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FORMULATION AND EVALUATION OF LEFLUNOMIDE LOADED PLURONIC LECITHIN ORGANOGEL FOR TREATMENT OF RHEUMATOID ARTHRITIS

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ABSTRACT

This study aims to develop and assess an organogel comprising pluronic lecithin and a nonsteroidal anti-inflammatory medication (Flurbiprofen) for topical use. This study created and evaluated four formulations of pluronic lecithin in an organogel. A variety of parameters, including appearance, drug content, viscosity, pH, and in vitro diffusion testing, were assessed for each formed organogel. Organogels are generally thermodynamically stable materials that have been investigated as bioactive agent delivery matrix. An effort has been made to comprehend the characteristics of organogels, different kinds of organogelators, and some uses of the organogels in controlled delivery in the present work.

Key words: drug delivery, biocompatibility, gel, gelator, and organogel.

1. 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.

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.

2. 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

Formulation	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.

3. 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.

4. 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

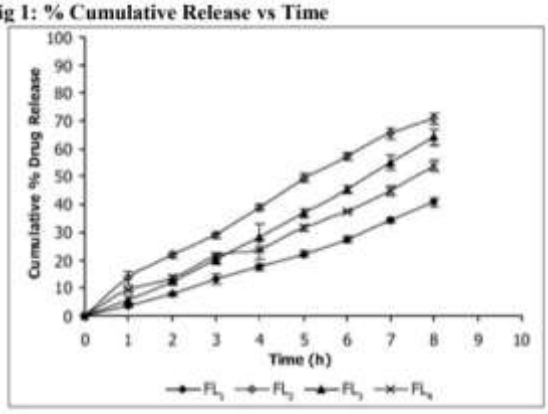

Fig. 1: *In vitro* release profile of flurbiprofen through dialysis membrane-70

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

5. DISCUSSION AND CONCLUSION

One of the most promising medication delivery methods is transdermal application, which avoids drug inactivation due to GI tract enzymes and pH effects and bypasses the first pass metabolism.The drug's bioavailability is boosted and it offers a continuous method of delivery at rates that are almost identical to those of an intravenous infusion. Patient compliance is increased, the delivery is non-invasive, and hospitalization is not necessary. For a medication to penetrate the skin, it must be hydrophilic, lipophilic, and have a favorable partition coefficient. It should also be thermodynamically active. The drug's preformulation research was carried out. Through the analysis of its organoleptic characteristics, Flurbiprofen was found to be an odorless, bitter-tasting, white or slightly yellow crystalline powder. Flurbiprofen is less soluble in water and more soluble in organic solvents, according to the findings of qualitative solubility tests. 3.89 was discovered to be the partition coefficient, which is appropriate for transdermal medication administration. Flurbiprofen's partition coefficient was found to be more than 1, indicating that it has a lipophilic nature. Using a microscope approach, the average particle size of flurbiprofen was discovered to be 7.145 micrometers. It was found that the melting point was 110–112 0 The transdermal anti-inflammatory gels, which included lecithin and pluronic as well as flurbiprofen, were made and assessed according to a variety of criteria. Formulations were optimized by adjusting the lecithin %. These formulations were then assessed for pH, drug concentration, and rheological characteristics including viscosity. All of the findings were good. A research on the in vitro release of each of the four formulations was assessed. All formulations were studied for eight hours, and the findings are shown in Table 5, which indicates that Flurbiprofen's cumulative% Release profile for Formulations

F2 and F4 is satisfactory after eight hours. On the other hand, the F2(3% lecithin) formulation produced the shown linear curve. This suggests that there is more medication penetration across the membrane in PLO Gel. The results of the stability research showed that all of the chosen formulations (F2 and F4) were sufficiently stable at various temperatures (40 C, which is almost the same range as stated in the Merck Index and indicates that the medication is crystalline in nature). Flurbiprofen's preformulation research produced findings that were good enough to choose the medication for a transdermal drug delivery system. For 45 days, there was no change in the drug concentration, phase separation, pH, rheological characteristics, color, or odor at any temperature (0 C, 250 C, or room temperature). Therefore, it might be said that the formulation was chemically and physically stable. The explanation above makes it rather evident that, out of all the created formulas, F2(3% lecithin) is the best one. According to this research, 3% lecithin would increase the drug's (flurbiprofen) permeation. For transdermal distribution, the organogel formulation with 3% lecithin, 20% pluronic, and flurbiprofen is recommended since it offers the best drug penetration.

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