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RESEARCH ARTICLE

Formulation and Evaluation of Transdermal patches of Maloxicam using Solvent Casting Technique

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Abstract:

The purpose of the research work to formulate and evaluate transdermal patches of maloxicam polymers containing drug by solvent casting method. Transdemal patches were prepared with different ratios of combination of polymers like Pectin, Ethyl cellulose and PVP. The prepared patches were evaluated for different physicochemical evaluations like thickness, drug content, moisture uptake, folding endurance, moisture loss and in-vitro diffusion. *in-vitro* diffusion study is to show the release rates and extent of drug release from dosage form. The cumulative percentage of drug released was found to be the highest (99.29%) from formulation M-2. The Higuchi's plot has shown the regression value (r^2) of 0.995, which indicated that diffusion mechanism, is influencing the drug release. In order to confirm this fact, Peppa's plot was drawn which has shown a slope value of 0.690, which confirms that the diffusion mechanism is involved in the drug release was of non–fickian diffusion type. Hence formulation M-2 was selected as the optimised formulation by virtue of its drug release kinetics.

Key words: Meloxicam, Transdermal Patches, Ethyl Cellulose, Pectin, PVP.

INTRODUCTION:

Transdermal drug delivery patches have been in the market for over a decade. Transdermal drug delivery system (TDDS) has been an increased interest in the drug administration via the skin for both local therapeutic effects on diseased skin (topical delivery) as well as for systemic delivery of drugs. 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.[1] Among the wide variety of novel drug delivery systems, the transdermal delivery of drugs for the systemic treatment of diseases has acquired increasing interest in recent years due to its potential in avoiding the hepatic first pass effect, thus achieving high systemic bioavailability of drugs, which undergo either considerable or extensive first-pass metabolism and they are capable of sustaining the drug release for prolonged period of time.[2] Meloxicam is non-steroidal anti- inflammatory drug chemically heterogeneous large groups of drugs which suppress inflammation in a manner similar to steroids, but less side effects of sedation, respiratory depression, or addiction then steroids. They are widely used for the treatment of inflammatory disorders and painful conditions such as rheumatoid arthritis, gout, has pH dependent solubility and permeability. Meloxicam is highly effective in wound healing through non steroidal anti inflammatory action. Efficiency and stability of Meloxicam can be enhanced by using dermal route. Due to the recent advances in technology and the incorporation of the drug to the site of action without rupturing the skin membrane transdermal route is becoming the most widely accepted route of drug administration. The objective of the research work to developed transdermal patches of maloxicam with different ration of polymer using solvent casting method.

Material and Method:

2.1. Material:

Meloxicam was received as a gift sample from Zee Laboratory PVT Ltd, Ponta Sahib, Himachal Pradesh. Ethyl Cellulose was purchased from Himedia laboratories, Mumbai, India. PVP and Pectin was received as gift sample from Torrent Pharmaceutical Pvt. Ltd, Ahmadabad, Gujarat. Span 80 and Propylene Glycol were purchased from Himedia laboratories, Mumbai. All other materials and chemicals used were of either pharmaceutical or analytical grade.

.2. Methods:

2.2.1. Fabrication of Transdermal Patches:

Transdermal patches were fabricated using different polymers containing drug by solvent casting method.[3-4] Adhesive patches containing MX were prepared by dissolving polymers individually or in combinations in suitable solvents namely ethanol and dichloromethane. Propylene glycol (30%v/v) of polymer composition was used as a permeation enhancer. Then the solution was poured into a glass ring, which was covered with funnel. The solvent was allowed to evaporate at ambient conditions [temperature, 32°C and relative humidity (RH), 45%] for 24 h. Aluminium foil was used as backing film and the prepared patches were stored in desiccators for further studies. Table 1 enlists the composition of different formulations prepared using varying amounts of the polymers.

Varying amounts of the polymers.

Table 1. Formula for Fabrication of Transdermal Patch containing Meloxicam

Formulation code	Drug (mg)	Pectin (%)	EC (%)	PVP (%)
M- 1	50	1	–	–
M-2	50	2	–	–
M-3	50	–	1	–
M-4	50	–	2	–
M-5	50	–	–	1
M-6	50	–	–	2

Notes: Volume of solution used for all formulation is 10 ml; permeation enhancer used is propylene glycol (30% v/v)

Evaluation of Transdermal Patches[5-8]

Physiochemical evaluation

Thickness:

Thickness of transdermal patch was taken randomly using screw gage at various locations on Matrix film. The value reported must be the mean of three sets of experiments.

Folding endurance:

The folding endurance was measured manually for the prepared film. A strip of film is cut evenly and folded at the same place till it breaks. The number of times the film could be folded at the same place without breaking gives the exact value of folding endurance.

Drug content:

100 mg portion of film was weighed accurately and dissolved in 100 ml of ethanol (95%), then shaked the resulting mixture vigorously to dissolve. The sample was Withdrawn, filtered and scanned at wavelength of drug using UV spectrophotometer.

Moisture uptake:

Weigh individually the films and kept them in desiccators containing calcium chloride at room temperature for at least 24 hrs. remove the films from desiccators and exposed to 4% relative humidity (RH) using saturated solution of potassium chloride in a another desiccator until a constant weight is achieved.

$$\% \text{ Moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Final weight}} \times 100$$

Drug entrapment study

To assess the total drug present in ethosomal patch and to find out drug entrapped in stored vesicular system study was carried out for a period of four weeks. Samples were withdrawn at an interval of 2 weeks and study was performed as mentioned earlier in the thesis under the drug entrapment efficiency by ultra centrifugation.

Moisture loss

The formulations (n=3) were kept in a desiccator at room temperature (37°C) and then exposed to an atmosphere of 98% RH using anhydrous calcium chloride and weighed after 3 days . The percentage of moisture loss was calculated as the difference between initial and final weight.

***In-vitro* Diffusion Study:**

The *in-vitro* diffusion study is carried by using Franz Diffusion Cell. Egg membrane is taken as semi permeable membrane for diffusion. The Franz diffusion cell has receptor compartment with an effective volume approximately 60 ml and effective surface area of permeation 3.14sq.cms. The egg membrane is mounted between the donor and the receptor compartment. A two cm^2 size patch taken and weighed then placed on one side of membrane facing donor compartment. The receptor medium is phosphate buffer pH 7.4. The receptor compartment is surrounded by water jacket so as to maintain the temperature at 37 ± 0.5°C. Heat is provided using a thermostatic hot plate with a magnetic stirrer. The receptor fluid is stirred by Teflon coated magnetic bead which is placed in the diffusion cell.

During each sampling interval, samples are withdrawn and replaced by equal volumes of fresh receptor fluid on each occasion. The samples withdrawn are analyzed spectrophotometrically at wavelength of drug.

Kinetics Modeling of Drug Dissolution Profiles

To analyse the in vitro release data various kinetic models were used to describe the release kinetics. The dissolution profile of the all formulations was fitted to higuchi and Korsmeyer–Peppa's model to ascertain the kinetic modeling of the drug release and mechanism of drug release**.**

Higuchi model [9]:

Higuchi described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion Eq. (1) A large number of modified release

dosage form contain some sort of matrix system. In such instances, the drug dissolves from the matrix. The dissolution pattern of the drug is dictated by water penetration rate (diffusion controlled). In higuchi model, a plot of % drug released versus square root of time is linear.

$Q = Kh\ t1/2$ ---------- (1)

Where, Kh = Constant t = Time.

Korsmeyer–Peppas model [10]

Korsmeyer et al derived a simple relationship which described drug release from a polymeric system Eq. (4). To find out the mechanism of drug release, drug release data was fitted in Korsmeyer–Peppas model, log of % cumulative drug release versus log of time.

Korsmeyer et al derived a simple relationship which described drug release from a polymeric system Eq. (2). To find out the mechanism of drug release, drug release data was fitted in Korsmeyer–Peppas model, log of % cumulative drug release versus log of time.

$Mt / M\infty = Ktn$ ---------- (2)

Where, $Mt / M\infty$ = Fraction of drug released at time t, K = Rate constant, n = Release exponent.

In this model, the value of n characterizes the release mechanism of drug as described as follows. For the case of cylindrical tablets, $0.45 \leq n$ corresponds to a Fickian diffusion mechanism, $0.45 < n < 0.89$ to non-Fickian transport, $n = 0.89$ to Case II (relaxational) transport, and $n > 0.89$ to super case II transport. To find out the exponent n the portion of the release curve, where $Mt / M\infty < 0.6$ should only be used.

Stability studies

Stability study was carried out for meloxicam transdermal patch at two different temperatures i.e. refrigeration temperature (4 ± 2 °C) and at room temperature (25 -28±2°C) for 4 weeks. The formulation subjected for stability study was stored in borosilicate container to avoid any sort of interaction between the transdermal patch and glass of

container, which may affect the observations. The ethosomal patch were analysed for any physical changes such as color and appearance, entrapment study and drug content.[11]

Result and Discussion:

Evaluation of Transdermal Patches:

The thickness of prepared transdermal patch was found to be 0.80 mm thick, showing uniform thickness throughout the distribution which confirms uniform dispersion of in prepared patch. The thicknesses of all batches are nearly similar which indicates the physical uniformity of prepared patches. The drug content analysis of the prepared formulation has shown that the process adopted for casting the films in this investigation is capable of giving films uniform drug content and minimum intra batch variability. Folding endurance values of all formulations indicates good strength and elasticity and can maintain the integrity with general skin folding. The moisture uptake of drug is a function of Pectin, PVP/EC ratios. This may be attributed to the higher polydispersity index and solubility parameter of pectin and PVP as compared to those of EC. Thereby, it has a high affinity for water and induces higher moisture uptake as the Pectin, PVP ratio in the films increased. The formulation M-2 (2% Pectin) gives higher value of moisture loss, which is due to its hydrophilic nature and formulation. M-3 (1% EC) gives low value, which is due to its hydrophobic nature.

Table 2: Physicochemical evaluation of the prepared patches

Formulation code	Thickness (mm)	Drug content (mg)	Moisture uptake	Folding endurance	Moisture loss
M-1	0.31±0.01	98.96±0.63	4.40±0.015	282±1.0	3.907±0.05
M-2	0.35±0.04	98.82±0.26	6.613±0.01	260±1.5	6.143±0.01
M-3	0.28±0.02	96.96±0.76	1.614±0.03	272±2.0	1.858±0.01
M-4	0.34±0.05	97.52±0.26	2.662±0.02	255±2.5	2.00±0.014
M-5	0.29±0.01	96.96±0.70	1.965±0.02	276±2.00	2.599±0.31
M-6	0.29±0.02	93.82±0.26	2.187±0.15	270±1.52	2.540±0.10

**All values are represented as mean ±SD (n=3)*

In-vitro Diffusion Study:

The objectives in the developments of in-vitro diffusion study are to show the release rates and extent of drug release from dosage form. The study was carried out for 24 hours duration; all results were shown on table and represented graphically. The cumulative percentage of drug released was found to be the highest (99.29%) from formulation M-2. Figure 1 exhibits the dissolution profile obtained for formulation M-2. The Higuchi's plot has shown the regression value (r2) of 0.995, which indicated that diffusion mechanism, is influencing the drug release. In order to confirm this fact, Peppa's plot was drawn which has shown a slope value of 0.690, which confirms that the diffusion mechanism is involved in the drug release was of non–fickian diffusion type. Hence formulation M-2 was selected as the optimised formulation by virtue of its drug release kinetics.

Table 3: *In-vitro* Diffusion Study for transferral patch (Batch M-2)

S.no	Time in (hr)	% Drug released*
1	0	0.00
2	1	21.45 ± 1.88
3	2	34.54 ± 2.18
4	3	46.02 ± 2.36
5	4	58.56 ± 2.22
6	6	67.23 ± 2.65
7	8	77.34 ± 2.82
8	12	82.56 ± 3.11
9	18	89.34 ± 2.96
10	24	99.29 ± 1.01

**Values are represented as mean ±SD (n=3)*

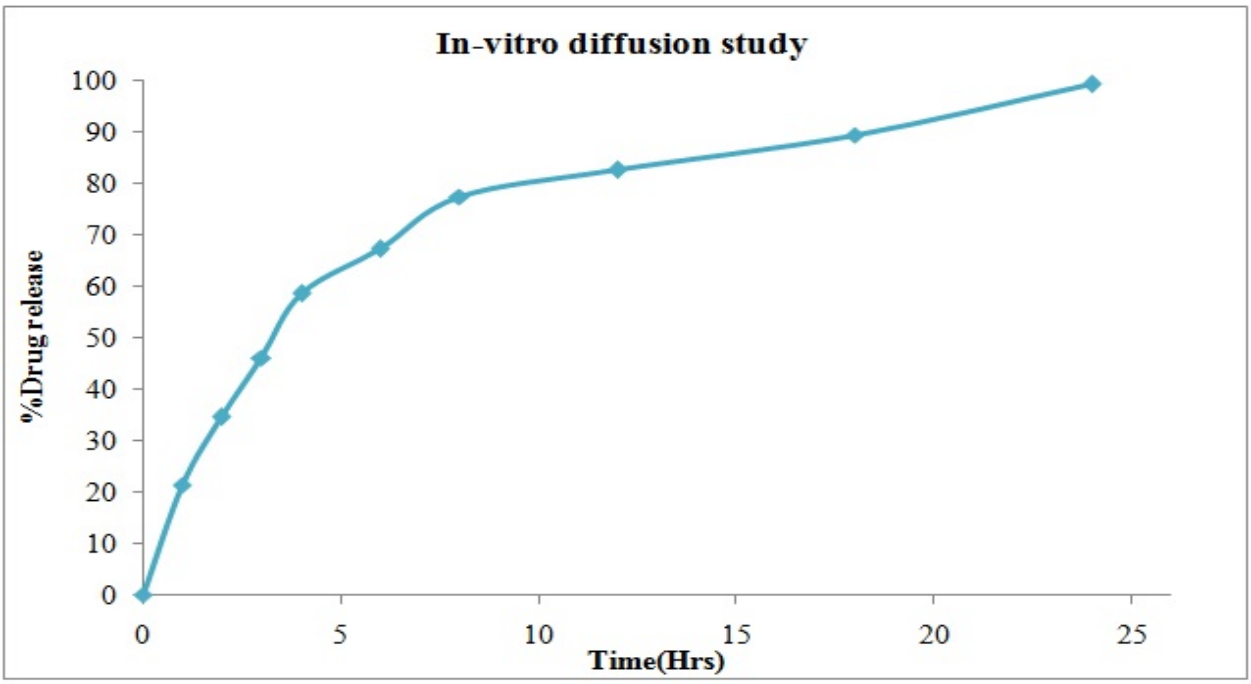

Figure 1: *Invitro* Diffusion Study for transdermal patch (Batch M-2)

Kinetics modelling of drug dissolution profiles

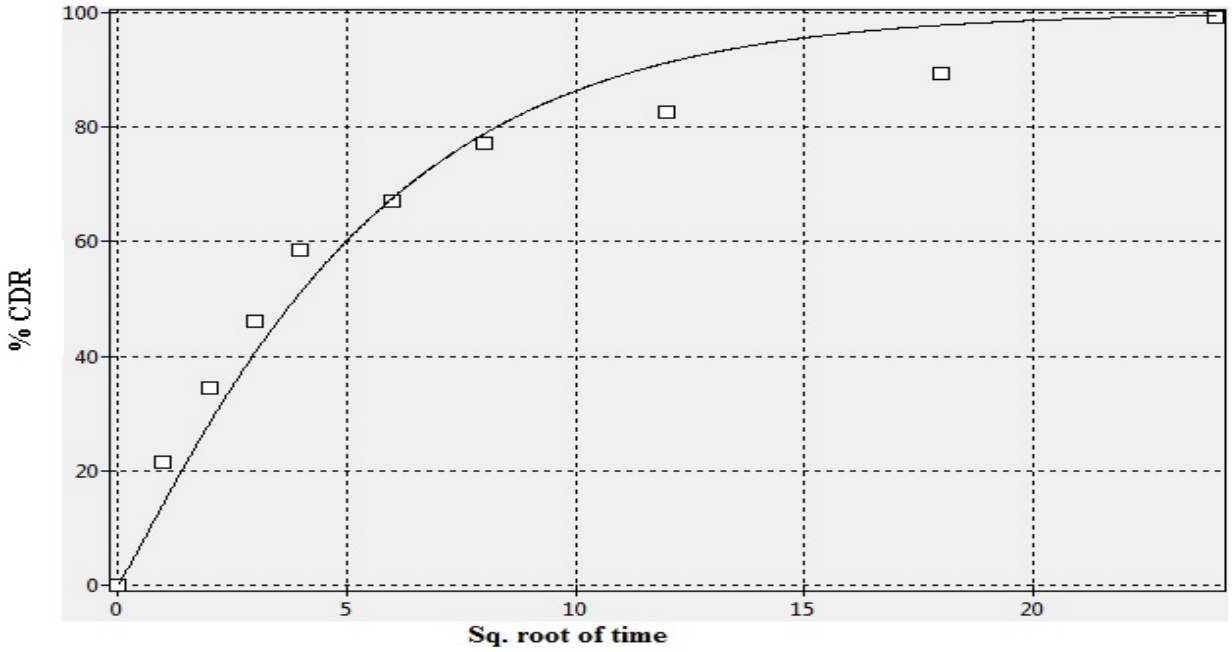

Figure 2: Higuchi release plot

The *in vitro* release data of selected formulation was also subjected to model fitting analysis to know the mechanism of drug release from the formulations by treating the data

according to Higuchi equation and peppa's model. The results are showed that the release of drug from the patches might have followed zero order kinetics. Also, was obtained for indicating a zero order release pattern from the higuchi model value of R^2=0.989 suggest that it follows super case II transport it indicates that drug releases, which means the drug release rate does not change over time and the drug is released by zero-order mechanism.

In vitro release test is widely used because of its simplicity and reproducibility. Moreover, it has been shown that drug diffusion through matrix was influenced by the drug-polymer interaction. However, in vitro tests are very useful in the quality control of finished TDDS. Drug released in 24 h was found to be the highest for formulation M-2 and diffusion mechanism involved in the drug release was of non–fickian diffusion type. Hence formulation M-2 was selected as the optimised formulation by virtue of its drug release kinetics.

Stability studies

Transdermal patch (Batch M-2) was observed for any change in appearance or colour for the period of 4 weeks. There was no change in appearance in formulation throughout the period of study. The stability of drug was further confirmed by spectral data and there was no change observed.

TABLE 4: Different parameters after 30 days in different storage condition

Storage condition	Thickness ±SD (mm)	Folding endurance±SD	Drug content%±SD
Accelerated	0.35±0.04	260±1.5	98.82±0.26
Normal	0.35±0.04	260±1.5	98.82±0.26

Transdermal delivery offers several advantages over oral routes for controlled drug delivery viz., bioavailability of drug for a longer time than the oral dosage forms, evading of hepatic first-pass metabolism, avoid the chemical or metabolic degradation, the delivery of the API can be immediately discontinued (e.g., upon occurrence of adverse reactions).

Conclusion:

The transdermal formulation and the prototype patch were shown to be efficacious, safe, stable and non-irritant to skin. The formulation M-2 (2% Pectin) has shown optimum release in concentration dependent manner. The obtained results are encouraging for further studies, which deals with the application of the presently reported findings to human skin permeation, involving in vivo tests.

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