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Formulation and evaluation of transdermal patches of etodolac for topical application

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ABSTRACT

Etodolac transdermal patches formulated with PEG-400 as plasticizer and polymers HPMC and ethyl cellulose by solvent casting method are quite stable, there is no interaction between drug and formulation component on the basis of physical appearance and FTIR data. The average weight of the patches (2.54 cm^2) was found to be ranging from 158 to 165 mg. The thickness of the patches ranged from 0.245 to 0.346 mm and was found to be dependent on the polymer ratio. The patches were able to withstand 43 to 78 folds at same place in the folding endurance test. All the formulations were able to incorporated uniform quantity of drug in them ranging from 98.5 to 99.2 %. The results of moisture content study revealed that increase in concentration of HPMC was directly proportional to the moisture content in the patches with F6 exhibiting the highest moisture (7.25%) while F1 exhibiting the lowest (5.11%). The drug was released ranging from 88.3 to 60.7 % in various formulations. The regression coefficients of the graphical representation of the mathematical models reveal that the release of etodolac from the patches can be described by Korsemeyer-Peppas model. The expression relates that the drug released from the patches is due to diffusion of drug from the polymeric matrix of the patch and is primarily diffusion controlled.

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Introduction

Controlled release medication may be defined as the permeation-moderated transfer of an active material from a reservoir to a target surface to maintain a predetermined concentration or emission level for a specified period of time.[1] Transdermal drug delivery system can be defined as the controlled release of drugs through intact skin.[2] It provides controlled release of the drug and produces a steady blood- level profile leading to reduced systemic side effects and, sometimes, improved efficacy over other dosage form. In addition transdermal dosage form is user-friendly, convenient, painless, and offers multi -day dosing, it generally leads to improved patient compliance.[3]

In recent years, various drug delivery systems have been developed which provide sustained release therapy via a sub-dermal insert. Systems have been disclosed which also provide drug delivery systems suitable for transdermal drug administration. Several anti-inflammatory agents have been previously attempted to be formulated as transdermal patches in order to avoid the gastric irritation associated with the NSAIDs. Transdermal patches of fentanyl, salicylate, buprenorphine and diclofenac have already been approved by USFDA for clinical application.

Etodolac is a NSAID that exhibits onset of action in 30 min and attains peak plasma concentration in 1 to 2 h. A single oral dose elicits its effects for up to 4 to 5 h leading to frequent administration of drug to maintain steady state concentration.[4] Several formulations have been attempted to produce controlled and sustained release of etodolac for reducing its administration frequency.[5-9]

In the present research work, we prepared transdermal patches of anti-inflammatory drug etodolac with an objective to reduce the dosing frequency of the drug. The transdermal patches are also expected to reduce the gastric irritancy caused due to the oral administration of NSAIDs. The prepared transdermal patches will be evaluated for various parameters like weight variation, thickness, folding endurance, drug content, percentage of moisture content, *in-vitro* release study etc.

Material and Methods

Etodolac (Yarrow Pharmaceuticals, Mumbai), Hydroxypropyl methylcellulose (HPMC, CDH, New Delhi), ethyl cellulose (EC, CDH, New Delhi), Polyethylene glycol (PEG, Merck) were used for the study.

Preformulation Studies[10]

The preformulation studies were carried out in the terms of tests of identification like physical appearance, melting point and λ_{max}. It also includes solubility profile of drug in various solvents (water, HCl, ethanol and acetone) and determination of partition coefficient (butanol-water)[11]. FT-IR spectrum of the sample of etodolac was obtained and examined for the presence of characteristic peaks.

Preparation of Calibration Curve in methanol[12]

A stock solution (100 µg/ml) of pure drug was prepared by dissolving 5 mg etodolac in 50 mL of methanol. From this stock solution, the working standard solutions at 1.0, 2.5, 5, 10, 20, 30 and 50.0 µg/ml concentrations were prepared by suitable dilution. A standard

curve was constructed against absorbance and concentration.

Preparation of Transdermal Patches[13]

The matrix transdermal patches containing etodolac was prepared by solvent evaporation technique using different ratios of HPMC and ethyl cellulose. The backing layer was casted by pouring 4% PVA solution in the petri-plates lined with aluminum foil, followed by drying at 60ºC for 3-4 h in hot air oven.

In the process of formulation, initially, the polymer (HPMC) was taken in a beaker with a solvent dichloromethane: methanol (2:1) and was allowed to completely swell for a duration of 1 hour. Subsequently, with continuously stirring, ethyl cellulose was added. Afterward, the plasticizer (PEG 400) and permeation enhancer (SLS) were added and mixed uniformly for the few minutes duration. Finally, the drug was incorporated with continuous stirring to mix well. The resultant homogenous dispersion was spread over a backing membrane. The prepared films were cut to size, wrapped in aluminum foil and stored in the desiccator for further study. Table 1 describes the composition in formulating the transdermal patches.

Evaluation of Transdermal Patches

Small patches of 2.54 cm^2 area were cut from the stored films and the evaluation of various parameters was carried out on the patches.

Weight Variation

The patches were subjected to mass variation by individually weighing randomly selected patches. Such determinations were carried out for each formulation.

Thickness

The thickness of each patch was measured by using screw gauge at different positions of the patch and the average was calculated.

Folding endurance

Folding endurance was determined by repeatedly folding one patch from the same place till it broke. The number of times the film could be folded from the same place without breaking/ cracking gave the value of folding endurance.

Percentage moisture content

The prepared transdermal films were weighed individually and kept in desiccators containing fused calcium chloride at room temperature for the duration of 24 hours. After 24 hours, the films were re-weighed and the percentage moisture content was determined by the given formula

Percentage of moisture content = Initial weight – Final weight x 100/Initial weight

Drug content determination

For determining the drug content, an area of 10 cm^2 of the patch was cut and dissolved in 10 ml of phosphate buffer (pH 7.4). After that, 0.1 ml volume was withdrawn from the solution and diluted with the phosphate buffer to 10 ml in a volumetric flask. The absorbance of the solution was taken at 277 nm by using UV spectrophotometer.

***In-Vitro* Permeation Study**

In-vitro permeation studies of the patches were carried out by using Franz diffusion cell with a receptor compartment capacity of 60 ml. The formulated patch of surface area of 0.64 cm^2 was placed in between the dialysis membrane and the donor compartment and then dialysis membrane was mounted between the donor and receptor compartment of diffusion cell. The receptor compartment of diffusion cell was filled with phosphate buffer saline pH 7.4. The

whole assembly was fixed on a magnetic stirrer and the solution in the receptor compartment was constantly and continuously stirred magnetic beads at 50 rpm; the temperature was maintained at 37±0.5°C. The 1 ml aliquots were withdrawal at different time intervals (0, 1, 2, 3, 4, 6 and 24 h) and analyzed the drug content by UV at 277 nm. The receptor phase was replenished with an equal volume of phosphate buffer (37°C) at each sample withdrawal, the cumulative amount of drug permeated per square centimeter of patches were plotted against time. Percent drug permeated and log % DRP was calculated and tabulated.

Results and Discussion

Preformulation studies

Preformulation testing is the primary step towards the rationale development of dosage forms of drug substance. It is an investigation of the physical and chemical properties of drug substance alone and when combined with excipients. The overall objective of preformulation study is to have information that is useful for the formulator in developing stable, effective and safe dosage form. The sensory organ (eye, tongue, skin and nose) have been used to perform the organoleptic evaluation of etodolac. The melting point has been determined using open capillary method and the result of the same is reported uncorrected for environmental factors (Table 2).

Compatibility study by FTIR

The FTIR spectrum of etodolac (figure 1a) exhibited significant peaks of C-N stretch, C=O stretch, C-O-C stretch, N-H and O-H stretch and the peaks were compared to the standard spectra available at NIST. No deletion of the characteristic peaks of etodolac was found in the FTIR spectrum of the physical mixtures of drug and polymer (figure 1b, 1c).

The calibration curve of etodolac was constructed in methanol at concentration range of 1.0-50.0 µg/mL. The λmax was found to be 277 nm and was used for all the analysis of drug (Figure 2).

Evaluation of transdermal patches

The evaluation of the patch was performed as per reported procedures and the result is reported in table 3.

The average weight of the patches (2.54 cm^2) was found to be ranging from 158 to 165 mg. The weights were found to be consistent in various patches of same batch. The thickness of the patches ranged from 0.245 to 0.346 mm and was found to be dependent on the polymer ratio. A higher concentration of HPMC in the polymeric matrix led to an increase in the thickness of the patch.

The folding endurance test results indicated that the patches did not break and maintained their integrity with general skin folding when applied. The thinner the film patches were found to be more flexible. The patches were able to withstand 43 to 78 folds at same place. It was also observed that the higher concentration of the hydrophilic polymer (HPMC) caused an increase in the flexibility of the patches.

All the formulations were able to incorporated uniform quantity of drug in them ranging from 98.5 to 99.2 %. The complete incorporation of drug in the patches was indication that the method adopted for formulation of the patches was able to produced patches with minimum variability.

The results of moisture content study revealed that increase in concentration of HPMC was

directly proportional to the moisture content in the patches with F6 exhibiting the highest moisture (7.25%) while F1 exhibiting the lowest (5.11%). The low moisture content in the patches suggests the formation of stable patches that do not become brittle and dried on storage.[14]

The *in vitro* release profile of etodolac from the patches was studied using Franz diffusion apparatus. The result revealed that the patches were able to sustain the release of drug for more than 24 h during the study. The drug was released ranging from 88.3 to 60.7 % in various formulations. It was found that as the concentration of HPMC increased in the formulation, the release of drug decreased that may be attributed to the low movement of the poorly soluble drug in the hydrophilic matrix of the patch. The release data was mathematically and graphically explored for studying the type of release that the drug might follow from the patches. The data was subjected to kinetic modeling using zero order, first order, Higuchi and Kosemeyer-Peppas models (Figure 3-6).

The slope and regression coefficient of the drug released and the various applied kinetic models has been presented in table 4.

Conclusion

Etodolac exhibits great potential for administration via transdermal route for the treatment of several pain conditions. The objective of the present investigation was to evaluate the transdermal films of etodolac for its applicability to reduce the dosing frequency of the drug. It may be concluded that transdermal drug delivery system of etodolac can provides better compliance than conventional drug delivery system due to reduced dose and prolonged release of the drug. The patch formulation of etodolac can be of particular benefit for topical treatment of chronic pain conditions.

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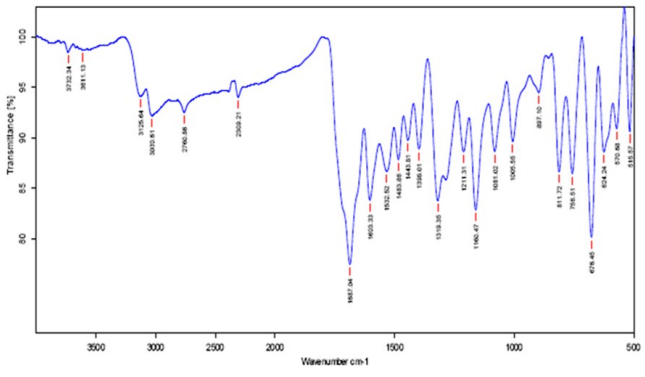

Figure 1 (A) FTIR spectra of etodolac

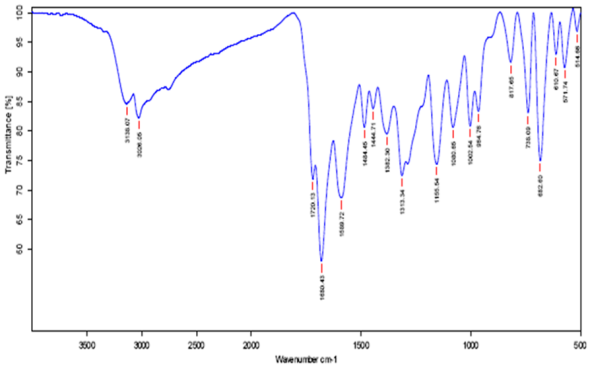

Figure 1(B) FTIR spectrum of HPMC + etodolac

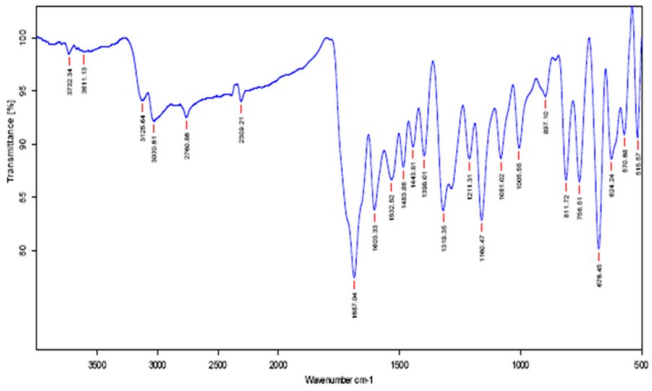

Figure 1(C) FTIR spectrum of EC + etodolac

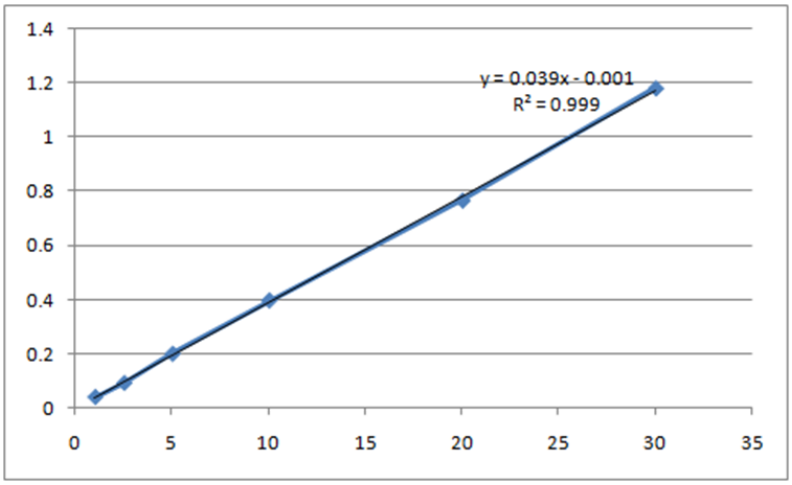

Figure 2 Calibration curve of etodolac in methanol

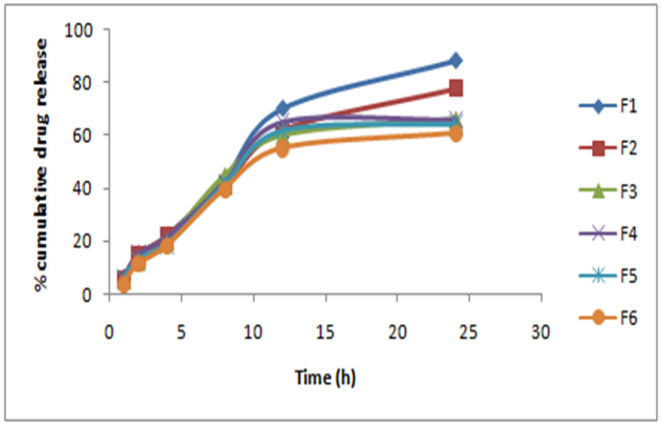

Figure 3 Zero order release graph of etodolac patches

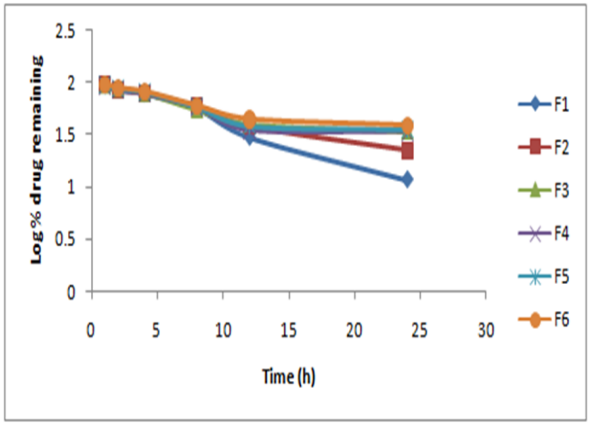

Figure 4 First order release graph of etodolac patches

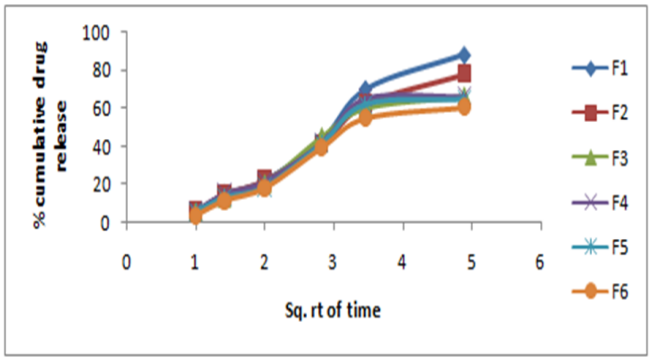

Figure 5 Higuchi release graph of etodolac patches

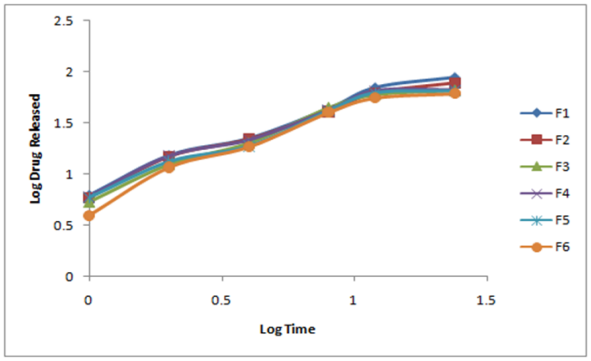

Figure 6 Korsemeyer-Peppas release of etodolac patches

Table 1 Composition of Transdermal patch formulations

S.No	For-mulation	Ratio of poly-mer (EC: HPMC)	Total wt. of Poly-mers (mg)	Solvent (DCM:methanol, 2:1) (ml)	Plasticizer (PEG-400) (mg)	Permea-tion en-hancer (SLS) (mg)	Etodolac (mg)
1	F1	8:2	1000	30	200	80	100
2	F2	7:3	1000	30	200	80	100
3	F3	6:4	1000	30	200	80	100
4	F4	4:6	1000	30	200	80	100
5	F5	3:7	1000	30	200	80	100
6	F6	2:8	1000	30	200	80	100

Table 2 Organoleptic features of etodolac

S. No.	Characteristic	Observed Results
1	Color and appearance	White, powder
2	Taste	Slightly Bitter
3	Odor	Odorless
4	Melting Point	148-151°C
5	Solubility	Soluble in methanol, chloroform; slightly soluble in ethanol; insoluble in water

Table 3 Physiochemical features of Transdermal Patches

	Thickness (mm)	Average weight (mg)	Moisture content (%)	Drug content (%)	Folding Endurance
F1	0.245	161	5.11	98.7	43
F2	0.261	165	6.18	99.2	45
F3	0.275	163	6.56	98.5	47
F4	0.315	158	6.73	98.9	53
F5	0.322	161	7.03	99.2	67
F6	0.346	159	7.25	99.1	78

Table 4 Statistical data of kinetic modeling of drug release from patch

	Zero Order		First Order		Higuchi		Korsemeyer-Peppas	
	Slope	R^2	Slope	R^2	Slope	R^2	Slope	R^2
F1	3.627	0.917	-0.040	0.986	22.3	0.971	0.846	0.977
F2	3.129	0.911	-0.027	0.976	19.34	0.975	0.811	0.973
F3	2.692	0.817	-0.020	0.876	17.13	0.927	0.829	0.957
F4	2.672	0.792	-0.020	0.818	17.04	0.903	0.776	0.949
F5	2.648	0.804	-0.019	0.838	16.83	0.910	0.796	0.956
F6	2.493	0.822	-0.017	0.872	15.85	0.931	0.877	0.946

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