Indian Journal of Novel Drug Delivery

IJNDD

An Official Publication of Karnataka Education & Scientific Society

Research Article

A Comparative Study: Solution Stability and Dissolution Behavior of Solid Dispersions Curcumin

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ARTICLE DETAILS

Article history:
Received on 10 June 2010
Modified on 13 August 2010
Accepted on 19 September 2010

Keywords:
Curcumin
Solution Stability
Solid Dispersions
In-vitro release

ABSTRACT

Curcumin (CU), a yellow pigment obtained from *Curcuma longa* shows profound biological activities. Literature reveals that CU is insoluble in water and susceptible to higher pH. This work is focused firstly to study the susceptibility of curcumin in water, various pH conditions in presence and absence of ascorbic acid (AA), tartaric acid (TA) and citric acid (CA) by a simple UV absorption method and secondly to prepare and evaluate curcumin solid dispersions (CSD) by physical mixtures, hot melt method and solvent evaporation method using PEG-4000, PEG-6000 and PVP K-30 as carriers. Drug, carrier ratio for physical mixtures and hot melt method was 1:1, 1:4 and 1:8; drug, carrier and adsorbent (micro crystalline cellulose) ratio in solvent evaporation method was 1:1:2. Selected formulations with better solubility were studied for TLC, FTIR, SEM, X-ray diffraction studies, in vitro release and in vitro absorption studies using everted rat gut technique. Results indicated that the CU and CSD were unstable in solution; the stability was more in acidic pH and decrease as the pH increases. Presence of AA, TA and CA in solution enhanced the CU aqueous stability relatively by 3 folds in pH 7.4 however more degradation was observed in CSD solutions in pH 7.4 even in presence of these acids. Hot melts of drug with PEG 6000 in 1:8 ratio showed maximum solubility of 1mg/ml than that of other CSDs. Maximum in vitro release was observed by hot melts than that of other CSDs. Hot melts showed burst release in 10 min followed by the degradation of curcumin in aqueous solution indicating occurrence of rapid hydrolytic reaction. In vitro absorption of hot melts and pure curcumin in rat gut was insignificant as the permeability of both were negligible.

INTRODUCTION

Curcumin, a yellow pigment obtained from *Curcuma longa* is been used from the time immemorial as a dietary supplement, coloring agent, spice and also for curing the diseases. A vast research revealed that turmeric and curcumin has a wide spectrum of therapeutic effects such as antiinflammatory[1], antibacterial[2], antifungal[3], anticancer[4] antispasmodic [5], antioxidant [6], antiamoebic[8], anti HIV[9], antidiabetic [10], antifertility [11] etc. It is also reported that the curcumin is safe up to 8g/day [12-14]. Curcuminioids, the oleoresins, derived from ethanolic extraction of turmeric are mainly responsible for yellow color and are considered responsible for the biological activity.

Curcumin is practically insoluble in water and highly susceptible for pH change. It is reported that curcumin exhibits keto-enol tautomeric forms[15]. In neutral and acidic condition curcumin exhibits bis keto form. In acidic condition curcumin acts as a powerful hydrogen donor [15]. In basic pH above 8 enolate form of the curcumin predominates and acts as a powerful electron donor a mechanism more typical for antioxidants.

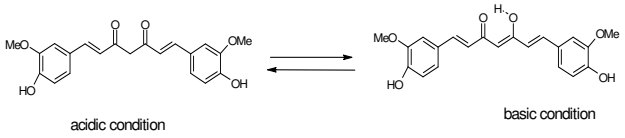

Figure 1: Curcumin in acidic and basic condition

It is also reported that curcumin undergo degradation up to 90% in serum free 0.1M phosphate buffer of pH 7.2 at 37^0 C. The decomposition of curcumin was pH dependent and occurs faster under neutral and basic pH condition[16].

Solid dispersion (SD) is one of the commonly used methods to improve the solubility, dissolution characteristics and bioavailability of the poorly soluble drug[17]. It involves a dispersion of one or more active ingredients in an inert carrier or matrix in solid state prepared by melting, dissolution in solvent or melting-solvent method[17]. The technique has been used for a wide variety of poorly aqueous soluble drugs such as nimesulide[18], tenoxicam[19], nifedipine[20], nimodipine[21].

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The current research is undertaken to study the degradation of curcumin in various pH solutions and also to study the influence of citric acid, tartaric acid and ascorbic acid on the solution stability of curcumin. Another objective of the study is to improve the aqueous solubility of curcumin by solid dispersions method.

MATERIALS AND METHODS

Curcumin was generously gifted by Natural remedies, Bangalore and Sami labs Bangalore. PVP, PEG 6000, PEG 4000, and Micro crystalline cellulose were purchased from Merck Chemie Pvt. Ltd., Mumbai. All the other regents used were of laboratory grade and used as they procured.

Solution Stability Studies of Curcumin.

Curcumin is reported to be highly susceptible to pH and light [16]. In order to quantify the instability of curcumin in aqueous medium as well as in various pH conditions such as pH 1.2, 6.8 and 7.4, a simple spectroscopic method was adopted. A stock solution of 100µ/ml solution of curcumin was prepared in methanol. 1 ml solution (100µ/ml) of curcumin in methanol was transferred to the 24 ml distilled water to obtain the l curcumin concentration of 4µ/ml solution. The absorbance of the resultant solution was immediately measured at 425 mn using Shimadzu UV Visible Spectrophotometer (UV-1700 pharmaspec) at different intervals of 5 min against blank. The absorbance was read at zero time was considered to be as 100 %. This procedure was repeated with the different buffer solutions of 0.1M pH 7.4, 6.8 and 1.2. The effect of citric acid, ascorbic acid and tartaric acid in pH 7.4 and pH 6.8 curcumin buffer solutions was studied[22].

Curcumin Solid Dispersions

Solid dispersions of curcumin were prepared by three methods; physical mixtures hot melt method and solvent evaporation method as in Table 1.

1. Physical Mixtures

Physical mixtures of curcumin were prepared using PEG-6000, PEG-4000 and PVP K 30 in 1:1, 1:4 and 1:8. Drug and the carrier were mixed properly using mortar and pestle. These physical mixtures were preserved in polyethylene bag in desiccators until further use[17].

2. Hot melt method (Hot melts)

In this method, nine solid dispersions of curcumin were prepared with curcumin and polymer ratios of 1:1, 1:4 and 1:8 by using PEG-6000, PEG-4000 and PVP K 30 carriers. The carrier was melted at 60^0C; curcumin was dispersed in molten carrier with constant stirring. Finally the molten dispersion was then poured into the specially designed zero sized capsule molds to attain the shape of the zero sized capsules[17].

3. Solvent evaporation method

In Solvent evaporation method, drug, carrier were dissolved in alcohol along with microcrystalline cellulose (MCC) which acts as an adsorbent 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 drug: carrier: adsorbent ratio was kept 1: 1: 2. The solid dispersions were preserved from moisture content and light in desiccators for the further studies[17].

Evaluation of solid dispersion

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 25 $\pm$ 5 ^{0}C until equilibrium was attained. 5 ml of the supersaturated solution filtered through 0.22 micron Millipore filters and 1 ml of the filtrate was further diluted suitably with methanol and the absorbance was read at 425 nm against blank. Each experiment was performed in triplicate (coefficient of variation [CV] < 3%)[23].

TLC studies

Interaction of the drug with the carrier was studied by TLC method. Chloroform and methanol in 9.25:0.75 ratio was used as mobile phase and Silica gel G was Stationary phase. The spots were detected under UV light as well as fluorescence light and Rf values were noted[24].

FTIR studies

Instrument used was Shimadzu FTIR-8700 spectrophotometer. In this study, potassium bromide disc method was employed. Both pure drug and its solid dispersions were subjected to IR studies.

The powdered sample was intimately mixed with IR grade potassium bromide. The mixture was then compressed into transparent disc under high pressure using special dies. The disc was placed in IR spectrophotometer using sample holder and spectrum was recorded[23].

Scanning Electron Microscopy (SEM) 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[25].

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 X-ray 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.

Table 1: Solid dispersions of curcumin

Formulation code	Method	Curcumin	PEG 6000	PEG4000	PVP – K30	MCC
H1	Hot melt method	1	1	-	-	-
H2	Hot melt method	1	4	-	-	-
H3	Hot melt method	1	8	-	-	-
H4	Hot melt method	1	-	1	-	-
H5	Hot melt method	1	-	4	-	-
H6	Hot melt method	1	-	8	-	-
H7	Hot melt method	1	-	-	1	-
H8	Hot melt method	1	-	-	4	-
H9	Hot melt method	1	-	-	8	-
S1	Solvent evaporation method	1	1	-	-	2
S2	Solvent evaporation method	1	-	1	-	2
S3	Solvent evaporation method	1	-	-	1	2
P1	Physical mixture	1	1	-	-	
P2	Physical mixture	1	4	-	-	
P3	Physical mixture	1	8	-	-	
P4	Physical mixture	1	-	1	-	
P5	Physical mixture	1	-	4	-	
P6	Physical mixture	1	-	8	-	
P7	Physical mixture	1	-	-	1	
P8	Physical mixture	1	-	-	4	
P9	Physical mixture	1	-	-	8	

The diffractometer used was STOE / STADI-P powder X-ray diffractometer with Germanium monochromated Cu $K\alpha_1$ (λ=1.54056 A^0) radiation in transmission mode. The sample was rotated during the data collection to reduce orientation effects, and the data was recorded using a curved photosensitive detector (PSD). The X ray was measured in the range of 2θ=10 to 60 at steps of (10 ^{0}) at ambient temperature[23].

***In vitro* release studies of optimized solid dispersions:**

In vitro dissolution studies were performed for selected formulations showing improved solubility in each method of solid dispersion using Electrolab- USP Dissolution test apparatus. Distilled water, 500 ml, Type II apparatus, temperature of 37±0.1^{0}C, 75 rpm were set parameters for dissolution process. 5 ml of the sample withdrawn filtered through Whatman filter paper No1. 1 ml of the filtrate was made up to 10 ml with methanol in 10 ml volumetric flask. Suitable dilutions were further made when required. The absorbance of the samples was read at 425 nm against blank.

***In vitro* absorption studies of solid dispersion**

Pure curcumin and H3 formulation were selected for in vitro absorption as the H3 formulation showed better aqueous solubility compared to the other solid dispersions. The male albino rats, fasted for 24hrs, weighing 200g were anesthetized with di-ethyl-ether and killed by cervical dislocation, the abdomen opened, and the smail intestine washed out in situ with warm, Krebs'- ringer solution. Krebs–Ringer solution was prepared by combining 6.3g NaCl, 0.35g KCl, 0.14g $CaCl_2$, 0.16g KH_2PO_4 , 0.15g $MgSO_4 \cdot 7H_2O$, 2.1g $NaHCO_3$, and 5g glucose in one liter of distilled water. The lumen was carefully cleared from mucus by rinsing with a pH 7.4 buffer solutions (Krebs–Ringer solution). An intestinal segment of the first 6- cm length was removed and transferred to oxygenated Krebs–Ringer solution. It was washed thoroughly with warm Krebs–Ringer solution. The proximal extremity of the intestine was turned back and ligated on a glass rod to form an everted bag. The other part of the everted sac was attached to the canula for sampling the drug solution. Entire assembly was placed in organ bath maintained at 37$\pm$ 2^{0}C in Krebs–Ringer solution for a stabilization period of 15 min with aeration of 95 % oxygen and 5 % CO_2. Then the Krebs-Ringer solution was replaced with drug solution keeping the aeration unaltered. At the intervals of 15 min, 30 min, 45 min, 60 min and 90 min, 0.5 ml of the solution was sampled from the everted gut and the drug content was analyzed 425 nm. Fresh Krebs–Ringer solution of 0.5 ml replaced immediately after each sampling.

Aqueous stability of H3 formulation in pH 7.4, 6.8 and 1.2

Aqueous stability studies of curcumin solid dispersions were carried out as per the procedure mentioned for solution stability of curcumin. A stock solution of 100µ/ml solution of curcumin solid dispersion was prepared in methanol. 1 ml of this stock solution was transferred to the 24 ml distilled water to obtain the final curcumin concentration of 4µ/ml solution. The absorbance of the resultant solution was immediately measured at 425 mn using Shimadzu UV Visible Spectrophotometer, UV-1700 pharmaspec at different intervals of 5 min against blank. The absorbance was read at zero time was considered to be as 100 %.

RESULTS AND DISCUSSION

Solution stability studies of curcumin

Lower concentration (4µ/ml or 10.8 µ M) of curcumin in methanol was studied as higher concentration of curcumin in solution shows precipitation of curcumin. The plot of logarithmic concentration verses time indicates that the curcumin was follows first order

kinetics. The degradation constant (k) was calculated by multiplying slope with 2.303. Half life (t ½) of the reaction was calculated by the following equation. Table 2 represents the k value and t ½ values.

$k = 2.303 \times slope$

$t_{½} = 0.693/k$

Table 2: Solution stability data of curcumin in different pH solutions

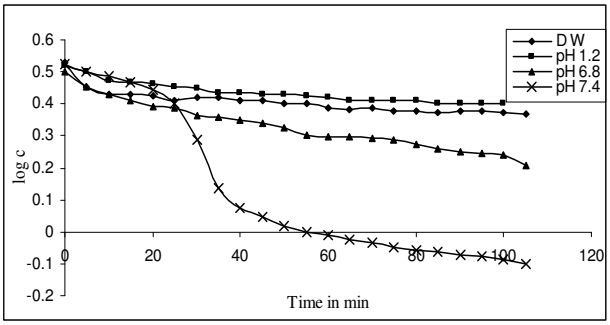
Sample	k- Value	$t_{1/2}$ (min)
DW	0.002303	300.9119
pH 1.2	0.002303	300.9119
pH 6.8	0.005297	130.8312
pH 7.4	0.0152	45.59271
pH 7.4+aa	0.002073	334.3465
pH 7.4+ta	0.001842	376.1398
pH 7.4+ca	0.005297	130.8312
pH 6.8+aa	0.005758	120.3647
pH 6.8+ta	0.004376	158.3747
pH 6.8+ca	0.005297	130.8312

The results revealed that the Curcumin was unstable in the all aqueous solutions. The amount of curcumin remained after 105 min in various pH conditions as follows pH 1.2 > Distilled water > pH 6.8 > pH 7.4 and the data is given in Table 3 and Figure 2.

Table 3: Cumulative amount of curcumin remaining after 105 min

pH	% Amount of drug remained after 105 min			
	Pure Curcumin	1% Ascorbic acid (w/v)	1%Tartaric acid (w/v)	1% Citric acid (w/v)
1.2	75 %	NC	NC	NC
Water	69.3 %	NC	NC	NC
6.8	51 %	60.63 %	62.85 %	60.49 %
7.4	23.62	77.27 %	78.47 %	60.85 %

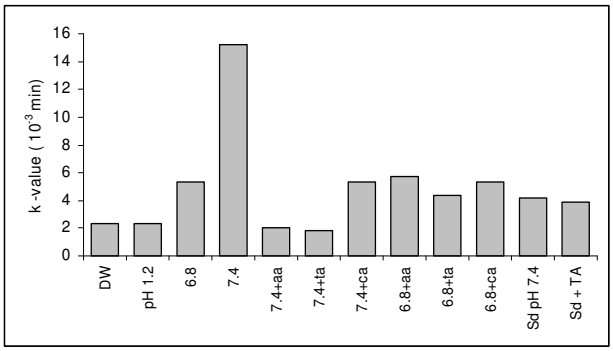
NC: Not conducted



DW= Distilled water

Figure 2: Comparative degradation profile of curcumin in different buffers (log C vs time)

The addition of 1% w/v ascorbic acid, tartaric acid and citric acid to the pH 7.4 curcumin buffers solution showed a significant improvement in the curcumin stability which is approximately 3 folds. Furthermore, the addition of these acids to curcumin pH 6.8 buffer solutions showed improvement in the stability but not significantly as seen in buffer pH 7.4 as the curcumin was more stable in pH 6.8 than pH 7.4 as shown in Figure-3. Student –T test of this data by reveals the significant improvement of the solution stability by the addition of acids in pH 7.4. However, in pH 6.8, the addition of tartaric acid was found to enhance the stability significantly then that of other acids as given in Table 4.



aa (ascorbic acid), ta (tartaric acid), and ca (citric acid)

Figure 3: Comparative degradation profile of curcumin in different buffers in presence and absence of various acids in different buffers

Table 4: Effect of acids on the aqueous stability of curcumin obtained from student-t- test

Sample	Acids	P value	Level of significance
pH 7.4	TA	<0.01	Significant
	AA	<0.01	Significant
	CA	<0.01	Significant
pH 6.8	TA	<0.01	Significant
	AA	>0.05	Not Significant
	CA	>0.05	Not Significant

Solid dispersions of curcumin

The solubility of all solid dispersions were given in the below Table 5. All the solid dispersions showed improvement in solubility when compared to pure drug.

Table 5: Solubility profile of various solid dispersions and pure drug

Formulation	Solubility (mcg/ml)
H1	33.14
H2	50.54
H3	10344.77
H4	5.77
H5	18.08
H6	43.26
H7	29.79
H8	37.82
H9	42.01
S1	6.36
S2	8.95
S3	8.54
P1	20.59
P2	42.34
P3	46.78
P4	29.21
P5	31.88
P6	33.31
P7	19.75
P8	36.23
P9	38.83
Pure drug	2.68

Solid dispersions by hot melt method had good solubility when compared with solid dispersions prepared by

solvent evaporation method and physical mixtures. Best formulation from each method was chosen for further characterization studies; H3 formulation by hot melt method, S2 formulation by solvent evaporation method and P3 formulation by physical mixture.

TLC of solid dispersions showed as in Figure 4 showed three distinct spots 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) [24]. This test conforms that there is no interaction between the drug and the carriers.

P= Pure drug, HM= hot melt, SE=Solvent evaporation

Figure 4: TLC studies of curcumin and its solid dispersions

The IR spectrographs of pure drug, excipients and solid dispersions which indicted no interaction of curcumin with carriers. The chemical structure curcumin shows the functional groups of phenolic OH, C=O and aromatic C=C which shows the peaks at 3500-3300 cm^{-1}, 1625 – 1640 cm^{-1} and 1520 – 1400 cm^{-1} in the IR spectrum. These peaks were observed in both pure drug as well as in solid dispersion indicating no interaction between drug and polymer (Figure 5-7).

From the SEM studies it was observed that the 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 (Figure 8).

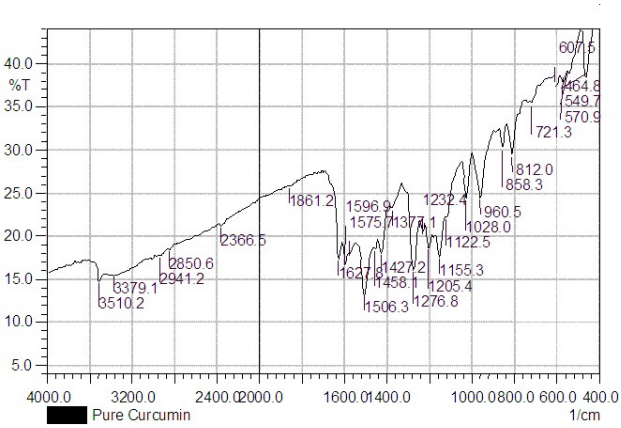


Figure5: IR spectrograph of pure curcumin

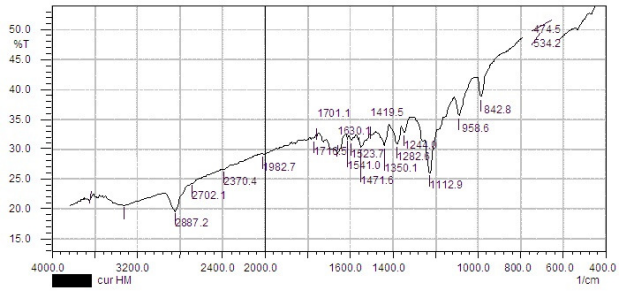


Figure 6: IR spectrogram of curcumin solid dispersion by hot melt method

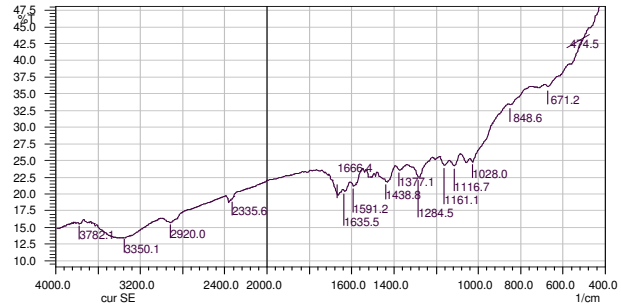
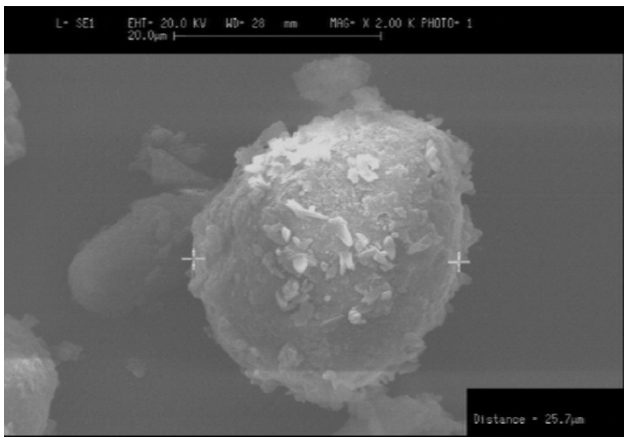


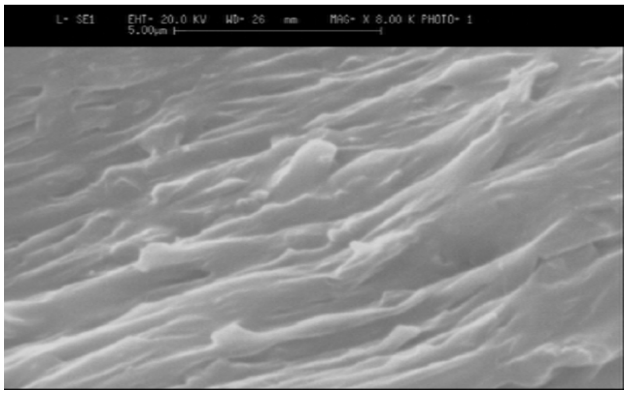
Figure 7: IR spectrogram of curcumin solid dispersion by solvent evaporation method- Drug: Microcrystalline cellulose : PVP K 30 (1:2:1)

Figure 9 shows the X ray diffraction studies of pure curcumin, S2 and H3 formulations indicated the decrease in the intensity of curcumin in solid dispersion.

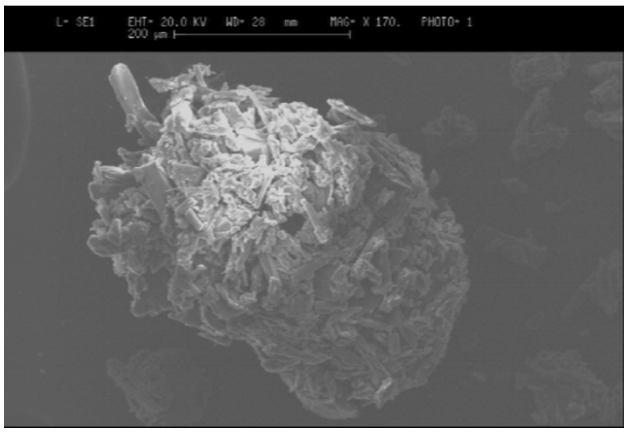
Figure 10 shows the in vitro dissolution of pure curcumin, S2 and H3 carried out in distilled water. H3 formulation showed the immediate release of curcumin in the dissolution media. However reduction in the drug content was observed after 10 min of the study, this may be due to hydrolytic reaction of curcumin. S2 formulation showed 8.5 % release after 90 min, this may be due to less solubility of the solid dispersion in distilled water. Pure curcumin showed the least release of about 2.6 % in the medium after 90 min.



(a)



(b)



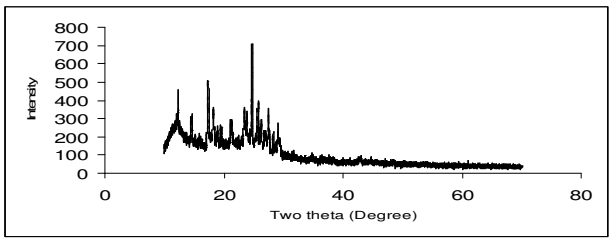
(c)

(a) Curcumin (b) hot melts (c) solid dispersion by solvent evaporation method

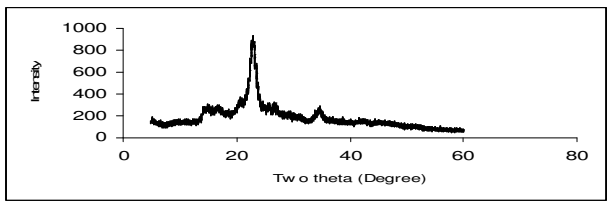
Figure 8: SEM Photo graphs of pure drug and formulations

In vitro absorption studies of solid dispersion

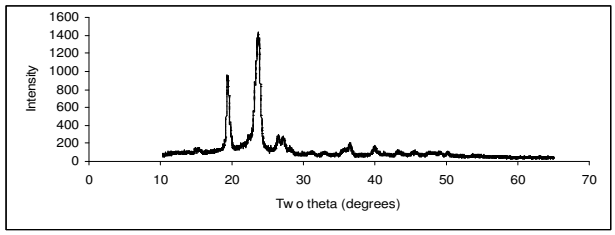
Figure 11 shows the In vitro absorption studies showed that very negligible amount of the curcumin is absorbed in the intestine even though the solubility of curcumin is enhanced the solid dispersion technique as less than 100 mcg is absorbed up to 90 min.



(i)



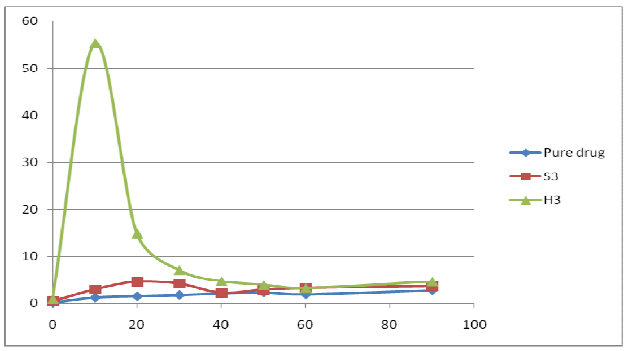
(ii)



(iii)

(i) Curcumin (ii) Curcumin solid dispersion by hot melt (H3) (iii) Curcumin solid dispersion bysolvent evaporation (S2)

Figure 9: X- ray diffraction studies of pure drug and formulations



S3: Solid dispersion by Solvent evaporation; **H3:** Solid dispersion by hot melt

Figure 10: *In vitro* dissolution profile of pure curcumin and solid dispersions

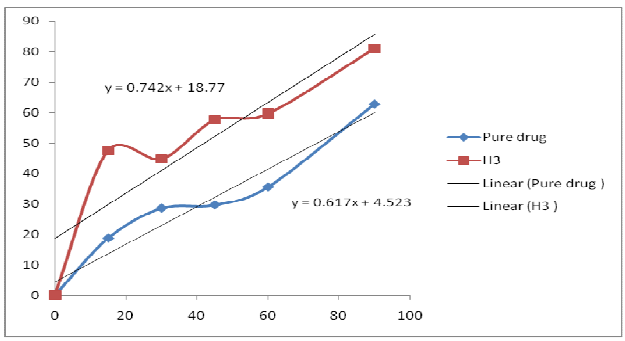


Figure 11: *In vitro* absorption studies of pure curcumin and H3 formulation

Aqueous stability study of H3 formulation.

Aqueous solubility study of solid dispersion carried at pH 7.4 revealed that the degradation of curcumin was more when compared to the pure curcumin. This degradation may be the result of more exposure of the curcumin to the aqueous media in molecular state which hastens the hydrolytic reaction. The addition of Tartaric acid, Ascorbic acid and citric acid improves the aqueous stability but not significantly as we saw in pH 7.4 with pure curcumin. Similar results were seen with pH 6.8 and 1.2 as hydrolytic reaction was the major driving parameter for the curcumin degradation.

CONCLUSION

From the above experiment, curcumin is found to be unstable in solution form. Stability increases in acidic and decreases as the pH increases. Addition of tartaric acid, ascorbic and citric acid to the solution increases the aqueous stability by 3 folds in pH 7.4 in pure form. Amongst three acids, tartaric acid and ascorbic acid found to increase the stability in a greater extent. Solid dispersions of curcumin enhance the aqueous solubility. Hot melt method with PEG 6000 was found suitable for improving the solubility when compared to physical mixtures and solvent evaporation method. Though the solid dispersion improves the aqueous solubility but drastically reduces the aqueous stability. The presence of Tartaric acid, Ascorbic acid and Citric did not significantly improves the aqueous stability, however these acids reduce the pH and aids the curcumin degradation by basic pH. In vitro release studies also supports this concept as burst release was seen with in 10 min later the curcumin tend to degrade in aqueous media. The permeability of curcumin in solid dispersion from rat intestine was found less and was insignificant as seen with the parent molecule. Further studies can be conducted to improve the permeability of curcumin from the intestine.

Finally form this experiment, it was noticed that enhancing the solubility of curcumin by solid dispersion does not really helpful because of increased hydrolytic degradation of curcumin in fine form. In Vitro absorption of the solid dispersion was also found limited may be due to the same hydrolytic reaction.

ACKNOWLEDGMENT

We thank Natural remidies laboratories, Bangalore and Sami labs, Bangalore for providing the gift samples.

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