The use of a novel microwave antisolvent-precipitation technique for the synthesis of bioactive nanoparticles

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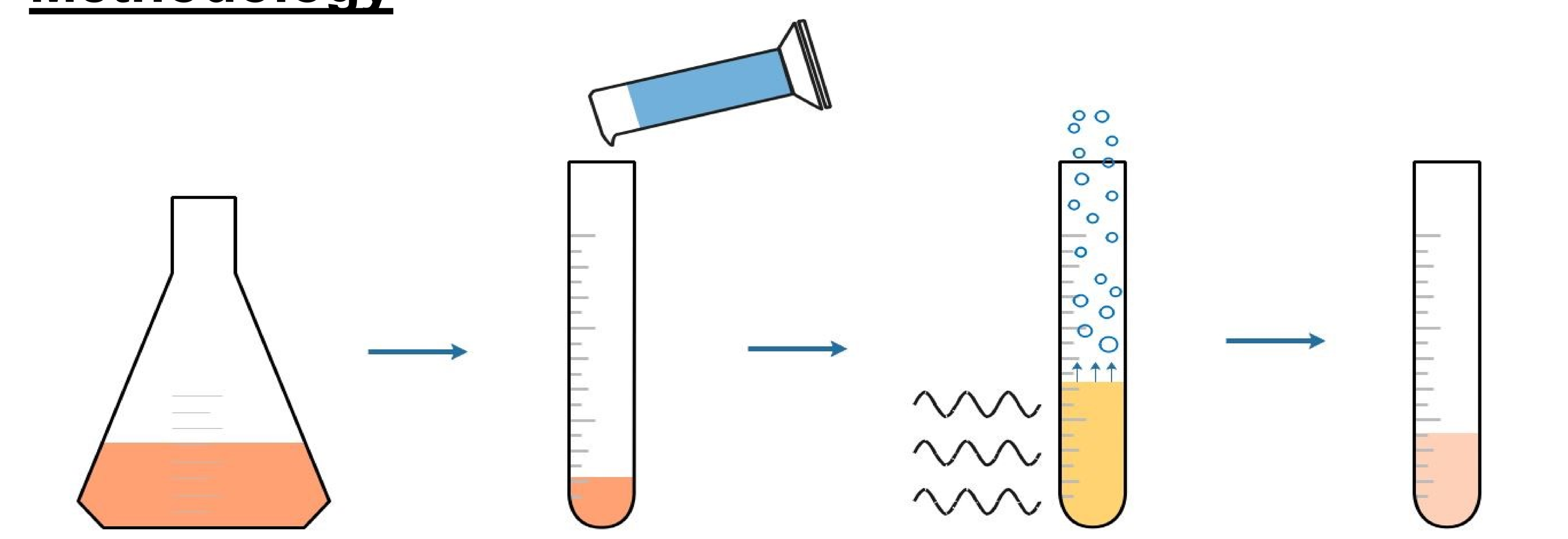
Introduction

- A wide variety of bioactive compounds are present in plant and animal products which can provide numerous health benefits. However, many suffer limited oral bioavailability due to their poor aqueous solubility.
- Nanonisation of bioactive compounds can drastically increase dissolution velocity and ultimately improve the bioavailability of bioactive compounds upon consumption.
- Microwave antisolvent precipitation (MAP) represents a novel nanoparticle fabrication technique. Microwaves can provide rapid and selective heating which results in effective solvent removal which it was hoped could create a 'second wave' of high supersaturation after mixing solvent and antisolvent phases.

Methodology



1. Dissolve bioactive compound in solvent
2. Add anti-solvent to solvent
3. Apply microwave energy for solvent evaporation
4. Obtain nano-suspension

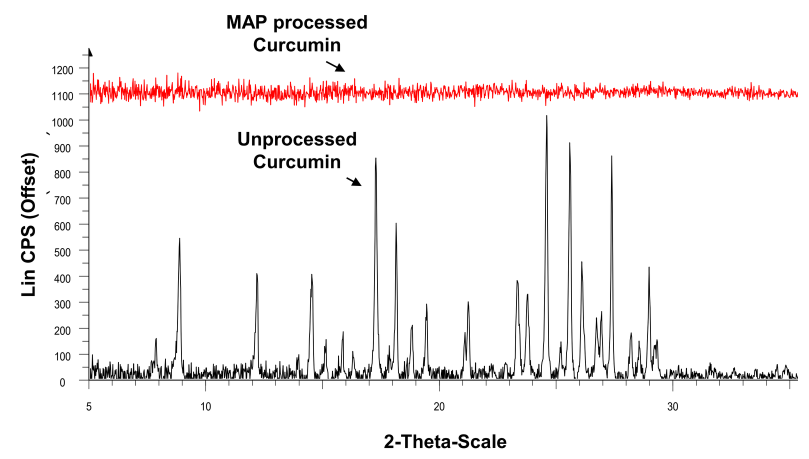
Effect of Processing and Formulation Parameters

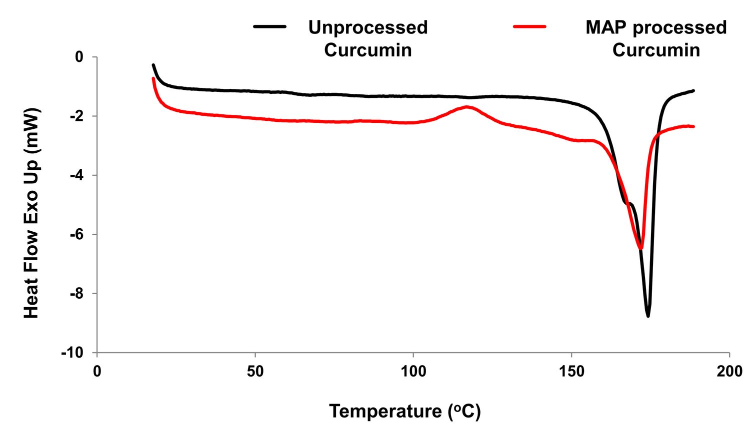
- The effects of various processing and formulation parameters on the particle size and polydispersity index (PDI) of curcumin, a model water-insoluble bioactive compound, were investigated.
- Smaller particle sizes were achieved using lower pressures, greater solvent concentrations, and lower solvent : antisolvent (SAS) ratios. The power-time split and hence, the rate of solvent evaporation, was found to have no effect on particle size.

Pressure (kPa)	Average Size (nm)	PDI	Concentration (mg/ml)	Average Size (nm)	PDI
0	119 ±6	0.15	0.5	ND	ND
-90	179 ±1	0.06	1	254 ±84	0.40
-93	169 ±6	0.07	2	165 ±2	0.18
-96	148 ±10	0.07	4	148 ±10	0.09
Power-Time Split	**Average Size (nm)**	**PDI**	**SAS Ratio**	**Average Size (nm)**	**PDI**
20W, 10mins	159 ±13	0.09	1:7.5	235 ±30	0.07
50W, 4mins	148 ±10	0.07	1:10	169 ±2	0.14
100W, 2mins	135 ±3	0.13	1:20	152 ±4	0.06
200W, 1 mins	148 ±2	0.15	1:30	148 ±10	0.07

Solid State Characterisation

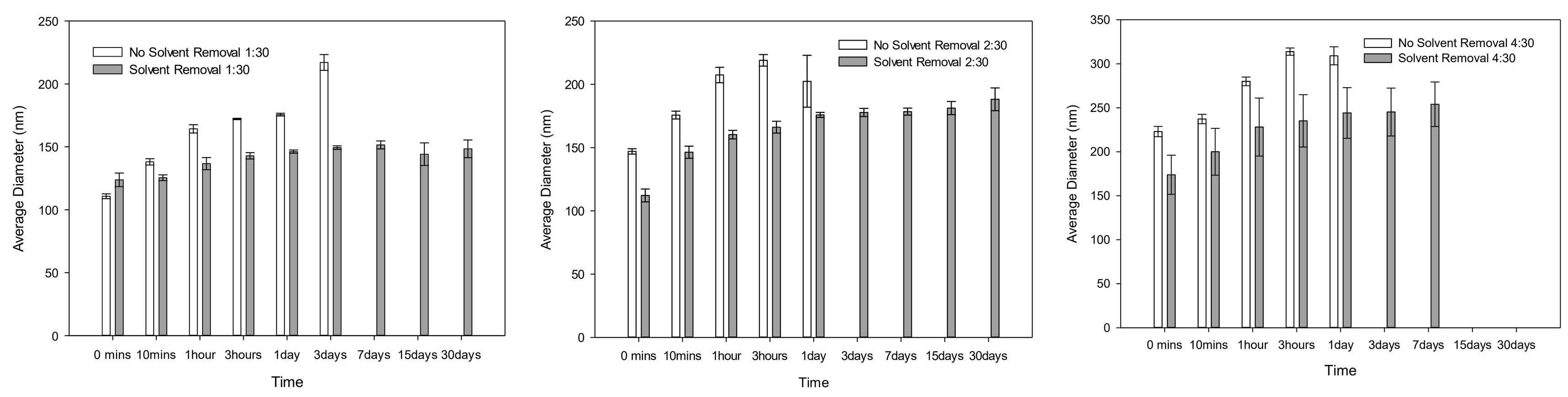
- X-ray diffraction (XRD) and differential scanning calorimetry (DSC) studies were performed on both unprocessed curcumin, and curcumin which had undergone the MAP technique.
- XRD studies showed the disappearance of the sharp, characteristic crystalline peaks of curcumin once the MAP technique was used.
- DSC studies showed a significant reduction in the enthalpy of melting for curcumin which had undergone the MAP technique compared with unprocessed curcumin.
- Both the XRD and DSC studies are in agreement with each other and show that curcumin is transformed from a crystalline, to a more amorphous morphology after the MAP technique is used; this enhances dissolution velocity.



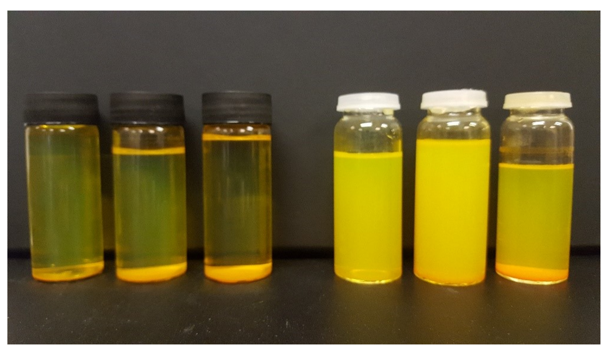


The Impact of Solvent Removal on Nanosuspension Stability

- The MAP technique is capable of rapidly removing solvent from SAS mixtures. Therefore, the impact of solvent removal on nanosuspension stability at different SAS ratios was assessed:



- At every SAS ratio used, the use of the MAP technique to remove solvent was found to produce nanosuspensions which were stable for significantly longer periods than those in which there was no solvent removal.
- This is because, there is a far greater amount of diffusible solute (curcumin) present in nanosuspensions which did not undergo the MAP technique due to the presence of solvent.
- Diffusible solute will preferentially attach onto larger nucleated particles over time through Ostwald Ripening which promotes increased particle size, polydispersity and instability.



Stability of curcumin nanosuspensions after 15days at increasing SAS ratios in which there had been (SR), and had not been (NSR) solvent removal. Left to right 1) NSR 1:30, 2) NSR 2:30, 3) NSR 4:30, 4) SR 1:30, 5) SR 2:30, 6) SR 4:30.

Conclusions

- In this study, the MAP technique has been successfully used to produce amorphous curcumin nanoparticles suspended in aqueous media with a high degree of monodispersity and stability. The nanoparticles produced will have enhanced dissolution velocity and improved bioavailability.
- The MAP technique is a rapid process which utilises one of the alternate sources of green energy (microwave heating) used in both food and pharmaceutical industries; thus the developed MAP technique could have useful application in both these fields.

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