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RESEARCH ARTICLE

DESIGN AND EVALUATION OF KETOPROFEN AS TRANSDERMAL PATCHES USING DIFFERENT POLYMERS

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ABSTRACT

Transdermal delivery provides a leading edge over injectables and oral routes by increasing patient compliance and avoiding first pass metabolism thus increases bioavailability and efficiency of drugs. This route of administration may be particularly significant in infants and children because of their greater surface area to weight ratio. This delivery system is an effective means for introducing drugs into the blood stream by applying a patch to skin. Matrix type transdermal patches remain the most popular as they are easy to manufacture. Ketoprofen is one of the most useful NSAIDs, which require controlled release due to its short biological half-life of 1.5 to 2 h. The drug is widely used in the treatment of many types of inflammatory and arthritic diseases such as rheumatoid arthritis and osteoarthritis also used for frozen painful stiff shoulder, in tendinitis, muscular pain and swelling resulted from trauma. The aim of this study was to develop and evaluate transdermal patches of ketoprofen employing various polymers to achieve controlled release in order to minimize adverse effects associated with oral administration.

INTRODUCTION

Over the number of decades, drug delivery systems have enormously increased their performances, moving from simple pills to sustained/controlled release and sophisticated programmable delivery systems. Meanwhile, drug delivery has also become more specific from systemic to organ and cellular targeting (Pillai, 2001). Drug delivery by oral route has significant drawbacks like poor bioavailability due to hepatic metabolism (first pass) and the tendency to produce rapid blood level spikes (both high and low), leading to a need for high and/or frequent dosing, which can be both cost prohibitive and inconvenient (Chien, 1992). New drug delivery systems (NDDS) are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the delivery of drug to a particular tissue (Chien, 1992). Transdermal drug delivery constitutes one of the most important routes of NDDS due to its numerous advantages over conventional delivery methods including oral and parenteral route. As a result, the research into transdermal drug delivery has greatly increased over the past few years. This is evident from the remarkable achievements of pharmaceutical technologists who have made transdermal drug delivery systems (TDDS) the most successful non-oral systemic drug delivery and also a highly successful commercial venture.

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The technology has a proven record of FDA approval since the first transdermal patch was approved in 1981 (Scopolamine patch). Transdermal drug delivery uses the skin as an alternative route for the delivery of systemically acting drugs. These systems deliver medicines via the skin portal to the systemic circulation at a predetermined rate and maintain clinically effective concentrations over a prolonged period of time (Chien, 1992)

"*Transdermal drug delivery systems are adhesive, drug containing devices of defined surface area that deliver a pre-determined amount of drug to the surface of intact skin at a pre-programmed rate. These systems provide drug systemically at a predictable rate and maintain the rate for extended periods of time (Roberts, 1997)***".**

MATERIALS AND METHODOS

Materials used: Ketoprofen was kindly supplied by Themis Laboratory, Mumbai. Ethyl cellulose (EC) and Carbopol 934 were purchased from CDH Laboratories and NR chemicals, Mumbai respectively. HPC was procured from Sigma Aldrich Bengaluru. All other chemicals and solvents used were of analytical grade.

Experimental Animals: Swiss albino rats weighing between 160 to 180 G and swiss albino mice weighing between 20 to 30 G were used in this study. Animals were procured from Sri Amrutha industries, Sangli, Maharashtra and were acclimatized for seven days under standard housing conditions

like, room temperature of 24 ± 1°C; relative humidity 45-55% with 12:12 h light/dark cycle. The animals were habituated to laboratory conditions for 48 h prior to the experimental protocol to minimize any nonspecific stress.

Drug profile: Ketoprofen (Roberts *et al.*, 2003; Pharmacopoeia of India, 1996; Moffat, 1987; United states pharmacopoeia, 1985; http://www.kspcdic.com./ketoprofen review; Tripathi, 2003).

Mechanism of action: During inflammation, pain and fever, arachidonic acid is liberated from phospholipids fraction of cell membrane. Arachidonic is then converted by cyclooxygenase and lipoxygenase to prostaglandins, bradykinins, leukitrienes etc which are the chemical mediators for the above conditions, ketoprofen mainly acts by inhibiting the action of both cyclooxygenase and lipooxygenase.

Analytical methods

Determination of λmax: 100 mg of ketoprofen was dissolved in 100 ml of methanol and further diluted with pH 7.4 buffer, suitable dilutions were made and finally scanned for maximum absorbance using Hitachi U-2000 spectrophotometer (double beam) in the U.V range from 180 to 360 nm. Average of triplicate readings was taken.

Table 1. Calibration curve data of ketoprofen

Sl.No.	Concentration (µg/ml)	Absorbance* ± SD
1	0	0.000
2	2	0.180 ± 0.08
3	4	0.360 ± 0.22
4	6	0.540 ± 0.16
5	8	0.709 ± 0.10
6	10	0.900 ± 0.12

*Average of three determinations

Construction of calibration curve of ketoprofen: 100 mg of ketoprofen was accurately weighed and dissolved in 25 ml of methanol in a 100 ml volumetric flask and the volume was made up to the mark using methanol. The above prepared solution of ketoprofen was subsequently diluted with phosphate buffer of pH 7.4 to get 2, 4, 6, 8, 10 µg/ml of the final solution. Then the absorbance was measured by Hitachi U-2000 spectrophotometer at 260 nm using phosphate buffer of pH 7.4 as blank. Average of triplicate readings was taken.

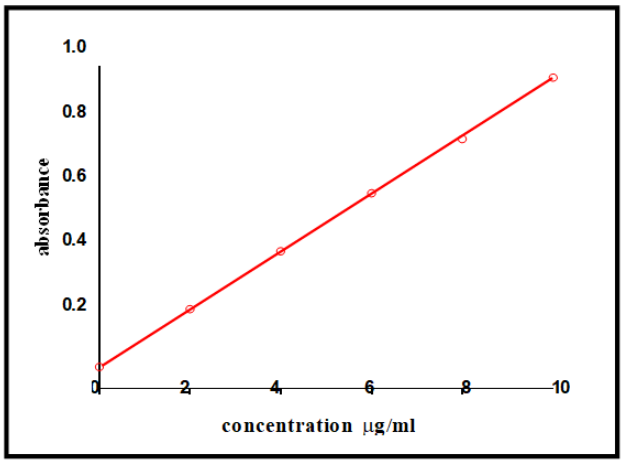

Figure 1. Calibration curve of ketoprofen

Preformulation studies of the model drug

Melting point determination (Atherden, 2002)

Melting point of the drug was determined by taking a small amount of the drug in a capillary tube closed at one end and was placed in Thiel"s melting point apparatus and the temperature at which the drug melts was noted. Average of triplicate readings was taken.

Partition coefficient (Priyanka arora, 2002; Alfred Martin, 1991)

A drug solution of 1mg/ml was prepared in n-octanol. 25 ml of this solution was taken in a separating funnel and shaken with an equal volume of phosphate buffer of pH 7.4 (aqueous phase) for 10 min and allowed to stand for 2 h. After suitable dilution both the phases were analyzed for the drug concentration using UV spectrophotometer. Partition coefficient was calculated by taking the ratio of the drug concentration in n-octanol to drug concentration in aqueous phase. Average of three readings was taken.

Permeability coefficient (Potts, 1992): The permeability coefficient of drug was calculated by

"Potts and Guy equation",

$\log Kp = -2.7 + 0.71 \times \log Ko/w - 0.0061 \times$ Molecular weight

Where,

logKp = Permeability coefficient

Ko/w= Partition coefficient

Infrared (IR) absorption spectroscopy (Fregany , 2003; Bremecker, 1984)

To investigate any possible interaction between the drug and the polymer (EC) IR spectrum of pure drug (ketoprofen) and its physical mixture was obtained on perkin elmer 1600 series (USA). The spectra were recorded over the wavenumber range of 4000 cm^{-1} to 400 cm^{-1}.

Formulation of matrix type transdermal patches

Matrix type transdermal patches of ketoprofen were prepared by method of solvent casting on mercury surface. Initially, EC patch with and without span 80 (F1 and F2) were prepared by keeping drug and polymer ratio of 1:3 and then patches containing combination of EC: carbopol (F3, F4, F5) and EC:HPC (F6, F7, F8) were prepared according to the formulae given in Table 4**.** The drug loaded patches were prepared by dissolving required quantity of the drug in 10 ml solvent blends of ethanol and dichloromethane (1:1). Then, polymer (150 mg), dibutyl phthalate (plasticizer) at a concentration of 30% w/w of the polymer, span–80 (2.5% w/w of polymer) was also dissolved in respective solvent blends. Carbopol and HPC were added in solvent blend at concentrations of 2.5%, 5% and 7.5% w/w of the polymer (carbopol was neutralized using triethanolamine before addition) and stirred to get a homogeneous dispersion. The dispersion (2 ml) was poured within a glass bangle (3.66 cm) on the surface of mercury in a Petri dish. The rate of evaporation was controlled by inverting a funnel over the mercury and dried at 40°C for 8 h in hot air oven.

Table 2. The formulae of transdermal patches containing ketoprofen

Sl.No.	Ingredients	Formulation codes							
		F1	F2	F3	F4	F5	F6	F7	F8
1	Ketoprofen (mg)	50	50	50	50	50	50	50	50
2	EC (mg)	150	150	150	150	150	150	150	150
3	Span 80	-	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%
4	Dibutyl phthalate	30%	30%	30%	30%	30%	30%	30%	30%
5	Carbopol	-	-	2.5%	5%	7.5%	-	-	-
6	HPC	-	-	-	-	-	2.5%	5%	7.5%

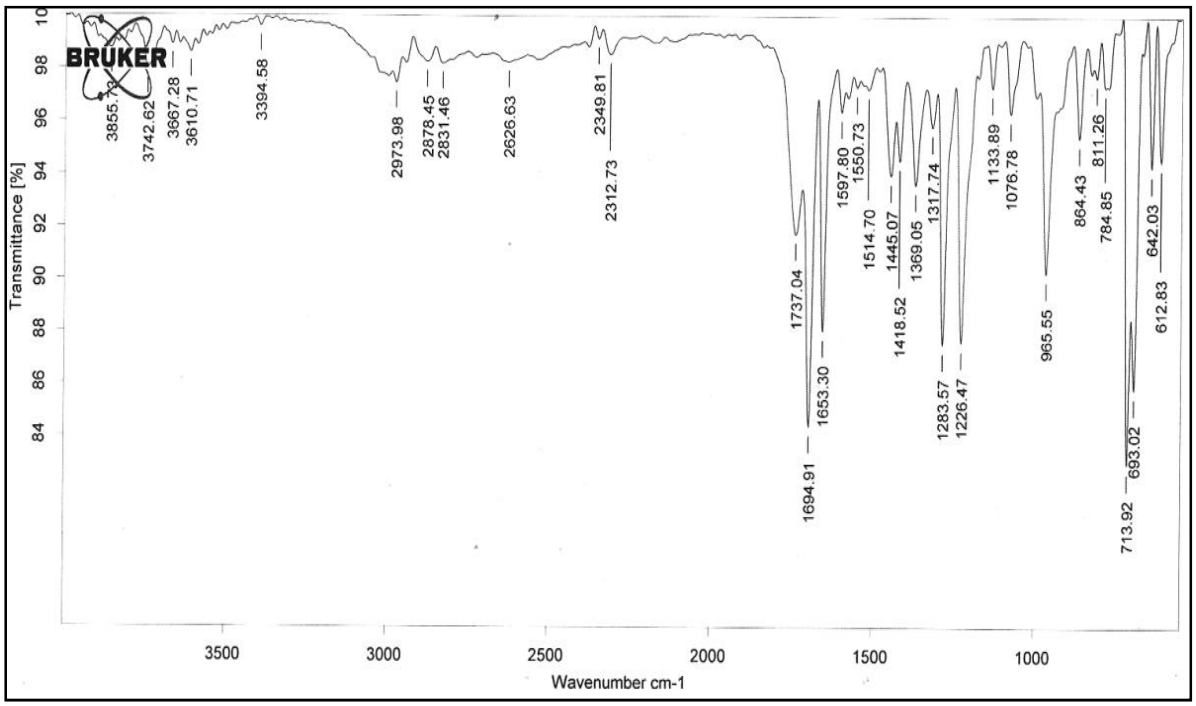

Figure 2. FTIR spectra of ketoprofen

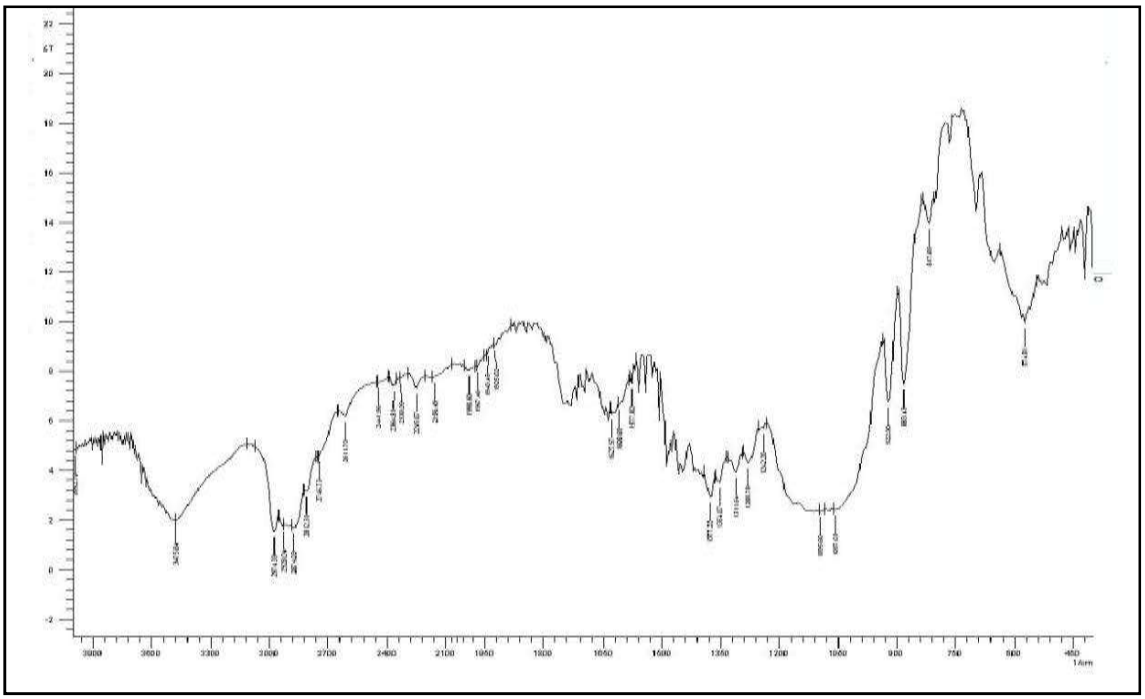

Figure 3. FTIR spectra of EC

After drying, obtained patches were packed in aluminium foil and stored in desiccators at room temperature for further studies.

Evaluation of transdermal patches of ketoprofen

Physicochemical characteristics of patches

- Physical appearance
- Weight uniformity
- Thickness uniformity
- Folding endurance
- Water vapour transmission
- Drug content uniformity
- *In vitro* drug release studies of patches through rat abdominal skin

Physical appearance: All the transdermal patches were visually inspected for color, clarity, flexibility and smoothness.

Weight uniformity: The dried patches were weighed on afcoset digital balance. The average of five observations was taken as a weight of the patch.

Thickness uniformity (Raghavendra, 2000): Patches thickness was measured by a screw gauge (mitutoyo Japan) at five different random points on the patch. The average of five observations was taken.

Folding endurance (Volland, 1999): The folding endurance was measured manually for the prepared patches. A strip of patches (3×3 cm) was cut evenly and repeatedly folded at the same place till it breaks.

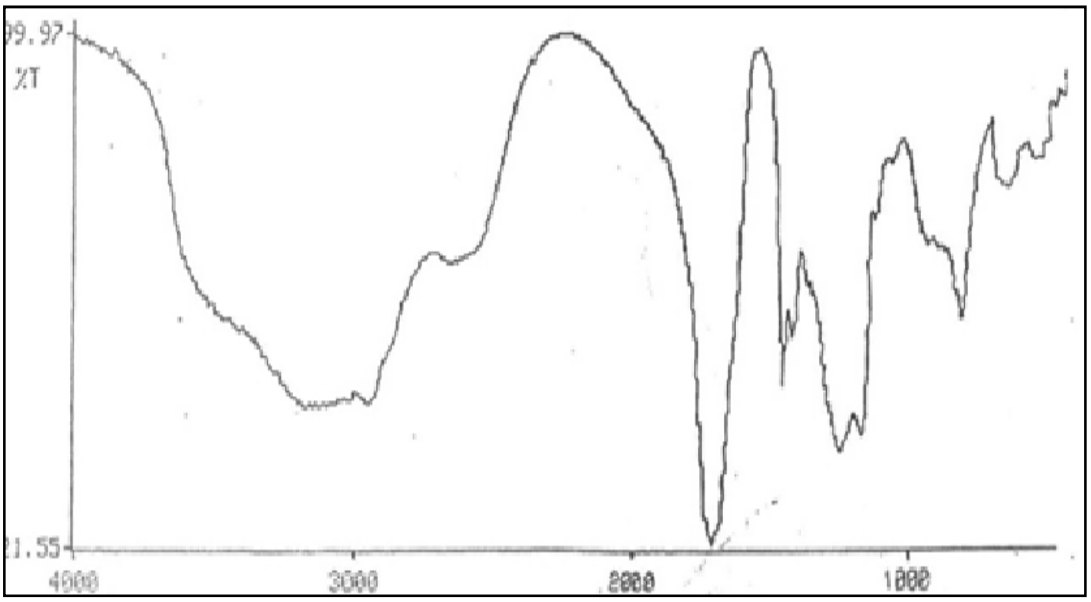

Figure 4. FTIR spectra of carbopol 934

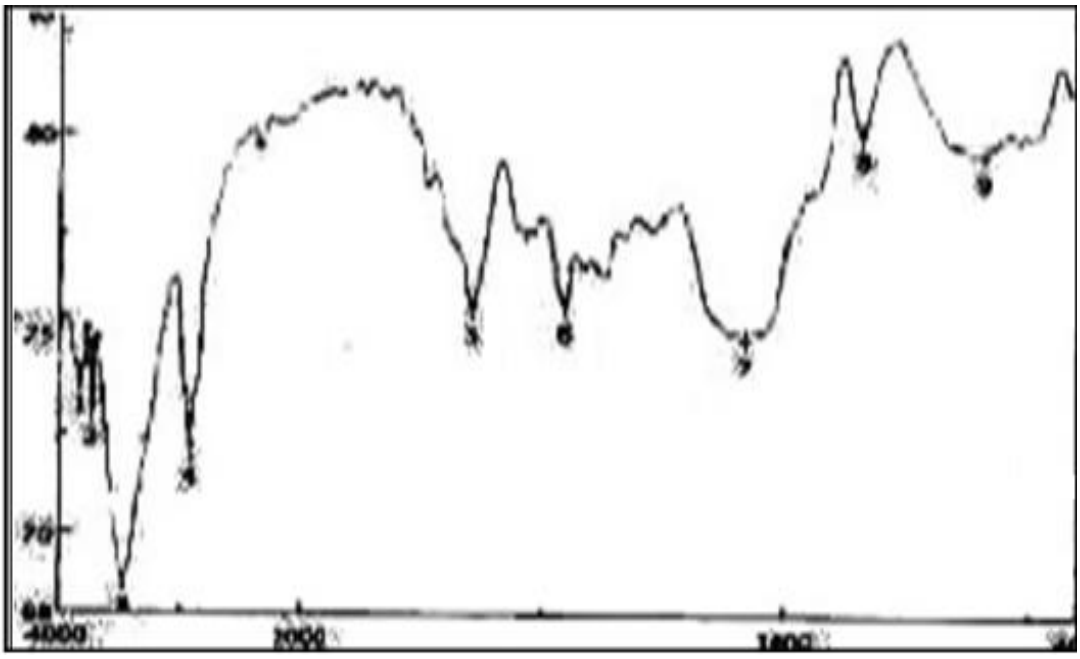

Figure 5. FTIR spectra of HPC

The number of times the patches could be folded at the same place without breaking gave the exact value of folding endurance.

Water vapour transmission studies (Kusum devi *et al.*, 2003): Glass vials of equal diameter were used as transmission cells. These cells were washed and dried in an oven. About 1 gm of fused calcium chloride was taken in the cells and patch of area equivalent to brim of vial (1.36 cm^2) was fixed with the help of an adhesive. The cells were weighted accurately and kept in a close dessicator containing saturated solution of potassium chloride (200 ml). The humidity inside the dessicator was measured by a hygrometer and it was found to be 84% RH. The cells were taken out and weighed after 1, 2, 3, 4,5, 6, and 7 days of storage. The WVT was calculated by taking the difference in the weight of the patches before and at regular intervals of 24 h for a total period of seven days. Water vapour transmission rate was calculated using the following formula, WVT rate = WL/SWhere, W is the water vapour transmitted in G, L is the thickness of the patch in cm and S is the exposed surface area in square cm.

Drug content uniformity (Bhalla, 1991): Transdermal patches of 1.168 sq.cm area was cut into small pieces and transferred into 100 ml volumetric flask. 25 ml of methanol was added and volume made up to 100 ml with phosphate buffer of pH 7.4. shaken for 4 h to extract the drug. After suitable dilution, the drug content was analysed spectrophot- ometrically at 260 nm against blank. Average of 3 determinations was taken for each film.

***In vitro* drug release studies of patches through rat abdominal skin**

Preparation of the rat skin (Flynn, 1981**):** The swiss albino rats were sacrificed by decapituation. The fresh abdominal skin was excised from swiss albino rats weighing 170-190 gm. The abdominal skin of excised hairless rat skin was separated along the epidermal junction and was kept under a steam of 60°C water for exactly 50 seconds. The heat-treated skin was cleared of its subcutaneous fatty substances and immediately kept in normal saline solution to flatten and smooth. This step maintained the integrity and viability of the skin.

Permeation studies (Chien, 1991): The release profile of ketoprofen from transdermal films was performed by using fabricated keshary-Chien diffusion cell. The patch (area 1.168 cm^2 = 10 mg of drug) was placed on rat abdominal skin and mounted between the donor and receptor compartment of the diffusion cell the receptor compartment was filled with 35 ml phosphate buffer of pH 7.4 and the temperature was maintained at 37 ± 1°C The samples were withdrawn every hour (replaced with 1 ml fresh buffer to maintain sink condition) and their concentrations were measured in UV- spectrophotometer at 260 nm.

RESULTS

Table 3. Preformulation studies of ketoprofen

Sl.No.	Drug	Melting point °C	Partition coefficient (P)	Log P	Log Kp
1	Ketoprofen	96	6.80	0.83	-3.661

Table 4. Physical parameters and drug content of transdermal patches

Formulation codes	Physical appearance	Weight* (mg)	Thickness* (µm)	Folding endurance*	% Drug content*
F1	++	260.3 ± 0.13	112.12 ± 0.22	112.23 ± 1.12	98.5 ± 0.25
F2	++	271.2 ± 0.12	166.24 ± 0.12	176.24 ± 0.98	99.1 ± 0.35
F3	++	274.6 ± 0.23	148.38 ± 0.10	198.44 ± 1.21	98.9 ± 0.37
F4	++	252.4 ± 0.09	129.44 ± 0.08	189.20 ± 1.94	97.2 ± 0.27
F5	++	249.6 ± 0.18	174.56 ± 0.04	190.30 ± 0.96	98.1 ± 0.36
F6	++	272.4 ± 0.42	146.24 ± 0.06	202.30 ± 1.48	97.8 ± 0.41
F7	++	270.6 ± 0.36	152.39 ± 0.05	212.60 ± 0.54	98.5 ± 0.25
F8	++	278.6 ± 0.54	144.78 ± 0.03	189.70 ± 0.78	98.5 ± 0.35

→ The figure inside the parenthesis denotes the standard deviation values
* → Average of three observations
++→ Satisfactory

Table 5. Water vapour transmission data of transdermal patches

Formulation codes	Cumulative amount of water vapour transmitted in grams in days							WVT rate constant (G.cm/cm^2.24h)
	1st	2nd	3rd	4th	5th	6th	7th	
F1	0.02	0.04	0.06	0.08	0.10	0.12	0.13	6.4×10^{-3}
F2	0.02	0.04	0.06	0.07	0.09	0.10	0.11	8.5×10^{-3}
F3	0.02	0.04	0.05	0.07	0.08	0.09	0.10	6.9×10^{-3}
F4	0.01	0.01	0.03	0.04	0.06	0.08	0.09	4.18×10^{-3}
F5	0.03	0.08	0.13	0.18	0.22	0.26	0.32	22.3×10^{-3}
F6	0.04	0.07	0.11	0.14	0.17	0.21	0.29	15.8×10^{-3}
F7	0.04	0.08	0.14	0.19	0.25	0.30	0.36	21.2×10^{-3}
F8	0.03	0.07	0.10	0.12	0.16	0.19	0.22	13.2×10^{-3}

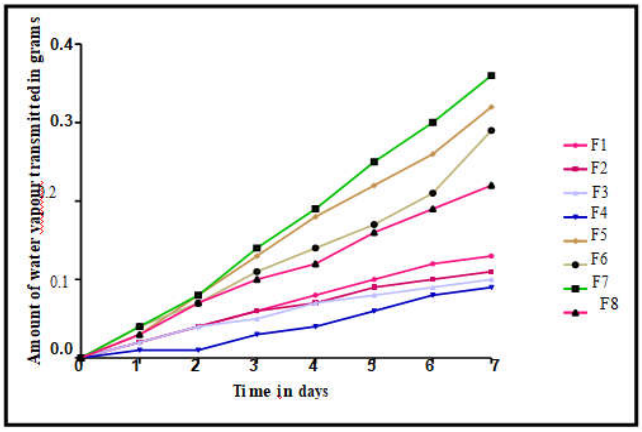

Figure 6. Water vapour transmission profiles of transdermal patches

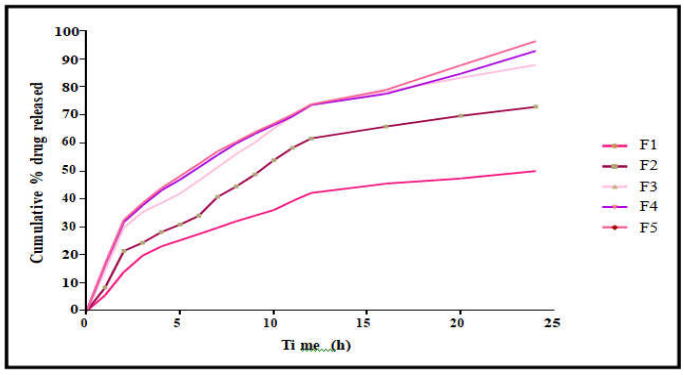

Figure 7. Comparative *in vitro* permeation rate profiles of drug from EC patches and EC: carbopol patches through rat abdominal skin

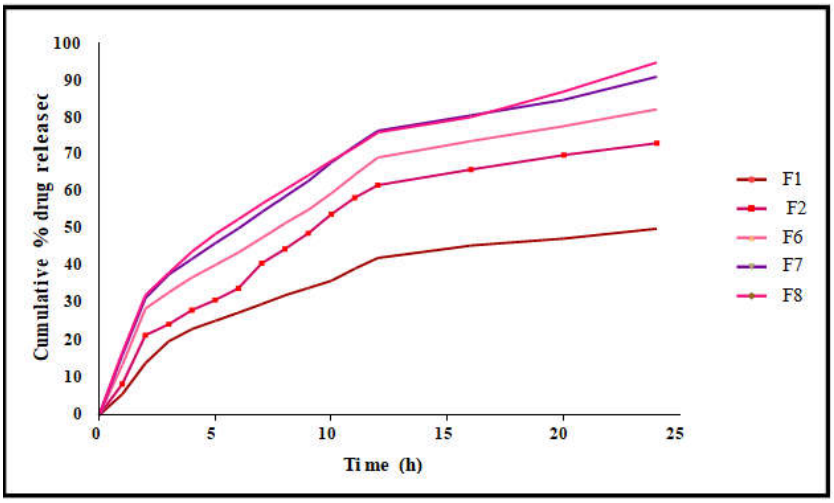

Figure 8. Comparative *in vitro* permeation rate profiles of drug from EC patches and EC:HPC patches through rat abdominal skin

***Table 6. In vitro* drug permeation data from transdermal patches through rat abdominal skin**

		Cumulative percent of drug released (± SD, n=3)							
Sl.No	Time (h)	Formulation codes							
		F1	F2	F3	F4	F5	F6	F7	F8
1	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
2	1	5.68 ± 0.14	8.42 ± 0.21	13.50 ± 0.12	16.23 ± 0.23	16.94 ± 0.23	14.67 ± 0.47	16.63 ± 0.34	17.02 ± 0.56
3	2	14.05 ± 0.22	21.56 ± 0.32	28.74 ± 0.34	31.55 ± 0.43	32.35 ± 0.43	29.94 ± 1.10	31.95 ± 0.57	32.75 ± 0.58
4	3	19.92 ± 0.45	24.51 ± 0.11	33.07 ± 0.65	37.91 ± 0.98	38.35 ± 0.25	35.48 ± 0.47	37.93 ± 0.46	38.75 ± 0.78
5	4	23.21 ± 0.21	28.31 ± 0.41	37.10 ± 1.12	42.08 ± 0.45	44.09 ± 0.45	38.80 ± 0.49	43.28 ± 0.67	44.12 ± 0.67
6	5	25.41 ± 0.34	31.03 ± 0.54	40.45 ± 0.54	46.34 ± 0.45	48.80 ± 0.83	42.19 ± 0.56	47.18 ± 0.58	48.43 ± 0.97
7	6	27.64 ± 0.23	34.20 ± 0.25	43.86 ± 0.85	50.30 ± 0.65	52.83 ± 1.12	46.82 ± 0.46	51.56 ± 0.95	52.84 ± 0.85
8	7	29.93 ± 0.54	40.95 ± 0.41	47.73 ± 0.99	54.73 ± 1.10	56.93 ± 0.50	51.55 ± 0.94	56.02 ± 0.46	57.34 ± 0.78
9	8	32.26 ± 0.45	44.74 ± 0.21	51.68 ± 0.63	58.86 ± 0.49	60.72 ± 0.52	56.38 ± 0.34	60.18 ± 0.84	60.75 ± 0.93
10	9	34.24 ± 0.28	49.00 ± 0.53	55.31 ± 0.65	63.07 ± 0.29	64.58 ± 0.97	60.53 ± 0.34	63.63 ± 1.30	64.22 ± 1.28
11	10	36.26 ± 0.65	54.14 ± 0.84	59.80 ± 0.52	68.13 ± 0.88	68.51 ± 0.49	65.54 ± 0.36	66.76 ± 1.10	67.35 ± 0.73
12	11	39.48 ± 0.30	58.60 ± 0.76	64.76 ± 0.99	72.51 ± 1.23	72.1 ± 1.11	69.87 ± 1.45	69.92 ± 0.84	70.53 ± 0.67
13	12	42.38 ± 0.29	61.98 ± 1.10	69.44 ± 1.34	76.59 ± 0.94	76.16 ± 0.41	74.27 ± 0.83	73.92 ± 0.84	74.14 ± 0.57
14	16	45.72 ± 0.68	66.19 ± 0.56	73.81 ± 1.12	80.72 ± 0.48	80.27 ± 0.85	78.76 ± 0.93	77.98 ± 0.46	79.37 ± 0.86
15	20	47.57 ± 0.58	70.10 ± 1.23	77.87 ± 0.57	84.93 ± 0.86	87.19 ± 0.89	83.71 ± 0.67	85.23 ± 0.46	88.22 ± 0.74
16	24	50.23 ± 0.48	73.29 ± 0.43	82.39 ± 0.94	91.16 ± 0.94	95.04 ± 0.94	88.36 ± 0.26	93.42 ± 0.36	96.88 ± 0.47

Table 7. The flux and permeability coefficient data of transdermal patches of ketoprofen

Formulation codes	Flux (µg/cm^2/min)	Permeability coefficient (cm/h)
F1	48.77	6.64×10^{-3}
F2	73.29	7.39×10^{-3}
F3	82.39	8.39×10^{-3}
F4	91.16	9.37×10^{-3}
F5	95.04	9.6×10^{-3}
F6	88.36	8.97×10^{-3}
F7	93.42	9.48×10^{-3}
F8	96.88	9.99×10^{-3}

Table 8. Mathematical modelling and comparative kinetic values obtained from all transdermal patches of ketoprofen

Formulation codes	Zero order equation		Higuchi's equation		Korsemeyer's Peppas equation	
	Ko (%mg/h)	r	K_h (%mg)	r	n	r
F1	3.6910	0.7950	14.1160	0.9872	0.6280	0.9746
F2	4.1629	0.8157	15.8754	0.9825	0.6510	0.9773
F3	4.7234	0.7092	18.2148	0.9899	0.5346	0.9813
F4	5.2567	0.6587	20.3532	0.9880	0.5149	0.9837
F5	5.3675	0.6536	20.7854	0.9907	0.5066	0.9855
F6	5.0774	0.7142	19.5746	0.9897	0.5392	0.9835
F7	5.2485	0.6503	20.3274	0.9908	0.5035	0.9851
F8	5.3661	0.6711	20.7474	0.9933	0.5031	0.9862

Where, K_h= Higuchi release rate constant, K_o= release rates constants or zero order, n=release rate exponent of Korsemeyer"s Peppas model and r = correlation coefficient

Conclusion

The present study demonstrated the successful design of transdermal patches of ketoprofen using EC and blends of EC:carbopol and EC:HPC at different ratios by incorporating suitable permeation enhancers like span-80 to produce overall prolonged drug release up to 24 h.

The following conclusions were drawn from the present investigation,

- Preformulation studies on ketoprofen were found satisfactory to design as transdermal patches.
- FT-IR studies confirmed no interaction between the drug and polymers.
- Thin, flexible, smooth and transparent patches were obtained with EC a lone, blends of EC:carbopol and EC:HPC at different ratios.
- Thickness, mass, folding endurance and drug content were found to be uniform and reproducible with low SD values.
- Water vapour transmission (WVT) through all batches of transdermal patches containing ketoprofen followed zero order kinetics.
- All patches prepared with the blends of EC:carbopol and EC:HPC showed sustained and prolonged release of drug up to 24 h compared to patch prepared with EC alone.
- Comparatively, EC:HPC transdermal patches showed higher flux and drug release than EC:carbopol patches.
- In case of EC:carbopol and EC:HPC patches, flux and drug release rate increased with the increase in the concentrations of hydrophilic polymers i.e., carbopol and HPC.
- The highest percentage of drug release i.e., 95.04% and 93.42% was observed with EC:carbopol and EC:HPC patches respectively at 7.5% ratio.
- The release of the ketoprofen from all batches of patches followed predominantly Higuchi kinetic model.
- Based on Korsemeyer Peppas model the mechanism of drug release from transdermal patches was concluded as non–Fickian diffusion controlled (anomalous diffusion).

From the overall *in vitro* permeation studies it could be concluded that the transdermal patches of ketoprofen prepared with blends of polymers (EC:carbopol and EC:HPC) at different ratios holds potential for transdermal delivery of model drug to systemic circulation which gives a slow and controlled release up to 24 h. These patches may also provide an added advantage of circumventing gastric disturbances and other side effects associated with oral administration of the model drug, ketoprofen. However, there is a scope for pharmacodynamic and pharmacokinetic evaluation of these systems in animals and human volunteers to confirm these findings.

REFERENCES

Alfred Martin, James Swarbrick, Arthur Cammarata. 1991. Polymer Science. 3rd ed. Bombay: K. M. Varghese company.

Atherden LM. 2002. Analytical methods. 8th ed. Oxford medical publication.

Bhalla HL, Shah AA. 1991. Controlled release matrices for ketoprofen. Indian drugs, 28(9):420-22.

Bremecker KD, Strempel H, Klein G. 1984. *J Pharm Sci.,* 73:548.

Chien YW. 1992. Concepts on systems design for rate controlled drug delivery. 2nd ed. New York: Marcel Dekker Inc.

Chien YW. 1992. Novel drug delivery systems. Drugs and the pharmaceutical sciences. New York: Marcel Dekkar Inc; 50-797.

Chien YW. 1992.Transdermal drug delivery and delivery systems. 2nd ed. New York: Marcel Dekker Inc.

Chien YW.1991. Systemic drug delivery of pharmacologically active molecule across the skin. Vol 100. New york.

Flynn GL, Durrheim H, Huguchi WI. 1981. Permeation through hairless mouse skin II:membrane sectioning techniques and influence on alkanol permeabilities. *J Pharm Sci.,* 70(1):52-56.

Fregany A, Mohammed, Hussin Khedr. 2003. Preparation and in vitro/in vivo evaluation of the buccal adhesive properties

of slow-release tablets containing miconazole nitrate. *Drug Dev Ind Pharm.,* 29(3):321-37.

Kusum devi V, Saisivam S, Maria GR, Deepti PU. 2003. Design and evaluation of matrix diffusion controlled transdermal patches of verapamil hydrochloride. *Drug Dev Ind Pharm.,* 29(5):495-503.

Moffat AC, Jackson JV, Moss MS, Widdop B. 1987. Analytical and toxicological data. 2nd ed. London: The pharmaceutical press.

Pillai O, Dhanikula AB, Panchagnula R. 2001. Drug delivery: Odyssey of 100 years. *Curr Opin Chem Biolm*, 5:439–446.

Potts RO, Guy RH. 1992. Predicting Skin Permeability. *Pharm Res.,* 9:663-669.

Priyanka arora, Biswajit mukherjee. 2002. Design, development, physicochemical and in vitro,in vivo evaluation of transdermal patches containing diclofenac di ethylammonium salt. *J Pharma Sci.,* 91(9):2078-88.

Raghavendra K, Doddayya H, Dr. Marihar SC, Patil CC, Habbu PV. 2000. Comparative evaluation of polymeric films for transdermal application. The Eastern Pharmacist, XLIII (513):109-111.

Roberts L Jackson, Marrow D Jason. 2003. Analgesic-antipyretic, anti-inflammatory agents and drugs used in the treatment of gout. 10th ed. New York: Mc graw Hill Medical Publishing Division.

Roberts MS. 1997. Targeted drug delivery to the skin and deeper tissues: role of physiology, solute structure and disease. *Clin Exp Pharmacol Physiol,* 24(11):874-9**.**

Tripathi KD. 2003. NSAID"s and antipyretic, analgesics. 5th ed. New Delhi: Jaypee brothers Medical publishers.

United states pharmacopoeia XXI – NF XVI, USP conventions. Rockville, Maryland USA; 1985. <10. Error! Hyperlink reference not valid. review.

Volland C, Wollf M, Kissel T. 1999. The influence of terminal gamma-sterilization on captopril containing [D,L-lactide-co-glycolide] microspheres. *J Control Release.,* 31:293-305.

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