Research Article

Formulation and *In-Vitro* Characterization of Zaltoprofen Transdermal Patch Using Different Polymers

A. Chatterjee*, S. Mohan, Himanshu M. Varshney, M. Jaimini, Bhupendra S. Chauhan
Department of Pharmaceutics, Jaipur College of Pharmacy, Sitapura, Jaipur, Rajasthan, India.
*Corresponding author's E-mail: a.chatterjee@mail.com

ABSTRACT

Transdermal Drug Delivery System can be considered as one of the most promising systems for the application of some of the active medicament to the site, particularly for the localized action. Increasing numbers of drugs are being added to the list of therapeutic agents that can be delivered to the systemic circulation through skin. Attempts were made to prepare transdermal patches of Zaltoprofen. The transdermal patch was prepared by solvent casting technique employing mercury as substrate. Various formulations were designed using HPMC K-100M, PVA, and PVP K-30 as matrix polymers, individually or in combination. PEG 400 and Propylene Glycol (PG) were employed as plasticizers and were incorporated in the concentration of 30% w/w in the formulations. The patch was characterized by various physicochemical characteristics viz. folding endurance, surface flatness, tensile strength and percentage moisture content, along with the *in vitro* drug release and skin permeation. Percentage cumulative amounts of the drug released in 12 h from each of the formulations were found to be in the range of 93.40 to 97.78 %. *In vitro* drug release was found to follow zero order kinetics. The transdermal patch of Zaltoprofen, a NSAID, was prepared to deliver the drug component through the intact skin. The patch were developed and evaluated for the drug release, and found to more convenient delivery system since it bypasses the hepatic drug metabolism.

Keywords: Hydroxy propyl Methyl Cellulose (HPMC K-100M), *In Vitro* Drug Release, Polyvinyl Alcohol (PVA), Polyvinyl pyrollidone (PVP K-30), Transdermal Drug Delivery, Zaltoprofen.

INTRODUCTION

The transdermal route for the administration of drugs has been identified as one of the potential route for the local and systemic delivery of the drugs. Transdermal route has various advantages over conventional modes of drug administration including the ability to avoid problems of gastric irritation, pH, and emptying rate effects and potentially avoids hepatic first pass metabolism and certainly improves patient compliance.[1] It excludes the variables that affect drug absorption from the gastrointestinal tract such as pH, enzymatic activity and drug food interactions.[2] This approach of drug delivery is more pertinent in case of chronic disorders, such as hypertension, which require long term dosing to maintain therapeutic drug concentration.[3] Although the highly organized structure of stratum corneum forms an effectual barrier to the penetration of the drugs into the skin, which must be modified/changed if poorly penetrating drugs are to be administered. The uses of various penetration enhancers have significantly increased the number of drug molecules suitable for the transdermal delivery.[4] The safest and the most widely employed penetration enhancer is water which enhances the hydration and reduces the resistance of the skin.[5, 6]

The present work is aimed at the development of transdermal drug delivery system of Zaltoprofen which is an anti-inflammatory drug. Zaltoprofen is a Non Steroidal Anti-inflammatory Drugs (NSAIDs) and fall under the class of propionic acid derivative, which has the powerful anti-inflammatory and analgesic effects on inflammatory pain. Zaltoprofen is a preferential COX-2 inhibitor, selectively inhibits PGE-2 production at the site of inflammation. Zaltoprofen specifically blocks the nociceptive response induced by bradykinin. Zaltoprofen inhibits the activation of COX-1, COX-2 and 12- LOX, which leads to the inhibition of bradykinin induced responses including the release of Substance-P. Therefore Zaltoprofen blocks the B2 receptor mediated signaling pathway on the primary sensory neuron without actually having any interaction with B2 receptors. The peak plasma levels of Zaltoprofen are obtained after 1.6 hours of intake. Zaltoprofen has a plasma half-life of 4 hours and is largely metabolized in liver. About 62 % of these metabolites are eliminated in the urine as conjugates and 3% is excreted in unchanged form. The plasma protein binding of Zaltoprofen is 99.6 %.[7, 8] The Matrix type transdermal patches were prepared by solvent casting technique employing a aluminium foil as a substrate by using the combinations of HPMC K-100M, PVP K-30 and PVA. The present work is aimed at developing a matrix dispersion type transdermal drug delivery of Zaltoprofen to ensure acceptable drug release with the use of optimum polymers or the combination of polymers and thereby to avoid first pass metabolism and achieve prolonged duration of action.

MATERIALS AND METHODS

Materials

Zaltoprofen was obtained as gift sample from IPCA Labs Ltd, Ratlam. PVP K-30 was purchased from CDH (P) Ltd., New Delhi and Aluminum foil was obtained from Hindalco

industries, Silvassa. PVA and HPMC were supplied by CDH Fine Chemicals, India. Polyethylene Glycol 400 and Propylene glycol were procured from Fischer Scientific, Mumbai and S.D. Fine Chemicals, Mumbai, respectively. All other chemicals used were of analytical grade.

Methods

Drug polymer interaction studies

The drug and polymer compatibility studies were carried out to check the compatibility between drug and various polymers. It was necessary to confirm that drug was not interacting with polymers under experimental conditions and shelf life.

UV analysis: The aqueous solutions of the pure drug and the patches containing Zaltoprofen were filtered through whatman filter paper and scanned for UV absorption between 200 and 400 nm.

FT-IR: Fourier Transform Infrared is the preferred method of infrared spectroscopy. In infrared spectroscopy, IR radiation is passed through a sample. Some of the infrared radiation is absorbed by the sample and some of it is passed through (transmitted). The resulting spectrum represents the molecular absorption and transmission, creating a molecular fingerprint of the sample. Like a fingerprint no two unique molecular structures produce the same infrared spectrum. This makes infrared spectroscopy useful for several types of analysis. Fourier Transform Infrared (FT-IR) spectrometry was developed in order to overcome the limitations encountered with dispersive instruments. *Sample Scanning:* The samples were scanned in 400-4000 wave number range, using KBr pellet technique.[9]

Differential Scanning Calorimetry: Differential Scanning Calorimetry (DSC) measures the temperatures and heat flows associated with transitions in materials as a function of time and temperature in a controlled atmosphere. These measurements provide quantitative and qualitative information about physical and chemical changes that involve endothermic or exothermic processes, or changes in heat capacity. Differential scanning calorimetry (DSC) monitors heat effects associated with phase transitions and chemical reactions as a function of temperature. In a DSC the difference in heat flow to the sample and a reference at the same temperature, is recorded as a function of temperature. The reference is an inert material such as alumina, or just an empty aluminum pan. The temperature of both the sample and reference are increased at a constant rate. Since the DSC is at constant pressure, heat flow is equivalent to enthalpy changes: and can be either positive or negative. In an endothermic process, such as most phase transitions, heat is absorbed and, therefore, heat flow to the sample is higher than that to the reference. Hence ΔdH/dt is positive. Other endothermic processes include helix-coil transitions in DNA, protein denaturation, dehydrations, reduction reactions, and some decomposition reactions. In an exothermic process, such as crystallization, some cross-linking processes, oxidation reactions, and some decomposition reactions, the opposite is true and ΔdH/dt is negative.[10]

DSC was carried out on Shimadzu DSC-60 at Temp range- 35^0C-300^0C; Rate – 20^0C per min; Atmosphere-Air.

Formulation of transdermal patches

The matrix type transdermal patches containing Zaltoprofen were prepared by solvent casting technique employing mercury as substrate.[11] The casting solutions were prepared by dissolving appropriate polymers and plasticizers in suitable solvents using magnetic stirrer for 20 min to get uniform dispersion. Plasticizers were added at a concentration of 30 % w/w of polymers. The solution was then transferred quantitatively to glass bangle kept wrapped with aluminum foil in petridish. Controlled solvent evaporation was achieved by placing an inverted funnel over the petridish. These were left undisturbed at room temperature for 24 hours. The patches were retrieved intact by slow lifting of the rings from the aluminum foil and were kept in the desiccator for the further evaluation (Table 1).[12]

Table 1: Composition of Zaltoprofen Transdermal Patches

Formulation Code	Drug Conc. (mg)	Polymer	Casting Solvent	Plasticizer
A1	80	HPMC:PVP K-30	Ethanol	_
A2	80	HPMC:PVP K-30	Ethanol	PG
A3	80	HPMC:PVP K-30	Ethanol	PEG 400
B1	80	PVA:PVP K-30	Ethanol	_
B2	80	PVA:PVP K-30	Ethanol	PG
B3	80	PVA:PVP K-30	Ethanol	PEG 400
C1	80	HPMC:PVA	Ethanol	_
C2	80	HPMC:PVA	Ethanol	PG
C3	80	HPMC:PVA	Ethanol	PEG 400

Characterization of Zaltoprofen transdermal patches

The prepared transdermal patches were evaluated for uniformity of thickness, weight variation, percent flatness, tensile strength, hardness, folding endurance, drug content uniformity, surface pH, and *in vitro* permeation.

Thickness

The thickness of transdermal patches was measured at three different places using a micrometer and the average values were calculated.[13]

Weight variation

Weight variation was determined by weighing three patches individually, from each batch and the average weight was calculated.[14]

Flatness

The constriction of patches cut out from a drug loaded matrix patch is an indicator of its flatness. Longitudinal strips were cut out from the prepared medicated patch, the lengths of each strip were measured and then variation in the lengths due to the non-uniformity in flatness was measured. Flatness was calculated by measuring construction of strips and a zero percent constriction is equal to a hundred percent flatness.

$$Constriction\ (\%) = l1 \text{-} l2/ l2\ x\ 100$$

Where l_1 = initial length of each strip, l_2 = final length of each strip.[15]

Tensile strength

Mechanical properties of the polymeric patches were conveniently determined by measuring their tensile strength.[16] The tensile strength of the patches was determined by using a tensile strength instrument. Average reading of three patches was taken as the tensile strength. The transdermal patch was fixed to the assembly, the weights required to break the patch was noted, and simultaneously elongation was measured with the help of a pointer mounted on the assembly and calculated the tensile strength of the patch using the following formula

$$T.S. =\ break\ force/\ a.b\ (1 + \Delta L/L)$$

Where a, b and L are width, thickness and length of the patch respectively.

ΔL is the elongation of patch at break point.

Break force = Weight required to break the patch (Kg) [16]

Hardness

Hardness test was performed on three different patches individually from each batch by fabricated hardness instrument and the average was calculated. Hardness apparatus consists of a wooden stand of 8 cm in height, and a top area of 8 x 8 cm. A hole of 0.2 cm diameter was made in the centre of the wooden top. A small plastic pan was fixed horizontally on to one end of a 2 mm thick smooth iron rod, whose other end had been reduced to sharp point. This rod, having the pan on its upper end, was inserted into the hole of the wooden top and its lower sharp end was placed on a metal plate.

An electric circuit was made through a 3-volt battery in such a way that the bulb lighted up only when the circuit was completed through the contact of the metal plate and the sharp end of the rod. The sample patch was placed between the metal plate and the sharp end of the iron rod and weights were gradually added on to the pan and the total weight required to penetrate the patch, which was indicated by the lighted bulb, was noted. [17]

Folding Endurance

The folding endurance was measured manually for the prepared patches. It is expressed as number of times the patch is folded at the same place either to break the patch or to develop visible cracks. This is important to check the ability of sample to withstand folding. This also gives an indication of brittleness. [18]

Moisture Uptake

Weighed films were kept in a desiccator at room temperature for 24 h. These were then taken out and exposed to 65% relative humidity using saturated solution of Potassium chloride in a desiccator until a constant weight was achieved. % moisture uptake was calculated as given below. [19]

$$\% \ moisture\ uptake$$
$$= \{(Final\ weight - Initial\ weight)$$
$$/\ Initial\ weight\} \ X\ 100$$

Drug Content Uniformity

In order to determine the uniform distribution of the drug in the patches, the content uniformity test was carried out employing the pharmaceutical standard by means of a UV/Visible spectrophotometer. The transdermal patch of specified area (3.14 cm²) was dissolved in 100 ml pH 7.4 phosphate buffer. This was then shaken in a mechanical shaker for 2 hour to get a homogeneous solution and filtered. A blank was performed using a drug free patch treated similarly. The drug content in each formulation was determined by measuring the absorbance at 338.80 nm after suitable dilution using a UV/visible spectrophotometer. [20]

In vitro permeation study

The *in vitro* skin permeation from the prepared polymeric patches across the cellophane membrane was studied using a modified Keshary Chien diffusion cell. [21] The receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4. It was placed on a magnetic stirrer for uniform distribution. The patches to be studied were placed in between the donor and the receptor compartment in a way that the drug releasing surface faced toward the receptor compartment. The samples were withdrawn at different time intervals and analyzed for drug content spectrophotometrically at 338.80 nm. The cumulative percent drug permeated at various time intervals were calculated and plotted against time.

RESULTS AND DISCUSSION

Analysis of Drug

The identity of the compound was confirmed by comparison with an authentic sample and verifying the presence of functional groups in an unknown molecule was done by IR spectra. The IR spectrum was analyzed for important chromophoric groups. The FTIR spectra showed peaks at 2978, 2716, 2685, 1710, 1670 and 1281 cm^{-1}. The peaks are shown in fig. and DSC thermogram of Zaltoprofen showed a sharp peak at 136.5^{0}C (Figure 1-3).
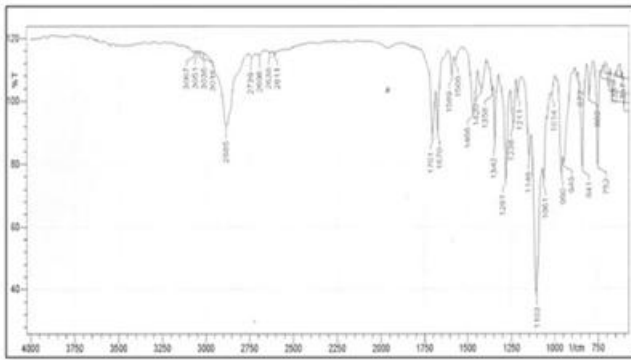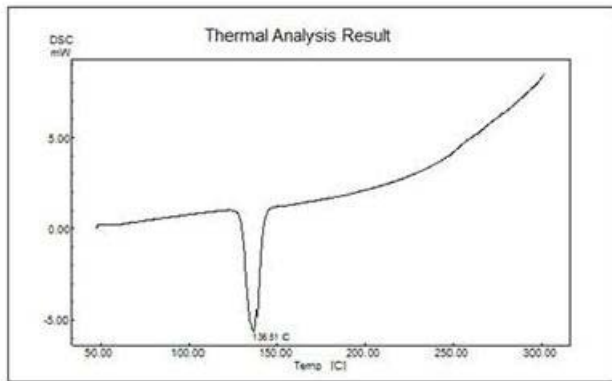
Figure 1: FT-IR of pure Zaltoprofen

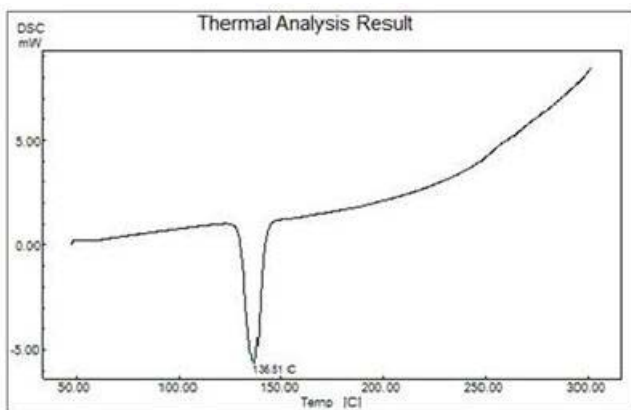**Figure 2:** DSC Curve of pure Zaltoprofen

Figure 3: DSC Curve of optimized formulation

Drug-excipient compatibility study

Compatibility of drug and excipient was determined by FT-IR analysis of the respective drug and polymer. It was found that there was no significant interaction between the drug and the excipient (Figure 4).

Evaluation of prepared film

Matrix type transdermal patches of Zaltoprofen were prepared using HPMC K-100M, PVA and PVP K-30 as film formers by solvent casting method using ethanol as solvent. Incorporation of PG and PEG 400 at a concentration of 30% w/w as a plasticizer yielded smooth and flexible patches. No interaction was found between the drug and polymers.

The physicochemical evaluation study reveals that all formulations measured weight and thickness with low SD values. Flatness study showed that none of the formulations had the difference in the strip lengths before and after longitudinal cut, suggesting 100% flatness, and thus they could maintain a smooth surface when applied onto the skin. The folding endurance measures the ability of patch to withstand pressure and it was found to be satisfactory. The result indicated that the patches would not break and would maintain their integrity with general skin folding when used.
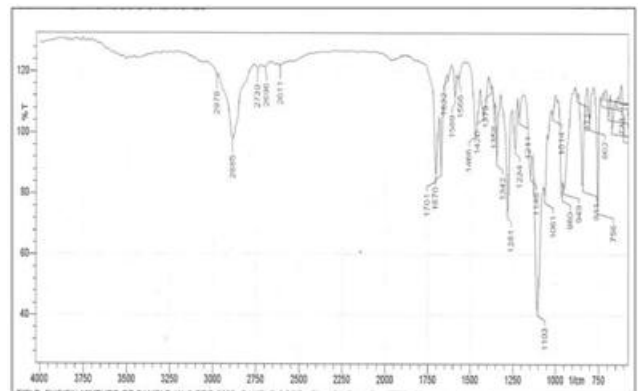

Figure 4: FT-IR Spectra of polymer and Zaltoprofen

Patches require certain amount of hardness to withstand the mechanical shocks in handling, packaging and at the time of application. The hardness of the patch varied from 230 gm. to 254 gm. Uniform drug distribution is one of the important characteristics of a transdermal patch that ensures the uniform reproducible sustained release of the drug from the patch. Estimation of drug content suggested that the drug is uniformly distributed all over the patches (Table 2).

In-vitro Characterization

Release of the drug from transdermal patches was found to be controlled by the physiochemical properties of the drug and delivery form, as well as physiological and physicochemical properties of the biological membrane.
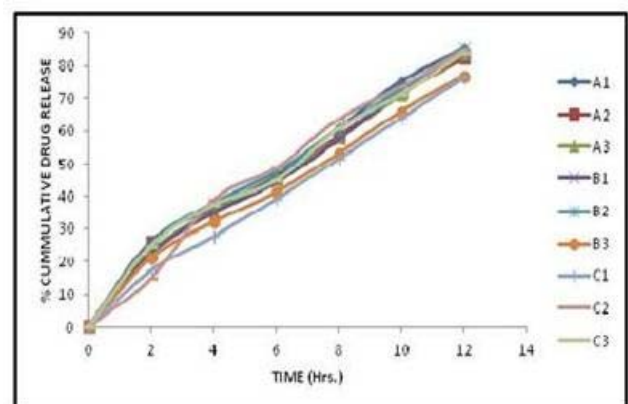

Figure 5: Zero Order Release

The cumulative percent drug permeation was found to be higher in case of PVP K-30 and PVA containing polymer matrix having PG as plasticizer. The cumulative percent of

drug released from formulations of A series was 85.07 %, 82.50 % and 83.69 % from A1, A2, A3 respectively. From B series the cumulative release was 83.73 %, 85.45 % and 76.81 from B1, B2, and B3 respectively. For Formulation series C, it was found to be 76.34 %, 84.91 % and 83.81 % from C1, C2, and C3 respectively. The cumulative percent

drug permeation was found to be higher in case of PVP K-30 and PVA containing polymer matrix having PG as plasticizer i.e. formulation code B2 was found to have maximum release and was found to be more optimized (Figure 5-8).

Table 2: Characterization of Transdermal Patches

| Formulation Code	Thickness (mm)	Weight Variation (mg)	Tensile Strength (kg/mm^2)	Hardness	Folding Endurance	Moisture Uptake (%)	Drug Content (%)	Flatness (%)
A1	0.303±0.004	153.1 ± 1.25	0.473 ± 0.036	250 ± 3.09	272	4.77 ± 0.01	74.54	100
A2	0.318±0.001	155.1 ± 1.45	0.449 ± 0.057	230 ± 3.54	289	4.29 ± 0.08	79.83	100
A3	0.352±0.003	151.1 ± 1.23	0.394 ± 0.046	238 ± 4.43	289	5.04 ± 0.03	76.74	100
B1	0.334±0.001	158.4 ± 1.35	0.409 ± 0.035	254 ± 4.16	248	5.43 ± 0.05	75.34	100
B2	0.331±0.002	157.1 ± 1.05	0.426 ± 0.071	238 ± 4.43	246	5.25 ± 0.03	76.15	100
B3	0.341±0.002	159.1 ± 1.25	0.386 ± 0.055	240 ± 3.54	259	5.12 ± 0.07	80.42	100
C1	0.327±0.002	148.1 ± 1.23	0.473 ± 0.036	241± 4.16	255	4.04 ± 0.03	74.59	100
C2	0.332±0.003	149.1 ± 1.23	0.426 ± 0.071	240 ± 3.54	248	4.22 ± 0.03	76.12	100
C3	0.334±0.001	147.1 ± 1.23	0.386 ± 0.055	237 ± 3.54	248	4.21 ± 0.03	75.66	100
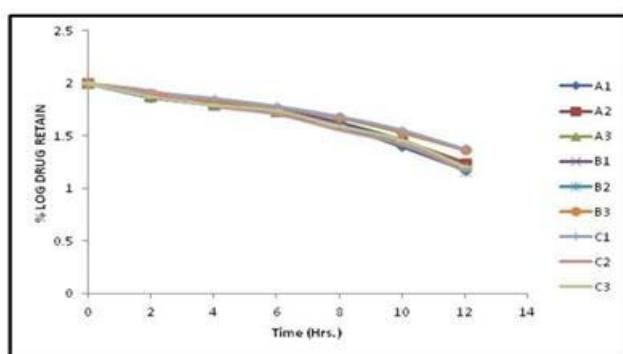
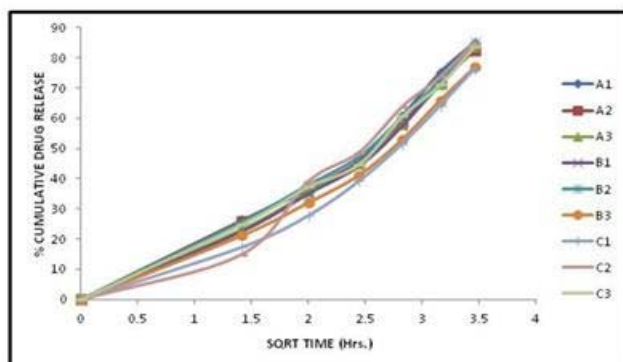
Figure 6: First Order Release Plot
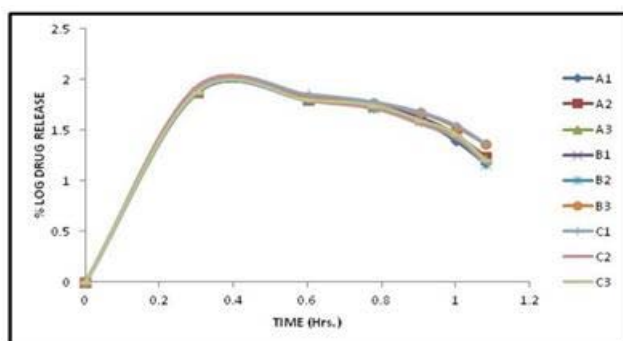

Figure 7: Higuchi Release Plot

Figure 8: Korsmeyer-Peppas Release Plot

CONCLUSION

From the above evaluation studies of the transdermal patches, it may be concluded that transdermal drug delivery system of Zaltoprofen can be designed and formulated, which can provides better compliance than conventional drug delivery system.

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