FORMULATION AND EVALUATION OF A MONOLITHIC DRUG-IN-ADHESIVE TYPE PATCH CONTAINING TENOXICAM

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Abstract:

Tenoxicam (TX) is a well-established nonsteroidal anti-inflammatory agent with analgesic actions achieved by inhibiting prostaglandin synthesis. Administration of tenoxicam through the transdermal route offers many advantages over the oral dosage form as it avoids the problems associated with the other routes of administration, 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. The aim of the present investigation was to formulate and evaluate a monolithic drug-in-adhesive type patch containing Tenoxicam (TX) using various polymers like Hydroxy Propyl Methyl Cellulose (HPMC), Ethyl Cellulose (EC) and carbopol and plasticizers by solvent casting technique. The prepared transdermal patches were then evaluated for their physicochemical properties. The *in-vitro* release studies revealed that the release was sustained upto 24h and it follows zero order kinetics (r^2 – 0.998). Finally, the patch formulation containing TX (G 7) selected through our *in-vitro* study. As a patient friendly and once a day dosing therapeutic system, the Transdermal patches incorporating TX could be promising in the pasture of Controlled drug delivery.

Keywords: Transdermal, Tenoxicam, Solvent Casting Technique, Patches

Introduction:

Patches are groundbreaking drug delivery systems planned for skin application with the goal of attaining a systemic effect. Use of various characteristic Polymer in appropriate blending is an effective method for providing new materials. As a substitute for the oral route, transdermal drug delivery enables the avoidance of gastrointestinal absorption, with its associated pitfalls of enzymatic and pH associated deactivation. This method also allows for reduced pharmacological dosaging due to the shortened metabolization pathway of the transdermal route versus the gastrointestinal pathway. The patch also permits constant dosing rather than the peaks and valleys in medication level associated with orally administered medications. Multi-day therapy with a single application, rapid notification of medication in the event of emergency, as well as the capacity to terminate drug effects rapidly via patch removal, are all further advantages of this route [1-4].

Tenoxicam (TX) is a well-established nonsteroidal anti-inflammatory agent with analgesic actions achieved by inhibiting prostaglandin synthesis [5]. Like other oxicam derivatives, TX 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 [6]. 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 [7]. 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 [8]. Therefore, the transdermal film delivery system is a viable alternative route for the administration of TX. 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 [9]. TX shows side effects akin to that of other NSAIDs; it causes epigastric pain, nausea, vomiting, dyspepsia and indigestion [10] and increases the risk of renal failure or bleeding [11]. It also has severe effects on the liver and biliary tract, leading to hepatitis in high doses, and it increases liver enzyme activity. Administration of tenoxicam through the transdermal route offers many advantages over the oral dosage form [12-14] as it avoids the problems associated with the other routes of administration [15], 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 [16-19].

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* investigations.

Materials and methods:

Chemicals:

TX was a gift sample obtained from Sun Pharmaceuticals Ltd (India). The polymers such as Hydroxy propyl methyl cellulose (15 cps) [S.d. fine Chemicals], Ethyl cellulose (20 cps) [S.d. fine Chemicals] and Carbopol (15 cps) [S.d. fine Chemicals] were purchased. All other chemicals were of analytical grade.

Determination of partition coefficient

The partition coefficient of TX was carried out in n-octanol/phosphate buffer pH 7.4 (11). The two phases were shaken together initially to ensure mutual saturation. An accurately weighed quantity of TX was dissolved in 100 ml of the n-octanol phase and shaken at 25°C for 24 h against 50 ml aqueous phase in a sealed container. 1 ml of the solution was then transferred to a 10 ml centrifuge tube containing 1ml of water saturated with n-octanol. The tube was gently shaken for 24 h at 25^{o}C and centrifuged at 3000 rpm for 10 min The separated n-octanol phase was assayed by UV spectroscopy to determine its residual concentration and hence the amount partitioned into the aqueous phase. The partition coefficient was expressed as the concentration of drug in the n-octanol phase (% w/v) divided by the concentration in the aqueous phase.

Investigation of Physicochemical Compatibility of Drug and Polymer

The physicochemical compatibility between TX and polymers used in the films was studied by using Fourier Transform Infrared (FTIR) Spectroscopy.

Fabrication of patches:

Table no 1 enlists the composition of different formulations prepared using varying amounts of the polymers. Transdermal patches were prepared by the solvent evaporation technique [20,21]. Adhesive patches containing TX were prepared by dissolving polymers individually or in combinations in suitable solvents namely dichloromethane and ethanol. Propylene glycol (30%v/v) of polymer composition was used as a permeation enhancer. The solution was poured into a glass ring which is covered with funnel. The solvent was allowed to evaporate at ambient conditions for 24 h. The patches were then covered with backing membrane cut into appropriate sizes, packed in aluminium foil and stored in a desiccator for further studies.

Physicochemical Characterization of TX Transdermal Patches

Thickness, Weight variation and Drug content

The thickness of the patch at three different points was determined using thickness gauge and the patches were then weighed individually using digital balance to determine the weight of each patch taken out from the casted film. The patches were subjected to weight variation by individually weighing ten randomly selected patches. Such determinations were carried out for each formulation. Films of specified area were cut and weighed accurately [22]. Pieces were taken into a 100 ml volumetric flask containing phosphate buffer (pH 7.4), and the flask was sonicated for 8 h [23]. A blank was prepared in the same manner using a drug-free placebo patch of same dimensions. The solution was then filtered using a 0.45-µm filter and the concentration is found in respective nm.

Folding endurance test

Folding endurance test was carried out by folding the patch at the same point a number of times till it broke [24]. The test was carried out to check the efficiency of the plasticizer and the strength of the film prepared using varying ratios of the polymers. The test was carried out in triplicate.

Moisture Uptake

Accurately weighed films of each formulation (n = 3) were kept in a desiccator which is maintained at 79.5% relative humidity (saturated solution of aluminium chloride) at room temperature and weighed after 3 days [25]. The percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight.

Moisture Loss

Accurately weighed films of each formulation (n = 3) were kept in a desiccator and exposed to an atmosphere of 98% relative humidity (containing anhydrous calcium chloride) at room temperature and weighed after 3 days

[26]. The percentage of moisture loss was calculated as the difference between initial and final weight with respect to initial weight

Water Absorption Capacity

Three film units of each formulation were kept in an atmosphere of relative humidity RH = 82% for one week and the difference in weight of the film was taken as the water absorption capacity for that film [27].

Water Vapor Transmission Rate

For water vapor transmission studies glass vials of equal diameter were used as transmission cell [28]. These transmission cells were washed thoroughly and dried in an oven. About 1 gm of anhydrous calcium chloride was taken in the cell and the polymer film was fixed over the brim with the help of the solvent. The cell were accurately weighed and kept in a closed desiccators containing saturated solution of potassium chloride to maintain a humidity of 84% RH. The cells were taken out and weighed after 1, 2, 3, 4, 5, 6 and 7th day.

Tensile strength and Percentage elongation at break

Mechanical properties of the film were evaluated using an "Instron Tensile Strength tester" (Series IX Automated Material Testing System). A film strips with the dimension (15 cm x 7.5 cm) and free from air bubbles (or) physical imperfections was prepared and cut it in a Dumbell shape, before fed into the equipment. This test was carried out with 50% humidity at 20^{o}C [29]. The crosshead speed employed were 100mm/min, with the full-scale load range of 500 Kgf. The force and percentage elongation were measured, when the films were broken. Measurements were run in three replicates for each formulation.

***In-vitro* Drug Release Studies:**

A Franz diffusion cell was used for drug release study from the formulations [30-32]. Phosphate buffered saline (PBS; 20 ml, pH 7.4) was used as the receptor fluid. The receptor fluid was agitated at 600 rpm by a Teflon-coated magnetic stirrer. The area of donor compartment exposed to receptor compartment was 3.14 cm^2. The semi permeable membrane was mounted between the donor and receptor compartment. The TX drug matrix was placed on one side of the dialysis membrane. The receptor compartment was surrounded by a water jacket to maintain a temperature at 37 ± 0.5°C during the drug release study. Samples were collected from the sampling port at every six hour and were replaced with equal volume of fresh receptor fluid. The collected samples was subjected to examine for its absorbance under UV spectrophotometry.

RESULTS AND DISCUSSION:

Monolithic drug-in-adhesive transdermal drug delivery system containing TX was prepared by using different polymeric ratios of hydroxyl propyl methyl cellulose, carbopol and hydrophobic polymer of ethyl cellulose in combination or individual. The formulations made were evaluated for their physico-chemical characterization and *in-vitro* drug release.

The preformulation study indicates that the drug possesses sufficient lipophilicity, which meets the requirements of formulating it into a transdermal patch. Apart from physical characteristics, compatibility between a drug and polymer is a factor in determining the effectiveness of polymeric delivery systems. Herein, to consider compatibility between polymer and drug, we refer to interaction with no alteration in the chemical structure of the polymer or the drug. The possible drug-polymer interaction was studied by IR of placebo films and TX loaded matrix films. FTIR techniques have been used here to study the physical and chemical interactions between drug and excipients used. These results suggest that there is no interaction between the drug and polymers used in the present study.

Table 2 lists various physico-chemical parameters computed for all the formulations. (Thickness, weight variation, content uniformity, moisture uptake, moisture loss, water vapor transmission rate and tensile strength). The thickness of the patches varied from 0.29 ± 0.02 to 0.40 ± 0.01. The drug content analysis and the weight uniformity of the prepared formulation have shown that the process adopted for casting the films in this investigation is capable of giving films with uniform drug content and with minimum intra batch variability. Folding endurance values of matrix films was found within 229 – 293 no of folds, indicating good strength and elasticity. Folding endurance test results indicated that the patches would maintain the integrity with general skin folding when applied. The percentage moisture uptake in the formulation G7 has shown the lowest value of moisture absorption 1.543 ± 0.03 which may be due to the hydrophobic nature of the polymer used in it. The formulation G 7 shows higher value of moisture loss 9.858 ± 0.01 which is due to its hydrophilic nature and formulation G 3 shows low value of 2.558 ± 0.01 which is due to its hydrophobic nature. The high moisture absorption capacity and water absorption capacity was found in G 2 as 5.431 ± 0.1 and 3.458 ± 0.08 respectively which also revealed its high hydrophilicity. The formulation G 2 has shown maximum water vapor transmission of 8.428 X 10^{-6} among all the patches. This may be due to the presence of high hydrophilic nature of the polymer.

In-vitro Dissolution Studies

The Reservoir type TDDS of TX were prepared and characterized on the basis of *in-vitro* drug release. The cumulative percentage of drug released in 24 h was found to be the highest (99.28%) from formulation G7. Figure ix exhibits the dissolution profile obtained for formulation G7. The Higuchi's plot has shown the regression value of 0.998, which indicated that diffusion mechanism influencing the drug release. In order to confirm this fact, Peppa's plot was drawn which has shown slope value of 0.701, which confirms that the diffusion mechanism involved in the drug release was of non – fickian diffusion type. Hence formulation G7 was selected as the optimized formulation by virtue of its drug release kinetics. Table 3 and figure 1 shows the diffusion kinetics data and comparative *invitro* graph for all the formulaitons.

Conclusion:

The transdermal formulation and the prototype patch were shown to be efficacious, safe, stable and non-irritant to skin. The formulation G 7 has shown optimum release in concentration independent manner. While release kinetics (Higuchi's plot) of drug is the zero-order process, suggesting that the outwards moving of drug from the adhesive is associated with the diffusion process. The obtained results are encouraging for the further development of this novel drug delivering technology for the skin.

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Table 1. Composition of Transdermal Patches Using TX

Formulation code	**HPMC (%)**	**EC (%)**	**Carbopol (%)**	**Permeation enhancer**
G1	1	-	-	Propylene glycol (30% V/V)
G2	2	-	-	
G3	-	1	-	
G4	-	2	-	
G5	-	-	1	
G6	-	-	2	
G7	1	-	1	
G8	1	1	-	
G9	-	1	1	

Table 2. Physicochemical Evaluation of Transdermal Films of TX

Formulation Code	Thickness (mm) ± SD	Weight Uniformity ± SD*	Drug content (%)	Folding Endurance ± SD*	Moisture uptake ± SD*	Moisture Loss ± SD*	Water Absorption capacity ± SD*	Water Vapor Transmission Rate ($mg/cm^2/hr$)	Tensile Strength Kgf/cm^2 & Percentage Elongation
G1	0.31 ± 0.01	88.73±0.54	99	229± 1	4.440±0.01	3.807±0.05	2.508±0.15	$5.050 X10^{-6}$	421.25 & 0.322
G2	0.40 ± 0.01	193.20±0.23	98	293±2	6.413±0.01	8.473±0.01	3.458±0.08	$3.247 X10^{-6}$	291.61 & 0.254
G3	0.39 ± 0.03	96.16±0.50	99	272±2	1.984±0.03	2.558±0.01	1.153±0.131	$5.689 X10^{-5}$	308.34 & 0.286
G4	0.34 ± 0.05	192.50±0.25	99	282± 1	2.652±0.02	5.84±0.014	1.558±0.083	$3.788 X10^{-6}$	175.55 & 0.295
G5	0.35 ± 0.04	92.53±0.25	99	260±1	1.952±0.02	7.599±0.31	2.629±0.283	$8.428 X10^{-6}$	696.21 & 0.266
G6	0.29 ± 0.02	178.37±0.86	99	270±1	2.187±0.15	3.540±0.10	2.827±0.054	$4.169 X10^{-6}$	289.18 & 0.382
G7	0.31 ± 0.02	176.67±0.51	99	255±2	1.614±0.03	9.858±0.01	2.133±0.131	$3.619 X10^{-5}$	338.34 & 0.206
G8	0.36 ± 0.01	185.84±0.42	99	276±2	2.662±0.02	5.540±0.10	1.98±0.083	$7.588 X10^{-6}$	295.55 & 0.265
G9	0.28 ± 0.02	193.33±0.51	99	290±4	1.965±0.02	8.599±0.31	2.629±0.283	$6.428 X10^{-6}$	296.21 & 0.286

*Average of three determinants for each parameter.

Table 3 Diffusion Characteristics for TX Formulations

Batch Code	Regression For *In-Vitro* Plot (R^2)	Regression For Higuchi's Plot (R^2)	Slope For Peppa's Plot (n)
G1	0.994	0.949	0.840
G2	0.997	0.933	0.707
G3	0.993	0.953	0.794
G4	0.993	0.957	0.850
G5	0.985	0.976	0.707
G6	0.995	0.950	0.794
G7	0.990	0.974	0.701
G8	0.990	0.961	0.669
G9	0.996	0.950	0.805

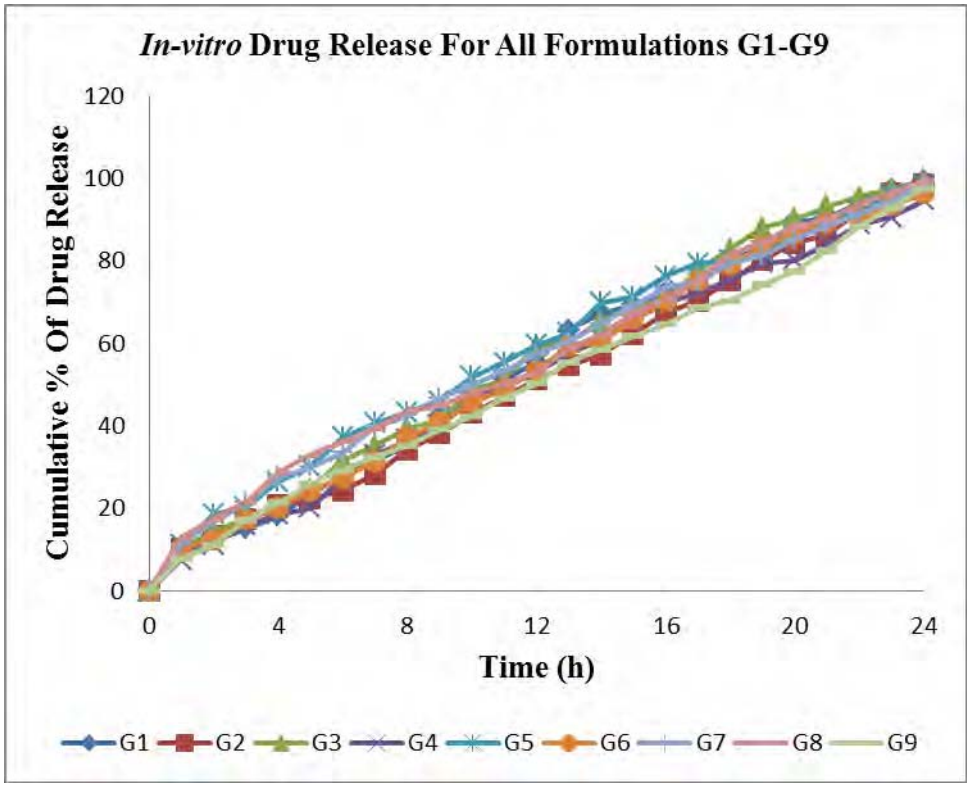

Figure 1: *Invitro* drug release of all formulations G1-G9