Optimisation of the Production of Ketoprofen Nanosuspensions using a Continuous Flow Millireactor

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Introduction

Nanotechnology has attracted considerable interest as a means of improving the dissolution rates and bioavailability of poorly soluble drugs. The production of nano-sized particles using top-down (size reduction) approaches requires high energy/pressure input, while bottom-up approaches (typically antisolvent precipitation as in this study) involve minimal mechanical energy input and may confer advantages of size uniformity and scalability. Here, we reported the use of a flow millireactor for continuous generation of ketoprofen nanosuspensions, assessing production optimisation and performance. A Design of Experiment (DoE) approach was used to identify optimal production characteristics while also assessing dissolution behaviour compared to batch reactor-generated nanosuspensions and mechanical sieved reconstituted microsuspension. This study aims to develop a platform for the continuous manufacture of a viable formulation for a poorly soluble drug.

Method

Ketoprofen (KTP) nanosuspensions were produced using a 3D printed miniaturised continuous stirred tank reactor (mCSTR, 3 mL) and a batch reactor (Figure 1) via antisolvent precipitation. Optimisation of the nanosuspension production method was conducted using 2^3 full factorial design (Table 1) with the following parameters: concentration of stabilising agent, polyvinyl pyrrolidone vinyl acetate 64 (PVPVA 64) at 5% and 10% w/v, solvent flow rate (0.5 and 1.0 mL/min) and stirring rate (250 and 500 rpm). KTP and PVPVA 64 were dissolved in ethanol (solvent phase) and deionised water (antisolvent phase) respectively prior to the antisolvent precipitation process. The physicochemical properties of the samples were characterised using dynamic light scattering (DLS), transmission electron microscopy (TEM) and wide-angle X-ray scattering (WAXS). The dissolution profiles of nanosuspensions were compared between the optimised nanosuspensions and a microsuspension (125-180 µm) of the same composition.

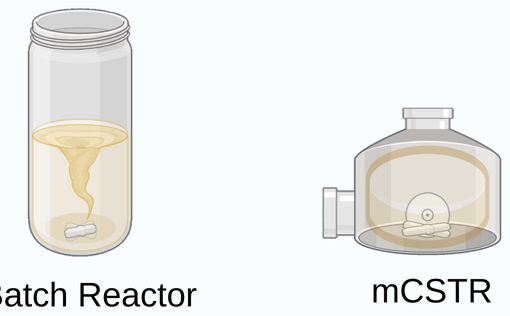

Figure 1: Illustrations of reactors. Batch reactor is a borosilicate vial (27.5 × 72 mm, 28.25 mL), mCSTR is a 3D printed resin model (16 × 16 mm, 3 mL).

Results

A similar optimised condition (DoE 7) at 5% w/v stabilising agent, 1.0 mL/min flow rate and 500 rpm stirring rate for both reactors was predicted using the JMP® Pro 17 best model approach. The continuous production of nanosuspensions using the mCSTR generated smaller KTP particles but at a broader size distribution compared to the batch reactor-generated nanosuspension (Figures 2-3). However, no significant difference ($p > 0.05$) in dissolution profile (Figure 4) and initial dissolution rate (Table 2) among nanosuspensions was noted but they were significantly ($p < 0.05$) higher compared to the microsuspension. This could be ascribed to the particle size reduction and amorphization of KTP (Figure 5). Optimised nanosuspensions showed an ability to maintain their particle size below 500 nm up to day 10 of preparation.

Table 1: List of conditions based on 2^3 full factorial design. The optimum condition predicted by the model was highlighted.

DoE	[PVPVA] (% w/v)	Solvent Flow Rate (mL/min)	Stirring Rate (rpm)
1	5	0.5	250
2	10	0.5	250
3	5	0.5	500
4	10	0.5	500
5	5	1.0	250
6	10	1.0	250
7	5	1.0	500
8	10	1.0	500

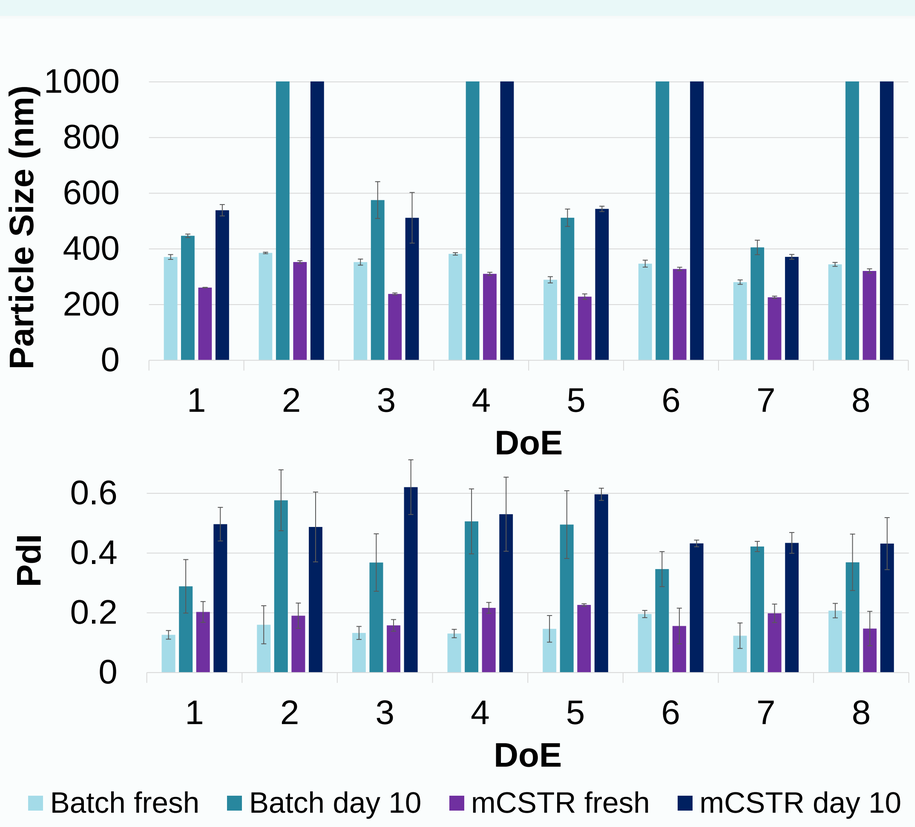

Figure 2: Hydrodynamic diameter and polydispersity index (PdI) of nanosuspensions measured using DLS.

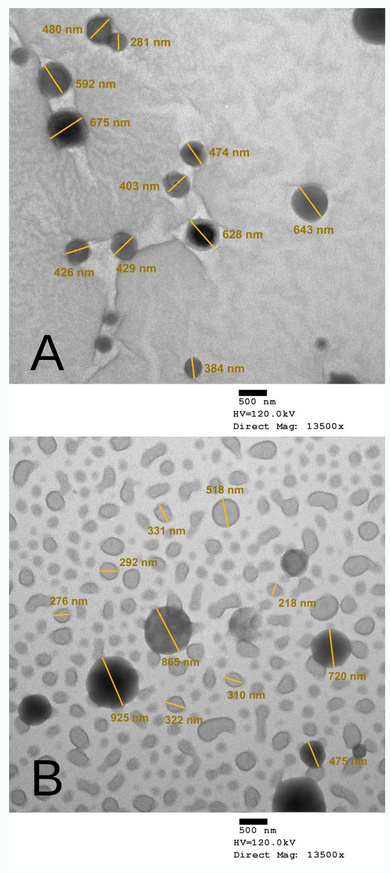

Figure 3: TEM image of (A) batch and (B) mCSTR suspension.

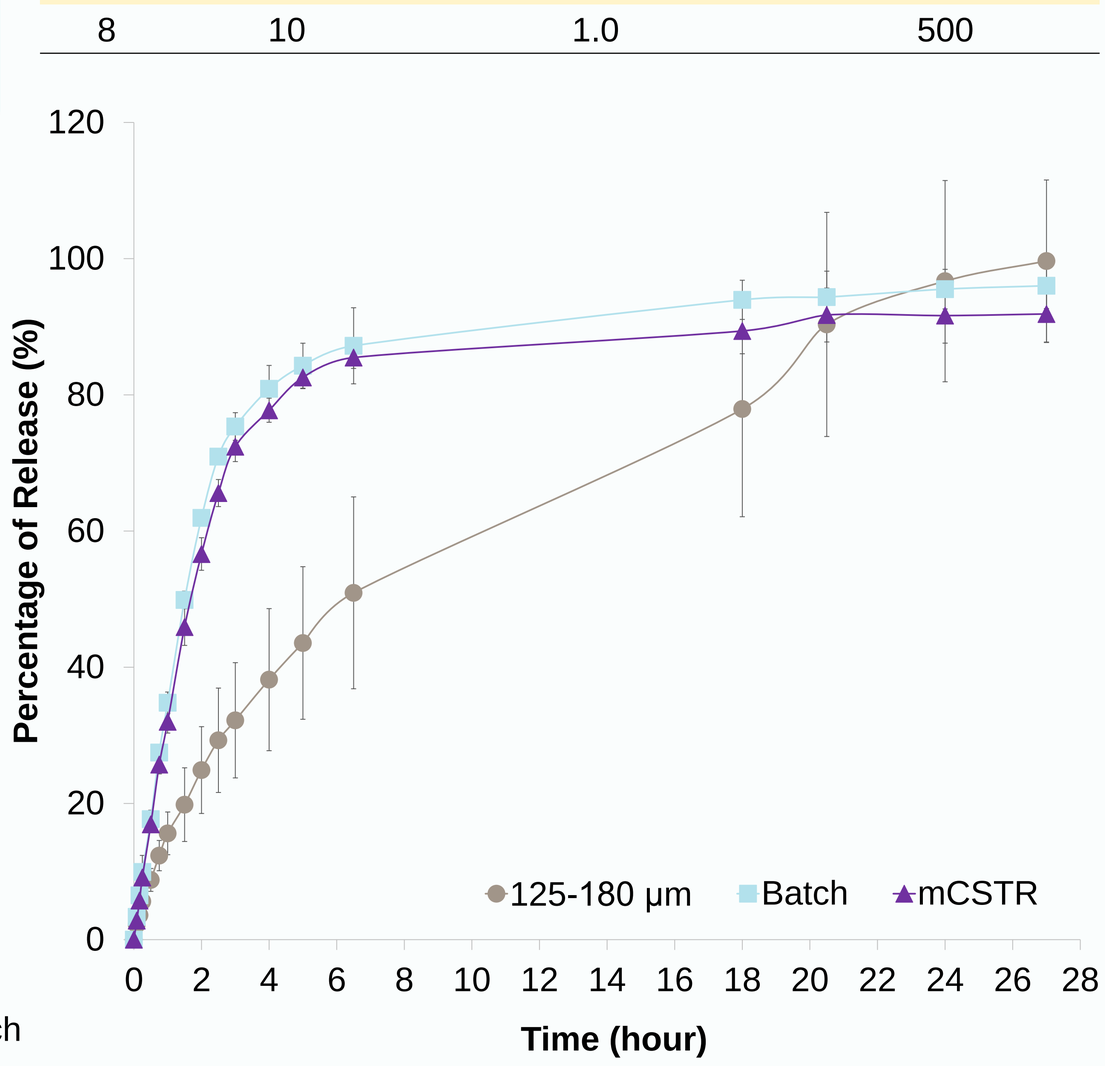

Figure 4: Dissolution profile of fresh sample, n = 3.

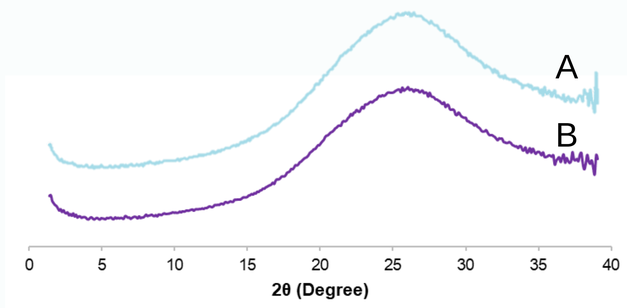

Figure 5: Diffractogram of (A) batch and (B) mCSTR nanosuspension.

Table 2: Initial dissolution rate of fresh sample, n = 3.

KTP	Dissolution Rate (%/min ± SD)	
	10 mins	30 mins
125-180 µm	0.36 ± 0.09	0.29 ± 0.06
Batch	0.65 ± 0.30	0.59 ± 0.04
mCSTR	0.57 ± 0.11	0.56 ± 0.03

Conclusion

No significant difference in dissolution profile was reported between mCSTR and batch reactor-generated nanosuspension. Therefore, continuous production of nanosuspensions using mCSTRs represents a promising approach in that this method potentially offers a higher throughput production than the batch reactor without detriment to characteristics or performance.

Acknowledgement: This research was supported by the Engineering and Physical Sciences Research Council (EPSRC) (EP/V050796/1).