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Research Article

FORMULATION AND *IN-VITRO* CHARACTERIZATION OF MONOLITHIC MATRIX TRANSDERMAL SYSTEMS USING HPMC/EUDRAGIT S 100 POLYMER BLENDS

KEVIN C. GARALA[1*], ANIL J. SHINDE[2], PRATIK H. SHAH[3]

[1]Department of Pharmaceutics, Atmiya Institute of Pharmacy, Kalawad Road, Rajkot-360005, Gujarat State, India
[2]Department of Pharmaceutics, Bharati Vidyapeeth College of Pharmacy, Morewadi, Kolhapur-416013, Maharashtra State, India.
[3]Department of Clinical Pharmacology, University of Aberdeen, UK.
E-mail: kevin_garala@rediffmail.com
Tel.: +91-9974664666

ABSTRACT

In the present work, monolithic matrix transdermal systems containing tramadol HCl were prepared using various ratios of the polymer blends of hydroxy propyl methyl cellulose (HPMC) and Eudragit S 100 (ES) with triethyl citrate as a plasticizer. A 3^2 full factorial design was employed. The concentration of HPMC and ES 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 (Jasco V-530) at λ_{max} 272 nm. The experimental results shows that the transdermal drug delivery system (TDDS) containing ES in higher proportion gives sustained the release of drug.

Keywords: HPMC, Eudragit S 100, Tramadol HCl, Transdermal Delivery.

INTRODUCTION

Controlled drug release systems can be assembled from either polymers or pumps. Because of their small size and lower cost, polymers are most widely employed[1]. As polymer science has developed over the past two centuries with the number of innovative 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 practicable 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].

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 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[5]; the reduction of fluctuations in plasma levels of drugs[6] 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[7]. 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[8,9, 10]. 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[11, 12].

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/ES 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 monolithic systems, the drug is dissolved or dispersed in the polymer system – diffusion of drug from the drug/polymer matrix controls the overall rate of its release from the device.

EXPERIMENTAL

Materials

Tramadol HCl was a gift sample from Rantus Pharma Pvt Ltd. (Hyderabad, India). Eudragit S 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.

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[13]. The partition

coefficient of drug ($K_{0/w}$) was calculated using the following formula:

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

Preparation of monolithic matrix systems using hpmc/es blends

The transdermal films containing HPMC and ES with 20% wt/wt of tramadol HCl, 5% wt/wt of plasticizer (i.e. triethyl citrate) prepared by film casting technique on the mercury[14, 15]. 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.

Factorial design

It is desirable to build up a suitable pharmaceutical formulation in shortest possible time using least number of man-hours and raw materials. Traditionally pharmaceutical formulations after developed by changing one variable at a time approach. The method is time consuming in nature and requires a lot of imaginative efforts. Moreover, it may be difficult to develop an ideal formulation using this classical technique since the joint effects of independent variables are not considered. It is therefore very essential to understand the complexity of pharmaceutical formulations by using established statistical tools such as factorial design. In addition to the art of formulation, the technique of factorial design is an effective method of indicating the relative significance of a number of variables and their interactions.

Factorial Design is one type of Experimental Design especially applicable for mixture. The "design of experiments" (DOE) is a set of statistical techniques that allows the experimenter to select the most influential factors on an experimental response and to obtain their optimum values. The DOE will provide the appropriate set of experiments to perform in the laboratory to obtain the maximum information with the minimum number of experiments.

A 3^2 full 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 ES (X_2) were selected as independent variables. The percentage drug release was selected as dependent variable. The data were 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 full factorial design are indicated in Table 2.

A statistical model incorporating interactive and polynomial terms was used to calculate the responses (Y).

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1X_1 + b_{22}X_2X_2 \quad (2)$$

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_{12}, 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 2 factors are simultaneously changed. The polynomial terms (X_1X_1 and X_2X_2) are included to investigate the nonlinearity.

Table 1: Full factorial experimental design layout

Trials	Variable Level In Coded Form	
	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

Table 2: Values Amount of Variables in a 3^2 Full Factorial Design

Coded Values	Actual Values	
	X_1 = HPMC (mg)	X_2 = ES (mg)
-1	325	325
0	425	425
1	525	525

Evaluation of transdermal films

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

Thickness

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

Folding endurance

Folding endurance of patches was determined by repeatedly folding a small strip of film (2 cm x 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[16].

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.

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[17, 18].

$$Constriction\ (\%) = (l1 - l2)/l2 \times 100 \quad (3)$$

Where, I_1 is the initial length of strip and I_2 is the final length of strip.

Percentage of moisture content

The films were weighed individually and kept in 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[19].

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

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[20].

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

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 minutes. After filtration, the drug was estimated spectrometrically at wavelength of 272 nm and determined the drug content.

***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[21], has been fabricated as semi-permeable membranes for biomedical application[22]. The cellophane membrane (cellulose acetate membrane) was used for the determination of drug from the prepared transdermal matrix type patches[23]. The cellulose acetate membrane having a pore size 0.45µ was mounted between the donor and receptor compartment of the diffusion cell[24]. 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 ± 0.5 °C, because the normal skin temperature of human is 32 °C[22, 25, 26]. 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.

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[27] the TDDS samples were stored at 40 ± 0.5 °C and 75 ± 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 ± 0.5°C and 75 ± 5 % RH for 6 months using programmable environmental test chamber (Remi, India). The samples were evaluated for physicochemical parameters and drug diffusion.

RESULTS AND DISCUSSION

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[13]. 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[28]. 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[29]. 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.

Table 3: Partition coefficient of tramadol HCl

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

Evaluation of transdermal films

Flatness Study

An idyllic patch should be formulated in such a way that it possesses a smooth surface and it 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 through out 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 applied onto skin.

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 break and would maintain their integrity with general skin folding when used. The results of folding endurance shown in Table 4. It was found to be high in patches containing higher amount of the ES.

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 shown in Table 4. Tensile strength test results showed that the patch contains HPMC in higher amount were less strengthens. There is increase in tensile strength with increase in ES in the polymer blend.

Table 4: Result of thickness, flatness, folding endurance and tensile strength

Trials	Thickness (mm)	Flatness (%)	Folding Endurance	Tensile Strength (kg/cm^2)
1	0.14 ± 0.05	99.99 ± 0.002	111 ± 2.33	0.458 ± 0.015
2	0.16 ± 0.01	100.00 ± 0.001	142 ± 0.66	0.627 ± 0.045
3	0.19 ± 0.03	100.01 ± 0.002	174 ± 1.66	0.742 ± 0.021
4	0.16 ± 0.08	100.02 ± 0.001	99 ± 0.51	0.409 ± 0.012
5	0.20 ± 0.06	100.01 ± 0.001	133 ± 2.33	0.602 ± 0.023
6	0.24 ± 0.01	99.95 ± 0.003	161 ± 1.66	0.715 ± 0.019
7	0.19 ± 0.04	99.98 ± 0.001	80 ±1.34	0.343± 0.002
8	0.25 ± 0.02	100.00 ± 0.002	109 ± 2.66	0.559 ± 0.007
9	0.27 ± 0.05	100.01 ± 0.002	149 ± 1.03	0.649 ± 0.014

Results are the mean of triplicate observations ± SD

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 are shown in Table 5. The moisture content varied to a small extent in all nine trials. 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 the prepared transdermal film was low, which could help the formulations remain stable and from being a completely dried and reduce brittleness during storage.

Moisture uptake

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 5. The percentage moisture uptake was also found to increase with increasing concentration of hydrophilic polymer, HPMC. The moisture uptake of the transdermal formulations was also low, which could protect the formulations from microbial contamination and also reduce bulkiness of films.

***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[30,31]. 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.

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[32, 33]. 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*[34]. 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 5. The percentage of drug release at each time interval was calculated and plotted against time. The drug release profile is shown in Figure 1.

Initially there was rapid release of drug from the patch as shown in Figure 1. This rapid drug release (burst effect) from the prepared transdermal patch, which might be due to rapid dissolution of the surface drug[35, 36]. The burst release can be useful for dermal penetration of drugs[17]. 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[32]. 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[37].

Table 5: Result of moisture content, moisture uptake, drug content and drug release

Trials	Moisture Content (%)	Moisture Uptake (%)	Drug Content (%)	Drug Release (%)
1	3.12 ± 0.03	5.25 ± 0.03	99.84 ± 0.02	73.12 ± 0.24
2	2.80 ± 0.02	4.77 ± 0.01	99.92 ± 0.03	68.52 ± 0.15
3	2.54 ± 0.01	3.97 ± 0.02	99.85 ± 0.04	58.96 ± 0.42
4	3.59 ± 0.08	6.02 ± 0.08	99.99 ± 0.02	78.02 ± 0.18
5	3.43 ± 0.04	5.43 ± 0.05	99.82 ± 0.04	71.72 ± 0.22
6	3.28 ± 0.02	4.29± 0.08	99.63 ± 0.06	63.81 ± 1.04
7	4.89 ± 0.03	6.79 ± 0.02	98.93 ± 0.03	80.25 ± 0.28
8	4.51 ± 0.05	5.12 ± 0.07	99.94 ±0.11	74.18 ± 0.91
9	4.39 ± 0.04	5.04 ± 0.03	99.91 ± 0.09	70.54 ± 0.09

Results are the mean of triplicate observations ± SD

The trial 3 containing the higher proportion of the Eudragit shows only 58.96 % drug release within 12 h which was the lowest amount of the drug release among the all nine trials. Whereas the highest amount of the drug release was observed in trial 7 (i.e. 80.25 %) 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 ES is required.

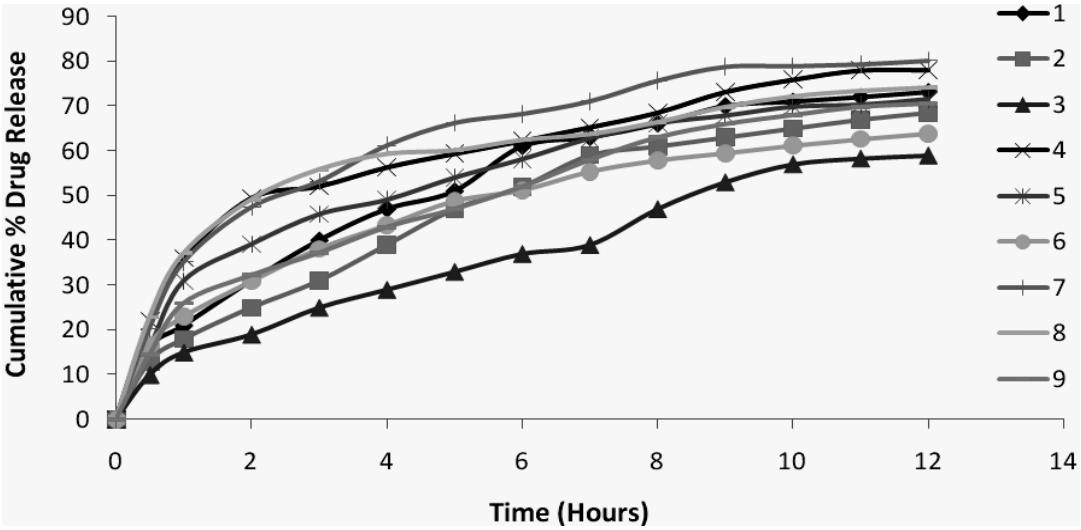

Fig. 1: Drug release profile

The response surface plot for the drug release is shown in Figure 2. It is clearly observed that the drug release was increased with increasing the concentration of HPMC and inversely proportional to the amount of ES.

The final polynomial equation (Equation 6) shows the effect of dependent variables on the response.

Final Polynomial Equations:

$Y = 71.0133 + 4.0617\ X_1 - 6.3467\ X_2$ (6)

The positive X_1 coefficient indicates that as the concentration of X_1 (HPMC) increases; there is increase in the release of drug. The negative X_2 coefficient indicates that as the concentration of X_2 (Eudragit S 100) increase, the drug release from the matrix was decrease.

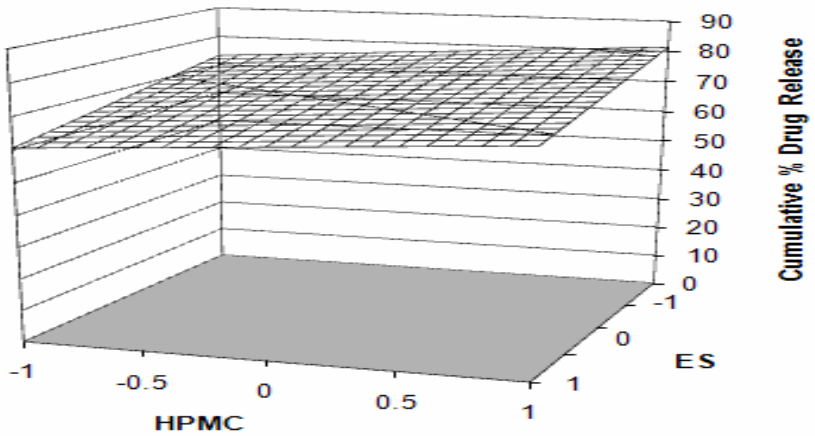

Fig. 2: Response surface plot for drug release

The different *in-vitro* drug release profiles from the different blends of HPMC and ES 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, it was found that the formulation 3 is most promising indicating sustained the release of drug. Hence it was decided to use it for the stability studies.

Stability study

In the present work stability study was carried out for selected formulation (trial 3) at 40 ± 0.5 °C and 75 ± 5 % RH for six months using 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 stability period are given in Table 6.

Table 6: Results after stability period

Test Parameters	Results
Thickness (mm)	0.19 ± 0.02
Flatness (%)	100.01 ± 0.001
Folding Endurance	185 ± 1.33
Tensile Strength (gm/cm^2)	0.738 ± 0.011
Moisture Content (%)	2.51 ± 0.02
Moisture Uptake (%)	4.02 ± 0.05
Drug Content (%)	99.84 ± 0.04
Drug Release (%)	58.11 ± 0.03

Results are the mean of triplicate observations ± SD

The data, after stability period, of evaluation parameters of transdermal patch were found nearly same as those of patch, before the stability period. The comparison between the drug release before and after stability period shown in Figure 3. From comparison graph, it was conclude that the release of drug after stability period was same as before stability period. Hence, stability study indicates that the formulation is quite stable at accelerated conditions.

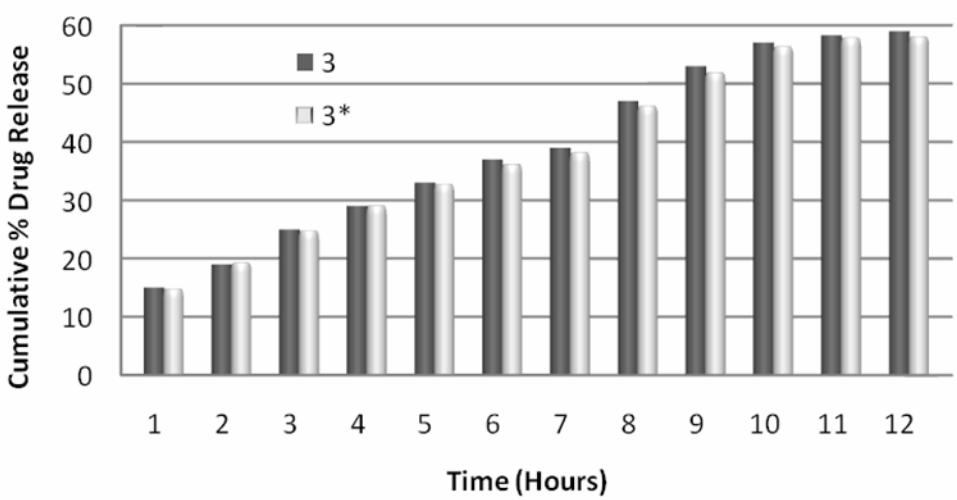

Fig. 3: Comparison of drug release profile of trial 3 and 3* 3* indicates result after stability period

CONCLUSION

Medicated monolithic matrix transdermal systems can be prepared from blends of HPMC and ES showed good mechanical performance. When high mechanical performance is required, higher amount of ES in the blends have to be used. *In-vitro* drug release profile indicates that the drug release is sustained with increasing the amount of ES in the blends. The result of stability studies of selected optimized trial (trial 3) 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.

HPMC/ES polymer blends could have potential to formulate TDDS as they have 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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