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Development of novel transdermal self-adhesive films for tenoxicam, an anti-inflammatory drug

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ABSTRACT

Aim: The purpose of this study was to develop transdermal films (TFs) with the addition of different polymer ratios that incorporated 0.5% tenoxicam in order to ensure maximum controlled and sustained drug release capacity. Tenoxicam is a non-steroidal anti-inflammatory drug (NSAID) widely used in the treatment of rheumatic diseases and characterized by its efficacy and reduced side effects in comparison to other NSAIDs.
Main methods: Transdermal films of tenoxicam were designed with the Eudragit L30D-55copolymer with permeation enhancers like polyethylene glycol (PEG) and propylene glycol (PG) incorporated at different concentrations using the casting evaporation technique. Evaluations of these formulae were performed through mechanical characterizations and Fourier Transform Infrared Spectroscopy [FTIR]. In-vitro release studies were performed during 24 h using diffusion cells. The film formulations with optimum in vitro-release rate have been taken up for testing of the anti-inflammatory effects and the sustaining action of tenoxicam. The in-vivo studies performed included carrageenan-induced hind paw edema and skin biopsies in Wistar rats.
Key findings: Formulation (F7) had the best effective combination [glycerol (0.25 g), PEG200 (0.5 g), PEG400 (1 g) and PG (10%) and 0.5% dispersed drug] among all of the tenoxicam TF formulations studied. Also, this formula had the highest release value than formula 1 (F1) that contains [glycerol (2.5 g), PEG200 (0.5 g), PEG400 (0.5 g) and 0.5% dissolved drug] or a commercially available gel after 24 h. FTIR revealed that there was an interaction between the polymer and the drug. The drug–polymer interaction occurring between tenoxicam and Eudragit L30D-55 seems to cause a drag effect, leading to a delay of the tenoxicam release from the Eudragit L film.
Significance: When the films were applied half an hour before the subplantar injection of carrageenan in the hind paw of Wistar rats, it was observed that formula F7 provided maximum inhibition of paw edema in rats over 24 h in contrast to both formula F1 and the marketed piroxicam gel as a reference. This was also confirmed histopathologically from skin biopsies. Thus, we show that tenoxicam can be formulated into transdermal films to sustain its release characteristics, and the polymeric composition of PEG200/PEG400 at a ratio of 1:2 and 10% PG was found to be the best choice to manufacture tenoxicam TF.

Introduction

Drug-loaded transdermal films are a mechanism to deliver a drug based on application of pharmaceutical technology. Numerous controlled or sustained delivery systems have been described whereby the active ingredient has been dissolved or dispersed within these films (Hadgraft and Guy 1989; Prausnitz et al., 2004). The profile of tenoxicam side effects is similar to that of other NSAIDs; it causes epigastric pain, nausea, vomiting, dyspepsia and indigestion (González and Todd, 1987) and increases the risk of renal failure or bleeding (Al-Obaid and Mian, 1993). It also has severe effects on the liver and biliary tract, leading to hepatitis in high doses, and it increases liver enzyme activity (Information for Health Professionals, 2006). Administration of tenoxicam through the transdermal route offers many advantages over the oral dosage form (Kim and Simon 2011; Ammar et al. 2011; Vartiainen et al. 2001) as it avoids the problems associated with the other routes of administration (Thong et al. 2007), such as improving patient compliance in long term therapy, bypassing first pass metabolism, sustaining drug delivery, maintaining a constant and prolonged drug level in plasma, minimizing inter- and intra-patient variability, and making it possible to interrupt or terminate treatment when necessary (Nicoli et al. 2006; Beverley and Barrie, 2004; Rathbone et al., 2003; Brian, 2001; Chien, 1987). However, transdermal delivery is limited to drugs used in low doses, with low melting points and molecular weights and a solubility of greater than 1 mg/ml in water and mineral oil (Prausnitz, 2004; Naik et al. 2000; Misra 1997).

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Films are innovative drug delivery systems intended for skin application with the goal of achieving a systemic effect. They do not allow water to be released from the skin surface and therefore increase drug transport by augmenting the water content of the stratum corneum. Polymer blending is an effective method for providing new materials for a variety of applications. Plasticizing agents are generally essential to overcome the brittleness of the films. Brittleness is an inherent quality attributed to the complex/branched primary structure and weak intermolecular forces of natural polymers. Plasticizers soften the rigidity of the film structure and increase the mobility of the polymer chains by reducing the intermolecular forces, thus improving their mechanical properties (Bergo and Sobral, 2007; Padula et al., 2007). Use of polyethylene glycol (PEG) at 0.25% and 0.5% resulted in a reduced tensile strength (TS) and water vapor permeability rate (WVPR) of the film but an increase in percent elongation (%ε) (Srinivasa et al. 2007; Wiles et al. 2000). PEG is a biocompatible polymer with excellent biocompatibility that is non-toxic (Zhang et al. 2002). It is often blended or compounded with other polymers to be used in the field of drug controlled release (Chandy et al. 1998). Glycerol improves film flexibility and reduces film puncture strength (Gontard et al. 1993).

Tenoxicam is a well-established nonsteroidal anti-inflammatory agent with analgesic actions achieved by inhibiting prostaglandin synthesis (Morof et al., 1988). Like other oxicam derivatives, tenoxicam has been found to be approximately 99% protein bound with a mean elimination half life of 67 h, which allows the administration of a daily single oral dose of 20 mg (Nilson, 1994). Tenoxicam is widely used in various musculoskeletal disorders, arthritis, toothaches, dysmenorrheal and symptomatic relief of pain and inflammation. The drug undergoes substantial hepatic first-pass metabolism. This creates a need for an alternative route of administration, which can bypass the hepatic first pass metabolism (Priyanka and Biswajit, 2002). Tenoxicam is also a very good antioxidant (Vartiainen et al. 2001). The required amount of NSAIDs to achieve anti-inflammatory and analgesic effects is lower when applied topically than compared to an oral dose. This also limits the common side effects NSAIDs, namely gastrointestinal irritation (British pharmacopoeia 2007, Martindale 2007). Therefore, the transdermal film delivery system is a viable alternative route for the administration of tenoxicam. However, because systemic absorption of nonsteroidal anti-inflammatory drugs from topical formulations has been documented, caution should be exercised when prescribing these formulations to patients with a history of peptic ulcers (Zimmerman et al. 1995).

The aim of the present study was to develop transdermal films with various ratios of polyethylene glycol (PEG 200 or PEG 400), propylene glycol (PG) and glycerol together with tenoxicam using the casting evaporation technique. An attempt was also made to establish the best possible combination of polymeric ratios to ensure maximally controlled and sustained drug release capacity. This will allow for drug delivery at a controlled rate across intact skin to achieve a therapeutically effective drug level for a longer period of time. Evaluations of the formulated films were done via physicochemical, in vitro and in vivo investigations. In vivo studies included carrageenan-induced hind paw edema and skin biopsy.

Materials and methods

Materials

Tenoxicam was given as a gift from M/s Ranbaxy Lab Cipla Ltd., [Mumbai], India. Eudragit L30 D-55 (methacrylic acid–ethyl acrylate copolymer) (1:1) was purchased from Rohm, Germany. Polyethylene glycol 200 and 400 were obtained from Loba Chemia, [Mumbai,] India. Polyvinyl alcohol was obtained from Fluka Chemie GmbH, Switzerland. Glycerol and propylene glycol were obtained from Loba Chemia, [Mumbai], India. All other ingredients were of analytical grade. Carrageenan was purchased from Sigma Chemical Company, [St. Louis], MO, USA. Cellophane dialysis membrane (M.W. cutoff 3600 Da) was purchased from Fisher Scientific, Ltd., Loughborough, [Leicestershire], UK. Feldene gel was from Pfizer Co. [Egypt], batch No. 013, manufactured 5/2009, exp. date 11/2011 RG. No. 2002/22414. The animals used for in vivo experiments were twenty five young adult male Wistar rats weighing 180–250 g from the [Department of Central Animal House] at (NODCAR).

Methods

Preparation of tenoxicam

First method (drug dissolved). Polyvinyl alcohol (2.5 g) (PVA) was dissolved in 25 ml distilled water with heating at 70 °C to obtain a clear 10% solution. Different amounts of plasticizer were added to the PVA solution described in Table 1 and then mixed well with the different amounts of PEG 400 and propylene glycol as permeation enhancers. Tenoxicam was completely dissolved in 3 ml 0.1 N NaOH and then added to the PVA/plasticizer/enhancer solution. The mixture was cooled to 30 °C. One milliliter of Eudragit L30D-55 was added and mixed. After thorough mixing, the mixture was left to stand until all air bubbles had disappeared, at which point it was poured into a clean, dry Petri dish. The polymer solution was left to dry at room temperature in a dust-free atmosphere. After they had dried thoroughly, the films were taken out and stored in desiccators.

Second method (drug dispersed). The previous method was repeated but the drug was dispersed into the solution of PVA and plasticizer as illustrated in Table 1.

Evaluation of the physicochemical properties of the films

Water content. The prepared films were marked and immersed in distilled water for 24 h, then placed between two pieces of filter papers to remove excess water. The swollen films were weighed (electronic analytical balance, JT3003, Shimadzu, [Kyoto], Japan.), and left to dry at room temperature until a constant weight was obtained.

Table 1
Table of prepared formulations.

Serial no.	Film code	Eudragit L30D55 (ml)	10% PVA (ml)	Glycerol (g)	PEG 200 (g)	PEG 400 (g)	PG%	0.1 N NaOH (ml)	Drug (0.5%)
1	Plain film (drug free)	1	2.50	–	–	–	–	–	–
2	(F1)	1	2.50	0.50	0.50	–	–	3	Dissolved
3	(F2)	1	2.50	0.50	–	0.50	–	3	Dissolved
4	(F3)	1	2.50	0.50	–	0.50	–	–	Dispersed
5	(F4)	1	2.50	0.33	–	0.67	–	3	Dissolved
6	(F5)	1	2.50	0.25	–	0.75	–	3	Dissolved
7	(F6)	1	2.50	–	–	1.00	5%	–	Dispersed
8	(F7)	1	2.50	0.25	0.50	1.00	10%	–	Dispersed