

Formulation, Development and Evaluation of Etoricoxib containing Transdermal patches in Arthritis management.

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ABSTRACT

Transdermal drug delivery has made an important contribution to medical practice. It is a medicated patch that delivers a specific amount of medication through the skin into the blood stream. An advantage of a transdermal drug delivery route over other types of medication delivery is that the patch provides a controlled release of the medication into the patient, usually through either a porous membrane covering a reservoir of medication or through body heat melting thin layers of medication embedded in the adhesive. The present investigation was aimed to formulate transdermal patches of non steroidal anti-inflammatory drug, Etoricoxib using solvent evaporation technique and evaluated for physicochemical parameters like thickness, weight variation, moisture content, folding endurance, drug content values and In vitro drug release. Five batches of transdermal patches were prepared using different concentrations of PEG (poly ethylene glycol). The final optimized formulation was found to be thick, opaque and flexible with folding endurance of >200, having drug content 96.23% and drug release was found to be 75.1% over 12 hrs. It was concluded that transdermal patch formulation of Etoricoxib enhanced its bioavailability by releasing the drug to its target site and avoiding first-pass effect.

Keywords: Transdermal drug delivery system, controlled release, Etoricoxib, drug diffusion, arthritis.

Introduction

During the past few years, interest in the development of novel drug delivery systems for existing drug molecules has been renewed. The development of a novel delivery system for existing drug molecules not only improves the drug's performance in terms of efficacy and safety but also improves patient compliance and overall therapeutic benefit to a significant extent. Transdermal Drug Delivery System (TDDS) are thus can be defined as self contained, discrete dosage forms which are also known as "patches", When patches are applied to the intact skin, deliver 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 drug across a patient's skin.[1]

The main objective of transdermal drug delivery system is to deliver drugs into systemic circulation into the skin through skin at predetermined rate with minimal inter and intra patient variation. Currently transdermal delivery is one of the most promising methods for drug application. It reduces the load that the oral route commonly places on the digestive tract and liver. It enhances patient compliances and minimizes harmful side effects of a drug caused from temporary over dose and is convenient in that transdermal patches delivered drugs that require only once weekly application.

This will improve bioavailability, more uniform plasma levels, longer duration of action resulting in a reduction in dosing frequency, reduced side effects and improved therapy due to maintenance of plasma levels up to the end of the dosing interval compared to a decline in plasma levels with conventional oral dosage forms. Transdermal delivery not only provides controlled, constant administration of drugs, but also allows continuous input of drugs with short biological half lives and eliminates pulsed entry into systemic circulation, which often causes undesirable side effects. [2]

The developments of TDDS is a multidisciplinary activity that encompasses fundamental feasibility studies starting from the selection of drug molecule to the demonstration of sufficient drug flux in an *ex vivo* and *in vivo* model followed by fabrication of a drug delivery system that meets all the stringent needs that are specific to the drug molecule (physicochemical, stability factors), the patient (comfort and cosmetic appeal), the manufacturer (scale up and manufacturability) and most important economy. [3]

The first transdermal system, Transderm SCOP was approved by FDA in 1979 for the prevention of nausea and vomiting associated with travel. Most transdermal patches are designed to release the active ingredient at a zero order rate for a period of several hours to days following application to the skin. [4]

Recently Serpell M *et al*, concluded that clinical practice TDS was well tolerated and patients were satisfied with their therapy also Bae J *et al*, demonstrated that topically applied leflunomide can be delivered effectively on arthritis joints, possibly allowing better compliance in rheumatoid arthritis patient by avoiding leflunomide side effects and Romualdi P *et al* also concluded that residual fentanyl remaining in

the patch after use is at the lowest end of the range used in commercial fentanyl patches, minimizing the potential for abuse and misuse. [5, 6, 7]

Advantages of TDDS

- Avoids chemically hostile GI environment (drug degradation in acidic and basic environments is prevented).
- No GI distress and the factors like Gastric emptying, intestinal motility, transit time, do not affect this route as in oral route.
- Avoidance of significant presystemic metabolism (degradation in GIT or by the liver) and therefore need lower doses.
- Allows effective use of drugs with short biological half-life.
- Allow administration of drugs with narrow therapeutic window because drug levels are maintained within the therapeutic window for prolonged periods of time.
- Reduced inter and intra patient variability.
- Enhance therapeutic efficacy, reduced fluctuations (rapid blood level spikes-low and high) due to optimization of blood concentration – time profile.
- Reduction of dosing frequency and enhancement of patient compliance.
- Provides controlled plasma levels of very potent drugs.
- Can provide adequate absorption of certain drugs.
- Avoids the risk and inconveniences of parenteral therapy (Painless method of drug administration).
- Drug input can be promptly interrupted simply by removal of the patch when toxicity occurs.
- Provides suitability of self medication. [8,9]

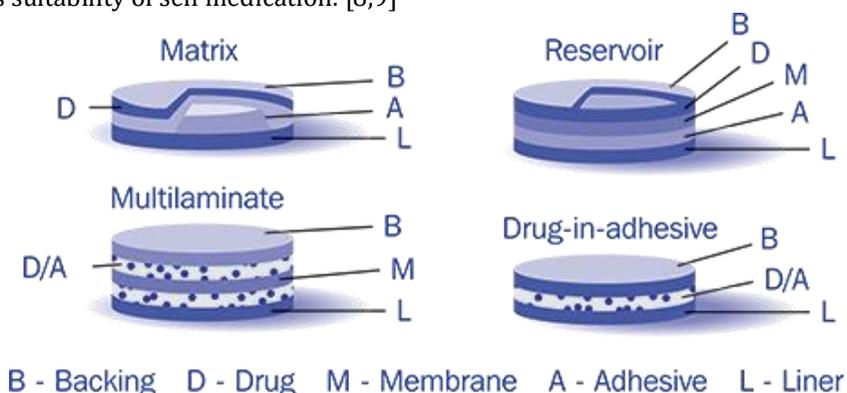


Fig.1 Types of transdermal patches.

Osteoarthritis is the most common rheumatic disease and is the principal source of pain and disability in the elderly. Non-steroidal, anti-inflammatory drugs (NSAIDs) are the drugs of choice for managing a variety of acute and chronic inflammation and chronic degenerative orthopathies. The major drawback associated with anti-inflammatory drug use is the preponderance of gastrointestinal (GI) side effects caused by the majority of agents. It is generally recognized that these GI side effects occur due to the biosynthesis of prostaglandins (PGs) and other arachidonic acid metabolites interfering with the drug in the gastric mucosa. The most common GI adverse effects include GI perforations, ulcerations, and bleeding, each of which may require hospitalization. Consequently, there is a need for a NSAID delivery system with improved GI tolerance that would retain its therapeutic efficacy. The NSAID-mediated toxicity is often dose related. Thus, a reduction in serum concentration should also lessen the risk of producing potentially serious systemic adverse effects secondary to NSAIDs (e.g., induced PG inhibition, namely acute renal insufficiency, nephritic syndrome, NSAID gastropathy, prolonged bleeding time, and fluid retention). This necessitates the need for an alternative route of administration, a route that can bypass gastrohepatic metabolism of the drug. [10]

Etoricoxib is a member of a new class of agents called Coxibs. Etoricoxib is a potent, orally active cyclooxygenase-2 (COX-2) specific inhibitor within, and significantly above, the clinical dose range. Two isoforms of cyclooxygenase have been identified: cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). COX-1 is responsible for prostaglandin-mediated normal physiologic functions such as gastric cytoprotection and platelet aggregation. Inhibition of COX-1 by nonselective NSAIDs has been associated with gastric damage and inhibition of platelet aggregation. COX-2 has been shown to be primarily

responsible for the synthesis of prostanoid mediators of pain, inflammation, and fever. Selective inhibition of COX-2 by etoricoxib (within the clinical dose range) decreases these clinical signs and symptoms with decreased potential for GI toxicity and effects on platelet aggregation. [11]

The potential of transdermal drug delivery systems has been demonstrated in recent years with the approval of several medicines for use by patients who are unable to use conventional dosages route, like oral administration or injection. To enhance the TDDS potential to include other drug candidate many researchers have been exploring enhancement approach to increase the permeability of various drugs through the skin.

The present study deals with the fabrication of transdermal patches at the target site to deliver drug in a controlled manner. The developed patches will be able to be effective in arthritis disease and better patient compliance. [12, 13]

Materials and Methods

Chemicals and reagents-

The drug Etoricoxib was procured as a gift samples from Kusum health care, (Rajasthan), India. Other reagents were of Analytical grade.

Solubility-

Solubility of drug was checked by dissolving them in different solvents. Solubility is the property of a solid, liquid or gaseous chemical substance called solute to dissolve in a solid, liquid or gaseous solvent to form a homogeneous solution of the solute in the solvent. The drug was qualitative tested for its solubility in various solvents. It was determined by shaking 10mg of drug in different solvents in test tube for several hrs as per Indian Pharmacopoeia 2010. The results obtained by solubility testing are given in the table, in which the notation was given as per the Indian pharmacopoeia 2010. (Table. 1)

Table. 1- Solubility of Etoricoxib

Solvent	Etoricoxib
Water	Practically insoluble
Methanol	Freely soluble
Chloroform	Freely soluble
Ethanol	Soluble
NaOH	Insoluble
Sulphuric acid	Insoluble

Estimation of Etoricoxib by UV Spectroscopy

Determination of Drug- Standard solution (100µg/ml) of pure Etoricoxib was prepared. The pure drug solution was scanned on UV spectrophotometer, which showed maximum absorbance at 237 nm for Etoricoxib. (Fig. 3)

Experimental procedure

Preparation of standard stock solution-

10 mg of drug Etoricoxib accurately weighted was dissolved in 100 ml of ethanol in a volumetric flask and volume made up to get the concentration of 1000µg/ml.

Preparation of Working Standard Solution-

From stock solution of Etoricoxib 0.2, 0.4, 0.6, 0.8, 1.0 1.2, 1.4, 1.6, 1.8, 2.0 ml etc of solution was taken and diluted up to 20 ml in a volumetric flask and volume made up to get the standard drug solution of 2, 4, 6, 8, 10, 12, 14, 16,18,20 µg/ml. Absorptivity of Etoricoxib was observed at 237 nm. (Table. 2) (Fig. 2)

Estimation of Etoricoxib by UV Spectroscopy

Table. 2 - Calibration curve data of Etoricoxib

S.No.	Concentration (µg/ml)	Absorbance
1.	2	0.300
2.	4	0.52
3.	6	0.790
4.	8	0.850
5.	10	1.012

6.	12	1.168
7.	14	1.324
8.	16	1.480
9.	18	1.636
10.	20	1.794

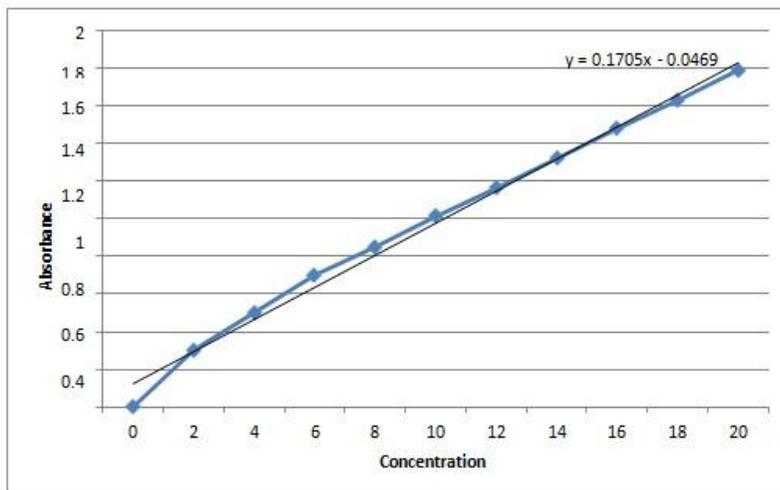


Fig. 2 - Calibration curve of Etoricoxib

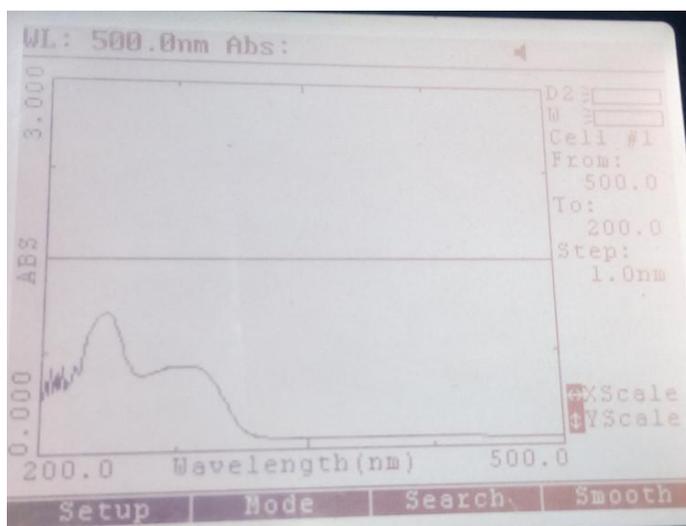


Fig. 3 - UV spectra of Etoricoxib

Formulation of Matrix type transdermal patch

Transdermal patches of Etoricoxib was prepared by solvent evaporation technique by incorporating different concentration of polymer, hydroxyl propyl methyl cellulose (HPMC) or Ethyl cellulose (EC) along with suitable solvent . The polymer was dissolved in the solvent to get polymer solution. 50mg of Etoricoxib was added to the above solution and stirred continuously until the drug was soluble in the polymer solution. Poly ethylene glycol (PEG) was added as plasticizer to increase the plasticity of the transdermal patch. Isopropyl alcohol and dichloromethane were added as diluents. [14, 15]

The polymer solutions were prepared by dissolving appropriate polymers, plasticizer in suitable vehicle using a magnetic stirrer. The drug was added slowly to the solution and dissolved by continuous stirring for 30 min to get a clear solution. Then the solution was spread separately uniformly in the petri dish, and the solution was separated by the aluminum foil partition. The mould was kept for one day. After 24 h, the dried

patches were then detached from the petri dish and patches were cut to generate transdermal patch of 2.0 cm in diameter. The formulated patches were stored in desiccators. (Table.3) (Fig. 3)

Table. 3 -Composition of transdermal patches

S.No	Formulation code	Etoricoxib (mg)	PEG4000 (mg)	PEG 6000 (ml)	HPMC (10cps) (gm)	Dichloromethane (ml)	Isopropyl alcohol (ml)
1.	F1	50	500	-	2	q.s	q.s.
2.	F2	50	700	-	2	q.s	q.s.
3.	F3	50	-	2	2	q.s	q.s.
4.	F4	50	-	3	2	q.s	q.s.
5.	F5	50	-	4	2	q.s	q.s.



Fig. 4- Transdermal patch of Etoricoxib F3 formulation

Evaluation of transdermal patches-

The prepared transdermal patches were evaluated for various parameters such as:

Physical Characterization- The physicochemical parameter such as thickness, uniformity of weight, tensile strength, content uniformity test, moisture content, moisture uptake, drug content uniformity and folding endurance of various patches were determined. (Table. 4)[16]

Thickness-

The thickness of the patch was determined by measuring the thickness at the random sites on the formulated patches using micrometer screw gauge and the average thickness was determined. (Table. 4)[17]

Uniformity of weight-

Weight variation is studied by individually weighting 10 randomly selected patches and calculating the average. (Table. 4)[18]

Folding endurance-

The folding endurance was measured manually for the prepared patches. Folding endurance of the film was determined by repeatedly folding a small strip of film (2cm×2cm) at the same place till it breaks. The number of times, the film could be folded at the same place either to break the film or to develop visible cracks, gave the evaluation of folding endurance. (Table. 4)[19]

Drug content-

An area of film 1cm² was cut and dissolved in sufficient quantity of methanol. The volume was made upto 10ml. 1ml was then withdrawn from this solution and diluted to 10ml. The absorbance was then measured at 237nm spectrophotometrically. (Table. 4)

Percentage moisture content-

The prepared patch were weighed individually and kept in a desiccators containing calcium chloride at room temperature for 24 h. The patch is weighed again after a specified interval until they show a constant weight. (Table.4) [20, 21]

The percentage moisture content is calculated using following formula

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

***In- vitro* dissolution study-**

The release rate determination is one of the most important studies to be conducted for all controlled release delivery system. The dissolution studies of patches are very important because one needed to maintain the drug concentration on the surface of stratum corneum consistently and substantially greater than the drug concentration in body to achieve a constant rate. The dissolution of patches was performed using USP basket type dissolution apparatus. The patches were placed in basket with their drug matrix exposed to phosphate buffer 7.4 all dissolution studies were performed at $37 \pm 0.5^\circ \text{C}$ at 50 rpm with each dissolution jar carrying 900ml of buffer. Sample was withdrawn at different time interval and analyzed using a UV spectrophotometer at 237 nm. (Fig.5) [22]

Result

The transdermal patches were prepared by solvent evaporation method and the prepared transdermal patches were evaluated for their physicochemical characteristic such as appearance, weight variation, thickness, folding endurance, drug content moisture uptake and *in vitro* drug release study.

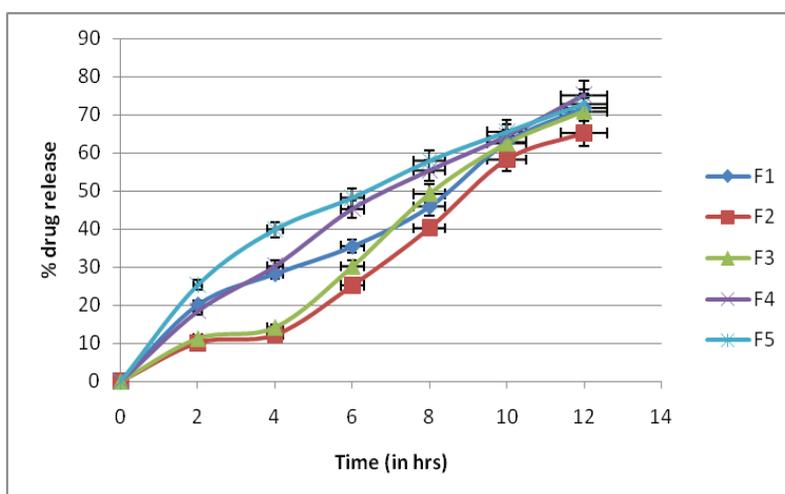
Table. 4 - Evaluation of Transdermal patches

S.No.	Formulations	Appearance	Thickness (mm)	Drug content (%)	Folding endurance	Weight variation (mg/2cm ²)	% moisture content
1.	F1	Thin, opaque and flexible	0.29±0.01	97.32	<150	0.030±0.009	4.12±0.015
2.	F2	Thin, transparent and not Flexible	0.25±0.01	99.10	<150	0.050±0.005	3.94±0.057
3.	F3	Thick, opaque and flexible	0.30±0.04	97.65	>200	0.045±0.005	3.54±0.017
4.	F4	Thick, transparent and flexible	0.33±0.05	96.23	>200	0.040±0.005	3.24±0.017
5.	F5	Thick, opaque and flexible	0.40±0.05	98.20	>200	0.057±0.007	4.24±0.017

***In- vitro* dissolution study-**

The best available tool today which can at least quantitatively assure about the biological availability of a drug from its formulation is its *in vitro* dissolution test.

The *in vitro* release studies revealed that F4 formulation released the drug till 12 hrs in controlled manner without burst effect and F1 and F5 formulations showed burst effect initially because of less plasticity in patches, the patches did not withstand for much and released drug in burst manner initially, where as in formulation F2 and F3 the release of drug was not maximum up to 12 hrs. (Fig. 4)

**Fig. 5- *In- vitro* drug release profile**

Discussion

Transdermal drug delivery system is a most suitable system for a long term treatment or for a multi dose treatment because transdermal patches are prepared for a long period of time in a single dose providing treatment from a day to even up to seven days. TDDS also increase the bioavailability of drug by avoiding the first pass metabolism and increase the therapeutic efficacy of drug by reaching into the systemic solution. Polymers Hydroxy propyl methyl cellulose (HPMC) was selected on the basis of their adhering property and non toxicity.

The result of the finding showed excellent property and controlled release. Result from present study concluded that etoricoxib with Hydroxy propyl methyl cellulose (HPMC), Ethyl cellulose (EC) and with incorporation of poly ethylene glycol (PEG-4000) produce smooth, and transparent film.

The prepared transdermal patches were evaluated for their physicochemical characteristic such as appearance, weight variation, thickness, folding endurance, drug content, and in vitro drug release study. The physical appearance of the various formulations in terms of their transparency, smoothness, flexibility, stickiness and opaque properties were recorded.

Appearance- The formulation F1 was found to be thin, opaque, and flexible, formulation F2 was found to be thin, transparent, not flexible, formulation F3 was found to be thick, opaque and flexible, formulation F4 was found to be thick, opaque and flexible, and clear with very less presence of bubbles. On the basis of flexibility and appearance formula F4 was found to be on optimum scale. [23]

All these formulation were prepared and the formulation F4 was selected for the final formulation.

Thickness- The thickness of the formulations F1 to F5 was found to be 0.29 ± 0.01 mm, 0.25 ± 0.01 mm, 0.30 ± 0.04 mm, 0.33 ± 0.05 mm, 0.40 ± 0.05 mm respectively. (Table. 4)

Weight variation- The weight variation of the formulation F1 was found to be 0.030 ± 0.005 mg/2cm². Formulation F2 was found to be 0.057 ± 0.009 mg/2cm². So this formulation was rejected because in this formulation the weight variation was observed very high. Formulation F3 was found 0.045 ± 0.005 mg/2cm². This formulation was not good. Formulation F4 was found to be 0.040 ± 0.005 mg/2cm² in this formulation the weight variation was observed less and this formulation was selected for the final formulation and formulation F5 was found to be 0.057 ± 0.007 mg/2cm². (Table. 4)

Drug content- The drug content for the formulation prepared was 97.32%, 99.10%, 97.65%, 96.23% and 98.20% for F1, F2, F3, F4, and F5 respectively. (Table. 4) [24]

Folding endurance- The folding endurance was found to be for formulation F1= <150, formulation F2= <150, formulation F3= >200, formulation F4= >200 and formulation F5= >200. The folding endurance measures the ability of patch to withstand rupture. It was found to be satisfactory. The result indicated that the patches would not break and would maintain their integrity with general skin folding when used. (Table. 4)[25]

The moisture content in the patches ranged from $4.24 \pm 0.015\%$ to 3.24 ± 0.017 . The lower moisture content in the formulations helps them to remain stable and become a completely dried and brittle film and also prevents the material from bacterial growth. (Table. 4)

The percentage drug release from F4 formulation was found to be 75.1% in 12 h which was higher when compared to other formulations. The release of drug from F4 formulation was in controlled manner which delivered the drug to its target site in controlled manner without burst effect and it resulted in attaining the desired action. (Fig.5)[26, 27]

Conclusion

A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. The patch provides a controlled release of the medication into the patient, usually through either a porous membrane covering a reservoir of medication or through body heat melting thin layers of medication embedded in the adhesive. The preliminary study confirms the suitability of ethyl cellulose and hydroxy propyl methyl cellulose (HPMC) for formulating transdermal drug delivery system of Etoricoxib. The permeation of Etoricoxib from different polymeric membranes was found more with hydroxy propyl methyl cellulose (HPMC) than Ethyl cellulose (EC). Hence it can be concluded that the prepared transdermal patches will deliver the drug at the target side and the developed patches will be able to be effective in Osteoarthritis by relieving the pain and result in patient compliance. The results revealed that transdermal patch formulation of Etoricoxib enhanced its bioavailability by releasing the drug to its target site and avoiding first-pass effect and metabolism in the gut mucosa, also it increases patient compliance due to decreasing dose frequency.

Future aspects

The transdermal patch may be an underutilized tool for management of acute and chronic pain. With improved delivery and a wider range of analgesics, we expect the popularity and applicability of this modality to deliver drugs to increase. In current scenario, transdermal route of drug delivery system in comparison with oral treatment as the most successful innovative research area in new drug delivery system, with around 40% of the drug delivery candidate products under clinical trials related to transdermal or dermal system. The transdermal drug delivery systems (TDDS) have been designed as an alternative, safest and easy route for systemic drug delivery.

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