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EVALUATION OF SOLID-STATE FORMS OF CURCUMINOIDS

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Keywords:

Curcuminoids, Solid-state screening, Powder X- ray diffraction, Differential scanning Calorimetry, Dissolution studies

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ABSTRACT: Curcuminoids are dietary phytochemicals obtained from dried rhizomes of turmeric plant (*Curcuma longa*). Curcuminoids are mixture of curcumin, demethoxy curcumin and bisdemethoxy curcumin in which curcumin is a major constituent. Several polymorphic forms of curcumin were reported. The present study relates to the preparation of different solid forms of curcuminoids and to study the influence of other constituents of curcuminoids on the polymorphic behaviour of curcumin. The developed solid forms were characterized by various spectral methods like Fourier Transform Infrared Spectroscopy (FTIR), Powder X- ray diffraction (PXRD), Differential Scanning Calorimetry (DSC) and Scanning Electron microscopy (SEM). On crystallization from ethanol and upon melt crystallization, curcuminoids underwent transformation into an amorphous form. Grinding did not affect the polymorphic nature of curcuminoids. These findings suggest that curcuminoids undergo polymorphic modifications very similar to curcumin.

INTRODUCTION: Predominance and importance of polymorphism occurring in pharmaceutical compounds are well recognized, especially in pharmaceutical community. Different crystal arrangements or crystal lattices are possible for any particular compound. Polymorphic changes can be induced by heat, stress, pressure, and humidity conditions or solvent mediated processes. Different polymorphs of the same substance can have different physical properties such as melting point, chemical reactivities, dissolution rate and bioavailability due to differences in molecular packing.

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The change of the polymorphic form frequently causes clinical failures once it is on the market. Hence, it is very important to prepare and select the right form from the beginning during drug discovery and development. The extent of polymorphic transitions depends on the processing conditions and the relative stability of the polymorphs [1, 2].

Curcuminoids are extracted from rhizomes of *Curcuma longa (family: Zingiberacae)*, commonly known as turmeric, which are responsible for yellow-orange coloration to turmeric powder and possess a camphoraceous odour. Turmeric contains 3-5% curcuminoids. Naturally occurring curcuminoids contain mixture of 77% curcumin[1, 7-bis (4-hydroxy-3-methoxy-phenyl)-1, 6-heptadiene-3,5dione], 17% demethoxycurcumin[4-hydroxycinnamoyl - (4 – hydroxyl – 3 - methoxy cinnamoyl methane)] (DMC) and 6%

bisdemethoxycurcumin (bis-(4-hydroxy cinnamoyl) methane) (BDMC). The curcuminoids differ in their chemical structure and melting points. Curcumin is the most important constituent which is responsible for the biological activities of turmeric. Curcuminoid derivatives with Alteration in chemical structure in structure can influence the physiological activity, leading to variation in pharmacokinetic parameters [5-7].

A large number of studies demonstrated the potential biological activity of curcumin. According to these studies, curcumin was reported to exhibit anti-inflammatory, antioxidant, anticarcinogenic, antiviral and antimicrobial activity. Besides these, curcumin has a variety of potentially therapeutic properties, such as anti angiogenic, immunomodulatory, antithrombotic, wound healing, antistressor, antilithogenic, cardioprotective, neuroprotective, antidiabetic and chemoprotective activities. It has been reported that not only the curcumin the other curcuminoids, DMC and BDMC are also responsible for antioxidant activities as well as hepatoprotective activity [8, 9].

The fast growing research on curcuminoids suggests that, DMC and BDMC show a broad range of potent therapeutic applications. The presence of BDMC was found to be a better cytotoxic agent than curcumin and DMC. BDMC showed greater antitumor, antipromoter, and anticarcinogenic activities than curcumin or DMC [10, 11]. The problems associated with curcumin/curcuminoids i.e. low aqueous solubility and poor bioavailability may be addressed through the studies on development of new polymorphic forms. With this background, the present study mainly focuses on the polymorphic behaviour of curcuminoids and to investigate the polymorphic nature of curcumin in presence of other minor constituents.

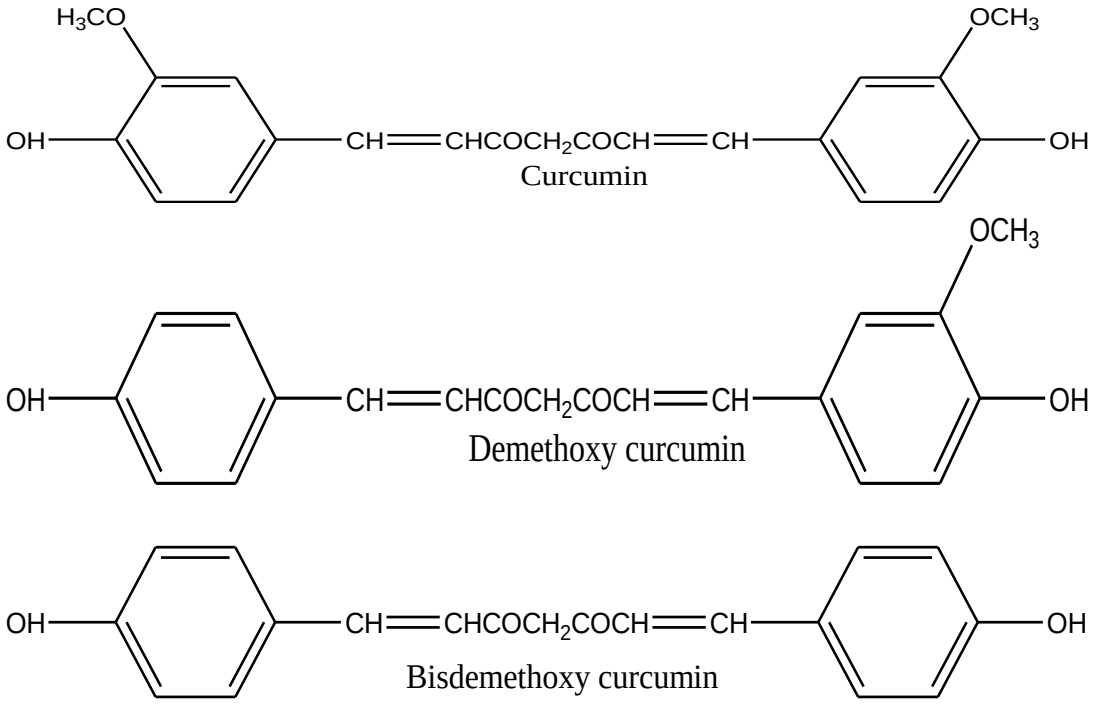


FIG.1: STRUCTURES OF CURCUMINOIDS

Three crystalline forms of curcumin, namely forms 1- 3 and an amorphous form were reported. Six Polymorphs form I - VI of curcumin were reported in the patent literature. Of these, Form III is a meta-stable form, form II & form V are 1, 4-dioxane solvates and form VI is a methyl acetate solvate [12, 13].

However, there was no matching in the PXRD and DSC data reported for forms 1-3 and patented forms I to VI. Curcumin, forms 1-3 were obtained from dried rhizomes of turmeric plant *curcuma longa* from Indian source.

No polymorphic forms of DMC has been reported so far. Two crystalline forms I and II of BDMC were reported by using solvent evaporation method using ethyl acetate and acetonitrile respectively [14].

The polymorphic transformations of polymorphs of curcumin from form 1 into form2 and 3 in presence of ultrasound and additives were reported [15].

The objective of the present work is to study the polymorphic behaviour of curcuminoids where curcumin is present along with other constituents Demethoxy curcumin (DMC) and Bisdemethoxy curcumin (BDMC) through preparing various solid forms of curcuminoids, under different experimental conditions, and to characterize them by spectroscopic, thermal and microscopical analysis.

MATERIALS AND METHODS:

Materials:

Curcuminoids sample was gifted by Indo Necop Chemical Pvt Ltd, Vinkonda. Curcumin was procured from sd Fine chemicals, Mumbai, India. Different solvents used in the study like ethanol, isopropanol, methanol etc were procured from Merck, Mumbai, India.

Preparation of solid forms by different crystallization techniques: [16, 17]

Crystallization from isopropanol:

200mg of curcuminoids was dissolved in 25ml of isopropanol & allowed to evaporate at room temperature. Then the crystals formed was filtered, dried and designated as solid form A.

Crystallization from methanol:

200mg of curcuminoids were dissolved in 25ml ethanol and heated to make a supersaturated solution and cooled to temperature of 10°C. Then the formed crystals was filtered, dried and designated as solid form B.

Solvent drop grinding method:

500mg of curcuminoids was ground in mortar and pestle for about one hour in clock wise direction incorporating 2-3 drops of methanol. The obtained product was collected and designated as solid form C.

Dry grinding method:

500mg of curcuminoids was ground in mortar and pestle for about one hour in clockwise direction. After one hour the product was collected and designated as solid form D.

Crystallization from melt:

100mg of curcuminoids were melted at 190°C and then immediately cooled to room temperature in ice to a glassy state and designated as solid form E.

Characterization methods: [18, 19]

Fourier transform infrared spectroscopy (FTIR):

The FTIR spectra were acquired on a BRUKER model 65 with OPUS software at room temperature from 4000-400 cm^{-1}. Standard KBr pellets were prepared from 100mg of KBr pressed under 15,000 lbs and solid forms containing 2-3mg were used. Interpretation of the IR spectra was based on the identification of the functional groups represented by specific wave numbers.

Differential scanning Calorimetry (DSC):

The thermal behaviour of solid forms of curcuminoids was measured with Mettler Toledo 821^e DSC module for thermal analysis; 6-7 mg of weighed samples (Mettler M3 microbalance) of each Solid form was placed in crimped 40µL aluminium pans. Each sample was heated from 40 to 500 at a ramp rate of 10°C/min. The instrument was preventively calibrated with Indium as a standard reference. A purge gas of nitrogen was passed over the pans with a flow rate of 20mL/min. The temperature and enthalpies were calculated by the software (STAR ^{e} software) by integrating the transition areas associated and normalizing the weight of each sample.

Powder X-ray diffraction (PXRD):

Powder X-ray diffraction patterns of solid forms of curcuminoids were performed on Shimadzu 7000 diffractometer. The divergence and scattering slits were set at 1.0mm, and the receiving slit was set at 0.3 mm. Diffraction patterns within the 2θ range of 10-80° were recorded at room temperature using Cu Kα radiation at following conditions: tube voltage of 40 kV, tube current of 30 mA, step-scan mode with the step size of 0.02°, 2θ and counting

time 00.6sec/temp. The diffractograms were analyzed using Spectris diffraction software.

Scanning Electron Microscopy:

Morphological studies were performed using Scanning Electron Microscope (SEM) with Energy – Dispersive X-ray Analysis (EDAX) System (model CARL- ZEISS EVO MA 15). The samples were observed at 10,000 X magnification with an accelerating voltage of 20kV. Powder samples of curcuminoids were mounted onto aluminium stubs using double sided adhesive tape and sputter coated with a thin layer of gold at 10 torr vaccum before examination.

Dissolution profile:

Dissolution studies of solid forms were was performed according to the USP standard dissolution apparatus Type II (Electro Lab, TDT-08L, Dissolution tester, USP) at 37 ºC ±0.5 ºC at a paddle speed of 100rpm. 10mg of sample was placed into the vessel containing 900ml of distilled water. At specific intervals, 5ml aliquots of the dissolution medium was sampled and replaced with buffer, filtered (pore size 0.45µm) and assayed spectrophotometrically at 430 nm (UV-Double beam spectrophotometer, UV- 1800, Shimadzu) to determine the amount of drug dissolved. The dissolution experiments were conducted in triplicate and standard deviation was also calculated.

RESULTS AND DISCUSSION:

Characterization of solid forms by FTIR, PXRD & DSC:

(i) Input material of Curcuminoids:

IR spectroscopy is an important tool for the characterization of chemical nature of the molecule, and is used to distinguish the solid forms of curcuminoids, results are shown in Table1. The IR spectrum of input material displayed all the characteristic bands which were in agreement with literature data of curcumin. It exhibited a strong absorption band at 3511cm^{-1} due to hydroxyl group, and a strong C=O stretching vibration at 1628 cm^{-1}. A medium intense absorption band was observed at 1599 cm^{-1} owing to the aromatic C=C stretching vibration of curcumin, a phenolic C-O stretching vibration was observed at 1427 cm^{-1}.

Powder X-ray diffraction patterns of input sample of curcuminoids displayed characteristic 2θ values at 17.3 (100), 23.5 (41), 25.7 (41), 23.9 (35), 24.7 (35), 14.8 (34), 18.2 (34), 27.4 (21), 21.3 (19), 19.5 (17), 29.0 (17), 15.9 (17), 12.2 (16), 26.2 (16), 29.4 (15), 18.9 (12), 27.0 (12) which correspond to curcumin form 1, indicating that the input material of curcuminoids contains curcumin in form 1.

DSC thermogram of input material of curcuminoids showed a single melting endotherm at 172.1 ºC (ΔH 58 j/g) with onset temperature and endset temperatures at 164.4ºC and 179.3ºC respectively. When compared to curcumin form 1, there is a difference in melting endotherm observed which may be due to the presence of other curcuminoids DMC, BDMC.

From the above FTIR, PXRD and DSC data, it may be confirmed that the input material consists of curcumin polymorph 1.

Comparative FTIR spectra, PXRD patterns and DSC thermograms of all solid forms were shown in **Fig. 2, 3** and **4** respectively.

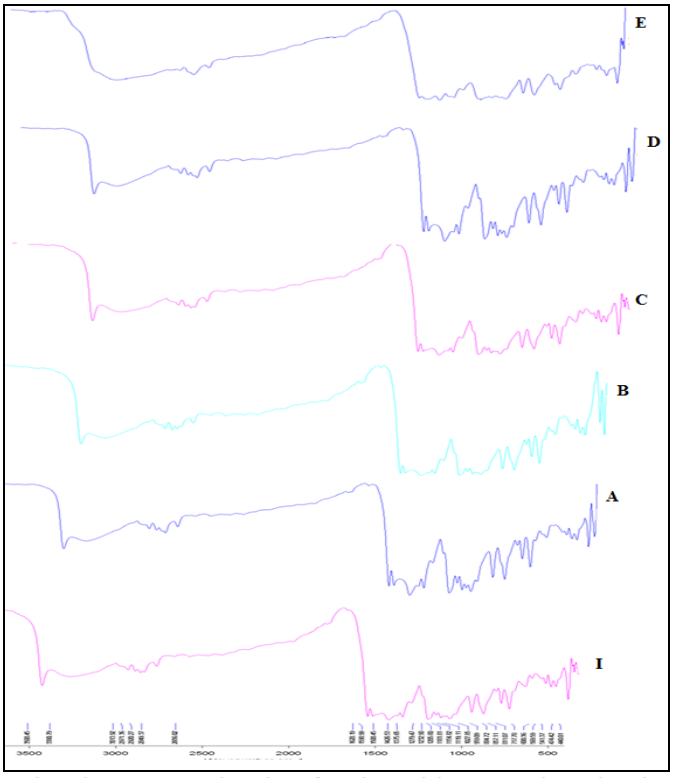


FIG. 2: FTIR SPECTRA OF SOLID FORMS OF CURCUMINOIDS CURCUMINOIDS (I) INPUTMATERIAL (A) SOLID FORM A (B) SOLID FORM B (C) SOLID FORM C (D) SOLID FORM D (E) SOLID FORM E

(ii) Commercial sample of curcumin:

The IR spectrum of curcumin displayed all the characteristic bands. It exhibited strong absorption band at 3510cm^{-1} due to hydroxyl group, and a strong C=O stretching vibration at 1627 cm^{-1}. A strong absorption band was observed at 1602 cm^{-1} owing to the aromatic C=C stretching vibration of curcumin, a phenolic C-O stretching vibration was observed at 1429 cm^{-1}.

Powder X-ray diffraction patterns of input sample of curcuminoids displayed characteristic 2θ values at 17.3 (100), 9.0 (75),25.2 (69), 12.3 (59), 17.7 (56), 24.7 (52), 24.7 (52), 18.2 (51), 27.4 (48), 14.6 (47), 23.4 (41), 23.7(35), 21.3 (34), 26.2 (29), 19.5 (27) which correspond to curcumin polymorph 1, indicating that curcumin sample exists as form 1.

According to the USP general chapter on X-ray diffraction, the agreement in the 2θ-diffraction angles between specimen and reference is within ±0.2° for the same crystal form, while relative intensities between specimen and reference may vary considerably due to preferred orientation effects [20].

DSC thermogram of curcumin showed a single melting endotherm at 180.0 °C (ΔH 51 j/g) with onset temperature and endset temperatures at 175.5°C and 182.5°C respectively. The melting endotherm was similar to the melting endotherm of curcumin form 1 (181.4°C) indicating that curcumin exists as form 1.

From the above data it is confirmed that input material of curcuminoids and curcumin sample contains curcumin form 1. Though curcuminoids contain a mixture of curcumin, DMC and BDMC, its solid state behaviour is similar to its major constituent curcumin. The other constituents DMC and BDMC did not show any distinct crystalline properties in the curcuminoids.

In this study, various solid forms of curcuminoids were prepared by employing different processing conditions like crystallization of solvents with isopropanol and methanol, solvent drop grinding, neat grinding and melting crystallization and the resulting solids were designated as solid forms A, B, C, D and E respectively.

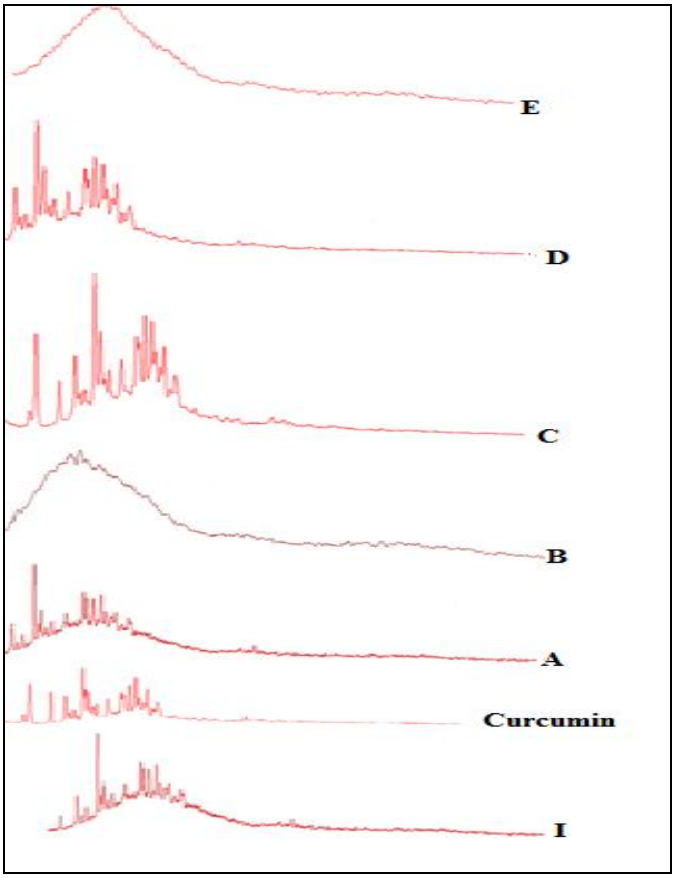


FIG. 3: PXRD PATTERNS OF SOLID FORMS OF CURCUMINOIDS (I) INPUT MATERIAL (A) SOLID FORM A (B) SOLID FORM B (C) SOLID FORM C (D) SOLID FORM D (E) SOLID FORM E

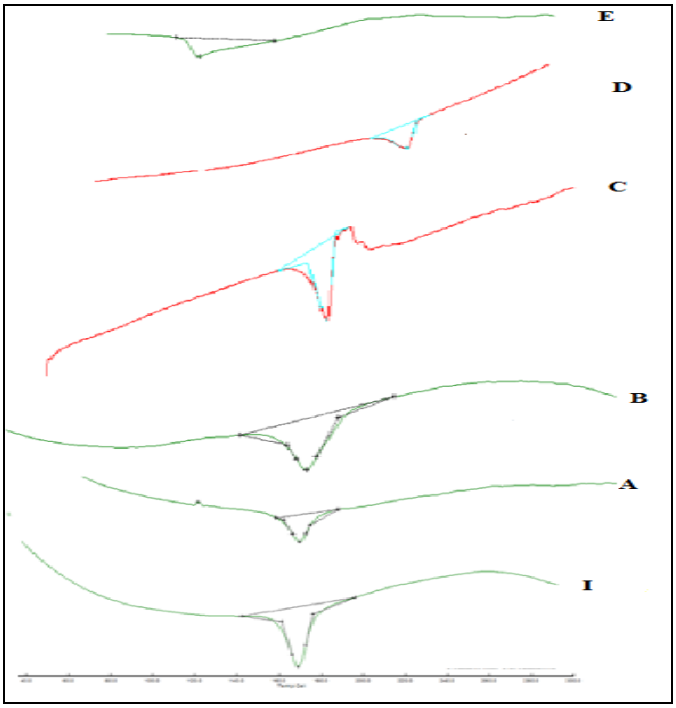


FIG. 4: DSC THERMOGRAMS OF SOLID FORMS OF CURCUMINOIDS (I) INPUT MATERIAL (A) SOLID FORM A (B) SOLID FORM B (C) SOLID FORM C (D) SOLID FORM D (E) SOLID FORM E

(iii) Solid form A:

The IR spectrum of solid form A, obtained from crystallization of isopropanol, displayed all the characteristic bands which were similar to the Input material of curcuminoids as shown in **Fig.1**. It exhibited significant absorbance bands at 3511, 1628, 1599 and 1427 cm^{-1}.

The diffraction lines of solid form A displayed prominent 2θ values at 17.2 (100), 24.7 (95), 23.3 (75), 25.7 (68), 21.2 (56), 14.6 (48), 18.2 (45), 22.8 (44), 29.4 (39), 27.4 (39), 26.2 (38), 26.7 (38), 25.2 (36), 22.4 (34) corresponding to curcumin form 1, indicating that solid form A, existed as curcumin form 1. The PXRD behaviour of solid form A is similar to input material of curcuminoids. Curcumin, on crystallization from isopropanol was reported to be crystallized as form 1. In curcuminoids, curcumin also exists in form 1 upon crystallization from isopropanol and the presence of DMC and BDMC did not alter the polymorphic nature of curcmin. DSC trace of solid form A, depicts a single melting endotherm at 172.8 °C (ΔH 45 j/g) with onset temperature and endset temperatures at 166.5°C and 176.9°C respectively. The melting endotherm is similar to that of melting endotherm of input material of curcuminoids. No solution mediated transformation was observed during crystallization from isopropanol.

From the above data, it may be concluded that the input material curcuminoids did not undergo any polymorphic transformation. Curcumin, on crystallization from isopropanol was reported to be crystallized as form 1. Also in curcuminoids, curcumin exists in form 1 upon crystallization from isopropanol. The presence of DMC and BDMC did not contribute to the crystalline properties in the curcuminoids and also did not alter the polymorphic nature of curcmin.

(iv) Solid form B:

The IR spectrum of solid form B obtained from crystallization of ethanol displayed all the characteristic bands very similar to input material curcuminoids as shown in Fig. It displayed characteristic absorption bands at 3511, 1628, 1599 and 1427 cm^{-1}.

A different polymorphic behaviour was noticed Incase of solid form B, crystallized from ethanol. The PXRD pattern of solid form B was found to possess low intensity peaks at 2θ values at 24.7 (100), 23.4 (92), 28.1 (43), 30.5 (37), 14.4 (10), 12.3 (10) corresponding to curcumin form 1 and peaks 2θ values at 22.0 (80), 20.4 (53), 26.7 (30), 32.3 (27), 18.1 (27), 15.7 (12), 13.8 (10) corresponding to curcumin form 2 suggesting that solid form B exists as a mixture of forms 1 & 2 and amorphous form. The crystalline nature of curcuminoids was significantly reduced on crystallization from ethanol. However, it was reported that curcumin was transformed into form 2 when crystallized from ethanol [12]. The partial transformation of curcumin form 1 into a mixture of form 2 and an amorphous phase may be due to effect of DMC and BDMC present in curcuminoids.

DSC trace of solid form B, depicts a single broad melting endotherm at 172.1 °C (ΔH 39 j/g) with onset temperature and endset temperatures at 165.9°C and 182.2°C respectively. No significant change in the melting endotherm was observed but the shape of the endotherm was broader than the melting endotherm of input material which may be due to partial transformation of curcumin form 1 into mixture of form 2 and amorphous form.

(v) Solid form C:

It is well known that grinding or milling is one of the manufacturing processes in pharmaceutical industry. Grinding process can modify the physical and chemical properties of drugs, such as introduction of a significant lattice strain within the crystalline drug, alteration of crystallinity of drug, reduction of particle size, and induction of polymorphic transformation of drug polymorphs [21].

The IR spectrum of solid form C obtained by solvent assisted grinding displayed all the characteristic bands which are similar to input material. It showed significant absorption bands at 3511, 1628, 1599 and 1427 cm^{-1}.

Diffraction spectra of solid form C exhibited signature 2θ values at 17.3 (100), 24.6 (55), 18.1 (54), 25.6 (48), 14.5 (44), 23.4 (43), 27.3 (38), 23.8 (34), 12.2 (31), 26.1 (26), 21.2 (25), 19.6 (22), 17.9

(20), 29.0 (19) Correspond to curcumin polymorph 1. The PXRD behaviour of solid form C was similar to input material of curcuminoid suggesting that, solvent assisted grinding did not alter the polymorphic behaviour of curcuminoids.

Addition of few drops of solvent act as catalyst and facilitates the polymorphic transformation. Incorporation of solvent molecules into a solid form influences the intermolecular interactions in the crystal structure [22]. In case of solid form C, curcuminoids upon solvent assisted grinding neither resulted in the formation of pseudo polymorphs nor underwent any polymorphic transitions.

It was reported that curcumin readily forms co-crystals with phenolic compounds such as resorcinol, pyrogallol, etc by solvent assisted grinding method using ethanol as a solvent [12]. But, Curcumin present in curcuminoids did not form co-crystal with DMC or BDMC upon solvent assisted grinding.

The DSC behaviour of solid form C furnished a melting endotherm at 171.1°C (ΔH 55 j/g) with onset temperature and endset temperatures at 162.04°C and 175.6°C respectively. The melting endotherm was similar to the endotherm of input material. But it is relatively sharp when compared to input material.

(vi) Solid form D:

The IR spectrum of solid form D was obtained from neat grinding, displayed all the characteristic bands which were similar to input material. It showed absorption bands at 3511, 1628, 1599 and 1427 cm^{-1}.

Diffraction lines recorded for solid form D showed significant 2θ values at 17.3 (100), 9.0 (69), 24.7 (58), 25.6 (54), 18.2 (54), 14.6 (44), 23.5 (43), 23.8 (37), 27.4 (37), 12.2 (31), 26.1 (31), 21.2 (28), 19.5 (23), 29.1 (21), 26.9 (20) corresponding curcumin form 1. It was observed that grinding did not induce any polymorphic transition. Solid form D seemed not to be altered by neat grinding.

A small broad melting endotherm was observed for solid form D in DSC trace, at 171.6 °C (ΔH 65 j/g) with onset temperature and endset temperatures at 165.2°C and 175.6°C respectively. No significant difference was observed when curcuminoids were subjected to neat grinding, suggesting that curcumin did not undergo any polymorphic change in curcuminoids.

(vi) Solid form E:

The IR spectrum of solid form E, obtained from crystallization from melt, displayed characteristic bands which were in agreement with curcuminoids. It exhibited strong absorption band at 3380 cm^{-1} due to hydroxyl group. A phenolic C-O stretching vibration was observed at 1427 cm^{-1}. The absence of C=O stretching vibration and slight shifting of aromatic C=C stretching vibration from 1599 to 1581 cm^{-1}, indicate the possible polymorphic change in solid form E.

A significant difference was observed in the PXRD pattern of solid form E. crystallization from melt significantly decreased the crystallinity of curcuminoids suggesting the distortion of structure induced by crystallization from melt. No sharp peaks were observed for solid form E indicating the amorphous nature. Generally crystallization from melt and quench cooling of a crystalline drug results in amorphous phase and curcumin was reported to exist in amorphous form on melt crystallization [23].

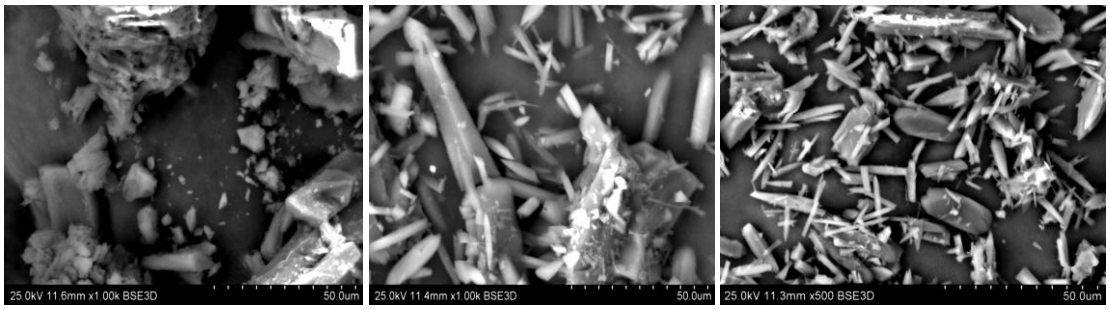
There was a significant change in DSC behaviour of solid form E. It exhibited a small broad endotherm at 64°C with onset temperature and endset temperatures at 58°C and 86°C respectively. The broadening of the endotherm may be due to the solid- solid transition of form 1 of curcumin into amorphous form. This difference in thermal behaviour suggests that, curcuminoids underwent a significant polymorphic change under melt crystallization Conditions, similar to curcumin. However, amorphous form of curcumin was reported to be crystallized to form 1 upon heating, but the amorphous phase of curcuminoids did not show any such transformation.

From the above data, it was confirmed that Curcumin present in curcuminoids transformed into amorphous form under melt crystallization conditions.

4.2 SEM analysis:

Microscopical analysis plays a prominent role in Characterization of solid dosage forms solid dosage forms. Differences in crystal habit may strongly influence the particle orientation; modify flowability, packing, compaction, and compressibility and dissolution characteristics of a drug. Solid-liquid interface interactions can alter the roundness of the interfaces, change crystal growth kinetics and enhance or inhibit growth at certain crystal faces, resulting in different habits (acicular, plates, tabular, bladed, prismatic etc) [24].

The SEM photographs of curcuminoids solid forms developed from different processing conditions are represented in **Fig. 5**. The SEM pictures reveal that the crystals of the solid forms represent differences in size, morphology and surface.



A B C

FIG. 5: SCANNING ELECTRON MICROSCOPIC PHOTOGRAPHS OF SOLID FORMS OF CURCUMINOIDS IAE (AT 500 MAGNIFICATION) (A) INPUT MATERIAL (B) SOLID FORM A (C) SOLID FORM E

The crystal shape of input material is irregular aggregates of small size crystals, whereas clusters of long rod like structures were observed for solid form A. On the other hand, solid form E showed irregular particles.

Dissolution profile:

The results of *in vitro* dissolution study are shown in **Fig.6**. There were observed marked differences in dissolution behaviour of the solid forms and input material of curcuminoids. The dissolution rates were found to be increased to 97.9±1.3 and 96±3.5 for solid forms B and E respectively at 80min, when compared to input material (94.3±0.5). The dissolution rate was comparatively low for the solid form D (76.3±0.7). The other solid forms of curcuminoids, showed dissolution rates in the order of 82.4±2.3 and 90.2±1.7 for solid forms A and C respectively. The variation in dissolution rates of solid forms may be associated with differences in melting behaviour, degree of crystallinity and presence of polymorphic forms of Curcuminoids. There was an increase in dissolution rate observed for solid forms B and E when compared to input material, which may be due to transformation of curcumin into an amorphous form.

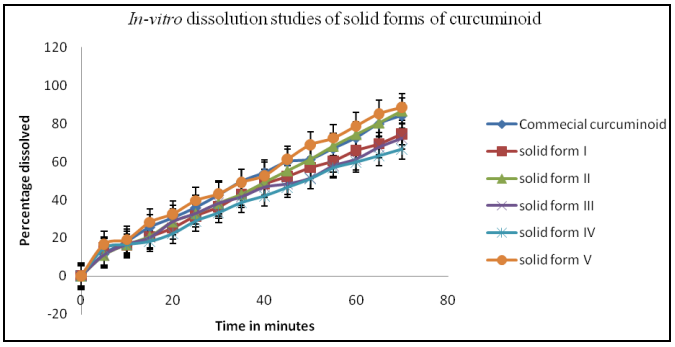


FIG.6: *IN-VITRO* DISSOLUTION STUDIES OF SOLID FORMS OF CURCUMINOIDS

CONCLUSION: The solid-state characterization of curcuminoids demonstrated interesting polymorphic behaviour of its constituents present in the form of a mixture. The input material of curcuminoid was similar to curcumin polymorph 1. Curcuminoids, on recrystallization from ethanol underwent polymorphic transformations resulting in a mixture of forms 1&2 and a predominant amorphous form. Upon melt crystallization also, similar transformation into amorphous form was resulted. The dissolution rates of these amorphous forms (solid forms B and E) were found to be increased. The poor dissolution observed with curcuminoids was improved by converting into amorphous forms.

Curcuminoid on crystallization from isopropanol or upon solvent assisted and neat grinding did not undergo any polymorphic changes. The coexistence of the curcumin, DMC and BDMC in curcuminoids studying their polymorphic behaviour presents an interesting aspect of modifying their properties. The solid- state behaviour of curcuminoids was mainly due to its major constituent curcumin, while DMC and BDMC did not contribute to the overall crystalline properties probably owing to the amorphous nature of DMC or to the low percentage of BDMC in the curcuminoids. The differences in the reported polymorphic forms of curcumin i.e., curcumin forms 1-3 and the patented forms I to VI may be due to variations in the purity of curcumin.

In conclusion, the present work underlines the importance of polymorphic behaviour of curcuminoids and its major constituent, curucmin for their therapeutic potential.

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