IJPSR (2012), Vol. 3, Issue 04 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 24 November, 2011; received in revised form 24 February, 2012; accepted 20 March, 2012

PREPARATION AND CHARACTERIZATION OF CIPROFLOXACIN LOADED TRANSDERMAL PATCHES

Priyanka Rathore*, Ruchi Bhatia and Satish Nayak

Bansal College of Pharmacy, Bhopal, Madhya Pradesh, India

Keywords:
Ciprofloxacin,
Transdermal patch,
Permeation

Correspondence to Author:

Priyanka Rathore

Bansal College of Pharmacy, Bhopal,
Madhya Pradesh, India

ABSTRACT

The aim of this research was to formulate a matrix-type transdermal therapeutic system containing drug ciprofloxacin with different ratios of hydrophobic (ethyl cellulose) polymer by solvent evaporation technique, using 15% w/w of dibutyl phthalate to the polymer weight, incorporated as plasticizer. Different concentrations of isopropyl myristate were used to enhance the transdermal permeation of Ciprofloxacin. Formulated transdermal films were physically evaluated with regard to thickness, weight variation and drug content. All prepared formulations showed good physical stability. *In-vitro* permeation studies of formulations were performed by using Franz diffusion cells. Formulation T3 showed best *in-vitro* skin permeation through goat skin as compared to all other formulations. The release profile of the optimized formulation T3 indicated that the permeation of the drug from the patches was governed by a diffusion mechanism. Formulation T3 showed highest flux among all other formulations. These results indicate that the formulation containing highest amount of isopropyl myristate gives better penetration of ciprofloxacin through goat skin.

INTRODUCTION: Continuous intravenous infusion is recognised as a superior mode of drug administration not only to bypass a first mass metabolism but also to maintain a constant and prolong drug level in the body [1, 2].

A closely monitored intravenous infusion can provide the advantages of both direct entry of drug into the systemic circulation and control of circulating drug levels [3, 4]. However, such mode of drug administration entails certain risks and therefore necessitates hospitalization of the patients and close medical supervision of administration [5, 7].

So to provide continues drug infusion through an intact skin, several transdermal therapeutic systems have been developed for topical aplication on to the intact skin surface to control the drug delivery and its subsiquent permeation through the skin tissue [8, 9, 10].

Ciprofloxacin hydrochloride (3-quinoline carboxylic acid, 1- cyclopropyl- 6- fluoro- 1, 4- dihydro- 4- oxo- 7- (1-piperazinyl)-, mono-hydrochloride, monohydrate) (CP) is a quinolonecarboxylic acid derivative with high antibiotic activity against gram-positive and gram-negative bacteria.

The development of a controlled release system for CP is very interesting for post-surgery prophylaxis, for combating skin infections, soft tissues, joints and bones. Inhibition of topoisomerase (DNA gyrase) enzymes, which inhibits relaxation of super coiled DNA and promotes breakage of double stranded DNA.

MATERIAL AND METHODS: Ciprofloxacin was purchased from Druid Pharma Limited, Kolkata, India. Ethyl cellulose was a generous gift from Maan Pharmaceuticals Ltd., Ahmedabad, India. Dibutyl pthalate and isopropyl myristate were procured from Sigma chemicals Ltd. All other chemicals and solvents were of analytical reagent grade.

Preparation of Transdermal Patches: Transdermal patches containing ciprofloxacin were prepared by solvent evaporation techniques in glass petri plate. The backing membrane was casted by pouring a 1.5% (m/v) polyvinylalcohol (PVA) solution followed by drying at 60^{o}C for 6 hrs. Drug reservoir was prepared by dissolving ethyl cellulose (EC) in choroform : methanol (1:1) mix. 15%w/w Dibutylpthalate was used as the plasticizer. The drug 100mg (chloroform: methanol) was added into the homogenous dispersion under slow stirring with a magnetic stirrer. The uniform dispersion was casted on PVA backing membrane and dried at room temperature. The film was stored in a desiccator [6, 14].

Physicochemical Characterization of Films [11, 13, 15]:

Thickness: Micrometer was used to calculate the thickness of the patches and mean values were calculated**.**

Weight Variation: Weight variation was determined by individually weighing randomly selected patches.

Drug Content: Patches of specified area (1 cm^2) were dissolved in 5 mL of dichloromethane and the volume was made up to 10 mL with phosphate buffer (pH 7.4); dichloromethane was evaporated using a rotary vacuum evaporator at 45°C. A blank was prepared using a drug-free patch treated similarly. The solutions were filtered through a 0.45 µm membrane, diluted suitably and absorbance was read at 274nm in a double beam UV-Vis spectrophotometer.

In-vitro **Drug Release Profile:** The dissolution test was performed using a U.S.P. Pharmacopoeia dissolution paddle apparatus using glass beaker containing 900 ml phosphate buffer (pH 7.4) and a paddle speed of 50 rev/min. The patch was tied with the help of thin copper rod and was carefully placed at the bottom centre of the vessel [12]. The paddles were lowered to a height 2.5 cm above the patches.

The apparatus was equilibrated to 37±0.5^{o}C, the temperature of the skin surface. Five millilitres samples were collected at appropriate time intervals up to 12 h and consequently sink conditions were maintained and the determination of the ciprofloxacin content was per- formed by UV spectrophotometer at 277nm against blank. Thus, cumulative percent drug release against time were plotted [16-19].

In-vitro **Permeation Procedure:** The *in-vitro* permeation studies were conducted using vertical type Franz diffusion cell having a receptor compartment capacity of 50 ml. The excised goat skin was mounted between the half cells with the dermis in contact with the receptor fluid (phosphate buffer pH 7.4) and was equilibrated for 1 hour. The area available for diffusion was about 1.21cm^2. The donor cell was covered with an aluminium foil to prevent evaporation of vehicle. The fluid in the receptor compartment was maintained at 37±0.5^{o}C. Under these conditions the temperature of the skin surface was approx. 32^{o}C.

Patches with a surface area of 3 cm^2 were cut by a punch, and then applied to the epidermal side of the skin with a slight pressure, and the holders containing the skin and formulation were then placed on diffusion cells using a spring clamp. The receiver compartment of each cell was filled with 2.5 ml phosphate buffer (pH 7.4). Samples were withdrawn (2ml each time) periodically from the receiver cell and an equal volume of phosphate buffer was added to keep the volume constant and the ciprofloxacin content determined by UV at 277nm. Each experiment was carried out for 10 h to achieve a steady permeation rate.

Data Analysis: The cumulative amount of ciprofloxacin permeated through the skin was plotted as a function of time. The slope of the linear portion of the plot was calculated as the flux. The lag-time was determined by extrapolation of the linear portion of the cumulative amount of drug permeated versus the time on the abscissa.

TABLE 1: COMPOSITION OF TRANSDERMAL PATCHES

Ingredients	Formulation codes		
	T1	T2	T3
Ciprofloxacin	100mg	100mg	100mg
Ethyl cellulose	150mg	200mg	250mg
Dibutylpthalate	20%w/w of total polymer	20%w/w of total polymer	20%w/w of total polymer
Methyl alcohol: chloroform	01:02:00	01:02:00	01:02:00
Isopropyl myristate	5.00%	10.00%	15.00%

Note: 20%w/w of dibutyl phthalate to the polymer weight, incorporated as plasticizer

RESULTS AND DISCUSSIONS:

Physicochemical Characterization of Films: The results of the physicochemical characterization of the patches are shown in **Table 2**. The thickness ranged between 150+4.12 and 180+5.51µm, which showed their uniformity in thickness. Slight changes in weights among the patches was observed with all formulations and ranged from 12+0.37 mg and 10.45±0.35 mg. Drug content ranged from 96.2±2.14% to 98.1±2.94%, which indicates good uniformity among all formulations. This result indicates that the process employed to prepare patches in this study was capable of producing patches with uniform drug content and minimal patch variability.

TABLE 2: PHYSICOCHEMICAL CHARACTERIZATION OF DIFFERENT TRANSDERMAL PATCHES

Parameters	T1	T2	T3
Thickness (µm)	150+4.12	165+4.35	180+5.51
Weight variation (mg)	12+0.37	10.11+0.30	10.45+0.35
Drug Content (%)	96.2+2.14	97.6+2.93	98.1+2.94

In vitro drug release profile of the different transdermal formulations were determined in phosphate buffer saline (pH 7.4) and the formulations showed a sustained release profile up to 10 hrs. (**fig. 1**). Ciprofloxacin was released steadily with lower burst effect *in-vitro*. *In-vitro* drug permeation studies were conducted and higher permeation was observed after 10 hrs with different formulation (T1, T2, T3). This can be attributed to a well known permeation enhancer properties. The maximum amount of CP that permeated during the 10 hr of the study was 96.64% from formulation T3 (**fig. 2**). The flux was calculated by dividing the cumulative amount of drug permeated per cm^2 of the skin with time.

The corresponding flux values were ranging from 2.538 to 2.857 µg cm^{-2} hr^{-1}. Formulation T3 shows highest flux among all the formulation (**table 3**). Formulation T3 shows 1.21 fold enhancements in drug permeation. This result indicate that the formulation containing 15% Isopropyl myristate give better penetration of CP through goat skin.

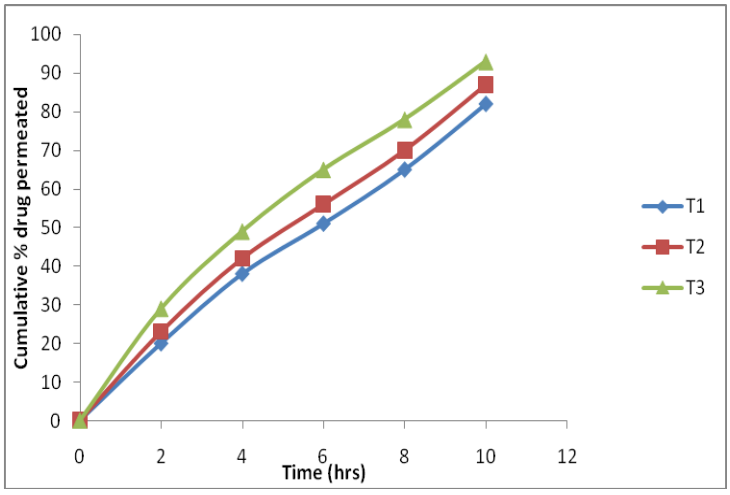

FIG. 1: *IN-VITRO* DRUG RELEASE PROFILE OF TRANSDERMAL PATCHES LOADED WITH CIPROFLOXACIN

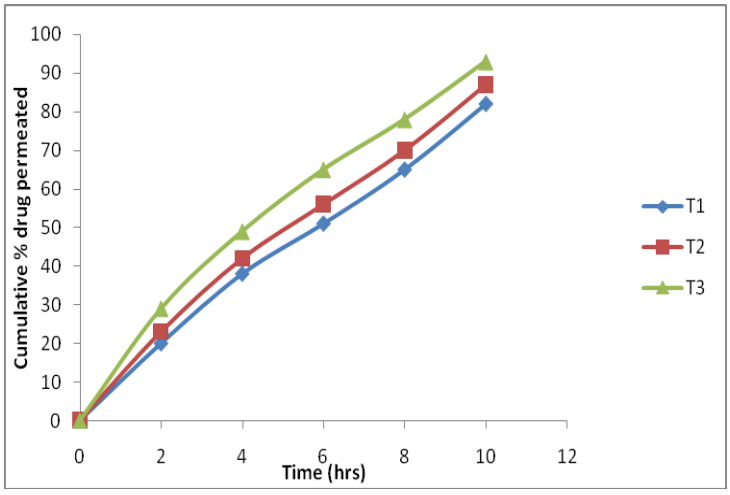

FIG 2: *IN-VITRO* PERMEATION STUDIES OF TRANSDERMAL PATCHES LOADED WITH CIPROFLOXACIN

TABLE 3: DATA ANALYSIS OF PERMEATION STUDIES

Formulations code	Steady state flux (µg/h cm^2)	Permeability coefficient (cm/h)	Diffusion coefficient (cm^2/s)
T1	2.538	0.00005076	0.00000021
T2	2.684	0.00005368	0.00000024
T3	2.857	0.00005714	0.00000027

CONCLUSION: It could be concluded that the transdermal patches have potentiality in transdermal administration of ciprofloxacin. All formulation showed good physicochemical properties like thickness, weight variation, and drug content. The *in-vitro* release data showed that drug release from the patch formulation was dependent upon diffusion mechanism. Effect of penetration studies indicated that as the concentration of penetration enhancer i.e., isopropyl myristate increased drug permeation also increased. Thus, the transdermal patches we made could provide the delivery of drug at a controlled rate across intact skin and might be used in clinical situation.

ACKNOWLEDGEMENT: The authors would like to thank Druid Pharma Limited, Kolkata, India and Maan Pharmaceuticals Ltd., Ahmedabad, India, for providing us gift samples of ciprofloxacin and ethyl cellulose.

REFERENCES

1. Arora P, Mukherjee B: Design, development, physical, and *in vitro* and *in vivo* evaluation of transdermal patches containing diclofenac diethylammonium salt. J Pharm Sci 2002, 91: 2076-2089.
2. Assandri A, Canali, S, Giachetti C: Local tolerability and pharmacokinetic profile of a new transdermal delivery system, diclofenac hydroxyetylpyrrolidine plaster. Drugs Exptl Cli. Res 1993; 19: 89-95.
3. Barry BW: Novel mechanisms and devices to enable successful transdermal drug delivery. Eur J Pharm Sci 2001; 14: 101-114.
4. Chein YW: Transdermal drug delivery systems and delivery systems.
5. Deasy PB, Mcdaid DM: Formulation Development of Transdermal drug delivery system for Amlodipine base. Int J Pharm 1996; 133: 71-83.
6. Keith AD: Polymer matrix consideration for transdermal devices. Drug Dev Ind 1983; 9: 605- 621.
7. Krishna R, Pandit JK: Transdermal delivery of propranolol. Drug Dev Ind Pharm 1994; 20:2459–2465.
8. Koteswar UN: Preparation and Evaluation of Captopril transdermal matrices. Indian drugs 1992; 29: 680-8.
9. Kusum DV, Saisivam S, Maria GR, Deepti PU: Design and evaluation of matrix diffusion controlled transdermal patches of verapamil hydrochloride, Drug Dev Ind Pharm 2003; 29: 495–503.
10. Lea and Febiger:Libermann and Lachman. Pharmaceutical dosage forms. 1990:2nd ed.: 265.
11. Lee PJ, Ahmad N, Langer R: Evaluation of chemical enhancers in the transdermal delivery of lidocaine. In J Pharm 2006; 308: 33-39.
12. Limpongsa E, Umprayn K: Preparation and evaluation of diltiazem hydrochloride diffusion- controlled transdermal delivery system. AAPS PharmSciTech 2008; 9(2):464-70.
13. Liu Y, Fang L, Zheng H, Zhao L, Xinyu G, Zhonggui H: Topical use patch containing diclofenac diethanolamine salt. Asian Journal of Pharmaceutical Sciences 2007; 2 (3): 106-113.
14. Marcel Dekker,Delivery Fundamentals and Applications 2nd ed. New York:, Inc. 1987; 524-552.
15. Patel RP, Patel G, Baria A: Formulation and evaluation of transdermal patch of Aceclofenac. International Journal of Drug Delivery 2009; 1: 41-51
16. Sadashivaih R, Dinesh BM, Patil UA, Desai BG, Raghu KS: Design and *In-vitro* Evaluation of Haloperidol lactate transdermal patches containing ethyl cellulose–povidone as film formers. Asian J Pharm2008; 2:43-9.
17. Squillante E, Needham T, Zia H: Solubility and i*n-vitro* transdermal permeation of Nifedipine. Int J Pharm 1997, 159: 171-80.
18. Tipre DN, Vavia PR: Formulation optimization and stability study of transdermal therapeutic system of nicora- ndil. Pharm Deve Tech 2002; 7: 325-332.
19. Vijayan V *et al*: Development and Physiochemical, *In-Vitro* Evaluation of Antihypertensive Transdermal Patches. J Pharm Sci & Re 2010; 2(3): 171-177.

****