
PHARMACEUTICAL TECHNOLOGY

***IN VITRO* EVALUATION OF TRANSDERMAL PATCHES OF FLURBIPROFEN WITH ETHYL CELLULOSE**ARFAT IDREES¹, NISAR UR RAHMAN², ZEESHAN JAVAID^{3*}, MUHAMMAD KASHIF¹, IRFAN ASLAM¹, KHIZAR ABBAS³, TALIB HUSSAIN⁴¹Faculty of Pharmacy and Alternative Medicine, The Islamia University of Bahawalpur, Pakistan²Faculty of Pharmacy, COMSAT Institute of Information Technology, Abbotabad, Pakistan³Akson College of Health Sciences, Mirpur University of Science & Technology, Mirpur, AJ & Kashmir, Pakistan⁴University College of Pharmacy, University of the Punjab, Lahore, Pakistan

Abstract: This study was aimed to determine effects of penetration enhancers and plasticizers on drug release from rationally designed formulations of flurbiprofen based transdermal drug delivery system. Matrix type transdermal patches were formulated with ethyl cellulose (EC) as a polymer by using plate casting method. The plasticizers such as propylene glycol (PG) and dibutyl phthalate (DBP), and enhancers such as Span 20, Tween 20, sodium lauryl sulfate (SLS), isopropyl myristate (IPM) and ethanol (EtOH) were formulated in different concentrations in the patches. Such different combinations of polymer with various enhancers and plasticizers in patches were evaluated for their effect on the physicochemical properties and drug release behavior of flurbiprofen. The drug release study was carried out by the paddle-over-disk method and permeation of drug was performed by Franz diffusion cell using rabbit skin. Patches having ethanol with ethyl cellulose showed more uniformity in the physical properties while the smoothness and clarity of patches containing sodium lauryl sulfate were not satisfactory. The drug release from patches followed Higuchi and Korsmeyer-Pappas model while maximum drug release was obtained by isopropyl myristate (903 µg). It was concluded that the patches having ethyl cellulose with isopropyl myristate and propylene glycol are more useful for transdermal patches of flurbiprofen.

Keywords: transdermal patches, ethyl cellulose, flurbiprofen, kinetic models, permeation enhancers

Certain side effects like ulceration, nausea and vomiting are reported for non-steroidal anti-inflammatory drugs (NSAIDs) if they are administered by oral route of administration. To exempt these kinds of side effects, such drugs required to be administered by some alternative routes of administration. Transdermal patches have shown potential for administration of such drugs, as they transfer the drug into general circulation through the skin and hence, bypass the gastrointestinal tract. Moreover, constant plasma levels are achieved by administering the drug through transdermal route (1). The selection of transdermal drug delivery system (TDDS) is advantageous as it can maximize the rate of transfer of drug into systemic circulation and can also reduce its time of stay in the skin tissues if properly formulated with some permeation enhancers.

The metabolism of drug, that is primary factor in oral delivery system, is markedly minimized by administering the drug through skin. For efficient transdermal drug delivery system, the drug must be able to penetrate the skin barrier and reach the target site. Transdermal patches are also responsible for the sustained release of drug through skin into the blood stream (2). Hence, NSAIDs patches not only remove above mentioned side effects but also improve the patient compliance, avoid first pass effect and maintain a controlled release of drug (3). Flurbiprofen is a chiral non-steroidal anti-inflammatory drug (NSAID) having comparative efficacy with other NSAIDs like ibuprofen and diclofenac. It possesses anti-inflammatory, analgesic and antipyretic activity but can also be employed in the treatment of rheumatoid arthritis, vernal keratocon-

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junctivitis and ocular gingivitis (4). Recent studies have proved its role in the inhibition of colon tumor. Various investigators are attracted towards the quantification of flurbiprofen in the body fluids (5).

It's of remarkable value that the polymers are being used in different roles for developing various drug delivery systems, e.g., ethyl cellulose is widely used as a rate retarding polymer in TDDS due to its lipophilicity that does not allow it to be dissolved by the diffusion medium (6). The enhancers are primarily used to assist the absorption of the penetrant through the skin. Literature reveals the role of various chemical agents as permeation enhancers like Span 20 (7), Tween 20 (8), IPM (9), SLS (10) and ethyl alcohol (11).

The major objectives of this study is to prepare and evaluate various batches of flurbiprofen patches by using different combinations of polymer and enhancers as well as compare the efficiency of various enhancers. It was designed to explore the flurbiprofen interaction with matrix excipients in TDDS, mathematical modeling and critical evaluation of drug release kinetics. Moreover, the influence of unilaminated matrix formulations of flurbiprofen on various characteristics such as physical appearance, weight uniformity test, thickness variation test, folding endurance and percent flatness were also evaluated.

EXPERIMENTAL

Materials

Flurbiprofen was a gift sample by Hamaz Pharmaceuticals, Pakistan. Other materials were purchased as: ethyl cellulose (~5.1 cps) from Sigma Chemicals, USA; Tween 20, Span 20, sodium lauryl sulfate and toluene from BDH, UK; isopropyl myristate from Panreac Quimica, USA; polyvinyl alcohol from Sigma Chemicals, Japan; ethanol, propylene glycol, dibutyl phthalate, chloroform, potassium dihydrogen orthophosphate and sodium hydroxide pellets from Merck, Germany.

Preparation of backing membrane

Polyvinyl alcohol (PVA) is being used for the preparation of backing membrane (7). Four percent w/v solution of PVA was continuously stirred with double distilled water in conical flask on the hot plate magnetic stirrer at 800 rpm for 2 h at 80°C. After cooling, the solution, degassing of the PVA solution was done for 3 min using ultrasonic bath (JenKen PS-08A 1.3L) at 30°C for at least 10 min. Then, 15 mL of the prepared solution was poured in the glass Petri dishes having an area of approximately 61 cm² and finally dried in open air for 24 h.

Development of unilaminated matrix patches

The unilaminated transdermal patches were prepared by solvent evaporation technique (12). Hundred milliliters of the solvent (toluene and chloroform (1 : 1, v/v) for ethyl cellulose) was taken in conical flask in which measured amounts of polymer, enhancer and plasticizer were added gradually and allowed to dissolve. At the end, flurbiprofen was dispersed in the matrix solution.

Twenty milliliters of the above solution was poured in Petri dish, which already had backing membrane. The solution was dried at room temperature by using inverted funnel to avoid rapid evaporation. When the solvent was completely evaporated, the dried patch was removed from Petri dish and wrapped in the aluminum foil. Wrapped film was labeled and stored in cool container. The dried films were cut with the diameter of 1.54 cm². About 10–12 patches were obtained from one Petri dish.

Weight uniformity test

The weight uniformity of randomly selected patches from each formulation was checked by digital weighing balance in triplicate. Every triplicate gave uniformity in weight and the average value was similar to an individual patch. So the mean value is zero in almost all the formulations and the patches showed minimum deviation in weight (13).

Thickness variation test

For variation in thickness, micrometer screw gauge was used. For all formulations, a single patch was checked at three different places and the mean value was used to elaborate the variation in the thickness (14).

Folding endurance

The folding endurance is the number of folds which are required to cleave the matrix film (15). The test clarifies the efficiency of plasticizer in the each patch. The value was determined by repeatedly folding each patch at the same axis until it cleaved. The number of times a film could be folded at the same axis without breaking will give the value of folding endurance (16).

Percent flatness

The percentage flatness was determined by cutting the transdermal film into three strips; two strips from either sides or one at the centre. The length of each strip was calculated after constriction in the films. Minimum constriction in the films resulted in maximum flatness (17).

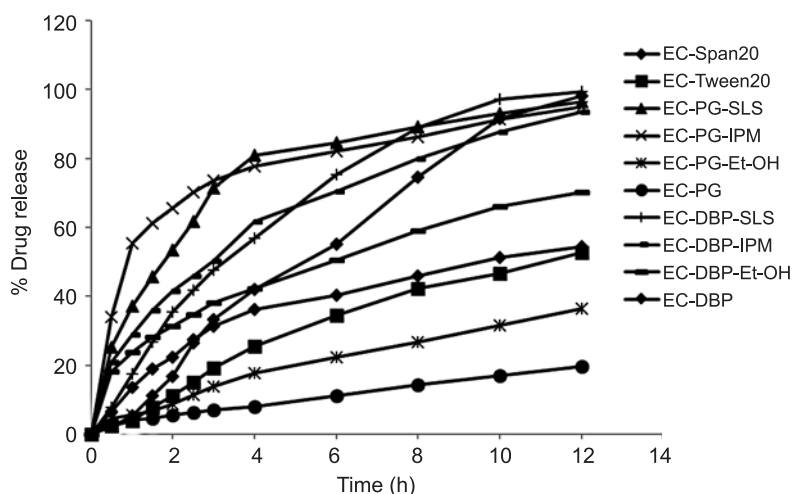


Figure 1. Effect of various enhancers (Span 20, Tween 20, SLS, IPM and EtOH) on the release profile of flurbiprofen patches using dibutyl phthalate (DBP) and propylene glycol (PG) as plasticizers

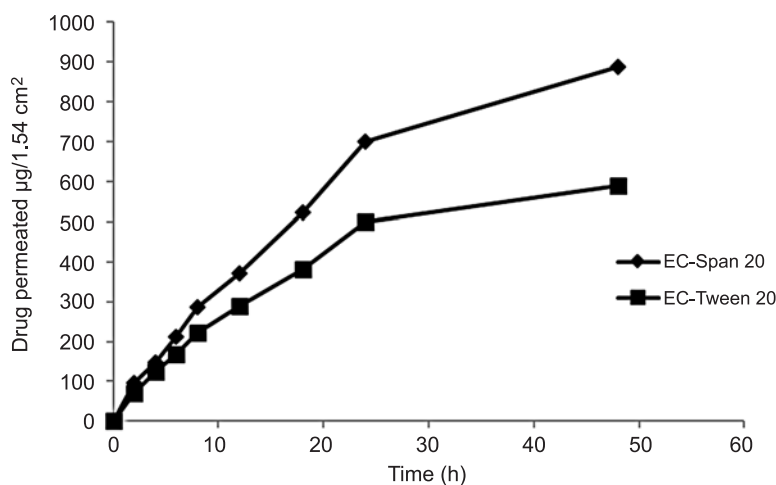


Figure 2. Effect of Span 20 and Tween 20 on the permeability profile of flurbiprofen patches

Drug content uniformity test

Drug content uniformity was evaluated for the confirmation that the drug is distributed evenly in the glass Petri dish. To calculate the uniformity of drug in patches; the patches without drug were also formulated and considered as blank. Each patch was put into conical flask containing 50 mL of dichloromethane (DCM), covered with aluminium foil to avoid evaporation of solvent and stirred continuously at 600 rpm at hot plate magnetic stirrer at 30°C for 24 h. The entrapped air bubbles were

removed by sonication for 15 min. The solution was then filtered through filter paper. After a suitable dilution (up to 200 times), the solutions were analyzed on double beam UV-Vis spectrophotometer (Irmeco-U2020, Germany) at the wavelength of 247 nm for flurbiprofen.

In vitro drug release studies

The dissolution test was performed by using paddle over disk method (USP apparatus 5). Due to the unavailability of commercial patch retainer or

Table 1. Formulation of transdermal flurbiprofen patches using EC with various enhancers (1 : 1) and plasticizers.

Formulation ingredients	Formulations									
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
EC (mg)	600	600	600	600	600	600	600	600	600	600
Span 20 (mg)	600	–	–	–	–	–	–	–	–	–
Tween 20 (mg)	–	600	–	–	–	–	–	–	–	–
IPM (mg)	–	–	600	–	–	–	–	600	–	–
Ethanol (mg)	–	–	–	600	–	–	–	–	600	–
SLS (mg)	–	–	–	–	600	–	–	–	–	600
PG (mg)	–	–	210	210	210	210	–	–	–	–
DBP (mg)	–	–	–	–	–	–	210	210	210	210
Flurbiprofen (mg)	50	50	50	50	50	50	50	50	50	50
Chloroform (mL)	50	50	50	50	50	50	50	50	50	50
Toluene (mL)	50	50	50	50	50	50	50	50	50	50

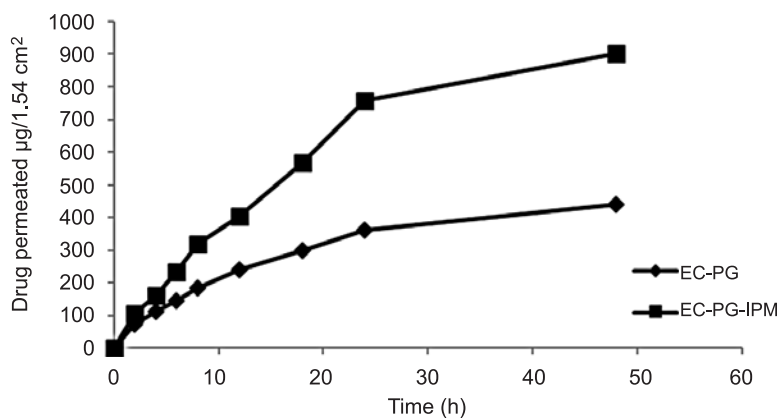


Figure 3. Effect of isopropyl myristate (IPM) and propylene glycol (PG) on the permeability profile of flurbiprofen patches

sandwich patch holder, the disk assembly was prepared by using watch glass (3 inches in diameter), 120 µm mesh stainless steel net and plastic coated stainless steel clips (18).

The patch of an area of 1.54 cm² having 1.22 mg of drug was placed against the watch glass and retained in position with the stainless steel mesh by using stainless steel clips. The disk assembly was designed in such a way that it could hold the system flat with the release surface of patch facing upward and parallel to the bottom of the paddle blade. Moreover, the disk assembly also minimized the “dead” volume between the patch holder and the bottom of the dissolution vessel. For dissolution studies, vessels were filled with 500 mL of phosphate buffer solution (PBS pH 7.4) maintained at 32

± 0.5°C. The disk assemblies holding patches were placed at the bottom of vessels with the release surfaces facing upward and were centered using a glass rod. The stirring speed was set at 50 rpm. Samples of about 5 mL each were collected at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10 and 12 h with an automated fraction collector (Pharma Test, Germany) after filtering through Millipore filters. The withdrawn sample volume was replaced with equivalent fresh volume of media already maintained at 32 ± 0.5°C. Measured amount of samples were analyzed at λ 247 nm using a UV-Vis spectrophotometer (Irmeco U2020, Germany). A calibration curve showing the measured absorbance of known concentrations of flurbiprofen was constructed to measure the amount of flurbiprofen released from withdrawn samples at

Table 2. Physicochemical properties of flurbiprofen transdermal patches.

Formulation Code	Patch	Smoothness	Clarity	Overall appearance	Weight variation (g) ± SD	Thickness variation (mm) ± SD	Folding endurance	Flatness %	% Content ± SD
Q1	EC-Span 20	+	+	Satisfied	0.066 ± 0.00	0.32 ± 0.00	143	99.99	96.53 ± 0.012
Q2	EC-Tween 20	+	+	Satisfied	0.053 ± 0.00	0.27 ± 0.00	129	99.96	97.66 ± 0.006
Q3	EC-PG-IPM	+	+	Satisfied	0.061 ± 0.00	0.35 ± 0.00	119	99.89	97.02 ± 0.02
Q4	EC-PG-EtOH	++	++	Satisfied	0.05 ± 0.00	0.23 ± 0.00	101	99.93	98.21 ± 0.015
Q5	EC-PG-SLS	+	×	Unsatisfied	0.059 ± 0.01	0.29 ± 0.01	97	99.91	96.77 ± 0.020
Q6	EC-PG-No enhancer	++	++	Satisfied	0.048 ± 0.00	0.22 ± 0.00	88	99.94	98.81 ± 0.006
Q7	EC-DBP-No enhancer	++	++	Satisfied	0.046 ± 0.00	0.23 ± 0.00	94	99.93	100.71 ± 0.006
Q8	EC-DBP-IPM	+	+	Satisfied	0.067 ± 0.00	0.35 ± 0.00	131	99.92	98.98 ± 0.006
Q9	EC-DBP- EtOH	++	+++	Satisfied	0.049 ± 0.00	0.25 ± 0.00	113	99.9	101.13 ± 0.025
Q10	EC-DBP-SLS	+	×	Unsatisfied	0.066 ± 0.00	0.32 ± 0.00	99	99.91	100.35 ± 0.015

(+) level of satisfaction, (×) level of dissatisfaction, (SD) standard deviation

specified time intervals as shown in Figure 5. All the test samples were run in 5 different vessels and average values of absorbance were taken, which were later correlated with calibration curve to analyze the amount of drug released. The drug release constants and correlation coefficient (r^2) were obtained by applying zero order (19), first order (20), Higuchi (21), Korsmeyer-Pappas (22) and Hixson-Crowell models (23).

***In vitro* permeation study across the rabbit skin**

In vitro permeation study was performed only on the formulations having satisfactory physicochemical characteristics and showed maximum amount of drug release during *in vitro* dissolution test. The reason for such a selection was based on the assumption that the formulations, which have shown maximum amount of drug release during *in vitro* evaluation, will eventually permeate maximum amount of drug through rabbit skin. The formulations containing Span 20, Tween 20, IPM and EtOH as enhancers were studied using Franz diffusion cell (24).

For permeation study, Franz diffusion cell with an area of 1.76 cm² was used while rabbit skin was used as a permeation medium. Phosphate buffer solution (pH 7.4) was filled in the receptor compartment up to 12 mL while temperature was maintained at 37 ± 1°C by circulating water at constant temperature in the outer jacket of the receiver compartment. The temperature had to be set at 37 ± 1°C in order to produce the temperature reading of the formulation in the receptor compartment at 32 ± 1°C. Actually, the loss of heat occurs in the plastic tubes that connect the Franz cell with the thermostatic water bath. The rabbit skin membrane was carefully placed over the open end of the receptor compartment and the patch of an area of 1.54 cm² was placed over the membrane. The glass disk, i.e., the donor compartment was placed over receptor compartment and both compartments were kept in position with the help of the stainless steel clamp. To avoid evaporation, the junction of the two compartments was wrapped with adhesive tape. The whole assembly was kept on magnetic stirrer and the receptor fluid was kept stirring continuously during test by using magnetic bars at speed of 600 rpm. Samples (1 mL) were with-

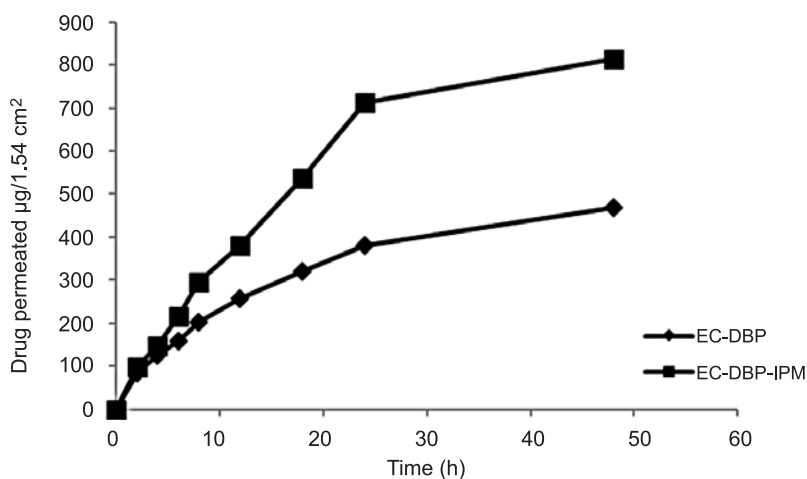


Figure 4. Effect of isopropyl myristate (IPM) and dibutyl phthalate (DBP) on the permeation of drug through rabbit skin

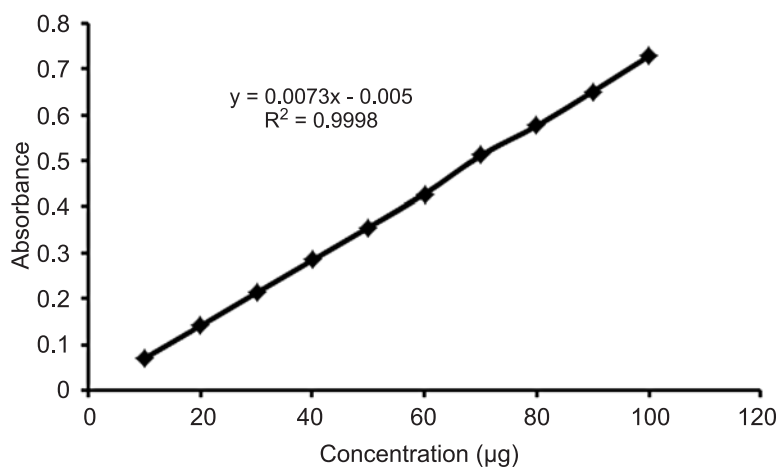


Figure 5. Calibration curve prepared to measure the amount of flurbiprofen released from withdrawn samples at specified time intervals

drawn at 0, 2, 4, 6, 8, 10, 12, 18, 24 and 48 h and replaced by an equal volume of receptor fluid at each sampling time. All the samples were analyzed for the drug contents on UV-Vis spectrophotometer at λ of 247 nm (25).

RESULTS AND DISCUSSION

Physicochemical evaluation

Regarding smoothness and clarity, all the formulations were found satisfactory except the formulation containing SLS (patches Q5 and Q10). All the

films were found to be uniform in weight and thickness variation, with low standard deviation (SD) values. The folding endurance ranges from 88 (patch Q6) to 143 (Q1) and percent flatness were also satisfactory. Experimental findings for physical appearance, weight variation, thickness variation, folding endurance and percent flatness have been presented in Table 2.

Drug contents

Table 2 shows the results for the drug content uniformity in percentage. It is evident from the

Table 3. The drug release constants and correlation coefficient (r_c) obtained from various models for various formulations.

Formulation Code	Zero order		1st order		Higuchi model		Korsmeyer-Peppas		Hixon-Crowell	
	k_0	r^2	k_1	r^2	k_H	r^2	n	r^2	$k_H C$	r^2
Q1	8.912	0.9812	0.151	0.9354	23.821	0.8319	0.908	0.9863	0.044	0.9672
Q2	4.906	0.9544	0.066	0.9906	13.313	0.8714	0.808	0.982	0.02	0.9847
Q3	11.041	-0.5069	0.397	0.9661	32.82	0.8138	0.353	0.9342	0.109	0.9117
Q4	11.075	-3.2477	0.534	0.6979	33.743	0.1351	0.240	0.9399	0.121	0.3605
Q5	3.334	0.9268	0.04	0.9686	9.17	0.9209	0.727	0.9944	0.013	0.9573
Q6	1.769	0.9125	0.019	0.935	4.881	0.9275	0.708	0.9914	0.006	0.9281
Q7	10.282	0.8034	0.229	0.9852	28.831	0.9495	0.622	0.978	0.064	0.9984
Q8	9.798	0.364	0.241	0.9552	28.306	0.9901	0.461	0.9955	0.067	0.8933
Q9	7.278	0.2796	0.131	0.7638	21.059	0.9864	0.444	0.9982	0.037	0.6466
Q10	5.676	0.5362	0.086	0.8074	16.284	0.9739	0.505	0.974	0.025	0.7326

results that there is no significant difference in the drug content uniformity. The range for drug contents is 96.52% (patch Q1) to 100.71% (patch Q7). The test indicates that the drug is distributed uniformly in the patches developed by plate casting method.

In-vitro drug release studies

All the prepared transdermal matrix patches were subjected to dissolution test and the data obtained for drug release were plotted as percentage drug *versus* time in hours. The formulations Q1 and Q2 do not contain plasticizers as Span 20 and Tween 20 both act as plasticizer too. The amount of drug release from all the formulations are 98, 52, 95, 36, 95, 20, 54, 94, 70 and 98% for the formulations Q1, Q2, Q3, Q4, Q5, Q6, Q7, Q8, Q9 and Q10, respectively, at the end of 12 h. The formulations containing Span 20 and SLS as enhancers showed maximum release. The release data (0–12 h) were fitted to different kinetic models in order to determine the effect of all the enhancers on the release kinetics. The drug release constants and correlation coefficient (r^2) obtained from zero order, first order, Higuchi, Korsmeyer-Peppas and Hixon-Crowell models fitted for transdermal patches have been shown in Table 3. It is apparent that the release of drug from transdermal patches Q7, Q8, Q9 and Q10 followed Higuchi model as the values of coefficient of correlation (r^2) are most linear for these formulations. It also suggested that the predominant release mechanism from these patches is diffusion. The diffusional coefficient 'n' values obtained from

Korsmeyer-Peppas model show a combination of fickian and non fickian release mechanisms from the patches that confirms the diffusion as well as erosion of the patch surface. Thus, as a whole, it can be said that the release of drug from patches is slow, controlled and followed diffusion mechanism (26).

In vitro permeation studies

The cumulative amount of the drug permeated (Q_n) for the selected formulations have been mentioned in Table 4. The increased permeation caused the increased amount of drug in receptor compartment. The results clearly show that maximum amount of drug is released by samples containing EC, PG, IPM, whereas the minimum amount is released by the samples containing EC and PG. Detailed discussion of these factors is given as follows.

Effect of Span 20 and Tween 20 on permeation of drug through rabbit skin

The result indicates that the rapid release of drug occurs when the patch is in a good contact with the rabbit skin. Span 20 (enhancer) releases more amount of drug in receptor compartment as compared to Tween 20 as well as from the patches in which no enhancer was included. This is mainly due to the increased receptor-solvent permeation caused by marked partitioning of drug from matrix to the solvent, which then dragged it to the receptor cell membrane (27). Table 4 and Figure 2 show that Span 20 increases the rate of permeation of drug. Span 20 permeates 888 μ g of drug from the rabbit

Table 4. Cumulative amount of drug release ($\mu\text{g}/1.54 \text{ cm}^2$) by various enhancers permeated through rabbit skin.

Time (h)	Cumulative amount of flurbiprofen $\mu\text{g}/1.54 \text{ cm}^2$					
	EC-Span 20	EC-Tween 20	EC-PG	EC-PG-IPM	EC-DBP	EC-DBP-IPM
0	0	0	0	0	0	0
2	96	69	73	105	84	98
4	147	124	111	162	124	146
6	211	167	145	235	159	216
8	286	221	184	320	202	296
12	372	289	239	403	257	381
18	522	382	298	568	321	537
24	698	500	360	759	381	713
48	888	589	439	903	467	814

skin while patch containing Tween 20 permeates 589 μg of drug. This amount of drug release by way of permeation by both Span 20 and Tween 20 is less than the amount released from *in vitro* drug release profile during dissolution study. The formulations which are without plasticizers (Span 20, Tween 20) are self-operating as plasticizers. The results show 25% enhancement in the permeation of drug due to Span 20 (7).

Effect of IPM and PG on the permeation of drug through rabbit skin

The formulations containing EC as polymer and IPM as enhancer with and without PG as plasticizer were studied for the permeation of drug. The results show that in the presence of IPM, increased amount of drug was released as compared to the patch which did not contain IPM. Table 4 and Figure 3 clearly show the amount of drug permeated through rabbit skin. IPM is able to release 903 μg of drug as compared to 439 μg of drug released in the absence of IPM. This amount of drug release by IPM and PG is less than the amount released during *in vitro* drug release. IPM acts as a fluidizer of intercellular lipids and affects the lipid-rich phase in the stratum corneum, so decreases its barrier function (28). The increased amount of drug released by IPM can also be displaced by its intermediary polar nature that caused its penetration into the polar portion of stratum corneum. The increased subdivision of drug in both phases by the use of IPM cause the maximum amount of drug partitioning in the skin as well as in the dissolution medium (29). Therefore, IPM doubles the release of drug when combined with EC and PG.

Effect of IPM and DBP on the permeation of drug through rabbit skin

When IPM was studied with another plasticizer DBP with EC as polymer, the results indicated that 814 μg of drug is released in the presence of IPM and DBP as compared to 467 μg by the formulation which contain only DBP. This amount of drug release by IPM and DBP is less than the amount released during *in-vitro* drug release profile during dissolution study. IPM acts as a conveyer for the drug to permeate through skin barrier and DBP (plasticizer) diffuses and softens the polymer particles by reducing polymer-polymer bonding such as hydrogen bonding and forms its own bonds with the polymer lattice that promotes the latex coalescence and film formation. This results in the decreased strength of polymer and allows IPM to transport the drug through this softened film. So the physico-chemical properties of a patch may vary with this effect (30, 31).

CONCLUSION

The present study suggests that ethyl cellulose releases the drug more effectively in almost all the formulations containing five different enhancers and two plasticizers. The patch having EC, PG and IPM shows maximum amount of drug permeated through rabbit skin membrane. Patches having no enhancer also show increased permeability in the presence of plasticizer (DBP), which also acts as permeability enhancer, whereas the release of drug from patches is controlled and followed diffusion mechanism. On the bases of aforementioned discussion it can be concluded that the patches having ethyl cellulose

with isopropyl myristate and propylene glycol are more useful for transdermal patches of flurbiprofen.

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