International Journal of PharmTech Research
CODEN (USA): IJPRIF ISSN : 0974-4304
Vol.4, No.3, pp 1055-1064, July-Sept 2012

Solubility and Dissolution Rate Enhancement of Curcumin Using Kollidon VA64 by Solid Dispersion Technique

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Abstract: Curcumin is natural occurring, highly lipophilic, main pharmacological active phytochemical compound of turmeric. Insolubility in water at acidic or neutral pH and its incomplete absorption leads to poor bioavailability. The aim of present study was to increase solubility and dissolution rate enhancement of curcumin by solid dispersion technique. For solid dispersion preparation, Kollidon VA 64 polymer was selected as a hydrophilic carrier. Solid dispersion was prepared in a combination of Curcumin and Kollidon VA64 in a weight ratio of 1:1, 1:2 and 1:3 by solvent evaporation and solvent change precipitation method. SDs prepared in a 1:2 ratio by solvent evaporation showed 100% drug release in 30 min compared to its equivalent physical mixtures 50% and solvent change precipitated SDs product 65% after 60 minutes of dissolution. Saturation solubility studies also indicated that solvent evaporated SDs showed markably increased solubility compared to others. Physical characterizations of solvent evaporated solid dispersion in comparison to its physical mixtures by SEM, DSC, FTIR and PXRD revealed a change in solid state from pure crystalline phase to high-energy amorphous phase. Studies suggested that the Curcumin solid dispersions prepared using Kollidon VA 64 by solvent evaporation method can be employed for solubility and dissolution enhancement thus leading to bioenhancement.
Keywords: Curcumin, Kollidon VA64, Solid dispersion (SD), Physical mixture (PM).

Introduction

As per the report by Technology Catalysts International, 35 to 40 % of the screened New Chemical Entities (NCEs) suffer from poor aqueous solubility (1). The solubility or the dissolution rate of the drug is a key factor determining its rate and extent of absorption after oral administration. A poor solubility of the drug leads to detraction from its inherent efficacy by affecting the drug bioavailability. Also with the advances in high throughput screening techniques, a sharp rise has been observed in the number of poorly-soluble drug candidates. Hence one of the most challenging tasks faced by modern pharmaceutical scientists is designing a formulation for a poorly soluble drug such that the drug is available in a more soluble form after administration.

Several approaches have been reported for enhancing the solubility and hence the dissolution rate of poorly soluble drugs including a) Micronisation to increase the surface area ; b) use of surfactants as solubilisers; c) forming water soluble complexes with cyclodextrins; d) manipulating the solid state of the drug with the aim of decreasing the drug crystallinity ;e) prodrug formation etc (2). Recently, liquid-solid compaction technique has

been explored as a novel work area for enhancing solubility of poorly soluble drugs (3, 4).

Solid dispersion is one of the majorly used strategies to increase the dissolution rate of poorly water soluble drugs and thus the bioavailability (5, 6). Solid dispersion (SD) technique comprises of dispersion of one or more active ingredients in inert carriers at solid state and can be prepared by fusion, solvent, or solvent–fusion methods (7, 8).The main contributing factor responsible for dissolution enhancement by solid dispersion technique includes enhanced surface area, increased surface wetting property of drug and size reduction (6,9,10).

Curcumin, a yellow pigment obtained from turmeric (*Curcuma longa*) has been used since ancient time as a dietary supplement. Curcumin is regarded as one of the most valuable drug as it has wide range of pharmacological actions like antibacterial, antifungal, antioxidant, anti amoebic anti-inflammatory, anticancer, anti- HIV, anti- diabetic ,antispasmodic (11, 12, 13, 14, 15, 16, 17, 18). Its poor solubility and slow dissolution rate responsible are the contributing factors for its low bioavailability which is about 60% (19).

The work performed here describes the use of Kollidon VA 64 as a hydrophilic carrier to enhance dissolution of Curcumin. This study also investigates the effect of two different methods for solid dispersion preparation on dissolution of curcumin. Solid dispersions obtained were characterized for PXRD, SEM, DSC and FTIR to elucidate the mechanism involved in dissolution enhancement.

Experimental:

Materials

Synthetic Curcumin was obtained as a gift sample from Aptuit Laurus Pvt. Ltd., India and Kollidon VA64 was procured from BASF, Germany. Glacial acetic acid and Sodium acetate trihydrate was procured from S.D. Fine Chem. Ltd. Mumbai, India. Other reagents used were of analytical grade.

Preparation of Solid dispersion

Curcumin solid dispersion was prepared by solvent evaporation and solvent change precipitation method. Solid dispersions were prepared in drug polymer weight ratio of 1:1, 1:2 and 1:3 (SD1, SD2 and SD3). Solvent evaporation method involves dissolution of a weighed amount of drug and polymer in 100ml acetone separately followed by addition of polymer phase to drug phase at constant mechanical stirring 2000 rpm (Remi Stirrer, Mumbai, India) at room temperature. The solvent evaporation and drying of resultant product was carried out in vacuum oven (Model OV-11, JEIO Tech, Korea). In solvent change precipitation method, organic phase containing drug and aqueous phase containing polymer were prepared in above specified ratio and volume. Organic phase was added to aqueous phase with constant mechanical stirring causing precipitation of solubilised drug phase. Stirring was continued for 20 min in both the cases. The product was filtered and washed with deionized water following drying at 60 °C for 4h. The dried samples were pulverized using mortar and pestle and passed through 60 mesh sieve to get uniform particle size distribution. PMs were also prepared manually in same ratio (PM1, PM2 and PM3) .The obtained samples were stored in vacuum desiccators till further studies.

Drug Content analysis

An amount of sample (10mg) was weighed accurately and dissolved in 10 ml glacial acetic acid (AR). The solution was sonicated for 10 min and the sample was centrifuged at 10000 rpm for 5 min. The supernatant was diluted with suitable quantity of methanol. The absorbance was recorded at 420 nm through UV-Visible Spectrophotometer. The drug content was determined by using a standard curve plotted as a plot of absorbance versus concentration.

Saturation Solubility studies

Apparent saturation solubility measurement was performed by standardized shake flask method (BOEKEL shaking hot tub, USA) by keeping at 37 °C at an rpm of 20 for 48h. Apparent solubility was determined in deionized water and pH 1.2 buffers. For solubility study, an excess amount of the samples (20mg) was dispersed into 10 ml of media. After 48 hrs of shaking, samples were filtered through 0.2µm membrane filters (PALL life sciences, India) and the filtrate was appropriately diluted with the medium used for solubility analysis. The measurement was conducted using UV-visible spectrophotometer (Shimadzu UV-1650, Tokyo, Japan) at 427 nm.

In vitro drug release studies

Powder dissolution study was carried out using eight stations USP apparatus II (Electrolab, TDT-08L, India) in 900 ml of pH 4.5, acetate buffer at a temperature of 37±0.5 °C at 100 rpm. A powdered sample (equivalent 30 mg curcumin) was introduced directly into the dissolution medium. At regular time intervals of 15, 30, 45 and 60 min, suitable amount of sample (10 ml) was withdrawn and same amount replaced by fresh medium to maintain the sink

condition. The withdrawn samples were suitable diluted and analyzed through UV-Visible spectrophotometer at 427 nm. All studies were carried out in triplicates.

Contact angle measurement

For the contact angle measurement G10 Contact angle meter (KRUSS, Germany) was used. In this study Static contact angles method was adopted to measure the contact angle**.** A compressed disc of the powder (100 mg) with flat surface was made at 3-4 kg/cm^2 hardness. A solid disc was prepared for plain drug and SDs. Method involved dropping a single drop of distilled water (25 µl) on the disc surface and the contact angle was determined at 10 and 180s after equilibrium. Measurement was carried out in triplicate for each sample.

Moisture Uptake Study

The moisture uptake for prepared SDs was determined gravimetrically. A weighed amount of samples (100 -200 mg) were placed in crucibles at accelerated condition of temperature and humidity, 40 ±2 °C and 75 ± 5% RH respectively in environmental test chamber (Thermo lab, INDIA,) and weighed at different time points (Citizen, Mumbai, India).Observations for changes in moisture content were taken after 7 days.

Stability study

For stability analysis, known amount (n = 3) of the sample was kept in aluminum capped glass vials at 40 ± 2 °C and 75 ± 5% RH for 2 months in environmental test chamber (Modern Industrial Corporation, INDIA). After 30 and 60 days, the samples were taken out and analyzed for the drug content.

Scanning Electron Microscopy (SEM)

Morphological evaluation of the treated samples and plain drug was performed by scanning electron microscope. Scanning electron micrographs were taken using a Philips XL 20 (Philips, Eindhoven, Netherlands). Samples were fixed on an aluminum stub with conductive double sided adhesive tape (Leit-Tabs, Plano GmbH, Wetzlar, Germany) and coated with gold in an argon atmosphere (50 Pa) at 50mA for 50 s (Sputter Coater, Bal-Tec AG, Liechtenstein).

Fourier Transform Infrared (FTIR) Spectroscopy

FTIR spectra were recorded on samples prepared in potassium bromide (KBr) disk using a PERKIN ELMER FTIR spectrophotometer (Spectrum RX1, USA). Samples were prepared in KBr disk by means of a hydrostatic press. The scanning range was 500 to 4000 cm^{-1} and the resolution was 4 cm^{-1}.

Differential Scanning Calorimetry (DSC)

DSC analysis was performed using PERKINELMER DSC Pyris -6 (USA) on 2 to 8 mg sample. Samples were heated in open aluminum pans at a rate of 10°C/min in 40 to 240 °C temperature range under nitrogen flow of 20 mL/min using an empty sealed pan as a reference.

X-ray Powder Diffractometry

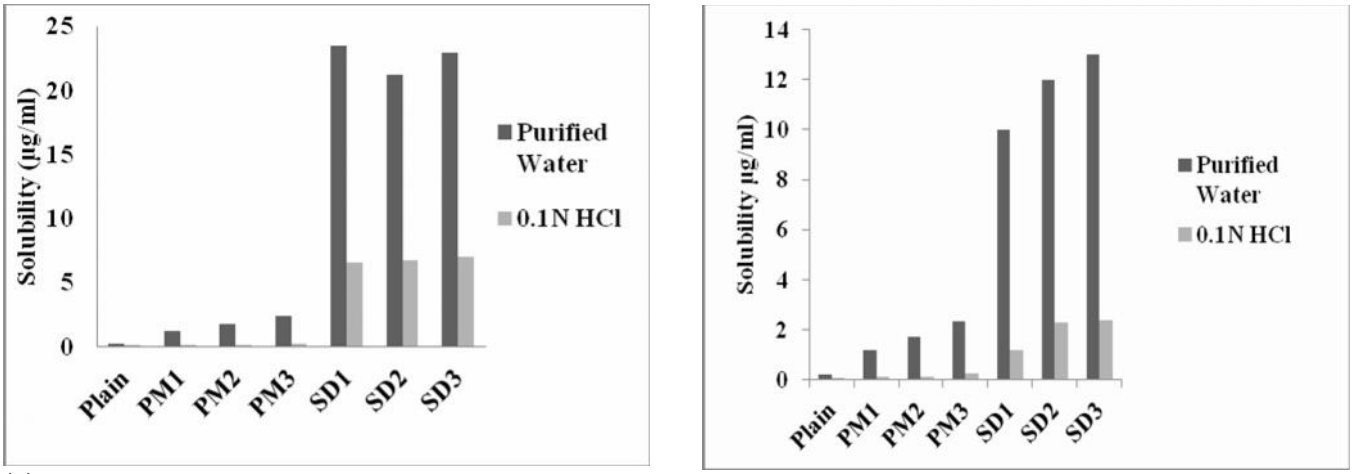
X-ray powder diffraction patterns were recorded on a Jeol JDX 8030 x-ray diffractometer (Tokyo, Japan) using Ni filtered, CuKα radiation, a voltage of 40 kV, and a 25-mA current. The scanning rate employed was 1° min^{-1} over the 0 to 70° diffraction angle (2θ) range.

Results and discussion

Drug content and Solubility studies

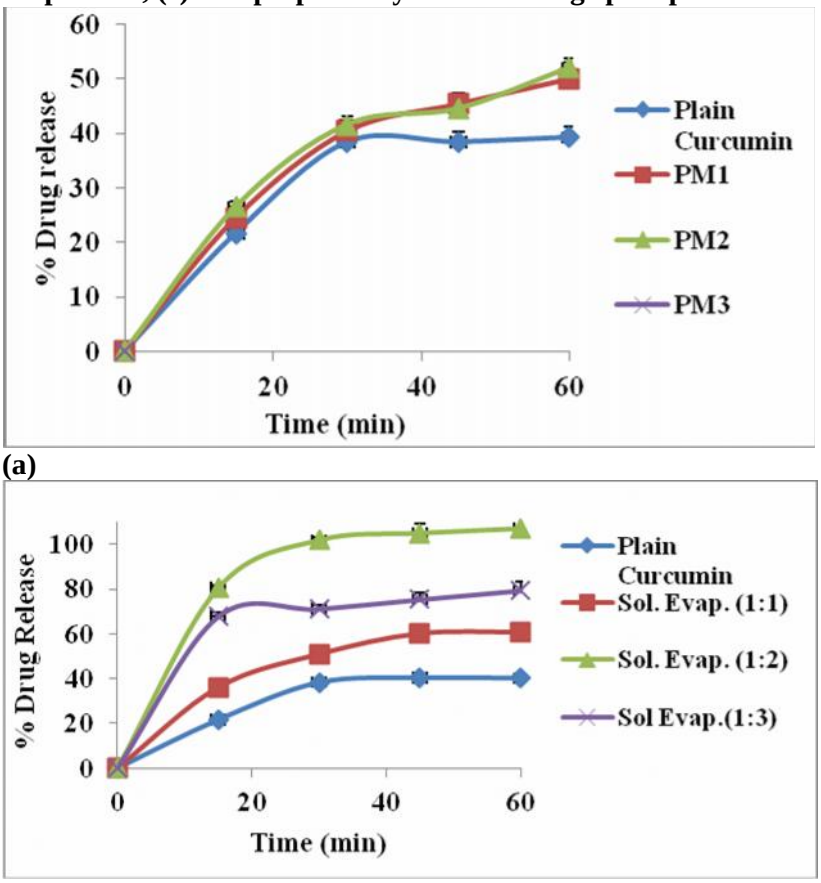
The drug content was found to be good and uniform among the different batches of prepared samples and ranged from 98.5 to 99.43%. The saturation solubility was performed in deionized water and pH 1.2 buffer media in triplicate. The solubility profile of Curcumin, physical mixture and solid dispersion of curcumin with various concentration of Kollidon VA 64 are shown in figure 1a and 1b. Plain Curcumin was practically insoluble in water. The solubility of plain curcumin and its physical mixture in water and 0.1N HCl was very low and produced imprecise results due to limitation of analytical system. Whereas solid dispersions prepared by solvent evaporation and solvent change precipitation method reported higher solubility than pure curcumin and its physical mixtures. SDs prepared by solvent evaporation showed 100 fold increase in solubility in both the medium compared to pure drug whereas this improvement was 20 fold with respect to physical mixture. This ratio for SDs prepared solvent change precipitation method was 50 and 10 with respect to pure drug and physical mixture. The increase in solubility might be attributed to formation of soluble complex of curcumin and Kollidon VA64. The increase in solubility was found almost similar irrespective of polymer concentration. This might be due to release inhibiting property of polymer at higher concentration or attainment of saturation solubility by curcumin.

Figure1: Comparative solubility profile of pure cucumin, PMs with (a) SDs prepared by solvent evaporated method, (b) SDs prepared solvent change precipitation method.



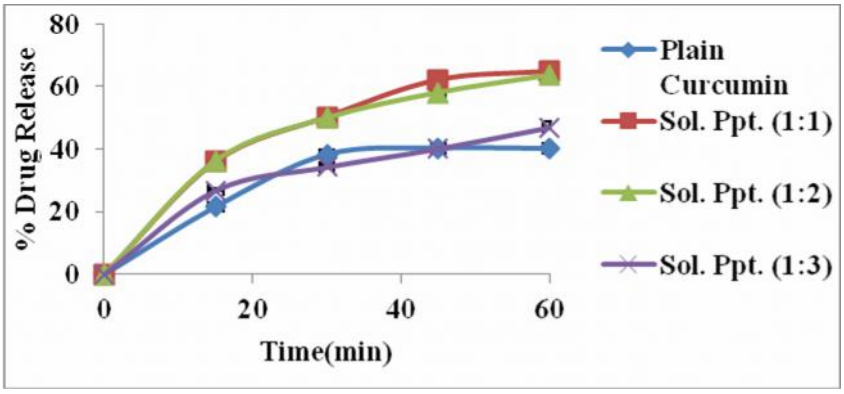
(a) **(b)**

Figure 2: Comparative dissolution profile of curcumin with (a) PMs, (b) SDs prepared by solvent evaporated, (c) SDs prepared by solvent change precipitation method.



(a)

(b)



(c)

In vitro drug release

In vitro drug release profile for different batches is shown in figure 2. During dissolution study, plain curcumin and its physical mixtures showed 39% and 50% drug release respectively at the end of 60 min. Whereas SDs prepared by solvent change precipitation method showed maximum 65% (SD1) drug release after 60 min and SDs prepared by solvent evaporation showed 100% drug release (SD2) after 30 min. The low dissolution rate observed with SD3 prepared by solvent evaporation and SD2, SD3 prepared by solvent change precipitation. This effect might be due presence of high concentration of Kollidon VA64 polymer causing agglomeration of drug particles and retard in the release of drug. In case of solvent change precipitation method, micron size particles with increased surface area and improved surface wetting property were found to be responsible for solubility and dissolution enhancement. Washing treatment with deionized water leading to removal of water soluble polymer from the particles surface might also be one of the reasons for low dissolution rate and solubility in case of SDs prepared by solvent change precipitation technique. SDs prepared by solvent evaporation method showed complete drug release and high solubility compared to earlier method hence it was further characterized. Dispersion of drug into glassy matrix of amorphous polymer (Kollidon VA64), transition of solid drug from crystalline to amorphous form, reduced particle size and improved surface wetting are the mechanisms responsible for dissolution rate enhancement of solvent evaporated SDs .These mechanisms are supported by data obtained from PXRD, DSC, SEM and contact angle studies.

FTIR

FTIR spectroscopy was also performed to characterize interaction between Curcumin and Kollidon VA64 in solid state. FTIR spectra were recorded in 500-4000 cm^{-1} range.The FTIR spectra of Curcumin, Physical mixture and solid dispersions were shown in figure 3. Pure curcumin showed stretching vibration of C=O (1640-1700) and –OH (3400) group appeared at wave number 1629 and 3404 cm^{-1} respectively whereas ether group (-C-O-) observed at 1119 and 1028 cm^{-1}. Polymer Kollidon VA 64 showed presence of a stretching band of ester (-COO) at 1734 cm^{-1}. The stretching vibration of above all mentioned functional group were found to be within range in all solid dispersions as well as in physical mixture indicating absence of any significant chemical interaction in solid state.

DSC

The DSC thermograms of Curcumin, Kollidon VA 64, PMs and solid dispersion are shown in figure 4. Absence of thermal peak reveals amorphous state of polymer Kollidon VA 64. A single sharp endothermic peak at 185.45 $^{\circ}C$ was observed corresponding to melting point of pure curcumin with enthalpy of fusion 513.84 J/g. In all PMs with increased Kollidon VA 64 concentration, the DSC curve showed broadening of endothermic peak with significant lowering in melting temperature and the enthalpy of fusion of curcumin. The decrease of enthalpy of fusion of PMs may be a result of solubilizing effect of Kollidon VA64 during heating process due to its low melting temperature. The presence of broadened melting endotherm indicates presence of excess of curcumin. This shows that a crystalline form of curcumin was still present, conferring the results from X-ray diffraction studies. Whereas all SDs showed no endothermic peak of curcumin. The complete absence of thermal endotherms indicates dispersion of drug in the polymer phase which was also conferred by scanning electron micrograph. This results support the process, transition of crystalline curcumin to amorphous solid solution state which also may be responsible for an increase in dissolution.

Figure3 : FTIR spectra of (a) curcumin, (b) Kollidon VA 64, (c) PM1, (d) PM2, (e) PM3, (f) SD1, (g) SD2 and (h) SD3

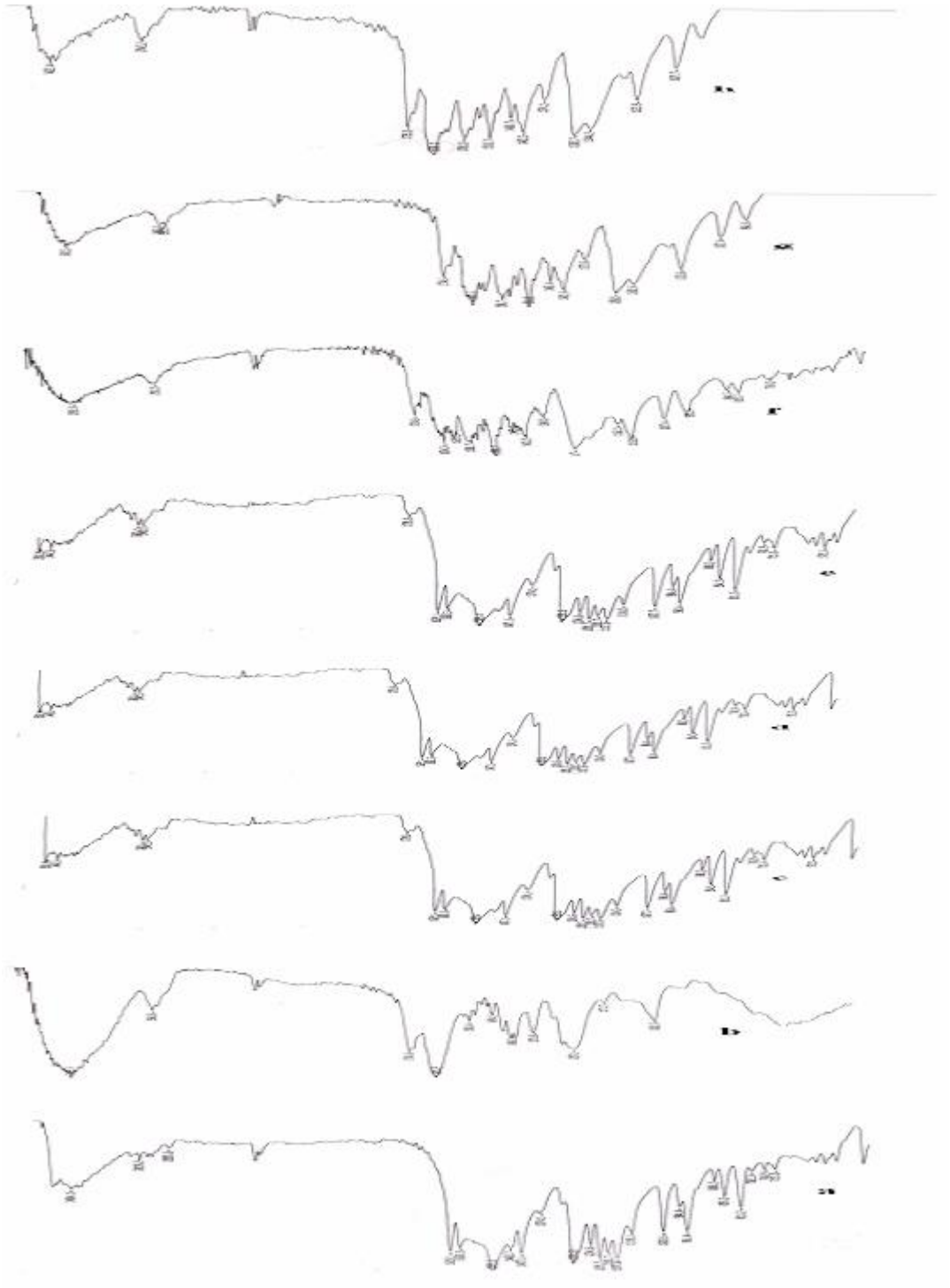
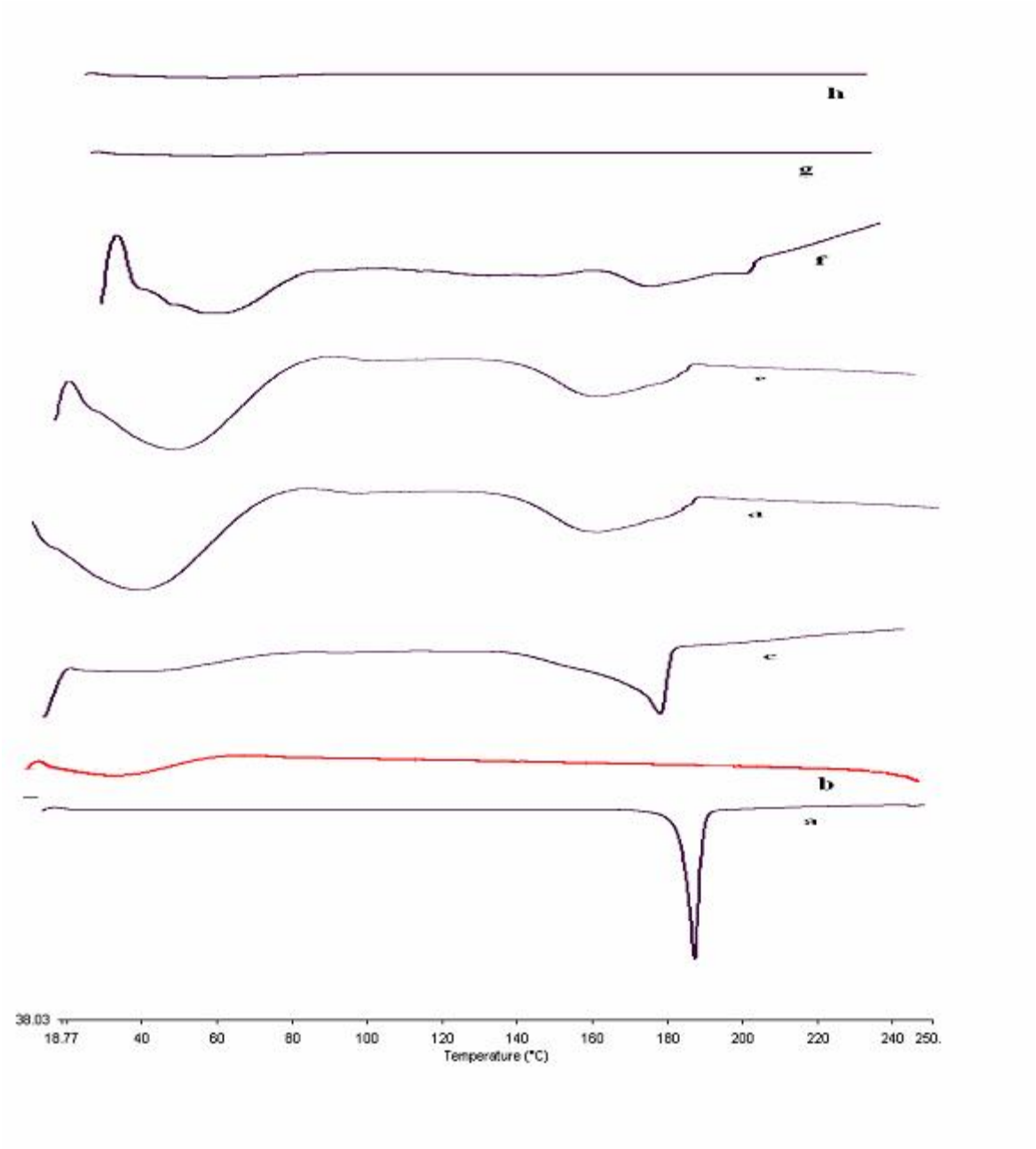


Figure 4:Comparative DSC thermogram of (a) Curcumin, (b) Kollidona VA 64, (c) PM1, (d) PM2, (e) PM3, (f) SD1, (g) SD2 and (h) SD3



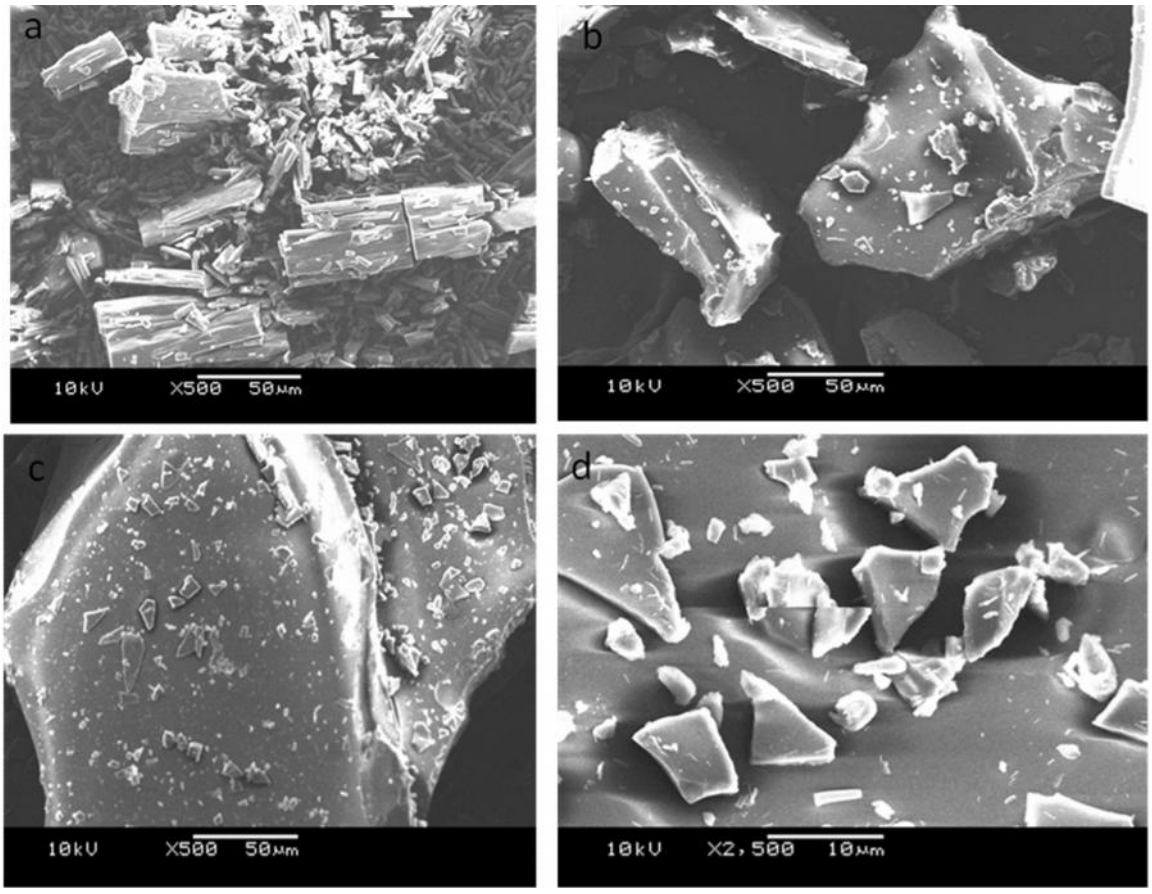
Contact angle measurement

In a static contact angle measurement, the size of the drop does not alter during the measurement but surface interaction at the boundary can cause the contact angle to change considerably with time. Depending on the type of time effect the contact angle can increase or decrease with time. It was observed that with plain drug showed higher contact angle even after 60 seconds of equilibrium while polymer treated drug showed very less or no contact angle after equilibrium time. This effect might be due migration of hydrophilic polymer coating from solid surface to liquid surface. The results are tabulated in table1.

Table1. Contact angle [°] (n=3, ±SD)

Samples	Contact angle	
	t=0	t=60 seconds
Pure Curcumin	81±2	71±2
PM1	60±2	55±1.5
PM2	55±1.5	54±2
PM3	50±1	40±2
SD1	30±2	22±1
SD2	18±1.5	10±3
SD3	10±1.5	8±2

Figure5: Scanning electron micrograph of (a) Curcumin, (b) SD1, (c) SD2 and (d)SD3



Moisture uptake and Stability studies

The moisture uptake study is important to check hygroscopic nature of the prepared crystals. No significant change in moisture content was observed after subjecting them to accelerated condition of temperature and humidity. The accelerated stability studies showed that there was no considerable change in drug content after study duration. Drug content was found to be same as initial day i.e. approximately 98%.

Scanning Electron Microscopy

Scanning electron micrograph of Curcumin and solid dispersions are shown in figure 5. In SEM studies pure curcumin was found as flat, broken needle shape of different sizes. Whereas solid dispersions showed irregular triangular shaped particle with reduced size embedded in polymer phase. Increased polymer concentration provides more dispersing medium for drug to remain in embedded form and plays an important role during solubilization and dissolution study.

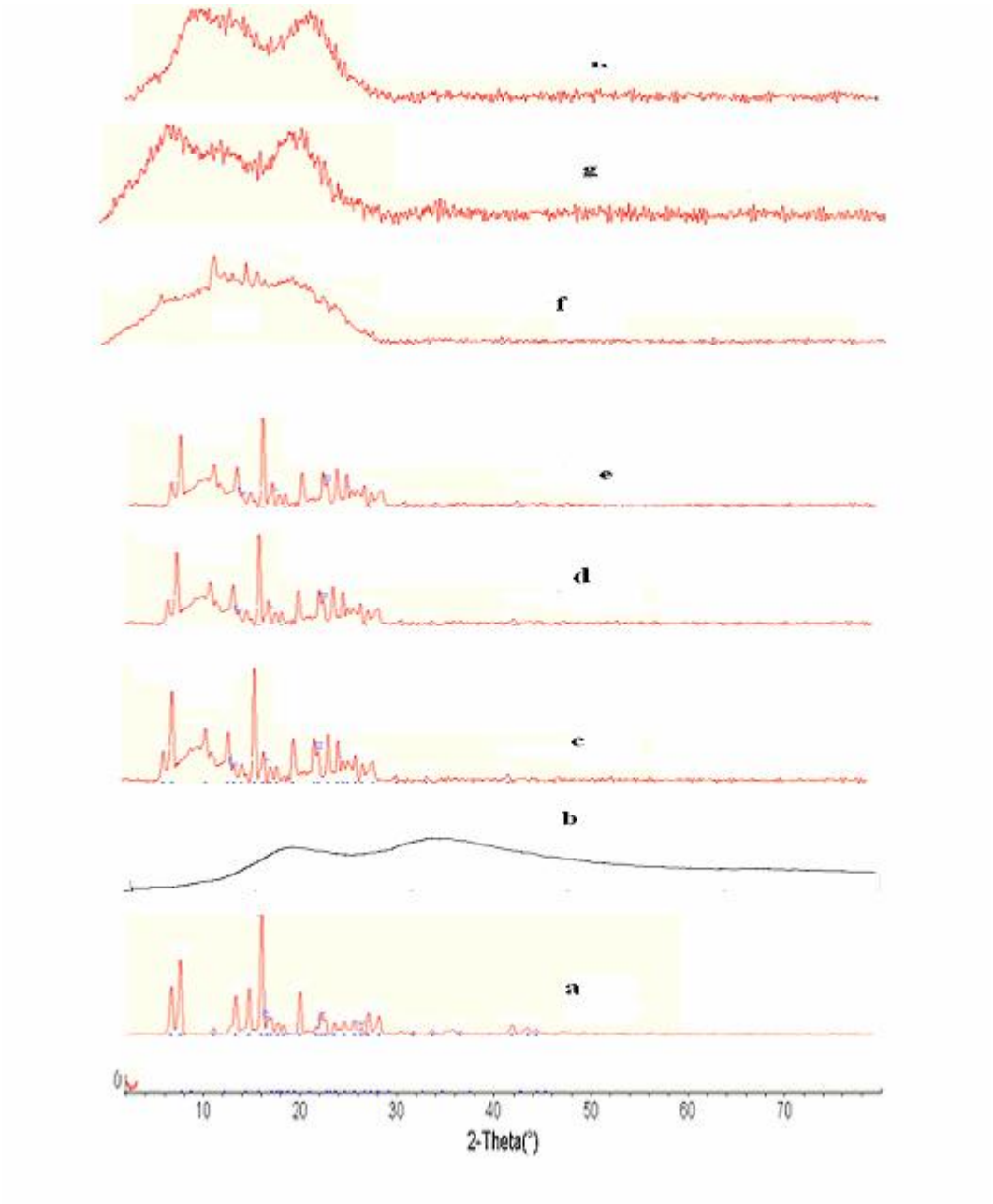
PXRD

The powder X-ray diffractograms of plain curcumin, physical mixtures and solid dispersions were shown in Fig. 6. X-ray diffractograms of pure curcumin showed characteristic peaks at diffraction angle of 2θ at 7.86, 8.78, 12.18, 14.46, 15.84, 17.14, 21.08 etc. revealing that curcumin is present as a crystalline form. Kollidon VA 64 powder is amorphous in nature. The solid dispersions prepared with increased concentration of Kollidon VA64 indicated disappearance of crystallinity of curcumin and transition to amorphous states. The amorphous state powder has better solubility and dissolution rate compared to crystalline (20).

Conclusion

From the study it was concluded that solvent evaporated solid dispersion showed better solubility and dissolution rate as compared to solvent precipitated SDs. This indicated solvent treatment and inclusion of hydrophilic polymer contributes to enhanced dissolution.

Figure 6. Powder X-ray diffractogram of (a) Curcumin, (b) Kollidona VA 64, (c) PM1, (d) PM2, (e) PM3, (f) SD1, (g) SD2 and (h) SD3



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