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NOVEL PLURONIC LECITHIN ORGANOGEL SYSTEM FOR TRANSDERMAL DELIVERY OF LEFLUNOMIDE IN RHEUMATOID ARTHRITIS MANAGEMENT

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic autoimmune disorder characterized by persistent joint inflammation, pain, and progressive disability. Conventional oral administration of leflunomide, a disease-modifying antirheumatic drug (DMARD), is associated with gastrointestinal disturbances, hepatic toxicity, and variable bioavailability. To overcome these limitations, the present study was undertaken to formulate and evaluate a leflunomide-loaded pluronic lecithin organogel (PLO) for transdermal delivery. The organogel was prepared by incorporating leflunomide into a pluronic-lecithin system, optimized for drug loading, spreadability, viscosity, and stability. Physicochemical characterization, pH determination, and in vitro drug release studies were performed, along with ex vivo permeation across rat skin. The prepared PLO gel exhibited satisfactory physicochemical properties, sustained release behavior, and enhanced drug permeation compared to conventional formulations. Stability testing confirmed minimal drug degradation and acceptable storage characteristics. The findings suggest that PLO-based leflunomide gel has the potential to bypass first-pass metabolism, reduce systemic toxicity, and provide a more targeted therapeutic effect in rheumatoid arthritis management.

I. INTRODUCTION

The fundamentals of successful formulation are to deliver the active substance at target organ with minimal discomfort and side effects. In this respect, transdermal route excels because of avoidance of hepatic first pass metabolism, typical peak trough plasma profile, ease of administration etc. Drug delivery through the skin has been used to target the epidermis, dermis and deeper tissues and for systemic delivery. The major barrier for the transport of drugs through the skin is the stratum corneum, with most transport occurring through the intercellular region.

A topical gel is a gel substance, which often contains some form of medicine and is applied to the skin or the mucus membranes. . In most cases a topical gel is clear and it tends to be more readily absorbed by the skin than is a lotion or ointment. Individual drugs have different degrees of penetration. A balance between lipid and aqueous solubility is needed to optimize penetration, and use of prodrug esters has been suggested as a way of enhancing permeability. Methods of Preparation of gels include fusion method, cold method, and dispersion method [1-5] Pluronic lecithin organogel is mainly composed of Pluronic F-127, soya lecithin, and IPP/IPM. In general, it is made up of two phases, first pluronic phase (aqueous phase) and second lecithin phase (oil phase), i.e., pluronic gel combined with a lecithin.

Pluronic gel (aqueous phase):

Pluronic gel is prepared by taking specified amount of Pluronic F-127 NF in ice cold water, agitating continuously and placing the mixture overnight for complete dissolution of Pluronic F-127. About 0.2% w/w potassium sorbate is added as preservative.

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Lecithin phase (oil phase):

Lecithin phase is prepared by taking specified amount of lecithin, IPP/IPM, and 0.2-0.3% w/w sorbic acid as preservative, then keeping the mixture overnight for complete dissolution of lecithin [10].

Advantages of Pluronic Lecithin Organogel System . [11-15]:

Pluronic lecithin organogel have following advantages over other transdermal drug delivery system:

• More stable than other types of gel.
• Easy to formulate.
• Have a high uptake capacity for active drugs.
• Do not grow mold if the gel becomes contaminated.
• Enhanced the drug penetration through the skin.
• The drug would penetrate to the subjacent tissues attaining high concentrations in the affected muscles / joints, while maintaining low blood levels.
• Poorly water soluble drug can be easily formulated using PLO.
• They can substitute for oral administration of medication when that route is unsuitable.
• They are less greasy and can be easily removed from the skin.
• Localized effect with minimum systemic side effects.

II. MATERIALS AND METHODS

2.1 Procurements of Drug and Excipients:

Flurbiprofen was obtained from sun pharma India Ltd., Mumbai. Pluronic F-127 was obtained from Sigma Aldrich, Delhi. Lecithin was purchased from Ruchi soya Pvt. Ltd.Isopropyl myristate and Polyethylene glycol 400 was purchased from SDFCL, Potassium sorbate and Sorbic acid was purchased from CDH, Potassium di hydrogen phosphate was purchased from Sunchem, Di sodium hydrogen phosphate, Sodium chloride and Sodium hydroxide was procured from Merck and n-octanol from Triza.

Table:1 Different Formulation of PLO

Formulations	Ingredients (%)							
	Drug		Oil Phase			Aqueous Phase		
	Flurbiprofen	PEG 400	Soya Lecithin	Sorbic Acid	Isopropyl Myristate	Pluronic F-127	Potassium sorbate	Distilled water
F-1	3	10	1	0.2	100	20	0.2	100
F-2	3	10	3	0.2	100	20	0.2	100
F-3	3	10	5	0.2	100	20	0.2	100
F-4	3	10	7	0.2	100	20	0.2	100

2.2 Method of Preparation of PLO: (by Cold Method)

The various formulation of PLO was developed with different compositions. Four formulations of different compositions were made as given in (Table 1). All the 4 formulation were coded from F1 to F4. Pluronic Lecithin Organogel is a two phase's based gel. It is made up of 2 phases an oil phase and a aqueous phase.

Oil Phase was prepared by mixing soya lecithin and sorbic acid in appropriate quantity of isopropyl myristate. The mixture was kept overnight at room temperature in order to dissolve its constituents completely. Aqueous phase was prepared by dispersing weighed amount of pluronic F-127 and potassium sorbate in cold water. The dispersion was stored in refrigerator for effect for effective dissolution of Pluronic F-127. The next day, active ingredient Flurbiprofen was dissolved in Polyethylene glycol-400 and mixed with the lecithin-isopropyl solution. Polyethylene glycol-400 was used for solubilization of Flurbiprofen. Finally, aqueous phase (70%) was slowly added in oil phase (30%) with stirring using mechanical stirrer. Following PLO formulations were prepared by altering the concentration of Lecithin, while keeping the concentration of Pluronic and other excipients and drug unchanged.

III. EVALUATION PARAMETERS

1) Measurement of pH

The pH of various gel formulations was determined by using digital pH meter. The measurement of pH of each formulation was done in triplicates and average values were calculated. The data show in table.

2) Viscosity study

Brookfield digital viscometer (model DV-I+, Brookfield Engineering Laboratory, INC., USA)

was used to measure the viscosity (in poise) of the prepared gel formulations. The spindle (T-D) was rotated at 10 rpm. The viscosity of formulations was more correct which was near to 100% torque. Samples were measured at 30 ± 1° C. Reading was detected 30 sec after measurement was made, when the level was stabilized. The data show in table.

3) Drug content

1 g of the prepared gel was dissolved in 100ml of ethanol. 1ml of this solution was further diluted to 100ml. Then absorbance was measured at 247nm. Drug content was calculated using the equation, which was obtained by linear regression analysis of calibration curve of drug in ethanol. The data show in table.

4) In vitro Diffusion studies

Phosphate buffer of pH 7.4 was used for in vitro release as a receptor medium. The egg membrane was used in franz- diffusion cell. The 1g of gel sample was applied on the membrane and then fixed in between donor and receptor compartment of diffusion cell. The receptor compartment contained phosphate buffer of pH 7.4. The temperature of diffusion medium was thermostatically controlled at 37±1ºC and the medium was stirred by magnetic stirrer at 100 rpm. The sample at predetermined intervals were withdrawn and replaced by equal volume of fresh fluid. The samples withdrawn were spectrophotometrically estimated using phosphate buffer pH as 7.4 a blank at 247 nm. The data show in table.

IV. RESULTS

1) Measurement of pH

The pH of various gel formulations was determined by using digital pH meter as mentioned. The Results are shown in (Table 2).

Table 2: pH of different formulation of gel

S. No	Formulations	pH
1	F1	5.5 ± 0.1
2	F2	6.22 ± 0.17
3	F3	6.01 ± 0.17
4	F4	6.40 ± 0.17

2) Viscosity

The viscosity of Gel formulations were measured by Brookfield digital viscometer as mentioned earlier. The results are shown as below in (Tab 3).

Table 3: Viscosity of different formulations

S. No	Formulations	Viscosity (poise)
1	F1	2908 ± 1.67
2	F2	3160 ± 40
3	F3	3248 ± 21.34
4	F4	3417 ± 9.34

3) % Drug Content

% Drug content was calculated by U.V. method at 248nm. For calculation of drug content 1 g of the prepared gel was dissolved in 100ml of ethanol. 1ml of this solution was further diluted to 100ml. Then absorbance was measured at 247-248nm. Then results are shown in (Table 4).

Table 4: Drug Content of different formulation of gel

S. No	Formulations	% Drug content
1	F1	94.66 ± 0.19
2	F2	97.48 ± 0.68
3	F3	97.25 ± 0.52
4	F4	96.51 ± 0.27

4) In-vitro release study

In-vitro release study was done to obtain release profiles of the prepared gel formulations by the method mentioned. The study was performed upto 8 hrs. The results are shown in (Table 5).

Table 5: In-vitro Release study in PBS 7.4 pH

		% Drug release			
S. No	Time (hrs)	F1	F2	F3	F4
1	0	0	0	0	0
2	1	3.45	12.66	4.98	9.871
3	2	5.78	21.49	11.67	12.18
4	3	9.87	28.97	19.56	20.62
5	4	12.02	39.55	26.67	23.71
6	5	22.45	48.89	35.87	28.57
7	6	25.67	57.77	44.56	38.27
8	7	30.69	65.86	51.65	44.82
9	8	39.88	70.95	64.67	55.53

The above results indicate that, for good drug release from the gel, optimized amount of lecithin & Pluronic is required. Further increase or decrease in concentration of lecithin above or below the optimized concentration may hamper & disturb the skin penetration of gel and hence affect the release profile of the drug. This might be due to the extensive formation of network like structure.

Fig 1: % Cumulative Release vs Time

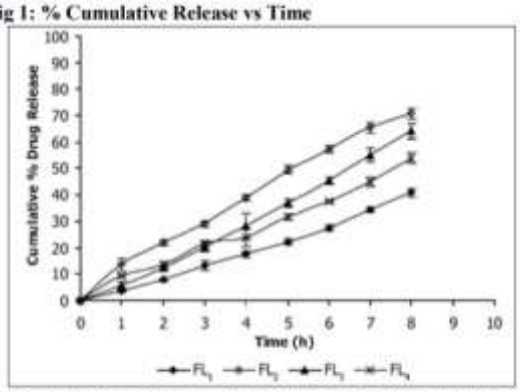

Fig. 1: *In vitro* release profile of flurbiprofen through dialysis membrane-70

In vitro release rates through dialysis membrane of the four flurbiprofen formulations developed, FL_1 (-◆-), FL_2 (-○-), FL_3 (-▲-) and FL_4 (-*-)

5) Stability Studies

The stability testing provides evidence on the variation of the quality of a drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and establishes a shelf life for the drug product and recommended storage conditions. Stability studies should include testing of those attributes of the drug product that are susceptible to change during storage and are likely to influence quality, safety, and/or efficacy. The testing should cover the physical and chemical attributes.

Stability of formulations

The optimized formulations from all the four formulations were selected and subjected to the accelerated stability testing. Formulation were kept at 400 C, 250 C & room temperature for 45 days & evaluated for following parameters:

i) Physical stability:

The gel formulations were evaluated in terms of physical character like phase separation & change in colour, odour & rheological parameters. Physical stability testing was done by visual inspection of the formulation on day 1 and then on 45th

ii) Chemical stability:

The gel formulations were evaluated for % drug content. The % drug content day. of the formulations were determined, by method given .on day 1 and then on 45th day and results were reported.

From the Evaluation studies results reported above; two formulations F2 & F4 were selected as optimized PLO formulations. They were than subjected to 45 days Accelerated Stability studies as per the method reported. The results of Accelerated Stability are shown in (Table 6) below:

Table 6: Accelerated Stability studies of formulations

		F2			F4		
S. No	Parameters	40°C	25°C	Room Temp	40°C	25°C	Room Temp
1	pH	6.65	6.23	6.22	6.1	6.3	6.4
2	Viscosity in cps	3141	3160	3128	3402	3417	3409
3	Phase separation	No	No	No	No	No	No
4	Spreadability	Good	Good	Good	Good	Good	Good
5	%Drug content	71.78	70.95	70.59	54.56	55.60	55.58

V. DISCUSSION AND CONCLUSION

The study successfully developed and evaluated a novel leflunomide-loaded pluronic lecithin organogel for transdermal application in rheumatoid arthritis therapy. The formulation demonstrated favorable stability, excellent spreadability, and controlled release with enhanced permeation across the skin. Compared to conventional oral therapy, the PLO-based system offers the advantages of improved patient compliance, reduced gastrointestinal side effects, and localized therapeutic action. These results highlight the potential of transdermal leflunomide delivery as a promising alternative strategy for long-term management of rheumatoid arthritis. Future work should focus on in vivo pharmacokinetic and pharmacodynamic studies, as well as clinical evaluation, to validate the therapeutic efficacy and safety of this novel delivery system.

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