



Development and optimization of Felodipine–sorbitol co-crystal embedded mucoadhesive buccal films for enhanced ex vivo permeation

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Abstract

Background: Felodipine is a poorly water-soluble calcium-channel blocker with low systemic bioavailability after oral administration, attributed in the thesis to extensive first-pass metabolism and poor aqueous solubility. The present study investigated a combined crystal-engineering and buccal-film strategy to improve the aqueous solubility and ex vivo buccal permeation of felodipine.

Methods: Felodipine co-crystals were prepared by solvent-drop grinding with sorbitol, L-ascorbic acid, and oxalic acid at a 1:1 drug:coformer ratio. The highest-solubility co-crystal was further screened at 1:1, 1:1.5, and 1:2 ratios. The selected felodipine–sorbitol co-crystal was characterized by microscopy, SEM, FTIR, and PXRD. Co-crystal-loaded buccal films were prepared by solvent casting and optimized using a 3² factorial design with HPMC E15 and PVA as independent variables. Drug permeation at 8 h and mucoadhesive strength were the principal responses.

Results: The reported saturation solubility of felodipine was 1.97 mg/100 mL, compared with 3.2 mg/100 mL for the felodipine–sorbitol co-crystal. FTIR showed shifts in characteristic bands and PXRD showed a diffraction pattern distinct from the parent materials, supporting formation of a new solid form. Across the nine experimental film batches, the reported 8-h permeation response ranged from 65.52% to 96.82%, while mucoadhesive strength ranged from 4.3 to 8.4 g. The experimentally evaluated optimized formulation (F4) showed 94.59% ex vivo permeation at 8 h through goat buccal mucosa. Kinetic analysis gave R² values of 0.975, 0.861, 0.992, 0.684, and 0.981 for zero-order, first-order, Higuchi, Hixson–Crowell, and Korsmeyer–Peppas models, respectively, with n = 0.653.

Conclusion: Felodipine–sorbitol co-crystallization combined with a mucoadhesive buccal-film platform produced a formulation with improved aqueous solubility and substantial ex vivo buccal permeation. The findings support further development, including confirmatory *in vivo* pharmacokinetic and bioavailability studies.

Keywords: Felodipine, pharmaceutical co-crystal, sorbitol, buccal film, mucoadhesion, factorial design, ex vivo permeation, Korsmeyer–Peppas

Introduction

Felodipine is a dihydropyridine calcium-channel blocker used in the management of hypertension. The thesis reports that the drug is poorly soluble in water and has approximately 15% oral bioavailability because of extensive first-pass metabolism [1]. These characteristics make formulation approaches that improve dissolution while reducing exposure to gastrointestinal and hepatic first-pass processes relevant to formulation development.

Buccal drug delivery provides access to the highly vascularized oral mucosa and can reduce exposure to gastrointestinal degradation and hepatic first-pass metabolism. Mucoadhesive films can prolong contact with the mucosa and provide a convenient dosage form that can be removed when required [2, 5]. The performance of such systems depends on film-forming and mucoadhesive polymers, mechanical integrity, hydration, surface pH, and the physicochemical properties of the incorporated drug.

Pharmaceutical co-crystallization is a crystal-engineering approach in which an active pharmaceutical ingredient and a suitable coformer are assembled into a new multicomponent crystalline phase. The thesis describes co-crystallization as a means of modifying physicochemical properties such as solubility and dissolution while retaining the intrinsic pharmacological activity of the API [6, 8]. Previous work has also demonstrated the feasibility of combining co-crystal technology with buccal films, including piroxicam co-crystal films [9].

Accordingly, the present investigation combined felodipine co-crystallization with sorbitol and mucoadhesive buccal-film technology. The study screened three coformers, characterized the selected co-crystal, optimized HPMC E15/PVA concentrations using a 3² factorial design, and evaluated the resulting films for physicochemical properties, mucoadhesion, and ex vivo permeation.

Materials and Methods

1. Materials

Table 1: Materials used for preparation and evaluation of felodipine co-crystal embedded buccal films.

Material	Function	Source (as reported in thesis)
Felodipine	Active pharmaceutical ingredient	Sai Mirra Innopharm Pvt. Ltd.
Sorbitol	Coformer, plasticizer and sweetening agent	Vopec Pharmaceuticals Pvt. Ltd.
HPMC E15	Buccoadhesive/film-forming polymer	Vopec Pharmaceuticals Pvt. Ltd.
PVA	Buccoadhesive polymer	Vopec Pharmaceuticals Pvt. Ltd.
Menthol	Flavoring agent	Vopec Pharmaceuticals Pvt. Ltd.
PEG 400	Plasticizer	Aman Scientifics Pvt Ltd.

2. Preformulation studies

The physical appearance of felodipine was examined. Solubility was assessed in water, pH 6.5 phosphate buffer, ethanol, DMSO, and DMF. A calibration curve was prepared in pH 6.5 phosphate buffer by measuring absorbance at 364 nm. Drug–excipient compatibility was assessed by FTIR using KBr pellets scanned from 4000 to 500 cm⁻¹ on a Shimadzu FTIR-8400S instrument ^[10].

3. Preparation and screening of felodipine co-crystals

Felodipine was co-crystallized with sorbitol, L-ascorbic acid, and oxalic acid at a 1:1 molar ratio using the solvent-drop grinding method. Felodipine and the coformer were triturated using a mortar and pestle while ethanol was added dropwise with continuous grinding. The resulting solid was recovered as a freely flowing powder. The coformer producing the highest solubility was subsequently investigated at drug:coformer ratios of 1:1, 1:1.5, and 1:2.

Saturation solubility was determined by dispersing co-crystal equivalent to 100 mg of drug in 100 mL water, agitating for 24 h on a rotary shaker, diluting suitably, and measuring felodipine spectrophotometrically at 364 nm. Selected co-crystals were characterized by optical microscopy, SEM, FTIR, and PXRD.

4. Optimization of co-crystal-loaded buccal films

A two-factor, three-level (3²) full factorial design was implemented in Design-Expert® version 11. The independent variables were HPMC E15 (X1; 300, 600, and 900 mg/film) and PVA (X2; 150, 300, and 450 mg/film). The principal responses were 8-h drug permeation (Y1) and mucoadhesive strength (Y2). The design consisted of nine experimental formulations (F1–F9), as shown in Table 2. The design objectives were to maintain drug permeation within the desired range and maximize mucoadhesive strength.

Table 2: 3² factorial design combinations used for preparation of felodipine co-crystal embedded buccal films.

Formulation	PVA (mg)	HPMC E15 (mg)
F1	450	900
F2	300	300
F3	300	600
F4	150	600
F5	450	300
F6	150	300
F7	450	600
F8	150	900
F9	300	900

5. Preparation of buccal films

For the formulation corresponding to 600 mg HPMC E15 and 150 mg PVA, the polymers were dispersed/dissolved in 20 mL distilled water with 0.8 mL PEG 400 and stirred at 800 rpm for 1 h. Menthol (1 mL) was then incorporated under stirring at 1000 rpm at room temperature until a clear viscous polymeric solution was obtained. Felodipine co-crystals equivalent to the target drug load were added gradually with stirring to obtain uniform distribution. Entrapped air was removed, the solution was cast on a fabricated glass mould, and the film was dried at room temperature. Dried films were peeled, cut to the required size, and stored in double-wrapped aluminium foil. The thesis reports a target dose of 5 mg felodipine equivalent per 2 × 2 cm film; 12.5 mg co-crystal was considered equivalent to 5 mg felodipine.

6. Film characterization

Films were visually examined and characterized by SEM, weight variation, thickness, folding endurance, swelling, drug content, surface pH, percentage moisture loss,

mucoadhesive strength, and ex vivo permeation. Weight was determined from three randomly selected 2 × 2 cm films. Thickness was measured at multiple locations using a calibrated digital vernier caliper. Folding endurance was determined by repeatedly folding the film at the same line until breakage. Swelling was measured after immersion in simulated saliva using the change in weight relative to the initial film weight.

Drug content was determined from three film units dissolved in 100 mL pH 6.5 phosphate buffer, followed by filtration, suitable dilution, and UV analysis at 364 nm. Surface pH was measured after wetting the film. Moisture loss was determined after three days in a desiccator containing anhydrous calcium carbonate. Mucoadhesive strength was measured using a two-arm balance and fresh sheep buccal mucosa; the force required for detachment after a 5-min contact period was recorded in grams.

7. Ex vivo buccal permeation

Fresh goat buccal mucosa was collected and used within 2 h of sacrifice. Underlying connective tissue was removed and

the mucosa was trimmed to approximately 500 μm thickness. Permeation was studied in a Franz diffusion cell at 37 ± 0.5 °C. The thesis describes pH 6.8 phosphate buffer in the donor compartment and pH 6.5 ± 0.5 phosphate buffer in the receptor compartment in the detailed method; the results section reports pH 6.5 for both compartments. Samples were withdrawn at 1-h intervals up to 8 h and analyzed by UV spectrophotometry at 364 nm.

Permeation data for the optimized formulation were fitted to zero-order, first-order, Higuchi, Hixson–Crowell, and Korsmeyer–Peppas models. Model fit was compared using R^2 , and the Korsmeyer–Peppas diffusional exponent (n) was used to interpret the release mechanism.

Results and Discussion

1. Preformulation and analytical characterization

Felodipine was described as a pale white/off-white solid. The reported solubility assessment classified the drug as poorly soluble in water, sparingly soluble in pH 6.5

phosphate buffer, freely soluble in ethanol, and highly soluble in DMSO and DMF. The calibration curve was established over 0–50 $\mu\text{g/mL}$ at 364 nm (Figure 1).

Figure 1: Calibration curve of felodipine in pH 6.5 phosphate buffer at 364 nm (reproduce from thesis Figure 8).

FTIR spectra of felodipine and the drug–excipient system showed the characteristic functional-group bands reported in the thesis, including N–H stretching, C–H stretching, C=O stretching, C=C stretching, and CH₃ C–H bending. The co-crystal spectrum showed shifts in the N–H, C–H, and C=O regions, with the thesis identifying bands near 3376.43, 2948.28, and 1699.72 cm^{-1} as showing notable shifts. These changes were interpreted as evidence of intermolecular interactions between felodipine and sorbitol (Figure 2).

Figure 2. FTIR comparison of felodipine and felodipine–sorbitol co-crystal, including characteristic band shifts (reproduce from thesis Figures 12 and 16).

2. Co-crystal screening and characterization

Table 3: Saturation solubility values reported for felodipine and screened co-crystals. The numerical fold-change values are calculated directly from the thesis-reported solubilities.

Sample	Solubility (mg/100 mL)	Relative to felodipine
Felodipine	1.97	1.00-fold
Felodipine–sorbitol co-crystal	3.20	1.62-fold
Felodipine–L-ascorbic acid co-crystal	2.50	1.27-fold
Felodipine–oxalic acid co-crystal	2.20	1.12-fold

Sorbitol produced the highest reported solubility among the three screened coformers and was therefore selected for further ratio screening. Optical microscopy and SEM were used to examine the morphology of the prepared co-crystals (Figure 3). PXRD showed a diffraction pattern distinct from the parent felodipine and sorbitol materials, with changes in peak pattern/intensity interpreted in

the thesis as supporting formation of a new solid form (Figure 4).

Figure 3. Microscopic and SEM morphology of the prepared felodipine–sorbitol co-crystal (reproduce from thesis Figures 14 and 15).

Figure 4. PXRD patterns of sorbitol, felodipine, and felodipine co-crystal (reproduce from thesis Figures 17–19).

3. Factorial optimization

Table 4: Design-of-experiment responses used for factorial optimization, as reported in the thesis.

Formulation	PVA (mg)	HPMC E15 (mg)	8-h permeation response (%)	Mucoadhesive strength (g)
F1	450	900	68.63	8.4
F2	300	300	92.79	4.8
F3	300	600	87.93	5.6
F4	150	600	88.64	4.3
F5	450	300	84.21	6.5
F6	150	300	96.82	4.5
F7	450	600	82.75	6.8
F8	150	900	73.52	5.3
F9	300	900	65.52	6.2

The response-surface analysis indicated that increasing HPMC E15 and PVA concentrations reduced the reported 8-h permeation response, with HPMC E15 described as having a stronger release-retarding effect (Figure 5). Conversely, increasing both polymer concentrations increased mucoadhesive strength, with PVA described as contributing substantially

to adhesion (Figure 6).

Figure 5. Response-surface representation of the effects of HPMC E15 and PVA on 8-h drug permeation (reproduce from thesis Figure 20).

Figure 6. Response-surface representation of the effects of HPMC E15 and PVA on mucoadhesive strength (reproduce from thesis Figure 21).

Table 5: Statistical parameters reported for the factorial response models.

Response	Adjusted R^2	Predicted R^2	Model P value	Adequate precision	CV (%)
Drug release/permeation at 8 h	0.8259	0.7277	0.0022	11.3974	5.48
Mucoadhesive strength	0.8820	0.7549	0.0007	15.0594	7.70

The reported model statistics indicate statistically significant response models ($P < 0.05$), with adequate-precision values substantially above 4 for both responses. The adjusted and predicted R^2 values

were 0.8259 and 0.7277 for the 8-h permeation response and 0.8820 and 0.7549 for mucoadhesive strength, respectively. The thesis reports a desirability value of 1.00 for the optimization procedure.

Table 6: Point-prediction/validation values reported in the thesis. The reported error is calculated as $(\text{predicted} - \text{observed})/\text{predicted} \times 100$.

Optimization parameter	Predicted	Observed	Reported error (%)
Drug permeation at 8 h (%)	96.82	94.59	2.30
Mucoadhesive strength	8.4	6.82	18.8

4. Physical evaluation of buccal films

Table 7: Physical and mucoadhesive properties of the nine experimental films, compiled from the thesis Tables 13–19.

Formulation	Weight (mg)	Thickness (mm)	Folding endurance	Swelling index	Surface pH	Moisture loss (%)	Mucoadhesive strength (g)
F1	35.49	0.33	314	5.48	6.3	1.89	4.5
F2	72.32	0.35	312	4.89	6.5	2.14	4.8
F3	53.60	0.32	305	4.50	6.4	2.25	6.5
F4	88.24	0.34	310	5.23	6.4	1.36	4.3
F5	61.07	0.36	318	4.98	6.6	1.56	5.6
F6	43.50	0.35	309	5.62	6.4	1.19	6.8
F7	74.81	0.35	305	5.20	6.3	2.32	5.3
F8	53.52	0.34	313	5.25	6.5	2.21	6.2
F9	96.42	0.36	304	5.28	6.4	1.92	8.4

The films were reported to be clear and transparent, suggesting visually uniform drug distribution. Film weight varied from 35.49 to 96.42 mg, while thickness ranged from 0.32 to 0.36 mm. Folding endurance ranged from 304 to 318 folds. Swelling indices ranged from 4.50 to 5.62, surface pH ranged from 6.3 to 6.6, and moisture loss ranged

from 1.19% to 2.32%. These data are summarized in Table 7.

Drug content ranged from $69.26 \pm 0.2\%$ to $98.16 \pm 0.3\%$ across F1–F9 (Table 8). The thesis states that 12.5 mg felodipine co-crystal corresponds to 5 mg felodipine equivalent.

Table 8: Drug-content results for the experimental films.

Formulation	Drug content in co-crystal (%)
F1	78.56 ± 0.2
F2	82.51 ± 0.1
F3	98.16 ± 0.3
F4	91.10 ± 0.9
F5	84.62 ± 0.6
F6	73.25 ± 0.9
F7	69.26 ± 0.2
F8	88.54 ± 0.9
F9	72.82 ± 0.8

5. Ex vivo buccal permeation

Table 9: Ex vivo cumulative drug permeation (%) through goat buccal mucosa as reported in the thesis. Dashes indicate values not visible in the extracted thesis table; these should be verified against the original laboratory record/figure before submission.

Time (h)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	19.96	22.25	22.54	20.14	18.97	11.78	11.85	16.74	20.41
2	35.78	39.46	31.92	37.49	24.96	18.01	26.01	31.32	35.57
3	44.61	45.27	47.23	46.21	41.14	24.36	33.36	45.86	45.83
4	63.19	56.83	53.32	55.32	57.49	31.49	42.17	54.65	56.09
5	78.32	61.44	65.41	60.88	66.03	45.62	57.71	63.52	64.82
6	87.93	74.78	82.90	72.30	81.89	63.90	65.21	74.61	75.63
7	—	81.75	82.10	88.48	72.86	73.52	79.04	86.12	—
8	94.59	—	—	—	—	—	82.75	—	—

The optimized formulation identified in the thesis was evaluated further using goat buccal mucosa. The detailed optimized-formulation profile reported for F4 showed progressive permeation from 20.14% at 1 h to 94.59% at 8 h (Figure 7).

The permeation profile was described as relatively steady over the study period.

Figure 7. Ex vivo permeation profile of the optimized felodipine co-crystal buccal film (F4) through goat buccal mucosa over 8 h (reproduce from thesis Figure 33).

6. Release/permeation kinetics

Table 10: Kinetic-model fitting parameters for the optimized formulation (F4).

Model	R ²	Interpretation in thesis
Zero order	0.975	Highest linearity among tested models
First order	0.861	Lower fit than zero order
Higuchi	0.992	Strong diffusion-related fit
Hixson–Crowell	0.684	Lower fit
Korsmeyer–Peppas	0.981	Strong fit; n = 0.653

The highest R² among the tested models was obtained with the Higuchi model (0.992), while the zero-order model also showed a high R² of 0.975. The Korsmeyer–Peppas model gave R² = 0.981 with n = 0.653. The thesis interprets n = 0.653 as non-Fickian transport, consistent with a combination of diffusion and erosion-controlled processes. The kinetic plots are represented by the zero-order, first-order, Higuchi, Korsmeyer–Peppas, and Hixson–Crowell plots in the original thesis (Figures 34–38).

Discussion

The study demonstrates a formulation strategy in which two complementary barriers to felodipine delivery—poor aqueous solubility and gastrointestinal/hepatic first-pass exposure—were addressed through co-crystallization and buccal administration, respectively. Sorbitol was selected from the screened coformers because the reported solubility of the felodipine–sorbitol co-crystal (3.2 mg/100 mL) exceeded those of the L-ascorbic acid and oxalic acid co-crystals (2.5 and 2.2 mg/100 mL, respectively) and the parent drug (1.97 mg/100 mL).

The FTIR shifts and altered PXRD pattern provide spectroscopic and solid-state evidence consistent with formation of a distinct felodipine–sorbitol solid form. However, the available thesis data do not include single-crystal X-ray diffraction, DSC, or a full quantitative crystallographic assignment; therefore, the solid-form characterization should be described as supportive rather than definitive at the molecular-structure level.

Polymer concentration materially affected the film responses. Higher HPMC E15 levels were associated with lower 8-h permeation responses, consistent with the release-retarding role described in the thesis, whereas higher polymer concentrations generally increased mucoadhesive strength. The factorial models showed significant model P values and adequate precision, supporting the usefulness of the selected design space for formulation screening.

The optimized formulation displayed substantial *ex vivo* permeation, reaching 94.59% at 8 h in the reported goat-buccal-mucosa study. The Higuchi and Korsmeyer–Peppas fits indicate an important diffusion component, while the Peppas exponent (n = 0.653) was interpreted by the thesis as non-Fickian transport. These findings support continued investigation of the formulation as a buccal delivery platform.

Importantly, the present work is an *in vitro/ex vivo* formulation study and does not directly establish systemic bioavailability. The thesis title refers to enhanced bioavailability, but no *in vivo* pharmacokinetic dataset is reported in the experimental results. Accordingly, the present manuscript frames bioavailability improvement as a potential consequence requiring confirmation rather than as an established outcome.

Conclusion

Felodipine–sorbitol co-crystallization increased the reported aqueous solubility of felodipine from 1.97 to 3.2 mg/100 mL. The selected co-crystal showed FTIR and PXRD changes consistent with formation of a new solid form and was successfully incorporated into HPMC E15/PVA mucoadhesive buccal films. A 3² factorial design demonstrated the influence of polymer concentrations on permeation and mucoadhesive strength. The optimized formulation reported in the thesis exhibited 94.59% *ex vivo* permeation at 8 h through goat buccal mucosa, with kinetic analysis indicating substantial diffusion contribution and non-Fickian transport (n = 0.653). Further studies should include confirmatory solid-state characterization, stability testing, mucosal-safety assessment, and *in vivo* pharmacokinetic/bioavailability evaluation before clinical translation.

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