Research Article

[Modasiya & Patel, 3(3): Mar., 2012]

ISSN: 0976-7126

INTERNATIONAL JOURNAL OF PHARMACY & LIFE SCIENCES

Studies on solubility of curcumin

M. K. Modasiya[1]* and V. M. Patel[2]

1, JJT University, Jhunjhunu, (R.J.) - India

2, APMC College of Pharmaceutical Education and Research, Himatnagar, (Gujarat) - India

Abstract

Curcumin is coming from the *Curcuma longa* which gives golden color and have the biological importance. As per the survey it is water insoluble, the poor solubility and wettability of curcumin leads to poor dissolution and hence shows poor bioavailability. The present study is aimed at increasing solubility of drug using solid dispersion technique. The solid binary systems were prepared using different drug: polymer ratio (1:1, 1:4 and 1:8) with polyethylene glycol 4000 and 6000 by different techniques like physical mixing, melting method and solvent evaporation method. PVP K 30 was also used as a polymer. The formulations were characterized by scanning electron microscopy, thin layer chromatograpy, compatibility study, diffraction study and *in vitro* dissolution rate studies. The solubility of drug increased linearly with the increase in polymer concentration. The solid dispersion of drug prepared by hot melt method demonstrated higher drug dissolution rates in comparison to solid dispersion prepared by physical mixtures, solvent evaporation method and pure curcumin.

Key-Words: Curcumin, Solid dispersion, Hot melt method, PEG

Introduction

Oral bioavailability of a drug depends on its solubility and/or dissolution rate, and dissolution may be rate determining step for appearance of medicinal effect, therefore efforts to increase dissolution of drug with limited water solubility is often needed. Many methods are available to improve these characteristics, including salt formation, micronization and addition of solvent or surface active agents. Solid dispersion (SD) is one of these methods, and involved a dispersion of one or more active ingredients in an inner carrier or matrix in solid state prepared by melting, dissolution in solvent or melting solvent method[1].

A huge investigation exposed that turmeric and curcumin has an extensive variety of curative property such as antiinflammatory[2], antibacterial[2], antifungal[3], anticancer[4] antispasmodic [5], antioxidant [6], antiamoebic[8], anti HIV[9], antidiabetic [10], antifertility [11] etc. Curcumin, a golden color attained by Curcuma longa is been used from the time immemorial as a nutritional complement, coloring means, spice and also for therapeutic the purpose. It is also accounted that the curcumin is safe and sound up to 8g/day [12-14].

*** Corresponding Author**

E-Mail: m_chandni2004@yahoo.co.in

Curcuminioids, the oleoresins, resultant by ethanolic extraction of turmeric are mainly liable for golden color and are believed liable for the natural actions. In neutral and acidic situation curcumin shows bis keto form. In acidic condition curcumin performs as an influential hydrogen patron [15-16].

For improving solubility, dissolution behavior and on set of action solid dispersion is one of the preferable technique[17]. It rivet a spreading of one or more drug component in an inert transporter or matrix in solid state set by melting, dissolution in solvent or melting solvent method[17]. The method has been used for a broad range of weakly water soluble active ingredients such as nimesulide[18], tenoxicam[19], nifedipine[20], nimodipine[21]. The aim of the present work is carried out to develop the water solubility of curcumin by solid dispersions process.

Material and methods

Curcumin as a drug and other non drug component like PVP, PEG 6000, PEG 4000, and Micro crystalline cellulose were obtained by the Sehat Pvt. Ltd., Gujarat, Himatnagar. All the other regents used were of laboratory grade and used as they acquired.

Curcumin solid dispersions[17]

Solid dispersions of curcumin were prepared to improve bioavailability by many the following methods among them hot melt method and solvent evaporation methods are common (Table 1).

Physical Mixtures

They were prepared by using drug/PEG-6000, PEG-4000 and PVP K 30 in 1:1, 1:4 and 1:8. Curcumin and polymers were mixed uniformly using by triturating. These physical mixtures were preserved in polyethylene bag in desiccators until further use.

Hot melt method

In this method, the carriers such as PEG 6000 and PEG 4000 were selected. The drug to polymer ratio was kept 1:1, 1:4 and 1:8. The carrier was first melted in the china dish at about 60 ^{0}C and the drug was dispersed in the molten mixture with constant stirring. The dispersion was poured immediately into the molds (specially designed for filling into the capsule) and cooled immediately.

Solvent evaporation method

In solvent evaporation method, drug and the carrier were dissolved in alcohol and the adsorbent like micro crystalline cellulose (MCC) were dispersed in the same medium with constant stirring. Alcohol was evaporated under low pressure to get the solid dispersion. In this method, PEG 6000, PEG 4000 and PVP-K-30 were used as carriers and MCC was used as adsorbent. Drug: carrier: adsorbent ratio was kept 1: 1: 2. The product obtained was free flowing unlike the solid dispersions obtained by hot melt method. The solid dispersions showing good water solubility from the above methods were further studied evaluated.

Evaluation of solid dispersion[18]

All solid dispersions from different methods were initially screened for their aqueous solubility. The solid dispersion showing better solubility were further screened drug excipient interaction studies including TLC and FTIR. The morphological changes were measured by SEM and X-Ray diffraction studies. In vitro release studies and in vitro absorption studies in rat were carried out to understand the release profile of the formulation.

Solubility of solid dispersions

Excess of solid dispersion was dispersed in the 30 ml of distilled water to get the super saturated solution with constant shaking for 24 hrs at ambient temperature until equilibrium was attained. 5 ml of the supersaturated solution filtered through Whatman filter paper No 1 and 1 ml of the filtrate was further diluted suitably with methanol and the absorbance was read at 425 nm. Solubility studies were performed for pure drug, physical mixtures and solid dispersion from both hot melt method as well as solvent evaporation method[19].

Thin layer chromatograpy studies

TLC method was used to check the interaction of the drug with the polymer. A proper ratio of chloroform and methanol was used as mobile phase and as a stationary phase silica gel G was used. The spots were detected under UV light as well as fluorescence light and R_f values were noted[20].

IR studies

Spectrophotometer was used in this study by applied potassium bromide disc method. An IR study was applied for both pure active ingredient and solid dispersions. The powdered sample was closely mixed with IR grade potassium bromide. The mixture was then compacted into clear disc under high pressure using special dies. The disc was placed in IR spectrophotometer using sample holder and spectrum was recorded[21].

Scanning electron microscopy studies

Pure drug as well as solid dispersions was sputtered coated using pelco gold palladium coaters. The surface morphology of the layered sample was examined using SEM. The sample were placed in an evacuated chamber and scanned in a controlled pattern by an electron beam. Interaction of the electron beam with the specimen produces a variety of physical phenomenon that detected, are used to form images and provide information about the specimens[21].

X-ray diffraction studies

Crystalline compounds give characteristic X-ray diffractogram. This pattern of diffraction is useful for the identification of compound. Quantitative analysis of Xray powder diffraction technique is a measurement of a series of d spacing, the interplanar spacings from the position of the diffraction peaks. The diffraction angle is a recorded in terms of 2θ and all 2θ values are readily converted to d-values expressed in angstroms units for a given wave length of X rays. The sample was rotated during the data collection to reduce orientation effects, and the data was recorded using a curved photosensitive detector. The X ray was measured in the range of 2θ=10 to 60 at steps of (100) at ambient temperature[21].

Results and Discussion

Curcumin is practically water insoluble and have poor bioavailability. In order to improve its water solubility, solid dispersions of curcumin were prepared by both hot melt method and solvent evaporation method. In hot melt method, PEG-4000, PEG-6000 were chosen as carriers. The ratios of drug to carrier were 1:1, 1:4 and 1:8. The effect of 1% w/w Tween 80 was also investigated on the solubility of solid dispersions. PEG 4000, PEG 6000 and PVP K 30 were selected as carriers for solvent evaporation method. The solubility of curcumin was further compared with physical mixtures in the same drug to carrier ratios. The formulation showing good solubility was optimized.

The optimized formulations were further studied for in vitro release studies, IR, TLC, SEM and X ray analysis. Solubility of curcumin was increased in all solid dispersions and physical mixtures when compared to pure drug (Table 1). Solubility of curcumin in solid dispersion of curcumin with PEG 6000 (1:8) by hot melt method was increased about 1000 folds when compared to the solubility of pure curcumin. In case of solid dispersion with PVP K 30 by solvent evaporation method, solubility of curcumin was lesser then the value observed in the case of hot melt method. These two formulations were further studied for IR, TLC, SEM and X ray analysis.

In vitro dissolution of selected solid dispersions and pure curcumin were carried out in distilled water. Dissolution profile of pure curcumin, curcumin solid dispersions by hot melt method (SDHM) and by solvent evaporation method (SDSE) after 90 min were found to be 2.6 %, 10.03 % and 8.5 % respectively (Figrure1). The SDHM was released the drug completely into the medium 122 % in 10 min. Reduction in the drug content was observed after 10 min of the study. The hydrolytic reaction of curcumin could be the reason for the reduction of drug content. In case of solid dispersion by solvent evaporation method (SDSE), the release was lesser about 8.5 % of curcumin was released after 90 min where as pure curcumin showed the least release of about 2.6 % in the medium.

TLC studies were carried out for the pure drug and its selected solid dispersions using chloroform: methanol (9.25:0.75) mobile phase on a silica gel G stationary phase. Three spots were seen in all the samples at the similar Rf values. These spots can be identified as curcumin (Rf-0.96), demethoxy curcumin (Rf- 0.94) and bis demethoxy curcumin (Rf- 0.88-0.9). This test conforms that there is no interaction between the drug and the carrier (Table 2).

SEM studies of pure curcumin and solid dispersions were carried out in order to analyze the change in surface morphology of pure drug as well as solid dispersions. Pure drug particles were spherical in shape while solid dispersion obtained from hot melt method were plane and uniform indicating that drug is soluble in the PEG 6000 and converted into amorphous state which could be the reason for improvement of solubility. In case of solid dispersion obtained from solvent evaporation method, the particles were roughly spherical and the drug particles and the carrier were adsorbed on the adsorbent (Figure 2-6).

X ray diffraction studies of pure curcumin and its solid dispersions were investigated from the angle of 10 ^{0} to 70 $^{0.}$ The intensity vs angle (2θ in degrees) was plotted which showed the decrease in intensities of curcumin in solid dispersion (Figure 7-9).

IR spectrographs of pure drug, its solid dispersions and excipients were taken by the Shimadzu FTIR 8700 instrument. From the data obtained, it can be inferred that curcumin did not interact with the carriers. As the peaks shown due to functional groups of the pure curcumin was also observed in the solid dispersions IR spectrum. For example phenolic OH showed its peak in the range of 3500-3300 cm^{-1} in all the formulations. The peak due to the carboxyl group (C=O) was observed in both SDHM and SDSE at around 1625 – 1640 cm^{-1}. Three characteristic peaks in the range of 1520 – 1400 cm^{-1} conforms the aromatic unsaturation (C=C) as in Table 3.

This study clearly revealed that the preparation of solid dispersions of PEG-6000 with curcumin by hot melt method, physical mixture, and solvent evaporation method led to enhanced dissolution properties. The highest improvements in solubility and *in-vitro* drug release were observed in solid dispersion prepared with PEG-6000 by hot melt method. The dissolution rates of solid dispersion prepared by physical mixtures and solvent evaporation method were higher than that of pure drug. Thermal analysis indicated that drug is present in an amorphous form at high concentration of PEG 6000. Solid dispersion prepared by hot melt method are extremely important from a commercial point of view as it improves dissolution profile of poorly soluble drug like curcumin.

References

1. Chiou WL, Riegelman S. Pharmaceutical applications of solid dispersion systems. *J Pharm Sci. 1971*, **60:** 1281Y1302.
2. Negi PS, Jayaprakash GK, Jagan MRL, Sakariah KK; Antibacerial activity of turmeric oil; a byproduct from curcumin manufactuer. *J. Agric. Food Chem.* 1999; 47: 4297-300.
3. Apisariyakul A, Vanittanakomm N, Buddhasukh D. Antifungal activity of turmeric oil extracted from Curcuma longa (Zingiberaceae). *J. Ethnopharmacol.*1995; 49:163–169.
4. Ghatak N, Basu N. Sodium curcuminate as an effective antiinflammatory agent. *Indian J. Exp. Biol.*1972; 10; 235–236.
5. Itthipanichpong C, Ruangrungsi N, Kemsri W, Sawasdipanich A. Antispasmodic effects ofcurcuminioids on isolated guinea pig ileum and rat uterus. *J. Med. Assoc.Thai*.2003; 86: 299-309.
6. Ruby AJ, Kuttan G, Dinesh BK, Rajasekharan KN, Kuttan R. Antitumor and antioxidant activity

of natural curcuminoids. *Cancer Lett.* 1995; 94: 79–83.
7. Dhar ML, Dhar MM, Dhawan BN, Mehrotra B N and Ray C. Screening of Indian plants for biological activity: *I. Indian J. Exp.Biol*. 1968; 6: 232–247.
8. Dhar ML, Dhar MM, Dhawan BN, Mehrotra B N and Ray C. Screening of Indian plants for biological activity: I. *Indian J. Exp.Biol.* 1968; 6: 232–247.
9. Mazumdar A, Raghavan K, Weinstein J, Kohn K W, Pommer Y, Inhibition of human immunodeficiency virus type-1 integrase by curcumin. *Biochem. Pharmacol*.1995; 49; 1165–1170.
10. Halim EM, Ali H. Hypoglycemic, hypolipidemic and antioxidant properties of combination of curcumin from Curcuma longa Lin. and partially purified product from *Abroma augusta* Lin. In streptozotocin induced diabetes. *Ind. J. Clinic. Biochem.* 2002; 17(12): 33-43.
11. Garg SK, Effect of Curcuma longa (rhizomes) on fertility in experimental animals. Planta Med. 1974; 26: 225–227.
12. Kapoor LD. Handbook of Ayurvedic Medicinal Plants, CRC Press, Boca Raton, Florida, 1990, p. 185.
13. Bharath LD, Anushree K, Agarwasl MS, Shishodia S. Curcumin derived from turmeric Curcuma longa); Phytochemicals in cancer chemoprevention; 349- 387.
14. Kiuchi F, Goto Y, Sugimoto N, Akaon N,Kondo K, Tsuda Y . Nemotodial activity of turmeric. Chem. *Pharm. Bull* Tokyo. 1993;41(a):1640-1643.
15. Ravindranath V, Chandrasekhara N. In vitro studies on the intestinal absorption of curcumin in rats. *Toxicol.* 1981; 20:251–257.
16. Wang YJ, Pan MH, Chang AL, Hsieh CY, Lin JK. Stability of curcumin in buffer solutions and characterization of its degradation products. *J. Pharmaceut. Biomed. Anal.* 1997; 15:1867-1876.
17. Moore, J.W., Flanner, H. Mathematical comparison of dissolution profiles. *Pharmaceutical Technology. 1996*, **20:** 6, 64-74.
18. Newa, M., Bhandari, K., Jong Oh K,, Seob, J., Jung Ae, K., Bong Kyu, Y., Jong Soo,W., Han Gon, C., and Chul Soon, Y. Enhancement of Solubility, Dissolution and Bioavailability of Ibuprofen in Solid Dispersion Systems, *Chem. Pharm. Bull. 2008*, **56:** 4, 569-574.
19. Modi A, Tayade P. Enhancement of Dissolution Profile by Solid Dispersion (Kneading) Technique. *AAPS PharmSciTech*. 2006; 7(3): Article 68.
20. Ansari MJ, Ahmad S, Kholi K, Ali J, Khar RK. Stabilityindicating HPTLC determination of curcumin in bulk drug and pharmaceutical formulations. *Journal of Pharmaceutical and Biomedical Analysis*, 2005 Sep. 1; 39(1-2):132-138.
21. Mahmoud El-Badry ,Gihan Fetih ,Mohamed Fathy, Improvement of solubility and dissolution rate of indomethacin by solid dispersions in Gelucire 50/13 and PEG4000. *Saudi Pharmaceutical Journal* (2009) 17, 217–225.

Table 1: Solubility data of pure drug and solid dispersions (SD)

S/ No.	Type	Carrier	Figure Grade	D:C Ratios	Solubility (µ/ml)
1	Pure drug		A		2.677
2	SD: Physical mixture	PEG 6000	B	1:1	20.585
3			C	1:4	42.343
4			D	1:8	46.778
5		PEG 4000	E	1:1	29.205
6			F	1:4	31.882
7			G	1:8	33.305
8	SD: Hot melt method	PEG 6000	H	1:1	33.138
9			I	1:4	50.543
10			J	1:8	1034.6
11		PEG 4000	K	1:1	5.774

ISSN: 0976-7126

12			L	1:4	18.075
13			M	1:8	43.263
14	Solid dispersions + 1% Tween 80	PEG 6000	N	1:1	43.76
15			O	1:4	151.4
16			P	1:8	33.38
17		PEG 4000	Q	1:1	11.8
18			R	1:4	11.631
19			S	1:8	9.874
20	SD: Solvent evaporation method	PEG 6000	U	1:2:1	6.5
21		PEG 4000	V	1:2:1	8.87
22		PVP-K-30	W	1:2:1	9.2
D: C Ratio – Drug: Carrier ratio					

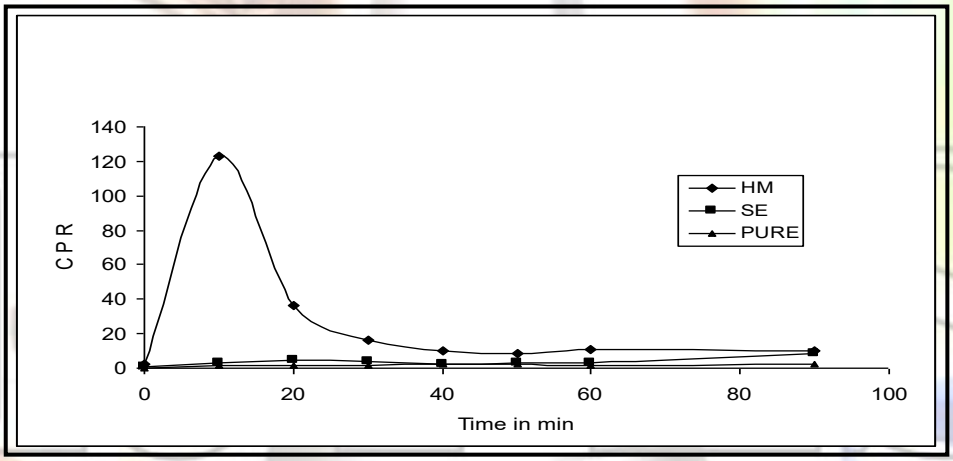

Fig. 1: In vitro dissolution profiles of pure Curcumin and solid dispersions

Table 2: TLC data of Rf values and distance traveled by the curcumin and its solid dispersions

Sample	Pure curcumin		SDHM		SDSE	
	Sample front (cm)	R_f Value	Sample front (cm)	R_f Value	Sample front (cm)	R_f Value
Curcumin	4.9	0.98	4.8	0.96	4.9	0.98
Demethoxy Curcumin	4.7	0.94	4.6	0.92	4.6	0.92
Bis-demethoxy Curcumin	4.5	0.9	4.4	0.88	4.4	0.88

Solvent front = 5 cm
R_f value = Distance traveled by the sample / Distance traveled by the solvent

ISSN: 0976-7126

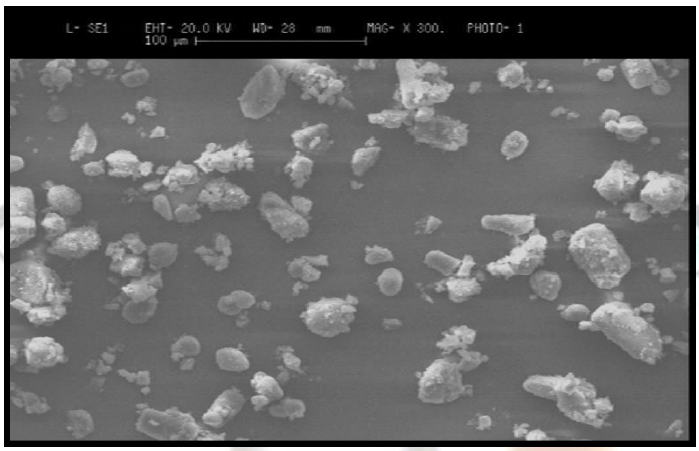

Fig. 2: SEM of pure curcumin

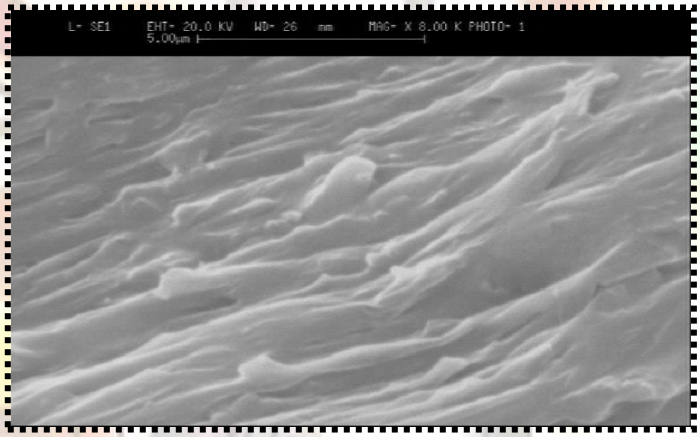

Fig. 3: SEM of curcumin SD by HM (sample 1)

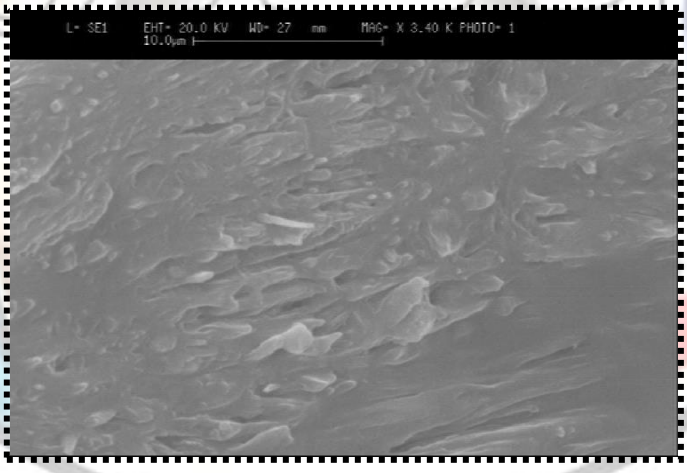

Fig. 4: SEM of curcumin SD by HMM (sample 2)

ISSN: 0976-7126

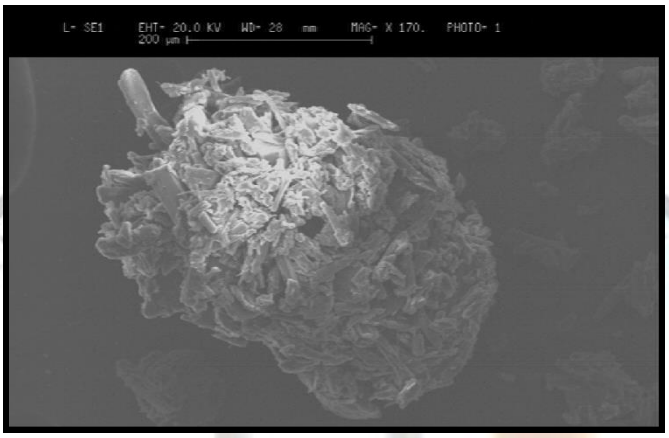

Fig. 5: SEM of curcumin SD by SEM (sample 1)

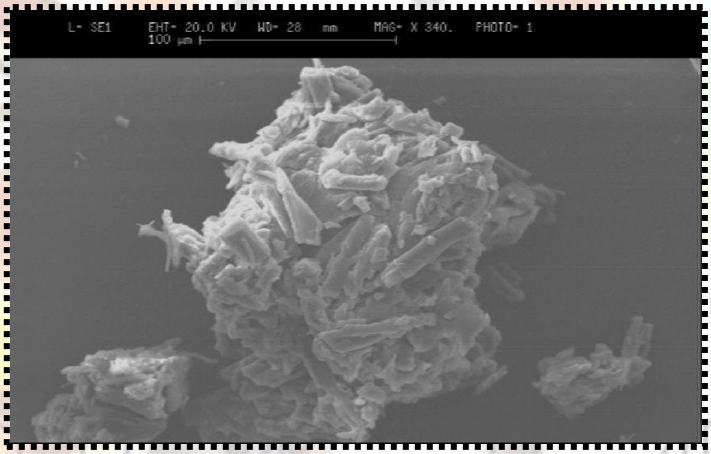

Fig. 6: SEM of curcumin SD by SEM (sample 2)

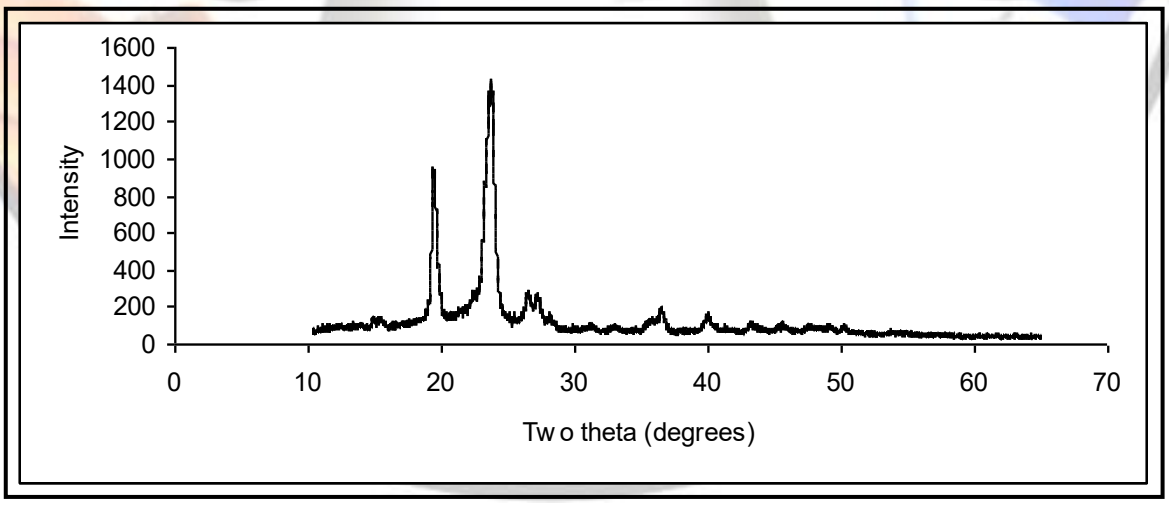

Fig. 7: X-ray diffraction studies of pure curcumin

ISSN: 0976-7126

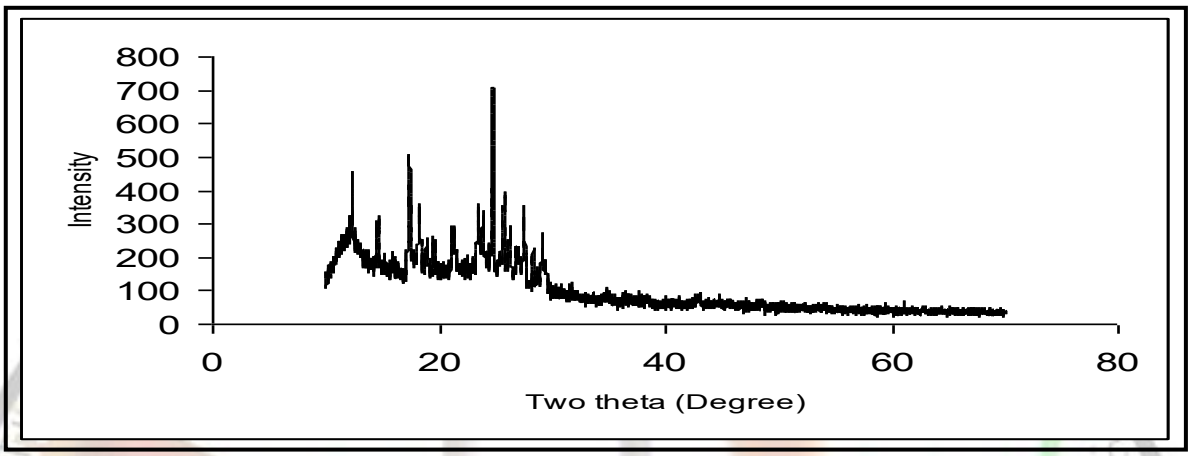

Fig. 8: X-ray diffraction studies of SD of curcumin by HMM

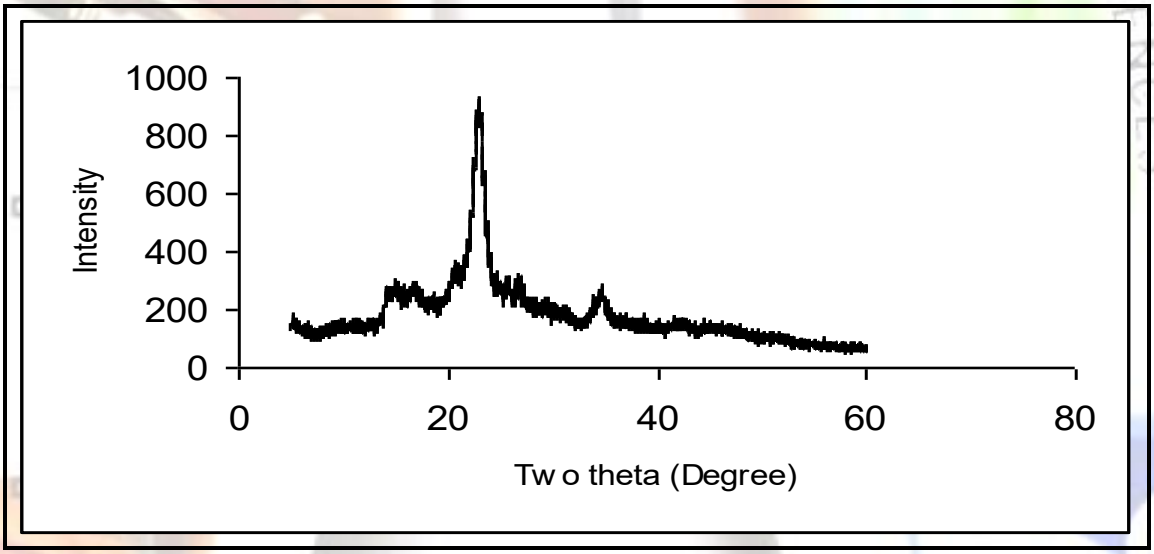

Fig. 9: X-ray diffraction studies of SD of curcumin by SEM

Table 3: Compatibility studies of curcumin and its solid dispersion by IR spectrograph

Functional groups	Wave number in 1/cm			
	Range	Pure drug	SDHM	SDSE
Phenolic OH	3500-3300	3510.2	3782.1(D) and 3413.8(Ex)	3782.1(D) and 3350(Ex)
C=O	1750-1650	1627.8	1630.1	1635.5
C=C	1650-1550	1596.9	1593.1	1591.2
Ar C=C	1400-1600 (3 peaks)	1506.3 1458.1 1427.2	1523.7 1471.6 1419.5	Not labeled Not labeled 1438.8