$\mathbf{S}(T) = \mathbf{S}(T_{ref}) + \mathbf{Cp}\ln\left(\frac{T}{T_{ref}}\right) \qquad (5)$$

If we assume that both the solid's and the solute's molar heat capacity **Cp** are independent of temperature, the enthalpy and entropy at a temperature T may be calculated from known values at a reference temperature T_{ref} as shown in the equation above.

For the molar entropy and enthalpy associated with the dissolution process, the temperature effect described by eq 5 is only important if there is a difference between the **Cp** of the solid and the **solute in solution** ($\Delta\mathbf{Cp}_{S\rightarrow L}$). Combining eqs 5 and 1 demonstrates that for systems where $\Delta\mathbf{H}_{mix}$ and $\Delta\mathbf{S}_{mix}$ are temperature dependent over the interval of interest, solubility data are to be described by a three-parameter model (eq 6):

$$\ln(x_A) = a - b/T + c\ln(T)$$
$$\ln\left(\frac{x_A(T)}{x_A(T_r)}\right) = b\left(\frac{1}{T} - \frac{1}{T_{ref}}\right) + c\ln\left(\frac{T}{T_{ref}}\right) \qquad (6)$$

with

$$a = \Delta\mathbf{S}_{S\rightarrow L} - \mathbf{Cp}/R$$
$$b = \Delta\mathbf{H}_{S\rightarrow L} - \Delta\mathbf{Cp}_{S\rightarrow L}T_{ref}/R$$
$$c = \Delta\mathbf{Cp}_{S\rightarrow L}/R$$

Values for the difference in **Cp** between the solid and its melt ($\Delta\mathbf{Cp}_{S\rightarrow melt}$) can be measured using DSC and are of the order of 100 J/(mol K) (see for instance data of Granberg and Rasmusson[7]) The $\Delta\mathbf{Cp}$ between the solid and solute in solution is, however, not easily determined and is not necessarily equal to the $\Delta\mathbf{Cp}$ between the solid and its melt. Since $\Delta\mathbf{Cp}_{S\rightarrow L}$ is not a measurable quantity, these authors prefer to include the effect of $\Delta\mathbf{Cp}$ in the activity coefficient which then becomes a three-parameter function:

$$\ln(\gamma(T)) = \frac{1}{RT}\left(\Delta\mathbf{H}_{mix}(T_{ref}) + \Delta\mathbf{Cp}_{S\rightarrow L}(T - T_{ref}) - T\left(\Delta\mathbf{S}_{mix}(T_{ref}) + \Delta\mathbf{Cp}_{S\rightarrow L}\ln\left(\frac{T}{T_{ref}}\right)\right)\right) \qquad (7)$$

Combining eqs 2, 3, and 7 we arrive at the equation that describes the temperature dependence of solubility in the most general of ways:

$$\ln(x_A(T)) = \ln(x_A^{id}(T)/\gamma_A) \rightarrow$$
$$\ln(x_A(T)) = \frac{1}{RT}\left(-(\Delta\mathbf{H}_m + \Delta\mathbf{H}_{mix}(T_{ref}) + \Delta\mathbf{Cp}_{S\rightarrow L}(T - T_{ref})) + \frac{1}{R}\left(\Delta\mathbf{S}_m + \Delta\mathbf{S}_{mix}(T_{ref}) + \Delta\mathbf{Cp}_{S\rightarrow L}\ln\left(\frac{T}{T_{ref}}\right)\right)\right) \qquad (8)$$

Note this is essentially a three-parameter model as for many systems the heat and entropy of melting are known from DSC measurements.

(5) Mullin, J. W. *Crystallization*, 4th ed.; Equation 3.18; Butterworth-Heinemann: Woburn, MA, 2001; p 98, ISBN 0 7506 4833 3.
(6) Lewis, G. N.; Randall, M.; Pitzer, K. S.; Brewer, L. *Thermodynamics*, 2nd ed.; McGraw-Hill: New York, 1961.
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2.5. Solubility Data. To get a better understanding of typical crystallisation yields for cooling crystallisations we evaluated the parameters in eq 6 for 93 systems in the literature.[7–17] For all these systems the heat of fusion, the melting point, and temperature-dependent solubility data were available in a number of solvents or solvent mixtures. In addition to these data we analysed 20 AstraZeneca systems based on 9 AstraZeneca compounds for which data could not be revealed. Equation 6 was fitted to the data by varying the solubility at the reference point $x(T_{ref})$, the dissolution enthalpy $\Delta\mathbf{H}_{S\rightarrow L}$, and the heat capacity difference $\Delta\mathbf{Cp}_{S\rightarrow L}$ until the relative error was minimised:

$$\text{average relative error} = \left(\frac{1}{N_{exp}}\Sigma_i^{N_{exp}}\left(\frac{x_i(\text{predicted})}{x_i(\text{measured})} - 1\right)^2\right)^{0.5} \quad (9)$$

The initial fit assumed that $\Delta\mathbf{Cp}_{S\rightarrow L} = 0$, fitting just $x(T_{ref})$ and $\Delta\mathbf{H}_{S\rightarrow L}$. If the average error could not be reduced below 6%, the fit was repeated and $\Delta\mathbf{Cp}_{S\rightarrow L}$ was allowed to vary as well.

The fitting results are presented in Table 1. It is clear that in most cases (85%), $\Delta\mathbf{Cp}_{S\rightarrow L}$ could be assumed to be zero. For those sets where the three-parameter model was required (15%), $\Delta\mathbf{Cp}_{S\rightarrow L}$ was positive in all but two cases. This means that the solubility rises faster with increasing temperature than the two-parameter model can predict.

In general the error in the solubility measurement is too large for $\Delta\mathbf{Cp}_{S\rightarrow L}$ to be determined. For instance for paracetamol $\Delta\mathbf{Cp}_{melt}$ was determined at 100 J/mol K,[7] but the data was well fitted with the two-parameter model.The exception seems to be systems in which hydrates are formed (caffeine hydrate, lamivudine hydrate). There are a number of other systems for which $\Delta\mathbf{Cp}_{S\rightarrow L} > 0$. In analogy to the hydrates this may indicate that solids have converted to a solvate, or there are very strong interactions between the solvent and the solute.

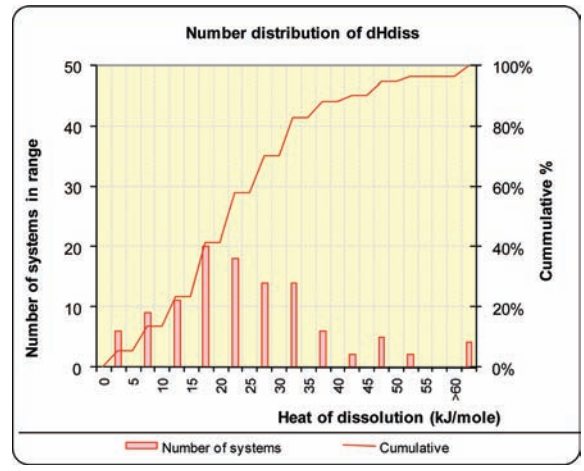

Figure 3. **Distribution of the systems over the heat of dissolution at 20 °C.**

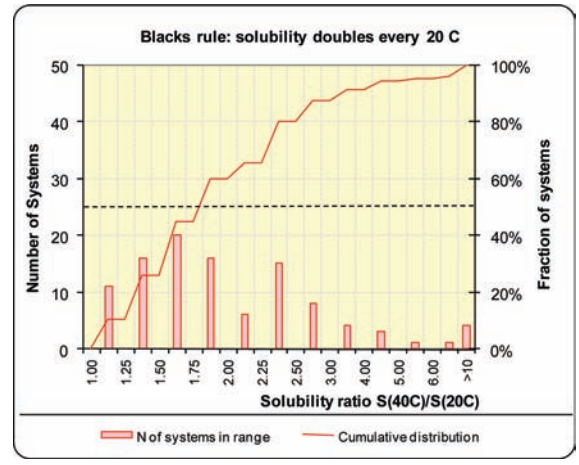

Figure 4. **Distribution of the systems over the solubility increase for a 20 °C rise in temperature.**

2.6. General Temperature Dependence: "Black's Rule". In order to get a feel for the general temperature dependence of solubility, the distribution of the molar heat of dissolution ($\Delta\mathbf{H}_{S\rightarrow L}$) was evaluated (Figure 3). It is clear that the distribution of $\Delta\mathbf{H}_{S\rightarrow L}$ is very wide (5−100 kJ/mol) with a median of about 25 kJ/mol—about 5 kJ/mol lower than the average $\Delta\mathbf{H}_m$ at 30 kJ/mol.

Equation 6 was used to calculate the solubility ratio for a temperature rise of 20 °C using the solubility at 40 °C relative to the solubility at 20 °C. The distribution of this solubility ratio is plotted in Figure 4; the median of the curve lies at a solubility ratio of 2, indicating that on average the solubility has doubled, thus supporting "Black's rule" which states that solubility doubles every 20 °C.[3] This rule may be compared to a similar heuristic that states that reaction rate doubles every 10 °C; it holds in general.

"Black's rule" is a qualitative heuristic rule that can be used for solvent selection after an initial solubility screen is performed. Furthermore, in order to obtain solubility data that are reproducible to within ±4%, it is necessary to control the temperature to ±1 °C. The (regrettably) common practice of measuring and quoting solubility data at "room temperature"

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Table 1. **Tabulated results of fitting the data to the general solubility equation**

cmpd	solvent	ΔH_m (J/mol)	T_m (K)	T_{ref} (K)	X_{ref} (−)	ΔH_{diss} (J/mol)	ΔCp (J/mol K)	fit error (%)	γ (−)	X(40 °C)/X(20 °C) (%)	ref
niflumic acid	water	36800	476	308	5.87×10^{-6}	5378		0.6	568	115	8
niflumic acid	water + 10% ethanol	36800	476	308	9.74×10^{-6}	7888		0.7	360	123	8
niflumic acid	water + 20% ethanol	36800	476	308	1.57×10^{-5}	10903		0.9	237	133	8
niflumic acid	water + 30% ethanol	36800	476	308	3.20×10^{-5}	14773		1.2	126	147	8
niflumic acid	water + 40% ethanol	36800	476	308	8.25×10^{-5}	28249		3.5	63.8	210	8
niflumic acid	water + 50% ethanol	36800	476	308	2.31×10^{-4}	36591		1.5	26.9	261	8
niflumic acid	water + 70% ethanol	36800	476	308	0.00164	38687		3.6	3.95	276	8
niflumic acid	water + 90% ethanol	36800	476	308	0.0105	31166		2.2	0.531	226	8
niflumic acid	ethanol	36800	476	308	0.0225	23658		2.8	0.213	186	8
niflumic acid	ethanol + 10% ethyl acetate	36800	476	308	0.0310	20764		1.4	0.146	172	8
niflumic acid	ethanol + 30% ethyl acetate	36800	476	308	0.0456	19033		0.5	0.0960	165	8
niflumic acid	ethanol + 50% ethyl acetate	36800	476	308	0.0558	12222		1.2	0.0685	138	8
niflumic acid	ethanol + 60% ethyl acetate	36800	476	308	0.0607	9894		0.9	0.0601	130	8
niflumic acid	ethanol + 70% ethyl acetate	36800	476	308	0.0608	7294		0.3	0.0569	121	8
niflumic acid	ethanol + 80% ethyl acetate	36800	476	308	0.0533	1410		0.1	0.0577	104	8
niflumic acid	ethanol + 90% ethyl acetate	36800	476	308	0.0397	4183		0.2	0.0819	112	8
niflumic acid	ethyl acetate	36800	476	308	0.0264	4615		2.2	0.124	113	8
caffeine hydrate	water	20300	509	308	0.00319	38030	1005	3.2	16.8	351	8
caffeine hydrate	water + 10% ethanol	20300	509	308	0.00558	44208	953	1.6	10.9	407	8
caffeine hydrate	water + 20% ethanol	20300	509	308	0.00897	49161	855	3.6	7.61	452	8
caffeine hydrate	water + 30% ethanol	20300	509	308	0.0129	54331	1243	3.9	5.53	572	8
caffeine hydrate	water + 40% ethanol	20300	509	308	0.0183	47122	676	5.1	3.68	409	8
caffeine hydrate	water + 50% ethanol	20300	509	308	0.0211	46489	616	4.6	3.18	396	8
caffeine	water + 60% ethanol	20300	509	308	0.0260	37845		3.5	2.39	270	8
caffeine	water + 70% ethanol	20300	509	308	0.0220	32004		4.1	2.51	232	8
caffeine	water + 80% ethanol	20300	509	308	0.0160	25896		2.7	3.05	197	8
caffeine	water + 90% ethanol	20300	509	308	0.00790	19727		2.2	5.47	168	8
caffeine	ethanol	20300	509	308	0.00216	18523		2.8	19.5	163	8
caffeine	ethanol + 10% ethyl acetate	20300	509	308	0.00303	21154		2.4	14.7	174	8
caffeine	ethanol + 20% ethyl acetate	20300	509	308	0.00407	23594		1.4	11.5	186	8
caffeine	ethanol + 30% ethyl acetate	20300	509	308	0.00478	22395		3.0	9.53	180	8
caffeine	ethanol + 40% ethyl acetate	20300	509	308	0.00560	22075		1.9	8.08	178	8
caffeine	ethanol + 50% ethyl acetate	20300	509	308	0.00621	21660		3.1	7.23	177	8
caffeine	ethanol + 60% ethyl acetate	20300	509	308	0.00730	19528		2.1	5.89	167	8
caffeine	ethanol + 70% ethyl acetate	20300	509	308	0.00765	16471		2.2	5.29	154	8
caffeine	ethanol + 80% ethyl acetate	20300	509	308	0.00746	15934		1.8	5.37	152	8
caffeine	ethanol + 90% ethyl acetate	20300	509	308	0.00654	17983		0.8	6.38	160	8
caffeine	ethyl acetate	20300	509	308	0.00489	13407		1.2	7.79	142	8
paracetamol	methanol	27100	444	293	0.0820	17753		1.8	0.279	159	7
paracetamol	ethanol	27100	444	293	0.0670	14240		1.4	0.342	145	7
paracetamol	1-propanol	27100	444	293	0.0460	14007		1.2	0.498	144	7
paracetamol	isopropyl alcohol	27100	444	293	0.0460	14786		1.1	0.498	147	7
paracetamol	*n*-butanol	27100	444	293	0.0390	13043		0.8	0.587	141	7
paracetamol	acetone	27100	444	293	0.0360	15789		1.5	0.636	151	7
paracetamol	water	27100	444	293	0.00154	19907		1.5	14.9	169	7
paracetamol	ethyl acetate	27100	444	293	0.00490	16439		1.8	4.67	154	7
paracetamol	acetonitrile	27100	444	293	0.0064	24132		1.4	3.60	188	7
paracetamol	toluene	27100	444	293	2.22×10^{-4}	2560	−1387	1.74	103	145	7
carbamazepine[b] FIII	mesitylene	29300	447	293	3.31×10^{-4}	35489		2.2	47.9	254	9
carbamazepine FIII	cumene	29300	447	293	5.52×10^{-4}	34413		2.0	28.7	247	9
carbamazepine FIII	*cis*-decalin	29300	447	293	7.42×10^{-5}	39180		3.2	214	279	9
carbamazepine FIII	bButOAc	29300	447	293	0.00305	31295		2.3	5.19	227	9
carbamazepine FIII	1-octanol	29300	447	293	0.00401	30933		2.7	3.96	225	9
carbamazepine FIII	1-hexanol	29300	447	293	0.00410	31327		2.3	3.87	227	9
carbamazepine FIII	1-heptanol	29300	447	293	0.00385	32857		0.5	4.12	237	9
carbamazepine FIII	2-heptanone	29300	447	293	0.00406	31125		2.2	3.91	226	9
carbamazepine FIII	cyclohexanone	29300	447	293	0.0210	29008		2.6	0.755	214	9
carbamazepine FIII	ethoxybenzene	29300	447	293	0.00394	31573		2.1	4.03	229	9
carbamazepine FIII	anisole	29300	447	293	0.00813	30646		2.3	1.95	223	9
carbamazepine FIII	bromobenzene	29300	447	293	0.00857	31051		2.2	1.85	226	9
carbamazepine FIII	NMP	29300	447	293	0.145	24399		3.7	0.109	190	9
carbamazepine FIII	DMA	29300	447	293	0.0970	25981		3.6	0.164	198	9
carbamazepine FIII	DMF	29300	447	293	0.0290	29813		3.4	0.547	219	9
cefotaxime Na	methanol	45092	435	293	0.00104	2417		0.9	2.29	107	11
cefotaxime Na	acetone	45092	435	293	0.00120	3234		0.8	1.98	109	11
cefotaxime Na	ethanol	45092	435	293	2.93×10^{-4}	21233		1.8	8.10	175	11
lamivudine[c] hydrate	water	26106	451	298	0.00697	48470	2111	6.3	4.52	613	12
lamivudine hydrate	methanol	26106	451	298	0.00510	18348	415	1.1	5.18	180	12
lamivudine anhydr	ethanol	28167	451	298	0.00302	19361		2.7	6.58	166	12

Table 1. **Continued**

cmpd	solvent	ΔH_m (J/mol)	T_m (K)	T_{ref} (K)	X_{ref} (−)	ΔH_{diss} (J/mol)	ΔCp (J/mol K)	fit error (%)	γ (−)	X(40 °C)/ X(20 °C) (%)	ref
lamivudine anhydr	1-propanol	28167	451	298	0.00238	21909		4.4	8.50	178	12
lamivudine anhydr	2-propanol	28167	451	298	0.00160	19925		1.6	12.5	169	12
lamivudine anhydr	*n*-butanol	28167	451	298	0.00205	20409		3.9	9.78	171	12
lamivudine anhydr	*s*-butanol	28167	451	298	0.00166	23917		2.3	12.4	187	12
lamivudine anhydr	ethyl acetate	28167	451	298	2.34×10^{-5}	34482		5.2	942	247	12
lamivudine anhydr	acetone	28167	451	298	3.11×10^{-4}	28352	1026	2.9	66.8	274	12
lamivudine anhydr	acetonitrile	28167	451	298	2.26×10^{-4}	28361		6.0	93.7	210	12
stearic acid[d]	ethanol	56590	343	303	0.0133	90675		1.1	8.89	1079	14
stearic acid	methanol	56590	343	303	0.00336	99947		4.2	39.9	1376	14
stearic acid	ethyl acetate	56590	343	303	0.0175	87843		1.1	6.50	1002	14
stearic acid	acetone	56590	343	303	0.0114	92639		1.5	10.7	1136	14
ibuprofen	water	25280	349	298	9.02×10^{-7}	50401		5.8	2.97×10^{05}	375	15
ibuprofen	octanol	25280	349	298	0.342	37364		0.8	0.715	266	15
ibuprofen	octanol−water	25280	349	298	0.256	40078		0.9	0.974	286	15
ibuprofen	isopropyl myristate	25280	349	298	0.178	34517		1.7	1.35	247	15
ibuprofen	chloroform	25280	349	298	0.377	25955		1.4	0.600	198	15
ibuprofen	cyclohexane	25280	349	298	0.112	46752		5.7	2.33	341	15
hydroquinone[e]	water	27105	443	293	0.0101	25107	447	0.0	2.29	217	16
hydroquinone	acetic acid	27105	443	293	0.0350	19838		2.6	0.660	168	16
hydroquinone	methanol	27105	443	293	0.117	7911		1.6	0.198	123	16
hydroquinone	ethanol	27105	443	293	0.184	6386		1.5	0.126	118	16
hydroquinone	2-propanol	27105	443	293	0.147	15499	−198	0.5	0.157	143	16
hydroquinone	ethyl acetate	27105	443	293	0.0924	11648		0.6	0.250	136	16
hydroquinone	*n*-butyl acetate	27105	443	293	0.112	8879		2.4	0.206	126	16
AZ[f] cmpd **1**	1-propanol			293	0.00149	28027	364	2.6		229	
AZ cmpd **1**	*n*-butanol			293	0.00168	26825	364	7.0		222	
AZ cmpd **1**	methanol			293	0.00149	36883		4.1		263	
AZ cmpd **1**	1-octanol			293	0.00188	27692		0.0		207	
AZ cmpd **1**	*p*-xylene			293	4.20×10^{-4}	405		0.0		101	
AZ cmpd **1**	tetrahydrofuran			293	0.00707	15727		0.0		151	
AZ cmpd **1**	2-methoxyethanol			293	0.0120	16909		0.0		156	
AZ cmpd **1**	chlorobenzene			293	3.00×10^{-4}	23564		0.0		186	
AZ cmpd **1**	cyclohexane			293	2.70×10^{-4}	12219		0.0		138	
AZ cmpd **1**	cyclohexanone			293	0.00514	28562		0.0		212	
AZ cmpd **2** salt	MeOH			293	0.00102	16366	516	4.8		175	
AZ cmpd **3**	MeCN/water			288	2.34×10^{-5}	23564	1371	4.6			
AZ cmpd **4**	MeCN			293	0.00575	19883	483	1.6		191	
AZ cmpd **5**	DMSO/EtOAc			296	0.00116	32947		2.0			
AZ cmpd **6** salt	IPA			293	0.00592	19292	533	3.2		190	
AZ cmpd **7**	IPA			295	0.00492	25428	639	0.9			
AZ cmpd **8**	7% water/ *n*-butanol			277	4.09×10^{-5}	36897		4.0			

[a] The two-parameter model was fitted (**ΔCp** is blank); where the error was more than 6%, the three-parameter model is fitted. [b] Carbamazapine: enthalpy of melting from ref 10. [c] Lamivudine: enthalpy of melting from ref 13. [d] Stearic acid; enthalpy of melting from Wikipedia. [e] Hydroquinone; enthalpy of melting from ref 17. [f] AZ cmpds **1**−**8**: Data measured at AstraZeneca.

is expected to introduce errors of ±20%, if ambient temperatures vary between 15 and 25 °C.

Black's rule also demonstrates that, on average, cooling crystallisations may be expected to give a ∼88% yield if the temperature of a saturated solution is reduced by 60 °C:

$$\text{Yield} = 1 - \frac{x(T_{ref})}{x(T_{ref} + \Delta T)} = 1 - \frac{1}{2^{\Delta T/20}} = 1 - \frac{1}{2^{60/20}} = 88\% \quad (10)$$

Note that 50% systems will give better yields, and that 50% may not be suitable for cooling crystallization. However, all solutes evaluated in this study had at least one solvent from which a reasonable cooling crystallization was thermodynamically feasible (with the exception of the cefotaxime sodium salt).

2.7. General Feasibility of Cooling Crystallisation. In addition to yield, a good crystallisation solvent also results in a reasonable volume productivity. Typically, if the solubility at the higher temperature (T_H) is in the range of 50−150 g/L the system will be considered dilute for practical purposes. If the concentration is too high, the final slurry may be to dense or immobile.

Note that the temperature T_H can be limited by a number of factors including chemical stability of the API, enantiotropic transitions, and solvent boiling point (although pressurised crystallisations can be run on-plant). Plant constraints can also limit T_H as it is unadvisable to filter supersaturated solutions or transfer fluids very close to their boiling point. If the maximum system temperature is limited to 60 °C or less, a cooling crystallisation may not be feasible.

There is also a minimum concentration at the end of the crystallisation ($T = T_L$). If the final solubility is too low (<5 g/L), then precipitation of impurities is more likely, compromising product quality. The lower temperature limit is determined

by plant capability and practicalities around washing and drying. T_L is preferably in the range of 5−20 °C.

In summary, the key criteria for a cooling crystallisation are:

(1) $T_H > \sim 60$ °C
(2) Solubility equal to 50−150 g/L at T_H
(3) $T_L + 60 < T_H$
(4) Solubility > 5 g/L at T_L

Using Black's rule, a solvent with a solubility of 5−20 g/L at 20 °C will have a solubility of 40−160 mg/mL at 80 °C and thus fulfills all criteria if the boiling point of the solvent is greater than 80 °C. Since Black's rule is approximate, lower-boiling solvents may also be suitable.

It follows that, for a system with $T_H > 60$ °C, in general a cooling crystallisation is feasible if one can find a solvent with a solubility of 5−20 mg/mL at room temperature.

3. Case Study

This case study illustrates how crystallisation processes are arrived at for different stages of development. The development compound in this study has three crystal modifications: Form 1 which is the desired, stable form; Form 2 which is a metastable form monotropically related to Form 1, and a hydrate.

3.1. Early Development. Early development is characterised by a shortage of material and time and the prioritisation of manufacture over yield and robustness; only a couple of kilos of material are required. The starting point of crystallisation development is often the reaction mixture.

In this case study the reaction system was biphasic: an organic solvent and aqueous hydrochloric acid. On completion of the reaction, the aqueous phase was removed and the organic phase washed first with a solution of aqueous potassium carbonate and finally with water. Ethyl acetate was identified as a suitable solvent for both this reaction and the isolation by crystallisation.

The final reaction mass (after washes) was used as the starting point of the crystallisation development (32 mg/mL product in ethyl acetate saturated with 3.7% w/w water). To arrive at a suitable yield the solution needed to be concentrated. Twenty percent of the initial volume was distilled off. This increased the product concentration to 40 mg/mL and reduced the water level to 2.6% w/w. To ensure Form 1 was obtained the solution was then seeded with Form 1 and cooled to room temperature. The overall yield was 78%.

Two batches were made in 100 L vessels resulting in ~1.3 kg of 99.2% w/w assay and 0.2 area % relative substances.

Comment on Robustness. During the distillation water and ethyl acetate are removed so the solute concentration increases. The solubility of the product reduces sharply with decreasing water content (Figure 5). A typical equipment setup does not control the level of reflux, and different levels of refractionation may be experienced at different scales. This makes it hard to control/predict the change of the water concentration. There is therefore a major risk of producing the unwanted Form 2, because (i) if not enough water is removed, the seed may dissolve and the system will eventually nucleate Form 2, or (ii) if too much water is removed, the supersaturation may increase dramatically and Form 2 may nucleate before seeding.

In addition to the sensitivity with regards to the distillation, the above process cannot avoid the presence of water; thus, there is an additional risk of formation of the hydrate.

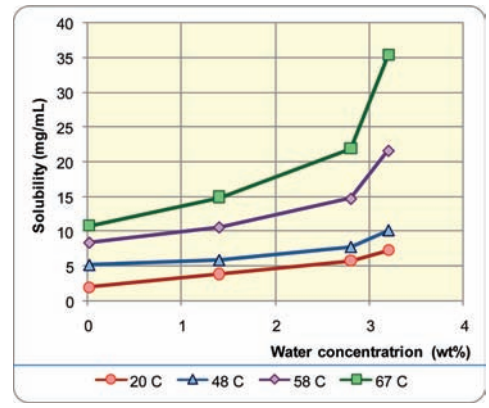

Figure 5. **Effect of water on solubility at a range of temperatures.**

3.2. Development for Manufacture. Later in development when 50−1000 kg of material is required, robust manufacture of product with a consistent quality becomes more important. In this context, quality is typically defined by the level of various impurities, the polymorphic form, and particle properties such as size and shape.

Following on from early development, the chemistry route to the product was completely changed, resulting in new processes and the introduction of a "Pures" step—a final recrystallisation of the product to control the quality. Having established that ethyl acetate/water mixtures are unsuitable, the work flow outlined in section 2.7 was used to identify a suitable solvent.

Using Form 1 as starting material, the solubility was measured in nine solvents using the gravimetric method. The solubilities in mg/mL of solvent are shown in Figure 6.

Three of these solvents have solubilities in the required range of 5−20 mg/mL. 1-Propanol was preferred to ethanol for two reasons. The boiling point is 19 °C higher (97 °C vs 78 °C). According to Black's rule this will allow a doubling of the volume productivity. Moreover, the yield will also be greater. 1-Propanol was preferred to 2-butanol because the higher (61%) room temperature solubility is likely to allow higher volume productivity (the boiling points are similar 97 °C vs 99 °C).

At this point we could have attempted a cooling crystallisation using the procedure outlined in the Experimental Section. However, to validate the workflow we measured the solubility curve for Form 1 in 1-propanol gravimetrically. The results are shown in Figure 7 and are compared with Black's rule.

The data confirm the assertion that 5−20 mg/mL solubility at 20 °C is sufficient to move towards a cooling crystallisation:

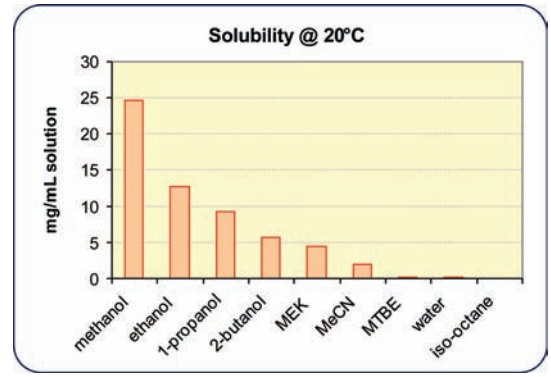

Figure 6. **Solubility data in a range of solvents at 20 °C.**

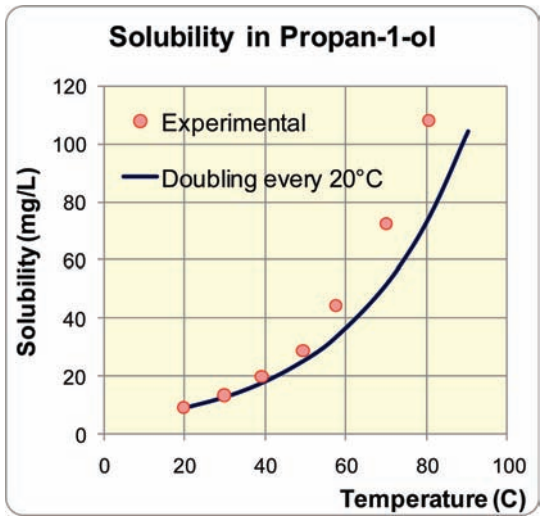

Figure 7. **Solubility vs temperature of compound 1 (Form 1) in 1-propanol.**

using 1-propanol starting at 80 °C and cooling to 20 °C should have a yield of 91% and a volume productivity of 91 g/L. This is only slightly above the predictions based on Black's rule: 87% yield at 76 g/L.

This was verified by carrying out a cooling crystallisation from 1-propanol using the 5 g procedure outlined in the Experimental Section. On heating to 80 °C all solid dissolved (100 g/mL) and after the final 20 °C hold (over the weekend) the final liquid concentration was 12.5 mg/mL, corresponding to less than 0.6 g (12.5%) of product. The isolated weight of product was 4.2 g, corresponding to 84% of the starting material. XRD confirmed that it was Form 1.

The small discrepancy between the measured yield (84%) and that predicted from the solubility data (>91%) is not unusual at this scale and usually arises from losses of material to the equipment.

3.3. Experimental Section. *Solubility Curve Using HPLC.* A slurry of Form 1 in solvent was made up at the highest temperature required (~70 °C) and equilibrated for 2 h. A slurry sample was withdrawn and filtered rapidly. The solid was analysed by powder X-ray diffraction, and the liquors were analysed by HPLC against an external standard. The temperature was reduced, and further samples were withdrawn after equilibration times of at least 2 h. Comparison of the powder X-ray diffraction patterns with reference patterns of Form 1 showed that no transformations occurred during the cool down.

Gravimetric Solubility Measurement. For each measurement, 40 mg of Form 1 was added to 5 mL of solvent in a test tube, and the slurry was agitated using a magnetic flea while the slurry was placed inside a Stem block and controlled at the required temperature. After slurrying overnight the suspension was allowed to settle, and a known volume of the supernatant was withdrawn using a syringe filter and added to a preweighed foil dish. The syringe was preheated for system temperatures above room temperature. The amount of solute in the sample was determined after the solution had evaporated to dryness.

Solubility Curves in Ethyl Acetate/Water Mixtures. To determine the influence of water on the solubility of Form 1 in ethyl acetate, four mixed solvent samples were prepared using varying amounts of water. The water contents were 0.02%, 1.38%, 2.80%, and 3.24% (all w/w). Solubility curves were measured using the HPLC method.

Crystallisation Process. Solute (5 g) is added to a 100 mL jacketed vessel fitted with an overhead stirrer, a condenser, and a thermocouple. Then 50 mL of solvent is added and the slurry heated to a batch temperature of 80 °C. If required, solvent could be added in small aliquots until all the solid is dissolved. The solution is cooled to 65 °C and seeded with 0.05 g of the preferred form. After holding for 2 h, the suspension is cooled to 55 °C over 4 h and then to 20 °C over a further 4 h. After at least a 10 h hold the liquors are sampled. After filtration the solid is washed with 10 mL of solvent and dried in a vacuum oven.

Water Content. The water content was measured using Karl-Fischer analysis using a CA-100 instrument from Mitsubishi Chemical Corporation, fitted with a coulometric cell and using Aquamicrometer FLS solution.

HPLC. The mobile phase was 1:1 acetonitrile:water/1% TFA. Two drops of solution were diluted into 1.5 mL of the mobile phase. Analysis was performed in an Agilent 1100 machine fitted with a Luna C18(2) 3 μm column. Flow rate was 1 mL/min. Column temperature was 40 °C. Sample injection volume was 5 μL. Run time was 8.1 min. Detector wavelength was 254 nm.

Powder X-ray Diffraction. Dried samples were prepared on silicon wafer mounts and analyzed using the Siemen's D5000 X-ray diffractometer. The sample was exposed for 1 s per 0.02° θ over the range 2° to 40° 2θ in continuous scan, $\theta-\theta$ mode.

4. Conclusions

This study demonstrates that in general one can find a solvent that gives a viable, high-yielding, cooling crystallisation for a particular solute. Our solvent selection methodology is based on a few simple criteria and solubility measurements at one temperature close to ambient conditions using the 'Black's rule' as a first guide to solubility at other temperatures.

Black's rule states that solubility doubles every 20 °C. A thorough analysis of the literature data has shown that 20 °C is indeed the correct median temperature rise to use, but in reality the doubling temperature does of course vary significantly depending on the solvent−solute systems.

Applying this methodology to an in-house development compound successfully led to a cooling crystallisation. Further application of our methodology has subsequently resulted in cooling crystallisations on more than ten other in-house products not described in this paper.

We conclude that cooling crystallisations should be the norm, unless there are other processing constraints arising for instance from chemical stability, solute melting point, or enantiotropic transitions.

Acknowledgment

The authors thank Tim Murray, Ric Cooke, Kathryn Arnott, and Rebecca Southworth for their assistance in the experimental work described in this paper.

Received for review June 6, 2009.

OP9001438