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Original Article

Formulation and *In-vitro* evaluation of transdermal patch of Lornoxicam by using hydrophilic and hydrophobic polymers

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ABSTRACT

The purpose of this work is to develop and evaluate matrix-type transdermal patch containing drug Lornoxicam with different ratios of hydrophilic (PVA) and hydrophobic (Ethyl cellulose) polymeric systems, in which 4 % w/v of Tween 80 as penetration enhancer and 10 % w/v of PEG 400 as plasticizer in dichloromethane and methanol (4:1) solvent system by using Solvent Evaporation Technique. Formulated transdermal films were physically evaluated with regard to thickness, weight variation, drug content, tensile strength, folding endurance, percentage moisture loss, percentage moisture uptake, and water vapour transmission rate. Drug excipients compatibility studies are confirmed by using FTIR Spectrums. *In-vitro* permeation studies of formulations were prepared by using Franz diffusion cells. Mechanism of drug release was determined by Korsmeyer-Peppas equation. The 'n' values were found in the range of 0.836-1.159. It indicated that the formulation follows diffusion mechanisms of both non-Fickian and super case II transport. The kinetic studies showed that, formulation F-1 follow zero order while formulations F-2 to F-7 follow fist order. These results indicate that the formulation F3 {poly vinyl alcohol: Ethyl cellulose (1:1)} has shown optimum release of 79.34% with its action sustained for 24 hours time period.

Keywords: Formulations, Transdermal patch, Lornoxicam, PVA, Solvent evaporation technique.

INTRODUCTION

Rheumatic diseases have affected mankind since ages and one of the commonest inflammatory conditions in the developing countries. Rheumatoid arthritis forms a major prototype of rheumatic diseases and is a common cause of disability. Rheumatoid arthritis is an extra vascular immune complex disease and disorder of cell-mediated immunity leads to chronic inflammation, granuloma formation and joint destruction. The etiopathogenesis of rheumatoid arthritis involves divers and complex factors such as genetic background rheumatic factor, immune complexes, compliant activation, lymphocytes, arachidonic acid metabolites, free oxygen radicals, etc. Currently synthetic drugs form a major line of treatment in the management of arthritis. These agents act at various sites in the schema of pathogenic mechanisms. An important problem in the drug therapy in the elderly rheumatoid arthritis patients is the lack of compliance. They have other illness for which they are taking medicines, thus are unable to take medication of rheumatoid arthritis on time due to confusion. Transdermal delivery thus offers a better route of delivery, reported to have better patient compliance by reducing frequency of administration of the drug. Lornoxicam is one of the newer and potent NSAIDs that inhibit the prostaglandin synthetase cyclo-oxygenase and act as useful anti-inflammatory agent to control rheumatoid arthritis and other related conditions. Though Lornoxicam is very effective anti-inflammatory agent its conventional therapy suffers from serious drawbacks like non-compliance due to frequent dosing and various side effects like gastro-intestinal irritation and ulcerogenicity. The purpose of this work is to develop a new modified delivery of Lornoxicam which can avoid its systemic side effects as well as minimize its frequency of administration by sustaining the drug release. In this aspect TDDS of Lornoxicam can be considered as useful alternative to conventional deliver system. Additionally, Lornoxicam is having molecular weight, partition coefficient, and daily dose which make it an ideal candidate for TDDS [1].

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MATERIALS

Lornoxicam (Micro Labs, Bangalore), Poly vinyl alcohol (Shreeji chemicals, Mumbai), Ethyl cellulose (Shreeji chemicals, Mumbai), Dichloromethane (S.D. Fine Chem. Ltd., Mumbai), Methanol (S.D. Fine Chem. Ltd., Mumbai), Polyethylene Glycol-400 (S.D. Fine Chem. Ltd., Mumbai), Octanol (S.D. Fine Chem. Ltd., Mumbai), Tween 80 (S.D. Fine Chem. Ltd., Mumbai).

EXPERIMENTAL WORK

Preformulation studies: The various Preformulation studies were performed for Lornoxicam which includes melting point, pH (1 % solution of Lornoxicam in Dichloromethane: Methanol- 4:1), Solubility, Partition Coefficient (using 1-Octanol as Organic phase & Phosphate buffer as aqueous phase).

Preparation of transdermal patches of Lornoxicam[2]: Transdermal patches of Lornoxicam were prepared by solvent evaporation technique for the formulations as shown in Table 1.0. Solutions PVA and EC were prepared separately in dichloromethane: methanol (4:1) mixture. The two polymeric solutions were mixed to which weighed amount of Lornoxicam was added slowly. To the mixture, PEG 400 (0.6 ml), and Tween 80 (0.2 ml) were added and mixed. The drug-polymer solution was casted in Teflon plate with area of 28 cm^2 which is wrapped by aluminium foil. The plate was kept aside for drying at room temperature for 24hrs.

EVALUATION OF TRANSDERMAL PATCHES OF LORNOXICAM:

Drug-excipient compatibility studies [3]: The Infrared (IR) spectra were recorded using an FTIR by the KBr pellet method and spectra were recorded in the wavelength region between 4000 and 400 cm^{-1}. The spectra obtained for Lornoxicam, polymers, and physical mixtures of Lornoxicam with polymers were compared.

Thickness uniformity [4, 5, 6]: The thickness of patches was measured by using electronic caliper, with a least count of 0.01 mm.

Uniformity of weight [2]: The patch of size 1x1 cm^2 was cut and weight of each patch was taken individually, the average weight of the patch was calculated.

Tensile strength [2, 4]: Tensile strength of the patches was determined with Universal Strength Testing Machine (Hounsfield, Slinfold, and Horsham, U.K.). It consisted of two load cell grips. The lower one was fixed and upper one was movable. The test film of size (4 × 1 cm^2) was fixed between these cell grips and force was gradually applied till the film broke. Tensile strength is expressed as follows

$$\text{Tensile Strength} = \frac{\text{Tensile load at Break}}{\text{Cross sectional area}}$$

Folding endurance [2, 3, 4, 7, and 6]: strip of patch (2 x 2 cm^2) was cut and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of folding endurance.

Percentage moisture loss [2, 7, 8]: The patches were weighed individually and kept in a desiccator containing calcium chloride. The final weight was noted when there was no change in the weight of individual patch. The percentage of moisture content was calculated as a difference between initial and final weight with respect to final weight.

$$\% \text{ Moisture Loss} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}} \times 100$$

Percentage moisture uptake [2, 7, 9]: The patches were weighed accurately and placed in a desiccator where a humidity condition was maintained by using saturated solution of potassium chloride. The patches were kept until uniform weight is obtained, then taken out and weighed. The percentage of moisture uptake was calculated as follows:

$$\% \text{ Moisture Uptake} = \frac{\text{Final Weight} - \text{Initial Weight}}{\text{Final Weight}} \times 100$$

Water vapour transmission (wvt) rate [2, 5, 6]: About 1 g of fused calcium chloride was taken in vials and the patches measuring 1 cm^2 area were fixed over the brim with the help of an adhesive. They were weighed accurately and initial weight was recorded, and then kept in a closed desiccator containing saturated solution of potassium chloride to maintain 80-90 % RH. The cells were taken out and weighed after 24 hrs. The amount and rate of water vapor transmitted was calculated by the difference in weight using the formula.

$$\text{Water vapor transmission rate} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Time x area}}$$

Drug content uniformity [2, 3, 7]: The patches of size 1 cm^2 was cut and placed in a 100 ml volumetric flask. The contents were stirred using a magnetic bead for 24 hrs. Subsequent dilutions were made with phosphate buffer (pH 7.4). The absorbance of the solution was measured against the corresponding blank solution at 379 nm using UV-visible spectrophotometer.

***In- vitro* release studies [2, 7, 9]:** The fabricated patch were cut into 1 cm^2 and placed on the commercial semi permeable membrane and attached to the Modified diffusion cell such that the cell's drug releasing surface towards the receptor compartment which was filled with 200 ml of phosphate buffer solution of pH 7.4 at 37±10 ^{0}C and was stirred magnetically. The aliquots (5 ml) was withdrawn at predetermined time intervals and replaced with same volume of phosphate buffer of pH 7.4. The samples were analysed using UV spectrophotometer at 379 nm.

Kinetic modelling of drug release:

***Zero-order equation*:** To analyze the mechanism of drug release from the patches, the release data were fitted to the following equations:

$$Q = K_0t$$

Where Q is the amount of drug released at time t, and k0 is the release rate.

First-order equation:

$$In(100-Q) = ln100 - K_1t$$

Where Q is the percent of drug release at time t, and k1 is the release rate constant.

Higuchi's equation:

$$Q = K_2 \sqrt{t}$$

Where Q is the percent of drug release at time t, and k_2 is the diffusion rate constant.

Peppas Model: The Peppas model is widely used when the release mechanism is not well known or when more than one type of release phenomenon could be involved 'n' value could be used to characterize different release mechanism.

Peppas-Korsmeyer equation is given as

$$\%R = Kt^n$$

$$Log \%R = Log K + Log t$$

Where,

R= Drug release, K= constant, n= slope, t=time.

The mechanism of drug release was generally determined based on the 'n' value and was given in table no.2

RESULTS AND DISCUSSION

Preformulation studies: Composition of different formulations containing Lornoxicam is shown under table no: 1. The Preformulation study were performed for Lornoxicam and mentioned in table no.3

Drug - excipient compatibility studies: FTIR spectra of Lornoxicam, PVA and EC alone were compared with FTIR spectrum of the physical mixture of Lornoxicam, PVA and EC. The spectrum of Lornoxicam showed a characteristic peaks at 3417 cm^{-1} (N-H stretching), 1637 cm^{-1}(C=O stretching), 1082 cm^{-1} (S=O stretching), 3059 cm^{-1} (C-H stretching), 1539 cm^{-1} (C=C stretching), 1327 cm^{-1} (C-N stretching) and 621 cm^{-1} (C-Cl stretching) indicating purity of the drug. The characteristic peaks of Lornoxicam were prominently observed in FTIR spectra of Physical mixture (Lornoxicam, PVA and EC) with slight shift in their positions and characteristic peaks for PVA and EC were also observed in the spectrum of Physical mixture.

EVALUATION TESTS OF PREPARED PATCHES: The various evaluation results are reported in table no. 4 and the results for invitro drug release were recorded in table no.5.

Kinetic modelling of drug release: The results were recorded in table no.6. The results followed the release profile of Lornoxicam followed Peppas kinetics in different formulation. Mechanism of drug release from formulations was determined by Korsmeyer-Peppas equation where exponent 'n' indicated mechanism of drug release. The 'n' value range was found to be 0.836-1.59 and drug release follows non-Fickian and super case II transport. The drug release kinetics studies showed that, formulations F-1 follow zero order while formulations F-2 to F-7 follows fist order.

CONCLUSION

The method of preparation of transdermal patches of Lornoxicam presented in this research work is simple. All formulation also showed good physicochemical properties like thickness, weight variation, drug content, folding endurance, moisture content and moisture uptake. The *in-vitro* release data showed that drug release from the patch formulation have been affected by types of polymer and concentration of polymer. The transdermal drug delivery system F-1 (PVA alone) showed the highest drug release, but lasts only for 9 hrs. The transdermal drug delivery system F-2 (EC alone) showed lowest drug release but successfully prolonged the release. Thus, formulations F-3 to F-7 were developed using different ratios of PVA and EC, in order to achieve better release along with sustained action. All the formulations carried PEG400 as plasticizer and Tween 80 as permeation enhancer. The formulation F-3 containing PVA: EC (1:1) showed better release for sufficiently long period, up to 24 hrs and emerged as ideal formulation for Lornoxicam.

From the above studies, it is revealed that the present work was a satisfactory preliminary study of improving patient compliance of Lornoxicam by development of transdermal Drug delivery system using PVA and EC.

Table 1: COMPOSITION OF DIFFERENT FORMULATIONS CONTAINING LORNOXICAM

Formulations	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**
Lornoxicam (mg)	8	8	8	8	8	8	8
PVA (mg)	300	-	150	240	60	180	120
EC (mg)	-	300	150	60	240	120	180
Di chloro methane: Methanol (4:1ml)	7	7	7	7	7	7	7
PEG 400 (ml)	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Tween 80 (ml)	0.2	0.2	0.2	0.2	0.2	0.2	0.2

PVA = Poly vinyl Alcohol, EC=Ethyl cellulose, PEG 400=Polyethylene glycol-400

Table 2: MECHANISM OF DRUG RELEASE BASED ON '**n**' VALUE

Value of 'n'	**Mechanism**
0.5	Fickian Diffusion (Higuchi Matrix)
	Non- Fickian Transport
0.89	Case – II transport (Zero Order Release)
Higher than 0.89	Super Case II Transport

Table 3: PREFORMULATION DATA FOR LORNOXICAM

Property	**Result**
Melting point	224-226 ^{0}C
λ_{max}	379 nm
P^H	3.52
Solubility	40.98 µg/ml
Partition Coefficient	1.6

Table 4: EVALUATION REPORTS OF PREPARED LORNOXICAM TRANSDERMAL PATCHES

Formulation	**Thickness (mm)**	**Weight uniformity (gm)**	**Tensile strength (Kg)**	**Folding endurance**	**% moisture absorption (%)**	**% moisture loss (%)**	**Water vapor transmission rate (gm cm^{-2}h^{-1})**	**Drug content uniformity**
F1	0.184	0.0346	3.71	94.33	7.028	13.09	0.0041	0.283
F2	0.197	0.0331	2.96	67.87	1.680	10.73	0.0021	0.259
F3	**0.171**	**0.0292**	**3.53**	**87.66**	**6.7**	**9.426**	**0.0038**	**0.277**
F4	0.178	0.0371	3.41	81.33	5.691	9.166	0.0030	0.273
F5	0.166	0.0336	3.17	66.66	2.006	3.220	0.0025	0.275
F6	0.209	0.0332	3.34	80.33	3.651	7.44	0.0025	0.266
F7	0.183	0.0331	3.26	75	2.927	5.17	0.0028	0.271

Table 5: *IN -VITRO* RELEASE DATA OF LORNOXICAM TDDS

S.No.	Time (Hrs)	Percentage cumulative drug release						
		F1	F2	F3	F4	F5	F6	F7
1	0	0	0	**0**	0	0	0	0
2	0.5	8.2	1.95	**1.01**	2.89	1.28	2.65	3.18
3	1	15.69	3.46	**2.89**	8.76	2.61	5.54	5.31
4	2	25.36	7.89	**6.48**	17.21	8.22	7.98	8.63
5	3	35.85	10.21	**14.32**	22.69	11.14	13.49	10.21
6	4	46.36	15.22	**16.21**	31.64	14.46	16.26	12.17
7	5	52.36	17.46	**20.11**	37.28	17.54	20.74	18.61
8	6	64.98	22.32	**29.22**	43.21	21.63	23.61	21.86
9	7	79.36	27.46	**32.69**	57.32	25.64	27.24	26.44
10	8	95.88	32.21	**37.21**	61.32	30.61	32.29	32.47
11	9	99.26	38.43	**43.73**	69.67	36.21	38.86	39.39
12	10		41.28	**46.98**	76.96	42.64	43.68	41.51
13	11		45.11	**54.23**	88.98	49.11	48.25	48.78
14	12		48.67	**62.87**	92.65	52.16	54.21	54.35
15	24		52.71	**79.34**	96.47	60.14	69.85	62.76

Table 6: TDDS RESULTS OF MODEL FITTING FOR LORNOXICAM

Formulation Code	Zero Order	First Order	Higuchi/ Matrix	Peppas	
				r^2	N
F1	0.992	0.673	0.952	0.993	0.836
F2	0.717	0.834	0.915	0.973	0.991
F3	**0.896**	**0.980**	**0.962**	**0.976**	**1.138**
F4	0.779	0.897	0.911	0.961	0.957
F5	0.815	0.894	0.924	0.655	1.591
F6	0.875	0.964	0.955	0.985	0.911
F7	0.825	0.905	0.922	0.967	0.881

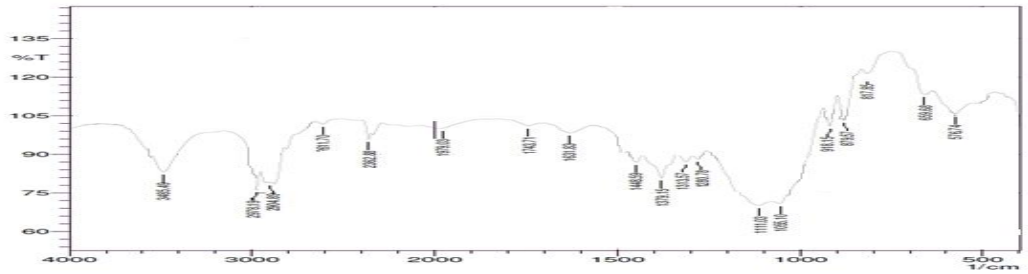

Figure.1: FTIR Spectrum of Lornoxicam

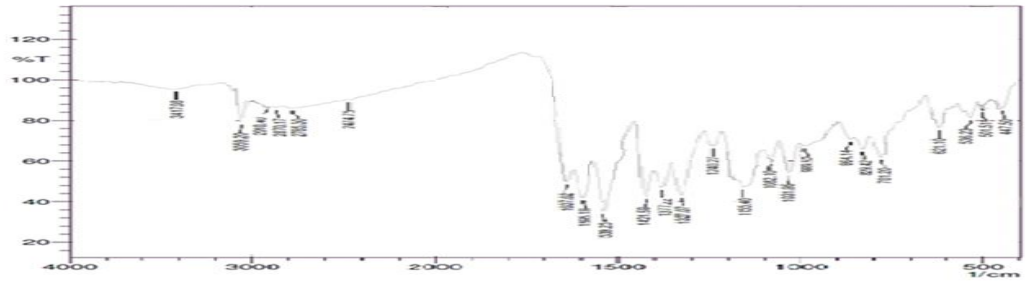

Figure.2: FTIR Spectrum of Ethyl cellulose

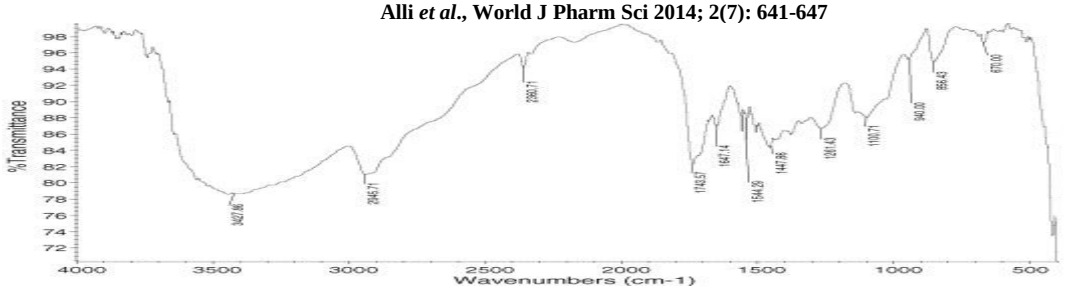

Figure.3: FTIR Spectrum of Poly vinyl alcohol

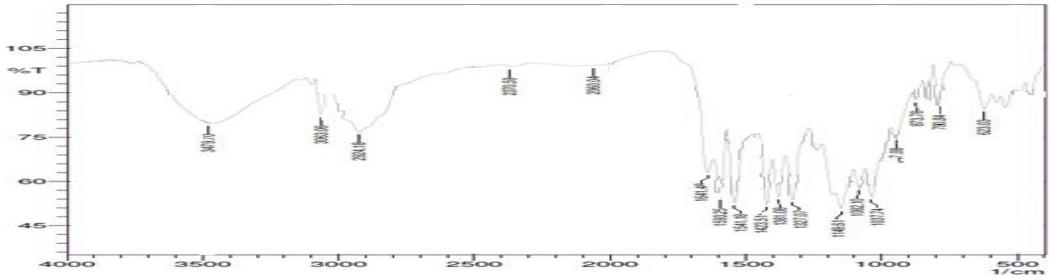

Figure. 4: FTIR spectrum of Lornoxicam, PVA and Ethyl cellulose

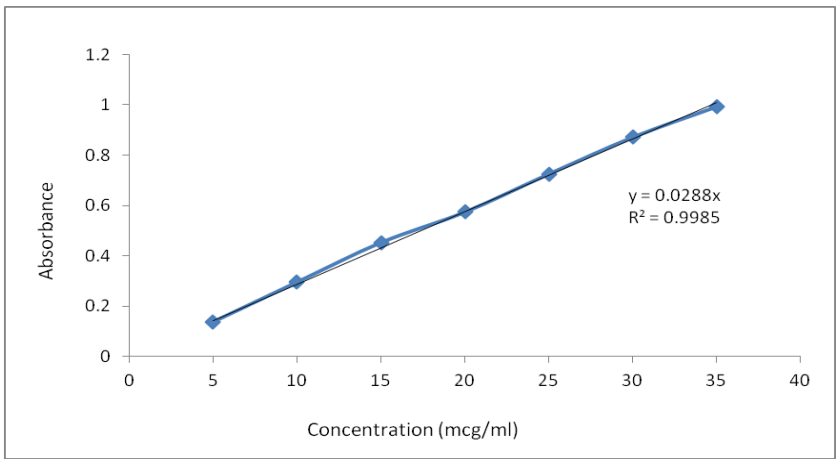

Figure 5: Calibration curve of Lornoxicam in phosphate buffer pH 7.4 at λ_{max} 379 nm

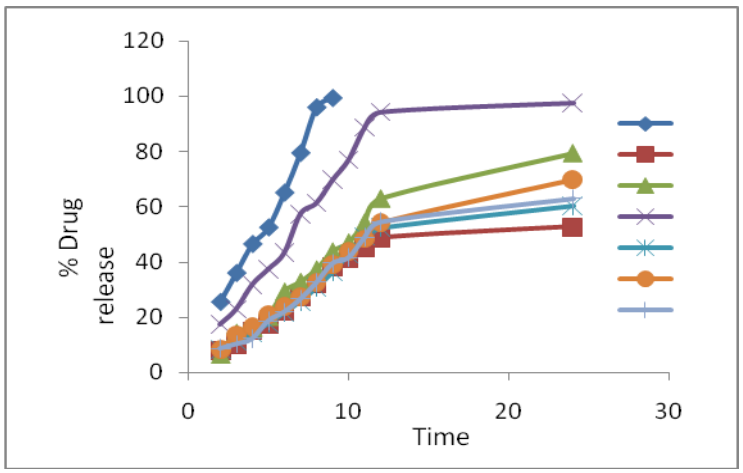

Figure 6: Cumulative % drug release profile for Lornoxicam TDDS

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