Development and *in-vitro* evaluation of Etoricoxib loaded Transdermal Film containing MWCNT

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Abstract

Nanocomposites are materials that integrate either a unit of nanoscale material or multi-units of nanoscale material into a matrix of a standard substance. The main purpose of the current study is to fabricate and evaluate nanocomposite transdermal films of Etoricoxib. The transdermal films of etoricoxib were developed with a mixture of polymers *viz.* Eudragit RL-100 and HPMC K4M, with or without different percentages of multi-walled carbon nanotubes (MWCNT, 1, 3, 5, and 10%, w/w of total polymer) using solvent casting method. Various parameters including FT-IR, DSC, drug content, folding endurance, moisture content, moisture uptake, water vapour permeability (WVP), and *in-vitro* drug release employing Franz diffusion cell were assessed for the prepared films. The absence of interaction between the drug and polymers was confirmed by FT-IR and DSC studies. The thickness of the resulted films was within the range of 0.33±2.76 µm to 0.43±2.76 µm. The weights of prepared films were between 85.1±1.3 mg to 85.15±0.8 mg. The drug content was measured to be between 4.486 and 5.993 mg. The folding endurance of the developed films ranged from 237.33±7.8 to 342±6.5. The moisture content (%) was between 5.91 ± 1.2% and 8.84 ± 4.0%, whereas the percent moisture uptake of prepared films was observed to be between 8.23 ± 2.1% and 12.38 ±3.6%. The WVP of films was found to be 97.08 ± 0.57 g/m^2/day to 194.17 ± 0.81 g/m^2/day. *In-vitro* release studies revealed that formulation F4 prepared with an equal amount (50:50) of Eudragit RL-100 and HPMC K4M, and 5% MWCNT shows the highest drug release after 24 hr of study.The above results imply that the nanocomposite films could be an effective tool for transdermal delivery of etoricoxib and could act as a better prospect in replacing the oral dosage form.

Keywords: Transdermal films, Etoricoxib, Nanocomposite, Folding endurance.

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1. Introduction

Chronic degenerative diseases such as osteoarthritis, rheumatoid arthritis, lower back pain, and tendinitis are associated with inflammatory conditions which inflict pain and could impair normal activities [1,2]. The inflammation and pain are caused by prostaglandins that are secreted by the Cyclooxygenase (COX) enzyme at the site of injury. In these conditions, non-steroidal anti-inflammatory drugs (NSAIDs) are the first-line drugs to mitigate inflammation and associated pain [3]. Out of various classes, cyclooxygenase-2 (COX-2) enzyme inhibitors are widely accepted due to their selectivity toward the receptor. In the beginning, COX-2 inhibitors were recommended for the oral route of administration. However, their chronic administration resulted in gastric ulcers, bleeding, and cardiovascular events [4]. Etoricoxib, a selective inhibitor of isoform 2 of the COX enzyme, acts by blocking the COX-2 enzyme and thereby decreasing the formation of arachidonic acid to prostaglandins which results in reduced pain and inflammation [5]. In addition, etoricoxib shows poor solubility in an aqueous medium and subsequent low dissolution resulting in its low bioavailability, which limits its administration through the oral route. On the other side, etoricoxib is having favourable properties for transdermal drug delivery, including 358.8 g/mol of molecular weight, 2.79 log p-value [6], 134-138°C of melting point, and oral doses as lowest as 30 mg [6]. Therefore, the transdermal route would offer superiority over other routes in reducing gastric irritation, providing taste masking, and prolonged release of etoricoxib.

Administration of drug through transdermal route certainly has many advantages over the widely used oral route as the former offers a huge and varied surface area for the absorption of drug, avoids first-pass metabolism of drug both in intestine and liver, easy administration with self-administration option, harsh environment of the gastrointestinal tract (GIT), and better patient compliance [7,8]. When compared with the parenteral route, drug administration *via* the transdermal route avoids needle phobia and infections at the administration site [9]. For drug delivery across the skin, two kinds of dosage forms are employed *viz.* semisolid dosage forms such as ointment, creams, and gels, and films and patches or transdermal drug delivery systems. However, each of them has limitations. For example, semisolid preparation lacking in providing persistent contact with the skin surface because there is a possibility of being rub-off by the patient's clothes and other daily activities [9]. On the contrary, films and patches are fabricated such that contact with the skin surface can be maintained for long period. Between them, transdermal films have superiority in their manufacturing simplicity compared to patches. Transdermal films are considered as medicated adhesive system which is capable of delivering incorporated drugs in desired concentration into the bloodstream following their application on the skin surface [10]. Medicated transdermal films are minimally composed of three ingredients with one each of bioactive, polymer, and suitable plasticizer and showed lower occlusive nature due to their thin and flexible nature compared to patches [11]. In addition, these films are having wide applications including transdermal, oral, buccal, and sublingual routes [12].

Nanocomposites are defined as materials that integrate either a unit of nanoscale material or multi-units of nanoscale material into a matrix of a standard substance such as ceramic, metal, and polymer [13]. Among them, polymeric nanocomposite, involving polymer and nanomaterial as the continuous phase and filler, respectively, has superiority in terms of processability, tailoring to different forms, availability in various forms and nature, and stability [14]. With the incorporation of nano-fillers into the polymeric matrix, a film not only improves mechanical strength and thermal stability but also provides controlled drug release. In addition, nano-fillers can also ameliorate other desired properties including electronic, optical, and magnetic [15]. Various types of nano-fillers can be used to develop nanocomposites including metals such as silica, clay, iron, or carbon-derived including carbon nanotubes (CNTs), nanofibers, graphene oxide, and fullerene [16].

Among all, CNTs are being widely used as a reinforcing filler for various nanocomposites because of their extraordinary strength and high aspect ratio. In addition, CNTs are most preferred for high technology applications where electrical properties are desired as they show excellent electrical conductivity [17-19]. CNTs are comprised of big cylindrical molecules with a hexagonal arrangement of sp2 hybridized carbon

atoms with a wall composed of either rolling up of a single-walled graphene sheet (SWCNT) or rolling up of greater than one graphene sheet (MWCNTs) [20,21]. CNTs of both kinds are existing as both ends of the tube are capped with fullerenes (alignment of carbon networks into a hemispherical structure), which are twisted up by graphene sheets. Out of the two, SWCNTs have a distinct wall with a tiny width which makes them appropriate as drug delivery vehicles. On contrary, MWCNTs are characterized by defects in their nanostructure leading to their poor stability, but modification friendly [22]. Basically, there are three different ways of interaction between drugs and CNTs: (i) entrapment of drugs within a CNT bundle or CNT mesh, (ii) attachment of the drug to the outer wall of the CNTs through functional groups, and (iii) the application of channels of CNTs as nanocatheters [23].

In the present study, the goal was to formulate nanocomposite transdermal films of Etoricoxib by solvent casting method, and the objective behind the study was to evaluate different parameters including film thickness, variation in weight, drug content, folding endurance, moisture content, moisture uptake, WVP, and *in-vitro* studies along with compatibility studies with FTIR and DSC analysis.

2. Materials and method

2.1 Materials

Etoricoxib was received as a gratis sample from Hetero Drugs, Hyderabad, India. HPMC K4M and Eudragit RL100 were obtained as gift samples from Ranbaxy Laboratories, and Evonik Degussa Pvt. Ltd., Mumbai, India, respectively. MWCNT was procured was obtained from Platonic Nanotech Pvt. Ltd., Godda, Jharkhand, India. The other chemicals employed in this research investigation were of analytical grade and used without any modification.

2.2 FTIR analysis

FTIR studies of pure etoricoxib and pure polymers (Eudragit RL 100 & HPMC K4M) and MNCNT along with the selected film (F4) were carried out by using FTIR Spectrophotometer (FT-IR Perkin Elmer 1600 series USA) using KBR pellets technique.

2.3 Differential scanning calorimetry (DSC) analysis

DSC analysis of pure etoricoxib and individual polymers (Eudragit RL 100 & HPMC K4 M), and film F4 were carried out by using DSC 60 thermal analyzer. All the samples underwent heating in a nitrogen purge of 100 (ml/min) from ambient temperature to 250°C.

2.4 Development of transdermal films

Etoricoxib transdermal films were prepared to employ the solvent casting method [24]. Etoricoxib transdermal film comprises different proportions of HPMC K4M and Eudragit RL 100 polymers as mentioned in Table 1. Polymers were measured accurately and then added to the solvent mixture with 50:50 of methanol: dichloromethane mixture (50:50). To this add 20% glycerol and stirred on the magnetic stirrer for 35 minutes. After getting a clear polymer solution, the etoricoxib and nanoparticles filler (MWCNT) of the desired amount was added to the polymer solution and mixed thoroughly for 2hr to uniformly disperse them, followed by pouring in petri plate. For nanocomposite films, the nanocomposite is added according to the amount depicted in Table 1.

Table 1. Composition of transdermal films of Etoricoxib

Ingredients	F1	F2	F3	F4	F5
Etoricoxib (mg)	300	300	300	300	300
Eudragit RL 100 (mg)	750	750	750	750	750
HPMC K4M (mg)	750	750	750	750	750
Glycerol (mg)	250	250	250	250	250
MWCNT (mg)	-	15	45	75	150
Methanol (ml)	25	25	25	25	25
Dichloromethane (ml)	25	25	25	25	25

2.5 Thickness and weight variation

A vernier caliper (BVK Technology, Hyderabad, India) was employed to measure the thickness of each film at three different points, followed by the calculation of mean thickness. For the weight variation test, three film samples from each formulation were taken. Film samples were weighed separately employing Shimadzu AUX 220 analytical digital balance and then the average weight is calculated.

2.6 Folding endurance

For folding endurance, a film with a known dimension (2cm × 1cm) was taken and folded frequently at a distinct place till it splits into two parts. The number of times the film was folded before breaking represents folding endurance [25].

2.7 Drug content

The known area of the films was placed in 10 mL of solvent mixture (50:50) in a volumetric flask, followed by their agitation in a water bath shaker (Remi, India) at 37° for one day. Whatmann filter paper No. 1 was used to filter the resulted solutions and appropriately diluted to analyze the drug content using Shimadzu double beam U.V spectrometer at 234 nm.

2.8 Moisture content and moisture uptake

The drug-loaded films were accurately weighed and placed in a desiccator carrying a saturated solution of $CaCl_2$ (29%RH) at ambient conditions for 24hrs. Afterwards, the films were individually measured to obtain a weight unchanged. The moisture uptake (%) of films was determined by dividing the initial weight of films by the difference in weight between the final and initial weight of films [26]. For moisture uptake, the accurately measured films that remained in desiccators at ambient temperature (32°C) for 24 hrs were removed and placed at 75% RH until a fixed weight is attained [11].

2.9 Water vapour permeability

For WVP study, glass tubes (25ml) were selected and filled with 20 ml of DW. Thereafter, the weight of individual tubes was taken 1 hr previous to placing films on the opening of test tubes. The area accessible for vapour permeation to occur was 2.060 cm^2 and tubes were kept at an ambient temperature of 32°C for 24 hrs. The final weight of the test tubes was measured after 1 hr of completion of the study and the WVP was measured by employing the below equation [24].

$$\mathrm{WVP} = \frac{\mathrm{W}}{\mathrm{A}} \ \left(\frac{\mathrm{g}}{\mathrm{m}^2} \times 24\ \mathrm{h}\right)$$

Where W is the mean weight loss (g) of containers and A is the area (m^2) of the displayed surface.

2.10 In-vitro drug release studies:

The release of etoricoxib from the film was carried out *in-vitro* with employing a vertical Franz diffusion cell having 3.8cm^2 of displayed surface area and 22 ml of receptor compartment volume. The jacketed diffusion cell is having provisions of entry and exit for the passage of water to keep the temperature at 32±0.5°C. A piece of dialysis membrane was soaked in pH 7.0 phosphate buffer for a period of one day to maintain equilibrium. Thereafter, the desired film specimen was placed on the equilibrated membrane and was instantly kept secure between the chambers. A Teflon-coated magnetic bead at 500 rpm was employed to stir the receptor medium. Samples of 0.5 ml were withdrawn from the receptor compartment at a predetermined point of times (1/2, 1, 2, 3, 4, 5, 6, 7, 8, and 24 hr) and replaced with the same volumes of fresh buffer kept at equal temperature. The samples obtained were analysed using a UV-Spectrophotometer [24].

3. Results and discussion

The etoricoxib-loaded transdermal films were developed employing the solvent evaporation method using equal volumes each of dichloromethane and methanol as a solvent system. Among all the formulations, F1 was prepared without nanocomposite & F2, F3, F4, and F5 were prepared using different nanocomposite concentrations (1%, 3%, 5%, and 10%), respectively. All the developed films were presented in Figure 1.

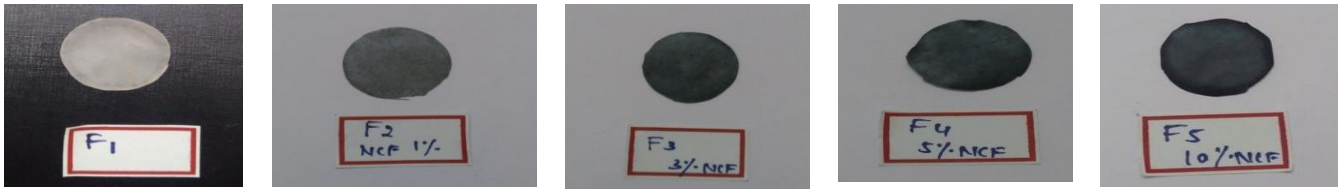

Figure 1. Pictures of prepared film batches

FTIR spectrum (Figure 2a) of etoricoxib exhibited characteristic peaks at 2958.80 cm^{-1} for CH_3 stretching, 1598.99 cm^{-1} for C=C stretching, 1143.79 cm^{-1} for S=O stretching, and 781.17 cm^{-1} C-Cl stretching. The selected formulation (F4) demonstrated the same peaks as pure drug and polymers without the addition of new peaks, which confirms there is no interaction between the drug, polymers and MWCNT. DSC thermogram (Figure 2b) of pure etoricoxib demonstrate a sharp endothermic peak at 134.61° C and the spectrum of Eudragit RL 100 shows peak at 141.43°C, respectively representing the melting point. However, the thermogram of the selected film formulation did not display any sharp peak with heating ranging from 0°C to 250°C. This was attributed to the existence of a minute quantity of etoricoxib in the film.

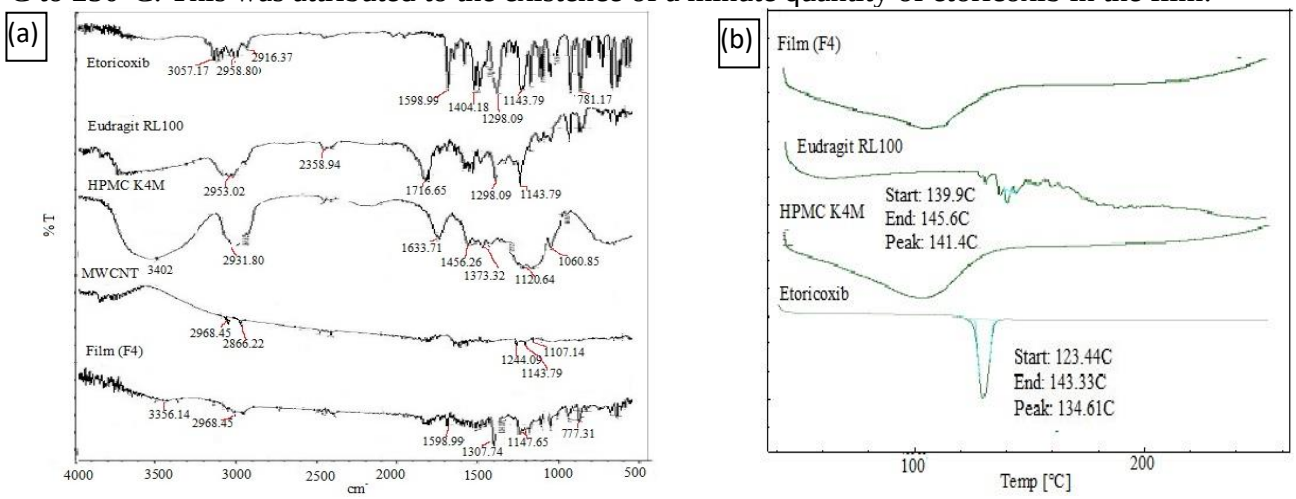

Figure 2: (a) FTIR spectra of Etoricoxib, Eudragit RL 100, HPMC K 4 M, MWCNT, and F4 formulation, (b) DSC thermograms of Etoricoxib, Eudragit RL 100, HPMC K 4 M, and F4 formulation

The results obtained from various physicochemical studies are displayed in Table 2. The thickness of all the films was within the range of 0.33±2.76 µm to 0.43±2.76 µm. The weights of prepared films varied between 85.1±1.3mg to 89.15±0.8mg. This illustrates variable amounts of polymers and MWCNT have no such notable effect on weight variation. The drug-loaded films displayed good drug content uniformity. It indicates that all formulations would show a high degree of consistency. The folding endurance values were found to be ranged from 237.33±7.8 to 342±6.5. It was observed that an increase in nanocomposite percentage in the film indicates that decrease in folding endurance values. Among all formulations, F1 showed high folding endurance which indicates the probity and shapes with inherent folding of the skin when tested on it.

Table 2. Obtained results from physiochemical studies.

Film code	Weight variation (mg)	Thickness (µm)	Drug content (mg)	Folding endurance
F1	87.8 ± 3.8	0.33± 2.76	5.277	342± 6.53
F2	89.15 ± 0.8	0.36±1.50	4.486	318.33 ± 2.62
F3	88 ± 0.9	0.43±2.76	5.993	277 ± 6.16
F4	85.1 ± 1.3	0.33±2.76	4.972	242.33 ± 6.77
F5	88.5 ± 1.3	0.36±1.50	5.907	237.33 ± 7.84

The moisture content (%) was in the range of 5.91 ± 1.2% to 8.84 ± 4.0% (Figure 3a) and moisture uptake (%) of prepared films was between 8.23 ± 2.1% and 12.38 ±3.6% (Figure 3b). The WVP of films was

observed to be 97.08 ± 0.57 g/m^2/day to 194.17 ± 0.81 g/m^2/day. The WVP increased with an increase in nanocomposite concentration in etoricoxib film.

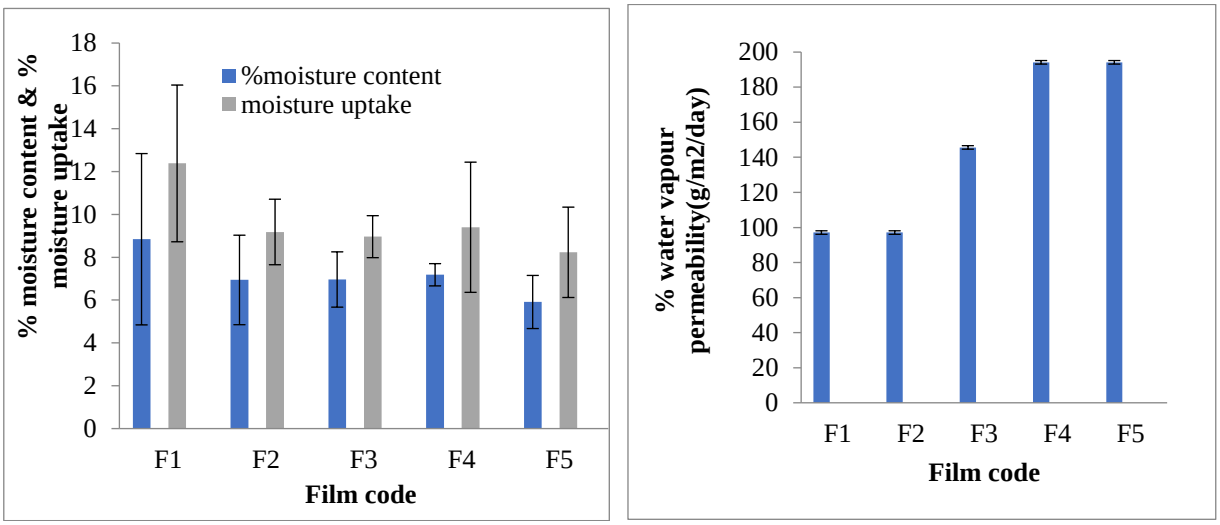

Figure 3. Results obtained from (a) percent moisture content & percent moisture uptake, (b) WVP studies

The *in-vitro* release studies of all the formulations are illustrated in Figure 4. It revealed that formulation F4, prepared with 1% MWCNT shows the highest drug release of 58.158±9.20% after 24 hrs of study. However, formulation F4 exhibited a higher correlation coefficient value (0.943) for zero-order, compared to other formulations. All the formulations demonstrated diffusion as the drug release mechanism because the correlation coefficient values were measured to be between 0.773 and 0.922. Based on *in-vitro* drug release and kinetics of drug release along with other physicochemical parameters, formulation F4 is selected as the best formulation.

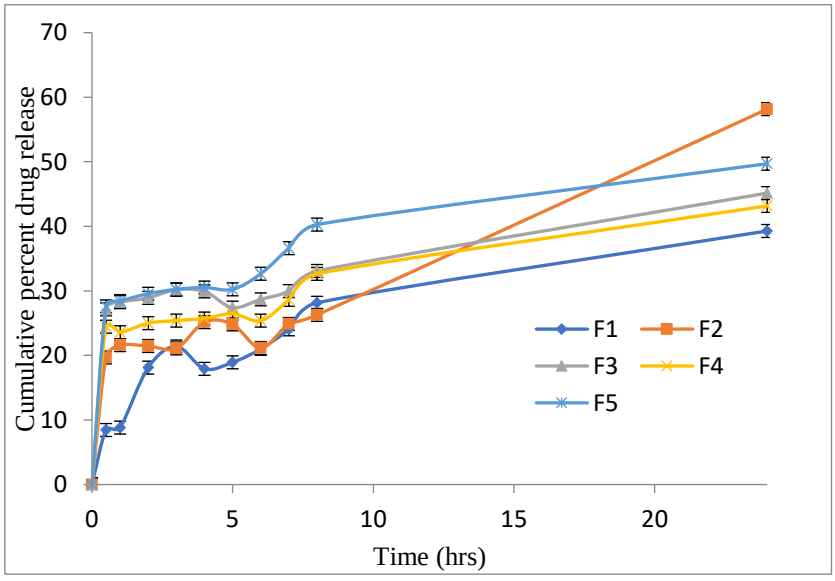

Figure 4. *In-vitro* drug release profile of all the film formulations.

4. Conclusion

A total of four nanocomposite transdermal films of etoricoxib were prepared with Eudragit RL-100, HPMC K4M and different percentages of nanocomposite employing solvent casting technique and compared with the etoricoxib film without nanocomposite. The prepared films have been evaluated for different parameters. The FT-IR and DSC investigations confirmed the absence of drug-polymer interaction. From the

in-vitro studies, it was found that films showed better drug release characteristics. From kinetics of release and drug release mechanism, F4 followed zero-order kinetics and drug release is through the diffusion mechanism.

Conflict of interest:

The author declares that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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