International Journal of Pharmaceutical Science and Research
ISSN: 2455-4685; Impact Factor: RJIF 5.28
Received: 05-07-2019; Accepted: 07-08-2019
www.pharmacyjournal.net
Volume 4; Issue 4; October 2019; Page No. 27-37

Formulation development and evaluation of Lornoxicam gel

Manish Mukati[1], Raju Choukse[2], Sourabh Jain[3], Dr. Karunakar Shukla[4]
[1-4] Dr. APJ Abdul Kalam University, Indore, Madhya Pradesh, India

Abstract
The transdermal anti-inflammatory gels containing Lornoxicam & different polymers, were prepared and evaluated for different parameters like pH, drug content & rheological properties like viscosity & spredability and results found were all satisfactory. The Results indicates that PLO gel shows better results than Carbopol Gel. All eleven formulations were also evaluated for *In-vitro* drug release study. Study was carried for 8 hrs for all formulation and results reported in table 9.3 shows that, the Formulation F-2 and F-4 showed good cumulative % Drug Release profile of Lornoxicam in 8 hr. But the linear curve shown in fig. 9.1 was obtained from F-2 formulation. The cumulative amount permeated from Carbopol gel through membrane was found to be 67% which was less than PLO Gel formulations. This indicates that PLO Gel has more drug permeation across the membrane than carbopol gel.

Keywords: Lornoxicam, Gel, NSAID, carbopol 934, Trandermal delivery

Introduction
Gel is defined as "semisolid system consisting of dispersion made up of either small inorganic particles or large organic molecules enclosing and interpenetrated by liquid". Gels are also defined as semi-rigid system in which the movement of dispersing medium is restricted by an interlacing three-dimensional network of particles or solvated macromolecules of dispersed phase. A high degree of physical or chemical cross-linking may be involved. A gel may consist of twisted matted strands often wound together by stronger types of Vander walls forces to form crystalline and amorphous regions throughout the system [3].

Types of Gel
Single phase gels are the gels in which macromolecules are uniformly distributed throughout the liquid with no apparent boundaries between the dispersed macromolecules and the liquid.
Two phase gels are the gels in which the gel consists of floccules of small distinct particles, two-phase gel system often referred as Magma.

Classification of Gels
- **Hydrogels-Hydrogel:** (also called Aquagel) is a network of polymer chains that are water-insoluble, sometimes found as a colloidal gel in which water is the dispersion medium. Common ingredients are e.g. polyvinyl alcohol, sodium polyacrylate, acrylate polymers and copolymers with an abundance of hydrophilic groups.
- **Organogels-An organogel:** is a non-crystalline, non-glassy thermoreversible (thermoplastic) solid material composed of a liquid organic phase entrapped in a three-dimensionally cross-linked network. The liquid can be for example an organic solvent, mineral oil, or vegetable oil. The solubility and particle dimensions of the structurant are important characteristics for the elastic properties and firmness of the organogel. Often, these systems are based on self-assembly of the structurant molecules.
- **Xerogels-A xerogel:** is a solid formed from a gel by drying with unhindered shrinkage. Xerogels usually retain high porosity (25%) and enormous surface area (150–900 m^2/g), along with very small pore size (1-10 nm). When solvent removal occurs under hypercritical (supercritical) conditions, the network does not shrink and a highly porous, low-density material known as an aerogel is produced. Heat treatment of a xerogel at elevated temperature produces viscous sintering (shrinkage of the xerogel due to a small amount of viscous flow) and effectively transforms the porous gel into a dense glass [18].

Criteria for Selection of Drug
A wide range of drugs have been incorporated within PLO for transdermal delivery. The skin is, however, a good barrier to drug permeation and drug flux is known to be low. In fact, drug absorption following application to the skin is so low that only a few drugs have been formulated for transdermal delivery.
An ideal drug for transdermal delivery is:
- A potent chemical with a daily dose of a few milligrams (in man).
- A small molecule.
- One that has a high lipid solubility and reasonable water solubility.
- Non-irritating and non-sensitizing to the skin.
- Drug having short half-life.
- Drug should not be metabolized in the skin itself while permeating through it [30].

Lornoxicam has been selected because it meets most of the above requirements.

Objective of Work
The objective of the present study is to formulate and evaluate Pluronic lecithin organogel of Anti-inflammatory drug (Lornoxicam). Lornoxicam (chlortenoxicam) is a non-

steroidal anti-inflammatory drug (NSAID) of the oxicam class with analgesic, anti-inflammatory and antipyretic properties. It is available in oral and parenteral formulations. Lornoxicam is used for inflammatory disease of the joints, osteoarthritis, pain following surgery as well as pain in the lower back and hip.

Drawbacks associated with Lornoxicam are as follows:

- Slightly soluble in water.
- Cause gastrointestinal disturbances, like ulcers.
- Have some toxicity when given intravenously / orally.

So by present study an attempt has been made to bypass the above disadvantages of lornoxicam by administration by formulating the drug topically by incorporating it in pluronic lecithin base.

By this we are aiming to achieve the following objectives:

- Gastrointestinal side effects may be bypassed.
- Penetration of the drug through the skin may be enhanced.
- Lornoxicam which is a poorly water soluble drug can be easily formulated using organic solvent.
- Uptake capacity of drug in the system may be enhanced.
- Systemic toxicities might be minimized.
- Gel prepared may be thermodynamically stable.
- Growth of molds or microorganisms may be avoided even after contaimination of the product and hence the shelf life of the product will be increased.

Pluronic lecithin organogel will also offer an added advantage, which is that by the inclusion of pluronics as cosurfactants in organogel will make organogelling feasible with lecithin of relatively lesser purity. By this, the overall cost of the product can be decreased.

Materials and Method

Lornoxicam and lecithin were received as a gift sample from Unichem Laboratories, Mumbai, India and Ruchi Soya Pvt. Ltd. Indore, India respectively. Pluronic F-127 was procured from Sigma Aldrich, Delhi. Isopropyl myristate, polyethylene glycol-400, sorbic acid and potassium sorbate were supplied by CDH Pvt. Ltd., Delhi, India. All other chemicals were of analytical grade. List of material and their supplier name is given below.

Table 1: List of Material used and Supplier name

S.No.	Material	Supplier Name
1.	Lornoxicam	Unichem Lab. Ltd, Mumbai
2.	Pluronic F-127	Sigma Aldrich, Delhi
3.	Lecithin	Ruchi soya Pvt. Ltd., Indore
4.	Isopropyl myristate	SDFCL
5.	Potassium sorbate	CDH
6.	Sorbic acid	CDH
7.	Polyethylene glycol 400	SDFCL
8.	Potassium di hydrogen phosphate	Sunchem
9.	Di sodium hydrogen phosphate	Merck
10.	Sodium chloride	Merck
11.	Sodium hydroxide	Merck
10.	n-octanol	Triza
11.	Liquid paraffin	SDFCL

Equipment: List of Equipments and their supplier name is given below.

Table 2: List of Equipments used and Supplier Name

S.No.	Equipments	Supplier name
1.	UV/VIS Double beam Spectrophotometer	Shimadzu 1601 – Double beam UV/VIS
2.	pH meter	MK VI
3.	Electronic Balance	Contech
4.	Optical Microscope	Labomed
5.	Melting point Apparatus	Rolex
6.	Dessicator	SD
7.	Mechanical stirrer	Remi motors
8.	Dona Balance	Dhona Instrument Ltd

Methods of Preformulation Studies of Lornoxicam

1. Identification of drug

The identification of drug was done by UV spectrophotometric method reported by Nemutlu *et al* (2005) [31]. The small amount of drug is dissolved in 0.05 N NaOH and scanned in UV range 200-600 nm in UV Double beam spectrophotometer. The highest peak was determined, which is the λ_{max} for the Lornoxicam. The spectral data from this scan was used for the preparation of standard curve of Lornoxicam.

2. Preparation of standard curve

a. Standard curve of lornoxicam in 0.05 N NaOH

Standard stock solution of Lornoxicam was prepared by dissolving 100 mg drug in 100 ml 0.05 N NaOH (i.e.1000µg/ml). Aliquot of this solution are further prepared by taking 10 ml of above solution and diluting it upto 100 ml (i.e. 100 µg/ml). From the above solution further dilutions are prepared in range of 5-35 µg/ml. Absorbances were taken on UV Double beam spectrophotometer at 376 nm against 0.05 N NaOH as a blank. From these absorbance's, the standard curve is plotted. Standard curve equation and regression value is obtained. The absorptivity coefficient of drug at desired wavelengths was determined.

b. Standard curve of lornoxicam in 7.4 PBS

Standard stock solution of Lornoxicam was prepared by dissolving 10 mg drug in 10 ml 7.4 PBS (i.e.1000µg/ml) containing 12mg of Tromethamine. This solution was then sonicated for complete dissolution of drug. Aliquot of this solution are further prepared by taking 10 ml of above solution and diluting it upto 100 ml (i.e. 100 µg/ml). From the above solution further dilutions are prepared in range of 4-24 µg/ml. Absorbances were taken on UV Double beam spectrophotometer at 376 nm against 7.4 PBS as a blank. From these absorbance's, the standard curve is plotted.

Standard curve equation and regression value is obtained. The absorptivity coefficient of drug at desired wavelengths was determined.3) Determination of Solubility

a. Qualitative Solubility

Qualitative solubility analysis for Lornoxicam was done by dissolving 5 mg of drug in 5 ml of solvent. Different solvents such as distilled water, 0.1N HCl, 0.05 N NaOH, 7.4 pH Saline phosphate buffer, 9 pH Phosphate buffer, 4 Phosphate buffer, 2 pH phosphate buffer, Ethanol, Methanol, Acetone and Chloroform were used to determine the solubility of drug.

b. Quantitative Solubility

Quantitative solubility analysis for Lornoxicam was done by taking 5 ml each solvent and adding drug into the solvent till saturation of solvent. Different solvents were used for the solubility determination like distilled water, 7.4pH Saline phosphate buffer, 3.6pH Phosphate buffer, 0.1N HCl and 0.05 N NaOH. This is done to determine the capacity of the solvent for dissolving the drug in it. The concentration of drug is measured by UV spectrophotometric technique.

3. Partition Coefficient

Partition coefficient determination of Lornoxicam was done by simple shaking flask method. The 10 mg of drug was dissolved in 10 ml of distilled water and 10 ml of Carbon tetra chloride in separating funnel. The separating funnel was shaken well for 3-4 hours and then allowed to stand for at least for 1 hour for phase separation. After that the water phases was separated out and the concentration of drug was measured spectrophotometrically after suitable dilution at 376 nm.

$$P_{o/w} = C_{oil}/C_{water}$$

4. Melting Point-Melting point determination of Lornoxicam was done by using Melting Point Apparatus. In that method the presealed capillary were filled by the small amount of drug. Then capillary and thermometer were placed in Melting Point Apparatus. Capillary was observed for melting the drug. The temperature when the drug starts to melt and the temperature when drug complete melting was noted.

5. Particle Size

Particle size determination of Lornoxicam was done by optical microscopy using stage micrometer. A very little amount of drug was taken on slide with a drop of liquid paraffin on it. Particle size of 100 particles was observed under microscope. Then the average particle size of the drug was calculated.

Least Count = Stage/Ocular

7. Drug- excipient interaction study

A small amount of drug substance with excipients (like plronic F-127, lecithin, potassium sorbate, sorbic acid, isopropyl myristate, PEG 400, triethanolamine, carbopol 934, oleic acid, ethanol and propylene glycol) that is, physical mixture of the drug and excipients (in 1:1 ratio were prepared to have maximum likelihood interaction between them) was placed in a vial, and rubber stopper was placed on the vial and sealed properly. A storage period of 2 weeks at 60°C, and the same sample was retained for 2 months at 40°C. After storage the sample were observed physically for liquefaction, caking, odour or gas formation, discolouration.

Experimental Work

Results of Preformulation Studies of Lornoxicam

1. Identification of drug

The highest peak was found at 376 nm. Zero order derivative UV spectrophotometric methods were used for the analysis of lornoxicam. The solutions of the drug samples were prepared in 0.05 N NaOH and scanned in UV. The UV scan of the drug sample (fig. 7.1) showed highest peak at 376 nm which is nearby to the standard value reported in the Merck index.

The peak detection spectra of Lornoxicam in 0.05 N NaOH is given below in Fig. 7.1.

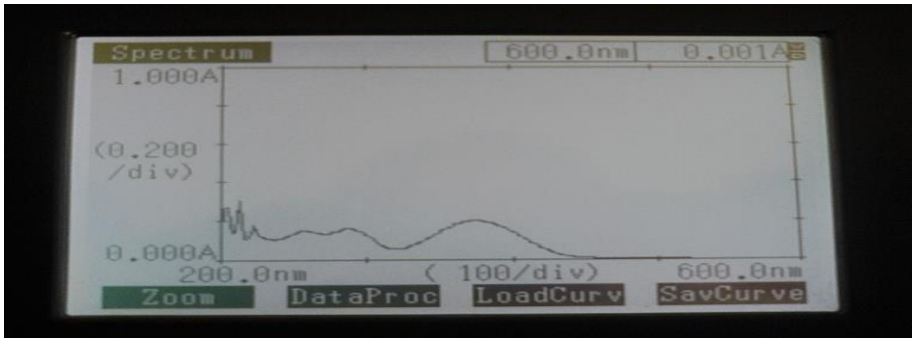

Fig 1: Peak Detection (λ_{max}) for Lornoxicam in 0.05 N NaOH

1. Organoleptic Properties

Organoleptic properties of the drug sample were found to be as given in table below.

Table 3: Organoleptic properties of Lornoxicam

Organoleptic properties	Results
Colour	Orange to Yellow powder
Crystallinity	Amorphous in nature
Taste	Slightly bitter in taste
Odour	Odourless

The above results are found similar to properties of Lornoxicam reported in Merck index.

2. Partition Coefficient

Partition Coefficient of Lornoxicam was found to be 1.7. The above value of partition coefficient is nearby to the value of partition coefficient reported in Merck index for Lornoxicam. The partition coefficient shows that the drug is lipophilic in nature which makes it suitable for transdermal

delivery via Pluronic lecithin organogel.

3. Melting Point

Melting Point of Lornoxicam was found in range of 225-228^{0}c which falls under the melting point range specified in Merck index. This shows that the drug is pure. The drug starts melting at 225º c and completes melting at 228º c which indicates amorphous nature of drug.

4. Solubility Properties

Qualitative Solubility: The results of Qualitative solubility of the drug in different solvents are given below in the table 7.2.

Table 4: Qualitative Solubility of drug in different solvents

Solvents(5ml)	Solubility Properties of the drug(5mg)
Distilled Water	+
0.1N HCl	+++
3.6 pH Buffer	++
7.4 pH Buffer	+++
9.2 pH Buffer	+++
Ethanol	++
Methanol	++
Chloroform	++
Acetone	+++
Hexane	+
0.05 N NaOH	++++

+ Insoluble
++ Poorly soluble
+++ Slightly soluble
++++ Freely soluble

The results showed that Lornoxicam is insoluble in distilled water & hexane and very less solubility in organic solvents like ethanol, methanol, chloroform & acetone but the drug showed good solubility in alkaline solvents like 7.4 pH buffer and 9.2 pH buffer. The drug showed high solubility in 0.05 N NaOH, which indicates the acidic nature of the drug.

Quantitative Solubilit

The results of Quantitative solubility of the drug are given below in the table 7.3.

Table 5: Quantitative Solubility of drug in different solvents

Solvent	Concentration of drug in solvent
0.05 N NaOH	6.306 mg of drug was present in 1ml of 0.05 N NaOH
0.1N HCl	0.664 mg of drug was present in 1 ml of 0.1N HCl
3.6 pH Buffer	0.732 mg of drug was present in 1 ml of 3.6 pH buffer
7.4 pH Buffer	0.92 mg of drug was present in 1 ml of 7.4 pH buffer
9.2 pH Buffer	1.224 mg of drug was present in 1 ml of 9.2 pH buffer

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

5. Standard Curve

Standard curve of the drug in 0.05 N NaOH & 7.4 PBS was prepared by method reported by Nemutlu *et al* (2005) [31]. The absorbances were taken out at 376 nm.

a. Standard curve of lornoxicam in 0.05 N NaOH

Absorbance's of the drug at 376 nm in 0.05 N NaOH are given below in table 7.4.

Table 6: Absorbances of Lornoxicam at 376 nm in 0.05 N NaOH

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

Standard curve of Lornoxicam in 0.05 N NaOH at 376 nm is shown below in fig. 7.2

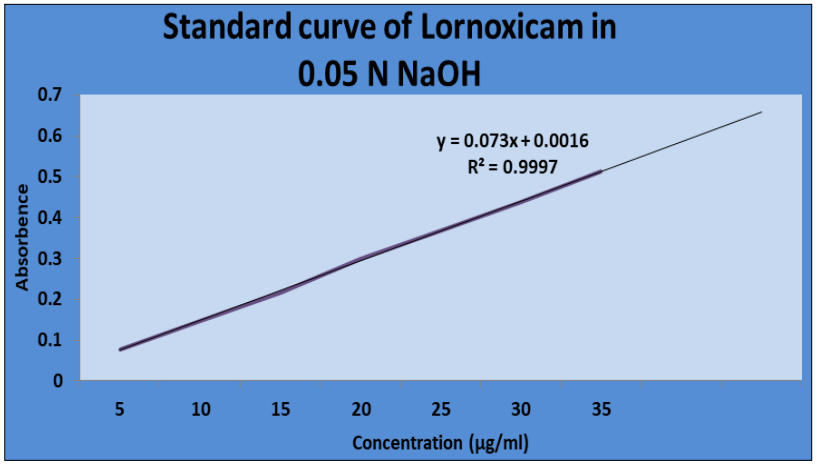

Fig 2: Standard Curve of Lornoxicam in 0.05 N NaOH

b. Standard curve of lornoxicam in PBS 7.4

Absorbances of the drug at 376 nm in PBS 7.4 are given below in table 7.5.

Table 7: Absorbances of Lornoxicam at 376 nm in PBS 7.4

S. No.	Concentration (µg/ml)	Absorbance
1	0	0
2	4	0.1672
3	8	0.3354
4	12	0.4885
5	16	0.6515
6	20	0.8225
7	24	0.9663

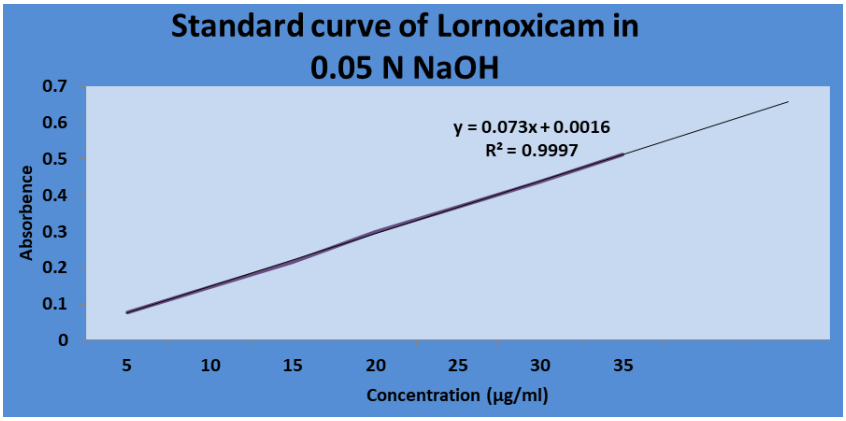

Fig 3: Standard Curve of Lornoxicam in 7.4 PBS

Fig. 7.2 & 7.3 showed linearity in the range of 5-35 µg/ml & 4-24 µg/ml with regression coefficient of 0.9997 & 0.9996 respectivily. This shows that the drug follows Beer's Lambert Law in these ranges.

7) Particle Size

The results of the Microscopic evaluation for the measurement of particle size of the drug particles are given below in table 7.6.

Table 8: Particle Size Distribution of Lornoxicam

S. No.	Size Range	Mid-Point (M. P.)	No. of Particles (N)	M. P. × N	M. P. × N × L. C. (d)
1.	0-1	0.5	06	03	5.82
2.	1-2	1.5	09	13.5	12.15
3.	2-3	2.5	11	27.5	53.35
4.	3-4	3.5	27	94.5	183.33
5.	4-5	4.5	23	103.5	200.79
6.	5-6	5.5	24	132	256.06
			∑n=100		∑d=714.5

Least Count (L. C.) = 1.94

Particle size was found to be 7.145 µm. Particle size distribution pattern depicted in fig. 7.4 shows that drug particles are distributed in a range of 1-6 µm and maximum number of particles are present in size range of 4-6 µm. This distribution pattern also indicates that the drug is amorphous in nature.

From the above data particle size distribution graph is plotted which is shown in fig. 7.4.

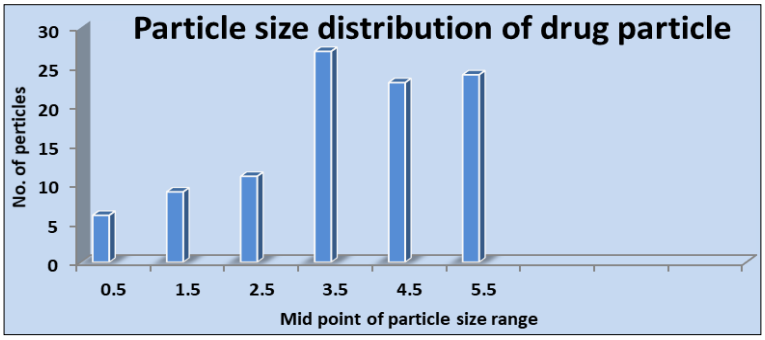

Fig 4: Particle Size Distribution of Drug (Lornoxicam)

8. Drug- Excipient Compatibility studies

Drug-Excipient Compatibility is performed by method described in section 7.1. This study is done to find out compatibility between the drug and excipients.

From the results given in table 7.7, it can be concluded that there is no interaction between excipients and drug. The drug and excipient are compatible with each other and can be used for formulation of Gel.

The results of Drug-Excipient Compatibility studies are shown in table 7.7.

Table 9: Drug-Excipient Compatibility Observations

S.No.	Additives (50 mg each) with drug	Observation at 60°C for 2 weeks	Observation at 40°C for 2 month	Remarks
1.	Drug (ornoxicam)	No interaction	No interaction	Accepted
2.	Drug + pluronic F-127	No interaction	No interaction	Accepted
3.	Drug + lecithin	No interaction	No interaction	Accepted
4.	Drug + isopropyl myristate	No interaction	No interaction	Accepted
5.	Drug + PEG 400	No interaction	No interaction	Accepted
6.	Drug + potassium sorbate	No interaction	No interaction	Accepted
7.	Drug + sorbic acid	No interaction	No interaction	Accepted
8.	Drug + Triethanolamine	No interaction	No interaction	Accepted
9.	Drug + carbopol 934	No interaction	No interaction	Accepted
10.	Drug + Oleic acid	No interaction	No interaction	Accepted
11.	Drug + Ethanol	No interaction	No interaction	Accepted
12.	Drug + propylene glycol	No interaction	No interaction	Accepted

Formulation of Transdermal Gel

Method of Preparation of Pluronic Lecithin Organogel:

The ten formulation of PLO were developed with different composition as given in Table 8.1. All the ten formulation were given coded as F1, F2, F3, F4, F5, F6, F7, F8, F9 & F10.

Pluronic Lecithin Organogel is a microemulsion based gel. It is made up of 2 phases, an oil phase and an aqueous phase. Ten PLO formulations were prepared by altering the concentration of Lecithin and Pluronic, while keeping the concentration of other excipient and drug unchanged.

Oil Phase was prepared by mixing soya lecithin (different amount of lecithin from 1 – 9 gm in different formulations) and sorbic acid (0.2 gm) in appropriate quantity of isopropyl myristate (quantity sufficient to 100ml). 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 (from 5 – 30 gm in different formulations) and potassium sorbate (0.2 gm) in cold water (quantity sufficient to 100 ml). The dispersion was stored in refrigerator for effect for effective dissolution of Pluronic F-127.

The next day, active ingredient lornoxicam (0.5 gm) was dissolved in Polyethylene glycol-400 (15 ml) and mixed with the prepared oil phase. Polyethylene glycol-400 was used for solubilization of Lornoxicam. Finally, aqueous phase (70%) was slowly added in oil phase (30%) with stirring using mechanical stirrer.

Table 10: Composition of Pluronic Lecithin organogel of Lornoxicam

Content		F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-10
Drug	Lornoxicam (gm)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
	PEG 400 (ml)	15	15	15	15	15	15	15	15	15	15
Oil Phase (%)	Soya Lecithin (gm)	1	3	5	7	9	3	3	3	3	3
	Sorbic acid (gm)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	02
	Isopropyl Myristate q.s. (ml)	100	100	100	100	100	100	100	100	100	100
Aqueous Phase (%)	Pluronic F-127 (gm)	20	20	20	20	20	5	10	15	30	25
	Potassium 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

Method of Preparation of Carbopol Gel

For preparation of Carbopol gel, Carbopol 934 was finely dispersed in 50:50 propylene glycol: water and stirred continuously at 300 rpm for 3 hrs. Then, the Lornoxicam (0.5 gm) was finely dispersed in of propylene glycol (15 ml) and then added to the carbopol mixture and mixed for 1hr. The dispersion was then neutralized and made viscous by the addition of triethanolamine.

Table 11: Composition of Carbopol gel of Lornoxicam

S. No.	Ingredients %	Formulation code F11
1.	Lonoxicam	0.5 gm
2.	Carbopol 934	2 gm
3.	Oleic acid	2.5 ml
4.	Ethanol	30 ml
5.	Propylene glycol	20 ml
6.	Triethanolamine	0.5 ml
7.	Distilled water	100 ml q. s.

Evaluation Studies of Transdermal Gel

Methods for Evaluation Studies of Transdermal Gel

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 [30].

2. Viscosity study

Brookfield digital viscometer (model DV-I+, Brookfield Engineering Laboratory, INC., USA) was used to measure the viscosity (in cps) of the prepared gel formulations at room temperature. The spindle (T-D) was rotated at 5 rpm. Reading was measured after 30 sec when the level of the gel was stabilized [30, 37].

3. Spreadability

Concentric circles of different radii were drawn on a graph paper and a glass plate of 100 ± 5 g was fixed onto it. Weighed amount of Gel (1 g) was transferred to the centre of this plate and allowed to spread over an area of 2 cm diameter on the glass plate. The other glass plate of 100 ± 5 g was placed gently on the spreaded gel. Again the gel was allowed to spread and the spread diameter was recorded after 1 minute. Then subsequent glass plates were added one by one and the spread diameter of the gel was recorded after 1 minute of each addition. Glass plates were added till the spread diameter became constant. Results were presented as the spreading area being a function of the applied mass [2].

4. Drug content

To determine the drug content 1 g of the prepared gel was dissolved in 100ml of 0.05 N NaOH. One ml of this solution was further diluted to 100ml. Then absorbance was measured at 376 nm in UV Double beam spectrophotometer against 0.05 N NaOH as a blank. Drug content was calculated using the equation, which was obtained by linear regression analysis of calibration curve of drug in 0.05N NaOH.

6. *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 keshary-chien 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 7.4 as a blank at 376 nm.

Result and Discussion

Result of Evaluation Studies of Transdermal Gel

1. Measurement of pH

The pH of various gel formulations was determined by using digital pH meter as mentioned in section 9.1.

The pH of skin is around 6.8. The results given in table 9.1 shows that pH of all the formulations was found to be in the range of 5.9 to 6.5, which is around to the pH of skin. This shows that formulations are fit for Transdermal use.

2. Viscosity

The viscosity of Gel formulations were measured by Brookfield digital viscometer as mentioned in section 9.1.

The viscosity of all the formulation was found in the range of 2912 to 3234 poise given in above table 9.1.The results shows that with the increase in polymer concentration i.e. lecithin and pluronic there is increase in viscosity of Pluronic lecithin organogel. This increase in viscosity is might be due to formation of complex and stabilized network, which is because of the synergistic contribution of both phospholipid and polymeric cosurfactant molecules, in their respective hydrated state (strong hydrogen bonding with water). The viscosity of F11 formulation, which is a carbopol gel, is less than Pluronic lecithin organogels, which might be due to the weak hydrogen bonding between carbopol and water/polar solvent in carbopol gel as compare to lecithin and pluronic with water in Pluronic lecithin organogel.

3. % Drug Content

The percent Drug content was calculated by method mentioned in section 9.1. For calculation of drug content 1 gm of the prepared gel was dissolved in 100ml of 0.05 N

NaOH. One ml of this solution was further diluted to 100ml. Then absorbance was measured at 376nm in UV Double beam spectrophotometer against 0.05 N NaOH as a blank. The results are shown in table 9.1.

All the gel formulations showed drug content in the range of 93 to 99%, indicating uniform distribution of drug throughout the base and high uptake capacity of drug in the base. Results also reveals that PLO gels have higher % drug content than Carbopol gel, which indicates superiority of former on latter.

Table 12: pH, Viscositiy and % Drug content of different formulation of gel

S. No.	Formulations	pH	Viscosity (cps)	% Drug content
1.	F1	5.9 ± 0.1	2912 ± 1.67	93.96 ± 0.17
2.	F2	6.4 ± 0.17	3145 ± 40	93.77 ± 0.63
3.	F3	6.03 ± 0.17	3179 ± 21.34	96.25 ± 0.52
4.	F4	6.27 ± 0.17	3174 ± 9.34	99.51 ± 0.27
5.	F5	5.93±0.16	3234 ± 24.33	99.49 ± 0.13
6.	F6	6.06 ± 0.06	3028 ± 25.67	96.86 ± 0.36
7.	F7	6.03 ± 0.16	3149 ± 18	95.85 ± 0.71
8.	F8	5.86 ± 0.06	3150 ± 19.33	98.46 ± 0.32
9.	F9	6.16 ± 0.16	3113 ± 14.33	98.32 ± 0.38
10.	F10	5.96 ± 0.16	3162 ± 15.67	97.15 ± 0.15
11.	F11	6.0 ± 1	2959 ± 18.33	93.67 0.83

4. Spreadability

The Spreadability of various gel formulations was determined by method mentioned in section 9.1. Quantity of gel taken was 1 gm & initial diameter was taken 2 cm for measurement of spreadability. The observations are shown in table 9.2.

Table 13: Spreadability of different formulations

		Spread diameter of different gel formulations (cm)										
S. No.	No. of plates placed on gel	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
1.	1	2.1	2.6	2.3	2.6	2.5	2.12	2.3	2.3	2.5	2.0	2.2
2.	2	2.5	2.76	2.6	2.8	2.7	2.16	2.4	2.38	2.7	2.4	2.5
3.	3	2.62	2.84	2.7	3.0	2.8	2.28	2.7	2.45	2.72	2.7	2.7
4.	4	2.7	2.93	2.8	3.2	3.1	2.36	2.8	2.56	2.79	2.8	2.86
5.	5	2.78	3.0	3.0	3.3	3.2	2.44	2.86	2.66	2.8	2.9	2.98
6.	6	2.8	3.08	3.1	3.36	3.25	2.48	3.0	2.75	2.83	3.0	3.08
7.	7	2.88	3.16	3.2	3.38	3.26	2.52	3.16	2.8	2.85	3.2	3.12
8.	8	2.9	3.24	3.3	3.40	3.27	3.55	3.18	2.84	2.86	3.34	3.14
9.	9	2.9	3.26	3.4	3.41	3.27	3.55	3.18	2.84	2.87	3.36	3.14

The spreadability of all the formulations was found in the range of 2.9 to 3.55 cm (in diameter). Spreadability is significantly influenced by the structural stability and rheological behavior of organogel, which in turn depends upon type of organic solvent, concentration of gelators or cosurfactants, or type and amount of polar solvents. The results show that spreadability of F2, F3, F4, F5, F6, F7 & F10 were found good, which might be due to the optimized amount of cosurfactant, organic and polar solvents. The spreadability of Carbopol gel was also found good, this shows structural stability and good rheological behavior of Carbopol gel.

1) *In-vitro* release study

In-vitro release study was performed to obtain release profiles of the prepared gel formulations by the method mentioned in section 9.1. The study was performed for 8 hrs. The results are shown in table 9.3.

The Results shows that cumulative % release profile of Pluronic lecithin organogel is better than Carbopol Gel (F-11)**.** This might be due to the good skin penetrability of Lecithin compared to that of Carbopol.

The results also revealed that maximum *in-vitro* cumulative % drug release of Lornoxicam in 8 hrs was observed from F-2 formulation. Formulation F-3, F-4 & F-10 also showed good release profile.

The above result indicates that, for good drug release from the gel, optimized amount of lecithin & Pluronic is required. Further increase or decrease in concentration of lecithin & Pluronic 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 between lecithin and pluronic.

From the above *In-vitro* % drug release data given in table 9.3, a curve is plotted, to demonstrate the *In-vitro* drug release profile of all the eleven Gel formulations. The curve is shown in Figure 9.1 & 9.2.

Table 14: *In-vitro* Release study in PBS 7.4 pH

		% Drug release from gel formulations										
S. No.	Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
1.	0	0	0	0	0	0	0	0	0	0	0	0
2.	1	6.63	9.28	5.92	7.871	3.80	4.9	5.22	5.48	6.28	8.05	5.93
3.	2	14.37	19.19	16.67	16.18	10.97	10.97	8.76	9.99	15.7	17.78	13.75
4.	3	23.52	32.59	27.46	26.62	20.12	20.96	10.87	18.13	26.23	30.91	25.08

5.	4	39.09	40.73	38.69	39.71	31.49	30.86	18.49	28.13	34.89	40.99	34.58
6.	5	51.83	56.56	43.43	51.57	39.98	39.09	28.13	37.50	42.98	55.01	41.71
7.	6	59.62	66.87	53.51	62.27	51.11	43.65	38.7	2.81	51.57	64.30	51.74
8.	7	68.19	81.02	65.1	71.82	61.16	54.26	49.0	50.06	60.23	75.98	56.79
9.	8	78.18	90.13	83.94	80.53	70.28	60.50	60.94	66.25	71.51	85.62	65

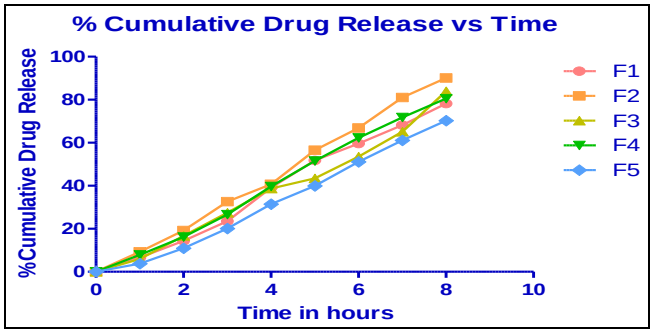

Fig 5: % Cummulative Drug Release Profile of formulation F-1 to F-5

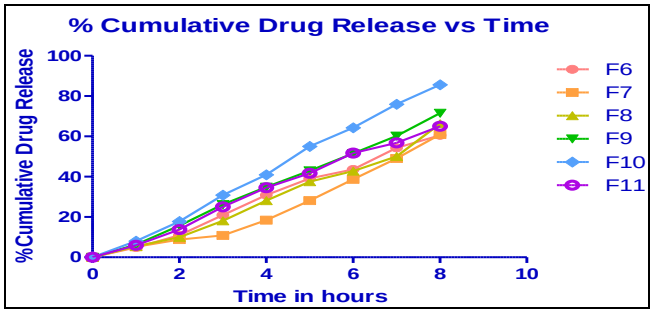

Fig 6: % Cummulative Drug Release Profile of formulation F-6 to F-11

Stability studies

The stability testing provides evidence on how 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 ten formulations were selected and subjected to the stability testing for 90 days. Formulation were kept at 40^0C, 25^0C & room temperature for 90 days & evaluated for following parameters:

i) Physical stability: The gel formulations were evaluated in terms of physical character like phase separation & rheological parameters. Physical stability testing was done by visual inspection of the formulation at 15 days interval for 3 months.

ii) Chemical stability: The gel formulations were evaluated for % drug content. The % drug content of the formulations were determined, by method given chapter 9, section 9.1, at 15 days interval for 3 months.

From the Evaluation studies results reported in chapter 9, two formulations F-2 & F-4 were selected as optimized PLO formulations. They were than subjected to 90 days Stability studies. The optimized gel formulations F2 & F4 were evaluated in terms of physical character & chemical character like phase separation, rheological parameters, pH & % Drug Content.

The results of Stability studies are shown in Table 10.1 & 10.2.

Table 15: Stability studies of F2 at Room Temperature (R.T.), 25°c & 40°c

S. No.	Time (Days)	pH			Viscosity (cps)			% Drug Content		
		R. T.	25°c	40°c	R. T.	25°c	40°c	R. T.	25°c	40°c
1.	0	6.6	6.6	6.5	3122	3112	3152	90.36	90.40	90.42
2.	15	6.5	6.6	6.6	3145	3115	3155	90.40	90.42	90.44
3.	30	6.5	6.3	6.8	3133	3122	3149	90.32	90.33	90.37
4.	45	6.4	6.6	6.7	3150	3104	3164	90.27	90.35	90.35
5.	60	6.4	6.4	6.7	3148	3118	3148	90.22	90.30	90.29
6.	75	6.5	6.5	6.9	3131	3106	3160	90.12	90.31	90.31
7.	90	6.5	6.2	6.9	3112	3102	3142	90.04	90.26	90.26

Table 16: Stability studies of F4 at Room Temperature (R.T.), 25°c & 40°c

S. No.	Time (Days)	pH			Viscosity (cps)			% Drug Content		
		R. T.	25°c	40°c	R. T.	25°c	40°c	R. T.	25°c	40°c
1.	0	6.3	6.5	6.2	3124	3120	3132	80.62	80.44	80.28
2.	15	6.3	6.3	6.3	3135	3132	3140	80.44	80.34	80.40
3.	30	6.5	6.6	6.6	3140	3134	3134	79.87	79.47	79.34
4.	45	6.7	6.5	6.5	3134	3136	3142	80.35	80.35	80.35
5.	60	6.6	6.6	6.7	3145	3125	3135	80.33	80.23	80.38
6.	75	6.6	6.6	6.7	3146	3134	3144	80.37	80.40	80.40
7.	90	6.9	6.8	6.9	3132	3140	3148	80.26	80.42	80.40

After 90 days stability studies it was found that there was no phase separation, no change in colour, odour and texture, in both the gel formulations (F-2 and F-4) and spredability was also found to be good at different temperature conditions.

The results of Stability study shown in table 10.1 & 10.2 indicated that the two selected formulations (F-2 and F-4) were stable enough at different temperature conditions (40^0C, 25^0C, room temperature) for 90 days as there was very slight change in drug content, viscosity and pH. Thus it may conclude that formulation were physically and chemically stable.

Summary and Conclusion

The transdermal drug delivery is one of the promising route of drug delivery system, since it by passes the first pass metabolism, avoids inactivation of drugs by pH effects and enzymes present in GI tract, provides a continuous mode of administration at rates approaching zero order similar to that provided by an intravenous infusion, increase the half life of the drug, the delivery is non-invasive, no hospitalization is required, and improves patient compliance.

Any drug for its permeation through skin should be potent, must be lipophilic as well as hydrophilic in nature, optimum partition coefficient etc, this prompted us to carryout the present study. The preformulation study for the drug was conducted. The λmax of Lornoxicam was found at 376 nm, which is comparatively same as given in Merck Index. This

shows that the drug is pure. By the determination of organoleptic properties, it was observed that the Lornoxicam is orange to yellow coloured amorphous powder, bitter in taste and odourless drug. Results of qualitative solubility studies shows that the Lornoxicam is more soluble in alkaline solvents and insoluble in water. This indicates acidic nature of the drug. Results of quantitative solubility shows that Lornoxicam has highest solublility in 0.05N NaOH and solubility of Lornoxicam increases with the increase of pH, which indicates that the ionization of drug increases with the elevating pH.

The partition coefficient was found to be 1.7, which is suitable for transdermal drug delivery, the obtained value of partition coefficient of Lornoxicam was more than 1 which showed that the Lornoxicam is lipophilic in nature. The average particle size of Lornoxicam was measured by microscopy method was found to be 7.145 micrometer. The melting point was observed at 225-227 ^{0}C and this range is nearly same as reported in Merck Index, it shows the drug is amorphous in nature. The standard curve of Lornoxicam was prepared in phosphate buffer 7.4 and in 0.05N NaOH, the r^2 values was obtained 0.999 and 0.999 respectively, which shows linearity of absorbance between the range of 5-35 ug /ml. The preformulation study of Lornoxicam showed satisfactory results to select the drug for transdermal drug delivery system.

The transdermal anti-inflammatory gels containing Lornoxicam & different polymers, were prepared and evaluated for different parameters like pH, drug content & rheological properties like viscosity & spredability and results found were all satisfactory. The Results indicates that PLO gel shows better results than Carbopol Gel.

All eleven formulations were also evaluated for *In-vitro* drug release study. Study was carried for 8 hrs for all formulation and results reported in table 9.3 shows that, the Formulation F-2 and F-4 showed good cumulative % Drug Release profile of Lornoxicam in 8 hr. But the linear curve shown in fig. 9.1 was obtained from F-2 formulation. The cumulative amount permeated from Carbopol gel through membrane was found to be 67% which was less than PLO Gel formulations. This indicates that PLO Gel has more drug permeation across the membrane than carbopol gel.

On the basis of results of Evaluation studies two formulations F-2 & F-4 were selected and subjected to 90 days Stability studies. Stability study indicated that the selected formulations (F-2 and F-4) were stable enough at different temperature conditions (40^{0}C, 25^{0}C, room temperature) for 90 days as there was no change in drug content, phase separation, rheological properties and pH. Thus it may concluded that formulation were physically and chemically stable.

It is clear from above discussion that F-2 and F-4 are better formulation among all the prepared formulations.

References

1. Ardente AJ, Barlow BM, Burns P, Goldman R, Baynes RE. Vehicle effects on *in vitro* transdermal absorption of sevoflurane in the bullfrog, Rana catesbeiana. Environmental Toxicology and Pharmacology. 2008; 25:373-379.
2. Ahmad FJ, Alam MA, Khan ZI, Khar RK, Ali M. Development and *In-vitro* evaluation of an acid buffering bio adhesive vaginal gel for mixed vaginal infection. Acta Pharm. 2008; 58:407-419.
3. Ansel HC, Allen VL, Popovich GN. Pharmaceutical Dosage Forms and Drug Delivery Systems. 2001; 4:376-380.
4. Belgamwar VS, Pandey MS, Chauk DS, Surana SJ. Pluronic lecithin organogel. Asian journal of pharmaceutics, 2008, 134-138.
5. Belgamwar VS, Pandey MS, Surana SJ. Topical delivery of flurbiprofen from Pluronic Lecithin organogel. Indian journal of pharmaceutical sciences. 2009; 71(1):87-90.
6. Byrav PDS, Medhi B, Prakash A, Patyar S, Wadhwa S. Lornoxicam: a Newer NSAID. IJPMR. 2009; 20(1):27-31.
7. Cevc G. Lipid vesicles and other colloids as drug carriers on the skin. Advanced Drug Delivery Reviews. 2009; 56:675-711.
8. Cevc G, Mazgareanu S, Rother M. Preclinical characterization of NSAIDs in ultradeformable carriers or conventional topical gels. International Journal of Pharmaceutics. 2008; 360:29-39.
9. Chandra A, Sharma PK, Irchhiaya R. Microemulsion-based hydrogel formulation for transdermal delivery of dexamethasone. Asian J Pharm. 2009; 3(1):30-36.
10. Dhamankar AK, Manwar JV, Kumbhar DD. The novel formulation design of o/w microemulsion of ketoprofen for improving transdermal absorption. Int J Pharm Tech Res. 2009; 1(4):1449-1457.
11. Dreher F, Walde R, Walther R, Wehrli E. Interaction of a lecithin microemulsion gel with human stratum corneum and its effect on transdermal transport. Journal of Controlled Release. 1997; 45:131-140.
12. Dumortier G, Grossiord JL, Agnely F, Chaumeil JC. A review of poloxamer 407 pharmaceutical and pharmacological characteristics. Pharm. Research. 2006; 12:2709-28.
13. Finch PM, Knudsen L, Drummond PD. Reduction of allodynia in patients with complex regional pain syndrome: A double-blind placebo-controlled trial of topical ketamine. International Association for the Study of Pain (Elsevier). 2009; 146:18-25.
14. Gattani SG, Gaud RS, Chaturvedi SC. Formulation and evaluation of transdermal films of ondansetron hydrochloride. Indian Drugs. 2006; 43(3):245-251.
15. Grahame R. Transdermal non-steroidal anti-inflammatory agents. Brit. J Clin. Pract. 1995; 49:33-35.
16. Helen R, Christopher T, Jenna L, Charles M. *In-vitro* transcutaneous delivery of ketoprofen and polyunsaturated fatty acids from a pluronic lecithin organogel vehicle containing fish oil. Journal of Pharmacy and Pharmacology. 2006; 58(7):903-908.
17. Hoffman SB, Yoder AR, Trepanier LA. Bioavailability of transdermal methimazole in a pluronic lecithin organogel (PLO) in healthy cats. J Vet Pharmacol Therapeutics. 2002; 25(3):189-93.
18. “http://en.wikipedia.org/wiki/Gel"
19. “http://en.wikipedia.nystatin/wiki”../../entrez/utils/fref.fcgi
20. Indurwede, N.H., Biyoni, K.R., Nekhat, P.D., Garg, N., Chopra, V.S., 2001. Formulation, evaluation and comparison of gels containing different cox-2 inhibitors. Indian Journal Medical Sciences. 55, 549-552.
21. Jain KG, Ahmed F. Adapalene pretreatment increases

follicular penetration of clindamycin: *In-vitro* and *in-vivo* studies. Indian J Dermatol Venereol Leprol. 2007; 73(5):326-329.
22. Kannaiyan S, Muthuprasanna P, Vardhareddy V. Effect of carbopol gel in stable liposomes and their enhanced antipyretic effect. Asian J Pharm. 2009; 3(3); 257-260.
23. Kumar R, Katare OP. Lecithin organogels as a potential phospholipid-structured system for topical drug delivery: a review. A. A. P. S. Pharm. Sci. Tech. 2005; 6(2):E298-3
24. Kumar Rani S. Preformulation studies of methotrexate for assessing its suitability for transdermal vesicular drug delivery. Int J of Pharma Excip. 2006; 5(3):93-97.
25. Lachman L, Lieberman HA. The Theory and Practice of Industrial Pharmacy, 1990; 3:534.
26. Lakshmi PK, Devi GS, Bhaskaran S, Sacchidanand S. Niosomal methotrexate gel in the treatment of localized psoriasis: Phase Me and phase II studies. Indian J Dermatol Venereol Leprol. 2007; 73(3):157-161.
27. Lin J, Zhang W, Jones A, Doherty M. Efficacy of topical non-steroidal anti-inflammatory drugs in the treatment of osteoarthritis: meta-analysis of randomized controlled trials. BMJ, 2004, 324-329.
28. Loganathan V, Jaswanth A, Sulaiman A, Rajaseskaran A, Manimaran S, Kumar Senthil B. *et al*. The effects of polymers and permeation enhancers on release of flurbiprofen from gel formulation. Indian J Pharm. Science, 2001, 200-204.
29. Murdan S. A Review of pluronic lecithin organogel as a topical and transdermal drug delivery system. Hospital pharmacist. 2005; 12:267-279.
30. Murthy TEGK, Kishore VS. Formulation and evaluation of transdermal gels of diltiazem hydrochloride. Indian J Pharm Educ Res. 2008; 42(3):272-276.
31. Nemutlu E, Demircan S, Kir S. Determination of lornoxicam in pharmaceutical preparations by zero and first order derivative UV spectrophotometric methods. Pharmazie. 2005; 60(6):421-425.
32. Patel HJ**,** Patel JS, Desai BG, Patel KD. Design and evaluation of amlodipine besilate transdermal patches containing film former. Int J of Pharma Res and Dev. 2009; 7:1-12.
33. Preformulation A need for Dosage Form Design Pharmainfo_net.mht
34. Remington. The Science and Practice of Pharmacy. 20: 745-747.
35. Rosenow DE, Albrechtsen M, Stolke D. A comparison of patient-controlled analgesia with lornoxicam versus morphine in patients undergoing lumbar disk surgery. Anesthesia & Analgesia (International Anesthesia Research Society). 1998; 86:1045-1050.
36. Ruiz MA, Clares B, Morales ME, Gallardo V. Preparation, rheological study, and characterization of an organogel as a system for transdermal release of active principles. Pharm. Development Technology. 2007; 12(6):637-44.