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*Research Article*

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# Application of Pharmaceutical QbD for Enhancement of the Solubility and Dissolution of a Class II BCS Drug using Polymeric Surfactants and Crystallization Inhibitors: Development of Controlled-Release Tablets

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***Abstract.*** The aim of this study was to apply quality by design (QbD) for pharmaceutical development of felodipine solid mixture (FSM) containing hydrophilic carriers and/or polymeric surfactants, for easier development of controlled-release tablets of felodipine. The material attributes, the process parameters (CPP), and the critical quality attributes of the FSMs were identified. Box–Behnken experimental design was applied to develop space design and determine the control space of FSMs that have maximum solubility, maximum dissolution, and ability to inhibit felodipine crystallization from supersaturated solution. Material attributes and CPP studied were the amount of hydroxypropyl methylcellulose (HPMC; $X_1$), amount of polymeric surfactants Inutec®SP1 ($X_2$), amount of Pluronic®F-127 ($X_3$) and preparation techniques, physical mixture (PM) or solvent evaporation (SE; $X_4$). There is no proposed design space formed if the Pluronic® content was below 45.1 mg and if PM is used as the preparation technique. The operating ranges, for robust development of FSM of desired quality, of Pluronic®, Inutec®SP1, HPMC, and preparation technique, are 49–50, 16–23, 83–100 mg, and SE, respectively. The calculated value of *f2* was 56.85, indicating that the release profile of the controlled-release (CR) tablet (CR-6) containing the optimized *in situ*-formed FSM was similar to that of the target release profile. Not only did the ternary mixture of Pluronic®, HPMC with Inutec®SP1 enhance the dissolution rate and inhibit crystallization of felodipine, but also they aided Carbopol®974 in controlling felodipine release from the tablet matrix. It could be concluded that a promising once-daily CR tablets of felodipine was successfully designed using QbD approach.

**KEY WORDS:** Box–Behnken design; dissolution; felodipine; QbD; solid mixture.

## INTRODUCTION

The last decade has seen a significant transformation in pharmaceutical quality regulation from an empirical process to a more science and risk-based approach. There are two approaches for pharmaceutical development, the empirical and systematic (pharmaceutical quality by design, QbD) approaches. QbD is a systematic risk-based, proactive approach to pharmaceutical development that begins with predefined objectives and emphasizes product and process understanding and process control based on sound science and quality risk management (1). Thus, QbD is concerned with the achievement of certain predictable quality with desired and predetermined specifications through relating the critical material attributes and critical process parameters (CPP) to the critical quality attributes (CQAs) of drug product. It uses multivariate experiments to understand product and process and to establish a design space through design of experiments (DOE) (2).

DOE is an organized method to determine the relationship between the inputs and outputs of a process. In pharmaceutical development, factors or input variables are the raw material attributes and CPP while outputs are the CQAs such as solubility and dissolution. Each unit operation has many input variables and CQAs, it is impossible to experimentally investigate all of them. Researchers have to use prior knowledge and risk management to identify critical input and output variables and process parameters to be investigated by DOE (3).

Felodipine is a model drug of the Biopharmaceutical Classification System (BCS) class II. It is used for treatment of chronic hypertension. Increasing the solubility of the sparingly water soluble drug and controlling its release rate from the product is critical during the development of a controlled-release (CR) tablet (4). Several formulation techniques have been used to improve dissolution rate of felodipine such as micronization (5), solid dispersion (6–8), and co-grinding (9). However, these techniques suffer from problems that prevent its commercial use such as physical

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instabilities, limited improvement of dissolution, and crystallization from the supersaturated solution generated by dissolution of the amorphous drug (4,6,10,11).

Literature lacks any data about the application of QbD for pharmaceutical development of felodipine solid mixture (FSM) containing hydrophilic carriers and/or polymeric surfactants reported to be solubility enhancers and crystallization inhibitors. The developed FSM with enhanced solubility and dissolution facilitates the development of CR tablets for once-daily administration of felodipine. Thus, the aim of this study was identification of CQAs and the material attributes of the FSMs (amount and type of hydrophilic carriers and/or surfactants) and determination of the process parameters for their preparation. Box–Behnken experimental design was applied to develop space design and determine the control space of the optimized FSMs that have maximum solubility, maximum dissolution, and ability to inhibit felodipine crystallization from supersaturated solution. The optimized FSM was used to prepare CR tablets having zero-order release kinetics for once daily administration.

## MATERIALS AND METHODS

### Materials

Felodipine was kindly obtained from Alkan Pharmaceutical Industries (Egypt). Polyethylene oxide (PEO, Mol.Wt. 7,000,000, Aldrich Chemical Co., USA), Carbopol® 974 (BF Goodrich, USA) were used as retardant polymers. Polyethylene Glycol (PEG 4000 and PEG 6000) and lactose monohydrate was provided by Merck (Darmstadt, Germany). Hydroxypropyl methylcellulose (HPMC; METHOCEL™ E5LV) was obtained from Colorcon Limited, UK. Polyvinyl pyrrolidone (PVP K25) was obtained from Fluka (Buchs, Switzerland). Pluronic® (F-68 and F-127; BASF Corporation, Chemical division, Parsippany, NJ, USA), linear polyfructose (inulin) grafted with hydrophobic lauryl chains (Inutec® SP1) was kindly donated from BENEO-Bio Based Chemicals (Belgium), arginine and leucine (Sigma, St Louis, USA), and magnesium stearate (Prolabo, France) Prosolv® SMCC 90 was kindly provided by RJS (Rosenberg, Germany). Ethanol, disodium hydrogen phosphate, and potassium dihydrogen phosphate were purchased from El-Nasr pharmaceutical chemicals company (Cairo, Egypt).

### Methods

#### *Identification of Material Attributes of Excipients Used for the Preparation of FSMs*

*Screening the Effect of Different Hydrophilic Carriers and Polymeric Surfactants on the Solubility of Felodipine.* The effect of different carriers on the solubility of felodipine was studied by formulating physical mixtures (PM) of felodipine with nine different carriers (PEG 4000, PEG 6000, PVP K25, Pluronic® F-68, Pluronic® F-127, HPMC, Inutec® SP1, leucine, and arginine) in three different ratios 1:3, 1:5, and 1:10. The PMs were prepared by mixing the drug with each of the aforementioned carriers in a mortar with a pestle for 2 min to obtain homogeneous mixtures. To determine the solubility of felodipine in these systems, a known excess of each system was shaken with 10 mL distilled water in an amber-colored glass vial, then left in a shaking water bath (GLF Corp., Burgwedel, Germany) at room temperature (25°C) for 24 h. The samples were withdrawn, centrifuged (Haraeus, Pennsylvania, USA) at 5,000 rpm for 10 min and their absorbance were measured spectrophotometrically at $\lambda_{max}$ 363.6 nm (UV-1601 PC, Shimadzu, Kyoto, Japan). The experiments were carried out in triplicate,

*Screening the Inhibitory Effects of Different Hydrophilic Carriers and Polymeric Surfactants on Crystallization of Felodipine from Supersaturated Solutions.* To achieve the best results in solubilization, the drug must be maintained in a solubilized form in supersaturated solutions with minimum crystallization. Thus, an experiment was conducted to determine the inhibitory effect of the previously mentioned polymers on the crystallization of felodipine from its supersaturated solution (12). In the vessels of the dissolution apparatus (Model VK 700; Vankel Corp., USA), 100 mg of each hydrophilic carrier was dissolved in 190 mL distilled water, 10 mg drug was dissolved in 10 mL ethyl alcohol and added to each vessel to form supersaturated solutions of felodipine (50 μg/mL). The paddle rotated at a speed of 100 rpm and the temperature was maintained at 37°C. Samples were withdrawn at predetermined time intervals, centrifuged at 5,000 rpm for 10 min and analyzed spectrophotometrically at $\lambda_{max}$ 363.6 nm

#### *Preparation of FSMs with the Selected Variables Using Box–Behnken Design*

*Design of Experiment.* Box–Behnken statistical screening design was used to optimize and evaluate the effects of the material attributes and CPPs on the solubility and *in vitro* dissolution of FSMs. A three-factor, three-level design used is suitable for exploring quadratic response surfaces and constructing second-order polynomial models with Design Expert (Version 7.0.0, Stat-Ease Inc., Minneapolis, MN, USA).

The Box–Behnken design was specifically selected since it requires fewer runs than a central composite design (13), in cases of three or four variables. The nonlinear computer-generated quadratic model is given as:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 + b_{11}X_1^2 + b_{22}X_2^2 + b_{33}X_3^2$$

where, $Y$ is the measured response associated with each factor level combination, $b_0$ is an intercept, $b_1$ to $b_{33}$ are regression coefficients computed from the observed experimental values of $Y$, and $X_1$, $X_2$, and $X_3$ are the coded levels of independent variables. The terms $X_1X_2$ and $X^2_i$ ($i$=1, 2, or 3) represent the interaction and quadratic terms, respectively. Materials attributes, CPP (process input) and CQAs (process output) selected are shown in Table I. Materials attributes studied were the amount of polymer HPMC ($X_1$), hydrophilic surfactants Inutec® SP1 ($X_2$), and Pluronic® F-127 ($X_3$). CPPs were PM or solvent evaporation (SE) as the method of preparation of FSMs ($X_4$). The CQAs were the initial maximum solubility after 30 min ($Y_1$), the equilibrium

**Table I.** Process Inputs and CQAs of FSMs in Box–Behnken Design

| Variables | Levels | | |
|---|---|---|---|
| | Low | Medium | High |
| Independent (process inputs) | | | |
| Material attributes | | | |
| $X_1$=amount of polymer HPMC (mg) | 50 | 75 | 100 |
| $X_2$=amount of polymeric surfactants, Inutec SP1 (mg) | 0 | 15 | 30 |
| $X_3$=amount of Pluronic F127 (mg) | 0 | 25 | 50 |
| Critical process parameter (CPP) | | | |
| $X_4$=preparation technique | PM | – | SE |
| Dependent (CQAs) | Successful operating ranges | | |
| $Y_1$=maximum solubility after 30 min (μg/mL) | $Y_1 \geq 75$ μg/mL | | |
| $Y_2$=equilibrium solubility after 24 h (μg/mL) | $Y_2 \geq 45$ μg/mL | | |
| $Y_3$=dissolution efficiency DE (%) | $75\% \leq Y_3 \leq 95\%$ | | |

solubility after 24 h ($Y_2$; which indicates solubility after crystallization) and the dissolution efficiency ($Y_3$). The optimum formulation of this study was selected to have maximum solubility and dissolution rate and minimum crystallization from supersaturated solution.

*Preparation of FSMs.* FSMs were prepared by PM and SE techniques (batch size was 20 times the weight of each FSM). In SE technique, felodipine and HPMC were dissolved or dispersed in ethanol, then the polymeric surfactants were added to the drug/HPMC dispersion. The resulting mixture was dried in a 45°C oven for 24 h. The solid mixtures were then scraped out with a spatula and stored in desiccators at room temperature. Different solid mixtures of felodipine were prepared using the following excipients: HPMC, Pluronic® F127, and Inutec® SP1. Table II depicts the composition of the prepared FSMs.

### *Evaluation of FSMs Prepared Using Box–Behnken Design*

*Determination of Initial Maximum Solubility and Equilibrium Solubility (CQAs) of the Prepared FSMs in Distilled Water.* A known excess amount of each FSM was added to 10 mL distilled water in amber-colored glass vials and left in a thermostatically controlled shaking water bath maintained at 25°C for 24 h. A sample was withdrawn after 30 min to determine the initial maximum solubility ($Y_1$) and another one was taken after 24 h to determine the equilibrium solubility ($Y_2$) which corresponds to drug concentration after the possible crystallization from the supersaturation solution (14). The samples were centrifuged at 5,000 rpm for 10 min and the concentration of the drug in the supernatant was determined spectrophotometrically at $\lambda_{max}$ 363.6 nm. All experiments were conducted in triplicates.

*In Vitro Dissolution of Felodipine from the Prepared FSMs in 0.5% Sodium Lauryl Sulfate Solution.* The release characteristics of felodipine from the prepared FSMs were determined according to the USP dissolution II paddle method at a rotation speed of 50 rpm in 500 mL 0.5% sodium lauryl sulfate (SLS) solution at 37±0.5°C using a dissolution tester. An accurately weighed amount of each of the prepared systems equivalent to 10 mg of felodipine was placed in each vessel. The paddle was placed at 2.5 cm from the bottom of the vessel. At appropriate time intervals of 5, 10, 15, 20, 30, 45, and 60 min, aliquots each of 5 mL were withdrawn from the dissolution medium and replaced with an equivalent amount of the fresh dissolution medium in order to maintain the volume in the vessel constant. The withdrawn samples were centrifuged at 5,000 rpm for 10 min and analyzed spectrophotometrically for felodipine content by measuring the absorbance at $\lambda_{max}$ 363.6 nm against 0.5% SLS solution as a blank. Each experiment was carried out in triplicate.

For assessment and comparison, the dissolution profiles were evaluated on the basis of the dissolution efficiency parameter (DE, $Y_3$) at 60 min (15,16), defined as;

$$\text{Dissolution efficiency (DE60 (\%))} = \int_0^t \frac{y.dt}{y_{100}.t}.100$$

where the integral is the area under the dissolution curve up to dissolution time $t$ and $y_{100}$ is the area of the rectangle described by 100% dissolution at the same time.

### *Development of Design Space of FSMs Having Optimum Quality*

The relationship between the process inputs (material attributes and process parameters) and CQAs were described in the design space. Design space was determined from the common region of successful operating ranges for multiple CQAs (Table I). The successful operating ranges for the maximum solubility ($Y_1$), equilibrium solubility ($Y_2$), and dissolution efficiency ($Y_3$) DE60 (%) were ≥75 μg/mL, ≥45 μg/mL, and $75\% \leq Y_3 \leq 95\%$, respectively. It is expected that operation within the design space will result in a product possessing the desired CQAs.

### *Determination of Control Strategy of the Optimized FSMs*

A control strategy is designed to ensure that a product of required quality will be produced consistently (2). The acceptable range of material attributes were determined based on design space.

The impact of storage of the optimized FSM at ambient temperature on product specifications and quality was

**Table II.** Composition and CQAs of FSMs Prepared by SE and PM Techniques

| FSM no. | HPMC (mg) $X_1$ | Inutec (mg) $X_2$ | Pluronic (mg) $X_3$ | Preparation technique $X_4$ | Max solubility (μg/mL) $Y_1$ | Equilibrium solubility (μg/mL) $Y_2$ | DE $Y_3$ |
|---|---|---|---|---|---|---|---|
| 1 | 50 | – | 25 | SE | 25.94 | 10.61 | 69.10 |
| | | | | PM | 15.12 | 7.60 | 44.62 |
| 2 | 100 | – | 25 | SE | 23.30 | 13.41 | 66.15 |
| | | | | PM | 14.28 | 6.31 | 47.84 |
| 3 | 50 | 30 | 25 | SE | 38.06 | 24.53 | 87.20 |
| | | | | PM | 32.85 | 18.38 | 51.99 |
| 4 | 100 | 30 | 25 | SE | 33.61 | 30.45 | 78.40 |
| | | | | PM | 43.35 | 27.93 | 42.34 |
| 5 | 50 | 15 | – | SE | 13.80 | 6.03 | 70.00 |
| | | | | PM | 9.13 | 7.32 | 47.61 |
| 6 | 100 | 15 | – | SE | 11.90 | 8.49 | 59.06 |
| | | | | PM | 7.74 | 6.76 | 29.02 |
| 7 | 50 | 15 | 50 | SE | 113.35 | 37.26 | 59.04 |
| | | | | PM | 35.22 | 35.70 | 54.62 |
| 8 | 100 | 15 | 50 | SE | 132.40 | 58.24 | 85.10 |
| | | | | PM | 28.09 | 47.15 | 43.10 |
| 9 | 75 | – | – | SE | 3.25 | 2.60 | 65.88 |
| | | | | PM | 2.21 | 1.62 | 41.99 |
| 10 | 75 | 30 | – | SE | 15.42 | 11.45 | 54.32 |
| | | | | PM | 19.39 | 16.48 | 36.45 |
| 11 | 75 | – | 50 | SE | 105.81 | 24.19 | 73.10 |
| | | | | PM | 29.35 | 23.97 | 50.55 |
| 12 | 75 | 30 | 50 | SE | 51.40 | 48.04 | 79.14 |
| | | | | PM | 49.50 | 48.50 | 46.47 |
| 13 | 75 | 15 | 25 | SE | 57.83 | 22.18 | 75.80 |
| | | | | PM | 31.62 | 23.58 | 57.85 |
| 14 | 75 | 15 | 25 | SE | 40.53 | 17.54 | 70.74 |
| | | | | PM | 28.04 | 23.24 | 38.37 |
| 15 | 75 | 15 | 25 | SE | 36.09 | 20.34 | 67.35 |
| | | | | PM | 27.77 | 23.35 | 40.22 |
| 16 | 75 | 15 | 25 | SE | 36.26 | 24.30 | 69.00 |
| | | | | PM | 23.85 | 16.82 | 43.55 |
| 17 | 75 | 15 | 25 | SE | 39.39 | 24.47 | 71.67 |
| | | | | PM | 28.49 | 23.63 | 36.21 |

All the prepared mixtures contain 10 mg drug

studied. The optimized FSM was stored in a glass vial wrapped in aluminum foil and kept in a dessicator at ambient temperature for 6 months. The stored samples were evaluated for solubility and dissolution as previously mentioned.

For easier manufacturing of CR tablets of felodipine, the impact of drying the alcoholic solution of the optimized FSM in the presence of silicified microcrystalline cellulose (Prosolv® SMCC90), a commonly used tablet excipients, on FSM quality was also studied. This alternative approach was called *in situ*-formed FSM. The optimized *in situ*-formed FSM was evaluated for solubility and dissolution as previously mentioned.

### *Thermal Analysis of the Optimized FSM*

Differential scanning calorimetry was performed using Shimadzu (DSC-50, Japan). Samples (4 mg) were placed in flat-bottomed aluminum pan and heated at a constant rate of 10°C/min in an atmosphere of nitrogen in a temperature range of 20–250°C. The differential scanning calorimetry (DSC) studies were performed for the pure drug, fresh optimized FSM, stored optimized FSM and optimized *in situ*-formed FSM.

### *Preparation of the CR Tablets Containing the Optimized In Situ-Formed FSM*

The alcoholic dispersion of felodipine with HPMC, Inutec ®sp1 and Pluronic® F-127 was mixed with Prosolv® SMCC90, left to dry for 1 h in an oven set at 50°C. The *in situ*-formed FSM was blended with lactose monohydrate, the retardant polymer (PEO and/or Carbopol® 974) and finally magnesium stearate was incorporated. Biconvex tablets were made by compressing 200 mg of each of the tested powder blends in a concave punch of diameter 9 mm using a single-punch tablet machine. The compression force was maintained constant to determine the effect of the components on the hardness of the prepared tablets. Table III depicts the composition of the CR tablets. Different concentrations of PEO and/or Carbopol® 974 were used to retard the drug release and linearize the

**Table III.** Composition of the CR Tablets Containing the Optimized *In Situ*-Formed FSM

| | Release retardant | | | |
|---|---|---|---|---|
| CR tablets | PEO 7,000,000 (%) | Carbopol® 974 (%) | Lactose monohydrate | Prosolv® SMCC 90 (mg) |
| CR-1 | 20 mg (10) | | 42.5 | 50 |
| CR-2 | | 20 mg (10) | 42.5 | 50 |
| CR-3 | 30 mg (15) | | 32.5 | 50 |
| CR-4 | | 30 mg (15) | 32.5 | 50 |
| CR-5 | 40 mg (20) | | 22.5 | 50 |
| CR-6 | | 40 mg (20) | 22.5 | 50 |
| CR-7 | 15 mg (7.5) | 15 mg (7.5) | 32.5 | 50 |
| CR-8 | 25 mg (12.5) | 5 mg (2.5) | 32.5 | 50 |
| CR-9 | | 50 mg (25) | 12.5 | 50 |
| CR-10 | | 40 mg (20) | 102.5 | 50 |

All CR tablets contain 85 mg *in situ*-formed FSM (containing 5 mg drug, 45.8 mg HPMC, 9.5 mg Inutec, and 24.7 mg Pluronic)
All CR tablets contain 2.5 mg magnesium stearate as lubricant (CR-10 contains 5 mg plain felodipine)

release profile to almost zero order. CR-10 (contains 5 mg plain felodipine) was formulated to study the effects of the polymers used for formulation of FSMs (Pluronic® F-127, HPMC and Inutec® SP1) on the *in vitro* release of the drug.

The dissolution of felodipine from the prepared CR tablets was performed in 500 mL phosphate buffer pH=6.5 containing 0.5% SLS (4) as previously mentioned.

## RESULTS AND DISCUSSION

Figure 1 shows the flow diagram of the different unit operations of the manufacturing process for CR tablets of felodipine. Felodipine, polymeric surfactant, and/or hydrophilic carrier are used to prepare FSMs using different preparation techniques (solvent wetting (SW), SE, PM or cogrinding). FSM is then blended with Prosolv® SMCC90, lactose monohydrate and PEO and/or Carbopol® for 10 min. The blend is then lubricated with magnesium stearate for 2 min and finally compressed into CR tablets. Based on scientific understanding and prior knowledge, the preparation of FSM, having high solubility and dissolution rate with minimum crystallization, is the most important unit operation for the development of CR tablets of felodipine.

### Identification of the Potential CQAs and Manufacturing Process (CPPs) of FSMs Required for Development of CR Tablets

According to QbD, pharmaceutical development includes identifying potential *CQAs* of the drug product, determining material attributes of excipients, selecting an appropriate manufacturing process (CPPs) and defining a *control strategy* (3). The potential CQAs of FSMs required for development of CR tablets were identified to be maximum solubility, minimum crystallization from supersaturated solution and maximum dissolution rate of felodipine. Figure 2 depicts the fishbone diagram that identifies potential variables that can have an impact on the desired quality attributes of FSM.

Four methods of preparation could be used for preparing FSM (Fig. 2). Preliminary studies were performed for selecting the appropriate method of manufacture. Solid mixtures of felodipine with the previously mentioned hydrophilic carriers and surfactants in ratio 1:5 were prepared by PM, SE, SW (8),

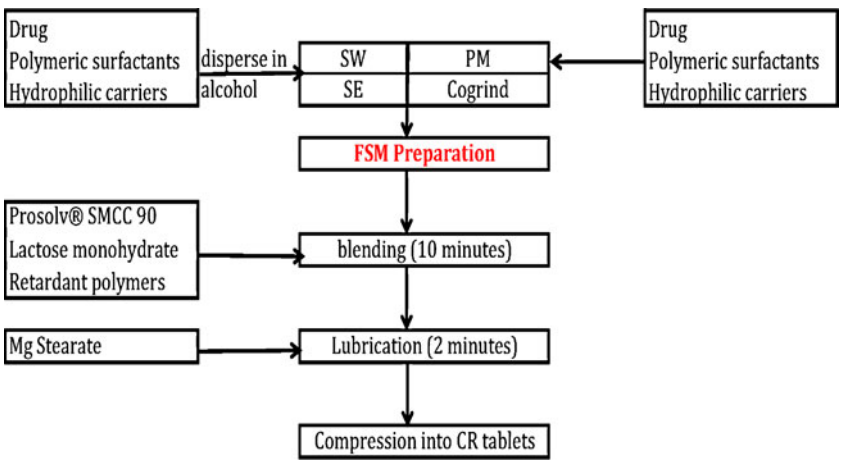


**Fig. 1.** The flow diagram of the different unit operations of the manufacturing process for CR tablets of felodipine

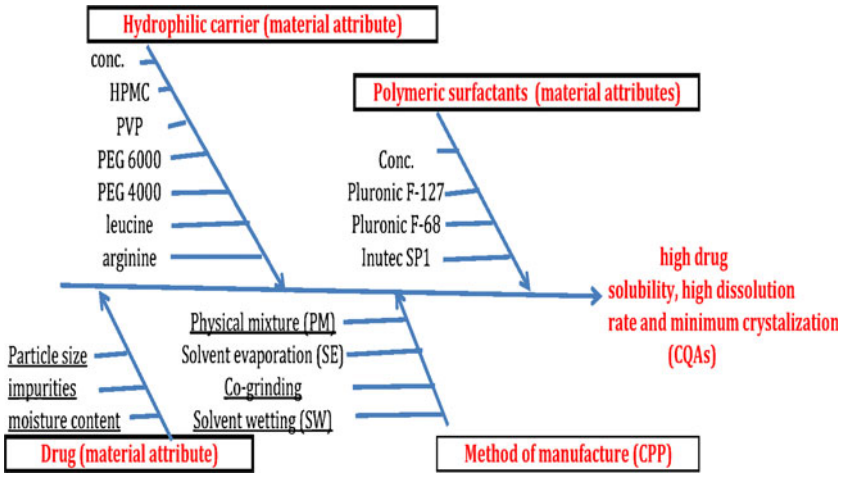


**Fig. 2.** Fishbone diagram that identifies potential variables that can have an impact on the desired quality attribute of FSM (*underlined* low-risk variable)

and cogrinding techniques (9). It was found that the mean solubility of the FSMs prepared using SE technique was significantly higher than that obtained from the other methods of manufactures ($p<0.0001$) and they can be arranged in descending order as follows: SE>PM~SW~cogrinding. Thus SE and PM techniques were selected to be the CPPs for development of FSM (PM technique was used for comparison).

The physical properties of solid felodipine such as particle size (material attributes of drug) was considered as low-risk variables that had no impact on the CQAs of FSMs because felodipine was dissolved in ethyl alcohol when prepared as FSM using SE technique.

## Identification of Material Attributes of Excipients Used for the Preparation of FSMs

*Screening the Effect of Different Hydrophilic Carriers and Polymeric Surfactants on the Solubility of Felodipine.* Various hydrophilic carriers and surfactants were used to enhance the solubility of felodipine (Fig. 2). In order to obtain a suitable polymer to solubilize felodipine, FSM with each of these excipients were prepared using PM technique. The equilibrium solubilities of the different felodipine physical mixtures in distilled water are shown in Fig. 3. The physical mixtures with the polymeric surfactants, Pluronic® F-127 or Inutec® SP1, significantly increased the equilibrium solubility of felodipine. The effect of the polymeric surfactants on the solubility is improved by increasing their concentrations. The physical mixtures of felodipine: Pluronic® F-127 (1:3, 1:5, and 1:10) improved the solubility of felodipine from 0.5 μg/mL (pure felodipine) to 24.12, 38.66, and 86.78 μg/mL, respectively. The solubilities of 1:3, 1:5, and 1:10 felodipine/Inutec® SP1 PMs were 14.30, 31.23, and 53.85 μg/mL, respectively. These results indicated that the wetting, solubilizing, and surface active effects of Pluronic® F-127 and Inutec® SP1 were the main mechanisms of the increasing solubility of felodipine (17–20).

The physical mixtures with the other hydrophilic carriers increased the solubility of felodipine two to four times due to the limited and/or lack of their surface active and solubilizing properties. The limited increase in solubil-

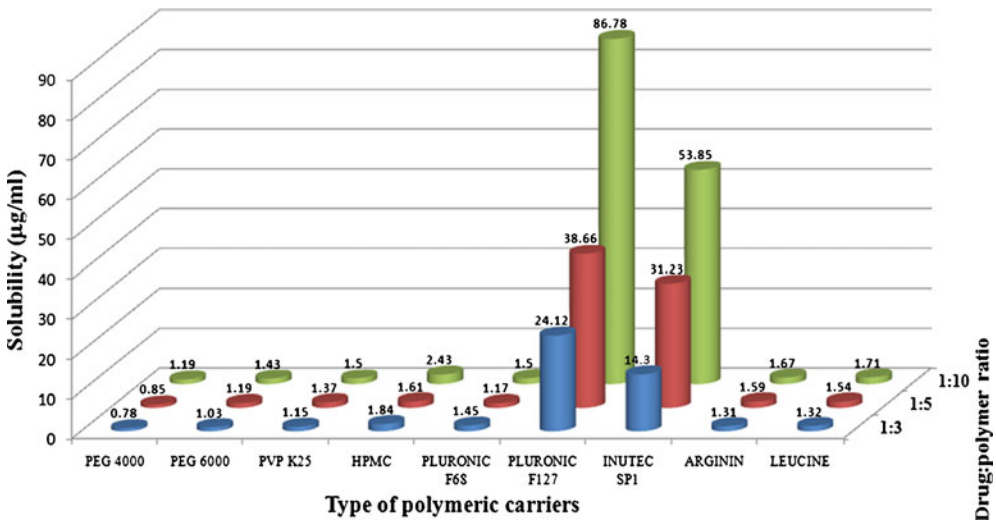


**Fig. 3.** Effect of different hydrophilic carriers and surfactants on the saturated solubility of felodipine in distilled water

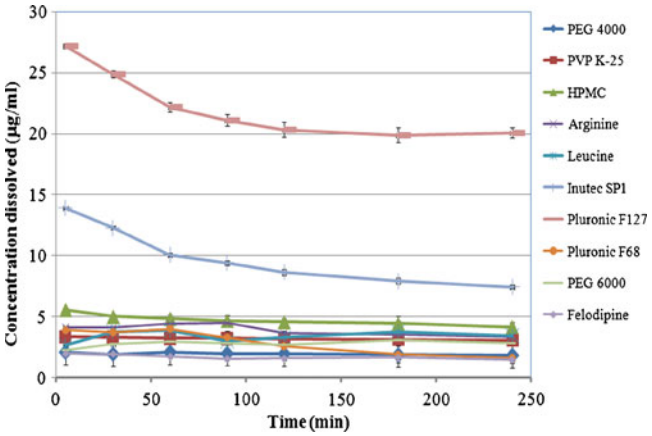


**Fig. 4.** The inhibitory effects of the hydrophilic polymers and polymeric surfactants on the crystallization of felodipine from supersaturated solution

ity of felodipine was due to the mild wetting effect of the hydrophilic carriers.

*Screening the Inhibitory Effects of Different Hydrophilic Carriers and Polymeric Surfactants on Crystallization of Felodipine from Supersaturated Solutions.* It is obvious that all the hydrophilic carriers and surfactants increased the solubility of felodipine through developing supersaturated solutions. Since the nucleation rate is dependent on the concentration, creating a highly supersaturated system leads to rapid nucleation of felodipine particles and precipitation from solution (12). The ability of polymers to inhibit crystallization of felodipine from a supersaturated solution were evaluated by adding a concentrated solution of felodipine to distilled water in which the polymers had been dissolved at concentration 500 µg/mL (corresponding to the highest drug/polymer ratio, 1:10) and then by measuring the solution concentration as a function of time.

The initial solution concentration of felodipine that was obtained by addition of the concentrated drug solution was 50 µg/mL. As shown in Fig. 4, in the absence of polymer, the concentration of felodipine rapidly declines until it reaches a concentration of 1.77 and 1.51 µg/mL at 1 and 4 h, respectively. Pluronic ® F 127 and Inutec ®SP1 maintained felodipine solution concentration above 22 and 10 µg/mL, respectively, after 1 h. It was reported that inclusion of polymeric surfactants in formulation with poorly soluble drug maintained solution concentrations that were higher than the equilibrium solubility of crystalline drug due to solubilizing effect and surface activity of the polymeric surfactants (8,21).

The other polymers also maintained solution concentration of felodipine above its equilibrium solubility but at a remarkable lower level than that obtained by Pluronic ® F 127 and Inutec ®SP1. HPMC maintained the supersaturation of felodipine at 4.86 and 4.18 µg/mL at 1 and 4 h, respectively (Fig. 4). The inhibition of crystallization and crystal growth by polymers have been previously reported (22–24). HPMC was found to have stabilizing and inhibitory effects on the solubilized drugs. This could be explained in terms of nucleation retardation in which association of the drug molecule with HPMC molecule occurs through hydrogen bonding due to presence of many hydroxyl binding sites in HPMC (11,12,25,26). Konno *et al.* reported that the crystal growth of felodipine is greatly inhibited in the presence of cellulose polymers such as HPMC (12).

## Optimization of CQAs of the Prepared FSMs

System components were selected based on their ability to form FSMs having the highest solubility, maximum dissolution, and maximum inhibition of drug crystallization from supersaturated solution. The polymer (HPMC) and polymeric surfactants (Pluronic® F-127 or Inutec® SP1), that significantly solubilized felodipine and remarkably maintained its solution concentration above supersaturation, were selected to prepare FSMs using PM and SE techniques.

In order to rapidly obtain the optimal FSMs, Box–Behnken experimental design was applied in this study. Material attributes and CPP studied were the amount of HPMC ($X_1$), amount of polymeric surfactants Inutec® SP1 ($X_2$), amount of polymeric surfactants Pluronic® F-127 ($X_3$), and preparation techniques ($X_4$). The CQAs were initial maximum solubility after 30 min ($Y_1$), the equilibrium solubility after 24 h ($Y_2$), and the dissolution efficiency ($Y_3$). The composition and responses of these formulations are summarized in Table II.

The process inputs and response variables were related using polynomial equation with statistical analysis through Design-Expert® software. As shown in Table IV, the approximation of response values of log ($Y_1$) and SQRT ($Y_2$) based on the quadratic model was the most suitable. The values of the coefficients of material attributes are related to the effect of these variables on the CQAs. The larger

**Table IV.** Mathematical Equations that Link Material Attributes and Process Parameter to CQAs of FSMs Prepared According to Box–Behnken Design

| Response | Model | $R^2$ | Adjusted $R^2$ | Predicted $R^2$ | Reduced regression equations for the responses |
|---|---|---|---|---|---|
| $Y_1$ | Quad. | 0.9574 | 0.9438 | 0.9148 | SE<br>$\text{Log}(Y_1)=0.586+0.035X_2+0.039X_3-0.00056X_2X_3-0.00051X_2^2-0.00021X_3^2$<br>PM<br>$\text{Log}(Y_1)=0.386+0.046X_2+0.032X_3-0.00056X_2X_3-0.00051X_2^2-0.00021X_3^2$ |
| $Y_2$ | Quad. | 0.9552 | 0.9472 | 0.9323 | $\text{Sqrt}(Y_2)=1.199+0.001X_1+0.137X_2+0.043X_3+0.00041X_1X_3-0.0022X_2^2$ |
| $Y_3$ | Linear | 0.7982 | 0.7852 | 0.7548 | SE<br>$Y_3=65.23+0.216X_3$<br>PM<br>$Y_3=38.86+0.216X_3$ |

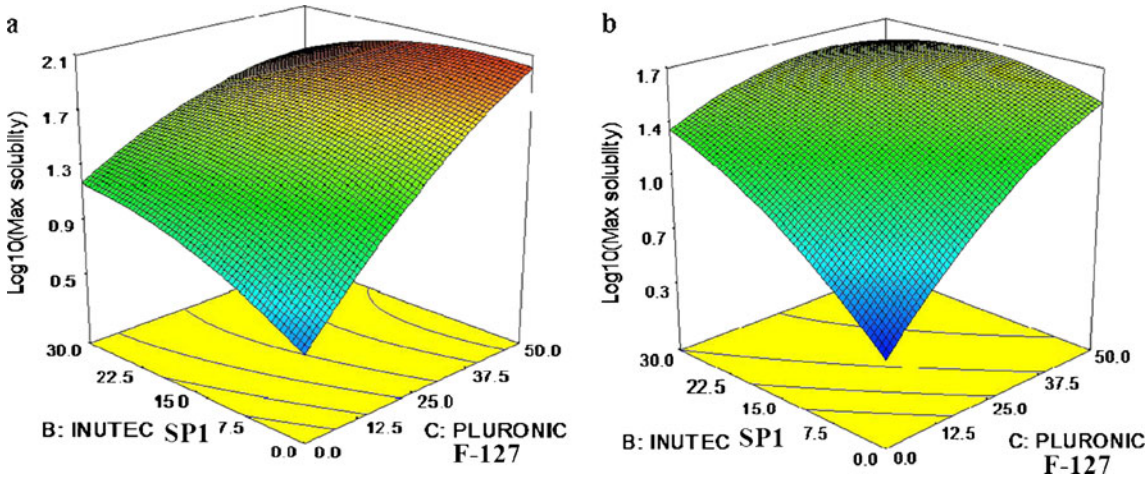


**Fig. 5.** Response surface (3D) plot of the effects of Inutec and Pluronic F-127 on the maximum solubility of FSMs prepared by SE (**a**) and PM (**b**) techniques

coefficient means the material attribute has more potent influence on the response.

Table II shows that maximum solubility after 30 min varied between 2.2 and 132.4 μg/mL. The highest values of maximum solubilities were obtained by FSMs containing the highest Pluronic® F-127 content and prepared by SE techniques (FSMs 7, 8 and 11). This result was similar to earlier studies which reported that solid dispersions of felodipine with Pluronic® F-127 by supercritical antisolvent precipitation methods enhanced the solubility and dissolution of felodipine (14). Based on the calculated model for the maximum solubility using SE and PM techniques, response surface (3D) plot are shown in Fig. 5a, b, respectively. The effect of Inutec® SP1 on maximum solubility differed according to the level of Pluronic® F-127 in FSM. At lower levels of Pluronic® F-127, increasing Inutec® SP1 content continuously increased the solubility of felodipine. However, at the highest levels of Pluronic® F-127, increasing Inutec® SP1 content up to 15 mg in FSM maintained higher values of felodipine solubility followed by slight reduction of solubility values. As shown in Table II, FSM 12 prepared by SE (50 mg Pluronic and 30 mg Inutec® SP1) had approximately half the maximum solubility of FSM 11 prepared by the same technique (50 and 0 mg Inutec). Thus, higher content of both Pluronic® F-127 and Inutec® SP1 had a negative effect on the maximum solubility of FSMs especially those prepared by SE technique. This could be due to the possible interaction of both polymeric surfactants. The amount of HPMC had limited and nonsignificant effects on the initial maximum solubility of felodipine ($Y_1$; $P$=0.6651).

From Table IV, it can be inferred that the three material attributes have a significant effect on equilibrium solubility ($Y_2$). However, the preparation technique had a nonsignificant effect on $Y_2$ ($P$=0.1849). Figure 6a, b shows response surface (3D) plots of the effect of the different material attributes on the average equilibrium solubility of FSMs prepared by both SE and PM techniques. It is obvious that the highest equilibrium solubility was obtained when using

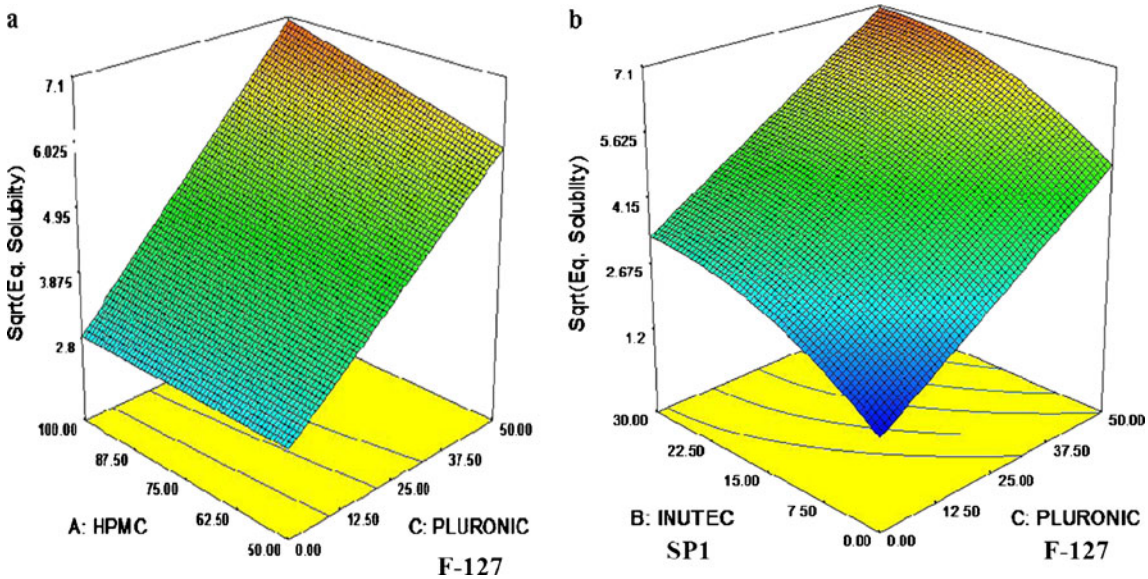


**Fig. 6.** Response surface (3D) plot of the effect of the different material attributes on the average equilibrium solubility of FSMs prepared by both SE and PM techniques, **a** HPMC/Pluronic F-127, **b** Pluronic F-127/Inutec SP1

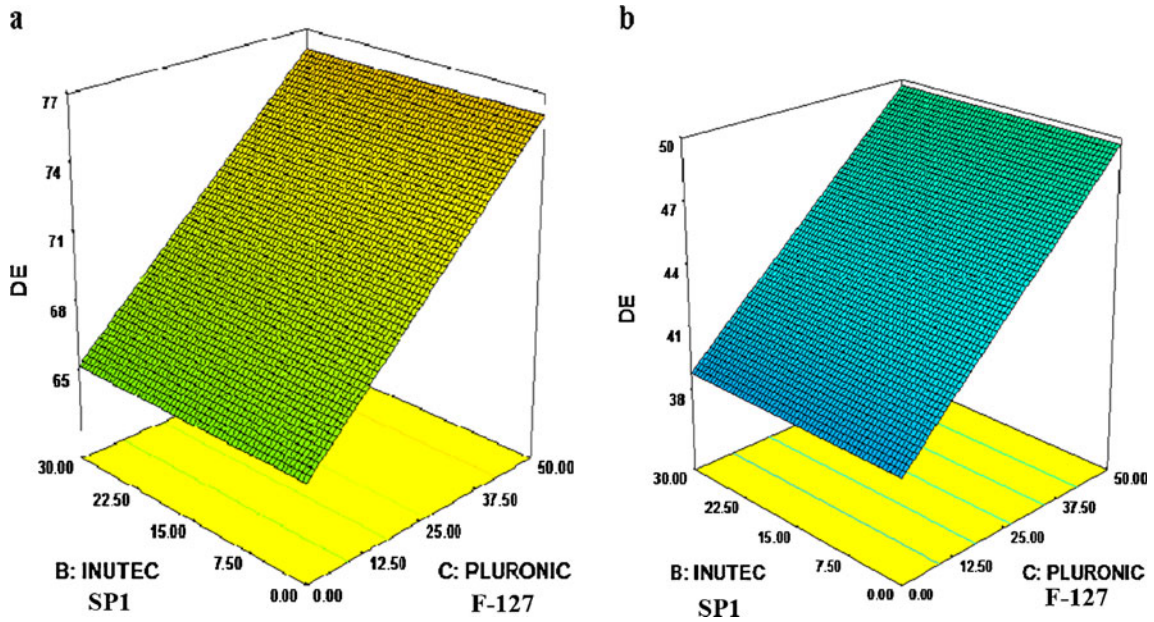


**Fig. 7.** Response surface (3D) plot of the effects of Inutec and Pluronic F-127 on the dissolution efficiency of FSMs prepared by SE (**a**) and PM (**b**) techniques

the material attributes in their maximum levels. This could be due to the ability of the three polymers to inhibit crystallization of felodipine from supersaturated solution as previously confirmed. The relatively large coefficient of $X_2$ in the polynomial equation for $Y_2$ (Table IV) indicates that the amount of Inutec® SP1 in the prepared FSMs is extremely important in retarding the crystallization of felodipine.

Table IV shows that the approximation of response values of $Y_3$ based on the linear model was the most suitable. Figure 7a, b shows response surface (3D) plots of the effect of both Pluronic® F-127 and Inutec® SP1 on the dissolution efficiency of FSMs prepared by SE and PM techniques, respectively. It is obvious that only the content of Pluronic® F-127 in the prepared FSMs ($X_3$) and the preparation technique ($X_4$) had significant effects on the dissolution efficiency of felodipine ($Y_3$; Table IV).

## Development of Design Space of the Prepared FSMs

The aim of the optimization of pharmaceutical formulations is generally to determine the levels of input variables from which a robust product with high quality may be produced. The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality is termed the design space (2). Working within the design space is not considered as a change and nearly gives the desired product quality of the optimum CQAs. However, movement out of the design space is considered to be a change and gives a pharmaceutical product of low quality. Design space could be determined from the common region of successful operating ranges for the three CQAs (responses). These responses were combined to determine an

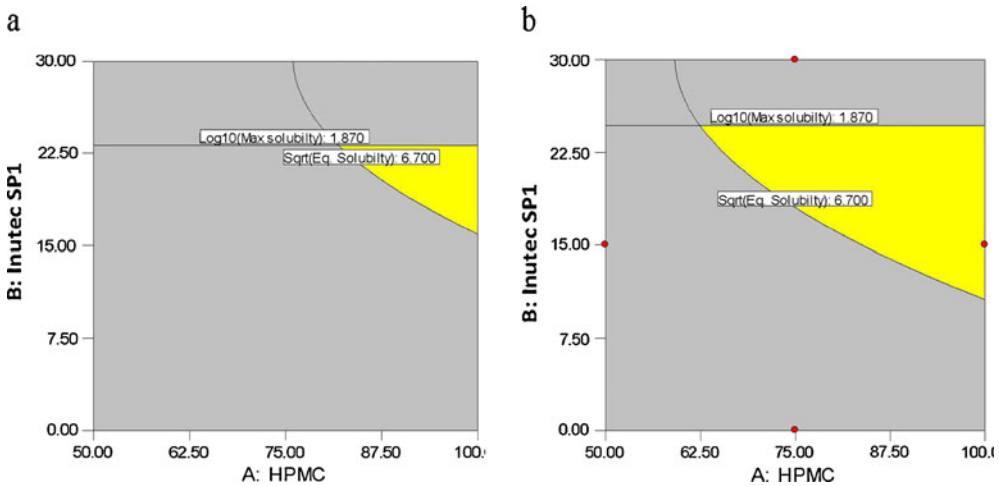


**Fig. 8.** Design space of FSMs prepared by SE comprised of the overlap region of ranges for the three CQAs using Pluronic® content of 45.1 mg (**a**) and 50 mg (**b**)

**Table V.** Predicted and Observed Responses (CQAs) of Optimized FSM (Fresh and Stored)

| Variables | Amounts (mg) | Response | Observed values (fresh) | Predicted values | Observed values (stored) |
|---|---|---|---|---|---|
| Amount of HPMC ($X_1$) | 91.33 | Maximum solubility ($Y_1$) | 110.2 μg/mL | 90.36 μg/mL | 104.3 μg/mL |
| Amount of Inutec ($X_2$) | 18.72 | Equilibrium solubility ($Y_2$) | 58.7 μg/mL | 49.02 μg/mL | 54.3 μg/mL |
| Amount of Pluronic ($X_3$) | 49.19 | DE60 (%) ($Y_3$) | 72.4% | 75.9% | 71.5% |
| Preparation technique ($X_4$) | SE | | | | |

all over optimum region. Figure 8a, b shows the proposed design space, comprised of the overlap region of ranges for the three CQAs using Pluronic® F-127 content of 45.1 and 50 mg, respectively. There is no proposed design space was formed if the Pluronic ®content was below 45.1 mg and if PM is used as the preparation technique.

### Determination of Control Strategy of the Prepared FSMs

The control strategy of the optimized FSMs was determined to ensure process performance and product quality. The control space (or normal operating ranges) is defined as the upper and/or lower limits for the critical material attributes and CPP between which the parameters are routinely controlled during production in order to assure reproducibility (3). The control space should be within the design space. If the control space is much smaller than the design space, the process is then considered robust. It is obvious that increasing the Pluronic® F-127 content in FSMs remarkably increases the design space. In case of low levels of Pluronic® F-127, the optimum ranges of Inutec® SP1 and HPMC are 16–23 and 83–100 mg, respectively. However, in case of high levels of Pluronic® F-127, the optimum ranges of Inutec® SP1 and HPMC are 11–23 and 63–100 mg, respectively (Fig. 8). Thus, the operating ranges (control space), for robust development of FSM of desired quality, of Pluronic® F-127, Inutec® SP1, HPMC, and preparation technique are 49–50, 16–23, 83–100 mg, and SE, respectively.

An FSM satisfying these criteria was prepared and evaluated. The FSM composition is reported in Table V, along with the predicted and observed responses. An optimum response was found with $Y_1$, $Y_2$, and $Y_3$ of 110.2 μg/mL, 58.7 μg/mL, and 72.45% at $X_1$, $X_2$, and $X_3$ values of 91.33, 18.72, and 49.19 mg, respectively, using SE technique. To verify these values, the optimum formulation was prepared according to the above values of input variables and subjected to previous tests. The predicted and observed values of CQAs of the optimum formulation are nearly similar. A good agreement is obtained between the model prediction and experimental observation. Thus, the validity of the model was established.

The effect of storage of the optimized FSM at ambient temperature for 6 months on the CQAs was studied. It was found that there was no significant difference between the CQAs of fresh and stored FSMs (Table V). Figure 9 shows DSC thermogram of the felodipine (having characteristic endothermic peak at about 142°C), freshly prepared, stored, and *in situ*-formed FSMs. The disappearance of the endothermic peak in the thermogram of the freshly prepared FSMs indicates the conversion of felodipine from the crystalline into the amorphous state which explains high solubility of the optimized FSMs. The reappearance of very small endothermic peak in the thermogram of the stored FSM indicates slight crystallization of the amorphous felodipine without affecting the CQAs of the optimized FSMs.

### Preparation of *In Situ*-Formed FSM

The difficulty of grinding the hard scales of the optimized FSM prepared by SE technique, to be easily incorporated into the CR tablets, encouraged us to study the effect of drying the alcoholic dispersion of the optimized FSM in presence of Prosolv® SMCC90 (a commonly used tablet filler). This alternative approach was called *in situ*-formed FSM. Both of the optimized FSM and *in situ*-formed optimized FSMs have identical DSC thermograms indicating the ability of the two operating approaches to prepare FSM of the desired quality (Fig. 9). The *in situ*-formed FSM approach facilitates the manufacture of tablet using a technique similar to wet granulation technique.

### Preparation of the CR Tablets Containing the Optimized *In Situ*-Formed FSM

Development of CR tablets of sparingly soluble drug should involve both increasing the solubility of the drug and

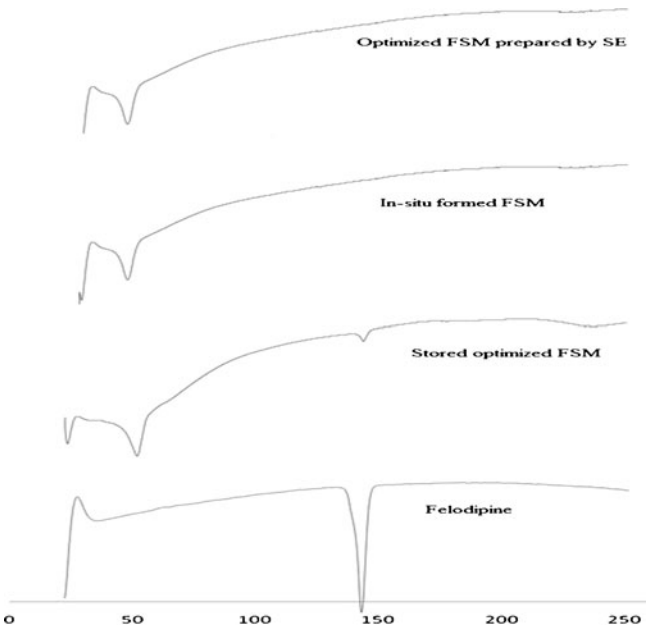


**Fig. 9.** DSC thermograms of the felodipine, stored optimized FSM, fresh optimized FSM and optimized *in situ*-formed FSM

controlling its release rate from the tablet. All the powder blends of the CR tablets showed good flow properties due to the presence of Prosolv® SMCC90. Figure 10 shows release profiles of felodipine from CR tablets in phosphate buffer pH=6.5 containing 0.5% SLS showing the values of time required for the release of 75% of the drug ($t_{75\%}$). It is obvious that the drug was rapidly released at lower concentration of retardant polymers due to lesser degree of swelling leading to increased regions of low microviscosity in the gel structure for the drug to channel through resulting in faster drug release (27). In general, tablets prepared with Carbopol® 974 showed higher control of release over PEO used in the same ratio. This could be explained by the fact that Carbopol® 974 polymers exhibit higher swelling than PEO resulting in an increase of the diffusional path length of drug and the consequent reduction of drug release. In addition, the thick gel layer formed on the swollen film surface is capable of preventing matrix disintegration and controlling additional water penetration (28). However, tablets made with PEO form weaker gels which tend to be eroded more quickly (29). CR-7 containing a mixture of PEO and Carbopol® 974 (1:1, *w*/*w*) remarkably retarded the release of the drug ($t_{75\%}$=22.5 h). This could be due to the formation of interpolymer complex between Carbopol® 974 and PEO through hydrogen bond formation and this hydrophobic complex retards the release of the drug (30). Increasing the concentration of Carbopol® 974 in the tablet matrix above 15% had nearly no effect on drug release but resulted in linearization of the release profile to almost zero order.

To study the effects of the polymers used for formulation of felodipine solid mixture (Pluronic® F-127, HPMC and Inutec® SP1) on the *in vitro* release of the drug, the release of felodipine from CR-10 was performed. It is obvious that CR-10 showed the highest drug release ($t_{75\%}$=5.85 h). This observation confirms that the prolongation of the release time might be due to an interaction between Pluronic® F-127, Carbopol® 974, and HPMC which retards the disintegration of the tablet matrix (4). It was reported that the release of drug from HPMC/Carbopol® 974 may be hindered due to a 3D network like structure formed by interpolymer complexation following the penetration of dissolution medium into the tablet. Thus, Pluronic® F-127 and HPMC had dual action in the developed CR tablets of felodipine. Not only did their ternary mixture with Inutec® SP1 enhanced the dissolution rate and inhibited crystallization of felodipine, but also they aid Carbopol® 974 in controlling felodipine release from the tablet matrix.

The release profiles of the CR-6 tablet containing the optimized *in situ*-formed FSM and the target release model (zero-order releasing about 100% of drug in 16 h and deduced form the dissolution profile of a marketed extended release tablet of felodipine) are presented in Fig. 11. These release profiles were compared using the fit factor, similarity factor (*f2*; 31). The calculated value of *f2* was 56.85 indicating that the release profile of the CR-6 tablet containing the optimized *in situ*-formed FSM was similar to that of the target release profile.

## CONCLUSION

In this study, QbD was applied for pharmaceutical development of FSM, containing hydrophilic carriers and/or polymeric surfactants, reported to be solubility enhancers and crystallization inhibitors for development of CR of felodipine. Box–Behnken experimental design was applied to develop space design and determine the control space of FSMs. There was no proposed design space is formed if the Pluronic ®content was below 45.1 mg and if PM is used as the preparation technique. The operating ranges (control space), for robust development of FSM of desired quality, of Pluronic® F-127, Inutec® SP1, HPMC, and preparation technique are 49–50, 16–23, 83–100, and SE, respectively. The release profiles of CR tablet containing the optimized *in situ*-formed FSM was comparable to that of the target release profile deduced form the dissolution profile of a marketed extended release tablet of felodipine. The mixture of Pluronic® F-127 and HPMC had a dual action. In the optimized FSMs, they enhanced the dissolution rate and inhibit crystallization of felodipine. However, they aided Carbopol® 974 in controlling felodipine release from the CR tablet matrix. Our results proposed that pharmaceutical QbD and DOE were successfully applied for enhancement of the solubility and dissolution of a class II BCS drug and development of promising once-daily CR tablets of felodipine.

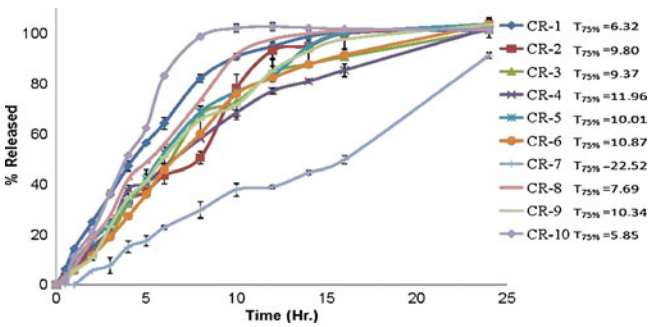


**Fig. 10.** The release profiles of felodipine from the CR tablets containing the optimized *in situ*-formed FSM in phosphate buffer pH=6.5 containing 0.5% SLS (showing the values of time required for the release of 75% of the drug ($t_{75\%}$))

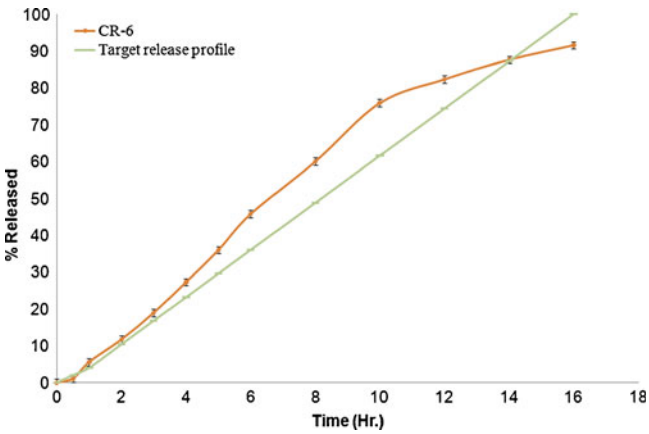


**Fig. 11.** *In vitro* release of felodipine from CR-6 tablets containing the optimized *in situ*-formed FSM and the target release profile

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