RESEARCH ARTICLE

Development and Evaluation of Fast-dissolving Oral Film of Poorly Water-soluble Drug Felodipine

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Abstract

Aim: The objective of the presented research work was to develop and evaluate fast-dissolving oral film containing solid dispersion of Felodipine (FnFDFs) for improvement of its water solubility, dissolution, and oral bioavailability by avoiding the first pass metabolism, providing faster onset of action and avoidance of problem of dysphasia. **Materials and Methods:** First, solid dispersion (SDP) of Felodipine was prepared using solvent evaporation method using PVP-K30 as hydrophilic polymeric carrier in different proportions. FnFDFs were prepared using solvent casting method and optimized using Box–Behnken design by applying design-expert. The concentration of HPMC-E5 (40–45% w/w) as a film forming polymer, propylene glycol (10–15% w/w of polymer) as a plasticizer, and croscarmellose (1–5% w/w) as disintegrating agent was selected as independent variables and tensile strength, disintegration time and percentage drug dissolution was selected as a response variables. Further, FnFDFs were evaluated based on uniformity of mass, thickness, percentage drug content, folding endurance, surface pH, moisture uptake, percentage swelling, percentage elongation, tensile strength, *in vitro* disintegration time, *in vitro* percentage drug dissolution or release study, stability study, surface morphology using scanning electron microscope, *ex vivo* permeation study, and *in vivo* pharmacokinetic study. **Results and Discussions:** Fourier transform infrared and differential scanning calorimetry analysis revealed the compatibility between drug and excipients. Results of evaluation of FnFDFs suggested satisfactory performance for all the parameters. FnFDFs indicated *in vitro* disintegration time of 22.84 ± 0.31 s and *in vitro* percentage drug dissolution of 97.09 ± 1.54% up to 10 min, thus suggested faster drug dissolution. Moreover, *in vivo* pharmacokinetic study in rats revealed faster absorption and around 90% of oral bioavailability up to 1–2 h for FnFDFs through the buccal administration in comparison with that slow absorption and around 20% of oral bioavailability up to 3 h for oral suspension of Felodipine through gastrointestinal tract. **Conclusion:** Based on the results, it was concluded that fast-dissolving oral film contained SDP of drug may provide the merits of faster onset of action, avoidance of extensive first-pass metabolism, enhanced bioavailability, and improved patient compliance for the delivery of poorly water-soluble drug such as Felodipine.

Key words: Bioavailability, Felodipine, Solid dispersion and fast-dissolving oral film of solid dispersion of Felodipine

INTRODUCTION

Felodipine is a calcium-channel blocker which is used as antihypertensive and antianginal drug. It is poorly water-soluble drug which undergoes extensive first-pass metabolism and thus has oral bioavailability of around 15%.[1,2] Delivery of poorly water-soluble drugs by the oral route has been difficult due to insufficient amount of drug dissolved for absorption from the gastrointestinal tract.[3] Although, there are number of formulation strategies have been employed to enhance the dissolution rate of poorly soluble drugs such as particle size reduction, modification of crystal habits, salts formation, complex

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formation with cyclodextrin, use of surfactants, solid dispersions (SDP), fast-dissolving oral films (FDFs), lipid-based formulations, and prodrug approaches.[4,5] Preparation of SDP is a better approach for improving drug solubility because it is easier to produce and more applicable.[6] Fast-dissolving dosage forms were initially prepared for providing substitute to conventional solid dosage forms to achieve better patient compliance.[7] In addition, fast-dissolving oral films (FDFs) showed a great potential over other dosage forms for the delivery of poorly soluble drugs since they provide distinct advantages including rapid disintegration and dissolution in the oral cavity thus increase bioavailability with faster onset of action and avoidance of first-pass effect.[8] Due to high permeability of oral mucosa, it allows direct access of drug to the systemic circulation and avoids the first pass metabolism.[9] FDFs represent an advantageous dosage form, especially for geriatric and pediatric patients.[10,11] Quality by design as a more holistic approach can be applied to assure the quality of the product. It provides a basis for optimizing and improving the manufacturing operation.[12]

MATERIALS AND METHODS

Materials

Felodipine was obtained as a gift sample from Cipla Ltd. HPMC-E5, croscarmellose and methyl cellulose were obtained as a gift sample from Signet Chemicals. All other chemicals were purchased from Loba chemicals.

Methods

Solubility determination

The solubility of Felodipine was determined using saturation solubility method. An excess amount of Felodipine was added to 10 ml of distilled water, phosphate buffer pH 6.8, ethanol, and acetonitrile separately in a glass vials. The content of vials was mixed vigorously for 30 min, and further solutions were shaken mechanically to equilibrate. After 72 h, the content of each vial was centrifuged for 10 min at 2500 rpm. The supernatant of each vial was filtered through 0.45 µ membrane filter and then, filtrate was diluted suitably with solvent. The concentration of Felodipine was analyzed using double beam UV visible spectrophotometer (UV1800, Shimadzu, Japan) at 237.1 nm against blank.[13]

FTIR analysis

FTIR spectrum of the HPMC-E5, PVP-K30, Felodipine, physical mixture of Felodipine with HPMC-E5, and physical mixture of Felodipine with PVP-K30 was recorded using FTIR spectrophotometer (FTIR-84008, Shimadzu, Japan) to study the incompatibility over the wavelength range of 4000–400/cm by preparing a dispersion of samples in KBr.[14,15]

DSC analysis

DSC-Thermogram of HPMC-E5, PVP-K30, Felodipine, physical mixture of Felodipine with HPMC-E5, and physical mixture of Felodipine with PVP-K30 were recorded using DSC (DSC-60, Shimadzu, Japan) to study the incompatibility. The heating rate of 10°C/min in the range of 3−400°C under inert nitrogen environment at a flow rate of 40 ml/min was used. The samples (2−3 mg) were put in aluminum sampling pan against empty aluminum pan as reference standard.[14,16]

Preparation of SDP of Felodipine

SDP of Felodipine was prepared using solvent evaporation method using PVP-K30 as hydrophilic polymeric carrier in drug:polymer ratio of 1:1, 1:2, 1:3, and 1:4 to find out the best ratio based on the improvement of water solubility. Weighed amount of Felodipine and PVP-K30 was dissolved in ethanol to get a clear solution and was further stirred continuously at 40°C until complete solvent gets evaporated to obtain solid mass. Then, solid mass was passed through the sieve no. 44 and stored in a desiccator until used for further studies.[15-17]

Formulation of FnFDFs

FnFDFs were prepared using solvent casting method by dissolving weighed amount of SDP of Felodipine (equivalent weight of 10 mg of Felodipine), HPMC-E5 (40–45% w/w), and propylene glycol (10–15% w/w of polymer) in 10 ml of distilled water with continuous stirring on a digital magnetic stirrer at 800 rpm for 1 h. Subsequently, required amount of croscarmellose (1–5% w/w), methyl cellulose (1.2% w/w), tween-80 (2% w/w), citric acid (1% w/w), disodium EDTA (0.5% w/w), sorbitol (2% w/w), peppermint oil (Q.S.), and indigo carmine (Q.S.) was gradually added to the casting solution under constant stirring at 1200 rpm at room temperature until a clear solution was obtained. As solution became clear, casting solution was then stirred for 4 h at 100 rpm to disappear entrapped air blisters. The resulting solution was then casted on a fabricated glass mold lubricated with glycerin and allowed to dry completely at room temperature to form film. The dried films were carefully separated from the glass mold and cut to produce six square-shaped FnFDFs of 2 cm^2 with an approximate weight of 150 mg and were stored in double wrapped aluminum foils.[18,19]

Optimization of FnFDFs

Formulation of FnFDFs was optimized using Box–Behnken design by applying design-expert to obtain desired and optimum characteristics. HPMC-E5 (A), propylene glycol (B), and croscarmellose (C) were selected as an independent variable and tensile strength (R1), disintegration time (R2), and percentage drug dissolution (R3) were selected as dependent or response variables. Subsequently, the experimental design was analyzed for various models such as quadratic, linear, 2FI, and mean to find out the best fit model on the basis of

responses of the dependent variables. Further, statistical validity using ANOVA and cube plots were established to find the compositions of the optimized formulation.[9,20,21]

Evaluation of FnFDFs

Uniformity of mass

Twenty randomly selected FnFDFs were weighed on digital balance. Films of 2 cm^2 were cut from the different places of the casted film and then, average mass were calculated.[18]

Thickness

It was determined using digital vernier caliper at five different points of films including four corners and middle point.[18]

Percentage drug content

FnFDFs (2 cm^2 film containing equivalent of 10 mg of Felodipine) were dissolved in phosphate buffer pH 6.8. The samples were filtered using 0.45 µ membrane filter, diluted, and analyzed for percentage drug content by double beam UV visible spectrophotometer (UV1800, Shimadzu, Japan) at 237.1 nm.[22]

Folding endurance

It was determined by repeatedly folding the film at the same place until it broken. The number of folding times that film had taken to broke was noted and considered as folding endurance.[23]

Surface pH

FnFDFs were moistened with distilled water and pH at the metaphase of water and film was recorded using pH meter (MKVI, Systronics, Ahmedabad).[24]

Moisture uptake

It was determined by placing FnFDFs (2 cm^2) in a desiccator for 24 h to ensure the complete drying of the film before the actual test. FnFDFs were then weighed in dry form and further placed at 75% of RH for 1 week. Then FnFDFs were reweighed and percentage increased weight as a moisture uptake was noted.[22]

Percentage swelling

It was determined by placing previously weighed FnFDFs (2 cm^2) in a beaker and then poured 50 ml of phosphate buffer pH 6.8 on it. The increased weight of the FnFDFs was calculated after 60 min by removing it from beaker using the following formula:

$$\% S=(Ws-Wi)/Wi\times100$$

Where, % S is percentage swelling, Ws is the weight of swollen film , and Wi is initial weight of film at zero time.[25]

Percentage elongation

It was determined by stretching FnFDFs with sufficient force required to exceed the elastic limit of the film up to the breaking of the film. It was calculated by using following equation:[23]

% Elongation=Increase in length at breaking point (cm)/ Original length (cm) ×100.

Tensile strength

FnFDFs (2 cm^2) were placed and fixed between two clamps of tensile tester positioned at the distance of 2 cm and load or force required to break the film was measured by pulling the bottom clamp with 30 inch/min. Then, tensile strength was calculated using the following formula:[26,27]

Tensile strength (N/m^2)=Load at failure × 100/cross-sectional area of the film.

In vitro disintegration time

FnFDFs (2 cm^2) were allowed to disintegrate by putting them in a 20 ml of phosphate buffer pH 6.8 in glass petri plate with mild agitation. The time at which FnFDFs broke or disintegrated was noted as disintegration time with stopwatch.[22]

In vitro drug dissolution or release study

The *in vitro* drug dissolution test of FnFDFs (2 cm^2 film containing equivalent of 10 mg of Felodipine) was carried out using USP paddle type dissolution testing apparatus (TDT-08L, Electrolab, Mumbai) and phosphate buffer pH 6.8 (300 ml) as dissolution medium up to 10 min. A piece of metal wire was attached with FnFDFs to avoid their floating property in dissolution medium and then placed at the bottom of the vessel. This study was performed at 37 ± 0.5°C and stirring rate of 50 rpm. Further, aliquots of 1ml was collected at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, and 10 min and 1 ml of the fresh dissolution medium was added to the vessel to maintain the volume of dissolution medium. Collected aliquots were filtered using 0.45 µ membrane filters and subsequently analyzed using double beam UV visible spectrophotometer (UV1800, Shimadzu, Japan) at 237.1 nm against blank. The percentage drug dissolution was calculated and further mechanism of drug release was determined by fitting the dissolution data into various kinetic models using DDsolver 1.0 software.[22,28]

Stability study

The stability study of optimized and validated FnFDFs was performed as per ICH Q1A guidelines to assess their physical and chemical stability. FnFDFs were stored in two different conditions at 25 ± 2°C/60 ± 5% RH and 40 ± 2°C/75 ± 5% RH up to 6 months. The samples were collected at 0, 30, 60, 90, 120, and 180 days and were analyzed for the estimation of physical parameters such as appearance and weight of film

and chemical parameter such as percentage drug content and surface pH.[9,25]

Surface morphology using scanning electron microscope (SEM)

Surface morphology of optimized and validated FnFDFs was observed using SEM (JEOL, JSM 5600, USA) at accelerating voltage of 0.5 kv–30 kv, resolution of 3.5 nm, and magnification of X18-1500X. The sample of film was placed in a sample holder of SEM and images were developed to observe surface morphology.[24,29]

Ex vivo permeation study

Ex vivo permeation study for optimized and validated FnFDFs (2 cm^2 film containing equivalent of 10 mg of Felodipine) was performed by using a Franz diffusion cell and membrane of porcine oral mucosa. Phosphate buffer pH 6.8 (13 ml) was used as a diffusion medium of receptor compartment and temperature was maintained at 37 ± 0.5°C. FnFDFs was fixed on the membrane at mid of receptor and donor compartment and diffusion medium was stirred at low speed. Further, aliquots of 1 ml was collected at 0, 1, 2, 3, 4, 6, 7, 8, 9, and 10 min and 1 ml of the fresh dissolution medium was added to the receptor compartment to maintain the volume of the diffusion medium. Collected aliquots were filtered using 0.45 µ membrane filter and subsequently analyzed using double beam UV visible spectrophotometer (UV1800, Shimadzu, Japan) at 237.1 nm against blank.[30]

In vivo pharmacokinetic study

In vivo pharmacokinetic study for FnFDFs was approved by the Institutional Animal Ethical Committee (IAEC) of Acropolis Institute of pharmaceutical education and research, Indore (Reg. No: 1627/PO/Re/S/2012/CPCSEA). Animals (7–8-week-old, male Sprague-Dawley rats were used and were accommodated with easy access of food and water at room temperature under ambient condition) were divided into three groups as follows: Group-1 was the control group which was treated with saline, group-2 was the standard group which was treated with standard formulation, and group-3 was the test group which was treated with FnFDFs. Animals of standard group were treated with 1 ml of suspension containing 10 mg of Felodipine by oral administration. Then, FnFDFs of 2 cm^2 (containing equivalent of 10 mg of Felodipine) were cut into four small pieces and were placed between the cheeks of oral buccal cavity of rats of test group. Subsequently, aliquots (blood sample) of 0.25 ml were withdrawn from the tail vein and collected in a heparin-containing capillary tube at 0, 0.25, 0.5, 1, 2, 3, 6, 12, 24, and up to 48 h. Further, plasma was separated from blood using protein precipitation method by mixing it with 1 ml of acetonitrile and 5 ml of isopropyl alcohol (as internal standard) with vortexing and centrifuged for 10000 rpm up to 10 min. Then, supernatant was collected, mixed with mixture of acetonitrile:water (7:3) and analyzed by HPLC. Further, the concentration of Felodipine in plasma was determined and plotted with respect to time and meaningful *in vivo* pharmacokinetic parameters were calculated.[31-33]

RESULTS AND DISCUSSIONS

Solubility determination

Results of this study suggested the poor aqueous solubility of Felodipine in distilled water (0.0436 ± 0.001 mg/ml), phosphate buffer pH 6.8 (0.0424 ± 0.001 mg/ml), and suggested high solubility in organic solvents such as ethanol (0.916 ± 0.013 mg/ml) and acetonitrile (0.731 ± 0.011 mg/ml).

FTIR analysis

Recorded FTIR spectrums of different components are shown in Figure 1. FTIR spectrums of a physical mixture of Felodipine with HPMC-E5 and physical mixture of Felodipine with PVP-K30 showed the major peaks of both the components when compared to that of single-component spectrum. There were no incompatibilities found between drug and excipient in their physical mixture.

DSC analysis

DSC-Thermograms of different components are shown in Figure 2. Thermogram of HPMC-E5 showed a very small peak at 281.11°C which indicated its melting point. Thermogram of PVP-K30 showed a broad endothermic peak at 92.34°C indicated the melting point of PVP-K30. Thermogram of Felodipine showed the sharp endothermic peak at 147.32°C indicated the melting point of Felodipine and the high intensity of peak also revealed the highly crystalline nature of Felodipine. Thermogram of a physical mixture of HPMC-E5 and Felodipine showed one small sharp endothermic peak at 146.83°C indicated the presence of Felodipine and suggested no incompatibility. Low intensity of the peak of Felodipine also revealed the suppression of its crystalline behavior in a mixed form with HPMC-E5. Thermogram of a physical mixture of PVP-K30 and Felodipine showed one endothermic peak at 146.24°C indicated the presence of Felodipine and suggested no incompatibility. The reduced intensity of the peak of Felodipine revealed its presence in molecular dispersion form with PVP-K30.

Preparation of SDP of Felodipine

Results revealed a maximum increase in the water solubility for the drug–polymer ratio of 1:3 in comparison with 1:1 and 1:2. However, SDPs had not shown any significant increase in the solubility of Felodipine on further increasing ratio up to 1:4.

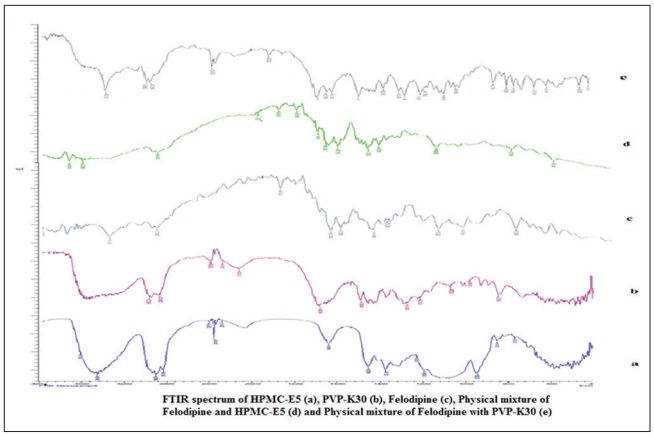

Figure 1: Recorded FTIR spectrums of different components

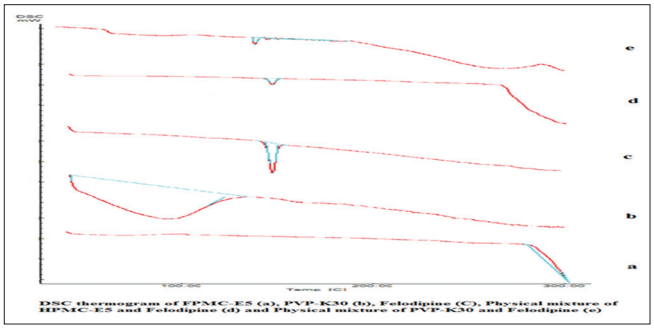

Figure 2: Recorded DSC-thermograms of different components

Formulation of FnFDFs

FnFDFs were prepared by using solvent casting method. Each film contained SDP of the equivalent of 10 mg of Felodipine. The casting solution was prepared in distilled water without the use of organic solvent and was casted on fabricated glass mold to yield films of uniform size of 2 cm^2 with an approximate weight of 150 mg.

Optimization of FnFDFs

There were total 13 runs for Box–Behnken experimental design as shown in Table 1, which were trialed in a randomized fashion to avoid chances of bias. The effects of different levels (low, medium and high) of independent variables on response variables were investigated. The linear model was found be the best fit for all response variables.

Effect of independent variables on tensile strength

The effects A, B, and C on the tensile strength were determined and recorded in the form of cube plot as shown in Figure 3. It suggested the increased value of tensile strength with the increased concentration of both HPMC-E5 and propylene glycol. However, the optimum combination of HPMC-E5 and propylene glycol also affected the tensile strength significantly. The change in concentration of croscarmellose had not shown any significant variation on the tensile strength of FnFDFs. It revealed the improved mechanical strength of the FnFDFs at a higher concentration of HPMC-E5 and propylene glycol.

Effect of independent variables on disintegration time

The effects of A, B, and C on the disintegration time were determined and recorded in the form of cube plot as shown in Figure 4. It suggested decreased disintegration time with the increased concentration of croscarmellose and propylene glycol and increased disintegration time with the increased concentration of HPMC-E5. However, HPMC-E5 being a hydrophilic polymer in combination with propylene glycol had not found to cause any significant increase in disintegration time. It revealed fast disintegration of the FnFDFs at a higher concentration of croscarmellose and propylene glycol.

Effect of independent variables on percentage drug dissolution

The effects of A, B, and C on the percentage drug dissolution were determined and recorded in the form of cube plots as shown in Figure 5. It suggested increased percentage drug dissolution with the increased concentration of propylene glycol and croscarmellose. However, the increased concentration of HPMC-E5 caused very slight decrease in percentage drug dissolution from FnFDFs but being hydrophilic in nature, it had not affected significantly and facilitated a better dissolution of Felodipine in proper combination with propylene glycol. It revealed over 97% of drug dissolution at a higher concentration of propylene glycol and croscarmellose.

The statistical data of ANOVA test and linear equations for tensile strength, disintegration time, and percentage drug dissolution are shown in Table 2. R^2 values were found to be more than 0.9 for all response variables and the difference between adjusted and predicted R^2 value was also found to be below 0.2. It indicated that linear model could be used to navigate the design space. Further, formulation of FnFDFs was validated using an optimized concentration of independent variable and validated results are shown in Table 3. Validated values of response variables were found to be close to that of optimized values.

Evaluation of FnFDFs

Uniformity of mass

Results of determination of uniformity of mass, thickness, % drug content and folding endurance of FnFDFs are shown in Table 4. The average mass of optimized and validated FnFDFs was found to be 148.13 ± 0.69 mg. The mass of the film cut from the different places was found to be uniform.

Table 1: Box–behnken experimental design for FnFDFs

Batch No.	Independent variables		
	HPMC-E5 (A) %	Propylene glycol (B) %	Croscarmellose (C) %
FnFDF-1	42.5	15	1
FnFDF-2	40	12.5	1
FnFDF-3	42.5	10	5
FnFDF-4	40	15	3
FnFDF-5	45	10	3
FnFDF-6	42.5	12.5	3
FnFDF-7	42.5	15	5
FnFDF-8	40	10	3
FnFDF-9	45	15	3
FnFDF-10	40	12.5	1
FnFDF-11	40	12.5	5
FnFDF-12	45	12.5	5
FnFDF-13	42.5	10	1

Table 2: Summary of statistical analysis of linear model for FnFDFs

Parameters	Observed values for		
	Tensile strength	Disintegration time	Percentage drug dissolution
R^2	0.9232	0.9445	0.9783
Adjusted R^2	0.8976	0.9260	0.9711
Predicted R^2	0.8323	0.8755	0.9577
SD	0.0007	0.6515	0.2252
% CV	0.3357	3.00	0.2356
Linear equation	R1=+0.1589+0.0009A+0.0004B+ 0.00002C	R2=−28.5663+1.1965A+ 0.0515B−0.2458C	R3=+122.9653−0.6632A+0.03 05B+0.0547C

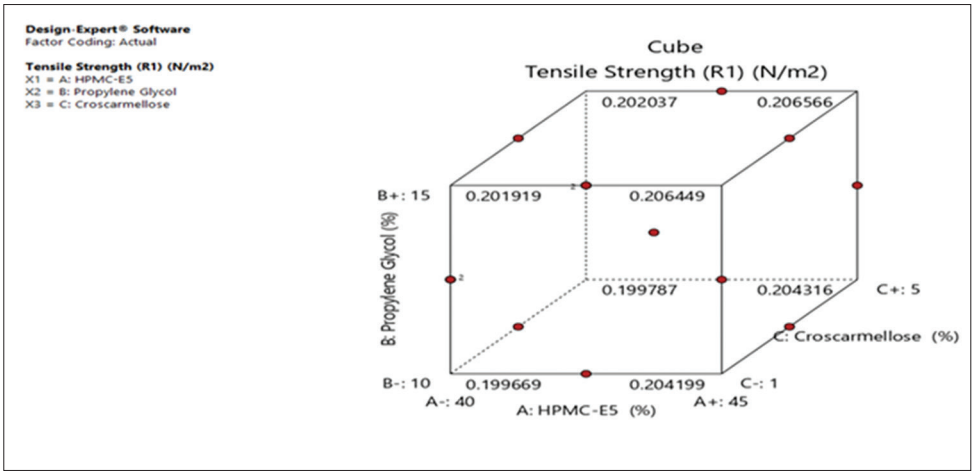

Figure 3: Cube plot of effects of A, B, and C on the tensile strength of FnFDFs

Thickness

The thickness of optimized and validated FnFDFs was found to be 0.246 ± 0.013 mm. Results revealed increased thickness of FnFDFs with increased concentration of HPMC-E5 and propylene glycol. The thickness of the film cut from the different places was found to be uniform.

Percent drug content

Percent drug content of optimized and validated FnFDFs was found to be 98.62 ± 1.11%. Results suggested a good uniformity of content in the FnFDFs without any significant variation.

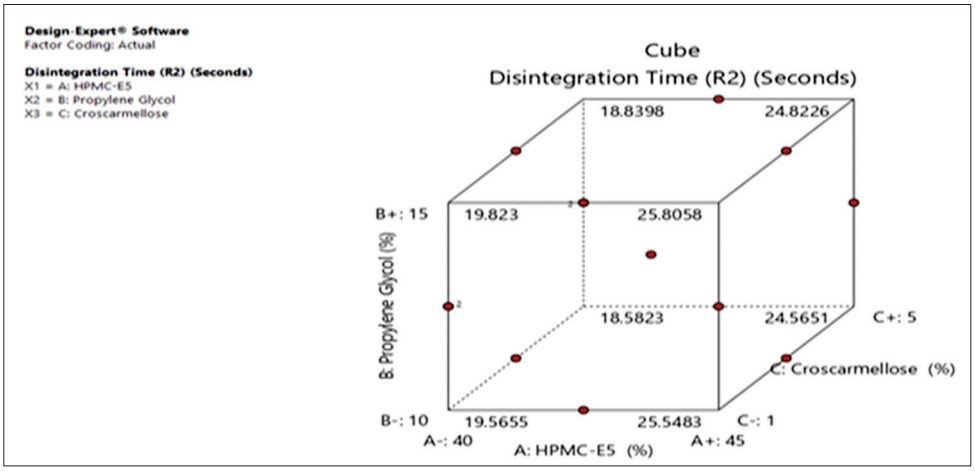

Figure 4: Cube plot of effects of A, B, and C on disintegration time of FnFDFs

Table 3: Optimized and validated values of independent and response variables for FnFDFs

Type of variable	Variables	Optimized value	Validated value (*n*=3)
Independent	HPMC-E5 (% w/w)	44.6146	44.61
	Propylene glycol (% w/w)	14.4107	14.41
	Croscarmellose (% w/w)	4.6307	4.63
Response or dependent	Tensile strength (N/m^2)	0.2059	0.201±0.002
	Disintegration time (seconds)	24.4219	22.84±0.31
	Percent drug dissolution (%)	94.0669	97.09±1.54

Table 4: Results of uniformity of mass, thickness, % drug content and folding endurance (n=3)

S. No.	Batch No.	Uniformity of mass of 2 cm^2 of film (average weight of 20 films in mg±SD)	Thickness (average in mm±SD)	Percent drug content (average in %±SD)	Folding endurance (average of times folded±SD)
1	Batch No. 1	144.16±1.06	0.232±0.014	98.45±1.11	216±1
2	Batch No. 2	148.72±1.13	0.247±0.011	98.73±1.01	219±2
3	Batch No. 3	143.38±0.98	0.231±0.008	98.32±1.03	213±1
4	Batch No. 4	141.14±1.13	0.216±0.012	97.95±1.12	203±2
5	Batch No. 5	149.25±0.92	0.245±0.014	98.64±1.05	219±3
6	Batch No. 6	145.83±1.11	0.234±0.013	98.42±1.11	216±1
7	Batch No. 7	146.17±1.15	0.238±0.011	98.71±1.12	217±1
8	Batch No. 8	142.26±1.17	0.219±0.012	98.15±1.13	197±2
9	Batch No. 9	149.18±1.02	0.248±0.015	99.02±0.82	221±1
10	Batch No. 10	143.23±1.21	0.212±0.009	98.13±1.08	206±1
11	Batch No. 11	142.91±1.18	0.216±0.011	98.11±1.04	199±2
12	Batch No. 12	149.84±1.11	0.247±0.014	98.13±0.73	220±1
13	Batch No. 13	146.57±1.23	0.231±0.016	98.51±1.07	215±2
14	Optimized	148.13±0.69	0.246±0.013	98.62±1.11	221±1

Folding endurance

Folding endurance of optimized and validated FnFDFs was found to be 221 ± 1. Results suggested the increased value of folding endurance with increasing the concentration of HPMC-E5 and propylene glycol.

Surface pH

Results of determination of surface pH, moisture uptake, percentage swelling, and percent elongation are shown in Table 5. Surface pH of optimized and validated FnFDFs was found to be 6.75 ± 0.01. Results of this study indicated almost

normal pH which revealed no chances of irritation to the oral mucosa after its administration.

Moisture uptake

Percentage moisture uptake of optimized and validated FnFDFs was found to be 2.15 ± 0.04%. Results of this study revealed increased moisture uptake with increased concentration of propylene glycol. It also suggested the mild hygroscopic behavior of the FnFDFs when kept openly at high humidity.

Percentage swelling

Percentage swelling of optimized and validated FnFDFs was found to be 42.68 ± 0.52%. Higher percentage swelling of FnFDFs suggested its suitability for rapid release of Felodipine due to increased absorption of phosphate buffer pH 6.8.

Percent elongation

Percent elongation of optimized and validated FnFDFs was found to be 13.98 ± 0.92%. Results suggested the increased mechanical strength of FnFDFs with increased concentration of HPMC-E5 and propylene glycol.

Tensile strength

Overall results of determination of tensile strength, *in-vitro* disintegration time and *in-vitro* percent drug dissolution or release studies of FnFDFs are shown in Table 6. The tensile strength of optimized and validated FnFDFs was found to be 0.201 ± 0.002 N/m^2. It revealed the good mechanical strength of FDFs against rupture and breaks.

In-vitro disintegration time

In-vitro disintegration time of optimized and validated FnFDFs was found to be 22.84 ± 0.31 s. It revealed the

Table 5: Results of surface pH, moisture uptake, percentage swelling and percent elongation (***n*** = 3)

S. No.	Batch No.	Surface pH (average pH ±SD)	Moisture uptake (average %±SD)	Percentage Swelling (average %±SD)	Percent elongation (average %±SD)
1	Batch No. 1	6.65 ± 0.01	2.15 ± 0.03	40.65 ± 0.32	11.97 ± 1.11
2	Batch No. 2	6.62 ± 0.06	2.23 ± 0.02	39.41 ± 0.51	13.43 ± 1.12
3	Batch No. 3	6.69 ± 0.04	1.96 ± 0.02	41.07 ± 0.46	12.15 ± 1.11
4	Batch No. 4	6.71 ± 0.02	1.87 ± 0.01	41.76 ± 0.48	10.46 ± 1.02
5	Batch No. 5	6.74 ± 0.01	1.94 ± 0.03	42.37 ± 0.52	13.58 ± 1.11
6	Batch No. 6	6.61 ± 0.03	2.08 ± 0.01	41.09 ± 0.37	12.24 ± 1.13
7	Batch No. 7	6.68 ± 0.04	1.83 ± 0.04	40.75 ± 0.41	12.41 ± 1.12
8	Batch No. 8	6.63 ± 0.02	1.67 ± 0.05	41.49 ± 0.34	10.73 ± 1.11
9	Batch No. 9	6.65 ± 0.01	1.83 ± 0.04	40.98 ± 0.36	13.48 ± 1.12
10	Batch No. 10	6.66 ± 0.05	2.12 ± 0.06	41.07 ± 0.28	10.82 ± 1.14
11	Batch No. 11	6.73 ± 0.01	2.19 ± 0.01	41.16 ± 0.31	11.99 ± 1.12
12	Batch No. 12	6.62 ± 0.06	2.06 ± 0.01	42.78 ± 0.58	13.21 ± 1.12
13	Batch No. 13	6.69 ± 0.03	1.92 ± 0.02	39.97 ± 0.47	12.67 ± 1.11
14	Optimized	6.75 ± 0.01	2.15 ± 0.04	42.68 ± 0.52	13.98 ± 0.92

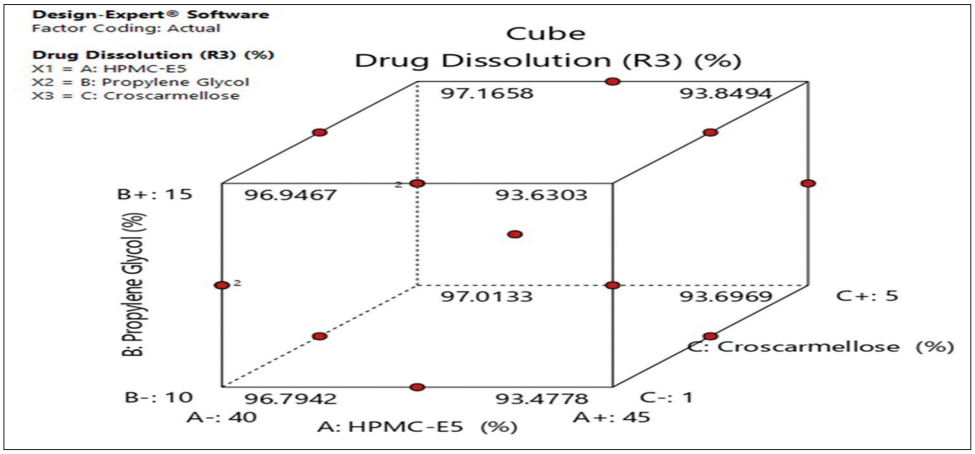

Figure 5: Cube plot of effects of A, B, and C on percentage drug dissolution of FnFDFs

Table 6: Results of tensile strength, disintegration time and % drug dissolution of FnFDFs (n=3)

S. No.	Batch No.	Tensile strength (average in N/m²±SD)	*In-vitro* disintegration time (average seconds±SD)	*In-vitro* percent drug dissolution (average %±SD)
1	Batch No. 1	0.204±0.002	22.21±0.05	95.37±1.14
2	Batch No. 2	0.201±0.001	20.19±0.09	96.98±1.13
3	Batch No. 3	0.202±0.001	22.20±0.11	95.26±1.08
4	Batch No. 4	0.202±0.002	19.18±0.08	97.14±1.05
5	Batch No. 5	0.205±0.003	25.17±0.07	93.69±1.11
6	Batch No. 6	0.204±0.002	22.18±0.09	95.32±1.12
7	Batch No. 7	0.205±0.001	21.22±0.10	95.67±1.06
8	Batch No. 8	0.200±0.002	18.19±0.06	97.04±1.12
9	Batch No. 9	0.206±0.001	26.17±0.04	93.73±1.11
10	Batch No. 10	0.201±0.002	20.21±0.07	96.35±1.13
11	Batch No. 11	0.200±0.002	19.22±0.08	97.12±1.09
12	Batch No. 12	0.205±0.001	24.21±0.09	93.52±1.11
13	Batch No. 13	0.201±0.002	22.19±0.11	95.31±1.12
14	Optimized	0.201±0.002	22.84±0.31	97.09±1.54

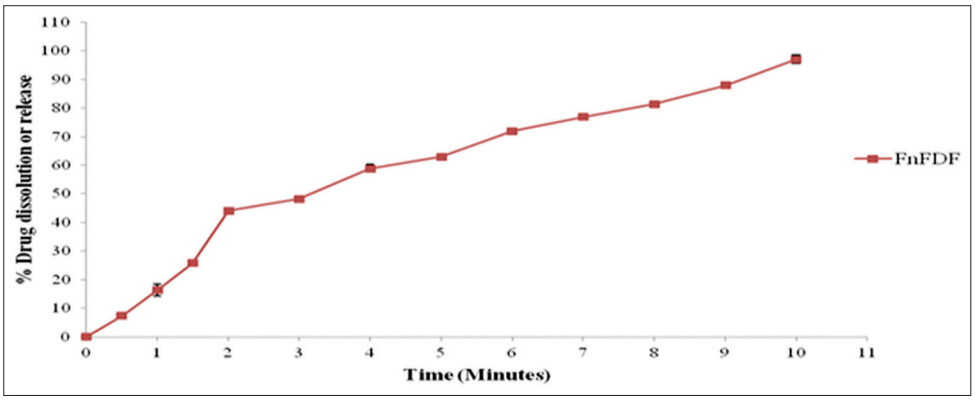

Figure 6: *In-vitro* percent drug dissolution of optimized and validated FnFDFs

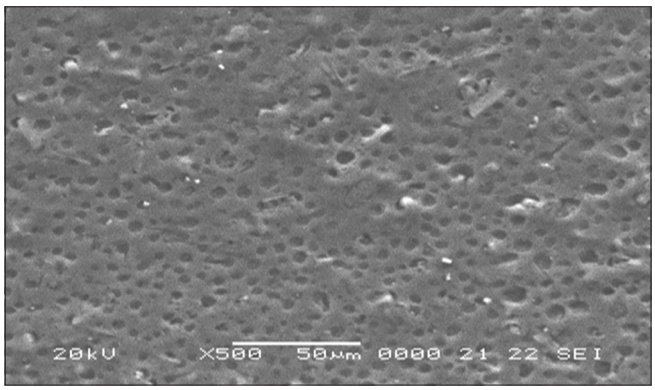

Figure 7: SEM image of FnFDFs

fast disintegration of the FnFDFs, and it facilitated faster dissolution of Felodipine.

In-vitro percent drug dissolution or release study

In-vitro percent drug dissolution of optimized and validated FnFDFs was found to be 97.09 ± 1.54%. Graph of *in-vitro* percent drug dissolution study for optimized and validated FnFDFs is shown in Figure 6. It revealed more than 97% drug dissolution up to 10 min and thus indicated faster and almost complete drug dissolution. Further, to study the drug release mechanism from FnFDFs, the data of *in-vitro* percent drug dissolution were fitted into various release kinetic models and R^2 values are shown in Table 7. The maximum R^2 value for FnFDFs was found to be 0.9844 in first-order model and it revealed first-order drug release from FnFDFs.

Stability study

Results of stability study of optimized and validated FnFDFs are shown in Table 8. Observations of study for both storage conditions indicated good physical and chemical stability based on the physical appearance, weight of film, percent drug content, and surface pH up to 6 months. However, FnFDFs stored at 25 ± 2°C/60 ± 5% RH had shown better stability in comparison with that stored at 40 ± 2°C/75 ± 5% RH.

Surface morphology using SEM

SEM image of FnFDFs is shown in Figure 7. It indicated smooth surface with pores of around 5-10 µ. The porous structure of the film suggested increased amorphous nature of the FnFDFs which could predict to be disintegrated and dissolved rapidly in the presence of dissolution medium.

Ex-vivo permeation study

The result of *ex-vivo* permeation study of optimized and validated FnFDFs is shown in Figure 8. *Ex-vivo* drug permeation of optimized and validated FnFDFs was found to be 89.98 ± 1.11% up to 10 min. It indicated around 90% drug permeation up to 10 min and thus suggested good tissue permeability of Felodipine from FnFDFs.

Table 7: Linear correlation coefficient (R^2) values of drug release kinetic modeling (n=3)

Drug release model	R^2 values
Zero-order model	0.8766
First order model	0.9844
Higuchi model	0.9609
Korsmeyer-Peppas modeland *n* values	0.9806 and 0.627

In-vivo pharmacokinetic study

Comparative results of *in-vivo* study for oral suspension of Felodipine and FnFDFs are shown in Table 9 and Figure 9. Various *in-vivo* pharmacokinetic parameters were calculated for oral suspension of Felodipine and FnFDFs as shown in Table 10. Maximum absorption of Felodipine from oral suspension was found to be 242.14 ± 0.027 µg/ml up to 3 h. However, maximum absorption of Felodipine from FnFDFs through oral buccal cavity was found to be 579.80 ± 0.046 µg/ml up to 1–2 h. The result of the present study revealed the fast and rapid absorption of Felodipine from FnFDFs through oral buccal cavity with the improved bioavailability of approximately 90% by avoidance of first-pass metabolism in comparison with its oral suspension.

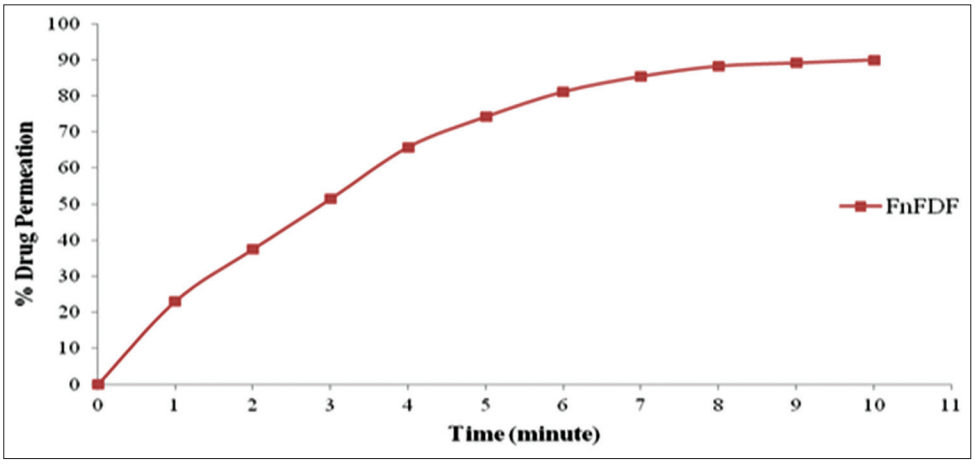

Figure 8: *Ex-vivo* drug permeation study of optimized and validated FnFDFs

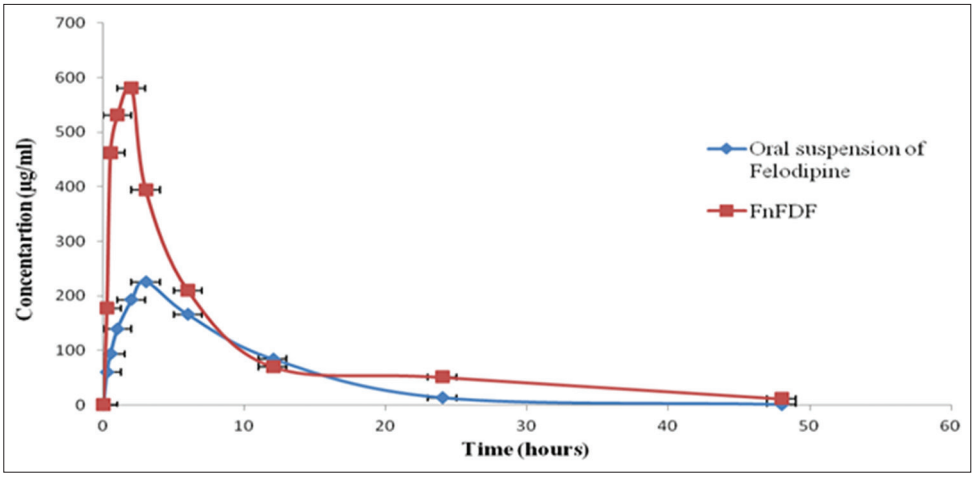

Figure 9: *In-vivo* study of an oral suspension of Felodipine and FnFDFs

Table 8: Results of stability study of FnFDFs (*n*=3)

Days	Storage at 25±2°C/60±5% RH for 6 months			
	Appearance	Weight (Avg. mg±SD)	Drug content (Avg. %±SD)	Surface pH (Avg. pH±SD)
0	Transparent	148.13±0.69	98.62±1.11	6.75±0.01
30	No Change	148.10±0.97	98.59±0.59	6.74±0.03
60	No Change	148.08±1.02	98.57±0.83	6.73±0.01
90	No Change	148.06±1.05	98.55±0.64	6.70±0.01
120	No Change	148.03±0.93	98.53±0.95	6.69±0.03
180	No Change	147.99±1.12	98.49±0.87	6.68±0.02
	Storage at 40±2°C/75±5% RH for 6 months			
0	Transparent	148.13±0.69	98.62±1.11	6.75±0.01
30	No Change	148.08±0.67	98.53±0.74	6.72±0.02
60	No Change	148.04±0.84	98.47±0.86	6.70±0.01
90	No Change	147.98±1.11	98.41±0.92	6.69±0.02
120	No Change	147.93±1.03	98.36±0.89	6.65±0.01
180	No Change	147.88±1.08	98.32±0.95	6.62±0.01

Table 9: Results of *in-vivo* pharmacokinetic study (*n*=3)

S. No.	Time (h)	Rat plasma drug concentration (average µg/ml±SD)	
		Oral suspension of Felodipine	FnFDFs
1	0	0±0.00	0±0.00
2	0.25	62.23±0.016	177.39±0.007
3	0.5	98.19±0.028	462.17±0.040
4	1	147.17±0.038	530.38±0.063
5	2	202.38±0.069	579.80±0.046
6	3	242.14±0.027	394.19±0.010
7	6	183.26±0.041	209.31±0.033
8	12	93.28±0.039	70.18±0.031
9	24	22.17±0.020	51.03±0.047
10	48	5.257±0.035	11.52±0.059

Table 10: *In-vivo* pharmacokinetic parameters

Parameters	Oral suspension of Felodipine	FnFDFs
C_{max} (µg/ml)	242.14±0.03	579.80±0.04
t_{max} (h)	3.14±0.05	1.34±0.03
Ka (µg/h)	0.691±0.18	3.694±0.02
Ke (µg/h)	0.112±0.03	0.026±0.002
AUC (µg/ml/h)	2975.75±3.75	4613.91±2.14
Vd (l)	0.037±0.002	0.014±0.003
$At_{1/2}$ (h)	1.00±0.04	0.187±0.019
$Et_{1/2}$ (h)	6.184±0.017	26.66±0.27
Cl_T (l/h)	0.0033±0.0003	0.0021±0.0001

CONCLUSION

Preparation of SDP of the Felodipine using solvent evaporation method with PVP-K30 up to 1:3 (drug to polymer ratio) found to remarkably increase the aqueous solubility of Felodipine. Results of evaluation parameters of optimized and validated FnFDFs revealed good mechanical strength, uniformity of content, optimum surface pH, faster disintegration time, almost complete drug dissolution or release, good *ex-vivo* permeation, and good stability up to six months. *In-vivo* pharmacokinetic study indicated faster absorption and around 90% oral bioavailability up to 1–2 h for Felodipine in form of FnFDFs through the buccal administration due to avoidance of first pass metabolism. Thus it can be concluded that FnFDFs could be commercially exploited for the treatment of hypertension using Felodipine with merits of faster onset of action, avoidance of extensive first pass metabolism, low dosage regimen, enhanced bioavailability and improved patient compliance.

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