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Research Article

Formulation and evaluation of matrix transdermal patches of meloxicam

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ABSTRACT

The present study deals with the formulation and evaluation of transdermal patches of meloxicam towards enhance its permeation through the skin and maintain the plasma level concentration. Transdermal patches were prepared by using polymers like Chitosan, HPMC 15cps and EC 20cps at various concentrations by solvent casting technique employing dibutyl phthalate as plasticizer and isopropylmyristate as permeation enhancer. The transdermal patches were evaluated for their physico-chemical properties and *in-vitro* drug release. The transdermal patches were found to be transparent and smooth in texture. Among the formulations studied, at the end of 12th hour, the minimum and maximum *in-vitro* drug release was observed for the formulations F12 and F4 i.e. $80.012 \pm 2.012\%$ and $98.365 \pm 3.012\%$. The mechanism of drug release was found to be Non-Fickian diffusion controlled. FT-IR studies revealed the integrity of the drug in the formulations.

Keywords: Transdermal Patches, Meloxicam, Chitosan, HPMC 15cps, EC 20 cps, *in-vitro* diffusion studies.

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INTRODUCTION

Transdermal drug delivery system has been in existence for a long time. In the past, the most commonly applied systems were topically applied creams and ointments for dermatological disorders the occurrence of systemic side-effects with some of these formulations is indicative of absorption through the skin¹. A number of drugs have been applied to the skin for systemic treatment. In a broad sense, the term transdermal delivery system includes all topically administered drug formulations intended to deliver the active ingredient into the general circulation².

Transdermal therapeutic systems have been designed to provide controlled continuous delivery of drugs *via* the skin to the systemic circulation³⁻⁴. Moreover, it over comes various side effects like painful delivery of the drugs and the first pass metabolism of the drug occurred by other means of drug delivery systems⁵.

Meloxicam and other NSAIDs the mechanism of release was diffusion mediated. The developed transdermal patches increase the efficacy of meloxicam for the therapy of arthritis and other painful muscular conditions⁶⁻⁸. Conventional systems of medication which require multi dose therapy have numerous problems and most recently, there is an increasing recognition that the skin can serve as the port provide continuous transdermal drug infusion into the

systemic circulation⁹⁻¹². Transdermal therapeutic systems are defined as self-contained, discrete dosage forms when applied to the intact skin deliver the drug through the skin at controlled rate to the systemic circulation¹⁵⁻¹⁹. So, in present study formulated, evaluated and *in-vitro* drug release studies of meloxicam.

MATERIAL AND METHODS

Meloxicam hydrochloride was received as a gift samples from Cadila Pharmaceutical, Ahmadabad and polymers are obtained from. Other chemicals used in the study were of analytical grade. Double-distilled water was used throughout the study.

Preparation of Transdermal Patches

The transdermal patches of Meloxicam were prepared using combination of three polymers *i.e.* (Chitosan, HPMC, EC) (Table 1) in a suitable solvent system by solvent casting technique. Calculated amount of meloxicam was dissolved in methanol and was dispersed in polymeric solution. Dibutyl phthalate is used as plasticizer (30% weight of polymer) and Isopropyl myristate served as permeation enhancer (5% weight of polymer) were added and stirred to form uniform mixture. The resultant mixture was poured into petridish having glass bangle (diameter 4.5 cm) lined with aluminum foil as a backing membrane. The prepared patches were

allowed to dry at room temperature for 24 hrs. For complete drying, the moulds were kept in a hot air oven maintained at $45 \pm 1^\circ\text{C}$ for another 4 hours. After complete drying, the patches were removed and stored in desiccator until used. The patches were smooth, flexible and could be cut to any desired size and shape²⁰⁻²⁶.

Evaluation of transdermal patches

The transdermal patches were evaluated for the following parameters.

Physical appearance

All the prepared patches were visually inspected for color, clarity, flexibility and smoothness.

Thickness uniformity

The thickness of the formulated film was measured at 3 different points using a mitutoyo thickness gage 7301 made in Japan thickness of three reading was calculated. Average thickness was determined.

Folding endurance

The folding endurance was determined to determine flexibility of film. The flexibility of the film is needed to handle the film easily and for comfortable, secured application of film on the wound. It was determined by repeatedly folding one film at same place till it breaks or folded up to 300 times manually. The number of times of film could be folded at the same place without breaking give the value of folding endurance.

Water absorption capacity

It is of utmost importance, if they are used for biological applications and wound healing. It is used to measure the capacity of film to absorb wound exudates. The initial weight of 1inch of dry film was noted. Then this film was placed in 15ml. of distilled water taken in Petri plate. The weight of the film was noted periodically at first hour, second hour, third hour and 24th hour. Every time after noting the weight, the film was placed in fresh water. Water absorption capacity of the film was calculated using a formula:

$$\% \text{ moisture absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Percentage moisture loss

The films were weighed accurately and kept in a desiccators containing anhydrous calcium chloride. After 3 days, the films weretaken out and weighed. The moisture loss was calculated using the formula:

$$\% \text{ moisture loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Water vapor transmission rate

Glass vials of 5 ml capacity were washed thoroughly and dried to a constant weight in an oven. About 1 g of fused calcium chloride was taken in the vials and the polymer films of 2.25 cm² were fixed over the brim with the help of an adhesive tape. Then the vials were weighed and stored in a humidity chamber of 80-90 % RH condition for a period of 24 h. The vials were removed and weighed at 24 h time intervals to note down the weight gain.

$$\text{Transmission rate} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Time} \times \text{Area}} \times 100$$

Tensile strength

Tensile strength of the film was determined with Universal strength testing machine (JUSTY, Tensile Testing Machine, JTM 50 digital). The sensitivity of the machine was 1 g. It consisted of two load cell grips. The lower one was fixed and upper one was movable. The test film of size (10 × 10 mm²) was fixed between these cell grips and force was gradually applied till the film broke. The tensile strength of the film was taken directly from the dial reading in kg. Tensile strength is expressed as follows:

$$\text{Tensile Strength} = \frac{\text{Tensile load at break}}{\text{Cross section area}}$$

Drug content

An accurately cut patch of 1cm² area was taken and added to a beaker containing 1 ml phosphate buffer solution of pH 7.4. The beaker was kept 24 hours with occasional shaking. The sample was analyzed drug content using UV spectrophotometer 248nm. This study was performed for 3 times for a single patch.

Table 1: Composition of Meloxicam Transdermal Patches

Formulation Code	Polymers			Plasticizer (30 % w/v) (DBT)	Permeation Enhancer (30% w/v) IPM
	Chitosan	HPMC	EC		
F1	5	-	-	30	5
F2	-	5	-	30	5
F3	2	3	-	30	5
F4	3	2	-	30	5
F5	3.5	1	0.5	30	5
F6	3	1.5	0.5	30	5
F7	2.5	1.5	1	30	5
F8	2.5	2.5	0	30	5
F9	3	1	1	30	5
F10	2	2	1	30	5
F11	2.5	2.5	0	30	5
F12	1.5	3.5	0	30	5

In vitro drug release studies

The *in vitro* evaluation was carried out in the modified Franz diffusion cell. This consists of an upper donor compartment and the lower receptor compartment, surrounded by water jacket for circulation of water to maintain the temperature inside at $32 \pm 1^\circ\text{C}$. The uniformity of solution in the receptor phase was maintained by stirring at high speed of 100 rpm (approximately) using a tiny magnetic bead the volume of receptor compartment was maintained at 60 ml and the diffusional surface area is 0.785 cm^2 . The receptor compartment was provided with the sampling port on one side, to withdraw sample at the predetermined time intervals for estimation of drug content by UV spectrophotometer.

Experimental conditions

The receptor medium was phosphate buffer solution of pH 7.4, temperature of the receptor medium was maintained at $37 \pm 2^\circ\text{C}$ throughout the experiment using water jacket. The donor compartment was in contact with ambient condition of atmosphere.

RESULT AND DISCUSSION

In the present study, Meloxicam transdermal patches were prepared by solvent casting method. Polymers used for this study Chitosan, HPMC, EC employing aluminum foil as the backing membrane, Dibutyl phthalate used as plasticizer and Isopropyl myristate as permeation enhancer.

Thickness

The transdermal patches were transparent, smooth, uniform and flexible. Thicknesses of transdermal patches were found to be in the range of $0.02266 \pm 0.0015 \text{ mm}$ to $0.03533 \pm 0.0025 \text{ mm}$ (Table 2). The low standard deviation values in the film thickness ensure uniformity of the patches prepared by solvent casting technique. The weights of formulations were found to be in the range of $0.1130 \pm 0.0040 \text{ gm}$ to $0.1736 \pm 0.0015 \text{ gm}$. This indicated that there is no significant weight variation in all formulations and are as shown in Table 2.

Folding endurance

In order to evaluate the flexibility, the films were subjected to folding endurance studies. The values in the range of 138 to 176 were observed in all batches. This revealed that the prepared films were having capability to withstand the mechanical pressure along with good flexibility. The formulation F6 was found to have lowest folding endurance, whereas formulation F4 was found to have highest folding endurance. The folding endurance results were shown in Table 2.

Percentage moisture uptake and loss

Among the formulations, F1 showed maximum moisture uptake *i.e.* $3.4533 \pm 0.2318 \%$ and F4 showed minimum moisture uptake *i.e.* $1.3433 \pm 0.1457\%$. The percentage moisture uptake results are as shown in Table 2. Among the formulations, F10 showed maximum moisture loss *i.e.* $4.3300 \pm 0.0360 \%$ and F1 showed minimum moisture loss *i.e.* $1.5150 \pm 0.2700\%$. The percentage moisture loss results are as shown in Table 2.

Tensile strength

The tensile strength was determined by using tensile strength tester (Test techno consultant, Vadodara) having the capacity of 10 kg. The results are as shown in Table 2. It was found that the formulation F4 and F1 shown maximum ($0.6130 \pm 0.0010 \text{ kg/cm}^2$) and minimum ($0.3250 \pm 0.0036 \text{ kg/cm}^2$) tensile strength respectively among all the formulations.

Bursting strength

The bursting strength was determined by using bursting strength tester (Test Techno Consultant, Vadodara) having the capacity of 10 kg. From results are as shown in Table 2, it is found that the formulation F4 and F8 shown maximum (2.9 kg/cm^2) and minimum (2.2 kg/cm^2) bursting strength respectively among all the formulations.

Drug content uniformity

The drug content uniformity of all the formulations was determined. The results of the drug content in all the formulations were found to be in the range of $96.5833 \pm 1.5593 \%$ to $98.4366 \pm 0.9281 \%$ and are as shown in Table 2.

In-vitro drug release

The results of the Table 3 indicated the cumulative percentage drug release of various formulations. The cumulative percentage of drug released in 12 h was found to be minimum and maximum for the formulations F4 and F10 *i.e.* $81.023 \pm 3.013 \%$ and $98.564 \pm 3.005\%$. The *in-vitro* release data obtained from different formulations of meloxicam was plotted for cumulative percent drug release versus time. First order plots are plotted by taking log cumulative percent drug remaining versus time. (Figure 1) To ascertain the drug release mechanism, the formulations were plotted for Higuchi diffusion plots (Figure 2) by taking cumulative percent drug release versus square root of time. The plots were found to be fairly linear and the regression coefficient values were nearer to 1 in all the cases. So it confirmed that the drug release mechanism was diffusion mechanism. The formulations were also treated to Peppas plot by taking log percent release versus log time (Figure 3). The plots are found to be fairly linear and the regression values are nearer to 1. The values of slope of Peppas suggest that the drug was released by Non-Fickian diffusion control (Anomalous diffusion) without any swelling.

CONCLUSION

The patches of Meloxicam prepared using the polymers HPMC 15cps, Chitosan and EC were of smooth surface, good appearance, uniform thickness and weight variation with minimum standard deviation. The ratio of hydrophilic and hydrophobic polymeric film formers affected the mechanical properties, percentage moisture uptake and rate of drug release. With increasing levels of EC in the formulations the release rates were lowered. It can be concluded that Meloxicam can be delivered by transdermal route in a controlled manner into the systemic circulation to maintain therapeutic drug levels for prolonged periods.

Table 2: Physical Characterization of Meloxicam Transdermal Patches

Formulation Code	Thickness (mm)* Mean \pm SD	Weight Variation (g)* Mean \pm SD	Folding Endurance* Mean \pm SD	Drug Content (%)* Mean \pm SD
F1	0.025 \pm 0.0030	0.1255 \pm 0.0052	146.3333 \pm 4.5092	97.4 \pm .45
F2	0.022 \pm 0.0030	0.1455 \pm 0.0025	163.6666 \pm 2.3025	97.98 \pm .42
F3	0.013 \pm 0.0015	0.1256 \pm 0.0041	169.0000 \pm 1.2563	99 \pm .255
F4	0.035 \pm 0.0025	0.1366 \pm 0.0025	155.6666 \pm 3.5263	97.37 \pm .48
F5	0.020 \pm 0.0032	0.1478 \pm 0.0063	136.3333 \pm 1.4415	96.00 \pm .48
F6	0.032 \pm 0.0015	0.1585 \pm 0.0048	152.0000 \pm 2.3632	97.52 \pm 1.4
F7	0.021 \pm 0.0010	0.1263 \pm 0.0036	152.6666 \pm 5.3652	97.99 \pm .79
F8	0.015 \pm 0.0020	0.2665 \pm 0.0074	136.3333 \pm 4.2635	98.82 \pm .39
F9	0.025 \pm 0.0032	0.2556 \pm 0.0045	140.6666 \pm 4.3652	97.9 \pm .79
F10	0.026 \pm 0.0020	0.2636 \pm 0.0012	150.3333 \pm 4.5665	98.82 \pm .39
F11	0.04 \pm 0.0032	0.4553 \pm 0.0036	146.6666 \pm 3.2365	97.9 \pm .70
F12	0.04 \pm 0.0032	0.2663 \pm 0.0063	142.0000 \pm 1.2556	98.5 \pm 2.5

*Average of three determination

Table 3(a): *In-vitro* Drug Release Studies

Time	Cumulative Percent Released					
	F1	F2	F3	F4	F5	F6
0	0.000 \pm 0.00	0.000 \pm 0.00	0.000 \pm 0.00	0.000 \pm 0.00	0.000 \pm 0.00	0.000 \pm 0.00
1	4.535 \pm 1.042	4.953 \pm 1.025	7.025 \pm 1.008	8.025 \pm 1.025	7.058 \pm 3.256	6.456 \pm 3.965
2	11.485 \pm 2.365	10.258 \pm 1.358	11.852 \pm 2.058	18.540 \pm 2.004	11.442 \pm 2.023	15.665 \pm 3.258
3	19.575 \pm 1.358	18.258 \pm 1.023	17.458 \pm 2.365	24.557 \pm 2.014	32.225 \pm 3.025	24.369 \pm 2.122
4	27.578 \pm 1.025	22.145 \pm 2.032	24.258 \pm 2.352	33.254 \pm 1.250	25.189 \pm 2.258	21.258 \pm 1.852
5	32.320 \pm 2.025	25.014 \pm 1.470	33.591 \pm 3.025	23.65 \pm 3.034	36.021 \pm 2.785	22.568 \pm 2.596
6	42.023 \pm 1.235	36.256 \pm 2.365	43.258 \pm 3.221	48.369 \pm 2.325	50.258 \pm 2.358	36.223 \pm 0.230
7	51.236 \pm 2.369	46.325 \pm 2.322	54.203 \pm 3.025	55.025 \pm 3.780	59.365 \pm 3.025	60.254 \pm 3.258
8	59.365 \pm 3.252	55.362 \pm 2.014	56.236 \pm 3.666	58.885 \pm 2.258	59.263 \pm 2.258	56.254 \pm 2.014
9	66.258 \pm 2.365	63.201 \pm 3.025	72.025 \pm 2.367	76.365 \pm 3.247	68.325 \pm 2.015	63.021 \pm 2.014
10	74.365 \pm 3.202	72.365 \pm 2.012	70.367 \pm 1.025	73.036 \pm 2.025	74.012 \pm 2.012	72.032 \pm 3.012
11	75.125 \pm 3.012	76.212 \pm 2.201	77.012 \pm 3.036	75.012 \pm 3.312	74.014 \pm 2.012	76.012 \pm 3.063
12	86.015 \pm 1.005	83.012 \pm 2.012	95.850 \pm 1.025	98.365 \pm 3.012	90.254 \pm 1.025	96.025 \pm 1.022

Table 3(b): *In-vitro* Drug Release Studies

Time	Cumulative Percent Released					
	F7	F8	F9	F10	F11	F12
0	0.000 \pm 0.00	0.000 \pm 0.00	0.000 \pm 0.00	0.000 \pm 0.00	0.000 \pm 0.00	0.000 \pm 0.00
1	8.025 \pm 1.025	6.456 \pm 3.965	7.025 \pm 1.008	4.535 \pm 1.042	7.058 \pm 3.256	4.953 \pm 1.025
2	18.540 \pm 2.004	15.665 \pm 3.258	11.852 \pm 2.058	11.485 \pm 2.365	11.442 \pm 2.023	10.258 \pm 1.358
3	24.557 \pm 2.014	24.369 \pm 2.122	17.458 \pm 2.365	19.575 \pm 1.358	32.225 \pm 3.025	18.258 \pm 1.023
4	33.254 \pm 1.250	21.258 \pm 1.852	24.258 \pm 2.352	27.578 \pm 1.025	25.189 \pm 2.258	22.145 \pm 2.032
5	23.65 \pm 3.034	22.568 \pm 2.596	33.591 \pm 3.025	32.320 \pm 2.025	36.021 \pm 2.785	25.014 \pm 1.470
6	48.369 \pm 2.325	36.223 \pm 0.230	43.258 \pm 3.221	42.023 \pm 1.235	50.258 \pm 2.358	36.256 \pm 2.365
7	55.025 \pm 3.780	60.254 \pm 3.258	54.203 \pm 3.025	51.236 \pm 2.369	59.365 \pm 3.025	46.325 \pm 2.322
8	58.885 \pm 2.258	56.254 \pm 2.014	56.236 \pm 3.666	59.365 \pm 3.252	59.263 \pm 2.258	55.362 \pm 2.014
9	76.365 \pm 3.247	63.021 \pm 2.014	72.025 \pm 2.367	66.258 \pm 2.365	68.325 \pm 2.015	63.201 \pm 3.025
10	73.036 \pm 2.025	72.032 \pm 3.012	70.367 \pm 1.025	74.365 \pm 3.202	74.012 \pm 2.012	72.365 \pm 2.012
11	75.012 \pm 3.312	76.012 \pm 3.063	77.012 \pm 3.036	75.125 \pm 3.012	74.014 \pm 2.012	76.212 \pm 2.201
12	97.365 \pm 3.012	96.025 \pm 1.022	95.850 \pm 1.025	86.015 \pm 1.005	90.254 \pm 1.025	80.012 \pm 2.012

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