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Research paper

A comparison between povidone-ethylcellulose and povidone-eudragit transdermal dexamethasone matrix patches based on in vitro skin permeation

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Abstract

The present study was designed to develop a suitable matrix type transdermal drug delivery system (TDDS) of dexamethasone using blends of two different polymeric combinations, povidone (PVP) and ethylcellulose (EC) and Eudragit with PVP. Physical studies including moisture content, moisture uptake, flatness to study the stability of the formulations and in vitro dissolution of the experimental formulations were performed to determine the amount of dexamethasone present in the patches were performed and scanning electron microscopy (SEM) photographs of the prepared TDDS were taken to see the drug distribution pattern. Drug–excipient interaction studies were carried out using Fourier transform infrared (FTIR) spectroscopic technique. In vitro skin permeation study was conducted in a modified Franz's diffusion cell. All the formulations were found to be suitable for formulating in terms of physicochemical characteristics and there was no significant interaction noticed between the drug and polymers used. In vitro dissolution studies showed that the drug distribution in the matrix was homogeneous and the SEM photographs further demonstrated this. The formulations of PVP:EC provided slower and more sustained release of drug than the PVP:Eudragit formulations during skin permeation studies and the formulation PVP:EC (1:5) was found to provide the slowest release of drug. Based on the above observations, it can be reasonably concluded that PVP–EC polymers are better suited than PVP–Eudragit polymers for the development of TDDS of dexamethasone.

Keywords: Dexamethasone; Transdermal patches; Eudragit; PVP; Ethylcellulose; In vitro skin permeation studies

1. Introduction

Transdermal drug delivery is the delivery of drugs across epidermis to achieve systemic effects. The success of transdermal patches lies in their commercialization. Transdermal patches control the delivery of drugs at controlled rates by employing an appropriate combination of hydrophilic and lipophilic polymers [1–4].

Dexamethasone, a synthetic glucocorticoid [5] suppresses inflammation [6] and normal immune response [7]. It is widely used as a therapeutic agent in alcohol withdrawal syndrome [8], cerebral oedema [9], congenital adrenal hyperplasia [5], nausea and vomiting specially associated with high dose of anticancer agents [10], high altitude disorder, cerebral malaria, opportunistic mycobacterial infections, respiratory disorders, skin disorders [5], rheumatism [11], meningitis, early mild carpal tunnel syndrome and as a diagnostic agent in Cushing's syndrome [12]. Commercial topical preparations of dexamethasone include dexamethasone aerosol, dexamethasone gel [13] among others. Although a good number of topical gel formulations of dexamethasone are available, they are not suitable for prolonged, controlled and systemic delivery of the drug through intact skin. Moreover, they are not a suitable drug delivery option to transdermal patches.

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Topical dexamethasone administered as an osmotic pump to brain tumor beds resulted in an increase in survival similar to systemic dexamethasone. To avoid complications of systemic steroid treatment, dexamethasone given topically is a more suitable alternative in such conditions [14]. Moreover, dexamethasone possesses most of the ideal physicochemical and biological properties, e.g. biological half-life ranging between 2 and 5 h, plasma protein binding nearly about 67%, a small dose ranging from 0.5 to 9 mg daily, hepatic first pass effect of the drug and gastric irritation upon oral administration [15], to be formulated into a transdermal patch type delivery system. A number of researchers have also reported some methodologies for increasing the transdermal absorption of dexamethasone from solution/gel formulation by employing iontophoresis [16] and phonophoresis [17,18]. But so far, no work related to the development of pre-filled transdermal patches of dexamethasone has been reported in the literature.

The system designs for transdermal patches include matrix, microreservoir, reservoir, adhesive and membrane–matrix hybrid. Matrix type transdermal patches remain among the most popular, as they are easy to manufacture.

The present study was designed to develop a suitable matrix patch type transdermal drug delivery system (TDDS) for dexamethasone employing various ratios of polyvinylpyrrolidone (PVP) and EC as well as PVP and Eudragit®. The aim was to compare the polymeric combinations in terms of in vitro skin permeation of the drug and to find out the best possible ratio of hydrophilic and lipophilic polymeric combination, which may be chosen for further studies.

2. Materials and methods

2.1. Materials

Ethylcellulose (ethoxyl content 47.5–49% w/w; viscosity 14 cps of 5% w/w solution, 80:20 toluene:ethanol solution at 25 °C, BDH Chemicals Ltd, Poole, England), Eudragit RL-100 (M/s Rohm Pharma GmbH, Darmstadt, Germany), polyvinylpyrrolidone (PVP; *K*-value 26–35, Hi-Media Laboratories Pvt. Ltd, Mumbai, India), di-*n*-butylphthalate (Central Drug House (Pvt) Ltd, Mumbai, India), chloroform (E. Merck Ltd, Mumbai, India) were obtained commercially. Polyvinyl alcohol (PVA; m.w 125,000), polyethylene glycol 400 and sodium chloride were purchased from S.D. Fine Chemicals Ltd, Boisar, India. Dexamethasone was received as a gift sample from M/s Bio-Ethicals Pharma Limited, Dharwad, India. All the chemicals were used as received without any further purification.

2.2. Preparation of films

TDDS composed of different ratios of EC and PVP as well as Eudragit® and PVP containing dexamethasone (∼1.2 mg/square centimeter patch) were prepared using the glass mould solvent evaporation technique [19]. Di-*n*-butylphthalate was incorporated as a plasticizer at a concentration of 20% w/w of dry weight of polymers. Backing membrane was cast by pouring and then evaporating 4% aqueous solution of polyvinyl alcohol in glass moulds covered on one side with aluminum foil, at 60 °C for 6 h. The matrix was prepared by pouring the homogeneous dispersion of drug with different blends of either type of lipophilic polymer (EC or Eudragit) with PVP in chloroform on the backing membrane in glass moulds. The above dispersion was evaporated slowly at 40 °C for 2 h to achieve a drug–polymer matrix patch. The dry patches were kept in desiccators until use.

2.3. Drug–excipient interaction study

The pure drug, dexamethasone and a mixture of it with the polymers, PVP, EC and PVP, Eudragit were mixed separately with IR grade KBr in the ratio of 100:1 and corresponding pellets were prepared by applying 5.5 metric ton of pressure in a hydraulic press. The pellets were scanned over a wave number range of 4000–400 cm^{-1} in Magna IR 750 Series II (Nicolet, USA) FTIR instrument.

2.4. Physical characteristics of the prepared films

The following physical studies were conducted:

2.4.1. Moisture content

The film was weighed and kept in a desiccator containing calcium chloride at 40 °C in a drier for at least 24 h or more until it showed a constant weight. The moisture content was the difference between the constant weight taken and the initial weight and was reported in terms of percentage (by weight) moisture content (Fig. 1).

2.4.2. Moisture uptake

A weighed film kept in desiccators at 40 °C for 24 h was taken out and exposed to two different relative humidity of 75% (saturated solution of sodium chloride) and 93%

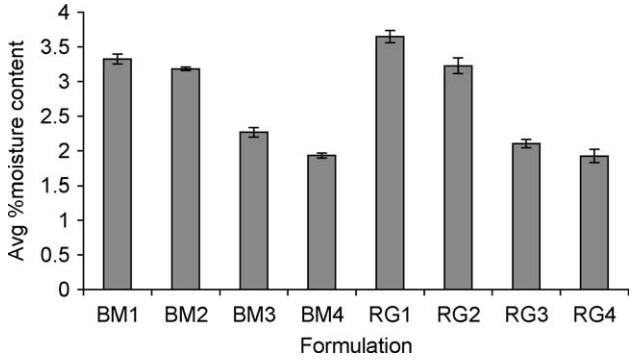

Fig. 1. Average percentage of moisture content (by weight) of different formulations. Data shows mean ($n=20$) ±SE.

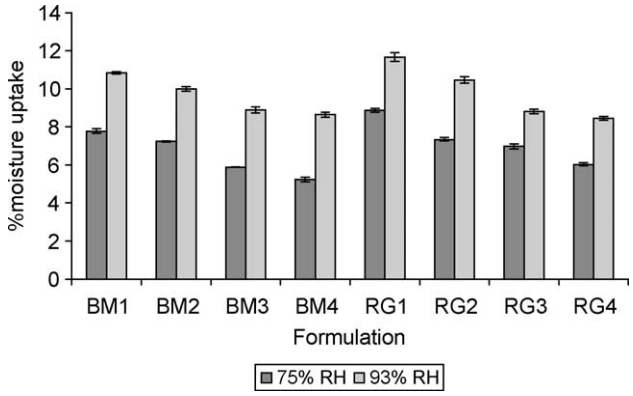

Fig. 2. Percentage moisture uptake (by weight) of the different formulations. Data shows mean ($n=20$) $\pm$SE.

(saturated solution of ammonium hydrogen phosphate) in two different desiccators, respectively, at room temperature. Then the weights were measured periodically to constant weights (Fig. 2).

2.4.3. Flatness

Longitudinal strips were cut out from the prepared medicated patches and the lengths of each strip were measured and then the variation in the lengths due to the non-uniformity in flatness was measured (Table 1). Flatness was calculated by measuring constriction of strips and a zero percent constriction was considered to be equal to a hundred percent flatness.

Constriction $(\%)=(l_1-l_2)/l_2\times 100$

Where l_1, initial length of each strip; l_2, final length.

2.5. Scanning electron microscopy

The external morphology of the transdermal patches was analyzed using a scanning electron microscope (JSM 6100 JEOL, Tokyo, Japan). The samples placed on the stubs were coated finely with gold palladium alloy and examined under the microscope.

2.6. Determination of drug content in the patches

An in vitro drug dissolution study was conducted using USP dissolution apparatus (Disso 2000, Labindia, Thane, India) in dissolution media (normal saline containing 20% v/v polyethylene glycol 400) keeping 1 cm^2 of patch. Aliquot samples were taken from the dissolution media at different time intervals until spectrophotometer readings became constant. The samples were analyzed spectrophotometrically at 244 nm and the amounts of drug present were calculated from the calibration curve (Table 2).

2.7. In vitro skin permeation studies

The in vitro skin permeation of dexamethasone from the selected TDDS through depilated mouse abdominal skin was conducted using a modified Franz diffusion cell. The study was conducted in accordance with the Helsinki declaration and animal care and facilities in Principles and Methods of Toxicology [19].

Normal saline containing 20% v/v of polyethylene glycol 400 was used as bathing solution [20] in the receptor compartment of a modified Franz diffusion cell. The selection of the receptor fluid is an important criterion in the in vitro skin permeation studies. Biphasic characteristics of the receptor fluid are desirable as the diffusion of drug molecules is through both aqueous and non-aqueous heterogeneous media. PEG 400 and normal saline are commonly chosen to provide the biphasic characteristics to the receptor fluid [21]. Moreover, PEG 400 is a non-interacting fluid for the receptor media [22]. The abdominal skin of Laca mice weighing 26 ± 2 g was used. Hairs on the abdominal area were removed using depilatory agent for 10 min about 12 h before sacrifice. Mice were sacrificed by cervical dislocation. Abdominal skin was excised and the fatty tissue attached to the dermis were removed carefully. The skin was mounted between donor and receiver compartments of the diffusion cell having capacity 300 ml with the epidermis facing upward into the donor compartment. The film of area 1 cm^2 to be tested was placed on the skin. The bathing solution in receiver compartment was

Table 1
Average thickness and flatness of the different formulations ($n=20$)

Polymeric blend	Formulation code	Ratio (w/w)	Strip length (cm)	Constriction of strip	Mean thickness (μm)	Mean flatness (%)
PVP–EC	BM1	3:2	2	0	58 ± 0.12^a	100 ± 0.03^a
PVP–Eudragit	RG1	3:2	2	0	67 ± 0.33^a	100 ± 0.10^a
PVP–EC	BM2	2:3	2	0	57 ± 0.27^a	100 ± 0.04^a
PVP–Eudragit	RG2	2:3	2	0	58 ± 0.87^a	100 ± 0.04^a
PVP–EC	BM3	1:4	2	0	59 ± 0.68^a	100 ± 0.07^a
PVP–Eudragit	RG3	1:4	2	0	64 ± 0.68^a	100 ± 0.08^a
PVP–EC	BM4	1:5	2	0	66 ± 0.92^a	100 ± 0.04^a
PVP–Eudragit	RG4	1:5	2	0	56 ± 0.57^a	100 ± 0.04^a

[a] Each value indicates the mean $\pm$SE ($n=20$).

Table 2
Drug concentration in the patches by in vitro drug dissolution study ($n=10$)

Formulation code	Average drug concentration (mg/cm^2)
BM1	1.1651 ± 0.055[a]
BM2	1.2985 ± 0.037[a]
BM3	1.1322 ± 0.060[a]
BM4	1.287 ± 0.092[a]
RG1	1.1564 ± 0.097[b]
RG2	1.1054 ± 0.069[b]
RG3	1.2852 ± 0.034[b]
RG4	1.1796 ± 0.082[b]

[a] Each value indicates the mean $\pm$ SE ($n=10$).
[b] Each value indicates the mean $\pm$ SE ($n=12$).

agitated with a magnetic stirrer at a temperature of 34 ± 1 °C maintained thermostatically. Samples (1 ml in each case) were withdrawn at regular intervals and fresh receptor fluid was added to maintain a constant volume of receptor fluid. The samples were analyzed spectrophotometrically at 244 nm and the drug content was determined from the calibration curve. A similar set was run simultaneously using the patch (without drug) at the donor compartment as a skin patch control system to avoid the influence of inherent extracts from the skin or leaching of any material from the patch without drug on the absorbance at 244 nm, at which the sample aliquots were analyzed spectrophotometrically.

3. Results

The physicochemical studies like moisture content, moisture uptake, flatness etc. provide information regarding the stability of the formulations. The moisture content and moisture uptake (Figs. 1 and 2) varied to a small extent in all the formulations studied. However, there was an increase in moisture content and uptake with an increase in hydrophilic polymers, PVP and Eudragit in matrix patches. The moisture content was found to be greater with the increase of Eudragit as compared to hydrophobic polymer EC. All the patches showed one hundred percent flatness (Table 1), which indicates no amount of constriction of the formulated patches. In vitro dissolution studies were carried out for the different formulations using USP dissolution apparatus using PEG 400 and normal saline as the dissolution fluid at 32 °C to determine the drug content in the patches. The average dexamethasone contents in the PVP–EC transdermal drug delivery systems BM1, BM2, BM3 and BM4 were found to be 1.1651, 1.2985, 1.1322 and 1.2873 mg/cm^2,

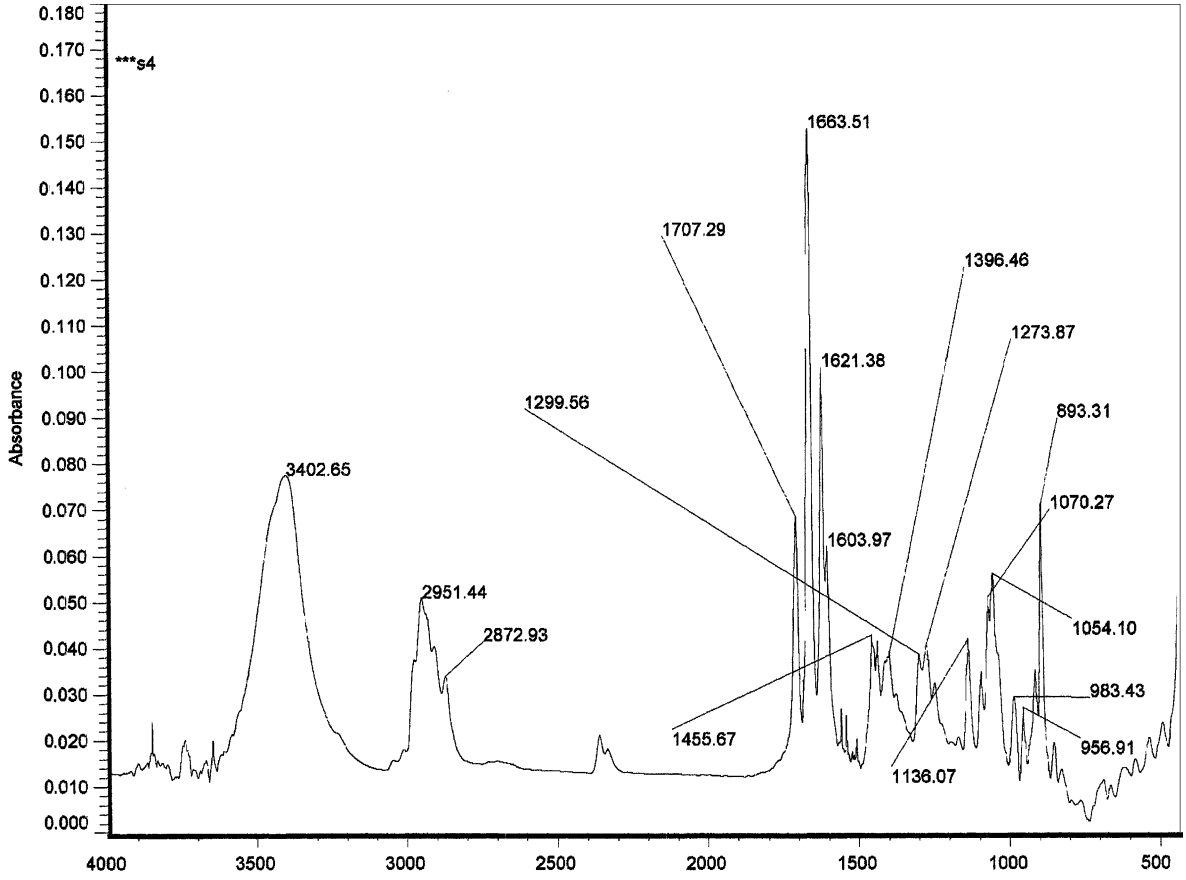

Fig. 3. IR spectra of the dexamethasone with ethylcellulose and polyvinylpyrrolidone.

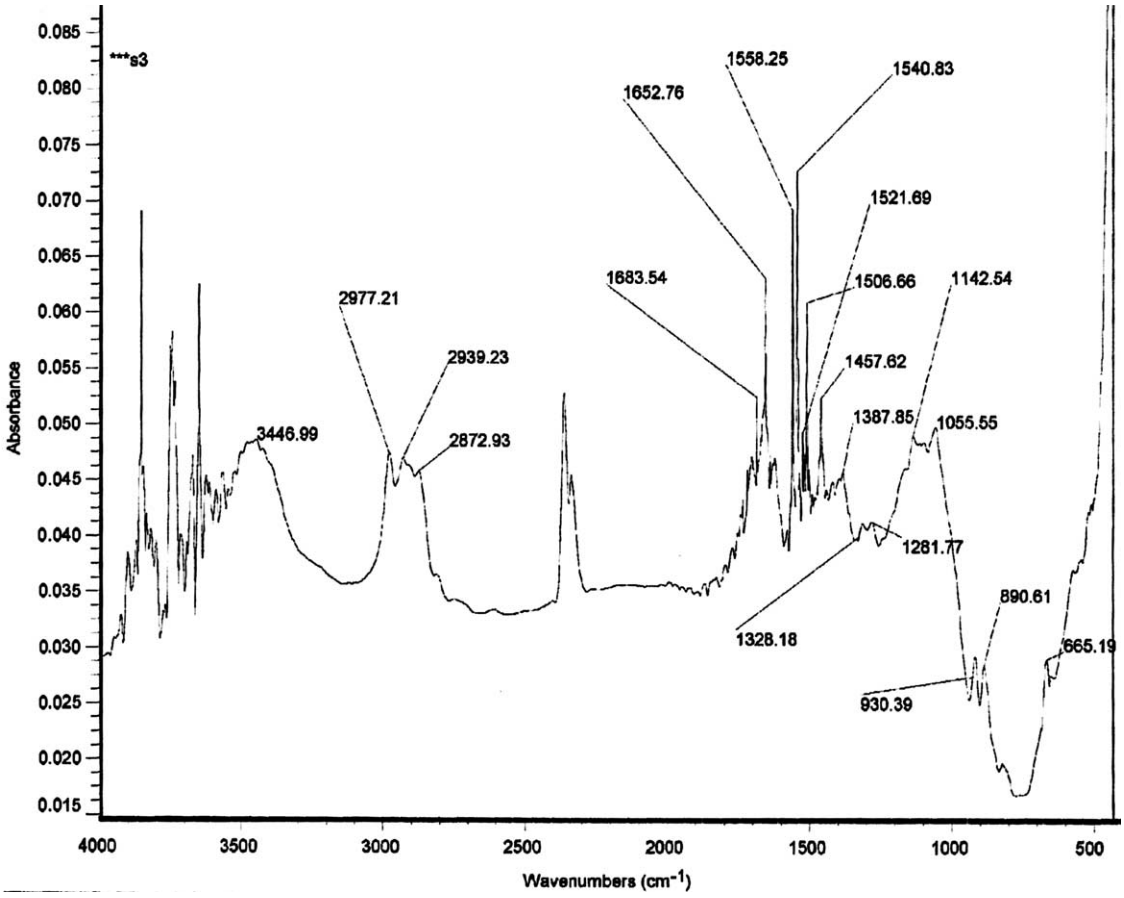

Fig. 4. IR spectra of dexamethasone with eudragit and polyvinylpyrrolidone.

respectively (Table 2). The drug content in the PVP–Eudragit TDDS RG1, RG2, RG3 and RG4 was 1.1564, 1.1054, 1.2825 and 1.1796 mg/cm^2 (Table 2), respectively. This demonstrates homogeneous distribution of the drug. This is further confirmed by SEM studies (Figs. 6 and 7). FTIR spectra were recorded to assess the interaction between the drug and excipients (Figs. 3–5). The figures showed no distinctive physical or chemical interactions between the drug and the polymers. There are some very minor changes in the peaks in the range of 2800–3500 cm^{-1}. This indicates that there may be some physical interactions related to the formation of weak to medium intensity hydrogen bonding between polymers.

An in vitro skin permeation study is predictive of in vivo performance of a drug. The study was carried out in a modified Franz's diffusion cell. Mean cumulative amounts of drug permeated from the patch after 20 h were found to be 0.758, 0.706, 0.598, 1.091, 0.186, 0.115, 0.090 and 0.080 mg/cm^2 in case of the formulation RG1 (PVP:Eudragit, 3:2), RG2 (PVP:Eudragit, 2:3), RG3 (PVP:Eudragit, 1:4), RG4 (PVP:Eudragit, 1:5), BM1 (PVP:EC, 3:2), BM2 (PVP:EC, 2:3), BM3 (PVP:EC, 1:4) and BM4 (PVP:EC, 1:5), respectively (Figs. 8 and 9). The permeation rate in both Eudragit and EC formulations decreased with increase in amount of EC and Eudragit except in formulation RG4 (Figs. 10 and 11). Again, when the rate of drug release was compared in both types of formulations, the Eudragit containing matrix patches showed a higher drug permeation rate.

3.1. Statistics

Data were analyzed using standard statistical methods.

4. Discussion

In this study, it was desired to design a TDDS of dexamethasone using a polymeric matrix film. This allows one to control the overall release of the drug via an appropriate choice of polymers [21] and their blends studied here, utilizing the different diffusion pathways created due to the blend of the polymers to produce overall desired steady and sustained drug release. Cumulative amounts of drug (dexamethasone) released per cm^2 from the different TDDS of varied ratio of PVP and EC (BM1–BM4) and PVP and Eudragit (RG1–RG4) showed variable release patterns (Figs. 8 and 9). The process of drug release in most of the controlled/sustained release devices including transdermal patches is governed by diffusion [23]. When this matrix

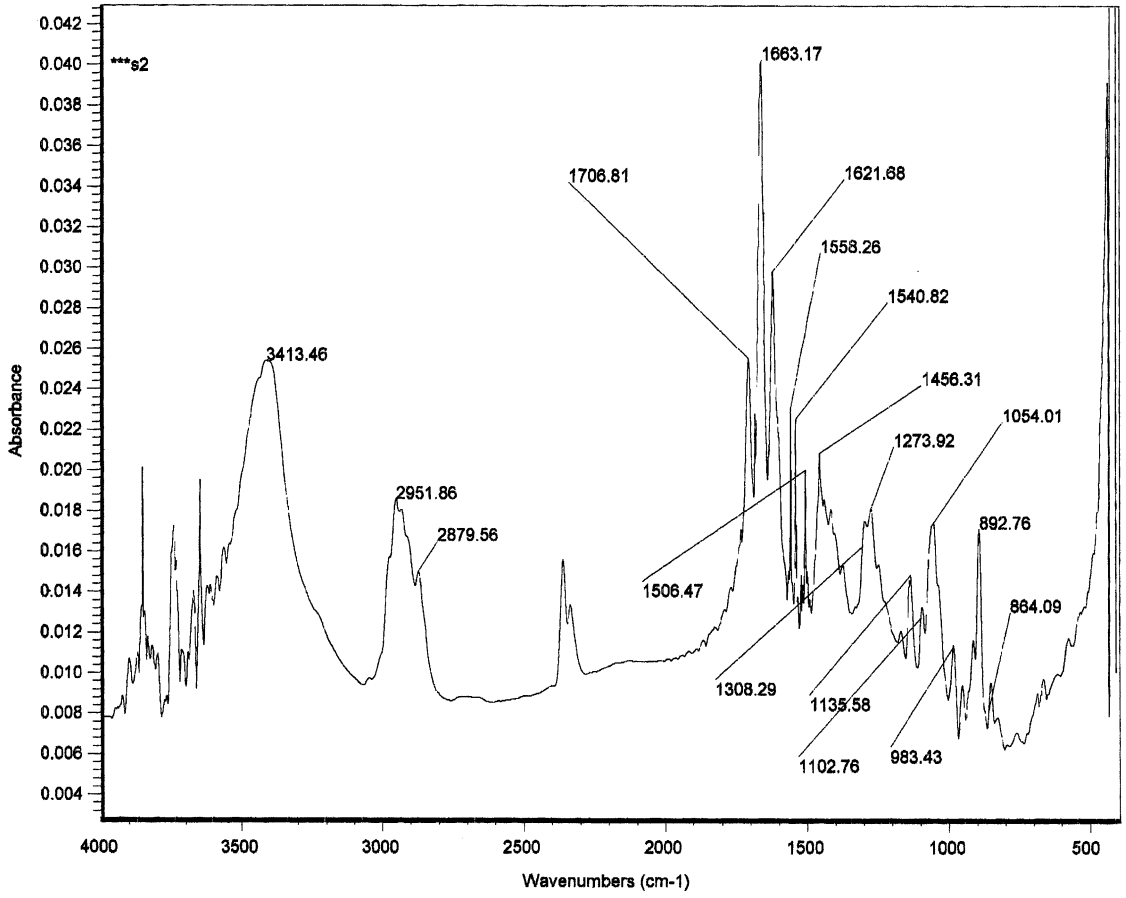

Fig. 5. IR spectra of pure drug, dexamethasone.

patch comes into contact with an in vitro study fluid, thermodynamically compatible with the polymer, the fluid is absorbed into the polymer matrix and this initiates polymer chain dissolution process in the matrix [24,25]. Polymer chain dissolution from the matrix surface involves two distinguishable steps [26,27]. The first step involves changes in entanglement of individual drug molecules at the matrix surface, which depends on the rate of hydration. The second step involves the transport of this molecule from the surface across the skin, adjacent to the matrix patch, initially to the surface and then to the bulk of the in vitro study fluid. Molecular diffusion through polymers is an effective, simple and reliable means of attaining sustained/controlled release of a variety of active agents [28].

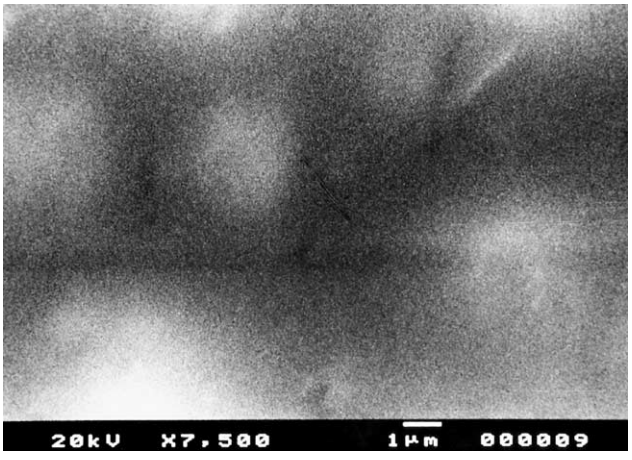

Fig. 6. SEM photograph of dexamethasone matrix patch containing ethylcellulose.

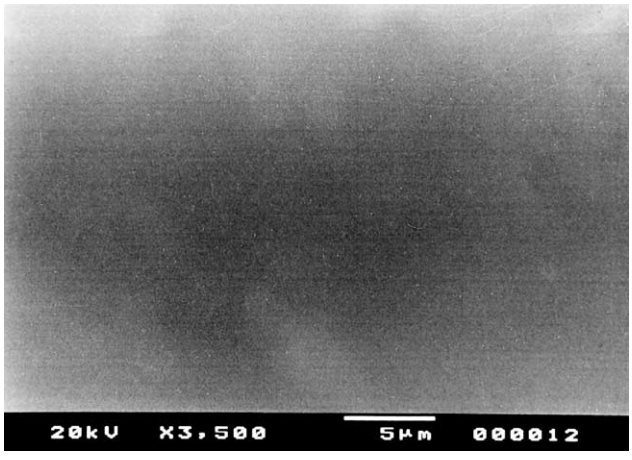

Fig. 7. SEM photograph of dexamethasone matrix patch containing eudragit.

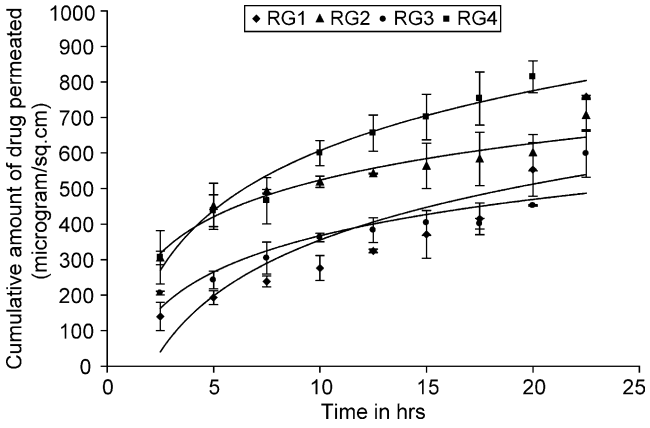

Fig. 8. In vitro skin permeation profile of dexamethasone incorporated in transdermal patches—RG1, RG2, RG3 and RG4. Data shows cumulative amounts of drug release against time; mean ($n=6$) ±SD.

When the active agent (drug) is released from the matrix in such a way that the rate of release of the drug remains constant, the release kinetics of the drug are believed to follow a zero-order kinetics [29]. Among the eight formulations studied, the formulations BM1 (PVP:EC, 3:2), BM2 (PVP:EC, 2:3) BM3 (PVP:EC, 1:4), BM4 (PVP:EC, 1:5), RG1 (PVP:Eudragit, 3:2), RG2 (PVP:Eudragit, 2:3) RG3 (PVP:Eudragit, 1:4) and RG4 (PVP:Eudragit, 1:5) appeared to follow similar patterns of drug release profiles, i.e. initially apparent zero-order and then first order release kinetics. Initially for first few hours the drug release, kinetic patterns followed zero-order drug release profiles and with the enhancement of time the release profiles gradually changed into the concentration dependent first order release kinetics. The drug polymer matrix initially ensured constant concentration of drug in in vitro study fluid, but afterwards, concentration dependent release kinetic made the reaction towards the first order kinetic.

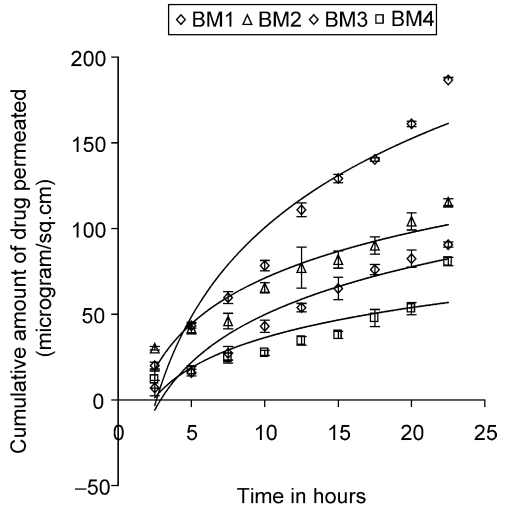

Fig. 9. In vitro skin permeation profile of dexamethasone incorporated in transdermal patches—BM1, BM2, BM3 and BM4. Data shows cumulative amounts of drug release against time; mean ($n=6$) ±SD.

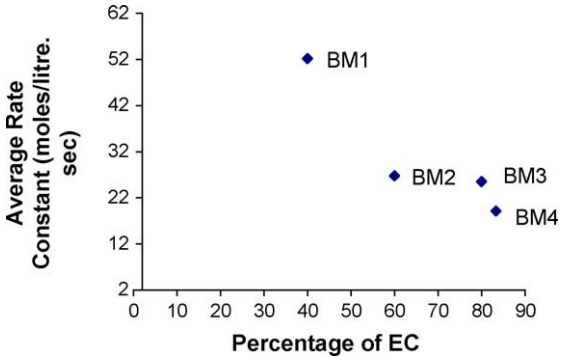

Fig. 10. Average rate constant (from Higuchian plots) against percentage of EC ($n=6$).

The release of a drug from a transdermal patch is controlled by the physico-chemical properties of the drug and the delivery form along with the properties of the biological membrane. Various release kinetics of dexamethasone from the various blends of the two different experimental polymeric combinations—'PVP and EC' and 'PVP and Eudragit'—through abdominal mouse skin may help us to consider some assumptions of behavioral changes of patches with respect to drug release due to the variation of polymeric composition in their blends. Diffusion of any molecule in a multi-polymeric matrix depends on structural and morphological parameters of the polymeric blend [30]. Diffusion in polymers occurs through the amorphous polymeric regions and diffusivity of drug molecule is related to the mobility of polymer chains and, thereby, to the free volume of the system [31]. For larger pores with respect to the size of drug molecules, diffusion occurs by localized activated jumps from one pre-existing cavity to another. Smaller pre-existing cavities may be unable to accommodate the larger diffusing drug molecules. Therefore, many monomer segmental rearrangements, by altering the mobility of polymer chains, may be involved in allowing the drug

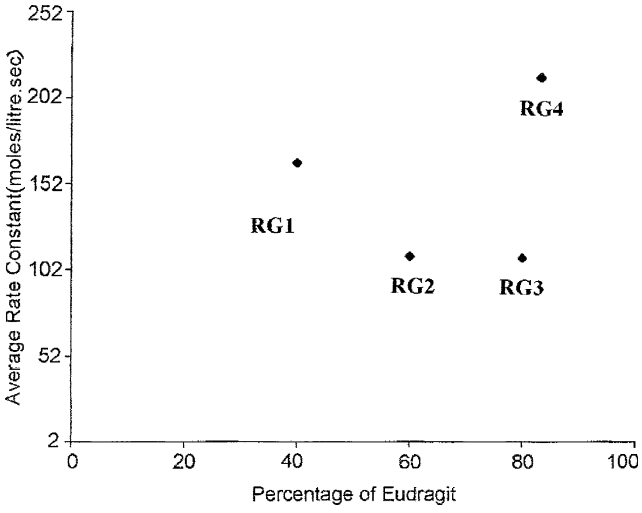

Fig. 11. Average rate constant (from Higuchian plots) against percentage of Eudragit ($n=6$).

molecules to diffuse. Thus, the matrices of various blends of the two categories of formulations (PVP:EC and PVP:Eudragit) had a definite influence on the diffusivity of dexamethasone, since the motion of a drug molecule is restricted by the variation of three-dimensional network of the polymer chains [27]. Drug–excipient interactions play a vital role with respect to release of drug from the formulation amongst others [32]. FTIR techniques have been used here to study the physical and chemical interactions between the drug and excipients used. In this present study, it has been observed that there is no chemical interaction between dexamethasone and the polymers used. Though there are some very minor changes in the peaks in the range of 2800–3500 cm^{-1} which indicates that there may be some physical interaction related to the formation of weak to medium intensity hydrogen bonding between polymers and the drug, but release and permeation studies showed that this type of interaction did not interfere with the release of drug from the PVP:EC polymer matrix. The changes in areas of some peaks occur simply due to mixing of components without any physical or chemical interactions.

Physical studies conducted on different polymeric films containing dexamethasone favored the combination of these polymers and their blends for preparation of transdermal patches. In vitro dissolution studies confirmed the homogeneous distribution of drug in the matrix patch (Table 2). SEM photographs (Figs. 6 and 7) further confirm this. They demonstrate the homogeneous dispersion of the drug in the matrices. A 100% flatness of all the formulations indicates (Table 1) no amount of constriction in formulated transdermal membrane strips. Thus this does not constrict when it is applied on to the skin. Moisture content and moisture uptake (Figs. 1 and 2) were found to increase with the increase of hydrophilic polymer, PVP in both types of formulations (BM and RG). The moisture content was found to be greater with the increase of Eudragit as compared to hydrophobic polymer EC. Significant changes in properties such as reduced crushing strength, increased total porosity and increased pore diameter of hydrophilic polymer containing polymer matrix due to water uptake were reported [33]. Moisture contents in our preparations were found to be low and they varied very little in the formulations.

When the release rate of the different formulations was studied, it was observed that release rate decreased with the increase in amount of EC in the formulation (Fig. 10). A more or less similar trend was studied in case of PVP:Eudragit formulations (Fig. 11), where an increase in amount of eudragit also decreased the release rate of drug except the formulation RG4 (PVP:Eudragit, 1:5). In this formulation, we find an abrupt increase in rate of release of drug. When PVP:EC formulations were compared against PVP:Eudragit formulations in terms of drug release rate, it was observed that rate of drug release was much higher in the case of Eudragit containing polymer matrix. Eudragit (polymethylmethacrylate) is known to have larger cavity size in its polymeric network [33] and thus, it may involve a faster mode of diffusion of dexamethasone from the PVP:Eudragit formulations as compared to the formulations of PVP–EC combinations. At a particular pH, the increase in rate of drug release with increased Eudragit L100 content in the formulations is explained by pore (and/weak points) formation in the film as a result of faster solubilization of Eudragit L100, thus creating channels for dissolution media to penetrate, resulting in faster dissolution of the drug [34].

In the formulation RG4 (PVP:Eudragit, 1:5), quantitatively much less PVP and an excess of eudragit (83.33%) to the polymer blend may have a little or no influence on the larger pre-existing cavities of the eudragit and thus, it may help the solvent molecule to loosen up the polymer matrix by increasing chain mobility and, thereby, result in an abrupt increase in release rate. This phenomenon may be due to sudden behavioral changes because of the mostly prevailing unaltered structure of the individual polymer network or an enormous change in polymeric blend network due to a little variation of eudragit from 80 to 83.33 [RG3 (80%), RG4 (83.33%)]. Nevertheless, one of the causes of variation in release profiles of drug molecules was the biological membrane (here abdominal mouse skin) as the skin of the same species of the animals was reported to vary release patterns [35–37].

5. Conclusion

The kinetic patterns among the formulations studied show that the formulations BM4 (PVP:EC, 1:5), RG1 (PVP:Eudragit, 3:2) and RG3 (PVP:Eudragit, 1:4) provided apparent zero-order kinetic patterns. When the average rate constants of these three formulations (Figs. 10 and 11) were compared, it was found that BM4 (PVP:EC, 1:5) had the slowest release rate of all the formulations studied. Based on the above observations, it can be reasonably concluded that PVP–EC polymers are better suited over PVP–Eudragit polymers for the development of TDDS of dexamethasone and the formulation BM4 (PVP:EC, 1:5) may be used for further pharmacokinetic and pharmacodynamic studies in suitable animal models.

Acknowledgements

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