Solid Dispersions of Curcumin

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Solid dispersions of curcumin was studied to increase its aqueous solubility. Different carrier such as HPMC, HEC, PVP, high molecular weight PEG such as 1500, 4000, 20000, poloxamers such as Cremophor and Lutrol-127 were used in the preparation. Both fusion and solvent methods were adopted for the preparation of solid dispersions. Curcumin was successfully solubilised using Cremophor and PEG 20000 to get a concentration of 18 mg/ml. Increase in rate of dissolution compared to the pure drug was observed. Release pattern may be by first order kinetics.

Turmeric, rhizome of Curcuma longa has been used down the ages as antisceptic, antibacterial, anti-inflammatory and a vermicidal agent[1]. Curcumin (diferuloyl methane) which is its main active compound has gained importance as a medicine as it exhibited pharmacological properties that include, anti-inflammatory[1], antineoplastic[2], hepatoprotective[3], and antioxidant[4] actions. Its antioxidant properties have been attributed to the phenolic group present in the molecule[4]. One of the major problems in the administration of curcumin has been its insolubility in the aqueous medium followed by its poor absorption in the GIT.

Solid dispersion technique has been used to increase the dissolution and absorptin of poorly soluble drugs by dispersing the drug in a highly water soluble carrier in a solid state. A number of freely soluble materials such as citric acid, bile acids, sterols and polymers such as polyethylene glycols and poly vinyl pyrrolidone have been described as carriers for solid dispersions[5]. Poloxamers, the new class of nonionic surfactants have been increasingly used as emulsifying agents for intravenous fat emulsions and has remarkable solubilising properties[6]. Two poloxamers were taken for the study-Cremophor RH 40, a macrogol ester which is polyethoxylated castor oil. It has been used as an emulsifying and solubilising agent[6]. The other poloxamer selected was Poloxamer 407 (Lutrol-127 or PF-127) which contians around 70% polyoxyethylene units. It is known for its low toxicity[7], excellent compatibility with other chemicals[7], high solubilising capacity for different drugs[8] and good release characteristics[9].

Solid dispersion technique was adopted to increase the solubility of curcumin. Carriers such as citric acid, mannitol, urea, tartaric acid, high molecular weight PEGs, PVP, HEC, MCC, dextrin and Cremophor and Lutrol-127 were studied. Curcumin (gift sample from SAMY CHEMICALS PVT. LTD.), Cremophor and Luitrol (gift sample from BASF, Bombay) and all other chemicals and reagents of AR grade were used in the study. Carrier and curcumin in the ratio of 1:1, 1:2 were used. Fusion and solvent evaporation methods were adopted for the preparation. In the fusion method[10], drug and the carriers were mixed thoroughly, melted on a heating mantle under constant temperature with continuos stirring, residue poured on a porcelain tile previously cooled in an ice bath for solidification, dried in a dessicator, pulverized and passed through sieve number 22. In the solvent method[11] drug and carriers were dissolved in a suitable solvent, evaporated on a boiling water bath with continuos stirring residue, poured on as porcelain tile previously cooled in an ice bath, solidified mass formed was dried in a dessicator, pulverized and passed through sieve number 22.

The solid dispersions prepared were further investigated to establish the identity of the drug in the system by TLC and IR analysis. These studies helped to rule out the possibility of either drug degradation or drug interaction with components of the system. Solubility studies of

Table 1 - Solid Dispersions of Curcumin

Carriers[1]	Ratio[2]	Solubility[3]	Code[4]
PEG 4000	1:5	9.94	1
PEG (4000+1500)	1:5	11.34	2
LUTROL	1:1	17.40	3
LUTROL	1:2	16.84	4
PVP	1:5	16.32	5
PEG 20000	1:1	18	6
CREMOPHOR	1:1	18	7
LUTROL	1:5	17.38	8
HEC	1:1	11.04	9

1- indicates carriers used in the preparation of solid dispersions, 2-Is the ratio of drug to carrier, 3-solubility shown in mg/ml, 4-number indicate the code given for formations.

curcumin and its dispersions were conducted in a thermostatic shaker water bath by shaking a saturated solution for 6 h at 37+/-1° at 120-130 strokes/min. Solid dispersions that have a solubility from 10-20 mg/ml were taken up for *in vitro* dissolution study. The selected solid dispersions and the solubility obtained is shown in Table 1.

Dissolution studies of the pure drug and the selected solid dispersions were carried out in USP XII dissolution apparatus. Solid dispersions equivalent to 25 mg of curcumin were placed in 500 ml of simulated gastric fluid maintained at 37°. Samples were withdrawn at intervals of 30 min. Dissolution was carried out for 2h at pH 1.2 after which the medium was replaced with simulated intestinal fluid at pH 6.8. The drug content of the samples were determined spectrometrically[12] at 430 nm using UV-Vis Shimadzu spectrophotometer.

Solid dispersions of curcumin could be successfully prepared with the carriers selected for the study such as urea, citric acid, mannitol, PVP, PEG 1500, PEG 4000, PEG 20000, poloxamers, HEC, tartaric acid and dextrin and curcumin showed good miscibility with all the carriers. Rapid solidification of the melts were observed when porcelain tile previously cooled in ice-bath was used. The molten mixture is cooled rapidly to entrap drug particles in matrix in as fine state as possible. The cooling rate of the solid obtained can influence the physical state of the solid obtained and the particle size of the crystals[10]. The melting point of urea is 132.7° and at this temperature it decomposes. Fusion method could not be employed for preparing the solid dispersions of curcumin with urea since the fusion temperature is 134°. Hence solvent method was adopted using methanol as the suitable solvent.

TLC ruled out the possible degradation of curcumin in the solid dispersions. Comparison of the spectra of pure curcumin and its solid dispersion showed that there had been no change in the structural assignments of pure curcumin and curcumin in solid dispersions. The results of the solubility studies of solid dispersions showed variation in the solubility. However, there was a considerable increase in the solubility of curcumin in all the cases. Solid dispersions that had a solubility between 10-20 mg/ml is given in Table 1. Solid dispersions prepared by using citric acid, tartaric acid, mannitol showed the least solubility with a solubility of less than 1 mg/ml. Carriers such as dextrin, HPMC, micro crystalline cellulose increased the solubility to a maximum extent of 5.88 mg/ml. From the Table 1 it is evident that the maximum solubility of 18 mg/ml was achieved in case Cremophor and PEG 20000. Polyethylene glycols which are highly crystalline are capable of entrapping low molecular weight compounds in their interstitial spaces[13]. Thus good solu-

Table 2 - Dissolution Data of Solid Dispersions

Formulation Code	Percent Release[1]	Regression Coeffecient[2]	Release Rate[3] K hr^{-1}
F1	74.04	0.944	0.0063
F2	82.22	0.965	0.00613
F3	90.25	0.992	0.01006
F4	92.61	0.922	0.0074
F5	84.28	0.988	0.0024
F6	90.32	0.985	0.0080
F7	90.31	0.982	0.00822
F8	94.65	0.879	0.0118
F9	74.15	0.959	0.006

1-cumulative percentage release at the end of 4 hours; 2-R^2 value of log of percent undissolved vs time (sigma minus plot, Ref.15); 3-calculated from slope X 2.303 of sigma minus plot.

bility was seen in case of all the solid dispersions prepared with PEG series.

Dissolution study was carried out to with those solid dispersions which had solubility of 10-20 mg/ml to find out their dissolution in the GIT. All the selected dispersions showed a good release rate when compared with pure curcumin. The maximum rate was observed when Lutrol was used as carrier. Formulations F8 followed by F4 showed the maximum release the former had a maximum release of 94.66% while F4 had a maximum release of 92.61%. From the dissolution study, Sigma minus plot[14] of log percentage drug undissolved versus time was plotted. Regression analysis was carried to calculate the coefficient of correlation and the rate of reaction. High correlation coefficient indicated that the release may be first order. Results of study are shown in Table 2. It has been observed that the reaction rate is in the order of F8>F3>F7>F4>F1>F2>F9>F5. Thus the nonionic surfactants Lutrol and Cremophor increased the solubility and release rate of curcumin considerably along with PEG 20000. The relase may be by first order kinetics.

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