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Original Article

Fabrication of Topical Pluronic Lecithin Organogel Containing Immunomodulatory Drug for Site-Specific Drug Delivery

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ABSTRACT

Background: Rheumatoid Arthritis is an Autoimmune disease, can be categorized by painful joints with limited treatment option. An Oral administration of Leflunomide for longer duration might lead to the Liver Toxicity. Hence, site specific delivery of an Immunomodulatory drug can be proposed for symptomatic relief of pain. **Materials and Methods:** Present study is focused on the formulation of Leflunomide using Pluronic Lecithin Organogel as a platform to enhance permeation through skin, bypass hepatic metabolism and to achieve local action. Prepared formulation was optimized by using 3^2 full factorial design and characterized for various parameters such as viscosity, physical form, pH, drug content, Spreadability, *in vitro* drug release profile and stability. **Results:** Optimized formulation of organogel showed (%) drug release up to 8 hr. Further, anti-inflammatory activity and Histopathology study of developed formulation confirmed safe and effective use for topical application. **Conclusion:** The study concluded that developed formulation is effective for topical treatment of Rheumatoid Arthritis. The study would be extended to assess the clinical application of preparation.

Keywords: Pluronic Lecithin Organogel, 3^2 full factorial design, Topical application, Rheological study, Anti-inflammatory activity, Histopathology study.

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INTRODUCTION

Rheumatoid Arthritis (RA) is an autoimmune condition that causes preliminary swelling and pain to the joints and progressively damage other organs too.[1,2]

Leflunomide is a Disease Modifying Anti-Rheumatic Drug (DMARD) that is preliminary used to cure inflammatory arthritis, such as rheumatoid arthritis. DMARDs work by modifying the underlying disease process rather than just treating the symptoms, and are used to reduce the development of the disease, reduce joint damage, and enhance long-term outcomes for patients. Leflunomide is thought to work by inhibiting the proliferation of immune cells that cause inflammation and damage in the joints. As per Biopharmaceutical Classification System, Leflunomide is categorized as BCS class II drug with low solubility but high permeability. The formulation available in market is only tablets that may lead to liver toxicity upon long term use. Hence, a formulation approach is desirable for minimizing systemic toxicity of drug without compromising its therapeutic potential.[3-5]

Pluronic Lecithin Organogel (PLO) is composed of both oil and aqueous phase. Oil phase is mainly containing Lecithin; to be dissolved in solvent Isopropyl Myristate. Poloxamer is dissolved in water and Preservative is added to both the phases. Both hydrophilic and hydrophobic drug can be incorporated in PLO. PLO has the capability for skin permeation and hence can be used for drug delivery to local along with systemic circulation.[6-8]

Leflunomide is a low molecular weight drug; 272 Dalton, with 2.8 Log P value make it a suitable candidate for the topical delivery, with added advantage of site-specific drug delivery. Present study deals with development of topical formulation of Leflunomide loaded PLO. The prepared formulation of PLO was optimized by means of 3^2 full factorial study design to check formulation variables which mainly affects physicochemical properties of drug and thereby drug release from formulation, rheological behavior.

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MATERIALS AND METHODS

Materials

Leflunomide was obtained as gift sample from Torrent Pharma Ltd., Ahmedabad, India. Poloxamer 407 and Poloxamer 188 were purchased from Sigma Aldrich, Germany, and soya lecithin was procured from Lipoid, Germany. All other chemicals used were of analytical grade.

Methods

The PLO was prepared by dispersing the oil phase into the aqueous phase. The leflunomide, sorbic acid and lecithin were dissolved in weighed quantity of Isopropyl Myristate to make oily phase. The accurately weighed amount of poloxamer 407 and Potassium sorbate were dissolved in cold distilled water to make aqueous phase. To prepare the PLO, the Poloxamer 407 was completely dissolved by keeping the aqueous mixture in a refrigerator at 4°C for 12 hr. The aqueous phase was stirred continuously and then oil phase was added dropwise. Mixture was kept under stirring further or few minutes to form a uniformly dispersed organogel.[9-11]

During Preliminary study, formulation variables and process variables were studied. By keeping process variables constant like temperature (15-20°C), stirring speed (400 rpm), stirring time (3 hr), addition rate (0.5 mL/min) constant; formulation variables like concentration of lecithin, concentration of poloxamer-407 and Aqueous: Oil phase ratio were studied (Table 1).

For the preparation of PLO gel, two types of surfactants Poloxamer-188 and poloxamer-407 was selected. When poloxamer 188 was used as surfactant, both oil and aqueous phase remain separate and liquid suspension was obtained. Gel was not formed. When poloxamer 407 was used as surfactant, each phase gets mix homogeneously and PLO was formed.

Experimental design

From the result of Preliminary batches, independent variables were selected for further study.

The suitable statistical model was finalized by taking consideration of independent variable and the sort of response predicted. Level factor is symbolized in full factorial design. 13 batches were prepared with consideration of 4 centre point.[12,13] The centre points confirm the minimal error in results. The experiments were conducted using the Design Expert software, specifically version 10.0.1.0. The layout of the idea is revealed in Table 2.

The 2D and 3D contour plots were established using reduced polynomial equation. To confirm the effect of experimental parameters for resultant parameters, the over lay plot was drawn. This is a prime prerequisite for the confirmation of consistency of the model.

Characterization

Organoleptic characteristics

The optimized PLO was measured for phase separation and other properties such as odor, color and texture.

Homogeneity test

Test is performed to check the presence of any gritty particles by rubbing it between thumb and finger.[14]

Gel transition Temperature

Poloxamer is showing thermo-gelling behavior i.e. at low temperature around 4-7°C, it dissolves in water and with elevation

Table 1: Formulation of Preliminary batch.

Ingredients	Formulation								
	M1	M2	M3	M4	M5	M6	M7	M8	M9
Drug (%)	1	1	1	1	1	1	1	1	1
Oil Phase									
Lecithin (%)	2	3	4	3	3	3	3	3	3
Sorbic acid (%)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
IPM q.s.	100	100	100	100	100	100	100	100	100
Aqueous phase									
Poloxamer 407 (%)	20	20	20	17.5	20	22.5	20	20	20
Potassium sorbate (%)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Distilled water q.s.	100	100	100	100	100	100	100	100	100
Ratio of aqueous and oil phase	75:25	75:25	75:25	75:25	75:25	75:25	70:30	75:25	80:20
Inference (consistency)	(+)	(+++)	(++)	(++)	(+++)	(+++)	(+)	(+++)	(++)

Table 2: Composition of batches formulated by using 3^2 factorial designs.

Batch no	Leflunomide (%)	Poloxamer 407 (%) (X1)	Distilled water q.s.	Lecithin (%)	Isopropyl Myristate q.s.	Ratio of Aqueous and Oil phase (X2)	Viscosity (cps)±SD	%Drug Release (at 8 hr)±SD
PL1	1	17.5	100%	3	100%	3:1	10948±288	69.83±3.49
PL2	1	17.5	100%	3	100%	3.5:1	10043±115	64.69±3.15
PL3	1	17.5	100%	3	100%	4:1	7705±197	62.49±2.49
PL4	1	18.75	100%	3	100%	3:1	11154±171	80.41±3.28
PL5	1	18.75	100%	3	100%	3.5:1	9279±124	78.28±4.08
PL6	1	18.75	100%	3	100%	4:1	9844±56	75.39±2.98
PL7	1	20	100%	3	100%	3:1	10217±105	89.34±1.91
PL8	1	20	100%	3	100%	3.5:1	11304±154	84.87±2.11
PL9	1	20	100%	3	100%	4:1	10010±137	82.17±3.55
PL10	1	18.75	100%	3	100%	3.5:1	8811±123	77.07±3.31
PL11	1	18.75	100%	3	100%	3.5:1	8592±53	78.28±4.98
PL12	1	18.75	100%	3	100%	3.5:1	7723±87	77.56±1.69
PL13	1	18.75	100%	3	100%	3.5:1	9954±105	79.61±2.8

Value are expressed as mean±SD; *n*=3.

in temperature, it swallows to form gel. Temperature at which Polymer solution transit to a gel state is defined as Gel Transition Temperature. Gel transition temperature is determined by placing an accurate amount of prepared formulation in a water bath, maintained at 4°C and then stirred at 100 rpm using a magnetic stirrer. Temperature was gradually elevated and monitored by placing thermometer in a beaker. Poloxamer shows swelling behavior with increase in temperature and convert to gel at defined temperature which was noted as Gel Transition Temperature.[15]

pH determination

The Calibrated digital pH meter was used to determine the pH of aqueous dispersion of Gel.[16]

Washability

Accurately weighed amount of gel was rubbed on a dorsal side of hand. Gel was allowed to dry. The dried layer of gel was kept under running tap water to observe the wash ability of gel.[17]

Microscopic study of organogel

The aqueous dispersion of gel (comprising of 0.5 gm of gel dispersed in 5 mL of water) was mounted on glass slide. The prepared glass slide was analysed using Optical Microscopy.

Spreadability

Spreadability is one of the important factors to be considered for topical application of semisolid formulation as it is resultant from composition of gel and its impact on Rheological behaviour. Spreadability was determined by placing 5 gm of gel on fixed slide and overlapping it with movable slide which is attached to a weighing pan. The weight was placed in a fraction to the pan and distance travelled by movable slide was measured. The Spreadability coefficient (S) is calculated using the following formula.[18]

$$S=(M \times L)\div T$$

Where S is dented for the Spreadability coefficient in g-cm/s, M is the load placed on the Pan, L is the distance moved by the slide in cm, and T is the time taken by the slide to move up to L.

Viscosity

The Brookfield Viscometer (DV-III Ultra, AMETEK Brookfield) was utilized to measure viscosity at a temperature of 25±5°C. The measurement was taken using a helipath T-F 96 spindle.[19] Further, Rheological behaviour of formulation at speeds of 10, 20, 30, 40, 50, 60, 70, 80, 90 and 100 rpm were measured.[20]

Drug content

To prepare the sample for analysis, a precisely weighed amount of Pluronic lecithin organogel was dispersed in 2-3 mL of methanol and subjected to ultrasonication for 30 min. The resulting mixture was then analysed using a UV spectrophotometer after appropriate dilution with methanol.[21]

In vitro release study

Dialysis bag (molecular weight cut off 12000-14000 Dalton) was filled with drug dispersion prepared by dispersing gel equivalent to 10 mg of drug in 5 mL Phosphate buffer saline, pH 5.5.

Diffusion media (100 mL) was stirred at 50 rpm using magnetic stirrer, at temperature 37±0.5°C. Dialysis bag was placed in acceptor compartment and diffusion was carried out for 8 hr. At different time interval, sample was collected and analyzed by measuring absorbance spectrophotometrically at 259 nm.[22]

Ex vivo permeation study

This study deals with the permeation of drug through animal tissue for topical application of prepared formulation. Ox ear tissue was procured from a nearby slaughterhouse and cleaned. The specimens composed of thick dorsal skin without cartilage, were cut and mounted on diffusion cells for carrying out the permeability study. At predetermined intervals, samples were withdrawn from well stirred receptor compartment containing Phosphate Buffer, pH 5.5 and analyzed for the amount of drug released. The sink condition was maintained by replenishing the medium with fresh buffer at the same volume as that of the withdrawn sample. Samples were analyzed by using UV spectrophotometer.

Flux and other parameters related to permeability of drug across the skin membrane can be calculated by plotting the data of *ex vivo* skin permeation vs time.[23,24] Based on straight line equation, following parameters were calculated.

$$Intercept = \text{lag}\,time(hr) = t_{lag} \quad \ldots\ldots\ldots (1)$$

$$Slope = Flux = J_{ss} \quad \ldots\ldots\ldots (2)$$

$$Permeability\ coefficient\ K_p = {}^{J_{ss}}/_{C_d};\ where\ administered\ dose = C_d \quad \ldots\ldots\ldots (3)$$

$$Diffusion\ coeficient\ D = {}^{h^2}/_{6 * t_{lag}},\ where, h = memberane\ thickness \quad \ldots\ldots\ldots (4)$$

In vivo study

Animal study was carried out in compliance with CPCSEA guidelines and licensed by the department's IAEC (SVU/DP/IAEC/2021/12/52). The study involved treating four groups of six animals each with different substances and measuring paw oedema volume at various time intervals after inducing paw oedema with carrageenan. The groups were a normal control group, a positive control group, a group treated with a standard marketed formulation (1 g), and a group treated with a leflunomide PLO gel formulation (1 g). Digital plethysmometer was used to determine the Anti-inflammatory activity. The following formula was utilized for the study.

$$\text{Percentage inhibition of edema} = \frac{(A-B)}{A}\ X\ 100 \quad \ldots\ldots\ldots (4)$$

Where, A represents the paw volume of the control group, and B represents the paw volume of the test drug treated group. The result is expressed as a percentage of the reduction in paw volume.[24]

Histopathological Studies

The mice abdominal skin was cut in measuring around 4 cm^2 area and glass slide was prepared. The specific amount of gel was applied on the skin and properties were compared with water which was taken as a control. The sample of skin was fixed using formalin solution and fixed using paraffin wax. The staining with haematoxylin and eosin was carried out on the sections of skin followed by observation and photographs.

Stability Study

A stability study was conducted according to ICH guidelines at two different temperature and humidity conditions, namely 25±2°C/60%±5% RH and 40±2°C/75%±5% RH, for 3 months. The samples were evaluated for their viscosity in cps and % drug release over 8 hr.

RESULTS AND DISCUSSION

Experimental Design

Leflunomide loaded PLO gel was developed using Response surface design as shown in Table 2. Total 13 batches were prepared as per Design Expert software and data were subjected for analysis which derived Polynomial equation as follows.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_1^2X_{11} + b_2^2X_{22} + b_{12}X_1X_2 \quad \ldots\ldots\ldots (5)$$

Where Y is the response i.e. Viscosity and % drug release; b_0 represents the intercept, (b_1 and b_2), b_{ij} (b_{12}) denotes the regression coefficients for the polynomial equation and indicates the independent formulation variable.

Polynomial equation for Viscosity,

$$Y1 = 9282.69 + 456.33X1 - 1460X2 - 25.41X12 + 380.59X22 - 16X1X2 \ldots\ldots\ldots (6)$$

Polynomial equation for Drug Release at 8 hr (%),

$$Y2 = 78.02 - 3.26X1 + 9.89X2 + 0.40X12 - 2.72X22 + 0.043X1X2 \ldots\ldots\ldots (7)$$

The magnitude of coefficient and a positive or negative sign of coefficient shows the impact of independent variables on dependent variables. Optimized batch was suggested by software upon selecting constraints. Checkpoint analysis was also performed to access the validity of a chosen model.

A statistical tool, ANNOVA was used to analyze the effects of independent variables on responses. Result of ANNOVA analysis can be graphically represented by using contour plots and three-dimensional response surface plots (Figure 1). This can be further used to optimize the values of selected independent variables to obtain desirable responses.

Effect of independent variables on Viscosity

The independent variable, which is the concentration of Poloxamer, has a direct effect on the dependent variable, which is the viscosity of PLO. Poloxamer molecules exist as individual chain in solution at lower concentration whereas at higher concentration, molecules of Poloxamer exhibits intermolecular interactions like cross linking and entanglement, imparts higher viscosity to the formulation.

On the other side; the plot shows that when ratio of aqueous: oil phase increases from 3:1 to 4:1, viscosity reduces. With increase aqueous: oil phase ratio; Oil phase concentration reduces resulting in decreased lecithin concentration. Lecithin act as an organogelator and hence reduced oil phase concentration was responsible for decreased viscosity of gel.

Effect of independent variables on %drug release at 8 hr

From the 2D plot and response surface plots, it can be established that concentration of Poloxamer is inversely proportional to %drug release. At lower concentration, Poloxamer dissolves in water and forms a solution, but with larger concentration, it forms a very viscous Gel like structure. Polymeric network of Gel entraps drug molecule in its structure; restricts rapid drug release.

As a ratio of aqueous to oil phase increases, %Drug release also increases. As an aqueous: oil phase ratio increases; due to aqueous

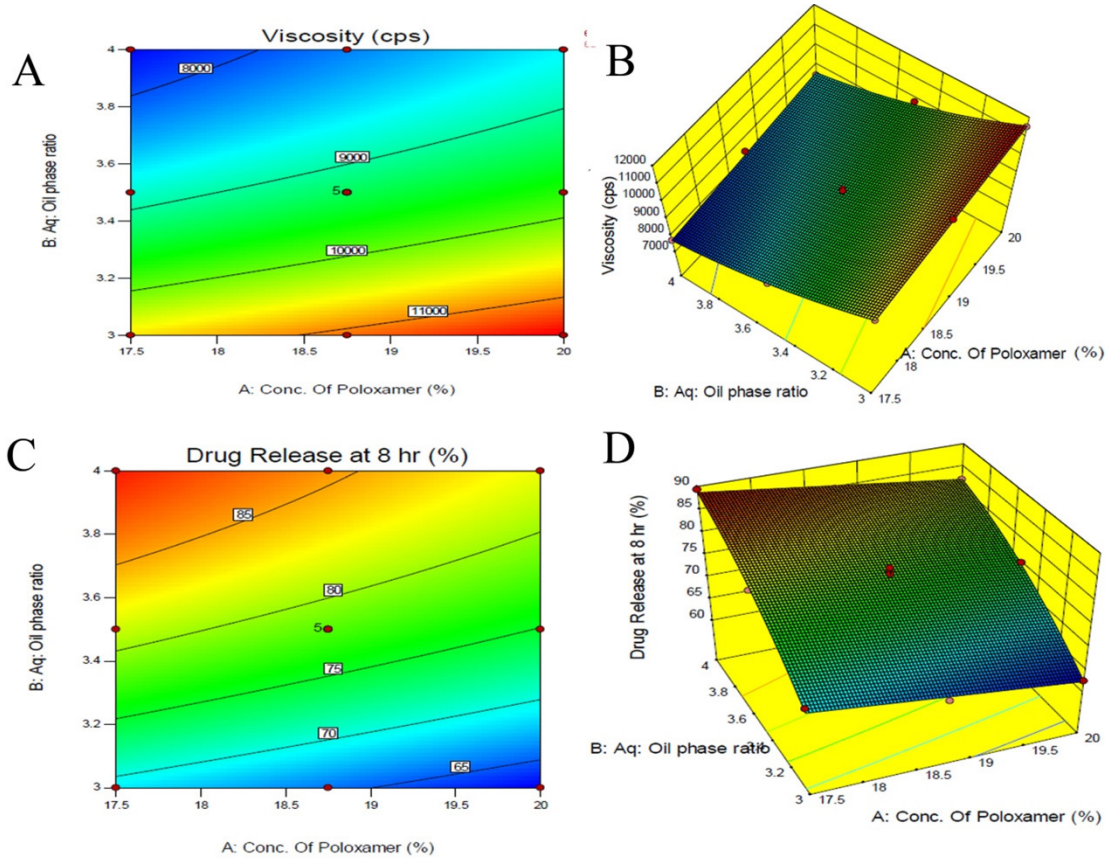

Figure 1: (A) Contour plot for effect of variables on Viscosity, (B) 3D Response surface plot for effect of variables on Viscosity, (C) Contour plot for effect of variables on %Drug release, (D) 3D Response surface plot for effect of variables on %Drug release.

Table 3: Check point analysis of Leflunomide loaded PLO.

Batch no.	X1	X2	Observed		Predicted		%Error	
			Viscosity (cps)	%DR (8 hr)	Viscosity (cps)	%DR (8 hr)	Viscosity (cps)	%DR (8 hr)
CK1	CK1	19.69	8577	82.69	8703	84.67	1.45	2.34
CK2	CK2	19.47	8583	82.69	8250	80.11	-4.04	-3.22
CK3	CK3	18.58	8825	81.21	8541	83.67	-3.33	2.94
CK4	CK4	17.69	8653	82.48	8972	79.98	3.56	-3.13
CK5	CK5	17.9	8963	80.36	8669	83.24	-3.39	3.46

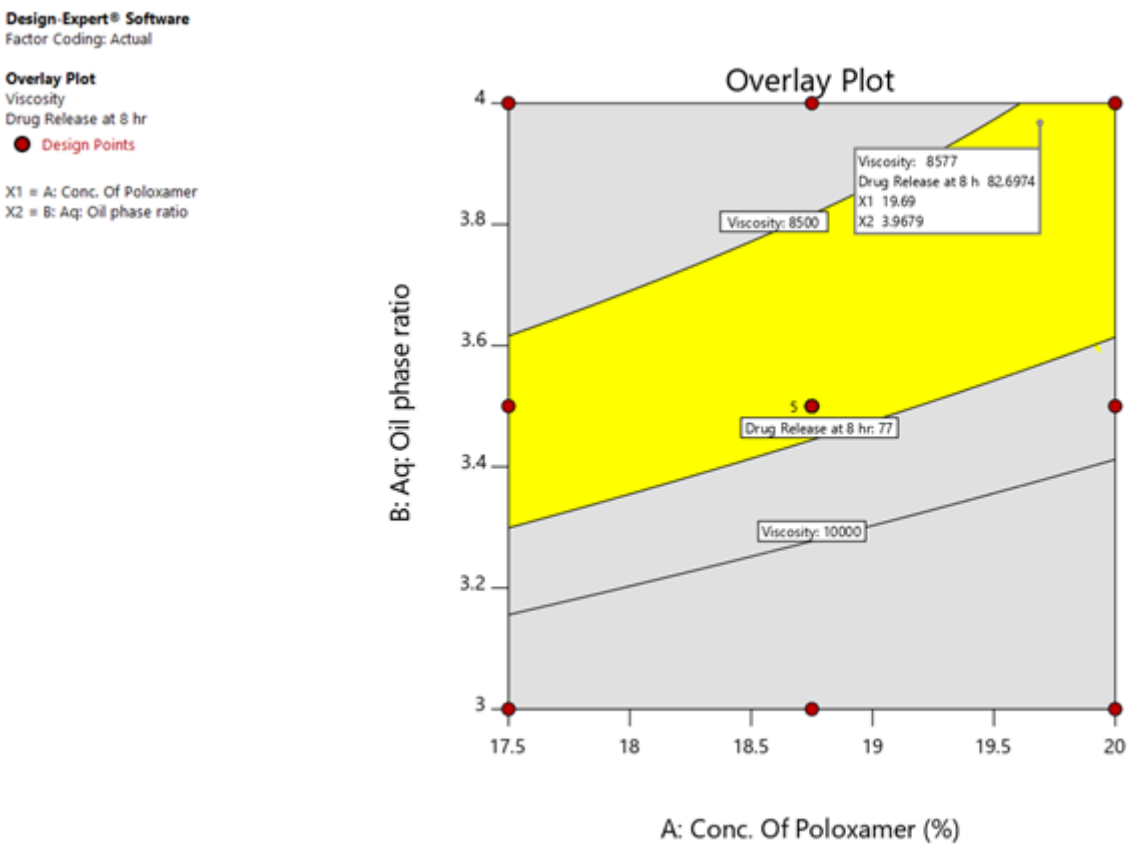

Figure 2: Overlay Plot.

Figure 3: Microscopic image of PLO.

phase increment gel become less stiff so drug escape out easily and rapid release obtained, hence %drug release increases.

The optimum batch of PLO was selected by setting the goal for the desirable responses. Overlay plot (Figure 2) facilitates the range of predicted batches which can be validated by preparing the actual batches and comparing the results (Table 3). Batches were selected with desirability close to 1.

Overlay plot having two distinct colours which predicted different value on concern of variables and response. The yellow colour suggests minimum and maximum limit of experimental

response. The best range of viscosity which software suggests is 8500-10000 and drug release at 8 hr is 77-85%

Characterization

Organoleptic characteristics

PLO was evaluated for organoleptic properties and found to with off white colour, odourless, smooth appearance.

Homogeneity test

PLO showed smooth texture and homogenous. Coarse particles were not observed in gel and found with optimal consistency.

Gel transition Temperature

Gel transition temperature for the optimized batch of PLO was found to be 29.3±3.05°C.

pH determination

An aqueous solution of PLO showed pH in the range of 5.92±0.85 which complies with pH of skin. Hence, developed PLO gel formulation is non-irritant to skin.

Washability

Applied PLO Gel on dorsal side of hand was washed out easily even after drying by keeping the hand under running water.

Microscopic study of Organogel

Prepared formulation was subjected for microscopic examination; which shows presence of oil globules entrapped within three-dimensional network of Polymer used as gelling agent (Figure 3).

Spreadability

Spreadability was measured by fabricated apparatus and was found to be in the range of 51.19±1.15%.

Viscosity

The Rheological behaviour of developed formulation was analysed using Brookfield Viscometer (Brookfield DV-III Ultra Rheometer). Formulation was sheared at variable speed ranging from 10, 20, 30, 40, 50, 60, 70, 80, 90 and 100 rpm, using spindle no.96. Rheogram was constructed using data of Rate of Shear and Shear Stress.

From the Rheogram, it can be concluded that upon application of Shear stress, viscosity was reduced and very less viscosity was observed at higher shear stress; indicating loss of polymeric structural network. Vice versa condition was observed with reducing the shear stress; i.e. structure regaining but not as original formulation. Hence, Shear thinning behaviour indicates Thixotropic flow of developed PLO gel. Viscosity of optimize batch was found to be 8501 centipoise by using Brookfield viscometer spindle T-F 96 helipath at 50 rpm; 25±5°C temperature.

Drug content

UV spectroscopy was used as an analytical method to determine the content of Leflunomide per gm of Gel. The Drug content was found to be in range of 99.12-96.61% for the same batch repeated thrice.

In vitro drug release

Optimized batch of PLO was subjected to Dialysis bag to study the *in vitro* drug release of developed formulation. Figure 4 showed initial burst release of drug due to presence of unentrapped drug on three-dimensional structure. Drug release data were subjected to different kinetic models which concluded that drug release from developed dosage form followed Higuchi model showing diffusion-controlled drug release.

Ex vivo permeation study

Study was performed by placing Ox ear skin as a semipermeable membrane in Franz diffusion cell. Drug permeation was observed for 8 hr and parameters were calculated using drug release data across the skin. Lag time was found to be 0.6 hr with high flux value of 10.96 mg/cm^2-h. Permeability coefficient was found to be 1.09 and diffusion coefficient 0.00027. Result showed satisfactory drug release through skin.

In vivo study

The paw volume of mice was noticeably decreased after applying both the standard marketed formulation and the developed Leflunomide PLO Gel. From 2 hr onwards, there was a significant reduction in paw volume observed for both the standard marketed formulation and the Leflunomide PLO Gel, compared to the positive control group. Interestingly, the mice treated with Leflunomide PLO Gel exhibited a greater reduction in paw volume at 4 hr compared to the standard marketed formulation. This result is summarized in Table 4.

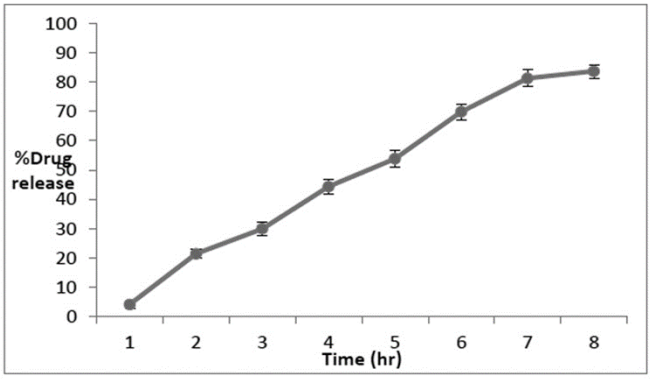

Figure 4: *In vitro* Drug Release from optimized Batch.

Table 4: **Effect of Leflunomide PLO gel on carrageenan-induced paws volume at different time intervals.**

Time (h)	Normal control (a)	Positive control (b)	Standard Marketed Formulation (c)	Leflunomide PLO gel (d)
0	0.8025±0.01109	0.8100±0.01683	0.7900±0.01472	0.8250±0.01555
1	0.8150±0.01555	0.8800±0.01080	0.8725±0.01493	0.8550±0.03663
2	0.7915±0.01797	1.008±0.01548***	0.8400±0.004082$^{###}$ (16.66%)	0.8950±0.02723$^{##}$ (11.21%)
3	0.7825±0.01797	1.055±0.02784***	0.8300±0.005773$^{###}$ (21.32%)	0.8000±0.009129$^{###}$ (25.29%)
4	0.7800±0.01871	1.080±0.01225***	0.8200±0.008165$^{###}$ (24.07%)	0.7500±0.01291$^{###\&}$ (30.55%)

All the statistical outcomes were stated in terms of mean±SEM; n=6;a vs. b, $^{***}p< 0.001$; b vs. c and b vs. d, $^{##}p<.01$, $^{###}p<0.001$; c vs. d, $^{\&}p< 0.05$.

Table 5: **Result of Stability study.**

Parameter	Before storage (0 day)	After 3-month storage (40±2°C/75%±5% RH)	After 3-month storage (25±2°C / 65%±5% RH)
Morphological Appearance	White, Gel form	White, Gel form	White, Gel form
Viscosity (cps)	8499±53.01	8459±125.60	8450±161.21
% Drug release (8 hr)	82.56±4.45	79.06±5.53	78.47±5.38

Value are expressed as mean±SD; n=3.

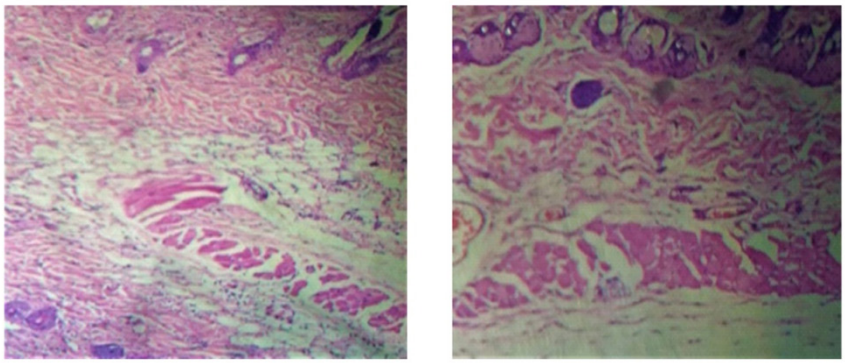

Figure 5: Histopathology of mice skin tretaed water (A) and Leflunomide PLO gel (B).

Histopathology study

The study findings indicate that there were no significant alterations observed in the microscopic composition of the removed skin sample from mice after being treated with the Leflunomide PLO gel and water for 24 hr (as shown in Figure 5). The epithelial layer and cellular structure of the skin remained unaffected, and there were no substantial modifications in the detailed structure of the mucosal morphology. These results lead to the conclusion that the organogel is safe to use topically and compatible with biological systems.

Stability study

A stability study was performed, in accordance with ICH guidelines, and the results are presented in Table 5. Based on these findings, it can be concluded that no significant changes were observed in the physical appearance, rheological behaviour of the formulation, and % drug release. Therefore, the formulation can be considered stable under the given storage conditions.

CONCLUSION

Leflunomide containing PLO gel was prepared by using different concentration of Poloxamer 407 and Ratio of Aqueous and Oil phase. PLO gel was optimized using 3^2 experimental designs. The optimized batch of PLO gel was evaluated for various physicochemical parameters. *In vitro* drug release study and *ex vivo* permeation study showed sufficient drug release. Optimized formulation exhibits satisfactory anti-inflammatory activity and Histopathology study on mice skin confirmed compatibility with

skin. Hence, developed formulation can be an alternate dosage form with available marketed formulation with added advantage of Patient compliance.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

RA: Rheumatoid Arthritis; **DMARD:** Disease Modifying Anti-Rheumatic Drug; **PLO Gel:** Pluronic Lecithin Organogel; **2D and 3D:** Two dimensional and three dimensional; **UV:** Ultraviolet; **ICH:** International Conference on Harmonization; **RH:** Relative humidity; **ANNOVA:** Analysis of Variance; **cps:** Centipoise; **rpm:** Rotations per minute.

SUMMARY

Present study deals with the formulation of Leflunomide loaded Pluronic Lecithin Organogel for topical application in symptomatic treatment of Rheumatoid Arthritis. Pluronic Lecithin Organogel was prepared by dispersing Oil phase into aqueous phase. Process and formulation variables were studied. Effect of formulation variables were analysed using 3^2 full factorial design by keeping process variables constant. Optimized formulation was selected by setting desirable goal and was characterized for various parameters like Gel transition temperature, pH, Drug content, Rheological behaviour, Spreadability, *in vitro* drug release behaviour, *ex vivo* permeation study, histopathology, *in vivo* study and stability study. *Ex vivo* permeation study showed significant drug release comparable to *in vitro* drug release study. The Anti-inflammatory activity of developed formulation confirmed desirable result compared to standard marketed formulation.

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