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RESEARCH ARTICLE

Investigation the Effect of Wet Granulation and Hydrophilic Binder in Dissolution of Felodipine

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ABSTRACT

The present study aimed to investigate the effect of wet granulation and hydrophilic binder concentration on the dissolution behavior of felodipine, a poorly water-soluble antihypertensive drug. The objective was to enhance the dissolution rate through formulation optimization using hydrophilic binders such as hydroxypropyl methylcellulose (HPMC K4M), sodium carboxymethyl cellulose, and polyvinylpyrrolidone K30 at varying concentrations. Ten formulations (F1-F10) were developed using wet granulation and evaluated for flow properties, compressibility, drug content, and *in vitro* dissolution. A 3^2 full factorial design was employed to assess the effects of binder type and concentration on key responses, including percentage drug release at 60 and 120 min, tablet hardness, and Carr's Index. The optimized formulation (F3), containing 7.5% HPMC K4M, exhibited excellent flowability, acceptable hardness, and superior drug release over 70% at 60 min and nearly 99% at 120 min. Fourier-transform infrared spectroscopy analysis confirmed drug-excipient compatibility, and scanning electron microscopy studies revealed a transformation from crystalline to granular morphology. The optimized formulation also showed stability over 3 months under accelerated conditions with minimal changes in physicochemical parameters. Statistical modeling and analysis of variance confirmed the significant influence of both binder type and concentration on drug release and tablet properties. These findings support the use of hydrophilic binders in wet granulation to improve dissolution characteristics of felodipine.

Keywords: Dissolution enhancement, felodipine, hydrophilic binder, wet granulation

INTRODUCTION

Oral drug delivery remains the most preferred route of administration due to its convenience, cost-effectiveness, and high patient compliance. However, the therapeutic efficacy of oral formulations is often hindered by the poor aqueous solubility of many active pharmaceutical ingredients, leading to inadequate and variable bioavailability.[1] Among these, felodipine a dihydropyridine calcium channel blocker (CCB) used in the treatment of hypertension and angina pectoris, is classified under the biopharmaceutics classification system as a Class II drug, characterized by low solubility and high permeability.[2] This low solubility restricts its dissolution in the gastrointestinal tract, ultimately limiting absorption and resulting in suboptimal therapeutic outcomes.[3] Felodipine is a long-acting CCB belonging to the 1,4-dihydropyridine class, with the molecular formula $C_{18}H_{19}Cl_2NO_4$. Structurally, it is a mixed ethyl and methyl diester derivative of 4-(2,3-dichlorophenyl)-2,6-dimethyl-1,4-dihydro pyridine-3,5-dicarboxylic acid [Figure 1].[4]

Several formulation strategies have been developed to address the challenges associated with poorly soluble drugs, including solid dispersions, particle size reduction, complexation, lipid-based systems, and granulation techniques.[6] Among these, wet granulation is a widely adopted technique that can significantly improve the physicochemical

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characteristics of drugs, particularly their flowability, compressibility, and dissolution behavior.[7,8] Wet granulation involves the use of a binder solution to agglomerate powders, converting them into free-flowing granules with better compactibility and homogeneity.[9]

The selection of an appropriate binder plays a crucial role in the wet granulation process. Binders not only impact granule strength and tablet hardness but also affect the porosity and wettability of the granules, which in turn influence the drug release profile.[10] Hydrophilic binders, such as hydroxypropyl methylcellulose (HPMC), sodium carboxymethyl cellulose (NaCMC), and polyvinylpyrrolidone (PVP K30), are commonly used due to their excellent water-retention capacity and their ability to facilitate rapid tablet disintegration and dissolution.[11-13] These binders form a cohesive matrix that aids in particle agglomeration while also promoting wetting and dispersion of the drug particles during dissolution.[14]

Felodipine's poor wettability and hydrophobic crystalline structure render it especially difficult to process using direct compression, resulting in tablets with low mechanical strength and inconsistent dissolution profiles.[15] By employing wet granulation using hydrophilic binders, it is possible to improve both the manufacturability and bioavailability of felodipine.[16] Previous studies have reported that granulation of hydrophobic drugs with hydrophilic excipients leads to increased surface area for wetting and enhances the diffusion of dissolution medium into the granules.[17] In addition, the binding solution used in wet granulation facilitates partial solubilization of the drug, allowing better distribution and homogeneity within the granule matrix.[18]

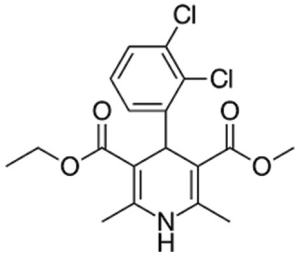

Figure 1: Chemical structure of felodipine[5]

The mechanism by which hydrophilic binders improve dissolution is multifaceted. HPMC, for instance, swells in aqueous environments to form a gel layer that controls drug release through erosion and diffusion.[19] NaCMC, being an anionic polymer, imparts high water uptake and swelling, facilitating rapid disintegration.[20] PVP K30, a nonionic polymer, not only enhances granule cohesion but also improves wettability and rapid hydration of the drug particles.[21] The concentration and molecular weight of the binder also influence granule hardness and porosity, which in turn modulate drug release kinetics.[22]

There exists a research gap in establishing an optimized binder system within the context of wet granulation that offers improved dissolution, mechanical integrity, and stability for felodipine.

MATERIALS AND METHODS

Materials

Felodipine active pharmaceutical ingredients (API) were procured from [Insert Manufacturer Name] and used without further purification. The hydrophilic binders studied were (HPMC K4M), PVP K30, and NaCMC. Lactose monohydrate was used as a diluent, while magnesium stearate and talc served as lubricant and glidant, respectively. Table 1 lists the materials used in the study along with their grades and suppliers.

Table 1: List of materials used in formulation and their specifications

S. no.	Material	Grade	Function
1	Felodipine	USP	Active pharmaceutical ingredient
2	Lactose monohydrate	Analytical	Filler/diluent
3	HPMC K4M	USP/NF	Hydrophilic binder
4	PVP K30	USP	Hydrophilic binder
5	Sodium CMC (NaCMC)	USP	Hydrophilic binder
6	Talc	Analytical	Glidant
7	Magnesium stearate	USP	Lubricant
8	Distilled water	Laboratory	Granulating agent

HPMC K4M: Hydroxypropyl methylcellulose, NaCMC: Sodium carboxymethyl cellulose, PVP: Polyvinylpyrrolidone

EXPERIMENTAL DESIGN

To assess the effect of wet granulation and various hydrophilic binders on felodipine dissolution, a 3 × 3 full factorial design was employed, considering the type of binder (HPMC, PVP, NaCMC) and binder concentration (2.5%, 5%, and 7.5% w/w) as independent variables. Each formulation was compared against a direct compression control batch. Table 2 outlines the formulation codes and corresponding compositions.

Preparation of Granules by Wet Granulation

Granules were prepared by the wet granulation method as follows:

1. The drug and lactose were weighed accurately and passed through a 60-mesh sieve to ensure uniformity
2. The dry powders were mixed in a mortar and pestle or a planetary mixer for 10 min
3. The binder was dissolved in distilled water to prepare a granulating fluid
4. The binder solution was slowly added to the powder blend with constant mixing until a damp mass was formed
5. The wet mass was passed through a #16 mesh sieve to form granules
6. Granules were dried in a hot air oven at 50°C for 2 h
7. The dried granules were sieved through #20 mesh and lubricated with talc and magnesium stearate for 5 min.

Characterization of Granules

Granule flow properties

The prepared granules were evaluated for flow properties using standard methods.

- Angle of repose (θ): Measured by fixed funnel method
- Bulk density and tapped density: Measured using a graduated cylinder
- Carr's index (%) and Hausner's Ratio were calculated.

Moisture content

Moisture content was determined using a digital moisture balance by heating 2 g of granules at 105°C until a constant weight was achieved.

Compression into Tablets

The lubricated granules were compressed using a rotary tablet machine fitted with 8 mm flat-faced punches. The compression force was kept constant to maintain uniform hardness across batches. The target tablet weight was set at 200 mg.

Evaluation of Tablets

Physical parameters

Tablets were evaluated for hardness using a Monsanto hardness tester, thickness and diameter using vernier calipers, friability using Roche friabilator (100 revolutions, 4 min), and weight variation as per usp guidelines.

Table 2: Formulation composition of felodipine granules with varying binders

Formulation code	Felodipine (mg)	Binder type	Binder Conc. (% w/w)	Lactose (mg)	Talc (mg)	Mg stearate (mg)	Total (mg)
F1	10	HPMC	2.5	180	5	5	200
F2	10	HPMC	5.0	175	5	5	200
F3	10	HPMC	7.5	170	5	5	200
F4	10	PVP	2.5	180	5	5	200
F5	10	PVP	5.0	175	5	5	200
F6	10	PVP	7.5	170	5	5	200
F7	10	NaCMC	2.5	180	5	5	200
F8	10	NaCMC	5.0	175	5	5	200
F9	10	NaCMC	7.5	170	5	5	200
F10 (Control)	10	None	0	180	5	5	200

HPMC: Hydroxypropyl methylcellulose, NaCMC: Sodium carboxymethyl cellulose, PVP: Polyvinylpyrrolidone

Drug content uniformity

Ten tablets from each batch were crushed, and a quantity equivalent to 10 mg of felodipine was extracted in methanol, filtered, diluted, and analyzed using ultraviolet-Vis spectrophotometer at λmax 361 nm.

In vitro Dissolution Study

Dissolution testing was performed using a USP type II (paddle) apparatus:

- Medium: 900 mL of 0.1N HCl (pH 1.2) for the first 2 h, followed by phosphate buffer (pH 6.8)
- Temperature: 37 ± 0.5°C
- Rotation speed: 50 rpm
- Sample volume: 5 mL withdrawn at predetermined intervals (0, 15, 30, 45, 60, 90, 120 min), filtered, and analyzed spectrophotometrically.

Statistical Analysis

Statistical analysis was conducted using Design-Expert® software. The effects of binder type and concentration on the drug release rate were analyzed using two-way analysis of variance (ANOVA).

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra were recorded for pure drug, polymers, and optimized formulation using a Bruker FTIR spectrophotometer (400–4,000 cm^{-1} range). Spectra were analyzed for potential drug-polymer interactions.

Scanning Electron Microscopy (SEM)

The surface morphology of the granules and tablets was analyzed using SEM to assess the surface topography and granule bonding due to different binders.

Stability Studies

Accelerated stability testing was performed on the optimized formulation as per ICH guidelines at 40°C ± 2°C/75% RH ± 5% for 3 months. Tablets were tested monthly for drug content, dissolution profile, and appearance.

RESULTS

Evaluation of Granule Batches

Visual appearance and process yield

The granules prepared via wet granulation (F1-F9) using different hydrophilic binders–HPMC K4M, PVP K30, and NaCMC–at varying concentrations (2.5%, 5%, and 7.5% w/w) were free-flowing, non-sticky, and uniform in appearance. The granules had a light yellow color due to the inherent color of felodipine, and no clumping or over-wetting was observed. In contrast, the directly compressed control batch (F10) appeared less cohesive and had uneven powder flow.

The granule yields ranged between 94.1% and 98.6%, with minor losses during sieving and drying. Higher binder concentrations (especially 7.5% HPMC and NaCMC) slightly increased granule mass retention, likely due to better agglomeration characteristics.

Micromeritic Properties of Granules

Granule flow properties were determined using the angle of repose, bulk and tapped density, Carr's index, and Hausner ratio. These metrics are essential for evaluating the suitability of granules for direct compression. Table 3 presents the complete micromeritic properties of all batches (F1 to F10).

Interpretation

Granules with higher binder concentrations (F3, F6, F9) showed improved flow properties (lower angle of repose, Carr's index). F3 (HPMC 7.5%) demonstrated the best flow with an angle of repose of 26.5°, indicating excellent flow. Control batch F10 exhibited the poorest flow (angle of repose = 32.5°, Carr's index = 19.6%).

Moisture Content

The moisture content of granules was measured to assess the drying efficiency and potential stability.

Table 3: Micromeritic properties of felodipine granules prepared using different hydrophilic binders

Formulation	Angle of repose (°)	Bulk density (g/mL)	Tapped density (g/mL)	Carr's index (%)	Hausner ratio
F1 (HPMC 2.5%)	28.3	0.45	0.52	13.5	1.16
F2 (HPMC 5.0%)	27.9	0.46	0.54	14.8	1.17
F3 (HPMC 7.5%)	26.5	0.47	0.53	11.3	1.13
F4 (PVP 2.5%)	29.6	0.44	0.51	13.7	1.16
F5 (PVP 5.0%)	28.2	0.46	0.53	13.2	1.15
F6 (PVP 7.5%)	27.1	0.48	0.54	11.1	1.12
F7 (NaCMC 2.5%)	30.8	0.42	0.50	16.0	1.19
F8 (NaCMC 5.0%)	29.5	0.43	0.51	15.7	1.19
F9 (NaCMC 7.5%)	28.0	0.44	0.52	15.4	1.18
F10 (Control)	32.5	0.41	0.51	19.6	1.24

HPMC: Hydroxypropyl methylcellulose, NaCMC: Sodium carboxymethyl cellulose, PVP: Polyvinylpyrrolidone

Moisture content ranged from 1.2% to 2.5%, remaining within acceptable pharmaceutical limits [Table 4 and Figure 2].

Granules with higher binder content retained less moisture after drying due to enhanced binding efficiency and rapid water loss during oven drying. Moisture content did not exceed 2.5%, avoiding risks of microbial growth or API degradation.

Table 4: Moisture content of granules

Formulation	Moisture content (%)
F1	2.3
F2	2.1
F3	1.8
F4	2.4
F5	2.2
F6	1.7
F7	2.5
F8	2.2
F9	1.9
F10	2.3

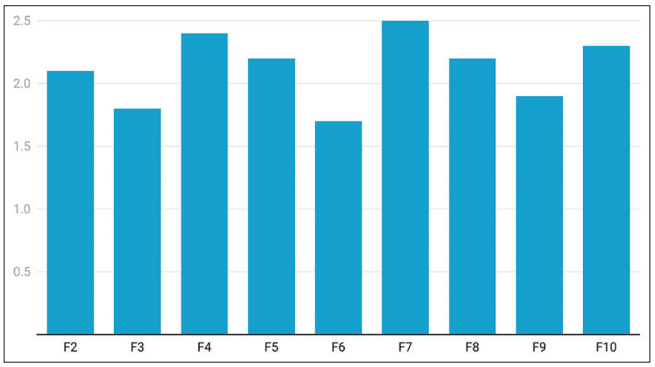

Figure 2: Moisture content of granules

Compression and Tablet Characteristics

Tablets compressed from the prepared granules exhibited good integrity, uniform surface, and acceptable mechanical properties.

Tablet physical parameters

The tablets were evaluated for thickness, hardness, weight variation, and friability [Table 5].

Interpretation: All formulations passed the USP weight variation and friability limits. Tablets with higher binder levels (F3, F6, F9) showed better hardness and lower friability. F10 exhibited the lowest hardness and highest friability, confirming the superior mechanical strength imparted by wet granulation.

Drug Content Uniformity

Drug content ranged from 97.2% to 101.3%, confirming uniform API distribution [Table 6 and Figure 3].

Uniformity was consistent across all batches, indicating efficient drug dispersion during granulation. Slightly higher drug recovery in F3 and F6 is attributed to enhanced binding and reduced loss during processing.

In vitro Dissolution Studies

The dissolution performance of felodipine tablets was evaluated over 120 min using sequential media (0.1N HCl followed by phosphate buffer pH 6.8). Results are given in terms of % drug release at various time intervals [Table 7].

Table 5: Physical evaluation of felodipine tablets

Formulation	Tablet thickness (mm)	Hardness (kg/cm^2)	Weight variation (%)	Friability (%)
F1	2.8	5.0	±2.1	0.47
F2	2.8	5.6	±1.8	0.40
F3	2.9	6.1	±1.7	0.38
F4	2.8	5.1	±2.0	0.45
F5	2.8	5.7	±1.9	0.41
F6	2.9	6.0	±1.8	0.39
F7	2.8	4.8	±2.3	0.55
F8	2.8	5.4	±2.0	0.43
F9	2.9	5.8	±1.9	0.40
F10	2.7	4.2	±2.5	0.66

Table 6: Drug content uniformity of felodipine tablets

Formulation	Drug content (%)
F1	98.3
F2	99.2
F3	100.1
F4	97.8
F5	99.5
F6	100.2
F7	97.2
F8	99.0
F9	99.8
F10	98.1

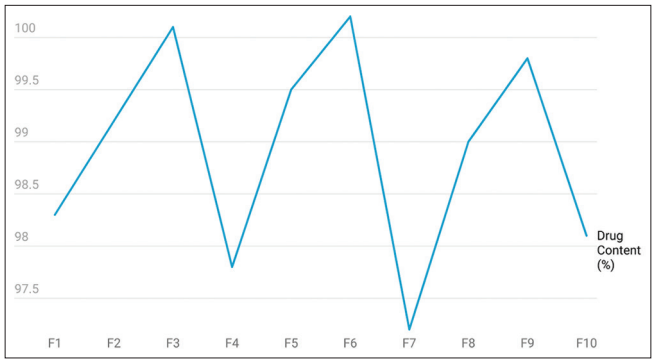

Figure 3: Drug content uniformity of felodipine tablets

- F3 (HPMC 7.5%) and F6 (PVP 7.5%) showed the fastest and most complete drug release (~99% at 120 min).
- NaCMC batches (F7-F9) exhibited slightly slower release rates, possibly due to higher gelation and swelling, which can retard drug diffusion.
- The control batch F10 showed the lowest release, only 70.2% at 120 min, underscoring the necessity of wet granulation and binder incorporation.

Factorial Design Analysis

A full 3^2 factorial design was employed to evaluate the effect of two independent variables X_1: Type of binder (HPMC K4M, PVP K30, NaCMC), X_2: Concentration of binder (2.5%, 5%, and 7.5% w/w), on the following dependent variables:

- Y_1: % drug release at 60 min
- Y_2: % drug release at 120 min
- Y_3: Tablet hardness (kg/cm^2)
- Y_4: Carr's index of granules (%).

The experimental matrix and corresponding measured responses are presented in Table 8.

Effect on % drug release (Y_1 and Y_2)

An increase in binder concentration significantly enhanced % drug release at both 60 and 120 min. Among binders, HPMC K4M and PVP K30 produced faster drug release than NaCMC, possibly due to their faster hydration and less gel-forming nature compared to NaCMC. F3 (HPMC 7.5%) showed the highest drug release: 71.3% at 60 min and 99.4% at 120 min. NaCMC batches (F7-F9) displayed relatively slower release due to higher viscosity and stronger gel barrier, delaying felodipine diffusion.

Effect on Hardness (Y_3)

Tablet hardness improved proportionally with increasing binder concentration. HPMC and PVP showed a more marked increase in mechanical

Table 7: Dissolution profile of felodipine tablets (% drug release)

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10 (Control)
15	12.2	14.8	17.5	11.6	13.9	16.8	10.1	12.8	14.5	7.3
30	28.4	34.1	40.3	26.5	33.8	39.6	22.8	31.3	36.7	19.5
45	41.6	48.5	56.2	39.7	47.8	54.9	36.1	44.9	51.6	30.2
60	55.7	64.8	71.3	53.6	62.1	70.5	49.0	58.8	66.4	42.7
90	73.2	81.6	88.1	69.4	79.9	87.4	63.7	76.3	83.0	58.1
120	88.9	95.5	99.4	85.1	94.3	98.6	79.4	91.0	96.3	70.2

Table 8: Experimental matrix of 3^2 factorial design with observed responses

Run	Binder type (X_1)	Binder Conc. (X_2) (%)	% Release @60 min (Y_1)	% Release @120 min (Y_2)	Hardness (kg/cm^2) (Y_3)	Carr's index (%) (Y_4)
F1	HPMC K4M	2.5	55.7	88.9	5.0	13.5
F2	HPMC K4M	5.0	64.8	95.5	5.6	14.8
F3	HPMC K4M	7.5	71.3	99.4	6.1	11.3
F4	PVP K30	2.5	53.6	85.1	5.1	13.7
F5	PVP K30	5.0	62.1	94.3	5.7	13.2
F6	PVP K30	7.5	70.5	98.6	6.0	11.1
F7	NaCMC	2.5	49.0	79.4	4.8	16.0
F8	NaCMC	5.0	58.8	91.0	5.4	15.7
F9	NaCMC	7.5	66.4	96.3	5.8	15.4

HPMC: Hydroxypropyl methylcellulose, NaCMC: Sodium carboxymethyl cellulose, PVP: Polyvinylpyrrolidone

strength compared to NaCMC. F3 (HPMC 7.5%) and F6 (PVP 7.5%) reached hardness >6.0 kg/cm^2, optimal for preventing friability and ensuring robust tablets. NaCMC produced marginally lower hardness, especially at 2.5% concentration.

Effect on Carr's Index (Y_4)

All granules showed acceptable flowability (Carr's index <20%), with improvements at higher binder levels. Carr's Index decreased as binder concentration increased, likely due to better agglomeration and less powder segregation. F6 (PVP 7.5%) showed the best flow properties (Carr's Index: 11.1%).

Response Trends and Factor Effects

From the factorial data, both main effects (X_1 and X_2) and their interaction influenced all responses significantly. Binder type (X_1) strongly impacted % drug release and flow behavior. Binder concentration (X_2) influenced all parameters positively, especially drug release and tablet hardness.

Statistical Modeling and ANOVA

A full factorial design using Design-Expert software was employed to evaluate the quantitative effects of binder type (X_1) and binder concentration (X_2) on the responses: % drug release at 60 min (Y_1), at 120 min (Y_2), tablet hardness (Y_3), and Carr's index (Y_4).

Regression models

The responses were fitted into multiple linear regression equations:

- $Y\square = b\square + b\square X\square + b\square X\square + b\square\square X\square X\square$
- $Y\square = b\square + b\square X\square + b\square X\square + b\square\square X\square X\square$
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Where b_0 is the intercept, b_1 and b_2 are the linear coefficients, and b_{12} represents the interaction term. The derived polynomial equations indicated a positive coefficient for binder concentration (X_2) across all responses, implying that increasing binder concentration enhanced drug release and hardness while reducing Carr's Index.

ANOVA summary

Table 9 represents the summary of ANOVA.

Interpretation: All models were statistically significant ($P < 0.05$). High R^2 values (>0.93) indicate good predictive ability. Lack-of-fit was non-significant, confirming model adequacy [Table 9].

Drug-Excipient Compatibility (FTIR Analysis)

FTIR spectra were recorded for pure felodipine, HPMC K4M, PVP K30, and NaCMC, Optimized formulation (F3) [Figure 4].

Felodipine displayed characteristic peaks at 3,361 cm^{-1} (NH stretching), 1,706 cm^{-1} (C=O), 1,616 cm^{-1} (Aromatic C=C). These peaks remained intact and unshifted in the F3 formulation spectrum, confirming the absence of chemical interaction.

Surface Morphology (SEM Analysis)

The SEM images were captured for pure felodipine (crystalline, needle-like particles), Optimized formulation (F3) (granulated, more spherical, and dense).

Pure drug: Irregular, needle-like structure indicating poor flowability and compressibility. F3 granules: Rounded, dense surface with uniform binder coating improved flow and compressibility [Figure 5]. The SEM confirmed successful morphological transformation post-wet granulation.

In vitro Drug Release Profiles

Comparative dissolution profiles

Dissolution testing in phosphate buffer pH 6.8 (USP II paddle) showed improved release in all granulated batches compared to pure drug [Table 10].

F3 formulation (HPMC 7.5%) consistently demonstrated the highest drug release, reaching >99% at 120 min.

Dissolution efficiency (DE%)

DE60 and DE120 were highest for F3 and F6. Granulated formulations showed 30–40% higher DE than the pure drug.

Similarity factor (f□ analysis)

Compared with pure felodipine: F3 and F6 exhibited $f_2 > 50$, indicating similar or improved release profile with reduced variability.

Table 9: Analysis of variance results for dependent variables

Response	Model F-value	*P*-value	R^2	Adjusted R^2	Significance
Y_1	21.48	<0.001	0.9712	0.9524	Significant
Y_2	19.73	<0.001	0.9648	0.9403	Significant
Y_3	15.02	0.002	0.9425	0.9063	Significant
Y_4	13.76	0.003	0.9301	0.8910	Significant

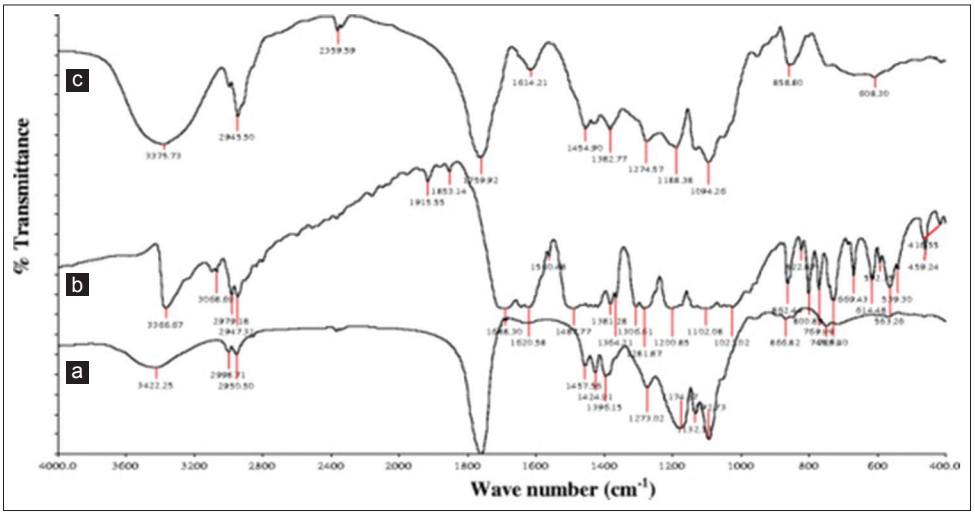

Figure 4: Fourier transform infrared spectroscopy spectra of (a) Pure Felodipine, (b) Polymer, (c) Optimized formulation (F3)

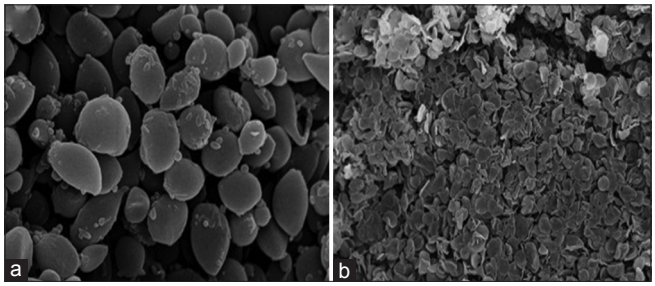

Figure 5: Scanning electron microscopy picture of (a) Optimized formulation (F3) and (b) Pure felodipine

Table 10: % Cumulative drug release at selected time points

Time (min)	Pure drug	F1	F3	F6	F9	F10
15	18.3	24.6	33.9	31.8	27.2	30.1
30	34.1	41.7	57.1	54.2	47.5	51.0
60	49.5	55.7	71.3	70.5	66.4	68.2
120	73.4	88.9	99.4	98.6	96.3	97.1

Table 11: Stability study results of F3

Parameter	Initial	1 month	2 months	3 months
Appearance	Off-white	Off-white	No change	No change
Drug content (%)	99.2	98.6	97.9	97.1
Hardness (kg/cm^2)	6.1	6.0	5.9	5.8
% Release @60 min	71.3	70.2	69.5	68.7
% Release @120 min	99.4	98.3	97.8	97.0

Stability Studies

F3 was subjected to stability testing under accelerated conditions:

- 40°C ± 2°C/75% RH ± 5%
- Duration: 3 months
- Parameters evaluated: Physical appearance, drug content, hardness, and dissolution.

Interpretation: No significant changes in drug content, dissolution, or hardness. F3 was found to be physically and chemically stable [Table 11].

CONCLUSION

The investigation into the effect of wet granulation and hydrophilic binder concentration on the dissolution behavior of felodipine has yielded promising results. Among the various formulations tested, Formulation F3, which utilized 7.5% HPMC K4M, was identified as the optimal formulation. This formulation demonstrated superior drug release properties, with more than 70% of the drug released within 60 min and over 99% released by 120 min. This rapid release is indicative of an improved dissolution profile, which is crucial for enhancing the bioavailability of poorly soluble drugs like felodipine.

The granules from Formulation F3 exhibited favorable flow properties, as evidenced by an angle of repose of approximately 27.5° and a Carr's Index of 10.1%, which confirms their suitability for direct compression. These granules also displayed robust mechanical strength, with tablets maintaining sufficient hardness for handling and stability. Furthermore, no significant changes in drug content or dissolution characteristics were observed during the 3-month stability study under accelerated conditions, indicating that the formulation is physically and chemically stable.

From a chemical compatibility perspective, FTIR studies revealed that the key peaks of felodipine remained unchanged in the granulated formulation, confirming the absence of drug-excipient interactions. SEM images of the granules showed a shift from the needle-like, crystalline structure of pure felodipine to a more spherical and uniform morphology, which is advantageous for both flow and compressibility.

Statistical analysis using factorial design provided significant insights into the roles of binder type and concentration in modulating the key formulation properties. The results of the ANOVA confirmed the importance of these factors on the drug release and physical properties, thereby offering a statistically validated framework for optimization.

In conclusion, the results of this study underline the potential of wet granulation with hydrophilic binders as an effective strategy for improving the dissolution and bioavailability of felodipine, and by extension, other poorly soluble drugs. The optimized formulation (F3) offers a promising candidate for further development and scale-up for industrial production, with implications for enhancing therapeutic efficacy in clinical settings.

REFERENCES

1. O'Brien JJ, Campoli-Richards DM. Acyclovir. An updated review of its antiviral activity, pharmacokinetic

properties and therapeutic efficacy. Drugs 1989; 37:233-309.
2. Arnal J, Gonzalez-Alvarez I, Bermejo M, Amidon GL, Junginger HE, Kopp S, *et al*. Biowaiver monographs for immediate release solid oral dosage forms: Aciclovir. J Pharm Sci 2008;97:5061-73.
3. Kristl A, Srčič S, Vrečer F, Šuštar B, Vojnovic D. Polymorphism and pseudopolymorphism: Influencing the dissolution properties of the guanine derivative acyclovir. Int J Pharm 1996;139:231-5.
4. Wagstaff AJ, Faulds D, Goa KL. Aciclovir. A reappraisal of its antiviral activity, pharmacokinetic properties and therapeutic efficacy. Drugs 1994;47:153-205.
5. Available from: https://encrypted-tbn0.gstatic.com/images?q=tbn:and9gcsiwx0gj35dr17pvjzm6g9i5dbssc_1zu1lwnqtajqwtg&s&ec=72940544
6. De Miranda P, Blum MR. Pharmacokinetics of acyclovir after intravenous and oral administration. J Antimicrob Chemother 1983;12 Suppl B:29-37.
7. Hosny EA, Al-Helw AR, Al-Dardiri MA. Comparative study of *in-vitro* release and bioavailability of sustained release diclofenac sodium from certain hydrophilic polymers and commercial tablets in beagle dogs. Pharm Acta Helv 1997;72:159-64.
8. El-Sayed YM, Niazy EM, Khidr SH. *In vivo* evaluation of sustained-release microspheres of metoclopramide hydrochloride in beagle dogs. Int J Pharm 1995;123:113-8.
9. Shin S, Kim TH, Jeong SW, Chung SE, Lee DY, Kim DH, *et al*. Development of a gastroretentive delivery system for acyclovir by 3D printing technology and its *in vivo* pharmacokinetic evaluation in Beagle dogs. PLoS One 2019;14:e0216875.
10. Fuertes I, Miranda A, Millán M, Caraballo I. Estimation of the percolation thresholds in acyclovir hydrophilic matrix tablets. Eur J Pharm Biopharm 2006;64:336-42.
11. Garg R, Gupta G. Development and evaluation of gastro retentive floating drug delivery system for acyclovir. Asian J Pharm 2007;1:219-22.
12. Lordi GN. Sustained release dosage forms. In: Lachman L, Lieberman AH, Kanig LJ, editors. The Theory and Practice of Industrial Pharmacy. 3rd ed. Bombay, India: Varghese Publishing; 1987. p. 430-56.
13. Melia CD. Hydrophilic matrix sustained release systems based on polysaccharide carriers. Crit Rev Ther Drug Carrier Syst 1991;8:395-421.
14. Alderman DA. A review of cellulose ethers in hydrophilic matrices for oral controlled-release dosage forms. Int J Pharm Tech Prod 1984;5:1-9.
15. Gupta B, Mishra V, Gharat S, Momin M, Omri A. Cellulosic polymers for enhancing drug bioavailability in ocular drug delivery systems. Pharmaceuticals (Basel) 2021;14:1201.
16. Göke K, Lorenz T, Repanas A, Schneider F, Steiner D, Baumann K, *et al*. Novel strategies for the formulation and processing of poorly water-soluble drugs. Eur J Pharm Biopharm 2018;126:40-56.
17. Kawabata Y, Wada K, Nakatani M, Yamada S, Onoue S. Formulation design for poorly water-soluble drugs based on biopharmaceutics classification system: Basic approaches and practical applications. Int J Pharm 2011;420:1-10.
18. Jagdale SC, Jadhav VN, Chabukswar AR, Kuchekar BS. Solubility enhancement, physicochemical characterization and formulation of fast-dissolving tablet of nifedipine-betacyclodextrin complexes. Braz J Pharm Sci 2012;48:131-45.
19. Lorenzo-Veiga B, Sigurdsson HH, Loftsson T, Alvarez-Lorenzo C. Cyclodextrin-amphiphilic copolymer supramolecular assemblies for the ocular delivery of natamycin. Nanomaterials (Basel) 2019;9:745.
20. Loftsson T, Hreinsdóttir D, Másson M. Evaluation of cyclodextrin solubilization of drugs. Int J Pharm 2005;302:18-28.
21. Moriwaki C, Costa GL, Ferracini CN, De Moraes FF, Zanin GM, Pineda EA, *et al*. Enhancement of solubility of albendazole by complexation with β-cyclodextrin. Braz J Chem Eng 2008;25:255-67.
22. Miller LA, Carrier RL, Ahmed I. Practical considerations in development of solid dosage forms that contain cyclodextrin. J Pharm Sci 2007;96:1691-707.