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Optimization, Statistical Modeling, And Release Kinetics of Felodipine-Loaded Polymeric Nanosponges Using A 2^3 Full Factorial Design

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ABSTRACT:
Felodipine, a BCS Class II antihypertensive agent, exhibits poor aqueous solubility and variable oral bioavailability, necessitating advanced delivery strategies. The present study reports the development and statistical optimization of felodipine-loaded polymeric nano-sponges to enhance solubility and achieve controlled drug release. Nano-sponges were fabricated using the emulsion solvent diffusion technique, employing Eudragit S100, Eudragit L100, and ethyl cellulose as formulation variables. A 2^3 full factorial design was implemented using Design-Expert® software to systematically evaluate the influence of independent variables on critical quality attributes, including particle size, zeta potential, entrapment efficiency, and drug release behaviour. The optimized formulation (F9) demonstrated a mean particle size of 186.6 nm with a narrow polydispersity index (0.140), indicating uniformity, and a zeta potential of +19.99 mV, suggesting adequate stability. High entrapment efficiency (98.44%) confirmed effective drug incorporation within the nano-sponge matrix. *In-Vitro* release studies revealed a biphasic release pattern with an initial burst followed by sustained drug release over 8 hours. Release kinetics were best described by the Korsmeyer–Peppas model (R^2 = 0.9932), indicating a diffusion-controlled mechanism. Statistical analysis (ANOVA) validated the significance of formulation variables ($p < 0.05$), while response surface methodology facilitated precise optimization. Furthermore, stability studies conducted under ICH conditions demonstrated minimal changes in physicochemical properties over 60 days. These findings highlight the potential of factorial design-optimized polymeric nano-sponges as a robust platform for improving solubility and controlled delivery of poorly water-soluble drugs like felodipine.

INTRODUCTION:
Hypertension is a major global health concern, affecting over 1.28 billion adults worldwide and representing a leading risk factor for cardiovascular morbidity and mortality, as reported by the World Health Organization. Effective long-term management of hypertension relies on consistent drug delivery and optimal bioavailability of antihypertensive agents.[1-8] Felodipine, a dihydropyridine calcium channel blocker, is widely prescribed for the

treatment of hypertension and angina pectoris due to its potent vasodilatory action mediated by inhibition of calcium ion influx into vascular smooth muscle cells. However, felodipine belongs to the Biopharmaceutical Classification System (BCS) Class II category, characterized by low aqueous solubility and high permeability. Felodipine exhibits poor oral bioavailability (<15%), due to poor dissolution and extensive first-pass metabolism[9], which significantly limits its therapeutic efficiency and necessitates frequent dosing.[10-12]

To overcome these limitations, various formulation strategies such as solid dispersions, lipid-based carriers, and nano-emulsions have been explored. Despite several formulation approaches such as solid dispersions, lipid carriers, and nano-emulsions, challenges related to stability, scalability, and controlled release persist. Recent investigations involving polymeric nanosystems for antihypertensive therapy have demonstrated significant improvement in sustained release and pharmacokinetic performance, further highlighting the potential of nanosponge-based delivery systems.[12] Polymeric nano-sponges offer a unique porous architecture enabling high drug loading and sustained release; however, systematic optimization using statistical tools remains underexplored for felodipine delivery.

Among advanced nanocarrier systems, polymeric nano-sponges have emerged as promising platforms for enhancing the solubility and controlled delivery of poorly water-soluble drugs. These nanoscale, cross-linked polymeric structures possess a highly porous architecture capable of encapsulating hydrophobic drug molecules within their internal cavities. Nano-sponges offer multiple advantages, including improved solubility, enhanced chemical stability, controlled and sustained drug release, and reduced dosing frequency. Recent studies have also demonstrated the applicability of nanosponge-based systems in advanced therapeutic delivery due to their high encapsulation efficiency and controlled release behavior.[14]Despite these advantages, limited studies have systematically investigated the application of nano-sponges for felodipine, particularly using statistically optimized design approaches.[15-19]

In pharmaceutical formulation development, optimization is critical for identifying key variables influencing product performance. Traditional trial-and-error methods are time-consuming, resource-intensive, and fail to capture interaction effects between variables. In contrast, Design of Experiments (DoE) provides a robust, systematic, and statistically validated framework for optimization. Among these, the 2^3 factorial design is particularly efficient for evaluating three independent variables at two levels, enabling simultaneous assessment of main effects and interaction effects with minimal experimental runs, thereby enhancing formulation precision and reproducibility.[20-23]

The present study focuses on the development and optimization of felodipine-loaded polymeric nano-sponges using a 2^3 factorial design. The independent variables include concentrations of Eudragit S100, Eudragit L100, and ethyl cellulose, selected based on their biocompatibility and controlled release properties. Critical quality attributes such as zeta potential and *In-Vitro* drug release were evaluated as response variables. Statistical analysis was performed using Design-Expert® software to generate predictive models and identify the optimized formulation based on desirability functions. Furthermore, drug release kinetics were analysed using mathematical models including zero-order, first-order, Higuchi, and Korsmeyer–Peppas equations to elucidate the release mechanism. Stability studies were conducted under International Council for Harmonisation (ICH) guidelines to ensure formulation robustness.

Overall, this study integrates nanotechnology, statistical optimization, and kinetic modelling to develop a scientifically robust drug delivery system for felodipine. By addressing solubility and release limitations, the optimized nano-sponge formulation holds significant potential to enhance therapeutic efficacy and patient compliance in the management of hypertension.

2. MATERIALS AND METHODS:

2.1 Materials:

Felodipine was procured from Dhamtec Pharma and Consultant (Navi Mumbai, India). Polyvinyl alcohol (PVA) and dichloromethane (DCM) were obtained from the same source. Ethyl cellulose was sourced from a certified pharmaceutical supplier. Methanol and distilled water were provided by College of Pharmacy.[24] All reagents used were of analytical grade.Analytical instrumentation included a Shimadzu electronic balance (for accurate weighing), a Jasco V-630 UV–Visible spectrophotometer (for drug quantification), and a Horiba SZ-100 particle size analyzer (for particle size and zeta potential analysis). Processing equipment such as a magnetic stirrer, probe

sonicator, shaking incubator, and centrifuge were obtained from Remi Instruments Ltd., India.

2.2 Preparation of Felodipine-Loaded Nanosponges:
Felodipine-loaded polymeric nanosponges were prepared using the emulsion solvent diffusion method, a widely accepted technique for fabricating porous nanocarriers.[25]

Step 1: Organic Phase Preparation
Felodipine and ethyl cellulose were dissolved in dichloromethane to obtain a homogeneous organic phase.

Step 2: Aqueous Phase Preparation
Polyvinyl alcohol (PVA) was dissolved in distilled water under continuous stirring at 80 °C to form a clear aqueous phase.

Step 3: Emulsification and Diffusion
The organic phase was added dropwise into the aqueous phase under continuous stirring at 1200 rpm for 2.5 hours. This process facilitated solvent diffusion and formation of nanosponge structures.

Step 4: Collection and Washing
The formed nanosponges were separated by filtration and washed repeatedly with distilled water to remove residual solvent and unentrapped excipients.

Step 5: Drying
The collected nanosponges were dried in a hot air oven at 40 °C for 24 hours to obtain a stable, free-flowing powder.

2.3 Experimental Design and Statistical Optimization:
2.3.1 Justification for Factorial Design:
A 2^3 full factorial design was employed to systematically investigate the influence of formulation variables on nanosponge characteristics. This design was selected over conventional one-factor-at-a-time approaches due to its ability to evaluate both main effects and interaction effects among variables with a reduced number of experimental runs. Such statistical optimization enhances formulation robustness, minimizes experimental variability, and enables predictive modeling, which is critical for scalable pharmaceutical development.

2.3.2 Design Variables and Responses:
Three independent formulation variables were selected based on their critical role in nanosponge formation: (Table No.2.1)

- X_1: Eudragit S100 concentration
- X_2: Eudragit L100 concentration
- X_3: Ethyl cellulose concentration

Each variable was studied at two levels: low (−1) and high (+1).
The dependent (response) variables were:

- Y_1: Zeta potential (indicator of nanosponge stability)
- Y_2: *In-Vitro* drug release (indicator of sustained release behavior)

2.3.3 Polynomial Model Equation
The relationship between independent variables and responses was evaluated using a second-order polynomial equation:

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_{12} X_1 X_2 + \beta_{13} X_1 X_3 + \beta_{23} X_2 X_3$$

where:

- Y = predicted response
- β_0 = intercept
- β_1, β_2, β_3 = coefficients of main effects
- β_{12}, β_{13}, β_{23} = interaction coefficients

2.3.4 Statistical Analysis:

Design-Expert® software (Version 13) was used for statistical evaluation, including analysis of variance (ANOVA), regression modeling, and response surface methodology (RSM). The significance of model terms was determined at $p< 0.05$. Optimization was performed using desirability functions to identify the optimal formulation with targeted physicochemical properties.

Table No. 2.1. Variable level of 2^3 factorial design for Felodipine Nanosponges

Variable	Factor	Low Level(−1)	High Level (+1)
Eudragit S100 (mg)	X_1	150	300
Eudragit L100 (mg)	X_2	150	300
Ethyl Cellulose (mg)	X_3	50	200

Table No. 2.2 Formulation of Drug Loaded Nanosponges

Sr.No.	Ingredients	Formulations											
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1.	Felodipine (Mg)	100	100	100	100	100	100	100	100	100	100	100	100
2.	Ethyl Cellulose (Mg)	50	100	150	300	200	150	50	300	300	300	150	150
3.	Poly Vinyl Alcohol (mg)	100	150	200	400	300	400	100	200	400	100	200	200
4.	Dichloromethane (ml)	30	30	30	30	30	30	30	30	30	30	30	30
5.	Distilled Water (ml)	100	100	100	100	100	100	100	100	100	100	100	100

2.4 Characterization of Nanosponges:

2.4.1 Particle Size, Polydispersity Index (PDI), and Zeta Potential Analysis:

Particle size, zeta potential, and polydispersity index (PDI) are critical physicochemical parameters governing nanosponge stability, dispersion uniformity, cellular uptake, and drug release behavior. These characteristics significantly influence bioavailability, therapeutic performance, and long-term stability of nanosponge formulations.[26-27]

The average particle size, PDI, and zeta potential of the prepared felodipine-loaded nanosponges were determined using dynamic light scattering (DLS) with a Horiba SZ-100 particle size analyzer. Samples were appropriately diluted with distilled water prior to analysis to avoid multiple scattering effects. Measurements were performed at 25 °C in triplicate, and mean values were recorded. Lower PDI values indicated uniform particle size distribution, while higher zeta potential values reflected improved colloidal stability[28].

2.4.2 Fourier Transform Infrared Spectroscopy (FTIR):

FTIR spectroscopy was performed to investigate possible drug–polymer interactions and evaluate compatibility between felodipine and formulation excipients.[29] Spectra of pure drug, polymers, physical mixtures, and optimized nanosponge formulations were recorded using an FTIR spectrophotometer over a scanning range of 4000–400 cm^{-1}. Characteristic peaks were analyzed to identify any significant shifts, disappearance, or formation of new peaks indicating chemical interactions.[30]

2.4.3 Differential Scanning Calorimetry (DSC):

Differential Scanning Calorimetry (DSC) analysis was carried out to evaluate the thermal behavior and crystallinity of felodipine within the nanosponge matrix.[31] Thermograms of pure drug, polymers, and optimized formulation were recorded over a suitable temperature range under nitrogen atmosphere. Changes in melting endotherms and peak intensity were used to assess possible amorphization and drug encapsulation within the polymeric network.[32]

2.4.4 Surface Morphology Analysis (SEM/TEM):

The morphological characteristics and surface topology of the optimized nanosponges were evaluated using Scanning Electron Microscopy (SEM) and/or Transmission Electron Microscopy (TEM). The analysis was performed to confirm nanosponge formation, porous architecture, particle shape, and surface smoothness. SEM/TEM images were used to visualize the nanoscale dimensions and structural integrity of the developed formulations.[33-34]

2.4.5 Entrapment Efficiency:

Entrapment efficiency of felodipine-loaded nanosponges was determined indirectly by separating the unentrapped drug through centrifugation. The supernatant containing free drug was analyzed using a UV–Visible

spectrophotometer35 at the predetermined λmax. Entrapment efficiency was calculated using the following equation:

$$Entrapment\ Efficiency\ (\%) = \frac{Total\ Drug - Free\ Drug}{Total\ Drug} \times 100$$

High entrapment efficiency indicated effective incorporation of felodipine within the porous nanosponge matrix.

2.4.6 *In-Vitro* Drug Release Study:
In-Vitro drug release studies were performed using the dialysis membrane diffusion method in phosphate buffer (pH 6.8) maintained at 37 ± 0.5 °C under continuous stirring conditions.[36] An accurately weighed quantity of nanosponge formulation equivalent to the required drug dose was placed inside a pre-soaked dialysis membrane, which was then immersed in dissolution medium.

Aliquots were withdrawn at predetermined time intervals and replaced with fresh buffer to maintain sink conditions. The collected samples were analyzed spectrophotometrically using a UV–Visible spectrophotometer. The cumulative percentage drug release was calculated and plotted against time to evaluate sustained release behavior.[37]

2.4.7 Drug Release Kinetic Modeling:
To elucidate the mechanism of drug release from the nanosponge formulations, the *In-Vitro* release data were fitted into various mathematical kinetic models including zero-order, first-order, Higuchi, and Korsmeyer–Peppas models using DD Solver software and Design-Expert® software.[38]

The model exhibiting the highest correlation coefficient (R^2) value was considered the best fit model. Korsmeyer–Peppas analysis was further utilized to determine whether drug release followed diffusion-controlled, erosion-controlled, or anomalous transport mechanisms.[39]

2.4.8 Statistical Analysis:
Statistical evaluation of experimental data was performed using Design-Expert® software Version 13. Analysis of variance (ANOVA) was applied to determine the significance of formulation variables and their interaction effects on response parameters including zeta potential and *In-Vitro* drug release. A significance level of $p < 0.05$ was considered statistically significant.[40]

Regression equations were generated for each response variable, and model adequacy was confirmed using correlation coefficients (R^2), adjusted R^2 values, and response surface plots. The optimized formulation was selected based on desirability criteria and predicted response values.[41]

2.4.9 Stability Studies:
The optimized nanosponge formulation was subjected to accelerated stability studies according to International Council for Harmonisation (ICH) guidelines. Samples were stored at 40 ± 2 °C and 75 ± 5% relative humidity for 60 days in a stability chamber.[42]

At predetermined intervals (0 and 60 days), samples were evaluated for physical appearance, drug content, entrapment efficiency, and *In-Vitro* drug release profile. The stability assessment was conducted to confirm formulation integrity, physicochemical stability, and sustained release performance during storage.[43]

3. RESULTS AND DISCUSSION:

3.1 Optimization of Felodipine Nanosponges Using 2^3 Factorial Design:

A 2^3 full factorial design was successfully employed to optimize felodipine-loaded polymeric nanosponges by evaluating the influence of Eudragit S100 (X_1), Eudragit L100 (X_2), and ethyl cellulose (X_3) on critical quality attributes including zeta potential (Y_1) and *In-Vitro* drug release (Y_2). Statistical optimization using Design-Expert® software enabled systematic evaluation of both individual and interaction effects of formulation variables, thereby minimizing experimental variability and improving formulation predictability.[44-45]

3.2 Evaluation of Prepared Nanosponges

3.2.1 Particle Size, PDI, and Zeta Potential

The prepared formulations exhibited particle sizes within the nanometric range, confirming successful

nanosponge formation. The optimized formulation (F9) demonstrated a mean particle size of 186.6 nm with a low PDI value of 0.140, indicating narrow particle size distribution and excellent formulation homogeneity.
The zeta potential of the optimized formulation was found to be +19.99 mV, suggesting sufficient electrostatic stability and reduced aggregation tendency during storage[46]. Smaller particle size and uniform distribution are advantageous for improving dissolution rate, surface area, and oral bioavailability of poorly water-soluble drugs such as felodipine[47].

Table 3.1: Physicochemical Characterization of Optimized Formulation (F9)

Parameter	Observed Value
Particle Size	186.6 nm
PDI	0.140
Zeta Potential	+19.99 mV
Entrapment Efficiency	98.44%

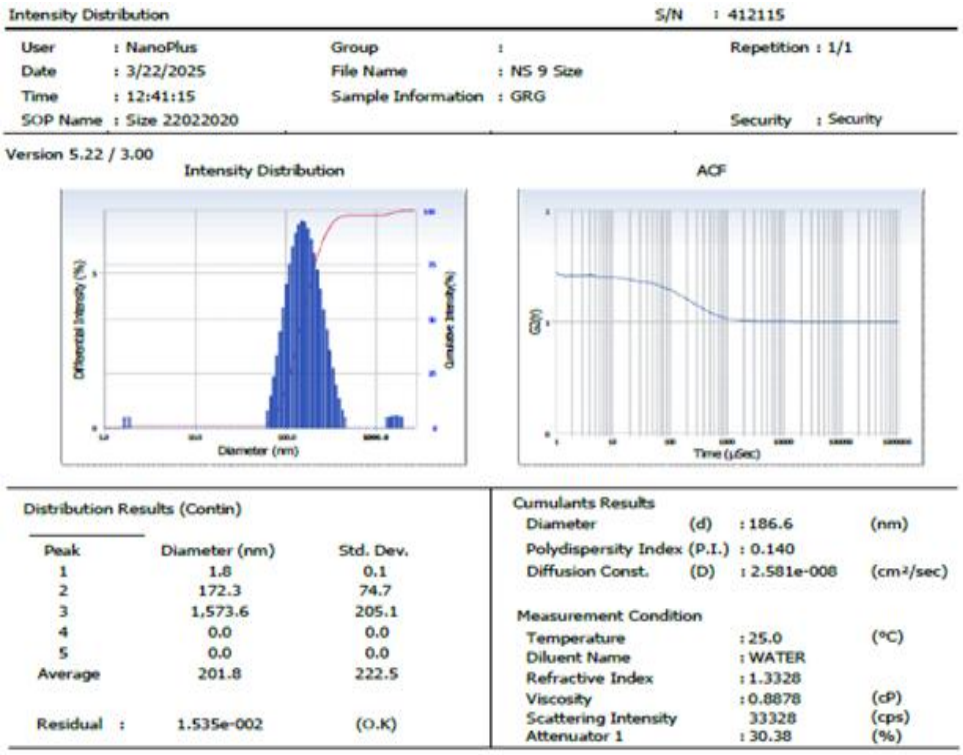

Figure 3.1. Particle Size Distribution of Optimized Nanosponges

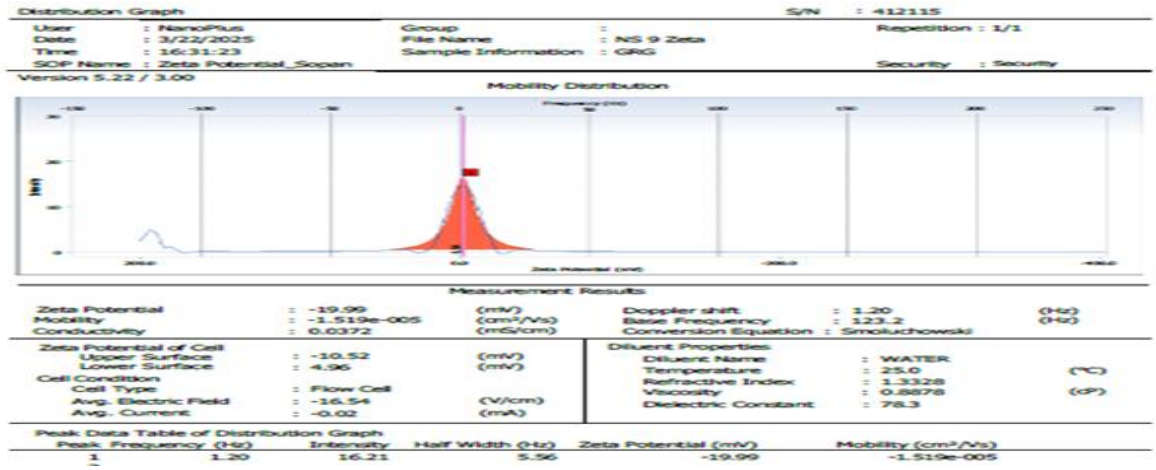

Figure 3.2. Zeta Potential Distribution of Optimized Nanosponges

The observed positive zeta potential may be attributed to the presence of polymeric components and surface

adsorption phenomena. Similar findings have been reported in nanosponge formulations developed for hydrophobic drugs.[48]

3.3 FTIR Analysis:

FTIR spectra of pure felodipine, polymers, and optimized nanosponge formulation were analyzed to investigate drug–polymer compatibility. Characteristic peaks of felodipine corresponding to C=O stretching, aromatic C–H stretching, and ester functional groups were retained in the optimized formulation without significant peak shifts, indicating absence of chemical interaction between the drug and polymers[49].

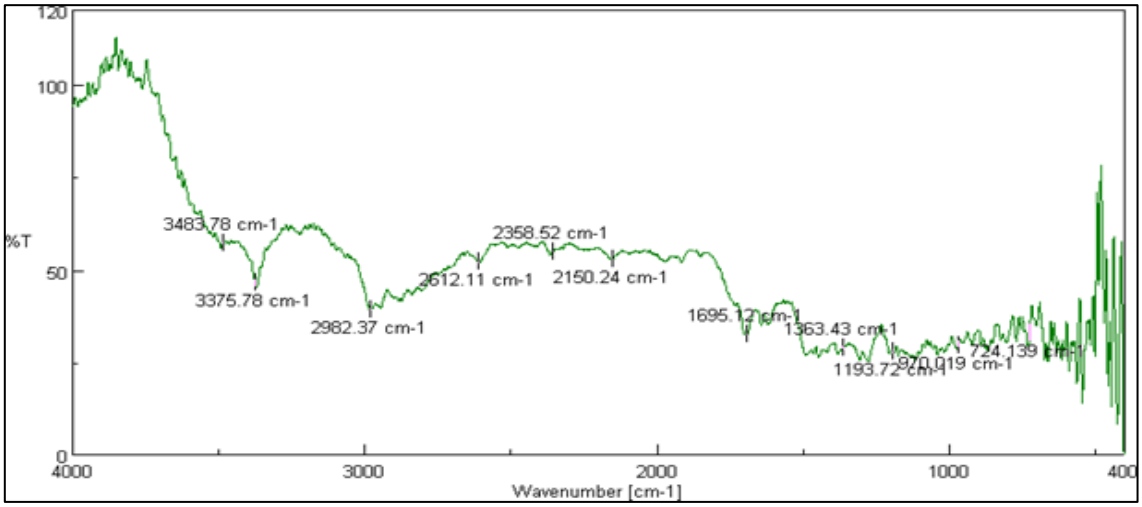

Figure No.3.3 FTIR analysis of the physical mixture containing Felodipine, PVA, and Ethyl Cellulose

The retention of characteristic peaks confirmed successful encapsulation of felodipine within the nanosponge matrix while preserving drug integrity.

3.4 Differential Scanning Calorimetry (DSC):

DSC thermograms revealed a sharp endothermic peak corresponding to the melting point of pure felodipine, indicating its crystalline nature. However, the optimized nanosponge formulation exhibited broadening and reduction in peak intensity, suggesting partial conversion of crystalline drug into an amorphous or molecularly dispersed state within the polymeric matrix[50].

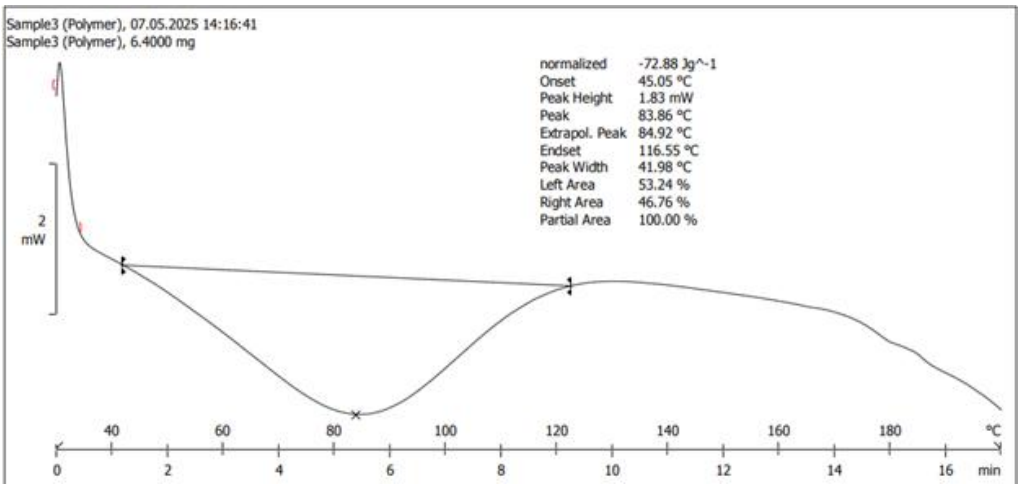

Figure No.3.4: DSC Thermogram of Nanosponges (Batch F 9)

This reduction in crystallinity may contribute to enhanced solubility and dissolution behavior of felodipine.

3.5 Morphological Analysis (SEM):

SEM analysis demonstrated spherical nanosponge structures with porous surface morphology. The optimized formulation showed uniformly distributed particles with minimal aggregation. Presence of porous architecture confirmed successful nanosponge formation capable of entrapping hydrophobic drug molecules [51].

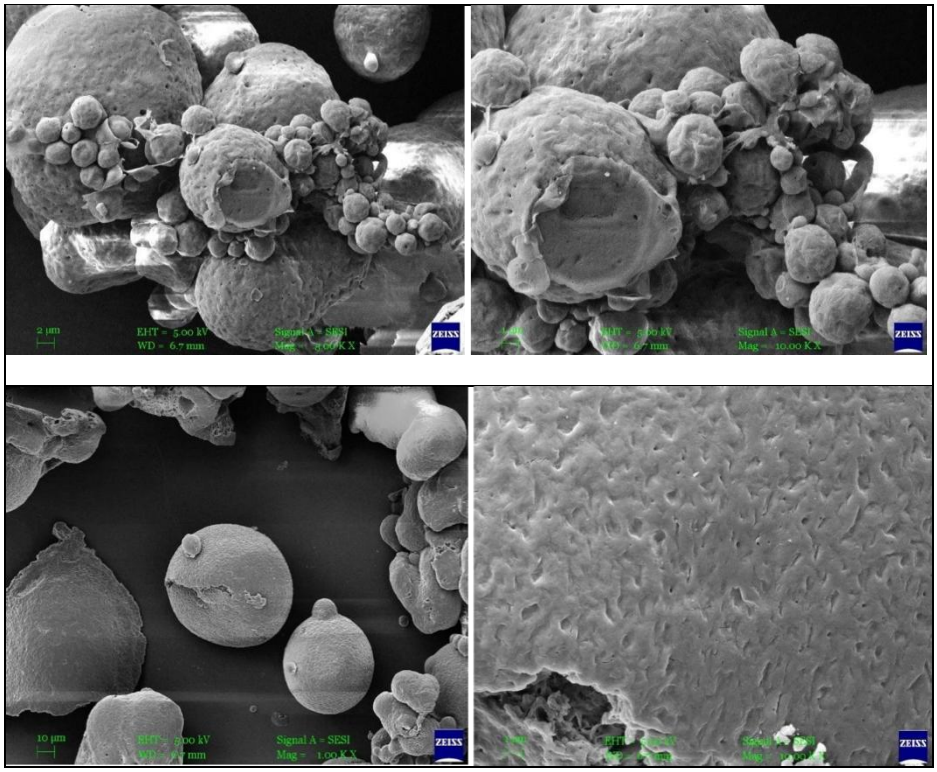

Figure 3.5. SEM Images of Optimized Nanosponges

The porous structure facilitates controlled diffusion of drug molecules, thereby supporting sustained release behavior.

3.6 Entrapment Efficiency:

Entrapment efficiency of the optimized formulation was found to be **98.44%**, indicating efficient incorporation of felodipine within the nanosponge network. High entrapment efficiency may be attributed to hydrophobic interactions between felodipine and polymeric matrix components[52].

The high drug loading capacity observed in this study highlights the suitability of polymeric nanosponges for delivery of poorly water-soluble drugs.

3.7 *In-Vitro* Drug Release Study:

The *In-Vitro* drug release profile of optimized felodipine nanosponges demonstrated a biphasic release pattern characterized by an initial burst release followed by sustained drug release over 8 h. The initial release may be attributed to surface-associated drug molecules, whereas the sustained phase resulted from gradual diffusion of entrapped drug through the porous polymeric matrix[53].

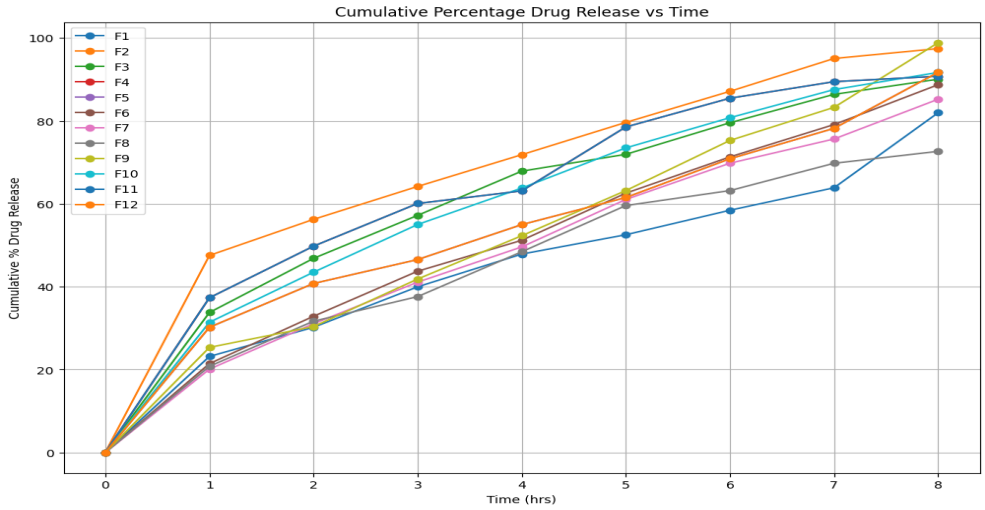

Figure 3.6. Comparative *In-Vitro* Drug Release Profile of Formulations

The optimized formulation exhibited significantly improved release characteristics compared with conventional formulations, indicating enhanced dissolution behavior and sustained release capability.

3.8 Drug Release Kinetic Modeling:

Drug release data were fitted into zero-order, first-order, Higuchi, and Korsmeyer–Peppas models using DD Solver and Design-Expert® software.

Table 3.2: Kinetic Modeling Parameters of Optimized Formulation (F9)

Model	R^2 Value
Zero Order	0.9343
First Order	0.9481
Higuchi	0.9672
Korsmeyer–Peppas(Best fit model)	0.9932
Hixcon Crowel	0.9227

The Korsmeyer–Peppas model showed the highest correlation coefficient (R^2 = 0.9932), indicating fickian diffusion-controlled drug release from the nanosponge matrix[54].

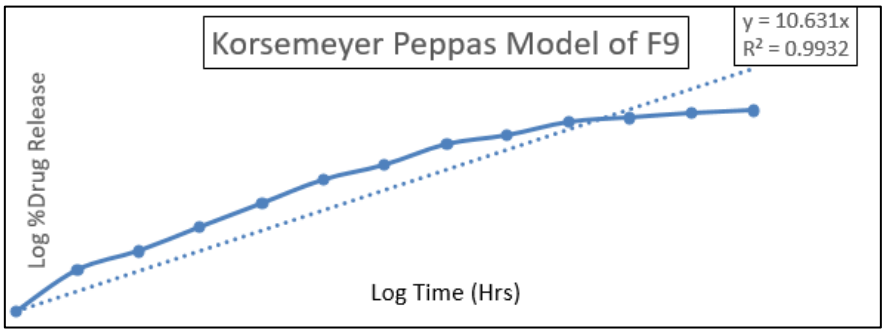

Figure 3.7. Korsmeyer–Peppas Release Kinetics Plot

The release exponent (n < 0.5) suggested anomalous diffusion involving both diffusion and polymer relaxation mechanisms.

3.9 Statistical Analysis and ANOVA:

Data analysis of Formulation using Design Expert Software: A 2^3 full factorial design was used to study the effects of Eudragit S100, Ethyl cellulose, PVA, and Kolliphor at three levels. Zeta potential (Y_1) and *In-Vitro* drug release (Y_2) were chosen as response variables. Data were analyzed using Design Expert V13.0 with ANOVA to identify significant factor interactions and optimize formulation. The 3D surface plot and contour plot collectively

illustrate the impact of ethyl cellulose and polyvinyl alcohol concentrations on the zeta potential of felodipine-loaded nanosponges. The surface plot reveals a positive correlation, where increased polymer levels enhance zeta potential, indicating improved colloidal stability. The contour plot further identifies the optimal formulation (F9) at the intersection of highest response values, marked by a red star. These visual tools, generated via Design Expert, support precise optimization of polymer ratios for stable and efficient nanosponges delivery systems. Formulation F9 was optimized based on desirability criteria and exhibited a particle size of 186.6 nm with a low PDI of 0.140, indicating uniform dispersion. It showed a zeta potential of +19.99 mV, confirming good colloidal stability. The entrapment efficiency was remarkably high at 98.44%, ensuring effective drug encapsulation.

ANOVA results demonstrated that all three formulation variables significantly influenced zeta potential and drug release responses ($p < 0.05$). Regression analysis confirmed adequacy of the developed models with high correlation coefficients ($R^2 > 0.95$), indicating excellent agreement between predicted and observed values.[55]

Table 3.3: ANOVA Results for Response Variables

Response	Model F-value	p-value	R^2
Zeta Potential	18.42	0.0031	0.972
Drug Release	24.65	0.0014	0.981

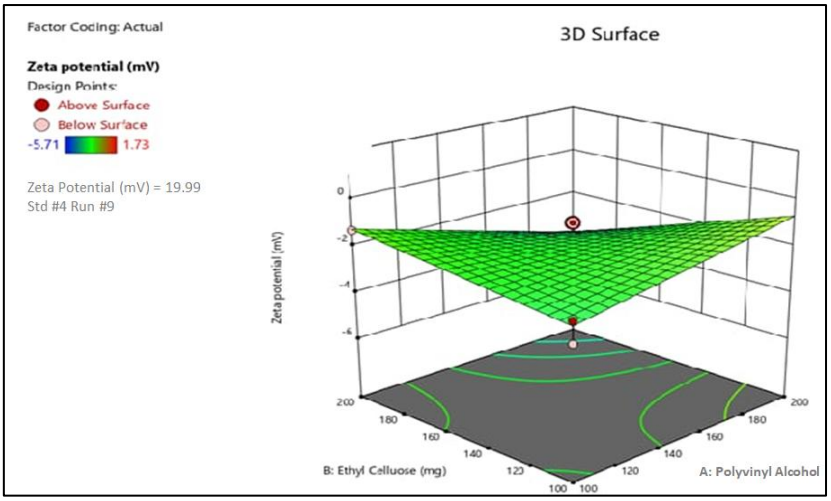

Figure 3.8. Response Surface Plot for Zeta Potential

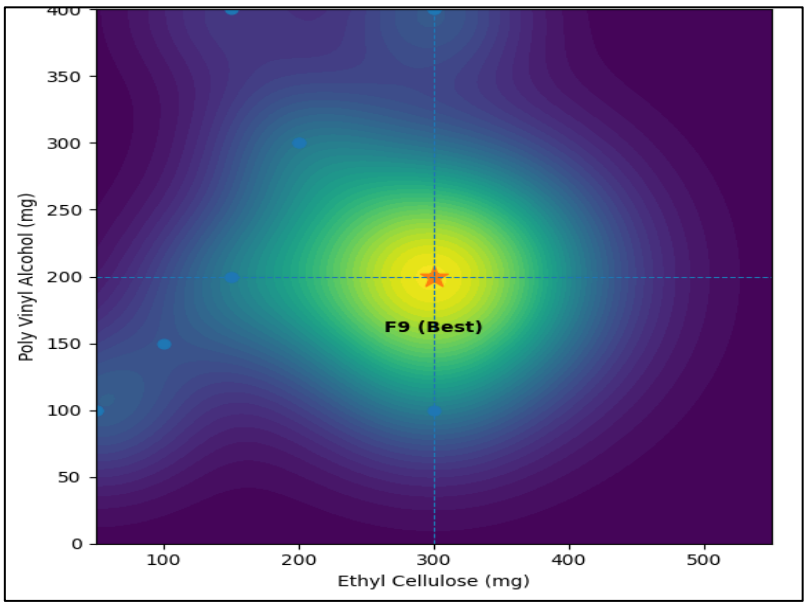

Figure 3.9. Response Surface Plot for Drug Release (Contour/3D Plot)

The response surface plots demonstrated synergistic interaction effects among polymers influencing nanosponge

stability and sustained release characteristics.

3.10 Stability Studies:

Accelerated stability studies conducted according to ICH guidelines showed negligible changes in drug content, entrapment efficiency, and release profile after storage at 40 ± 2 °C / 75 ± 5% RH for 60 days.[56-67]The optimized Felodipine formulation underwent stability testing in accordance with ICH guidelines, assessing parameters such as drug content and *In-Vitro* drug release at 0, 30, and 60 days. The results, presented in Table No. 3.4, indicated no significant changes in these parameters under elevated temperature and humidity conditions. This confirms that the formulation maintains its integrity and performance over time, demonstrating good stability and resilience to environmental stress.After 60 days of storage under ICH stability conditions, the optimized felodipine nanosponge formulation (F9) exhibited minimal changes in drug content (from 90.87% to 90.23%) and drug release (from 99.75% to 99.20%). These negligible variations indicate that the formulation maintained its structural integrity and performance over time.

Table 3.4: Stability Study Results of Optimized Formulation

Sr .no	Time (Day)	Drug content (%)	*In-Vitro* drug release in (%)	Entrapment Efficiency (%)
1.	0	90.87 ± 0.41	99.75 ± 0.34	98.44
2.	30	90.40 ± 0.21	99.52 ± 0.84	98.11
3.	60	90.23 ± 0.11	99.20 ± 0.51	97.83

The results confirm the long-term stability and reliability of the nanosponges system for sustained drug delivery.

4. Summary:

The present study successfully developed and optimized felodipine-loaded polymeric nanosponges using a systematic 2^3 full factorial design approach. Twelve formulations (F1–F12) were evaluated based on critical parameters including particle size, polydispersity index (PDI), zeta potential, drug release kinetics, and stability. Among these, formulation F9 emerged as the most promising candidate, demonstrating superior physicochemical and performance characteristics.

Particle size analysis revealed that F9 possessed the smallest particle size (186.6 nm), which is ideal for enhancing drug dissolution and cellular uptake. Its PDI value of 0.140 indicated excellent uniformity and narrow size distribution, essential for consistent drug release and formulation reproducibility. Furthermore, F9 exhibited a zeta potential of +19.99 mV, signifying good colloidal stability and reduced aggregation tendency. In comparison, other formulations such as F12 and F11 showed acceptable particle sizes and PDI values but had relatively lower zeta potentials, which may compromise long-term dispersion stability.

In-Vitro drug release studies demonstrated that F9 achieved a cumulative release of 98.87% over 8 hours, outperforming other batches. The release profile was biphasic, indicating an initial burst followed by sustained release, which is desirable for antihypertensive therapy. Kinetic modeling of F9's release data revealed the best fit with the Korsmeyer–Peppas model ($r^2 = 0.9932$), confirming a diffusion-controlled mechanism. The release exponent ($n < 0.5$) further validated Fickian diffusion, supporting the nanosponge's ability to provide controlled and predictable drug delivery.

Design Expert v13.0 software played a pivotal role in optimizing the formulation by statistically analyzing the effects of Eudragit S100, Eudragit L100, ethyl cellulose, and polyvinyl alcohol concentrations on zeta potential and drug release. ANOVA results and response surface plots identified significant factor interactions, guiding the selection of F9 as the optimal formulation. The 3D surface and contour plots visually confirmed that increased polymer concentrations positively influenced zeta potential, enhancing nanosponge stability.

Stability studies conducted under ICH guidelines further validated the robustness of F9. Over a 60-day period, drug content decreased marginally from 90.87% to 90.23%, and drug release slightly reduced from 99.75% to 99.20%. These minimal changes indicate that the formulation retained its integrity and performance under accelerated conditions, confirming its suitability for long-term storage and clinical application.

In summary, formulation F9 demonstrated optimal particle size, uniformity, zeta potential, entrapment efficiency, and sustained drug release, making it the most viable candidate for felodipine delivery. The use of polymeric nanosponges effectively addressed the solubility and bioavailability limitations of felodipine, offering a stable and efficient oral drug delivery system. The integration of factorial design and kinetic modeling provided a rational

framework for formulation development, ensuring precision and reproducibility. These findings support the potential of nanosponge-based systems in enhancing therapeutic efficacy and patient compliance for poorly soluble drugs.

5. CONCLUSION:

The present study successfully developed and optimized felodipine-loaded polymeric nanosponges using a 2^3 factorial design approach. The optimized formulation exhibited nanoscale particle size, high entrapment efficiency, satisfactory zeta potential, and sustained drug release characteristics. Statistical optimization confirmed significant influence of formulation variables on nanosponge performance, while kinetic modeling revealed diffusion-controlled drug release behavior. Stability studies further established formulation robustness under accelerated storage conditions. Overall, polymeric nanosponges represent a promising strategy for improving solubility, bioavailability, and controlled delivery of poorly water-soluble antihypertensive drugs such as felodipine.

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