Continuous Manufacturing of Ketoprofen Nanosuspensions using a Miniaturised Flow Reactor

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Background

- Continuous manufacturing has emerged as a transformative approach in pharmaceutical production as it avoids the intermittent processes inherent in traditional batch manufacturing.
- Transition from batch to continuous manufacturing solves various challenges, including fixed batch size, numerous sequential steps, interruptions and difficulties with upscaling batch processes.

Aim of Study

1. To identify the potential of a flow millireactor to continuously manufacture ketoprofen nanosuspensions in comparison to batch manufacturing.
2. 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) and a batch reactor (Figure 1) via antisolvent precipitation.
- Optimisation of the nanosuspension production method was conducted using 3^3 response surface design:
  1. Concentration of stabilising agent, polyvinyl pyrrolidone vinyl acetate 64 (PVPVA 64) at 2.5%, 5% and 10% w/v
  2. Solvent flow rate (0.25, 0.5 and 1.0 mL/min)
  3. Stirring rate (250, 500 and 1000 rpm)
- Samples investigation:
  1. Dynamic light scattering (DLS)
  2. Transmission electron microscopy (TEM)
  3. Wide-angle X-ray scattering (WAXS)
  4. Dissolution study

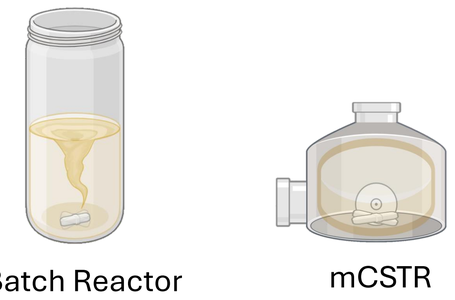
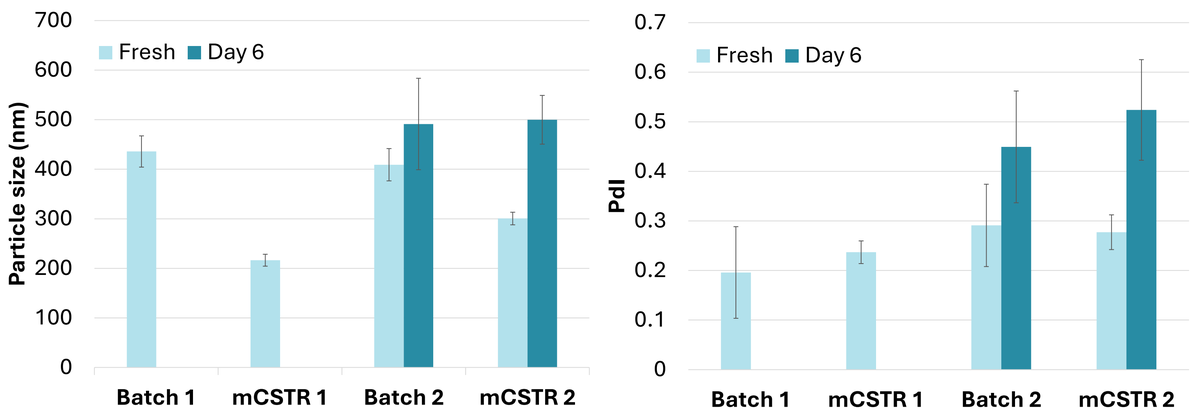


Figure 1: Illustrations of reactors. Batch reactor is a borosilicate vial (27.5 × 72 mm, 28.25 mL), mCSTR is a 3D printed resin model (16 × 16 mm, 3 mL).

Results

- Two conditions were selected to proceed with investigation:
  1. 2.5% w/v stabilising agent, 250 rpm stirring rate and 0.5 mL/min solvent flow rate – selected based on JMP® Pro 17 best model approach [Batch 1, mCSTR 1]
  2. 5.0% w/v stabilising agent, 1000 rpm stirring rate and 1.0 mL/min solvent flow rate – manually selected based on sample stability observation [Batch 2, mCSTR 2]
- mCSTR generated significantly ($p < 0.05$) smaller amorphous KTP particles with no significant difference ($p > 0.05$) in polydispersity index compared to the batch reactor (Figures 2-4).
- No significant difference ($p > 0.05$) in dissolution profile (Figure 5) and initial dissolution rate (Table 1) among nanosuspensions.



* Day 6 measurement for Batch 1 and mCSTR 1 were excluded as samples failed to resuspend

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

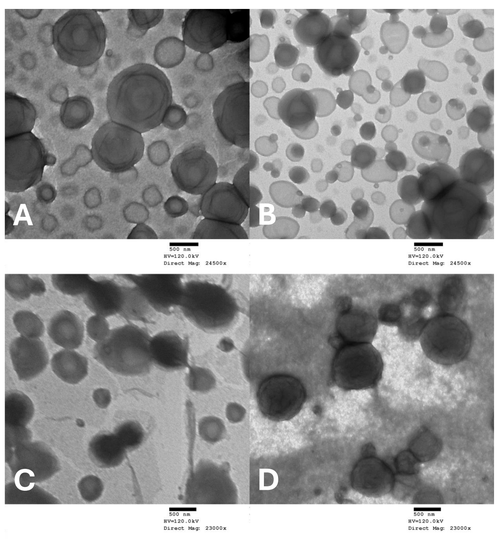


Figure 3: TEM image of fresh (A) Batch 1 and (B) mCSTR 1 (C) Batch 2 and (D) mCSTR 2 nanosuspension.

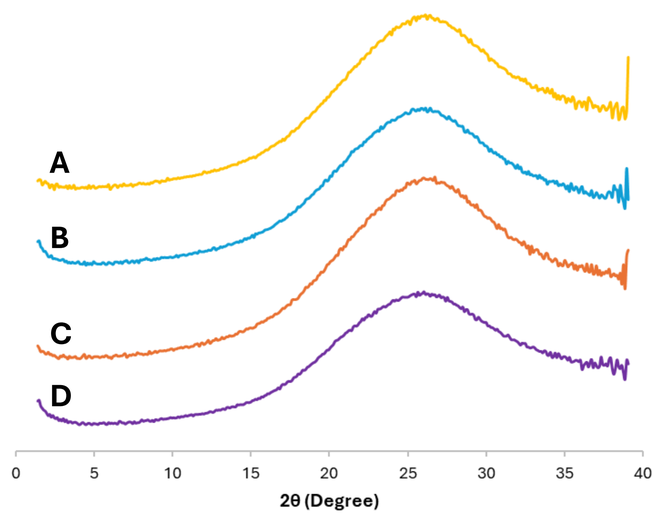


Figure 4: Diffractogram of fresh (A) Batch 1 and (B) mCSTR 1 (C) Batch 2 and (D) mCSTR 2 nanosuspension.

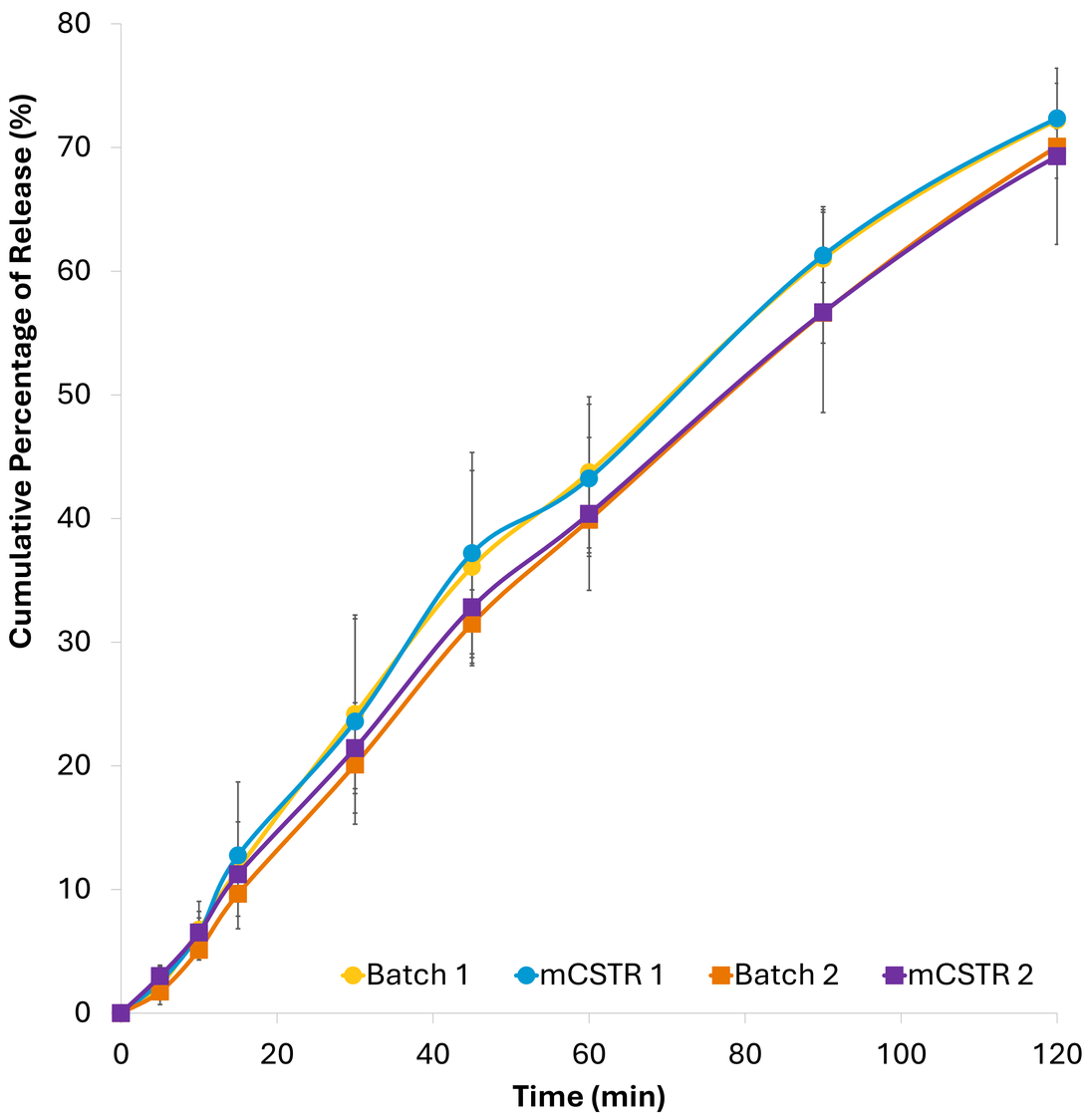


Figure 5: Dissolution profile of fresh sample, n = 3.

Table 1: Initial dissolution rate of fresh sample, n = 3.

Sample	Dissolution rate (%/min)	
	10 mins	30 mins
Batch 1	0.67 ± 0.23	0.81 ± 0.27
mCSTR 1	0.64 ± 0.18	0.79 ± 0.28
Batch 2	0.51 ± 0.08	0.67 ± 0.06
mCSTR 2	0.63 ± 0.15	0.69 ± 0.13

Conclusion

- No significant difference in dissolution profile was reported between mCSTR and batch reactor-generated nanosuspension.
- The continuous production of nanosuspensions using mCSTR therefore shows great promise as an alternative to batch reactors due to its potential for a higher throughput production yield.

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