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FORMULATION AND EVALUATION OF SPAN-60-BASED VALACYCLOVIR PRONIOSOMAL GEL FOR OCULAR DELIVERY

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ABSTRACT
Background: Ocular administration is a challenging route of drug delivery due to the eye's distinct anatomy and physiology. Valacyclovir is commonly prescribed to treat viral ophthalmological conditions. However, its poor permeability limits its effectiveness in ocular viral infections. In this study, valacyclovir proniosomal gels (F1-F14) have been prepared for ocular permeation. **Methodology:** The VCV proniosomal gel was prepared using varying ratios of cholesterol, Span 60, and lecithin via coacervation-phase separation. The prepared proniosomal gels were characterized for particle size and shape, viscosity, drug entrapment efficiency (EE%), surface morphology, zeta potential, and *in vitro* drug release. **Result and Discussion:** Data from experimentation indicate that all formulations prepared were found to have high entrapped efficiency (%), with the highest value being (90.70%) for F7. The final formulation showed a ZP of -27.40 ± 2 mV, a PDI of 0.231, and a vesicle size of 64.31 nm, indicating uniformly dispersed, nanosized vesicles well-suited for ocular drug delivery and exhibiting greater colloidal stability. **Conclusion:** The results from all fourteen formulations of in vitro drug release demonstrated that they all released their drug in a sustained manner for at least 10 hours following release. The patterns of drug release from the in vitro tests fitted into the Korsmeyer–Peppas model of drug release kinetics. Overall, the results show that using VCV in a proniosomal form enables prolonged, enhanced corneal permeation.

INTRODUCTION

An ocular drug delivery system (ODDS) is a dosage form used to deliver medication to the eye to treat conditions affecting or involving vision [1]. It might be as basic as sterile eye drops for the eye's surface or as sophisticated as implants for intraocular tissue [2–4]. Depending on the situation and intended outcome,

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the delivery medium for ODDS can take any shape, including wearable photoactivators, contact lenses, ophthalmic gels, eye drops, and optical inserts [5-7]. Ocular drug delivery is complex due to the eye's unique anatomy and physiology [8,9].

To effectively deliver drugs to the eye, a drug delivery system that can get past these obstacles must be developed. Because of their unique properties, proniosomes offer a viable alternative for ocular drug delivery systems [10]. Proniosomes are dry formulations of non-ionic surfactants and cholesterol that can be hydrated to form niosomes, vesicular systems used for drug delivery [11-13]. They facilitate dosing convenience and lower physical stability issues with liposomes and niosomes, including drug leakage, fusion, aggregation, distribution, transportation, and storage.

Since proniosomes can resolve the instability issues associated with liposomes and niosomes and potentially enhance the solubility, bioavailability, and absorption of many medications, they have emerged as the preferred vesicular carrier among other options [14,15]. It can encapsulate poorly soluble, hydrophilic, and hydrophobic medications and act as a barrier to prevent pH changes and enzymatic breakdown, while enhancing stability and shelf life [16–21]. Ocular herpes is treated with valacyclovir, a prodrug of acyclovir [22]. When applied topically, VCV HCl is degraded by enzymatic hydrolysis to produce acyclovir and valine [23]. Acyclovir has an oral bioavailability of about 10–20%, whereas valacyclovir has an oral bioavailability of up to 54% [24]. Acyclovir has an oral bioavailability of about 10-20%, whereas valacyclovir has an oral bioavailability of up to 54% [24], which is higher compared to acyclovir [25,26]. The BCS Class III drug valacyclovir has low ocular bioavailability with conventional formulations due to its limited corneal permeability and high aqueous solubility. Proniosomes of valacyclovir have been developed to enhance permeation and prolong ocular residence time, thereby overcoming valacyclovir's low ocular permeability and improving bioavailability. Its systemic distribution effectively reduces the risk of complications and recurrence when used to treat ocular infections by inhibiting viral replication in the eye [27–30].

Proniosomal gels are a potentially effective method for prolonging corneal contact, penetration, and residence times in the eye, which promotes sustained action and improved bioavailability [31-33]. The limitations of existing ocular drug delivery techniques are addressed in this research by employing valacyclovir proniosomes, which provide a more efficient and targeted approach to ocular antiviral therapy.

MATERIALS AND METHODS

Material

Valacyclovir was purchased from Yarrow Chem Pvt Ltd in Mumbai, India, and Span 60 from Loba Chemie Pvt Ltd (Mumbai, India). Cholesterol was obtained from Sisco Research Laboratories, and Soya Lecithin was purchased from Central Drug House Pvt. Ltd. in India. All other materials used in this study were of analytical grade.

PREFORMULATION STUDIES

UV-visible λ_{max} scan and Standard curve preparation

The stock solution was prepared by weighing 10 mg of the drug and dissolving it in sufficient phosphate buffer (pH 7.4) in a volumetric flask to achieve a concentration of 100 µg/mL. Various dilutions of 5, 10, 15, 20, 25, and 30 µg/mL were prepared in volumetric flasks using stock solutions. Samples have been scanned between 200 and 400nm using a UV-Vis spectrophotometer (LABMAN LMSP-UV 1900) to determine the λmax of the drug [34]. The absorbance of all dilutions was measured at the drug's λmax. A calibration curve was plotted between absorbance and concentration (µg/ml) [35,36].

Solubility

An excess amount of the drug was added to 25 ml of water in a conical flask to make a saturated solution. The flask was then placed in a shaking water bath at 25±1°C and 37±1°C for 24 hours. After 24 hrs, the solution was filtered, diluted if necessary, and assessed at 252nm. The practical was performed in triplicate [37].

Fourier Transform Infrared spectroscopy (FTIR) study

Fourier Transform Infrared (FTIR) spectroscopy (Thermoscientific Nicolet Summit LITE iD1) is used to identify the drug and assess its compatibility with various excipients. The FTIR spectrogram shows how excipients such as Span 60, cholesterol, and soya lecithin interact with the drug. The FTIR spectra can be obtained using the KBr method [38].

Method of Preparation of Proniosomal Gel of Valacyclovir

The coacervation-phase separation technique has been used to prepare valacyclovir proniosome gels. A total of 14 formulations (F1-F14) have been prepared, using valacyclovir and excipients in different combinations, as shown in Table 1. A diagrammatic representation of all steps of the method is given in Figure 1.

Accurately measured amounts of VCV, span 60 (surfactant), lecithin, and cholesterol were introduced into a glass beaker containing alcohol. The mixture was then properly mixed in a magnetic stirrer at 800rpm for 30 mins. To stop the solvent from escaping, the beaker was covered with aluminum foil. The mixture was then heated in a water bath at 60-70°C for approximately 5 minutes, or until the surfactant combination was fully dissolved. Following the addition of the aqueous phase, the mixture was heated again in a water bath to obtain a clear solution, which, upon cooling, formed a proniosomal gel [39,40]. To produce stable proniosomes with ideal vesicle properties and drug-release profiles, the concentration ranges were selected based on the literature and early optimization studies. Figure 2 depicts various formulations of valacyclovir proniosomal gel formulated in the research lab.

EVALUATION OF PRONIOSOMAL GEL

Viscosity

The Brookfield viscometer (AMETEK-DV1MRVTJ0) was used to assess the viscosity of the formulated proniosomal gel. via spindle size four, it was evaluated, as well as determining [41].

pH determination

The pH of the proniosomal gel formulations was measured with a pH meter (HPG SYSTEM-G 2020) [42].

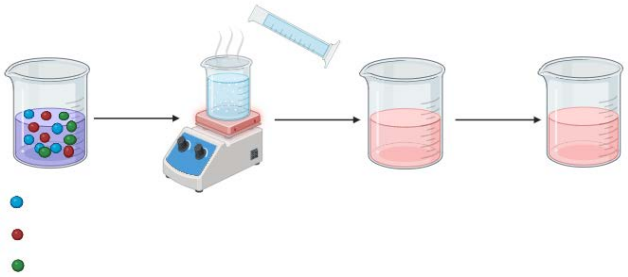

Figure 1: Coacervation Phase Separation Method

Figure 2: Various formulations of valacyclovir proniosomal gel

Table 1: Formulation table of Valacyclovir Proniosomal Gel

F. Code	Drug (mg)	Cholesterol (mg)	Span 60 (Extra pure) (mg)	Lecithin (mg)
F1	60	120	250	80
F2	60	90	90	60
F3	60	90	130	80
F4	60	90	250	100
F5	60	60	130	60
F6	60	60	130	100
F7	60	60	250	80
F8	60	90	90	100
F9	60	60	90	80
F10	60	120	130	100
F11	60	90	130	80
F12	60	120	90	80
F13	60	120	130	60
F14	60	90	250	60

Polydispersity Index (PDI) and Average Particle Size

The PDI and average particle size of the proniosomes were determined by the dynamic light scattering method. PDI is used to assess the particle-size distribution in the system. A homogeneous system is indicated by a PDI value near 0 (monodispersed), whereas a heterogeneous system is indicated by a value of 1. A PDI value greater than 0.7 indicates a non-uniform particle size distribution, or a polydisperse formulation. The dispersions were properly diluted with distilled water and measured to determine PDI and average particle size.

Zeta potential (ZP)

ZP is a measure of the physical stability of dispersion. ZP maintains stability due to the particle's electrostatic repulsion. The surface charge of nanoparticles in solutions can be evaluated using the zeta potential. The ZP of dispersions was determined using the Malvern Instrument (zeta sizer ver. 7.11).

Scanning Electron Microscopy (SEM)

The surface properties and particle shape have been evaluated using SEM. The proniosomes were placed on aluminum stubs and fixed using double-sided tape. The images of samples have been taken using an SEM instrument (ZEISS).

Entrapment Efficiency (EE%)

The amount of drug entrapped in the formulation was determined using the centrifugal method [15. To extract the unentrapped drug, the proniosomal gel was transformed into a niosomal dispersion and centrifuged at 15,000 rpm for 40 minutes at 50°C. Phosphate buffer was used to dilute the supernatant. The absorbance of the resultant solution was

measured at 252 nm. The following method was used to calculate the percentage of drug encapsulation:

$$EE\ (\%) = \frac{Total\ amount\ of\ drug - amount\ unentrapped}{total\ amount\ of\ drug} \times 100$$

In vitro diffusion studies

Drug release in vitro from proniosomal gels was studied using a diffusion apparatus (Franz) containing an egg membrane. An egg membrane was carefully cleaned and inserted between the donor and receptor compartments of the diffusion apparatus. A known weight of proniosomal gel was placed in the donor compartment, and a phosphate buffer at pH 7.4 was used as the receptor solution. A water jacket surrounded the receptacle chamber to control the temperature at 37 ± 1 °C.

The magnetic stirrer was connected to a hot plate with a thermostat that responded to temperature to keep the receptacle mixed. Samples were taken out of the receptacle at specific points in time and replaced with phosphate buffer at pH 7.4 to maintain the condition "sink". All samples taken from the receptacle were analyzed by spectrophotometry at 252 nm. All experiments were run in triplicate. [48-50].

Kinetics of drug release

The kinetics of drug release from the proniosomal gel were analyzed using DD Solver software. The in vitro release data obtained from the formulations were fitted to various mathematical models, including zero-order, first-order, Higuchi, Hixson–Crowell, and Korsmeyer–Peppas models. The most appropriate release model was selected based on model selection criteria, specifically the lowest sum of squared residuals (SSR) and the highest correlation coefficient (R^2) value.

RESULTS AND DISCUSSIONS

Determination of λmax and preparation of calibration curve

The way valacyclovir was released from the proniosomal gel was assessed using in vitro methods, and the quantitative characterization of the spectra of the valacyclovir samples was performed to find the wavelengths with the greatest absorbance (λmax) of valacyclovir in phosphate buffer (pH 7.4). As shown in Figure 3, the λmax for the valacyclovir buffered sample appears to be 252 nm with UV–visible spectrophotometry. The UV-visible absorbance of different dilutions of valacyclovir in PBS has been given in Table 2. The calibration curve has been plotted with absorbance on the y-axis and concentration on the x-axis, as shown in Figure 4. The R2 value of the graph is 0.9887, close to the acceptable value of 0.99 for a linear fit.

Table 2: Standard Calibration curve of Valacyclovir in Phosphate buffer 7.4

Concentration (µg/mL)	Absorbance
5	0.236
10	0.397
15	0.485
20	0.650
25	0.864
30	0.961

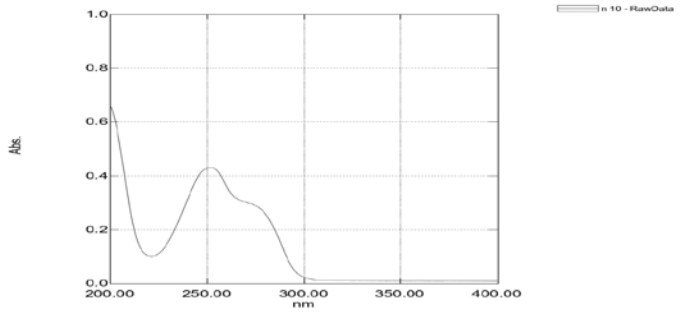

Figure 3: $\lambda_{max\ of}$ Valacyclovir phosphate in buffer 7.4.

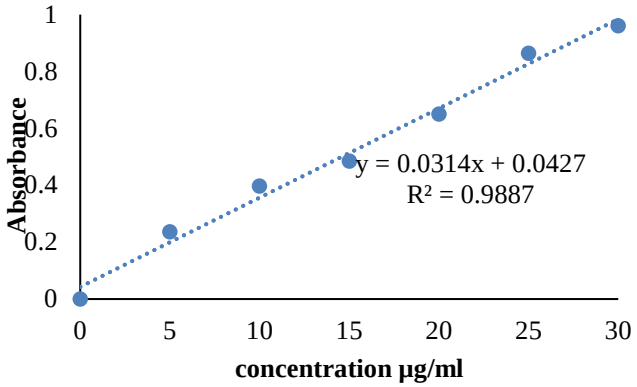

Figure 4: Calibration curve of VCV in Phospate buffer pH 7.4

Solubility

Valacyclovir is freely soluble in water, and its solubility was determined to be 164 mg/mL by the shake-flask method, close to the reported value of 174 mg/mL.

Fourier Transform Infrared Spectroscopy (FTIR) studies

FTIR spectroscopy was utilized to identify the drug and excipient. It is also used to assess the drug-excipient compatibility. Figure 5 displays the FTIR spectra of Valacyclovir, a drug-excipient mixture in physical form, and optimized formulations (F7). Some major FTIR recorded peaks of Valacyclovir are given in Table 3. Figure 5 shows no chemical reaction between the drug and the excipient, so no incompatibility was observed between them.

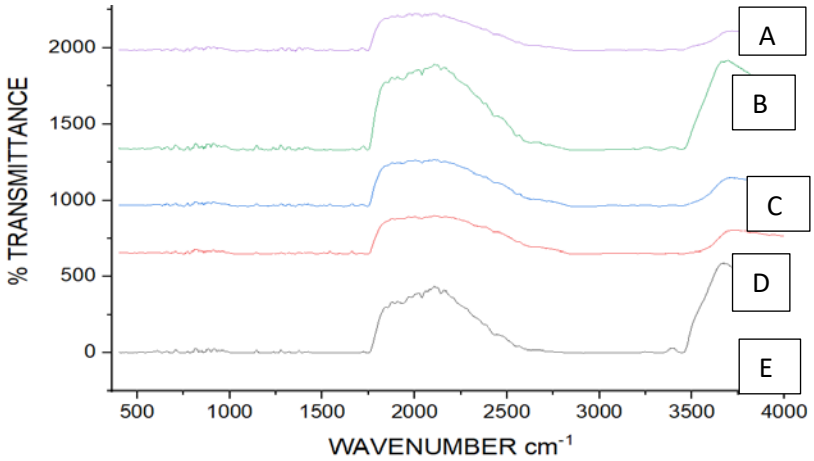

Figure 5: FTIR Spectrum (A): Valacyclovir, (B): Valacyclovir + Span60, (C): Valacyclovir + Span60 + Lecithin + Cholesterol, (D): Valacyclovir + Cholesterol, (E): Optimized formulation F7

Table 3: FTIR recorded peaks of Valacyclovir.

Observed peak	Characteristic peak	Bond	Functional Group
3321.459	3300-3500	-N-H	Amines
3446.751	3300-3500	-N-H	Amines
2911.487	2700-3300	C-H Stretch	Aromatics

Evaluation of Proniosomal Gel

Proniosomal gels have been characterized for various parameters, including pH, EE, drug loading, and viscosity, as shown in Table 4. All 14 formulations showed pH values of 6.12-6.96, which is within the ideal range, i.e., 6.5-7.5. Similarly, viscosity was found between 9-14 cP, which is also within the ideal range, i.e., below 15 cP. The optimized formulation has a viscosity of 9 cP, which is close to the natural viscosity of tear (1-10 cP).

Entrapment Efficiency (EE%)

The composition of proniosomes is a key factor in drug entrapment within the pro-vesicular system. The type of surfactant and the inclusion or exclusion of cholesterol play a crucial role in drug entrapment. Cholesterol was added to vesicles to prevent drug leakage by filling the spaces between the vesicle bilayers, thereby forming a more ordered or rigid membrane. The EE increases with the length of the saturated alkyl chain of the surfactant. The higher entrapment efficiencies of Span 60 pro vesicles were due to the longer saturated alkyl chain. In this research, the F7 formulation showed the highest entrapment, 90.7%, due to the maximum amount of span 60 (250 mg) and the lowest amount of cholesterol (60 mg) (47). It has been observed that high cholesterol levels, combined with reduced surfactant, reduce drug entrapment, as in F10, F12, and F13. Because it increases bilayer stiffness and competes with drug molecules for space within the vesicle membrane, excess cholesterol reduces EE. The table shows that the formulation with less surfactant has lower entrapment efficiency. The entrapment efficiency was not affected by lecithin.

Polydispersity Index (PDI) and Particle size analysis

The optimized Formulation F7 has a PDI of 0.231, indicating a uniform distribution, with an Av (Average vesicle size, Volume-Weighted Average) of 64.31 nm, as shown in Figure 6. The large average vesicle size is likely due to some of the formulation's lipophilic components, which include cholesterol and lecithin, and also because of Span 60, an oil-soluble surfactant that can interact with the lipophilic hydrocarbon chains of phospholipids to cause the vesicle's average size to expand. This interaction creates further competition between Span 60 and the phospholipid alkyl chains. The comparatively large vesicle size may be due to the way these molecules are packed within the vesicular membrane and reflects the rising particle-size effect [47].

Zeta Potential (ZP)

The optimized Formulation F7 has a PDI of 0.231, which is considered acceptable, with an Av + Average vesicle size (Volume Weighted Average) of 64nm, as shown in Figure 6. The large average vesicle size is likely due to some of the formulation's lipophilic components, which include cholesterol and lecithin, and also because of Span 60, an oil-soluble surfactant that can interact with the lipophilic hydrocarbon chains of phospholipids to cause the vesicle's average size to expand.

Table 4: Characterization of Proniosomes Gel Formulations

Formulation Code	pH	EE %	Viscosity (cP)	Polydispersibility index (PDI)	Zeta Potential
F1	6.27	78.58	14	0.528	-30.0
F2	6.17	70.7	9	0.604	-40.2
F3	6.76	83.16	12	0.473	-28.6
F4	6.22	64.9	10	0.780	-24.9
F5	6.41	72.65	10	0.338	-19.3
F6	6.12	72.21	9	0.478	-29.7
F7	6.96	90.7	9	0.231	-27.4
F8	6.35	69.06	11	0.632	-25.6
F9	6.72	73.93	13	0.515	-32.1
F10	6.19	65.0	9	0.463	-31.3
F11	6.47	73.4	12	0.339	-29.4
F12	6.81	64.63	11	0.534	-26.8
F13	6.54	62.36	9	0.732	-34.5
F14	6.28	78.46	11	0.665	-36.3

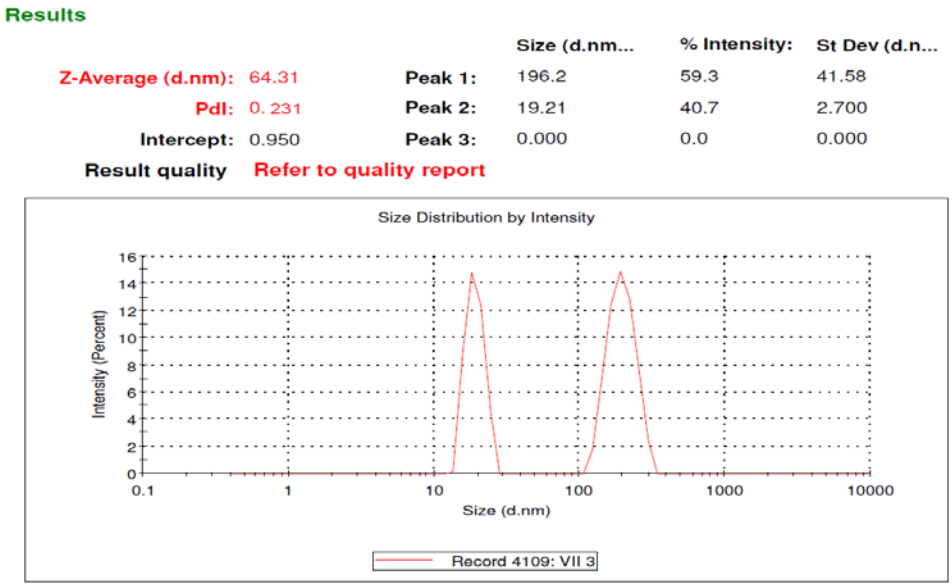

Figure 6: PDI of the optimized formulation F7

Scanning Electron Microscopy (SEM)

The SEM analysis of the optimized formulation (F7) was performed at a magnification of 9.00 KX, as shown in Figure 8. The particles were distinct and nearly spherical. Microscopically, round vesicle bodies of uniformly small size were observed. Since smaller vesicles tend to fuse more easily, it is thought that vesicles with smaller diameters penetrate the eye more effectively. The addition of Span 60 at various ratios has reduced vesicle diameters to some extent.

Percentage Drug Release

The in vitro DR profile of the valacyclovir-formulated proniosomes is summarised in Table 5, which presents the results after 10 hrs. Figure 9, depicts all of the formulations as having a sustained-release characteristic for more than 10 hours.

Kinetics of Drug Release

The in vitro release data for the optimized Proniosomal gel formulations were fitted to various kinetic models to determine the order and mechanism of drug release. The optimized formulation has shown the highest drug-release percentage (90.09%), as shown in Figure 10. The SSR, MSC, and R^2 values of each model are given in Table 6. It has been found that the drug release from the optimized formulation follows the Korsmeyer Peppas model based on the lowest SSR, and the highest R2 values of 27.2685 and 0.9956, respectively, and the n value of 0.5 shows the non-fickian mechanism, which means the drug is released by both diffusion and by swelling of the polymer. The MSC value was found to be highest, i.e., 5.0477, for the Korsmeyer Peppas model, indicating the best fit.

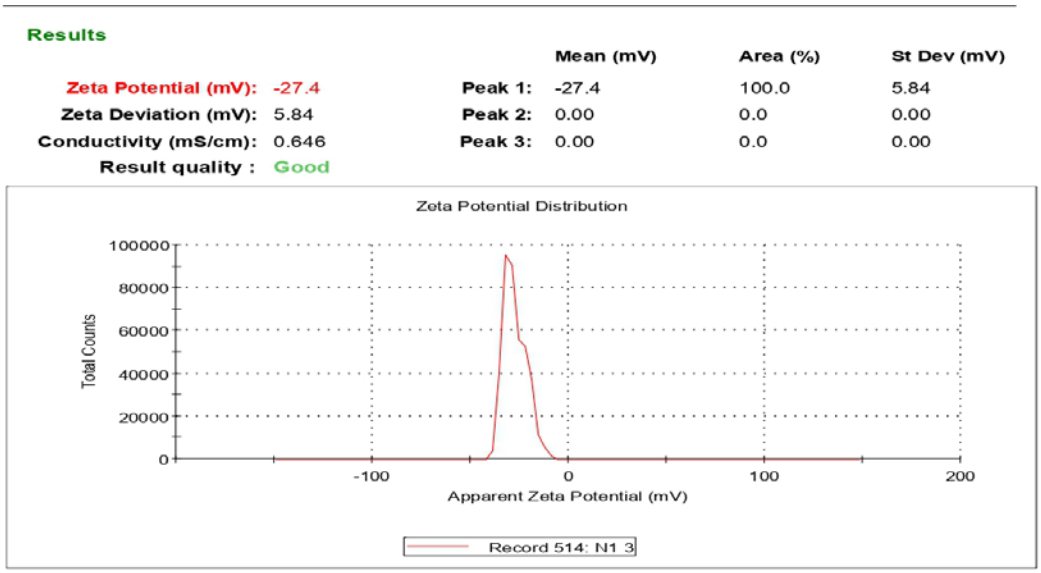

Figure 7: Zeta potential of Valacyclovir Proniosomal Gel for F7

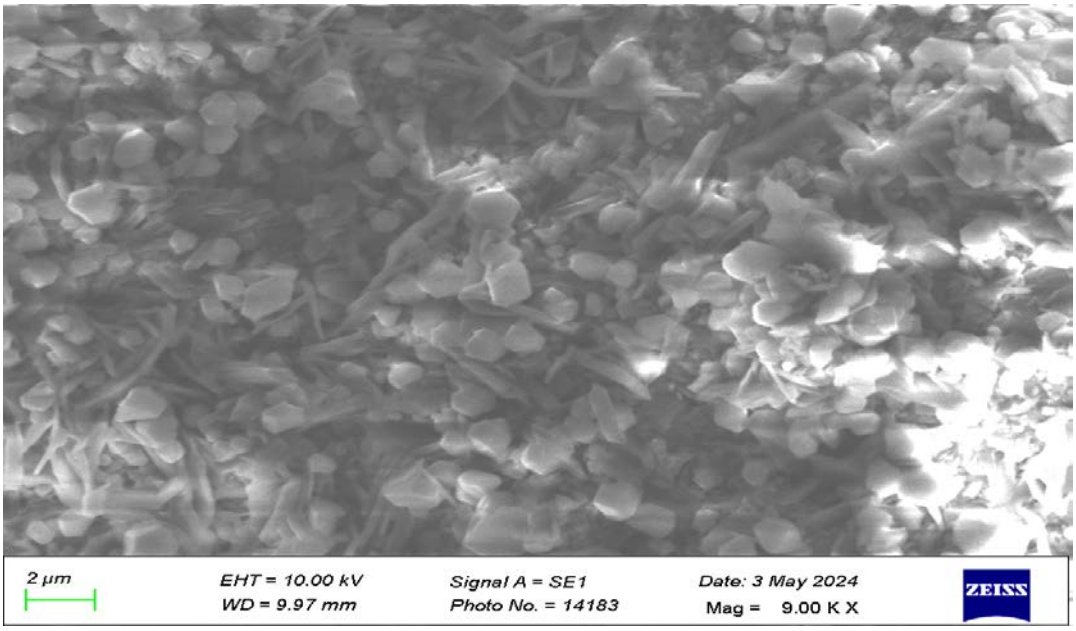

Figure 8: SEM image of the F7 formulation

Table 5: *In-vitro* drug release of various proniosomal gel formulations

Time (hr)	Cumulative % Drug Release													
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14
1	7.40	9.30	8.40	8.89	9.60	7.45	9.24	7.54	8.66	7.33	7.62	7.44	8.51	9.32
2	11.86	16.16	10.60	12.12	12.35	10.24	14.43	16.54	15.37	13.43	15.76	17.43	16.8	15.25
3	22.53	26.34	25.34	24.76	26.44	28.43	24.42	22.68	24.11	21.39	28.74	26.65	29.95	22.35
4	34.32	36.45	33.89	30.65	32.26	30.76	32.46	30.45	32.73	30.54	39.94	34.42	38.27	39.54
5	45.66	46.43	40.65	38.60	40.25	39.68	40.27	42.57	37.73	34.55	45.66	42.54	47.37	42.63
6	56.49	60.66	50.62	49.56	51.53	50.49	47.45	49.67	43.11	40.13	53.18	49.89	55.99	50.31
7	65.46	69.25	62.07	60.64	62.26	65.22	60.54	55.56	50.74	50.24	58.65	56.74	62.45	56.54
8	75.54	74.45	67.65	69.07	67.34	70.67	72.88	64.39	63.84	60.99	64.54	67.56	69.36	67.22
9	86.25	89.74	79.64	76.12	74.53	80.46	83.81	75.73	77.86	72.64	75.64	77.82	79.55	75.78
10	91.12	94.02	85.95	82.50	80.64	90.38	90.09	89.73	88.96	85.74	86.38	89.72	91.12	85.23

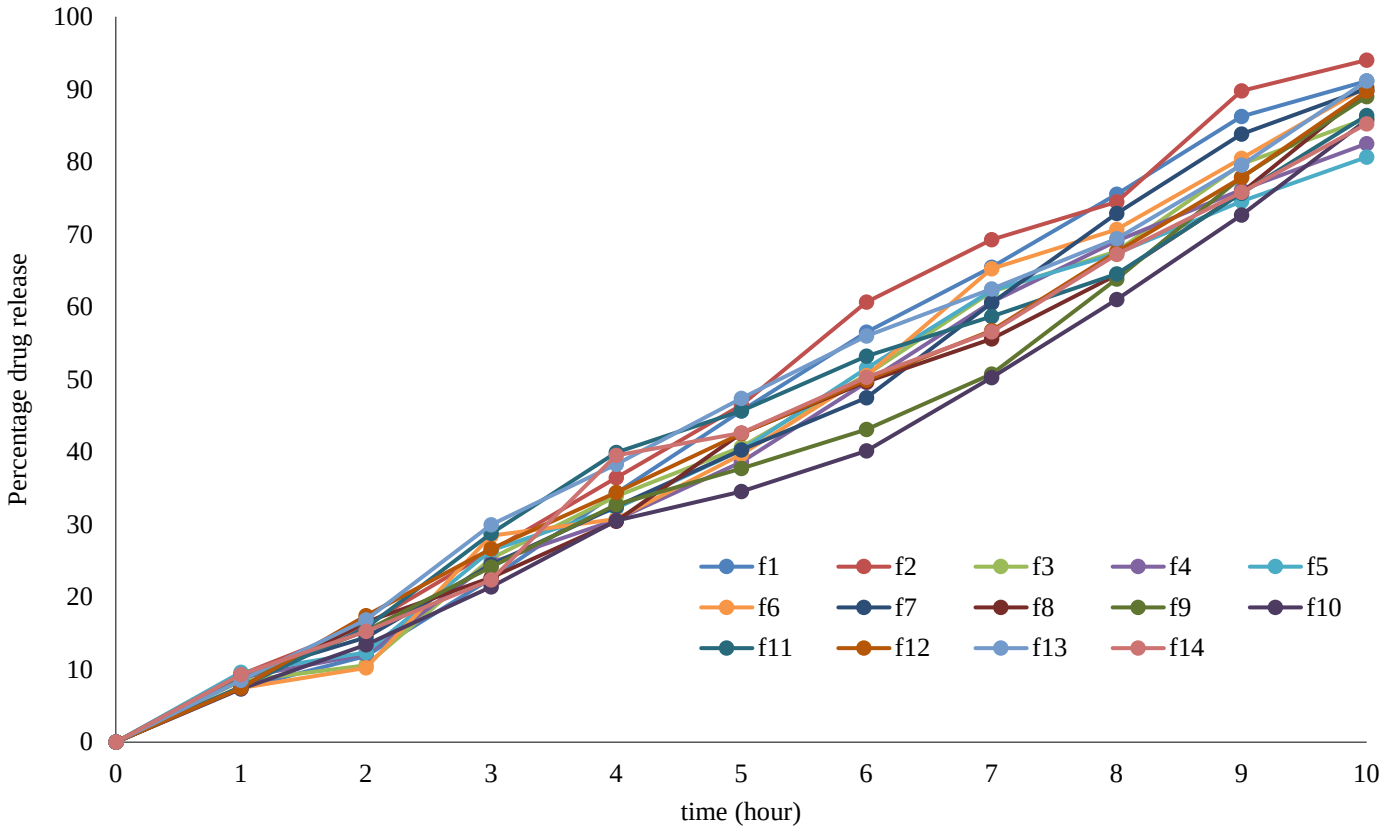

Figure 9: *In vitro* drug diffusion of valacyclovir from various proniosomal gel

Table 6: Kinetics of valacyclovir release from proniosomal gel

Kinetic models	R^2	R^2 Adjusted	SSR	MSC
Zero-order	0.994	0.9948	32.7438	5.047
First- order	0.945	0.9453	315.164	2.705
Higuchi	0.813	0.8131	933.647	1.619
Hixon-Crowell	0.970	0.9707	168.969	3.329
Korsmeyer Peppas	0.995	0.9956	27.2685	5.047

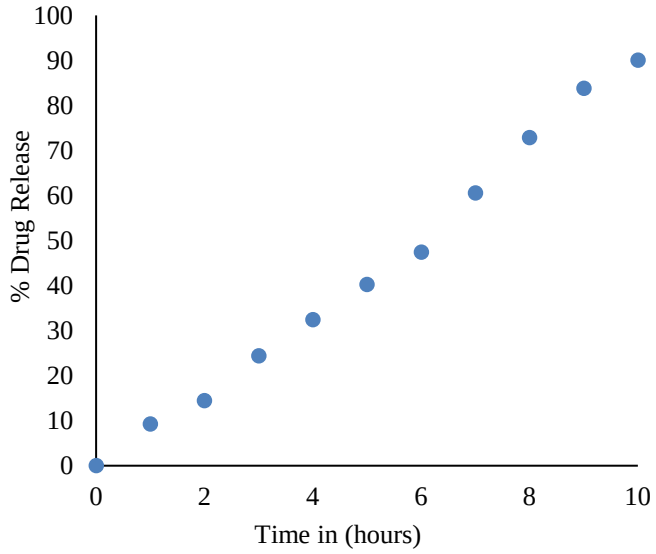

Figure 10: *In-vitro* DR of the optimized formulation (F7)

Stability Study

The optimized formulation was subjected to a stability investigation in compliance with ICH recommendations. Parameters such as vesicle size, viscosity, in vitro drug release, and visual appearance were evaluated. According to a three-month study, the formulation's stability is confirmed by the negligible changes in its viscosity, visual appearance, and in vitro drug release.

CONCLUSION

Proniosomes can enhance drug absorption, increase corneal contact time, and improve permeation and residence time in the eye. It has the potential to be a better form of delivery than conventional drug delivery. Valacyclovir Proniosomes gel was successfully formulated by the coacervation method and evaluated for various in vitro parameters. All the formulations showed controlled drug release. From the above results, it is proven that valacyclovir-loaded proniosomal gels showed higher bioavailability, enhanced permeation based on the permeation study on the goat cornea and prolonged ocular retention. However, the study lacks in vivo data; therefore, the potential of VCV proniosomes gel in animals will be evaluated in further animal studies.

FINANCIAL ASSISTANCE
NIL

CONFLICT OF INTEREST
The authors declare no conflict of interest.

AUTHOR CONTRIBUTION
The research work was done by Nyanbeni Y Kikon under the supervision of Shalu Verma, Nidhi Gairola, Alka Singh, and Tarun Parashar, who provided conceptual guidance, methodological support, critical evaluation of the results, and overall supervision throughout the study.

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