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Orginal Research Article

Synthesis and characterization of curcumin nanoparticles by hydrothermal method

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ABSTRACT

Curcumin (CRM) is a phytochemical that has potent antiproliferative effects against a variety of tumors in *vitro*. Curcumin, however, is limited in its clinical utility due to its poor solubility. Hydrothermal synthesis is a novel method that yields nanoparticles with narrow particle size distribution and high purity without further treatment the use of toxic solvents. Nanosized CRM with the average particle size of 186.2 nm was prepared by a simple hydrothermal process to enhance the aqueous solubility of CRM. Differential scanning calorimetry (DSC) and X-ray diffraction (XRD) analysis identifies that the particles are highly crystalline and revealed no polymorphic changes in CRM on hydrothermal treatment and scanning electron microscopy (SEM) identified that the CRM nano agglomerates. Zeta potential (ZP) results demonstrated the relative stability of nanosized CRM after hydrothermal treatment. Nanosized CRM particles exhibited greater solubility and hence dissolution rate as compared to the original drug. The present study offers a simple process that lacks the use of organic solvent, therefore, is green, and had good yield being a single-step process, to synthesize and to design nanosized CRM for better drug delivery applications.

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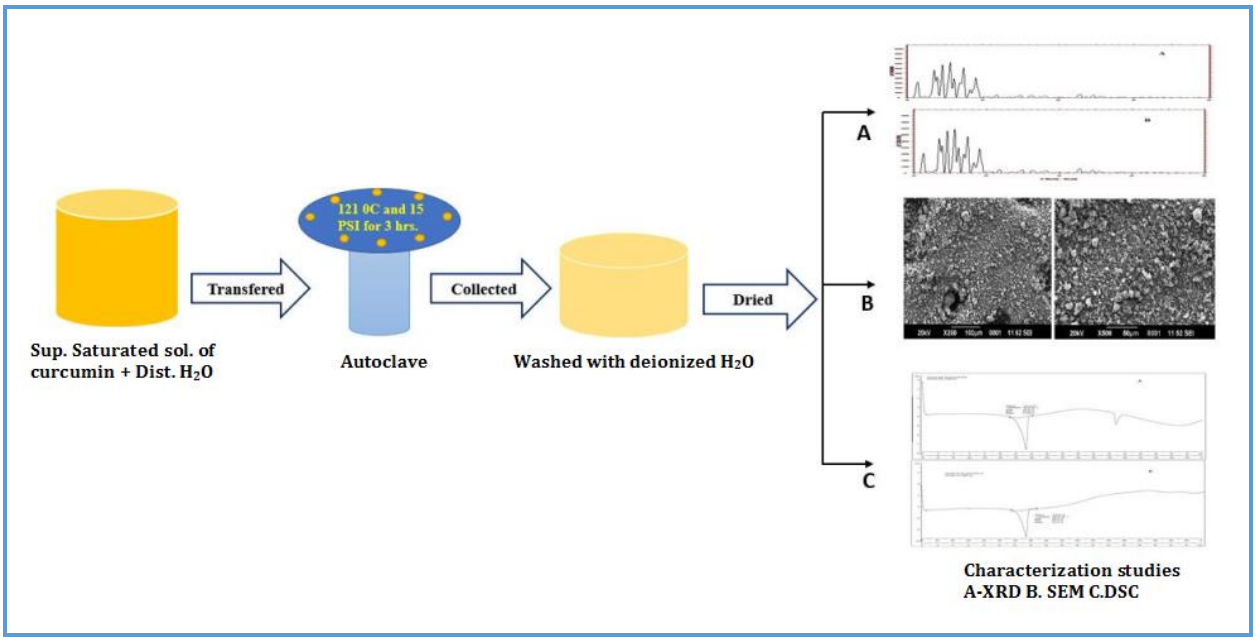
Graphical Abstract



Introduction

Nanoparticles are at the peak of nanotechnology systems. Their unique size-dependent properties make these materials superior and indispensable in numerous technological applications. Conventional techniques of nanomaterial synthesis such as micelle, inverse micelle, co-precipitation synthesis, and sol-gel not only require costly starting materials but also are long-lasting. Nowadays, nanomaterial synthesis processes with low cost as well as low environmental impact are gaining importance for different industries [1]. In an attempt to develop more environmentally friendly processes, supercritical fluids such as supercritical carbon dioxide [2–4] and supercritical water were used as greener alternatives to toxic organic solvents. Hydrothermal processing can be defined as any heterogeneous reaction in the presence of aqueous solvents at elevated conditions of temperature and pressure to recrystallize materials that are relatively insoluble under ordinary conditions. The hydrothermal technique is becoming one of the most important tools for advanced materials processing, particularly owing to its advantages in the processing of nanostructural materials for a wide variety of technological applications such as electronics, optoelectronics, catalysis, ceramics, magnetic data storage, biomedical, biophotonics, etc [5]. In recent years, commercial interest in hydrothermal synthesis was revived because few materials with improved properties have emerged that can be prepared under mild conditions of temperature and pressure. Hydrothermal synthesis is a novel method that yields nanoparticles with narrow particle size distribution and high purity without further treatment [3, 6–9] Approximately 40% or more of the new chemical entities being generated through drug discovery programs are poorly water-soluble. Most drugs have low bioavailability which is mainly accounted for due to poor aqueous solubility. To achieve greater bioavailability, there is a need for enhancement solubility of the

drug. Various approaches are carried out to enhance the solubility of the drugs. One such approach is via particle size reduction by synthesis of drug nanoparticles [10]. Nanosized drug particles exhibit greater solubility and hence dissolution rate as compared to an original drug [11, 12]. This could be due to the reduced particle size of drug particles which results in an increase in the effective surface area of the drug for dissolution. The CRM is the active constituent of turmeric (*Curcuma longa*) and has also been found to be beneficial in all three stages of carcinogenesis but it is not widely used because of its poor aqueous solubility. Despite, the effectiveness of CRM, its use in the clinic has been limited due to its hydrophobicity (solubility in water is ~0.6 μg/mL) and low in *vivo* bioavailability [13, 14]. In this study, nanoparticles were prepared by hydrothermal synthesis using CRM, a hydrophobic polyphenol as a model drug. The prepared CRM nanoparticles were characterized by particle size analysis, scanning electron microscopy (SEM), differential scanning calorimetry (DSC), and X-ray diffraction (XRD) analysis. Solubility measurement was performed to demonstrate the effect of size reduction on the solubility of CRM.

Experimental

Materials and methods

Curcumin and Tween 80® were obtained from Sigma Aldrich, all other chemicals were analytical grade reagents used as such without further purification.

Preparation of Curcumin nanoparticles

The nanometer-sized CRM is synthesized by a hydrothermal technique using a fully automatic vertical autoclave. A briefly supersaturated solution of the CRM in distilled water was prepared by placing an excess CRM in distilled water. The saturated solution was then transferred into a stainless-steel autoclave (Equitron, Model No. #7441STWL). The autoclave was sealed and maintained at 121 °C and 15 PSI pressure for 3 h. After hydrothermal processing, the autoclave was allowed to cool down to room temperature naturally. The resulting precipitate was collected and washed with deionized water several times and dried at room temperature. Under identical experimental conditions, Tween 80® was also used as surfactants to observe its effects on size and solubility.

Physical characterization of nano-sized CRM

Particle size (PS) and zeta potential (ZP) measurements

Particle size and polydispersity index were determined using a Malvern Zetasizer Nano ZS (Malvern Instrument, UK) based on dynamic light scattering. Briefly, a dilute solution of nano-sized CRM was prepared in double-distilled water. Size measurements were performed following the dilution (100 times) of the nano-sized CRM using water at 25 °C. The ZP was also measured in the same instrument at 25 °C. The nanoparticles were dispersed in deionized water. Then this dispersion was filled in zeta cells and placed in the zeta sizer [15, 16].

Surface morphology

The morphology of nano-sized CRM was examined by scanning electron microscopy (JSM 6390, Japan). The sample was dusted onto double-sided tape on an aluminum stub and coated with gold using a cold sputter coater to a thickness of 400 °A, and then imaged using a 20 kV electron beam at different magnifications [17].

Differential scanning calorimetric (DSC) evaluation

The physical nature of the nano-sized CRM was characterized using a DSC thermogram analysis (DSC 822c, Mettler Toledo). Sample (2 mg each of native curcumin and nanosized CRM) was sealed separately in a standard aluminium pan, the samples were purged in DSC with pure nitrogen gas set at a flow rate of 20 mL/ min, the temperature speed was set at 10 °C/min, and the heat flow was recorded from 30 to 350 °C [18].

X-ray diffraction studies (XRD)

XRD analysis was done to know the crystallographic structure of the nanosized CRM formulation. The patterns of native CRM and nanosized CRM were obtained using an X-ray diffractometer (Brucker AXS D8 Advance). The measurements were performed at a voltage of 40 kV and 25 mA. All samples were measured in the 2Θ angle range between 20 ° and 60 ° with a scanning rate of 3 °/min and a step size of 0.02 °[14].

Fourier transformed infrared (FT-IR)

Fourier transformed infrared (FT-IR) spectra of CRM was taken by using the KBr disk method (2 mg sample in 200 mg KBr). The scanning range was 450 to 4000 cm^{-1} and the resolution was 1 cm^{-1}. The obtained IR spectra of drug sample match with the standard IR spectra of CRM.

Solubility study of CRM and nanosized CRM

An equivalent quantity of native CRM and nanosized CRM was dissolved in water to observe the effect of hydrothermal treatment on the aqueous solubility of the formulation. Native CRM and nanosized CRM at a saturated concentration were prepared in 10 mL water and incubated in a shaker rotating at 100 rpm, 37 °C (Remi Lab, India) for 24 h. After 24 h the above solution was filtered and quantify the solubility of CRM was by UV-Visible spectroscopy [12].

Results and Discussion

In a quest of developing an ideal formulation for achieving small size, and for enhanced solubility of CRM, we have prepared nanosized CRM (based on hydrothermal process) in a view to getting maximum solubility without the use of excipients. After completion of the hydrothermal process, the resulting yellow solid products were washed with methanol, filtered, and then dried in the air in a laboratory oven at 60 °C.

Particle Size Analysis

The CRM nanoparticles were well formed with an average diameter of 186.2 nm. Curcumin nanoparticles were synthesized at 121 °C to reduce the particle size of the CRM. The variations in the particle size are shown in Figure 1. The particle size of the CRM decreased linearly from 479.0 to 186.7 nm. Nanosized CRM had a narrow size distribution with a polydispersity index (PDI) smaller than 0.3. size also can be affected by surfactants, which can adsorb on specific crystallographic faces, and solvents that adsorb similarly as well as regulate solubility. The use of surfactants allowed reducing the agglomerate size to about 152.3 nm [19].

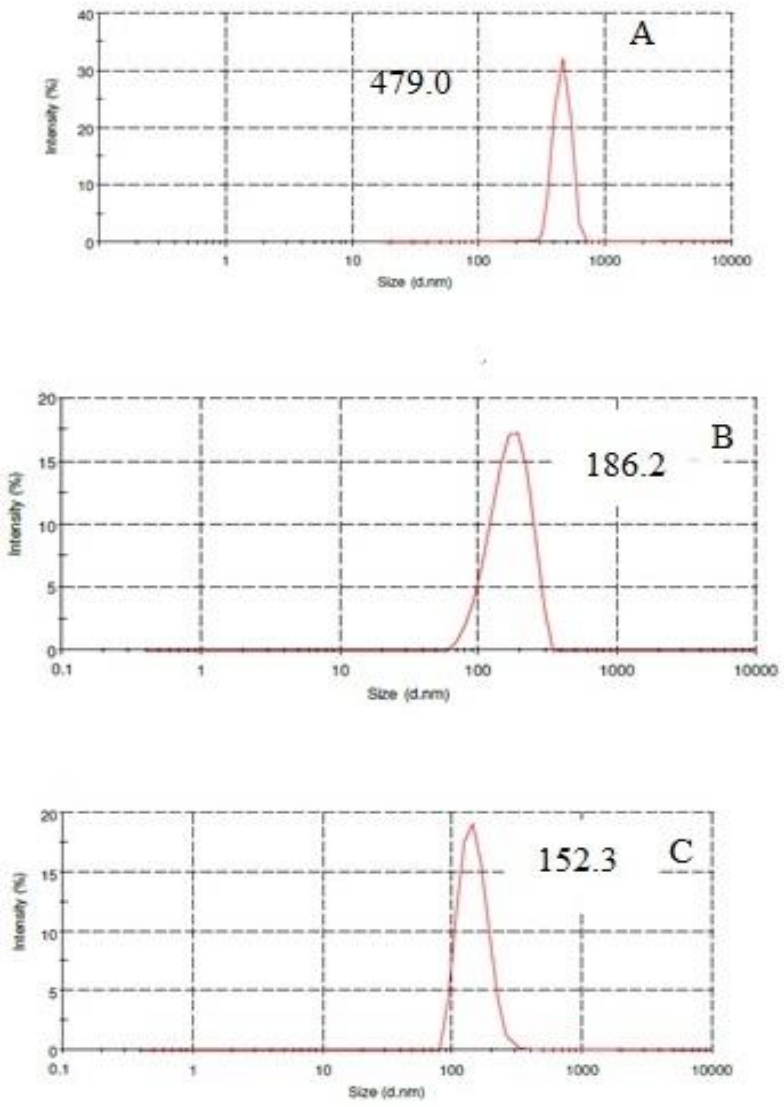


Figure 1. Particle size distribution of a) curcumin, b) hydrothermal treated curcumin and c) hydrothermal treated curcumin with surfactant

Zeta potential measurement

Zeta Potential is an important tool for understanding the charge on the surface and predicting the long-term stability of the nanoparticle. The ZP is an important and useful indicator to predict the stability of material on exposure to stress thermal and hydrolytic conditions. The ZP of CRM and nanosized CRM with surfactant were found to be -19.6 mV, -20.8 mV, and -19.4 mV respectively (Figure 2). The ZP of the nanoparticles had values that typically range from +100 mV to -100 mV. Nanoparticles with ZP values greater than +25 mV or less than -25 mV typically had high degrees of stability. The ZP measurements indicated no significant difference in the ZP value of the CRM and that of nanosized CRM deducing no change in the stability of material on canonization after hydrothermal processing.

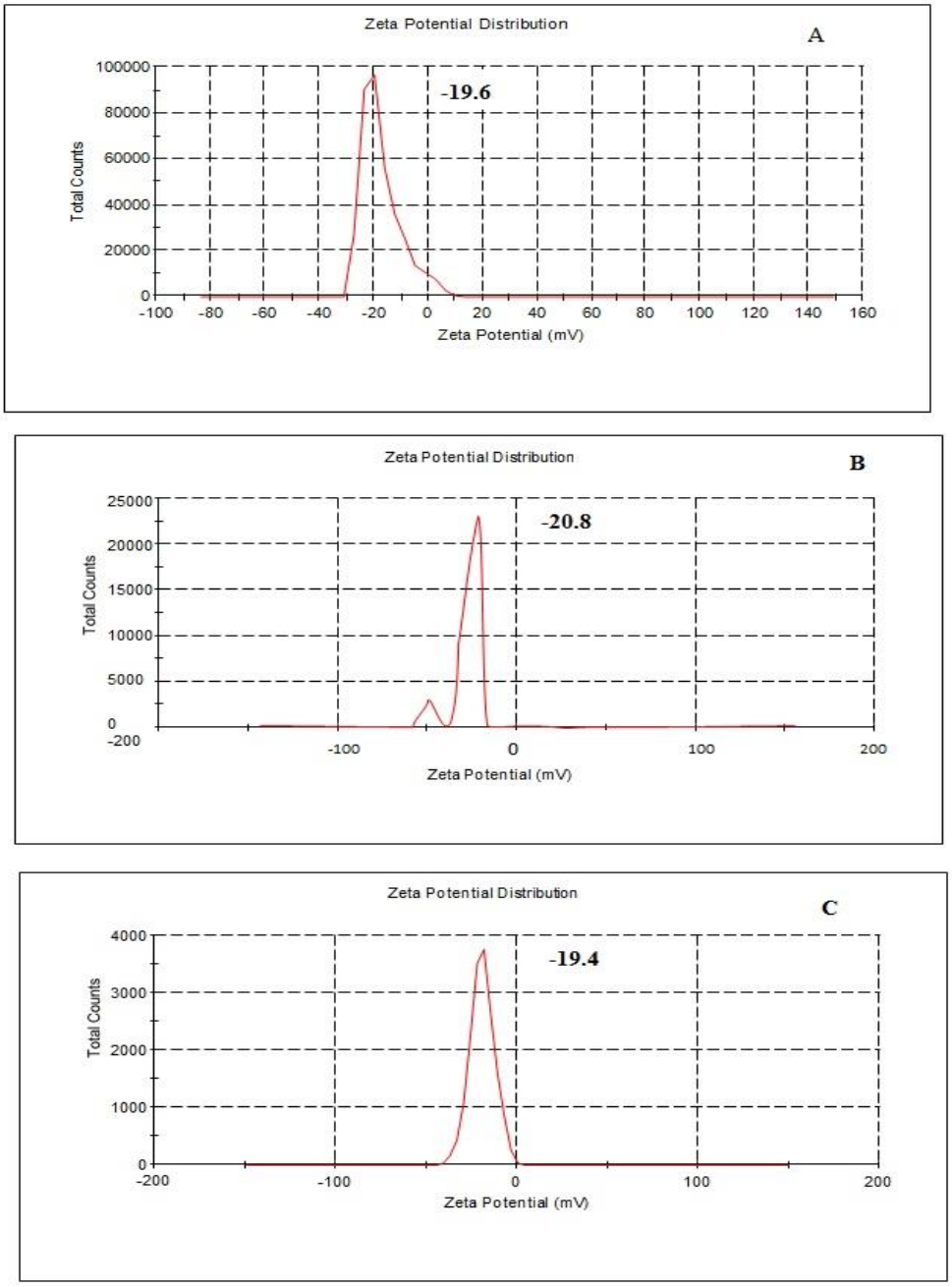


Figure 2. a) Zeta potential of native curcumin, b) nanosized curcumin obtained after hydrothermal process and c) nanosized curcumin with surfactant hydrothermal processed

Surface morphology

Figure 3 demonstrates the SEM images from the nanosized curcumin synthesized using the hydrothermal process. The product consisted of irregular nanoparticles with unclear surfaces along with the agglomerates. Surfactant introduction in the synthesis system does not alter the surface morphology of nanosized CRM.

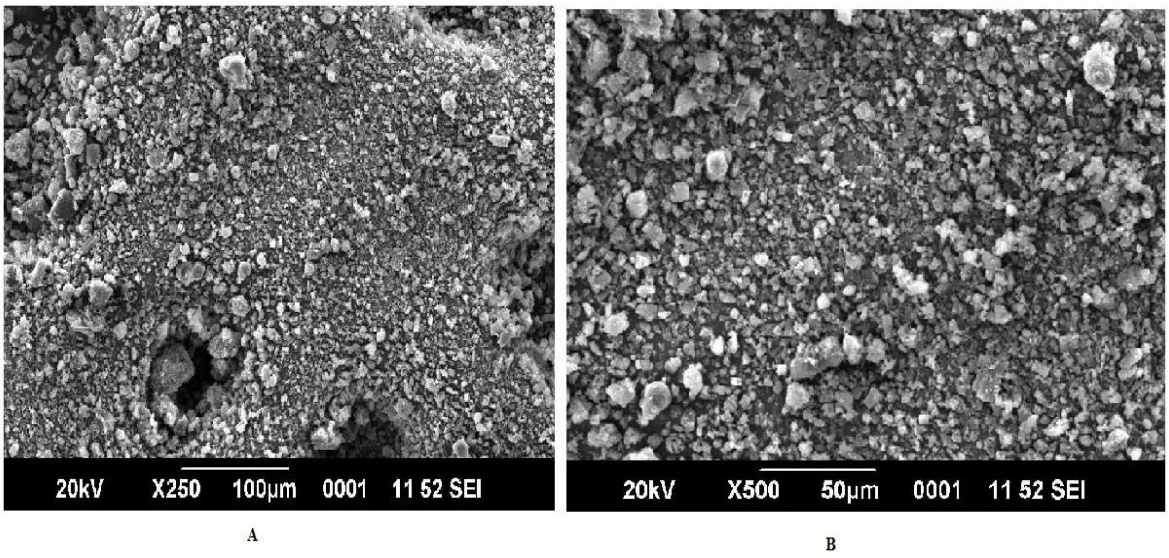


Figure 3. SEM micrographs of hydrothermally synthesized nanosized curcumin without surfactant (A) and with surfactant (B)

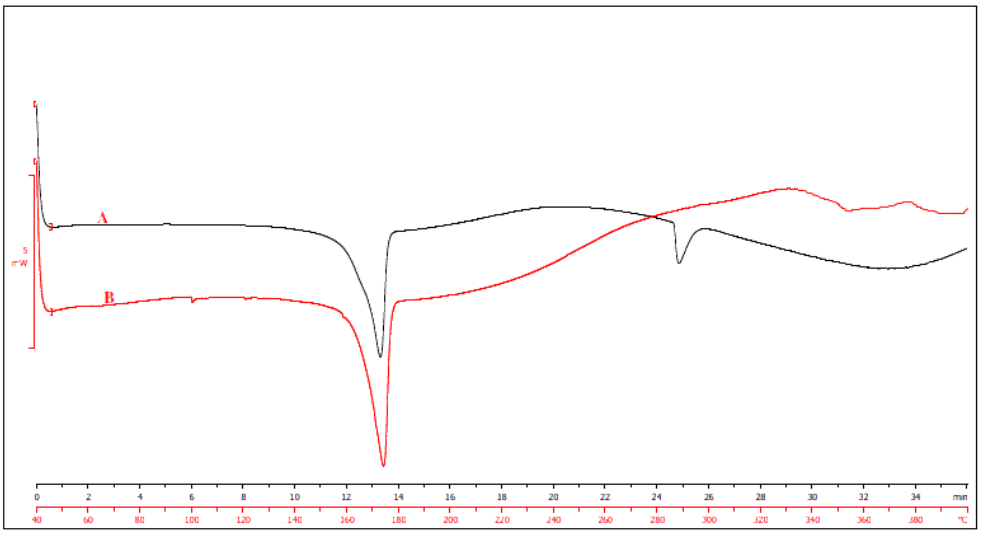


Figure 4. a) DSC thermogram of native curcumin, b) hydrothermal treated nanosized curcumin

Differential scanning calorimetric studies (DSC)

The endothermic peak of native CRM was found approximately at 172.64 °C (Figure 4). The DSC thermograms of native CRM and that of hydrothermally synthesized CRM nanoparticles were compared. A similar characteristic peak was observed in nanoparticulate CRM. It was found that there was no considerable change in the thermogram peak thus, indicating no physicochemical and polymorphic changes after the hydrothermal treatment of the CRM.

X-ray diffraction (XRD) study

The XRD study was further carried out to understand the nature of CRM nanoparticles formed as a result of hydrothermal treatment

(Figure 5**b**). The characteristics peaks of native CRM exhibited as shown in Figure 5**a** that demonstrated the traits of high crystalline structure. The diffraction peaks were following to the standard card no. of (JCPDS card 9-816 J). The XRD peak of bulk CRM and CRM nanoparticles are displayed in Figure 5**a**,**b** the average crystal size (d) was calculated based on the width of the peak by using the Scherrer's formula: $d = 0.94\ \lambda / \beta \cos\theta$ where, λ is the wavelength of X-ray used; β is the full width at half maximum and θ is the Bragg's angle of reflection. The average crystallite domain size was found to be 36 nm. No Significant difference in the intensity of the diffraction peaks of the samples is closely related to the degree of crystallinity of the samples after the hydrothermal treatment of the CRM.

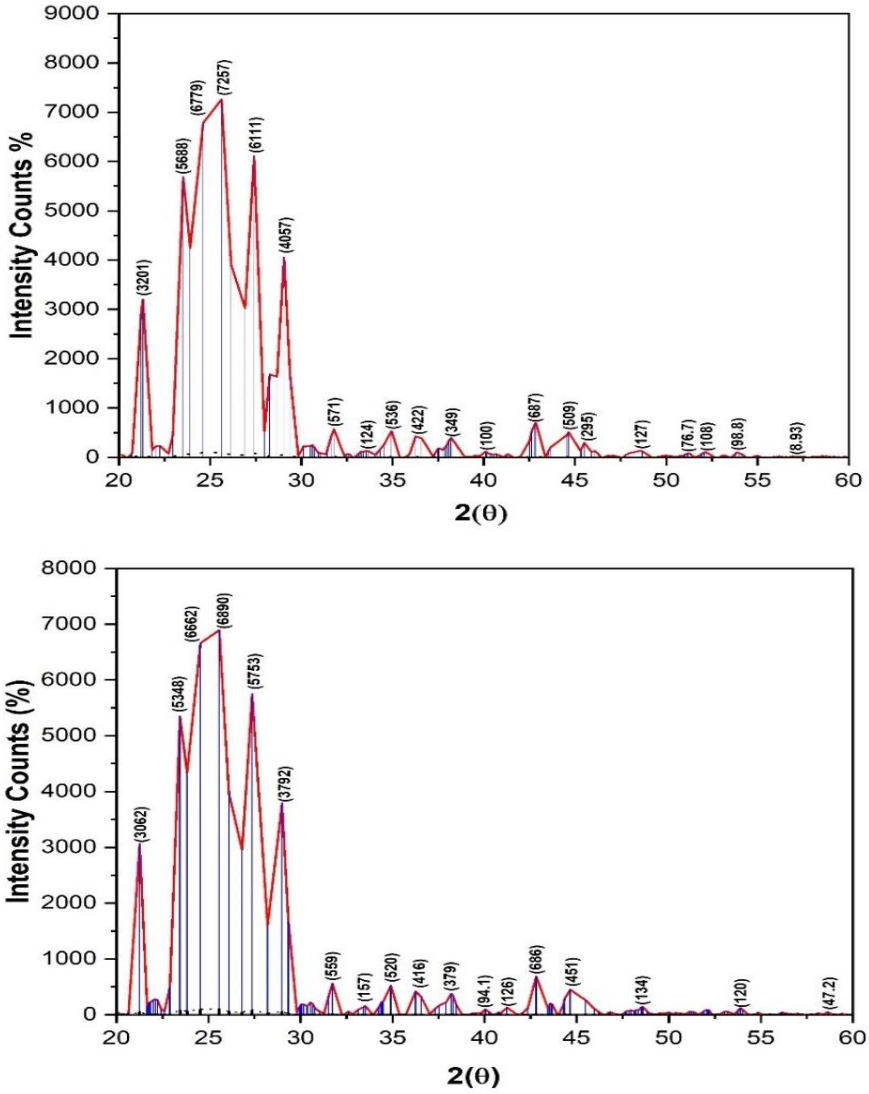


Figure 5. XRD pattern of a) native curcumin and b) nanosized curcumin

FT-IR studies

The FT-IR study was further carried out to understand the which functional groups present in the spectra of CRM nanoparticles formed as a result of hydrothermal treatment. In the FT-IR spectra of curcumin, (Figure 6) shows stretching vibrations at 1602 cm^{-1}

attributed predominantly to the overlapping stretching vibrations of aromatic (C-C) character. Infrared of curcumin show stretching vibration at 3013, 3502 cm^{-1} due to stretching vibration (=C-H) alkene (=C-H) alkane. Vibration C-H bend alkane at 1454 cm^{-1} and high intensity band at 1602 cm^{-1} attributed to the mixed vibrations including stretching carbonyl bond vibrations ν(C=O), in plane bending vibrations around aliphatic δ (C-C), δ (C=0) and in plane bending vibrations around aromatic δ (C-H) of keto and enol configurations and stretching vibrations around aromatic ν (C-C) bonds of keto and enolic form of curcumin [20]. Furthermore, significant intense band at 1281 cm^{-1} attributed to the bending vibration of the ν(C=O) phenolic band.

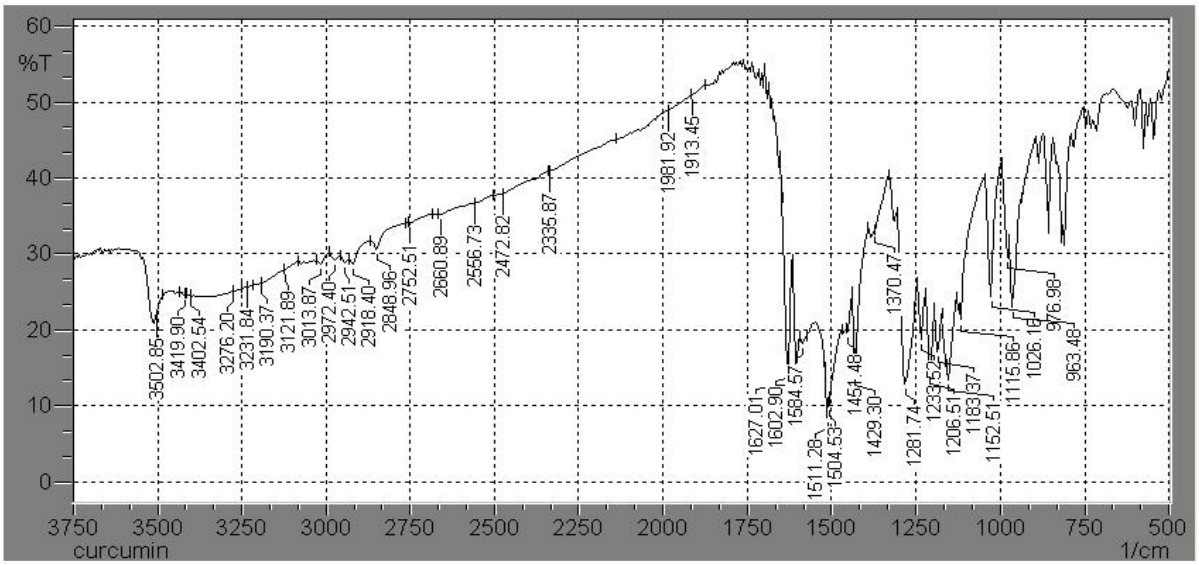


Figure 6. FT-IR pattern of Curcumin

Solubility studies

To confirm the effect of hydrothermal treatment on the solubility of CRM, solubility studies of resultant nanosized CRM was carried and the solubility of native curcumin was 3.756 µg/mL and that of nanosized CRM was 6.595 µg/mL demonstrating that hydrothermal treatment of CRM results 2-fold increase in solubility it could be attributed to a reduction in particle size of native CRM.

Conclusions

The enhancement of water solubility as well as stability will undoubtedly bring CRM to the head of existing anticancer therapeutic agents. In summary, we were employed a simple hydrothermal process to synthesize nanosized CRM with an average particle size of less than 200 nm. The crystalline nanosized CRM was confirmed by XRD and DSC respectively, demonstrating no change in the physical and polymorphic form of native CRM on hydrothermal treatment. Thus, the hydrothermal process can be considered an approach to develop drug particles with nanoparticle size and improved solubility without altering polymorphic form and stability.

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Disclosure Statement

No potential conflict of interest was reported by the authors.

Orcid

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