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Formulation and Evaluation of Solid Dispersion of Chrysin for Improved Bioavailability

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ABSTRACT

The objective of the present study was to prepared solid dispersion of chrysin for improving its aqueous solubility and in turn its oral bioavailability. I-opitmal design approach was used for preparing the solid dispersion of chrysin. A total of eight formulations were prepared using four different ratios of drug to carrier. Mannitol and PVP-K30 were used as the two different carriers to improve the solubility of chrysin by formulating SD using solvent evaporation method employing ethanol as the common solvent for the drug and the carrier. The solubility study of chrysin was performed in distilled water and was found to be 3.7 µg/mL. The particles were irregular to spherical in shape and the average particle size ranged from 34.90-38.09 µm for the particles. The yield of the SD was highest for F5 (93.2%) and least for F8 (91.14%). For all the formulations the yield was nevertheless higher than 90% suggesting a proper binary mixture formation. The drug content was found to be highest in the formulation SD4 (94.23 ± 0.351 %) and the lowest in formulation SD5 (91.18 ± 0.251 %).

Key words: Solid dispersion, chrysin, mannitol, PVP K30, solvent evaporation

1. INTRODUCTION

Absorption of drug and its therapeutic effectiveness get affected by solubility which is a significant physicochemical factor.[1] Poor aqueous solubility can lead to failure in formulation development process. The main reason behind inadequate bioavailability of drug is its low dissolution rate and low solubility in aqueous medium.[2] Therefore, to progress bioavailability of poorly water-soluble compounds like biopharmaceutical classification system class II and IV drugs, polymer matrix of various origin can be used. Various solubility enhancement methods have been introduced to triumph over this problem.[3,4]

The enhancement of oral bioavailability of poorly water-soluble drugs remains one of the most challenging aspects of drug development. The most commonly used techniques to increase dissolution rate are particle size reduction, salt formation and lyophilization, but all these methods have practical limitations like improper enhancement of solubility and all the drugs are not suitable for these techniques. To overcome all these, solid dispersion approach is successfully applied to improve the solubility and dissolution rate, there by bioavailability.[5]

Chrysin is a poorly water soluble phytoconstituent depicting solubility of just 3.03 µg/ml in water. The poor water solubility limits the use of this flavone despite having tremendous pharmacological potential.[6,7] Solid dispersion have been widely studied for improving solubility and in turn the bioavailability of hydrophobic molecules.[8-14] Hence it was envisioned to improve the aqueous solubility of chrysin by formulating it as solid dispersion using polymers like PVP K30 or Pluronic. The aim of this present investigation is to enhance solubility of chrysin by formulating as solid dispersions.

2. MATERIAL AND METHODS

2.1 Standard Curve for Chrysin

Chrysin 25 mg was weighed and dissolved in methanol in a 25 ml volumetric flask. The flask was shaken and volume was made up to the mark with methanol to give a solution containing 1000 µg/ml. From this primary stock solution, pipette out 2 ml and place into 100 ml volumetric flask. The volume was made up to mark with methanol to give a stock solution containing 20 µg/mL.

Appropriate volume of aliquots (1 to 10 ml) from chrysin secondary stock solution were transferred to different volumetric flasks of 10 ml capacity. The volume was adjusted to the mark with methanol to obtain concentrations of 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20 µg/mL. Absorbance of each solution against methanol as blank were measured at 212 nm.

2.2 Preparation of Solid Dispersion of Chrysin

The solid dispersion of chrysin was prepared using previously reported procedure to improve the solubility of the drug.[15,16] Briefly, 100 mg of chrysin was precisely weighed and placed in tared beaker. To this was added the required quantity of Mannitol or PVP-K30 and the solids were mixed thoroughly (Table 1). Ethanol (20 mL) was added to this mixture with stirring to dissolve the components and the components were stirred further for 10 min. The contents were poured in a petridish and the solvent was allowed to evaporate under mild heat (40°C). The residue left behind in the petridish was collected, dried properly, pulverized and sifted through sieve no. 80.

Table 1: Formulation table

Formulation Code	Chrysin (mg)	Mannitol (mg)	PVP-K30 (mg)
F1	100	100	-
F2	100	200	-
F3	100	300	-
F4	100	400	-
F5	100	-	100
F6	100	-	200
F7	100	-	300
F8	100	-	400

2.3 Solubility Analysis of Chrysin

25 mg of powdered chrysin was weighed and added into 25 mL of volumetric flask and the volume was made up to the mark with distilled water. The solution mixture was sonicated for 1h and a measured quantity of the solution was then filtered and the absorbance was taken.[17] The solubility was then calculated using the calibration curve.

2.4 Evaluation of Chrysin SD

2.4.1 Drug Content of Solid Dispersion

An accurately weighed 10 mg of the SD was taken in a 25mL volumetric flask and dissolved in methanol by sonication for 15 min. The volume was made up to the mark with methanol. A portion of the above solution was withdrawn and centrifuged for 10 min. 5 mL of the supernatant was suitably diluted and analyzed spectrophotometrically at 212 nm.

2.4.2 Solubility Study

An excess amount of the SD was transferred to stoppered Erlenmeyer flask and 25 mL of phosphate buffer pH 7.4 was added to it. The mixture was sonicated for 1 h and 2 mL of the solution was withdrawn, filtered through Whatman filter paper no. 40 and analyzed spectrophotometrically at 212 nm after appropriate dilution.

2.4.3 Dissolution Study

Accurately weighed formulation from each batch, equivalent to 25 mg of chrysin was added to 900 ml of dissolution media (phosphate buffer, pH 7.4) contained in USP dissolution apparatus II (Paddle type) and stirred at a speed of 50 rpm at 37 ± 0.5°C. 5 mL of sample were withdrawn at 5, 10, 15, 20 and 30 min and the medium was enriched with 5 ml of fresh dissolution media (37°C). The collected samples were analyzed after suitable dilution at 212 nm using UV-visible spectrophotometer against the phosphate buffer, pH 7.4 as blank. The dissolution of pure chrysin was studied similarly. The dissolution efficiency of SD at 15 min was determined from the release data.

2.5 DSC Study of Solid Dispersion

The thermal analysis of the formulated SD was done by differential scanning calorimetry. The SD was placed in the sample pan and introduced in the sample cavity of the instrument. The sample was gradually heated electrically from 30°C to 300°C and the changes in the thermogram were recorded.

2.6 X-ray Diffraction Study

The sample of chrysin and the solid dispersion were subjected to x-ray diffraction analysis in order to ascertain the crystalline form of the solid dispersion.

2.7 Particle Size of SD

SD particles are observed under microscope using calibrated ocular micrometer (ERMA) to calculate the average particle size of the solid dispersion. SD was dispersed in water and a drop of the dispersion was placed on glass slide and viewed under microscope. The number of divisions of ocular micrometer occupied by particles was counted.

2.8 Stability Study

The solid dispersion kept under accelerated conditions (4°C, RT and 40°C) for stability study in a stability oven for three months. At the end of the third month, the drug content in the solution under each storage condition was determined to assess the stability of the solid dispersion.

3. RESULTS AND DISCUSSION

3.1 Calibration Curve

The calibration curve of chyrsin was prepared according to the reported procedure using methanol as the solvent. The absorbance observed was plotted against the standard strength to obtain calibration curve along with the equation for straight line (Figure 1).

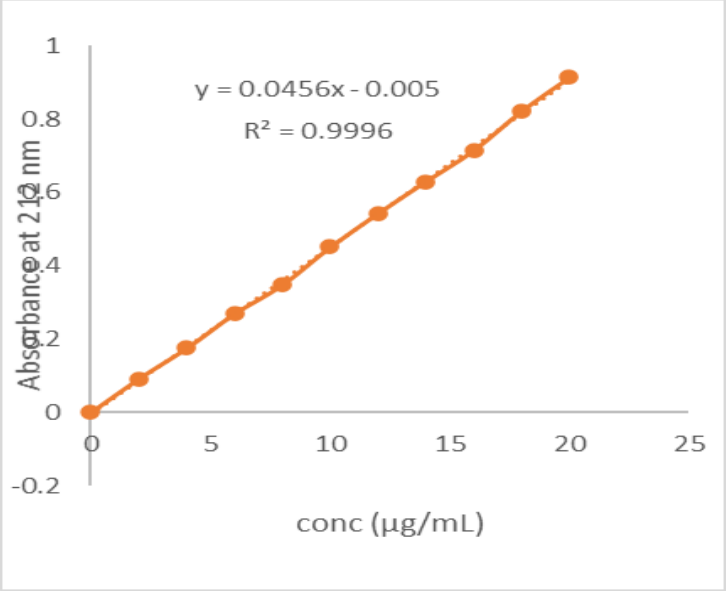

Figure 1: Calibration curve of chrysin

3.2 FT-IR Study

The FT-IR spectrum of chrysin and a physical mixture of chrysin was studied for characteristic stretching and bending vibrations occurring from the vibration of function groups and bonds. The spectrum of chrysin exhibited vibrations of C-O-C, C=O, O-H, C=C, C-H at 1020-1395 cm-1, 1740 cm-1, 3619-3743 cm-1, 1426-1547 cm-1, and 2879 cm-1 respectively (Figure 2).

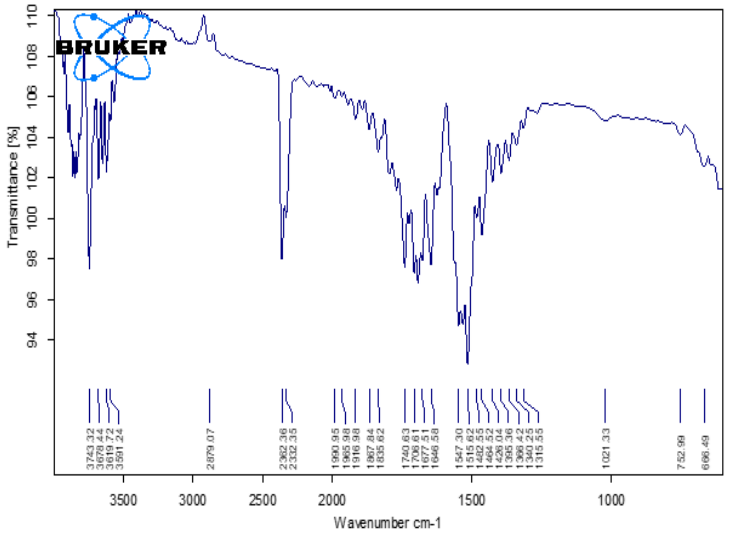

Figure 2: FT-IR Spectrum of chrysin

All the vibrations of chrysin were present in the physical mixture with mannitol (Figure 3) and PVP-K30 (Figure 4) suggesting that the drug was compatible with the components used for preparation of the solid dispersion.

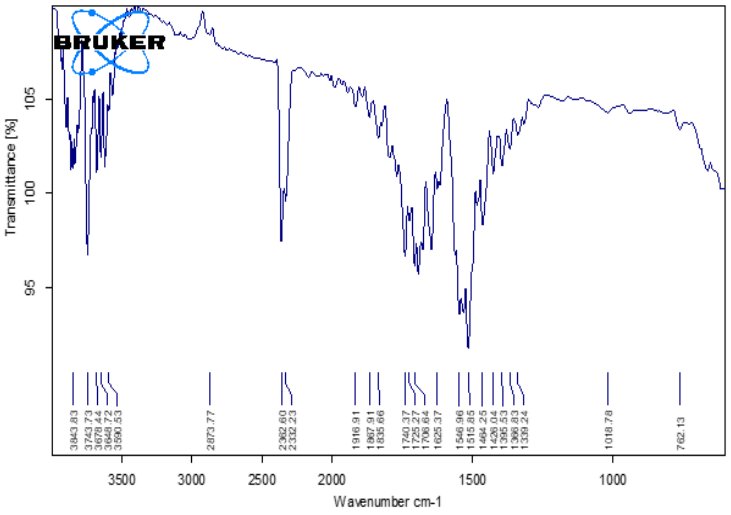

Figure 3: FT-IR spectrum of physical mixture of chyrsin and mannitol

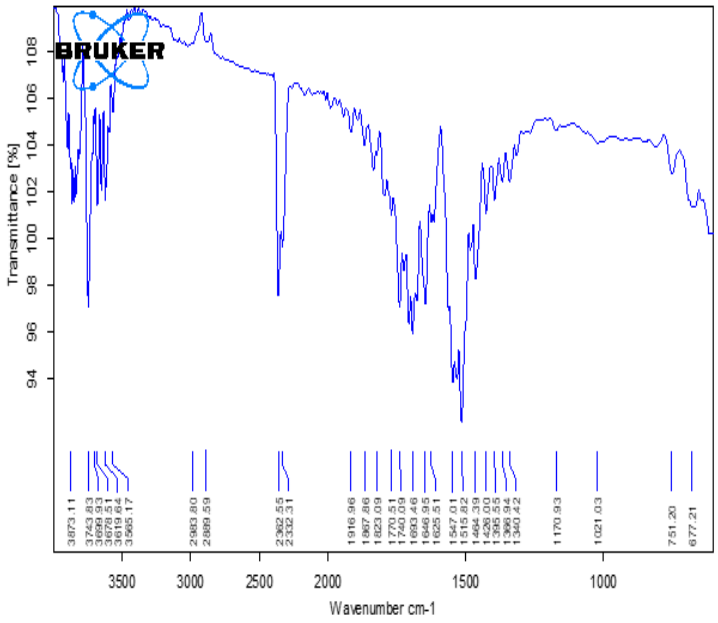

Figure 4: FT-IR spectrum of physical mixture of chyrsin and PVP-K30

3.3 Preparation of Solid Dispersion

I-opitmal design approach was used for preparing the solid dispersion of chrysin. A total of eight formulations were prepared using four different ratios of drug to carrier. Mannitol and PVP-K30 were used as the two different carriers to improve the solubility of chrysin by formulating SD. The SD were prepared using solvent evaporation method employing ethanol as the common solvent for the drug and the carrier. Solubilizing the drug and carriers in the solvent and evaporating the solvent resulted in the formation of SD with completing incorporation of the drug and carrier in each other.

3.4 Solubility of Chrysin

The solubility study of chrysin was performed in distilled water and the amount of drug solubilized was calculated by the calibration curve equation. It was found that only 3.7 µg drug was soluble in per ml of water.

3.5 Particle Size of SD

A calibrated ocular micrometer was used to measure the size of the SD particles under a microscope equipped with image analyzer. The particles were irregular to spherical in shape and the average particle size ranged from 34.90-38.09 µm for the particles. The particularly stable size was obtained as all the particles were finally passed through sieve of 100 mesh.

3.6 Yield of SD

The yield of the SD was highest for F5 (93.2%) and least for F8 (91.14%). For all the formulations the yield was nevertheless higher than 90% suggesting a proper binary mixture formation (Table 2).

Table 2: Yield and drug content in solid dispersion

Formulation	Weight of SD (g)	% Yield	Drug content (%)
F1	183.2	91.6	92.20 ± 0.321
F2	278.1	92.7	92.46 ± 0.404
F3	369.2	92.3	93.43 ± 0.251
F4	457.5	91.5	94.23 ± 0.351
F5	186.4	93.2	91.18 ± 0.251
F6	277.2	92.4	91.96 ± 0.543
F7	367.2	91.8	92.41 ± 0.327
F8	455.5	91.1	93.16 ± 0.211

3.7 Drug Content in SD

The drug content of the solid dispersion was evaluated in order to ascertain that each portion of the SD contained the same quantity of the drug. The drug content was found to be highest in the formulation SD4 (94.23 ± 0.351 %) and the lowest in formulation SD5 (91.18 ± 0.251 %).

3.8 Solubility Study of Chrysin in SD

The aqueous solubility of chrysin in the solid dispersion was studied by sonication method. It was found that all the formulations were able to significantly improve the aqueous solubility of chrysin (Table 3). The concentration of chrysin in solution was calculated using the calibration curve.

Table 3: Solubility of chrysin in aqueous media

Formulation	Solubility (µg/mL)	% increase	Times Increased
Chrysin	3.7	-	-
F1	4.2	13.51	1.13
F2	5.9	59.45	1.59
F3	8.4	127.02	2.27
F4	11.1	200	3
F5	4.1	10.81	1.10
F6	5.6	51.35	1.51
F7	7.9	113.51	2.13
F8	10.5	183.78	2.83

As visible from the results, mannitol was found to more significant in improving solubility compared to PVP-K30 carrier. Increasing the concentration of the carrier was able to improve the solubility. The increase in solubility ranged from 10.81 to 200.0% amounting to 1.10 to 3.0 times increase in aqueous solubility.

It was also evident that a 1:1 ratio of drug and carrier was not much effective in increasing solubility (13.51 % for F1 and 10.81% for F5). On the other hand, increasing the ratio to 1:2 and higher was able to tremendously increase the solubility of chrysin.

3.9 Dissolution Study of Chrysin for SD

The dissolution (drug release) of chrysin from the SD was studied using USP type II dissolution apparatus and the percent cumulative drug release at 15 min was considered as the criterion for selection of the best SD formulation (Figure 5).

As drug dissolution at 15 min was selected as the criteria for optimization of the independent variables (D:P ratio and polymer type), it was found that F4 containing 1:4 ratio of chrysin to mannitol was the best formulation of all with 46.16 ± 1.167 % drug release after 15 min and around 80% drug released at 30 min.

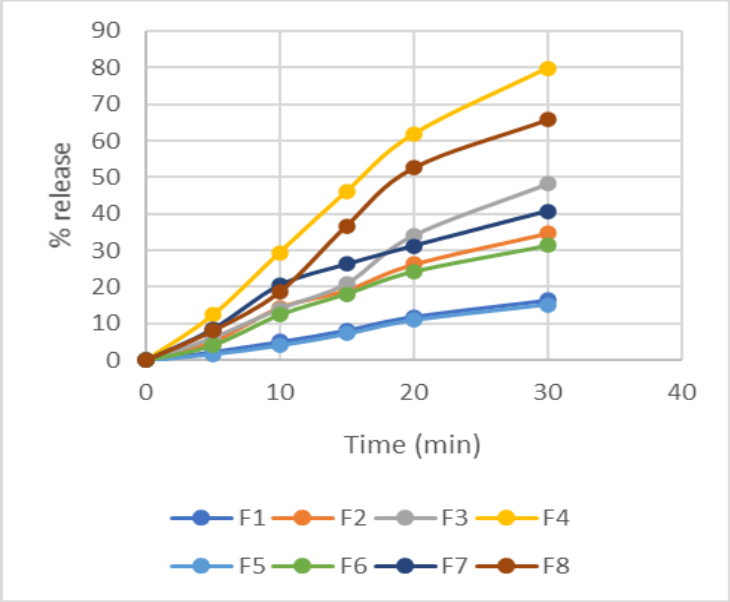

Figure 5: Cumulative release of chrysin from SD

3.10 Stability Study

The stability of SD was assessed at accelerated conditions of storage and the drug content was estimated at the end of three months of study (Table 4).

Table 4: Drug content in stability samples

Storage condition	Drug content (%)							
	F1	F2	F3	F4	F5	F6	F7	F8
4°C	92.16	92.34	93.11	94.01	91.1	91.8	92.25	92.97
RT	92.08	92.11	92.75	93.86	90.94	91.62	91.97	92.74
40°C	91.95	91.94	92.42	93.54	90.71	91.41	91.63	92.45

4. CONCLUSION

In the present study, chrysin, a flavanol with potential antioxidant action, was formulated as solid dispersion with an objective to improve its aqueous solubility. The improved/enhanced aqueous solubility in turn is known to improve the oral bioavailability of drugs. The solid dispersion formulation was effectively and in high yield, incorporating good amount of drug, obtained using mannitol PVP-K30 as the carrier and solvent evaporation method. The SD were able to increase the solubility of chrysin from 1.10 to 3.0 times. This suggests that formulating chrysin in SD improves the solubility and in turn is expected to improve bioavailability of chrysin, making it suitable to be effectively absorbed from nutraceutical formulations.

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