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Formulation and Evaluation of Hydrotropic Solid Dispersions of Curcumin

Krishna R Gupta*, Anita R Pounikar, Priyanka M Jaiswal and Milind J Umekar

Department of Pharmaceutical Chemistry, Smt. Kishoritai Bhoyar College of Pharmacy, New Kamptee, Nagpur, India

***Corresponding author:** Krishna R Gupta, Department of Pharmaceutical Chemistry, Smt. Kishoritai Bhoyar College of Pharmacy, New Kamptee, Nagpur, India, E-mail: krg1903@gmail.com

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Abstract

The hydrotropic solid dispersion may proper choice to preclude the use of organic solids so that simple, accurate and precise method could developed to enhance the solubility of poorly water soluble drugs. Solubility of curcumin is increased by using nicotinamide as a hydrotropic solid dispersing agent. Curcumin showed the maximum absorbance at 423 nm. At these wavelength, hydrotropic solid dispersing agent did not show any significant interference in the spectrophotometric study. The developed method were found to be linear in the range of 2-10 µg/ml with correlation coefficients (R) of 0.993. The developed method was validated according to ICH guidelines and values of accuracy, precision and other statistical parameters were found to be good in accordance with the prescribed values. As hydrotropic solid dispersing agent was used in the proposed method, the method can be said to be eco-friendly and it can be used to increase solubility of poorly soluble drugs.

Keywords: Curcumin; Nicotinamide; Hydrotropic solid dispersion formulation; Microscopic study

Introduction

The term hydrotropic agent was first introduced by Neuberg (1916), to designate anionic organic salts which, at high concentrations, considerably increase the aqueous solubility of poorly soluble solutes. The hydrotropic agents are defined as non-micelle-forming substances, either liquids or solids, organic or inorganic, capable of solubilizing insoluble compounds. Hydrotropic agents consist generally of two essential parts, an anionic group and hydrophobic aromatic ring or ring system [1].

The anionic group is important for high aqueous solubility, which is prerequisite for a hydrotropic substance. Also the planarity of the hydrophobic part has been emphasized as an important factor in the mechanism of hydrotropic solubilization. Hydrotropes commonly used includes sodium benzoate, sodium acetate, sodium salicylate, nicotinamide, urea, trisodium citrate, sodium ascorbate, piperazine, caffeine, potassium citrate etc. hydrotropic agents have been observed to enhance the solubility of various substances in water [2].

The powdered dry rhizome of the plant Curcuma longa, commonly called turmeric, is widely used as a colouring agent and spice in many food items. It contains wide variety of phytochemicals, including curcumin, demethoxycurcumin,

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bisdemethoxycurcumin, zingiberene, curcumenol, curcumol, eugenol, tetrahydrocurcumin, triethylcurcumin, turmerin, turmerones, and turmeronols. Curcumin is the phytochemical that gives a yellow colour to turmeric and is now recognized as being responsible for most of the therapeutic effects. Chemically described as-bis (4-hydroxy-3 methoxy phenyl)-1, 6 Heptadiene-3,5-dione, the aromatic ring systems, which are polyphenols are connected by two α, β-unsaturated carbonyl groups while the α, β-unsaturated carbonyl is a good Michael acceptor and undergoes nucleophilic addition. It is hydrophobic in nature and frequently soluble in acetone, ethanol, methanol, DMSO and oils [2].

Literature survey revealed that a variety of solubility enhancement methods viz. Complexation [3], Nano-particles formulation [4,5], Microencapsulation [6] Curcumine microparticales [7], Facile preparation [8] etc. but none of the methods were reported using hydrotropic solubilization for the curcumin, hence it was thought worthwhile to increase the solubility of curcumin by hydrotropic solid dispersion method (FIG. 1). The present study illustrate development and validation of simple, economical, selective, accurate, precise method for the solubility enhancement by using hydrotropic solid dispersion technique and validated as per ICH guidelines.

Structure of curcumin

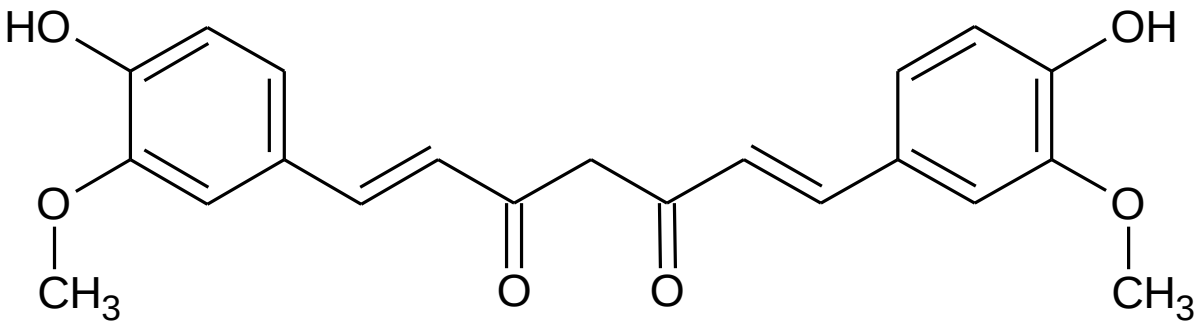


FIG. 1. **Structure of curcumin.**

Materials and Method

Chemicals and reagents

Curcumin was obtained as gift sample from protect laboratories, India. Nicotinamide, Sodium citrate, Sodium acetate, Sodium bicarbonate etc all hydrotropic agents used are of AR grade-LOBA Chemie Pvt. Ltd. (Mumbai, India) and distilled water used for the study.

Instrumentation

Jasco-UV module version V-630 series prominence JASCO UV was used for spectral measurements. Analytical balance-CONTECH, CAS-44 was used for weighing, Magnetic stirrer REMI BCMS-364 was used for stirring.

Selection of hydrotropic solid dispersion

Nicotinamide was used as a dispersing agent for enhancement of solubility of a drug. The selection was made after assessing the solubility in different hydrotropic solid dispersion like sodium acetate, sodium citrate, Sodium carbonate and Nicotinamide. Among these dispersion curcumin showed maximum solubility in Nicotinamide (TABLE 1).

TABLE 1. **Physico chemical properties of curcumin.**

Sr. No.	Physicochemical properties	Observation
1	Colour	Yellow
2	Odour	Characteristic
3	Nature	Amorphous
4	pH	7.45
5	Melting point	182°C-184°C

Method validation

The method was validated according to each guideline to study accuracy, linearity and precision [9,10].

Linearity: In order to find out linearity range of proposed UV-spectrophotometric method, studies were carried out by plotting absorbance of analyte against concentrations of the analyte.

Accuracy: Accuracy is expressed as the closeness of the results from standard samples to that of the actual known amounts to determine the accuracy of the proposed method, recovery studies were carried out by adding different amounts of bulk sample. The pre-analyzed formulation. The solutions were suitably diluted in the range and then each of the dilution was observed 6 times.

Precision: Precision is the level of repeatability of results as reported between samples analyzed on the same day (intra-day) and samples run on 3 different days (inter-day).

LOD: It is the lowest amount of analyte in a sample that can be detected but not necessarily quantities as an exact value under the stated, experimental conclusions. The detection limit is usually expressed as the concentration of analyte.

The standard deviation and response of the slope

LOD=3.3*standard deviation (σ)/s

LOQ: The quantitation limit of an analytical procedure is the lowest amount of an analyte in a sample which can be quantitatively determined with suitable precision and accuracy.

The standard deviation and response of the slope

LOQ=10*standard deviation (σ)/s

UV-Visible Spectophotometric Analysis

Preparation of calibration curve using methanol

For the selection of analytical wavelength 10 µg/ml solution of Curcumin in methanol was prepared by appropriate dilution of standard stock solution and scanned in the spectrum mode from 200 nm to 500 nm (FIG. 2). From the spectrum λmax of curcumin 423 nm was selected for the analysis. The calibration curve was prepared in concentration range of 2-10 µg/ml at 423 nm (TABLE 2).

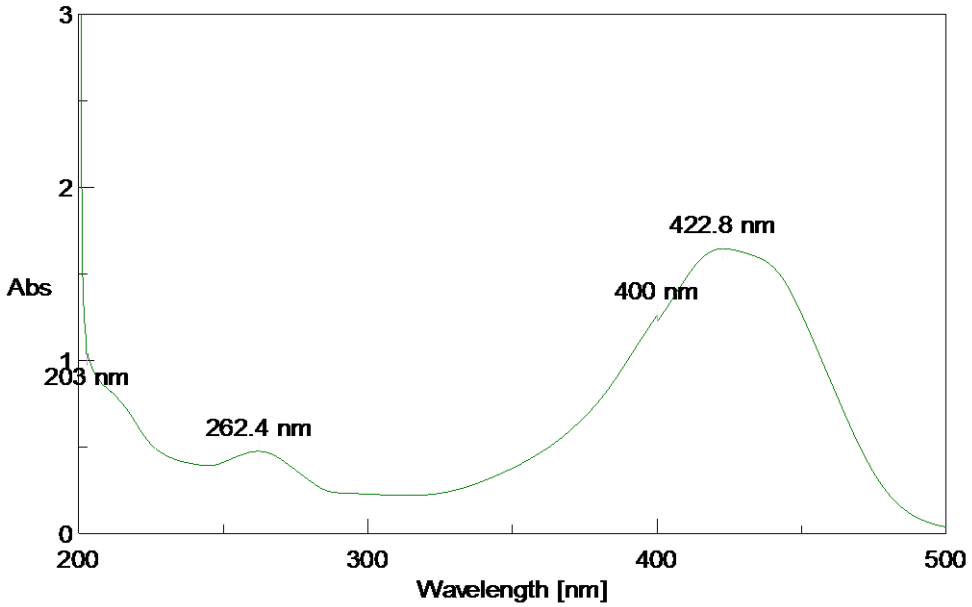


FIG. 2. **UV spectra of Curcumin in methanol.**

TABLE 2. **Observations of calibration curve.**

Sr No.	Concentrations (µg/ml)	Absorbance λ_{max}(423.0 nm)
1	2 µg	0.3976
2	4 µg	0.7070
3	6 µg	1.1134
4	8 µg	1.3675
5	10 µg	1.6476

A curve was plotted as absorbance vs. concentration and is shown in FIG. 3.

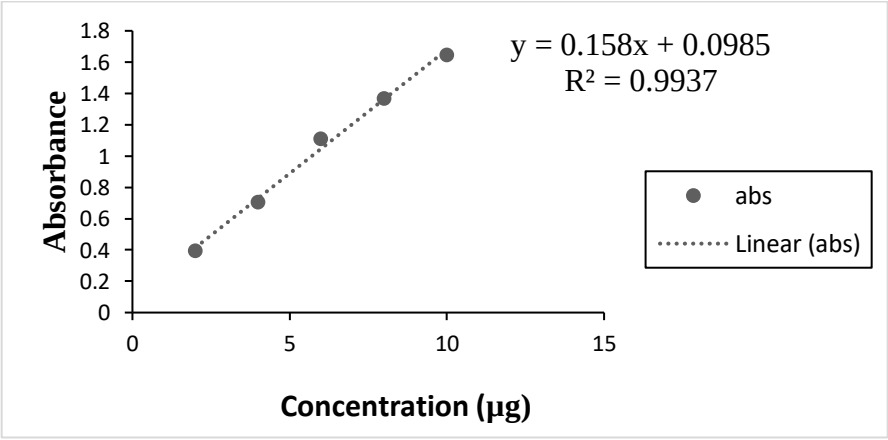


FIG. 3. **Calibration curve of Curcumin in methanol.**

Uv absorbance of curcumin in water

An accurately weighed quantity about 10 mg of Curcumin was dissolved in 25 ml distilled water. Further dilution to get 80 µg/ml (stock solution) scanned in the range 200 nm to 500 nm and absorbance taken at 423 nm (TABLE 3).

TABLE 3. **Absorbance in water.**

Sr. No.	Concentration (µg/ml)	Absorbance at 423 nm
1.	80 µg/ml	0.088 nm

Preparation of Hydrotropic Solid Dispersion

Sodium bicarbonate, sodium citrate and sodium acetate, nicotinamide were taken in molar (M) concentration as shown below in TABLE 4 and dissolved in 10 ml of distilled water. Heat the solution if necessary for making homogeneous mixture, up to 50-60°C. The solution was allowed to cool at room temperature. Then 0.1 M of Curcumin was added with continuous stirring. The above mixture was kept on magnetic stirrer for 24 h; filter the mixture, mass obtained was dried, collected and weighed. Similar procedure was followed for the preparation of solid dispersion of different concentrations.

TABLE 4. **Formulation of solid dispersion.**

Sr. No.	Hydrotropic agent	Drug
C1	Sodium acetate (1 M)	Curcumin (0.2 M)
C2	Sodium citrate (1 M)	Curcumin (0.2 M)
C3	Sodium bicarbonate (1 M)	Curcumin (0.2 M)
C4	Nicotinamide (1 M)	Curcumin (0.2 M)
C5	Nicotinamide (2 M)	Curcumin (0.2 M)
C6	Nicotinamide (1 M)	Curcumin (0.4 M)

Evaluation of Hydrotropic Solid Dispersion

Physicochemical properties

The physicochemical properties of the prepared hydrotropic solid dispersions were noted down and recorded in TABLE 5

TABLE 5. **Physicochemical properties of hydrotropic solid dispersion.**

Sr. No.	Colour	Weight(g)	Melting Point (°C)	pH
C1	Yellow	Not obtained	-	-
C2	Orange yellow	0.0403	186-188	7.0
C3	Yellow	Not obtained	-	-
C4	Yellow	0.3365	116-120	7.45
C5	Yellow	0.0492	192-194	7.0
C6	Yellow	0.0081	188-190	9.0

Saturation solubility

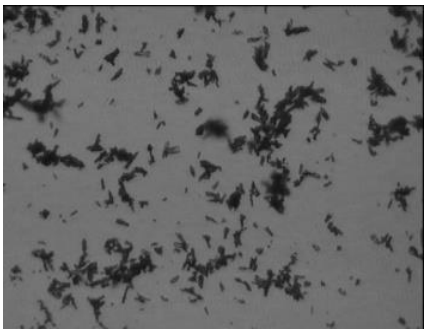
An accurately weighed quantity of pure Curcumin (25 mg) added to 25 ml hydrotropic agents solution and the mixture were allowed to stirred for 24 hours for solution gets saturated. The amount of curcumin solubilize in hydrotropic solution was estimated using UV spectrophotometric reading at 423 nm against blank (TABLE 6).

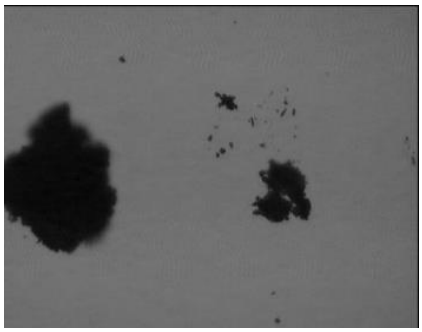
TABLE 6. **Saturation Solubility of hydrotropic solid dispersion.**

Sr.No.	Hydrotropic agent	Concentration of Hydrotropic agent	Absorbance at 423 nm	Concentration of Curcumin solubilized (g)
1.	Sodium acetate	2 M	0.2392	0.0135
2.	Sodium acetate	4 M	0.4665	0.0264
3.	Nicotinamide	2 M	2.5617	0.145

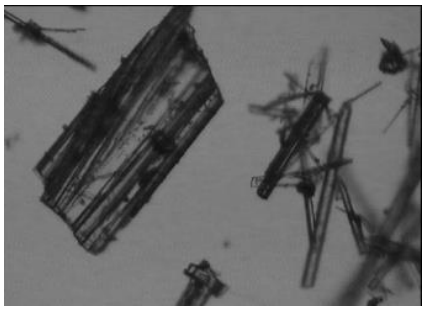
Motic microscopic evaluation

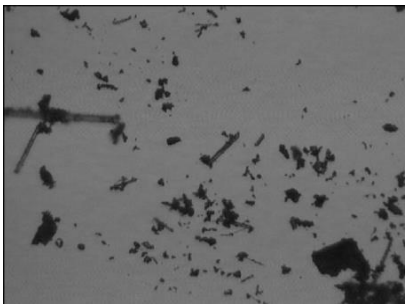
The captured motic microscopic images were displayed in FIG. 4.



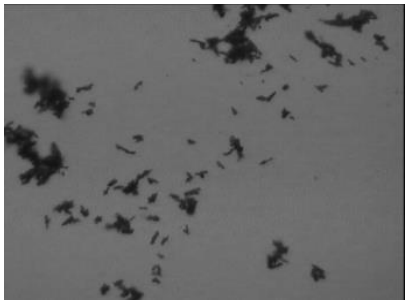


Pure curcumin C2. Sodium citrate: Curcumin (1 M: 0.2 M)





C4. Nicotinamide: Curcumin (1 M: 0.2 M) C5. Nicotinamide: Curcumin (2 M:0.2 M)



C6.Nicotinamide (1 M:0.4 M)

FIG. 4. **Motic microscopic images of prepared hydrotropic solid dispersion.**

Percentage yield

Weighed quantity of 1 M of Nicotinamide was dissolved in 10 ml of water and then 0.1 M of standard curcumin was added into it (TABLE 7).

TABLE 7. **Percentage yield of C4.**

Theoretical yield (M)	Practical yield (g)	% Practical yield
0.6055	0.3365	55.57%

Drug content

The drug content was evaluated by using UV spectrophotometer weighed quantity of solid dispersion was dissolved in 10 ml of water. From this 1 ml was pipette out and diluted with water up to 10 ml. Absorbance was noted down at 423 nm (TABLE 8).

The Drug content was calculated by using the equation:

$Cu=Au/As*Cs*d*V$

TABLE 8. **Drug content of C4 hydrotropic solid dispersion.**

Sr. No.	Weight of solid dispersion (mg)	Absorbance of Sample (C4)	Percent Estimation
1	10.1	0.0877	98.67
2	10.2	0.0881	98.15
3	10.4	0.0906	98.99
4	9.9	0.0877	100.66
5	10.2	0.0883	98.37
Mean			98.97
± SD			1.0016

Development of Ultraviolet Spectrophotometric Method

Accuracy

Accuracy of the proposed method was ascertained by taking curcumin dispersion alone because of poor solubility of curcumin. To analyze the concentration of curcumin 5 mg, 10 mg, 15 mg dispersion weighed and transferred to the volumetric flasks and volume made up to 10 ml with water. From above each solution 1 ml portion was pipette and diluted up to 10 ml with distill water.

Observation and Results

Observation and results of accuracy are given in TABLE 9.

TABLE 9. **Observation and results of Accuracy study.**

Sr. No.	Weight of solid dispersion taken (mg)	Absorbance Sample	Percent Recovery
1.	5.2	0.0457	99.87
2.	10.3	0.0899	99.18

3.	15.2	0.1354	101.23
Mean			100.09
± SD			1.0395

Precision

Precision of any analytical method is expressed as SD and RSD of series of measurement (TABLE 10). Precision of estimation by proposed method was ascertained by replicate analysis of homogeneous samples of Solid dispersion (TABLE 11).

TABLE 10. **Observation and results of Precision study.**

Sr. No.	Weight of solid dispersion (mg)	Absorbance of Sample (C4)	Percent Estimation
1	10.3	0.091	100.40
2		0.09	99.29
3		0.091	100.40
4		0.092	101.50
5		0.092	101.50
Mean			100.62
± SD			0.9230

TABLE 11. **Limit of detection and quantitation.**

Sr. No.	Limit	Result (µg)
1.	Limit of detection	0.3015
2.	Limit of quantitation	0.91366

Conclusion

The solid dispersions of Curcumin were developed using the concept of hydrotropic solubilization technique. Solid dispersions containing Nicotinamide as water-soluble carriers show more solubility; the quick onset of action and better extent of absorption is expected after oral administration of the HSDs. The curcumin hydrotropes prepared and validated as per ICH guidelines. The standard deviation and %RSD calculated for the methods are within the limits, indicating high

degree of precision of the methods. The results of the recovery studies performed indicate the proposed techniques can be said to be economical, convenient, and safe. It may be concluded that the proposed method of analysis is new, simple, cost-effective, environment-friendly, safe, accurate, and reproducible. The advantage is that the organic solvent is precluded, but not at the expense of accuracy. Definitely, there is further scope of these hydrotropes as solubilizing agent for the UV analysis of other poorly water soluble drugs. Hence we were successful in increasing the solubility of Curcumin, which will in turn increase its bioavailability possibly. These finding clearly implicates that the hydrotropic solid dispersion method modifies/interacts by weak binding with the chemical structure of Curcumin which possibly helps to increase its aqueous solubility.

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