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Toxicological Optimization and Assessment of Buccal Films Containing Felodipine Co-crystals to Enhance Bioavailability

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Abstract

The preformulation study of felodipine was carried out and it was found that the drug is poorly water soluble. The co-crystals were prepared using three different co-formers sorbitol, ascorbic acid, and oxalic acid. The solubility enhancement was observed in combination with sorbitol compared to other co-formers used. The characterization of co-crystals was performed like powder X-ray diffraction (PXRD), Fourier transform infrared (FTIR), and scanning electron microscopy (SEM) analysis. XRD results indicate the amorphous form of the drug. The co-crystals were embedded within the buccal film for sustained release of the drug. The buccal film was optimized by factorial design using hydroxy propyl methyl cellulose (HPMC) and polyvinyl alcohol (PVA) as independent variables. Two responses were chosen such as drug permeation and mucoadhesive strength for optimizing the buccal film. Based on desirability value (1.00), the formulation factors were found and observed value is closer to the predicted values. These results reveal that the model is validated. The morphology of buccal film was characterized with SEM analysis. The buccal film was tested for thickness, weight variation, folding endurance, drug content, moisture loss, surface pH, and swelling. The drug permeation kinetic study was performed in the optimized formulation and the results reveals that the mechanism of drug permeation follows diffusion from higher r^2 value for Higuchi kinetics (r^2 = 0.992) and the n value of Peppas model (n = 0.653) shows that the mechanism follows non-Fickian diffusion. Novel buccal adhesive co-crystal embedded patch offers innumerable advantages. While the water solubility of the drug is improved by two folds so that the permeation efficacy of the drug also improved, aided by increased bioavailability. Buccal patch exerts many advantages like ease of administration and withdrawal, avoiding first pass metabolism, low enzyme activity, enhancement of permeability and high patient compliance. Hence the novel formulation holds immense opportunities to be explored in terms of different drug candidates.

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INTRODUCTION

There are numerous ways to administer drugs to the body, including transdermal, transmucosal, parenteral, oral, and parenteral [1]. When comparing different medication delivery methods, transmucosal drug delivery has clear advantages over oral administration in terms of systemic impact. Buccal mucosa is the best transmucosal route for local and systemic medication administration among the available options [2, 3]. It is widely recognized that therapeutic chemicals absorbed from the oral mucosa allow for a direct entry of the medication into the bloodstream, avoiding first-pass hepatic metabolism and

gastrointestinal drug degradation, both of which are connected to peroral administration [4–6]. The most often used route for medication administration is the oral route [7]. Low therapeutic costs and patient comfort make the oral route a favorite Due to pain evasion and adaptability, oral dose forms make for more than 70% of commercially available drugs [8]. The most recently created dosage form for buccal administration is buccal films. In terms of comfort and flexibility, buccal film may be favored over buccal tablets. The pharmaceutical industry has increased its focus on films as dosage forms since they are cutting-edge, patient-friendly, and practical. Buccal film is the current topic of discussion. Compared to the majority of commercially available orally disintegrating tablets, which typically require special packaging, this dosage form is less friable [9, 10]. Additionally, these dose forms are pharmacoeconomic, self-administerable, and have improved patient compliance [11, 12]. The treatment of oral candidiasis and other fungal infections of the oral cavity has led to the development of numerous mucoadhesive buccal films that deliver medication locally. The development of dosage forms as a result of changes in oral drug administration included the transition from conventional solid dosage forms to variable release tablets/capsules, oral dispersible tablets, and ultimately the creation of fast mouth dissolving films (MDFs) [13]. MDFs are extremely thin films that are virtually exactly the size and form of postage stamps. They are simply placed on the tongue, where they quickly become hydrated by saliva and release the medication. The three main regions—the United States, the European Union, and Japan—have all approved MDFs for prescription use. These films appear to have a major market advantage over other oral dose forms that contain the same pharmacological active ingredients [14].

It acts primarily on vascular smooth muscle cells by stabilizing voltage–gate L-type calcium channels in their inactive conformation. Normally, L-type of calcium channels admit Ca+ and causes depolarization – excitation-contraction coupling through phosphorylation of myosin light chain leads to contraction of vascular smooth muscle result in elevation of blood pressure (BP). By inhibiting the influx of Ca+ in smooth muscle–cells, felodipine prevents Ca+-dependent myocyte contraction and vasoconstriction.

The aim of the present investigation was to formulate buccal films containing felodipine of dose 5 mg with thickness of about 2 mm and diameter less than 4 mm. Felodipine is a calcium-channel blocker used in the treatment of hypertension and angina pectoris. Being a dihydropyridine derivative felodipine has the advantage of being more selective as a vasodilator and having fewer cardiac effects than non-dihydropyridine calcium antagonists. This benefit is abolished by the poor bioavailability of the drug, which although being almost completely absorbed from the gastrointestinal tract is only 15% bio-available after oral administration. The poor oral bioavailability of felodipine was attributable to its extensive first-pass metabolism and the very low water solubility of the drug. The aqueous solubility of a given drug is a very critical factor, affecting drug efficacy and safety as it affects the drug dissolution parameters and the oral bioavailability. The efficacy of a drug can be severely limited by its poor aqueous solubility. The poor aqueous solubility and wet ability of the drug add to the difficulties encountered in drug formulation.

MATERIALS AND METHODS

Pre Formulation Study

Description of Drug

Physicochemical properties of drugs such as state, color, odor, and taste were physically examined and compared with the reported description of drugs.

Solubility of Pure Drug

Solubility tests were performed as a part of test for purity. Solubility of the drug was measured by 10 mg of drug in a test tube followed by addition of 0.1 mL of solvent. Addition of solvent was continued till the sample was dissolved completely. Solubility was recorded in form of the solvent required for solubilization of the drug powder.

Preparation of Standard Calibration Curve

Accurately weighed 10 mg of powdered drug was transferred to 100 mL volumetric flask. To this about 20 mL of phosphate buffer of pH 6.5 was added and the contents of the flask were shaken to effect the solution. Finally, volume in the flask was made up to the mark by using same solvent. A spectrophotometric method based on the measurement of absorbance at 364 nm in phosphate buffer of pH 6.5 was used in the present study for the estimation of felodipine.

Compatibility Study

Fourier transform infrared (FTIR) was the tool for solid state characterization of pharmaceutical solid. FTIR spectroscopy of pure drug, polymers, excipients and physical mixture were carried out on Shimadzu FTIR 8400S model to investigate any possible interaction between the drug felodipine and the utilized polymers (hydroxypropyl methylcellulose [HPMC], sorbitol). The samples were finely grounded with KBr to prepare the pellets under a hydraulic pressure of 600 psi and a spectrum was scanned in the wavelength range of 4000 and 500 cm^{-1} using Shimadzu FTIR spectrophotometer. The compatibility of drug in the formulation was confirmed by comparing FTIR spectra of pure drug with FTIR of its formulation.

PREPARATION OF FELODIPINE COCRYSTAL

The co-crystals of felodipine with various co-formers (viz., oxalic acid, L-ascorbic acid, and sorbitol) were synthesized by solvent drop grinding method. This method involves incorporation of felodipine and co-former with the addition of ethanol. The ethanol is added dropwise with continuous grinding. The ethanol used behaves as a catalyst, which enhances crystal formation. Briefly, felodipine and co-formers were taken in 1:1 ratio and mixed completely using mortar and pestle. The obtained product was ground to get a freely flowing powder. The solubility of resulting co-crystals was determined and selected co-former (co-crystal showing highest solubility) was further screened in order to select optimum co-former of felodipine as shown in Table 1.

The solubility of formulated co-crystals was determined and the drug with varying co-formers was evaluated for their solubility profiles. From the results the solubility of cocrystals formed with sorbitol showed highest solubility among three co-formers, so it was further screened in order to select optimum ratio of drug and co-former. Three ratios of drug:co-former were screened (1:1, 1:1.5, 1:2) as shown in Table 2.

OPTIMIZATION OF FELODIPINE CO-CRYSTALS EMBEDDED BUCCAL FILM

To understand the influence of formulation variables on the quality of formulations with a minimal number of experimental trials and subsequent selection of formulation variables to develop an optimized formulation using established statistical tools for optimization.

Mathematical modeling, evaluation of the ability to fit to the model and response surface modeling were performed with employing Design-Expert® software (Version 11). In a full factorial design, all the factors are studied in all the possible combinations. Hence, 3^2 factorial designs were chosen for the current formulation optimization study as shown in Table 3.

Table 1. Materials used in the formulation.

S.N.	Materials	Functional Category	Source
1	Felodipine	Active Pharmaceutical Ingredients (API)	Sai Mirra Inno pharm Pvt Ltd.
2	Sorbitol	Conformer, plasticizer, and sweetening agents	Vopec Pharmaceuticals Pvt Ltd.
3	HPMC	Buccoadhesive polymer	Vopec Pharmaceuticals Pvt Ltd.
4	PVA	Buccoadhesive polymer	Vopec Pharmaceuticals Pvt Ltd.

HPMC, hydroxypropyl methylcellulose; PVA, polyvinyl alcohol.

Table 2. Drug with different co-formers.

Co-formers	Drug: Co-formers
Sorbitol	1:1
L-ascorbic acid	1:1
Oxalic acid	1:1

Table 3. Drug and co-former (sorbitol) with different ratio.

S.N.	Drug and Co-former	Ratio
1	Felodipine-sorbitol co-crystals	1:1
2	Felodipine-sorbitol co-crystals	1:1.5
3	Felodipine-sorbitol co-crystals	1:2

Design of Experiment (DOE)

A two-factor and three-level factorial design was used as the experimental design. The independent variables studied were amount of HPMC E15 (X_1) and amount of PVA (X_2). Percentage drug release at 8 hours, (Y_1), and mucoadhesive strength (Y_2) were considered as dependent variables which are shown in Table 4.

Table 4. Factors and factor levels investigated in factorial experimental design.

Factors: Formulation Variables	Levels (mg/film)		
	-1	*0*	*+1*
HPMC E15	300	600	900
PVA	150	300	450
Response	***Goal***		
Drug release at 8th hour	In Range		
Mucoadhesive strength	Maximize		

HPMC, hydroxypropyl methylcellulose; PVA, polyvinyl alcohol.

Experimental Design

The factorial design is a technique that allows identification of factors involved in a process and assesses their relative importance. In addition, any interaction between factors chosen can be identified. Construction of a factorial design involves the selection of parameters and the choice of responses. Experimental runs were designed by Design Expert 11.0.1 (Stat Ease. Inc.) software following full factorial method, 3^2

Full factorial design was applied for examining two variables (factors) at three levels with a minimum of 9 runs as shown in Table 4. Totally nine felodipine buccal patch formulations were prepared employing selected combinations of the two factors as per 3^2 factorial and evaluated to find out the significance of combined effects of the two factor to select the best combination required to achieve the desired felodipine buccal patch as shown in Table 5.

PREPARATION OF BUCCAL FILM

Formulation of Buccal Films

The films containing felodipine co-crystals were prepared by dissolving 600 mg of HPMC-E15, 150 mg of PVA, and 0.8 mL of polyethylene glycol (PEG) 400 in 20 mL of distilled water with continuous stirring on magnetic stirrer at 800 rpm for 1 hour and then 1 mL of menthol isadded to the above solution under constant stirring at 1000 rpm at room temperature until a clear viscous polymeric solution was obtained. Then the weighed quantity of felodipine co-crystals were added slowly in the polymeric

solution and stirred on the magnetic stirrer to obtain a uniform distribution of the drug and then the entrapped air is removed before casting. The quantity of material to be taken is decided on the basis of surface area of the Petri dish. The resulting solution was then casted on a fabricated glass mold and allowed to dry completely at room temperature to form film. The driedfilms were carefully separated from the glass mold and cut to produce the desired sizerequired and were stored in double wrapped aluminum foils.

Table 5. Optimization table for buccal film.

Experiment	Design Factors	
	A: PVA (mg)	***B: HPMC (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

HPMC, hydroxypropyl methylcellulose; PVA, polyvinyl alcohol.

RESULTS AND DISCUSSION

Preformulation Study

Description of Drug

The appearance of the felodipine was visually observed. It was found that it was a pale white powder and it complies with the International Pharmacopeia (IP).

Solubility

Solubility tests were performed.

Calibration Curve of Felodipine

Calibration curve values of felodipine in pH 6.5 phosphate buffer were obtained.

Drug Polymer Compatibility Study

FTIR spectroscopy was the tool for solid state characterization of pharmaceutical solid. FTIR spectroscopy of pure drug, polymers, excipients, and physical mixture were carried out on Shimadzu FT-IR 8400S model to investigate any possible interaction between the drug felodipine and the utilized polymers (HPMC, sorbitol). The samples were finely grounded with KBr to prepare the pellets under a hydraulic pressure of 600 psi and a spectrum was scanned in the wavelength range of 4000 and 500 cm^{-1} using Shimadzu FTIR spectrophotometer. The compatibility of drug in the formulation was confirmed by comparing FTIR spectra of pure drug with FTIR of its formulation as seen in Tables 6 and 7.

INTERPRETATION OF INFRARED SPECTRA

Peak Values and Their Corresponding Functional Group

FTIR spectroscopy was used to detect the existence of interaction between felodipine and hydrophilic carriers used during preparation of buccal film. The spectrum of felodipine shows characteristic peaks of N-H stretching bond at 3368.79 cm^{-1}. The stretching band peak of 2949.94 cm^{-1} was due to stretching between C-H bond. The peak values of 1618.11 to 1686.20 cm^{-1} was due to stretching between C=O bond of carbonyl group. It was the strong bond lies in this group. The spectrum of peak values 1450 to 1600 cm^{-1} was due to the C=C stretching and 1382.33 cm^{-1} was due to CH_3 C-H bending. All the peaks corresponding to the respective bonds are shown in the Tables 8 and 9.

CHARACTERIZATION OF CO-CRYSTALS

Microscopic Characterization of Co-crystals

Microscopic characteristics of prepared co-crystals were observed by light microscope (Figure 1).

Table 6. Solubility test of pure drug.

S.N.	Solvent	Solubility
1	Water	Poorly soluble
2	pH 6.5 buffer	Sparingly soluble
3	Ethanol	Freely soluble
4	DMSO and DMF	Highly soluble

DMF, dimethyl formamide; DMSO dimethyl sulfoxide.

Table 7. Calibration curve of felodipine.

S.N.	Concentration (µg/mL)	Absorbance (nm)
1	0	0
2	10	0.045
3	20	0.082
4	30	0.121
5	40	0.159

Table 8. Interpretation of infrared (IR) spectra.

S.N.	Peak Value (cm^{-1})	Characteristic Functional Groups
1	3368.79	O-H stretching
2	2949.94	C-H stretching
3	1618.11–1686.20	C=O stretching
4	1450–1600	C=C stretching
5	1382.33	CH_3 C-H bending

Table 9. Solubility profile of co-crystals and pure drug.

S.N.	Drug/Co-former	Solubility (mg/100 mL)
1	Felodipine	1.97
2	Felodipine-sorbitol co-crystals	3.2
3	Felodipine-L-ascorbic acid co-crystals	2.5
4	Felodipine-oxalic acid co-crystals	2.2

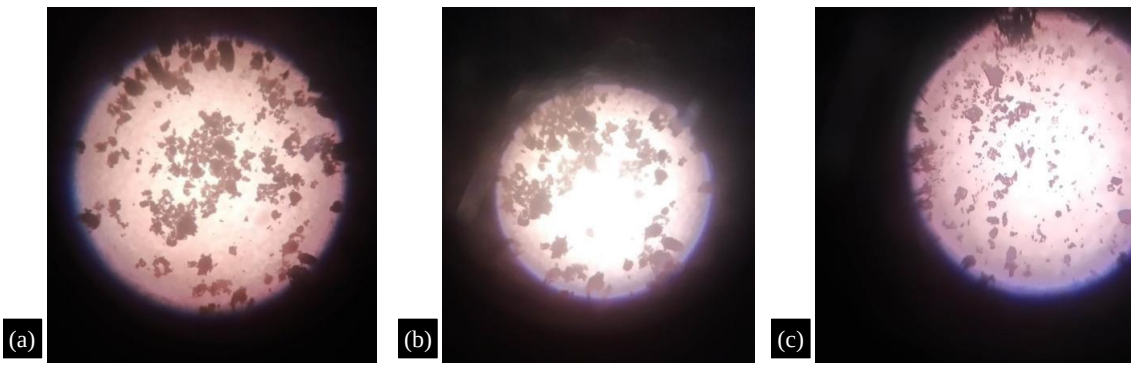


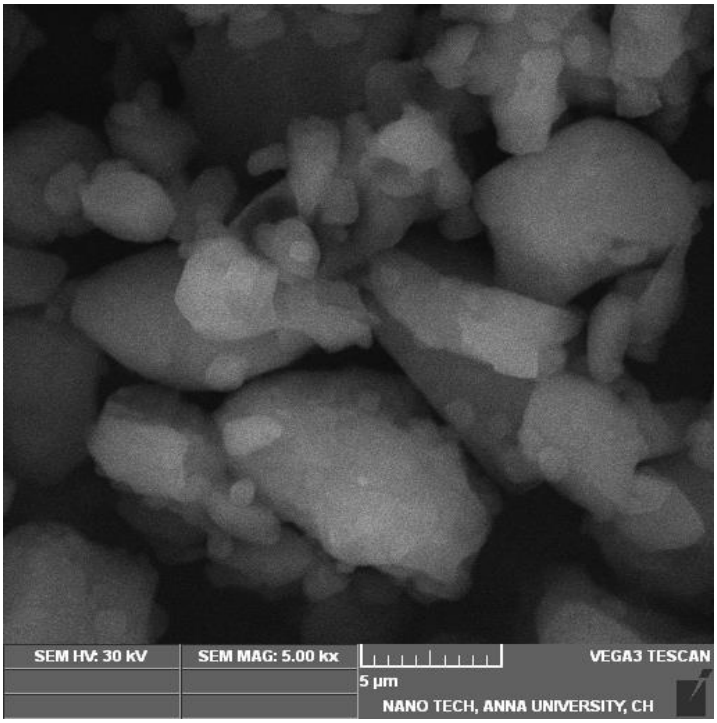
Figure 1. Microscopic images of co-crystals.

Morphological Characteristics of Co-crystals

The shape and surface characteristics of felodipine co-crystal was assessed by scanning electron microscopy (SEM) as shown in Figure 2.

Solubility Study of Co-crystals and Pure Drug

The co-crystals prepared with different co-formers have proved their potential to improve the solubility of drug. Co-crystals of felodipine:sorbitol have shown two folds more solubility than the parent drug.



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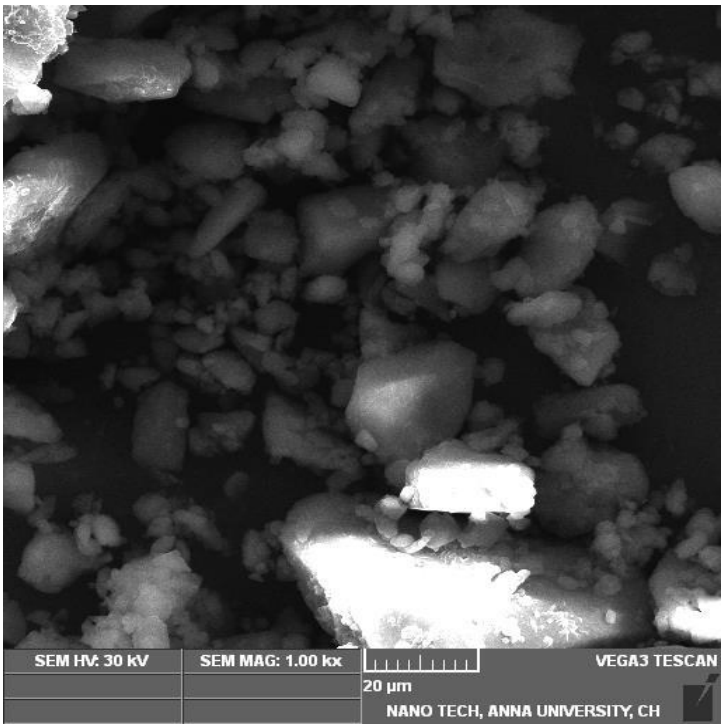

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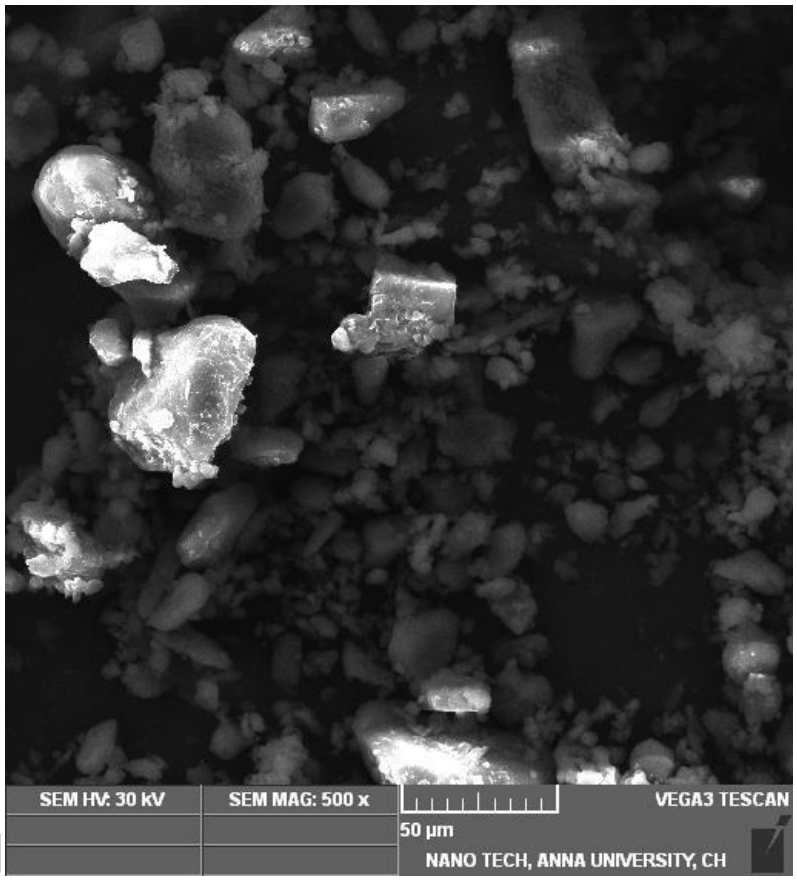

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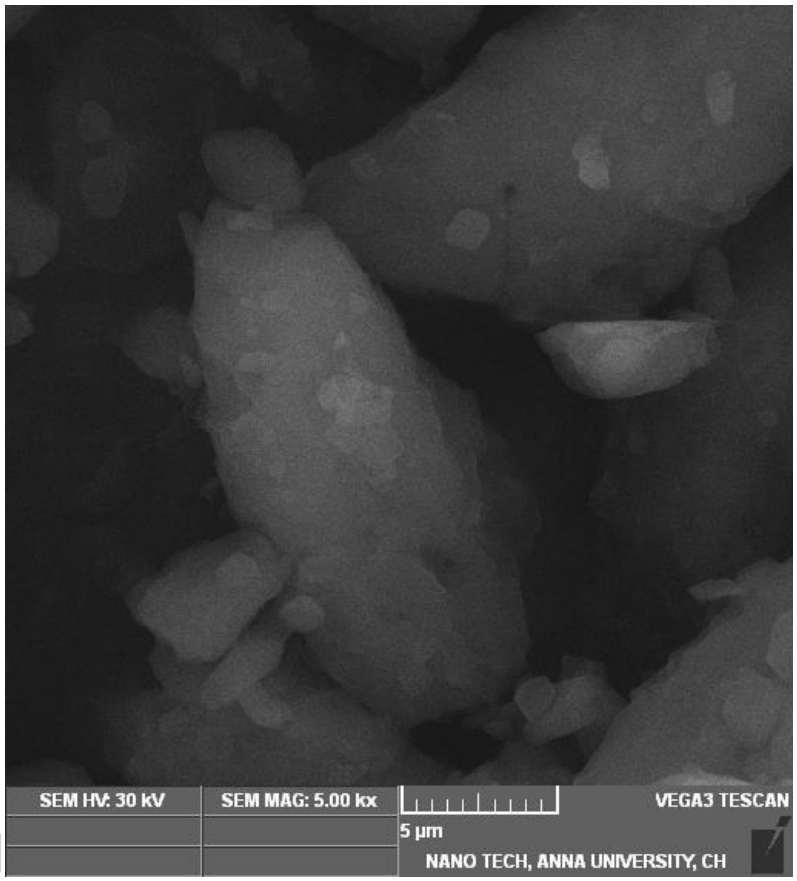

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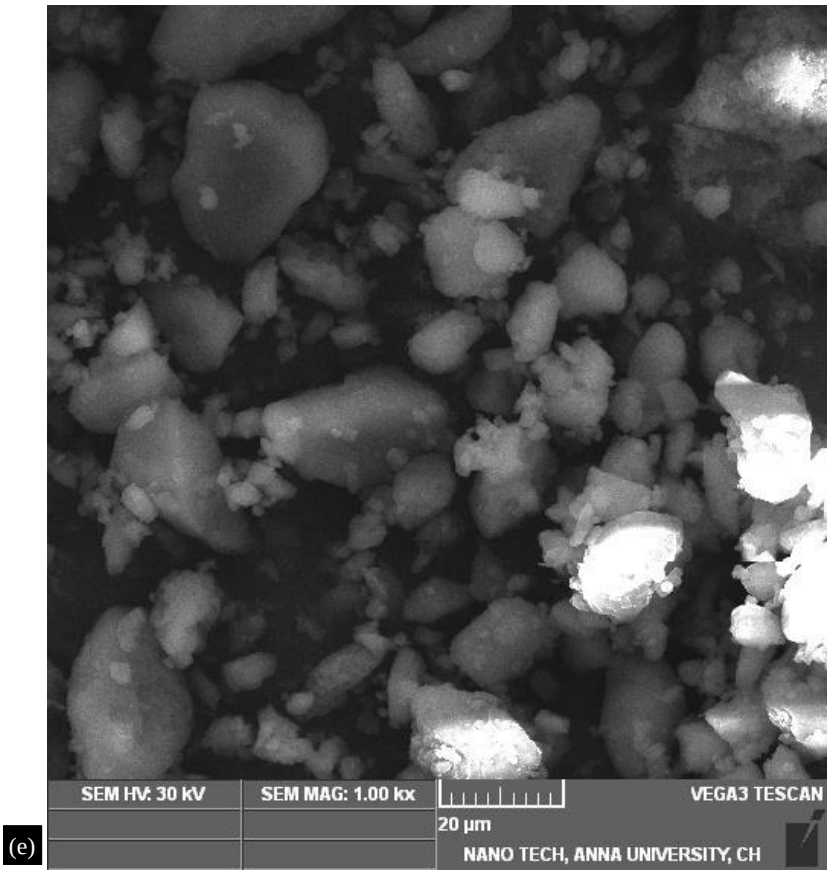

Figure 2. Scanning electron microscopy (SEM) images of felodipine co-crystals.

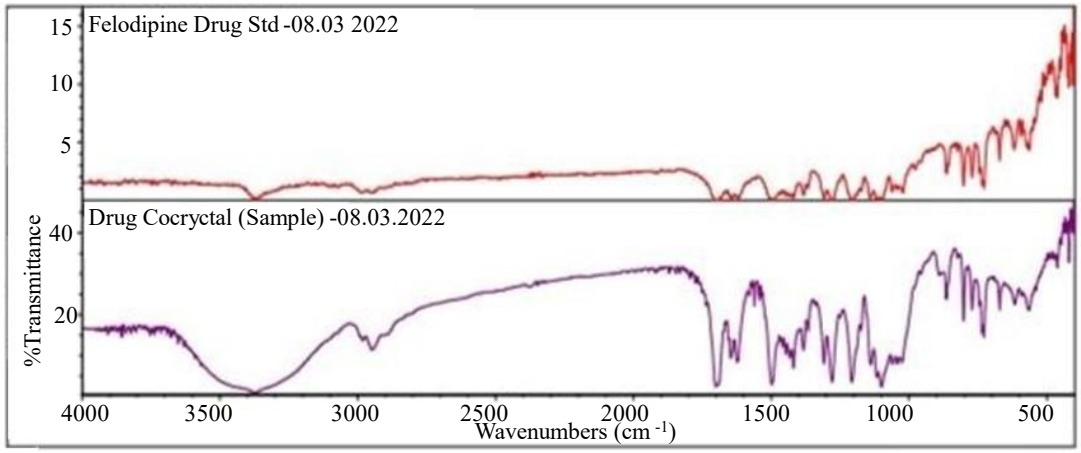

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Figure 3. Comparison between pure drug and drug co-crystal.

Infrared Spectroscopy

The FTIR analysis of the pure drug and felodipine co-crystal was done. IR spectra are as shown in Figure 3.

FTIR spectroscopy was used to detect the existence of interaction between felodipine and sorbitol co-former used during the preparation of cocrystal. When hydrogen bonding occurs between felodipine and the co-former, a shift in certain peaks, which OH affected by an interaction, can be observed in

felodipine spectra. In felodipine, the groups in which hydrogen bonding can occur are the amine group in the ring and the two carbonyl groups. When this hydrogen bonding occurs, bond energy at the N-H or C=O bond decreases and peak shift to lower frequencies is observed. This peak shift was most noticeable at the N-H stretch peak at 3376.43 cm^{-1}, C-H stretch at 2948.28 cm^{-1}, and the C=O stretch peak at 1699.72 cm^{-1}. These peaks shifting may be the probable group which involved in the bond formation with sorbitol to synthesize co-crystal.

Powder X-Ray Diffraction Study

Though single crystal X-ray diffraction (SXRD) is considered as the best technique to analyze the crystal at its atomic level, it is highly difficult to get single crystal suitable for SXRD analysis. Thus, powder XRD (PXRD) is widely used to confirm the co-crystal formation. Reduction in the peak intensity of the co-crystal was observed as compared to the pure drug and sorbitol. Further, some intense peaks with different angles other than drug specific angles were observed. The characteristic peaks of felodipine, sorbitol, and co-crystals were observed at their corresponding 2θ values. The diffractogram of felodipine cocrystal was found to be different from its parent material and more peaks were observed. The changes in diffraction pattern and increment in number of peaks were reported as evidence of formation of co-crystals.

OPTIMIZATION OF FELODIPINE CO-CRYSTALS EMBEDDED BUCCAL FILMS

The formulations were prepared as 9 sets using two variables following 3^2 factorial designs. Buccal films containing felodipine cocrystals were prepared by solvent evaporation technique. The optimized formulations selected by the design were prepared and the parameters were compared to the expected values. For systematic investigation of the factors, a full factorial design was employed.

On the basis of defined constraints for each independent variable, the Design Expert® 11 automatically generated the optimized formulation. The experiments were performed and the responses were obtained. The data are shown in Table 10.

Table 10. Results of independent variable and corresponding dependent variables.

	Factor 1	Factor 2	Response 1	Response 2
Trials	***PVA***	***HPMC***	***% Drug Permeation at 8 Hours***	***Mucoadhesive Strength***
	(mg)	(mg)	(%)	(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

HPMC, hydroxypropyl methylcellulose; PVA, polyvinyl alcohol.

Drug Permeation at 8 Hours

The 3D surface graph (Figure 4) illustrates that increasing the both polymer concentrations results in decreased drug release. Increasing the HPMC E15 concentration has more release retarding tendency. Thus, the formulations containing higher amounts of HPMC E15 has very less drug release at 8th hour.

Mucoadhesive Strength

The 3D surface graph (Figure 5) illustrates that on increasing the concentration of both the polymers results in increasing the mucoadhesive strength. Increasing PVA concentration increases mucoadhesive strength of the films considerably.

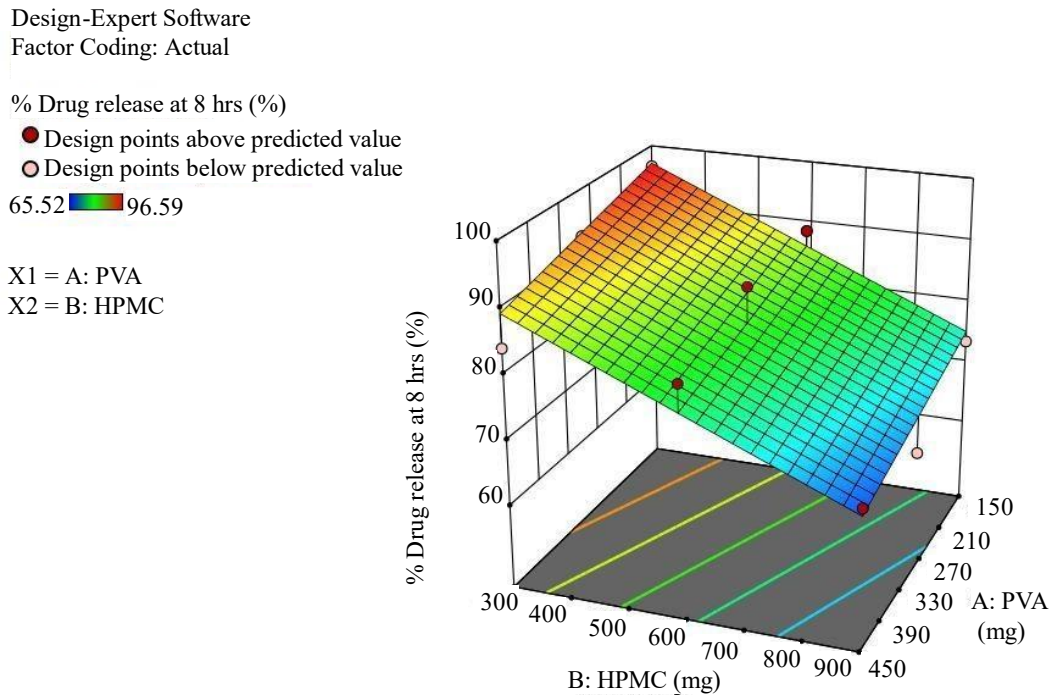


Figure 4. Effect of hydroxypropyl methylcellulose (HPMC) E15 and polyvinyl alcohol (PVA) on drug permeation.

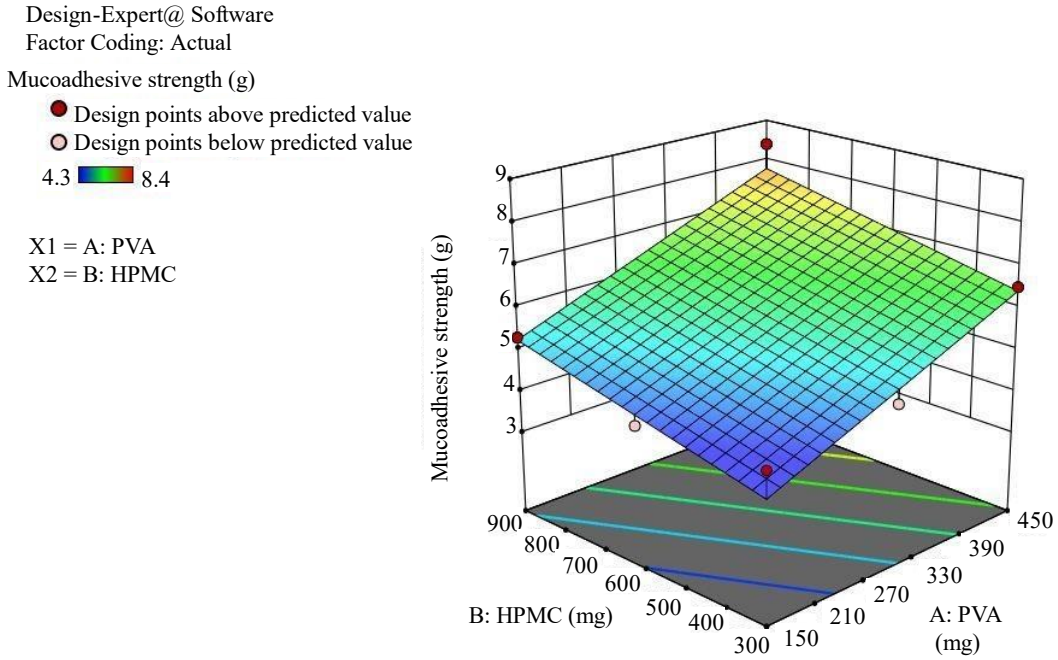


Figure 5. Effect of hydroxypropyl methylcellulose (HPMC) E15 and polyvinyl alcohol (PVA) on mucoadhesive strength.

Analysis of Variance (ANOVA)

Table 11 represents the statistical parameters such as adjusted R^2, predicted R^2, model P values, adequate precision, and percentage coefficient of variation (%CV). Based on Table 9, the responses time taken for drug release at 8 hours and mucoadhesive strength was well fitted to the linear and quadratic model with P value of <0.0500. Table 11 shows the adjusted R^2 for Y_1, and Y_2 which is in reasonable agreement with the predicted R^2. Adequate precision measures the signal-to-noise ratio.

A ratio greater than 4 is the desirable ratio indicating an adequate signal. This model can be used to navigate the design space. The results show that 90% of response variations in drug release at 8 hours and mucoadhesive strength could be described by factorial design as a function of main composition. So, it can be concluded that linear model was suitable model for analysis. The results are shown in Table 11.

Table 11. Response model and statistical parameters obtained from analysis of variance (ANOVA).

Responses	Adjusted R^2	Predicted R^2	Model *P* Value	Adequate Precision	%CV
Drug release at 8 hours	0.8259	0.7277	0.0022	11.3974	5.48
Mucoadhesive strength	0.8820	0.7549	0.0007	15.0594	7.70

Point Prediction

The felodipine co-crystals embedded buccal films were formulated and responses were measured. The software generated the optimized formulation and predicted the response based on the constraint. Then batch was formulated based on the suggested formulation and responses were observed. The observed values of responses were compared to the predicted values of the response and percentage error was calculated to validate the method. The observed value of Y_1 and Y_2 were in a close agreement to the predicted one. By this the validity of optimization procedure was proven. The point prediction is shown in Table 12.

Table 12. Point prediction of felodipine co-crystals embedded buccal films.

Point Prediction	Drug Permeation at 8 Hours (%)	Mucoadhesive Strength (min)
Predicted	96. 82	8.4
Observed	94.59	6.82
% Error	2.30	18.8

% error = (predicted value – observed value)/predicted value × 100.

EVALUATION OF FELODIPINE CO-CRYSTALS EMBEDDED BUCCAL FILMS

Appearance of the Film

The overall appearance was found to be clear and transparency was good which shows that the drug has distributed uniformly.

Patch Morphology

The shape and surface characteristics of felodipine co-crystal embedded buccal film was assessed by SEM as shown in Figures 6 and 7.

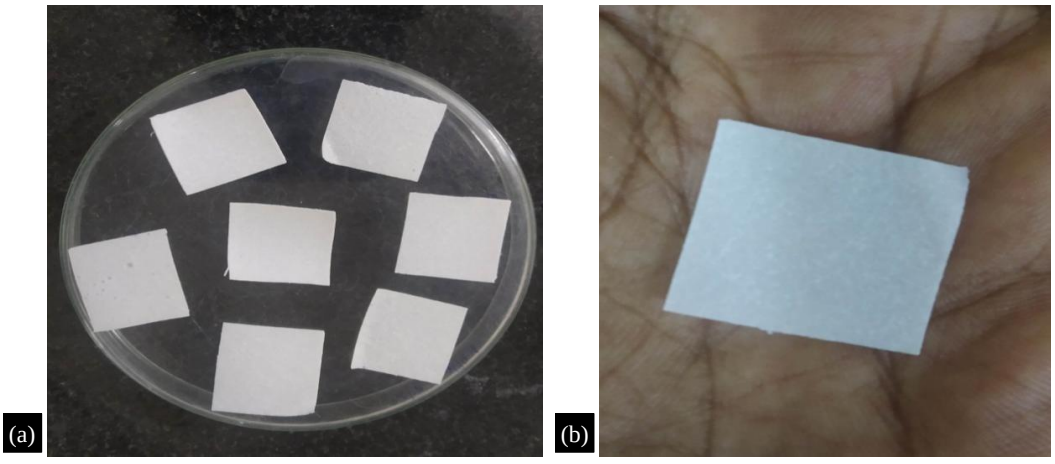
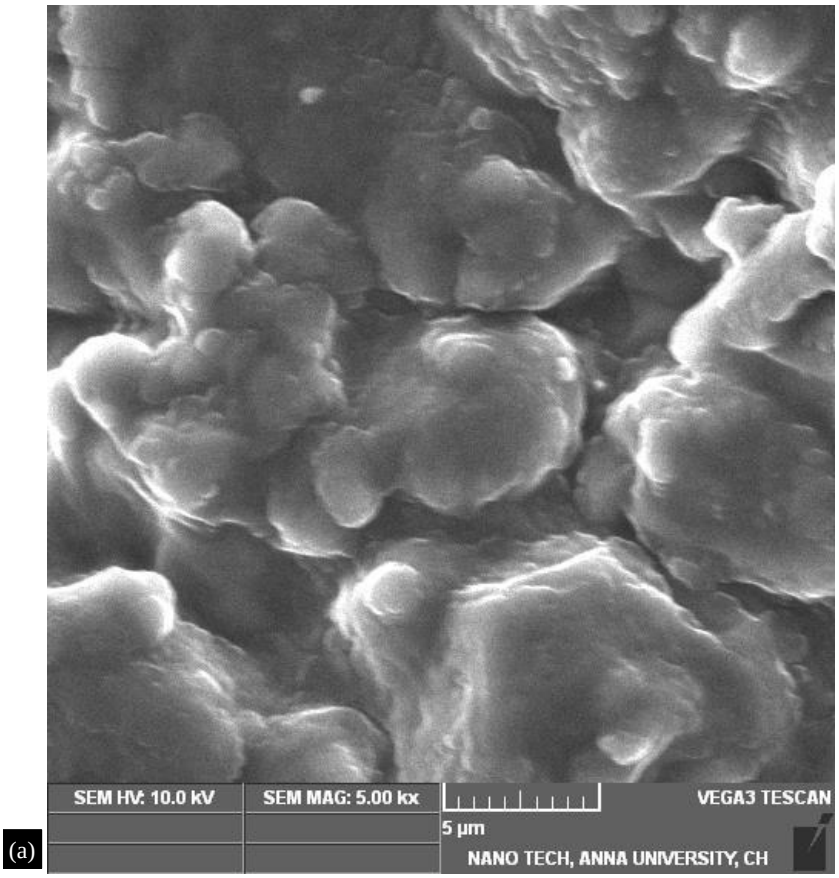


Figure 6. Images of buccal film.



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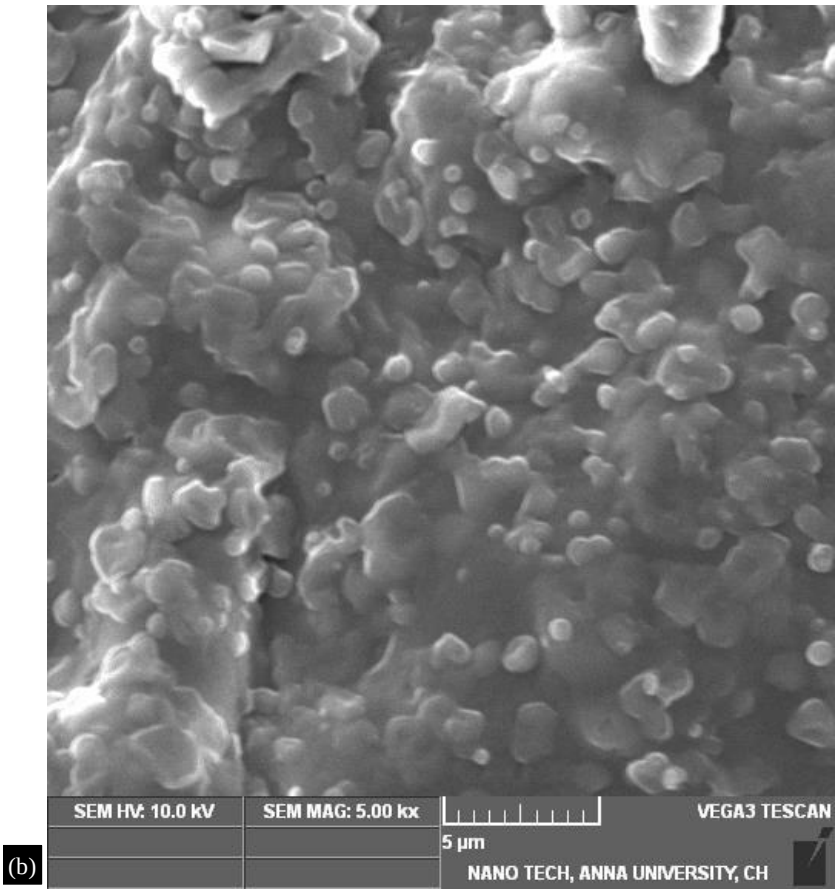

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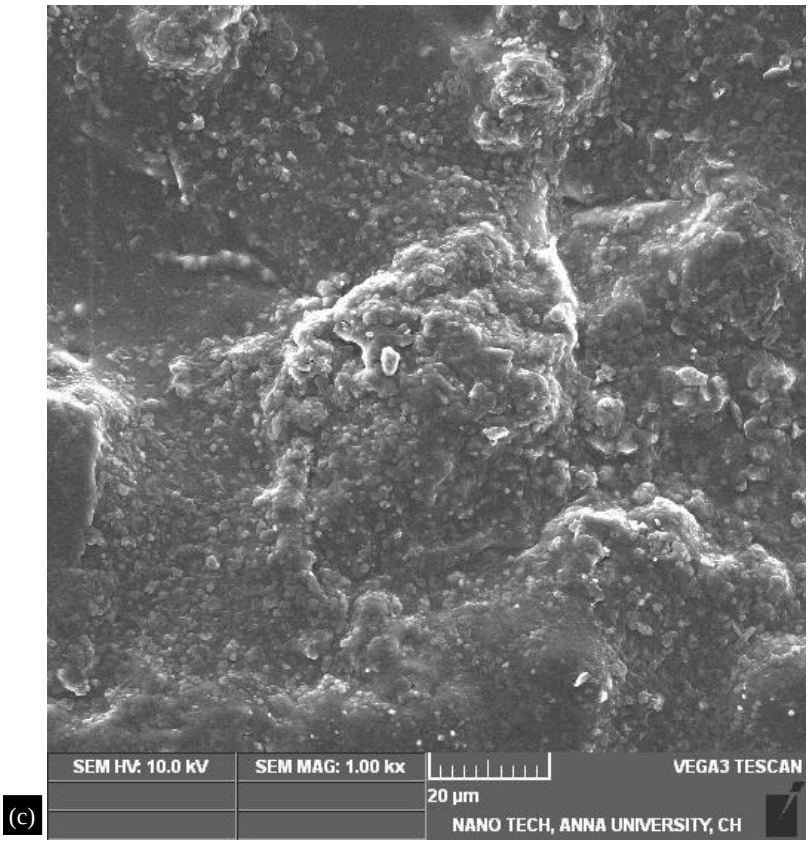

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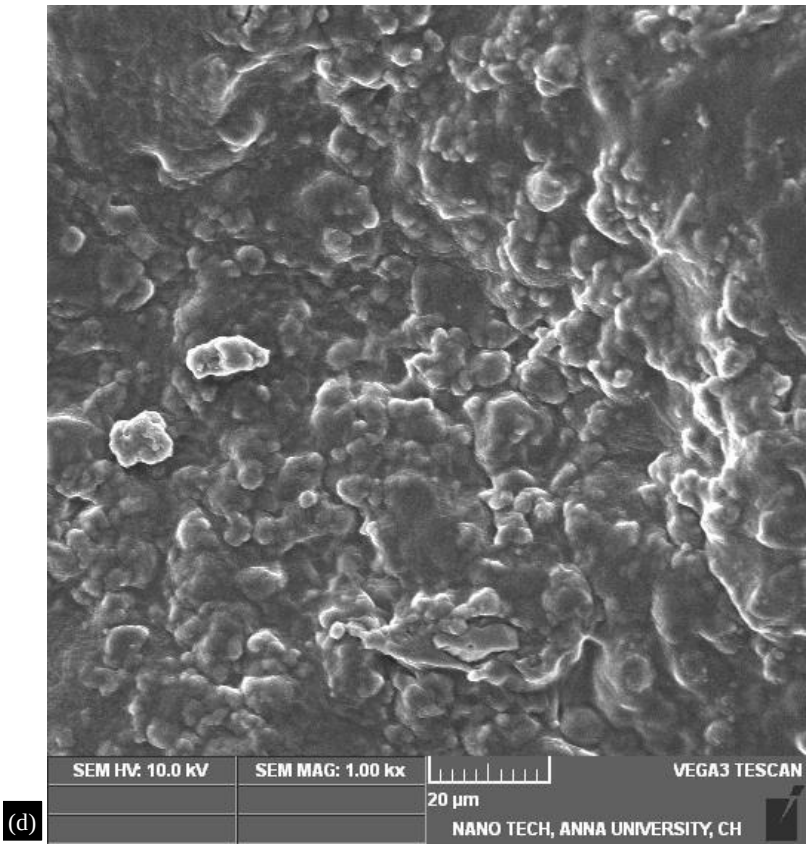

(d)

Figure 7. Scanning electron microscopy (SEM) images of felodipine co-crystals embedded buccal film.

Weight Variation

Three films of 2 × 2 cm size were cut randomly, and the patches were weighed individually on an electronic balance. The weight ranges from 35.49 to 96.42 nm.

T**able 13.** Weight variation of the film.

Formulation	Weight Variation
F1	35.49
F2	72.32
F3	53.6
F4	88.24
F5	61.07
F6	43.5
F7	74.81
F8	53.52
F9	96.42

Thickness of the Patch

The thickness of patch was directly related to drug content uniformity So it was essential to find uniformity in the thickness of the film. It can be measured by calibrated digital vernier calipers as seen in Table 13. The thickness was measured at different spots of the patch and average was taken. The film thickness ranged from 0.32 to 0.36 mm as shown in Table 14.

Table 14. Thickness of the film

Formulation	Film Thickness (mm)
F1	0.33
F2	0.35
F3	0.32
F4	0.34
F5	0.36
F6	0.35
F7	0.35
F8	0.34
F9	0.36

Folding Endurance

The folding endurance of the patch was used to estimate the mechanical strength of the patch to with stand the folding or the ability to withstand the brittleness. It was measured by repeatedly folding a patch at the same line before it breaks. The folding endurance was the number of times the film was folded without breaking.

Higher the folding endurance value greater was the strength of the patch. The highest folding endurance of 318 was achieved by formulation F5 as shown in Table 15.

Swelling Property

Simulated solution of saliva was prepared to check the swelling property of the patch. The initial weight of the patch was determined and placed in the pre-weighed stainless steel mesh. The system was dipped in the simulated saliva solution. The increase in the weight of the patch was noted by weighing the system at regular intervals. The degree of swelling was determined by the formula. The average swelling was found to be 5.62 as shown in Table 16.

Table 15. Folding endurance of the film.

Formulation	Folding Endurance
F1	314
F2	312
F3	305
F4	310
F5	318
F6	309
F7	305
F8	313
F9	304

Table 16. Swelling property of the film.

Formulation	Swelling property
F1	5.48
F2	4.89
F3	4.50
F4	5.23
F5	4.98
F6	5.62
F7	5.20
F8	5.25
F9	5.28

Surface pH

Patch was slightly wetted with help of water. The pH was measured by bringing the electrode in contact with the surface of the patch. The study was performed on three patches of each formulation and average was taken. The surface pH ranged from 6.3 to 6.6. as shown in Table 17.

Table 17. Surface pH of the film

Formulation	Surface pH
F1	6.3
F2	6.5
F3	6.4
F4	6.4
F5	6.6
F6	6.4
F7	6.3
F8	6.5
F9	6.4

Percent Moisture Loss

Moisture loss test was done to check the integrity of patch at dry condition and hygroscopicity of patch. Three patches of 2×2 cm^2 size were cut out and weighed accurately. Then the patch was rested in a desiccator Containing fused anhydrous calcium carbonate. After 3 days, the patches were removed, weighed and percentage weight loss were calculated as shown in Table 18.

Mucoadhesive Strength

Mucoadhesive strength was an important property to be determined because it ensures the attachment of dosage form and delivery of drug at the site of administration. The direct relationship between the

swelling index and adhesion strength has been described by many authors. Formulations F9 and F6 therefore showed highest bioadhesion due to their highest swelling index, thus ensuring adhesion of patch at the site of administration. On applying factorial design, the quadratic model was suggested by software and found to be significant with model *P* value of less than 0.0007 for each term was obtained which indicated that every model term was significant. The results are shown in Table 19.

Table 18. Percentage moisture loss of the film.

Formulation	% Moisture Loss
F1	1.89
F2	2.14
F3	2.25
F4	1.36
F5	1.56
F6	1.19
F7	2.32
F8	2.21
F9	1.92

Table 19. Mucoadhesive strength of film.

Formulation	Mucoadhesive Strength
F1	4.5
F2	4.8
F3	6.5
F4	4.3
F5	5.6
F6	6.8
F7	5.3
F8	6.2
F9	8.4

Drug Content

All the batches of the film contain 72.82 ± 0.8% to 98.16 ±0.3% of drug, which indicate that there is no loss of drug during preparation of the buccal film. All the batches of the film exhibit drug co-crystals content within limit, which is within the desirable range due to the equal distribution of drug in the solution. The results are shown in Table 20.

A total of 12.5 mg of felodipine co-crystal is equivalent to 5 mg of felodipine pure drug.

Table 20. Drug content of the film.

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

Ex Vivo Permeation Study

Ex vivo drug permeation through fresh goat buccal mucosa using Franz diffusion cell and the results are given in Table 21.

Permeation Study Parameters:

Donor compartment–phosphate buffer pH 6.5; receptor compartment–phosphate buffer pH 6.5; Apparatus–diffusion cell

Withdrawal time: 8 hours with 1-hour interval; volume withdrawn: 5 mL

Table 21. Ex vivo percentage drug permeation of the films

Time (Hours)	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	82.9	72.3	81.89	63.9	65.21	74.61	75.63
7		81.75		82.1	88.48	72.86	73.52	79.04	86.12
8				94.59		82.75			

Table 22. Evaluation of optimized felodipine co-crystals embedded buccal film.

Evaluations	Optimized Formulation Results
Weight (mg)	88.24
Thickness (mm)	0.24
Drug content (%)	98.16
Folding endurance	310
Swelling index (%)	5.23
Surface pH	6.4
Percentage moisture loss (%)	1.36

Table 23. Percentage drug permeation of optimized formulation.

Time (Hours)	Drug Permeation (%)
1	20.14
2	37.49
3	46.21
4	55.32
5	60.88
6	72.3
7	82.1
8	94.59

The optimized felodipine buccal film exhibits 94.59% permeation at 8 hours on goat buccal mucosa, the permeation profile was relatively steady and the amount consistently permeated with passage of time. The results are shown in Tables 22 and 23.

EX VIVO DRUG PERMEATION KINETICS OF OPTIMIZED FELODIPINE BUCCAL FILM

Examination of correlation coefficient (R^2) value indicated that the drug release followed a diffusion-controlled mechanism for the optimized Felodipine buccal film from the R^2 value. To study the drug release kinetics, data obtained from ex vivo permeation studies are plotted in various kinetic models. The curve fitting results of the release rate profile of the designed formulation gave an idea on the mechanism of drug release. Based on the "*n*" value 0.653 for the optimized formulation, the drug release was found to follow non-Fickian transport. This value indicates a coupling of the diffusion and erosion mechanism and indicates that the drug release was controlled by more than one process. Also, the drug release mechanism was best explained by zero order, as the plots showed the highest linearity, as the drug release was best fitted in zero order kinetics, it indicated that the rate of drug release was concentration independent. The results are shown in Table 24.

Table 24. Kinetic modeling of drug permeation.

Formulation	Zero-Order R^2	First-Order R^2	Higuchi R^2	Hixson-Crowell R^2	Korsmeyer-Peppas (R^2)	*n* Value
Optimized felodipine co-crystlas buccal film formulation	0.975	0.861	0.992	0.684	0.981	0.653

CONCLUSION

The preformulation study of felodipine was carried out and it was found that the drug is poorly water soluble. The co-crystals were prepared using three different co-formers sorbitol, ascorbic acid, and oxalic acid. The solubility enhancement was observed in combination with sorbitol compared to other co-formers used. The characterization of co crystals was performed using PXRD, FTIR, and SEM analysis. XRD results indicate the amorphous form of the drug.

The co-crystals were embedded within the buccal film for sustained release of the drug. The buccal film was optimized by factorial design using HPMC and PVA as independent variables. Two responses – drug permeation and mucoadhesive strength – were chosen for optimizing the buccal film.

Based on desirability value (1.00), the formulation factors were found and observed value is closer to the predicted values. These results reveal that the model is validated.

The morphology of buccal film was characterized with SEM analysis. The buccal film was tested for thickness, weight variation, folding endurance, drug content, moisture loss, surface pH, and swelling studies.

The drug permeation kinetic study was performed in the optimized formulation and the results reveal that the mechanism of drug permeation follows diffusion from higher R^2 value for Higuchi kinetics (R^2 = 0.992) and the *n* value of Peppas model (n = 0.653) shows that the mechanism follows non-Fickian diffusion.

Novel buccal adhesive cocrystal embedded patch offers innumerable advantages. While the water solubility of the drug is improved twofold so that the permeation efficacy of the drug also improved, aided by increased bioavailability. Buccal patch offers many advantages like ease of administration and withdrawal, avoiding first pass metabolism, low enzyme activity, enhancement of permeability, and high patient compliance.

Hence the novel formulation holds immense opportunities to be explored in terms of different drug candidates.

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