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Comments on "What if cocrystallization fails for neutral molecules? Screening offered eutectics as alternate pharmaceutical materials: Leflunomide-A case study"

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In a recent paper published in *Pharmaceutical Sciences* Bala and coworkers[1] characterized eutectic mixtures prepared from leflunomide and two monocarboxylic acids (adipic acid, picolinic acid), three dicarboxylic acids (maleic acid, malonic acid, sorbic acid), and two pyridine carboxamides (nicotinamide, isonicotinamide). The solid materials were subjected to infrared spectroscopic studies, powder X-ray diffraction analyses, and differential scanning calorimetric measurements to establish whether the materials were salts, cocrystals or eutectics. As part of the thermal studies the authors reported in Table 1 of their paper the endothermic melting point temperatures of the individual pure components and the respective eutectic mixtures. Table 2 of the paper[1] gives the experimental enthalpy of fusion data.

The purpose of this brief commentary is to provide journal readers with a comparison of the authors' experimental enthalpy of fusion data for leflunomide, adipic acid, picolinic acid, maleic acid, malonic acid, sorbic acid, nicotinamide, and isonicotinamide with published values taken from the pharmaceutical and chemical literature. Multiple literature values exist for the several of the individual mixture components. Such comparisons provide valuable information and can be used to assess the "quality" of the measured values. Large difference between values often, though not always, suggest that experimental errors may have been made in the course of performing the measurements. In the case of enthalpy of fusion data, large differences can also suggest possible polymorphism or the formation of solid solvates.

In Table 1 of this commentary, the measured enthalpies of fusion, along with published literature values are tabulated. The majority of the literature values were taken from a two-part compilation of phase transition enthalpies by Acree and Chickos [2, 3]. Included in Table 1 are the original references for the literature values. Examination of the numerical entries in Table 1

reveals that the enthalpy of fusion data reported by Bala and coworkers [1] differ significantly from many of the literature values. In fact, the data reported by Bala and coworkers are often significantly less than published literature values. For both adipic acid and nicotinamide the authors' values are approximately one-half of the published literature data. Differences in the melting point temperatures may result from slight impurities in the samples and from how different authors determine the experimental values. Some researchers report the melting point temperature as the onset of melting, whereas other researchers report the value of the peak temperature in the thermogram.

Table 1. Comparison of Measured Melting Point Temperatures and Enthalpies of Fusion for Leflunomide, Adipic Acid, Picolinic Acid, Maleic Acid, Malonic Acid, Sorbic Acid, Nicotinamide, and Isonicotinamide

Compound	Melting temperature (K)	Enthalpy of fusion (kJ/mole)	Reference
Leflunomide	442.5	2.69	[1]
	440.1	31.3	[4]
	444.4	30.9	[5]
	438.2	32.43	[6]
Adipic acid	428.7	14.17	[1]
		32.0	[7]
	423	35.89	[8]
	426.3	35.20	[9,10]
	419	33.7	[11]
	420.9	34.34	[12]
	424.5	37.32	[13]
	426.4	34.85	[14,15]
	425.3	39.03	[16]
	425.2	35.15	[17]
	423.9	34.0	[18]
Picolinic acid	411.4	15.36	[1]
	411	30.0	[19,20]
	408.9	23.1	[21]
Maleic acid	416.8	11.96	[1]
	411.9	26.9[a]	[22]
Malonic acid	412.1	15.19	[1]
	406	18.74	[8]
	407.5	23.1	[23]
Sorbic acid	409.8	11.98	[1]
	405.3	18.76	[24]
Nicotinamide	403.8	12.50	[1]
	401.2	23.7	[25]
	401.7	22.58	[26]

	401.6	20.5	[27]
	401.2	25.4	[28]
	401.4	23.2	[29]
	397.8	26.5 (Form I)	[30]
	379.0	20.1 (Form II)	[30]
	403.8	23.8	[31]
	401.6	25.5	[32]
	402	26.94	[33]
	401.6	23.97	[34]
	403.2	23.90	[35]
	401.6	24.50	[36]
	401.3	25.2 (Form I)	[37]
	387.7	29.7 (Form II)	[37]
	382.1	19.3 (Form III)	[37]
Isonicotinamide	406.0	17.50	[1]
	429.8	23.6	[38]
	428.6	24.5	[29]
	431	26.81	[33]
	428.4	23.1	[35]
	428.5	22.60 Form (II)	[39]

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