

FORMULATION AND CHARACTERIZATION OF LIPOSOMAL HYDROGEL OF BARICITINIB FOR MANAGEMENT OF DERMATITIS**Harsh Dubey*, Satkar Prasad****RKDF School of Pharmaceutical Sciences, Bhabha University, Bhopal (M.P.)***Corresponding Author's E mail: dubeyharsh3767@gmail.com

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ABSTRACT

Baricitinib is a selective Janus kinase (JAK) inhibitor widely used in the management of inflammatory skin disorders; however, its therapeutic efficacy through conventional dosage forms is limited by poor skin retention and the need for frequent application. The present study aimed to develop and optimize a Baricitinib-loaded liposomal gel for sustained topical drug delivery. Liposomes were prepared using the ethanol injection method by varying the concentrations of Soya phosphatidylcholine (4–9% w/v) and Span 80 (2–7% w/v), while maintaining the drug concentration (2% w/w) and ethanol volume (5 mL) constant. Six formulations (F1–F6) were evaluated for vesicle size and entrapment efficiency. Among them, formulation F5 exhibited the smallest vesicle size (185.50 ± 7.45 nm), highest entrapment efficiency ($73.45 \pm 0.78\%$), and a zeta potential of -36.52 mV, indicating good colloidal stability. The optimized liposomal dispersion was incorporated into a Carbopol gel and evaluated for physicochemical characteristics, including drug content, pH, spreadability, viscosity, and in vitro drug release. The optimized liposomal gel (LG3) demonstrated satisfactory drug content ($99.24 \pm 0.21\%$), skin-compatible pH (6.98 ± 0.07), appropriate viscosity (4628 ± 25 cps), and acceptable spreadability (10.18 ± 0.65 g·cm/sec). The formulation exhibited sustained drug release, achieving 99.24% cumulative release over 10 hours. Drug release kinetic analysis revealed that the release profile best fitted the Higuchi model ($R^2 = 0.9980$), indicating diffusion-controlled release. These findings suggest that the developed Baricitinib liposomal gel is a promising sustained-release topical drug delivery system with improved formulation characteristics and potential for enhanced therapeutic efficacy.

Keywords: Baricitinib, Liposomes, Liposomal Gel, Sustained Drug Release, Ethanol Injection Method, Soya Phosphatidylcholine, Span 80, Entrapment Efficiency, Topical Drug Delivery, Higuchi Model.

INTRODUCTION

Baricitinib is a selective and reversible inhibitor of Janus kinase (JAK) 1 and JAK2 that has gained considerable attention for the treatment of inflammatory and autoimmune disorders. By inhibiting the JAK–STAT signaling pathway, Baricitinib suppresses the production of pro-inflammatory cytokines involved in the pathogenesis of various dermatological diseases, including alopecia areata, atopic dermatitis, and other chronic inflammatory skin conditions¹.

Although Baricitinib has demonstrated significant clinical efficacy following oral administration, systemic therapy is often associated with adverse effects, including increased susceptibility to infections, hematological abnormalities, and hepatic dysfunction. Consequently, the development of an effective topical drug delivery system has emerged as an attractive strategy to achieve localized therapeutic action while minimizing systemic exposure².

Topical drug delivery offers several advantages, including direct drug application to the affected site, improved patient compliance, reduced dosing frequency, and avoidance of first-pass metabolism. However, the effectiveness of topical therapy is frequently limited by the barrier function of the stratum corneum, which restricts the penetration of many therapeutic agents. Therefore, advanced carrier systems capable of enhancing drug permeation and retention within the skin are required to improve treatment outcomes^{3,4}.

Liposomes are phospholipid-based vesicular carriers composed of one or more lipid bilayers surrounding an aqueous core. Owing to their biocompatibility, biodegradability, and structural similarity to biological membranes, liposomes have been extensively investigated as efficient drug delivery systems for topical and transdermal applications⁵. They are capable of encapsulating both hydrophilic and lipophilic drugs, protecting the drug from degradation, improving skin permeation, enhancing drug retention within the epidermis and dermis, and providing sustained drug release. The incorporation of surfactants such as Span 80 further improves vesicle flexibility and stability, facilitating enhanced interaction with the skin barrier⁶.

To improve patient acceptability and ease of application, liposomal dispersions are frequently incorporated into hydrogel systems. Liposomal gels combine the penetration-enhancing properties of liposomes with the desirable rheological characteristics of hydrogels, providing prolonged residence time at the application site, improved spreadability, controlled drug release, and enhanced formulation stability. Such systems are particularly advantageous for chronic dermatological disorders that require sustained local drug delivery⁷.

In the present study, Baricitinib-loaded liposomes were prepared using the ethanol injection method by varying the concentrations of Soya phosphatidylcholine and Span 80 to optimize vesicle characteristics and drug entrapment efficiency. The optimized liposomal formulation was subsequently incorporated into a Carbopol gel and evaluated for physicochemical properties, vesicle size, zeta potential, entrapment efficiency, drug content, pH, viscosity, spreadability, and *in vitro* drug release behavior. Furthermore, the release kinetics were analyzed using various mathematical models to elucidate the mechanism of drug release. The study aims to develop a stable and sustained-release liposomal gel of

Baricitinib that may improve topical therapeutic efficacy and patient compliance for the management of inflammatory skin disorders.

Material and methods

Preparation and Optimization of Liposomes

Liposomes were prepared by varying the concentrations of Soya phosphatidylcholine (Soya PC) and Span 80, while keeping the drug concentration (2% w/w) and ethanol volume (5 mL) constant, as shown in Table 6.4. Accurately weighed quantities of Soya PC and Span 80 corresponding to each formulation (F1–F6) were dissolved in ethanol containing the drug. The resulting lipid solution was added slowly to the aqueous phase under continuous stirring to facilitate vesicle formation. Stirring was continued until a uniform liposomal dispersion was obtained. Six formulations (F1–F6) containing 4–9% w/v Soya PC and 2–7% w/v Span 80 were prepared and evaluated to identify the optimized formulation based on vesicle characteristics and drug entrapment efficiency⁸.

Preparation of Liposomal Gel

Carbopol 934 (1% w/v) was accurately weighed and dispersed in approximately 80 mL of double-distilled water under continuous stirring at 800 rpm for 1 hour to obtain a uniform dispersion. Propylene glycol (10 mL) was then added with continuous stirring. The pH of the dispersion was adjusted to 6.8–7.0 by the dropwise addition of 0.05 N sodium hydroxide until a clear and transparent gel was formed. The final volume was adjusted to 100 mL using double-distilled water, and the gel was sonicated for 10 minutes to remove entrapped air bubbles.

The optimized liposomal dispersion equivalent to the required drug concentration (2% w/w) was slowly incorporated into the gel base with gentle stirring to obtain a homogeneous liposomal gel. The prepared formulations were stored in airtight containers for further evaluation.

Table 1: Composition of Baricitinib Liposomal Formulations (F1–F6)

Formulation Code	Baricitinib(% w/w)	Soya PC (% w/v)	Span 80 (% w/v)	Ethanol (mL)	Purified Water (q.s. to 100 mL)
F1	2.0	4	2	5	100 mL
F2	2.0	5	3	5	100 mL
F3	2.0	6	4	5	100 mL
F4	2.0	7	5	5	100 mL
F5	2.0	8	6	5	100 mL
F6	2.0	9	7	5	100 mL

Characterization of liposomes

Vesicle size

Microscopic analysis was performed to determine the average size of prepared Liposomes. Formulation was diluted with distilled water and one drop was taken on a glass slide and covered with cover slip⁹. The prepared slide was examined under trinocular microscopic at 400 X. The diameters of more than 150 vesicles were randomly measured using calibrated ocular and stage micrometer. The average diameter was calculated using the following formula:

$$\text{Average Diameter} = \frac{\sum n.d}{\sum n}$$

Where n = number of vesicles; d = diameter of the vesicles

Surface charge and vesicle size

The vesicles size and size distribution and surface charge were determined by Dynamic Light Scattering method (DLS) (Malvern Zetamaster, ZEM 5002, Malvern, UK). Zeta potential measurement of the liposomes was based on the zeta potential that was calculated according to Helmholtz–Smoluchowsky from their electrophoretic mobility¹⁰. For measurement of zeta potential, a zetasizer was used with field strength of 20 V/cm on a large bore measures cell. Samples were diluted with 0.9 % NaCl adjusted to a conductivity of 50 IS/cm.

Entrapment efficiency

Baricitinib entrapped within the liposomes was estimated after removing the untrapped drug¹¹. The untrapped drug was separated from the liposomes by subjecting the dispersion to centrifugation in a cooling centrifuge (Remi Equipments, Mumbai) at 18000 rpm at a temperature of 4°C for 45 minutes, where upon the pellets of liposomes and the supernatant containing free drug were obtained. The liposomes pellets were washed again with phosphate buffer to remove any untrapped drug by centrifugation. The combined supernatant was analyzed for the drug content after suitable dilution with phosphate buffer solution by measuring absorbance at 210 nm using Labindia 3000+ spectrophotometer.

$$\% \text{ Entrapment Efficiency} = \frac{\text{Theoretical drug content} - \text{Practical drug content}}{\text{Theoretical drug content}} \times 100$$

Characterization of Liposomes containing gel

Measurement of viscosity

Viscosity measurements of prepared topical liposomes based gel were measured by Brookfield viscometer using spindle no. 63 with the optimum speed of 10rpm.

pH measurements

pH of selected optimized formulations was determined with the help of digital pH meter. Before each measurement of pH, pH meter should be calibrated with the help of buffer solution of pH 4, pH 7 and pH 9.2. After calibration, the electrode was dipped into the vesicles as long as covered by the vesicles. Then pH of selected formulation was measured and readings shown on display were noted ¹².

Drug content

Accurately weighed equivalent to 100 mg of topical liposome gel was taken in 10 ml volumetric flask, add 5 ml of methanol and sonicate it for 10 min and after sonication volume was made upto 10 ml with methanol ¹³. This solution was mixed thoroughly and filtered using Whatman filter paper no.1. Then 0.1mL of filtered solution was taken in 10 mL capacity of volumetric flask and volume was made upto 10 mL with methanol. This solution was analyzed using UV-Spectroscope at $\lambda_{\max}$ 210 nm. Drug content of topical liposome based gel is shown in table.

Spreadability

Spreadability of formulation is necessary to provide sufficient dose available to absorb from skin to get good therapeutic response ¹⁴. An apparatus in which a slide fixed on wooded block and upper slide has movable and one end of movable slide tied with weight pan. To determine spreadability, placing 2-5 g of gel between two slide and gradually weight was increased by adding it on the weight pan and time required by the top plate to cover a distance of 6cm upon adding 20g of weight was noted, good spreadability show lesser time to spread.

$$\text{Spreadability (g.cm/sec)} = \frac{\text{Weight tied to Upper Slide} \times \text{Length moved on the glass slide}}{\text{Time taken to slide}}$$

In vitro drug diffusion study

The *in-vitro* diffusion study is carried by using franz diffusion cell. Egg membrane is taken as semi permeable membrane for diffusion ¹⁴. The Franz diffusion cell has receptor compartment with an effective volume approximately 60 mL and effective surface area of permeation 3.14sq.cms. The egg membrane is mounted between the donor and the receptor compartment. A two cm² size patch taken and weighed then placed on one side of membrane facing donor compartment. The receptor medium is phosphate buffer pH 7.4. The receptor compartment is surrounded by water jacket so as to maintain the temperature at 32 ± 0.5°C. Heat is provided using a thermostatic hot plate with a magnetic stirrer. The receptor fluid is stirred by Teflon coated magnetic bead which is placed in the diffusion cell.

During each sampling interval, samples are withdrawn and replaced by equal volumes of fresh receptor fluid on each sampling. The samples withdrawn are analyzed spectrophotometrically at wavelength 210nm of drug.

RESULTS AND DISCUSSION

Baricitinib-loaded liposomes were successfully prepared by varying the concentrations of Soya phosphatidylcholine (Soya PC) and Span 80 while maintaining the drug concentration (2% w/w) and ethanol volume (5 mL) constant. The composition of the six formulations (F1–F6) is presented in Table 1. The prepared liposomes were evaluated for vesicle size and entrapment efficiency to identify the optimized formulation.

As shown in Table 2, increasing the concentration of Soya PC and Span 80 from F1 to F5 resulted in a progressive reduction in vesicle size from 225.36 ± 6.42 nm to 185.50 ± 7.45 nm, along with a corresponding increase in entrapment efficiency from $65.28 \pm 0.74\%$ to $73.45 \pm 0.78\%$. This improvement can be attributed to enhanced lipid bilayer formation and increased drug incorporation within the vesicles. However, a further increase in lipid and surfactant concentration in formulation F6 caused the vesicle size to increase to 198.65 ± 6.14 nm, while entrapment efficiency decreased slightly to $72.18 \pm 0.62\%$, suggesting vesicle aggregation or membrane saturation at higher lipid concentrations.

Based on the smallest vesicle size and highest entrapment efficiency, formulation F5 was selected as the optimized liposomal formulation (Table 3). The vesicle size distribution of the optimized formulation is illustrated in Figure 1, demonstrating a narrow particle size distribution suitable for topical drug delivery. The optimized liposomes also exhibited a zeta potential of -36.52 mV (Figure 2), indicating good electrostatic stabilization and reduced tendency for vesicle aggregation during storage. The optimized liposomal formulation (F5) was incorporated into Carbopol gel to prepare three liposomal gel formulations (TG1–TG3). The physicochemical evaluation results are summarized in Table 4.

The drug content of the formulations ranged from $96.42 \pm 0.38\%$ to $99.24 \pm 0.21\%$, indicating uniform distribution of Baricitinib throughout the gel matrix. Among the formulations, TG3 exhibited the highest drug content ($99.24 \pm 0.21\%$), suggesting excellent formulation uniformity.

The pH values ranged between 6.82 ± 0.10 and 6.98 ± 0.07 , which are compatible with the physiological pH of the skin and therefore suitable for topical application without causing irritation. As the polymer concentration increased, the viscosity increased from 3158 ± 22 cps (TG1) to 4628 ± 25 cps (TG3), whereas spreadability decreased from 14.82 ± 0.86 g·cm/sec to 10.18 ± 0.65 g·cm/sec, demonstrating the expected inverse relationship between viscosity and spreadability. Overall, TG3 showed the most desirable combination of drug content, viscosity, pH, and spreadability and was selected for further in vitro release studies.

The in vitro drug release profile of the optimized liposomal gel (LG3) is presented in Table 5. The formulation exhibited a controlled and sustained release pattern throughout the study period. An initial release of 14.82% was observed within the first 0.5 h, which may be attributed to the drug adsorbed on or near the vesicle surface. Subsequently, drug release proceeded gradually, reaching 56.42% after 4 h, 84.76% after 8 h, and 99.24% after 10 h.

The sustained drug release observed from the liposomal gel can be attributed to the gradual diffusion of Baricitinib through the phospholipid bilayer followed by diffusion through the gel matrix. Such a release profile is advantageous for topical therapy because it prolongs drug residence time at the application site, minimizes frequent application, and may improve therapeutic efficacy.

The release data of the optimized liposomal gel (LG3) were fitted to different kinetic models, and the regression coefficients are presented in Table 6.

Among the evaluated models, the Higuchi model showed the highest regression coefficient ($R^2 = 0.9980$), followed closely by the Korsmeyer–Peppas model ($R^2 = 0.9979$), whereas the Zero-order and First-order models exhibited R^2 values of 0.9806 and 0.7920, respectively. These findings indicate that drug release from the liposomal gel primarily follows a diffusion-controlled mechanism, consistent with drug diffusion from phospholipid vesicles embedded within the gel matrix.

The excellent fit to the Higuchi model confirms that Baricitinib release occurred predominantly by diffusion through the hydrated polymeric network, making the optimized liposomal gel suitable for sustained topical drug delivery.

Table 2: Evaluations of liposomes for vesicle size and entrapment efficiency

Formulation	Vesicle Size (nm)	Entrapment Efficiency (%)
F1	225.36 ± 6.42	65.28 ± 0.74
F2	215.84 ± 5.68	67.45 ± 0.69
F3	205.72 ± 4.95	69.86 ± 0.81
F4	195.43 ± 5.21	71.92 ± 0.65
F5	185.50 ± 7.45	73.45 ± 0.78
F6	198.65 ± 6.14	72.18 ± 0.62

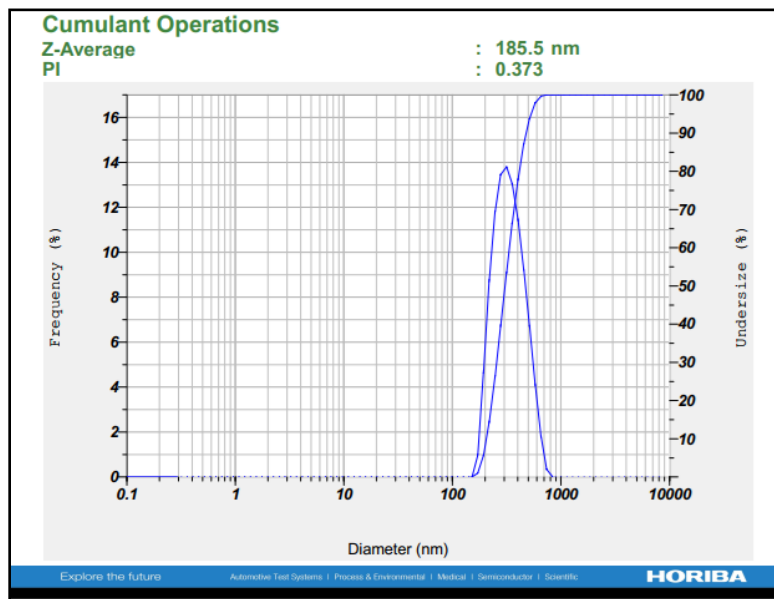


Figure 1: Vesicle Size of Optimized liposomes formulation F5

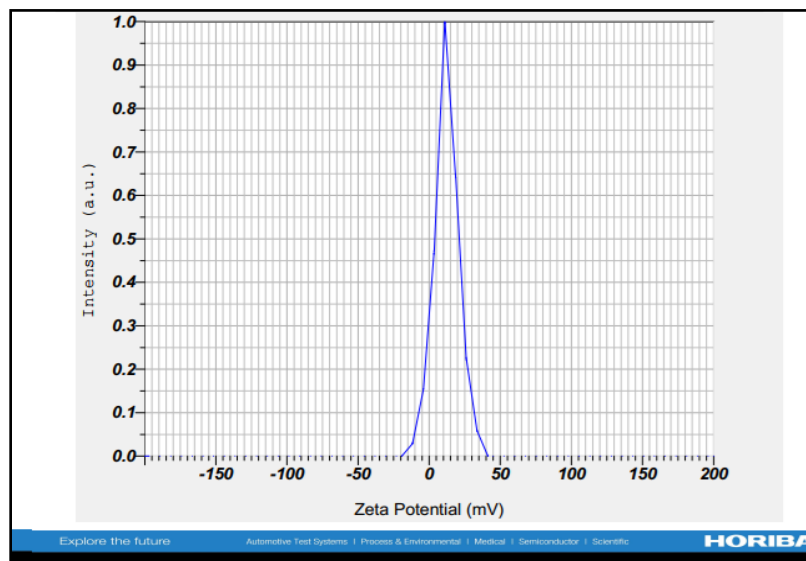


Figure 2: Zeta potential of Optimized liposomes formulation F5

Table 3: Vesicle size and entrapment efficiency of optimized formulation

Formulation Code	Vesicle Size (nm)	Entrapment Efficiency (%)	Zeta potential (mV)
F5	185.50 ± 7.45	73.45 ± 0.78	- 36.52

Table 4: Results of liposomes gel formulations

Code	Drug Content (%)	pH	Spreadability (g·cm/sec)	Viscosity (cps)
TG1	96.42 ± 0.38	6.82 ± 0.10	14.82 ± 0.86	3158 ± 22
TG2	98.16 ± 0.26	6.91 ± 0.08	12.36 ± 0.74	3865 ± 18
TG3	99.24 ± 0.21	6.98 ± 0.07	10.18 ± 0.65	4628 ± 25

Table 5: *In-vitro* drug release data for LG3

Time (h)	Square Root of Time (h) ^{1/2}	Log Time	Cumulative % Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
0.5	0.707	-0.301	14.82	1.171	85.18	1.930
1	1.000	0.000	23.65	1.374	76.35	1.883
2	1.414	0.301	38.94	1.590	61.06	1.786
4	2.000	0.602	56.42	1.751	43.58	1.639
6	2.449	0.778	71.28	1.853	28.72	1.458
8	2.828	0.903	84.76	1.928	15.24	1.183
10	3.162	1.000	99.24	1.997	0.76	-0.119

*Average of three reading

Table 6: Regression analysis data of liposomes gel formulation

Batch	Zero Order R ²	First Order R ²	Higuchi's Model R ²	KorsmeyersPeppas R ²
LG3	0.9806	0.7920	0.9980	0.9979

CONCLUSION

The present study successfully developed and optimized a Baricitinib-loaded liposomal gel for sustained topical drug delivery. Among the prepared formulations, F5 exhibited the smallest vesicle size, highest entrapment efficiency, and good colloidal stability. The optimized liposomal gel (LG3) demonstrated satisfactory physicochemical properties, high drug content, skin-compatible pH, appropriate viscosity, and sustained *in vitro* drug release. Drug release followed the Higuchi kinetic model, indicating a diffusion-controlled release mechanism. The developed liposomal gel represents a promising topical delivery system for Baricitinib with the potential to enhance therapeutic efficacy, prolong drug release, and improve patient compliance.

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