

FORMULATION AND CHARACTERIZATION OF DRUG IN ADHESIVE TRANSDERMAL PATCHES OF DICLOFENAC ACID

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ABSTRACT

The purpose of this research was to develop a matrix-type transdermal therapeutic system containing drug Diclofenac acid, Pressure Sensitive Adhesive (PSA) like acrylic adhesive by the solvent evaporation technique. Different concentrations of Labrasol, oleic acid and triacetin were used to enhance the transdermal permeation of diclofenac acid. Polyethylene monolayer film as a backing membrane and Silicone coated polyester film as a release liner preferred in preparation of transdermal patches. Formulated transdermal patches were physically evaluated with regard to percentage moisture absorption, thickness, weight variation, drug content, tensile strength, % elongation, folding endurance. All prepared formulations indicated good physical stability. *In vitro* skin permeation studies of formulations were performed by using Franz diffusion cells. Formulation containing 5% drug, 85% adhesive solution and 10% triacetin as permeation enhancer showed best *in vitro* skin permeation through human cadaver skin as compared to all other formulations. The results rate was found to follow zero order kinetics. These results indicate that the formulation F3 has shown optimum release in concentration independent manner. Stability study indicates that drug remains stable for six months and primary irritation study indicated that the transdermal patches are non-irritant.

Keywords: Transdermal Patch, Diclofenac acid, Pressure Sensitive Adhesive (PSA), Permeation enhancer, Stability.

INTRODUCTION

A recent approach to drug delivery is to deliver the drug into systemic circulation at predetermined rate using skin as a site of application. Transdermal drug delivery is one of the most promising methods for drug application. Increasing numbers of drugs are being added to the list of therapeutic agents that can be delivered to the systemic circulation via skin. The success of transdermal therapeutic system has created much interest in the pharmaceutical industry and has activated research activities related to it¹⁻². Transdermal delivery has many advantages over conventional modes of drug administration, it avoids hepatic first pass metabolism, potentially decreases side effects and improves patient compliance³. Drug delivery with transdermal patch systems exhibit slow, controlled drug release and absorption. The plasma drug concentration does not vary significantly over time. Transdermal delivery system is a growing market that is expected to expand in the near future with the discovery of new drug treatment applications and technologies⁴.

Diclofenac, one of the non-steroid anti-inflammatory drugs, shows therapeutic efficacy by means of inhibiting a biochemical reaction path which is necessary for the biosynthesis of a pain inducer, prostaglandin. Diclofenac acid is a drug which has the effects of pain

relief, antifebrile and anti-inflammation and is widely applicable in rheumatic arthritis, osteoarthritis, spastic spondylitis, acute gout and inflammation or gout of lesion after operation. However, diclofenac acid is orally administered for a long period of time; a peptic ulcer is induced along with other side effects such as anemia by hemorrhage. Transdermal route can by pass the first pass metabolism; also it is noninvasive and no chance of premature termination of therapy. So, transdermal delivery of diclofenac can overcome all the problem of conventional dosage forms⁵⁻⁷.

In the present investigation, twelve different formulations were formulated using different concentration of diclofenac acid, adhesive and permeation enhancers by solvent evaporation technique. The transdermal patches were evaluated for their physicochemical characteristics such as thickness, weight variation, tensile strength, folding endurance, content uniformity, permeability characteristics and stability studies.

MATERIALS AND METHODS

Diclofenac acid was purchased from Seva Fine chemicals, Ahmedabad. Triacetin and oleic acid were purchased from Merck chemicals limited. Pressure Sensitive Adhesive solution (Acrylate adhesive) was gifted from National Starch & Chemical Co.

Table 1: Composition of Tansdermal Patch

Formulation Code	Drug %*	Acrylic adhesive %w/w	Labrasol %*	Oleic Acid %*	Triacetin %*
F1	5%	85%	10%	-	-
F2	5%	85%	-	10%	-
F3	5%	85%	-	-	10%
F4	7.5%	85%	7.5%	-	-
F5	7.5%	85%	-	7.5%	-
F6	7.5%	85%	-	-	7.5%
F7	10%	80%	10%	-	-
F8	10%	80%	-	10%	-
F9	10%	80%	-	-	10%
F10	10%	85%	5%	-	-
F11	10%	85%	-	5%	-
F12	10%	85%	-	-	5%

*Based on solid content of adhesive solution

Preparation of Transdermal Patches

Accurately weighed diclofenac acid was dispersed in permeation enhancer solution in a 500ml stainless steel beaker. Adhesive solution was added to the drug-enhancer mixture and mixed properly using electric stirrer to prepare homogenous mixture. The above mixture was sonicated for few minutes to make the solution clear. The patch was prepared by casting the above mixture on release liner (Silicone coated polyester film) and allowed to dry at room temperature over night. The dried patches were laminated and cut into 9.61 cm² area and stored in polyethylene bag at 40°C/75% R.H. till the further evaluation.

Evaluation of Transdermal Patches

Drug-Excipient Compatibility Study

Drug-Excipient compatibility study was carried out on the basis of crystallization study. Crystallization study was carried out using different concentrations of drug, permeation enhancer and acrylic adhesive as shown in table 1. First of all, transdermal film was prepared in petridish using drug, permeation enhancer and adhesive solution and kept at 50°C/80% R.H. conditions for 1 month. Transdermal patches were observed for drug crystals by electron microscope and Scanning Electron Microscope.

The Transdermal patches were also evaluated for their physicochemical characteristics such as percent moisture absorption, thickness, weight variation, tensile strength and %elongation, folding endurance, content uniformity, permeability characteristics, skin irritation and stability studies.

Percent moisture absorption

The percent moisture absorption test was carried out to check the physical stability and integrity of the patches at high humid conditions. In the present study the moisture absorption capacities of the films were determined in the following manner. The patches were placed in dessicator containing saturated solution of aluminum chloride, keeping the humidity inside the dessicator at 80% R.H. After 3 days the films were taken and weighed the percentage moisture absorption of three films was found⁸.

$$\% \text{ Moisture absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Thickness

The thickness of the patches was measured at three different places using a screw gauge and the average was calculated⁹.

Weight variation

Each patch was weighed individually and average weight of three patches was found¹⁰.

Tensile strength and % Elongation

Tensile strength is the maximum stress applied to a point at which the film breaks. Elongation is defined as a measure of the capacity of a patch to deform prior to failure. Tensile strength and percent elongation of the patches were determined on tensile strength testing apparatus. Rectangular patch strips of 25.4mm X 50mm were fixed between the jaws of the instrument. The load on the strip was gradually increased to a maximum at a speed of 50mm/min. and the change in the length of the strips that occurred with increasing stress was measured. Tensile strength and percent elongation of three patches of each batch were measured¹¹.

Folding endurance

The folding endurance was measured manually for the prepared patches. It is expressed as number of times the film is folded at the same place either to break the film or to develop visible cracks. Folding endurance of the film was determined repeatedly by folding a small strip of film (2x2cm) at the same place till it breaks. The number of times the film could be folded at the same place without breaking gives the value of folding endurance¹².

Drug content

The content uniformity from patch to patch of the same batch was determined by removing the protective release liner and the patch was portioned out by cross cuts from each other. A sample cut patch was introduced into a 100 ml conical flask, 40 ml of methanol was added and vigorously agitated in a shaking apparatus for 15min and exposed in an ultrasound bath for 15min. Methanolic extract was poured into a 100 ml volumetric flask and extraction was repeated twice with 20 ml of methanol and the volumetric flask was made up to the mark with methanol. The concentration of diclofenac acid was determined by the following HPLC method: column, Licrospear (250 x 4.6 mm I.D., 5 µm); mobile phase (Methanol : Phosphate buffer pH 7.4 (50:50)); flow rate, 1.0 ml/min; column temperature, ambient temperature; internal standard, diazepam; detection wavelength, 280 nm; injection volume, 100 µl; Retention time, (9 min); Run time, (15 min).

In vitro drug permeation study

The skin samples were obtained from the abdomen of human cadavers within 48 hr of death. The skin samples were soaked in hot water and stored at -30°C until used. The skin samples were taken out of the freezer and allowed to remain at room temperature. Once they thawed out, the skin samples were soaked in normal saline for 30 min. and carefully checked for any macroscopic damage using a magnifying glass. A square section of the skin was positioned between two half of the cell with the stratum corneum side facing the donor compartment and the diffusion cell was made watertight by using a clamp and the excess skin trimmed off using scissors. *In vitro* release of diclofenac acid from various matrix systems was studied using Franz diffusion cell using human cadaver skin. The diffusion medium used during *in vitro* release study was phosphate buffer saline solution pH 7.4. The drug containing film with a support of backing membrane was kept in the donor compartment. The donor and receptor compartment hold together using clips of strong grip. The receptor compartment containing dissolution medium was maintained at 32 ± 5°C. The diffusion medium was stirred with magnetic bar to prevent the formation of concentrated drug solution layer below the standard membrane. The amount of drug permeated into the receptor solution was determined by removing 1ml of sample at fixed interval up to 24hrs. The withdrawn volume was replaced with an equal volume of fresh buffer solution. Permeation of the drug was determined by using HPLC method¹³.

Primary skin irritation Study

The patches were tested for their potential to cause skin irritation in healthy human volunteer. Placebo patches were applied to the 8 healthy volunteer and observed for any sign of redness, itching, erythema and edema for a period of 24 hr^{14, 15}.

Stability study

The developed transdermal patches were sealed in polyethylene-coated aluminum foils and kept at 25°C/65% R.H. & 40°C/75% R.H. for six months. The drug content of these patches was determined at different time interval in triplicate and patches was visually inspected for any physical changes brought about on storage.

RESULT AND DISCUSSION

Transdermal patches of diclofenac acid were prepared by solvent evaporation technique using acrylic adhesive to achieve a controlled release and improved bioavailability of diclofenac acid.

Crystallization of drug in a matrix significantly affects the efficacy and quality of the transdermal drug delivery system. Therefore, the cause and control of drug crystallization is of particularly interest in the development of efficient transdermal delivery systems. Microscopically examination of formulation F1 to F12 has shown that as the concentration of drug increases from 5 to 10%, drug was crystallized out in transdermal patches. Formulation F4 to F12 containing 7.5% to 10% of drug has shown drug crystal (Figure 1) in patch after some period while in formulation F1 to F3 containing 5% of drug, crystallization was not observed.

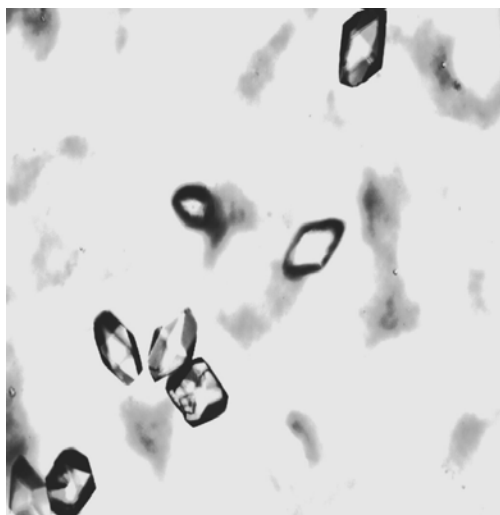


Fig. 1: Microscopic photograph of transdermal patch containing drug crystals

The prepared formulations were subjected to various physicochemical characteristics such as percent moisture absorption, thickness, tensile strength, % elongation, folding

endurance, drug content, and weight uniformity. The results are shown in Table 2.

Moisture absorption is an important part for drug diffusion to the skin because it is showing the extent of water uptake of patch from body tissues as well as from environment during application period. With moisture absorption of the patch, it is also important that the patch retains its mechanical integrity. Here, all the batches show moisture absorption ~13% and ~9% at 80% R.H. and 50% R.H. respectively which found to be satisfactory.

The thickness of the patches varied from 0.138 ± 0.0032 to 0.143 ± 0.0023 mm. The minimum standard deviation values assured that the process used for preparing the delivery system is capable of giving reproducible results. This fact is further confirmed by drug content and weight uniformity studies. In order to evaluate the flexibility, the films were subjected to tensile strength, % elongation and folding endurance studies. The tensile strength and % elongation of the patches was found vary with the nature of the adhesive and also enhancers. It was found to vary between 24.88 ± 0.16 to 31.71 ± 1.07 N/25.4mm and 254.76 ± 10.05 to 286.60 ± 2.66 % respectively. The values of tensile strength and % elongation of the patches was very identical to the innovator product. The value of folding endurance was found to be greater than 250 in all batches. This revealed that the prepared patches were having capability to withstand the mechanical pressure along with good flexibility. Drug content in all formulation was observed within the range of 93.08 ± 1.47 to 98.97 ± 0.51 , which was found to be satisfactory.

Table 2: Evaluations of Diclofenac Transdermal Patches

Formulation Code	Mean Thickness (mm)*	Weight Variation (mg/10cm ²)*	Tensile Strength (N/25.4mm)*	% elongation*	Drug content*
F1	0.140 ± 0.0029	140.0 ± 2.68	30.00 ± 0.81	283.94 ± 1.97	93.08 ± 1.47
F2	0.143 ± 0.0023	142.8 ± 1.85	31.71 ± 1.07	254.76 ± 10.05	95.88 ± 0.37
F3	0.141 ± 0.0028	143.8 ± 1.89	24.88 ± 0.16	274.60 ± 12.62	98.97 ± 0.51
F4	0.142 ± 0.0020	141.2 ± 2.18	25.19 ± 1.32	286.60 ± 2.66	97.50 ± 0.43
F5	0.141 ± 0.0023	140.6 ± 2.04	26.85 ± 1.60	275.75 ± 1.90	98.90 ± 1.20
F6	0.139 ± 0.0033	141.8 ± 1.69	29.19 ± 1.43	280.15 ± 7.80	96.69 ± 0.92
F7	0.141 ± 0.0030	141.9 ± 1.88	27.85 ± 0.89	260.45 ± 5.54	94.30 ± 0.79
F8	0.139 ± 0.0014	139.6 ± 2.80	28.85 ± 1.40	277.56 ± 9.30	95.21 ± 0.48
F9	0.138 ± 0.0032	142.0 ± 1.29	29.93 ± 0.75	280.89 ± 4.76	95.55 ± 1.43
F10	0.139 ± 0.0028	141.0 ± 1.72	27.79 ± 1.10	267.76 ± 3.56	94.99 ± 0.65
F11	0.140 ± 0.0024	141.4 ± 0.78	25.64 ± 0.80	281.93 ± 4.23	97.77 ± 0.44
F12	0.142 ± 0.0012	140.4 ± 1.65	26.10 ± 1.30	275.30 ± 5.78	98.22 ± 0.65

* Data represent mean (S.D.) (n=3)

The formulated transdermal patches were subjected to *in vitro* skin permeation study across human cadaver skin using Franz diffusion cell. Formulation F1 to F3 was subjected to *in vitro* drug release study because other formulations F4 to F12 has shown drug crystals. From the figure 2, it is clearly observed that drug release was in controlled manner. The drug release profile of formulation F1 showed a slow initial permeation, followed by increase in

permeation and in the late times, the value was decreased. There was no significant variation in the drug permeation value of batch F2, F3 and innovator batch. Formulation with triacetin (F3) was showing higher permeation ($35.46 \mu\text{g}/\text{cm}^2/24\text{hr}$) than the innovator and formulation F2. To achieve maximum bioavailability of drug through skin, high *in vitro* drug release is necessary.

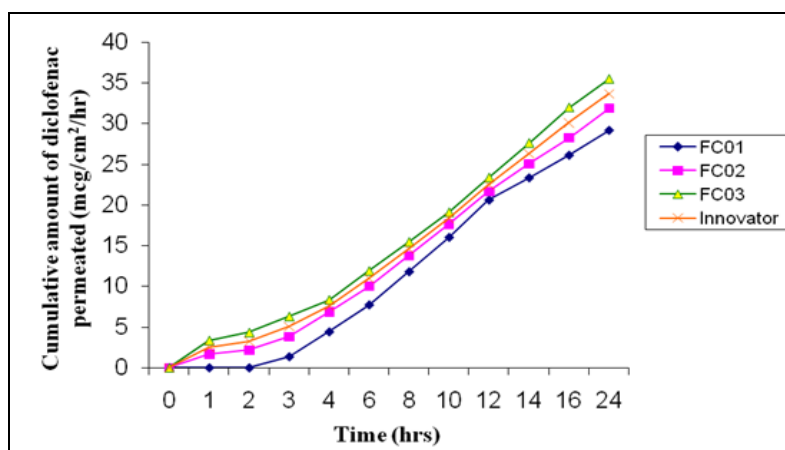


Fig. 2: Cumulative amount of drug release through skin

The skin irritation studies were also performed for the ideal patch (F3) to observe any visual skin irritation after the application of the patch to the humans. Patch does not cause any noticeable irritation on the skin throughout the study. Stability testing of formulation F3 was conducted for six months at different temperature conditions like 25°C/65% R.H. & 40°C/75% R.H. At specific interval of time, the patches were taken out to assay their drug content, appearance and texture and have shown satisfactory results.

CONCLUSION

Drug in adhesive type transdermal patches of diclofenac were prepared and the effects of various penetration enhancers on the permeation of diclofenac were studied. For this, Labrasol, Oleic acid and Triacetin were the permeation enhancers of choice for the percutaneous absorption of diclofenac. The adhesion properties of the patches were very satisfactory. Also, the prepared patches showed good uniformity with regard to drug content and drug release. Formulation F3 has achieved the targets of present study such as extended release, avoidance of first pass metabolism, reduced frequency of administration and thus may improve the patient compliance. In conclusion, the present data confirm the feasibility of developing diclofenac acid transdermal patches on an industrial scale.

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REFERENCES

- Misra AN. Controlled and Novel Drug Delivery. In: Jain NK, editors. *Transdermal Drug Delivery*. New Delhi, India: CBS Publisher and Distributor; 1997. p. 100-101.
- Chien YW. Transdermal therapeutic system. In: Robinson JR, Lee VHL. *Controlled Drug Delivery Fundamentals and Applications*. 2nd ed. New York: Marcel Dekker, Inc; 1987. p. 524-552.
- Keith AD. Polymer matrix consideration for transdermal devices. *Drug Develop Ind Pharm* 1983; 9: 605-621.
- Dittgen M. In: Muller, R.H. and Hildebrand, G.E. Eds., *Pharmazeutische Technologie, ModerneArzneiformen*, Wiss. Verl. Ges., Stuttgart; 1997. p. 81-104.
- Satoskar RS, Bhandarkar SD and Ainapure SS. In *Pharmacology and Pharmacotherapeutics*. 19th edition. Mumbai: Popular Prakashan; 2005. p. 171-173.
- Kriwet KM, uller-Goymann CC. Binary Diclofenac diethylamine-water systems, micelles, vesicles, and lyotropic liquid crystals. *Eur J Pharm Biopharm* 2002; 39(6): 234-238.
- Laurent B, Annette M, Jean-Pierre D Daniel-Henri M. Effects of diclofenac, aceclofenac and meloxicam on the metabolism of proteoglycans and hyaluronan in osteoarthritic human cartilage. *Br J Pharmacol* 2000; 131: 1413-1421.
- Kusum DV, Saisivam S, Maria GR, Depti PU. Design and evaluation of matrix diffusion controlled Transdermal patches of Verapamil Hydrochloride. *Drug Develop Ind Pharm* 2003; 29(5): 495-503.
- Amnuaitik C, Ikeuchi I, Ogawara K, Higaki K, Kimura T. Skin permeation of propranolol from polymeric film containing terpene enhancers for transdermal use. *Int J Pharm* 2005; 289: 167-178.
- Udupa N, Koteswar KB, Vasantha kumar. Formulation and evaluation of captopril transdermal preparations. *Indian Drugs*; 29(15): 680-850.
- Kulkarni R, Doddappa H, Marihal SC, Patil CC, Habbu PV. Comparative evaluation of polymeric films for transdermal application. *The Eastern Pharmacist*. 2000; 93(516): 109-11.
- Devi VK, Saisivam S, Maria GR, Deepti PU. Design and evaluation of matrix diffusion controlled transdermal patches of verapamil hydrochloride. *Drug Develop Ind Pharm* 2003; 29: 495-503.
- Kakkar AP, Ajay Gupta. Gelatin based transdermal therapeutic system. *Indian Drugs*; 29 (7): 308-311.
- Bureau of Indian Standards, Indian Standard Institute, New Delhi, 1997, No 4011, p. 273.
- Dey S, Malgope A. Preparation of carvedilol transdermal patch and the effect of propylene glycol on permeation. *Int J Pharmacy and Pharmaceutical Sciences* 2010; 2(1) Suppl 1: 137-143.