Impurity Occurrence and Removal in Crystalline Products from Process Reactions

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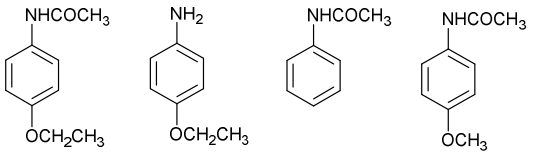
SUPPLEMENTARY INFORMATION

Data on the incorporation into phenacetin 61 **crystals of 4-phenetidine** 63**, acetanilide** 120 **and 4-methoxyacetanilide** 121



61 **63** **120** **121**

Crystal growth Compounds and solvents were purchased from Sigma-Aldrich. Phenacetin (50 mg) and one of each impurity were mixed to give samples containing each impurity as either 5%, 10% or 15% of the total number of moles of each sample. These samples were dissolved in methanol (1.5 mL) with heating to 35 °C to ensure dissolution in all cases. The solutions were allow to cool and partially (but not fully) evaporated in semi-covered (partially perforated) vials to allow growth of crystals of at least 0.5 × 0.5 × 0.2 mm dimensions. The crystals were isolated, washed with 0.4 mL of cold methanol, dried under vacuum and weighed.

Crystal dissolution For each impurity and concentration, individual crystals were subjected to a series of three partial dissolutions followed by analysis of the resulting solutions at each stage. The mass of the crystals determined the volumes of solvent used for complete dissolution, to give a concentration of 1.0 mg/mL, e.g. 6.0 mL was used for the complete dissolution of a crystal weighing 6.0 mg, with. 2.0 mL used for each of the three partial dissolution stages. At the beginning of the series of dissolutions, the crystal was placed in a sample vial. The correct volume of solvent was added and the crystal was observed partially dissolving. It was then removed and washed with a small quantity of cold hexane before being placed in a second sample vial to be further dissolved. This process was repeated for a third final stage giving complete dissolution. The solutions remaining in the sample vials were analysed by HPLC. Each of these experiments was repeated three times.

HPLC HPLC analysis on the products was conducted on an Agilent 1200 series HPLC, with a YMC-Pack ODSA column (250 x 4.6 mm, 5 μm). An isocratic 60:40 MeOH:H_2O solvent system was employed, at a flow rate of 1 mL/min and an injection volume of 10 μL. The detector was set at 254 nm and the oven temperature was ambient.

Table S1 Relative quantities (percentage area by HPLC) of impurity compounds **63**, **120** and **121** incorporated into crystals of phenacetin **61** determined at three successive dissolution stages.

Impurity	Mol % impurity in solution	% impurity in 1st dissolution layer	% impurity in 2nd dissolution layer	% impurity in 3rd dissolution layer
63	5, 10 or 15	<LOQ[a]	<LOQ[a]	<LOQ[a]
120	5	1.61 ± 0.01	0.31 ± 0.04	0.20 ± 0.01
120	10	2.28 ± 0.02	0.56 ± 0.02	0.45 ± 0.01
120	15	5.89 ± 0.03	1.44 ± 0.02	0.49 ± 0.03
121	5	2.88 ± 0.02	2.58 ± 0.01	2.53 ± 0.02
121	10	6.11 ± 0.01	5.23 ± 0.02	4.97 ± 0.01
121	15	7.64 ± 0.02	7.36 ± 0.04	6.52 ± 0.03

a 3.5×10^{-3} mg/mL