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FORMULATION AND EVALUATION OF TOPICAL GEL DELIVERY OF LORNOXICAM

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ABSTRACT

The aim of the present research work is to prepare and evaluate topical hydrogel of lornoxicam using different gelling agent for the treatment of inflammation. Lornoxicam is a highly selective cyclooxigenase-1 & cyclooxigenase-2 inhibitor used in the treatment of inflammation, pain and edema, rheumatoid arthritis and so on. Topical gel of Lornoxicam was formulated using triethanolamine (5%) as solvent, carbopol 934p as gelling polymer and various penetration enhancers. Formulated gel was evaluated with respect to different physiochemical parameters such as pH, viscosity, spreadability, gel strength. The in-vitro drug release rate of gel was evaluated using Franz diffusion cell with phosphate buffer 7.4 as the receptor medium. Stability studies carried out at different temperatures and humidity did not show any significant change in drug content, % CDR, viscosities and other parameters at the end of 12 weeks indicating that all the formulations were stable. It was concluded that Physiochemiclly stable and non-irritant Lornoxicam gel was formulated and the drug release increased with increase in concentration of penetration enhancer which is suitable for topical application.

KEYWORDS: Lornoxicam, hydrogel**,** Penetration enhancers, in-vitro, penetration enhancer, inflammation.

INTRODUCTION

Topical delivery can be defined as the application of a drug containing formulation to the skin to directly treat cutaneous disorders (e.g. acne) or the cutaneous manifestations of a general disease (e.g. psoriasis) with the intent of containing the pharmacological or other effect of the drug to the surface of the skin or within the skin [Apeksha et al, 2013].[1] Topical

gels are transparent or translucent semisolid formulations containing a high ratio of solvent/gelling agent [kumar et al, 2011].[2] Semi-solid formulation in all their diversity dominates the system for topical delivery. Topical application of drugs offers potential advantages of delivering the drug directly to the site of action and acting for an extend period of time. Skin is one of the most extensive and readily accessible organs on human body for topical administration and main route of topical drug delivery [Roychowdhary S, et al, 2012].[3]

GEL

Definition

Gels are 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 the dispersed phase [Mehetre VN, et al, 2013]. The USP defines gels as a semisolid system consisting of either suspension made up of small inorganic particles or large organic molecule interpenetrated by a liquid. The favorable properties of dermatological gel are thixotropic, good spreadability, greaseless, easily removable, emollient, and demulcent, nonstaining.[Saroha K et al, 2013].

Desired physicochemical properties of drug which required for formulation of topical hydrogels are

I) Drug should have a molecular weight of less than 500 Daltons.

II) Drug must have adequate hydrophilicity.

III) A saturated aqueous solution of the drug should have a pH value between 5 and 9.

IV) Drug highly acidic or alkaline in solution is not suitable for topical delivery [Munshi et al, 2012].

Table 1: Topical formulation.

Liquid preparation	Semisolid preparation	Solid preparation	Miscellaneous preparation
Liniment	Ointments	Topical	Transdermal drug delivery
Lotion	Cream	Powder	Tapes and Gauzes
Paint	Pastes	Poultices	Rubbing alcohol
Topical solution	Gels	-	Liquid cleanser
Topical tincture	Poultices	-	Topical aerosol

MATERIALS AND METHODS

Materials: Lornoxicam Gift sample from Alkem research Lab. Mumbai, Oleic acid Fizmerk India chemicals, Hapur (U.P), INDIA, Carbopol 934 Gift sample from Guapha Pharmaceuticals, INDIA, Glycerol Fizmerk India chemicals, Hapur (U.P), INDIA, Triethanolamine Qualikem fine chemicals, Vadodra, INDIA, Methanol RFCL, New Delhi, INDIA, Turpentine Oil, Gaupha Pharmaceutical, M.P. India.

Instruments

Digital electronic Balance (Modern business equipment and services pvt. Ltd, INDIA), Franz diffusion cell (Zenith glassware, Kolkata, INDIA), Melting point apparatus (Singhla Scientific industries, Ambala, INDIA), Hot air oven (D.K. Instruments And Chemicals, Ambala, INDIA), Mechanical stirrer (Singhla Scientific industries, Ambala, INDIA), UV-VIS Spectrophotometer (Model-1371, Electronic India, Parwanoo, H.P.), Fourier-Transform Infrared ray Spectrophotometer (FT-IR 8400, Shimadzu, JAPAN), Magnetic stirrer (Singhla Scientific industries, Ambala, INDIA), pH-meter (Electronic India, Parwanoo H.P).

METHODOLOGY

Determination of solubility of Lornoxicam

The solubility of Lornoxicam in distilled water and in Phosphate buffer solutions of pH 4.0, 5.0, 6.0, 6.8, 7.0, 7.2, 7.4, 7.6 and distilled water were determined. An excess amount of drug was added to 10ml of different solvent. The content were stirred continuously for 24 hours at 37^0C and allowed to equilibrate. After 24 hours the sample were withdrawn and filtered through membrane filter and the filtrate were suitably diluted with an appropriate solvent and analyzed spectrophotometrically (UV-1371, electronical India, INDIA) for lornoxicam concentrations, at 380 nm with reference to a corresponding calibration curve. Each experiment was done three times and the equilibrium solubility was taken as the average value.

APPARENT PARTITION COEFFICIENT STUDY

Equal volumes of each of distilled water , buffer solutions of pH 4.0, 5.0, 6.0, 6.8,7.2, 7.4, and isopropyl myristate (IPM) were previously saturated with each other by shaking together in shaker for 3 hours and the two phases were left to separate overnight. To each of the separated IPM phases, a known concentration of lornoxicam was added with gentle shaking until dissolved. The IPM phases containing dissolved drug were mixed with each of the other aqueous phases. The mixtures were then agitated for 6 hours at room temperature, and the

two phases were then separated again. The drug concentration in aqueous phases was determined spectrophotometrically at 380 nm, after suitable dilution. The results, treated according to Equation.

$$Partition\ Coefficient = \frac{Concentration\ in\ Organic\ Phase}{Concentration\ in\ Aqueous\ Phase}$$

FORMULATION LORNOXICAM HYDROGEL

Formulation table of lornoxicam hydrogel

S.No.	Composition	Formulation code (%w/w)									
		SHF 1	**SHF 2**	**SHF 3**	**SHF 4**	**SHF 5**	**SHF 6**	**SHF 7**	**SHF 8**	**SHF 9**	**SHF 10**
1.	LORNOXICAM	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	--
2.	CARBOPOL	1%	1%	1%	1%	1%	1%	1%	1%	1%	1
3.	OLEIC ACID	5	10	--	--	--	--	--	--	--	--
4.	PROPYLENE GLYCOL	--	--	5	10	--	--	--	--	--	--
5.	TURPENTINE OIL	--	--	--	--	5	10	--	--	--	--
6.	ISOPROPYL MYRISTATE	--	--	--	--	--	--	5	10	--	--
a.	PROPYL PARABEN	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7
7.	METHYL PARABEN	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35
8.	ETHANOL	5	5	5	5	5	5	5	5	5	5
9.	TRI ETHANOLAMINE	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs
10.	WATER	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs

EVALUATION OF LORNOXICAM GEL

Physical appearance & Homogenecity: Physical appearance and homogenecity of gel was observed visually.

pH

The pH of Lornoxicam gels were determined by using a calibrated pH meter (equiptronics). The readings were taken for average of three samples. The pH meter was calibrated before each use with standard 4, 7 and 9.2 buffer solutions.

Spreadibility study of Lornoxicam gel

The spreadibility of the gel formulations was determined at 24h after preparation, by measuring the spreading diameter of 1gm gel between two horizontal plates (20 x 20 cm^2) after 1 minute. The standardized weight tied on the upper plate was 220gm. The spreadibility was calculated by using the following formula.

$$S = M \times \frac{L}{t}$$

Where S is spreadibility, M is weight tied on upper slide. L is the length of glass slide, t is time taken.

Drug content

Drug content was determined by dissolving 0.2g of gel in 100 ml of phosphate buffer solution pH7.4. 1 ml of this solution was transferred into 10 ml volumetric flask and final volume was made by using phosphate buffer solution pH 7.4. Finally absorbance of prepared solution was measured at 378nm using UV visible spectrophotometer.

Determination of viscosity

The viscosity microemulsion was measured at 25°C with a Brookfield viscometer. (Brookfield DV–E) Viscosity of the samples was determined using a Brookfield digital viscometer with spindle number 63. The sample temperature was controlled at 25 ± 1^{0}c before the each measurement.

INFRA-RED SPECTROSCOPY

An IR spectrum reveals the characteristic peaks of all functional groups present in a sample. In order to ascertain successful entrapment, the drug, carbopol,and their mixture were subjected to FTIR studies. IR spectra of lornoxicam (LNR), carbapol (CP), physical mixture of carbapol and oleic acid (CP+OA) and gel formulation were recorded using Shimadzu model 8400, IR Spectrophotometer between the ranges of 500 $cm^{-1\ to}$ 4000 cm^{-1}.

In vitro drug release study

The *in vitro* drug release studies were performed by using Franz diffusion cell with cellophane paper. The water jacketed recipient compartment had total capacity of 30 ml and it had one arms for sampling and other side for water inlet and outlet. The donor compartment had internal diameter of 2.8 cm^2. The donor compartment was placed in such a way that it just touches the diffusion medium in receptor compartment. The receptor compartment contained phosphate buffer solution pH 7.4. That was maintained at 37°C ± 1°C (Mukhrjee *et al.*, 2005). The membrane was equilibrated before application of the microemulsion based Hydrogel equivalent to 8 mg of drug onto the donor side. 1ml of Samples was periodically withdrawn from the receptor compartment, replacing with the same amount of fresh PBS solution, and assayed by using a spectrophotometer at 378 nm.

Fig.: Modified Franz diffusion cell.

Preparation of standard calibration curve of lornoxicam in different phosphate buffer: Standard calibration curve of lornoxicam was prepared by making solutions of different concentration as follows: 0, 2, 4, 6, 8, 10 µg/ml in distilled water and different phosphate buffer (pH 4.0, 5.0, 6.0, 6.8, 7.0, 7.2, 7.4, 7.6.) and the absorbance was measured at 380 nm (Practically found).

RESULT AND DISCUSSION

SOLUBILITY PROFILE OF LORNOXICAM

Solubility studies helped to rationalize the choice of vehicle for gel formulation. LRN is poorly soluble in water (0.0385 ±0.01 mg mL–1). Among the different solubilizers screened, LRN exhibited the highest solubility in 5% triethanolamine solution (42.5 ± 0.36 mg mL–1). Solubility of LRN in\chloroform and in PBS pH7.4 was 0.26 ± 0.03 and 0.15 ± 0.05 mg mL–1 respectively. Hence 5% triethanolamine solution was selected as the vehicle of choice to formulate LRN gel, based on its solubilization capacity.

Table: Solubility Profile of Lornoxicam in Different Pbs.

S. No.	pH	Solubility (mg/ml)*
1.	4.0	0.370±0.065
2.	5.0	1.964±0.084
3.	6.0	2.699±0.023
4.	6.8	3.192±0.129
5.	7.0	4.528±0.106
6.	7.2	5.512±0.042
7.	7.4	9.425±0.174
8.	7.6	8.091±0.158

APPARENT PARTITION COEFFICIENT OF LORNOXICAM

The apparent partition coefficient results indicated an expected increase in the lipophilicity of the acidic drug, like lornoxicam, by decreasing the pH value.

Table: Apparent Partition coefficient of lornoxicam in PBS.

S. No.	System	Apparent Partition coefficient
1	IPM / pH 4 Buffer	26.130 ± 2.044
2	IPM / pH 5 Buffer	8.921 ± 0.282
3	IPM / pH 6 Buffer	4.234 ± 0.111
4	IPM / pH 7.4 Buffer	2.434 ± 0.104

Preparation of lornoxicam gel

The gel of lornoxicam with different concentration was prepared as mentioned in methodology.

EVALUATION OF GEL

Physical appearance & Homogenecity

The physical appearance of drug loaded gel was found to be off-white in color, smooth in texture and translucent. All the formulation was found to be homogenous.

pH

The pH of Lornoxicam gels were determined by using a calibrated pH meter (equiptronics) and pH of the gel were found to be 6.8±0.4 (n=3).

Spreadibility study of lornoxicam gel

All the formulated gel was evaluated for spreading diameter at 1 min, as a measure of stiffness. The result is shown in table.

S.No.	Formulation code	Spredability* g.cm/s
1.	F1	5.89 ± 0.13
2.	F2	5.45 ± 0.41
3.	F3	5.18 ± 0.28
4.	F4	6.79 ± 0.33
5.	F5	6.11 ± 0.47
6.	F6	5.25 ± 0.15
7.	F7	7.29 ± 0.24
8.	F8	6.14 ± 0.27
9.	F9	5.93 ± 0.28

Drug content study

The drug content study of formulation was found (89.12± 2.1) to 97.07± 0.014 performed & result is given in table.

S.No.	Formulation code	Drug content*(%v/w)
1	F1	93.81± 0.058
2	F2	95.44± 0.029
3	F3	97.07± 0.014
4	F4	94.90± 0.034
5	F5	96.52± 0.018
6	F6	92.55 ± 0.026
7	F7	89.12 ± 0.021
8	F8	90.42 ± 0.026
9	F9	89.87 ± 0.015

Viscosity study

Viscosity of hydrogel thickened microemulsion gradually increased with decrease in concentration of surfactant co-surfactant mixture in the formulation. The viscosity of the hydrogel thickened microemulsion of batches F1-F9 ranged from 4146-6383 cPs respectively.

S.No.	Formulation code	Viscosity* (cp)
1	F1	5291±11.02
2	F2	5839±11.00
3	F3	6383±10.35
4	F4	4756±10.27
5	F5	4812 ± 08.56
6	F6	5151± 12.36
7	F7	4146 ± 11.37
8	F8	4254± 09.67
9	F9	4460 ± 10.83

FT-IR studies: From the FTIR studies, all the characteristic peaks of Lornoxicam were present in the spectrum of drug and polymer mixture, indicating compatibility between drug and polymer. The spectra were recorded over the wave number range 4000-400 cm-1. The FTIR spectrum of Lornoxicam showed a characteristic peak at 3,065 cm−1 corresponding to NH stretching vibration. Intense absorption peak was found at 1,733 cm−1due to the stretching vibration of the C=O group in the primary amide. The stretching vibrations of the S=O group appeared at 1,034 cm-1. C–Cl bending vibration at 948 cm−1which indicates groups is match with structure of drug and confirms the purity of the drug. There is no shift of peaks or disappearance of principle peaks or modification of the principle peaks indicating

that there is no interaction between the drug and excipient. FT-IR spectrum of pure drug and its physical mixture is represented in figure 1 and 2.

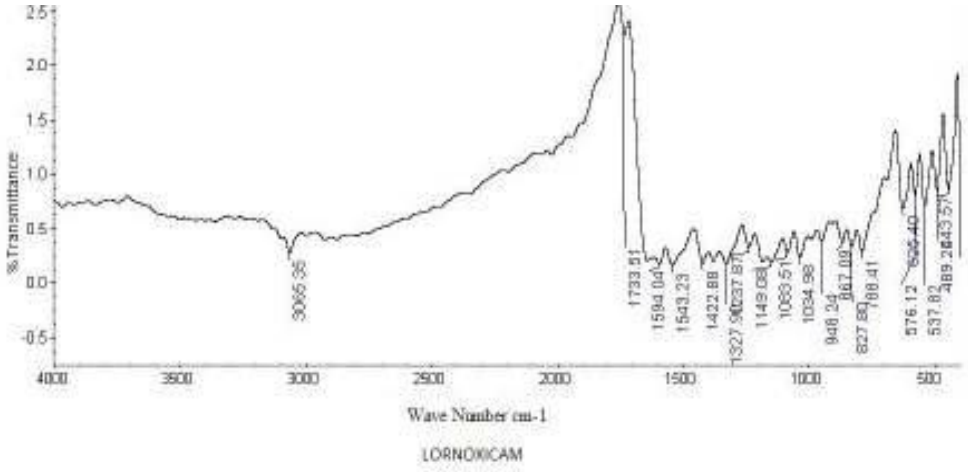


Fig: Ftir of Pure Lornoxicam.

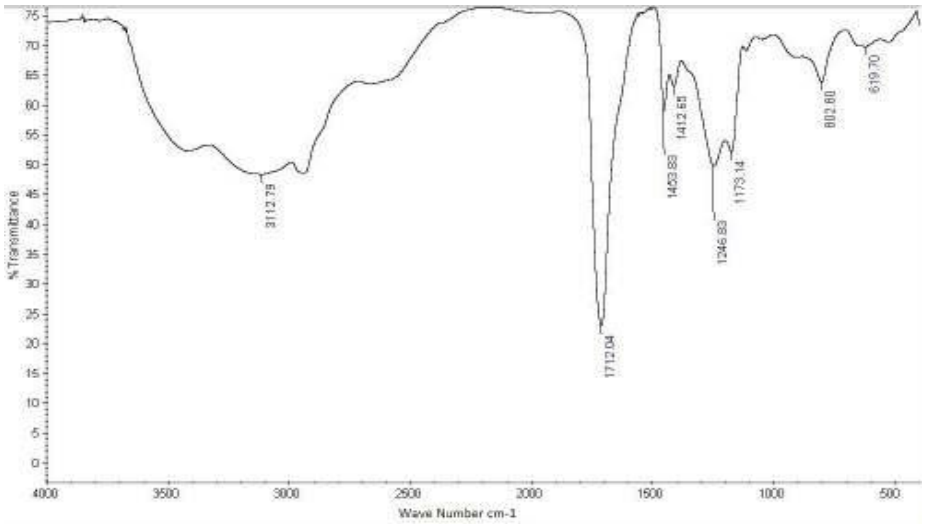


Fig: Ftir of Lornoxicam and Carbopol.

In vitro release study of gel

The release of the drugs from its microemulsified gel formulation can be ranked in the following descending order: F7 > F4 > F1> F8 > F5 >F2 > F9 > F6>F3, Where the amounts of the drug released after 8 hr were 82.17%, 80.75%, 78.91%, 70.72%, 64.09%, 57.84%, 53.12%, 42.90%, 38.14% respectively. The progressive increase in the amount of drug diffusion through membrane from formulation attributed to gradual decrease in the viscosity of hydrogel.

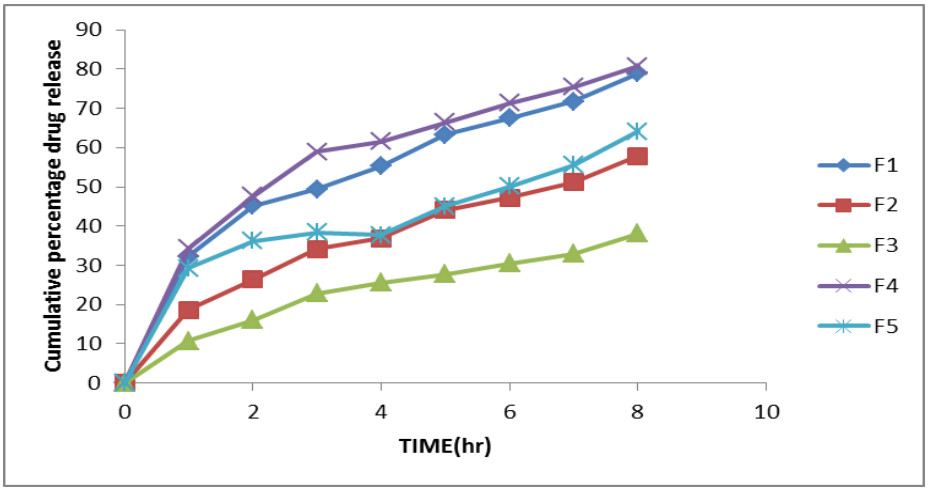


Fig: In-vitro dissolution profile in Franz Diffusion cell.

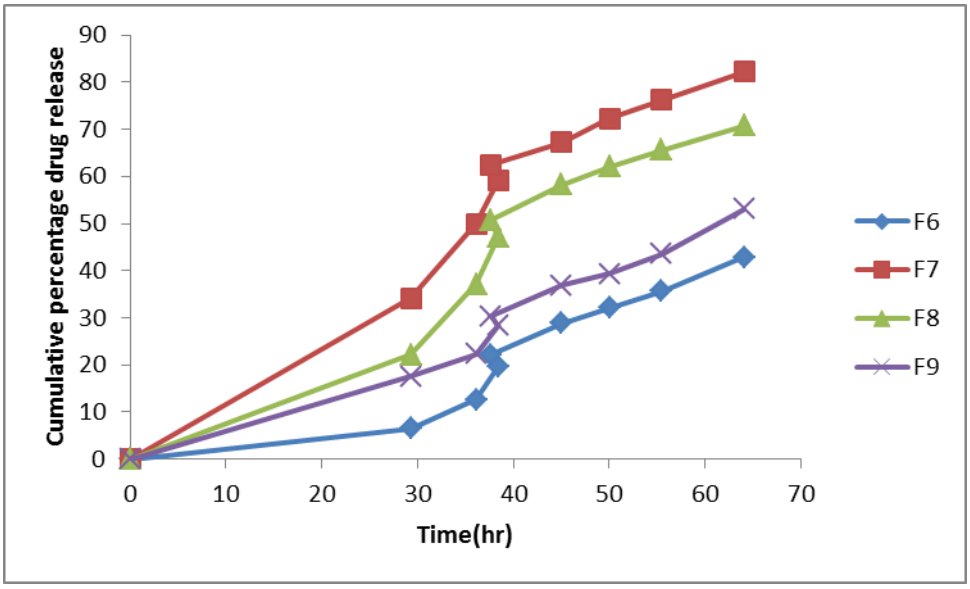
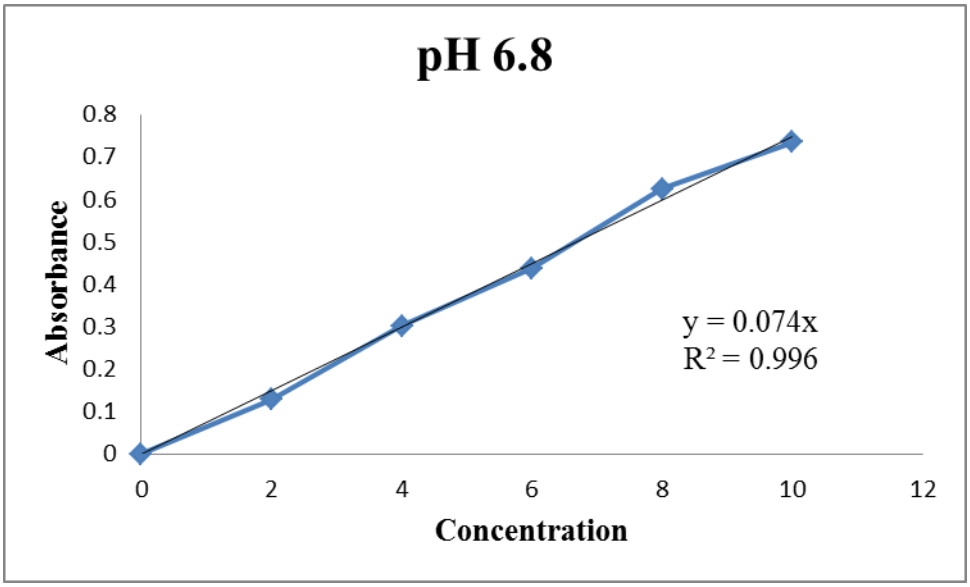
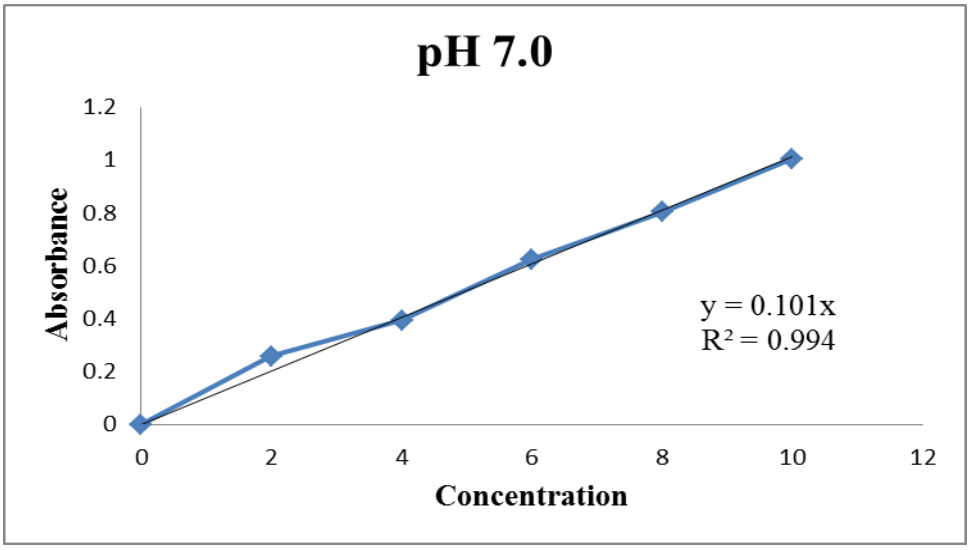


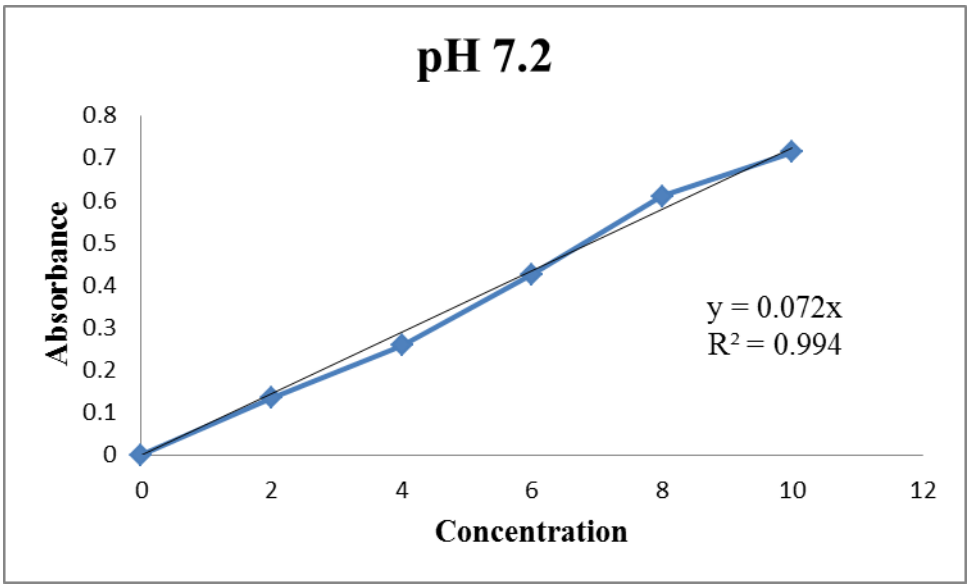
Fig: In-vitro dissolution profile in Franz Diffusion cell.

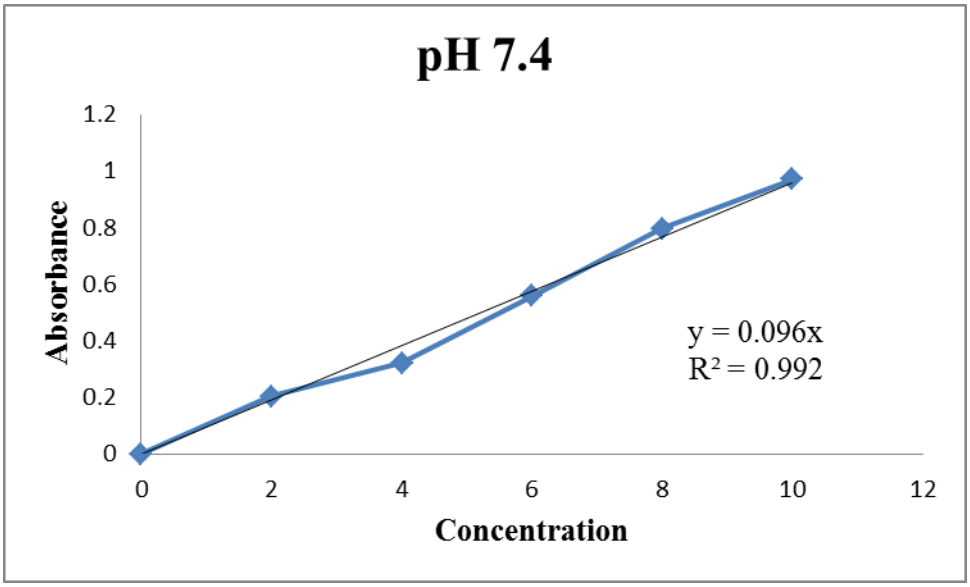
Preparation of standard calibration curve of lornoxicam in different phosphate buffer

Calibration curve of lornoxicam was prepared in different phosphate buffer. The concentration was increased in a predetermined way. Regression equation was calculated and utilized for solubility, partition coefficient and *In-vitro* drug release. The correlation coefficient and regression equation for phosphate buffer pH 7.4 was found to be 0.992


pH 6.8
Absorbance
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
2
4
6
8
10
12
Concentration
y = 0.074x
R² = 0.996


pH 7.0
Absorbance
1.2
1
0.8
0.6
0.4
0.2
0
0
2
4
6
8
10
12
Concentration
y = 0.101x
R² = 0.994


pH 7.2
Absorbance
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
2
4
6
8
10
12
Concentration
y = 0.072x
R² = 0.994



CONCLUSION

The hydrogel of lornoxicam with different penetration enhancer were successfully developed for topical delivery. Preformulation study of gifted sample was performed and all value found identical to standard. Evaluation and characterization including homogeneity, texture, colour, Spredability, drug content study, and *in-vitro* release profile were carried out.

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