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**Research Article**

# Formulation, Optimization and Evaluation of a Ribavirin-Loaded Liposomal Emulgel for Targeted Topical Antiviral Delivery

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**ABSATRACT**
The skin's stratum corneum act as major barrier and to overcome it while reducing the systemic toxicities associated with conventional dosage forms, this study is aimed to develop, optimize and evaluate a novel ribavirin-loaded liposomal emulgel for localized antiviral therapy minimizing systemic exposure. Ribavirin-loaded liposomes were prepared using a thin-film hydration technique and optimized using a Central Composite Design (CCD) to assess the effects of phospholipid and cholesterol concentrations on drug encapsulation and release. After optimization an ideal formulation contained 741.5 mg of phospholipid and 201.6 mg of cholesterol, which yielded a high entrapment efficiency of 82.3±0.38% and a cumulative in vitro release of 83.4±0.33% over 12h was selected. Scanning electron microscopy (SEM) revealed a smooth, spherical vesicular morphology with a zeta potential value of −35 mV, indicating good colloidal stability.an emugel was prepared by combining these optimized liposomes into a Carbopol 934. The resulting emulgel exhibited good dermatological properties, with a skin-compatible pH of 5.9±0.10, a viscosity of 12,580±0.79 cP, and a spreadability of 7.86±0.12 g·cm/s. The emulgel exhibited linear, zero-order release kinetics (83.52±0.62% over 420 min) and ex vivo skin permeation studies using excised goat skin showed good dermal retention with minimal flux into systemic circulation. These results show that the developed carrier system successfully crossed the epidermal barrier to establish a controlled therapeutic reservoir within target tissues, giving a stable and efficient formulation for the localized antiviral thrapy.

**Keywords:** Ribavirin, Liposomes, Emulgel, Carbopol 934, Thin-film hydration, localized antiviral therapy, optimize.

## INTRODUCTION

Cutaneous viral infections remain a significant clinical concern because of their frequent recurrence and their negative effect on patient quality of life. Although systemic antiviral therapy is widely used, oral and injectable dosage forms may produce variable drug exposure and undesirable adverse effects [1]. Topical drug delivery offers a good alternative for localized dermatological conditions, by increasing the accumulation of therapeutic drugs directly at the active site, reducing systemic exposure and its toxicities [2, 3]. Due to the skin's anatomy, effective topical delivery is restricted despite the advantages and to overcome this brick-and-mortar barrier, research has shifted toward advanced nano-carrier platforms to enhance dermal deposition, and provide controlled drug release [4].

Ribavirin-a synthetic, broad-spectrum antiviral nucleoside analogue possessing established efficacy against; a wide range of RNA and DNA viruses and its multi-mechanistic antiviral action were by[5]: inhibition of inosine monophosphate dehydrogenase (IMPDH) competitively, depletion of guanosine triphosphate (GTP) pool inside the cell, and the induction of lethal mutagenesis during viral RNA replication [6]. So, developing a localized delivery system is therefore essential to safely harness its therapeutic potential.

Encapsulating a hydrophilic molecule like ribavirin within liposomes protects the payload from enzymatic degradation, minimizes premature systemic clearance, and establishes a localized drug depot within the viable dermal layers [7] [8].

Due to the rheological limitation, incorporating liposomes into an emulgel matrix offers a advanced solution [9]. Emulgels combines the advantages of both emulsions and hydrogels, giving good spreadability, bio adhesion, a non-greasy texture, and along with considerable thermodynamic stability [10]. A combination of liposomes in an emulgel function as a dual-control delivery system: the gel matrix delivers macro-transport and skin retention, while the encapsulated liposomes control micro-permeation and sustained release of drug [11].
The present study mainly focuses to design, statistically optimize and evaluate a novel ribavirin-loaded liposomal emulgel for localized topical therapy [12].

## MATERIALS AND METHODS

### Determination of λmax and preparation of calibration Curve

Ribavirin was analysed using a UV–Visible spectrophotometer. The wavelength at which maximum absorption take place was determined in acetate buffer (pH 5.5), and calibration curve using standard solutions within the selected concentration range was prepared and recorded at 210nm [13].

### Drug- excipient compatibility study

Compatibility between ribavirin and formulation excipients was assessed by FTIR (Fourier-Transform Infra-red) spectroscopy. Distinctive peaks of the pure drug, excipients, and their physical mixture were compared to identify any evidence of chemical interaction [14].

### Preparation of ribavirin loaded liposomes

Ribavirin-loaded liposomes preparation was done using thin-film hydration technique. Phospholipid and cholesterol in different ratios (Table 1) dissolved using chloroform: ethanol (2:1 v/v) solvent mixture, after which the solvent was evaporation under reduced pressure to produce a thin film on the bottom of the flask. The dried film was hydrated with ribavirin solution, sonicated to obtain a uniform dispersion, and centrifuged to remove unentrapped drug before further characterization. [15, 29].

Table 1: Formulation Design of Ribavirin Loaded Liposome

| Formulation | DRUG (mg) | Phospholipid (mg) | Cholesterol (mg) | Chloroform:ethanol (2:1) (mL) |
|---|---|---|---|---|
| F1 | 100 | 500 | 100 | 15 |
| F2 | 100 | 700 | 100 | 15 |
| F3 | 100 | 500 | 300 | 15 |
| F4 | 100 | 700 | 300 | 15 |
| F5 | 100 | 458.6 | 200 | 15 |
| F6 | 100 | 741 | 200 | 15 |
| F7 | 100 | 600 | 58.6 | 15 |
| F8 | 100 | 600 | 341.4 | 15 |
| F9 | 100 | 600 | 200 | 15 |

### Evaluation of prepared liposomes

### Entrapment Efficiency (EE%)

To quantify the encapsulation of ribavirin, the free drug was separated from the liposomal dispersion by centrifuging at high speed, then; using UV-Visible spectrometry the free ribavirin in the supernatant was determined. The entrapment efficiency (EE%) was found by the equation [16]:

$$\boldsymbol{Entrapment\ efficiency}(\%) = \frac{\boldsymbol{Total\ drug - Actual\ drug}}{\boldsymbol{Total\ drug}} \times \mathbf{100}$$

### Liposomal Drug Content

Spectrophotometrically, the drug content of the ribavirin-loaded liposomes was determined. A quantity of liposomal dispersion (equivalent to a known theoretical amount of ribavirin) was measured; mixed with ethanol to disrupt the lipid vesicles and release the entrapped drug into ethanol then; using acetate buffer (pH 5.5) the volume was adjusted and mixed. After filtration, an appropriate quantity of the filtrate was diluted with the same and analyzed at 210 nm. The drug concentration was found using a standard calibration graph, and the percentage calculated as follows [17]:

$$\boldsymbol{Drug\ content\ of\ liposome}(\%) = \frac{\boldsymbol{Theoretical\ amount}}{\boldsymbol{Calculated\ amount}} \times \mathbf{100}$$

### Drug Release studies*; In Vitro*

The invitro release of ribavirin from the liposomes was found using the Franz diffusion cell method with an eggshell membrane as the dialysis barrier. A volume of the liposomal dispersion was introduced into the donor compartment, while acetate buffer (pH 5.5) filled in the receptor compartment with a steady temperature at 37°C under continuous stirring., volumes of buffer were withdrawn from the receptor medium at predetermined times, changing with same volume of fresh buffer, and analyzed using UV-Vis spectra. The drug release; cumulative percentage was calculated & graph was plotted against time [18].

**Formulation Optimization via Design of Experiments (DoE)**

A computer-aided optimization using a response surface methodology was executed via Design-Expert® software (Stat-Ease Inc.). A Central Composite Design (CCD) was selected to investigate the effects of two independent variables: phospholipid concentration and cholesterol concentration. Drug entrapment efficiency and drug release; *in vitro* were defined as the critical quality attributes (responses). A total of 13 experimental runs were generated. Statistical validation, contour plot analysis, and optimization were done to identify the optimized formulation variables on predetermined constraints [19].

**Characterization of the Optimized Liposomes**

The optimized liposomes were comprehensively characterized for its surface morphology, average particle size, polydispersity index (PDI), and zeta potential [20].

**Preparation and Evaluation of Liposome-Loaded Emulgel**

**Preparation of Liposome-Loaded Emulgel**

The liposomal emulgel was prepared first by gel base preparation- by hydrating Carbopol 934 in purified water for 24h. Seperately, oil-in-water emulsion was separately prepared by heating the liquid paraffin and Span 80 as oil phase and Tween 80, propylene glycol, methylparaben, and water as aqueous phase to 70–75 °C, followed by gradual mixing with continuous stirring and cooling to $25^0$C. Triethanolamine was used to neutralized the hydrated Carbopol gel, after which the incorporation of optimized ribavirin-loaded liposomal dispersion was done gently, to preserve vesicle integrity. Finally, the liposomal gel was blended with the emulsion to obtain a uniform liposomal emulgel, which was stored in airtight containers until further evaluation. [21].

Table 2: Formulation Table for 1%w/w Liposome Loaded Emulgel

| Ingredients | Quantity |
|---|---|
| Ribavirin loaded liposomes | Equivalent to 100mg ribavirin |
| Carbopol 934 | 1g |
| Liquid paraffin | 5g |
| Span 80 | 1g |
| Triethanolamine | q.s |
| Purified water | q.s to 10g |

**Evaluation of Liposome-Loaded Emulgel**

**Homogeneity and Physical Appearance**

Physicochemical properties of the liposomal emulgel was evaluated and Visual inspection was carried out to assess colour, consistency, homogeneity. 1 g of the formulation was mixed with 10 mL of distilled water and recorded the value using a digital pH meter; previously calibrated for pH measurement. Viscosity; determined at room temperature using a Brookfield viscometer by measuring the resistance of the formulation to spindle rotation under suitable operating conditions. Triplicate measurements were performed, and the mean values were recorded. [22], [23],[24].

**Spreadability**

The ease of topical application was assessed by evaluating the spreadability. A parallel-plate method was employed, in which a measured amount of emulgel; placed between two horizontal glass slides with a known weight applied to the upper slide. The time taken (in seconds) for the upper slide to travel a designated distance (in centimetre) under a constant load (gram) was recorded; calculated by the standard formulation [25]:

$$S = \frac{M \times L}{T}$$

Where:

S = Spreadability (g·cm/s)
M = Weight above the upper slide (g)
L = Length the slide moved (cm)
T = Time taken for slide to move (s)[23]

**In Vitro Drug Release Study**

Using a Franz diffusion cell, drug release kinetics of the emulgel were evaluated. A semi-permeable barrier (dialysis membrane or prepared eggshell membrane) was positioned between the donor and receptor compartments. The receptor chamber filled with Acetate buffer (pH 5.5), at 37°C, with continuous stirring to ensure sink conditions. A weighed quantity of the emulgel formulation was placed in the donor compartment and at scheduled time periods, volumes from the receptor medium were withdrawn, replacing with an equal of fresh buffer. Withdrawn sample analysed with UV–Visible spectrophotometry. The drug release; cumulative percentage was calculated and plotted against function of time [26].

**Skin Permeation and retention study; *Ex Vivo***

Skin permeation and retention; evaluated *ex vivo* study using a Franz diffusion apparatus fitted with goat skin obtained from a local registered slaughterhouse. The skin was carefully prepared, shaved, and placed between the compartments, with the stratum corneum faced on the donor chamber. Acetate buffer (pH 5.5) filled the receptor compartment and kept under constant stirring at 37°C. A known amount of the emulgel formulation was applied to the donor chamber & samples from the receptor chamber at intervals were withdrawn, replaced with fresh buffer, and quantified using UV to calculate the amount of ribavirin entered per unit area over time [27,28].

## RESULT AND DISCUSSION

**Calibration curve**

Calibration curve drawn over a concentration of 2–10µg/ml showed strict following of the Beer-Lambert law (R2>0.999), giving a reliable basis for remaining quantitative assessments (Figure 1).

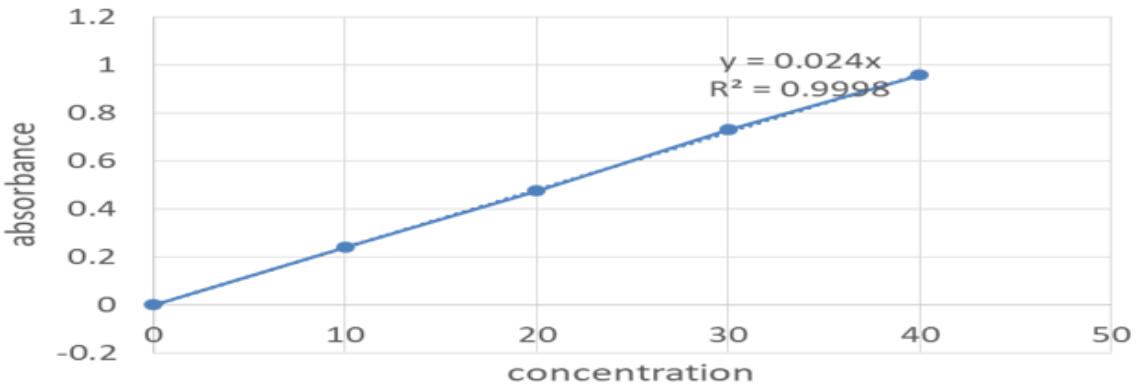



Fig. No.1; calibration curve of Ribavirin in Acetate buffer (pH 5.5)

**Drug–Excipient Compatibility (FTIR)**

Fourier-transform infrared (FTIR) spectrum (Figure 2) confirmed the compatibility between the drug and selected excipients. The IR bands of ribavirin, like the O-H/N-H stretching and C=O amide stretching, remained unchanged in the physical mixture with phospholipids and cholesterol. The lack of spectral shifting or new band appearance confirms the absence of chemical interactions, showing the structural integrity of the formulation components.

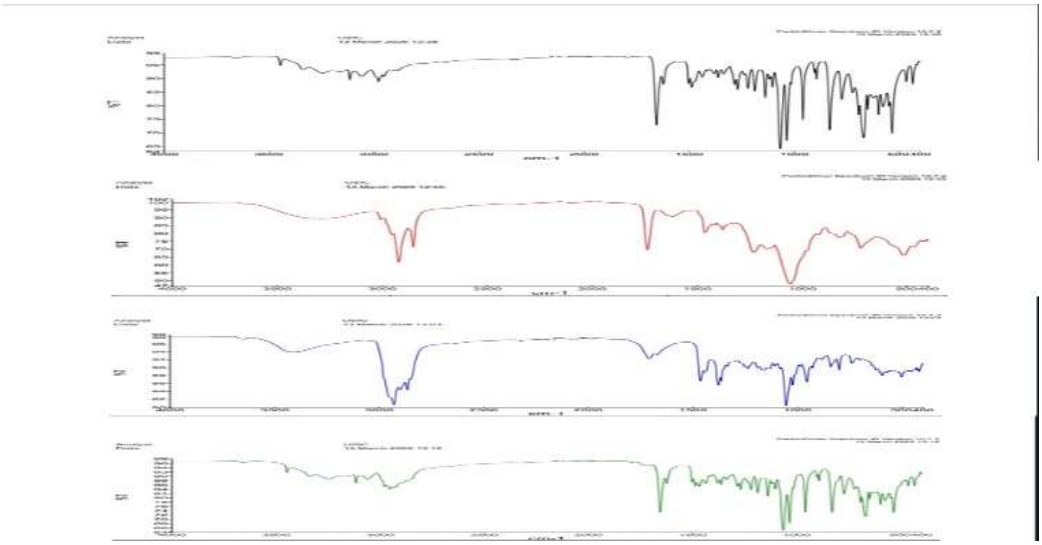


Fig No. 2. Report of FTIR of Ribavirin, Phospholipid, Cholesterol, and Mixture Compatibility

**Evaluation of Ribavirin Liposomes**

**Drug Content and Entrapment Efficiency (EE%)**

Drug content values were ranging from 48.5±0.11% to 82.8±0.03%, while the entrapment efficiency was from 49.5±0.69% to 83.1±0.79% for the prepared liposome formulations ; F1–F9

This is the same as vesicular formulation theories in which the optimal cholesterol minimizes fluidization induced drug loss.

**Drug Release studies; In Vitro test of Liposomes**

The *in vitro* data for all $F_1$-$F_9$ batches over a 12 hr period are given in figure.3 .

In this F6 achieved the highest drug release (83.4±0.33% at 12 hr). The release curves showed a biphasic sustained profile for all the batches. Initially faster release phase was obtained which was followed by a controlled, slower release phase. This confirms that an optimized phospholipid-to-cholesterol ratio balances bilayer elasticity with structural retention, preventing premature leaks by bursting while ensuring steady diffusion over extended durations.

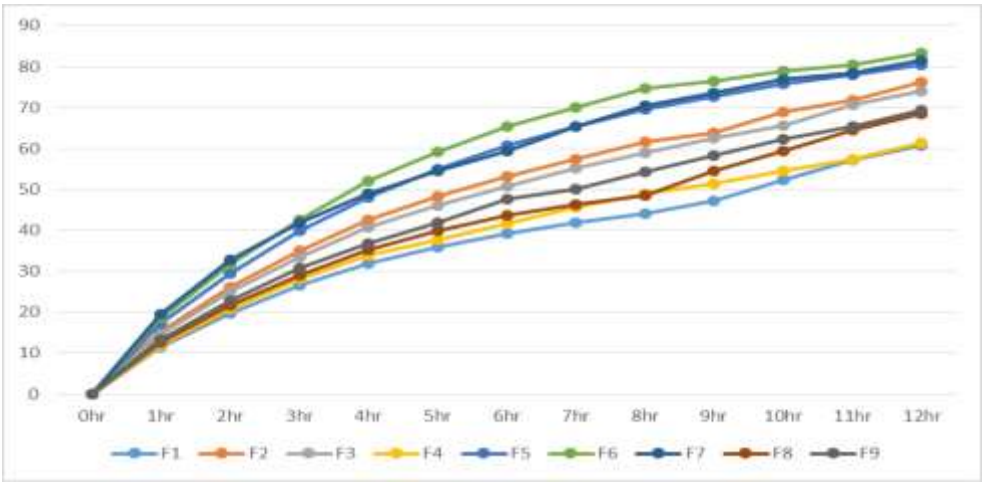



Fig no. 3 in vitro Release Data of Liposomes Formulation $F_1$ to $F_9$

**Formulation Optimization via Design-Expert®**

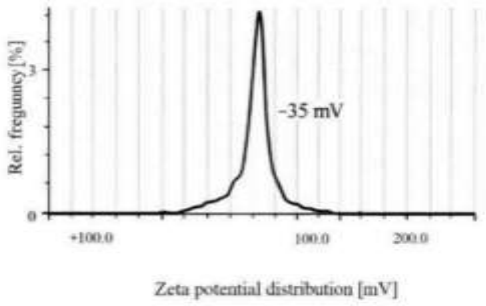
A Central Composite Design (CCD) was employed to systematically model and evaluate the effects of phospholipid and cholesterol levels on vesicle traits, optimization identified the definitive parameter criteria based on the responses entered for entrapment percentage and in vitro release

The formulation with 741.5 mg of phospholipid and 201.6 mg of cholesterol, with a maximum desirability score of 1.0 was established as

optimized. This composition corresponds closely with the experimental performance obtained in F6, which was chosen as the vehicle for the topical emulgel system.

**Characterization of the Optimized Liposome Formulation**

Surface morphology analysed with scanning electron microscopy (SEM) showed the optimized liposomes were uniform, and spherical, with nice boundary definition. A charge value of −35 mV was obtained as Zeta potential after analysis shown in Figure 4 &5.




| Result | | | |
|---|---|---|---|
| Mean zeta potential | -35 mV | Mean intensity | 785.7 k counts/s |
| Standard deviation | 0.6 mV | Filter optical density | 3.3047 |
| Distribution peak | -35.9 mV | Conductivity | 0.061 m S /cm |
| Electrophoretic mobility | -2.47 µm*cm/Vs | Transmittance | 70.3 % |

Figure 4: Zeta potential of optimized liposome formulation $F_6$

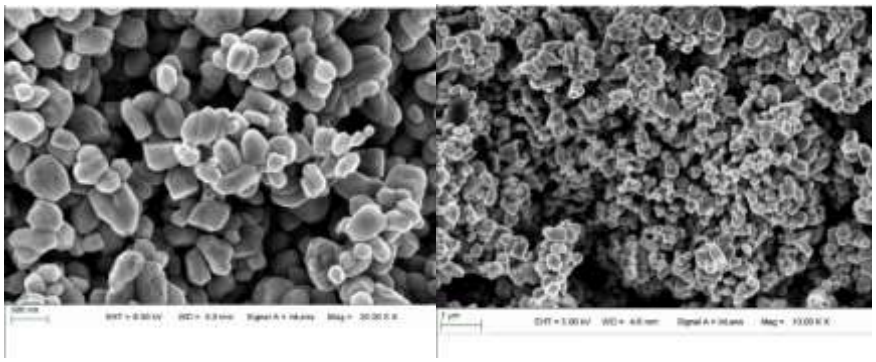


Figure 5: SEM Imaging of Optimized Liposome Formulation $F_6$ at 25x and 50x

**Evaluation of Liposome-Loaded Emulgel Physicochemical Characteristics**

Physicochemical evaluation of the liposomal emulgel was conducted and the formulation exhibited a pH value of 5.9±0.10, which was within the physiological range for human skin (4.5–6.0), reducing the chance of topical irritation. The viscosity was measured at 12,580±0.79 cP and the spreadability properties was measured at 7.86±0.12 g·cm/s. These results ensures comfortable application and reliable retention on the skin surface.

**In Vitro Release of Emulgel Matrix**

The cumulative drug release from the liposome-loaded emulgel matrix was found to be at 83.52±0.62% in a time of 420 min.

The emulgel followed a **zero-order release kinetics** after Mathematical modeling of the release data was done indicating the drug release rate remains constant over time and independent of the remaining drug concentration.

**Ex Vivo Skin Permeation and Retention Profile**

The *ex vivo* skin permeation study across excised goat skin showed minimal drug concentrations in the receptor medium, with

the majority of the active ribavirin successfully retained within the dermal tissue layers.

The optimized ribavirin-loaded liposomal emulgel demonstrated significantly higher skin drug retention in skin sample A ; ribavirin liposome loaded emulgel (57.34 ± 1.30%) compared with the sample B; plain ribavirin gel (12.48 ± 0.84%).

## DISCUSSION

The incorporation of ribavirin into liposomal vesicles followed by dispersion into a Carbopol-based emulgel provided a dual-delivery platform capable of improving drug localization, sustained release, and dermal retention.

Central Composite Design (CCD) was an effective statistical tool for optimization of the liposomal formulation. The concentrations of phospholipid and cholesterol significantly influenced vesicle characteristics, drug encapsulation efficiency, and drug release behavior. The optimized formulation containing 741.5 mg phospholipid and 201.6 mg cholesterol exhibited a high entrapment efficiency of 82.3 ± 0.38%, indicating efficient incorporation of ribavirin within the lipid bilayer. Excess cholesterol beyond the optimized level may reduce encapsulation by increasing membrane rigidity, while insufficient cholesterol can compromise vesicle stability.

The optimized liposomes demonstrated a cumulative drug release of 83.4 ± 0.33% over 12 hours, indicating a controlled and sustained release profile. The lipid bilayer acted as a diffusion barrier, preventing rapid drug release and maintaining prolonged therapeutic concentrations.

Scanning Electron Microscopy confirmed the production of smooth, spherical vesicles with uniform morphology, indicating successful preparation by the thin-film hydration technique. Furthermore, the zeta potential which was found to be −35 mV suggested excellent colloidal stability due to sufficient electrostatic repulsion between vesicles, thereby reducing aggregation during storage. These findings points to fact that the optimized liposomes possess desirable physicochemical characteristics for topical drug delivery.

Following incorporation into the Carbopol 934 emulgel base, the formulation exhibited suitable dermatological properties like easy and uniform application over the affected area, which are essential characteristics for patient acceptability.

The emulgel that was optimized had zero-order release kinetics, indicating concentration of drug is independent of the release. For topical formulations, maintaining a consistent drug dose concentration at the applied site of infection over an extended period; this type of release is particularly desirable. The controlled release behavior shown in the present study may be due to the combined diffusion resistance offered by both the liposomal lipid bilayer and the Carbopol gel matrix.

Ex vivo skin permeation studies by excised goat skin demonstrated high localized drug retention with minimal transdermal permeation. These findings indicate that the formulation effectively delivers ribavirin into the skin layers while limiting systemic absorption, thereby reducing the potential for systemic adverse effects.

## CONCLUSION

This study has developed a stable and highly efficient ribavirin-loaded liposomal emulgel optimized via Central Composite Design (741.5 mg phospholipid and 201.6 mg cholesterol). The optimized formulation achieved a high entrapment efficiency, excellent colloidal stability, and an ideal skin-compatible matrix featuring zero-order release kinetics. Most notably, ex vivo skin permeation studies demonstrated enhanced localized dermal retention with minimal transdermal systemic flux, confirming that the dual-carrier vehicle effectively circumvents the stratum corneum barrier to establish a controlled therapeutic depot within target cutaneous tissues. Overall, the developed liposomal emulgel is a promising topical delivery system for ribavirin has improved local drug retention and potential therapeutic benefits in the treatment of viral skin infections.

### Conflict of interest:

The authors have no conflicts of interest regarding this investigation.

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