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Formulation and Evaluation of Transdermal Drug Delivery System Containing Lornoxicam.

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ABSTRACT

The present study was undertaken to develop site-specific drug delivery system of lornoxicam for treatment of arthritis, pain etc., which has excellent activity on inhibition of cyclooxygenase-1 and cyclooxygenase-2 enzymes. Formulations were developed by various polymers such as Hydroxy propyl Cellulose and Eudragit RL-100 by solvent casting technique by utilizing plasticizer PEG-400 & DBT. The formulations were evaluated for thickness, folding endurance, weight variation, drug content, percent moisture loss & absorption, tensile strength etc. *In vitro* drug release study was also carried out by using PBS pH 7.4; the samples were analyzed UV-spectrophotometrically at 374 nm. Compatibility study was carried out by FT-IR and DSC, which revealed no interaction between drug and polymers. Formulations shown good uniformity of drug content, there was no any kind of effect on moisture loss test. Weight and thickness of the patches was found to be uniform. Formulation F6 shows the release of drug 96.74% at the end of 12 h and was considered as a best formulation. Accelerated stability study indicated the formulations were remained stable both physically and chemically. Formulations prepared with dibutyl phthalate have shown to effect on tensile strength and folding endurance when compared with PEG-400.

Keywords: Lornoxicam, Transdermal patch, physical characterization, *in vitro* release study, stability study.

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INTRODUCTION

Mostly the therapeutic agents are given to the patients in the conventional forms usually these produces a large range in the fluctuations of plasma drug concentrations leading to undesirable toxicity or poor effectiveness. These factors as well as other factors such as frequent dosing, unpredictable absorption etc., leads to the concept of the controlled drug delivery system or therapeutic system which deliver the doses at appropriate manner and in controlled way. A system that releases the therapeutic agents continuously in a predetermined pattern for a fixed period of time, either systemically or to a specified targeted organ is a controlled drug delivery system. The primary objectives of controlled drug delivery are to ensure safety and to improve efficacy of drugs as well as patient compliance and this is achieved by better control of plasma drug levels and by reducing frequency of administration. Transdermal drug delivery systems (TDDS) are defined as self-contained discrete dosage forms which, when applied to the intact skin, delivers the drug(s) through the skin at a controlled rate to the systemic circulation. The potential of using intact skin as the route of drug administration has been known for several years. The idea of using skin for delivery of drug is since ancient time [1]. Several ancient cultures used ointments, pastes, medicated plasters, and complex inductions in the treatment of various symptoms or disease. Historically, the medicated plaster can be viewed as the first development of transdermal drug delivery; this medicated plaster became very popular in Japan as over the-counter pharmaceutical dosage form. In recent times, development of transdermal delivery system started in 1970s, and in 1979, the first Transdermal patch of scopolamine was approved by USFDA for the treatment of motion sickness and later on nitroglycerine patch was marketed for the management of angina pectoris [2]. Hereafter, numbers of drugs viz. clonidine, nitroglycerine, fentanyl, oxybutonin, scopolamine, lidocaine and testosterone have been successfully delivered through transdermal route [3].

Transdermal drug administration generally refers to topical application of agents to healthy intact skin either for localized treatment of tissues underlying the skin or for systemic therapy. For transdermal products the goal of dosage design is to maximize the flux through the skin into the systemic circulation and simultaneously minimize the retention and metabolism of the drug in the skin [4]. A Transdermal Drug Delivery (TDD) System is a polymeric drug delivery system, which contains drug either in a reservoir with a rate-controlling membrane or dispersed in a polymer matrix. Drug is released from these devices though the skin and is taken up by the systemic circulation via blood capillaries. It reduces the load that the oral route commonly places on the digestive tract and liver. It enhances patient compliance and minimizes harmful side effects of a drug caused from temporary overdose. TDDS offers a number of advantages such as reduces the frequency of administration, easy termination of therapy, improves bioavailability, provides constant blood level in the plasma and suitable for unconscious patients [5]. For the last two decades, transdermal drug delivery has moved from a clinical reality to the point where it represents a viable diagnostic tool for non-invasive diagnosis. The first challenge is to effective transdermal system ultimately involves ensuring adequate drug permeability through the Stratum corneum (SC) [6]. To achieve and maintain therapeutic concentration of drug in blood, the resistance of the skin (stratum corneum) to diffusion of drugs has to be minimized to allow drug molecules to cross skin and to maintain therapeutic levels in blood. Innovative technologies ranging from chemical enhancers [7] to iontophoresis, electroporation [8], pressure waves generated by ultrasound or photoacoustic effects [9, 10] have been developed for to enhance Transdermal drug delivery for therapeutic and diagnostic purposes [11].

Lornoxicam is a non-steroidal anti-inflammatory drug with analgesic and inflammatory properties and it belongs to the class of oxicams. Lornoxicam is a potent inhibitor of both Cyclooxygenase-1 and Cyclooxygenase-2 enzymes. The mechanism of analgesic action is related to the inhibition of cyclooxygenase, which suppresses the production of prostaglandins and thromboxanes thereby reducing pain and inflammation. The analgesic activity was attributed to balanced inhibition of COX- 1 and COX-2 and release endogenous dynorphin and β endorphin with reported central analgesic activity. It readily penetrates into synovial fluid, the proposed site of action in chronic inflammatory arthropathies. Lornoxicam is a very effective Anti-inflammatory agent chronic pain management associated with Rheumatoid arthritis, Osteoarthritis [12].
The present study investigates the release profile of drug from Transdermal patch by utilizing various polymeric concentration and chemical enhancer.

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MATERIALS AND METHODS

Materials

Lornoxicam was a gift sample from Glenmark. Generics Pvt. Ltd, Daund, Pune India. Hydroxy propyl cellulose HiMedia Laboratories Pvt. Ltd. Mumbai, and Eudragit RL-100 Sigma life science, Dibutyl Phthalate (S. D. Fine Chem. Ltd., Mumbai), PEG 400 (Lobachemie Pvt. ltd) Dichloromethaneand Methanol was purchased from Loba chemicals, Mumbai. Dimethylsulphoxide Rankem chemicals, Mumbai. All other chemicals used were of analytical grade.

Methods

Preformulation study

It is necessary that certain fundamental properties of drug molecule and other derived properties of drug powder are determined. Preformulation testing is the first step in the rational development of dosage forms of a drug substance. The overall objective of Preformulation testing is to generate information needed to define the nature of the drug substance and useful to the formulator that provide a framework for the drug combination with pharmaceutical excipients in the dosage form in developing stable and bioavailable dosage forms that can be mass produced.

Confirmation of Drug

Confirmation of drug was carried out by Solubility study FTIR, Melting point determination by capillary method and DSC.

Solubility study

Solubility of LOR in water, 7.4 and 6.8 aqueous phosphate buffer was determined. Excess amount of LOR powder was added in conical flask containing 10 ml of aqueous phosphate buffer. The suspension was briefly sonicated and agitated at 32 °C on water bath shaker at 300 rev. / min for 24 hours until equilibration. Aliquot was withdrawn and then filtrated through 0.45 µm millipore filter and then diluted with solvent. The samples were analyzed by UV-spectrophotomettically at λmax 374 nm [13].

Drug-Excipients compatibility Studies [14]

The drug-excipients compatibility study was carried out by using FTIR and DSC.

Infrared Spectroscopy

FTIR spectra of plane drug lornoxicam and the mixture of polymers were taken to study the interaction between them. A mixture of lornoxicam with HPC and Eudragit RL-100 were mixed separately with IR grade KBr in the ratio of 100:1 and compressed using motorized pellet press at 15 tonnes pressure.comparision study between the mixtures of drug with polymer.

Differential Scanning calorimetry (DSC)

Firstly, melting point of drug was determine by capillary method then confirmed by DSC. Thermogram of lornoxicam was obtained using DSC. Drug-excipients compatibility study was performed by Differential Scanning calorimetry (DSC).

Method of Preparation of Transdermal patch

Formulations of LOR were prepared by the utilization of various polymers such as Hydroxy propyl cellulose (HPC) and Eudragit RL-100 with the aid of plasticizer PEG-400 and Dibutyl phthalate. Hydroxy propyl cellulose (Appropriate conc.) was dissolved in a 5 ml solvent (Dichlomethane/methanol) (4:1), previously dissolved by putting the solution on magnetic stirrer (rpm 60/min). Eudragit RL-100 (Appropriate conc.) was

also dissolved in a separate 5 ml (Dichlomethane/methanol), and then both the solution was added and mixes throughout. The drug was then added to the above polymeric solution along with different concentration of DBT and Polyethylene glycol, in the formulation F1 to F6 then optimized concentration of penetration enhancer (DMSO) was also added (0.2 ml) which is thoroughly mixed on magnetic stirrer to form a homogeneous mixture. The solution was then poured on the mercury placed in a glass petridish of area 36.29 cm^2 and dried at room temperature. After 24h, the dried patches were taken out and then patch was cut into the required size to deliver the equivalent dose containing of 8 mg of drug in each formulation then stored in a desiccators until to use [15].

Table 1: Composition of lornoxicam transdermal patch.

Ingredients	F1	F2	F3	F4	F5	F6
Drug (mg)	72	72	72	72	72	72
Hydroxy propyl cellulose (HPC) (mg)	50	50	250	350	100	100
Eudragit RL-100 (mg)	250	350	50	50	350	200
DMSO (ml)	0.2	0.2	0.2	0.2	0.2	0.2
Dibutylphalate (ml)	5%	-	5%	-	5%	-
PEG-400 (ml) (% w/w of polymers)	-	5%	-	5%	-	5%
Solvent(Dichloromethane: Methanol)(4:1) (ml)	10	10	10	10	10	10

CHARACTERIZATION OF TRANSDERMAL PATCHES

Drug Content Uniformity

The formulation (patch) was added to a beaker containing 100ml of PBS of pH 7.4. To check the uniformity of the drug in the patch, three patches were taken out from each batch. Each patch was then placed in volumetric flask containing 100 ml of PBS of pH 7.4, and then shaken to extract the drug from patch overnight period on magnetic stirrer. One milliliter of above resulting solution was withdrawn, and then added into 10 ml PBS of pH 7.4 and analyzed UV-spectrophotometrically at 374 nm using PBS of pH 7.4. The mean value was calculated [15]. The standard deviation of drug content was computed from the mean value.

Thickness uniformity

The thickness of the patches was measured by using micrometer (Mitutoyo, Japan) at three different points of the patch and the mean value was calculated. The standard deviation of thickness was computed from the mean value [15].

Surface pH

Surface pH of the patches was determined by the method described by Bottenberg et al. The patches were allowed to swell by keeping them in contact with 0.5 ml of double distilled water for 1 hour in glass tubes. The surface pH was then noted by bringing a combined glass electrode near the surface of the patch and allowing it to equilibrate for 1 minute [15].

Weight variation

Weight variation study was carried out by individually weighing 3 randomly selected patches. Such determination should be performed for each formulation. Patches from each batch were weighed individually and the average weight and SD was calculated [16].

Folding Endurance

The folding endurance of the patches was determined by repeatedly folding one Patch at the same place till it broke or folded up to 300 times, which is considered satisfactory to reveal good Patch properties. The number of times of Patch could be folded at the same place without breaking give the value of the folding endurance. This test was done on all the batches for three times [15, 16].

Tensile Strength

Tensile strength of the Patch was determined with "Texture analyzer" testing machine. It consists of two load cell grips. The lower one is fixed and upper one is movable. The test patch of specific size (3 x 1 cm^2) was fixed between these cell grips and force was gradually applied till the patch breaks. The tensile strength of the Patch was taken directly from the dial reading. The tensile strength of Patch was calculated by applying the following equation. Same procedure was repeated for three times and standard deviation was calculated from mean values [15, 16].

$$\text{Tensile Strength} = \frac{load\ at\ failure}{Area\ of\ Patch} \times 100$$

Percentage Moisture Loss Test

Percentage moisture loss was determined by keeping the patches (2 x 2 cm^2) in a desiccator containing anhydrous calcium chloride. After 3 days, the Patches were taken out, re-weighed and the percentage moisture loss was calculated using the following formula; [16, 17]

$$\text{Percentage Moisture loss } = \frac{Initial\ weight - Final\ weight}{Initial\ \ weight} \times 100$$

Percentage Moisture uptake Test (Moisture uptake)

Percentage moisture uptake was determined by keeping the Patches (2 x 2 cm^2) in a desiccator. A weighed film kept in desiccators at 40 ^{o}C for 24h was taken out and exposed to saturated solution of potassium chloride in order to maintain 84% RH. After 24hrs the patches are to be reweighed and determine the percentage moisture uptake from the below mentioned formula; [16, 17]

$$\text{Percentage Moisture Uptake } = \frac{Final\ weight\ - Initial\ weight}{Initial\ \ weight} \times 100$$

***In Vitro* drug release study**

The diffusion studies were performed so as to know the permeation of drug therough the barrier from the patch. The diffusion study was carried out by the utilization of cellophane membrane (0.4µ) using Franz diffusion cell. The cell consists of two compartment, the donor, and the receptor compartment. The donor compartment was open at the top and was exposed to atmosphere. The temperature was maintained at 32 ± 0.5^{o} C and receptor compartment was provided with sampling port. The diffusion medium used was phosphate buffer (pH 7.4). *In vitro* drug release study was performed by placing patch of known weight and dimension (2×2 cm^2) into small beaker containing 10ml of PBS pH 7.4. The beaker was then placed on magnetic stirrer at 30 rpm. At periodic interval, the samples were withdrawn and the drug content was analyzed at 374 nm against reference standard using PBS pH 7.4 as a blank on a UV–visible spectrophotometer (Shimadzu Inc., Japan). Then immediately known amount of PBS pH 7.4 was added. *In vitro* release data obtained was plotted and tabulated. The volume of diffusion cell was 25 ml. The diffusion was carried out for 12 hours and 1 ml sample was withdrawn at an interval of 30min, 1, 2,3,4,6,8,10 and 12 h. The same volume of phosphate buffer pH 7.4 was added to receptor compartment to maintain sink conditions and the samples were analyzed at 374nm in UV spectrophotometer [18].

Stability study

Stability study was performed on optimized formulation, according to ICH guidelines by storing replicates of Patches (packaged in aluminum foil) in a humidity chamber, with a relative humidity a temperature of 40±0.5 °C 70±5 RH%. At periodic intervals, the samples were taken out at 0, 15, 45, and 90 days and the period for their degradation of the patch was checked. Samples were also analyzed for drug content [17, 18]

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RESULTS AND DISCUSSION

Transdermal drug delivery system is one of the promising alternatives to oral dosage forms especially for drugs that are undergone to first pass metabolism. These developed formulations were intended to produce sustained release of drugs in the management of pain inflammation, Rheumatoid arthritis, osteoarthritis. The results of solubility study as well as physical properties are indicated in the below mentioned table. Melting point of a given drug was found to be in the range of 225-229^{0}C. It was also confirmed by differential scanning calorimetry at scanning range of 10^{0}C/min it exhibits a sharp melting exothermic peak at temperature of 224.65^{0}C as shown in figure. Drug - excipients interactions play a vital role with respect to release of drug from the formulation amongst others. FTIR techniques have been used here to study the physical and chemical interaction between drug and excipients used. Infrared (IR) spectra of LOR, physical mixture of LOR with excipients of HPC formulation and physical mixture of LOR with excipients of Eudragit RL-100 formulation are shown in Figure. Drug polymer compatibility study of pure drug, drug-polymer physical mixtures were analyzed by IR spectroscopy and Differential Scanning Calorimetry indicates that there were no interation between the excipients added and drug hence suitable for formulations. The thermogram of physical mixture of HPC and ERL; ratio of 1:1 were taken which showed no shifting in the thermograms proving that there were no drug-polymer interaction. Six formulations were prepared as part of the study using HPC and ERL at various concentrations. Polymers have been chosen, for to show the prolonged release as well as possesses a good film forming properties. PEG 400 and dibutyl phthalate was utilized as plasticizer for the preparation of patches. Composition of all formulations is shown in table 1; were found to be uniform and flexible proving the efficiency of the solvent casting method for the Transdermal patches. The transparency, uniformity and flexibility are needed for uniform drug distribution and proper handling.

Table 2: Preformulation data for lornoxicam

Description	Yellow Solid powder
Melting point	225-230^0
λ max	374nm
Partition coefficient (log P)	1.99
pH	3.82
pKa	4.7

Table 3: Solubility Determination

Media	Saturation solubility(mg/ml)
Water	0.034231
6.8pH	0.079773
7.4PH	0.086312

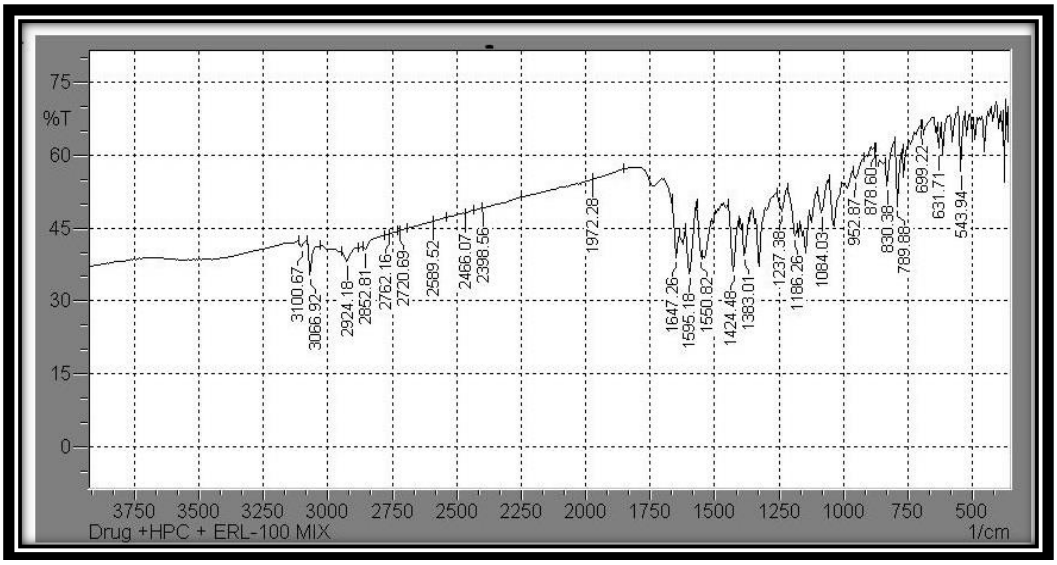

Fig. 1: FT-IR of drug + HPC+ Eudragit RL-100 (physical mixture)

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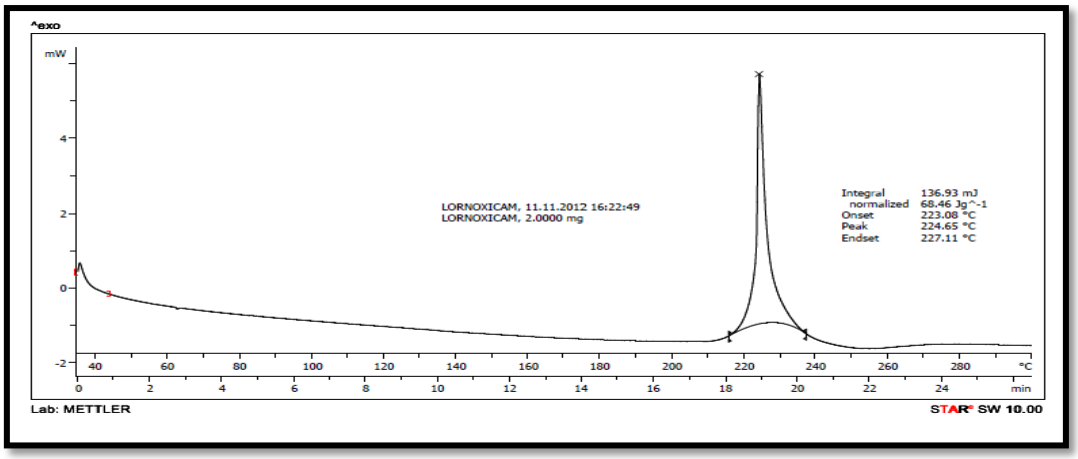

Fig.2: DSC thermogram of lornoxicam (pure drug)

The drug content of the formulations was determined according to procedure described in method. The drug content in percentage for all formulations was found to be in the range of 96.15±0.04 to and 99.15±0.03 of LOR. The results show that drug content was fairly uniform and did not deviate much from the mean. Film thickness was almost uniform in all the formulations and it was found to be in the range of 0.246±0.24 to 0.464±0.04 mm. Increase in thickness of the film might be due to the weight of polymer (HPC) and plasticizer (PEG). The average area of the patch was 0.502 sq. cm. Standard deviation was calculated for all aforesaid formulations. Results show that the thickness of the film was uniform with minimum variation. The folding endurance of the patch was found to be in the range of 189±0.03 to 267±0.15. The folding endurance measures the ability of patch to withstand rupture. The result indicated that the patches would not break and would maintain their integrity with general skin folding when used. Folding endurance was found to be highest for F3 and lowest for F2 as shown in table. Maximum concentration of HPC with DBP as plasticizer has maximum folding endurance while by lowering the conc of HPC with PEG400 showed least folding endurance. The value of folding endurance shows, the developed formulations exhibited good physical and mechanical properties. The tensile strength of the patches was found to vary with the nature of polymer and plasticizer used. HPC plasticized with DBP possessed high tensile strength while Eudragit RL100 plasticized with PEG possessed low tensile strength. The tensile strengths of drug loaded Patches are in the order of F3 > F4 > F5 > F6 > F1 > F2. The concentration of polymer (HPC) and plasticizer shows higher effect on tensile strength of patch. When the concentration of HPC increases accordingly then the tensile strength also increases. The plasticizer shows effect on tensile strength. Surface pH varied in the range of 5.3 & 6.0 indicating that no irritation will occur on the skin after applications of the patches.

Table 4: Physico-chemical characterization of prepared transdermal patch

Formulation Code	% Drug content (±SD)	Thickness (mm) (±SD)	Weight variation (mg) (±SD)	Tensile strength (kgmm-2) (±SD)	Folding endurance (±SD)	Surface pH
F1	96.15±0.04	0.246±0.24	153±0.02	0.169±0.21	212±0.01	5.4
F2	97.48±0.15	0.287±0.01	167±0.05	0.194±0.05	189±0.03	5.6
F3	99.12±0.03	0.464±0.04	194±0.01	0.278±0.13	267±0.15	5.7
F4	98.84±0.02	0.343±0.12	178±0.02	0.263±0.09	252±0.04	5.8
F5	97.28±0.14	0.269±0.02	164±0.03	0.229±0.17	236±0.16	6.0
F6	96.74±0.08	0.316±0.04	181±0.14	0.206±0.08	194±0.24	5.3

±SD=values are mean of triplicate; SD= Standard Deviation

The percentage moisture loss was noted for all the formulations in triplicate. It was observed that when the formulations were kept at very dry condition, the maximum moisture loss varied between 6.4 to 9.3 %. The amount of moisture loss might be due to less hindrance offered by added polymers and plasticizer like DBT. According to results obtained, the Percentage moisture absorption was more in formulations where high concentration of hydrophilic polymer is present. Formulation F4 possess the maximum percentage moisture absorption of 7.31±0.46 where as Formulation F1 had minimum moisture absorption. In general, it can be

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concluded that, HPC have more tendency to absorb moisture as compared to ERL. At the humid condition, percentage moisture absorption was more. However, there was no change in the integrity of the patch; which was observed by its physical appearance.

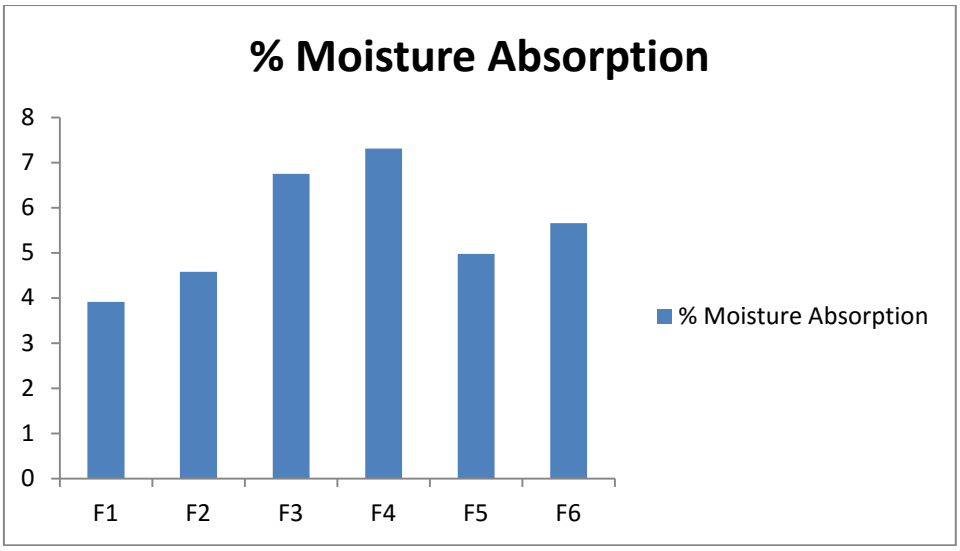

Fig. 3: Percentage moisture absorption from developed formulations

In-vitro release profile is an important tool that predicts in advance how a drug will diffuse and targeted. The results of in-vitro permeation studies of lornoxicam from transdermal patches are shown in figure. In the present study, hydrophilic (HPC) and hydrophobic (ERL-100) polymers were utilized to prepared patches. Formulation F2 exhibited 89.12 ± 0.4 % release at the end of 12h, while formulation F3 shows fast release 97.98 ±0.13 % at the end of 6 h. The cumulative amount of drug release was high from formulations containing maximum concentration of hydrophilic polymer (HPC) than hydrophobic polymer (ERL). The concentration of polymers played very important role to release the drug from matrix. Plasticizer would not affect in the release profile they only interfere in the mechanical properties of the patches. The prolonged and controlled release was found with the formulation F2; means presence of ERL contributes the release of drug.

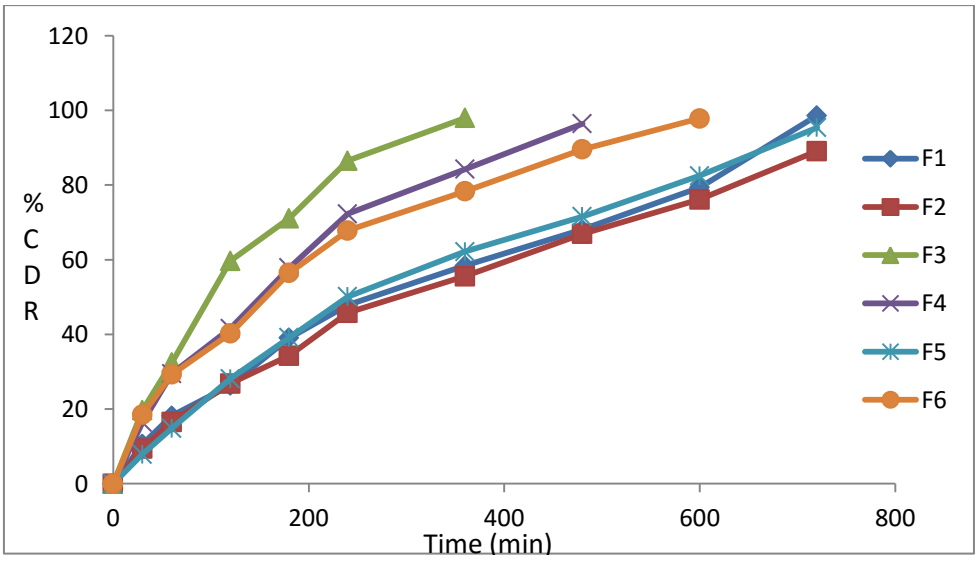

Fig. 4: *In- vitro* drug release study of formulation F1-F6

In-vitro drug release study indicated that the release of drug varied from the formulation batches according to the type and concentration of polymers utilized. The concentration of Eudragit RL-100 was increases gradually the release of drug was decreased. The concentration of hydroxy propyl cellulose was increases the drug release shows affect, increases release amount of drug. The F2 batch shows sustain drug

release 89.12 ± 0.4 % within 12 h but when compared batch F3 higher cumulative 97.98 ±0.13 % in vitro release which contained 250mg Hydroxy propyl cellulose and 50mg Eudragit RL-100 (5:1) ratio which shows effect in increases amount of release of drug in 6 h. The 2% of permeation enhancer shows increase amount of release of drug. The drug release from the patch is ordered as F3 > F4 > F5 > F6 > F2> F1.Accelerated Stability study was performed on optimized formulation (F2) at 40^{o}C temperature in a humidity chamber having 75 % RH for as per the ICH guidelines. The formulation was evaluated for physicochemical properties; drug content and in *vitro* drug release study, no major differences was found between evaluated parameters before and after ageing/storing and all were found to be in acceptable limits.

DISCUSSTION

Lornoxicam in combination with hydroxyl propyl cellulose, Eudragit RL 100C and with incorporation of PEG (5%) and DBT (5%) produced smooth, flexible and transparent films. Films developed with dibutylphthalate were found to hard texture as compared with the PEG-400.Formulation F3 which contain low concentration of Eudragit will release the drug at a faster rate when compared with other films. Formulation prepared with Eudragit will controlled the rate of release of drug. FT-IR spectral studies indicated there was no interaction between Lornoxicam and polymers used. From the above mentioned study, it was observed that thickness, weight variation, low moisture loss, low moisture absorption, tensile strength were suitable for maximum stability of the prepared formulations. The drug release rate increased when the concentration of hydrophilic polymer was increased.

CONCLUSION

The transdermal drug delivery system have shown as an alternative which avoiding hepatic first pass metabolism, maintaining constant blood levels for longer period resulting in a reduction of dosing frequency, improved bioavailability, and decreased gastrointestinal irritation that occur due to local contact with gastric mucosa and hence improved patient compliance. Based on the aforesaid study, plasticizers have significant effects on the mechanical properties of developed formulation but not on the release of drug. HPC polymer showed fast release of drug as compared to ERL-100. Therefore by the use of appropriate concentration of HPC and ERL can faster the release as well as prolong the release of drug. Further, in vivo studies have to be performed to correlate with in vitro release data for the development of suitable controlled release patches for Lornoxicam. Hence, in future such type of drug delivery system may utilize for the management of pain and inflammation.

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