International Journal of Pharmaceutics and Drug Research
ISSN: 2347-6346
Available online at http://ijpdr.com

Original Research Article

FORMULATION AND CHARACTERIZATION OF LIPID-BASED NANOCARRIERS FOR EFFECTIVE TREATMENT OF ARTHRITIS

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***Article History:**

Received: 20/02/2025
Revised: 16/03/2025
Accepted: 25/03/2025

ABSTRACT

The present study focuses on the formulation and characterization of solid lipid nanoparticles (SLNs) loaded with Baricitinib, aimed at enhancing its topical delivery for the effective treatment of arthritis. Baricitinib, a Janus kinase (JAK) inhibitor, has proven efficacy in managing inflammatory conditions, but its systemic administration is often associated with side effects. SLNs were developed using glyceryl tripalmitate, soy lecithin, and pluronic F-68 by the hot homogenization method followed by ultrasonication. Among the prepared formulations, F14 showed optimal particle size (210.32 nm), high entrapment efficiency (84.54%), drug content (99.55%), and a stable zeta potential (-36.48 mV). The optimized SLNs were incorporated into a gel base (G-2) using Carbopol 934P for topical application. Evaluation of the gel formulation revealed suitable pH (6.74), viscosity (3465 cps), good spreadability, and drug release properties. In vitro drug release studies demonstrated a sustained release profile, with 99.05% release over 12 hours, fitting best with the Higuchi model (R^2 = 0.9929). The results suggest that SLN-based gel formulations can be a promising carrier system for the topical delivery of Baricitinib in arthritis therapy, offering enhanced bioavailability and reduced systemic exposure.

Keywords: Baricitinib, Solid Lipid Nanoparticles, Arthritis, Topical Delivery, SLNs Gel, Drug Release, Entrapment Efficiency, Zeta Potential, In vitro Study.

INTRODUCTION

Arthritis is a debilitating inflammatory disorder affecting millions worldwide, characterized by joint pain, swelling, and progressive cartilage degradation. Among its various forms, rheumatoid arthritis (RA) is a chronic autoimmune condition that results in severe joint inflammation and systemic complications (Firestein *et al.*, 2017). Despite the availability of several therapeutic agents, limitations such as low bioavailability, systemic side effects, and poor patient compliance continue to hamper effective disease management.

Baricitinib, a selective Janus kinase (JAK) 1 and 2 inhibitor, has emerged as a promising therapeutic agent for RA due to its ability to block intracellular signaling pathways responsible for cytokine-mediated inflammation (Taylor *et al.*, 2019). However, the conventional oral delivery of Baricitinib is associated with limited aqueous solubility and risks of systemic adverse effects, necessitating alternative delivery strategies to enhance its efficacy and safety.

Lipid-based nanocarriers, such as solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs), have gained attention for

improving drug solubility, stability, and targeted delivery, particularly in chronic inflammatory diseases like arthritis (Mukherjee *et al.,* 2009; Mehnert and Mader, 2012). These nanocarriers can enhance the therapeutic concentration of Baricitinib at inflamed joints while minimizing off-target exposure, thus potentially improving treatment outcomes and reducing adverse effects.

The present study focuses on the formulation and characterization of Baricitinib-loaded lipid-based nanocarriers to develop a targeted, sustained, and efficient drug delivery system for the treatment of arthritis. By leveraging the advantages of lipid nanotechnology, this research aims to overcome the pharmacokinetic challenges associated with Baricitinib and enhance its therapeutic index in arthritic conditions.

MATERIALS AND METHODS

Materials

The materials used for the formulation development of solid lipid nanoparticles (SLNs) of Baricitinib included Baricitinib obtained from Bioplus Life Sciences Pvt. Ltd., Bangalore. Lipid components such as glyceryl tripalmitate, soy lecithin, and stearyl amine were sourced from S. D. Fine Chem. Ltd. and Hi Media, Mumbai. Surfactants like Pluronic F-68 and propylene glycol, along with stabilizers including carbopol 934p, methyl paraben, and propyl paraben, were procured from Loba Chemie Pvt. Ltd., Mumbai. Solvents such as methanol, ethanol, and chloroform were provided by Qualigens Fine Chemicals, Mumbai. Additional reagents such as potassium bromide, sodium chloride, hydrochloride, sodium hydroxide, and potassium dihydrogen phosphate were obtained from reputed chemical suppliers in Mumbai.

Methods

Preparation of Baricitinib loaded solid lipid nanoparticles

Solid lipid nanoparticles were prepared by using microemulsion technique (Muller *et al.,* 2007) and o/w microemulsions were initially prepared. The oil phase, lipophilic surfactant and continuous phase used are glyceryl tripalmitate, soy lecithin and pluronic F-68 (hydrophilic surfactant) respectively. The lipid and soy lecithin were melted at 70^{o}C and the drug was added with constant stirring. 10 ml of aqueous surfactant solution containing pluronic F-68 and drug heated at the same temperature was added to the melted lipid with mechanical stirring for 15 min. A clear microemulsion was obtained at a temperature close to the melting point of the lipid used. Stearyl amine was used as a positive charge inducer and added to melted lipid. Solid lipid nanoparticles were obtained by dispersing the warm o/w microemulsion which is added drop wise into ice cold water in a beaker under continuous stirring. After completion of stirring, the Solid lipid nanoparticles dispersion was subjected to ultrasonication for 15 min.

Study on the effect of lipid quantity

The effect of lipid quantity on the particle size was studied by varying one parameter, keeping the others constant. Three different batches of Solid lipid nanoparticles were prepared corresponding to varying concentrations of lipid such as 50, 100 and 200 mg keeping the amount of soy lecithin (1% w/w), stearyl amine (1% w/w), pluronic F-68 (1% w/v), stirring time (3 hours) and stirring speed (1500 rpm) constant.

Table 1: Composition of solid lipid nanoparticles by varying amount of Lipid

Components	Formulation code		
	F1	**F2**	**F3**
Drug	**10**	10	10
Lipid	**50**	100	200
Soy lecithin	**1**	1	1
Stearyl amine	**1**	1	1
Pluronic F-68 (1% w/v)	**1**	1	1
Stirring speed (rpm)	**1500**	1500	1500
Stirring time (hrs)	**3**	3	3

Study on the effect of formulation process variables

The effect of formulation process variables such as stirring time, stirring speed, surfactant concentration on the particle size was studied. From the results obtained, optimum level of those variables was selected and kept constant in the subsequent evaluations.

Effect of stirring time

Five different batches of Solid lipid nanoparticles were prepared corresponding to 1, 2, 3, 4, 5 hours of stirring time keeping the lipid concentration (50 mg), soy lecithin (1% w/w), stearyl amine (1% w/w), pluronic F-68 (1% w/v) and stirring speed (2000 rpm) constant (Muller *et al.*, 1997).

Table 2: Composition of Solid lipid nanoparticles by varying Stirring time

Components	Formulation code				
	F4	**F5**	**F6**	**F7**	**F8**
Drug	10	10	10	**10**	10
Lipid	50	50	50	**50**	50
Soy lecithin	1	1	1	**1**	1
Stearyl amine	1	1	1	**1**	1
Pluronic F-68 (1% w/v)	1	1	1	**1**	1
Stirring speed (rpm)	2000	2000	2000	**2000**	2000
Stirring time (hrs)	1	2	3	**4**	5

Effect of stirring speed

Four different batches of Solid lipid nanoparticles were prepared corresponding to 1000, 1500, 2000 and 2500 rpm of stirring speed keeping the lipid concentration (50 mg), soy lecithin (1% w/w), stearyl amine (1% w/w), pluronic F-68 (1% w/v) and stirring time (4 hours) constant.

Table 3: Composition of Solid lipid nanoparticles by varying Stirring speed

Components	Formulation code			
	F9	**F10**	**F11**	**F12**
Drug	10	10	**10**	10
Lipid	50	50	**50**	50
Soy lecithin	1	1	**1**	1
Stearyl amine	1	1	**1**	1
Pluronic F-68 (1% w/v)	1	1	**1**	1
Stirring speed	1000	1500	**2000**	2500
Stirring time	4	4	**4**	4

Effect of surfactant concentration

Four different batches of solid lipid nanoparticles were prepared corresponding to 0.5%, 1%, 1.5% and 2% w/v of pluronic F-68 keeping the lipid concentration (50 mg), soy lecithin (1% w/w), stearyl amine (1% w/w), stirring time (4 hours) and stirring speed (2000 rpm) constant.

Table 4: Composition of Solid lipid nanoparticles by varying amount Surfactant

Components	Formulation code			
	F13	**F14**	**F15**	**F16**
Drug	10	**10**	10	10
Lipid	50	**50**	50	50
Soy lecithin	1	**1**	1	1
Stearyl amine	1	**1**	1	1
Pluronic F-68 (1% w/v)	0.5	**1**	1.5	2
Stirring speed	2000	**2000**	2000	2000
Stirring time	4	**4**	4	4

Evaluation of solid lipid nanoparticles

Particle size and zeta potential

Particle size and zeta potential of the Solid lipid nanoparticles were measured by photon correlation spectroscopy using a Malvern Zetasizer (Jain *et al.,* 2009).

Entrapment efficiency

Entrapment efficiency was determined by dialysis method. Solid lipid nanoparticles entrapped Baricitinib were separated from the free drug by dialysis method (Krishnatreyya *et al.,* 2019). The above said formulations were filled into dialysis bags and the free Baricitinib dialyzed for 24 hours into 50 ml of phosphate buffer saline pH 7.4. The absorbance of the dialysate was measured at 252 nm against blank phosphate buffer saline pH 7.4 and the absorbance of the corresponding blank phosphate buffer saline pH 7.4 was measured under the same condition. The concentration of free Baricitinib could be obtained from the absorbance difference based on standard curve. Standard curve was made by measuring the absorbance at 252 nm for known concentrations of Baricitinib solution. The entrapment efficiency of the drug was defined as the ratio of the mass of formulations associated drug to the total mass of drug.

Total drug content

From the prepared Solid lipid nanoparticles formulation 1ml of suspension is dissolved in the 10 ml of phosphate buffer saline pH 7.4 and ethanol mixture. The amount of Baricitinib was determined using UV spectrophotometer at 252nm. The total drug content was calculated using calibration curve method (Mukherjee *et al.,* 2009).

Formulation of solid lipid nanoparticles incorporated gel

Preparation of gel base

Carbopol 934 (1-3%w/v Solid lipid nanoparticles based gel formulation i.e. G-1 of 1%w/v, G-2 of 2%w/v, G-3 of 3%w/v) was accurately weighed and dispersed into double distilled water (80ml) in a beaker. This solution was stirred continuously at 800 rpm for 1 hour and then 10ml of propylene glycol was added to this solution (Joshi and Patravale, 2008). The obtained slightly acidic solution was neutralized by drop wise addition of 0.05 N sodium hydroxide solutions, and again mixing was continued until gel becomes transparent. Volume of gel was adjusted to 100 ml and then sonicated for 10 min on bath sonicator to remove air bubbles. Final pH of the gel base was adjusted to 6.5. The same procedure was used to formulate SLN_S containing gel in which previously prepared SLN_S suspension was added. SLN_S preparation corresponding to 1% w/w of drug was incorporated into the gel base to get the desired concentration of drug in gel base.

Table 5: Formulation optimization of gel base

Ingredient (%)	G-1	G-2	G-3
Drug (Solid lipid nanoparticles equivalent to 1%)	1	1	1
Carbopol 934	1	2	3
Propylene glycol	0.2	0.2	0.2
Water (ml)	100	100	100

Evaluation of solid lipid nanoparticles incorporated gel

Measurement of viscosity

Viscosity measurements of prepared topical SLN_S based gel were measured by Brookfield viscometer using spindle no. 63 with the optimum speed of 10rpm (Kesharwani *et al.,* 2016).

pH measurements

pH of selected optimized formulations was determined with the help of digital pH meter (Patel *et al.,* 2012). 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.

Drug content

Accurately weighed equivalent to 100 mg of topical SLN_S gel was taken in beaker and added 20 ml of methanol (Gondrala *et al.*, 2015). This solution was mixed thoroughly and filtered using Whatman filter paper no.1. Then 1.0 mL 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-Spectroscopy at λ_{max} 252 nm.

Extrudability study

Extrudability was based upon the quantity of the gel extruded from collapsible tube on application of certain load. More the quantity of gel extruded shows better extrudability (Bagde *et al.*, 2022). It was determine by applying the weight on gel filled collapsible tube and recorded the weight on which gel was extruded from tube.

Spreadibility

Spreadibility of formulation is necessary to provide sufficient dose available to absorb from skin to get good therapeutic response (Al Haushey, 2024). 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 spreadibility, 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 10 cm upon adding 80g of weight was noted. Good spreadibility show lesser time to spread.

$$Spreadability = \frac{Weight\ tide\ to\ Upper\ Slide\ x\ Length\ moved\ on\ the\ glass\ slide}{Time\ taken\ to\ slide}$$

***In-vitro* drug diffusion study**

The *in-vitro* diffusion study is carried by using franz diffusion cell (Teeranachaideekul *et al.*, 2007). Egg membrane is taken as semi permeable membrane for diffusion. 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 cm^2 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 and analyzed spectrophotometrically at wavelength of 252nm.

RESULTS AND DISCUSSION

The present study focused on the formulation and characterization of Baricitinib-loaded solid lipid nanoparticles (SLNs) for enhanced topical delivery in arthritis treatment. The data from Table 6 indicate that among the 16 formulations (F1–F16), formulation F14

showed the most favorable characteristics, with the smallest particle size of 215.45 nm**,** highest entrapment efficiency **(**84.54%**),** and drug content (99.55%**).** Particle size is crucial for dermal penetration; smaller vesicles tend to penetrate deeper skin layers, facilitating improved drug delivery at the site of inflammation.

Further evaluation of formulation F14 (as shown in Table 7) confirmed its optimized profile, including a zeta potential of -36.48 mV, which suggests good colloidal stability due to electrostatic repulsion preventing aggregation. The stability and size were visually supported by Figure 1 and Figure 2, representing particle size distribution and zeta potential, respectively.

The SLNs were incorporated into gel formulations to enhance topical application convenience and retention. As shown in Table 8, gel formulation G-2 demonstrated favorable physicochemical properties, including viscosity of 3465 cps**,** pH 6.74 (close to skin pH), 99.12% drug content**,** good extrudability (176 g), and acceptable spreadability (11.36 g·cm/sec). These properties ensure user compliance, ease of application, and effective coverage of the affected area.

In vitro drug release studies (Table 9 and Table 10) showed that G-2 had a sustained drug release profile, reaching 99.05% cumulative release over 12 hours, which is ideal for prolonged therapeutic action in arthritis management. The release pattern supports the idea of controlled and targeted delivery via SLNs, reducing systemic side effects and enhancing local bioavailability.

The regression analysis **(**Table 11**)** revealed that drug release from G-2 followed Higuchi kinetics (R^2 = 0.9929) and Korsmeyer-Peppas model (R^2 = 0.9923), suggesting a diffusion-controlled release mechanism from the gel matrix, primarily driven by Fickian diffusion.

Overall, the findings support that SLN-based gels, particularly formulation G-2**,** provide a promising strategy for the topical delivery of Baricitinib, offering enhanced skin penetration, sustained release, and improved therapeutic potential in arthritis treatment.

Table 6: Result for particle size, entrapment efficiency and drug content of drug loaded solid lipid nanoparticles

Formulation Code	Particle size (nm)	% Entrapment Efficiency	% Drug Content
F1	**255.65**	**82.25**	**98.85**
F2	356.65	76.65	98.12
F3	283.32	74.45	97.14
F4	273.32	72.23	96.65
F5	255.65	80.23	97.66
F6	259.32	76.65	97.45
F7	**230.36**	**84.45**	**99.12**
F8	240.32	74.65	98.85
F9	270.36	70.32	98.65
F10	265.65	70.23	98.85

F11	**225.65**	**84.65**	**98.88**
F12	265.65	74.45	97.74
F13	273.32	65.65	97.85
F14	**215.45**	**84.54**	**99.55**
F15	230.32	80.32	98.65
F16	236.65	82.32	97.74

Table 7: Particle size and entrapment efficiency of optimized solid lipid nanoparticles

Formulation Code	Particle size (nm)	% Entrapment Efficiency	% Drug Content	Zeta potential (mV)
F14	210.32	84.54	99.55	-36.48

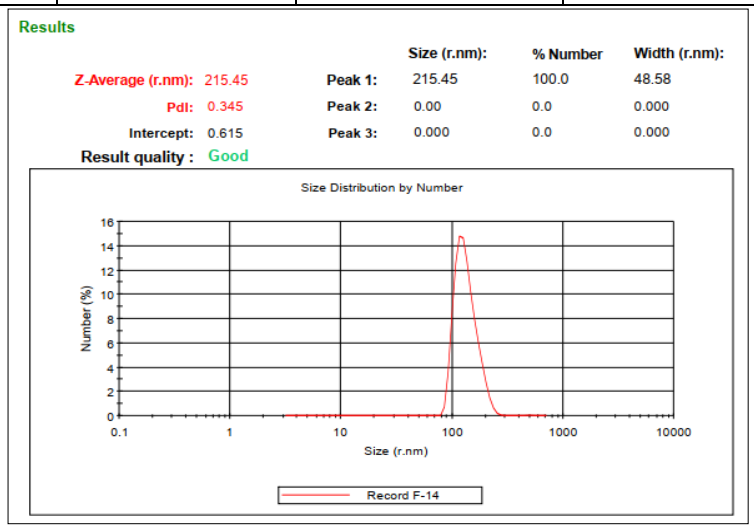

Figure 1: Particle size of optimized solid lipid nanoparticles formulation F14

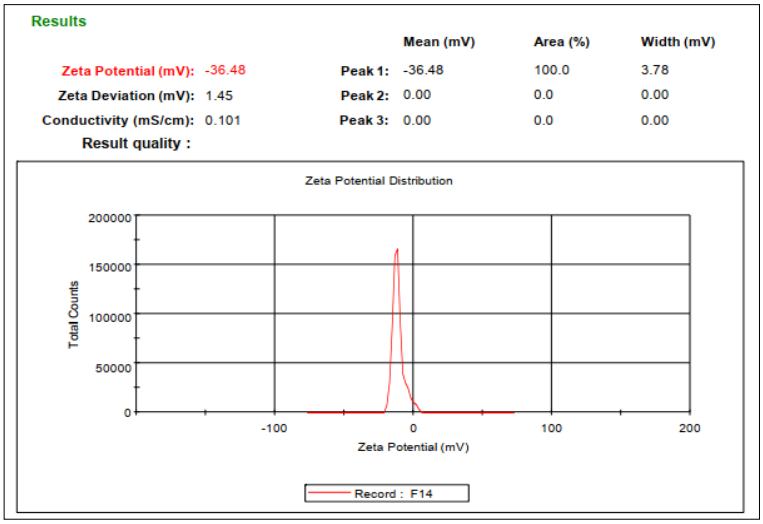

Figure 2: Zeta potential of optimized solid lipid nanoparticles formulation F14

Table 8: Characterization of SLNs gel

Gel formulation	Viscosity (cps)	pH	Drug Content (%)	Extrudability (g)	Spreadibility (g.cm/sec)
G-1	3572	6.95	98.45	170	12.25
G-2	3465	6.74	99.12	176	11.36
G-3	3345	6.32	97.65	183	10.25

Table 9: *In vitro* drug release study of gel formulation

S. No.	Time (hr)	% Cumulative Drug Release*		
		G-1	G-2	G-3
1	0.5	24.65	19.98	16.65
2	1	38.98	32.25	20.23
3	2	50.23	40.36	35.68
4	4	67.98	55.65	45.58
5	6	86.65	68.98	58.85
6	8	98.85	76.65	67.74
7	10	99.12	93.32	73.32
8	12	99.85	99.05	88.98

Table 10: *In vitro* drug release study of optimized gel formulation G-2

S. No.	Time (hr)	% Cumulative Drug Release*
1	0.5	19.98
2	1	32.25
3	2	40.36
4	4	55.65
5	6	68.98
6	8	76.65
7	10	93.32
8	12	99.05

Table 11: Regression analysis data of optimized gel formulation G-2

Batch	Zero Order	First Order	Higuchi	Korsmeyer Peppas
	R^2	R^2	R^2	R^2
G-2	0.9749	0.8459	0.9929	0.9923

CONCLUSION

The study successfully formulated and characterized solid lipid nanoparticles (SLNs) loaded with Baricitinib and incorporated them into a topical gel for the treatment of arthritis. Among all formulations, F14 exhibited the most favorable characteristics with a small particle size, high entrapment efficiency, and stable zeta potential. The optimized SLN formulation **(**G-2 gel**)** showed appropriate pH, viscosity, drug content, and excellent spreadability and extrudability suitable for topical use. In vitro release studies demonstrated sustained and controlled drug release over 12 hours, indicating enhanced retention and potential for prolonged therapeutic action. The release kinetics followed Higuchi and Korsmeyer-Peppas models**,** confirming diffusion-controlled release. Overall, the SLN-based gel formulation of Baricitinib offers a promising strategy for effective localized arthritis therapy, potentially improving patient compliance and reducing systemic side effects.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

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