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FORMULATION AND EVALUATION OF PLURONIC LECITHIN ORGANOGEL OF LORNOXICAM

[1]*Nitin Lodhe*, [2]*Dr. Kailas Biyani*
[1]*Research Scholar*, [2]*Supervisior*
[1,2] *School of Pharmacy, SunRise University, Alwar, Rajasthan, India*
Corresponding author email:-nitinlodhe87@gmail.com

Abstract:

Lornoxicam transdermal gel containing an appropriate enhancer for a controlled drug release was formulated. The aim of the present study is to prepare and evaluate novel topical drug delivery of lornoxicam by using pluronic lecithin based organogel. Formulations were developed using 30% oil phase and 70% aqueous phase. The formulated organogels were evaluated for appearance by psychorheological, in vitro diffusion study, drug content, viscosity, spreadability and pH. It was found that the pH of all the formulations is in the range of to 6-7 that suits the skin pH, indicating skin compatibility. This is the primary requirement for a good topical formulation. All formulation showed spreadability in the range of 13.83- 28.35gcm/sec. The finding of the study can be utilize for the development of organogel of the other drugs for the safer and effective topical delivery..

Keywords: Lornoxicam, organogel, FTIR, Drug release

INTRODUCTION:

Organogels:

Organogels are semi-solid systems, in which an organic liquid phase is immobilized by a three-dimensional network composed of self assembled, intertwined gelator fibers. Despite their majoritarily liquid composition, these systems demonstrate the appearance and rheological behaviour of solids. Organogels can be distinguished from hydrogels by their predominantly organic continuous phase and can then be further subdivided based on the nature of the gelling molecule: polymeric or low molecular weight (LMW) organogelators.

Lecithin Organogel:

The topical delivery has been attempted and made successful using several lipid-based systems viz vesicular systems, lipid microspheres, lipid nanoparticles, lipid-microemulsions, and polymeric gels. In a recent development, phospholipids in conjunction with some other additives have been shown to provide a very promising topical drug delivery vehicle known as lecithin organogels (LOs). LOs are thermodynamically stable, clear, viscoelastic, biocompatible, and isotropic gels composed of phospholipids (lecithin), appropriate organic solvent, and a polar solvent. LOs, the jelly-like phases, consist of a 3-dimensional network of entangled reverse cylindrical (polymer-like) micelles, which immobilizes the continuous or macroscopic external organic phase, thus turning a liquid into a gel. These systems are currently of interest to the pharmaceutical scientist because of their structural and functional benefits. Several therapeutic agents have been formulated as LOs for their facilitated transport through topical route (for dermal or transdermal effect), with some very encouraging results. The improved topical drug delivery has mainly been attributed to the biphasic drug solubility, the desired drug partitioning, and the modification of skin barrier function by the organogel components. Being thermodynamically stable, LOs are prepared by spontaneous emulsification and therefore possess prolonged shelf life. The utility of this novel matrix as a topical vehicle has further increased owing to its very low skin irritancy potential.

Materials and Methods:

Materials:

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Lornoxicam,pH7.4buffer, potassium dihydrogen phosphate, sodium hydroxide, disodium hydrogen phosphate, sodium hydroxide, n-octanol, Pluronic F-127, ecithin, isopropyl myristate, Sodiumsorbate, SodiumBenzoate, distilled water, ethanol,methanol, and acetone.

Methods: Preformulationstudies

1.Determination of solubility

a.Qualitative solubility

Qualitativesolubilityanalysisofdrugsweredonebydissolving5mgofdrugin 5 ml of distilled water and different solvents such as HCl (0.1N), NaOH (0.05N), Saline phosphate buffer (pH 7.4), Phosphate buffer(pH 9), Phosphate buffer(pH 4), phosphate buffer (pH 2), ethanol, methanol, acetone and chloroform wereused to determinethesolubilityofdrug.

b. Quantitative Solubility

Quantitative solubility analysis of drugs were done by 5 ml each solvent anddrug in gm(s) into the solvent till saturation of solvent. Differentsolvents wereused for the solubility determination like distilled water, Saline phosphate buffer(pH 7), Phosphate buffer(pH 3.6), HCl (0.1N)andNaOH (0.05N). This is done todeterminethecapacityofthesolventfordissolvingthedruginit.Theconcentrationofdrugismeasured byUVspectrophotometerat 376 nm.

Table 1Organolepticpropertiesof Lornoxicam

Organolepticproperties	**Results**
Colour	OrangetoYellowpowder
Crystallinity	Amorphousinnature
Taste	Slightlybitterin taste
Odour	Odourless

1) PartitionCoefficient

Partition Coefficient of Lornoxicam was found to be 1.7. The above value ofpartition coefficient is nearby to the value of partition coefficient reported in Merckindex for Lornoxicam. The partition coefficient shows that the drug is lipophilic innaturewhichmakesitsuitablefortransdermaldeliveryviaPluronicIecithinorganogel.

2) MeltingPoint

Melting Point of Lornoxicam was found in range of **225-228^{0}c** which fallsunder the melting point range specified in Merck index. This shows that the drug ispure. The drug starts melting at 225º c and completes melting at 228º c which indicatesamorphousnatureofdrug.

3) SolubilityProperties

Table.2QualitativeSolubilityofdrugindifferentsolvents

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Solvents(5ml)	SolubilityPropertiesofthedrug(5mg)
DistilledWater	+
0.1NHCl	+++
3.6pHBuffer	++
7.4pHBuffer	+++
9.2pHBuffer	+++
Ethanol	++
Methanol	++
Chloroform	++
Acetone	+++
Hexane	+
0.05NNaOH	++++

\+ Insoluble

++ Poorlysoluble

+++ Slightlysoluble

++++Freelysoluble

The results were showed that Lornoxicam is insoluble in distilled water &hexane and very less solubility in organic solvents like ethanol, methanol, chloroform&acetonebutthedrugwasfreelysolubleinalkalinesolventslike7.4pHbufferand 9.2 pH buffer. The drug showed high solubility in 0.05 N NaOH, which indicates theacidicnatureofthedrug.

Quantitative Solubility: The results of quantitative solubility of the drug are given below in the table.3.

Table.3QuantitativeSolubilityofdrugindifferentsolvents

Solvent	Concentrationofdruginsolvent
0.05NNaOH	6.306mgofdrugwaspresent in 1mlof0.05 NNaOH
0.1NHCl	0.664mgofdrugwaspresent in 1 mlof0.1NHCl
3.6pHBuffer	0.732mgofdrugwas presentin 1 mlof3.6 pHbuffer

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7.4pHBuffer	0.92mgofdrugwaspresent in 1 mlof7.4 pHbuffer
9.2pHBuffer	1.224mgofdrugwas presentin 1 mlof9.2 pHbuffer

The observations showed that the solubility of Lornoxicam increases with the increaseof pH from 3.0 to 9.0, which indicates that the ionization of drug increases with theelevatingpH.

5.)Standard Curve

Standard curve of the drugin 0.05 N NaOH& 7.4PBS wasprepared bymethodreported byNemutlu etal (2005).Theabsorbancesweretakenoutat376nm.

Table 4 AbsorbancesofLornoxicamat376nmin0.05 NNaOH

S. No.	**Concentration(µg/ml)**	**Absorbance**
1	5	0.076
2	10	0.147
3	15	0.216
4	20	0.298
5	25	0.367
6	30	0.438
7	35	0.513

Table 7Drug-ExcipientCompatibilityObservations

S.No.	**Additives (50 mg each)withdrug**	**Observation at 60°Cfor2 weeks**	**Observation at 40°Cfor2 month**	**Remarks**
1.	Drug(lornoxicam)	Nointeraction	Nointeraction	Accepted
2.	Drug+pluronicF-127	Nointeraction	Nointeraction	Accepted
3.	Drug+lecithin	Nointeraction	Nointeraction	Accepted
4.	Drug+isopropylmyristate	Nointeraction	Nointeraction	Accepted
5.	Drug+PEG400	Nointeraction	Nointeraction	Accepted
6.	Drug+Sodiumsorbate	Nointeraction	Nointeraction	Accepted
7.	Drug+Sodium Benzoate	Nointeraction	Nointeraction	Accepted

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8.	Drug+Triethanolamine	Nointeraction	Nointeraction	Accepted
9.	Drug+carbopol 934	Nointeraction	Nointeraction	Accepted
10.	Drug+Oleicacid	Nointeraction	Nointeraction	Accepted
11.	Drug+Ethanol	Nointeraction	Nointeraction	Accepted
12.	Drug+propyleneglycol	Nointeraction	Nointeraction	Accepted

A. Lornoxicam

Table 8. CompositionofPluronicLecithinorganogelofLornoxicam

CONTENT		L-1	L-2	L-3	L-4	L-5	L-6	L-7	L-8	L-9	L-10
DRUG	Lornoxicam (gm)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
	PEG400 (ml)	20	20	20	20	20	20	20	20	20	20
OILPHASE (%)	SoyaLecithin (gm)	1	3	5	7	9	3	3	3	3	3
	SodiumBenzoate (gm)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	02
	IsopropylMyristate q.s.(ml)	100	100	100	100	100	100	100	100	100	100
AQUEOUSP	PluronicF-127 (gm)	20	20	20	20	20	5	10	15	30	25

	Sodium Sorbate(gm)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
	Distilled water q.s.(ml)	100	100	100	100	100	100	100	100	100	100

Table 9. CompositionofCarbopolgelofLornoxicam

S.No.	**Ingredients%**	**Formulation codeL-11**
1.	Lonoxicam	0.5gm
2.	Carbopol934	3gm
3.	Oleicacid	2.5ml
4.	Ethanol	30 ml
5.	Propyleneglycol	20 ml
6.	Triethanolamine	0.5ml
7.	Distilledwater	100 ml q. s.

7. EVALUATION

7.1 Methodsforevaluationstudiesfortransdermalgel

1) Measurementof 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 averagevalueswerecalculated.

2) Rheological studiesa.)Viscosi tystudy

Brookfielddigitalviscometer(modelDV-I+,BrookfieldEngineeringLaboratory, INC., USA) was used to measure the viscosity (in poise) of the preparedgelformulations.Thespindle(T-D)wasrotatedat10rpm.Theviscosityofformulationswasmorecorrectwhichwasnearto100%torque. Sampleswereмeasured at 30 ± 1° C. Reading was detected 30 sec after measurement was made,whenthelevel was stabilized.

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b.)Spreadability

Concentric circles of different radii were drawn on a graph paper and a glass plateof 100 ± 5 g was fixed on it. Weighed amount of gel (1g) was transferred to thecentre of the plate and allowed to spread over an area of 2 cm diameter. The otherglass plate of 100 ± 5 g was placed gently on the spreaded gel. Again the gel wasallowedtospreadandthespreaddiameterwasrecordedafter1minute.Thensubsequent glass plates were added one by one and the spread diameter of the gel wasrecordedafter1 minuteofeachaddition.

3) Drugcontent

1 g of the prepared gel was dissolved in 100ml of ethanol. 1 ml of the solutionprepared was further diluted to 100ml. Then absorbance was measured at λ max. Drugcontent was calculated using the equation, which was obtained by linear regressionanalysisofcalibration curveofdrugs.

4) *Invitro*Diffusionstudies

Phosphate buffer of pH 7.4 was used for *in vitro* release as a receptor medium. Theegg membrane was used in franz- diffusion cell. The 1g of gel sample was applied onthemembrane and thenfixed inbetweendonorandreceptorcompartmentofdiffusion

cell.Thereceptorcompartmentcontainedphosphatebufferof pH7.4.Thetemperature of diffusion medium was thermostatically controlled at 37±1°C and themedium was stirred by magnetic stirrer at 100 rpm. The sample at predeterminedintervals were withdrawn and replaced by equal volume of fresh fluid. The sampleswithdrawn were spectrophotometrically estimated using phosphate buffer pH as 7.4 ablankat λmax.

Stability off ormulations

The optimized formulations from all the ten formulations were selected andsubjected to the stability testing for 90 days. Formulations were kept at 40^0C, 25^0C &roomtemperaturefor90days&evaluatedforfollowingparameters:

i) Physicalstability: Thegelformulationswereevaluatedintermsofphysicalcharacter like phase separation & rheological parameters. Physical stability testingwasdonebyvisual inspection oftheformulationat 15 days interval for3 months.

ii) Chemicalstability: Thegelformulationswereevaluatedfor%drugcontent.The

%drugcontentof the formulations weredetermined at15 daysinterval for 3 months.

From the Evaluation studies results reported in chapter 7, two formulationswere selected as optimized PLO formulations. They were than subjected to 90 daysstability studies. The optimized gel formulations were evaluated in terms of physicalcharacter & chemical character like phase separation, rheological parameters, pH & %drugcontent.

7.2 Resultofevaluationstudiesoftransdermal gel

A. Lornoxicam

1) Measurementof pH

ThepHofskinisaround6.8.Theresultsgivenintable7.1showsthatpHofall the formulations was found to be in the range of 5.6 to 6.4, which is around to thepHofskin. This showsthat

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formulations arefit fortransdermal use.

2) Viscosity

The viscosity of all the formulation was found in the range of 2953 to 3276poisegiveninabovetable7.1.Theresultsshowsthattheincreaseinpolymerconcentrationi.e.lecithinandpluronicthereisincreaseinviscosityofPluroniclecithin organogel. This increase in viscosity is due to formation of complex andstabilized because of the synergistic contribution of both phospholipid and polymericcosurfactant molecules, in their respective hydrated state (strong hydrogen bondingwith water). The viscosity of L-11 formulation, which is a carbopol gel, is less thanPluronic lecithin organogels,due to the weak hydrogen bonding between carbopoland water/polar solvent in carbopol gel as compare to lecithin and pluronic with waterinPluroniclecithin organogel.

3) Percentagedrugcontent

For calculation of drug content 1 gm of the prepared gel was dissolved in100ml of 0.05 N NaOH. One ml of the solution was further diluted to 100ml. Theabsorbance was measured at376nmin UV spectrophotometer against0.05 N NaOHasablank. Theresults arein table 9. .

The gel formulations were showed that drug content in the range of 95 to 99%,indicatinguniformdistributionofdrugthroughoutthebase.Resultsalsorevealsthat

PLOgelshavehigher%drugcontentthanCarbopolgel,whichindicatessuperiorityofformeron latter.

Table 10. pH,Viscositiyand%drugcontentofdifferentformulationof gel

S.No.	Formulations	pH	Viscosity(cps)	% Drugcontent
1.	L1	5.7	3165	99.23
2.	L2	6.2	3045	99.54
3.	L3	6.1	3242	96.92
4.	L4	6.27	2953	99.51
5.	L5	5.93	3178	99.29
6.	L6	6.4	3028	96.86
7.	L7	6.3	3276	98.85
8.	L8	5.9	2953	97.46
9.	L9	6.16	3143	97.32
10.	L10	6.06	3162	98.15
11.	L11	6.1	2999	95.67

4) Spreadability

Quantityofgelwastakenin1gm&initialdiameterwastakenmeasurement.Theobservations are recorded in table 10. .

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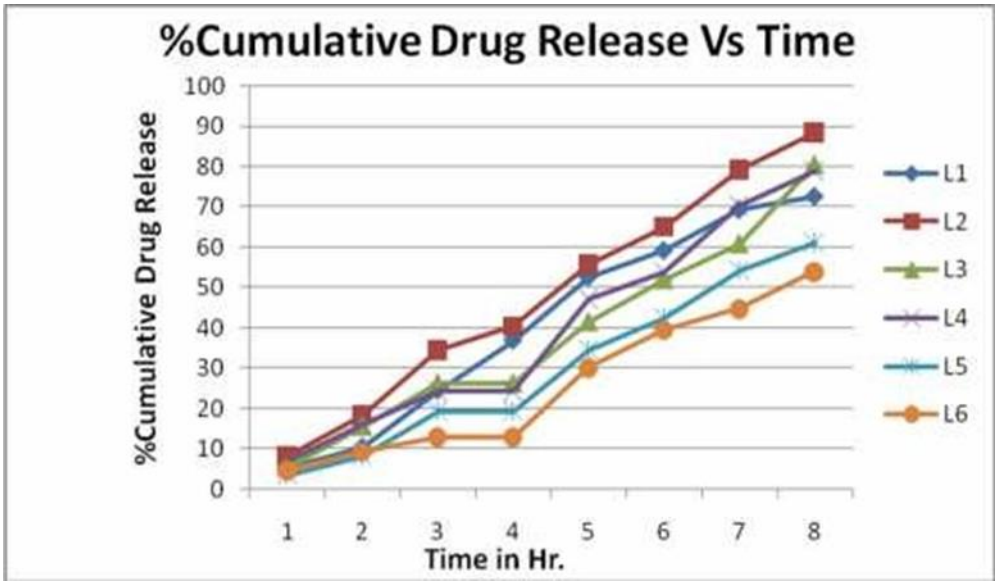

Fig.4%Cummulativedrugreleaseprofileof formulationL-1toL-6

After 90 days stability studies it was found that there was no phase separation,no change in color, odor and texture, in both the gel formulations (L-2 and L-4) andspredabilitywas alsofound to begoodatdifferenttemperatureconditions. The results of stability study shown in table 12 & 13 indicated that the twoselectedformulations(L-2andL- (40^0C,25^0C,roomtemperature)for90daysastherewasvery slightchange in drug content,viscosity and pH. Thus it may concluded that formulationwerephysicallyand chemicallystable. The transdermal anti-inflammatory gels containing Lornoxicam & differentpolymers, were prepared and evaluated for different parameters like pH, drug content&rheologicalpropertieslikeviscosity &spredability andresultsfoundwereallsatisfactory. The Results indicates that PLO gel shows better results than CarbopolGel.

Conclusion:

All formulation were also evaluated for In-vitro drug release study.Study was carried for 8 hrs for all formulations and results reported in table 7.3 showsthat, the Formulation L-2 and L-4 showed good cumulative % Drug Release profile ofLornoxicam in 8 hr. The cumulative amount permeated from Carbopol gel through membranewas found to be 65% which was less than PLO Gel formulations. This indicates that PLOGel hasmoredrugpermeation acrossthemembranethan carbopolgel.

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