Latin American Journal of Pharmacy
(formerly *Acta Farmacéutica Bonaerense)*
Lat. Am. J. Pharm. **37** (11): 2298-2311 (2018)

Received: July 3, 2018
Revised version: September 14, 2018
Accepted: September 15, 2018

Design, Preparation and Evaluation of Meloxicam Transdermal Patches using Flaxseed/Coriander Oils as Penetration Enhancers

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***SUMMARY*. Transdermal drug delivery patch is important for input of suitable drug at significant level to maintain plasma concentration for therapeutic efficacy. The present study discovered formulation and evaluation of transdermal patches using chitosan and thiolated chitosan, EC and PVP, Eudragit and PVP polymers in different ratios. Flaxseed oil and coriander oil were used as penetration enhancers in different concentrations (1, 2, 3, 4, 5, and 10%). Physicochemical properties the patches were evaluated for and in-vitro drug release. It was decided that amongst the formulations, FMLXE23, FLMXE35 and FMLXE47 which have 5% of flaxseed oil having maximum flux through rabbit skin while formulation FMLXE30, FMLXE42 and FMLXE54 containing 10% of coriander oil showed maximum flux. The drug mechanism was non-Fickian. The polymers used in the formulations have controlled the release pattern in transdermal patches. Flaxseed oil showed maximum flux at concentration 5% and coriander oil displayed maximum flux at 10% concentration.**

RESUMEN. El parche de administración transdérmica de fármacos es importante para la entrada de un fármaco adecuado a un nivel significativo para mantener la concentración plasmática de eficacia terapéutica. El presente estudio describe la formulación y evaluación de parches transdérmicos utilizando quitosano y quitosano tiolado, EC y PVP, Eudragit y polímeros de PVP en diferentes proporciones. El aceite de linaza y el aceite de cilantro se usaron como potenciadores de la penetración en diferentes concentraciones (1, 2, 3, 4, 5 y 10%). Se evaluaron las propiedades fisicoquímicas de los parches y la liberación de fármaco *in vitro*. Se comprobó que entre las formulaciones, FMLXE23, FLMXE35 y FMLXE47, que tienen un 5% de aceite de linaza, tienen un flujo máximo a través de la piel de conejo, mientras que la formulación FMLXE30, FMLXE42 y FMLXE54 que contiene 10% de aceite de cilantro mostró un flujo máximo. El mecanismo de la droga no era Fickiano. Los polímeros utilizados en las formulaciones han controlado el patrón de liberación en parches transdérmicos. El aceite de linaza mostró un flujo máximo a una concentración del 5% y el aceite de cilantro mostró un flujo máximo a una concentración del 10%.

INTRODUCTION

Transdermal drug delivery system (TDDS) is self-sufficient, distinct dosage forms also known as "patches" [1,2]. Patches applied to the unbroken skin and supply the drug through the skin at a controlled rate to the systemic circulation. TDDS are dosage forms designed to deliver a therapeutically effective amount of medication through a patient's skin [3].

The primary goal of the transdermal drug delivery system is to deliver drugs into the systemic circulation through the skin at a predetermined rate with negligible inter and intra-patient variation and avoiding first pass metabolism respectively [2]. Currently, transdermal delivery is one of the most auspicious methods for drug delivery. It increases patient compliance and reduces the harmful side effects of a drug caused by a temporary overdose and terminates the treatment when undesirable effects occur [3].

Meloxicam is a non-steroid anti-inflammatory drug which belong to enolic acid of NSAIDS. It is used to reduce pain, inflammation and also used to treat rheumatoid arthritis, osteoarthritis and ankylosing spondylitis [4]. Cyclooxygenase enzyme-2 (COX-2) are potently inhibited by as

KEY WORDS: meloxicam, patch, permeation enhancer, pharmacokinetics, polymer, transdermal.

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ISSN 0326 2383 (printed ed.)
ISSN 2362-3853 (on line ed.)

compared to COX-1 isoenzyme. Although toxicity of meloxicam is low, but when used orally its side effects are more. Such side effects include ulceration and perforation of gastrointestinal tract [5]. As long term uses of meloxicam produce significant gastrointestinal problems. So alternative route is required for meloxicam which could prevent those side effects which are associated with its oral administration and one of the methods which do not produce side effects associated with GIT is the delivery of drug through the skin. Skin is the major organ of the body is used for systemic delivery of drug [6]. Patches are mostly design for transdermal delivery of drug. Duan *et al.* [7] prepared patches for meloxicam by using chitosan, HPMC or polyvinyl alcohol. These polymers have hydrophilic components. Permeation enhancer used was polyamide amine denrdrimer. Kumar *et al.* [1] prepared meloxicam patch by using pectin as polymer matrix. This polymer is nontoxic and biodegradable. Patches have several advantages such as controlled release and self-application of patch on the skin. As compared to other drug delivery system such as gel, microemulsion, emulgel, cream and ointments, the best choice for meloxicam would be patch, because patient's compliance is more and offer accurate dosage form [9].

Hydrophobic polymers such as ethylcellulose have excellent film forming properties and are considered non-irritating, non-allergenic and non-toxic polymers. Due to the lower water permeability of this type of polymer delays release of the drug from the matrix. Therefore, hydrophilic polymers in combination with hydrophobic polymers are generally required in the preparation of the matrix type system of patches to control and maintain release of the drug [9].

However, the achievement of the transdermal drug delivery system is primarily related to the capability of the drug to enter the skin which is possible with the use of penetration enhancers. They act as polar and non-polar molecules by modifying the multilamellate pathway for penetration and even increasing the diffusivity of drugs across skin proteins [10]. Therefore, have a very important impact on the design and development of an effective product. The present study aims to develop and optimize the MXL transdermal matrix system using the varied ratio of hydrophilic (PVP), hydrophobic (EC) polymer and (EC), Eudragit and PE (Flax seed and Coriander oil) on drug release from matrix transdermal patches to study the *in vitro* release behavior of prepared patches, skin irritation and stability.

MATERIALS AND METHODS

Materials

Meloxicam was received as a gift sample (Leads Pharma Islamabad, Pakistan). Coriander seed oil and flaxseed oil were purchased to Marhaba Laboratories, Pvt., Ltd., Lahore; Eudragit, ethyl cellulose, and polyvinyl pyrrolidone to Dow Chemical Co. Midland USA, polyvinyl alcohol (PVA) to Sigma Aldrich, Germany, di-n-butylphthalate to Sigma Aldrich, Germany: potassium dihydrogen phosphate, methanol, ethanol, and NaOH to Merck, Germany. All chemicals used were of analytical grade.

Fabrication of transdermal patches without and with enhancer

MLX matrix type patches were developed using solvent evaporation techniques. Backing membrane was prepared using PVA and about 4% (w/v) solution of PVA was synthesized by dissolving 4 g of PVA in distilled water (IRMECO GmbH, IM-100, Germany) (Table 1). More distilled water was added to make the volume was made up to 100 mL in conical flask. The mixtures were heated up to 80 °C by using magnetic stirrer. The solution was cooled at room temperature and sonicator (Elma D78224, Germany) was used to remove entrapped air bubbles. About 12 mL of solution was cost on Petri dishes and dried at room temperature in open air. The drug polymer solution was prepared using a magnetic stirrer. When the drug and polymer were mixed properly then plasticizer (15% of polymer) was added. The petri dishes were allowed to cool at ambient condition by using funnel to control the evaporation. When the solution was dried completely than the film is removed and cut into 1.7 cm^2 areas.

Physicochemical Evaluation of Patches

All the patches formulations were evaluated for the following parameters.

Physical appearance

The prepared patches were evaluated visually for homogeneity, smoothness, transparency and color.

Fourier transform infrared spectroscopy

The drugs are alone and in combination with polymers were checked through FT-IR to check

Formulation Code	Drug Quantity	Polymer				Enhancer				Plasticizer	Ethanol
		Chitosan	Thiolated Chitosan	EC	PVP	Eudragit	PVP	Flaxseed oil	Coriander oil	Di-n-butyle phthalate	
FMLX1	120	1	1								
FMLX2	120	1.4	0.6								
FMLX3	120	1.7	0.3								
FMLX4	120	2:0	0.0								
FMLX5	120	0.6	1.4								
FMLX6	120	0.3	1.7								
FMLX7	120			5	0						
FMLX8	120			5	1						
FMLX9	120			3	1						
FMLX10	120			1	1						
FMLX11	120			1	3						
FMLX12	120			1	5						
FMLX13	120					5	0				
FMLX14	120					5	1				
FMLX15	120					3	1				
FMLX16	120					1	1				
FMLX17	120					1	3				
FMLX18	120					1	5				
FMLXE19	120	600	600					1%		15% of polymer	10 mL
FMLXE20	120	840	360					2%		15% of polymer	10 mL
FMLXE21	120	1020	180					3%		15% of polymer	10 mL
FMLXE22	120	1200	0.00					4%		15% of polymer	10 mL
FMLXE23	120	360	840					5%		15% of polymer	10 mL
FMLXE24	120	180	1020					10%		15% of polymer	10 mL
FMLXE25	120	600	600						1%	15% of polymer	10 mL
FMLXE26	120	840	360						2%	15% of polymer	10 mL

FMLXE27	120	1020	180						3%	15% of polymer	10 mL
FMLXE28	120	1200	0.00						4%	15% of polymer	10 mL
FMLXE29	120	360	840						5%	15% of polymer	10 mL
FMLXE30	120	180	1020						10%	15% of polymer	10 mL
FMLXE31	120			60	20			1%		15% of polymer	10 mL
FMLXE32	120			60	20			2%		15% of polymer	10 mL
FMLXE33	120			60	20			3%		15% of polymer	10 mL
FMLXE34	120			60	20			4%		15% of polymer	10 mL
FMLXE35	120			60	20			5%		15% of polymer	10 mL
FMLXE36	120			60	20			10%		15% of polymer	10 mL
FMLXE37	120			60	20				1%	15% of polymer	10 mL
FMLXE38	120			60	20				2%	15% of polymer	10 mL
FMLXE39	120			60	20				3%	15% of polymer	10 mL
FMLXE40	120			60	20				4%	15% of polymer	10 mL
FMLXE41	120			60	20				5%	15% of polymer	10 mL
FMLXE42	120			60	20				10%	15% of polymer	10 mL
FMLXE43	120					40	40	1%		15% of polymer	10 mL
FMLXE44	120					40	40	2%		15% of polymer	10 mL
FMLXE45	120					40	40	3%		15% of polymer	10 mL
FMLXE46	120					40	40	4%		15% of polymer	10 mL
FMLXE47	120					40	40	5%		15% of polymer	10 mL
FMLXE48	120					40	40	10%		15% of polymer	10 mL
FMLXE49	120					40	40		1%	15% of polymer	10 mL
FMLXE50	120					40	40		2%	15% of polymer	10 mL
FMLXE51	120					40	40		3%	15% of polymer	10 mL
FMLXE52	120					40	40		4%	15% of polymer	10 mL
FMLXE53	120					40	40		5%	15% of polymer	10 mL
FMLXE54	120					40	40		10%	15% of polymer	10 mL

Table 1. Composition of Meloxicam transdermal patch with different ratio of chitosan and thiolated chitosan, EC and PVP, Eudragit® and PVP, with and without permeation enhancer.

the interaction between the drugs and polymers. The FT-IR used was (Perkin Elmer, UK) ranging from 650-4000 cm. Sample of weight 8 mg was placed on the stage of machine and handle of machine was placed on the sample for generation of enough pressure. After that a sharp peaks of reasonable intensities were obtained.

Thickness

The patches prepared were evaluated for thickness uniformity. Microscrew gauge was used for thickness of patches [11].

Weight uniformity

Weighing balance (Model No. AX-200, Shimadzu, Japan), was used to weight the patches randomly collected from the formulation. The patches selected were 10 and digital electronic balance was used for the weighting of patches. Average weight of 10 patches were calculated and confirmed to single patch weight [12].

Folding endurance

To evaluate the efficiency of patches, folding endurance test was performed. The folding endurance value of patch was performed by rapidly folding a patch at the same point broke [12].

Moisture uptake (%)

From each formulation, 3 patches were selected randomly to determine the moisture uptake and weighed accurately. At room temperature these patches were placed on desiccator along with saturated solution of aluminum chloride to maintain humid condition. After 3 days the patches are removed from desiccator and weighed again. The individual % moisture uptake was calculated from the difference between the final and initial weight as the percentage of initial weight. After that average % moisture uptake was calculated [12].

Moisture loss (%)

From each formulation, three patches were selected randomly and weighed accurately. These patches were placed in desiccator at 37 °C along with dry condition maintain by the anhydrous calcium chloride. After 3 days the patches were removed from desiccator, weighed individually and the moisture loss was determined by difference b/w the initial weight and final weight as % age of initial weight [13].

Drug content

Drug content test was performed for the formulated patches, by placing the patch in 100 mL of volumetric flask, sonicated for 8 h. The solution was sonicated, filtered and drug contents were determined by using spectrophotometric (UV/Visible Spectrophotometer, Shimadzu 1800, Japan) at their respective wavelength of the drug [13].

Stability study

The patch selected for the study were kept for six month in incubator maintained at 37 ± 0.05 °C and 75 ± 5 % RH. After the interval of six month patches were removed from incubator and evaluated for physical appearance and the drug content [13].

Skin irritation study

Skin irritation was carried out by using rabbits having weight 2 to 2.5 kg. The dorsal surface of the rabbit was shaved with the help of razor to remove hair for applying patch and clean this surface by using spirit. The patch was applied on the clean surface with the help of tape for 24 h and then categorized into 5 ranking on the basis of response of the skin. Edema and erythema are ranked as 0 for non, 1 for slight, 2 for well defined, 3 for moderate, 4 for scar, and 5 for severe erythema and edema [14].

***In vitro* drug release studies of prepared patch**

Pharmatest Dissolution Apparatus (PTWS-11/P, Hamburg, Germany) were used for the dissolution study of prepared patches and also for evaluation of *in vitro* drug release according to the published method [15]. The patches were placed in the bottom of the each vessels of dissolution medium. These studies were carried out at 32 ± 0.5 °C at 50 rpm. Vessels were covered with lids and at specific time interval, 0, 0.05, 1, 1.5, 2, 4, 6, 8, 12, 20, and 24 h, samples of 5 mL were collected from dissolution medium and were simultaneously replaced with an equal volume of fresh dissolution medium. Spectrophotometer was used to analyze the drug in the dissolution medium at their respective wavelength using phosphate buffer pH 7.4 (pH Meter, Denver Model No. 215, USA) as a blank.

Drug Release Kinetics

Various kinetics models (Eqs. [**1**-**4**]) were applied according to the nature of data obtained from different formulation, to study release kinetics.

Zero Order Kinetics:

$$W = K_1 t \ldots \quad [\mathbf{1}]$$

where W = drug release at time t, and K_1 = rate constant for zero order release.

First Order Kinetics:

$$ln\ (100\text{-}W) = ln\ 100 - K_2\, t \ldots \quad [\mathbf{2}]$$

where W = drug release at time t, and K_2 = rate constant for first order release

Higuchi Model:

$$W = K_3 t^{1/2} \ldots \quad [3]$$

where W = drug release at time t, and K_3 = Higuchi dissolution rate constant.

Korsmeyer-Peppas:

$$M_t / M_\infty = K_4 t^n \ldots \quad [4]$$

where M_t / M_∞ = Function of released drug, K_4 = kinetic constant that represent structural and geometrical characteristics of device, and n = drug release diffusion exponent [16]. To represent different drug release mechanism or n values this model has been used. Drug release mechanism follow Fickian diffusion when n is equal 0.45 when the value of n is greater than 0.45 then it is non-Fickian. When the n value is equal to 0.89 then follow typical zero order release or case II transport [17] and when the n value is greater than 0.89 then it may follow super case II transport [18].

In vitro drug permeation study of meloxicam

To study permeation of selected drug meloxicam across the rabbit skin Franz Diffusion Cell Apparatus (Perme Gear, USA) was used and the already prepared skin was placed b/w donor compartment and receptor compartment and it was adjusted in a way that the stratum corneum of the skin facing donor compartments. The prepared patch was placed on the skin having drug releasing surface. The receptor compartment have phosphate buffer of pH 7.4 and at temperature 32 ± 0.05 °C the receptor fluids was maintain water Jackets and maintain the required temperature around the receptor compartments. Magnetics beads were also used to stirrer the receptor fluids. From the receptor compartments 2 mL of fluid were taken at regular interval of 0, 0.5, 1, 1.5, 2, 8, 12, 16, 20, and 24 h. To maintain sink condition same amount of water was added to receptor compartment which was drawn for sampling [19]. The samples drawn from the receptors compartment were analyzed spectrophotometrically against their respective were wavelength. The drug permeated from the patches were calculated and plotted against time. The flux was calculated from drug permeated per cm^2/h [20].

RESULTS

Physicochemical evaluation of patches without enhancer

The prepared patches were translucent, non-sticky of film and homogeneous. The weight and thickness of the patches were also approximately uniform. Low standard deviation shows that the patches have uniform weight. For the determination of thickness of patches Screw gauge was used. The patches having high quantity of Eudragit as compared to EC have high higher the moisture content. The chitosan and thiolated chitosan in ration of 0.3 and 1.7 have good physical characteristic and are responsible for controlled release of drug from patch. The formulation should contain small amount of moisture contents because it is necessary for stability, prevent the patch from microbial growth and also from dryness and brittleness. Such types of patches have 100% flatness, smooth and uniform surface for application onto the skin.

In vitro dissolution of patches

To confirm the sustain release performance, duration of drug release and reproducibility of rate dissolution is very much important. The drug release was faster from hydrophilic polymer as compared to hydrophobic and hydrophilic polymers or hydrophobic polymers were used in alone. This study was confirmed by dissolution. The polymer EC is nontoxic, nonirritant and non-allergic having good film properties which make it to form tougher film, but have low water permeability. It was observed that when the concentration of hydrophilic polymer increase the dissolution rate also increase and burst effect occur in formulation having high concentration of hydrophilic polymer. The lag time of hydrophilic polymer is very much little due to which bursting effect occur and could not maintain the concentration profile. Thermodynamic activity of the drug in the film increases due to high affinity of PVP for water. Maximum drug release was found from formulation having polymer ratio of 0.3:1.7 (C/TC), 1:5 (EC/PVP) and 1:5 (Eudragit/PVP). The increase of drug release is due to increase in PVP polymers. The formulation having polymer ratio 2:0 (C/TC), 5:0 (EC/PVP) and 5:0 (Eudragit/ PVP) have minimum drug release. This minimum drug release is due to increase concentration of chitosan and EC. Eudragit RL-100 containing patches showed slow release because these polymers are hydrophobic which decrease the release of drug from patches.

Meloxicam is NSAID drug used for management of pain, arthritis and ankylosing spondylitis. Transdermal drug delivery has some advan-

tages over the oral and parenteral drug delivery system [1,2]. In the present study polymers EC/PVP and Eudragit/PVP in different ratio were used with Meloxicam to study the release behavior of drug. From patches, the cumulative amount of drug permeated through centimeter square was calculated through the rabbit skin into the *in vitro* fluid and plotted against time, a straight was obtained from formulation having EC/PVP ratio of 3:1. The process of drug release from controlled release devices including transdermal patches is almost through the process of diffusion.

Release Kinetics of Patches

The amount of drug release during the dissolution study was further analyzed for evaluation of drug release from different formulation. Different kinetics models were used for release study of meloxicam. These models are zero order, first order, Higuchi and Korsmeyer-Peppas. Coefficient of correlation R^2 was calculated by using different kinetics models. The standards for choosing finest fit were maximum R^2 value, which shows the linearity of release data. The curve fitting determination of meloxicam is shown in tables. The data obtained from curve fitting shows that Meloxicam did not follow zero order kinetics which is clear from low value of R^2. The high linearity of R^2 indicates that meloxicam follow first order kinetics and Higuchi kinetics. The length of diffusion path increase as the time increase was explained by Higuchi diffusion model. Thus the release behavior of meloxicam shows that they follow first order release kinetics and Higuchi kinetics model. *In vitro* release data of Meloxicam were fitted in different kinetic model to explain the release behavior of drug from patches formulations. The n value obtained by this equation that the amount of drug released by non-Fickian diffusion predominated with all formulations (Table 2).

Visual and physical evaluation

The prepared patches of Meloxicam were smooth, clear, transparent, and homogeneous and non-sticky. The amount of Di-n-butyle phthalate used was 15% w/w of polymers to produce uniform and flexible patches of meloxicam and tizanidine. The plasticizer Di-n-butyle phthalate have good tensile strength and folding endurance of patches as compared to other plasticizer such as propylene glycol and polyethylene glycol. To increase the film forming properties preventing film cracking, desirable mechanical properties and increasing the flexibility the plasticizer is very much important in transdermal drug delivery system.

Thickness and Weight of Patches

The thickness of patches was measured with the help of micrometer screw gauge. The thickness range from 0.21 to 0.24 mm and the weight of patches also range from 38 to 39 mg. The low value of standard deviation shows that the patches have uniform weight and thickness (Table 3).

Folding Endurance

Appropriate folding endurance is necessary for cracks and ruptures. The folding endurance of prepared patches was good and was able to maintain integrity with general skin during use and would not break (Table 3).

Moisture uptake and loss

Moisture uptake and loss is also important for drug release and microbial contamination. When the moisture uptake is greater in patches causes microbial contamination and when microbial loss is greater than brittleness of patches occur. Appropriate level of moisture loss and uptake is necessary for stable and long term storage of patches (Table 3).

Flatness of patches

Flatness study indicates that the patches before and after cutting have the same length. The flatness of the patches was approximately 100%. Smooth surface of patches are necessary for application to the skin. High value of tensile strength and % elongation indicates that patches have good flexibility. To ensure the sustain delivery of drug through patches should have uniform and homogeneous distribution of drug (Table 3).

Drug contents

All the patches have approximately uniform drug contents as shown in tables. Among various batches the content of drug in patch ranges from 97.99% to 101.54% (Table 3).

Stability Study of the Patches

Stability Study of the Patches is shown in Table 4. At the beginning, during and at the end the accelerated stability shows that the tested

Formulation Code	Zero Order	First Order	Higuchi Order	Hixon Crowell	Korsmeyer-Peppas		Release mechanism
	R21	R22	R23	R24	R25	N	Non Fickian
FMLX1	0.923	0.923	0.956	0.978	0.967	0.623	Non Fickian
FMLX2	0.954	0.934	0.923	0.987	0.945	0.689	Non Fickian
FMLX3	0.987	0.967	0.989	0.967	0.962	0.634	Non Fickian
FMLX4	0.934	0.923	0.934	0.934	0.934	0.667	Non Fickian
FMLX5	0.953	0.967	0.967	0.934	0.954	0.701	Non Fickian
FMLX6	0.934	0.945	0.961	0.956	0.956	0.698	Non Fickian
FMLX7	0.964	0.945	0.923	0.967	0.978	0.656	Non Fickian
FMLX8	0.967	0.923	0.912	0.989	0.932	0.756	Non Fickian
FMLX9	0.988	0.998	0.993	0.992	0.934	0.907	Zero Order
FMLX10	0.976	0.981	0.977	0.987	0.985	0.898	Zero Order
FMLX11	0.945	0.983	0.923	0.934	0.954	0.864	Non Fickian
FMLX12	0.934	0.967	0.958	0.923	0.924	0.783	Non Fickian
FMLX13	0.934	0.945	0.961	0.956	0.956	0.698	Non Fickian
FMLX14	0.964	0.945	0.923	0.967	0.978	0.656	Non Fickian
FMLX15	0.967	0.923	0.912	0.989	0.932	0.756	Non Fickian
FMLX16	0.988	0.998	0.993	0.992	0.934	0.907	Zero Order
FMLX17	0.976	0.981	0.977	0.987	0.985	0.898	Zero Order
FMLX18	0.945	0.983	0.923	0.934	0.954	0.864	Non Fickian
FMLXE19	0.934	0.967	0.958	0.923	0.924	0.783	Non Fickian
FMLXE20	0.923	0.923	0.956	0.978	0.967	0.623	Non Fickian
FMLXE21	0.954	0.934	0.923	0.987	0.945	0.689	Non Fickian
FMLXE22	0.987	0.967	0.989	0.967	0.962	0.634	Non Fickian
FMLXE23	0.934	0.923	0.934	0.934	0.934	0.667	Non Fickian
FMLXE24	0.953	0.967	0.967	0.934	0.954	0.701	Non Fickian
FMLXE25	0.934	0.945	0.961	0.956	0.956	0.698	Non Fickian
FMLXE26	0.964	0.945	0.923	0.967	0.978	0.656	Non Fickian
FMLXE27	0.967	0.923	0.912	0.989	0.932	0.756	Non Fickian
FMLXE28	0.923	0.923	0.956	0.978	0.967	0.623	Non Fickian
FMLXE29	0.954	0.934	0.923	0.987	0.945	0.689	Non Fickian
FMLXE30	0.987	0.967	0.989	0.967	0.962	0.634	Non Fickian
FMLXE31	0.934	0.923	0.934	0.934	0.934	0.667	Non Fickian
FMLXE32	0.953	0.967	0.967	0.934	0.954	0.701	Non Fickian
FMLXE33	0.934	0.945	0.961	0.956	0.956	0.698	Non Fickian
FMLXE34	0.964	0.945	0.923	0.967	0.978	0.656	Non Fickian
FMLXE35	0.967	0.923	0.912	0.989	0.932	0.756	Non Fickian
FMLXE36	0.988	0.998	0.993	0.992	0.934	0.907	Zero Order
FMLXE37	0.976	0.981	0.977	0.987	0.985	0.898	Zero Order
FMLXE38	0.945	0.983	0.923	0.934	0.954	0.864	Non Fickian
FMLXE39	0.934	0.967	0.958	0.923	0.924	0.783	Non Fickian
FMLXE40	0.934	0.945	0.961	0.956	0.956	0.698	Non Fickian
FMLXE41	0.964	0.945	0.923	0.967	0.978	0.656	Non Fickian
FMLXE42	0.967	0.923	0.912	0.989	0.932	0.756	Non Fickian
FMLXE43	0.988	0.998	0.993	0.992	0.934	0.907	Zero Order
FMLXE44	0.976	0.981	0.977	0.987	0.985	0.898	Zero Order
FMLXE45	0.945	0.983	0.923	0.934	0.954	0.864	Non Fickian
FMLXE46	0.934	0.967	0.958	0.923	0.924	0.783	Non Fickian
FMLXE47	0.923	0.923	0.956	0.978	0.967	0.623	Non Fickian
FMLXE48	0.954	0.934	0.923	0.987	0.945	0.689	Non Fickian
FMLXE49	0.934	0.945	0.961	0.956	0.956	0.698	Non Fickian
FMLXE50	0.964	0.945	0.923	0.967	0.978	0.656	Non Fickian
FMLXE51	0.967	0.923	0.912	0.989	0.932	0.756	Non Fickian
FMLXE52	0.988	0.998	0.993	0.992	0.934	0.907	Zero Order
FMLXE53	0.976	0.981	0.977	0.987	0.985	0.898	Zero Order
FMLXE54	0.945	0.983	0.923	0.934	0.954	0.864	Non Fickian

Table 2. controlled release patches of meloxicam containing different ratio of C: TC, EC: PVP and Eudragit: PVP.

Formulation Code	Weight (mg ± SD)	Drug contents (%)	Thickness (mm ± SD)	Folding Endurance (times)	Moisture Absorbance (%)	Moisture Loss (%)	Hardness	Flatness (%)
FMLX1	22.23 ± .006	98.12 ± .034	0.20 ± .002	180	8.32 ± 1.3	7.3 ± 1.6	213 ± 1.3	100
FMLX2	22.67 ± .003	99.34 ± .034	0.21 ± .003	188	8.34 ± 1.6	7.5 ± 2.1	227 ± 1.8	99.98
FMLX3	22.12 ± .005	98.87 ± .023	0.22 ± .005	198	8.7 ± 1.30	8.2 ± 2.4	233 ± 2.1	99.96
FMLX4	23.23 ± .014	99.64 ± .031	0.21 ± .007	206	8.1 ± 1.90	7.8 ± 1.9	240 ± 1.9	99.98
FMLX5	23.89 ± .018	98.37 ± .121	0.23 ± .004	216	9.2 ± 1.40	8.8 ± 1.7	237 ± 1.6	100
FMLX6	23.34 ± .018	97.25 ± .023	0.24 ± .007	205	9.4 ± 1.70	8.6 ± 2.4	242 ± 1.8	99.88
FMLX7	22.21 ± .006	99.11 ± .034	0.21 ± .002	181	8.32 ± 1.3	7.5 ± 1.6	215 ± 1.3	99.78
FMLX8	22.45 ± .003	98.56 ± .034	0.23 ± .003	183	8.35 ± 1.6	7.3 ± 2.1	223 ± 1.8	99.92
FMLX9	23.14 ± .005	99.34 ± .023	0.21 ± .005	194	8.24 ± 1.3	8.3 ± 2.4	235 ± 2.1	99.90
FMLX10	23.25 ± .014	98.23 ± .031	0.22 ± .007	202	8.81 ± 1.9	7.6 ± 1.9	236 ± 1.9	99.85
FMLX11	23.56 ± .018	99.45 ± .121	0.22 ± .004	212	9.34 ± 1.4	8.7 ± 1.7	236 ± 1.6	99.56
FMLX12	23.45 ± .018	99.12 ± .023	0.24 ± .007	208	9.62 ± 1.7	8.8 ± 2.4	240 ± 1.8	99.92
FMLX13	38.23 ± .004	98.12 ± .034	0.21 ± .002	175	10.3 ± 1.3	7.3 ± 1.6	214 ± 1.3	100
FMLX14	39.67 ± .005	99.34 ± .034	0.23 ± .003	190	9.34 ± 1.6	8.1 ± 2.1	221 ± 1.8	100
FMLX15	39.12 ± .008	98.97 ± .023	0.24 ± .005	197	7.9 ± 1.30	7.9 ± 2.4	231 ± 2.1	99.98
FMLX16	37.23 ± .012	97.34 ± .031	0.23 ± .007	211	8.1 ± 1.90	8.2 ± 1.9	234 ± 1.9	100
FMLX17	36.89 ± .017	96.67 ± .121	0.25 ± .004	201	9.2 ± 1.40	7.8 ± 1.7	237 ± 1.6	99.98
FMLX18	38.34 ± .019	97.45 ± .023	0.24 ± .007	199	8.4 ± 1.70	7.3 ± 2.4	239 ± 1.8	99.99
FMLXE19	37.23 ± .034	98.35 ± .004	0.26 ± .008	191	10.4 ± 1.2	6.9 ± 1.9	248 ± 2.1	99.98
FMLXE20	38.45 ± .023	99.21 ± .043	0.27 ± .005	197	8.9 ± 1.50	6.5 ± 1.5	251 ± 2.8	99.98
FMLXE21	37.17 ± .021	97.32 ± .021	0.24 ± .004	208	9.2 ± 1.30	7.3 ± 2.1	237 ± 1.9	100
FMLXE22	38.56 ± .045	98.36 ± .004	0.26 ± .005	212	8.9 ± 1.50	7.8 ± 1.8	230 ± 1.7	99.99
FMLXE23	39.21 ± .005	98.34 ± .023	0.23 ± .008	231	9.4 ± 1.80	6.2 ± 1.9	238 ± 2.3	99.97
FMLXE24	38.19 ± .034	97.54 ± .012	0.22 ± .003	215	8.1 ± 1.30	7.3 ± 1.6	231 ± 1.9	100
FMLXE25	39.23 ± .006	99.12 ± .034	0.23 ± .002	178	10.32 ± 1.0	7.3 ± 1.6	212 ± 1.3	99.99
FMLXE26	38.67 ± .003	98.34 ± .034	0.22 ± .003	198	8.34 ± 1.60	8.1 ± 2.1	225 ± 1.8	100
FMLXE27	38.12 ± .005	99.97 ± .023	0.25 ± .005	195	9.9 ± 1.30	7.9 ± 2.4	237 ± 2.1	100
FMLXE28	39.23 ± .014	98.34 ± .031	0.22 ± .007	212	7.1 ± 1.90	8.2 ± 1.9	239 ± 1.9	100
FMLXE29	37.89 ± .018	97.67 ± .121	0.24 ± .004	221	8.2 ± 1.40	7.8 ± 1.7	234 ± 1.6	100
FMLXE30	38.34 ± .018	96.45 ± .023	0.25 ± .007	197	9.4 ± 1.70	7.3 ± 2.4	241 ± 1.8	99.99
FMLXE31	39.23 ± .033	99.35 ± .004	0.27 ± .008	196	10.4 ± 1.20	6.9 ± 1.9	245 ± 2.1	99.97
FMLXE32	39.45 ± .021	98.21 ± .043	0.26 ± .005	199	9.9 ± 1.50	6.5 ± 1.5	252 ± 2.8	100
FMLXE33	35.17 ± .029	98.32 ± .021	0.25 ± .004	205	8.2 ± 1.30	7.3 ± 2.1	243 ± 1.9	99.98
FMLXE34	37.56 ± .047	99.36 ± .004	0.28 ± .005	211	9.9 ± 1.50	7.8 ± 1.8	236 ± 1.7	100
FMLXE35	38.21 ± .008	97.34 ± .023	0.23 ± .008	211	8.4 ± 1.80	6.2 ± 1.9	234 ± 2.3	99.97
FMLXE36	39.19 ± .035	98.54 ± .012	0.24 ± .003	216	9.1 ± 1.30	7.3 ± 1.6	238 ± 1.9	100
FMLXE37	38.56 ± .045	98.36 ± .004	0.26 ± .005	212	8.9 ± 1.50	7.8 ± 1.8	230 ± 1.7	99.99
FMLXE38	39.21 ± .005	98.34 ± .023	0.23 ± .008	231	9.4 ± 1.80	6.2 ± 1.9	238 ± 2.3	99.97
FMLXE39	38.19 ± .034	97.54 ± .012	0.22 ± .003	215	8.1 ± 1.30	7.3 ± 1.6	231 ± 1.9	100
FMLXE40	39.23 ± .006	99.12 ± .034	0.23 ± .002	178	10.32 ± 1.3	7.3 ± 1.6	212 ± 1.3	99.99
FMLXE41	38.67 ± .003	98.34 ± .034	0.22 ± .003	198	8.34 ± 1.60	8.1 ± 2.1	225 ± 1.8	100
FMLXE42	38.12 ± .005	99.97 ± .023	0.25 ± .005	195	9.9 ± 1.30	7.9 ± 2.4	237 ± 2.1	100
FMLXE43	39.23 ± .014	98.34 ± .031	0.22 ± .007	212	7.1 ± 1.90	8.2 ± 1.9	239 ± 1.9	100
FMLXE44	38.45 ± .023	99.21 ± .043	0.27 ± .005	197	8.9 ± 1.50	6.5 ± 1.5	251 ± 2.8	99.98
FMLXE45	37.17 ± .021	97.32 ± .021	.24 ± .004	208	9.2 ± 1.30	7.3 ± 2.1	237 ± 1.9	100
FMLXE46	38.56 ± .045	98.36 ± .004	0.26 ± .005	212	8.9 ± 1.50	7.8 ± 1.8	230 ± 1.7	99.99
FMLXE47	39.21 ± .005	98.34 ± .023	0.23 ± .008	231	9.4 ± 1.80	6.2 ± 1.9	238 ± 2.3	99.97
FMLXE48	38.19 ± .034	97.54 ± .012	0.22 ± .003	215	8.1 ± 1.30	7.3 ± 1.6	231 ± 1.9	100
FMLXE49	39.23 ± .006	99.12 ± .034	0.23 ± .002	178	10.3 ± 1.3	7.3 ± 1.6	212 ± 1.3	99.99
FMLXE50	38.67 ± .003	98.34 ± .034	0.22 ± .003	198	8.34 ± 1.6	8.1 ± 2.1	225 ± 1.8	100
FMLXE51	38.12 ± .005	99.97 ± .023	0.25 ± .005	195	9.9 ± 1.30	7.9 ± 2.4	237 ± 2.1	100
FMLXE52	39.23 ± .014	98.34 ± .031	0.22 ± .007	212	7.1 ± 1.90	8.2 ± 1.9	239 ± 1.9	100
FMLXE53	37.89 ± .018	97.67 ± .121	0.24 ± .004	221	8.2 ± 1.40	7.8 ± 1.7	234 ± 1.6	100
FMLXE54	38.34 ± .018	96.45 ± .023	0.25 ± .007	197	9.4 ± 1.70	7.3 ± 2.4	241 ± 1.8	99.99

Table 3. Meloxicam transdermal patch physical parameters and drug contents and permeation enhancer.

Evaluation Parameter	F. Code	1st month	2nd month	3rd month	5th month	6th month
Drug contents	FMLXE6	99.45	99.26	99.23	98.67	98.98
	FMLXE12	99.78	98.89	98.56	97.78	97.23
	FMLXE18	99.23	98.78	97.78	98.48	98.12
	FMLXE24	99.86	99.45	99.67	99.23	99.10
	FMLXE30	99.78	98.89	98.56	97.78	97.23
	FMLXE36	99.86	99.45	99.67	99.23	99.10
Appearance	FMLXE6	No change	No change	No change	No change	No change
	FMLXE12	No change	No change	No change	No change	No change
	FMLXE18	No change	No change	No change	No change	No change
	FMLXE24	No change	No change	No change	No change	No change
	FMLXE30	No change	No change	No change	No change	No change
	FMLXE36	No change	No change	No change	No change	No change

Table 4. Physical stability of characteristics of meloxicam.

patches have approximately uniform drug contents, good flexibility and elastic properties, thus ensuring the stability of prepared patches.

Skin irritation studies

Skin irritation was carried out on rabbit skin by using score (erythema and edema). This study was carried out according to Draize patch test. According to this method score of less than 2 is considered negative means no skin irritation. Histopathology study also shows that no skin irritation occur during the study [2-3] (Table 5).

Formulation code	Visual Observation	
	Erythema	Edema
Control	0.00 ± 0.00	0.00 ± 0.00
Adhesive tape	0.94 ± 0.63	1.03 ± 0.76
Blank Patch	1.18 ± 0.67	1.05 ± 0.31
FMLXE6	0.98 ± 0.45	0.85 ± 0.45
FMLXE12	0.90 ± 0.34	1.04 ± 0.23
FMLXE18	0.86 ± 0.43	1.05 ± 0.23
FMLXE24	0.96 ± 0.23	1.06 ± 0.52
FMLXE30	1.02 ± 0.26	1.08 ± 0.56
FMLXE36	0.93 ± 0.34	1.03 ± 0.45
FMLXE42	0.98 ± 0.56	1.07 ± 0.53
FMLXE48	1.03 ± 0.34	1.09 ± 0.75
FMLXE54	0.95 ± 0.43	1.04 ± 0.32
Formaline	3.05 ± 0.65	3.4 ± 0.37

Table 5. Skin irritation studies of meloxicam transdermal patch.

In Vitro permeation study of meloxicam by using flaxseed oil and coriander oil as permeation enhancer

Figs. 1-9 show the amount of Meloxicam permeated through the rabbit skin for 24 h. Different amount of flaxseed oil was added to different formulation. Flaxseed oil added to the formulation was 1, 2, 3, 4, 5, and 10% (w/w) as permeation enhancers. The maximum flux of meloxicam was obtained when the concentration of flaxseed oil was 5%. Table 3 shows that the flux of the drug was increased when the concentration of oil increased. The amount of drug permeated through the rabbit skin was higher ($P < 0.05$) for formulation containing 5% flaxseed oil. The flux of formulations FMLXE23, FMLXE35, and FMLXE47 was higher as compared to control formulation. The formulation having flaxseed oil concentration between 5% and 10% have no significant differences.

Coriander oil as penetration enhancer in transdermal patch of meloxicam was investigated. Different concentration of coriander oil was used as permeation enhancer during *in vitro* experiment. The concentration of oil used was 1, 2, 3, 4, 5 and 10% (w/w). Flux data, permeability coefficient and lag time is given in Table 6. The result of flux indicates that by increasing the concentration the permeation also increases. The lag time was shorter between 5 and 10% (w/w) of coriander oil and permeability coefficient increase by increasing the concentration of oil. The formulations FMLXE30, FMLXE42 and

	Rabbit skin			
Formulation code	**Flux (μg/cm²·h) ± SD**	**Kp (cm/h) ± SD**	**ER**	**Tlag(h) ± SD**
Control	21.53 ± 1.72	0.689 ± 0.002	1.00	3.87 ± 0.006
FMLX1	21.21± 2.12	0.310 ± 0.006	1.34	3.08 ±0.004
FMLX2	35.23 ± 2.72	0.611 ± 0.003	3.32	3.35 ± 0.003
FMLX3	60.34 ± 1.93	0.987 ± 0.023*	7.19	2.75 ±0.006
FMLX4	87.23 ± 3.54	1.113 ± 0.034*	12.48	2.24 ± 0.008
FMLX5	112.34 ±3.22	3.112 ± 0.052*	15.85	2.13 ± 0.011
FMLX6	139.45 ± 4.23	4.431 ± 0.004*	17.84	1.43 ± 0.012
FMLX7	31.23 ± 2.12	0.902 ± 0.006	1.23	3.07 ±0.004
FMLX8	48.67 ± 2.72	1.564 ± 0.003	2.39	3.45 ± 0.003
FMLX9	86.45 ± 1.93	2.962 ± 0.023*	4.24	2.87 ±0.006
FMLX10	116.23 ± 3.54	4.112 ± 0.034*	5.58	2.34 ± 0.008
FMLX11	241.67 ± 4.23	5.564 ± 0.004*	7.94	1.56 ± 0.012
FMLX12	181.34 ±3.22	5.103 ± 0.052*	6.95	2.03 ± 0.011
FMLX13	29.23 ± 2.12	0.902 ± 0.006	1.21	3.12 ±0.004
FMLX14	45.67 ± 2.72	1.573 ± 0.003	2.34	3.67 ± 0.003
FMLX15	83.45 ± 1.93	2.987 ± 0.023*	4.21	2.98 ±0.006
FMLX16	115.23 ± 3.54	4.103 ± 0.034*	5.63	2.56 ± 0.008
FMLX17	179.34 ±3.22	5.112 ± 0.052*	6.98	2.13 ± 0.011
FMLX18	239.67 ± 4.23	5.621 ± 0.004*	7.88	1.87 ± 0.012
FMLXE19	31.23 ± 2.23	1.123 ± 0.007	1.32	2.97 ±0.004
FMLXE20	61.87 ± 2.34	1.987 ± 0.005	2.28	1.67 ± 0.003
FMLXE21	103.45 ± 1.56	3.123 ± 0.054*	4.34	1.98 ±0.006
FMLXE22	134.23 ± 3.23	4.321 ± 0.023*	5.98	2.21 ± 0.008
FMLXE23	211.67 ± 4.12	6.342 ± 0.007*	8.98	1.23 ± 0.012
FMLXE24	205.34 ±3.13	6.112 ± 0.072*	8.34	2.23 ± 0.011
FMLXE25	32.67 ± 2.12	0.934 ± 0.006	1.45	3.07 ±0.004
FMLXE26	49.27 ± 2.72	1.632 ± 0.003	2.78	3.45 ± 0.003
FMLXE27	87.78 ± 1.93	2.998 ± 0.023*	4.89	2.87 ±0.006
FMLXE28	117.45 ± 3.54	4.221 ± 0.034*	5.39	2.34 ± 0.008
FMLXE29	182.78 ±3.22	5.112 ± 0.052*	7.12	2.03 ± 0.011
FMLXE30	242.89± 4.23	5.473 ± 0.004*	8.22	1.56 ± 0.012
FMLXE31	29.23 ± 2.12	0.902 ± 0.006	1.21	3.12 ±0.004
FMLXE32	45.67 ± 2.72	1.573 ± 0.003	2.34	3.67 ± 0.003
FMLXE33	83.45 ± 1.93	2.987 ± 0.023*	4.21	2.98 ±0.006
FMLXE34	115.23 ± 3.54	4.103 ± 0.034*	5.63	2.56 ± 0.008
FMLXE35	239.67 ± 4.23	5.621 ± 0.004*	7.88	1.87 ± 0.012
FMLXE36	179.34 ±3.22	5.112 ± 0.052*	6.98	2.13 ± 0.011
FMLXE37	21.21± 2.12	0.310 ± 0.006	1.34	3.08 ±0.004
FMLXE38	35.23 ± 2.72	0.611 ± 0.003	3.32	3.35 ± 0.003
FMLXE39	60.34 ± 1.93	0.987 ± 0.023*	7.19	2.75 ±0.006
FMLXE40	87.23 ± 3.54	1.113 ± 0.034*	12.48	2.24 ± 0.008
FMLXE41	112.34 ±3.22	3.112 ± 0.052*	15.85	2.13 ± 0.011
FMLXE42	139.45 ± 4.23	4.431 ± 0.004*	17.84	1.43 ± 0.012
FMLXE43	31.23 ± 2.12	0.902 ± 0.006	1.23	3.07 ±0.004
FMLXE44	48.67 ± 2.72	1.564 ± 0.003	2.39	3.45 ± 0.003
FMLXE45	86.45 ± 1.93	2.962 ± 0.023*	4.24	2.87 ±0.006
FMLXE46	116.23 ± 3.54	4.112 ± 0.034*	5.58	2.34 ± 0.008
FMLXE47	241.67 ± 4.23	5.564 ± 0.004*	7.94	1.56 ± 0.012
FMLXE48	181.34 ±3.22	5.103 ± 0.052*	6.95	2.03 ± 0.011
FMLXE49	31.23 ± 2.23	1.123 ± 0.007	1.32	2.97 ±0.004
FMLXE50	61.87 ± 2.34	1.987 ± 0.005	2.28	1.67 ± 0.003
FMLXE51	103.45 ± 1.56	3.123 ± 0.054*	4.34	1.98 ±0.006
FMLXE52	134.23 ± 3.23	4.321 ± 0.023*	5.98	2.21 ± 0.008
FMLXE53	205.34 ±3.13	6.112 ± 0.072*	8.34	2.23 ± 0.011
FMLXE54	211.67 ± 4.12	6.342 ± 0.007*	8.98	1.23 ± 0.012

Table 6. Transdermal patches of meloxicam by using flaxseed oil and coriander oil as permeation enhancer through rabbit skin, values are mean and standard deviation of 3 determinations. *Kp is significantly different from control formulation, $p < 0.05$.

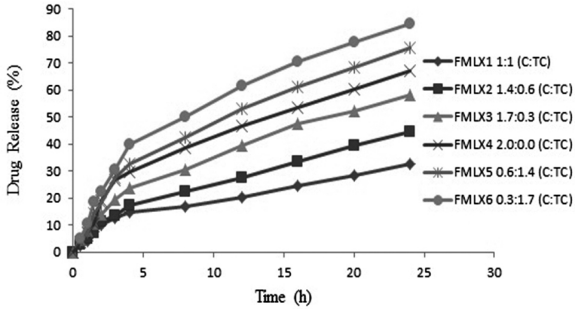

Figure 1. *In vitro* drug release of meloxicam from polymers chitosan and thiolated chitosan without permeation enhancer.

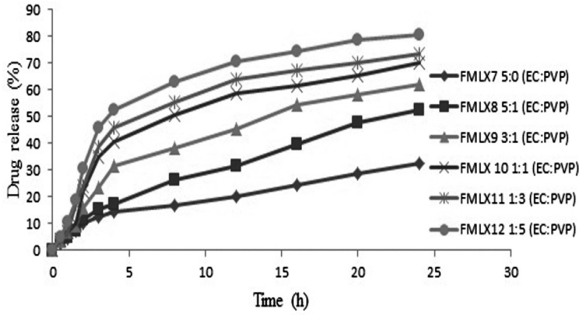

Figure 2. *In vitro* drug release of meloxicam from polymers EC/PVP without permeation enhancer.

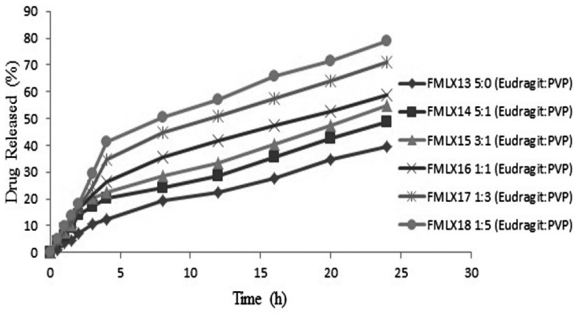

Figure 3. *In vitro* drug release of meloxicam from polymers Eudragit/PVP without permeation enhancer.

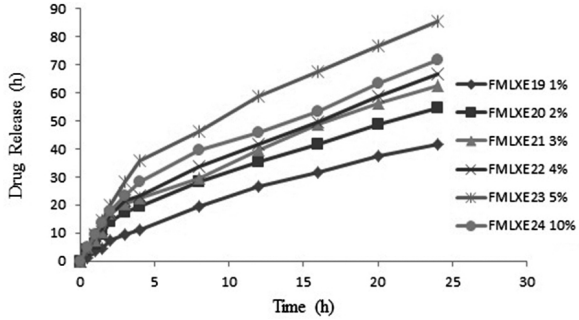

Figure 4. *In vitro* drug release of meloxicam from polymers chitosan and thiolated chitosan with permeation enhancer (flaxseed oil).

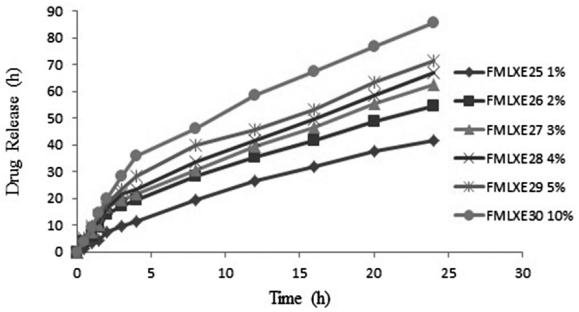

Figure 5. *In vitro* drug release of meloxicam from polymers chitosan and thiolated chitosan with permeation enhancer (coriander oil).

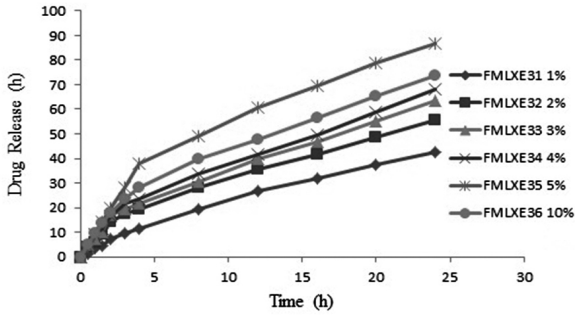

Figure 6. *In vitro* drug release of meloxicam from polymers EC/PVP with permeation enhancer (flaxseed oil).

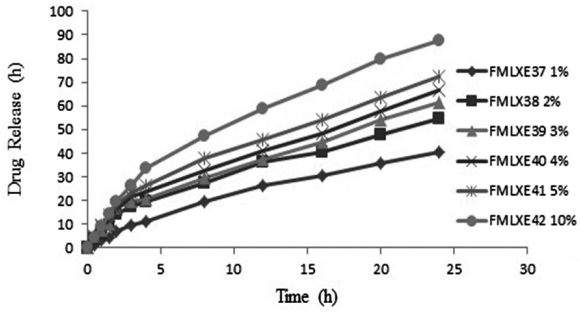

Figure 7. *In vitro* drug release of meloxicam from polymers EC/PVP with permeation enhancer (coriander oil).

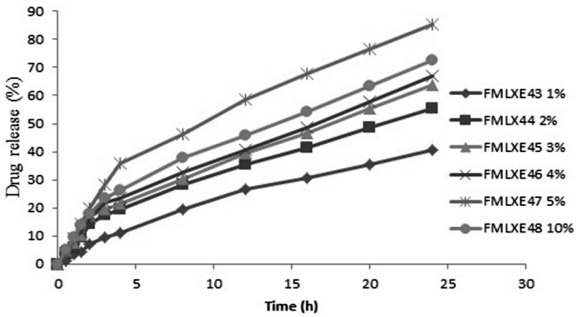

Figure 8. *In vitro* drug release of meloxicam from polymers Eudragit/PVP with permeation enhancer (flaxseed oil).

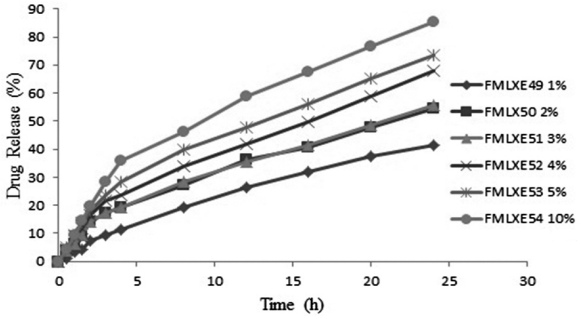

Figure 9. *In vitro* drug release of meloxicam from polymers Eudragit/PVP with permeation enhancer (coriander oil).

FMLXE54 having 10% (w/w) oil have maximum flux, Permeability coefficient, lag time and Enhancement ratio as compared to control formulation.

DISCUSSION

Moisture contents and moisture uptakes are very much are important for stability and release study of drug from patches [21]. Small amount of moisture is very much important for the stability of patches. It is also important to prevent the patch from brittleness and complete drying [23]. Small amount of moisture in patch also prevent the patch from microbial growth and contamination [22]. When the concentration of hydrophilic polymer PVP increases in the formation of patches the moisture content and moisture uptake also increases as shown in figures. As PVP is hydrophilic polymer and increase the capacity of moisture uptake. Same report was obtained by [22]. PVP change the structure of drug by changing drug from crystalline structure to amorphous and also increase the molecular spaces within the molecules [24]. To increase the permeability the polymers are mixed with other hydrophilic polymers [9]. FT-IR study was conducted for drug, polymer and excipient interactions and no interaction was found between drug, polymer and excipient. Polymers EC/PVP and drug compatibility was also studied. Polymers most commonly used in transdermal patches are C, TC, EC, PVP and Eudragit. The combination of C/TC, EC/PVP and Eudragit/PVP were used in transdermal patches in different ratio to formulate matrix type transdermal patches. Different ratios of polymers have different release characteristic. The formulations having highest concentration of PVP have bursting effect. This is due to highest concentration of hydrophilic polymers PVP. The bursting effect of PVP is due to little lag time which occurs in dissolution medium. The polymer ratio EC/PVP and Eudragit/PVP (1:1) in patches also give bursting effect which is due to high concentration of EC and Eudragit but showed controlled and sustained release. The polymers ratio 0.3:1.7, 3:1 and 5:1 C/TC, EC/PVP in formulation have best controlled release. The formulations having homogeneous distribution of polymers have best sustained release of drug. Inside the drug the intermolecular spaces are greater as compared to those between drug and polymers, but the polymers interact physically to the drug electrostatic movement [25]. *In vitro* study of the drug is very much important for *in vivo* drug release. When the formulation containing EC/PVP and Eudragit/PVP were compared in term of drug release behavior, it was concluded that the release was higher when using polymer matrix that contain Eudragit. This is due to the large cavity size in polymer network and causes faster release of MLX. At particular PH, the drug release increase from formulation containing Eudragit. Due to solubilization of Eudragit 100 channels are produced which are responsible for faster release of drug from dissolution medium [26]. So it was concluded that formulation containing drug and PVP/ EC provide slow release of drug as compared to formulation containing PVP/ Eudragit. So the best formulation found for slowest release of drug was EC/PVP (3:1) based on the physicochemical and *in vitro* release experiment. The formulation of MLX having polymer combination of C/TC (0.3:1.7), EC/PVP (3:1) and PVP/ Eudragit (5:1) were selected for further study with different permeation enhancers. The flaxseed oil contain oleic acid which the main component for permeation of drug. Riemma Pierre *et al.* [29] used oleic acid as permeation enhancer and obtained the same result by using 5-aminolevulinic. Same result was obtained by Aggarwal *et al.* [26] by using drug resperidone. The study showed that flaxseed oil increases the penetration of drug through transdermal patch. Coriander oil contains linalool 40.9 to 79.9%, geranyl acetate 2.3 to 14.2%, turpentine 0.1 to 13% and α pinene 1 to 7% and limonene. These components are responsible for permeation of drug. Similar result was obtained by Kuldeep & Eisha [26], by using linalool as permeation enhancer using drug curcumin. Galipoğlu *et al.* [28] also studied that limonene which is the component of coriander oil increase the permeation of donepezil.

CONCLUSION

On the basis of *in vitro* characterization of meloxicam transdermal patch it was concluded that it can be synthesize effectively when using polymer chitosan and thiolated chitosan in ratio of 03:1.7, ethyl cellulose (EC) and polyvinyl-pyrrolidone (PVP) in ratio of 3:1 and Eudragit and PVP in ratio of 5:1. The polymers in this ratio have controlled release pattern. It was also concluded that flaxseed oil and coriander both increase the permeation rate of Meloxicam by using Franz diffusion cell through rabbit skin.

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