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Research Article

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Solubility Enhancement Of Curcumin Using HPMC K 15M By Solvent Change Precipitation Method

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ABSTRACT: Curcumin naturally occurs from rhizhomes of Curcuma longa L., Zingiberaceae (Turmeric) is the most widely used phytoconstituent. It is highly Lipophilic, Insoluble in water at acidic or neutral pH. The major barrier to the clinical usefulness of Curcumin is its poor solubility and dissolution rate, hence leads to poor Bioavailability. . Many methods are available to improve these characteristics. Solid dispersion (SD) is one of these methods that involved a dispersion of one or more active ingredients in an inner carrier or matrix in solid state. The aim of the present study is to increase the solubility and dissolution rate enhancement of curcumin by solid dispersion technique. For solid dispersion preparation, HPMC K 15M is used as a hydrophilic carrier. It is prepared by combining the curcumin and HPMC K 15 M in a weight ratio of 1:1, 1:2, 1:3, and 1:4 by Solvent Change Precipitation Method.

KEYWORDS: Curcumin, Solid Dispersion, HPMC K15M, Solvent change Precipitation.

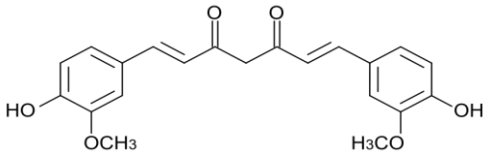
INTRODUCTION

The Solubility or the dissolution rate of the drug is a key factor determining its rate and extent of absorption after oral administration. A poor solubility of drug leads to detraction from its inherent efficacy by affecting the drug bioavailability. Hence one of the most challenging tasks faced by modern pharmaceutical scientists is designing a formulation for a poorly soluble drug such that the drug is available in a more soluble form after administration. [1][2]

Several approaches have been reported for enhancing the solubility and hence the dissolution rate of poorly soluble drugs including (i) Mironisation to increase the surface area; (ii) use of surfactant as a solubilisers; (iii) forming water soluble complexes with cyclodextrins; (iv) manipulating the solid state of drug with the aim of decreasing the drug crystalinity; (v) prodrug formation etc. [3] [4]

Solid Dispesion (SD) is one of the commonly used methods to improve the solubility, Dissolution characteristics and bioavailability of poorly soluble drug. The term 'Solid Dispersion' is define as the dispersion of one or more active ingredients in an inert hydrophilllic carrier or matrix at solid state prepared by melting, dissolution in solvent or melting solvent method.[5] [6]

Curcumin is a yellow pigment obtained from *Curcuma longa* and is been used from the time immemorial as the dietary supplement, colouring agent, spice and also for curing the diseases. A vast research and Curcumin has a wide spectrum of therapeutic effects such as anti-inflammatory, antioxidant, antifungal, antibacterial, anticancer, antiameobic, antidiabetic, antifertility etc. It is practically insoluble in water and is highly susceptible for the pH change. [7] [8]



Curcumin

Various water-soluble or water-swellable polymers with high molecular weight have been used in hydrophilic matrices, such as hypromellose (hydroxypropyl

methylcellulose (HPMC), hydroxypropylcellulose (HPC) and polyethylene oxide (PEO). HPMC is identified as the most popular polymer in matrix applications because of a number of key features and advantages

- Global regulatory acceptance.[9][10]
- Excellent stability and non-ionic nature (resulting in pH-independent performance). [11] [12]
- Ease of manufacture through direct compression or granulation.[13] [14]
- Versatility and suitability for various drugs and release profiles (because of different chemistries and viscosity grades being available).[15]
- Odourless and tasteless.[16]
- Extensively studied and understood.[17]
- Readily available[18]

In the present study we employed solid dispersion technique to improve dissolution of curcumin in acidic medium. Curcumin–HPMC K 15 M solid dispersions (SDs) in different ratios (1:1, 1:2, 1:3 AND 1:4) were obtained by Solvent Change Precipitation Method. The solubility, dissolution and physicochemical characterizations based on differential scanning calorimetry (DSC) and FTIR spectroscopy were evaluated. [19] [20]

MATERIALS AND METHODS

MATERIALS

All reagents were of analytical grade. Synthetic Curcumin was procured from Loba Chemie Pvt. Ltd., India and HPMC K 15M was procured from S D Fines, S.D. Fine Chem. Ltd. Mumbai, India.

METHODS

In this method both the drug and polymer is dissolved separately in an organic solvent- Acetone. The drug solution is then added drop wise in the organic solution containing polymer under over head stirring causing precipitation of solubilized drug phase. The precipitated product is then dried in an oven at 51 ° C till it gets dry. The dried powder is then passed through the sieve no. 44 to get uniform particle size. Different ratios of drug and curcumin were prepared. [21] [22] [23]

Table 2: Composition of Solid Dispersion of Curcumin

Ratio	Curcumin	HPMC K 15M
1:1	0.5 gm in 15 ml Acetone	0.5 gm in 15 ml Acetone
1:2	0.5 gm in 15 ml Acetone	1 gm in 15 ml Acetone
1:3	0.5 gm in 15 ml Acetone	1.5 gm in 15 ml Acetone
1:4	0.5 gm in 15 ml Acetone	2 gm in 15 ml Acetone

CHARACTERIZATION OF SOLID DISPERSIONS OF CURCUMIN

Drug Content Analysis

An amount of sample 10 mg was weighed accurately and dissolved in 10ml of Glacial acetic Acid. The solution was sonicated for 15 min and the sample was centrifuged at 10,000 rpm for 1 min at 25° C. the supernatant was diluted with suitable quantity of methanol. The absorbance was recorded at 425nm through uv visible spectrophotometer. The drug content was determined using a standard curve plotted as a plot of absorbance Vs concentration.

Saturation Solubility studies

Apparent saturation solubility measurement was performed by standardized shake flask method by keeping at 37 °C at an rpm of 20 for 48h. Apparent solubility was determined in Phosphate buffer pH 7.4. For solubility study, an excess amount of the samples (20mg) was dispersed into 10 ml of media. After 48 hrs of shaking, samples were filtered through 0.2µm membrane filters and the filtrate was appropriately diluted with the medium used for solubility analysis. The measurement was conducted using UV-visible spectrophotometer at 427 nm.

Flow Properties

The flow properties of SDs were characterized in terms of angle of repose, Carr index and Hausner 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 2.0cm above hard surface. The sample was poured till the time when upper tip of the pilesurface 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 2.0cm until the time when there was no more decrease in the volume. Bulk density (ρb) and tapped density (ρt) were calculated. Hausner ratio (HR) and Carr index (CI) were calculated according to the two equations given below:

$$HR = \rho t / \rho b$$

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

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 aluminium 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 Transforms 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

Drug Content and Saturation Solubility studies

The drug content was found to be good and uniform among the different batches of prepared samples and ranged from 65.73 to 80.71%. The solubility profile of Curcumin and solid dispersion of curcumin with various concentration of HPMC K 15M are shown in table. The saturation solubility was performed in Phosphate buffer pH 7.4, 0.1N HCl and in Distilled water in triplicate. Plain Curcumin was practically insoluble in water. Whereas solid dispersions prepared by solvent change precipitation method reported higher solubility than pure curcumin. The increase in solubility might be attributed to formation of soluble complex of curcumin and HPMC K15M. The increase in solubility was found almost similar irrespective of polymer concentration. This might be due to release inhibiting property of polymer at higher concentration or attainment of saturation solubility by curcumin. SDs prepared by Solvent change Precipitation showed 100 fold increases in solubility in Phosphate buffer pH 7.4, 0.1N HCl and in Distilled water compared to pure drug. The increase in solubility might be attributed to formation of soluble complex of curcumin and HPMC K15M. The increase in solubility was found almost similar irrespective of polymer concentration. This might be due to release inhibiting property of polymer at higher concentration or attainment of saturation solubility by curcumin.

Table 2: Percentage drug content of Solid Dispersion of Curcumin

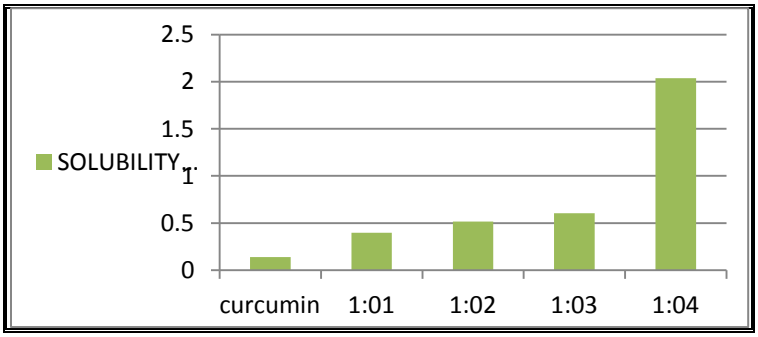
Ratio	Absorbance (425nm)	Dilution factor	Drug content
1:1	0.540	100	65.73 %
1:2	0.393	100	76.075%
1:3	0.402	100	75.44 %
1:4	0.327	100	80.719 %

Table 2: saturation solubility of Solid Dispersion of Curcumin

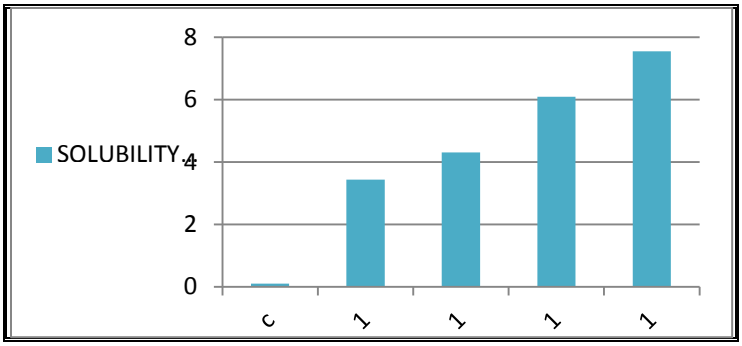
Ratio	Absorbance (425nm)			Solubility (µg/ ml)		
	Buffer pH 7.4	0.1N HCl	Distilled Water	Buffer pH 7.4	0.1N HCl	Distilled Water
1:1	0.186	0.560	0.391	0.3962	3.442	2.257
1:2	0.199	0.643	0.452	0.518	4.3157	3.128
1:3	0.208	0.812	0.617	0.60377	6.0947	5.485
1:4	0.36	0.951	0.853	2.0377	7.5578	8.857
Curcumin	0.159	0.243	0.312	0.141	0.1052	1.128

Figure1: Comparative solubility profile of pure cucumin in (a) Phosphate buffer pH 7.4 (b) 0.1N HCl (c) Distilled water.

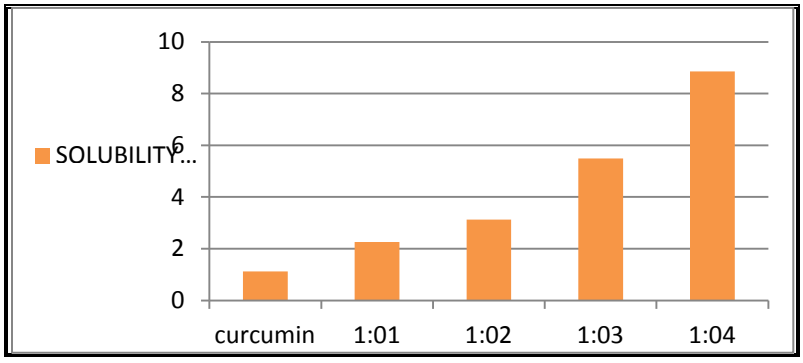
(a) Phosphate buffer pH 7.4



(b) 0.1N HCl



(c) Distilled water



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. The bulk density was found to increase in the ranges of 0.27 to 0.31 g/cc,tapped density of 0.35 to 0.44, Hausner's ratio of 1.38 or less indicating passable flowability, Carr's index was found between 22.72 to 27.78 indicating passable flowability. The good flowability of the solid dispersion was also evidenced with angle of repose which increases to 34.24° indicating good flowability. But still needs the incorporation of glidants during formulation of solid dosage form employing solid dispersion.

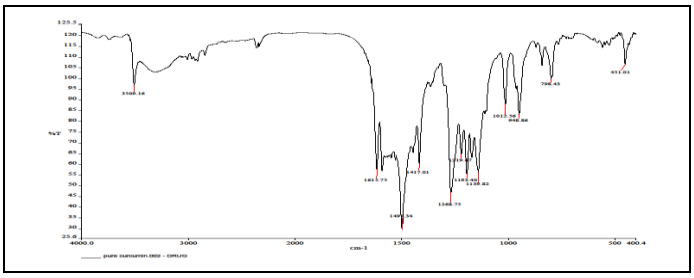
Table 2: flow properties of Solid Dispersion of Curcumin

Ratio	Angle of Repose	Bulk Density	Tapped Density	Hausner's Ratio	Carr Index
1:1	18.88°	0.2768 gm /cc	0.3582 gm /cc	1.2940	22.72 %
1:2	28.03°	0.334 gm /cc	0.4279 gm /cc	1.2811	21.94 %
1:3	36.30°	0.3143 gm /cc	0.4116 gm /cc	1.3095	23.63 %
1:4	34.24°	0.3187 gm /cc	0.4413 gm / cc	1.3846	27.78 %

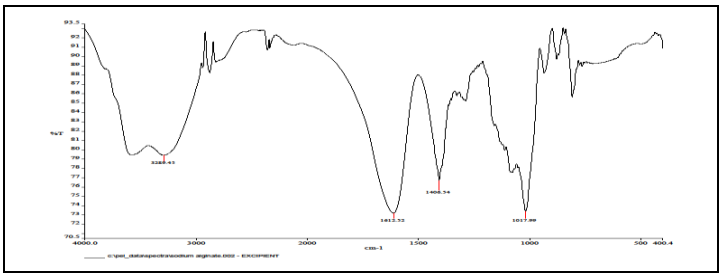
Fourier Transforms Infrared Spectroscopy (FTIR)

FTIR spectroscopy was used to assess the interaction between hydrophilic polymer and Curcumin in the solid state, since upon complexation, shifts or changes in the absorption spectrum may occur. The FTIR spectrographs of pure drug, HPMC K 15M and solid dispersions were taken which indicated no interaction of Curcumin with HPMC K 15M. The chemical structure of 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 FTIR spectrum. These peaks were observed in both pure drug as well as in solid dispersion indicating there was no change or shifting of the characteristic peaks in Curcumin Solid dispersion, suggested that there was no significant drug-polymer interaction which indicated the stable nature of the drug.

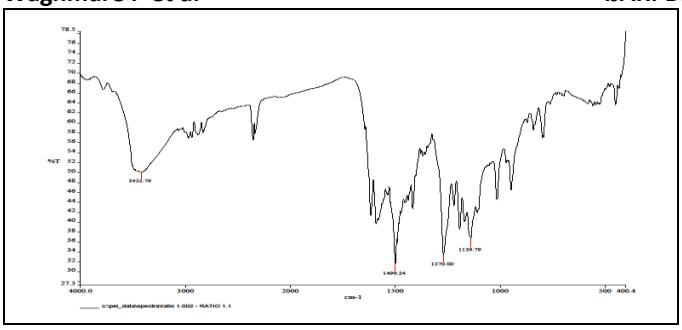
Pure drug curcumin

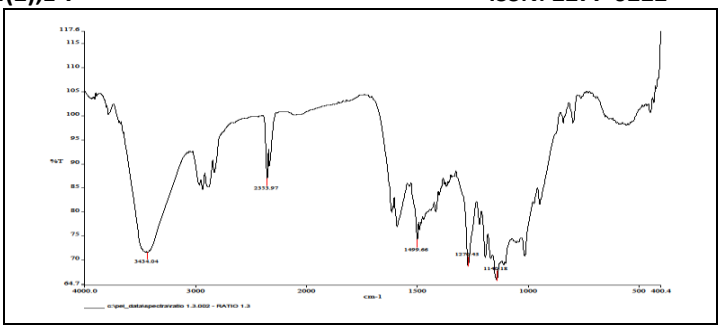


HPMC K 15 M

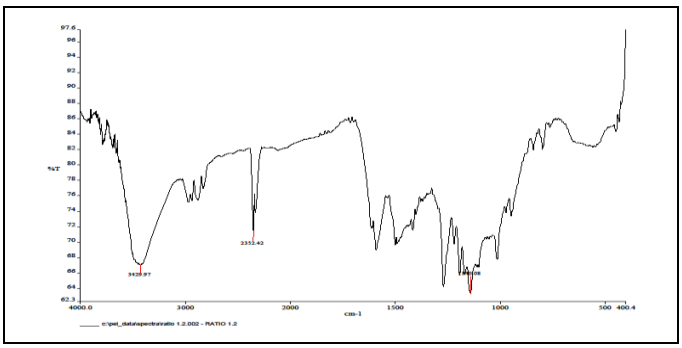


Ratio 1:1

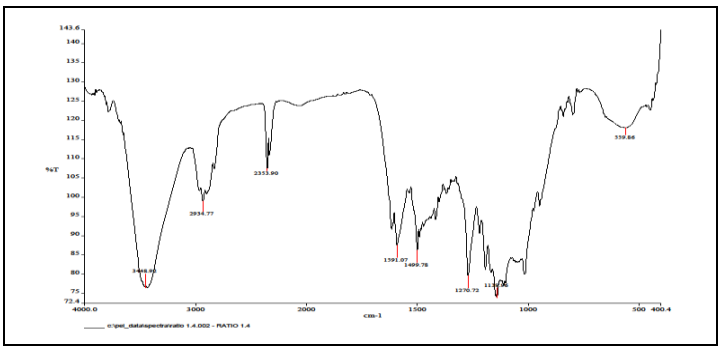




Ratio 1:2



Ratio 1:4



Ratio 1:3

Conclusion:

From the study it was concluded that solid dispersion prepared by solvent change precipitation method increases the solubility of Curcumin. HPMC K 15M can be used as a potential hydrophilic carrier for the improvement of solubility of Curcumin.

Further it can be concluded that continued extensive research on solid dispersion technology might strengthen the aim of better drug delivery system of improved bioavailability for the promising drug Curcumin with good safety profile and multiple targets for wider therapeutic application.

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