

Scalability and Batch vs. Continuous Processing of Anti-Solvent Co-Precipitation for the Production of Amorphous Solid Dispersions (ASDs)

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INTRODUCTION

Many Active Pharmaceutical Ingredients (APIs) exhibit poor aqueous solubility. Amorphous Solid Dispersions (ASDs), where the API is present in its amorphous form, have emerged as a means to enhance the aqueous solubility of APIs. Among the different methods that exist to produce ASDs, hot melt extrusion and spray-drying are already well-known and commonly used by pharmaceutical companies, while gaps still exist in the understanding of co-precipitation (CP), preventing it from being widely used at an industrial scale. In this work, the scalability of the ASD CP production process has been studied for the CP of the model API, hydrochlorothiazide (HCTZ), with two different polymers (Soluplus® and PVP-VA), based on previously published work (Myślińska et al., 2023). The objectives of the current project were to: (i) adapt the existing CP process from 10 mL vials to 100 mL and 1 L reactors, (ii) to evaluate the feasibility of undertaking CP by continuous, rather than batch, processing, and (iii) to characterise and compare the resulting products between the two batch reactor sizes and the batch versus continuous reactors.

METHODS

(1) The CP process previously reported at the EasyMax™ scale (Mettler Toledo 100 mL reactor) was adapted by using a peristaltic pump instead of a manual syringe for automatic addition of the API/polymer solution to the antisolvent (AS) which was held in the reactor vessel (Figure 1). For the feed solution, 1 g of API/polymer mixture [40/60 w/w] was dissolved in 20 mL ethanol. Whereas previously (at the 10 mL vial scale) hexane was used as AS, here both hexane and heptane were trialled as AS for the process.

(2) The CP process was scaled up to the OptiMax™ scale (500 mL in a Mettler Toledo 1 L reactor), using heptane as AS. Several stirring speeds and solution addition rates were trialled, using 5 g of API/polymer mixture [40/60 w/w] dissolved in 100 mL ethanol.

(3) The CP process was adapted from batch reactors to a Laminar Continuous Taylor Flow Reactor (LabII-HC) (LCTR®) system (150 mL reactor), where the ethanol API/polymer solution and heptane were separately and continuously pumped into the reactor (Figure 2).

Solid state characterisation of filtered and dried product was performed by DSC and PXRD. Thermogravimetric analysis was utilised to determine residual solvent content.

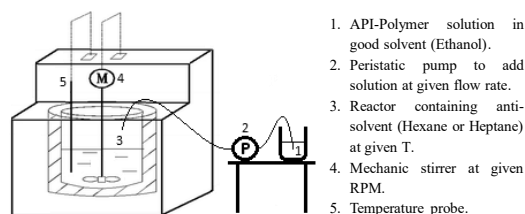


Figure 1. Schematic representation of an EasyMax™/OptiMax™ (Mettler Toledo) reactor CP process.

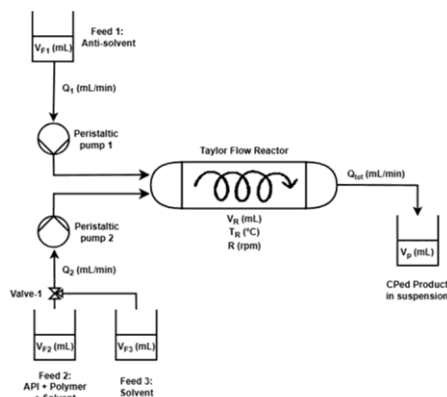


Figure 2. Schematic representation of the Continuous Taylor Flow Reactor (Laminar) CP process.

RESULTS

CP Process at the EasyMax™ (100 mL reactor) Scale

Results obtained using the pump were similar to previous results with the syringe (Myślińska et al., 2023) (Table 1). All products were ASDs (similar to what was observed at the 10 ml scale) and all were obtained in similar yields. Slightly higher yields were obtained when heptane was used as the AS compared to hexane experiments, but a significant increase in % residual solvent content (%RSC) values was observed, causing a decrease in glass transition temperature (T_g).

Table 1. Comparison of the results of Co-Precipitation of HCTZ between the EasyMax™, OptiMax™ and LCTR® reactors.

Sample composition	EasyMax™ results with hexane as AS		EasyMax™ results with heptane as AS		OptiMax™ results with heptane as AS		LCTR® results with heptane as AS	
	HCTZ + Soluplus®	HCTZ + PVP-VA	HCTZ + Soluplus®	HCTZ + PVP-VA	HCTZ + Soluplus®	HCTZ + PVP-VA	HCTZ + Soluplus®	HCTZ + PVP-VA
Yield (%)	64.82 ± 1.70	62.41 ± 2.70	68.45 ± 1.20	71.54 ± 0.16	75 – 85	77 – 82	32.38 ± 2.84	35.75 ± 1.87
RSC (%)	3.15 ± 0.05	4.43 ± 0.85	5.74 ± 0.67	5.10 ± 0.39	6.5 – 7.5	5 – 6	5.26 ± 0.28	5.06 ± 0.54
T _g (°C)	100.55 ± 0.55	120.40 ± 2.20	97.80 ± 1.92	122.01 ± 3.90	~ 85	~ 115	99.46 ± 0.91	125.31 ± 1.75
D ₅₀ (µm)	182.2 ± 14.2	145.9 ± 4.2	215.2 ± 5.7	159.3 ± 16.9	200 – 400	130 – 200	119.7 ± 1.6	102.3 ± 6.7

CP Process at the OptiMax™ (500 mL) Scale

Higher yields (80% ± 5%) were obtained for all ASD products compared to the EasyMax™, due to lower product losses. CP products were dried for 5 days at 60 °C, however RSCs were high (5.0 -7.5% w/w), leading to T_gs being lower than ASDs generated in the EasyMax™ (Table 1). The median particle size of CP products was found to be affected by both stirrer speed and solution addition rate.

Reducing the High Residual Solvent Content

RSCs obtained were considered excessive in the context of European safety regulations, and so several options were evaluated in an attempt to reduce the RSC: (1) Increasing the drying temperature, (2) using a more volatile AS (diethyl ether) to wash CP products, (3) using a more volatile AS (diethyl ether) to replace heptane as the AS in the reactor. A significant decrease in %RSC was observed when diethyl ether was used to wash CP products (3.7%), and the reduction was even more significant when this solvent was used as the AS directly in the CP process (2.0%), compared to increasing the drying temperature (4.8%).

CP Process in the Continuous LCTR®

Lower yields (34% ± 2%) were obtained for all ASD products in the LCTR®, compared to the batch reactors (Table 1), because of issues associated with linking the process with the filtration set-up. However, T_gs and RSCs were consistent with the values obtained at the EasyMax™ scale, compared to values obtained at the OptiMax™ scale where RSCs were higher, leading to lower T_gs. The median particle size of CP products was found to be the smallest of all the scales studied, which is promising for future tableting studies.

CONCLUSION

The HCTZ-polymer CP process is robust enough to be scaled up to 500 mL scale in batch reactors. This CP process was also shown to be suitable for continuous processing. As expected, the CP products were all ASDs, as characterised by DSC and PXRD. However, removal of residual solvent from CP products is a challenge. Samples with PVP-VA had lower median particle size than those with Soluplus®, but the smaller particle size did not result in a lower RSC. The use of diethyl ether, a more volatile AS, was found to facilitate a reduction in the %RSC of samples. Unfortunately, the use of diethyl ether as the main AS is not suitable at large scale due to health and safety issues. Ongoing studies are being conducted to investigate more and different process conditions and systems on the LCTR® system.

ACKNOWLEDGEMENT

This project is funded by a Trinity College Dublin Panoz Pharmaceutical Innovation Scholarship.

We would like to thank Laminar Co., Ltd. for the loan of their Taylor Flow reactor to University College Dublin and James Anderson from Analytik Ltd. for facilitating the loan and for useful discussions.

REFERENCES

1. Myślińska, M.; Stocker, M.W.; Ferguson, S.; Healy, A.M., A Comparison of Spray-Drying and Co-Precipitation for the Generation of Amorphous Solid Dispersions (ASDs) of Hydrochlorothiazide and Simvastatin. *Journal of Pharmaceutical Sciences*, 112, 2097-2114 (2023).