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Original Article

In vitro and *in vivo* evaluation of binary Solid dispersion of Curcumin by solvent evaporation technique

Suresh Kumavat*[1], Yogesh Chaudhari[1], Deepali Kenge[2], Rashmi Kokardekar[1], Avinash Bichave[3]

[1]Department of Pharmaceutics, HSNCB's Dr. L. H. Hiranandani College of Pharmacy, Ulhasnagar, Maharashtra, India
[2]Department of Pharmaceutics, VES College of pharmacy, Chembur, Mumbai, India
[3]Department of Quality Assurance, VES College of pharmacy, Chembur, Mumbai, India

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ABSTRACT

Curcumin, a natural pigment extracted from the plant *curcuma longa*, had wide range of pharmacological activities. However, its limited aqueous solubility and degradation at alkaline pH restricts its bioavailability. Solid dispersions were prepared with the objective of solubility and dissolution enhancement of curcumin using polyethylene glycol (PEG 4000)-polyvinylpyrrolidone (PVP K 30) combination carrier by solvent evaporation technique. Solid dispersions of curcumin in different ratios with Polymers were prepared and evaluated for its saturation solubility, drug content, flow properties, in vitro, in vivo by HPTLC method and Physical characterization by IR, DSC, and studies, in comparison with corresponding physical mixtures and drug. Studies revealed the changes in solid state during the formation of dispersion and justified the formation of high-energy amorphous phase from crystalline state of curcumin.

Keywords: Curcumin, Polyethylene glycol, Polyvinylpyrrolidone, Solid dispersion, Solubility, Bioavailability.

INTRODUCTION

Curcumin, obtained from the rhizomes of *Curcuma longa* L., Zingiberaceae (turmeric), is the most widely used phytochemical constituent in food industry. Indian and Chinese traditional systems of medicine have reported the use of turmeric for wound healing, anti-inflammatory and other pharmacological activities [1]. Following oral administration (upto 8 g per day), it is poorly absorbed and only traces of compound appear in blood. Curcumin is practically insoluble at acidic pH although soluble at alkaline pH; it undergoes rapid hydrolytic degradation[2,3]. Few attempts have been made to improve solubility of curcumin by its chemical derivatisation, complexation or interaction with macromolecules, e.g. gelatin, polysaccharides and protein, and cyclodextrin. But slow process of complexation, high molecular weight of cyclodextrins and pH of the processing medium may limit their practical utility[4].

Solid dispersion is one of the successful methods in improving drug dissolution and to obtain better bioavailability. Solid dispersion is defined as the dispersion of one or more active ingredients in an inert hydrophilic carrier or matrix at solid state prepared by the fusion, solvent or solvent-fusion method [5]. This system allows a particle size reduction of drug to nearly a molecular level. As this system exposed to aqueous media, the carrier is dissolved and the drug is released as very fine particles for quick dissolution and absorption. Hydrophilic synthetic polymers have been widely investigated as carrier substance for solid dispersions. Polyethylene glycol (PEG) and Polyvinylpyrrolidone (PVP) are amongst the most frequently used as the carriers. They can improve the solubility and dissolution of many poorly water soluble drugs.

In the present study we employed solid dispersion technique to improve dissolution of curcumin in acidic medium. Curcumin solid dispersions were prepared with the objective of solubility and dissolution improvement using PEG 4000-PVP K 30 combination carrier by solvent evaporation technique. Previous literature also revealed that the combination of two hydrophilic polymeric carriers like PEG and PVP could improve the solubility as well as dissolution profiles of various poorly aqueous soluble drugs. However, the Curcumin

Corresponding Author Address: Suresh Kumavat,** Department of Pharmaceutics, HSNCB's Dr. L. H. Hiranandani College of Pharmacy, Ulhasnagar, Maharashtra, India; **E-mail: srkkumavat@gmail.com

solid dispersion using PEG and PVP combination carrier was not reported. In the present investigation, we attempted to investigate the enhancement of the aqueous solubility and dissolution of Curcumin using the combination of these two different carriers. Curcumin: PEG 4000: PVP K30 solid dispersions (SDs) in different ratios (1:3:7, 1:5:5, and 1:7:3) were obtained by Solvent evaporation method. The solubility, dissolution and physicochemical characterizations based on differential scanning calorimetry (DSC) and FTIR spectroscopy were evaluated. The best ratios of curcumin: PEG 4000: PVP K30 was used by oral administration to rats. The bioavailability of curcumin in plasma concentration was measured by HPTLC methods [6,7].

MATERIAL AND METHODS

Materials: Curcumin 95% was procured from Neelam phytoextract, Mumbai, India. PEG 4000, PVP K30 was obtained as a gift sample from Ashland, Thailand. Methanol, Acetone analytical grade were procured from SD fine. The *in vivo* study was performed in accordance with the protocol approved by the Institutional Animal Ethics Committee (IAEC).

Methods: Solid dispersions of Curcumin: PEG 4000: PVP K30 in the weight ratio of 1:3:7, 1:5:5 and 1:7:3 were prepared by Solvent evaporation method. To the solution of curcumin (600 mg) in acetone (25 ml), the amounts of carriers were added. The minimum amount of methanol was added to in order to solubilize the PVP K-30. The solvents were removed under water bath at a temperature of 80^0C. The samples were taken and stored in the oven at the temperature of 70^0C for 48 hrs. The samples are then pulverized using mortar and pestle and then passed through a #40 sieve before analysis and kept in the desiccator. For comparison purposes, physical mixtures having the same ratios of curcumin and polymer were prepared by gently mixing the drug and the polymer in a glass mortar, and the mixtures were then passed through a #40 sieve [8, 9, and 10].

Determination of saturation solubility: The solubility of curcumin in pH1.2 (0.2 M HCL) and various concentrations of PEG 4000, PVP K30 were determined by adding excess amount of curcumin to glass vials containing 10 ml of aqueous solutions of polymer. These vials were shaken in a thermostatically water bath maintained at 37±0.5°C until equilibrium. The supernatants were filtered at the same temperature. The filtrates were suitably diluted with 0.2M Hydrochloric acid (HCL) and assayed spectrophotometrically at 428 nm for the concentration of curcumin. The solubilities of curcumin, physical mixtures and solid dispersions in 0.2M HCL (pH 1.2) were determined by following the aforementioned. All experiments were performed in triplicate [11].

Drug content: The drug contents in solid dispersion were determined by the UV-spectroscopic method. An accurately weighed quantity of solid dispersion equivalent to 5 mg of curcumin was transferred to a 100 ml volumetric flask containing 100 ml of methanol and dissolved. The solution was then filtered through the filter paper. One ml of solution was diluted 10 times with 0.2 M HCL buffer solutions and the absorbance was measured at 428 nm [12,13].

Flow Properties: The flow properties of PMs and SDs were characterized in terms of angle of repose, Carr index and Hausner's ratio. For determination of angle of repose (θ), the sample was poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2.0 cm above hard surface. The sample was poured till the time when upper tip of the pile surface touched the lower tip of the funnel. The $\tan^{-1}$ of the (height of the pile / radius of its base) gave the angle of repose. Sample was poured gently through a glass funnel into a graduated cylinder cut exactly to 10 ml mark. Excess sample was removed using a spatula and the weight of the cylinder with powder required for filling the cylinder volume was calculated. The cylinder was then tapped from a height of 2.0 cm until the time when there was no more decrease in the volume [14]. Bulk density (ρb) and tapped density (ρt) were calculated. Hausner's ratio (HR) and Carr index (CI) were calculated according to the two equations given below:

$HR = \rho t/\rho b$

$CI = (\rho t - \rho b)/\rho t \times 100$

In Vitro Dissolution Studies: All *in-vitro* dissolution studies were carried out using 900 ml of 0.2 M hydrochloric acid at (pH 1.2) 37 ± 0.5˚C as the dissolution medium in a USP Type II apparatus (TDT -08L, Electrolab) at a stirring speed of 100 rpm. To prevent photostability and simulate *in vivo* conditions, the release studies were conducted in dark. Accurately weighed solid dispersions and physical mixtures containing 500 mg of curcumin were used and sprinkled directly on the surface of the dissolution medium. One milliliter samples of dissolution medium were withdrawn at predetermined intervals and immediately replaced with an equal volume of the dissolution medium (maintained at 37 ± 0.5˚C) in order to maintain constant volume of dissolution medium. The withdrawn samples were filtered and analyzed for curcumin content at 428 nm and cumulative

percentage of curcumin dissolved was calculated. The amount of curcumin removed in each sample was compensated in the calculations. All experiments were performed in triplicate [15,16,17].

Differential Scanning Calorimetry: DSC analysis of prepared solid dispersions was performed using SII Nanotechnology (SIECKO) Model=EXSTAR DSC 6220, SOFTWARE=Muse, Measurement 6.9U. Samples were accurately weighed (10 mg) in aluminum pans, sealed and thermograms were obtained at the heating rate of 10˚C per min up to a temperature of 300˚C. Ultrahigh purity nitrogen was used as the purge gas at a flow rate of 50 ml/min. Alumina was used as a reference standard [18].

Fourier transforms infrared spectroscopy (FTIR): Potassium bromide discs were prepared by mixing a small amount of the sample with potassium bromide and mixture was compressed to form the disc. It is then scanned over a frequency range of 4000–500 cm^{-1}[19,20].

In vivo Characterization by HPTLC: From the data of *in vitro* release study suitable solid dispersion formulation was selected to carry out *in vivo* studies. After procurement of albino Wistar rats, these were acclimatized for 20 days before the conducting the experiment. Animals were divided into 3 groups, each having 6 male rats weighing approximately 200-250 g. Rats were fasted for 24 h before the studies, and during the course of the studies, water was available. Group I received normal saline at a dose of 1 mL/kg by oral route, group II received curcumin suspension in water at a dose of 2g/kg. Group III received optimized microsphere formulation suspension in water by oral route at a dose equivalent to 2g/kg of curcumin drug. Blood samples (1 mL) from the experimental rats were collected by retro-orbital plexus technique into a series of Eppendroff microcentrifuge tubes containing 0.2 mL of sodium citrate solution. The blood samples were collected at specific intervals 0.15, 1 and 2 hrs. The collected blood samples were centrifuged at a speed of 3000 rpm for 10 min and plasma was separated into other microcentrifuge tube by using micropipette. The drug was extracted from the plasma by adding 0.5mL of extraction reagent (95% ethyl acetate and 5% methanol), and vortexed at high speed on a cyclo mixer for 30 s, then all tubes were centrifuged at high speed for 5 min. The organic phase was separated and collected into another microcentrifuge tube and allowed to dryness. These dried samples were reconstituted with 0.5mL of methanol [21,22,and 23].

HPTLC instrumentation and condition: The samples were run through the 20.0 x 10.0 cm HPTLC plates silica gel 60 F_{254}(E Merk, darmstad, Germany) using mobile phase toluene: chloroform: methanol (5:4:1, v/v/v) of 8 mm bands with the application rate of 150 nl/second. The slit dimensions are (6.00 x 0.45 mm, Micro), with the scanning speed of 20mm/s, the absorbance was read at 428nm in the visible region of light the absorption maxima of curcumin spot, with a Camag HPTLC scanner operated by winCATS software. Data obtained through HPTLC analysis is further used to generate Bioavailability data. All the above experiments were performed in the ANCHROM test lab.

Calibration curve of curcumin: A stock solution of 0.1mg/ml in methanol was prepared by weighing 1mg of curcumin in 10ml of methanol. A series of curcumin concentration were spotted on TLC plates to obtain a final concentration of 100-500 ng/spot. The data of peak area versus drug concentration were treated by linear least square regression.

Linearity: In order to estimate detection (LOD) and quantification (LOQ) limits, we spotted blank methanol (n = 6) following the same method as explained under the section of chromatographic conditions and the standard deviation (σ) of the magnitude of analytical response was determined. The LOD was expressed as (LOD = 3.3σ/slope of curcumin calibration curve), whereas LOQ was expressed as (LOQ = 10σ/slope of curcumin calibration curve) [24,25].

RESULT AND DISCUSSION

Saturation solubility: The saturation solubility of pure Curcumin, various prepared curcumin solid dispersions using PEG 4000 and PVP K 30 in combination, as carriers and their respective physical mixtures in 0.2M HCL, pH 1.2 was measured. It is reported that the solubility of this drug is pH dependent. Therefore, the change in pH may hamper the results during solubility measurement from curcumin solid dispersion. So, to maintain pH constant, 0.2M, pH 1.2 was used. Pure Curcumin showed 0.45 ± 0.01 mcg/ml of saturation solubility. All of samples, both physical mixture and solid dispersions of curcumin showed an increase in drug solubility (Table 2). All physical mixtures showed higher saturation solubility as compared with pure curcumin. Again, curcumin solid dispersions showed higher saturation solubility than their respective physical mixtures of drug and carrier. This might be attributable to an improvement of wetting of drug particles and localized solubilization by the

hydrophilic polymeric carriers. Among various curcumin solid dispersions, solid dispersions SD3 combination of ratio (1:7:3) showed higher saturation solubility than its physical mixture and curcumin. Further it can be concluded that increasing the concentration of PEG 4000 has a marked higher effect of increasing the solubility as compared to PVP K30.

Percent drug content: The percentage drug content in various curcumin solid dispersions ranged from 96.54 ± 0.22 % and 99.54 ± 0.2 %, as reported in Table 1. This indicated that curcumin was uniformly distributed in all these prepared solid dispersions.

Flow properties: The bulk density, tapped density, angle of repose, Hausner's ratio and Carr's index values of the formulations are represented in Table 1. The bulk density was found in the ranges of 0.37 ± 0.17 to 0.46±0.21 g/cc, tapped density of 0.49 ± 0.14 to 0.52 ± 0.18, Hausner's ratio of 1.32 or less indicating poor flowability, Carr's index was found between 10.2 to 24.4 indicating poor flowability. The good flowability of the solid dispersion was also evidenced with angle of repose within range of 23.51 ± 0.11 to 33.19 ± 0.12°, which is around 35° indicating poor flowability. From the above data formulations needs the incorporation of glidants during formulation of solid dosage form employing solid dispersion.

In vitro drug release: The *in vitro* dissolution profiles of the drug (curcumin), various solid dispersions using PEG 6000 and PVP K 30 in combination and with their respective physical mixtures in 0.2M HCL buffer (pH=1.2) for 30 minutes are shown in (Fig 3-5). All of the physical mixture and solid dispersion samples showed improved dissolution over that of pure curcumin. The improved dissolution of curcumin is mainly attributed to increased wettability and accordingly solubility due to the higher level of hydrophilicity by the use of combination of polymeric carriers. Again, all of the solid dispersion samples revealed more improved curcumin dissolution than their respective physical mixture samples. This observation indicated that the increased dissolution of curcumin from curcumin solid dispersion due to presence of drug in amorphous state as compared the physical mixtures and pure drug, where drug is present in crystalline state. In case of various solid dispersions, the dissolution of solid dispersions using PEG 4000 and PVP K 30 combination (SD-3) was better than that of other solid dispersion and this was increased with the increase of polymer ratio of the PEG 4000 in the solid dispersion. Hence it may be concluded that the effect of solubility and dissolution by PEG 4000 has greater effect as compared to PVP K30, thus polymer PEG 4000 is better solubilizer as compared to PVP K30 It was also noticed that more than 90 % of drug released from solid dispersion using PEG 4000-PVP K 30 combination (SD-3, Drug:PEG 4000: PVP K 30 = 1:7:3) in 30 minutes. These observations are well correlated with the results of saturation solubility.

Fourier Transform Infrared Spectroscopy: FTIR spectroscopy was carried out to further elucidate the interaction between curcumin and Polymers in the solid state. (Fig 3-4) show the FTIR spectra of curcumin, physical mixtures and solid dispersions. The FTIR spectrum of pure curcumin showed an absorption band at 3510.45 cm^{-1}, assigned to the phenolic O-H stretching vibration. FTIR spectrum of PVP K-30 and PEG 4000 showed broad peaks at about 3050-3720 cm-1. The FTIR spectra of all physical mixtures were similar to the synthetic spectra producing by the addition of curcumin and both the polymers. This indicates no interaction between curcumin and Polymers. In particular, the O-H stretching vibration at 3510.45 $cm^{-1}$of all solid dispersions showed significant broadening of peaks in the region 3600–3400 cm^{-1}. It may be attributed to intermolecular hydrogen bonding. This interaction caused to change curcumin crystalline structure to amorphous form.

Differential Scanning Calorimetry: The DSC thermograms of curcumin, PEG 4000, PVP K30 and solid dispersions were illustrated in (fig 5-6). The DSC curve of pure curcumin showed a single sharp endothermic peak at 180.0°C, with the enthalpy of fusion was (ΔHf120.8 J/g, corresponding to the melting point of curcumin (Fig 5). DSC thermograms of PEG 4000 showed an endothermic peak around 51.5^0C indicating the melting point of the polymer and that of PVP K30 at 112.2^0Cindicating presence of residual moisture in PVP. In case of SD this endotherm broadened and was shifted slightly to lower temperature (110.5^0C) indicating the presence of residual moisture. The disappearance of thermal features of curcumin indicates that some interaction between curcumin and PEGs occurred. These findings may be due to the formation of an amorphous solid solution which has been known to cause an increase in drug dissolution. In case of PMs this endotherm broadened and was shifted slightly to lower temperature (162.3^0C). This may be due to solvent effect of molten polymer.

In vivo characterization: The HPTLC method for curcumin was successfully developed. The Rf value of the standard curcumin was found to be 0.28±0.007 (Fig 10). The calibration curve

obtained from the peak-area ratio (Y) and plasma concentration presented good linearity over the range (100~500ng/ml), the regression equation (Y = -425.4 + 13.87X, n=6, r^2=0.994) (Table 4, Figure 7). The LOD and LOQ were found to be 0.5 and 1.5 µg respectively which indicate adequate sensitivity of the method. From the plasma profile it was shown that the maximum concentration (C_{max}) values for plain curcumin and curcumin solid dispersion were 0.21±0.002 and 0.91±0.031µg/mL respectively and time to reach maximum concentration (T_{max}) values was 1 hr. The blood levels for curcumin and its solid dispersions at time interval of 0.15, 1 and 2 hrs were 95.53, 214.50 and 143.03 ng/ml of curcumin and 273.87, 918.27 and 346.84 ng/ml respectively and the AUC (extent of absorption) was also much higher in the case of curcumin solid dispersion when compared to plain curcumin$[AUC]_{0\text{-}2h}$was increased from 2135.17±78.15ng-hr/ml for curcumin to 5765.73±441.94ng-hr/ml for curcumin solid dispersion. From the above data the bioavailability has been increased by 2.7 folds.

CONCLUSION

Curcumin solid dispersions were prepared using PEG 4000-PVP K 30 combination carrier by solvent evaporation technique. It is found that the solubilizing capacity of polymer PEG 4000 is more as compared to PVP K30. The IR and DSC studies indicated the transformation of crystalline curcumin to amorphous curcumin in solid dispersion. The saturation solubility and *in vitro* dissolution studies showed a remarkable improvement in both the solubility as well as drug dissolution of solid dispersion as compare to physical mixtures and curcumin. This study concluded that the improved solubility as well as drug dissolution can be modulated by appropriate level of hydrophilic carriers.

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ETHICAL APPROVAL NUMBER: By IAEC (Institutional of Animal Ethics Committee): IAEC/PCEU-01/2013

Table 1: Ratios and codes for Curcumin, Physical mixtures and Solid dispersions

Excipients	Physical Mixture	Solid Dispersion	Drug: Polymer Ratio
Curcumin+ PEG 4000+ PVP K30	PM1 PM2 PM3	SD1 SD2 SD3	1:3:7 1:5:5 1:7:3

Table 2: Percent drug content of Curcumin solid dispersions and its physical mixture.

Formulation Codes	Ratio	Percent Drug Content (%)
PM1	1:3:7	99.54±0.2
PM2	1:5:5	97.50±0.13
PM3	1:7:3	98.97±0.29
SD1	1:3:7	99.03±0.2
SD2	1:5:5	96.54±0.22
SD3	1:7:3	98.69±0.41

Table 3: Flow properties of Physical mixture and Solid dispersions of Curcumin

Formulations	Bulk density (g/cc) (X ± S.D.)(n=3)	Tapped density (g/cc) (X ± S.D.) (n=3)	Carr's index (%)	Hausner's ratio	Angle of repose (^{0}) (X ± S.D.) (n=3)
PM 1	0.44±0.15	0.49±0.11	10.2	1.11	27.19±0.12
PM 2	0.41±0.18	0.52±0.18	21.1	1.26	26.46±0.22
PM 3	0.38±0.12	0.48±0.03	20.8	1.26	24.25±0.02

SD 1	0.41±0.12	0.51±0.19	19.6	1.24	26.11±0.23
SD 2	0.37±0.07	0.49±0.14	24.4	1.32	24.21±0.17
SD 3	0.46±0.01	0.52±0.01	11.5	1.13	23.51±0.11

Table 4: Linearity of Curcumin (n= 6)

Peak No.	Concentration (ng)	Average Area Under Curve (n=6)
1	100	787.91
2	200	2458.76
3	300	3853.11
4	400	5254.71
5	500	6325.59

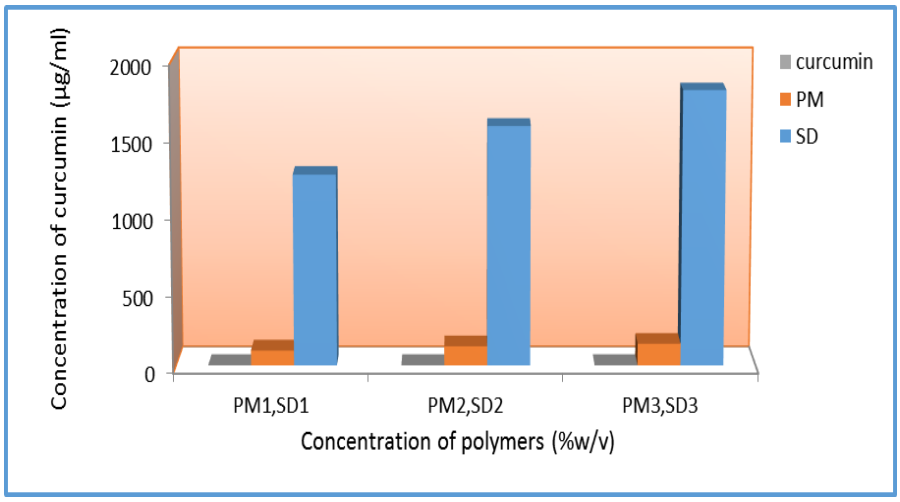

Fig 1: The Solubility of Curcumin, Physical mixtures and Solid dispersions of PEG 4000+PVP K30 at 37±0.5°C.

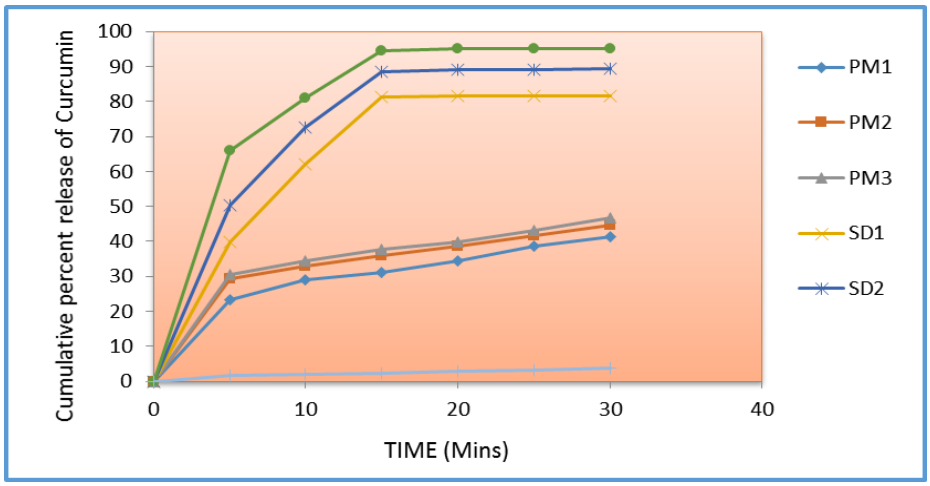

Fig 2: Comparative *in vitro* dissolution profile of Curcumin, Solid dispersion and its Physical mixture

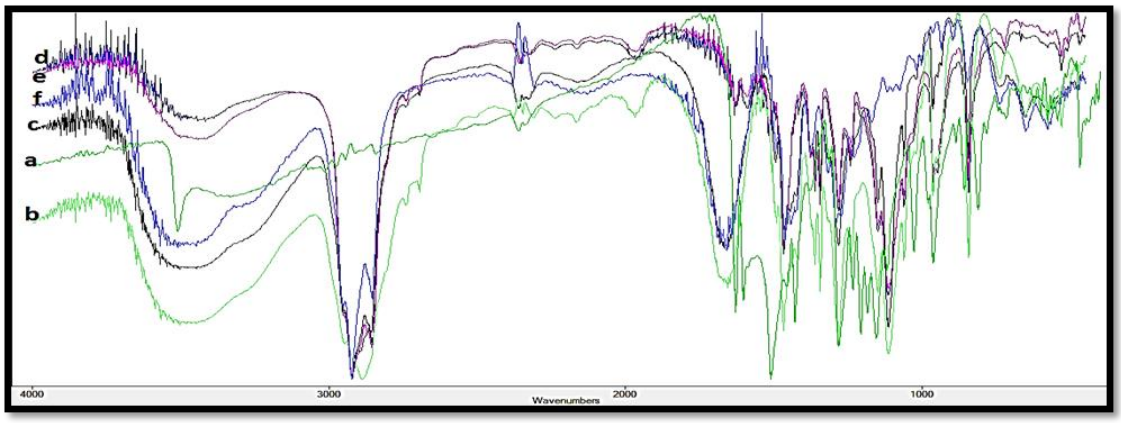

Fig 3: FTIR spectra of Curcumin (a), PEG 4000 (b), PVP K30 (c), and it's Solid Dispersion

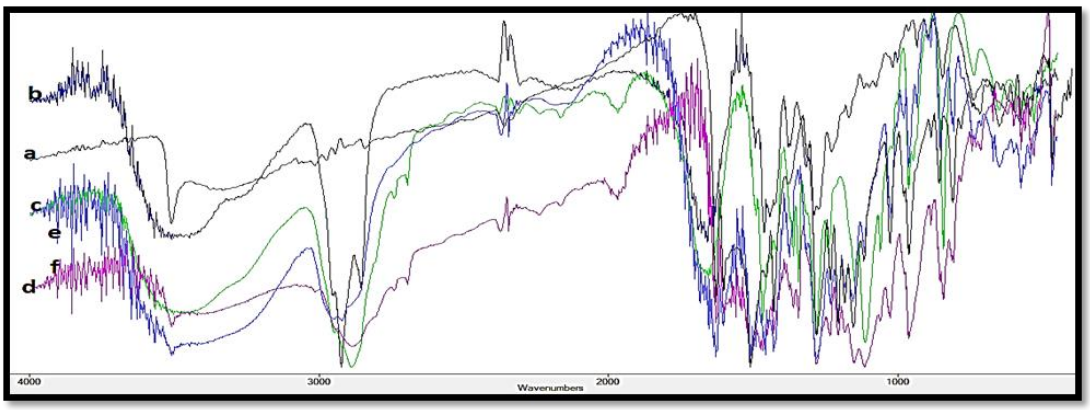

Fig 4: FTIR spectra of Curcumin (a), PEG 4000 (b), PVP K30 (c), and it's Physical mixture

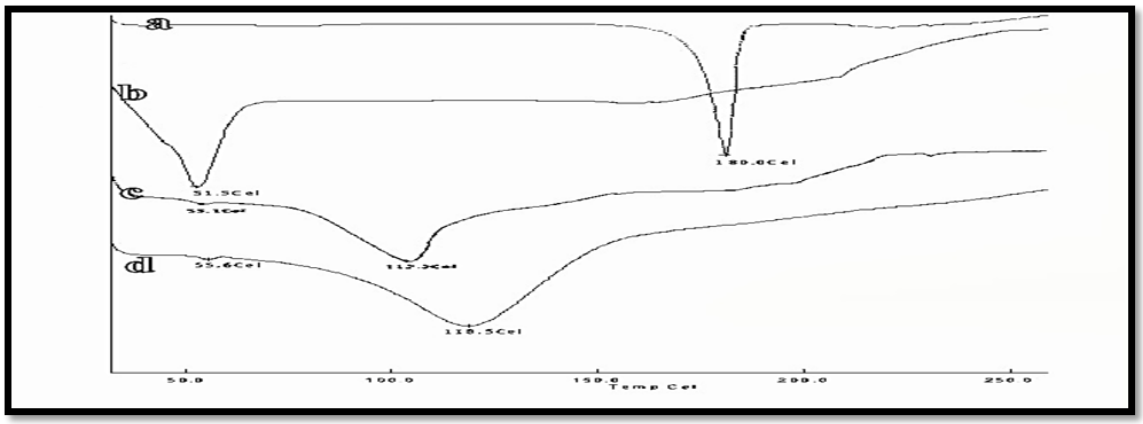

Fig 5: DSC data of Curcumin (a), PEG 4000 (b), PVP K30 (c) and Solid dispersion of ratio (1:7:3) (d).

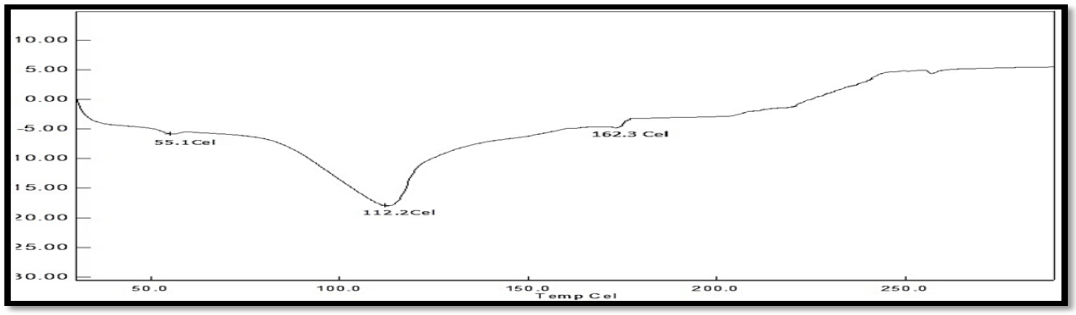

Fig 6: DSC data of Physical mixture of Curcumin, PEG 4000 and PVP K30 (1:7:3).

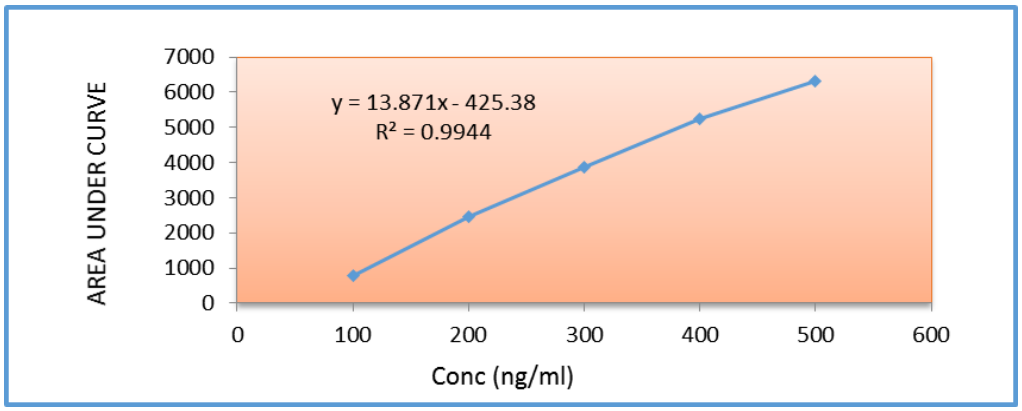

Fig 7: Linearity Curve of Curcumin

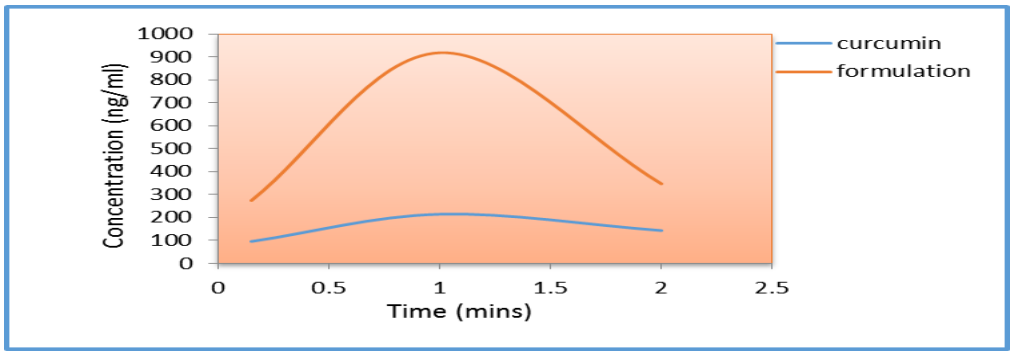

Fig 8: Plasma drug concentration profile after oral administration of Curcumin solid dispersion and plain Curcumin

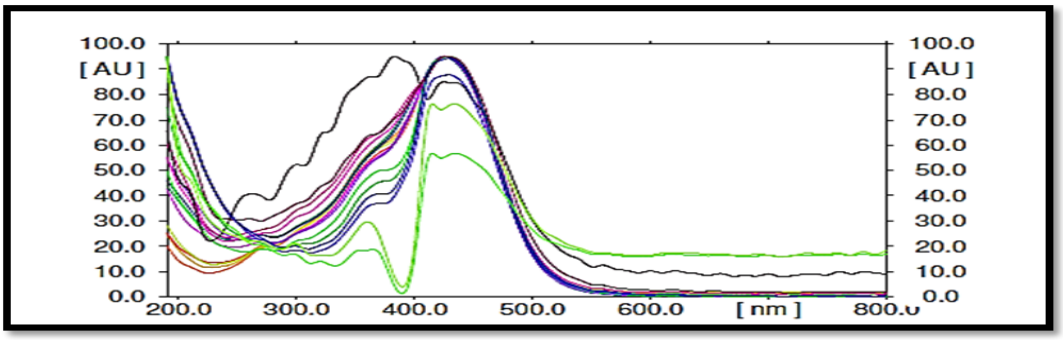

Fig 9: Superimposed Spectra of Curcumin and Samples

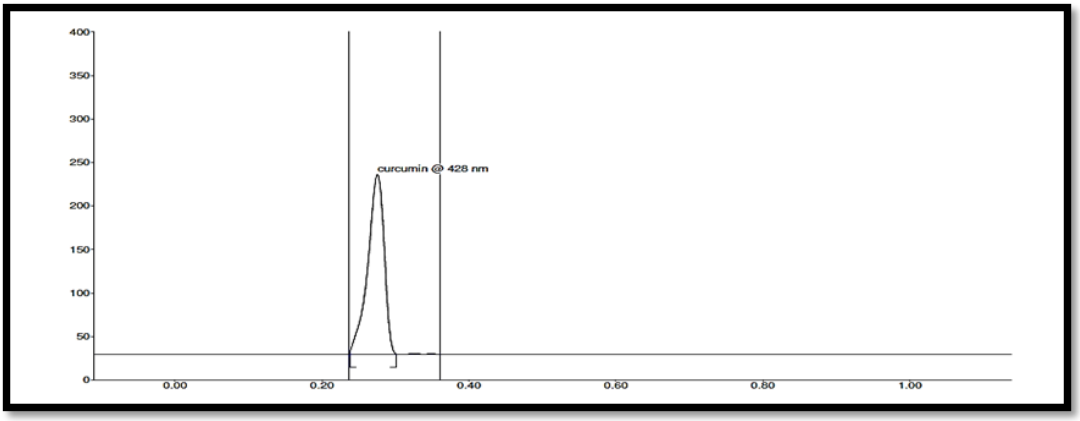

Fig 10: HPTLC Chromatogram of Curcumin (Rf 0.28±0.007)

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