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Formulation and Evaluation of Transdermal Patches for Chronic Pain Relief

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ABSTRACT: The skin has been used to apply various therapeutic agents and cosmetic products for a long period of time, but only recently the skin is being used as a route for drug delivery systems. Almost two third of the drugs available in the market are taken orally but they pose several problems like gastric degradation, first pass metabolism and low bioavailability thus showing low efficacy. Transdermal drug delivery systems (TDDS) show enhanced features and delivery of drugs through the patient's skin. TDDS show better therapeutic effects with minimum side effects and they are designed to release the drug at zero order rate following its application on the skin.

Millions of people worldwide suffer from arthritis, burdening healthcare systems with symptoms such as joint pain, inflammation, and decreased mobility. The preferred drugs prescribed to these patients include Diclofenac or other Non-steroidal anti-inflammatory drugs (NSAIDS). However, chronic consumption of these drugs is associated with gastric irritation and renal toxicity. Thus, new and innovative approaches to treating localized pain and inflammation are critical, making transdermal medication delivery methods that incorporate safer painkillers the need of the hour.This work centers on formulating transdermal patches using Etodolac, a relatively safer NSAID, so that relief in pain and inflammation control is achieved with the added advantage of mitigating the gastrointestinal adverse effects commonly associated with oral drug administrationthus augmenting the safety and tolerability profile of NSAID therapy. The versatility of the patch extends its application to a variety of conditions, including different forms of arthritis, muscle pain, and more. Our study encompasses the formulation of the transdermal patch, involving a carefully crafted combination of polymers, permeation enhancers and drug reservoirs to optimize drug release kinetics and enhance skin permeation.

KEYWORDS: Etodolac, Arthritis, pain relief, transdermal, patch, anti-inflammatory, NSAID

I. INTRODUCTION

Globally, it is anticipated that the prevalence of arthritis will keep rising due to aging populations, rising rates of obesity, and rising rates of injury. The global population with osteoarthritis was estimated to be 528 million in 2019; representing a 113% rise from 1990 while Rheumatoid arthritis affected 18 million individuals globally in 2019. People aged over 55-years make up about 73% of those with osteoarthritis and 55% of those with rheumatoid arthritis. Arthritis refers to a group of inflammatory joint diseases, with osteoarthritis and rheumatoid arthritis being the most prevalent types. Osteoarthritis is characterized by the gradual wearing down of the protective cartilage that cushions the ends of bones in the joints. On the other hand, rheumatoid arthritis is an autoimmune condition where the body's immune system mistakenly attacks the synovium, the lining of the membranes that surround the joints. Symptoms of arthritis include swelling, stiffness, inflammation in joint, joint damage, and pain particularly in weight-bearing joints like the knees, hips, and spine and decreased joint mobility. [1]

Etodolac

Etodolac is a selective COX-2 inhibitor and non-steroidal anti-inflammatory drug (NSAID) that has been demonstrated to be useful in treating symptoms of osteoarthritis and rheumatoid arthritis. Etodolac inhibits the enzyme cyclooxygenase-2 which is required to convert arachidonic acid into prostaglandins, thereby inhibiting the synthesis of prostaglandins and therefore decreasing the inflammatorymediators and reducing inflammation. It has an elimination half-life ($t_{1/2}$) of 6-8 hours in plasma, it ismetabolised in the liver and it is mainly excreted in the urine and a small quantity through biliary tract in faeces.[2]It is contraindicated in patients with renal impairment and should be used with caution in patients with liverdisorders.It shows adverse effects associated with NSAIDS like GI toxicity such as bleeding, ulceration, perforation, risk of direct renal injury, serious skin reactions, liver function test abnormalities, prolonged bleeding time, and rash.[3]Etodolac is a BCS Class 2 drug due to its high permeability and poor water solubility. Its chemical formula is $C_{17}H_{21}NO_3$. TheS-enantiomer is active.[4]

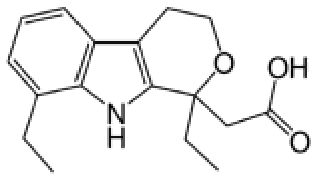

Fig. 1: Structure of Etodolac

Transdermal patch (TDP)

Transdermal drug delivery systems facilitate the transportation of drugs through the skin into the systemic circulation at a regulated pace. It allows the delivery of the drug in a controlled, continuous manner over an extended period. Transdermal patches offer numerous advantages over traditional oral medications. They offer a painless and non-invasive method for delivering substances directly into the body. Unlike oral medications, which may be subject to breakdown by stomach acids and significant liver degradation in the intestines, topical patches provide a superior technique for delivering medications that are poorly absorbed orally. These patches make it easier to administer medications gradually and steadily, which minimizes drug fluctuation and reduces the adverse effects of peak concentrations. In addition, they are very beneficial for users due to their ease of application, especially for those who may have difficulty swallowing tablets or prefer not to take drugs orally. Also, because of their continuous and extended period of activity they are favoured by users. These patches offer a dependable way to administer drugs while improving therapeutic efficacy by avoiding first-pass metabolism and gastrointestinal incompatibility. Additionally, drug administration stops when the patch is removed, providing patientsmore flexibility and control over their treatment plans. There are various types of Transdermal Patches (TDP) such as single-layered drug in adhesive, Multi-layered drug in adhesive, Reservoir system, Matrix system, Vapour Patch system.[5-8]Theideal properties of a drug that can be incorporated in a transdermal patch are shown in **Table 1**.[9]

Table 1: Ideal properties of drug for formulation as TDP compared with Etodolac

Srno.	Parameters	Properties	Etodolac
1	Half life	10 hours or less	6-8
2	Molecular weight	Less than 400 Da	287.35
3	Partition coefficient	Log P (Octanol-water) between 1.0 to 4.0	2.5
4	Melting point	Less than 200°C	145 – 148 °C

Drug-Matrix in Adhesive TDP is distinguished by the presence of a semisolid matrix that is in direct contact with the release liner and contains a drug solution or suspension as shown in **Fig. 2.** The skin-adhering component is incorporated into an overlay and encompasses the semisolid matrix in a concentric arrangement. Basic Components of TDP are Drug Reservoir / polymer Matrix, Membrane, Drug, Permeation enhancer, Backing membrane, Release liner, Plasticizer, Solvent system.[5]

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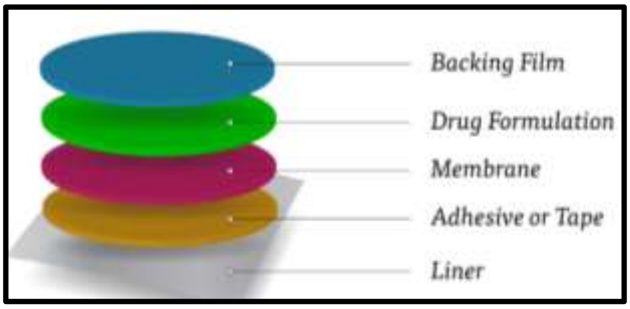

Fig.2: Components of Drug-Matrix in Adhesive TDP

This work aims to formulate a chronic pain relief transdermal patch that addresses the issues of the existing formulations used to treat arthritis, thereby reducing inflammation and pain while minimizing adverse effects on the stomach lining. Etodolac is a non-steroidal anti-inflammatory drug (NSAID) which selectively inhibits the enzyme cyclooxygenase-2 (COX-2) more than COX-1, blocking the production of prostaglandins, Etodolac helps alleviate pain, reduce inflammation, and improve joint function.[10] NSAIDS are being used to address the symptoms of arthritis, however their usage can lead to issues of GI irritancy, perforation, ulceration, bleeding.[3,11]Diclofenac is the most prescribed drug which shows GI irritancy and renal toxicity.[12,13] In comparison between Etodolac and Diclofenac, Etodolac is found to have better gastric tolerance and hence safer to use.[14] To eliminate the GI irritancy and other issues of gastrointestinal tract the transdermal route is preferred over the conventional oral route.

The given formulation is expected to be safer, efficacious and provide relief from the symptoms of arthritis. As per the WHO data the geriatric population suffers the most with Arthritis, as increase in age leads to various old age issues such as weakening of the bones and cartilages, decrease in mobility, degeneration of the bones and tissues and weakened immune system.[15] The formulated transdermal patches will increase patient compliance and tolerance due to ease of application and non-invasiveness thereby making it easy for use especially in the geriatric population.

II. MATERIALS AND METHODS

Materials

Etodolac IP was provided as a gift sample from the IPCA Laboratories, Mumbai. Hydroxypropyl Methyl Cellulose (HPMC), Polyethylene glycol 400 (PEG400), Dimethyl sulfoxide (DMSO), Chloroform and Methanol were procured from certified suppliers. Dynaplast was bought from the local pharmacy.

Equipment and instruments used: Electronic weighing scale, UV Visible spectrophotometer, Digital pH meter and Franz diffusion cell.

Methodology

Formulation Development

A number of TDPs were prepared using a combination of various polymers, plasticisers and penetration enhances. Each patch was evaluated to optimise the formulation further.

Preparation of blank matrix type transdermal patches

Blank transdermal patches were made without the incorporation of the drug in order to deduce a suitable formula for the patches in a petri plate of diameter 9.1 cm with an area of 65 sq. cm. Blank films of matrix type transdermal patch were prepared using solvent evaporation method using different combinations. The polymer was dissolved in a mixture of Chloroform: Methanol (1:1) as the solvent system to obtain the polymer solution. DMSO and PEG 400 were added to the mixture in the required quantities and the solution was stirred uniformly. The mixture of polymer solution was poured onto the petri plate in order to solidify via solvent evaporation method to form a uniform patch.

Preparation of Etodolac Patches

Drug loaded films of matrix type transdermal patches were prepared using solvent evaporation method. The drug was mixed in the prepared solvent system consisting of Chloroform: Methanol (1:1) to obtain the drug solution. To the

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drug solution, the polymer was added and stirred till a clear drug-polymer solution was obtained. DMSO and PEG 400 were added to the mixture in the required quantities and the solution was stirred uniformly. The mixture of drug-polymer solution was poured onto the petri plate in order to solidify via solvent evaporation method to form a uniform patch. Drug loaded matrix type transdermal patches were thus prepared.

Dose calculation for the patch:

For Etodolac, Dose= 150mg/patch of area 30 sq. cm., thus 325 mgs of Etodolac are required in 65 sq. cm. area of patch.

Pre-formulation studies: Etodolac

a. Determination of pH: The pH of Etodolac was determined using pH meter using freshly prepared 1% aqueous solution of the drug.

b. Determination of melting point: Melting point of Etodolac was determined by using sealed capillary tube method in Thiele's tube filled with paraffin oil.

Evaluation parameters for the transdermal patch[16-20]

a. Physical Appearance: The appearance of the patch is observed visually for colour, clarity, flexibility and smoothness.

b.Thickness: The thickness of a folded patch is determined by Vernier calliperat three different points and the mean thickness is calculated.

c.Weight Variation test: A random selection of prepared patches was weighed individually, in order to perform weight variation/ weight uniformity test.

d. Folding Endurance: A 30 cm^2 patch was prepared and was folded at the same point for multiple counts until the patch tore at the fold as depicted in **Fig. 3.** The number of folds determines the folding endurance of the patch.

Fig. 3: Measurement of folding endurance of the patch

e.Tensile Strength: The tensile strength of a patch was determined by the amount of force required in order to break the patch in half. A 30 cm^2 patch was subjected to test its tensile strength using an arranged weight balance on the stand. The patch was clipped one side to the stand firmly using the clamp and to the other extreme it was freely held by another firmly clipped clamp in a vertically transverse position. Later weights were added to the free rear end to measure the load required to break the patch. The arrangement is depicted in **Fig. 4.**

Fig. 4:Measurement of Tensile Strength

f. Drug Content - Assay: A 30 cm^2 patch was dissolved in phosphate buffer (pH-7.4) in a 100ml volumetric flask by keeping on a magnetic stirrer for 15 mins at 500 rpm. After the patch dissolved completely, dilutions of the solution were made and absorbance was measured using UV-Visible spectrophotometer.

g. In-vitro Drug Release Studies[21]: Diffusion was performed using a Franz Diffusion cell in order to determine the percent release of a drug from the patch into the receptor medium. The studies ran for 6/9 hours to determine the percent release of drug from the patch. It was carried out using a cellulose parchment paper, which resembles the skin, in contact with the patch; a buffer of pH 7.4 and the contents were kept on stirring using a magnetic stirrer to provide the sink condition for the release of the drug.

h.HET-CAM Assay: The Hen's Egg Test on Chorioallantoic Membrane (HET-CAM) assay allows the study of drug delivery and toxicologic

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analysis of angiogenic and anti-angiogenic molecules. The CAM assay is an in vivo animal model that involves the introduction of the formulation on the extra-embryonic membrane or CAM of the developing chick embryo. It was done as an alternative to Draize Rabbit's Eye Irritation test and used to determine the irritation potential of theformulation.[22,23]The basic ideology behind HET-CAM studies is to open an incubated hen's egg and expose the chorioallantoic membrane to the test substance, pure or diluted and to check for occurrence of any vascular injury, haemolysis or coagulation with the help of microscope. The time for reaction is recorded for a 5 min period and based on how much time is required for reaction to occur, the irritation score is calculated using the formula below.

Irritation Score = (301 - Ht)/300 * 5 + (301 - Ct)/300 * 7 + (301 - Lt)/300 * 9, where

Ht = Haemolysis time

Ct = Coagulation time

Lt = Vessel Lysis time

Table 2: Irritancy Score Category

Category	Irritation Score
Non-Irritative	0-0.9
Slightly Irritative	1-4.9
Moderately Irritative	5-8.9
Severely Irritative	9-21

III. RESULTS

Formulation Development:

Combination and permutations of various polymers like HPMC 5 cps, HPMC 15 cps and Ethyl cellulose were tried out, keeping the percentage of DMSO and PEG 400 constant as depicted in **Table 3.** After evaluation of the appearance, flexibility, thickness and folding endurance it was concluded that **F2** was the optimal formulation for the patch devoid of any drug (Blank patch).

Table 3: Selection of Polymer

Ingredients	F 1	F 2	F 3	F 4	F 5
HPMC 5cps	2.20%	-	-	1.10%	-
HPMC 15 cps	-	2.20%	-	-	1.10%
Ethyl Cellulose	-	-	2.20%	1.10%	1.10%
DMSO	0.70%	0.70%	0.70%	0.70%	0.70%
PEG 400 (5%w/v)	5.50%	5.50%	5.50%	5.50%	5.50%
Chloroform: Methanol (1:1) Solvent system	91.60%	91.60%	91.60%	91.60%	91.60%

The formulation **F2** was further optimised with respect to the type and concentration of plasticiser as depicted in **Table 4**. Formulation **F2.3** with a combination of PEG 400 as the plasticiser with HPMC 15 cps and DMSO in 1:1 Chloroform: Methanol solvent system yielded a transdermal patch with optimal properties, the formulation of which is summarised in **Table 5** and the film is depicted in **Fig. 5**

Table 4: Selection of Plasticizer

Ingredients	F 2.1	F 2.2	F 2.3	F 2.4
HPMC 15cps	2.30%	2.30%	2.10%	2.20%
DMSO	0.70%	0.70%	0.65%	0.70%
Dibutyl phthalate	2.00%	-	-	-
PEG 400 (5%w/v)	-	5.40%	-	-
PEG 400 (10%w/v)	-	-	10.35%	-
PEG 1500	-	-	-	5.10%
Chloroform:Methanol(1:1)	95.00%	91.60%	86.90%	92.00%

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Table 5: Final Formula for Blank Patch

Ingredients	**Formulation: F 2.3**
HPMC 15cps	2.10%
DMSO	0.65%
PEG 400 (10%w/v)	10.35%
Chloroform:Methanol (1:1) Solvent system	86.90%

Further, formulation F2.3 was further modified and three formulations F1, F2 and F3 were tried out along with incorporation of Etodolac as depicted in **Table 6**. Evaluation of all the patches was done and formulation F3 was found to give Etodolac TDP with optimal organoleptic properties, folding endurance as well as tensile strength. **(Fig. 6 and 7)**

Table 6: Formula table for Etodolac Patch

Ingredients	F 1	F 2	F 3
HPMC 15 cps	1.10%	2.20%	2.20%
Ethyl Cellulose	1.10%	-	-
DMSO	0.60%	0.60%	1.20%
PEG 400 (10%w/v)	10.20%	10.20%	10.10%
Chloroform:Methanol(1:1) Solvent system	85.90%	85.98%	85.40%
Etodolac	1.10%	1.10%	1.10%


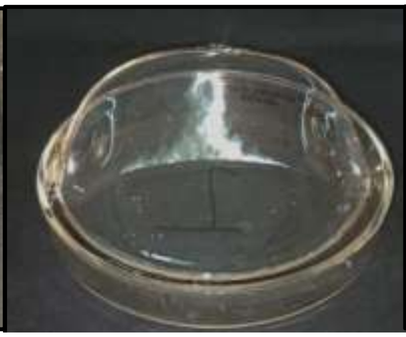
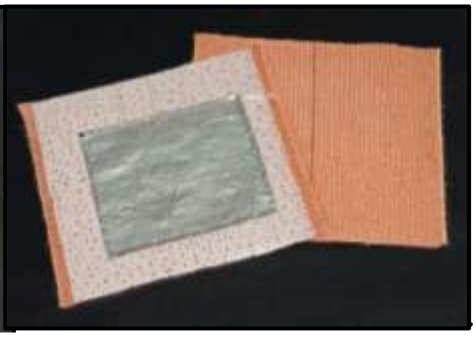

Fig. 5: F 2.3 Blank Patch Fig. 6: F 3 Etodolac Patch Fig. 7: Etodolac transdermal patch

Evaluation of Etodolac

The pH of Etodolac solution was found to be 7.4 and its melting point was found to be 146°C.

The λ_{max} of Etodolac in phosphate buffer of pH 7.4 was found to be 274 nm as shown in **Fig. 8**

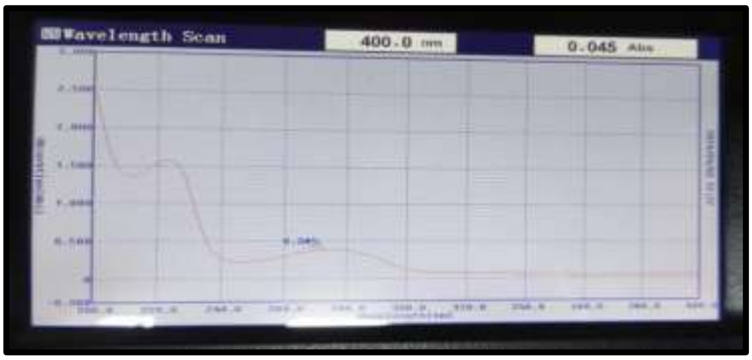

Fig. 8: UV spectrum of Etodolac

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A standard curve was prepared for Etodolac using the linear regression Analysis method as depicted in **Fig. 9**. The r^2 was calculated to be 0.998, which shows an efficient relation between the two parameters.

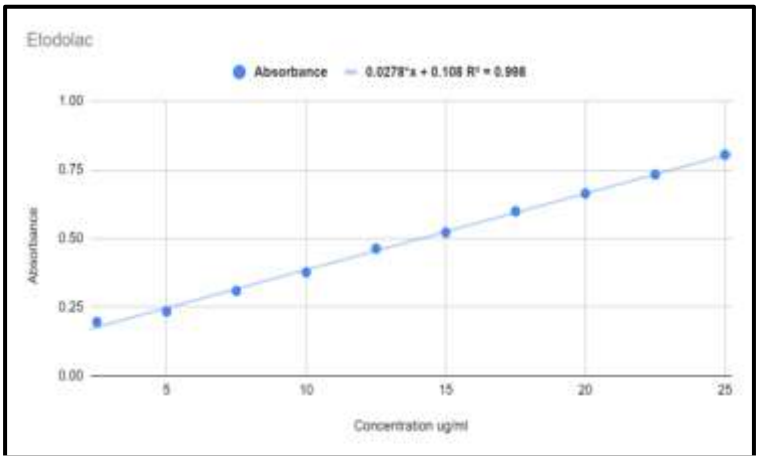

Fig. 9: Standard curve of Etodolac

Evaluation Parameters of Etodolac Transdermal Patches

The transdermal patches of Etodolac prepared using formulation **F3** were evaluated on the basis of various parameters as summarised in **Table 7.** Desired outcomes were achieved for all the parameters. The irritability score as per CAM assay **(Fig. 10)** was found to be 0.07, hence the formulation was categorised as non-irritant (**Table 2**)

Comparative study of formulated product and marketed product

Further the invitro drug release profile of the optimised Etodolac TDP was compared with a marketed Etodolac gel formulation using Franz diffusion cell. It was observed that the Etodolac TDP prepared by us showed a substantially better release of 72.5% than the marketed gel formulation that showed a release of only 49.65%. The comparison of the in vitro release is summarised in **Table 8**.

Table 7: Evaluation of Etodolac Transdermal Patch

Sr. No.	Tests	Observations	Inference
a.	Physical Appearance	Transparent and flexible	
b.	Folding Endurance	200+	Good Plasticity
c.	Thickness	0.06 cm	Within acceptable limits
d.	Tensile Strength	Patch endured 226.70 gm	7.56 gm/cm^2
e.	Assay	106%	98-102% (Allowed Limits)
i.	In-vitro Drug Release Studies.	72.5%over 8 hrs	
j.	CAM Assay	Score: 0.07	Non-irritant

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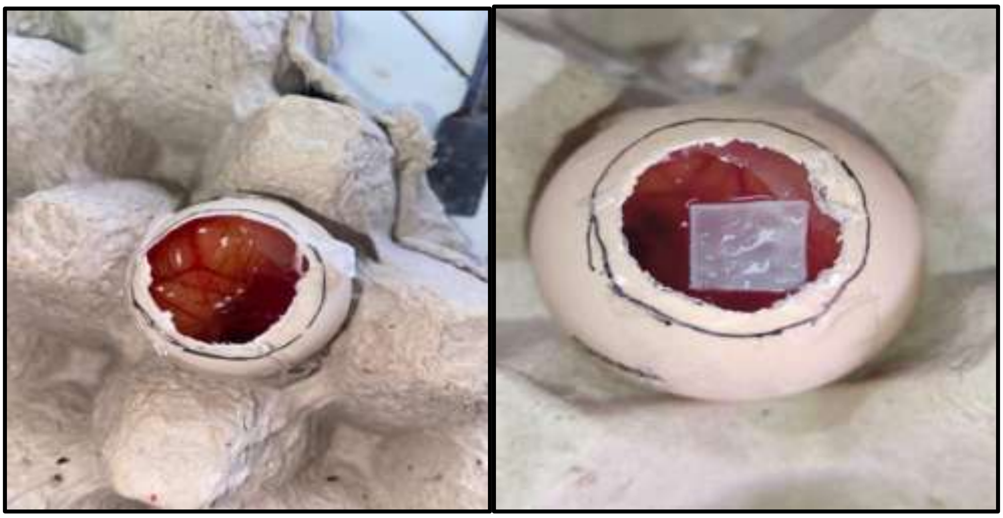

Fig. 10: CAM Assay

Table 8: Etodolac Patch vs Etova Gel Release

	Etodolac TDP	Etova Gel (Marketed Formulation)
Time (Hours)	8 hours	8 hours
Percent Release	72.50%	49.65%

IV. CONCLUSION

The aim of the project was to formulate a chronic pain relief transdermal formulation that addresses the issues of the existing formulations used to treat arthritis. Etodolac was chosen on the basis of its safety profile in comparison to diclofenac. A TDP was formulated to eliminate the issues associated with the existing formulations available in the market. A number of TDPs were made using different formulae and the most suitable one was selected on the basis of flexibility, smoothness, uniformity. The optimal patch was formulated with HPMC 15 cps as the polymer, Methanol: Chloroform as the solvent system, DMSO as the penetration enhancer and PEG as plasticizer. The final patch selected passed the evaluation tests conducted showing an in-vitro release of 72.5 % within 8 hours which was significantly better in comparison to the marketed gel formulation. Thus, the transdermal patch of Etodolac formulated showed promising results and it can be used practically for relieving chronic pain.

In conclusion, this approach has a potential to address the issues associated with chronic use of oral dosage forms of NSAIDS as TDPs of Etodolac offer significant advantages in terms of safety, reduced dose and dosing frequency, less side effects, increased patient compliance, ease of application especially for the geriatric population which includes major proportion of the arthritic population and thus catering to the problems of millions of people worldwide.

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