Sorbitan Monolaurate 20 as a Potential Skin Permeation Enhancer in Transdermal Patches

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KEY WORDS: matrix type transdermal patches, diclofenac diethylamine, sorbitanmonolaurate 20, rat skin

ABSTRACT

The objective of our present work was to prepare transdermal matrix patches containing the drug, diclofenac diethylamine with various polymeric combinations of polyvinylpyrrolidone and ethylcellulose and to study the mechanism of release of the drug from the patches and its skin permeation. Sorbitan monolaurate 20 (Span 20), a non-ionic surfactant was added to the concentrations (0.1% wt/vol), as a skin permeation enhancer to the drug, diclofenac diethylamine. In vitro skin permeation studies, with rat skin, using a modified Keshary-Chien diffusion cell, were carried out to establish the most favorable polymeric combination and the impact of Span 20 was also studied. Extensive electron microscopy studies were conducted and the underlying mechanism of drug release from the patches and its permeation through skin are discussed. Cumulative amounts of drug released, per cm^2 of patch after 48 hours, were found to be 2.6111 mg, 3.53 mg, 2.498 mg, 3.373 mg, 3.716 mg, and 4.983 mg, in the formulations PA-1 (PVP: EC 1:2), PA-2 (PVP: EC 1:2 with enhancer), PA-3 (PVP: EC 1:3), PA-4 (PVP: EC 1:3 with enhancer), PA-5 (PVP: EC 3:5), and PA-6 (PVP: EC 3:5 with enhancer), respectively. There was about a 29% to 30% enhancement of skin permeation of the drug using Span 20. It is concluded here that the formulation PA-3 is the slowest in terms of skin permeation of the prepared transdermal matrix patches for diclofenac diethylamine and that Span 20 may be the best choice amongst the skin permeation enhancers to permeate the drug steadily. Moreover, extensive electron microscopic studies were conducted to understand drug distribution in the patches, drug release from the patches, and the permeation of drug through skin.

INTRODUCTION

Groundbreaking drug delivery systems may allow formulation scientists to utilize chemicals that are otherwise difficult to use because of stability, toxicity or bioavailability problems. Drug administration with specific delivery systems can potentially facilitate the

delivery of drugs to the particular site of action, while reducing the undesired side effects, thus drastically increasing patient compliance. Nowadays, transdermal patch-type drug delivery systems are used as a new frontier for the administration of various drugs. Drugs are delivered directly to the systemic circulation through intact skin, bypassing hepatic "first-pass" metabolism, and provide controlled release of drugs for extended and safe use. The nonsteroidal anti-inflammatory drug, diclofenac, is used either topically or systemically to treat various disorders, such as rheumatism, osteoarthritis, osteoporosis, biliary colic, renal colic, dysmenorrhea, etc.[1-6] Ammonium salt (diclofenac diethylamine) is widely used for topical application.[7] The drug causes gastric irritation and undergoes hepatic first-pass metabolism and thus only 50% of drug reaches the circulation.[8] Moreover the drug possesses almost all characteristics needed for transdermal systemic formulations. Thus, the drug has reasonably been chosen to develop a transdermal formulation to increase patient compliance. We have been working on this delivery system for quite some time and have shown that polymeric matrix (PVP: EC 1:2) containing the drug has a potential skin permeation in vitro release profile through the abdominal skin.[9] So, here various other formulations having polymeric composition close to the previous best polymeric combination (PVP: EC 1:2) were studied to establish a potentially more favorable polymeric combination. The non-ionic surfactant, 0.1% wt/vol sorbitan monolaurate-20 (Span 20), was used to study its impact as an enhancer to skin permeation of the drug diclofenac diethylamine. Moreover, extensive electron microscopic studies were conducted in an effort to understand drug distribution in the patches, drug release from the patches, and the permeation of the drug through skin.

MATERIAL AND METHODS

Materials

Polyvinyl alcohol (mol wt. 125,000, viscosity of 4% aqueous solution at 32˚C, 50 cps) was purchased from S.D. Fine Chemicals Ltd., Boisar, India. Polyvinylpyrrolidone (K value 26-4 35) was purchased from HiMedia Laboratories Pvt. Ltd., Mumbai, India. Ethyl cellulose (ethoxy content, 47.5%-49%; viscosity, 14 cps in 5% wt/wt solution in 80:20 toluene; ethanol, 25˚C) was purchased from Central Drug House Pvt. Ltd., Mumbai, India. Sorbitan monolaurate-20 (Span 20) was purchased from Loba Chemie Ltd., Mumbai, India. Diclofenac diethylamine was given by Kothari Laboratory, Saugor, India. Di-n-butyl phthalate was purchased from SRL Pvt. Ltd. (Mumbai, India) All chemicals were used as received without any further purification.

Methods

Procedure for the preparation of patches

The patches were developed using the procedure mentioned earlier.[9] In brief, backing membrane was prepared in a 4% wt/vol aqueous solution of polyvinyl alcohol, placed in cylindrical glass molds, and dried at 60˚C for 6 hours. The drug matrix was cast using homogeneously mixed combinations of polyvinylpyrrolidone and ethylcellulose along with the drug (20% wt/wt of the total weight of the polymer) and the plasticizer, di-n-butyl pthalate (20% wt/wt of the total weight of polymer) on the backing membrane and dried at 40˚C for 4 hours. When the drug was mixed with the polymer-plasticizer mixture, 0.1% wt/vol enhancer (Span 20) was added.

Drug-excipient interaction study

The pure drug, diclofenac diethylamine and a mixture of it with the excipients, PVP, and EC were mixed separately with IR grade KBr in the ratio 100 to 1

Table 1. Composition of the Prepared Film Without Enhancer

S. No.	Formulation Code	Ratio of PVP: EC	Total weight of PVP and EC (mg)
1.	PA-1	1:2	500
2.	PA-3	1:3	500
3.	PA-5	3:5	500

Table 2. Composition of Prepared Film with Enhancer

S. No.	Formulation Code	Ratio of PVP: EC	Total weight of polymers PVP and EC (mg)	Enhancer (Span 20)
1.	PA-2	1:2	500	0.1 wt/vol of the polymer
2.	PA-4	1:3	500	0.1 wt/vol of the polymer
3.	PA-6	3:5	500	0.1 wt/vol of the polymer

and the pellets were prepared by applying 5.5 metric tons of pressure in a hydraulic press. These pellets were scanned over a wave number range of 4000 to 400 cm-1 in a Magna IR 750 series II FTIR instrument (Nicolet, Madison, Wis).

Evaluation of polymeric films

Physical characterizations of the prepared films were evaluated through the following physical studies: 1) moisture content, 2) moisture uptake, and 3) flatness (Tables 1 and 2).

Moisture content. The prepared films were weighed individually and kept in a dessicator containing silica at room temperature for 24 hours. The films were weighed again and again until they showed a constant weight. The percent moisture content was calculated using the following formula:

Percent moisture content = [Initial weight - Final weight/Final weight] □100

Moisture uptake. The weighed film was kept in a dessicator at room temperature for 24 hours. It was then taken out and exposed to 84% relative humidity using a saturated solution of potassium chloride in a dessicator until a constant weight was achieved. The percent moisture uptake was calculated by using the following formula:

Percent moisture uptake = [Final weight-Initial weight/Initial weight] □100

Flatness. One strip was cut one from the center and two from each side of the patches. The length of each strip was measured and the variation in length was measured by determining percent constriction. Zero percent constriction was considered equivalent to one hundred percent flatness. Percent constriction is defined as follows: Constriction (%) =(l_1-l_2)/ l_1 □ 100 where l_2 equals final length of each strip, and $l_1$equals initial length of each strip.

In vitro release-dissolution studies

It is desirable to maintain greater drug concentrations at the surface of *stratum corneum* than in the body. This is required to achieve a constant rate of permeation. The dissolution study, using USP Paddle Type Dissolution Apparatus, was carried out at 32°C at 50-rpm frequency of the paddle. PEG 400

(20% vol/vol) in normal saline was used as the dissolution media. The patches were tied with a thin copper wire and then placed in a jar. Samples were withdrawn at different time intervals and then analyzed using a UV spectrophotometer at 275 nm against blank. Dissolution was carried out for 4 different sets and corrected absorbance (Ca) was calculated using the formula:

$$Ca = {}^{n}_{i-1} A_i + \frac{V_s}{V_t} \sum_{i=1}^{n-1} A_i$$

Ai indicates absorbance of ith reading; Vs, volume of the sample, and Vt, volume of dissolution medium.

The amount of drug was calculated from the standard curve and percentage of drug released was determined using the formula below:

% of drug released = Da/Dt □100

Dt indicates the total amount of drug in the patch; and Da, the amount of drug released.

In vitro skin permeation study

The in vitro permeation studies were carried out in a modified Keshary-Chien diffusion cell with a capacity of 30 mL, using Sprague-Dawley male rat skin. The skin was used after the removal of adhering fat. A section of skin was cut and placed in the donor compartment, keeping the dorsal side upward, and the patch was placed on the skin with the drug matrix side towards the donor side and backing membrane on the upper side. The holder, containing the skin and the formulation, was placed on the receiver compartment of the cell containing the dissolution media (ie, PEG 400) (20% vol/vol) in normal saline. The temperature of the cell was maintained at 32˚C by circulating water jacket. This whole assembly was kept on a magnetic stirrer and the solution was stirred continuously using a magnetic bead. A similar set was run simultaneously without using the patch at the donor compartment as a skin control. The samples were withdrawn at different time intervals and replaced with equal amounts of dissolution media. Samples were analyzed spectrophotometrically at 275 nm and the amount of drug permeated per cm^2 of patch was calculated from the standard curve and plotted against time. The difference between the readings of drug skin permeation and skin control was used as the actual reading in each case.

Scanning electron microscopy

The external morphology of the skin and the transdermal patch (with and without enhancer) was analyzed using a scanning electron microscope. The skin was first fixed with the help of a fixative (ie, 4% glutaraldehyde) in 0.2 mol sodium phosphate buffer (pH 7.2-7.4). The skin was washed with buffer thoroughly and then subjected to dehydration with acetone. The moisture from the skin was removed by using increasing concentrations of acetone. The section of the skin was cut and mounted on stubs using an adhesive tape. The samples placed on the stubs were coated with gold palladium alloy using a fine coat ion sputter (JOEL, fine coat ion sputter JFC-1100). The sections were examined under scanning electron microscope (JSM 6100 JEOL, Tokyo, Japan). The abdominal skin of the rat was excised and the fat layer was removed, carefully keeping the underlying dermal tissues containing capillary network intact, using a sterile scalpel with the help of a high power magnifying glass. The process was conducted very quickly and the tissue was immediately used for experiments.

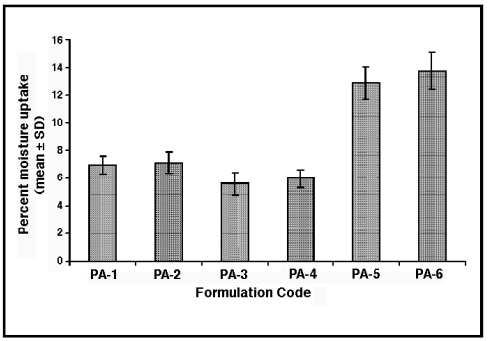

Figure 1. Percentage moisture uptake from diclofenac diethylamine containing different matrix films prepared by using different ratios of polyvinylpyrrolidone and ethyl cellulose. Data shows mean (n = 5) ± SD.

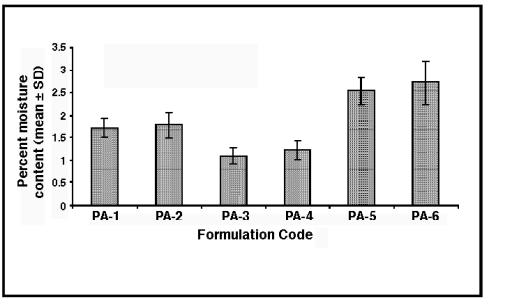

Figure 2. Percentage moisture content of diclofenac diethylamine containing different matrix films prepared by using different ratios of polyvinylpyrrolidone and ethyl cellulose. Data shows mean (n = 5) ± SD.

Statistics

Data were analyzed using the standard statistical methods.

RESULTS

Some important physicochemical parameters of the prepared formulations were evaluated in this study (Tables 1 and 2). The transdermal patches were exposed to 84% relative humidity and the percentage moisture uptake of the formulation was determined (Figure 1). It was observed that with an increasing percentage of hydrophilic polymer, PVP, in the formulations, moisture content increased. Interestingly, with the addition of Span 20 in the patches, little increase (statistically insignificant) of moisture was observed. A similar observation was made in the case of percentage moisture content (Figure 2).

A transdermal patch should possess a smooth surface and should not constrict with time, as the flatness study demonstrated. No constriction was observed in any of the prepared formulations; all of the surfaces were 100% flat (Table 3). Fourier transform infrared spectroscopy (FTIR) was carried out to assess the interaction between the drug and the excipients (Figures 3a and 3b). Graphs of drug and drug-excipients show that there is no interaction between the drug and excipients used.

Drug release from polymer matrix and drug dissolution ensures sustained reproducibility of rate and duration of drug release. Dissolution studies for different formulations were carried out using USP paddle type apparatus using PEG 400 and normal saline as dissolution fluid at 32˚C. An initial burst effect was observed in formulations PA-5 (PVP: EC 3:5 without enhancer) and PA-6 (PVP: EC 3:5 with enhancer) (Figure 4). In this figure the mean cumulative amount released for formulation PA-5 decreases in 4 hours compared to 3 hours. The reason could be the wide variation of data of drug release in two of the experiments, out of 4 performed. However, in Figure 5, which depicts in vitro skin permeation, no such discrepancies are seen in any of the formulations. Hence, an experimental error during sampling could be one possible reason for the decrease in the cumulative amount seen in the case of formulation PA-5 at the particular time point. In vitro skin permeation study is predictive of an in vivo performance of a drug. This study was carried out using different formulations in a modified Keshary-Chien cell using rat skin. Mean cumulative amounts of drug released per cm^2 of patch after 48 hours were found to be 2.6111 mg, 3.53 mg, 2.498 mg, 3.373 mg, 3.716 mg, and 4.983 mg, for the formula-

Table 3. Determination of Flatness of the Films

Formulation Code	PVP: EC	Film length (cm)	Amount of constriction in the strips	Flatness (%)
PA-1	1:2	2.5 ± 0.01*	0	100
PA-2	1:2 with enhancer (Span 20)	2.5 ± 0.01	0	100
PA-3	1:3	2.5 ± 0.005	0	100
PA-4	1:3 with enhancer (Span 20)	2.5 ± 0.005	0	100
PA-5	3:5	2.5 ± 0.004	0	100
PA-6	3:5 with enhancer (Span 20)	2.5 ± 0.004	0	100

*Data represents mean ± SE (n = 6)

tions PA-1 (PVP: EC 1:2), PA-2 (PVP: EC 1:2 with enhancer), PA-3 (PVP: EC 1:3), PA-4 (PVP: EC 1:3 with enhancer), PA-5 (PVP: EC 3:5), and PA-6 (PVP: EC 3:5 with enhancer), respectively (Figure 5). Again percentages of drug released per cm^2 of the patches after 48 hours were 13.05%, 17.65%, 12.49%, 16.86%, 18.58%, and 24.91%, for the formulations PA-1, PA-2, PA-3, PA-4, PA-5, and PA-6, respectively.

The study clearly indicates the skin permeation enhancement of the drug by using sorbitan monolaurate 20. About 29% to 30% enhancement of skin permeation is seen (Figure 5). With a little variation of ratio of PVP and EC from 1:2 to 3:5, an "initial burst effect" was noticed (Figure 4). Again, when skin permeation studies were conducted, the rates of skin permeation in those formulations (PA-5 and PA-6) were high. It may be because the formulations lost their polymeric chain network and provide an "initial burst" effect and an opening for the drug cluster for faster release through them.

EM Result

Electron microscopic studies were conducted to visualize drug penetration through the skin and its distribution in the matrix patches. The drug distribution in the matrix patches was a particulate distribution (Figure 6). The drug and the excipients were soluble in chloroform and no chemical interaction was noticed, when FTIR results were compared (Figure 3). Figure 7 shows one of the drug clusters on the skin surface during its entry through a skin appendage. This result confirms that the drug remains in cluster form when it reaches the surface. Figure 8 shows a drug cluster is passing through one of the skin appendages from the dorsal side to the ventral side of the skin. Figure 9 shows that drug clusters reached the ventral side of the skin. These figures clearly indicate that the drug, in cluster form, was transported from the dorsal side to the ventral side of the skin. In an experiment with a specially prepared skin, keeping the blood capillary network intact at the ventral side, it was shown that the drug reaches the ventral side of the skin (Figure 10). Again, this shows that the drug travels in cluster form, even when it passes through the skin, and that a drug particle reached the surface of blood capillaries to diffuse the drug molecules in the blood.

DISCUSSION

In this study, transdermal patch delivery systems, containing the well-established

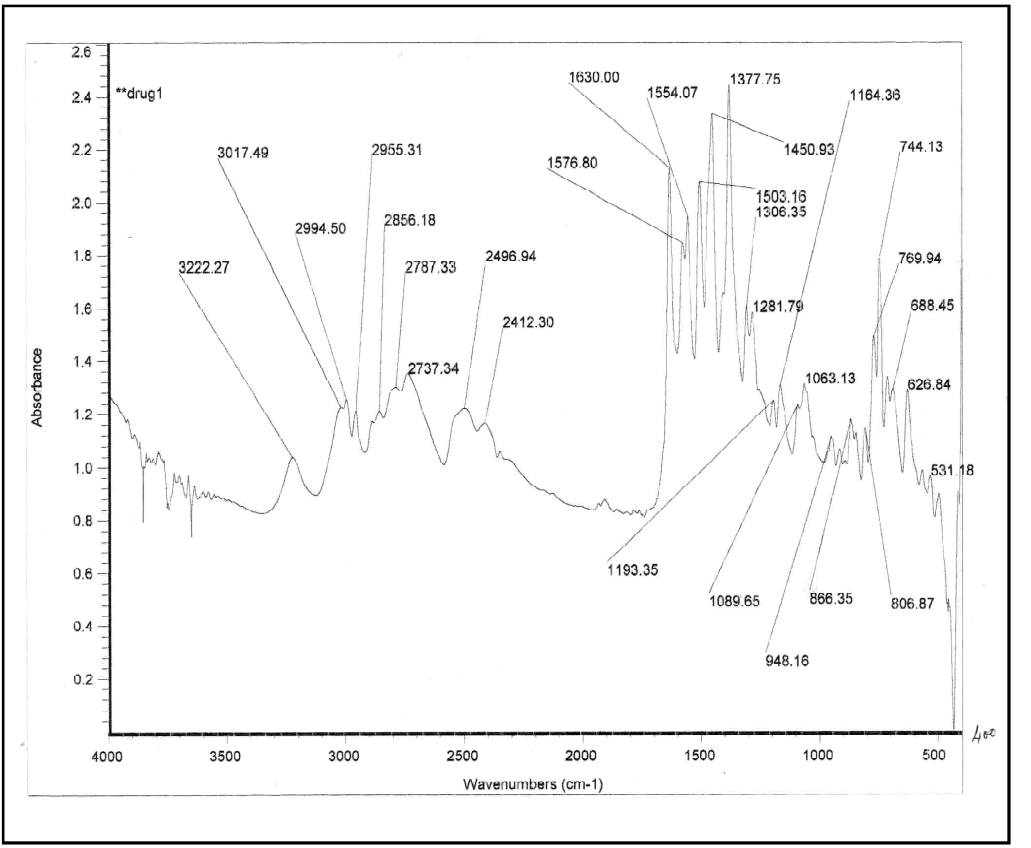

Figure 3A. IR spectra of pure drug.

nonsteroidal anti-inflammatory analgesic drug diclofenac diethylamine (diethylammonium salt of diclofenac) in various combinations of ethylcellulose-polyvinylpyrrolidone polymeric matrices with or without sorbitanmonolaurate 20 (Span 20) as skin permeation enhancer, were developed for percutaneous studies of transdermal drug delivery systems. The patches were subjected to in vitro permeation and permeation enhancement studies through rat skin using a modified Keshary-Chien diffusion cell. Some physicochemical parameters like moisture content, moisture uptake, and flatness were also carried out to evaluate the physicochemical stability of the formulation. An electron microscopic was used to visualize what actually happens when the drug diffuses through the skin and how it diffuses from the patch formulations. The drug molecules were distributed in the form of small clusters within the range of 1 to 3 µm. Though the drug, polymers, plasticizer, and enhancer are completely soluble in chloroform, the distribution of the drug in the polymer matrix was in a particulate distribution (Figure 6). Stability of a formulation primarily depends on the compatibility of the drug with the excipients. Hence, it is important to detect any possible chemical or physical interactions, since they can affect the bioavailability and stability of the drug.[10]

Drug-excipient interactions were studied using FTIR technique to understand the physical and chemical interactions that could occur in the drug and excipients. FTIR study implied that all the excipients are compatible with diclofenac diethylamine. Changes in

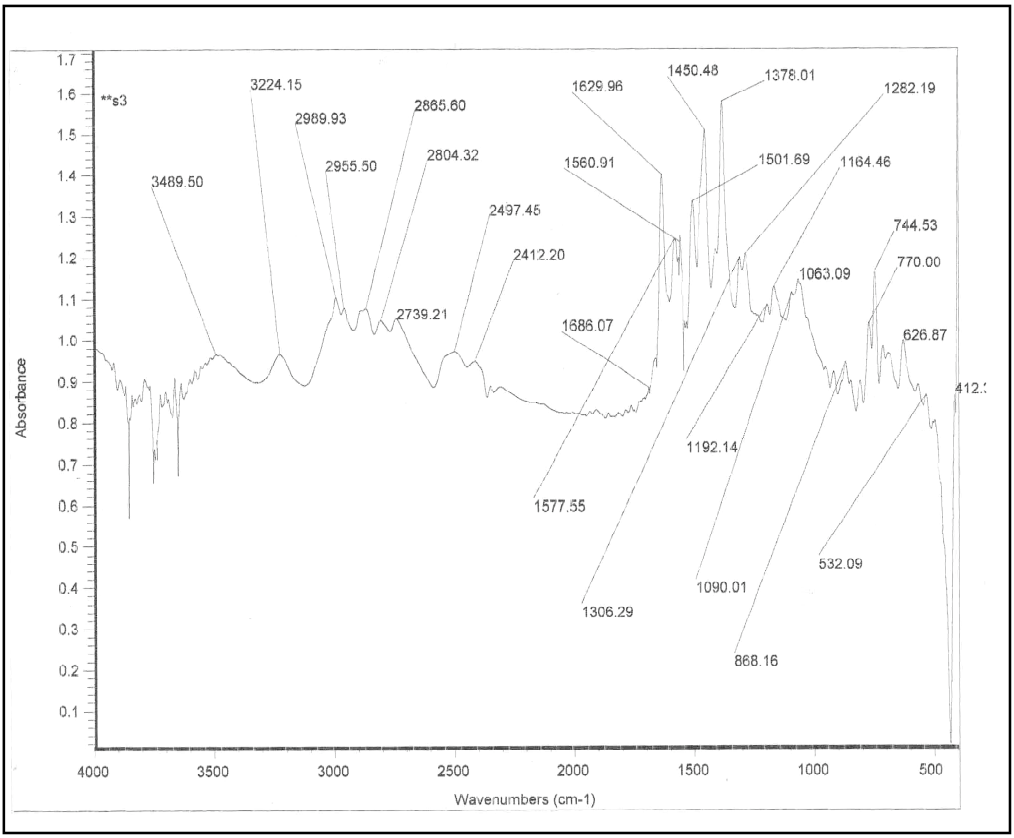

Figure 3B. IR spectra of drug and excipients.

areas of peaks occur simply due to mixing of components without any physical and chemical interactions. In our previous study,[9] we also found that there was no chemical interaction between diclofenac diethylamine and the same excipients using Thin Layer Chromatography technique. The intermolecular forces between drug molecules are stronger (ionic in nature), as compared to those between the drug and the polymers (ie, ionic drug and slightly polar matrix compounds). Drug molecules through electrostatic forces may form soluble polyion drug complex aggregates[11] surrounded by polymer molecules, which prevents drug aggregate precipitation while in the solution. Simultaneous precipitation of drug complexes with polymers takes place during the solvent evaporation technique.

As human skin is not easily available for experimentation, rat and mouse skin are frequently used for in vitro studies of skin permeation of drugs.[12-14] The selection of receptor fluid is an important criterion in the design of in vitro studies for transdermal drug delivery systems. Biphasic characteristics of the receptor fluid are desirable, since drug molecules are diffused through both aqueous and nonaqueous heterogeneous media. PEG 400, plus water or normal saline, is commonly chosen to provide the biphasic characteristics to the receptor fluid.[15] Moreover, PEG 400 is considered to be a non-interacting fluid for the receptor media.[16] Percutaneous absorption of the drug is believed to take place through various skin appendages (ie, sweat and sebaceous ducts, hair follicles, etc), at an early stage and at steady

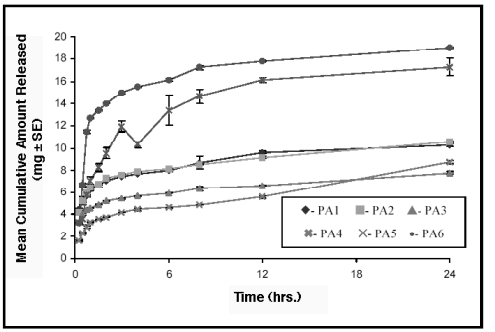

Figure 4. In vitro drug dissolution profiles of diclofenac diethylamine from different PVP and EC matrix patches in PEG400+Normal saline. Data shows mean ± SE (n = 4).

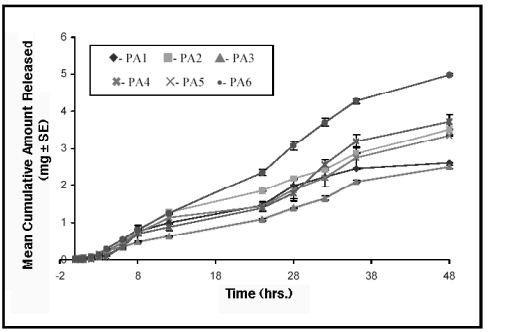

Figure 5. In vitro skin permeation of diclofenac diethylamine from different PVP and EC matrix patches, through rat abdominal skin. Data shows mean ± SE (n = 4).

state. These routes are considered significant, with the implication that various shunt pathways from one part of the skin to the other may result in the ultimate skin release profile of the drug.[17] The electron microscopic study of the dorsal sides of the skin, used for skin permeation studies after the application of the various patches, depicted no such distinctive changes of the skin condition, except some more flat physical surface appearances of the skin exposed to the formulation with enhancer (data not shown). This suggests that there is no harmful effect of Span 20, when used as a skin permeation enhancer at the concentration used in our study, in transdermal patch form, even after 48 hours of administration. Figure 7 shows one of the drug polyion complexes (shown by arrow 2) on the skin surface during their entry through skin appendage (shown by arrow 1). Figure 8 shows a drug cluster passing through one of the skin appendages from the dorsal side to the ventral side of the skin. Figure 9 shows that drug clusters reached the ventral side of the skin. These figures clearly indicate that the drug in cluster form was transported from the dorsal side to the ventral side of the skin. Again skin was specially prepared keeping the blood capillary network intact at the ventral side, and the experiment was conducted to monitor big drug complexes after diffusion through the epidermis. Of particular interest was how such a big cluster of drug molecules is absorbed through blood capillaries, when the capillary diameters are smaller. Interestingly, it was observed that a drug cluster reached the surface of blood capillary by diffusing the drug molecule through the capillary walls in the blood (Figure 10).

The scanning electron microscopic study showed skin permeation of soluble drug clusters through skin appendages and that small soluble clusters of drug molecules penetrate through the appendages to blood capillary walls, which then dissolve and penetrate as soluble molecules in the blood. This is established for the first time in this study. We strongly believe that soluble drug molecules of drug clusters not only penetrate through the intact skin texture, but they also permeate through the appendages. Based on this observation, we strongly believe that the diffusion of the drug through blood capillary walls plays a very significant rate-limiting role, as it does in the passage of the drug through epidermis. The skin permeation study may not clearly predict the blood level of the drug in transdermal patch formulations. There is little doubt that skin permeation can be enhanced by non-ionic surfactants, including sorbitan esters and polyoxyethylene sorbitan esters.[18-23]

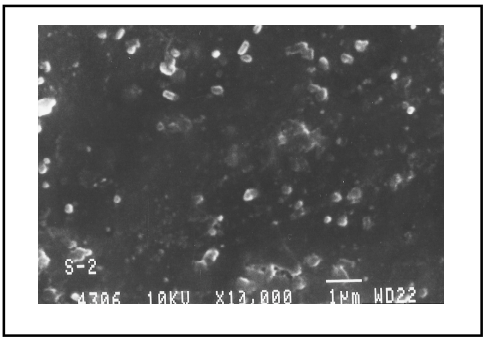

Figure 6. SEM photograph of the transdermal patch shows the distribution of the drug in the matrix as particulate distribution.

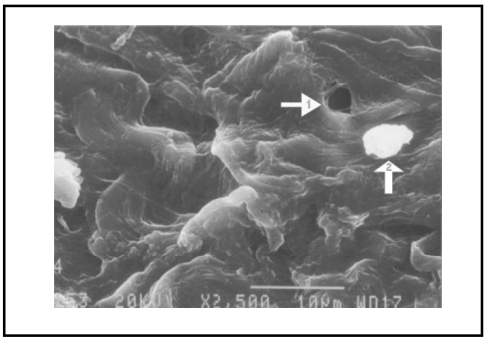

Figure 7. SEM photograph shows one of the drug particles on the skin surface during their entry through skin appendage.

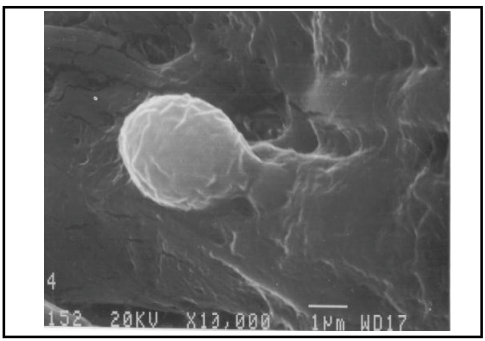

Figure 8. SEM photograph shows drug one cluster passing through one of the skin appendages from the dorsal side to the ventral side of the skin.

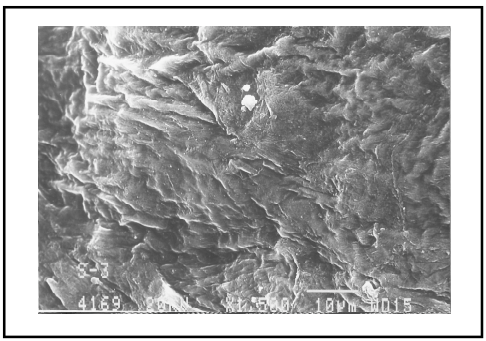

Figure 9. SEM photograph shows a drug cluster as such reached at the ventral side of the skin.

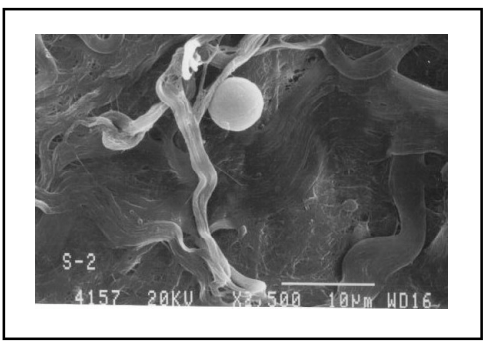

Figure 10. SEM photograph shows how a drug cluster proceeds for absorption through the wall of blood capillary at the ventral side of the skin.

The mechanism of penetration enhancement effects of the surfactants is primarily believed to be due to the promotion of membrane-vehicle partitioning tendency of the drug.[24] Penetration of the surfactants into the intracellular lipid phase of the membrane may also increase the degree of fluidity in this phase resulting in a decreased resistance to permeation.[25] Increase in this flux of the drug across the skin is mainly due to solvent drag effect.[26] The penetration of the solvent itself, and subsequent drag of the drug cluster with it, is the mechanism of drug release from the patches. Span 20 increases the quick partitioning of the drug in the solvent[16] and small drug-polyion complexes (approximately 3 μm are dragged by the solvent through the appendages, the average diameters of which are about 50 μm. The driving force behind this diffusive transport is a gradient in the chemical potential.[27] Some important physicochemical parameters of different formulated

patches were evaluated in this study. The moisture content and moisture uptake of the various formulations showed that with the increase in concentration of hydrophilic polymer and PVP, both the percentage of moisture content and that of moisture uptake increased (Figures 1 and 2). Again, 100% flatness (ie, no amount of constriction) was observed (Table 3). This finding demonstrates flat and smooth patch surface, a very important characteristic of transdermal patch type formulation. The percentage moisture content and moisture uptake was found to be maximal for formulation PA-5 and PA-6. A little bit of moisture content prevents the brittleness of the patches, while less moisture uptake indicates the stability of the formulation, since a greater amount of moisture uptake indicates bulkiness of the formulation. Moreover, the chance of microbial growth cannot be ignored. Polymer dissolution and drug release from polymeric matrix is known to ensure sustained release characteristics, as well as reproducibility of rate and duration of drug release.[28] In this study, we found that formulation (PVP: EC 3:5) with or without enhancer showed 'initial burst' release. This may be due to the presence of higher percentages of hydrophilic polymer polyvinylpyrrolidone, which might need a small "time lag" to establish a concentration profile in the patches, resulting in a burst release effect in the dissolution study.

When in vitro skin permeation of the drug from different formulations was compared, variable cumulative drug release profiles were observed in formulations PA-1 to PA- 6. Formulations, PA-1 to PA-6, had a zero order profiles of cumulative amounts of drug release over time. The formulation PA-3 (PVP: EC 1:3) had the slowest release, whereas the formulation PA-6 (PVP: EC-3: 5 with enhancer Span 20) had the fastest release of drug, among the formulations studied (Figure 5). After 48 hours, the percentages of drug permeated through the skin were about 12.5% (PA-3) and 25% (PA-6). When the enhancer, Span 20, was used in the same composition of the formulation PA-3, the percentage drug release was about 17% instead of 12.5% after 48 hours. For formulation PA-5 (ie, the same composition of PA-6 without enhancer), the percentage drug release was about 18.5% in 48 hours. Therefore, enhancing the capability of skin permeation of the diclofenac diethylamine drug by Span 20 is unambiguous. In fact, when the mean cumulative amounts of drug release through skin were studied, any of the polymeric combinations seem suitable for the preparation of transdermal matrix patches containing diclofenac diethylamine. Combinations of polymers used here provide a sustained release of the drug in all formulations and the enhancer reasonably increased (about 29-30%) the amount of drug released from the patches through the skin.

CONCLUSION

All the formulations may be chosen for further in vivo studies, except formulations PA-5 (PVP: EC 3:5) and PA-6 (PVP: EC with enhancer) because they show an initial 'burst effect'. The formulation PA-3 (PVP: EC 3:5) showed the slowest and sustained release of the drug through the skin. Using Span 20, there was about a 29% to 30% enhancement of skin permeation of the drug. Again, it is concluded here that the formulation PA-3 is the slowest in terms of skin permeation amongst the prepared transdermal matrix type patches for diclofenac diethylamine and Span 20 may be an option amongst the skin permeation enhancers for permeating the drug steadily through the skin. Further, the study demonstrates that the solvent drags the drug diclofenac diethylamine in the soluble cluster form through the

skin appendages, and they reach the wall of the blood capillaries.

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