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Influence of Crosslinking Agent on the Release of Drug from the Matrix Transdermal Patches of HPMC/Eudragit RL 100 Polymer Blends

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The present work was designed to develop suitable transdermal matrix patches using the polymer blends of hydroxy propyl methyl cellulose (HPMC) and Eudragit RL100 (ERL) with triethyl citrate as a plasticizer in group A and in group B, other than HPMC and ERL, crosslinking agent, succinic acid was added. A 3^2 full factorial design was employed for both groups. The concentration of HPMC and ERL were used as independent variables, while percentage drug release was selected as dependent variable. Physical evaluation was performed such as moisture content, moisture uptake, tensile strength, flatness and folding endurance. *In vitro* diffusion studies were performed using cellulose acetate membrane (pore size 0.45 μ) in a Franz's diffusion cell. The concentration of diffused drug was measured using UV-visible spectrophotometer (V-530, Jasco) at λ_{max} 272 nm. The experimental results shows that the transdermal drug delivery system (TDDS) containing ERL in higher proportion gives sustained the release of drug and patches containing crosslinking agent shows more release than those do not contains succinic acid.

Keywords: HPMC, Eudragit RL 100, crosslinking agent, tramadol HCl, transdermal delivery

1 Introduction

Controlled drug release systems can be constructed from either polymers or pumps. Because of their small size and lower cost, polymers are most widely used (1). As polymer science has developed over the past two centuries with the number of novel architectures, polymer-based products and pioneering process technologies are playing a very important role in medicine and pharmacy (2). Polymers are the backbone of a transdermal drug delivery system. Systems for transdermal delivery are fabricated as multilayered polymeric laminates in which a drug reservoir or a drug-polymer matrix is sandwiched between two polymeric layers: an outer impervious backing layer that averts the loss of drug through the backing surface and an inner polymeric layer that functions as an adhesive and/or rate-controlling membrane. One feasible attitude to minimize the device associated adverse skin reactions of transdermal therapeutic systems is to employee highly biocompatible polymers for their fabrication (3). Polymer should provide consistent, effective delivery of a drug throughout the product's intended shelf life or delivery period and have generally-recognized-as-safe status (4).

Hydroxy propyl methylcellulose (HPMC) is modified cellulose, a hydrophilic swellable polymer soluble in water. It is used as a coating agent, film former, stabilizing agent, suspending agent, tablet binder and a viscosity-increasing agent. In oral products, HPMC is primarily used as a tablet binder and as an extended release tablet matrix (5, 6). HPMC is widely used in oral, ophthalmic and topical pharmaceutical formulations.

Eudragit RL 100, poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1: 2: 0.2, is the copolymers of acrylic acid and methacrylic acid esters with a low content in quaternary ammonium groups. The ammonium groups are present as salts and make the polymer permeable. Eudragits are primarily used in oral capsule and tablet formulations as film-coating agents. Depending on the type of polymer used, films of different solubility characteristics can be produced (7, 8).

Transdermal drug delivery system (TDDS) has been an increased interest in the drug administration via the skin for both local therapeutic effects on diseased skin (topical delivery), as well as for systemic delivery of drugs. The skin as a site of drug delivery has a numbers of significant advantages over many other routes of drug administration, including the ability to avoid problems of gastric

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irritation, pH, and emptying rate effects; avoid hepatic first pass metabolism thereby increasing the bioavailability of drug; reduce the risk of systemic side effects by minimizing plasma concentrations compared to oral therapy; provide a sustained release of drug at the site of application; rapid termination of therapy by removal of the device or formulation (9); the reduction of fluctuations in plasma levels of drugs (10) and avoids pain associated with injections. The transdermal delivery can also eliminate pulsed entry into the systemic circulation, which might often cause undesirable side effects. Transdermal therapeutic systems may produce sustained, constant and controlled levels of drug in the plasma, thereby improving patient compliance, since frequent intake of the drug is not necessary. The skin as a route for systemic drug administration has become very attractive since the introduction of transdermal therapeutic systems in the form of patches. They utilize a natural and passive diffusion mechanism that allows substances to penetrate the skin and enter the blood stream. Transdermal therapy also has its some disadvantages, like, higher molecular weight candidates (>500 Dalton) fail to penetrate the stratum corneum without modifying the nature of stratum corneum, drugs with very low or high partition coefficient fail to reach systemic circulation and high melting drugs, due to their low solubility both in water and fat (11). The effective barrier properties of the skin may prevent the entry of drug molecules from the transdermal formulations. Molecules may activate allergic responses and the drug may be metabolized by mircoflora on the surface of skin or by enzymes in the skin (12–24). An ideal penetration enhancer reversibly reduces the barrier resistance of the stratum corneum without damaging the skin. The safest and most widely used penetration enhancer is water which increased hydration and diminishes the resistance of the skin (15, 16).

Tramadol HCl is used in the treatment of osteoarthritis. It has a molecular weight 299.8, melting point is 179°C–180°C and an octanol water partition coefficient 1.35 at pH 7, so it is suitable to administer through transdermal route. HPMC/ERL is chosen in order to study the release profile of the drug, Tramadol HCl from the monolithic matrix membranes made of hydrophilic and hydrophobic polymers respectively. In this study we also observed the influence of crosslinking agent, succinic acid on the *in vitro* drug release profile.

2 Experimental

2.1 Materials

Tramadol HCl was a gift sample from Rantus Pharma Pvt Ltd. (Hyderabad, India). Eudragit RL 100 was obtained from Degussa India Pvt. Ltd. (Mumbai, India). HPMC obtained from Colorcon Asia Pvt. Ltd. (Goa, India). 3M™ Scotchpack™ 9733 backing membrane and 3M™ Scotchpack™1022 release liner were obtained from 3M (USA). Cellulose acetate membrane was obtained from Sartorious Biotech GmbH (Germany). All other ingredients were used of pharmaceutical grade.

2.2 Determination of Partition Coefficient

The partition coefficient study was performed using *n*-octanol as the oil phase and phosphate buffer pH 7.4 as the aqueous phase. The two phases were mixed in equal quantities and were saturated with each other on a mechanical shaker at 37°C for 24 h. The saturated phases were separated by centrifugation. An equal volume (25 ml) of the two phases was placed in conical flasks and, to each 5 mg of drug was added. The flasks were shaken at 37°C for 6 h. The two phases were separated and were then analyzed for respective drug contents (17). The partition coefficient of drug ($K_{o/w}$) was calculated using the following formula:

$$K_{o/w} = \frac{\text{Concentration of Drug in Octanol}}{\text{Concentration of Drug in phosphate buffer pH 7.4}} \quad (1)$$

2.3 Preparation of Matrix Film using HPMC/ERL Blends

The transdermal films containing HPMC and ERL with 15% wt/wt of tramadol HCl, 5% wt/wt of plasticizer (i.e. triethyl citrate) in group A and 5% wt/wt of crosslinking agent (i.e. succinic acid) along with group A excipients in group B were prepared by film casting technique on the mercury (18, 19). Plasticizers are generally used to improve the mechanical properties of a polymer matrix. Hydrophilic ingredients were dissolved in water and hydrophobic ingredients were dissolve in dimethyl formamide, then mixed both solution and stir on magnetic stirrer to accomplished homogeneous mixture. The resulting solution was poured in a petri dish containing mercury. The solvent was allowed to evaporate at 40°C for 24 h to obtain medicated transdermal film. A backing membrane (3M™ Scotchpack™ 9733) and a release liner (3M™ Scotchpack™ 1022) on either side of the film were applied to complete the transdermal therapeutic system of tramadol HCl. The prepared tramadol HCl patches were store in dessicator until further use.

2.4 Factorial Design

A 3^2 factorial design was used in this study and two factors were evaluated, each at three levels; experimental batches were performed at all nine possible combinations as shown in Table 1. The amount of HPMC (X_1) and ERL (X_2) were selected as independent variables. The percentage drug release was selected as dependent variable. The data were

Table 1. Full factorial experimental design layout

	Variable level in coded form	
Trials	X_1	X_2
1	−1	−1
2	−1	0
3	−1	1
4	0	−1
5	0	0
6	0	1
7	1	−1
8	1	0
9	1	1

subjected to 3-D response surface methodology in PCP Disso 2.08 to determine the effect of polymers on the release of drug, dependent variable. The values of variables in a 3^2 Factorial Design are indicated in Table 2. A statistical model incorporating interactive and polynomial terms was used to calculate the responses.

$$Y = b_0 + b_1 X_1 + b_2 X_2 + b_{12} X_1 X_2 + b_{11} X_1 X_1 + b_{22} X_2 X_2 \quad (2)$$

Where, Y is the dependent variable, b_0 is the arithmetic mean response of the all trials, and b_i (b_1, b_2, b_{12}, b_{11} and b_{22}) is the estimated coefficient for the corresponding factor X_i (X_1, X_2, X_1X_2, X_{11} and X_{22}), which represents the average result of changing one factor at a time from its low to high value. The interaction term (X_1X_2) shows how the response changes when two factors are simultaneously changed. The polynomial terms (X_1X_1 and X_2X_2) are included to investigate the nonlinearity.

2.5 Evaluation of Transdermal Films

The physical parameters such as thickness, folding endurance, tensile strength, moisture content, moisture uptake and drug content were determined.

2.5.1. *Thickness*

Patch thickness was measured using digital micrometer screw gauge (Mitutoyo, Japan) at three different places and the mean value was calculated.

Table 2. Values amount of variables in a 3^2 factorial design

	Actual Values	
Coded Values	$X_1 = HPMC\ (mg)$	$X_2 = ERL\ (mg)$
−1	350	350
0	450	450
1	550	550

2.5.2. *Folding endurance*

Folding endurance of patches was determined by repeatedly folding a small strip of film (2 cm × 2 cm) at the same place till it broke. The number of time the film could be folded at the same place without breaking was the folding endurance value (20).

2.5.3. *Tensile strength*

The tensile strength was determined by using a modified pulley system. Weight was gradually increased so as to increase the pulling force till the patch broke. The force required to break the film was consider as a tensile strength and it was calculated as kg/cm^2.

2.5.4. *Flatness*

Three longitudinal strips were cut out from each film: one from the center, one from the left side, and one from the right side. The length of each strip was measured and the variation in length because of nonuniformity in flatness was measured by determining percent constriction, with 0% constriction equivalent to 100% flatness (21, 22).

$$\text{Constriction}\,(\%) = (l1 - l2)/l2 \times 100 \quad (3)$$

Where, $l1$ is the initial length of strip and $l2$ is the final length of strip.

2.5.5. *Percentage of Moisture Content*

The films were weighed individually and kept in a desiccator containing activated silica at room temperature for 24 h. Individual films were weighed repeatedly until they showed a constant weight. The percentage of moisture content was calculated as the difference between initial and final weight with respect to final weight (23).

$$\text{Percent Moisture Content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100 \quad (4)$$

2.5.6. *Percentage of Moisture Uptake*

A weighed film kept in a desiccator at room temperature for 24 h was taken out and exposed to 84% relative humidity (a saturated solution of aluminum chloride) in a desiccator until a constant weight for the film was obtained. The percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight (24).

$$\text{Percent Moisture Uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100 \quad (5)$$

2.6 Drug Content

A 5 cm^2 film was cut into small pieces, put into a 100 ml phosphate buffer (pH 7.4), and shaken continuously for 24 h. Then the whole solution was ultrasonicated for 15 min. After filtration, the drug was estimated spectrometrically at wavelength of 272 nm and determined the drug content.

2.7 *In vitro* Drug Release Study

In vitro drug release studies were performed by using a Franz diffusion cell with a receptor compartment capacity of 22 ml. Cellulose acetate, acetate ester of cellulose (25), has been fabricated as semi-permeable membranes for biomedical application (26). The cellophane membrane (27) (cellulose acetate membrane) was used for the determination of drug from the prepared transdermal matrix type patches. The cellulose acetate membrane having a pore size 0.45μ was mounted between the donor and receptor compartment of the diffusion cell (28). The prepared transdermal film was placed on the cellulose acetate membrane and covered with aluminum foil. The receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4. The whole assembly was fixed on a hot plate magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred using magnetic beads and the temperature was maintained at 32 $\pm$ 0.5°C, because the normal skin temperature of human is 32°C (26, 29, 30). The samples were withdrawn at different time intervals and analyzed for drug content spectrophotometrically. The receptor phase was replenished with an equal volume of phosphate buffer at each sample withdrawal.

2.8 Stability Study

Stability testing of drug products begins as a part of drug discovery and ends with the demise of the compound or commercial product. Food and Drug Administration (FDA) and International Conference on Harmonization (ICH) specifies the guidelines for stability testing of new drug products, as a technical requirement for the registration of pharmaceuticals for human use. According to the ICH guidelines (31) the TDDS samples were stored at 40 $\pm$ 0.5°C and 75 $\pm$ 5% relative humidity (RH) for 6 months. The samples withdrawn at 0, 30, 60, 90 and 180 days and analyzed for physicochemical parameters as well as drug diffusion. If significant change occurs at these stress conditions, then the formulation should be tested at an intermediate condition i.e. 30°C and 75% RH. In the present work, stability studies were carried out for selected formulations at 40 $\pm$ 0.5°C and 75 $\pm$ 5 % RH for 6 months using programmable environmental test chamber (Remi, India). The samples were evaluated for physicochemical parameters and drug diffusion.

Table 3. Partition coefficient of tramadol HCl

Trials	*Partition coefficient*	*Average partition coefficient*
1	1.3634	1.3606
2	1.3597	
3	1.3588	

3 Results and Discussion

3.1 Partition Coefficient Determination

n-Octanol and *in vitro* study fluid (here phosphate buffer, pH 7.4) are considered to be the standard system to determine drug partition coefficient between skin and *in vitro* study fluid (17). To measure the partitioning of drug between the skin and *in vitro* study fluid, the partition coefficient was determined using the formula shown in Experimental Section. The partition studies were performed in triplicate. The result shows mean of all these experiments and it shown in Table 3. Moreover, the logarithmic value of the partition coefficient of the drug in octanol-phosphate buffer, pH 7.4 (*in vitro* study fluid used by us) system, in our study showed that the value is well within the range of 0.8 – 3.0 (log P = 1.3606), which fulfills the requirements of formulating it into a transdermal patch (32). Drugs with a very low partition coefficient will not be well absorbed because they will stay on the skin surface and not partition into the stratum corneum (33). The biphasic nature of drug mimics the biphasic nature of skin, thus ensuring easy penetration through the skin. The results obtained indicate that the drug possesses sufficient lipophilicity, which meets the requirements of formulating it into a transdermal patch.

3.2 Evaluation of Transdermal Films

3.2.1. *Flatness Study*

An idyllic patch should be formulated in such a way that it possesses a smooth surface and should not constrict with time. Flatness studies were performed to judge the same. The result of flatness and thickness shown in Table 4 and low value of standard deviation indicates good uniformity. The results of the flatness study showed that none of the formulations had many differences in the strip lengths before and after their cuts indicating good uniformity of the polymers throughout the transdermal films. It indicates much closed to 100% flatness observed in the formulated patches. Thus, very minute amount of constriction was observed in the film of any formulation and it indicates smooth flat surface of the patches and these formulations can maintain uniform surface when they are administered onto skin.

3.2.2. *Folding endurance*

The folding endurance measures the ability of patch to withstand rupture. The folding endurance was measured manually and results indicated that the patches would not

Table 4. Result of thickness and flatness

Trials	*Thickness (mm)*	*Flatness (%)*	*Trials*	*Thickness (mm)*	*Flatness (%)*
A1	0.14 ± 0.02	100 ± 0.01	B1	0.14 ± 0.05	99.87 ± 0.02
A2	0.15 ± 0.08	99.97 ± 0.03	B2	0.15 ± 0.03	100.03 ± 0.06
A3	0.21 ± 0.09	100.01 ± 0.02	B3	0.20 ± 0.01	100.01 ± 0.01
A4	0.17 ± 0.01	99.96 ± 0.04	B4	0.16 ± 0.08	99.97 ± 0.03
A5	0.22 ± 0.06	100.03 ± 0.01	B5	0.21 ± 0.04	100.02 ± 0.04
A6	0.25 ± 0.01	99.84 ± 0.02	B6	0.26 ± 0.01	100.02 ± 0.05
A7	0.20 ± 0.04	99.95 ± 0.01	B7	0.21 ± 0.07	100.01 ± 0.01
A8	0.26 ± 0.03	100.01 ± 0.02	B8	0.25 ± 0.01	100.06 ± 0.05
A9	0.29 ± 0.04	100.01 ± 0.04	B9	0.29 ± 0.01	99.97 ± 0.02

Results are the mean of triplicate observations ± SD.

break and would maintain their integrity with general skin folding when used. The results of folding endurance are shown in Table 5. It was found to be high in patches containing a higher amount of the ERL. The value of folding endurance is significantly more in group B that was due to the presence of a crosslinking agent, succinic acid, to the formulations.

3.2.3. *Tensile strength*

The tensile strength results indicate the strength of film and the risk of film cracking. But, no sign of cracking in prepared transdermal films was observed, which might be attributed to the addition of the plasticizer, triethyl citrate. The results of tensile strength are shown in Table 5. Tensile strength test results showed that the patch contains HPMC in higher amount were less strengthens. There is an increase in tensile strength with an increase in ERL in the polymer blend. Tensile strength of transdermal films of group A is low as compared to that of group B.

3.2.4. *Moisture Content*

The physicochemical studies like moisture content and moisture uptake provide the information regarding the stability of the formulation. The moisture content was determined by keeping the drug matrix patches in a desiccator containing activated silica until they showed constant weight. The percentage moisture content was calculated from the weight differences relative to the final weight. The results of the moisture content studies for different formulations of both groups are shown in Table 6. The moisture content varied to a small extent in all the trials of group A. However, there was an increase in the moisture content with an increse in the hydrophilic polymer, HPMC in matrix transdermal patches. The moisture content of all trials of group B is considerably higher as compared to group A trials. That is because of the formation micro channels due to cross linking of polymers within the matrix, which means more moisture was retain into these channels. The moisture content of the prepared transdermal film was low, which could help the formulations remain stable and from being a completely dried and reduce brittleness during storage.

3.3 Moisture Uptake Studies

The percentage moisture uptake was calculated from the weight difference relative to the initial weight after exposing the prepared patches to 84% relative humidity (saturated ammonium chloride solution). The results of moisture uptake studies for different formulations are shown in Table 6. The percentage moisture uptake was also found to increase with increasing concentration of hydrophilic polymer, HPMC. The moisture uptake of the transdermal

Table 5. Result of folding endurance and tensile strength

Trials	*Folding Endurance*	*Tensile Strength (kg/cm^2)*	*Trials*	*Folding Endurance*	*Tensile Strength (kg/cm^2)*
A1	110 ± 2.51	0.464 ± 0.11	B1	116 ± 1.31	0.471 ± 0.12
A2	144 ± 1.66	0.635 ± 0.25	B2	148 ± 2.53	0.642 ± 0.08
A3	177 ± 1.45	0.750 ± 0.51	B3	185 ± 1.02	0.763 ± 0.02
A4	100 ± 1.21	0.418 ± 0.13	B4	102 ± 2.04	0.432 ± 0.12
A5	137 ± 2.97	0.615 ± 0.62	B5	141 ± 3.12	0.631 ± 0.11
A6	160 ± 1.06	0.720 ± 0.32	B6	169 ± 1.76	0.729 ± 0.05
A7	82 ± 1.04	0.351 ± 0.09	B7	93 ± 1.08	0.362 ± 0.10
A8	112 ± 2.21	0.568 ± 0.11	B8	115 ± 1.35	0.570 ± 0.07
A9	154 ± 2.93	0.658 ± 0.03	B9	158 ± 2.91	0.673 ± 0.08

Results are the mean of triplicate observations ± SD.

Table 6. Result of moisture content and moisture uptake

Trials	*Moisture Content (%)*	*Moisture Uptake (%)*	*Trials*	*Moisture Content (%)*	*Moisture Uptake (%)*
A1	3.18 ± 0.01	5.30 ± 0.04	B1	3.46 ± 0.01	5.88 ± 0.06
A2	2.75 ± 0.04	4.97 ± 0.01	B2	3.25 ± 0.06	5.45 ± 0.04
A3	2.61 ± 0.02	4.15 ± 0.03	B3	2.99 ± 0.11	5.14 ± 0.09
A4	3.69 ± 0.07	6.11 ± 0.05	B4	4.16 ± 0.09	7.11 ± 0.02
A5	3.55 ± 0.09	5.61 ± 0.08	B5	3.79 ± 0.02	6.48 ± 0.05
A6	3.32 ± 0.02	4.77 ± 0.09	B6	3.68 ± 0.05	6.03 ± 0.08
A7	4.90 ± 0.05	6.82 ± 0.03	B7	5.02 ± 0.01	7.45 ± 0.11
A8	4.61 ± 0.03	6.14 ± 0.01	B8	4.75 ± 0.07	6.71 ± 0.06
A9	4.48 ± 0.08	5.36 ± 0.02	B9	4.69 ± 0.04	6.05 ± 0.03

Results are the mean of triplicate observations ± SD.

formulations was also low, which could protect the formulations from microbial contamination and also reduce bulkiness of films. The physical evaluation of patches showed that the addition of succinic acid does not greatly affect the physical characteristic of the prepared transdermal patches.

3.4 *In vitro* Drug Release Study

The study was designed to formulate a transdermal therapeutic system of tramadol HCl using a polymeric matrix film. This allows one to control the overall release of the drug via an appropriate choice of polymers and their blends. The several diffusion pathways created due to the blend of the polymers to generate overall desired steady and sustained drug release from the patches. The manner by which drug release in most of the controlled/sustained release devices including transdermal patches is governed by diffusion (34, 35). Diffusion is naturally a probabilistic process described by the random walk of molecules. The polymer matrix has a strong influence on the diffusivity as the motion of a small molecule is restricted by the three-dimensional network of polymer chains. The alteration of the crosslinking and the modification of structural arrangements of polymers by using different blends of polymer were already reported (36).

When this matrix patch comes into contact with an *in vitro* study fluid, the fluid is absorbed into the polymer matrix and this initiates polymer chain dissolution process in the matrix. Polymer chain dissolution from the matrix surface involves two distinguishable steps (37, 38). 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 shift of this molecule from the surface across the diffusion membrane initially to the surface and then to the bulk of the *in vitro* study fluid. It is well known that the addition of hydrophilic component to an insoluble film former leads to enhance its release rate constant. This may be due to dissolution of the aqueous soluble fraction of the film, which leads to creation of pores and decrease of mean diffusion path length of the drug molecule to be released.

In vitro release profile is an important tool that predicts in advance how the drug will behave *in vivo* (39). Thus, we can eliminate the risk of hazards of components of transdermal therapeutic system because of direct experimentation in the living system. Drug release studies are also required for predicting the reproducibility of the rate and duration of drug release. The results of drug content and percentage drug release from the prepared medicated transdermal film are shown in Table 7. The percentage of drug release at each time interval was calculated and plotted against time. The different formulations have shown significant difference in the drug release. The drug release profiles of both the groups are shown in Figures 1 and 2.

Table 7. Result of drug content and drug release

Trials	*Drug Content (%)*	*Drug Release (%)*	*Trials*	*Drug Content (%)*	*Drug Release (%)*
A1	99.11 ± 0.12	79.54 ± 0.24	B1	99.46 ± 0.19	86.34 ± 0.58
A2	99.73 ± 0.09	73.63 ± 0.15	B2	99.73 ± 0.05	78.91 ± 0.73
A3	99.82 ± 0.17	64.85 ± 0.42	B3	99.84 ± 0.03	69.35 ± 0.32
A4	99.96 ± 0.06	84.25 ± 0.18	B4	99.85 ± 0.15	91.18 ± 1.02
A5	99.44 ± 0.05	78.91 ± 0.22	B5	98.12 ± 0.17	84.25 ± 0.29
A6	99.45 ± 0.31	73.28 ± 1.04	B6	98.72 ± 0.29	78.91 ± 0.12
A7	98.94 ± 0.11	91.18 ± 0.28	B7	99.59 ± 0.08	95.27 ± 0.04
A8	99.15 ±0.14	81.55 ± 0.91	B8	99.97 ± 0.01	89.73 ± 1.16
A9	99.53 ± 0.01	72.43 ± 0.09	B9	97.91 ± 0.14	81.55 ± 0.33

Results are the mean of triplicate observations ± SD.

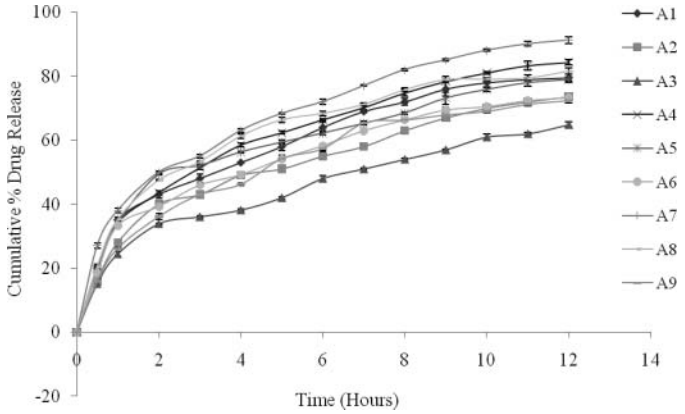

Fig. 1. Drug release profile of group A.

Initially, there was a rapid release of drug from the patch as shown in Figures 1 and 2. This rapid drug release (burst effect) from the prepared transdermal patch, which might be due to rapid dissolution of the surface drug (40, 41). The burst release can be useful for dermal penetration of drugs (42). When the 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 (37). The release profile of the dissolved drug can generally be described by the Fick's law and predicted that the cumulative mass released is proportional to the square root of time (43). The trial A3 and B3 containing the higher proportion of the Eudragit shows only 64.85% and 69.35% drug release within 12 hours which was the lowest amount of the drug release among the all trials of group A and group B, respectively. Whereas the highest amount of the drug release was observed in trial A7 (i.e. 91.18%) and in trial B7 (i.e. 95.27%) which contains the higher proportion of the hydrophilic polymer, HPMC. Hence for the sustaining the drug release from the matrix transdermal patch the higher concentration of ERL is desired.

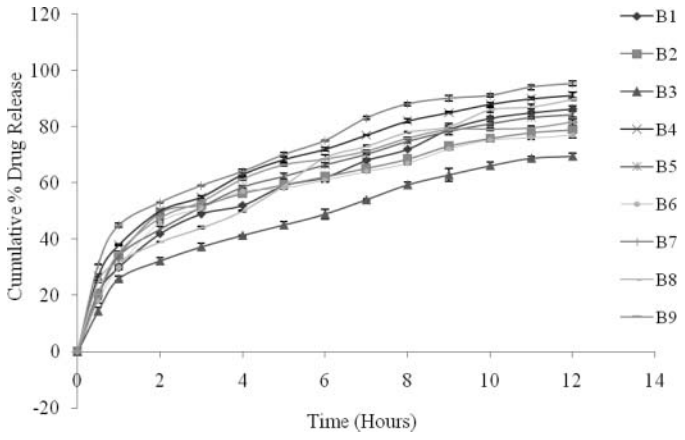

Fig. 2. Drug release profile of group B.

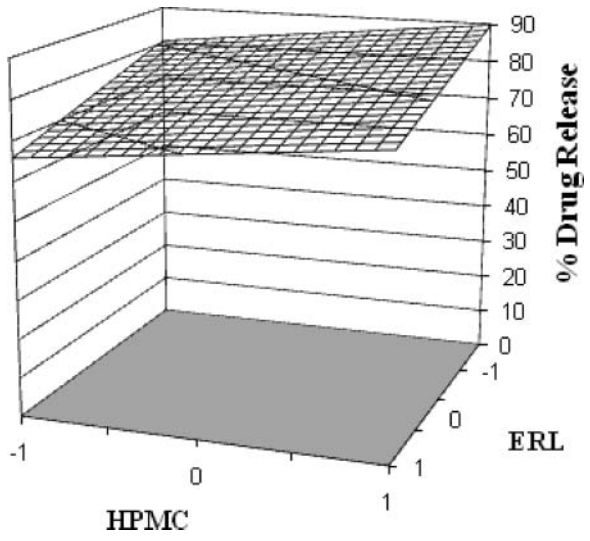

Fig. 3. Response surface plot (for drug release) of group A.

The response surface plot for the drug release, of both the group, shown in Figures 3 and 4. It is clearly observed that the drug release was increased with increasing the concentration of HPMC and inversely proportional to the amount of ERL. The incorporation of succinic acid as a crosslinking agent in the matrix is one of the methods to modulate the release of drug from the prepared patches. The results of *in vitro* drug release study show that the release of drug increases in the group B as compared to group A and that is because of the presence of succinic acid in group B trials. The incorporation of 5% w/w succinic acid increased the drug release from the prepared patches can be attributed to the change in the matrix properties and hence drug diffusivity and thermodynamic activity within the cross-linked transdermal patches. The trial B 7 shows 84.25% release in 12 h, which is the

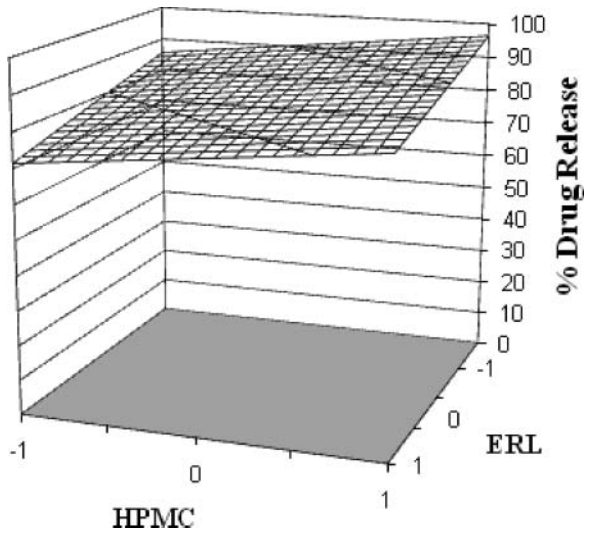

Fig. 4. Response surface plot (for drug release) of group B.

maximum concentration of drug release as compared to other formulations as that contain maximum amount of hydrophilic polymer and also due to presence of succinic acid.

Response (Y), Group A

R2 = 0.9539393

F = 62.1315299 (Significant correlation)
(@ alpha < 0.05, one-tailed)

Variable	CONSTANT	X_1	X_2	
Coefficient	77.7356	4.5233	−7.4017	
t-calculated	122.348	5.813	−9.512	
t-table	2.45	(@ alpha < 0.05, two-tailed)		(DF = 6)

Response (Y), Group B

R2 = 0.9768369

F = 126.516882 (Significant correlation)
(@ alpha < 0.05, one-tailed)

Variable	CONSTANT	X_1	X_2	
Coefficient	83.9433	5.3250	−7.1633	
t-calculated	183.222	9.490	−12.766	
t-table	2.45	(@ alpha < 0.05, two-tailed)		(DF = 6)

The final polynomial equation of both the groups (Equations 6 and 7) shows the effect of dependent variables on the response.

Final Polynomial Equations:
For group A:

$$Y = 77.7356 + 4.5233\ X_1 - 7.4017\ X_2 \qquad (6)$$

For group B:

$$Y = 83.9389 + 5.3183\ X_1 - 7.1567\ X_2 \qquad (7)$$

The positive X_1 coefficient of the both groups indicates that as the concentration of X_1 (HPMC) increases; there is an increase in the release of drug. The negative X_2 coefficient of group A and B indicates that as the concentration of X_2 (Eudragit RL 100) increase, the drug release from the matrix was decrease. While comparing the results of both the groups, the drug release is sustained for a longer time in trials of group A than that of the group B, that is because of the presence of a crosslinking agent in group B. The difference in the *in vitro* drug release profiles from the different blends of HPMC and ERL formulations could be attributable to the varied crosslinking networks of polymeric chains of the different blends of polymeric transdermal experimental formulations as tortuosity and diffusion pathway varied and they have thereby been reported to vary the release of drug and the duration of diffusion. Hence, the molecular diffusion through polymer matrix is an effective, simple and reliable means to achieve sustained/controlled release of a variety of active agents from the transdermal therapeutic system.

Thus, from the evaluation of transdermal patches of both the groups, it was found that the formulation A3 and B3 is most promising indicating sustained the release of drug. Hence it was decided to use it for the stability studies.

Table 8. Results of stability testing

Test Parameters	*A3*	*B3*
Thickness (mm)	021 ± 0.03	0.20 ± 0.02
Flatness (%)	100.01 ± 0.01	100.01 ± 0.01
Folding Endurance	116 ± 1.33	187 ± 0.66
Tensile Strength (gm/cm^2)	0.748 ± 0.23	0.761 ± 0.05
Moisture Content (%)	2.60 ± 0.01	2.97 ± 0.02
Moisture Uptake (%)	4.11 ± 0.04	5.09 ± 0.07
Drug Content (%)	99.80 ± 0.33	99.82 ± 0.03
Drug Release (%)	64.87 ± 0.08	69.02 ± 0.53

Results are the mean of triplicate observations ± SD.

3.5 Stability Study

In the present work, a stability study was carried out for selected formulation (A3 and B3) at 40 ± 0.5°C and 75 ± 5% RH for six months using a programmable environmental test chamber (Remi, India). The samples were evaluated for physicochemical parameters like thickness, flatness, folding endurance, tensile strength, moisture content and moisture uptake, drug content, as well as drug release. The results after the stability period are given in Table 8. The data, after stability period, of evaluation parameters of transdermal patch were found nearly same as those of patch, before the stability period. Hence, stability study indicates that the formulation is quite stable at accelerated conditions.

4 Conclusions

Medicated transdermal films can be prepared from blends of HPMC and ERL showed good mechanical performance. When high mechanical performance is required, a higher amount of ERL in the blends have to be used. An *in vitro* drug release profile of group A and B indicates that the drug release is sustained with increasing the amount of ERL in the blends. The incorporation of cross-linking agent, succinic acid, increased the drug release from the prepared. The result of stability studies of selected optimized trials (A3 and B3) indicates that the prepared transdermal patch retained their properties for longer period. Hence it is quite stable at storage until further use. Moreover, a general conclusion that can be drawn is that selection of a particular blend formulation can vary the diffusion of the drug

significantly. It may also be concluded that the addition of cross-linking agent to the HPMC/ERL systems could be a promising approach for altering the drug diffusion.

HPMC/ERL polymer blends could have the potential to formulate TDDS as they have a good film forming property and mechanical strength. However, the pharmacodynamic and pharmacokinetic evaluation of these systems in animals and human volunteers is necessary to confirm these findings.

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