ABSTRACT

Objective: Curcumin naturally occurs from rhizomes 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 hence leads to poor bioavailability. The aim of the present study is to increase the solubility of Curcumin. Method: Many methods are available to improve the solubility of Curcumin. Solid dispersion (SD) is one of the methods that involved a dispersion of one or more active ingredients in an inner carrier or matrix in solid state. For solid dispersion preparation, HPMC K 4M and HPMC K 15M is used as a hydrophilic carrier. It is prepared by combining the Curcumin and the polymers in a weight ratio of 1:1, 1:2, 1:3, and 1:4 by Solvent Change Precipitation Method. Result: It is found that the solid dispersion prepared using HPMC K 4M and HPMC K 15M increases the solubility of Curcumin. The increase in drug content was found only up to ratio 1:4 to the drug and polymer. In both the solid dispersion prepared using HPMC K 4M and HPMC K 15M. With the evidence of saturation solubility study, the solubility of solid dispersion increases in 0.1N HCl, Phosphate buffer pH 7.4 and distilled water, as the concentration of polymer increases. Conclusion: The solid dispersion prepared by solvent change precipitation method increases the solubility of Curcumin. HPMC K 15M and HPMC K 4M can be used as a potential hydrophilic carrier for the improvement of solubility of Curcumin which is the evidence of Drug content, Saturation solubility study, DSC and FTIR. And HPMC K 4M was found to be the superior hydrophilic carrier than HPMC K 15M to increase the solubility.
**Keywords** Curcumin, Solid Dispersion, HPMC K 4M, 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 after administration, the drug is available in a more soluble form. [1]

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) formation of prodrug etc. [2]

Solid Dispersion (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 hydrophilic carrier or matrix at solid state prepared by melting solvent method, melting or dissolution in solvent. [3]

Curcumin is a yellow pigment obtained from *Curcuma longa* and is been used from the time immemorial as the dietary supplement, coloring agent, spice and also for curing the diseases. A vast research and Curcumin has a wide spectrum of therapeutic effects such as antioxidant, antibacterial, anticancer, antiameobic, antifungal, antidiabetic, anti-inflammatory, antifertility etc. It is practically insoluble in water and is highly susceptible for the pH change. [4]

![Fig 1 Structure of Curcumin](image-url)
Hydroxy propyl methylcellulose is an odorless slightly off-white to white, tasteless, granular, free-flowing powder which is a synthetic modification of the natural polymer, cellulose. Specifically, it is a modification of alkali cellulose, which is produced when purified wood pulp is treated with 18% sodium hydroxide solution. Methyl and Hydroxypropyl ether groups are introduced into the molecule by reaction of the alkali cellulose with propylene oxide and methyl chloride respectively. The commercial HPMC’s degree of substitution with these methoxy and hydroxyl propyl groups will vary depending on the commercial use and properties desired. These added groups confer on the molecule its unique properties of being cold-water soluble, while at the same time exhibiting reversible gelation when heated and re-cooled. [5]

The reason for its widespread acceptance includes;
1. Solubility characteristics of the polymer in aqueous solvent systems, organic solvent systems and in gastrointestinal fluid
2. Noninterference with tablet disintegration and drug availability,
3. Flexibility, chip resistance and absence of taste and odor,
4. Stability in the presence of temperature and humidity,
5. Ability to incorporate color and other additives into the film without difficulty.
6. HPMC also play a potential to improve the solubility of low water soluble drug.

The present work examines the influence of different grades of hydrophilic polymer HPMC on solubility of poorly water soluble drug Curcumin. Different ratios of Solid dispersion (1:1, 1:2,1:3, 1:4) were prepared using polymers HPMC K4M and HPMC K 15M by Solvent Change Precipitation Method. The solid dispersion were then evaluated for its solubility in different solvents, its flow property, drug content and physicochemical properties based on differential scanning Calorimetry (DSC) and FTIR spectroscopy. [6]

MATERIALS AND METHODS
Materials
All reagents were of analytical grade. Synthetic Curcumin was procured from Loba Chemie Pvt. Ltd., India. HPMC K 4 M and HPMC K 15M were procured from S.D. Fine Chem. Ltd. Mumbai, India.
Methods
In this method both the drug (Curcumin) and polymers were dissolved separately in an organic solvent-Acetone. The drug solution was then added drop wise in the organic solution containing polymer under overhead stirring, causing precipitation of solubilised drug phase. The precipitated product was then kept in an oven at 51° C till it gets dry. The dried powder was then passed through the sieve no. 44 to get uniform particle size. Different ratios of Curcumin and polymers were prepared.

Table 1 Different ratios of Curcumin Solid Dispersion using HPMC K 4M

<table>
<thead>
<tr>
<th>Ratio</th>
<th>Curcumin (gm)</th>
<th>HPMC K 4M (gm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:1</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>1:2</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>1:3</td>
<td>0.5</td>
<td>1.5</td>
</tr>
<tr>
<td>1:4</td>
<td>0.5</td>
<td>2</td>
</tr>
<tr>
<td>1:5</td>
<td>0.5</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Table 2 Different ratios of Curcumin Solid Dispersion using HPMC K 15M

<table>
<thead>
<tr>
<th>Ratio</th>
<th>Curcumin (gm)</th>
<th>HPMC K 15M (gm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:1</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>1:2</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>1:3</td>
<td>0.5</td>
<td>1.5</td>
</tr>
<tr>
<td>1:4</td>
<td>0.5</td>
<td>2</td>
</tr>
<tr>
<td>1:5</td>
<td>0.5</td>
<td>2.5</td>
</tr>
</tbody>
</table>

CHARACTERIZATION OF SOLID DISPERSIONS OF CURCUMIN

Drug Content Analysis
An amount of Curcumin 10 mg was weighed accurately and dissolved in 10ml of Glacial acetic Acid. The solution was sonicated using Sonicator 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 using UV Spectrophotometer. The drug content was determined using a standard curve plotted as a plot of concentration Vs absorbance. [6]

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 Distilled water, 0.1N HCl, 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. [4]

**Flow Properties**

The flow properties of Solid Dispersions 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 pile surface touched the lower tip of the funnel. Thetan-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. [7]

Hausner ratio (HR) and Carr index (CI) were calculated according to the two equations given below:

HR = ρt/ρb

CI = (ρt– ρb)/ρt x 100

**Differential Scanning Calorimetry (DSC)**

Thermal behavior of Curcumin Solid Dispersion was analyzed using differential scanning Calorimetry instrument equipped with Stare computer program. DSC thermograms were recorded using differential scanning calorimeter. Approximately 2-5 mg of sample was heated in an open aluminum pan from 30-300°C at a scanning rate of 10°C/ min under a stream of nitrogen. [8]

**Fourier Transforms Infrared Spectroscopy (FTIR)**

In this study, potassium bromide disc method was employed. Pure drug and solid dispersions were subjected to FTIR studies. The 5mg 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 FTIR spectrophotometer using sample holder and spectrum was recorded. [9]
RESULTS AND DISCUSSIONS

Drug Content Analysis

As depicted in figure 2, the drug content was found to be good and uniform among the different batches of prepared samples. The drug content of solid dispersion prepared using HPMC K15M was in the range from 68.141 ± 0.0185% to 80.32 ± 0.015% and for the Solid dispersion prepared using HPMC K4M, the drug content was in the range from 70.651 ± 0.560% to 81.791 ± 0.171%. It was observed that, the drug content was increases as the concentration of polymer increases in Solid dispersion. The ratio 1:4 shows maximum drug content as compared to the other ratios. Low values of standard deviation in the drug content of Solid dispersion indicated uniform drug distribution in the entire prepared batches.

Saturation Solubility studies

The solubility profile of Curcumin and solid dispersion of Curcumin with various concentrations of HPMC K 15 and HPMC K4M were performed. The saturation solubility was performed in Distilled water, 0.1N HCl and in Phosphate buffer pH 7.4 in triplicate. Plain Curcumin was practically insoluble in water. Whereas solid dispersions prepared by solvent change precipitation method using polymers HPMC K4M and HPMC K 15M reported higher solubility than pure Curcumin. The increase in solubility might be attributed to formation of soluble complex of Curcumin and polymers HPMC K4M, HPMC K 15M. The increase in solubility was found almost similar irrespective of polymers concentration. This might be due to release inhibiting property of polymers at higher concentration or attainment of saturation solubility by Curcumin.
Figure 3 show that the solubility of pure Curcumin in Distilled water was found only 1.0 μg/ml which was almost negligible. Whereas the solid dispersion of Curcumin prepared using various polymers shows increased in solubility in Distilled water then the pure Curcumin. The solubility of Curcumin increases as the concentration of the Curcumin with the polymer increases. Ratio 1:4 shows highest solubility of Curcumin. Both the polymer HPMC K 4M and HPMC K 15M helps to increase the solubility of Curcumin Solid Dispersion. The solubility of Curcumin Solid Dispersions prepared using HPMC K 4M increases up to 9.77μg/ml. And the solubility of Curcumin Solid Dispersions prepared using HPMC K 15M increases up to 8.87μg/ml. The solid Dispersion prepared using HPMC K 4M shows more solubility of Curcumin in Distilled water than the solid Dispersion prepared using HPMC K 15M. The higher solubility of Curcumin by HPMC K 4M may probably be due to the low viscosity of HPMC having higher solubility.

Figure 4 Solubility of Curcumin Solid Dispersion in 0.1N HCl
Figure 4 shows that the solubility of pure Curcumin in 0.1N HCl is only 1.7µg/ml which is almost negligible. Whereas the solid dispersion of Curcumin prepared using various polymers shows increased in solubility in 0.1N HCl then the pure Curcumin. The solubility of Curcumin increases as the concentration of the Curcumin with the polymer increases. Ratio 1:4 shows highest solubility of Curcumin. Both the polymer HPMC K 4M and HPMC K 15M helps to increase the solubility of Curcumin Solid Dispersion. The solubility of Curcumin Solid Dispersions prepared using HPMC K 4M increases up to 17.25µg/ml. And the solubility of Curcumin Solid Dispersions prepared using HPMC K 15M increases up to 16.54µg/ml. The solid Dispersion prepared using HPMC K 4M shows more solubility of Curcumin in 0.1N HCl than the solid Dispersion prepared using HPMC K 15M. The higher solubility of Curcumin by HPMC K 4M may probably be due to the low viscosity of HPMC having higher solubility.

![Graph showing solubility of Curcumin Solid Dispersion in Phosphate Buffer pH 7.4](image)

**Fig 5 Solubility of Curcumin Solid Dispersion in Phosphate Buffer pH 7.4**

Figure 5 shows that the solubility of pure Curcumin in Phosphate Buffer pH 7.4 is only 0.11µg/ml which is almost negligible. Whereas the solid dispersion of Curcumin prepared using various polymers shows increased in solubility in Phosphate Buffer pH 7.4 then the pure Curcumin. The solubility of Curcumin increases as the concentration of the Curcumin with the polymer increases. Ratio 1:4 shows highest solubility of Curcumin. Both the polymer HPMC K 4M and HPMC K 15M helps to increase the solubility of Curcumin Solid Dispersion. The solubility of Curcumin Solid Dispersions prepared using HPMC K 4M increases up to 2.67µg/ml. And the solubility of Curcumin Solid Dispersions prepared using HPMC K 15M increases up to 2.05µg/ml. The solid Dispersion prepared using HPMC K 4M shows more solubility of Curcumin in Phosphate Buffer pH 7.4 than the solid Dispersion prepared using HPMC K 15M.
prepared using HPMC K 15M. The higher solubility of Curcumin by HPMC K 4M may probably be due to the low viscosity of HPMC having higher solubility.

**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.

**Table 3 Flow properties of Solid Dispersion of Curcumin prepared by using HPMC K 4M**

<table>
<thead>
<tr>
<th>Ratio</th>
<th>Angle of Repose (°)</th>
<th>Bulk Density (gm/cc)</th>
<th>Tapped Density (gm/cc)</th>
<th>Hausner’s Ratio</th>
<th>Carr’s Index (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:1</td>
<td>32.56 ± 0.100</td>
<td>0.3643 ± 0.0007</td>
<td>0.418 ± 0.0025</td>
<td>1.143 ± 0.0057</td>
<td>13.06 ± 0.520</td>
</tr>
<tr>
<td>1:2</td>
<td>33.56 ± 0.038</td>
<td>0.2753 ± 0.0004</td>
<td>0.316 ± 0.0020</td>
<td>1.147 ± 0.0032</td>
<td>13.5 ± 0.481</td>
</tr>
<tr>
<td>1:3</td>
<td>34.89 ± 0.025</td>
<td>0.334 ± 0.0001</td>
<td>0.385 ± 0.0030</td>
<td>1.145 ± 0.0062</td>
<td>13.32 ± 0.808</td>
</tr>
<tr>
<td>1:4</td>
<td>35.25 ± 0.108</td>
<td>0.3716 ± 0.0002</td>
<td>0.402 ± 0.0591</td>
<td>1.168 ± 0.0076</td>
<td>14.83 ± 0.30</td>
</tr>
</tbody>
</table>

The bulk density of Curcumin Solid Dispersion prepared by using HPMC K 4M was found to increase in the ranges of 0.3643 ± 0.0007 to 0.3716 ± 0.0002 g/cc, tapped density of Curcumin Solid Dispersion prepared by using HPMC K 4M 0.418 ± 0.0025 to 0.402 ± 0.0591, Hausner’s ratio of Curcumin Solid Dispersion prepared by using HPMC K 4M 1.168 ± 0.0076 or less indicating passable flowability, Carr’s index of Curcumin Solid Dispersion prepared by using HPMC K 4M was found between 13.06 ± 0.520 to 14.83 ± 0.30 indicating passable flowability. The good flowability of the solid dispersion was also evidenced with angle of repose which increases to 32.56 ± 0.100° to 35.25 ± 0.108° indicating good flowability.

**Table 4 Flow properties of Solid Dispersion of Curcumin prepared by using HPMC K 15M**

<table>
<thead>
<tr>
<th>Ratio</th>
<th>Angle Of Repose (°)</th>
<th>Bulk Density (gm/cc)</th>
<th>Tapped Density (gm/cc)</th>
<th>Hausner’s Ratio</th>
<th>Carr’s Index (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:1</td>
<td>31.98 ± 0.295</td>
<td>0.3645 ± 0.0026</td>
<td>0.414 ± 0.0025</td>
<td>1.133 ± 0.0037</td>
<td>12 ± 0.10</td>
</tr>
<tr>
<td>1:2</td>
<td>33.14 ± 0.032</td>
<td>0.2767 ± 0.0020</td>
<td>0.318 ± 0.0015</td>
<td>1.149 ± 0.005</td>
<td>13.02 ± 0.083</td>
</tr>
<tr>
<td>1:3</td>
<td>33.86 ± 0.363</td>
<td>0.334 ± 0.0025</td>
<td>0.388 ± 0.0030</td>
<td>1.161 ± 0.0011</td>
<td>13.89 ± 0.083</td>
</tr>
<tr>
<td>1:4</td>
<td>35.11 ± 0.143</td>
<td>0.3712 ± 0.0020</td>
<td>0.432 ± 0.0015</td>
<td>1.163 ± 0.0044</td>
<td>14.07 ± 0.044</td>
</tr>
</tbody>
</table>

The bulk density of Curcumin Solid Dispersion prepared by using HPMC K 15M was found to increase in the ranges of 0.3645 ± 0.0026 to 0.3712 ± 0.0020 g/cc, tapped density of Curcumin Solid Dispersion prepared by using HPMC K 15M 0.414 ± 0.0025 to 0.432 ± 0.0015, Hausner’s ratio of Curcumin Solid Dispersion prepared by using HPMC K 15M 1.163 ± 0.0044 to 1.163 ± 0.0044.
± 0.004 or less indicating passable flowability, Carr’s index of Curcumin Solid Dispersion prepared by using HPMC K 15M was found between 12 ± 0.10 to 14.07 ± 0.044 indicating passable flowability. The good flowability of the solid dispersion was also evidenced with angle of repose which increases to 31.98 ± 0.295° to 35.11 ± 0.143° indicating good flowability.

Differentia Scanning Calorimetry (DSC)

Figure 6 shows the DSC curve of pure Curcumin. The endothermic peak of pure Curcumin was observed at 175.64°C.
Figure 7 shows the DSC curve of Solid Dispersion of Curcumin prepared using HPMC K 4M. The solid dispersion shows no endothermic peak of Curcumin. This might be due to encapsulation of Curcumin in HPMC K 4M by formulating Solid dispersion.

![DSC curve of Solid Dispersion using HPMC K 4M](image1)

**Fig 8 DSC of Solid Dispersion using HPMC K 15M**

Figure 8 shows the DSC curve of Solid Dispersion of Curcumin prepared using HPMC K 15M. The solid dispersion shows no endothermic peak of Curcumin. This might be due to encapsulation of Curcumin in HPMC K 15M by formulating Solid dispersion.

Fourier Transforms Infrared Spectroscopy (FTIR): FTIR spectroscopy was used to assess the interaction between hydrophilic polymer and Curcumin in the solid state, since upon complication, shifts or changes in the absorption spectrum may occur. The FTIR spectrographs of pure drug and solid dispersions prepared using HPMC K 15m and HPMC K4M was taken which indicated no interaction of Curcumin with polymers. From figure 9, 10 and 11 it was indicated that, there was no change or shift in peaks, indicating no interaction between Curcumin and polymers used in formulation of Solid Dispersion.

![FTIR spectrograph of pure drug and solid dispersions](image2)
Figure 9 shows the FTIR spectrographs of pure Curcumin. The chemical structure of Curcumin contains the functional group OH which is indicated by its peak at 3509.16 cm\(^{-1}\). It also contains the functional group C=O at 1615.75 cm\(^{-1}\). Peak at 1497.34 indicates the presence of aromatic C=C group.
Figure 10 shows the FTIR spectrographs of Curcumin Solid Dispersion prepared using HPMCK 4M. The chemical structure of Solid Dispersion contains the similar functional groups OH, C=O, C=C which is indicated by its peaks.

![FTIR of Solid Dispersion using HPMC K 15M](image)

**Fig 11 FTIR of Solid Dispersion using HPMC K 15M**

Figure 11 shows the FTIR spectrographs of Curcumin Solid Dispersion prepared using HPMCK 4M. The chemical structure of Solid Dispersion contains the similar functional groups OH, C=O, C=C which is indicated by its peaks.

**CONCLUSION**

HPMC K 4M and HPMC K15M can be used as potential hydrophilic carriers for the improvement of solubility of Curcumin. The solubility of Curcumin from solid dispersions prepared by HPMC K15M was found to be low when compared with solid dispersion prepared by HPMC K4M. The study concluded that the solid dispersion prepared by Solvent Change Precipitation method (SD 1:4 ratio of drug: HPMC K 4M) shows higher solubility rate compared with other formulations and pure drug. Thus, HPMC K 4M was found to be the superior hydrophilic carrier in curcumin to carrier ratio of 1:4 to prepare solid dispersion by Solvent Change Precipitation method, which was evidenced by solubility profile with the altered crystallinity which was manifested in DSC. The study result concluded that the Solvent Change Precipitation method is suitable for development of solid dispersions of
curcumin. It is, however, suggested that further research on large scale be carried out by using other hydrophilic carriers.

**ACKNOWLEDGEMENT**

First of all I would like to say thanks to my College Dr. Bhanuben Nanavati College of Pharmacy for helping throughout my research and the principal Dr. Mayur Yergeri for his constant support and guidance.

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