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FORMULATION AND EVALUATION OF MOXIFLOXACIN-LOADED PRONIOSOMAL GEL FOR OCULAR DELIVERY

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ABSTRACT
Background: The management of ocular disorders is particularly arduous due to the eye's distinctive anatomy. The cornea serves as a crucial obstacle to medication absorption, restricting the effectiveness of conventional dosage regimens. To address this issue, a proniosomal gel has been developed, comprising a lipid bilayer that emulates the corneal cell membrane, thereby enhancing drug transport across the cornea and resulting in improved bioavailability. **Methodology:** The Moxifloxacin-loaded Proniosomal gel was developed by the coacervation phase separation method. To determine the physicochemical characteristics of the gel, various evaluation parameters were conducted, including viscosity, pH, FTIR, zeta potential, polydispersity index (PDI), particle size (PS), entrapment efficacy (EE), SEM, and in vitro studies. **Results and Discussion:** The F5 optimized formulation exhibited a maximum EE of 94.47±0.23%, an ideal pH of 6.8, a PS of 105.4 nm, a PDI of 0.3678, and a zeta potential within ±30 mV. *In-vitro* drug release and kinetic studies showed that proniosomal gel followed first-order kinetic characteristics of drug released and a biphasic drug release pattern (There is an initial rapid release of the drug, followed by a slower, controlled release over an extended period). **Conclusion**: Proniosomal gels as drug delivery carriers increased corneal contact, penetration, and retention time in the eye, resulting in sustained action and increased bioavailability.

INTRODUCTION

The eye is a sensitive organ and susceptible to disease. The microorganisms that cause eye infections might include bacteria, viruses, fungi, and even parasites. Infection with such bacteria in the eye may endanger normal eyesight [1]. Since the eye presents several physiological hurdles that limit the delivery of medication to the intended site through the ocular route, the successful administration of pharmaceuticals to the eye remains a significant challenge for researchers. Over the past several years, many novel, safe, and dependable ocular delivery systems have been developed to overcome the obstacles in the eye that limit the bioavailability of medications. These cutting-edge medication delivery technologies are anticipated to have a prolonged effect, significantly increasing efficiency and

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reducing eye-related challenges, thereby enhancing the bioavailability of drugs. Nanotechnology has revolutionized research, leading to the discovery of innovative approaches such as niosomes, liposomes, and Proniosomes [2]. Liposomes are popular drug carriers due to their ability to encapsulate both water-soluble and lipid-soluble drugs; however, their application is hindered by stability issues such as aggregation, fusion, drug leakage, and phospholipid breakdown in aqueous environments.

Niosomes, composed of nonionic surfactants and cholesterol, offer various benefits, including improved stability, ease of production, enhanced solubility, and increased bioavailability. Despite their benefits, niosomes remain susceptible to physical instability over time, including aggregation, leakage, and structural disruption during storage. A more resilient delivery system was required to overcome the instability of conventional vesicular carriers, leading to the development of proniosomes as a promising solution [3]. Proniosomes are an intriguing application of nanotechnology in drug delivery. Among the many developing technologies, proniosomes stand out as a viable platform for delivering a diverse variety of pharmacological agents due to their adaptability, stability, and efficiency [4]. Proniosome-based gel of Terconazole developed and induced by Ahmed et al. serves as a practical option for delivering antifungal agents deep into ocular tissues, offering a promising approach for treating persistent and hard-to-reach fungal keratitis [5]. Likewise, a Proniosome-based gel of Timolol maleate developed and induced by Lokapur et al. served as a promising alternative to conventional eye drops, offering improved penetration and prolonged drug release.

Moxifloxacin hydrochloride is a fluoroquinolone antibiotic used in ophthalmology to treat ocular infections. It is bactericidal and works by inhibiting DNA gyrase and topoisomerase, thereby preventing the replication of bacterial DNA. Moxifloxacin hydrochloride has been studied in several formulations for ocular administration, including eye drops, ointments, inserts, and sustained-release systems. Owing to their patient compliance and convenience of administration, eye drops are the most often used type. There are problems with traditional eye drops, namely their short precorneal residence duration and low bioavailability. The US Food and Drug Administration (USFDA) has authorized Moxifloxacin as a 0.5% w/v (Vigamox®) ophthalmic solution eyedrop for topical ocular application. The main drawback of topical ocular administration is precorneal drug elimination due to nasolacrimal drainage and quick tear fluid turnover [6]. Proniosomes represent a versatile and promising drug delivery system that has garnered significant attention in pharmaceutical research. These innovative vesicular carriers offer a novel approach to improving the delivery of both hydrophilic and hydrophobic drugs [7].

MATERIAL & METHOD

Materials

All chemicals employed were procured from reputable sources and were of analytical quality. Yarrow Chem Products, Mumbai, India, provided moxifloxacin hydrochloride (Moxi). Span 60 was acquired from Loba Chemie Pvt. Ltd., India. L-α-lecithin derived from soybean was procured from a central medicine house in India. Sisco Research Laboratories, India, provided cholesterol. Ethanol (99%) was procured from Changshu Hongsheng Fine Chemical Co., Ltd., India.

Preformulation Studies

Physical Appearance

The organoleptic characteristics of moxifloxacin powder, including colour and Odour, were investigated.

Melting Point

The capillary tube method was utilized to ascertain the melting point. A narrow capillary tube was filled with drug powder, which was then sealed from one side by melting. A thermometer and a capillary were put in a melting point apparatus. After some time at a specific temperature, the drug started melting, indicating the melting point of the drug. The reading was calculated in triplicate for accuracy [8].

Solubility

The method employed for solubility analysis was the shake flask method using a rotary flask shaker. Water was taken as a solvent. This method involves taking a sufficient quantity of the drug and then dissolving it in 25 mL of solvent. The mixture is then placed in a rotary flask shaker at a speed of 70-80 rpm for 3 hours. After saturation, the solution was filtered, diluted, and its absorbance was measured at 292 nm. The test was repeated in triplicate [8].

FTIR Analysis

Compatibility studies between the drug and excipient were conducted using FTIR to ensure that the pharmaceutical used in the formulation meets its pre-defined characteristics and is

compatible with the excipient. Calibrate FTIR using polystyrene film to ensure wavelength accuracy. Perform baseline correction before scanning the sample to eliminate background noise. The drug and excipients were taken in a 1:1 ratio and mixed with KBr in a mortar and pestle, from which pellets were formed using a hydraulic press at a pressure of 10 tons. The range from 400 cm^{-1} to 4000 cm^{-1} was used to scan the produced pellets [9,10].

Method of Preparation of Proniosomal Gel

The proniosomes were formulated by the coacervation phase separation technique. L-α-Lecithin, cholesterol, and surfactant were accurately weighed as listed in Table 1 and transferred to a clean beaker. To the above mixture, 2.5 mL of ethanol was added, and the mixture was stirred on a magnetic stirrer apparatus at 50°C until the lipids were completely dissolved. In the other beaker, the drug was dissolved in phosphate buffer (7.4) and incorporated into the above-molten lipid mixture. The mixture was stirred continuously for 10 minutes until it became a lucid liquid. White, creamy proniosomes were formed after the resulting mixture was allowed to cool for 24 hours at ambient temperature [11,12].

Table 1: Formulation ratio of proniosomal gel of moxifloxacin hydrochloride

Batch	Cholesterol (Mg)	Span 60 (Mg)	Lecithin (Mg)
F1	120	90	80
F2	90	170	80
F3	120	170	60
F4	60	250	80
F5	90	250	100
F6	60	90	80
F7	120	250	80
F8	90	90	60
F9	120	170	100
F10	60	170	60
F11	90	170	80
F12	60	170	100
F13	90	170	80
F14	90	90	100
F15	90	250	60

Ethanol, drug, and pH 7.4 phosphate buffer solution concentration are fixed for each formulation.

Evaluation of Prepared Proniosomes Gel

Entrapment efficacy

The quantity of drug successfully entrapped within the proniosomes can be accurately determined in triplicate (n = 3). Each Proniosome gel sample was centrifuged for 2 hours at 6000 rpm in a centrifuge. After centrifugation, the supernatant was collected in a volumetric flask, diluted if required, and measured spectrophotometrically using Shimadzu (UV 1900i) at 293 nm [13]. The results are expressed as mean ± standard deviation (SD). Entrapment efficiency was calculated using the formula:

$$EE\ (\%) = \frac{Moxifloxacin\ hydrochloride_{Total} - Moxifloxacin\ hydrochloride_{Supernatant}}{Moxifloxacin\ hydrochloride_{Total}} \times 100$$

pH

The pH was measured using a microprocessor pH-mV-Temp meter (Tishcon). The pH was examined by dispersing the electrode in a proniosomal gel, and the pH was recorded in triplicate to ensure accuracy. The compatibility of an ophthalmic formulation with sensitive ocular tissues is directly influenced by its pH. A solution's tolerance is usually higher, and it is less likely to irritate or sting when administered when its pH value is near the physiological pH of the eye, which is approximately 7.4 [14].

Viscosity

The proniosomal gel viscosity was calculated using a Brookfield viscometer using spindle no 4, and the rotational speed was adjusted to 50 rpm at 37°C. The viscosity of an ocular gel determines its flow properties & ease of administration. Higher viscosity formulations may have slower rates of drug release [15].

Zeta potential / Particle size & Polydispersibility Index (PDI)

The proniosomal gel zeta potential, polydispersity index, and particle size were measured using a Malvern zeta sizer. The formulation was diluted with phosphate buffer (pH 7.4) & agitated until a stable, homogeneous mixture was obtained. High oppositely charged forces between particles inhibit aggregation; hence, a greater zeta potential value indicates stability. A zeta potential of ±30 mV or greater is frequently recommended for stability. PDI measured size distribution homogeneity. Lower PDI indicates a narrow size range & increased homogenous particle sizes [16].

***In-vitro* drug release**

A Franz diffusion cell was used to perform an in vitro drug release study. The egg membrane was isolated using hydrochloric acid. The egg membrane placed between the donor and receptor compartments contained 2 ml of proniosomal gel. The temperature in the receptor compartment was controlled at 37°C. Samples were collected at hourly intervals for 8 hours and analyzed spectrophotometrically at 293 nm [17,18].

Release kinetics of the drug

The kinetics of drug release were determined using the DD solver software. DD Solver is a tool designed to simulate the kinetics of drug release using mathematical models. Model selection is generally based on statistical indicators such as the coefficient of determination (R^2), which measures the goodness of fit, along with other parameters like the Akaike Information Criterion (AIC). A smaller AIC value signifies a better balance between model fit and complexity. Based on the input data, the model with the highest R^2 was selected as the best fit for the generated formulation [19–21].

Surface morphology

The SEM study involves converting the proniosomal gel into a dry powder, which is then placed on a sample holder and subsequently coated with a conductive metal, either through sputter coating with gold or a gold-palladium alloy. The coating mitigates charging effects during SEM investigation. Adjust the voltage and beam current to the optimal levels for the gel being analyzed [11,22].

RESULT AND DISCUSSION

Pre-formulation parameters: Physical Properties

The Physical properties of Moxifloxacin hydrochloride were determined using organoleptic properties, and it was found to be light yellow in colour with no odour present in it.

Melting Point

The observed melting point of moxifloxacin was found to be 240°C, which is similar to the standard melting point of the drug.

Solubility

The sample was qualitatively analyzed for solubility in various solvents, including water and ethanol. The solubility is found to be 22.03 ± 0.82 mg/mL in water and 0.89 ± 0.07 mg/mL in ethanol. The result revealed that the drug is more soluble in water than in ethanol.

FTIR

The FTIR spectrophotometer was used to scan the pellets between 4000 and 400 cm^{-1}. The infrared spectra of the drugs, the physical mixing of the drug with excipients (including cholesterol, lecithin, and surfactant), and the optimized formulation F5 were compared, as shown in Figure 1. FTIR spectra of pure drug showed characteristic peak at 1045 cm^{-1}, 1454 cm^{-1}, 1624 cm^{-1}, 1702 cm^{-1}, 2424 cm^{-1}, 2524 cm^{-1}, 2941 cm^{-1}, and 3528 cm^{-1} indicating CH_2 bending, CH bond, C=O, NH_2, C-H, and O-H stretching. The FTIR spectra observed in the pure drug were also recognized in the physical combination and optimized formulation, indicating no apparent interaction between the drug and the excipients [15,23].

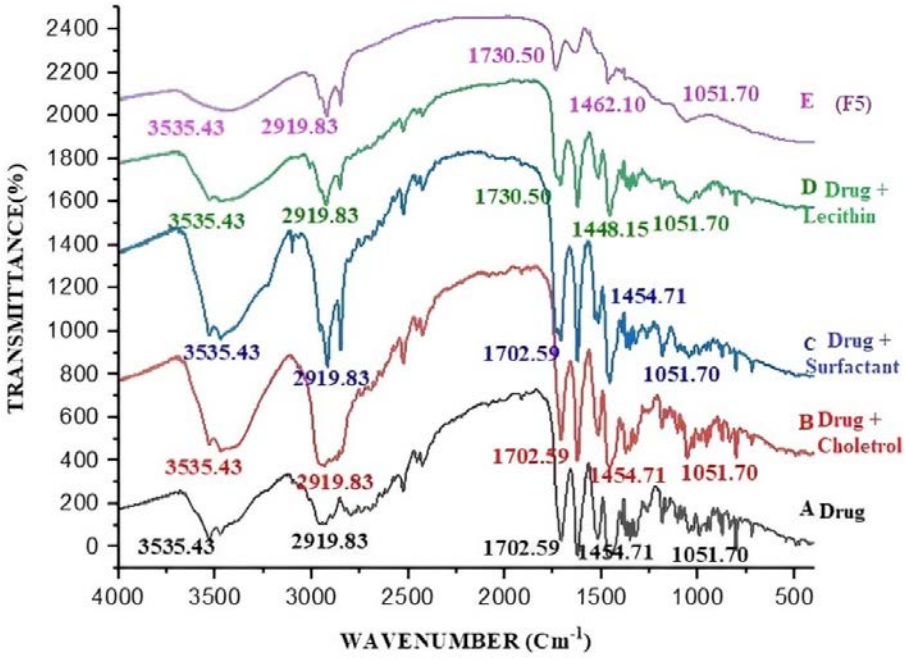

Figure 1: FTIR Spectrum representing the drug-excipients compatibility study and optimized formulation. (A) Drug, (B) Drug and Cholesterol, (C) Drug and Surfactant, (D) Drug and Lecithin, (E) Optimized Formulation (F5).

Evaluation of prepared proniosomes gel

Entrapment Efficiency

The entrapment efficiency (EE) of all 15 formulations ranged from 51.98 ± 0.33% to 94.47 ± 0.23%. Statistical analysis was conducted using one-way analysis of variance (ANOVA) and subsequently Tukey's post-hoc multiple comparison test to validate the observed variations in EE. The ANOVA results revealed a highly significant difference across the formulations ($F(14, 30) = 1395.13$, $p < 0.001$), indicating that the differences in EE were statistically significant. Post-hoc analysis revealed that formulation F5 had a considerably greater EE ($p < 0.05$) than the majority of other formulations. Only formulations with closely identical EE values, such as F11 & F15, exhibited no significant change. The results unequivocally demonstrate the enhanced encapsulation capability of F5, validating its designation as the optimum formulation. Table 2 represents the results of pH, viscosity, and entrapment efficacy of all formulations [24].

Table 2: Results of pH, viscosity & entrapment efficacy(EE)

Batch	pH Range	Viscosity (cps)	EE (%)
F1	6.5	10.3	66.03±0.59
F2	6.8	8.04	90.6±0.65
F3	6.5	10	75.01±0.42
F4	7.1	10.1	78.08±0.49
F5	6.8	12	94.47±0.23
F6	7.1	11.6	62.15±0.24
F7	7.6	12.2	89.74±0.5
F8	6.5	6.3	51.98±0.33
F9	7.6	15.6	54.29±0.07
F10	6.2	8.9	65.03±0.44
F11	7.6	12	91.03±2.8
F12	6.8	9.08	82.20±0.11
F13	7.1	10	86.02±0.29
F14	7.8	8.6	81.52±0.49
F15	6.5	12	92.59±0.26

Viscosity

The flow index (n) value of Moxifloxacin-loaded proniosomal gel was found to be less than one, indicating non-Newtonian shear thinning behaviour. This was determined by utilizing the power law model. According to the research studies [25].Semi-solid systems with nanocarriers typically exhibit pseudoplastic behaviour. The pseudoplastic behavior of the generated gel results from the combined effects of Brownian motion and shear-induced alterations, which intensify with increasing shear stress. Reduced viscosity occurs as polymer molecules orient their long axes in the flow direction with increasing shear stress [25]. When viscosity is high, the movement of drug-loaded vesicles and water molecules becomes limited, reducing the drug's diffusion coefficient. Consequently, the drug diffuses more slowly from the gel matrix into the tear fluid, resulting in a sustained and prolonged release. Thus, selecting the right viscosity range is vital to ensure that ocular proniosomal gels maintain therapeutic efficacy without compromising patient convenience.

pH

The pH of the ophthalmic preparation is critical for patient adherence. According to research studies, a pH range of 6.5 to 8.5 is acceptable for use without endangering the cornea. The pH value was in the range of 6.5 to 7.8 for all formulations, confirming its suitability for ocular application [26]. Khalil RM et.al. formulated lomefloxacin HCl proniosomal gel for ocular delivery. The pH of the optimized formulation was found to be 7.12 ± 0.4. In vivo studies establish that lomefloxacin HCl proniosomal gel demonstrated no ocular irritation or inflammation in rabbit models, confirming its safety profile [27]. Similarly, Eldeeb et.al. formulated brimonidine-tartrate proniosomal gel for ocular delivery, and in vivo pharmacodynamic studies in albino rats showed that the proniosomal gel showed no ocular irritation as assessed by the Draize test [29].

Zeta Potential

The zeta potential study suggests that the sizes of the produced vesicles are relatively heterogeneous. The magnitude of ZP shows the stability of the formulation. The ZP of the optimized proniosomal gel was found to be −29.87 mV, as shown in Figure 2 (A) below. Due to the free hydroxyl groups on the surfactant and cholesterol molecules, every proniosome surface is negatively charged. At neutral pH, lecithin's phospholipids contribute to its negative charge. The significant negative surface charge on particles predicts higher stability due to repulsive forces between particles of the same charge, thereby limiting the aggregation of colloidal particles.

According to the zeta potential result of the developed formulation, the particles remain suspended and are therefore considered stable. The particles have been suspended. It was shown that the formulation worked incredibly well when administered parenterally [16,28]. Due to the possibility of tear film and ocular epithelial membrane disruption, a high positive zeta potential can raise the risk of irritation. On the other hand,

certain proniosomal or niosomal systems have substantially negative zeta potential values, which provide good colloidal stability through electrostatic repulsion and decreased aggregation [31].

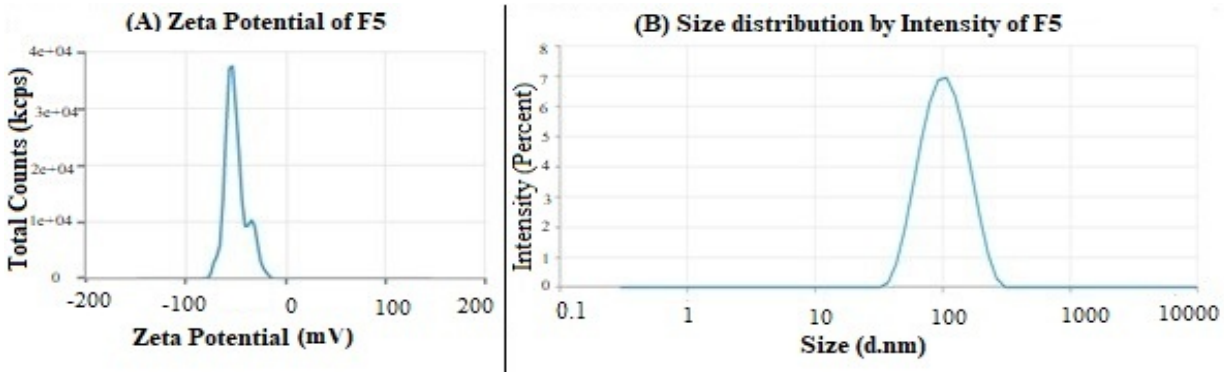

Figure 2. (A) Zeta potential of optimized formulation (F5) and (B) Particle size and PDI of optimized formulation (F5)

Particle size and Polydispersibility Index (PDI)

The particle size and PDI value of the optimized formulation F5 were found to be 105.4 nm and 0.3678, respectively, indicating significant dispersion and consistency of particle size within the formulation, as shown in Figure 2(B). The particle size of proniosomes was considerably influenced by the content of cholesterol, lecithin, charge incorporation, and the hydrophobicity of surfactants. Proniosomes' larger vesicles produced a high concentration of lecithin, which is less hydrophobic than Span 60. Increasing the span 60 increases hydrophobicity, thereby reducing vesicle size. The particle size increased significantly as cholesterol levels increased. All formulations have low polydispersity [4].

In vitro Release Study

The *in-vitro* release study was evaluated using the membrane diffusion technique. The release study was conducted over 10 hours. Proniosomes are widely recognized for their effective drug-release vesicles, characterized by a distinct biphasic pattern. Within the initial 2 hours, a rapid release (burst) of the drug occurred from the gel due to the drug's attachment to the surface of the surfactant. Later, the drug release was in a sustained pattern due to entrapment of the drug inside the vesicles. The longer alkyl chains, high transition temperatures, and low HLB improve drug entrapment, which in turn produces a more prolonged profile. Span 60-based formulation (proniosomal gel) showed prolonged release behavior. Span 60's strong hydrophobic properties and low HLB (~4.7) provide densely packed bilayers. Bilayer fluidity and drug leakage are further reduced by the hydrophobic tail length, which significantly strengthens van der Waals connections between surfactant molecules, guaranteeing long-term ocular retention and sustained release [32]. According to the results obtained, F5 showed the best sustained drug release. The initial release of the drug after 2 hours was found to be in the range of 22.32±0.03 to 60.84±0.49%, and the release of the drug after 10 hours was found in a range of 53.02±0.32% to 93.75±0.51%, as shown in Figure 3. The finding of the study reveals how the amount and type of surfactant, cholesterol, and lecithin influence the release of the drug from the gel [21,30].

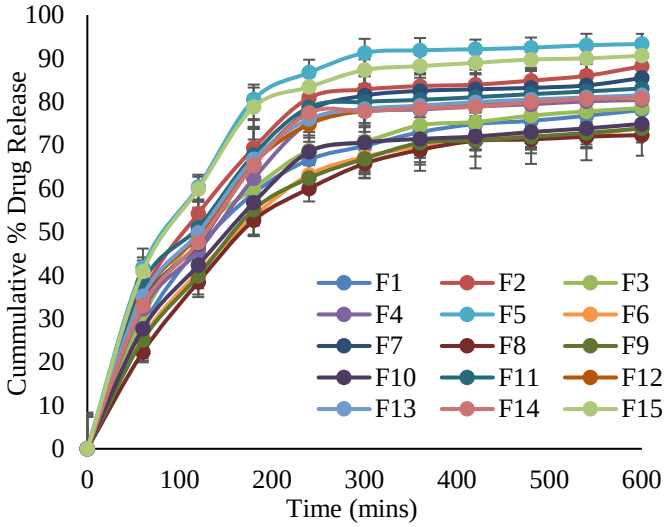

Figure 3: In vitro Release of Formulations F1 to F15

Drug Release Kinetics

The kinetics of drug release were examined for various kinetic models. The determination of R^2, R^2 Adjusted, and R^2 Predicted values indicates that the formulations follow a first-order kinetic model, which suggests that the release is diffusion-controlled from the proniosomal gel, as shown in Table 3. A greater R^2 value indicates an improved correlation between observed and predicted data. This suggests that the Fickian diffusion transport mechanism governs gel formulation release, that is, $n<0.5$ [21].

Surface Morphology

The SEM was performed on the optimized formulation F5 to verify the morphology at different magnifications, as shown in Figure 4. The proniosomal vesicles were found to be spherical vesicles, having smooth surfaces with no formation of aggregates at magnification at 2.00 k x and 10.00 k x; scale bar 100 nm and 20 nm, respectively [2,4].

Table 3. Kinetic Modelling of Formulation F5

Kinetic Model	R^2 Predicted	R^2	R^2 Adjusted	AIC
Zero-order	0.8039	0.119	0.1195	100.6
First order	**0.9950**	**0.982**	**0.9826**	**57.49**
Higuchi	0.9356	0.829	0.8292	82.61
Korsmeyer Peppas	0.9739	0.948	0.9425	71.47
Hixson Crowell	0.9907	0.955	0.9554	67.83

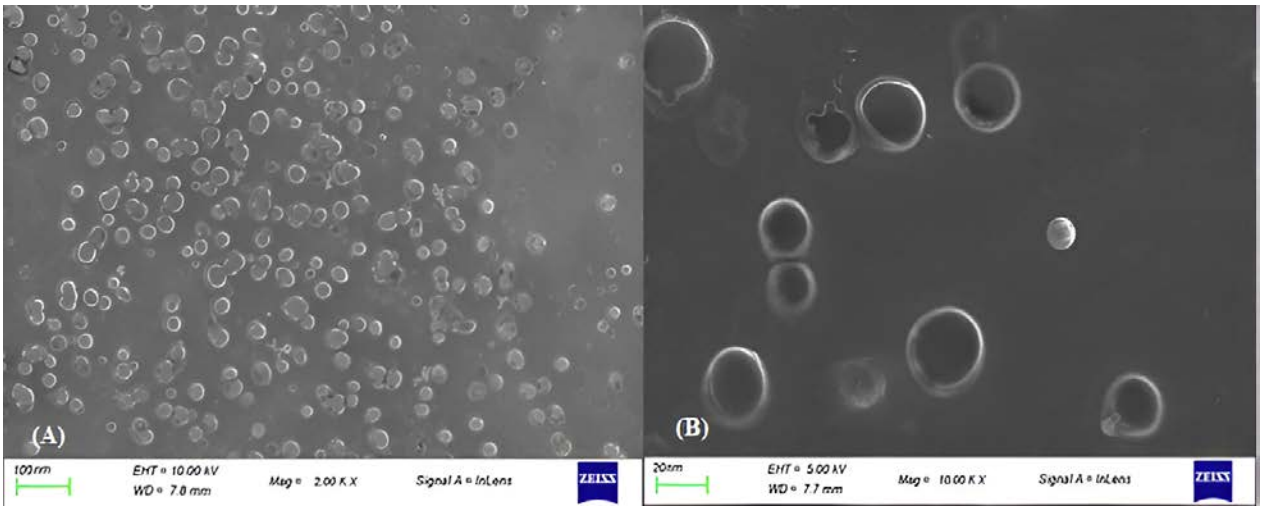

Figure 4: SEM Analysis of proniosomal gel (F5) (A) SEM spherical vesicle image at 2.00 kx magnification. (B) SEM surface morphology image at 10.00 kx magnification.

CONCLUSION

The optimized moxifloxacin-proniosomal gel (F5) achieved a high entrapment efficiency (94.47±0.23%). It sustained in vitro release (93.75±0.05% over 10 h), with excellent stability, retaining its particle size, zeta potential, and drug content during three months of storage. The pH (6.5–7.8) and zeta potential (−29.87 mV) supported ocular tolerability, while Span 60's low HLB and high hydrophobicity contributed to tight bilayer packing, reduced permeability, and prolonged drug retention.

In conclusion, proniosomes are promising platforms for ocular medication delivery. These dry formulations contain surfactant and carrier substances. For developing innovative ocular therapeutics, the capacity of proniosomes to increase medication absorption & retention in the eyes, along with their ease of handling and stability, makes them an appealing option. These are commonly used to deliver antibiotics, anticancer medicines, and anti-inflammatory agents. In addition to pharmacodynamic evaluations, such as anti-inflammatory efficacy, therapeutic onset & and intraocular pressure modulation, future research should incorporate thorough pharmacokinetic studies, including precise aqueous humor concentration time curves, half-life, and tissue distribution. For this formulation to be used in clinical ophthalmic applications, further research and in vivo studies will be necessary.

FINANCIAL ASSISTANCE

NIL

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Neha Kandpal, Kumari Kajal, and Saurav Chamoli contributed to the experimental work done in the manuscript. They also contributed to writing the first draft of the manuscript. The manuscript was reviewed and supervised by Yogita Ale. Mansi Butola supported the research work and assisted with data collection and the literature review.

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