ORIGINAL ARTICLE

A Systematic Approach for Dissolution Enhancement of Felodipine using Hydrophilic Polymers for Solid Dispersion Preparation

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Abstract

Aim: The aim of the study was to systematically explore hydrophilic polymers as carrier for dissolution enhancement using central composite design of experiment. **Materials and Methods:** Felodipine was chosen as drug prototype for this study. Influence of formulation and processing parameters such as drug: Polymer ratio, solid content of feed solution, inlet temperature, and aspirator percentage was studied on evaluation parameters such as percent yield and drug release of solid dispersions using a 3^4 central composite design of experiment. Effect of incorporation of surface active agent like polysorbate 80 on further increasing the *in vitro* dissolution was also studied. **Results and Discussion:** Conversion of crystalline drug into amorphous form in solid dispersions was confirmed by Differential scanning study and X-ray diffraction studies. *In vitro* dissolution study showed 55–60 fold increase in drug release within 60 min for spray dried solid dispersion as compared to untreated drug. *In vitro* drug release was enhanced to 64–70 fold as compared to drug when polysorbate 80 (Tween 80) was used as co-carrier for solid dispersion preparation. On basis of preliminary comparative dissolution trials PVP K 30 was selected as suitable carrier polymer for further trials. Outcome of design of experiment trials indicated that drug: Polymer ratio has maximum influence on drug dissolution from solid dispersions. Higher the ratio, more the drug release. Process yield is mainly dependent on feed solid concentration and aspirator speed. Low solid content of spraying solution and higher aspirator speed is required to get good process yield. **Conclusion:** The current study demonstrates that PVP K 30 is a suitable carrier polymer to generate stable solid dispersions to enhance drug dissolution using spray drying technology. Selection of appropriate formulation and processing conditions such as drug: polymer ratio, inlet temperature, aspirator speed and solid content of feed solution determines the quality, and performance of the solid dispersions.

Key words: Solid dispersions, spray drying, PVP K 30

INTRODUCTION

Introduction of combinatorial chemistry and high-throughput screening has resulted in numerous new potential drug candidates being investigated for their therapeutic efficacy. However, complex molecular structure of new chemical entities has resulted in drugs with poor drug dissolution rate leading to limited bioavailability which is a major challenge in preparing successful formulations in present times.[1] Preparation of solid dispersions, among others such as salt formation,[2] prodrugs preparation,[3] complexation,[4] drug particle size reduction,[5] preparation of micelles,[6] self-emulsifying drug delivery systems,[7] and many others are widely used to overcome this challenge. Improved wettability, size reduction coupled with amorphization of drug particles makes spray drying an effective technique to formulate solid dispersions for drug dissolution enhancement.[8,9] Polymers are widely used as carriers for amorphous solid dispersion preparation. The role of polymeric carrier is to inhibit recrystallization of drug from amorphous to crystalline form by entrapping drug molecules in polymer matrix. This helps to maintain drug in supersaturated, high energy amorphous state during

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dissolution and even *in vivo*. Solubility of drug and polymer in common solvent or solvent mixtures is an important criterion for selection of polymer for preparation of solid dispersion using spray drying technique.[10] In addition, polymers with high glass transition temperatures (Tg) are more suitable for preparation of stable solid dispersions as they are more effective in preventing molecular mobility of drug molecules and conversion of amorphous drug back to crystalline state.

In the present research, we have evaluated some hydrophilic polymers having high Tg as carriers for solid dispersion preparation using spray drying technology. Hydroxypropyl methyl cellulose (HPMC) and polyvinyl pyrollidone 30 (PVP K 30) have Tg values of 180°C and 168°C, respectively.[11] These polymers are soluble in various organic solvents as well as in hydro alcoholic solvents which further helps to deal with varieties of drugs.[12,13] Even though PVP K 30 is a high Tg polymer; many publications have highlighted instability concerns of solid dispersions prepared which it due to its inherent hygroscopic nature.[14-20] In addition, to study the interaction of formulation and processing parameters for preparation of high quality product with good reproducibility, a systematic study using principles of design of experiments (DoE) was undertaken.

In the present work, felodipine was selected for study. Poor water solubility of felodipine combined with extensive first pass metabolism results in limited bioavailability after oral administration;[21] hence, dissolution enhancement is required to achieve desired pharmacological response.[22,23]

MATERIALS AND METHODS

Materials

Felodipine was purchased from Nivedita chemicals Pvt. Ltd. (Mumbai, India), PVP K 30 and HPMC (PHARMACOAT® 603) were purchased from BASF SE (Mumbai, India) and Shin-Etsu respectively, Polysorbate 80 (Tween 80) was purchased from Merck Ltd. Analytical grade solvents were used for all the experiments.

Saturation solubility of felodipine at various pH conditions

1 g of felodipine was added in each of the media under stirring using mechanical shaker (Remi, India). The media selected for this study were purified water, 0.1 N HCl, pH 4.0 buffer, pH 6.8 phosphate buffer, and pH 8.0 phosphate buffer. The beaker containing drug and medium was stirred for 24 h to achieve equilibrium thereafter the aliquots from each of the media were filtered through 0.45 µm polyvinylidene fluoride (PVDF) filter, diluted with buffered media and then analyzed spectrophotometrically at 362 nm λmax

Formulation design

Procedure for preparation of formulations

Pure felodipine was dissolved in ethanol using magnetic stirrer (IKA® works Inc., USA) until a clear solution was obtained. The solution obtained was spray dried using spray dryer (mini spray dryer B290, BuchiLabortechnik AG, Switzerland) to prepare spray dried felodipine [A1 in Table 1]. Batches A2 and A3 were prepared by spray drying felodipine and HPMC solution. Solvent Ethanol and water in the ratio of 9:1 was used for these batches. Batch A4 was prepared by spray drying felodipine and PVP K 30.

Felodipine, PVP K 30 and Tween 80 in the ratio of 1:9:1 and 1:9:2 were dissolved in ethanol using magnetic stirrer until a clear solution was obtained after which the feed solution obtained were spray dried (A5 and A6). Ethanol was used as solvent system for batches A4–A6. Solid content of spraying solution for all the batches was kept at 10%.

Physical mixture of felodipine and HPMC in the ratio of 1:1 and 1:9 was designated as batches A7 and A8, respectively. Batch A9 was physical mixture of felodipine and PVP in the ratio of 1:9.

Spray drying process optimization using DoE

The study was designed to have optimized product with maximum percent yield of solid dispersions and *in vitro* drug dissolution in 0.1 N HCl and buffer pH 6.8 within 60 min. A 3^4 central composite design of experiment as suggested by MODDE software was selected for the study. The four independent formulation and process parameter selected were solid content of feed solution (X1), inlet temperature (X2), drug: Polymer ratio (X3), and aspirator percentage (X4). The three responses also identified as critical quality attributes were percent yield of solid dispersions (Y1), percent *in vitro* drug release at 60 min in 0.1 NHCl (Y2) and percent *in vitro* drug release at 60 min in buffer pH 6.8 (Y3). The specification and range selected for all the critical quality attributes were ≥50 and 30–100%, respectively.

Preparation of solid dispersions for DoE study

Felodipine and PVP K 30 in the ratio of 1:I, 1:5, and 1: 9 were dissolved in ethanol using magnetic stirrer until a clear solution was obtained. Three levels (15% and 30% and 45% w/w) of feed solution solid content were taken for study. The solution obtained was spray dried using spray dryer. Inlet temperature was varied at 3 levels (35°C, 55°C, and 75°C). Aspirator speed percentage was also varied at three levels (50%, 70%, and 90%). [Formulation and process parameters mentioned in Table 2]. Out of the 27 trials, spraying solution was not formed in four trials so they were no taken for further evaluation.

Table 1: Formulation details and process parameters

Batch no.	Formulation details					
	A1	A2	A3	A4	A5	A6
Felodipine (g)	5	5	5	5	3	3
PHARMACOAT 603 (g)	-	45	5	-	-	-
PVP K30 (g)	-	-	-	45	27	27
Tween 80 (g)	-	-	-	-	3	6
	Process parameters					
Inlet Temperature (°C)	60–70	60–70	60–70	60–70	75	75
Outlet Temperature (°C)	37–42	41–45	46–47	37–42	46–59	52–61
Aspirator (%)	90	90	90	90	90	90
Spray rate (g/min)	4–8	4–8	4–8	4–8	4–8	4–8
Nitrogen pressure (bar)	6	6	6	6	6	6
Spray flow rate (l/h)	473	473	473	473	473	473
Flow meter height (mm)	40	40	40	40	40	40

Table 2: Worksheet for design of experiment trials along with results

Batch no.	XI (%)	X2 (°C)	X3	X4 (°C)	Y1 (%)	Y2 (%)	Y3 (%)
N1	15	35	1:1	50	58.5	1.9	3.3
N2	15	75	1:1	50	36.5	1.1	1.3
N3	15	35	1:9	50	16.2	37.81	35.8
N4	15	75	1:9	50	12.6	46	53
N5	45	75	1:9	50	17	41	44
N6	15	35	1:1	90	71.5	2	2
N7	15	75	1:1	90	74	4.1	1.6
N8	45	75	1:1	90	37	4	3
N9	15	35	1:9	90	61.2	57	48
N10	45	35	1:9	90	11.9	44.28	53.82
N11	15	75	1:9	90	62	55	60
N12	45	75	1:9	90	46	41	52
N13	15	55	1:5	70	55	10.1	5.6
N14	45	55	1:5	70	27.16	6.2	6.3
N15	30	35	1:5	70	56.6	4.3	3.7
N16	30	75	1:5	70	66.33	0.8	7.7
N17	30	55	1:1	70	42.5	1.3	1.1
N18	30	55	1:9	70	51	33.27	36.15
N19	30	55	1:5	50	45.66	1	5.5
N20	30	55	1:5	90	60.67	1	3.6
N21	30	55	1:5	70	53.66	1.6	5.2
N22	30	55	1:5	70	64.44	6.25	2.79
N23	30	55	1:5	70	61.11	7.13	3.89

Evaluation studies

Scanning electron microscopy (SEM) imaging study

The SEM imaging of felodipine and solid dispersions were performed using scanning electron microscope (FEI Quanta 200, Oregon, USA).

Thermal analysis

Differential scanning study (DSC) study was performed on felodipine, physical mixture of felodipine and PVP K 30, initial and stability samples of solid dispersions (each containing 10 mg of felodipine) using model 910,TA instruments thermal analyzer (New Castle, USA). Nitrogen

gas at flow rate of 20 mL/min was used to maintain inert atmosphere. Accurately weighed quantities of samples (5 mg) were analyzed in hermetically sealed, pin holed aluminum crucibles. The samples were heated at a constant rate at 10°C/min over a temperature range of 30–300°C. An empty pan was used as a reference. Indium and zinc was used for calibration of temperature and heat flow, respectively.

Powder X-ray diffraction (PXRD) analysis

Powder XRD patterns of felodipine, physical mixtures of felodipine and PVP K 30, and solid dispersion were recorded in diffractometer (XRD 6000, Shimadzu, Japan) using Cu radiation. Diffractogram was run at a scanning speed of 4°/2θ. The samples were irradiated with monochromatic Cu K radiation (1.542 A°). Voltage and current of 40 kV and 40 mA, respectively, were used for the study.

Process yield (% w/w)

After completion of spray drying process, the powder collected in powder collector was collected form spray dryer and weighed accurately. Process yield was calculated using the following formula:

$$\% \text{ process yield} = \frac{\text{Weight of powder collected from cyclone collector}}{\text{Solid content of spraying solution}}$$

Particle size measurement (µm)

Solid dispersions samples were prepared in water for this study and measurements were recorded using Microtrac S3500 particle size analyzer (Microtrac., USA). The mean particle size was reported as an average of 3 measurements.

In vitro drug dissolution (%)

Dissolution studies of 10 mg pure drug, spray dried drug, physical mixture of drug and polymer and spray dried solid dispersion amount containing drug equivalent to 10 mg was carried out in USP type II apparatus dissolution tester (LabIndia, India). Rotation speed of paddle was kept at 50 rpm. Dissolution was carried for 60 minutes and 37 ± 0.5°C temperature was maintained The two dissolution media used were 900 mL each for 0.1 N HCl and buffer pH 6.8. At the end of 60 min, 10 mL aliquot liquid of dissolution medium was drawn out from dissolution jars, filtered through 0.45 µm PVDF filter, diluted and analyzed on HPLC (Thermo Scientific Dionex, Massachusettis, USA) at 362 nm λmax. The results were reported as mean of three readings ±standard deviation value.

Analysis of drug content (%)

The drug content in spray dried felodipine, physical mixture of drug and polymer, and solid dispersion was determined using UV spectroscopy and compared with drug alone. Accurately weighed solid sample equivalent to 10 mg of felodipine was transferred to 100 mL volumetric flask, diluted to 100 mL with mobile phase and sonicated for 30 min for complete solubilization of drug. The clear solution obtained after filtration through 0.45 µm filter was analyzed on HPLC at 362 nm λmax.

Stability studies

Solid dispersions (felodipine: PVP K30:1:9) were packed in 30 cc HDPE bottles with roll-on-pilfer-proof caps and incubated in stability chamber for 6 months at accelerated stability conditions (40°C, 75% r.h.) as per ICH guidelines. After incubation period samples were tested for assay, dissolution and changes in DSC.

RESULTS AND DISCUSSION

Saturation solubility study

Almost similar drug release (0.0005–0.0018 mg/mL) was observed in purified water (pH 6.37), 0.1 N HCl (pH 1.2), citrate buffer (pH 4), phosphate buffer (pH 6.8), and phosphate buffer (pH 8) from drug saturation solubility studies which indicated that felodipine is a pH independent poorly soluble drug.

DSC study

DSC spectra of felodipine, spray dried felodipine, physical mixture of felodipine, and PVP K 30 and solid dispersion initial and after 6 months storage at accelerated stability conditions are shown in Figure 1. Presence of endothermic melting peak of felodipneat approx. 145.14°C in pure felodipine, spray dried felodipine, and physical mixture of felodipine and PVP K 30 indicated non conversion of drug to amorphous form. Complete disappearance of melting point peak of felodipine in initial and stability samples indicated presence of drug in amorphous state and generation of stable formulation.

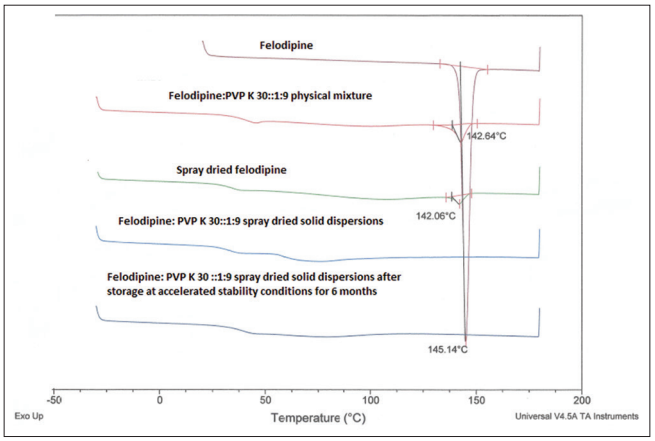

Figure 1: DSC curves of felodipine, spray dried felodipine, physical mixture of felodipine and PVP K 30, and initial and accelerated storage stability samples

SEM imaging study

SEM images of solid dispersion powder of felodipine: PVP K 30:1:9 show perfectly spherical particles with smooth surface as compared to irregular shaped particles with sharp edges in felodipine [Supplementary Figure S1] indicating formation of solid dispersions.

XRD diffraction study

Characteristic peaks of felodipine at 2θ of 10.2°,16.58°, and 23.3° were seen in diffractogram of drug and physical mixture of drug and polymer, which were not observed with spray dried formulation confirming the conversion of crystalline drug in solid dispersion [Figure 2].

Particle size study

Particle size of solid dispersions tested was between 5.7 ± 0.5 µm and 15.5 ± 0.5 µm indicating uniform particle size distribution.

Drug content analysis

Drug content of all the experimental batches was within 98–102% indicating content uniformity.

In vitro dissolution

Drug release from drug, spray dried drug and physical mixture of drug with polymer was not more than 5% indicating the requirement of preparation of solid dispersion for enhancing the drug dissolution. Not more than 10% drug release was observed from solid dispersions prepared using HPMC as carrier polymer which was attributed to less wetting tendency of formulation in dissolution media [Table 2]. Solid dispersions prepared using PVP K 30 as carrier polymer showed 55% (55 fold increase) and 60% (60 fold increase) of drug released in 0.1 NHCl and buffer pH 6.8 respectively in 60 min. Dissolution profile of solid dispersions stored at accelerated stability conditions for 6 months was found to be stable. *In vitro* drug release was enhanced to 63 and 70 fold in 0.1 NHCl and buffer pH 6.8, respectively, in 60 min [Tables 2 and 3] as compared to pure drug when tween 80 was used as co-carrier for solid dispersion preparation due to faster wetting and distribution of the solid dispersion in dissolution media.

Design of experiment study results and interpretation

Effect of formulation and processing parameters on evaluation parameters such as percent yield and percent drug release in 0.1N HCl and buffer pH 6.8 was checked using graph of summary of FIT plot [Figure 3]. Values for model fit (R^2) and model predictability (Q^2) were close to 1. <0.3 difference between R^2 and Q^2, model validity and reproducibility value of more than 0.25 and 0.5, respectively, confirmed the reliability of selected model [Supplementary Table T1].

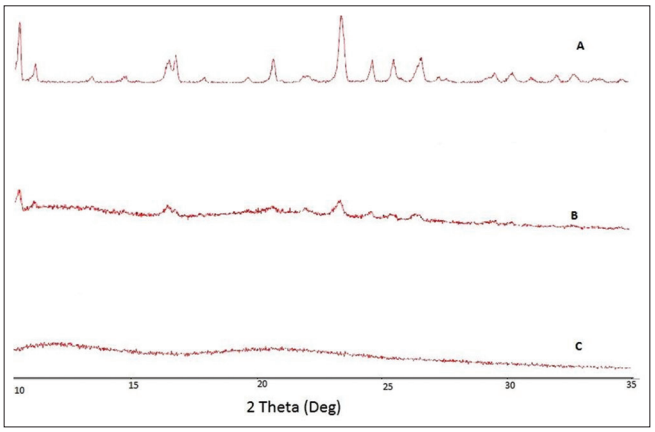

Figure 2: XRD spectra of felodipine, physical mixture of felodipine and PVP K 30, and solid dispersion (A) Felodipine (B) Felodipine: PVPK30 (1:9) physical mixture; (C) Felodipine: PVPK 30 (1:9) spray dried solid dispersion

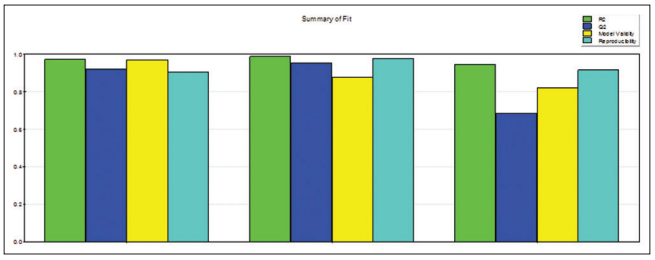

Figure 3: Summary of FIT plot. Dissolution in acid (at the end of 1 h) Dissolution in buffer (at the end of 1 h) Process yield

Table 3: *In vitro* dissolution results

Formulation	Drug dissolution in 0.1N HCl after 1 h (%)	Drug dissolution in buffer pH 6.8 after 1h (%)
Felodipine pure drug	0.75±0.8	0.42±0.3
A1	2.01±1.2	2.05±0.7
A2	9.65±0.5	10.0±1.2
A3	11.39±0.7	9.56±0.7
A4	55±0.5	60±0.9
A5	55±0.8	65±0.8
A6	64±0.7	70±0.38
A4 after storage at accelerated conditions stability for 6 months	52±1.7	58±1.2
A7	4.20±1.0	3±0.9
A8	5.16±0.8	4.2±0.4
A9	3.8±0.5	4.3±1.0

Influence of variables on process yield study

Main effect plots [Supplementary Figures S2-S4] obtained from MODDE 9.1.1 software reveal that when varying solid content from low to high while keeping other factors constant (at their average) major effect was observed on process yield. Slight decrease in process yield in batches with up to 30% solid content was observed but when solid content was further raised to 45% drastic decrease in process yield was seen. When aspirator speed was varied from low to high while keeping other factors constant (at their average) major effect was observed on process yield, on increasing the aspirator speed increase in process yield was observed. Varying inlet temperature from low to high while keeping other factors constant, moderate effect was observed on process yield, with increase in temperature increase in process yield was observed.

From contour plot [Figure 4], it is also revealed that with low solid content and high aspirator speed maximum process yield was achieved depicted by more grey areas in the graph. This phenomenon is demonstrated by the following set of examples from Table 2.

In batch N10 where high solid content of spray solution was used (solid content: 45%, inlet temperature: 35°C, w/w and aspirator speed 90%) product yield obtained was only 11.9%. when solid content in batch N 13 was reduced to 15% while keeping other variables same product yield increase to 61.2%. In trial with low aspirator speed percentage, batch N4 (inlet temperature: 75°C, solid content: 15% w/w and aspirator speed 50%) poor yield 12.6% was again observed. In batch N11 all formulation and process parameters were kept similar to similar N4 except aspirator speed % was increased to 90% which resulted in high process yield of 62%.This phenomenon can be attributed to increase in spray solution viscosity with increase in solid content resulting in bulky spray droplets which are not dried sufficiently thus sticking to each other and walls of drying cylinder resulting in poor yield. With low aspirator speed again bulky droplets are formed due to less atomization resulting in poor yield of the final product.

Influence of variables on percent in vitro drug release in acid

Main effect plot in supplementary Figure S5 suggested that varying drug: polymer (D: P) ratio from low to high while keeping other factors constant (at their average) drug release in acid did not increase significantly till 1:5 drug: polymer ratio. Significant drug release was observed at drug: polymer ratio 1:9.

Area highlighted in grey in contour plot [Figure 5] also suggested that drug release >50% after 1 h in acid was observed in high drug: polymer ratio of 1:9, low solid content and high aspirator speed % irrespective of inlet temperature.

Influence of variables on percent in vitro drug release in buffer

Main effect plot [Figure S5] suggested that varying drug: polymer ratio from low to high while keeping other factors constant (at their average) drug release in buffer did not increase significantly till 1:5 drug: polymer ratio, after which a significant drug release was observed at drug: polymer ratio 1:9.

Contour plot in Figure 6 also confirmed that high drug: polymer ratio of 1:9 was required to obtain drug release more than 50% after 1 h in buffer.

Purple color regions in contour plots in Figure 5 and 6 also indicated that *in vitro* drug release in acid and buffer was significantly low at low drug: polymer ratio up to 1:5, even though inlet temperature and solid content of spray solution were high.

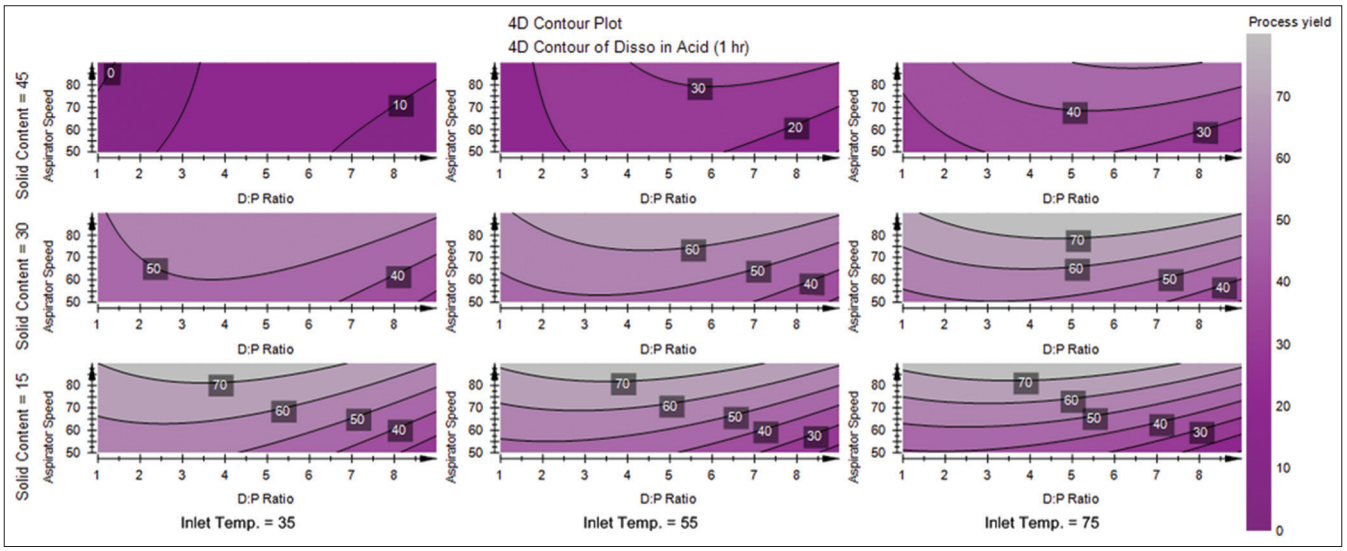

Figure 4: Contour plot for process yield

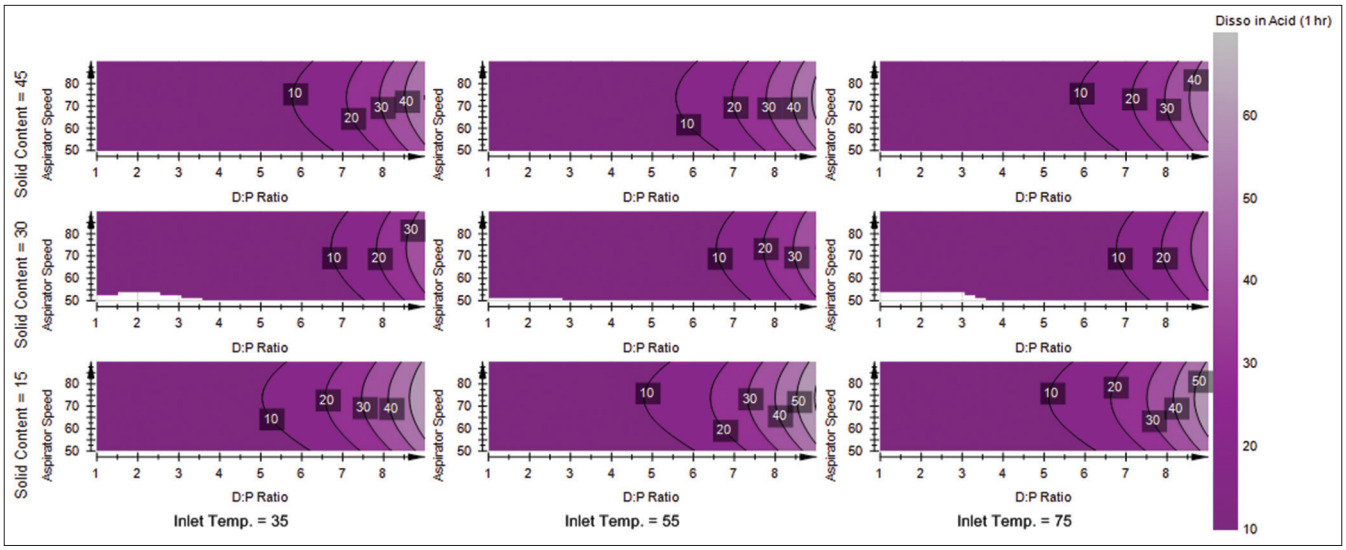

Figure 5: Contour plot for dissolution in acid

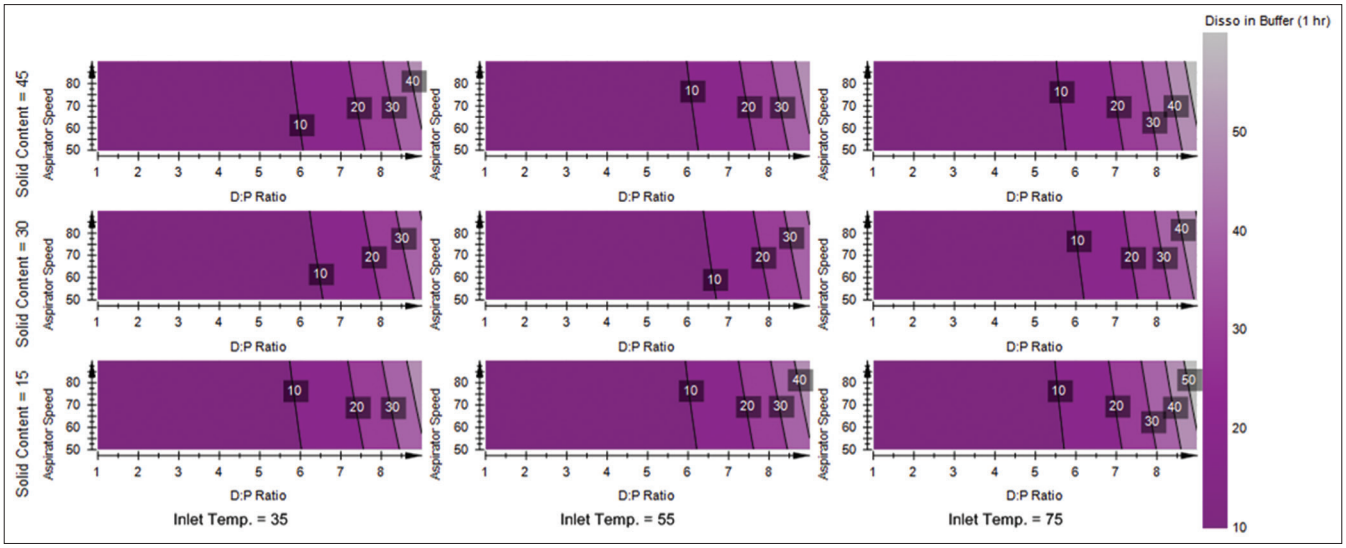

Figure 6: Contour plot for dissolution in buffer

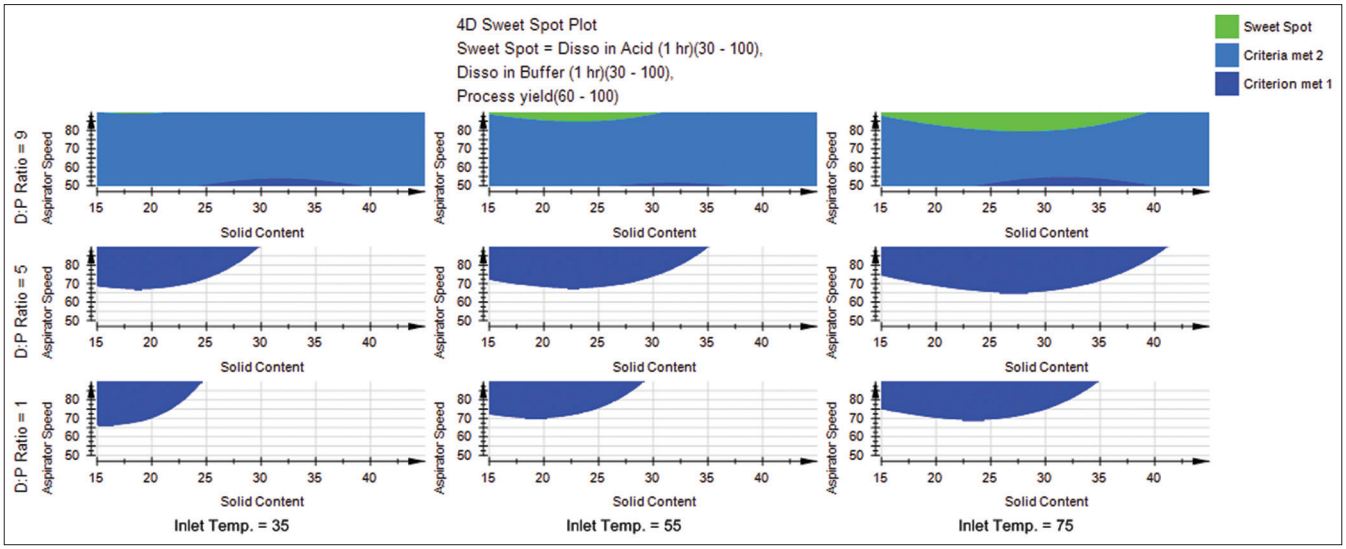

Figure 7: Response surface plot showing 4D sweet spots

Sweet spot study

Response surface plot showing 4D sweet spots in Figure 7 depicts different conditions in different colors schemes. Sweet spot marked in green color indicates area where all critical quality attributes mentioned in Table 2 (percent drug dissolved in acid and buffer and percent process yield) are within the specified limits. Sky blue, dark blue, and white color indicates areas where two, one or none CQA, respectively, are within the selected limits.

From the plot it was concluded that batch with drug: polymer ratio of 1:9, inlet temperature of 75°C, solid content up to 30% w/w and aspirator speed percent of more than 80% would show a desired result within predefined specification. This interpretation was confirmed by results of trial 11 where percent process yield of 62%, percent drug dissolution of 55% and 60% in acid and buffer, respectively, was obtained.

CONCLUSION

Preparation of solid dispersions using spray drying technique for dissolution enhancement of poorly soluble drug using hydrophilic carrier polymers was successfully evaluated. PVP K 30 was selected as carrier polymer for dissolution enhancement based on preliminary comparative dissolution trials. DSC and XRD studies confirmed complete conversion of crystalline drug to amorphous form in prepared solid dispersions. To study the effect of spray drying formulation and process parameters on solid dispersion characteristics a central composite design of experiment was used. The optimum batch was selected based on maximum value of process yield and percentage of drug dissolution in acid and buffer at the end of hour. *In vitro* dissolution study showed 55–60 fold increase in drug release within 60 min for spray dried solid dispersion as compared to pure drug. *In vitro* drug release was further enhanced to 64–70 fold as compared to drug when polysorbate 80 was used as co-carrier for solid dispersion preparation. Stability results revealed that solid dispersions generated were stable for 6 months in accelerated storage stability conditions. The current study demonstrates that PVP K 30 is a suitable carrier polymer to generate stable solid dispersions to enhance drug dissolution using spray drying technology and selection of appropriate formulation and processing conditions such as drug: polymer ratio, inlet temperature, aspirator speed, and solid content of feed solution determines the quality and performance of the solid dispersions.

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Source of Support: Nil. **Conflicts of Interest:** None declared.

SUPPLEMENTARYTABLE

Table T1: Summary of FIT plot values

	Drug release in acid	Drug release in buffer	Process yield
R^2 (model fit)	0.9721	0.9879	0.9450
Q^2(predictability)	0.9220	0.9543	0.6847
Model Validity	0.9693	0.8780	0.8194
Reproducibility	0.9048	0.9779	0.9168

SUPPLEMENTARYFIGURES

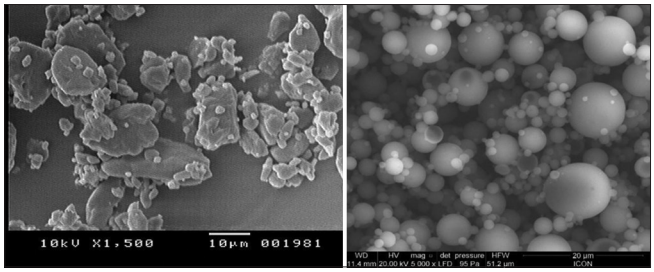

Figure S1: SEM image of felodipine drug and solid dispersion with PVP k 30 as carrier polymer. Felodipine, Felodipine: PVP K 30:1:9 solid dispersion

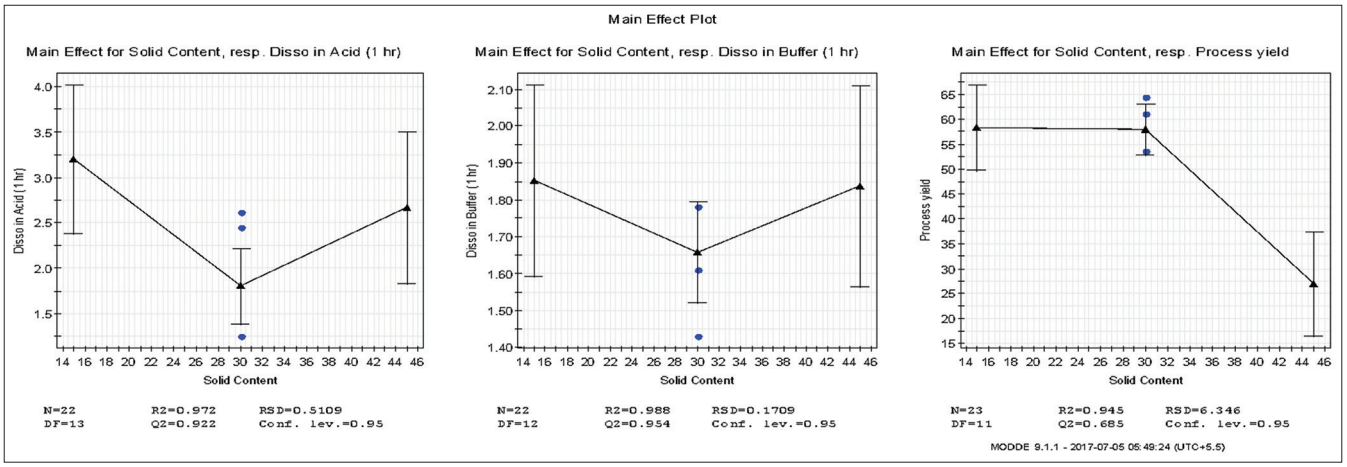

Figure S2: Main effect plot for solid content

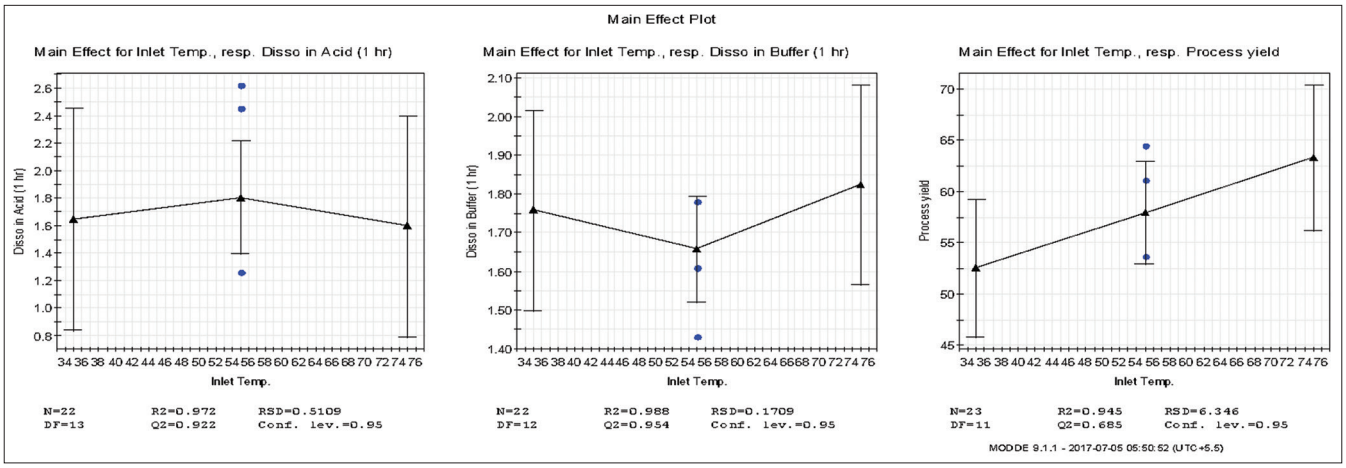

Figure S3: Main effect plot for inlet temperature

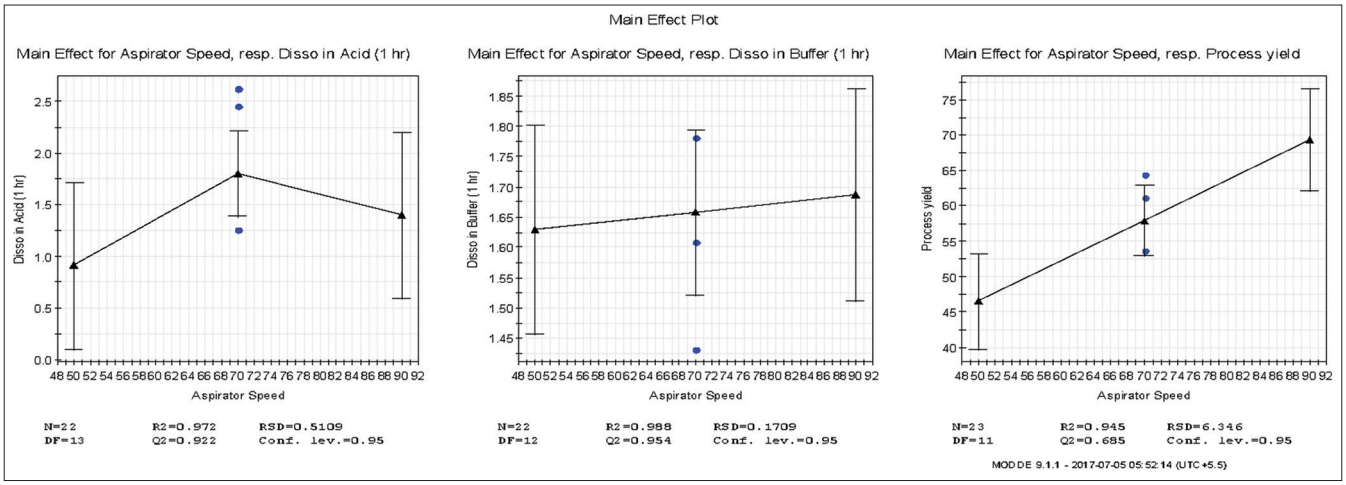

Figure S4: Main effect plot for aspirator speed percentage

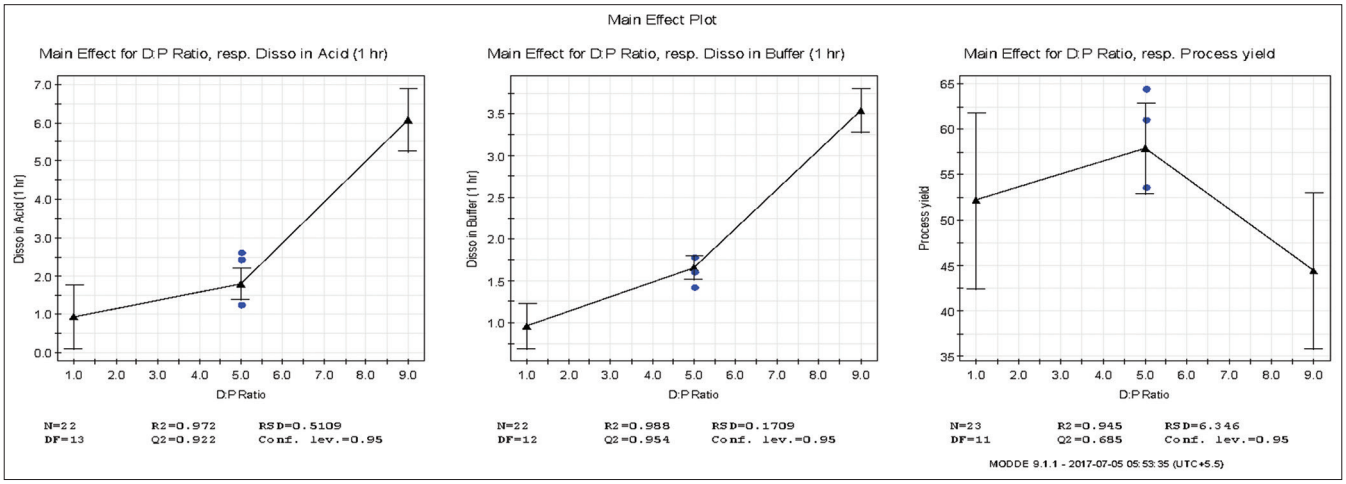

Figure S5: Main effect plot for drug: polymer ratio