ENHANCEMENT OF SOLUBILITY AND DISSOLUTION RATE OF CURCUMIN BY SOLID DISPERSION TECHNIQUE

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ABSTRACT

Curcumin, a naturally occurring highly lipophilic molecule has wide range of pharmacological activities. However, its limited aqueous solubility and degradation at alkaline pH restricts its bioavailability. Solid dispersions (SD) of curcumin-polyethylene glycol (PEG 4000, 6000) in the ratio of 1:3, 1:5, and 1:10 were prepared in an attempt to increase the solubility and dissolution by fusion method. Physical characterization by IR, DSC studies, in comparison with corresponding physical mixtures revealed the changes in solid state during the formation of dispersion and justified the formation of high-energy amorphous phase. Both solubility and dissolution of curcumin solid dispersions were significantly greater than those observed for physical mixtures and intact curcumin and it was observed that the dissolution of PEG 4000 was higher as compared to PEG 6000 in 30 mins. The powder DSC thermogram indicated that the amorphous curcumin was obtained from all solid dispersions. This may aid in improving bioavailability and dose reduction of the drug.

Key words: Curcumin, Fusion method, Solid Dispersion, Amorphous phase.

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. Following oral administration (upto 8 g per day), it is poorly absorbed and only the traces of compound appear in blood^{1,2}. Curcumin is practically insoluble at acidic pH. At alkaline pH although soluble, it undergoes rapid hydrolytic degradation^{3,4}. Few attempts have been made to improve solubility of curcumin by its chemical derivatization, complexation or interaction with macromolecules, e.g. gelatin, polysaccharides and protein, salt formation and cyclodextrins. But slow process of complexation, high molecular weight of Cyclodextrins, in vivo conversion into acidic or basic forms of the salt drug and pH of the processing medium may limit their practical utility. Solid dispersion is one of the successful methods in improving drug dissolution and to obtain better bioavailability^{5,6}. 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 method⁷. 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 absorption⁸. Hydrophilic synthetic polymers have been widely investigated as carrier substance for solid dispersions. PEG is amongst the most frequently used as the carrier. It can improve the solubility and dissolution of many poorly water-soluble drugs^{9,10}. In the present study we employed solid dispersion technique to improve dissolution of curcumin in acidic medium. Curcumin-PEG 4000 and PEG 6000 (PEG) solid dispersions (SDs) in different ratios (1:3, 1:5, and 1:10) were obtained by Fusion method. The solubility, dissolution and physicochemical characterizations based on differential scanning calorimetry (DSC) and FTIR spectroscopy were evaluated¹¹.

MATERIALS AND METHODS

Materials

Curcumin extract 95% was generously gifted by Neelam Phytoextract. PEG 4000 and PEG 6000 and other chemicals and reagents were obtained from Luba Chemicals. All reagents were of analytical-reagent grade.

Methods

Solid dispersions of curcumin: PEG 4000 and PEG 6000 in the weight ratio of 1:3, 1:5 and 1:10 were prepared by Fusion method. Solid dispersions were prepared by melting the accurately weighed amounts of carriers (PEG 4000, PEG 6000) in a water bath at a temperature of 60°C and the drug was dispersed in the molten solution. Weight amount of curcumin 600mg was taken in petri dish and required amount of carriers (PEG 4000, PEG 6000) were added to prepare required drug to carrier ratio for formulations¹². Then the mixture was heated under controlled temperature to melt drug and carrier with continuous stirring. The melted preparation was transferred to the refrigerator for just 5 mins to solidify. The solid dispersions prepared were pulverized and sifted (40#) sieve and stored in a desiccator.

Preparation of physical mixture

Drug and carriers physical mixture were prepared by slightly grinding drug curcumin and carriers (PEG 4000, PEG 6000) in mortar for 2 min at the required drug/carriers ratio. Then the powder was passed through the sieve no#40. The resulted product was stored in desiccator to carry out further analysis.

Characterization of physical mixtures and solid dispersions of curcumin

Solubility studies

The solubility of curcumin in pH 1.2 (0.2 M HCL) and various concentrations of PEG 4000, PEG 6000 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 temperature¹³. 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.

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. 1 ml of this solution was diluted 10 times with 0.2 M HCL buffer solutions and the absorbance was measured at 428 nm¹⁴.

Flow Properties

The flow properties of PMs and SDs were characterized in terms of angle of repose, Carr index and Hausner ratio¹⁵. 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 2.0cm 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 repose¹⁶. 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 2.0cm until the time when there was no more decrease in the volume. Bulk density (pb) and tapped density (pt) were calculated. Hausner ratio (HR) and Carr index (CI) were calculated according to the two equations given below:

$$\text{HR} = \text{pt}/\text{pb}$$

$$\text{CI} = (\text{pt} - \text{pb})/\text{pt} \times 100$$

Dissolution studies

All *in-vitro* dissolution studies were carried out using 900 ml of 0.2 M hydrochloric acid at (pH 1.2) $37 \pm 0.5^\circ\text{C}$ as the dissolution medium in a USP Type II apparatus (TDT -08L, Electrolab) at a stirring speed of 100 rpm. 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 $37 \pm 0.5^\circ\text{C}$) 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.

Physical characterization

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.

Fourier transform infrared spectroscopy (FTIR)

The potassium bromide discs were prepared by mixing a small amount of the sample with potassium bromide and powder mixture was compressed to form the disc. It is then scanned over a frequency range of 4000–500 cm^{-1} .

RESULTS AND DISCUSSIONS

Solubility studies

The solubility of curcumin was determined at 37°C in purified water as well as in aqueous buffer solution at pH 1.2. The solubility of curcumin in purified water at 37°C was $0.432 \pm 0.01 \mu\text{g/ml}$ and pH 1.2 was $0.45 \pm 0.01 \mu\text{g/ml}$, very similar to the solubility in purified water. The solubility profile of curcumin in various concentrations of PEG 4000 and PEG 6000 was shown in Figure 1. Curcumin was practically insoluble in water. A significant increase in its solubility was observed as the concentration of both PEG was increased. It was suggested that both PEG might form the soluble complex with curcumin. The solubility of curcumin in aqueous solutions of the two selected polymers at different concentrations is shown in Figure 1. The solubility increased linearly, though marginally in the PEG 6000 solutions ($R^2 = 0.9766$ and slope = 0.052) suggesting very weak interactions between curcumin and PEG 6000. Solutions of PEG 4000 exhibited linear and significantly greater increase in the solubility of curcumin as the concentration of PEG 4000 was increased ($R^2 = 0.9856$, slope = 0.0807) signifying approximately 2-fold greater solubility than that obtained in the PEG 6000 solutions. This might be attributed to improved wetting in the presence of PEG 4000 or association between the functional groups of PEG 4000 and curcumin^{17,18}. The higher solubility of curcumin in the solutions of the carriers suggests greater miscibility of curcumin into the carrier and thus higher probability of solid solution formation during the formulation of the solid dispersion. The higher solubility of curcumin in the solutions of the carriers suggests greater miscibility of curcumin into the carrier and thus higher probability of solid solution formation during the formulation of the solid dispersions shown in Figure 1. The solubility of curcumin at pH 1.2 was very low. For physical mixtures, a slight increase in curcumin solubility compared to the solubility of curcumin in the same medium was found. In all solid dispersion systems, the curcumin solubility was markedly higher than that of pure curcumin and physical mixtures. The increase in curcumin solubility was linear with respect to the weight fraction of the polymers. At 1:10 curcumin-PEG 4000 solid dispersions, the increase in curcumin solubility at pH 1.2 was approximately 4-fold, respectively compared with 1:10 curcumin-PEG 6000. The higher solubility of curcumin by PEG 4000 may probably be due to the low molecular weight of PEG having higher solubility^{19, 20}.

Drug content

The drug content was found in the range of 96.13 to 99.9% indicating the acceptability of fusion method for preparation of solid dispersions. Low values of standard deviation in drug content of PMs and SDs indicated uniform drug distribution in the entire prepared batches Table 2.

Table 1: Composition and codes of physical mixtures and solid dispersions

Excipients	Physical mixture	Solid dispersion	Drug:polymer ratio
PEG 4000	PM1 PEG 4000 1:3	SD1 PEG 4000 1:3	1:3
	PM2 PEG 4000 1:5	SD2 PEG 4000 1:5	1:5
	PM3 PEG 4000 1:10	SD3 PEG 4000 1:10	1:10
PEG 6000	PM4 PEG 6000 1:3	SD4 PEG 6000 1:3	1:3
	PM5 PEG 6000 1:5	SD5 PEG 6000 1:5	1:5
	PM6 PEG 6000 1:10	SD6 PEG 6000 1:10	1:10

Table 2: Percent drug content in physical mixtures and solid dispersion of PEG 4000 and PEG 6000 in mass ratio of 1:3, 1:5, and 1:10 respectively

Formulations code	Drug content (%) (X $\pm$ S.D.)
PM 1	99.78 $\pm$ 0.34
PM 2	99.56 $\pm$ 0.14
PM 3	99.92 $\pm$ 0.12
SD 1	98.26 $\pm$ 0.41
SD 2	96.13 $\pm$ 0.4
SD 3	96.58 $\pm$ 0.23
PM 4	99.04 $\pm$ 0.13
PM 5	99.00 $\pm$ 0.05
PM 6	99.63 $\pm$ 0.06
SD 4	97.46 $\pm$ 0.26
SD 5	98.50 $\pm$ 0.57
SD 6	98.20 $\pm$ 0.35

Table 3: Flow properties of physical mixture and solid dispersions of curcumin

Formulations	Bulk density (g/cc) (X $\pm$ S.D.)	Tapped density (g/cc) (X $\pm$ S.D.)	Carr's index (%)	Hausner's ratio	Angle of repose ($^{\circ}$) (X $\pm$ S.D.)
PM 1	0.43 $\pm$ 0.27	0.51 $\pm$ 0.21	15.6	1.18	25.59 $\pm$ 0.12
PM 2	0.42 $\pm$ 0.23	0.54 $\pm$ 0.24	22.2	1.28	21.37 $\pm$ 0.42
PM 3	0.45 $\pm$ 0.25	0.52 $\pm$ 0.31	13.4	1.15	24.15 $\pm$ 0.22
PM 4	0.42 $\pm$ 0.32	0.5 $\pm$ 0.19	16	1.19	27.31 $\pm$ 0.23
PM 5	0.39 $\pm$ 0.27	0.52 $\pm$ 0.24	25	1.33	21.47 $\pm$ 0.47
PM 6	0.41 $\pm$ 0.23	0.54 $\pm$ 0.28	24	1.31	31.61 $\pm$ 0.11
SD 1	0.41 $\pm$ 0.24	0.55 $\pm$ 0.27	25.4	1.34	27.37 $\pm$ 0.16
SD 2	0.42 $\pm$ 0.12	0.57 $\pm$ 0.31	26.3	1.35	22.21 $\pm$ 0.29
SD 3	0.45 $\pm$ 0.17	0.55 $\pm$ 0.23	18.18	1.22	23.43 $\pm$ 0.17
SD 4	0.46 $\pm$ 0.34	0.62 $\pm$ 0.26	25.8	1.34	32.61 $\pm$ 0.14
SD 5	0.38 $\pm$ 0.41	0.55 $\pm$ 0.31	30.9	1.44	22.42 $\pm$ 0.27
SD 6	0.42 $\pm$ 0.24	0.51 $\pm$ 0.21	17.6	1.21	28.47 $\pm$ 0.38

Figure 1: Solubility profile of curcumin in various concentrations of PEG 4000 and PEG 6000 at 37 $\pm$ 0.5 $^{\circ}$ C **Figure 2: The solubility of curcumin, physical mixtures and solid dispersions at PEG 4000 at 37 $\pm$ 0.5 $^{\circ}$ C**

Figure 3: The solubility of curcumin, physical mixtures and solid dispersions in PEG 6000 at $37\pm0.5^\circ\text{C}$

Figure 4: Dissolution profile of pure curcumin, physical mixture and solid dispersion of PEG 4000

Figure 5: Dissolution profile of pure curcumin, physical mixture and solid dispersion of PEG 6000

DCS OF CURCUMIN

DSC OF PEG 4000

DSC OF PEG 6000

DSC OF PHYSICAL MIXTURE OF PEG 4000 AND CURCUMIN

Figure 6: DSC data of curcumin, polymers, physical mixtures, and solid dispersions

Figure 7: FTIR spectra of Curcumin (a), solid dispersion of PEG 4000 (b), PEG 6000 (c)

Figure 8: FTIR spectra of curcumin (a), physical mixtures of PEG 4000 (b), PEG 6000(c)

Figure 9: FTIR spectra of curcumin (a), PEG 4000 (b), PEG 6000 (c)

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 0.38 ± 0.41 to 0.46 ± 0.34 g/cc, tapped density of 0.51 ± 0.21 to 0.62 ± 0.26 , Hausner's ratio of 1.44 or less indicating good flowability, Carr's index was found between 13.4 to 30.9 indicating poor flowability. The good flowability of the solid dispersion was also evidenced with angle of repose within range of 21.37 ± 0.42 to $32.61 \pm 0.14^\circ$, which is around 33° indicating good flowability. But still needs the incorporation of glidants during formulation of solid dosage form employing solid dispersion.

Dissolution studies

The dissolution profile of pure drug, physical mixtures and solid dispersions are shown in (Figure 5). Both physical mixtures and solid dispersions showed enhanced dissolution rate as compared with pure drug. Solid dispersion increased the solubility and maximizing the surface area of the drug that came in contact with the dissolution medium as the carrier dissolved. Dissolution rate of PEG 4000 was higher as compared to the PEG 6000. This might be due to the low molecular weight of polymer which increases the solubility of the curcumin compared to the high molecular weight polymer. The pure curcumin exhibited the slowest dissolution rate because of its hydrophobicity that caused the powder to float on the surface of the dissolution medium and prevented its surface contacting the medium²². In all cases, the dissolution rates of curcumin solid dispersions were remarkably enhanced compared to their corresponding physical mixtures and pure curcumin. Several mechanisms have been proposed to account for the increase in the dissolution kinetic of drug from solid dispersions. These mechanisms include the reduction of drug crystallite size, a solubilization effect of carrier, an absence of drug aggregation and agglomeration, an improvement in drug wettability, the conversion of drug to the amorphous state^{22,24}. The increased in curcumin dissolution from these solid dispersions can thus be contributed by several factors such as an excellent wettability, which could be observed clearly from the solid dispersion since it rapidly left the surface and was dispersed in the bulk of the dissolution medium, a markedly increase in curcumin solubility, the solubilizing effect of the carrier, an absence of aggregation and agglomeration and the formation of high energy amorphous state as confirmed by DSC, FTIR.

Differential scanning Calorimetry

The DSC thermograms of curcumin, PEG 4000, PEG 6000, physical mixtures (1:10) and solid dispersions were illustrated in Figure 7. The DSC curve of pure curcumin showed a single sharp endothermic peak at 180.0°C , with the enthalpy of fusion was 119.8 J/g, corresponding to the melting point of curcumin figure (6)²⁵. DSC thermograms of PEG 4000 showed an endothermic peak around 51.5°C and that of PEG 6000 at 65.3°C , indicating the melting point of the polymers. In case of PMs this endotherm broadened and was shifted slightly to lower temperature (140°C). The decrease of the enthalpy of fusion of curcumin in physical mixtures was the result of the solubilizing effect of PEGs during heating process; only that part of curcumin which is in excess shows a melting endotherm. On the other hand, all solid dispersion systems showed no endothermic peaks of curcumin. 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 dissolution²⁶.

Fourier Transform Infrared Spectroscopy

FTIR spectroscopy was carried out to further elucidate the interaction between curcumin and PEGs in the solid state shows 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 O-H stretching vibration. FTIR spectrum of PEGs showed broad peaks at about 3050 – 3438 cm^{-1} due to O-H stretching, 2891 cm^{-1} (CH_2 Symmetry)²⁶. The FTIR spectra of all physical mixtures were similar to the synthetic spectra producing by the addition of curcumin and PEGs. This indicates no interaction between curcumin and PEG. In particular, the O-H stretching vibration at 3507 cm^{-1} of all solid dispersions was disappeared. Therefore, the solid dispersions show an interaction such as the intermolecular hydrogen bonding between curcumin and Polymers. This interaction caused to change curcumin crystalline structure to amorphous form.

CONCLUSION

The study concluded that the solid dispersion prepared by Fusion method (SD 6, 1:10 ratio of drug: PEG 4000) shows higher dissolution rate compared with other formulations and pure drug. The study shows that the dissolution rate of Curcumin can be enhanced to a great extent by solid dispersion technique. The study result concluded that the Fusion method is suitable for development of solid dispersions of curcumin with PEGs. It is, however, suggested that further research on large scale be carried out by using other hydrophilic carrier.

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