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Original Article

Design and Characterization of Microwave Irradiation Assisted Amorphous Solid Dispersion of Resveratrol

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ABSTRACT

Background: One of the emerging solutions for facing the solubility as well as dissolution issues of poorly soluble drugs is formulation approach by dispersing drugs in hydrophilic carriers. **Objectives:** Present study aims in enhancing the solubility of resveratrol by amorphous solid dispersion technique. **Materials and Methods:** Solid dispersions were prepared by microwave irradiation where the irradiation time and the drug: carrier ratios were optimized using Design of Experiments by the effect of these critical parameters on solubility as a response variable. **Results and Discussion:** Solubility of the fabricated amorphous solid dispersions were analyzed and optimized at 1:5 drug: carrier ratio with an irradiation time of 5 min. Different characterization techniques like infrared spectroscopy, particle size, differential scanning calorimetry etc., were performed in order to study and prove the process of amorphization. The results of powder X-ray diffraction studies, scanning electron microscopic studies certainly highlighted the conversion of crystalline form of resveratrol into an amorphous form along with reduced particle size of 41 times in solid dispersion than that of pure resveratrol. **Conclusion:** With the present work, it can be concluded that microwave irradiation is an absolute approach in preparation of amorphous solid dispersions.

Keywords: Microwave irradiation, Amorphous solid dispersion, Resveratrol, Soluplus, Design Expert, Solubility enhancement.

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INTRODUCTION

Many drugs have poor absorption because of low solubility and are usually better absorbed in upper parts of small intestine.[1] Because of the poor solubility and less dissolution rate of BCS class II and class IV drugs, dissolution is the parameter which becomes a challenging task during formulation of a dosage form.[2] Conversion of drugs into solid dispersions by the aid of inert carriers is a promising technique which is easily manufacturable and feasible in order to address the poor solubility problem with practically insoluble or very slightly soluble drugs.[1] Solid dispersions are mixture of two components which are mostly a hydrophilic polymer matrix with one or more hydrophobic drugs. Formulation of solid dispersions of poorly soluble drugs is one of the methods of choice to improve solubility even at industrial level.[3] In an amorphous solid dispersion, the drug usually gets miscible with the polymer at a molecular level resulting in enhancing dissolution or absorption compared to crystalline form of the drug.[4]

Amorphous stabilized approaches increase the solubility of bioactive and actives by overcoming the crystal lattice energy yielding a non-crystalline, amorphous form which is thermodynamically metastable than the crystalline form resulting in enhancement of both solubility and bioavailability.[5] Various methods used for manufacturing of Amorphous Solid Dispersions (ASDs) include: simple fusion; hot melt extrusion; electrospinning; microwave irradiation; solvent methods like solvent evaporation, spray drying, freeze drying, supercritical fluid etc; hot melt encapsulation; melt agglomeration; vacuum drying and rotary evaporation.[6,7] Use of hydrophilic polymers as carriers during dispersions prevents recrystallization of drugs in amorphous solid dispersions as they are supersaturated. So, wise selection of carrier is needed in order to prepare effective amorphous solid dispersions.[1]

Various carriers that can be employed in fabrication of amorphous solid dispersions include synthetic polymers (PVP, PVP-VA, PVA etc.,) natural polymers (HPMC, HPC, HPMCP, HPMC-AS etc.,) and other naturally occurring dispersants (corn starch, trehalose, inulin etc.,).[8] Soluplus® is one of the carrier/polymers that is extensively being studied for its solubility enhancing as well as matrix forming ability.[9] Soluplus chemically is a graft co-polymer of polyvinyl caprolactam-PVA-PEG. Soluplus is a feasible

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polymer to hold a hydrophobic drug as it contains a lipophilic core.[10] Other carriers that are widely used in the preparation of solid dispersions include polyvinylpyrrolidone, poloxamer 407 i.e., Pluronic® which is a non-ionic block copolymer of polyoxyethylene-polyoxypropylene having solubilizing effect.[11] The drawback of amorphous forms is that they are thermodynamically unstable when compared to crystalline forms and so they are converted into amorphous solid dispersions which are stable because of polymer systems employed during their fabrication.[12] Thermodynamic solubility (which states the amount of the drug substance dissolves) have a significant role in determining solubility of poorly soluble compounds as well as plays a key role in dissolution of the drug.[3]

Amorphization of certain drugs by various techniques including microwave irradiation have physical instability issue because of the nature of drug and polymers employed. The drug will recrystallize which can be overcome by in situ amorphization technique where the drug will be formulated as such in crystalline form and the formulation before administration (may be hours, days or weeks if travelling) will be amorphized in situ. It helps in conversion of drug in crystalline nature into amorphous form with no physical stability issues throughout the shelf-life period. For few drugs like tibolone, microwave irradiation of its physical mixture even though didn't change the crystalline nature of drug into amorphous form, still resulted in reduced particle size which enhanced dissolution than that of solid dispersions containing larger crystalline particles of drug that are prepared by conventional methods.[13]

Employing higher concentrations of carriers during preparation of solid dispersions makes it easy to formulate and when microwave irradiation method is employed, as the waves penetrate through the samples, there will be better contact and interaction between the drug and carrier polymers. Adding poloxamer as an aid helps in enhancing solubility providing synergistic effect by expediting the release. Because of hydrophilic nature on the surface of the carrier, they get in contact rapidly with the dissolution medium and resulting in better drug release from the dispersions than from the pure drug. Microwave irradiation results in collisions between the molecules producing molecular movement at faster rate and helps in amorphization of drug.[1]

Resveratrol is one of the widely used polyphenolic phytochemicals that is synthesized by various plants and is usually found naturally in berries, grapes etc. It possesses several properties and is able to exhibit anti-oxidant, cardioprotective, anti-inflammatory activities along with improvement of cognitive behaviour.[14] Various studies reported poor solubility of resveratrol along with confirmation of its poor bioavailability; which encouraged in developing drug delivery systems of resveratrol with enhanced solubility and bioavailability.[15] The present study focussed on solubility enhancement of resveratrol using hydrophilic carrier by amorphous solid dispersion approach using microwave irradiation technique. Fabrication and development of amorphous solid dispersions was optimized for irradiation time and amount of carrier by Design of Experiment (Design-Expert) software.

MATERIALS AND METHODS

Materials

Resveratrol was used as model compound which was purchased from Herbo Nutra Extracts Pvt. Ltd., Polymers were obtained as gift samples from BASF and Evonik, all the other chemicals used were of high-grade purity.

Methods

UV-visible spectrophotometric method

Primary stock solution of concentration 1 mg/mL i.e., 1000 µg/mL was made by dissolving 10 mg of pure resveratrol in 10 mL of ethanol. Then a secondary stock solution of concentration 100 µg/mL was made by taking 1 mL of primary stock solution and making up to 10 mL using respective buffer solution (hydrochloric acid buffer pH 1.2 or acetate buffer pH 4.5 or phosphate buffer pH 6.8 or phosphate buffer pH 7.4 or distilled water). Absorption maximum was observed by scanning the solutions of concentration 100 µg/mL (i.e., secondary stock solution) from 800 nm to 200 nm and the spectrum was recorded. 0.1, 0.2, 0.3, 0.4 and 0.5 mL of secondary stock solution was pipetted out into volumetric flasks and solutions of concentrations 1, 2, 3, 4, 5 µg/mL respectively and by making up the volume to 10 mL using various buffers and distilled water, solutions were prepared, absorbances were recorded at respective absorption maxima and calibration of resveratrol was carried out.[16]

Solubility study

Solubility studies of pure resveratrol and fabricated amorphous solid dispersions were carried out by equilibrium solubility studies as per WHO protocol. The highest therapeutic dose of the drug must be dissolved or mixed with 250 mL of respective solvent or the buffer system. The highest dose of resveratrol is 1000 mg. An equivalent dose was maintained by adding 100 mg of pure resveratrol into 25 mL of buffer (in triplicate). The solubility studies were carried out by constant stirring of the solution for 24 hr using rotary shaker and the solution was filtered using Whatman filter paper and the filtrate was analyzed using UV spectrophotometer against buffer as blank at respective absorption maxima (λ_{max}). The procedure was carried out using hydrochloric acid buffer, acetate buffer, two phosphate buffers of pH 1.2, 4.5, 6.8, 7.4 respectively and in distilled water. Similarly, 10 mg resveratrol equivalent dose of solid dispersion was added into 2.5 mL of distilled water (in triplicate) and after 24 hr shaking, solubility was analyzed using spectroscopic method developed earlier.[17]

Experimental Design

Selection of carrier

In order to narrow down the tedious process of analyzing the solubility of individual physical mixtures and to know about the feasibility with the polymer, a quick profiling of solubility study by taking different ratios of bioactive:carrier (1:1, 1:3, 1:5 and 1:10) using different polymers like soluplus, eudragit L100-55, eudragit RS100, kolliphor P188G, kolliphor P407G, kollidon 90F, kollidon VA64, crospovidone XL10, PVP K30 and betadex was done along with pure active in order to mimic the conditions of solubility testing studies. The physical mixtures were taken and mixed with respective solvent, followed by sonication for 30 min. The volume of solvent taken was according to equilibrium solubility protocol as per WHO. The solutions were filtered using whatmann filter paper and the filtrate (diluted if necessary) was analyzed using UV-visible spectrophotometer and thermodynamic solubilities were determined in distilled water, hydrochloric acid buffer pH 1.2, acetate buffer pH 4.5, phosphate buffers pH 6.8 and 7.4.[17,18]

Formulation and optimization by DoE

The concentration/amount of drug in the prepared solid dispersions was kept constant (1 part) and the amount of the carrier was varied from 1 to 10 parts (1, 5 and 10). Based on the review of literature and preliminary studies, two critical parameters i.e., drug: carrier ratio (1:1 to 1:10) and microwave irradiation time (5 min-15 min) were chosen for the study. A full factorial design with two factors at three levels i.e., 3^2 factorial design was selected and a total of 9 experiments were performed. Solubility (mg/mL) was selected as response which is Critical Quality Attribute (CQA) for the DoE design.[12] The design space is shown in Table 1.

Preparation of ASDs

Microwave irradiated amorphous solid dispersions were prepared in different ratios of resveratrol to soluplus.[12,19] Physical mixtures of different mass ratios were taken into microwave safe container and subjected to microwave irradiation at 900 W power in a microwave oven (Morphy Richards Model 27CGF). Only one sample was irradiated at a time with varying time intervals. The obtained product after irradiation was pulverized, sieved using 60# and stored for further studies.

Resveratrol and soluplus were mixed in different ratios according to the DoE design. Amorphous solid dispersions were fabricated with varying drug (resveratrol): carrier (soluplus) ratios like 1:1, 1:5 and 1:10 for different time intervals like 5 min, 10 min and 15 min according to the runs provided in the design using Design Expert 13 trial version.

Preparation of physical mixture

The physical mixture of resveratrol with soluplus with same ratio as that of optimized formulation was prepared to evaluate various parameters and to compare with that of microwave irradiated amorphous solid dispersion. Accurately weighed drug and carrier were taken in a mortar, triturated thoroughly, sieved using 60# and stored for further analysis.[1]

Fourier Transform Infrared spectroscopic studies (FTIR)

FTIR spectra of pure resveratrol, soluplus, Resveratrol-Soluplus Physical Mixture (R-S PM) and optimized formulation i.e., Resveratrol-Soluplus Microwave Irradiated Solid Dispersion (R-S MISD) were obtained using Attenuated Total Reflectance (ATR) module of infrared spectrophotometer (ATR-FTIR, Shimadzu, IRSpirit). Then the spectra were recorded over the range of 4000 cm^{-1} to 650 cm^{-1}.[1,20]

Differential Scanning Calorimetry (DSC) studies

DSC studies of pure resveratrol, soluplus, physical mixture i.e., R-S PM and optimized formulation i.e., R-S MISD were carried out using DSC calorimeter (Shimadzu, DSC 60 Plus) to study the thermal behaviour of samples. Empty pan was used as a reference and all the samples of 3-5 mg each were packed in individual aluminium pans and were scanned at the rate of 10°C/ min in the range of 30°C to 300°C under nitrogen atmosphere.[1,15,21]

Table 1: 3^2 factorial design space and effect of critical parameters on solubility.

Run #	A: Drug: Carrier (ratio)	B: MI time (min)	R1: Solubility (mg/mL)
1	1	5	0.697
2	5	10	2.613
3	5	5	2.759
4	10	5	2.751
5	1	10	0.589
6	5	15	2.589
7	1	15	0.594
8	10	10	2.335
9	10	15	1.905

Particle size

The average particle size and Polydispersity Index (PDI) of pure resveratrol, soluplus, resveratrol-soluplus physical mixture and optimized formulation of resveratrol-soluplus MISD were determined by Dynamic Light Scattering (DLS) method using LABINDIA Nano Plus particle size analyzer.[10]

Field Emission Scanning Electron Microscopy (FESEM) studies

Surface morphology of pure resveratrol, soluplus, R-S PM and R-S MISD were studied using scanning electron microscope (FEI, QUANTA FEG 250). The samples were subjected to sputter coating with gold and palladium alloy prior to analysis in order to make samples conductive and the images were observed at 10 kV accelerated voltage.[1]

Powder X-ray Diffraction (XRD) analysis

Powder XRD analysis of pure drug, carrier, physical mixture and optimized amorphous solid dispersion were carried out to know about the crystallinity of the samples. XRD analysis was performed using BRUKER D8 Advance diffractometer using Cu radiation (λ=1.54 A°) at a voltage of 40 kV and a current of 40 mA from 2° to 50° 2θ angle at a rate of 2°/min with a step size of 0.02° and counting time of 0.5 s/step.[1,12,13]

Statistical analysis

Design Expert software trial version 13 was used for optimization of amorphous solid dispersions. ANOVA and numerical as well as graphical optimization were done in order to know the effect of independent variables on solubility. Data was expressed as Mean±S.D. for three different experiments. $p<0.05$ was considered to be statistically significant.[1,10]

RESULTS AND DISCUSSION

UV-visible spectrophotometric method

Absorption maxima of resveratrol was found to be at 312 nm in hydrochloric acid buffer pH 1.2; at 312 nm in acetate buffer pH 4.5; at 306 nm in phosphate buffer pH 6.8; at 312 nm in phosphate buffer pH 7.4 and 304 nm in distilled water. Standard calibration was performed for resveratrol in various buffers i.e., hydrochloric acid buffer pH 1.2, acetate buffer pH 4.5, phosphate buffer pH 6.8, phosphate buffer pH 7.4 and distilled water and were found to be linear in the Beer's range of 1-5 µg/mL and the calibration curve was shown in Figure 1.

Solubility Studies

Solubilities of resveratrol in various buffers and distilled water were determined and found to be 28.5431 ± 2.3361 µg/ml in pH 1.2 buffer, 17.0420 ± 3.7605 µg/ml in pH 4.5 acetate buffer, 29.3447 ± 7.4727 µg/ml and 28.6149 ± 8.4940 µg/ml in pH 6.8 and 7.4 buffers respectively, and 52.6606 ± 4.0960 µg/ml in distilled water. Resveratrol was found to be more soluble in distilled water which is 0.053 mg/mL. As solubility of resveratrol is high in distilled water, further solubility studies of amorphous solid dispersions were carried out in distilled water.

Selection of carrier

Solubility studies of physical mixtures of resveratrol using various carriers in different ratios were carried out and the samples were analysed in hydrochloric acid buffer pH 1.2 and acetate buffer pH 4.5 and phosphate buffer pH 7.4 at 312nm; phosphate buffer pH 6.8 at 306nm; distilled water at 304nm respectively.

Based on the values, the carriers with following ratios were selected for studies:
Resveratrol 1:5 Soluplus,
Resveratrol 1:5 Kolliphor P188G,
Resveratrol 1:3 Kolliphor P407G,
Resveratrol 1:5 PVP K30.

As the solubilities of microwave irradiated solid dispersions of kolliphor and PVP was less than 1mg/mL and also the solid dispersions of kolliphor were physically unstable during the process of microwave irradiation, kolliphors were not considered further.

Taking all these into consideration, soluplus was found to be more promising carrier. Hence, soluplus was considered for further studies using DoE and the ratio was optimized using the software.

Formulation and optimization by DoE

Solubility results of experiments performed according to design were given in Table 1. Fit summary of the response was analyzed and quadratic model was suggested with predicted R^2 of 0.9599 which is in reasonable agreement with the adjusted R^2 of 0.9911 and an adequate precision of 30.045 indicating adequate signal to noise ratio. Analysis of variance was performed to evaluate critical parameters affecting on solubility of amorphous solid dispersions. Both the factors individually as well as in combination i.e., two-way interaction have shown significant effect as depicted in Table 2. It was observed that there is very significant increase in solubility of drug with increase in amount of carrier and microwave irradiation time though resulted in increase in solubility, had less impact. The coefficients of critical parameters were as in the equation below:

$$\text{Solubility}=-0.153563+0.972408\times \text{Drug: Carrier} - 0.021586\times \text{MI time}-0.008471\times \text{Drug: Carrier} * \text{MI time}-0.063491\times \text{Drug: Carrier}^2+0.001473\times \text{MI time}^2$$

The 3D surface plot effect of drug: carrier ratio and microwave irradiation time on solubility is shown in Figure 2a. The model was found to be statistically significant and the plot showing predicted vs actual values of the model was given in Figure 2b. Numerical and graphical optimization of the design was carried out and the overlay plot showing graphical optimization of the

design was given in Figure 2c. Subsequent to optimization, post analysis of the design was carried out at confirmation location #1 with drug: carrier ratio 1:5 and microwave irradiation time of 5 min and 3 runs were performed and solubilities were found to be 2.732 mg/mL, 3.015 mg/mL, 2.836 mg/mL; and analyzed depicting the model is robust as data mean observed was 2.86 mg/mL which is very close to the predicted mean i.e., 2.84 mg/mL confirming that the design and model were significant and optimized. The design was optimized numerically with lower limit of solubility of 1 mg/mL and graphical optimization was carried out to obtain an overlay plot. Post analysis was done after optimization of design using confirmation location at 1:5 drug: carrier ratio at 5 min microwave irradiation.

Solid dispersions were prepared by Microwave Irradiation (MI) technique using domestic microwave oven with Soluplus as carrier using resveratrol in ratios of 1:1, 1:5 and 1:10 as per the runs in design expert. All the solid dispersions were analyzed for solubility and stored at room temperature for further analysis. Optimized amorphous solid dispersion was used for further studies along with physical mixture.

Fourier Transform Infrared spectroscopic studies (FTIR)

FTIR spectrum of pure resveratrol extract showed broad peak at 3250-3400 cm^{-1} corresponding to polyphenolic groups, stretching vibrations because of benzene ring exhibited peaks at 1450-1600 cm^{-1}, peaks at 1600-1650 cm^{-1} are due to aromatic double bonds

Table 2: Estimated effect of critical parameters on solubility (Response 1).

ANOVA for selected factorial (Quadratic) model						
Analysis of variance table: (Sum of squares-Type III-Partial)						
Source	**Sum of Squares**	**d_f**	**Mean square**	**F-value**	***p*-value***	
Model	7.47	5	1.49	179.87	0.0006	Significant
A-Drug: Carrier	4.35	1	4.35	523.94	0.0002	
B-MI time	0.2243	1	0.2243	27.00	0.0138	
AB	0.1459	1	0.1459	17.56	0.0248	
A^2	3.21	1	3.21	386.50	0.0003	
B^2	0.0027	1	0.0027	0.3265	0.6077	
Residual	0.0249	3	0.0083			
Cor Total	7.50	8				

* - *p*-values less than 0.05 indicate model terms are significant.

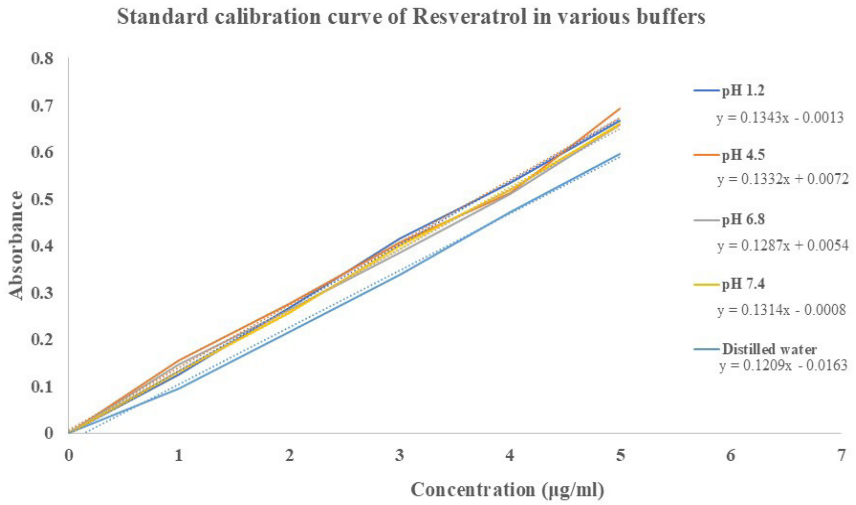

Figure 1: Standard calibration curve of resveratrol in various buffers.

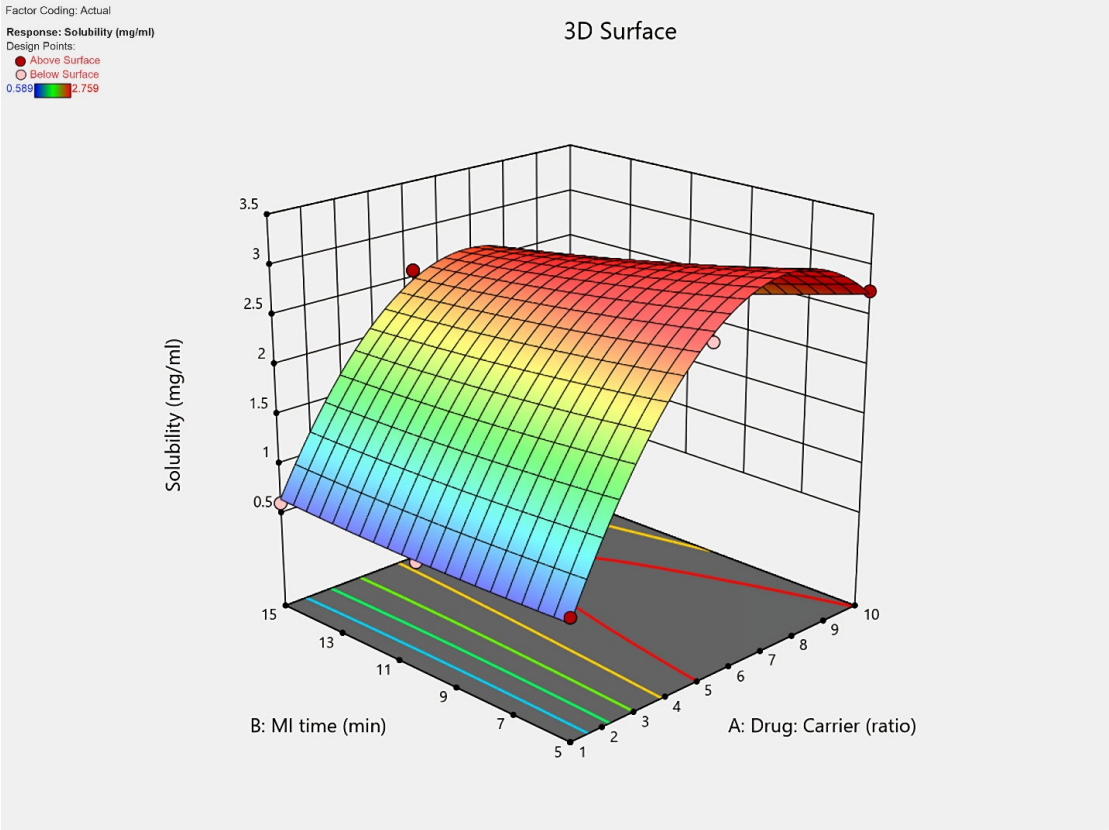

Figure 2a: 3D surface plot showing effect of drug: carrier ratio and microwave irradiation time on solubility.

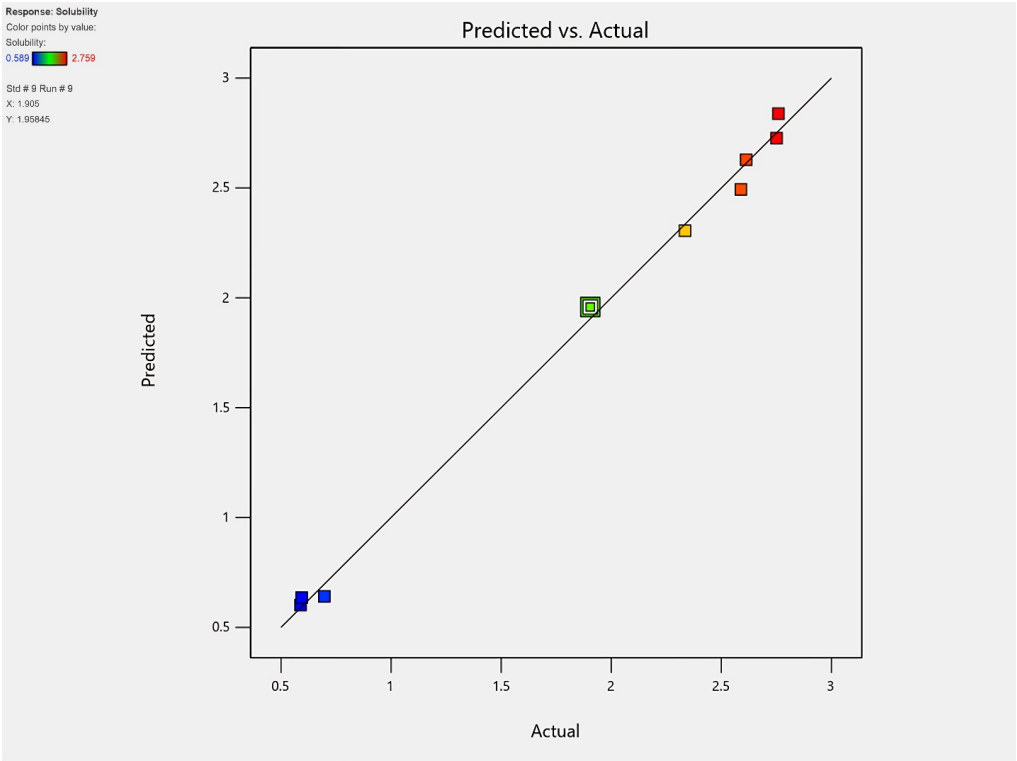

Figure 2b: Plot showing predicted vs actual values of the model.

and at 825-1050 cm^{-1} which indicates trans olefinic bands i.e., bending vibration of C=C-H.[22,23] The characteristic peaks of resveratrol were clearly observed in spectra of physical mixture as well as amorphous solid dispersion as depicted in Figure 3.

Differential scanning calorimetric studies

All the thermograms were shown in Figure 4. DSC thermogram of pure resveratrol showed exothermic peak at 267.67°C. DSC thermogram of soluplus exhibited a broad endothermic peak at 60.64°C. DSC thermogram of R-S PM and R-S MISD showed a broad endothermic peak around 61°C indicating the glass-transition temperature of the soluplus and broad endothermic peak at 280.23°C of resveratrol in thermogram of R-S PM and the absence of sharp endothermic peak in thermogram of R-S MISD indicates amorphization of drug.[16,24]

Particle Size

The average particle size of pure resveratrol was found to be 10.26±2.89 µM with PDI of 0.971; solid dispersion of resveratrol and soluplus possessed 41 times lower particle size and the average particle size, PDI. D10, D50 and D90 of all the samples were given in Table 3.

FESEM studies

From scanning electron micrographs as in Figure 5, it was observed that pure resveratrol and R-S PM depicted well defined crystal structure of drug; in soluplus and R-S MISD, the particles were not clearly seen indicating glassy solution like texture indicating amorphous nature and dispersion of drug in the carrier in case of solid dispersion.[2,25]

Powder XRD analysis

Resveratrol pure extract exhibited crystalline nature depicted by characteristic peaks at 6.67°, 13.31°, 16.44°, 22.43°, 23.48°, 25.32° and 28.38°. Soluplus was found to be amorphous in nature. Few peaks of resveratrol were observed in R-S PM representing the crystalline nature of drug in the physical mixture. In R-S MISD, there is no sharp peak at any of the diffraction angle where distinct crystalline peaks of resveratrol were observed as in Figure 6 indicating the amorphous nature of the drug rather

Table 3: Particle size analysis by Dynamic Light Scattering (DLS).

Sl. No.	Sample	Average particle size (µM)	Polydispersity Index (PDI)	D10 (µM)	D50 (µM)	D90 (µM)
01	Pure resveratrol	10.26±2.89	0.971	3.65±1.03	48.79±27.01	124.19±14.12
02	Soluplus	0.06±0.00	0.046	0.05±0.00	0.06±0.00	0.08±0.01
03	R-S PM	0.37±0.15	0.245	0.04±0.00	0.04±0.00	4.55±4.53
04	R-S MI SD	0.25±0.12	0.171	0.04±0.00	0.05±0.00	0.06±0.00

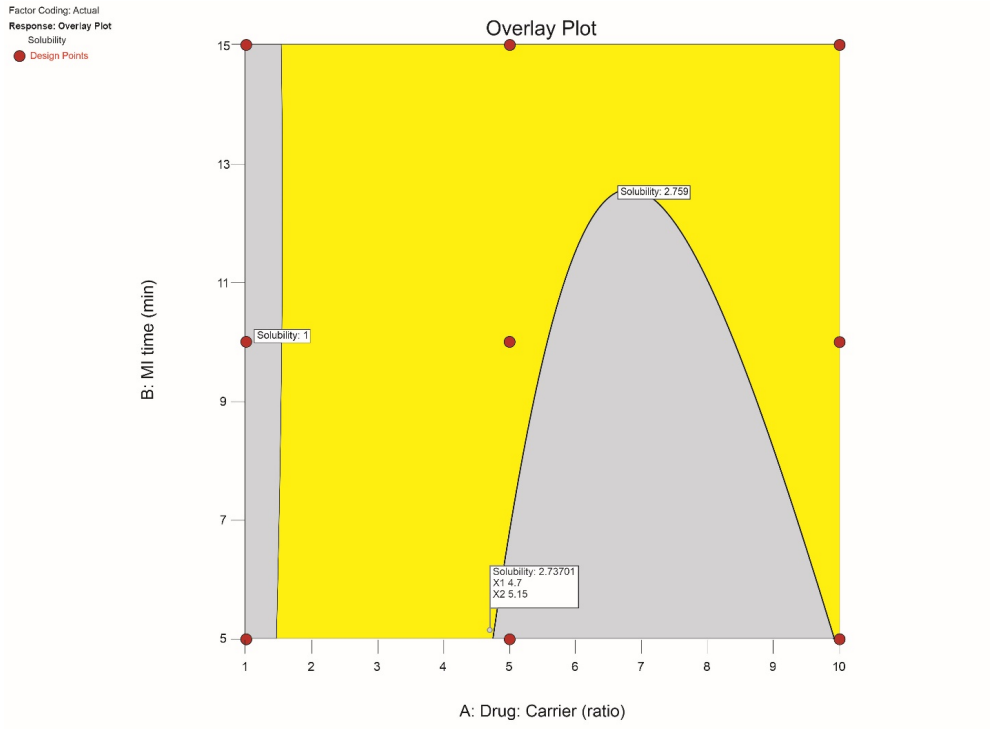

Figure 2c: Overlay plot showing graphical optimization of design.

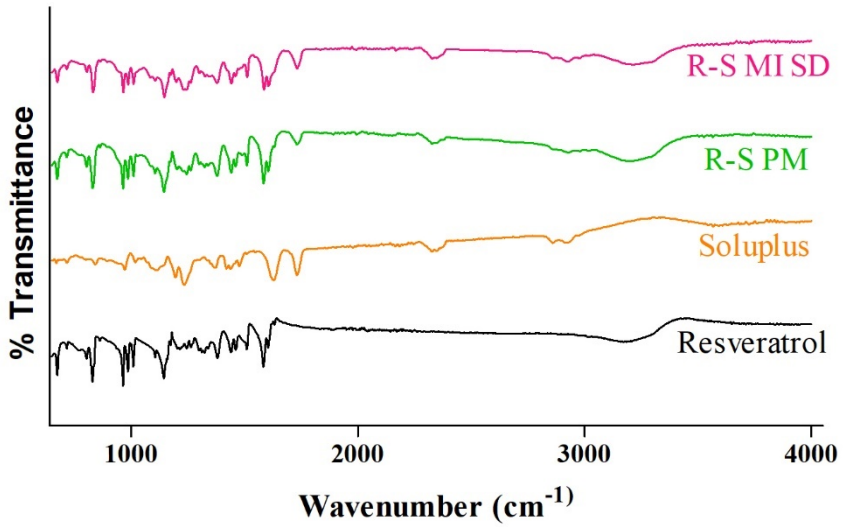

Figure 3: FTIR spectra of a.Resveratrol, b.Soluplus, c.R-S PM and d.R-S MI SD.

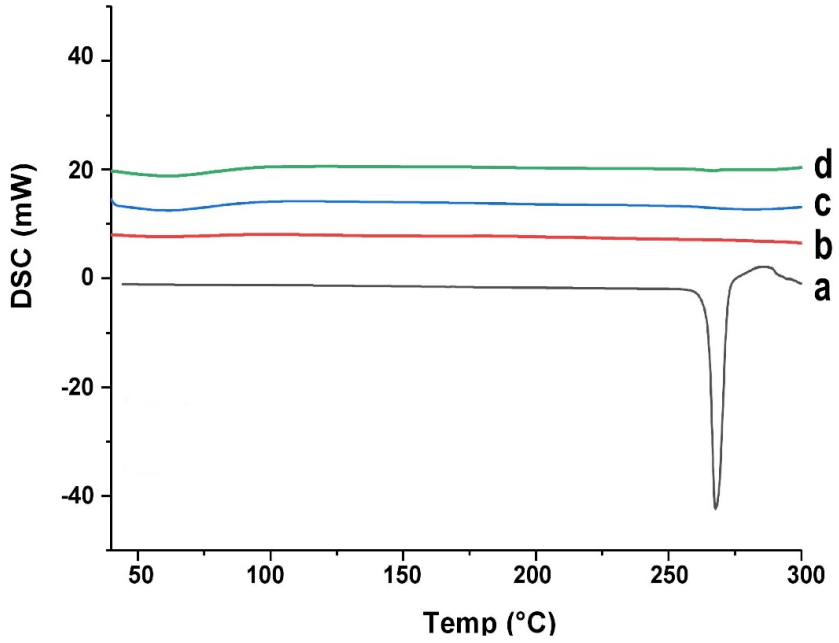

Figure 4: DSC thermograms of a. Resveratrol, b. Soluplus, c. Physical mixture and d. Optimized ASD

than its crystalline form.[2] The intensities of peaks were reduced in the range of 8 to 166-fold at various 2θ values. The intensities at 6.67º, 13.31º, 16.44º, 22.43º, 23.48º, 25.32º and 28.38º are 156151, 27977, 96687, 10647, 6014, 22760 and 11032 for pure resveratrol and 941, 794, 1153, 1339, 723, 582 and 912 for solid dispersion respectively. The reduction in intensities of peaks in the physical mixture and solid dispersions indicated the conversion of crystalline form of the drug into an amorphous form.

DISCUSSION

Resveratrol, a crystalline natural bioactive compound, was used as a model drug in this study. Resveratrol has low solubility issue along with its poor bioavailability. As evident in the literature, the solubility of resveratrol was 5.6 µg/mL and the third generation solid dispersion prepared with the addition of surfactant showed a 2-fold higher solubility than the solid dispersion without surfactant and the solubility increased 8-fold when poloxamer was added instead of soluplus alone as a carrier.[26] Amorphous solid dispersions of resveratrol were prepared by microwave irradiation using different carriers and optimized with soluplus as an effective carrier, which increased the solubility of resveratrol by 54-fold. The use of microwave irradiation has been reported in the literature as a method to prepare solid dispersions at a power of 900 W.[27] Considering the same, critical quality attributes such as irradiation time and drug: carrier ratio, this method was optimized using factorial design.

The disappearance of endothermic peak in the thermogram and peaks in the diffractogram confirmed the conversion of

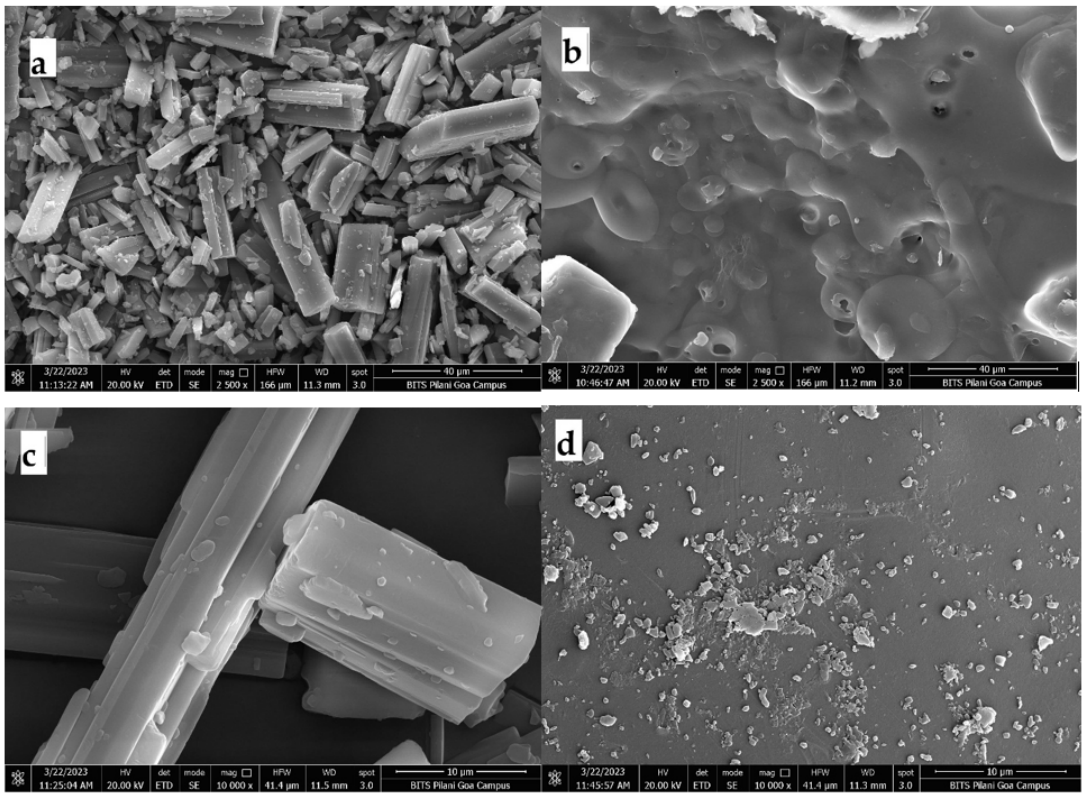

Figure 5: SEM images of a. pure resveratrol, b. soluplus, c. R-S PM and d. R-S MISD.

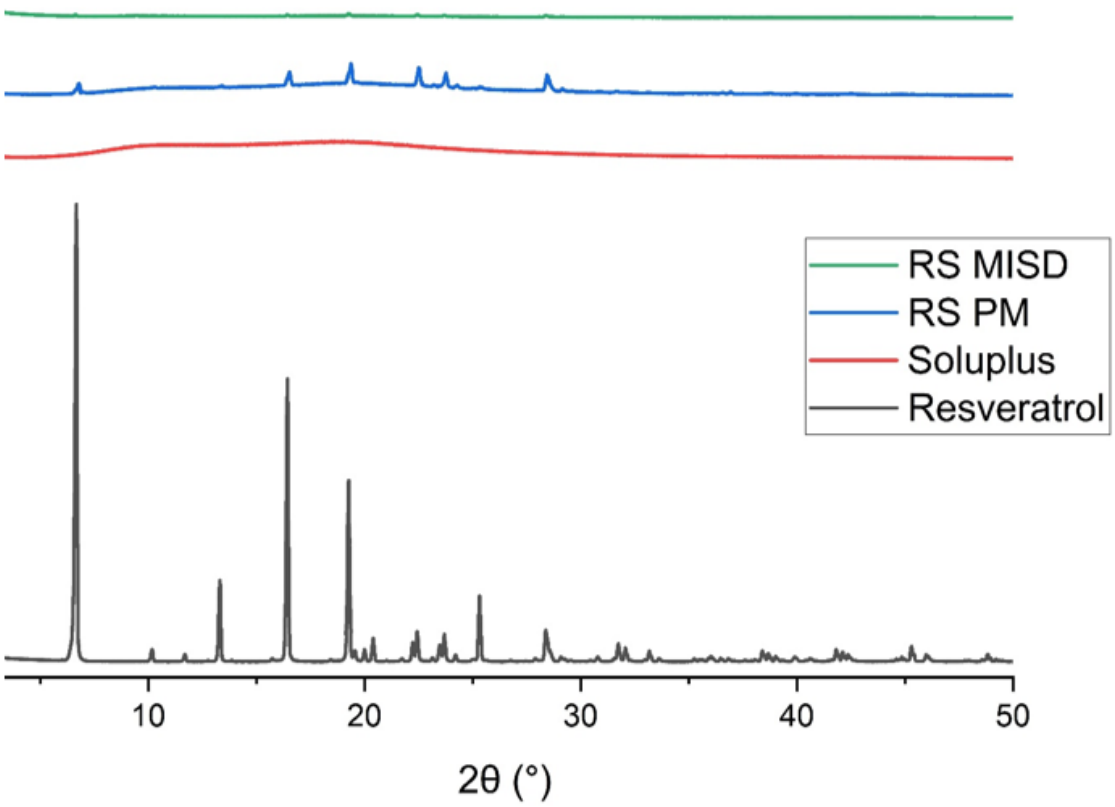

Figure 6: XRD patterns of pure resveratrol, soluplus, R-S PM and R-S MISD.

crystalline form of the resveratrol into an amorphous form. The literature indicates that the use of microwave radiation in the preparation of solid dispersions can convert the crystalline form of a drug into an amorphous or microcrystalline form.[28] This study showed a decrease in the intensity of the peaks, which was reduced by a factor of 166 at certain characteristic diffraction angles, confirming the possibility of amorphization of resveratrol. The images from scanning electron microscope clearly depicted the morphology of pure resveratrol extract which appeared as glass crystals which are not seen in the micrograph of the solid dispersion. The dissolution behaviour exhibited spring effect and this was achieved by 41-fold reduction in the particle size in the solid dispersion compared to extract.

CONCLUSION

With the present work, it can be concluded that microwave irradiation is an absolute approach in preparation of amorphous solid dispersions. Work was carried out using resveratrol as a model drug with soluplus as a carrier. Optimization of drug: carrier ratio as well as irradiation time was done using Design Expert (DoE). The amorphous solid dispersions yielded by microwave irradiation were superior in solubility and the optimized formulation was characterized by various characterization techniques like FTIR, PXRD, DSC, SEM etc., and the results of various studies proved successful conversion of crystalline form of drug into an amorphous form with reduced particle size and poly-dispersity index. The work depicts the use of microwave irradiation technique in enhancing the solubility of poorly soluble compounds by amorphous solid dispersion approach.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ASDs: Amorphous solid dispersions; **BCS:** Biopharmaceutical classification system; **PVP:** Polyvinyl pyrrolidone; **PVP-VA:** Polyvinyl pyrrolidone-vinyl acetate; **PVA:** Polyvinyl alcohol; **HPMC:** Hydroxypropyl methyl cellulose; **HPC:** Hydroxypropyl cellulose; **HPMCP:** Hydroxypropyl methyl cellulose phthalate; **HPMC-AS:** Hydroxypropyl methyl cellulose acetate succinate; **PEG:** Polyethylene glycol; **WHO:** World Health Organization; **DoE:** Design of Experiments; **CQA:** Critical quality attribute; **UV:** Ultraviolet; **FTIR:** Fourier Transform InfraRed; **ATR:** Attenuated total reflectance; **R-S PM:** Resveratrol-Soluplus physical mixture; **MISD:** Microwave irradiated solid dispersion; **DSC:** Differential scanning calorimetry; **PDI**-Polydispersity index; **DLS:** Dynamic light scattering; **FESEM:** Field emission scanning electron microscopy; **XRD:** X-ray diffraction; **PXRD:** Powder X-ray diffraction; **ANOVA:** Analysis of variance; **S.D:** Standard deviation; **MI:** Microwave irradiation.

SUMMARY

Poor solubility of drugs is one of the leading problems in current pharmaceutical industries during formulation development and optimization. The present study demonstrates the use of microwave irradiation technique to design an amorphous solid dispersion which exhibited nearly 50-fold increase in solubility of resveratrol. Irradiation time and drug: carrier ratio were optimized using Design Expert. The optimized amorphous solid dispersion exhibited good solubility, reduced particle size and confirmed conversion of crystalline form of resveratrol into an amorphous form by FESEM, DSC and PXRD studies.

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