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

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Bioactive compounds

- These are the extra-nutritional components in food which are capable of providing numerous health benefits upon consumption.
- A wide variety of Bioactive Compounds (BC's) can be found in nature.
- However, unfortunately many BC's suffer limited oral bioavailability which is often due to their poor aqueous solubility.

Nanonisation Techniques

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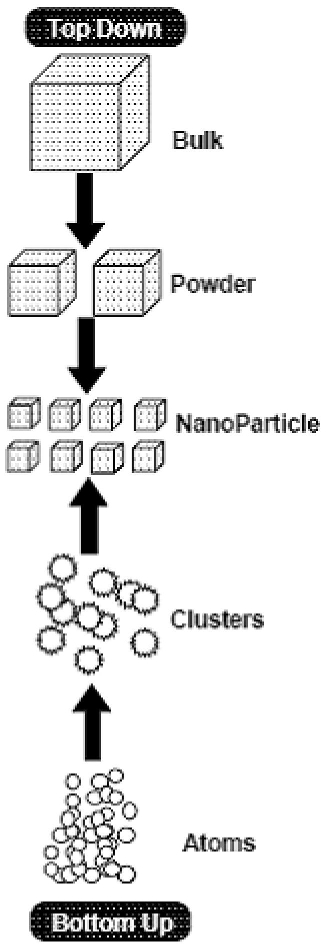

Figure 1: Top Down Vs Bottom Up

- Top Down Techniques- E.g High Pressure homogenisation and milling.

  ➢ These techniques are generally well established and typically capable of processing large throughputs with a high energy demand.

- Bottom Up Techniques- E.g. Antisolvent precipitation, and spontaneous emulsification.

  ➢ These techniques are generally less energy intensive and give greater control over particle properties.

Top Down vs Bottom Up Image, Gitam University, http://www.gitam.edu/eresource/nano/NANOTECHNOLOGY/synthesis_and_processing_of_nano.htm, Accessed 17/11/16

Microwave Antisolvent Precipitation (MAP) Technique

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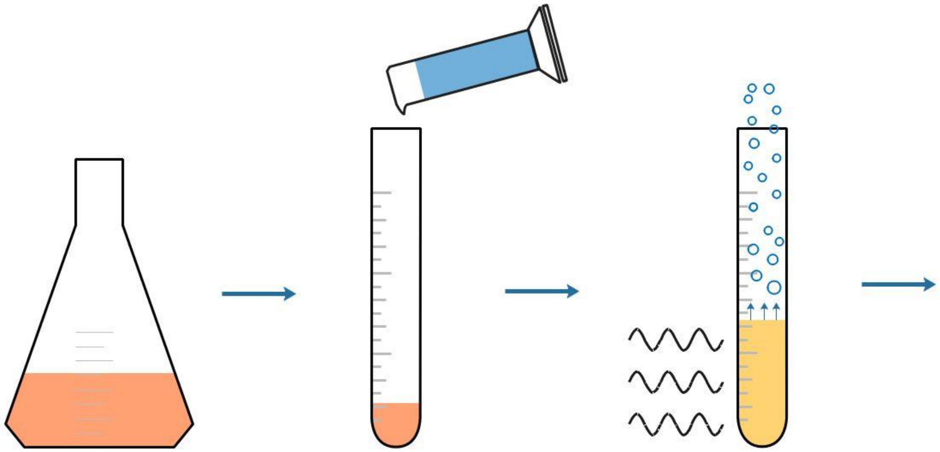

1. Dissolve bioactive compound in solvent
2. Mix antisolvent with solvent
3. Apply microwave energy for solvent evaporation
4. Obtain Nanosuspension

In this study:

Bioactive Compound- **Curcumin**

Solvent- **Ethanol**

Antisolvent- **Water**

Huge reduction in solvent quality and 'first wave' of supersaturation. However the reaction is incomplete.

Rapid solvent removal through microwave heating further reduces solvent quality and generates a 'second wave' of high supersaturation.

Nanosuspension has greatly enhanced physical stability due to solvent removal.

Effect of Processing and Formulation Parameters on Particle Size

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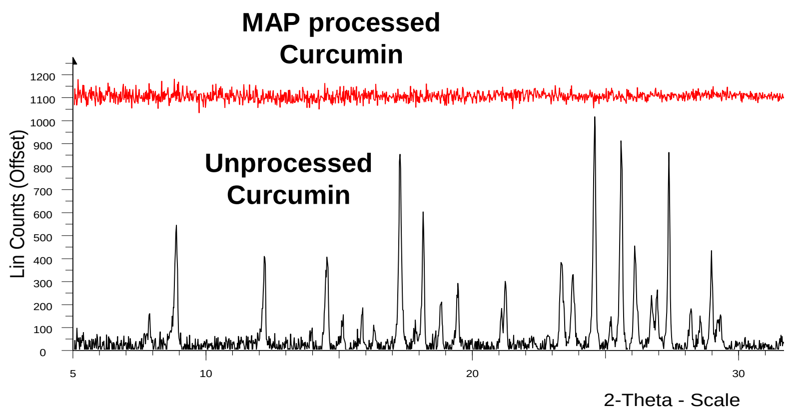
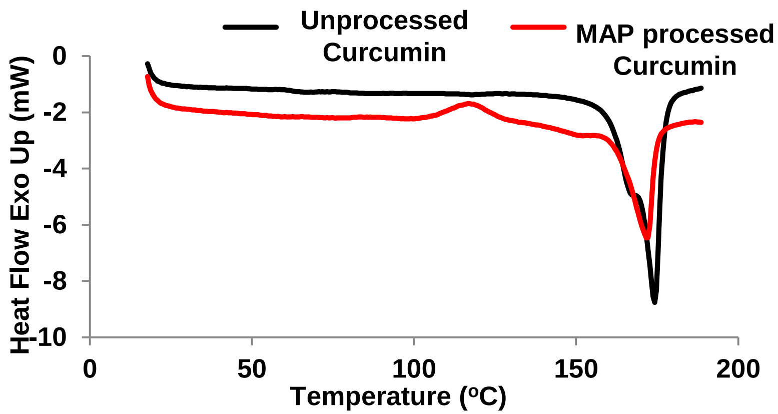
Pressure (kPa)	Average Size (nm)	PDI	Concentration (mg/ml)	Average Size (nm)	PDI
0	191 ±6	0.15	0.5	ND*	ND*
-90	179 ±1	0.06	1	254 ±84	0.40
-93	169 ±6	0.07	2	165 ±2	0.18
-96	148 ±10	0.07	4	148 ±10	0.09
Power-Time Split	**Average Size (nm)**	**PDI**	**SAS Ratio**	**Average Size (nm)**	**PDI**
20W, 10mins	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

*ND- Not Determined

Solid-State Characterisation

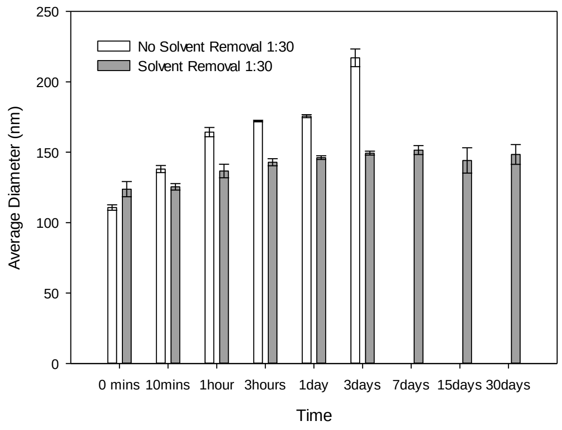
- X-ray Powder Diffraction (XRD) and Differential Scanning Calorimetry (DSC) was performed to assess changes in the degree of crystallinity of curcumin post-processing.

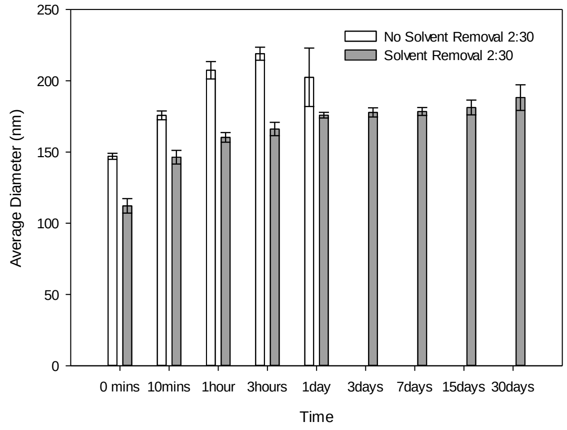


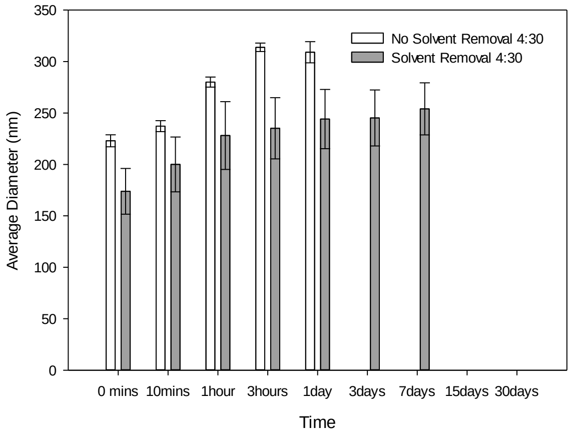


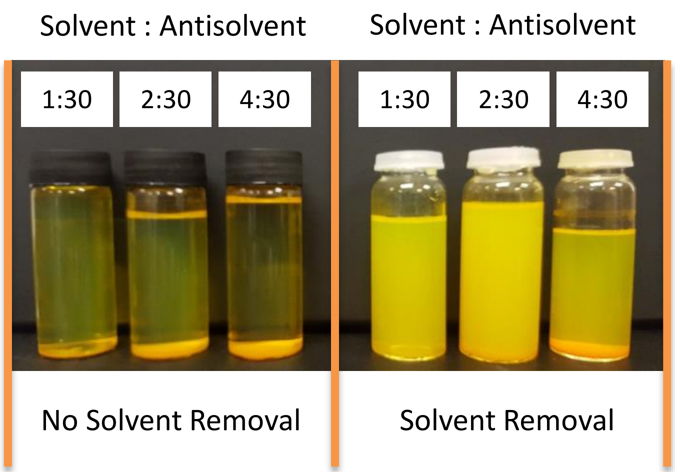
- XRD studies shown the disappearance of the sharp, characteristic crystalline peaks of curcumin once the MAP technique was performed.
- Both the XRD and DSC studies are in agreement with each other and show that curcumin in transformed from a highly crystalline, to a more amorphous morphology post-processing.
- DSC studies showed a significant reduction in the enthalpy of melting of curcumin once the MAP technique was used.

Impact of Solvent Removal on Nanosuspension Stability









Visual appearance of nanosuspensions after 15days

- At all SAS ratio's solvent removal through the MAP technique dramatically improved the physical stability of nanosuspensions from durations of ~1day to in excess of 1 week.
- MAP is a rapid technique which can be completed in a matter of minutes – but, nanosuspension stability can be dramatically improved through use of this process.

New Hypothesis

- The driving force for precipitation comes, almost entirely from the solvent-antisolvent mixing step.

- Solvent removal causes a negligible amount of precipitation in comparison.

- However, solvent removal is very important for the long term stability of curcumin nanosuspensions and can be quickly achieved using the MAP technique.

Conclusions

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- Curcumin has been successfully nanosized from an average particle diameter of ~20μm to ~0.15μm.
- Nanosuspensions were produced which exhibited relatively low polydispersity (PDI < 0.1) and significantly improved stability over samples produced in which there was no solvent removal.
- The MAP technique is a rapid process which utilises one of the alternate sources of green energy used in both food and pharmaceutical industries. Thus, this technique could have useful application in both these fields.