Electronic Supplementary Material (ESI) for CrystEngComm.


# Particle Formation Pathways and Polymorphism of Curcumin Induced by Ultrasound and Additives During Liquid Antisolvent Precipitation

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## Experimental

**Materials:** Curcumin (from *Curcuma longa* (Turmeric) >65% curcumin), sodium dodecyl sulfate (SDS) (99+ % A.C.S. reagent), Tween 80, bovine serum albumin (BSA), hydroxypropyl methyl cellulose (HPMC; 80−120 cPs, FCC), and polyvinyl pyrrolidone (PVP) were purchased from Sigma-Aldrich Inc. India. Ethanol was purchased from Changshu Yangyuan Chemicals, China. Solvents used in experimental work were analytical grade reagents. All these chemicals were used without further purification. Deionized Millipore water was used as an antisolvent.

**Precipitation of Curcumin Particles:** Organic solution of curcumin in ethanol (5 mg/mL) was introduced in water (100 mL) containing surfactant (0.02 wt% in water) or without surfactant, maintained at a constant temperature (1° C) quickly in presence of ultrasound. The ultrasound horn was immersed in antisolvent. The tip (1″ ID) of an ultrasound horn (Sonics, USA) was directed over a surface of solvent-antisolvent mixture solution such that the solution can be dispersed instantaneously by vibrations (at 100% ultrasound amplitudes for 10 min). A jacketed glass vessel of 7 cm diameter and L/D ratio of 1.7 was used. The vessel volume was approximately 500 mL. For without ultrasound case, curcumin particles were precipitated with mechanical stirring at 1200 rpm for 10 min using an overhead agitator. The agitator used was a three bladed pitch blade turbine with diameter of 4 cm.

**Characterization of Particles***:* Particle morphology of curcumin was examined using SEM mode on Field Emission-SEM (JSM 7600F, JEOL Japan). The AFM analysis was done using Bruker Multimode 8 with ScanAsyst scanning mode. Surface morphology and selected area electron diffraction (SAED) analysis of curcumin particles was carried out using transmission electron microscopy (HR-TEM, JEM2100, from Japan) operating at 200 kV available with ICT Mumbai and (HR-TEM, FEI Technai G2 F20, FE TEM, USA) operating at 200 kV available with NIPER Mohali. Curcumin particles suspensions were diluted with deionized water and then drop of sample was placed on copper grid coated with carbon and drop was air-dried before analysis. The curcumin suspensions were freeze-dried using Martin Christ (ALPHA 2-4 LD plus) freeze dryer for overnight with temperature and vacuum conditions of -43°C and 0.090 mbar respectively. The lyophilized curcumin powder was then used for X-Ray powder diffraction (XRPD) analysis using X-Ray Diffraction System (XRD), (D8 Discover, Bruker AXS GmbH, Germany). Freely available Mercury software Version 3.1 was used to assign crystal planes using crystallographic information file (CIF) available in the literature[42]. The CIF was also used for molecular packing analysis using Mercury software. TGA-DSC analysis was carried out using NETZSCH STA 449F3 Jupiter ® -simultaneous TGA-DSC (Germany) in temperature range of 30-1000° C, with heating rate of 10 degree/min. Fourier-Transform Infrared Spectroscopy analysis of curcumin powders and as received curcumin was carried out using Thermoscientific Nicolet iS10 spectrophotometer. For FTIR analysis blank air spectra was recorded and then sample spectra was recorded by placing curcumin powder on the surface pane where beam is projected and FTIR was recorded. Enough sample was kept to avoid any interference in recording from surrounding.

**Table.S 1. Form of precipitated curcumin particles without stabilizer and with stabilizers.**

| Precipitation Condition | Curcumin Form |
|---|---|
| No stabilizer and no ultrasound | Form 1 (Monoclinic) |
| No stabilizer and 105 W ultrasound | Form 3 (Orthorhombic) |
| SDS and 105 W ultrasound | Form3 (Orthorhombic) |
| Tween 80 and 105 W ultrasound | Form 3 (Orthorhombic) |
| BSA and 105W ultrasound | Form 3 (Orthorhombic) |
| HPMC and 105 W ultrasound | Form 3 (Orthorhombic) |
| PVP and 105 W ultrasound | Form 2 (Orthorhombic) |

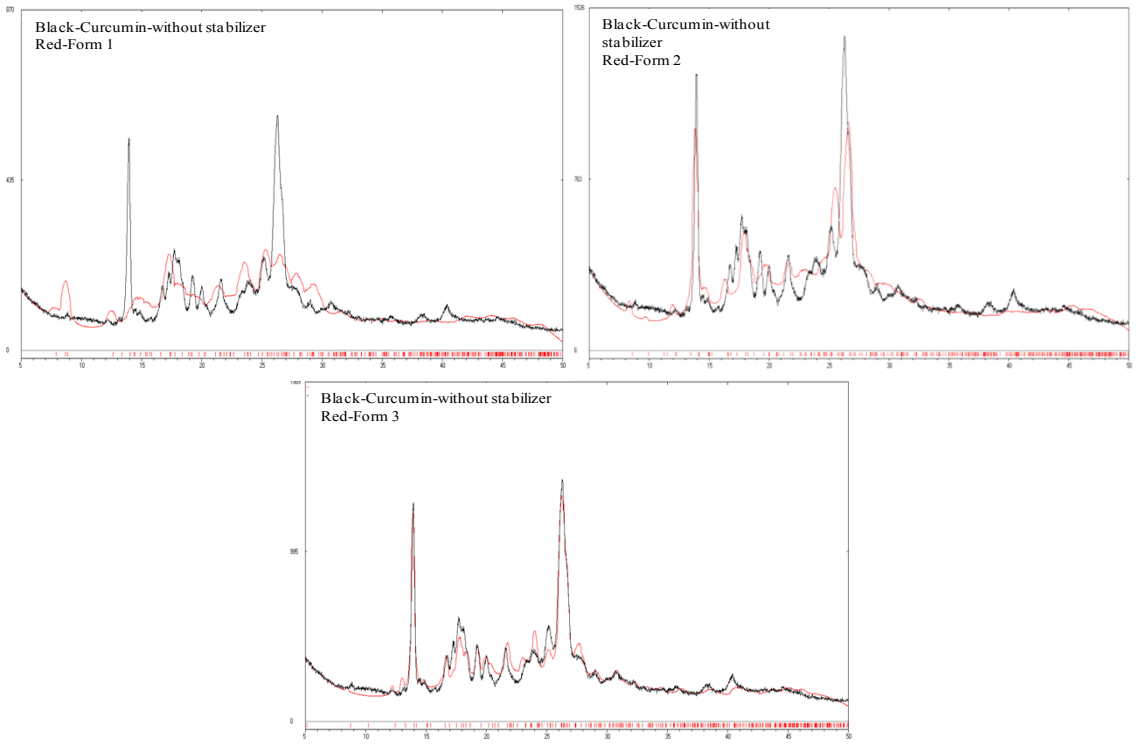



**Figure S1. PXRD pattern of curcumin particles precipitated with ultrasound and without stabilizer, compared with PXRD patterns of Curcumin Form 1, Form 2, and Form 3.**

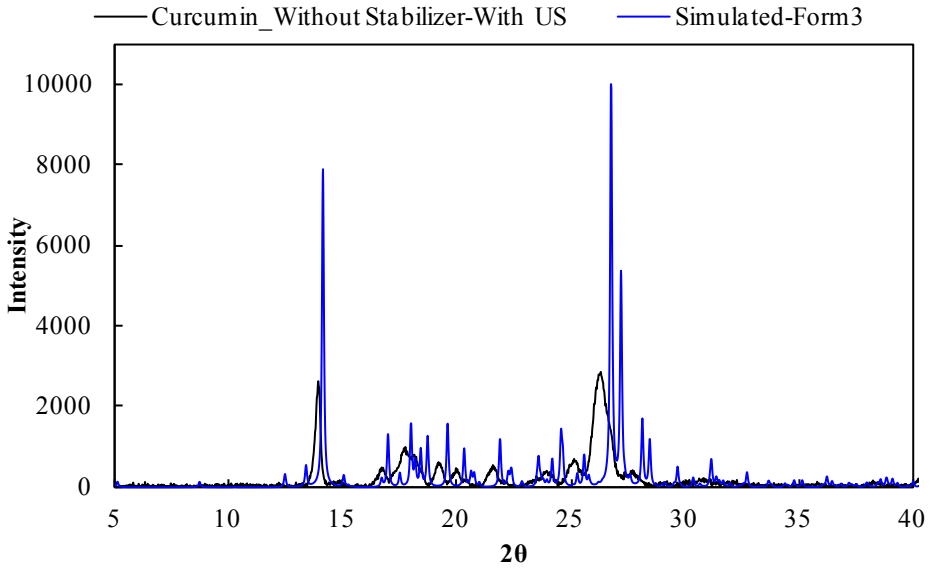



**Figure S2. PXRD pattern of curcumin particles precipitated with ultrasound and without stabilizer, compared with simulated Form 3.**

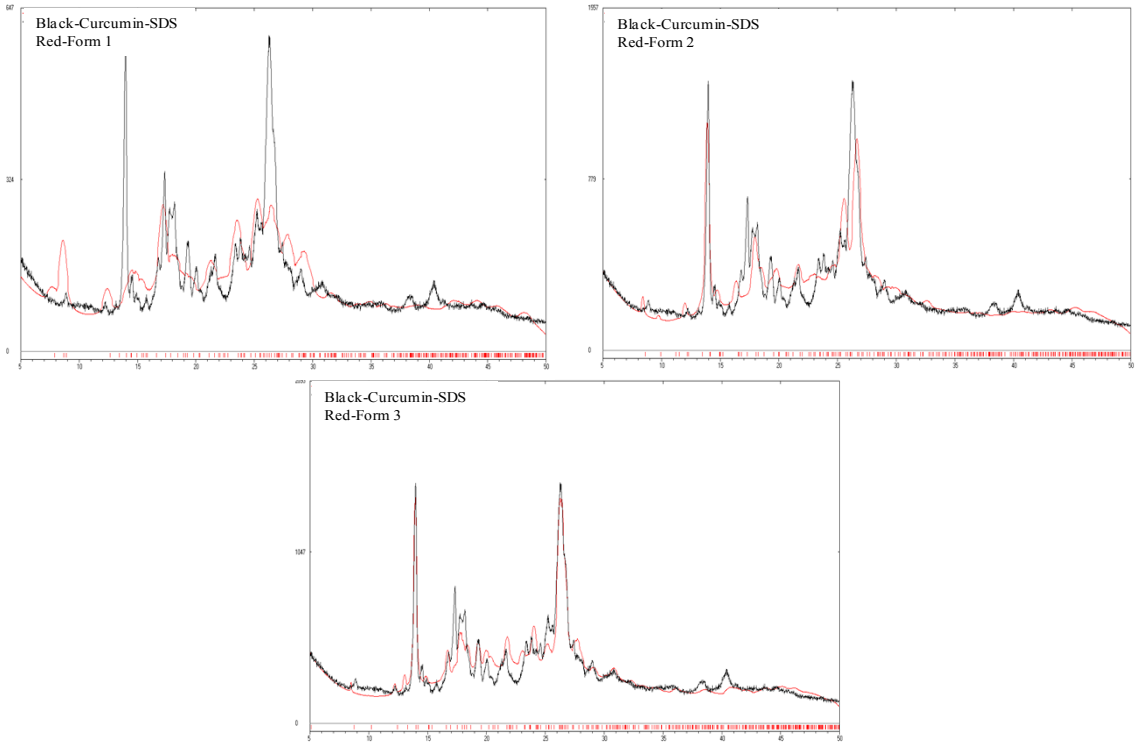



**Figure S3. PXRD pattern of curcumin particles precipitated with ultrasound and SDS, compared with PXRD patterns of Curcumin Form 1, Form 2, and Form 3.**

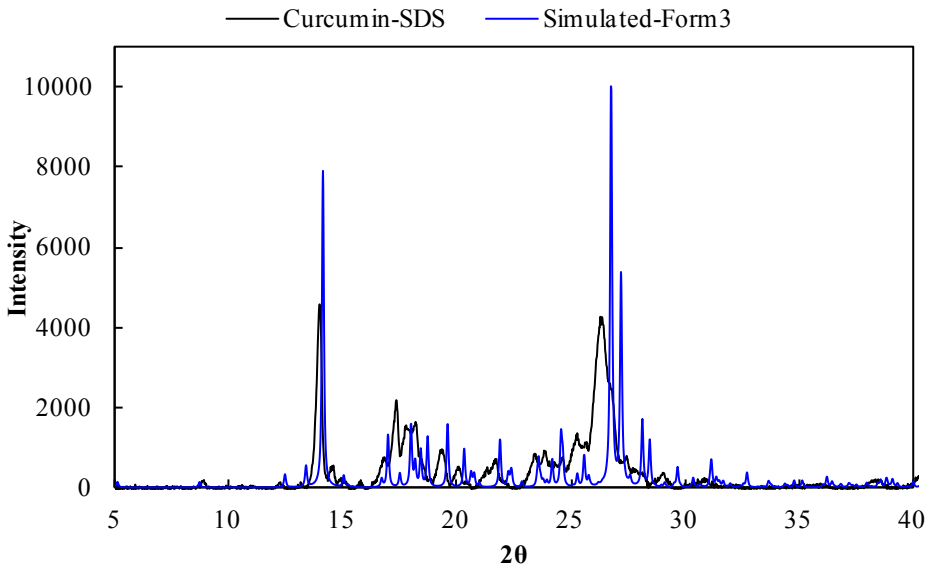



**Figure S4. PXRD pattern of curcumin particles precipitated with ultrasound and SDS, compared with simulated Form 3.**

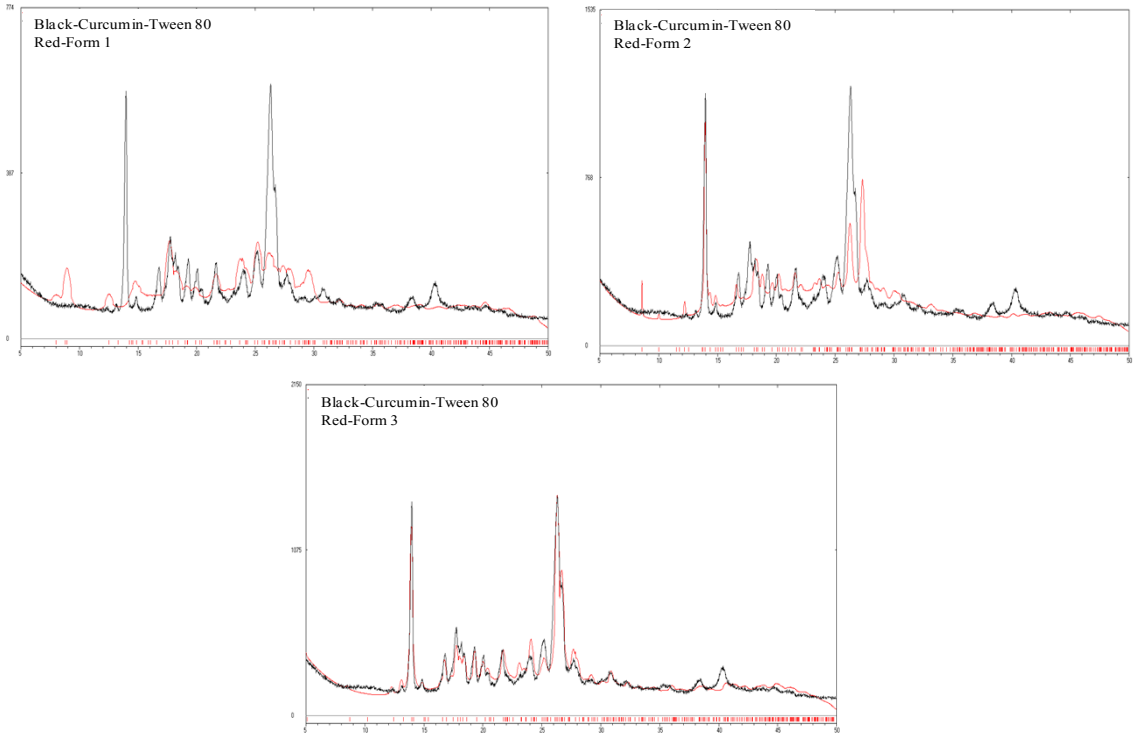



**Figure S5. PXRD pattern of curcumin particles precipitated with ultrasound and Tween 80, compared with PXRD patterns of Curcumin Form 1, Form 2, and Form 3.**

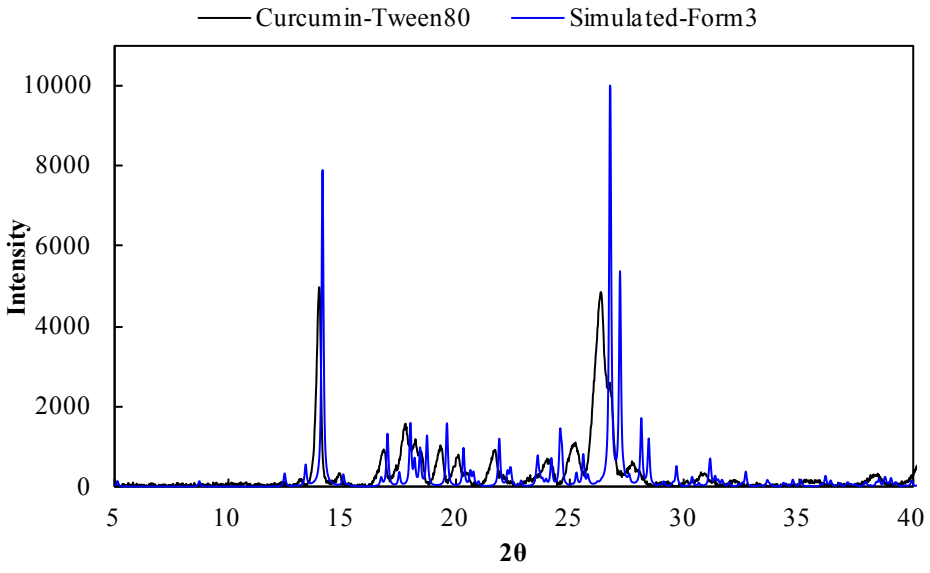



**Figure S6. PXRD pattern of curcumin particles precipitated with ultrasound and Tween 80, compared with simulated Form 3.**

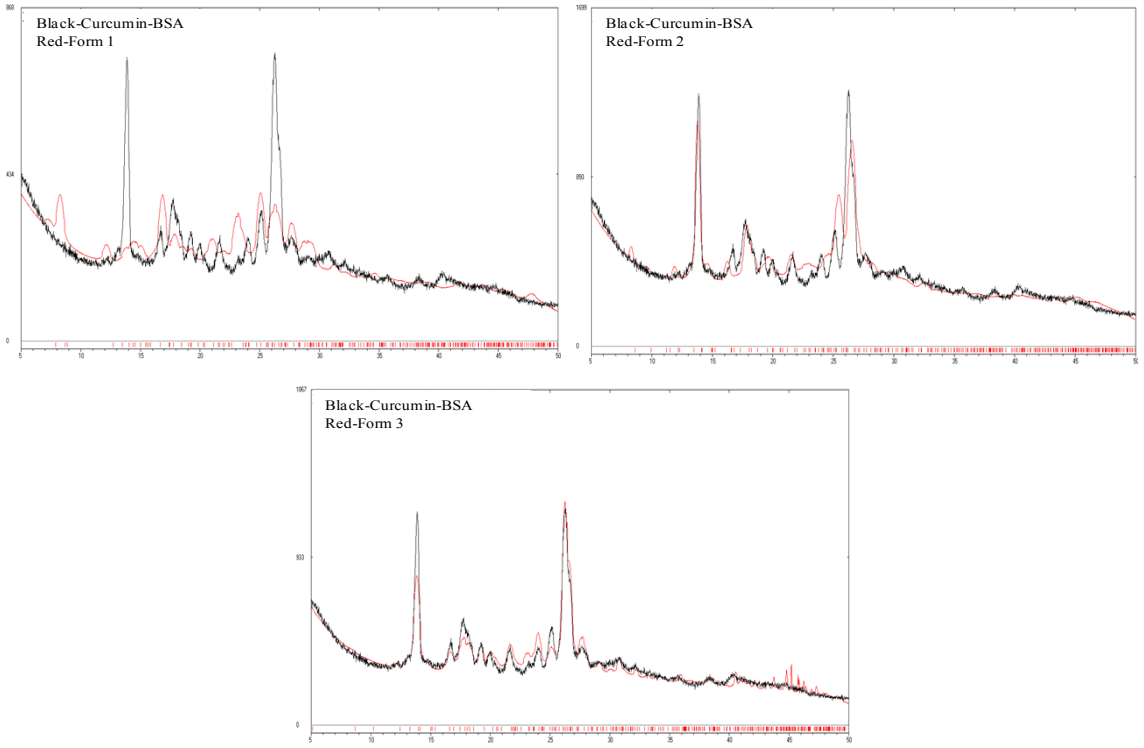



**Figure S7. PXRD pattern of curcumin particles precipitated with ultrasound and BSA, compared with PXRD patterns of Curcumin Form 1, Form 2, and Form 3.**

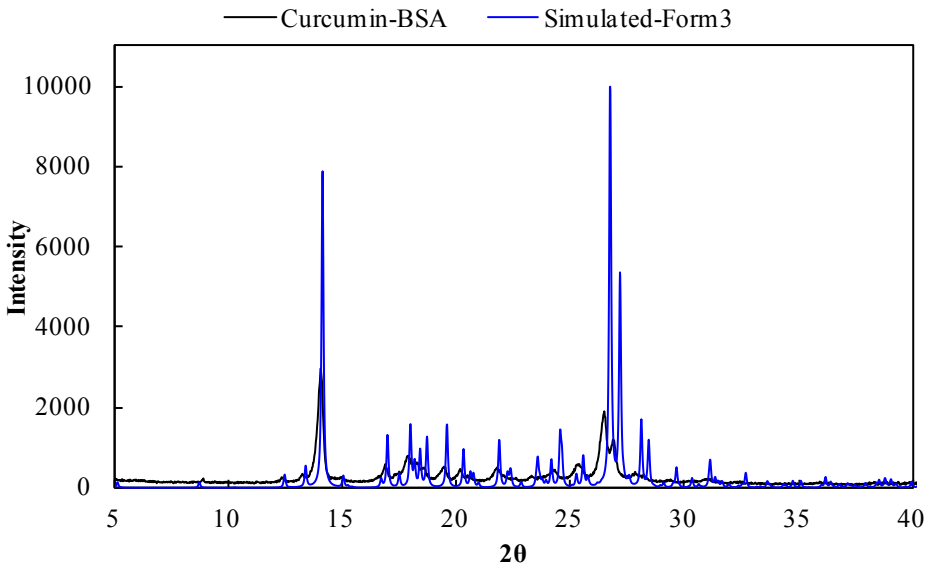



**Figure S8. PXRD pattern of curcumin particles precipitated with ultrasound and BSA, compared with simulated Form 3.**

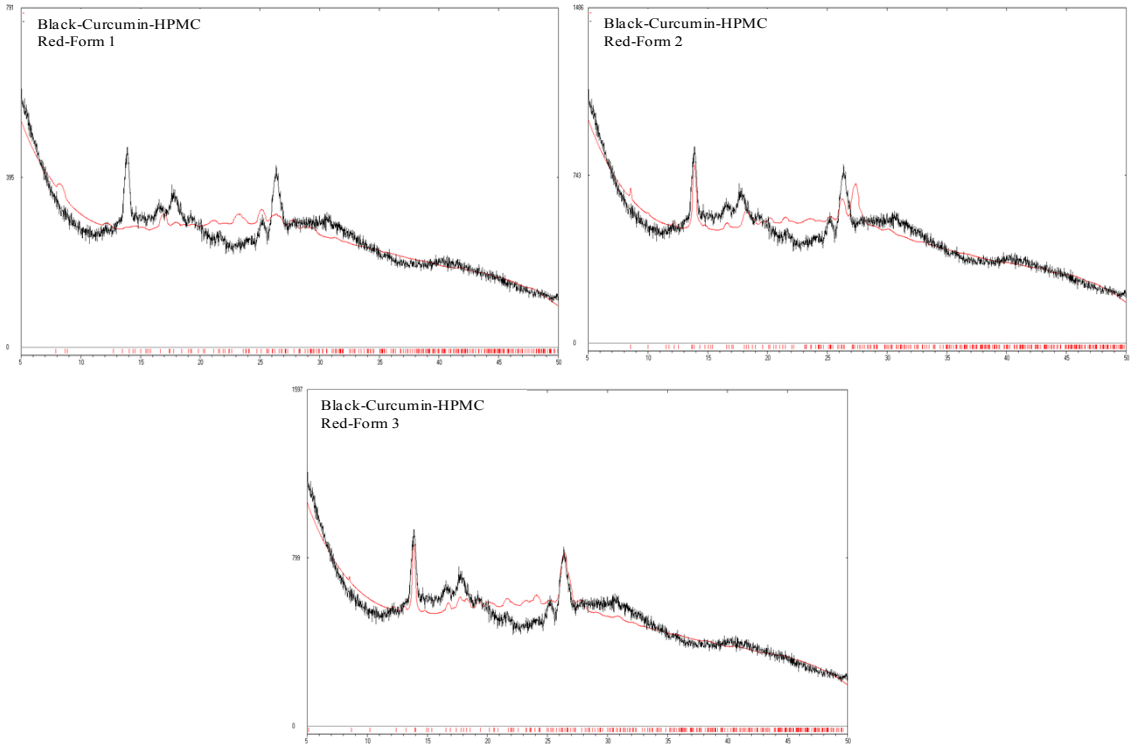



**Figure S9. PXRD pattern of curcumin particles precipitated with ultrasound and HPMC, compared with PXRD patterns of Curcumin Form 1, Form 2, and Form 3.**

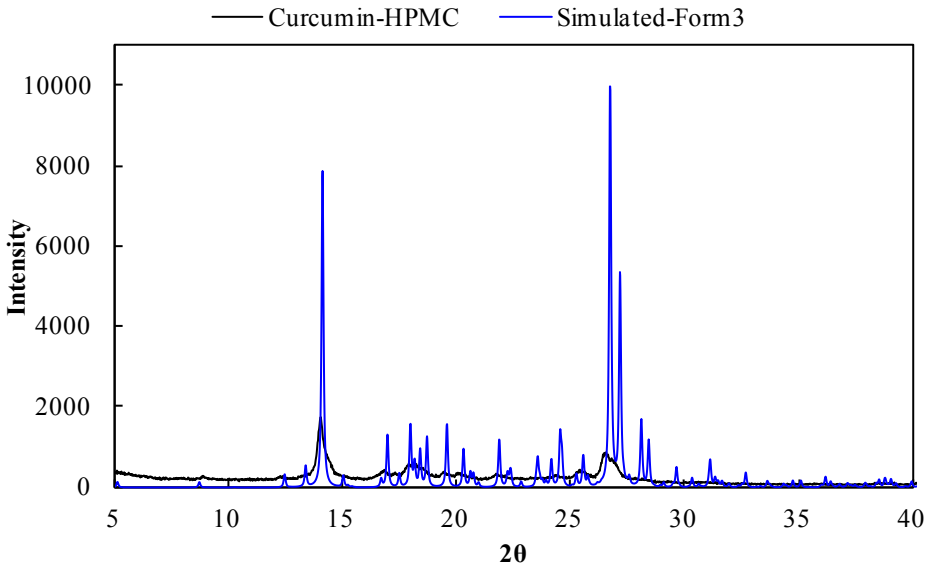



**Figure S10. PXRD pattern of curcumin particles precipitated with ultrasound and HPMC, compared with simulated Form 3.**

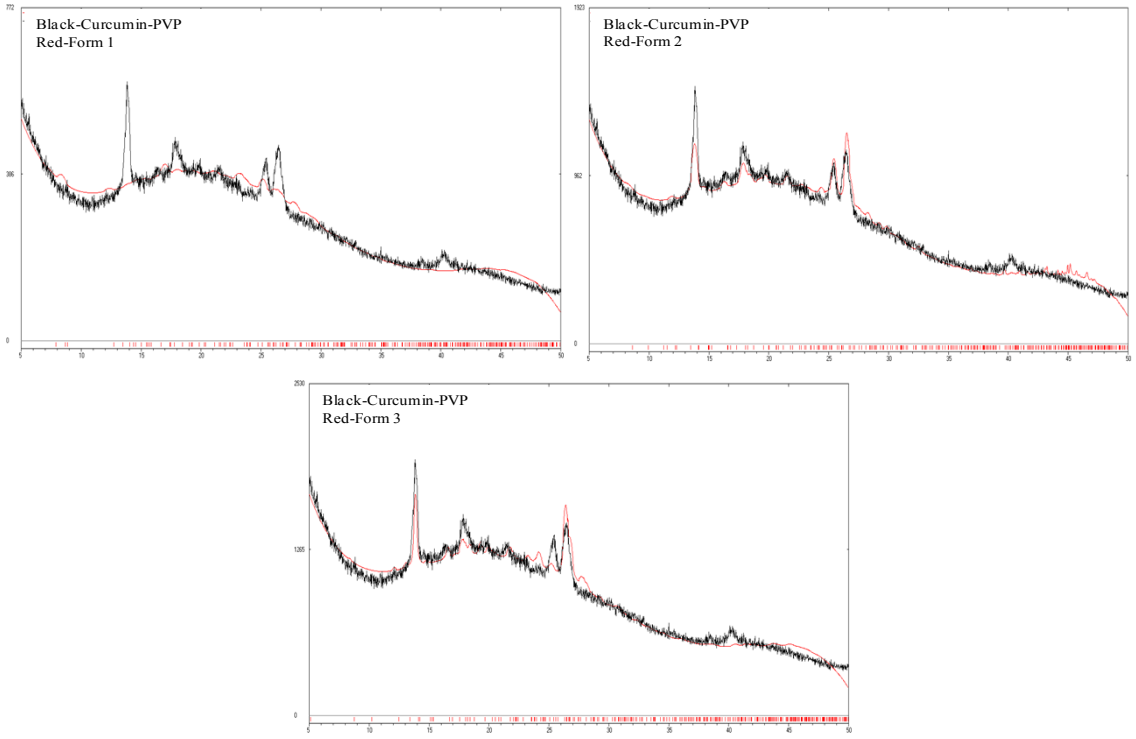



**Figure S11. PXRD pattern of curcumin particles precipitated with ultrasound and PVP, compared with PXRD patterns of Curcumin Form 1, Form 2, and Form 3.**

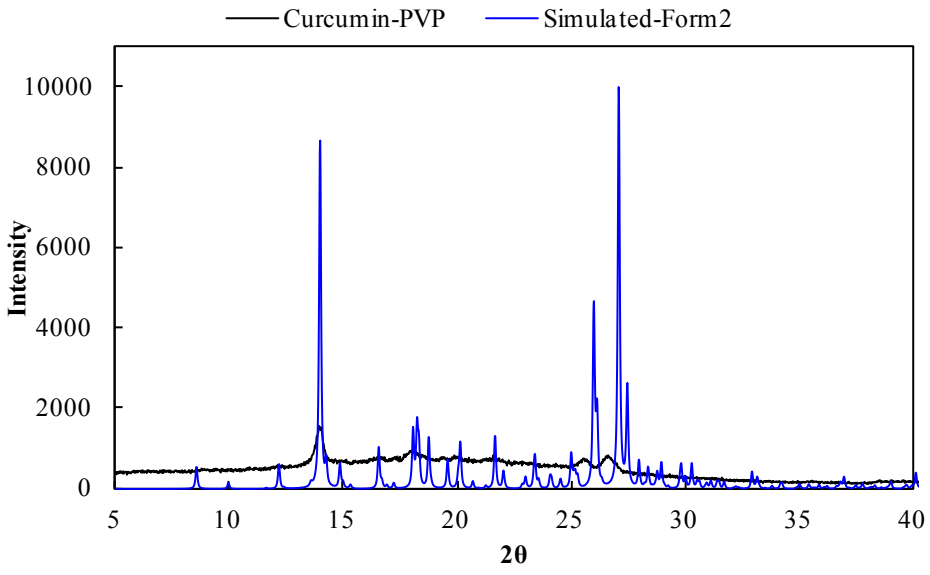



**Figure S12. PXRD pattern of curcumin particles precipitated with ultrasound and PVP, compared with simulated Form 2.**

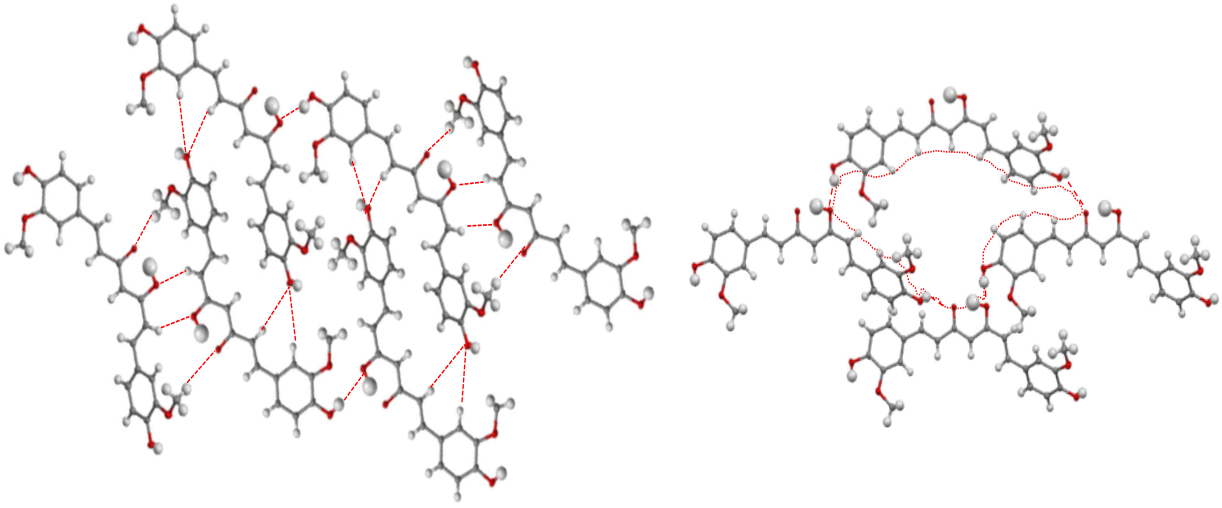


**Figure S13. Hydrogen bonding and molecular packing in monoclinic form (Form 1) resulting in formation of macrocyclic ring[16].**

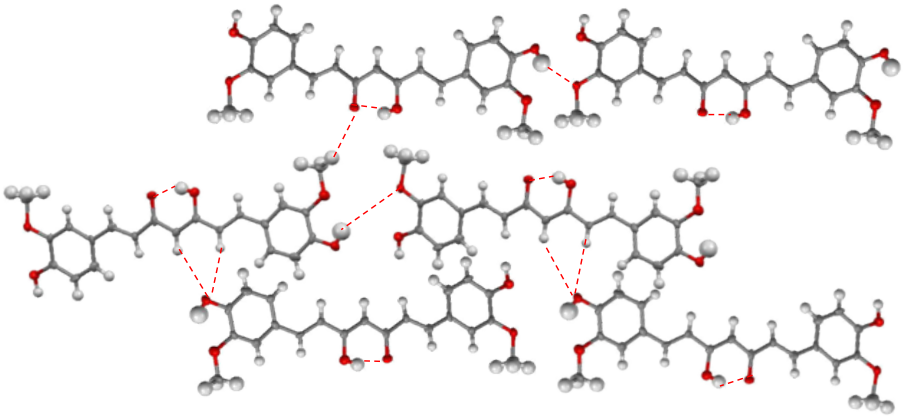


**Figure S14. Hydrogen bonding and molecular packing in orthorhombic form (Form 2) resulting in planar structure [16].**

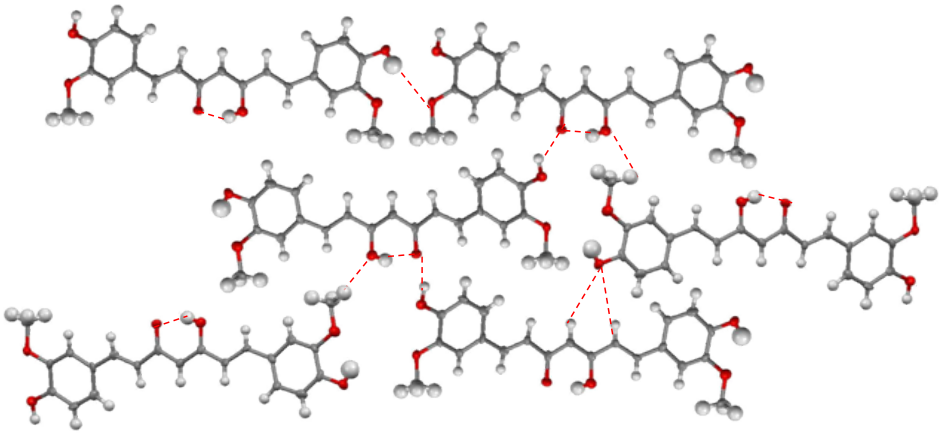
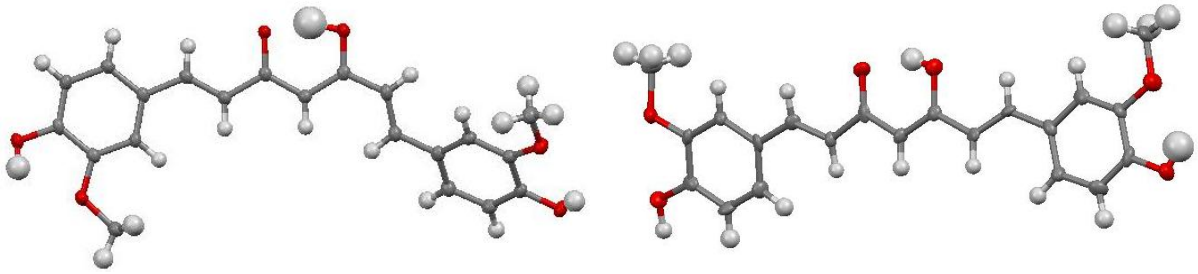


**Figure S15. Hydrogen bonding and molecular packing in orthorhombic form (Form 3) resulting in planar structure [16].**



Monoclinic form Orthorhombic form

**Figure S16. Twisted confirmation in monoclinic form (Form 1) and Linear and Planar confirmation in orthorhombic form (Form 2 and 3)[16].**

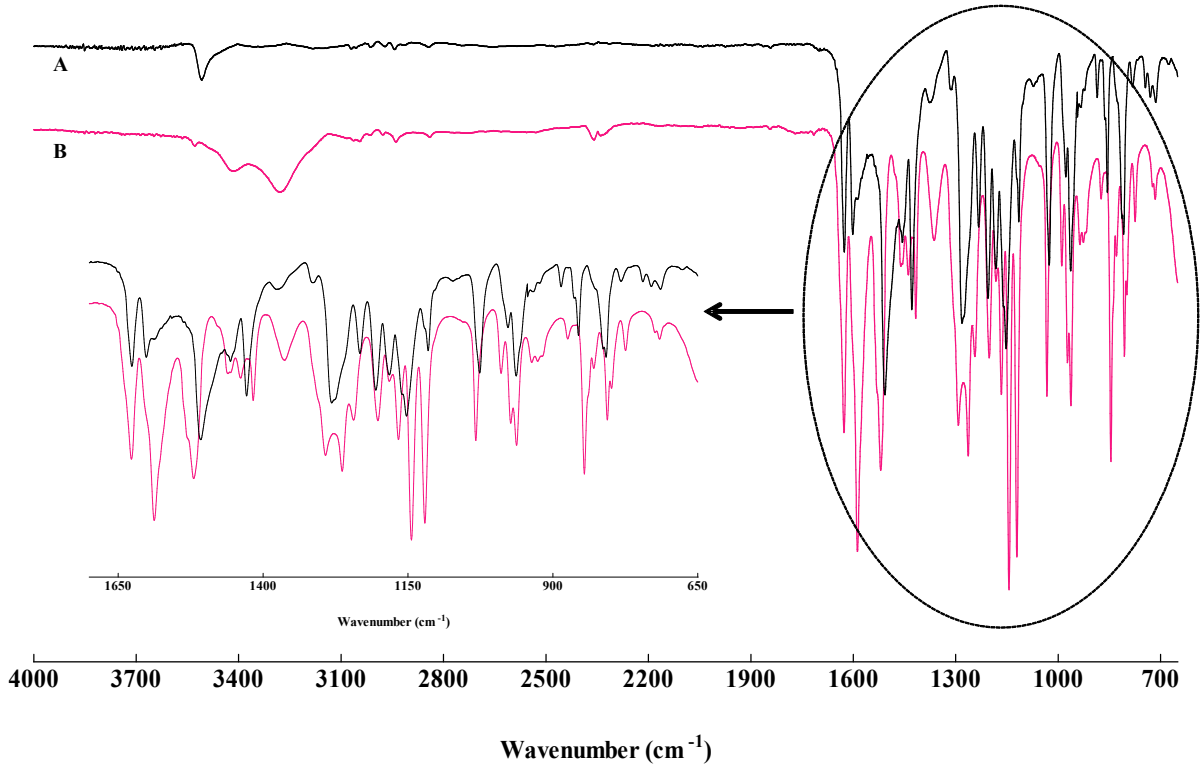



**Figure S17. FTIR spectra of (A) Curcumin precipitated without Ultrasound and without surfactant, and (B) Curcumin precipitated with Ultrasound and without surfactant. Changes in –OH region are visible upon change in form from monoclinic to orthorhombic.**

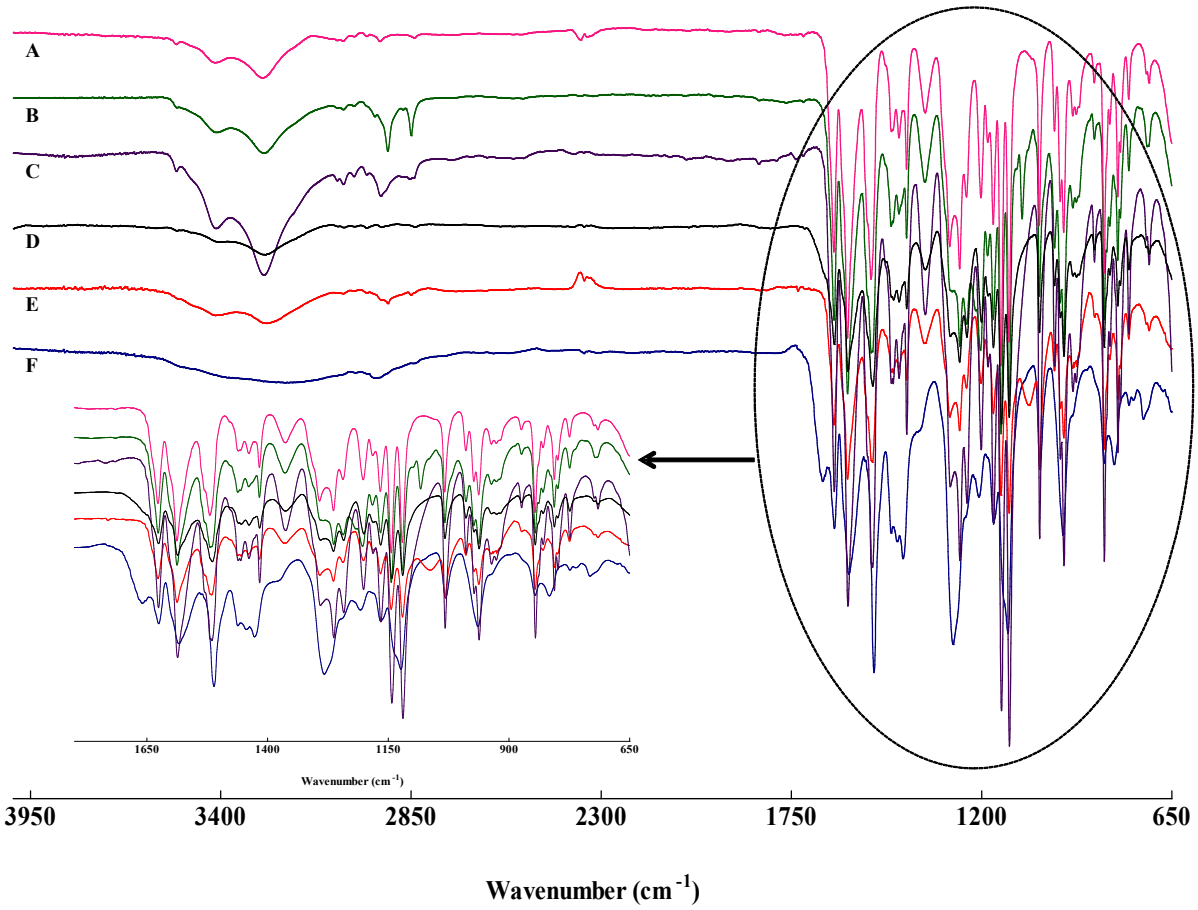



**Figure S18. FTIR spectra of Curcumin precipitated with Ultrasound and (A) without surfactant, (B) with SDS, (C) with Tween 80, (D) with BSA, (E) with HPMC, (F) with PVP. Differences in peak in area of –OH stretching for different stabilizers are evident.**

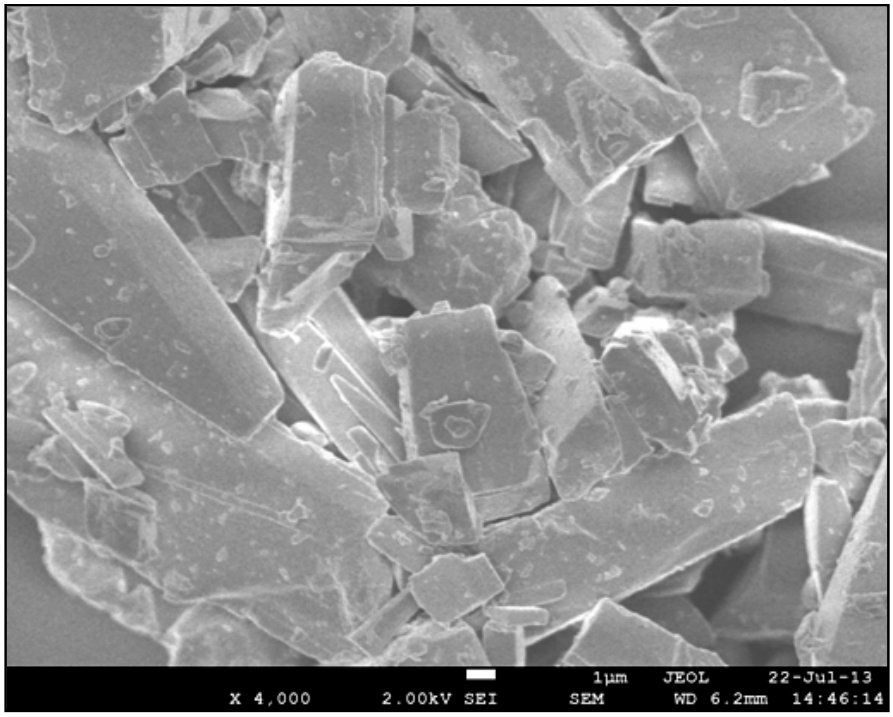



**Figure S19. SEM micrograph of as received curcumin.**