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Development and Characterization of Nifedipine Loaded Liposomal *In-Situ* Gel For the Effective Of Anal Fissure

Prashant Raghav[*1], Dr. Sachin Kumar[2]

[1]Research Scholar, NKBR College of Pharmacy and Research Centre Meerut-Hapur Road,Phaphunda, Uttar Pradesh India - 245206

[2]Professor, NKBR College of Pharmacy and Research Centre Meerut-Hapur Road,Phaphunda, Uttar Pradesh India -245206

[*]**Corresponding author:**

Prashant Raghav

Email ID: prshantraghav772@gmail.com

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ABSTRACT

The current research intended to improve and evaluate a liposomal in-situ gel formulation for the sustained topical delivery of nifedipine. Preformulation studies confirmed the drug's physicochemical compatibility, solubility, and stability. By using thin film hydration approach nifedipine-loaded liposomes were prepared and evaluation done for entrapment efficiency (82.7± 0.46 %), particle size (180.4 nm), zeta potential (−22.3 mV) and polydispersity index (0.461). The optimized liposome (NL1) was incorporated into a Carbopol 934-based in-situ gel and evaluated for clarity, pH, gelling time, viscosity, drug content, and gelation temperature. In-vitro relief studies presented continued drug delivery up to 96.24% over 24 hours, and release kinetics best fit the Korsmeyer-Peppas model ($R^2 = 0.993$), indicating anomalous diffusion. The formulation remained stable over 3 months, suggesting potential for enhanced therapeutic efficacy and patient compliance in topical nifedipine delivery.

Keywords: *Anal fissure, Nifedipine, Thin film hydration, Liposomes,*

1. INTRODUCTION

Anal fissure is a common anorectal condition characterized by a linear tear in the anal canal epithelium, usually located at the posterior midline below the dentate line. Acute fissures are superficial and short-term, whereas chronic fissures persist for more than six weeks and often present with fibrotic edges, exposed sphincter fibers, and associated symptoms like pain, bleeding, and spasms. The underlying pathophysiology involves a vicious cycle of mechanical trauma, sphincter hypertonia, reduced blood flow (ischemia), and impaired wound healing.[1,2]

These fissures often result from hard stools, prolonged diarrhea, childbirth trauma, or anorectal procedures. Internal sphincter spasm exacerbates ischemia and delays healing, making treatment challenging. Conservative treatment is the first line of management and includes dietary fiber, sitz baths, and stool softeners. If ineffective, pharmacological agents such as topical calcium channel blockers (e.g., nifedipine) or nitroglycerin are used to relax the internal sphincter and improve local perfusion. Among these, nifedipine has shown promising results due to its vasodilatory and muscle-relaxing properties. In refractory cases, botulinum toxin injections or surgical intervention (Lateral Internal Sphincterotomy) may be considered, though the latter carries a risk of incontinence. Recent advances in drug delivery, such as liposomes and in-situ gels, offer targeted and sustained release at the site of action, improving therapeutic outcomes and patient compliance. [3, 4]

These novel formulations enhance drug bioavailability, minimize systemic side effects, and are particularly useful in chronic fissures where long-term drug presence is beneficial. This study explores the development of a liposome and in-situ gel-based delivery system for nifedipine to enhance the management of chronic anal fissures.[5]

2. MATERIALS AND METHODS

2.1 Materials

Nifedipine was sourced from Indiamart Pvt. Ltd., with excipients such as soya lecithin and cholesterol procured from SRL Chem Pvt. Ltd. Solvents including chloroform and ethanol were of analytical grade. All materials used were of pharmacopeial quality, and distilled ultrapure water (Millipore Direct Q, Merck) was used throughout.

2.2 Preformulation Studies

Preformulation studies aim to assess the physicochemical and mechanical properties of nifedipine to facilitate the development of a stable and effective liposomal in-situ gel formulation.

2.2.1 Organoleptic Properties

Nifedipine was evaluated for its color, odor, and texture. The drug appeared as a yellow crystalline powder, odorless, and tasteless, confirming its known identity and initial quality.

2.2.2 Melting Point

The melting point of nifedipine was determined using the capillary method with a digital melting point apparatus. The observed melting range (169–172°C) was consistent with pharmacopeial standards, confirming purity.

2.2.3 Fourier Transform Infrared Spectroscopy (FTIR)

FTIR analysis was conducted to confirm drug identity and evaluate drug–excipient compatibility. A pellet of nifedipine with potassium bromide (KBr) was prepared under 5.5 metric tones of pressure and scanned over a range of 4000–450 cm^{-1}. Characteristic peaks corresponding to ester (C=O), aromatic (C=C), and NO_2 groups were identified and compared with standard references (B.P., 2009), indicating chemical integrity and no significant interaction with excipients.

2.2.4 Solubility Studies

Solubility profiling was performed in distilled water, phosphate-buffered saline (PBS, pH 7.4), ethanol, methanol, chloroform, and DMSO at 37 ± 1°C. Nifedipine exhibited poor aqueous solubility but was freely soluble in ethanol and chloroform, supporting the choice of solvents for liposome formulation.

2.2.5 Partition Coefficient

The partition coefficient (Log P) was evaluated between n-octanol and PBS (pH 7.4) to estimate lipophilicity. A suitable Log P value (~2–3) confirmed the potential for effective incorporation into lipid-based vesicles such as liposomes.

2.2.6 Bulk and Tapped Density, Compressibility Index, and Hausner's Ratio

To assess flow properties:

- **Bulk Density**: ~0.45 g/cm^3
- **Tapped Density**: ~0.56 g/cm^3
- **Carr's Index**: ~19.64% (acceptable flow)
- **Hausner's Ratio**: ~1.24 (indicating good compressibility and flow)

2.2.7 UV-Visible Spectrophotometric Method Development [6]

A UV-Vis method was developed to detect nifedipine at various stages. λmax was found to be 238 nm in PBS (pH 7.4). Calibration curves were constructed using serial dilutions (10–60 µg/mL), showing excellent linearity ($R^2 > 0.998$).

2.3 Formulation of Nifedipine-Loaded Liposomes

Liposomes were developed using the THF method with the aid of a rotary evaporator. Various formulations of nifedipine-loaded liposomes were developed**.** To formulate nifedipine-loaded liposomes, 10 mg of nifedipine was combined with varying concentrations of 8 mL of chloroform and 2 mL of ethanol, soya lecithin (600–900 mg) and cholesterol (100–400 mg). The resulted solution was kept in a 250 mL RBF and subjected to rotary evaporation at 80 rpm within a thermo-statically maintained water bath maintained at 40°C, under a vacuum pressure of 900 mm Hg for 30 minutes. A uniform dry lipid film was formed by slow solvent evaporation, then hydrated with PBS (pH 6.8) and swirled to produce a milky liposomal suspension. After centrifugation at 3000 rpm for 30 minutes, the liposomes were isolated, characterized, and stored for further evaluation. [7]

2.4 Liposomal Characterization [8]

- **Particle size & PDI**: Measured using Zeta-sizer Nano ZS (Malvern, UK).
- **Zeta potential**: Evaluated to assess colloidal stability.
- **Entrapment efficiency (%EE)**: Determined via ultracentrifugation at 11,000 rpm (4°C, 2 hr), followed by spectrophotometric drug quantification at 242 nm.
- **SEM analysis**: Morphology examined post-gold coating using Hitachi SEM under vacuum at 10 kV.

2.5 Formulation of nifedipine loaded liposomal *in-situ* gel

A Carbopol 934-based gel was developed by dispersed 1 g of polymer in distilled water with 10 g of propylene glycol, followed by stirring at 800 rpm for 60 minutes to obtain a liposome-compatible topical base. The mixture was then neutralized by the gradual addition of triethanolamine until the pH reached 7.2. The optimized nifedipine-loaded liposomes were subsequently incorporated into the prepared 1% (w/v) Carbopol gel using an electric mixer at 25 rpm for 2 minutes. [9,10]

2.6 Evaluation of In-situ Gel

- **Clarity**: Visual inspection against black/white backgrounds.
- **pH**: Measured to ensure topical compatibility (target: ~6.8).
- **Gelation time/temp**: Assessed using the Miller and Donovan method in temperature-incremental water bath (4°C to gel point).[11]
- **Viscosity**: Determined using Brookfield viscometer (Spindle 6, 100 rpm).
- **Drug content**: Quantified via UV spectroscopy at 238 nm after solubilization in methanol/PBS.[12]

***2.7 In-vitro* drug delivery**

The in vitro delivery of nifedipine from the *in situ* gel was assessed using a Franz diffusion cell, where a pre-swollen cellophane membrane was mounted between the donor and receptor chambers, and the system was stirred continuously in PBS (pH 6.8) at 200–250 rpm for uniform diffusion. The temperature was maintained at 37 °C by circulating warm water through the jacket of the Franz diffusion cell. At predetermined time intervals (0, 0.25, 0.5, 1, 2, 4, 6, 8, 12, 16, and 24 hours), 0.5 mL samples were taken and instantly changes with an similar vol of fresh PBS (pH 6.8) to preserve sink. The collected samples were then evaluated using UV spectrophotometry.

2.8 *In-vitro* drug release kinetics studies

An investigation was conducted on the medicine delivery from the liposomal in-situ gel by analyzing the release data using the Higuchi equation, zero-order kinetics, and first-order kinetics. Analysis of the data using the Korsmeyer Peppas model allowed for the identification of the process by which the substance is released.

2.9 Stability Study

The drug retention capacity of vesicles in a in-situ gel formulation was evaluated by subjecting the gel to various temperatures. The gel was stored in airtight vials with a capacity of 10ml at a temperature of 4 ± 2ºC and at room temperature for duration of 45 days. The drug content was measured at various time periods to ascertain the percentage.

3. RESULT

3.1 Pre-Formulation Studies

3.1.1 Organoleptic properties

Organoleptic evaluation revealed that the nifedipine is a white to a yellow, odorless, and crystalline powder. the organoleptic properties of nifedipine as shown in Fig. 1 and Table 1.

Figure 1: Nifedipine powder.

Table 1: Comprehensive Physiological Properties of nifedipine

Parameter	Result
Colour	Yellowish
Physical form	Crystalline powder
Odour	Odourless
Taste	Slightly bitter
Melting Point (Observed)	MP1: 170°C, MP2: 172°C, MP3: 172°C; Mean: 171°C
Melting Point (Reported)	171–175°C (Indian Pharmacopoeia)
Solubility in Distilled Water	0.5 mg/mL
Solubility in Ethanol	2.8 mg/mL
Solubility in DMSO	40 mg/mL
Solubility in Methanol	0.3 mg/mL
Solubility in Chloroform	1.7 mg/mL
Solubility in PBS (pH 7.4)	10 mg/mL

Nifedipine is a yellowish, crystalline powder that is odourless and slightly bitter in taste. The melting point was determined using a digital melting point apparatus (Stuart SMP30) and found to range between 170–172°C, with a mean value of 171°C, closely matching the reported pharmacopeial range of 171–175°C (Indian Pharmacopoeia). Solubility studies revealed that nifedipine exhibits very poor solubility in water (0.5 mg/mL) and methanol (0.3 mg/mL), moderate solubility in ethanol (2.8 mg/mL) and chloroform (1.7 mg/mL), and high solubility in DMSO (40 mg/mL). It also showed good solubility in phosphate-buffered saline (PBS, pH 7.4), with a value of 10 mg/mL. These properties are essential for guiding the formulation strategy for liposomal drug delivery systems.

3.2 Preparation of calibration curve and Determination of λ_{max}

The spectrum of nifedipine was examined and the wavelength of nifedipine was found to be 238 nm which is as according to standard values**.** Then the selected wavelength of 238 nm was used for the further studies. The dilutions were prepared in the concentration range 10-60 µg/ml. The result of the linearity curve of nifedipine was found to be R^2 0.9879 (**Below Fig**).

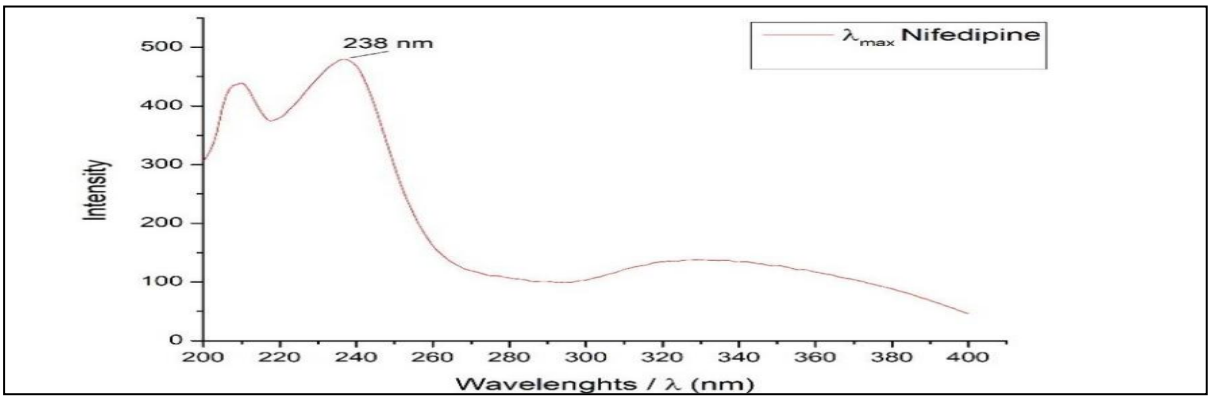

Figure 2: UV Absorption spectra of nifedipine in PBS (PH 7.4) with absorption maximum at 238 nm.

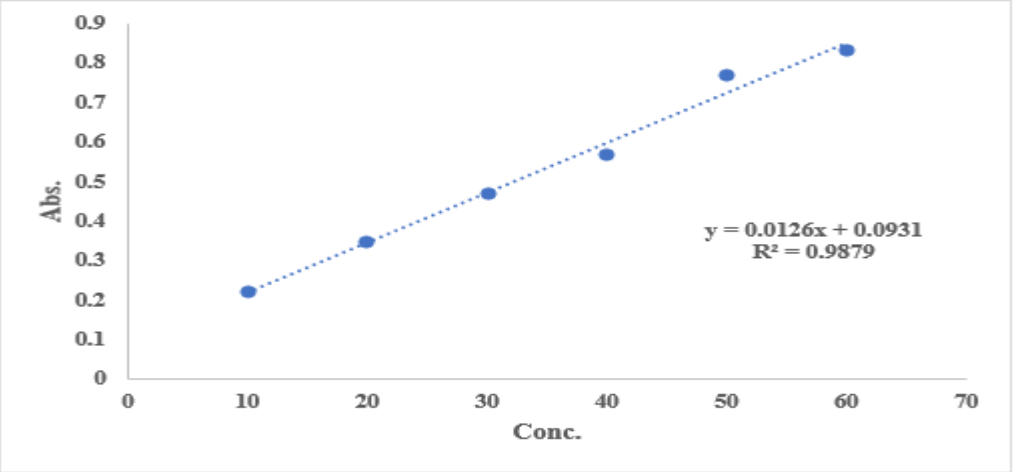

Figure 3: Linearity curve of nifedipine in PBS in PH 7.4 at 238 nm.

3.3 FT-IR spectrum of nifedipine

The FTIR spectrum of the pure nifedipine powder revealed a characteristic N–H stretching vibration at 3326 cm^{-1}. Additional absorption bands at 3236 cm^{-1} and 2997 cm^{-1} correspond to aromatic C–H stretching. A distinct band at 2841 cm^{-1} is associated with aliphatic C–H stretching from methyl groups (–CH_3). The ester group exhibited a notable C=O stretching band at 1677 cm^{-1}. Bands observed at 1648 cm^{-1} and 1617 cm^{-1} are attributed to the pyridine moiety. A strong peak at 1526 cm^{-1} signifies N–H bending vibrations, while the band at 1493 cm^{-1} corresponds to C–H bending. Prominent C–O stretching vibrations appeared at 1224 cm^{-1}, and stretching bands in the region of 829–712 cm^{-1} were characteristic of C–N vibrations, particularly within aryl-nitrogen groups [62,63] (Fig. 4).

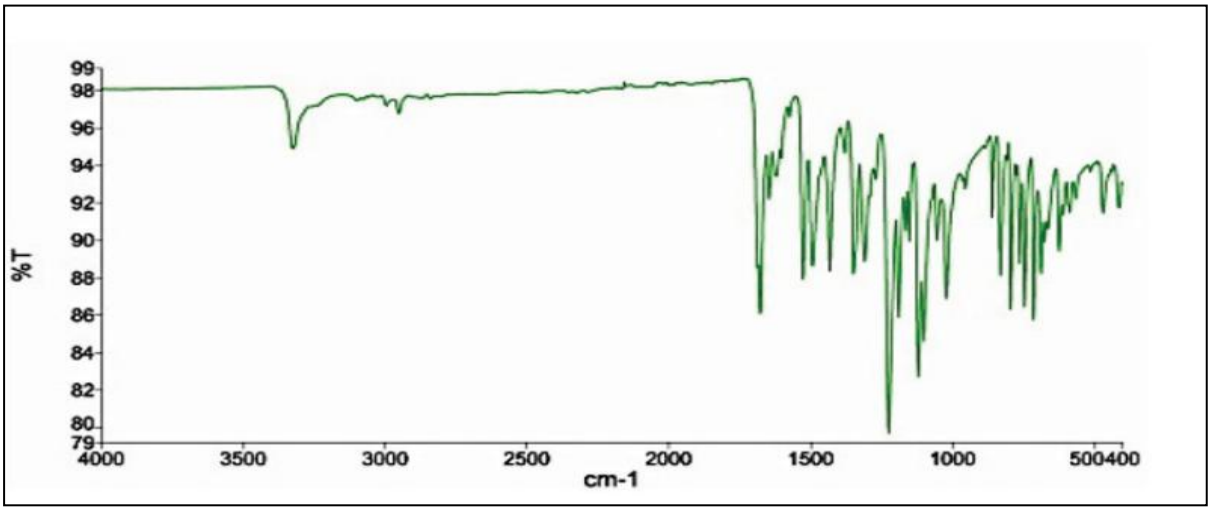

Figure 4: FTIR Spectrum of nifedipine.

3.4 Evaluation of nifedipine loaded liposome

3.4.1 Entrapment efficiency (%EE)

The EE of all formulations ranged from 56 ± 0.70 % to 82.7± 0.46%. Among the formulations, Formulation NL1 exhibited the highest entrapment efficiency at 82.7± 0.46% (Table 2). The data indicates that the entrapment efficiency of liposomal as the soya lecithin concentration.

Table 2: Entrapment efficiency (%) of different formulations of nifedipine loaded liposome.

S. No.	Formulation	Entrapment efficiency (%)
1.	NL1	82.7± 0.46%
2.	NL2	81± 0.36%
3.	NL3	76 ± 0.11%
4.	NL4	72.7 ± 0.12%
5.	NL5	78.2 ± 0.52%
6.	NL6	75 ± 0.12%
7.	NL7	56 ± 0.70 %

3.4.2 Particle size analysis and polydispersity index

An instrument Litesizer 500 used to analyze the prepared formulation NL1 particle size, and it was create to be 180.4 nm. This result demonstrates that the prepared transethsomoal possess nano-sized particles, indicating their suitability for penetration through the skin. The PDI of the liposomes was analyzed to be 0.461, indicating a uniform particle size distribution and narrow dispersion within the formulations (Fig. 5).

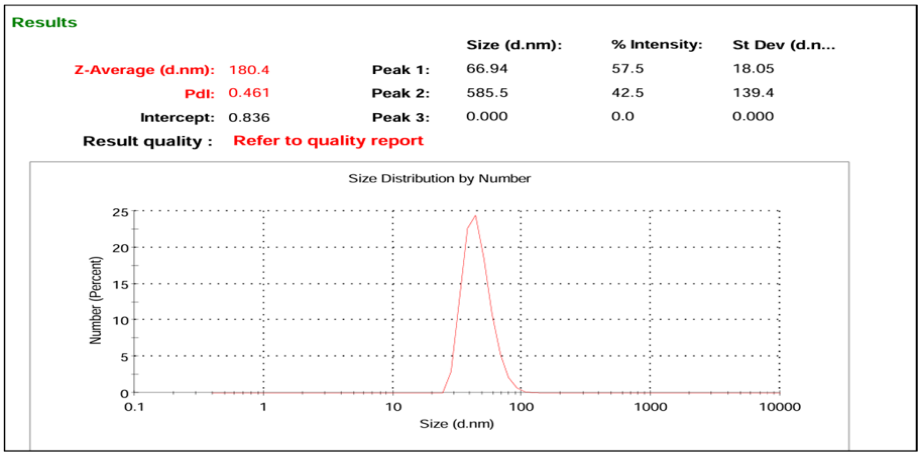

Figure 5: Particle size of Optimized Formulation NL1.

3.4.3 Zeta potential

An increase in zeta potential leads to enhanced repulsion between charged particles, resulting in improved stability against aggregation. The optimized liposome formulation exhibited a zeta potential of -22.3 mV, indicating good stability (as depicted in below).

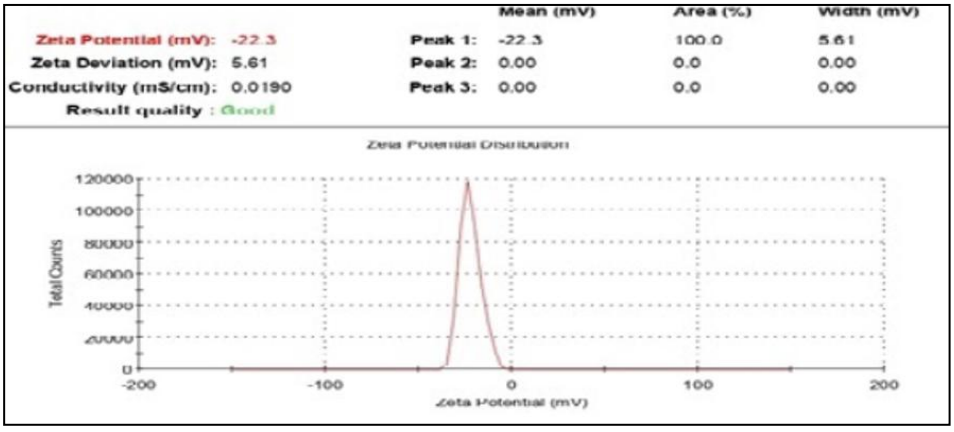

Figure 6: Zeta Potential of Optimized Formulation NL1.

3.4.4 Shape and surface morphology of particles (scanning electron microscope)

The surface and shape of prepared preparation was by SEM. The liposomes prepared by thin film hydration have good particles distribution, smooth surface, spherical shape (Figure. 7).

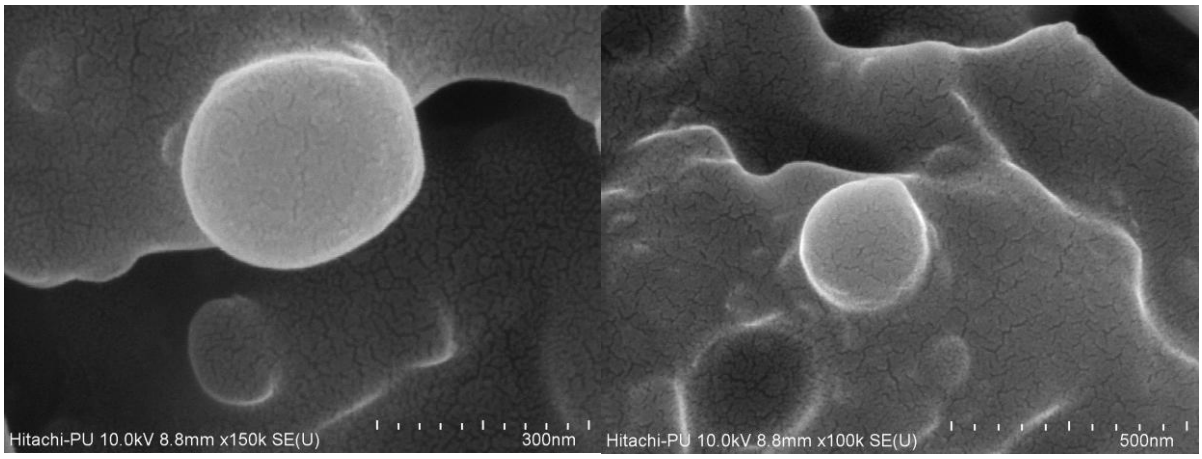

Figure 7: Scanning electron micrograph of nifedipine loaded liposomes.

3.5 Characterization of nifedipine loaded liposomal *in-situ* gel

Out of the 7 batches of liposomes, the NL1 batch exhibited the best encapsulation efficiency (%EE), and zeta potential (ZP). This batch was then used to create *in-situ* gel formulations using carboxyvinyl polymer carbomer [Carbopol 934].

Table 3: Analysing of nifedipine laden liposomal *in situ* gel

Parameters	**Formulation**
Physical appearance	Yellowish brown
Drug content (%)	93±0.87
pH	6.4±0.34
Gelling Time (sec.)	62±0.56
Viscosity (cps)	18457±67.8
Gelation Temperature (°C)	35.12±0.321

3.6 In-vitro diffusion study

The % in-vitro drug release profile of liposome insitu gel formulation was perfomed by the dialysis membrane The *in-vitro* drug delivery data of the nifedipine-loaded liposomal *in-situ* gel can be found in Table 4 and Fig. 8**.** The *in vitro* relief research finds the *in-situ* gel achieved a high drug release of 96.24 ± 0.132% after 24 hours, indicating efficient sustained delivery.

Table 4: *In-vitro* drug release study

Sr No.	Time (hours)	%CPR
1.	0	0 ± 0.000
2.	0.25	3.01 ± 0.036
3.	0.5	5.31 ± 0.012
4.	1	8.19 ± 0.213
5.	2	15.56 ± 0.218

6.	4	35.17 ± 0.310
7.	6	47.5 ± 0.324
8.	8	67.12 ± 0.412
9.	12	86.09 ± 0.124
10.	16	92.65 ± 0.156
11.	24	96.24 ± 0.132

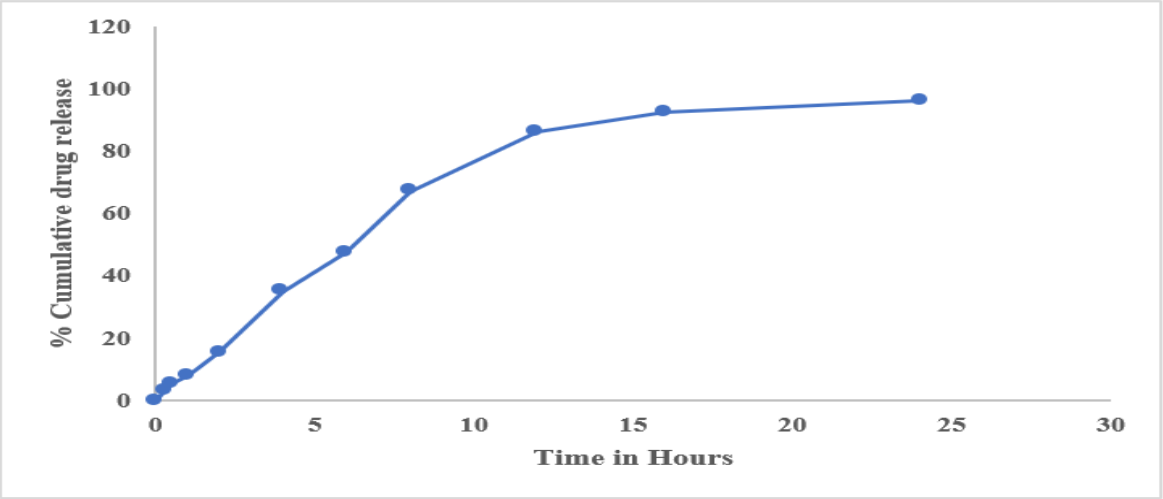

Figure 8: % Cumulative drug release of prepared insitu gel formulation.

3.7 *In-vitro* drug release kinetics studies

The delivery rate was established by computing the gradient of the relevant graphs, and the coefficient of determination (R^2) was also assessed. The model fitting data for the release kinetics of nifedipine loaded liposomal *in-situ* gel. Among the different models, the Peppas model exhibited the highest R^2 value, indicating the best fit for the data. This observation was further confirmed by plotting the cumulative drug delivery % against the time (hr), where the R^2 value ranged between 0.993.

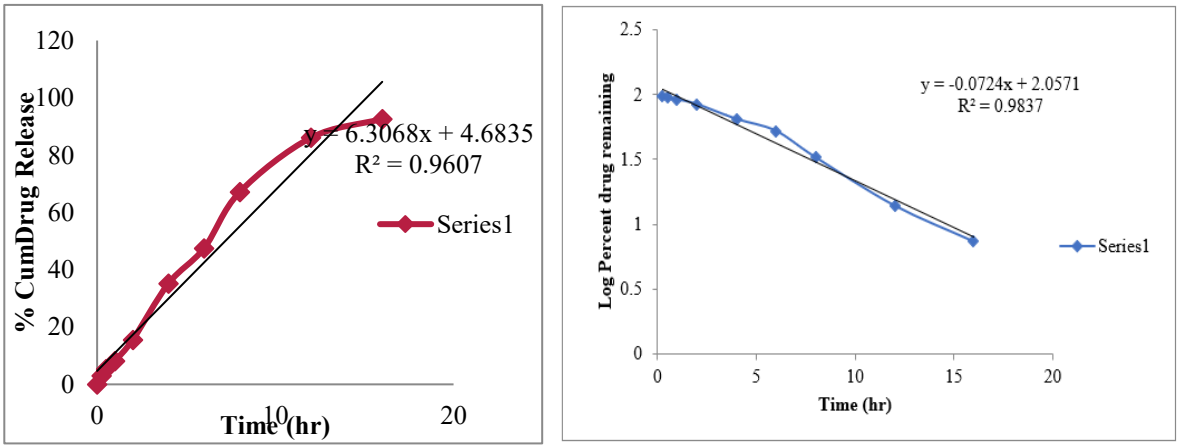

Figure 9: Zero order and First order plot of *in situ* liposomal gel respectively.

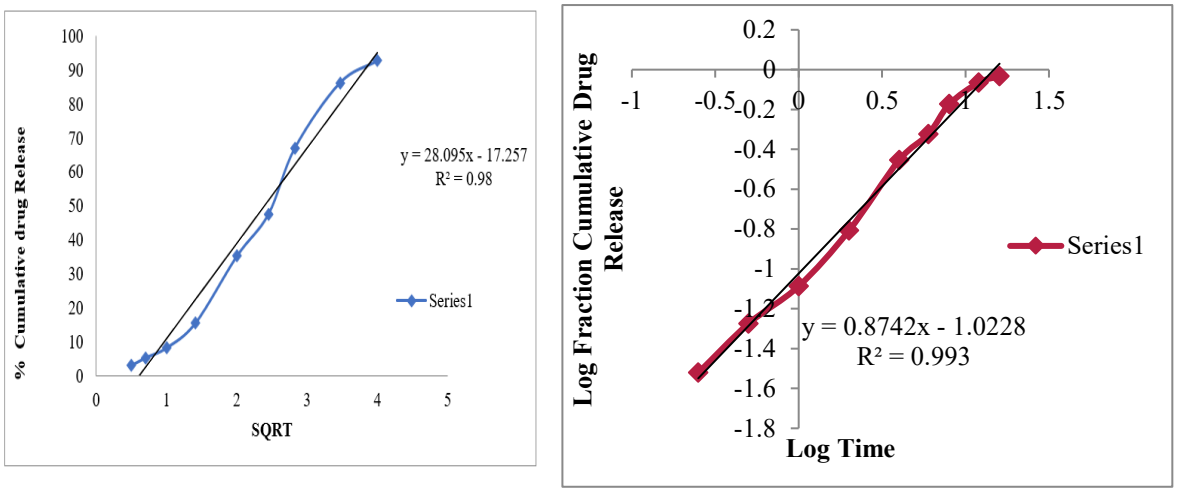

Figure 10: Higuchi and Peppa's plot plot of *in situ* liposomal gel respectively

3.8 Stability studies

The developed in-situ gel formulation demonstrated stability for three months, with no changes observed in its physical appearance, pH, or gelling time (**Table 5).**

Table 5 Stability data of *in situ* nasal gel at 0, 3 and 6 months.

Parameters	For 0 month	For 2 months	For 3 months
Physical Appearance	Yellowish brown	Yellowish brown	Yellowish brown
pH	6.4±0.23	6.4±0.10	6.4±0.109
Gelling Time (sec)	62±0.181	62±0.111	61±0.165

4. DISCUSSION

The study focused on the preparation of a nifedipine-loaded liposomal in-situ gel aimed at enhancing transdermal drug delivery. Initially, preformulation studies including organoleptic evaluation, solubility, melting point, FTIR, and UV spectroscopic analysis confirmed the identity and properties of nifedipine. Among all formulations, NL1 was optimized based on high entrapment efficiency (82.7± 0.46 %), desirable particle size (180.4 nm), and a stable zeta potential (-22.3 mV). SEM images confirmed spherical, smooth-surfaced liposomes.

The optimized liposomes were incorporated into a Carbopol 934-based in-situ gel, which exhibited good clarity, pH (6.4 ± 0.34), viscosity (18457 ± 67.8 cps), gelation temperature (35.12°C), and high drug content (93 ± 0.87%). In-vitro diffusion studies showed a sustained release of 96.24% over 24 hours. Kinetic modeling revealed that the drug release followed Korsmeyer-Peppas kinetics (R^2 = 0.993). Stability studies confirmed the physical and chemical stability of the gel for up to 3 months.

5. CONCLUSION

A stable, effective nifedipine-loaded liposomal in-situ gel development was successfully developed and optimized. The formulation NL1 demonstrated excellent encapsulation, favorable particle size, and sustained drug release behavior. Integration into a Carbopol gel matrix preserved drug integrity, allowed for controlled release, and exhibited promising pH, viscosity, and gelling properties suitable for transdermal application. The formulation followed Korsmeyer-Peppas release kinetics, suggesting a diffusion-controlled and polymer relaxation mechanism. Overall, the study establishes a potentially effective platform for topical nifedipine delivery, combining the benefits of liposomes and *insitu* gel systems.

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