Formulation and Evaluation of Transdermal Proniosomal Gel Containing Vildagliptin for Enhanced Anti Diabetic Therapy Through Sustained Drug Release

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***Abstract*—Vildagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor widely used in the management of Type II diabetes mellitus. However, its short biological half-life necessitates frequent dosing, which may reduce patient compliance. Proniosomal gel systems offer a promising vesicular drug delivery approach capable of improving drug stability and providing sustained drug release.**

Objective: The present study aimed to formulate and evaluate a proniosomal gel of Vildagliptin to achieve controlled drug release and enhance its therapeutic performance.

Methods: Vildagliptin proniosomal gels were prepared using the coacervation phase separation method with Span 40, Span 60, soya lecithin, cholesterol, and ethanol. Eight formulations (F1–F8) were developed by varying the concentrations of non-ionic surfactants. Preformulation studies, including melting point determination, solubility analysis, UV spectroscopy, and FTIR compatibility studies, were performed. The prepared formulations were evaluated for vesicle size, drug content, entrapment efficiency, and in vitro drug release. Release kinetics were analyzed using various mathematical models.

Results: FTIR studies confirmed the compatibility of Vildagliptin with the selected excipients. Vesicle size analysis demonstrated uniform vesicle formation predominantly within the 20–40 µm range. Entrapment efficiency ranged from 86.07% to 92.29%, while drug content varied between 88.48% and 94.24%. Formulation F8 exhibited the highest drug content (94.24%) and entrapment efficiency (92.29%) along with sustained drug release, showing 67.84% cumulative drug release after 8 hours. Drug release from the optimized formulation best fitted the Korsmeyer–Peppas model, indicating a diffusion-controlled release mechanism.

Conclusion: The developed Vildagliptin proniosomal gel demonstrated satisfactory physicochemical characteristics, high drug entrapment, and sustained drug release. The optimized formulation (F8) showed promising in vitro performance and may serve as a potential controlled-release delivery system for improving the therapeutic efficacy of Vildagliptin. Further in vivo studies are recommended to establish its clinical applicability.

***Index Terms*—Vildagliptin, Proniosomal gel, Vesicular drug delivery, Entrapment efficiency, Sustained release, DPP-4 inhibitor, Controlled drug delivery.**

I. INTRODUCTION

Innovative solutions have been sought, even though no single medication delivery method has been able to satisfy all of the requirements in recent years. To accomplish either targeted or controlled distribution, a number of innovative methods covering a range of administration routes have been developed. The main goals of innovative medication delivery are to minimize side effects and maintain a steady and effective drug level in the body. Additionally, it targets drug distribution and localizes drug activity using drug carriers.[1]

Vesicular drug delivery techniques that employ colloidal particle carriers, such as liposomes or niosomes, have definite benefits over traditional dosage forms. Proniosomal gels share structural similarities with liposomes and niosomes, despite being more stable and offering a number of advantages. Both liposomes and niosomes have a bilayer.[2]

Because colloidal particulate carriers, like liposomes or niosomes, can act as drug reservoirs, carry

hydrophilic drugs by encapsulation or hydrophobic drugs by partitioning them into hydrophobic domains, and modify the particle composition or surface to alter the drug release rate and/or the affinity for the target site, these drug delivery systems have demonstrated clear advantages over conventional dosage forms.[3]

The vesicles are predominantly composed of phospholipids or non-ionic surfactants These two types of vesicles are referred to as liposomes and niosomes. The size, charge, thermodynamic phase, lamellarity, and bilayer elasticity of vesicles are all influenced by the composition of the vesicles. These physicochemical properties significantly impact vesicle behavior and, consequently, their effectiveness as a drug delivery method.[4]

Proniosomes or dry niosomes are vesicular drug delivery systems. Proniosomes are made up of a bilayer of a non-ionic surfactant, a hydrophilic end oriented outward, and a hydrophobic end that remains in the core. Regarding the stability issue, proniosomes are physically more stable during storage and transport than noisome Technically, proniosomes are promising drug carriers as they possess greater chemical stability and lack many disadvantages associated with liposomes, such as high-cost and variable purity problems of phospholipids. Proniosomes are promising delivery systems for lipophilic drugs.[5]

Some of the Advantages of Proniosomes include[6]

- Avoiding problem of physical stability like aggregation, fusion, leaking.
- Avoiding hydrolysis of encapsulated drugs which limiting the shelf-life of the dispersion.
- The storage makes proniosomes a versatile delivery system with potential for use with a wide range of active compounds.
- Biodegradable, biocompatible and non-immunogenic to the body.
- Shows controlled and sustained release of drugs due to depot formation.
- Furthermore, unacceptable solvents are avoided in proniosomal formulations. The systems may be directly formulated into transdermal patches and doesn't require the dispersion of vesicles into polymeric matrix.

Vildagliptin (VLG) is dipeptidyl peptidase-4 (DPP-4) inhibitor, mostly used for treatments of Type II Diabetics Mellitus. It enhances a glucose-dependent insulin secretion from a pancreatic β-cell as well as suppresses inappropriately elevates glucagon secretion through the α-cell.6 Vildagliptin has rapid metabolism and short elimination half-life of about 1.6 to 2.5 hour

II. MATERIALS AND METHODS

Materials

Vildagliptin was obtained from Medreich Pvt. Ltd Bengaluru. Soya lecithin was procured from Sonic Biochem Extraction Ltd., Indore. SPAN 40, SPAN 60, cholesterol and ethanol were obtained from S D Fine Chem Limited, Mumbai. All the reagents were used without any purification. Phosphate buffer solution pH 7.4 was prepared as described in the Indian pharmacopoeia.

Preformulation studies

Determination of melting point of the drug

The melting point of Vildagliptin was determined by the capillary tube method using a digital melting point apparatus. The observed melting point was compared with the reported value to confirm the identity and purity of the drug.

Fourier Transform Infrared Spectroscopy (FTIR) Studies Drug–excipient compatibility studies were carried out using FTIR spectroscopy. The infrared spectra of pure Vildagliptin and its physical mixture of soya lecithin, cholestrol, span 40, span 60 . The spectra were recorded over the range of 4000–500 cm^{-1} using an FTIR spectrophotometer. The characteristic peaks of the drug and physical mixture were compared to evaluate any possible drug–excipient interactions.

Determination of absorption maximum (λmax) of the drug

A solution of Vildagliptin (10 µg/mL) was prepared using phosphate buffer pH 7.4 . The solution was scanned in the wavelength range of 200–400 nm using a UV–Visible spectrophotometer to determine the absorption maximum (λmax). The maximum absorbance of Vildagliptin was observed at 204 nm.

Method: Preparation of Proniosomal Gel by Coacervation Phase Separation;

Accurately weighed amount of surfactant (Span 40), lecithin, cholesterol and drug Vildagliptin will be taken in a clean and dry wide mouthed glass vial and alcohol (3ml) is added to it. After warming, all the ingredients were mixed well with a glass rod, open end of the glass bottle was covered with a lid to prevent the loss of solvents from it and warmed over water bath at

60°C- 70°C for about 5-10 min until the surfactant mixture was dissolvingcompletely Then the Phosphate Buffer Solution (pH 7.4) is added and warmed on a water bath till clear solution is formed which is converting into Proniosomal gel on cooling. The obtained gel is preserved in the same glass bottle in dark condition.[7-8]

Table 1: Formulation design for the preparation of vildagliptin proniosomal gel

Formulation Code	Drug (mg)	Cholesterol (mg)	Soya lecithin (mg)	Span 40 (mg)	Span 60 (mg)
F1	100	100	100	100	-
F2	100	100	100	200	-
F3	100	100	100	400	-
F4	100	100	100	600	-
F5	100	100	100	-	100
F6	100	100	100	-	200
F7	100	100	100	-	400
F8	100	100	100	-	600

Characterization of Vildagliptin Proniosomal gel[9-10]

a. Vesicle size analysis

A drop of Proniosomal gel with distilled water formulation is added on glass slide without cover slip to observe the formation of Proniosomes. Vesicle size analysis was carried out using an optical microscope with a calibrated eye piece micrometer. About 150 Proniosomal gel were measured individually, average was taken and their size distribution range and mean diameter were calculated.

b. Entrapment Efficiency determination

The entrapment efficiency of Vildagliptin Proniosomal gel was determined after hydration with distilled water. 2 ml of distilled water was added to the Proniosomal gel equivalent to 2 mg of drug then the mixture was shaken manually for 2min. For the separation of unentrapped Vildagliptin, the Proniosomal gel suspension was subjected to centrifugation on a cooling centrifuge at 25000 rpm for The For the separation of un entrapped drug. The clear supernatant (0.1 ml) was taken and diluted to 10ml with methanol and water solution and absorbance was recorded at 204 nm using UV visible spectrophotometer then calculates the percentage drug in each formulation.

c. In-vitro diffusion study

The release of drug was determined by using the treated cellophane membrane mounted on the one end of open tube, containing formulations. The dialysis tube was suspended in 500 ml beaker, containing 150 ml pH 7.4 buffer. The solution was stirred at 100 rpm with the help of magnetic stirrer at 37 ± 0.5 °C. Perfect sink conditions were maintained during the drug release testing. The samples were withdrawn at suitable time interval (at 1, 2, 4, 6, 8, 12 hrs). The diffusion medium was replaced with same amount of fresh pH 7.4 buffer solutions to maintain the volume 200 ml throughout the experiment. The drug content in the withdrawn samples (1ml) were analyzed by UV spectrophotometer at λmax 204 nm after making the volume up to 10 ml with pH 7.4 buffer and cumulative % of drug released was calculated and plotted against time (t). The rate and release mechanism of Vildagliptin from the formulations were analyzed by fitting the release data in to various kinetic model.

d. Release kinetics:

Drug release kinetics of all proniosomal gel formulations was evaluated using zero-order, first-order, Higuchi, and Korsmeyer–Peppas models.Zero-order describes concentration-independent release, while first-order describes concentration-dependent release.The Higuchi model indicates drug release primarily by diffusion from an insoluble matrix.The Korsmeyer–Peppas model uses the diffusional exponent (n) to determine the release mechanism: $n \leq 0.45$ indicates Fickian and $0.45 < n < 0.89$ indicates anomalous release.The equation used was $\%R = Kt^n$,

or log %R = log K + **n log t**, where R = drug release, K = release constant, n = diffusional exponent, and t = time.

e.Stability studies as per ICH guidelines

Stability testing studies was performed at refrigerated condition for 3 months as per ICH guidelines. The optimized formulation was kept at 4 ± 2°C and 75 ± 5% RH in stability chamber. At the end of 0, 45, 90 days intervals regularly tested for % entrapment and drug release were fixed as physical parameters for stability testing.

Proniosomal gel Formulation Incorporated into Carbopol gel base

Carbopol 940P gels (0.5-2.0% w/w) will be prepared by dispersing in required water and soaked for 24 hours. Vildagliptin-loaded Proniosomal gel (100 mg) and pure drug (100 mg), each dispersed in alcohol, will be added separately to the gels. Alcohol will act as a distributing agent. The gel will be neutralized with Triethanolamine and mixed with Glycerine(moisturizer), Methyl and Propyl parabens (preservatives) under continuous stirring until a clear, homogeneous gel forms

Evaluation of Proniosomal gel

- Appearance

The prepared gels were examined for clarity, Color, homogeneity, presence of foreign particles.

- pH

1gm of gel was dispersed in 100 ml distilled water and the pH was examined using digital pH meter.

- Spreadability studies

Bachhav et al., carlier presented a method for determining spreadability. Spreadability was assessed by dropping 0.5 gm gel in a marked circle on a glass plate with a diameter of 1 cm. A glass plate of identical size was put over it, with care taken to prevent air bubbles from becoming trapped between the two slides. For 5 minutes, a weight of 500 g was kept on the upper glass plate to evenly distribute the gel. The increase in diameter caused by the gel spreading was noticed as spreadability indication Then calculate using the formula.

Spreadability = weight tied to upper slide (g) × length of lass slide(cm)

Time taken in sec

- Viscosity

The viscosity measurement was carried out at room temperature to maintain uniform testing conditions and to minimize any temperature-induced variations in viscosity. Each sample was allowed to equilibrate for a few minutes before measurement to ensure stable readings. The obtained viscosity values were expressed in centipoise (cP) and recorded at different spindle speeds to study the rheological behavior of the gel. The rheological data helped in understanding the flow characteristics, spreadability, and structural integrity of the formulation. A formulation with appropriate viscosity ensures ease of application, good patient compliance, and sustained drug release from the gel base, based on specific rules**:**

- The width of the spindle has an inverse correlation with the viscosity range.
- The rotor speed is indirectly proportional to the viscosity range.

In-vitro diffusion study:

An in vitro diffusion study of formulated gels was carried out on the franz diffusion cell.

Franz diffusion membrane was used as a diffusion membrane. The diffusion cell was

filled with phosphate buffer pH 7.4, diffusion membrane was mounted on the cell. The

temperature was maintained at 34-37°C. At predetermined time points, 5 ml samples

were withdrawn from the acceptor compartment, replacing the sampled volume with

phosphate buffer pH 7.4, after each sampling, for a period of 12 hrs. The samples

withdrawn were filtered and used for analysis. Blank samples were run simultaneously

throughout the experiment to check for any interference. The amount of diffused drug

was determined at 204 nm using on UV visible spectrophotometer, Shimadzu UV 1800.

Stability

Stability studies were performed for 3 months as per ICH guidelines for optimized formulation. Drug content, pH and % CDR at 12hrs were fixed as evaluation parameter for stability study. Stability study was carried out by storing the prepared Proniosomal gel at intermediate study condition 30°C+2°C and 65 ± 5% RH for a period of 3 months duration. The parameters were checked at 3 months intervals as per ICH guidelines.

III. RESULT AND DISCUSSION

- The melting point of pure Vildagliptin was determined by the capillary tube method and was found to be within the reported range of 148–155°C. The observed average melting point was 153°C, confirming the purity and identity of the drug.
- Vildagliptin was found to be soluble in water, phosphate buffer pH 6.8 and pH 7.4. vildagliptin also freely soluble in methanol.
- The UV spectrum of Vildagliptin (10 µg/ml) scanned between 200–400 nm showed a maximum absorbance (λmax) at 204 nm, which was selected for further analytical studies. The calibration curve exhibited excellent linearity (R^2 = 0.9995), confirming the suitability of the analytical method.
- FTIR studies showed that the characteristic peaks of Vildagliptin were retained in the physical mixture with only minor shifts, confirming the absence of significant drug–excipient interactions and indicating good compatibility between the drug and excipients.
- Vesicle size analysis demonstrated that the majority of vesicles were distributed within the 20–40 µm range, indicating uniform vesicle formation and good reproducibility of the preparation method.
- Entrapment efficiency of the prepared Proniosomal gel ranged from 86.07% to 92.29%. Formulation F8 exhibited the highest entrapment efficiency, indicating efficient incorporation of Vildagliptin into the Proniosomal gel vesicles.
- Drug content ranged from 88.48% to 94.24%. All formulations exhibited satisfactory drug loading and acceptable content uniformity, indicating efficient incorporation of the drug during formulation.
- Among all the formulations, F8 was selected as the optimized formulation as it exhibited the highest drug content (94.24%), satisfactory entrapment efficiency (92.29%), and the less cumulative drug release (67.84%) after 8 hours, indicating its superior formulation performance.

The in-vitro drug release data were fitted to various kinetic models. The optimized formulation showed the best fit to the Korsmeyer–Peppas model, indicating diffusion-controlled drug release from the Proniosomal gel matrix.

Solubility analysis of vildagliptin

Table 2: Solubility analysis of vildagliptin

Media	Solubility (mg/ml)	Volume of solvent in ml/gm (ml)	Solubility Criteria
Water	49.056	20.38	soluble
Methanol	124.8	8.013	Freely soluble
Ethanol	16.5	60.61	Sparingly soluble
Buffer pH 6.8	47.55	21.03	soluble
Buffer pH 7.4	48.63	20.56	soluble

Standard calibration for vildagliptin:

Table 3: Data for Standard calibration of vildagliptin

Concentration	Average Absorbance (204nm)
10µg/ml	0.188 ± 0.0015
20µg/ml	0.376 ± 0.0046
30µg/ml	0.564 ± 0.0051

40µg/ml	0.776 ± 0.0111
50µg/ml	0.946 ± 0.0085

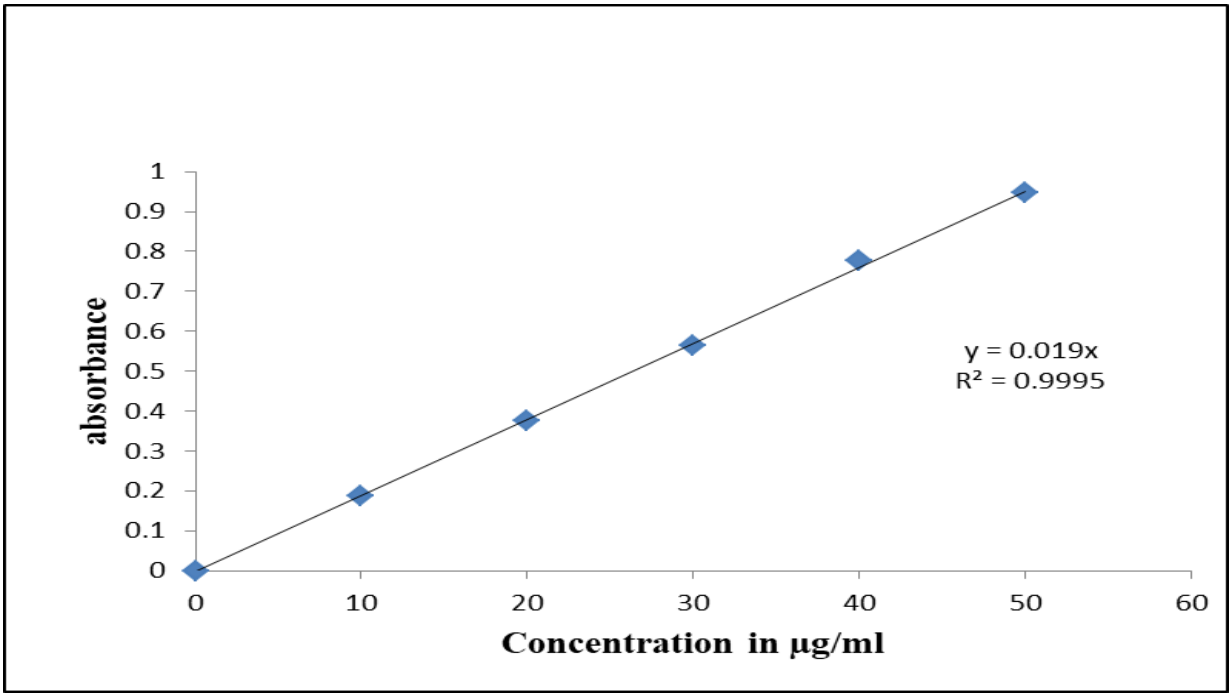

Figure 1: Standard calibration curve for vildagliptin

Compatibility studies by FT-IR

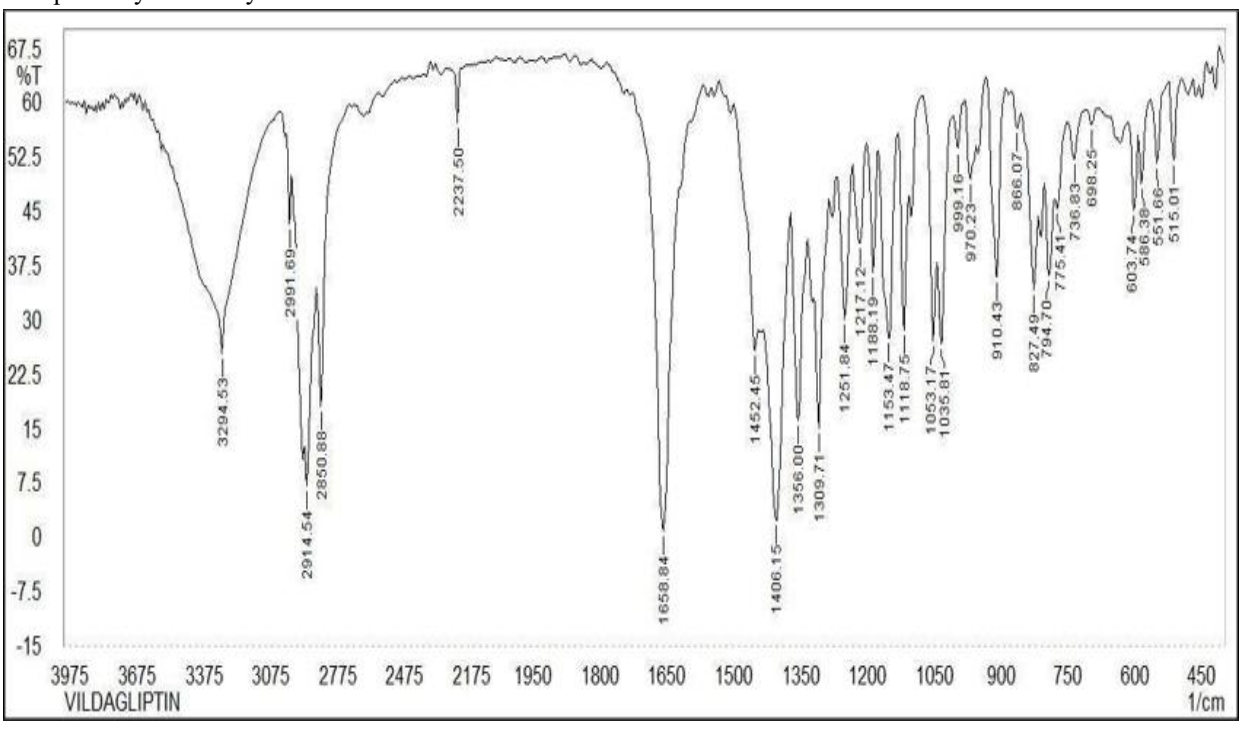

Figure 2 : FT-IR spectrum of Vildagliptin

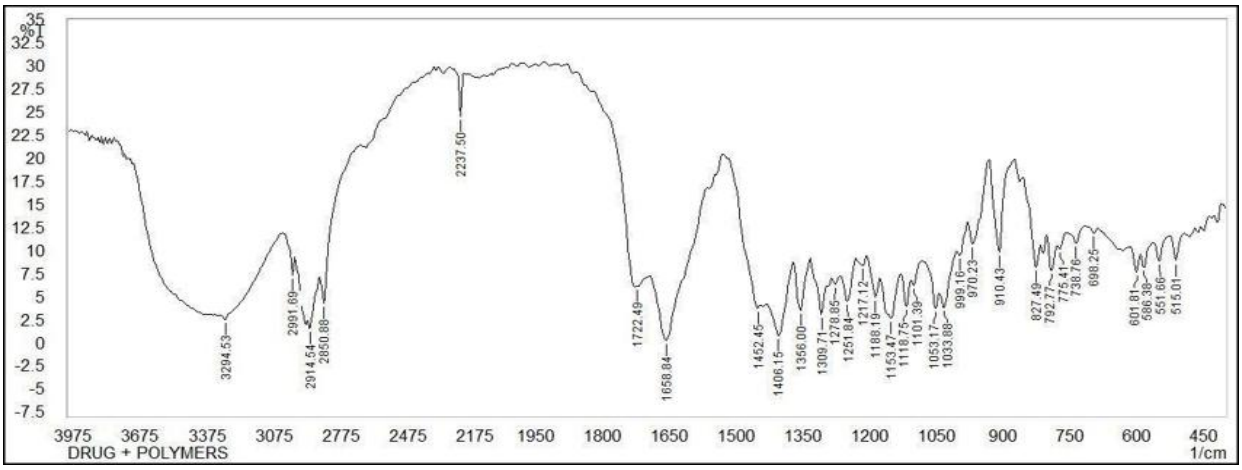

Figure 3 : FTIR spectrum of drug

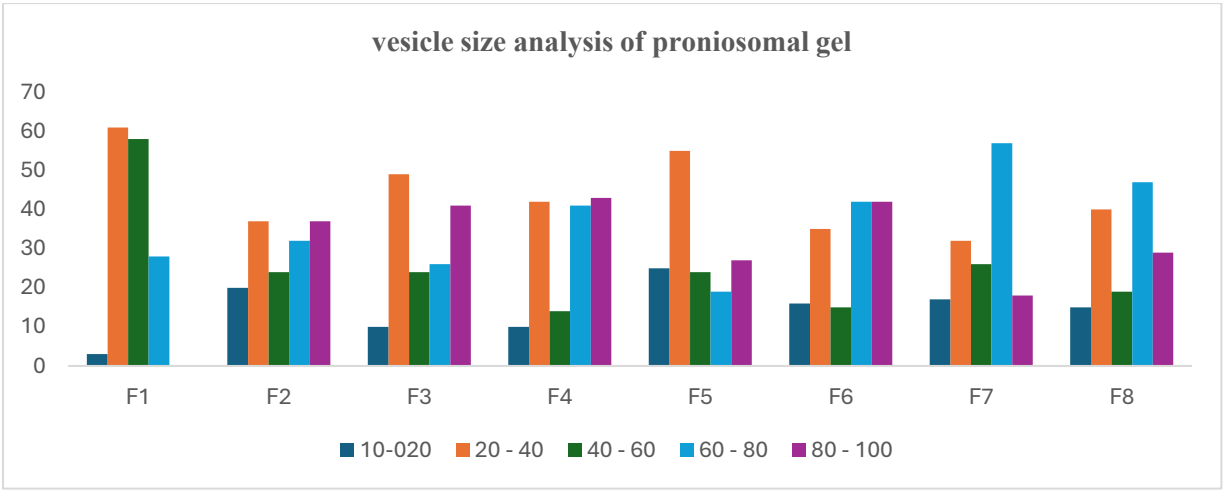

Figure 4 : FTIR spectrum of drug and polymers mixture

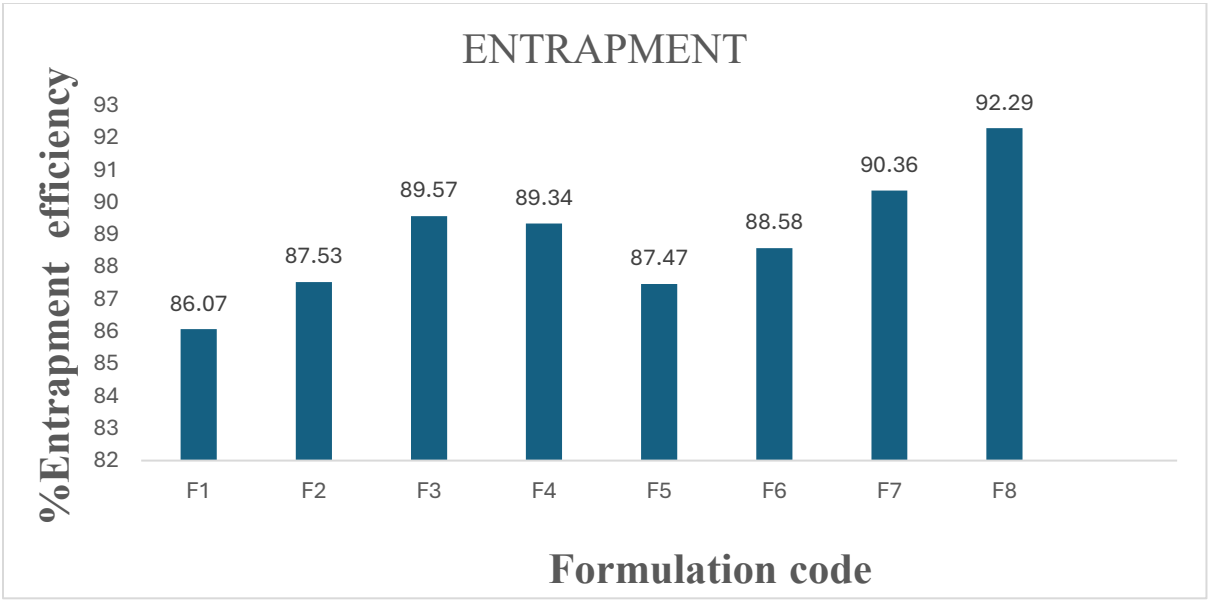

Figure 5 : Drug Entrapment

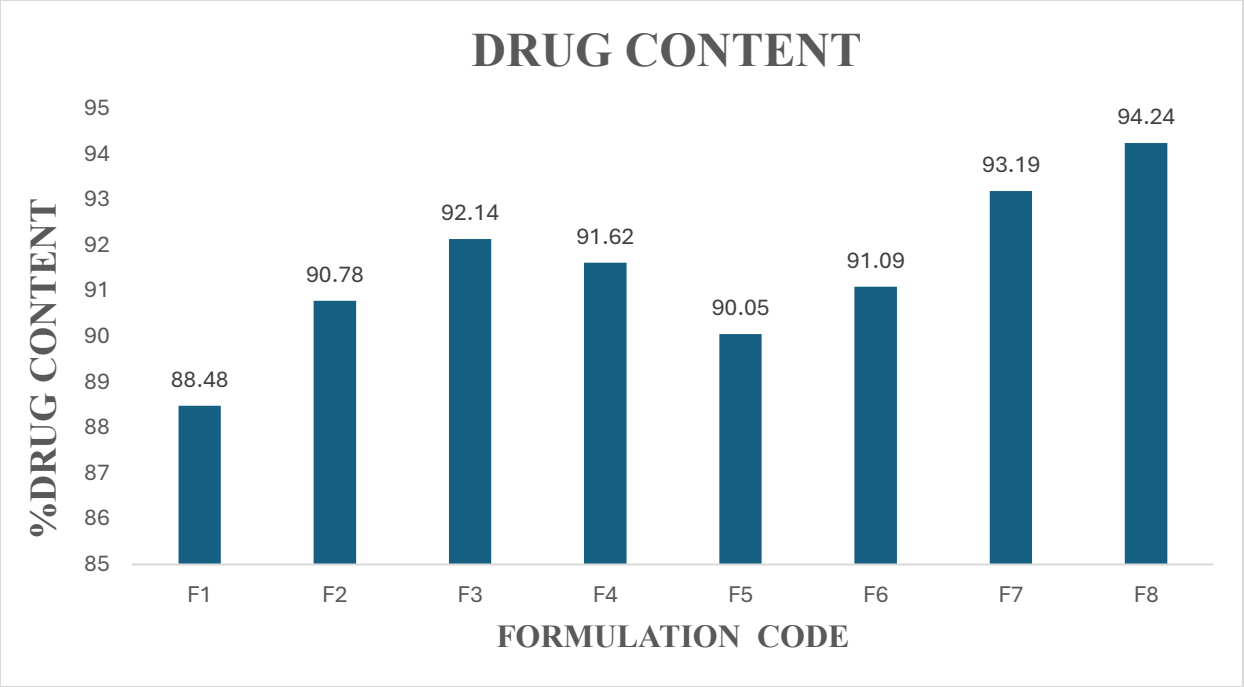

Figure 6 : Drug content

In-vitro drug release

Table 4: Invitro drug release study of formulation F1-F8

Time(hrs)	% Cumulative Drug Release							
	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
0.5	21.66	35.64	18.33	27.19	23.58	18.7	18.49	12.23
1	28.45	41.86	22.51	34.92	32.31	26.9	33.83	18.10
2	41.21	46.20	30.86	41.72	43.56	42.3	48.66	22.46
4	48.21	56.22	45.82	51.33	50.51	55.01	54.69	28.59
6	58.51	66.50	49.56	60.01	60.32	65.9	67.90	40.61
8	72.14	72.24	67.10	68.44	69.18	71.1	69.75	60.81
12	79.72	75.3	70.61	71.49	79.48	76.8	72.30	67.84

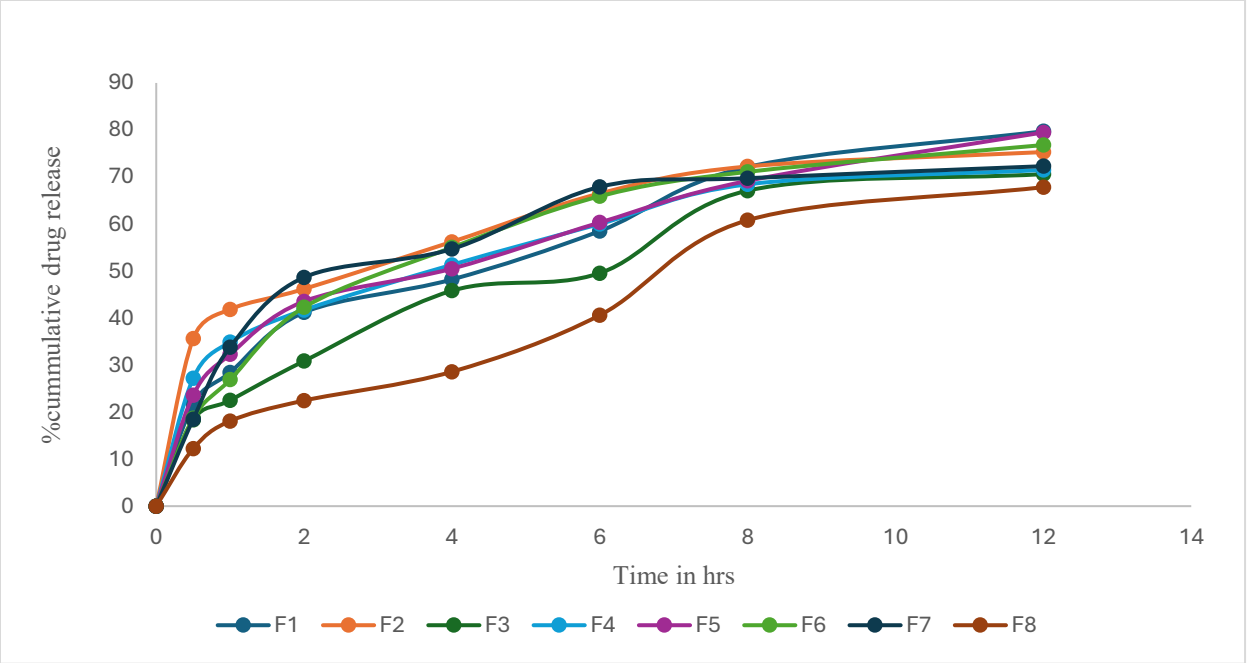

Figure 7 : % cumulative drug release

Table 5: Data for different kinetic model

F.CODE	ZERO ORDER	FIRST ORDER	HIGUCHI	K-PEPPAS MODEL	
				R^2	'n' VALUE
F1	0.846	0.966	0.98	0.98	0.405
F2	0.689	0.858	0.913	0.97	0.259
F3	0.866	0.939	0.981	0.98	0.478
F4	0.743	0.883	0.945	0.98	0.305
F5	0.814	0.959	0.975	0.98	0.306
F6	0.788	0.922	0.967	0.96	0.422
F7	0.688	0.827	0.916	0.94	0.309
F8	0.938	0.948	0.959	0.93	0.562

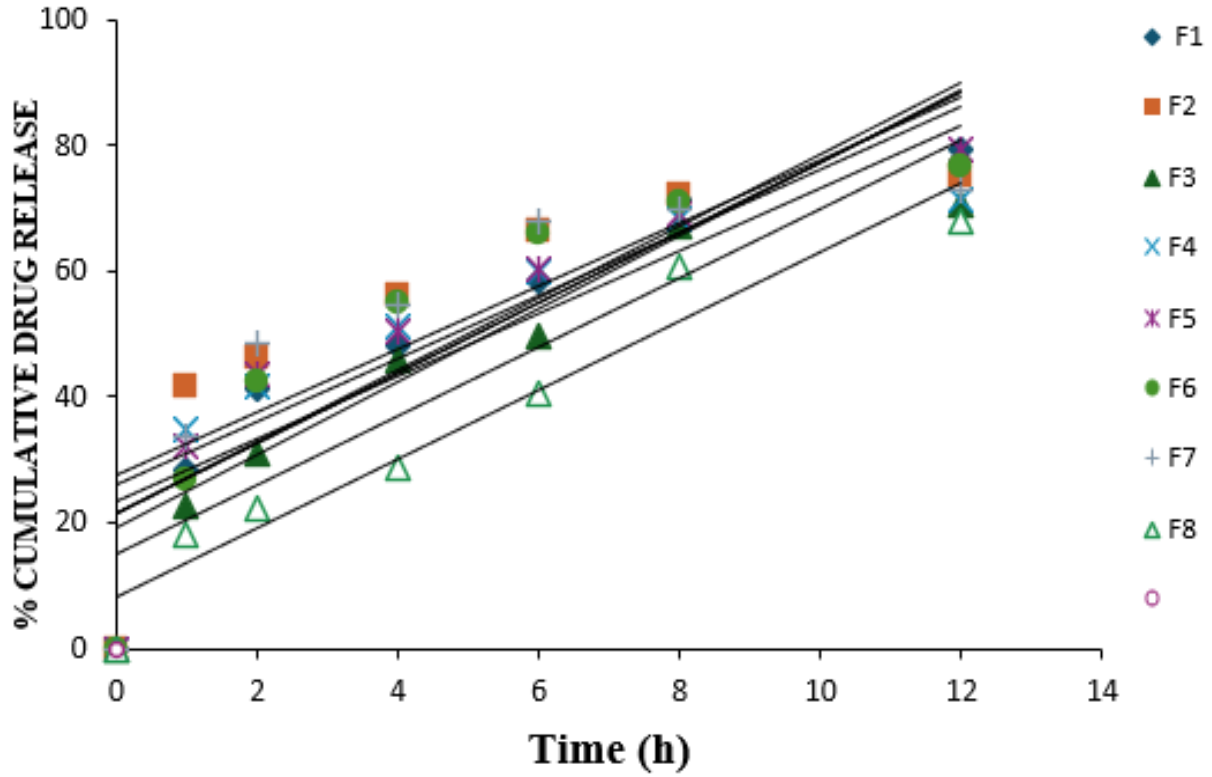

Figure 8 :Zero order release kinetic profile of formulation F1-F8

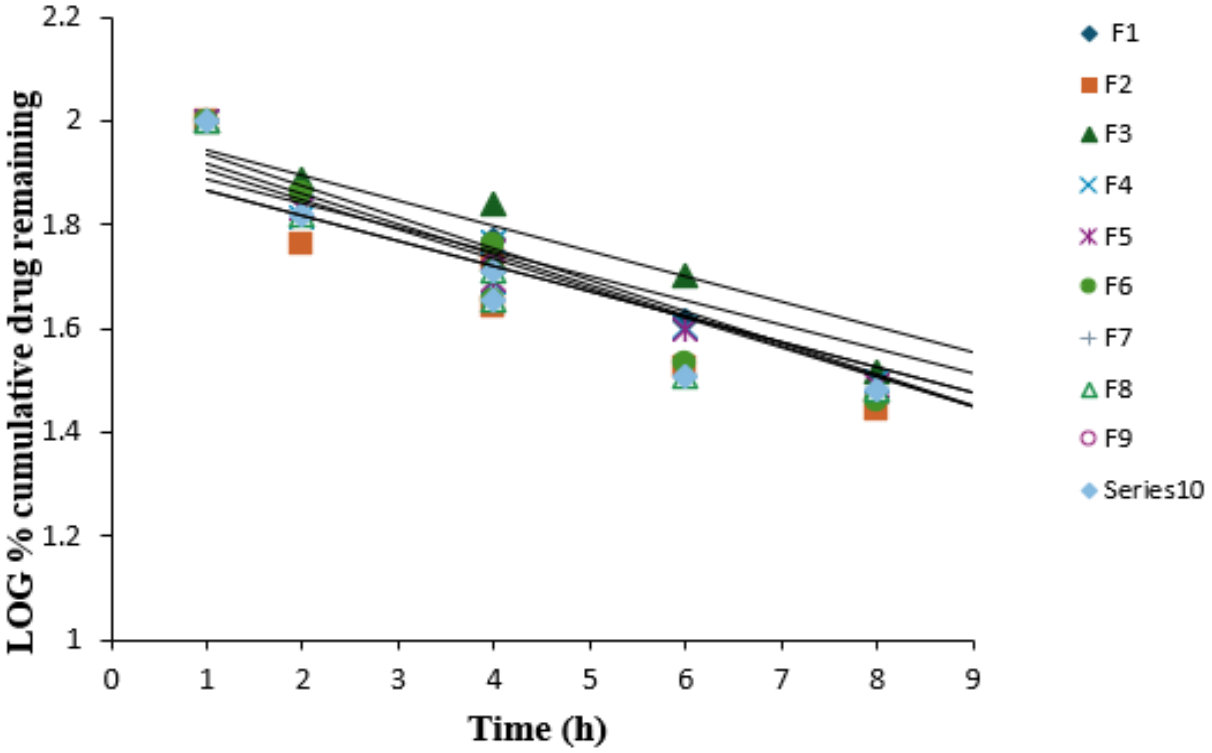

Figure 9: First order release kinetic profile of formulation F1-F8

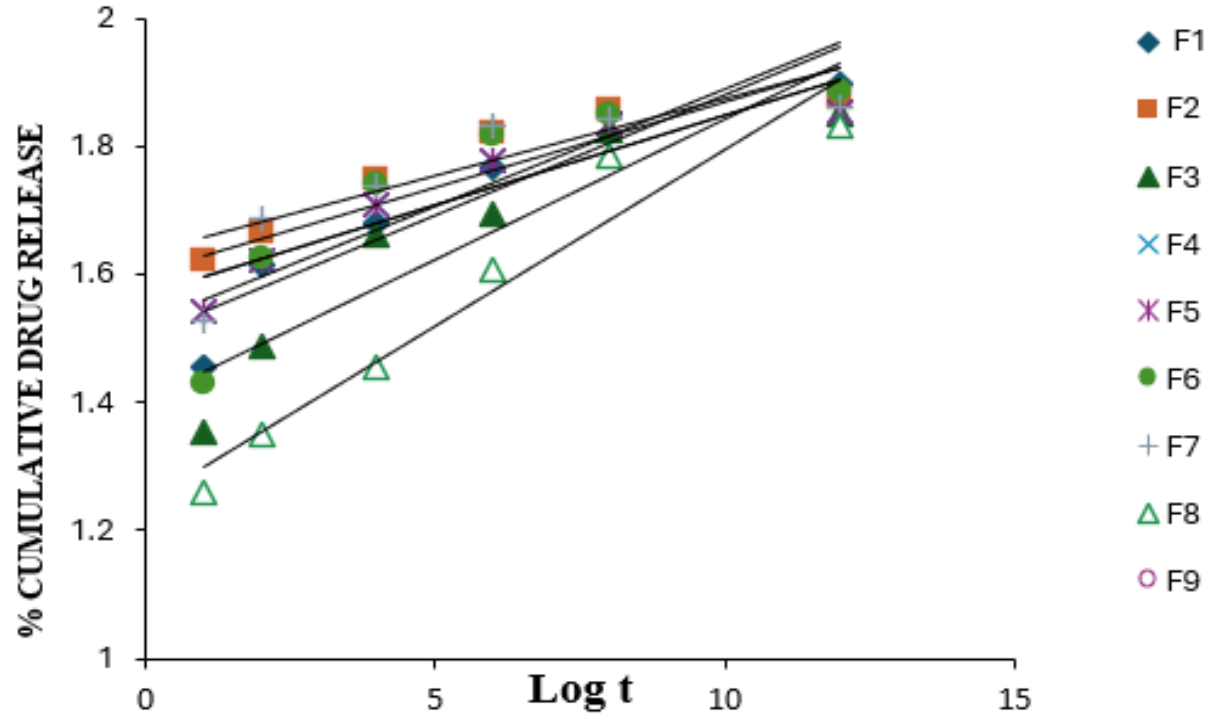

Figure 10: Higuchi release kinetic profile of formulation F1-F8

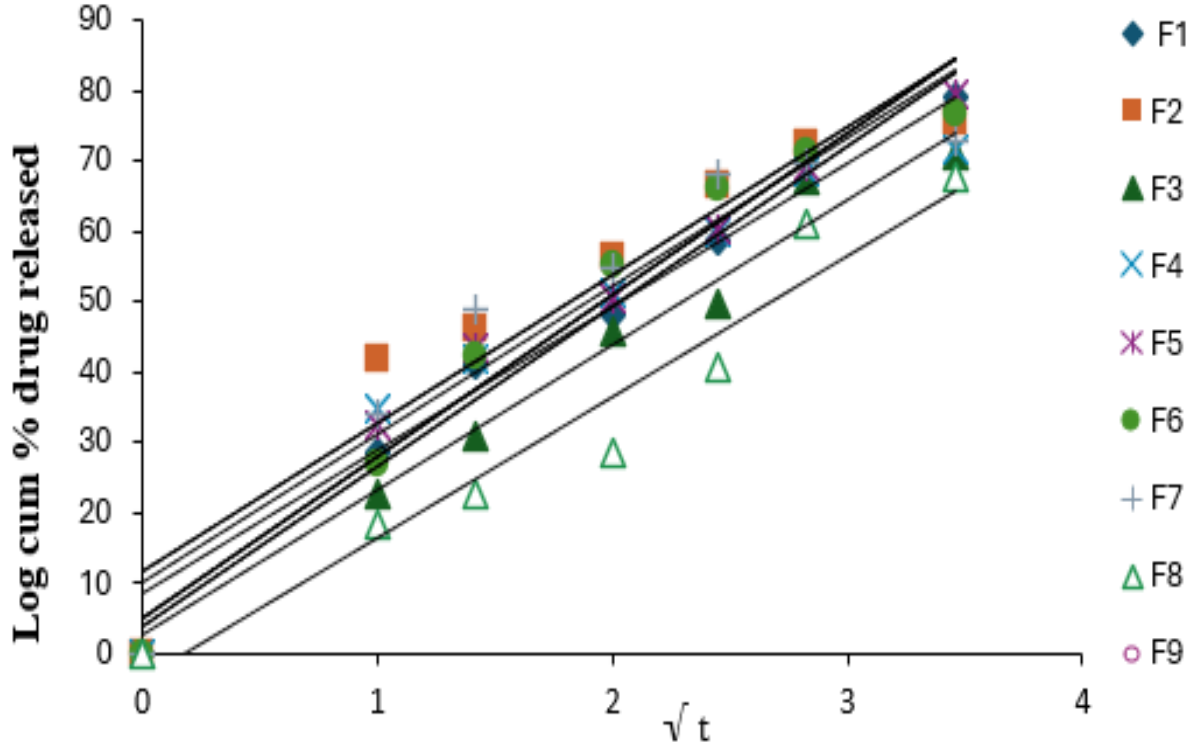

Figure 11: Peppas release kinetic profile of formulation F1-F8

IV. RESULTS OF MODELING FITTING

Table 6: Data for different kinetic model

F.CODE	ZERO ORDER	FIRST ORDER	HIGUCHI	K-PEPPAS MODEL	
				R^2	'n' VALUE
F1	0.846	0.966	0.98	0.98	0.405
F2	0.689	0.858	0.913	0.97	0.259
F3	0.866	0.939	0.981	0.98	0.478
F4	0.743	0.883	0.945	0.98	0.305
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F6	0.788	0.922	0.967	0.96	0.422
F7	0.688	0.827	0.916	0.94	0.309
F8	0.938	0.948	0.959	0.93	0.562

Stability studies of proniosomal gel

Table 7: Results of stability studies

Parameters	Duration in days		
	0	45	90
% DC	91.37	90.86	89.71
% CDR	67.84	66.67	65.45

Proniosomal gel Incorparation into Carbopol gel base

The optimized proniosomal gel was corporated into gel by the use of Carbopol 934 containing 1% w/w gel was found to be suitable for gelling the proniosomal gel because of desirable consistency.

Table 8: Spreadability, Viscosity, pH and % drug content of proniosomal gel

Formulation code	Spreadability	Viscosity	pH	% Drug content
F8-G1	7.2 ± 0.04	7340 ± 77.14	6.4 ± 0.19	94.54 ± 0.23

➢ *In vitro* drug release study

Table 9: Drug release study of F8-G1

Time in hrs.	F8
0	0
0.5	8.25
1	12.3
2	16.3
4	22.5
6	30.05
8	41.5
12	49.5

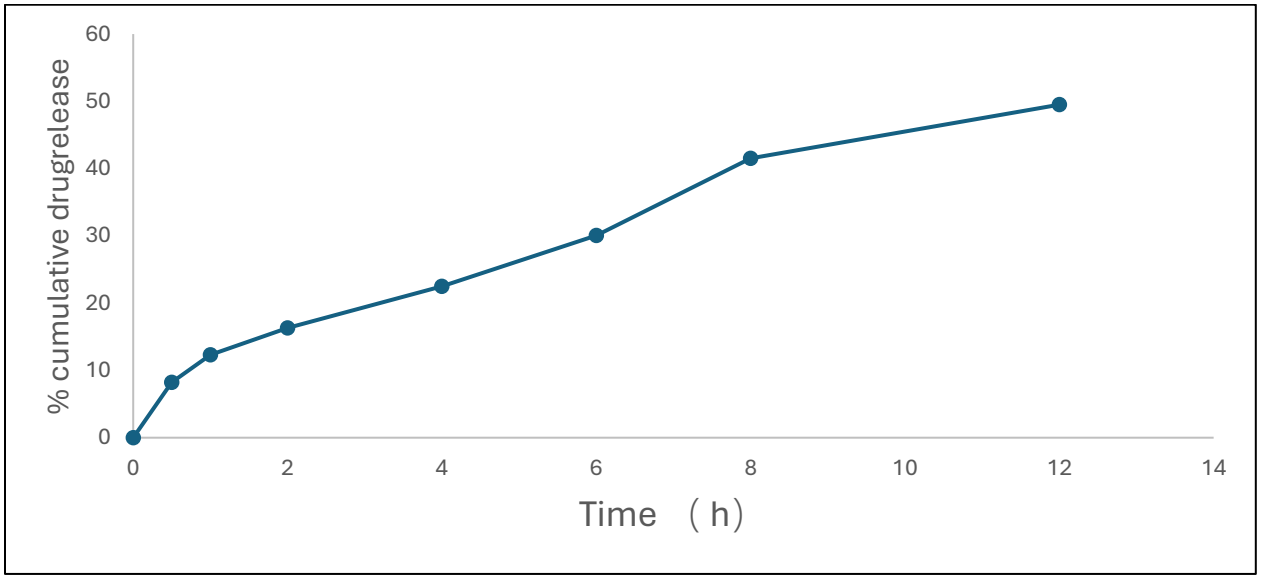

Figure 12: %Cumulative drug release of F8-G1.

Table 10: Release kinetic profile of F8-G1

Time in hrs.	Log T	√T	% CDR	Log % CDR	% Drug remaining	Log % drug remaining
0	0	0	0	0	100	2
0.5	0.000	1.000	9.25	0.966	90.74	1.958
1	0	1	12.3	1.08	87.3	1.94
2	0.30	1.14	16.3	1.21	83.7	1.92
4	0.60	2	22.5	1.35	77.5	1.88
6	0.90	2.28	30.34	1.48	69.66	1.84
8	1.20	4	41.5	1.61	58.5	1.76
12	1.38	4.89	49.5	1.69	50.5	0.70

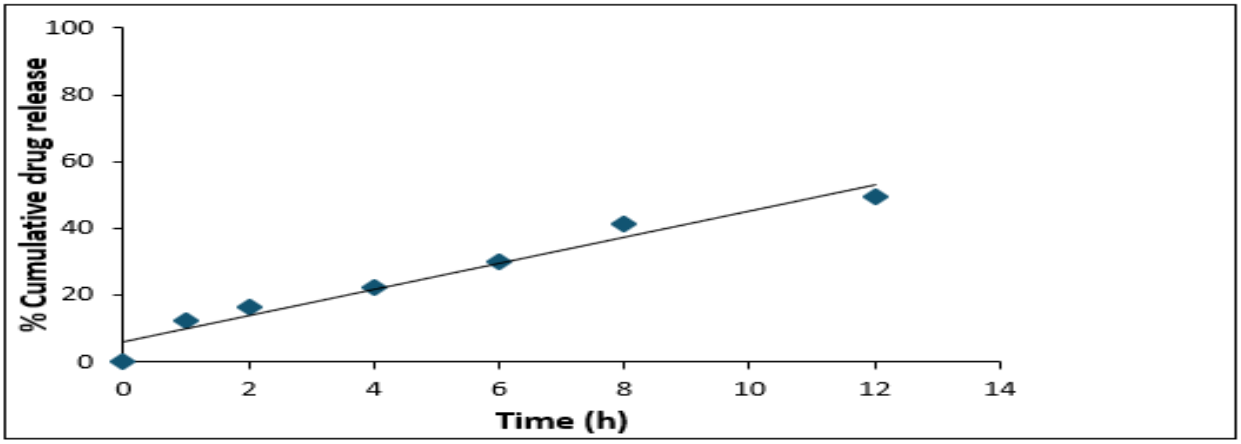

Figure 13: Zero order release kinetic profile of formulation F8-G1

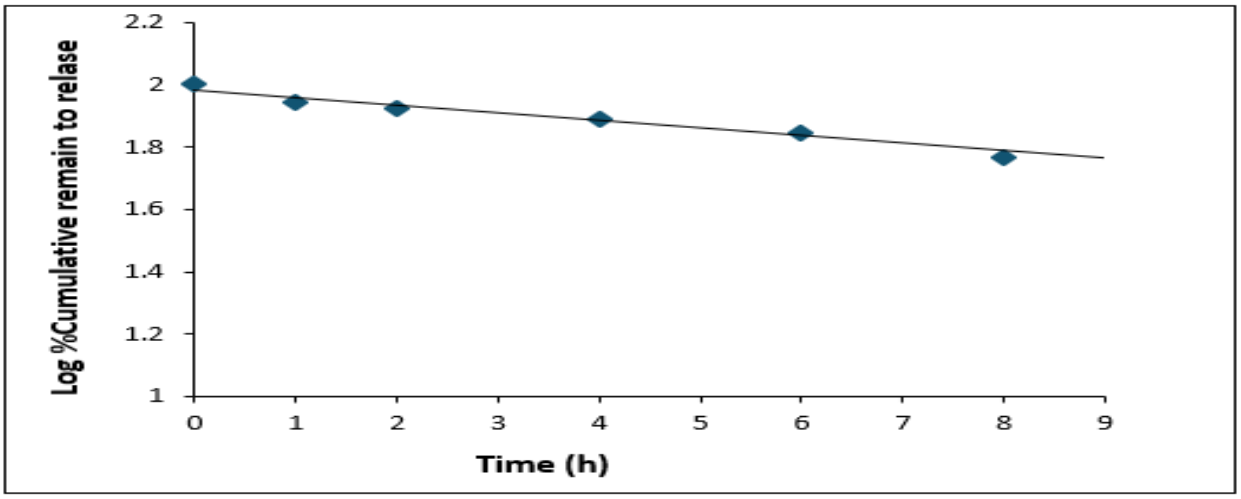

Figure 14: First order release kinetic profile of formulation F8-G1

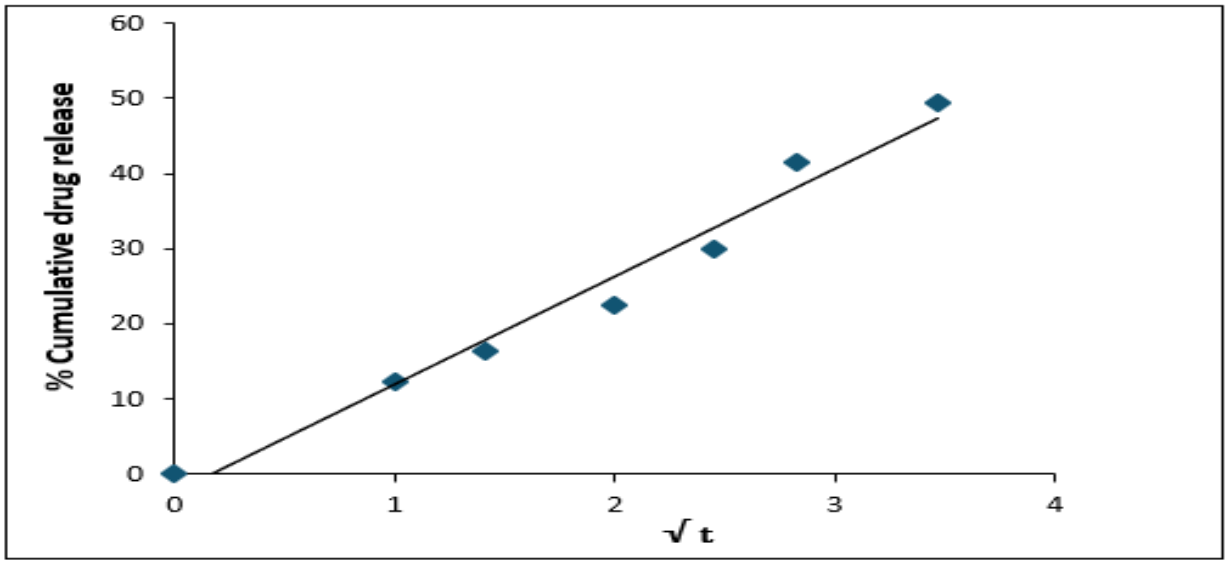

Figure 15: Higuchi release kinetic profile of formulation F8-G1

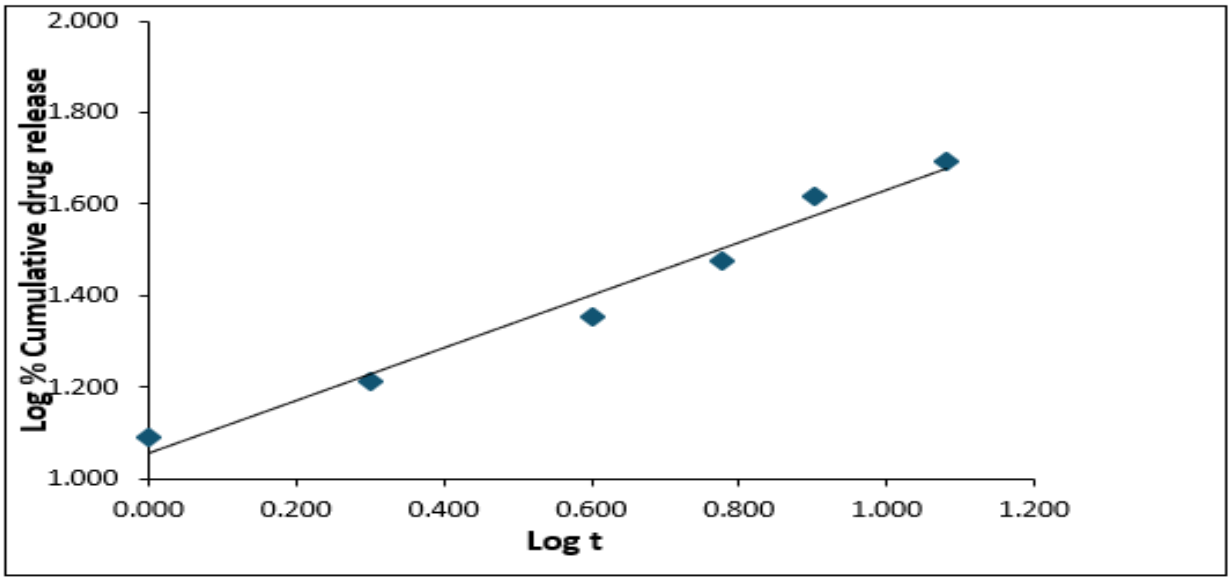

Figure 16: Peppas release kinetic profile of formulation F8-G1

V. RESULTS OF MODELING FITTING

Table 11: Data for different kinetic model

Formulation code	Zero order	First order	Higuchi	Peppas model	
				r^2	n value
F8-G1	0.902	0.937	0.995	0.653	0.5374

Stability studies

Table 12: Results of stability studies

Parameters	Duration in days		
	0	45	90
% DC	90.82	89.72	88.43
% CDR	49.5	48.6	48.4

IV. CONCLUSION

- The present study was successfully formulated and evaluated Vildagliptin proniosomal gel using the coacervation phase separation method. The prepared formulations exhibited satisfactory physicochemical properties, good drug–excipient compatibility, uniform vesicle formation, high drug content, and excellent entrapment efficiency. Among all the formulations, F8 was identified as the optimized formulation, demonstrating the highest drug content (94.24%), entrapment efficiency (92.29%), and sustained drug release over 8 hours. The release kinetics followed the Korsmeyer–Peppas model, indicating a diffusion-controlled mechanism of drug release. Overall, the developed proniosomal gel showed promising potential as a controlled drug delivery system for Vildagliptin, which may improve therapeutic efficacy and patient compliance. However, further *in vivo* pharmacokinetic and pharmacodynamic studies are required to confirm its clinical

effectiveness and establish its suitability for therapeutic application. Stability studies of selected formulation F8 showed that, negligible changes in drug content, and % CDR and revealed that the formulations are stable on storage.

- The optimized F8 formulation was incorporated into carbopol 934 gel. The prepared formulations were evaluated for various parameters and study observed from the prepared gel.
- The In vitro drug release study of Proniosomal gel F8G1- showed sustained release, with %CDR values. The results confirm that the gels can retain the drug for prolonged periods.

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