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On the effect of added impurity on crystal purity of urea in an oscillatory baffled crystallizer and a stirred tank crystallizer

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ABSTRACT

Previous work has indicated that crystals produced in oscillatory baffled crystallisers (OBC) from a relatively 'pure' starting environment gave statistically higher purities than that in stirred tank crystallisers (STC) under comparable conditions. In this work, a known amount of biuret (the impurity) was added to the 'pure' urea system and the results show that the OBC still produced higher purity crystals than the STC, although these purity values were statistically lower than from the 'pure' environment in both vessels. By evaluating crystallisation rates of both urea and biuret, we noticed that these rates are higher in the STC than in the OBC, which would have led to small crystals in the former vessel. The CSD data however gave the opposite result where the CSD is wider with more, large crystals in the STC than in the OBC, in particular in the presence of added impurity. These larger crystals are likely formed due to agglomeration coupled with incorporation of impurity, which leads to a lower purity.

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1. Introduction

Crystallisation is an important purification tool in pharmaceutical and chemical industries [1,2], as any unwanted impurity can cause defect in product quality or side effects in patients [3,4], consequently the production of high purity crystals is paramount. Cooling crystallisation is one of the more popular forms of crystallisation and involves lowering the solution temperature beyond its saturation point to induce nucleation [5]. Generally a decrease in crystal purity is attributed to either mother liquor entrapped between agglomerating single crystals or specific impurity being included in the growing crystals [6].

A stirred tank crystallizer (STC) is often used to carry out crystallisations in the pharmaceutical industry and generally consists of a large jacketed vessel fitted with an impeller to mix the contents. This is a well understood process with Regulatory approval and has advantages of optimised productivity and flexibility of processing multiple drugs. The STC is however prone to poor mixing and heat transfer [7], depending on the type of impeller used, leading to problematic scale up and inconsistent crystal qualities. Efficient mixing and heat transfer leading to better temperature control are key parameters in cooling crystallisation and can be achieved in the oscillatory baffled crystallizer (OBC) [8–10] which has attracted increasing attention from the pharmaceutical industry. Previous investigations [11] have shown that higher purity crystals were obtained in the OBC under all comparable conditions. This was likely caused by the combination of a higher supersaturation level obtained in the STC with a lower temperature required to induce nucleation. This allowed less time for crystal growth and subsequently smaller single crystals that were more likely to agglomerate when mixing became poorer due to increased solid loading upon further cooling in the STC [12]. The aim of this work is to extend the previous research by investigating the effect of an impure starting environment on the final crystal purity at different cooling rates and mixing intensities.

2. Experimental set-up, calibration and procedures

2.1. Experimental system

The OBC consists of a glass column 76 mm in diameter and 1 L in volume, with a working volume of 0.5 L. Two stainless steel orifice baffles are connected by metal rods to form a baffle string; these are attached to a linear actuator above the OBC vessel. Different oscillation amplitudes and frequencies can be delivered by the actuator via a control box, therefore providing the oscillatory motion within the column. The outer diameter, orifice diameter and spacing of the baffles are 72 mm, 35 mm and 52 mm respectively, giving the overall surface

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Nomenclature

f	Frequency of Oscillation [Hz]
N_S	Agitator Speed [s^{-1}]
x_o	Centre-to-Peak Oscillation Amplitude [m]
ω	Angular Frequency [rad s^{-1}]
% AI	Percentage Added Impurity
SE	Standard Error
SD	Standard Deviation

area of the baffle string as 13,320 mm^2. The temperature within the column was achieved by controlling the jacket temperature using a water bath (Grant Instruments GP 200/R2), thus enabling different linear cooling rates to be operated.

The STC is a jacketed glass vessel, 90 mm in diameter, with a total volume of 1 L and a working volume of 0.6 L. A stainless steel two-blade flat-paddle impeller, 60 mm in diameter, was used to generate mixing and was centrally aligned within the vessel. The impeller was attached to an overhead stirrer to control the rotation speeds. Four stainless steel wall-baffle inserts were added into the system to aid mixing. The total surface area of the impeller and wall baffles in contact with the solution is 3070 mm^2. Temperature control was identical to that used in the OBC. The schematic illustration of both STC and OBC is given in Fig. 1.

To ensure comparable experimental conditions, the power density or dissipation rate was kept approximately equal. The determinations of power density are well documented for both the STC [13] and OBC [9]. The mixing conditions for each crystallizer are outlined in Table 1.

2.2. Experimental compound

Urea was the model compound and its chemical structure is shown in Fig. 2. This compound was selected as it is relatively safe, highly soluble in water, stable and has only one known polymorph under normal process conditions. Technical grade urea was sourced from VWR with an average initial purity of 95%.

For the 'impure' tests, specific amounts of impurity (biuret with an average purity of 97% from Acros Organics) were added into both vessels to investigate its effect on crystal purity. Biuret is a main condensation product of two urea molecules [14] and its structure (Fig. 3) is similar to that of urea.

When urea crystallises as a pure compound it forms long, needle-like crystals. This habit is distorted when impurity is present within the crystal [14], becoming a more cubic shape as the incorporation of biuret increases towards 5 wt%. This change in habit can be used to verify whether any impurity is being incorporated into the product crystal.

Table 1
Mixing conditions and corresponding mixing intensities.

Mixing intensity (W m^{-3})	OBC			STC
	Frequency [f] (Hz)	Angular frequency [ω] (Hz)	Centre-to-peak amplitude [x_o] (mm)	Stirrer speed [N_s] (RPM)
20	0.6	3.77	10	104
170	1.2	7.54	10	201
750	2	12.57	10.5	351

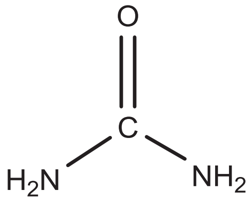

Fig. 2. Chemical structure of urea.

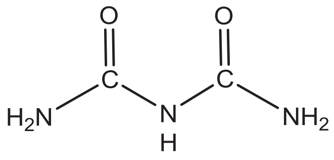

Fig. 3. Chemical structure of biuret.

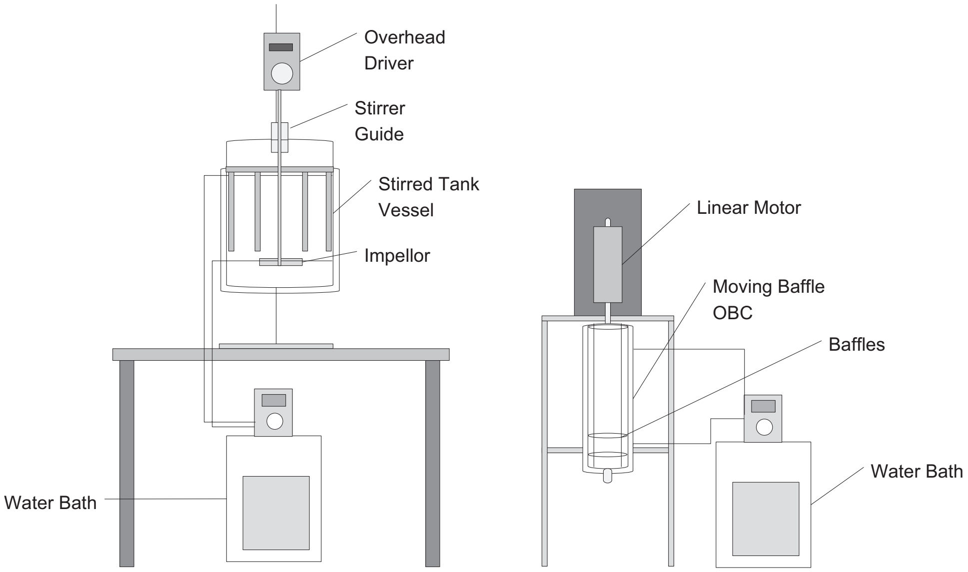

Fig. 1. Schematic illustration of STC and OBC set-up.

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