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Influence of Polymeric System and Loading Dose on Drug Release from Alfuzosin Hydrochloride Transdermal Films

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SUMMARY. **In the present study, the influence of polymeric concentration, its blend and drug loading dose on the in vitro drug release pattern of alfuzosin hydrochloride from its transdermal patches has been investigated. Ratio of EC and PVP and drug loading dose were selected as independent variables and their influence on the percentage drug released at 24 h (Q_{24}), drug release rate (KH) and time taken for 50% drug release ($t_{50\%}$) were studied using statistical experimental designing. Ratio of EC and PVP was found to be the main influential factor for all the dependent variables studied. Drug loading dose was also found to influence the dependent variables but to a lesser extent. Physicochemical parameters of the prepared patches were also evaluated. This study could be used as a screening method for further development of transdermal delivery of alfuzosin hydrochloride and skin permeation studies.**

INTRODUCTION

Benign prostatic hypertrophy (BPH), often alternatively referred to as benign prostatic hyperplasia, is a condition characterized by a nodular enlargement of prostatic tissue leading to obstruction of the urethra. In a large community-based survey, lower urinary tract symptoms (LUTS) secondary to BPH were reported in 25% of men aged >50 years [1]. LUTS including urinary frequency, nocturia, incomplete emptying, and urinary hesitancy are often associated with BPH. These symptoms can be caused by altered function of the smooth muscle tone that is regulated by the alpha1-adrenergic receptors in the prostate and its capsule, the bladder base and neck, and the prostatic urethra [2]. Presumably alpha1-adrenergic receptor antagonists may be implicated in the pathophysiology of BPH and may cause relaxation of smooth muscles, improve in urine flow and reduction in LUTS [3]. Consequently, American health care policy and research (AHCPR) guidance recommended alpha-blockers as a first-line therapy for BPH. Alfuzosin hydrochloride is an alpha-adrenergic receptor blocker approved by FDA for the symptomatic treatment of BPH. It is available in three bioequivalent formulations: an immediate release standard form, typically 2.5 mg three times per day, a 5-mg sustained-release form given twice per day, and a 10-mg once daily sustained-release form [4,5]. The absolute bioavailability of alfuzosin is about 49% under fed condition, while the corresponding value under fasting condition is around 25% [6]. This shows that food has a significant impact on the oral absorption of alfuzosin. This originates the need of an alternative route of administration, which can bypass the hepatic first-pass metabolism. Transdermal route is an alternative choice of route of administration for such drugs. Transdermal patches offer added advantages such as maintenance of constant and prolonged drug level, reduced frequency of dosing, minimization of inter- and intrapatient variability, self administra-

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tion, and easy termination of medication, leading to patient compliance [7].

The transdermal permeation can be treated as a diffusion process through a selectively permeable membrane. The concentration of the applied solute species at the surface layers is not usually equal to but related to its concentration in the applied vehicle in accord with the vehicle/stratum corneum sorption isotherm. The linear isotherm can be defined in terms of the distribution coefficient between the vehicle and the stratum corneum. It is considered that the transdermal flux is directly proportional to the concentration difference across the skin barrier [8]. Drug permeation through the skin following transdermal delivery is also influenced by various design factors such as polymer species, internal structure of the polymer matrix and drug loading dose. The effects of the above mentioned factors must be elucidated in detail for developing an optimum delivery system, first in vitro and then in vivo. In the present study, we have verified the effects of polymeric concentration, its blend and drug loading dose on the in vitro drug release pattern of alfuzosin hydrochloride from its transdermal patches.

MATERIALS AND METHODS

Materials

Alfuzosin hydrochloride was obtained as a gift sample from Cipla Ltd (Mumbai, India). Ethyl Cellulose (EC; ethoxy content 47.5–49%, viscosity 14 cps in 5% w/w solution in 80:20 toluene/ethanol at 25 °C) was purchased from BDH Chemicals Ltd., Poole, England. Polyvinylpyrrolidone (PVP; K value: 26–35) and Polyvinylalcohol (PVA) were purchased from HiMedia Laboratories Pvt. Ltd, Mumbai, India and S.D. Fine-Chem. Ltd. Boisar, India, respectively. Di-n- Butylphthalate was purchased from Central Drug House (P) Ltd., Mumbai, India.

Full Factorial Design

A 3^2 full factorial design was used in development of dosage form and two factors were evaluated, each at three levels. In the present investigation, ratio of EC and PVP (X_1) and drug loading dose (X_2) were selected as independent variables. The percentage drug dissolved at 24 h (Q_{24}), drug release rate (K_H) and time taken for 50% drug release ($t_{50\%}$) were chosen as dependent variables. Ratio of EC and PVP was evaluated at 60:40 (-1), 50:50 (0), and 40:60 (+1), while alfuzosin loading dose was evaluated at 30% (-1), 40% (0), and 50% (+1) of total polymer weight. The levels for these two parameters were determined from the preliminary trials. Design-Expert software (Version. 7.1.3, Stat-Ease Inc., Minneapolis, USA) was used for the generation and evaluation of the statistical experimental design.

Preparation of Transdermal Films

Experimental transdermal films were prepared at all possible combinations (Table 1). Films composed of different ratios of EC and PVP containing alfuzosin hydrochloride (~1.05mg/square centimeter patch) were prepared by solvent evaporation technique. Di-n-butylphthalate was incorporated as a plasticizer at a concentration of 30% w/w of dry weight of polymers. Alfuzosin hydrochloride was dissolved in chloroform followed by addition of polymers and plasticizer with constant stirring. The matrix was prepared by pouring the homogeneous dispersed solution on 4% PVA backing

Run	Factors		Observed Responses [c]		
	X_1[a] (EC:PVP)	X_2[b] (Drug loading)	Q_{24}	K_H	$t_{50\%}$
1	-1	-1	68.93 (± 1.87)	14.3 (± 0.54)	16.51 (± 0.66)
2	0	-1	76.25 (± 0.99)	15.39 (± 1.32)	15.23 (± 0.62)
3	+1	-1	85.24 (± 1.67)	17.85 (± 1.22)	11.98 (± 0.72)
4	-1	0	70.82 (± 1.62)	14.81 (± 0.51)	15.70 (± 0.81)
5	0	0	78.58 (± 1.08)	17.42 (± 0.68)	12.67 (± 0.33)
6	+1	0	86.82 (± 1.55)	19.50 (± 0.77)	10.50 (± 0.52)
7	-1	+1	72.25 (± 2.16)	17.79 (± 0.92)	12.10 (± 0.83)
8	0	+1	79.52 (± 1.86)	18.42 (± 0.62)	11.23 (± 0.76)
9	+1	+1	90.1 (± 1.94)	20.79 (± 1.00)	09.64 (± 0.44)

Table 1. Composition and observed responses from randomized runs in 3^2 full factorial design. [a] Levels of ratio of EC: PVP (X_1) as 60:40(-1), 50:50(0) and 40:60(+1). [b] Levels of drug loading (X_2) as 30%(-1), 40% (0) and 50% (+1). [c] Data shown are mean of three determinations and figure in the parantheses indicates standard deviation.

membrane in a flat bottomed petridish, covered with perforated aluminum foil, and dried at 40 °C for 24 h. The dry patches were removed and kept in desiccators until use.

Evaluation of Physicochemical Parameters

Percentage Moisture Uptake

Accurately weighed films kept in a desiccator at normal room temperature for 24 h were taken out and placed in desiccators containing 100ml of super saturated solution of potassium chloride to maintain 84 % relative humidity until a constant weight for the films were obtained. The percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight [9]. The percentage moisture absorption at laboratory ambient condition (300 C and 64 % RH) was also calculated.

Percentage Moisture Content

The prepared films were weighed individually and kept in a desiccator containing activated silica at room temperature until it showed a constant weight. The percentage of moisture content was calculated as a difference between initial and final weight with respect to final weight [9].

Flatness

Longitudinal strips were cut out from the prepared patches. The length of each strip was measured, and than variation in the length due to the nonuniformity in flatness was measured. Flatness was calculated by measuring constriction of strips, and a 0 % constriction was considered to be 100 % flatness [9].

Folding Endurance

This was determined by repeatedly folding the film at the same place until it broke. The number of times the film could be folded at the same place without breaking gave the value of folding endurance.

FTIR Study

The pure drug, alfuzosin HCl and mixture of it with the polymers (PVP, EC) were mixed separately with IR grade KBr in the ratio of 100:1 and corresponding pellets were prepared by applying pressure in a hydraulic press. The pellets were scanned over a wave number range of 4000-400 cm^{-1} in fourier transform infrared spectrophotometer (Perkin Elmer, Switzerland).

Scanning Electron Microscopy (SEM)

The surface morphology of the films was recorded with a Jeol Scanning Electron Microscope (Model: JSM 5200, Japan). The samples were mounted on an aluminium stab by using a double-sided adhesive tape. Then it was placed in an ion coater unit (Model: IB-2, Hitachi, Tokyo, Japan) for gold coating (200 Å). During gold coating process the samples were exposed to vacuum of 10^{-50} mm. Afterwards, an accelerating voltage of 25 kV was applied and the image was photographed by Asia Pentex Camera of 35 mm film.

In-Vitro Drug Release Studies

In vitro skin permeation studies for transdermal delivery systems are more useful compared to dissolution studies but still for routine quality control studies and screening of formulations [10,11], in vitro drug release studies may be carried out. The *in vitro* drug release studies for all the transdermal films were carried out using USP Basket Type dissolution rate test apparatus (Tab machine®, Mumbai, India) in 900 ml of normal saline as dissolution media maintained at 32 ± 0.5 °C at 50 rpm for 24 h. The patches were placed in respective baskets with their drug matrix exposed to dissolution media. Samples were withdrawn at predetermined time intervals and analyzed spectrophtometrically (Double beam u.v and visible spectrophotometer, Elico India Ltd.) after suitable dilution. Each dissolution study was performed three times and average value was taken. The percentage of alfuzosin hydrochloride released at various time intervals was calculated and analyzed by plotting.

RESULTS AND DISCUSSION

Evaluation of Physicochemical Parameters

A summary of the results of physicochemical studies has been presented in Table 2. The result of the moisture uptake (%) and moisture content (%) studies revealed that the moisture uptake/content was found to increase with increasing concentration of hydrophilic polymer PVP. The moisture uptake was increased at higher humidity conditions as compared to at ambient conditions. The low moisture uptake at laboratory ambient condition (3.063 ± 0.795 to 5.341 ± 1.438%) protects the material from microbial contamination and bulkiness of the patches. Again a small moisture content (3.077 ± 1.179 to 5.427 ± 1.395%) in the formulations helps them to remain stable and from being a

Runs	Moisture uptake [a] (%)		Moisture content [a] (%)	Flatness [a] (%)	Folding endurance [a]
	RH 64%	RH 84%			
1	3.063 (± 0.795)	5.884 (± 0.623)	3.115 (±0.628)	100	38.666 (± 0.577)
2	3.960 (± 1.198)	6.954 (± 1.168)	3.873 (±1.172)	100	35 ± (1.000)
3	5.338 (± 2.917)	8.086 (± 1.202)	5.289 (±1.494)	100	36.333 (± 1.154)
4	3.081 (±0.872)	5.879 (±0.224)	3.116 (±0.287)	100	37 ± (1.000)
5	3.911 (±0.883)	6.956 (±1.086)	3.879 (±0.251)	100	35 ± (1.000)
6	5.346 (±2.043)	8.079 (±1.183)	5.328 ±(1.754)	100	37 ± (1.000)
7	3.065 (±1.231)	5.885 (±0.764)	3.077 (±1.179)	100	38.666 (± 0.577)
8	3.965 (±1.084)	6.899 (±0.829)	3.891 (±0.887)	100	36 ± (1.732)
9	5.341 (±1.438)	8.083 (±2.108)	5.427 (±1.395)	100	35.333 (± 0.577)

Table 2. Physicochemical properties of transdermal films. [a] Data shown are mean of three determinations and figure in the parantheses indicates standard deviation.

completely dried and brittle film. The results of flatness study showed that none of the formulation had the difference in the strip lengths before and after their cuts, thus indicating 100% flatness. It indicates 0% constriction in the patches and thus they could maintain a smooth surface when applied onto the skin leading to intimate contact and hence better drug permeation. Folding endurance study assured about its flexibility.

FT IR Study

The IR spectra of alfuzosin hydrochloride and physical mixture of drug and polymers showed all characteristic bands of alfuzosin hydrochloride. In case of IR spectra of matrix film containing drug and polymers, changes in the area of C-O-C skeletal vibration in 1200 to 1000 cm^{-1} range (Fig. 1) of glucose unit in cellulosed polymer appeared, showing differences of glucose bond orientation solid dispersion. Basically no change of frequency and shape of alfuzosin hydrochloride bands were noticed, which infers no significant redistribution of electronic density in the structure of organic molecule. This indicates no strong interaction between the drug and the polymers, in the film prepared by the solvent casting method.

Scanning Electron Microscopy (SEM)

The surface morphology of the formulation (run 6) was studied with SEM (Fig. 2). Due to fairly good solubility of alfuzosin hydrochloride in the polymeric system, homogenously distributed drug particles were observed.

In vitro Drug Release Studies

Effects of the variables on the *in vitro* drug release from the transdermal patches were studied by statistical experiment designing. Design

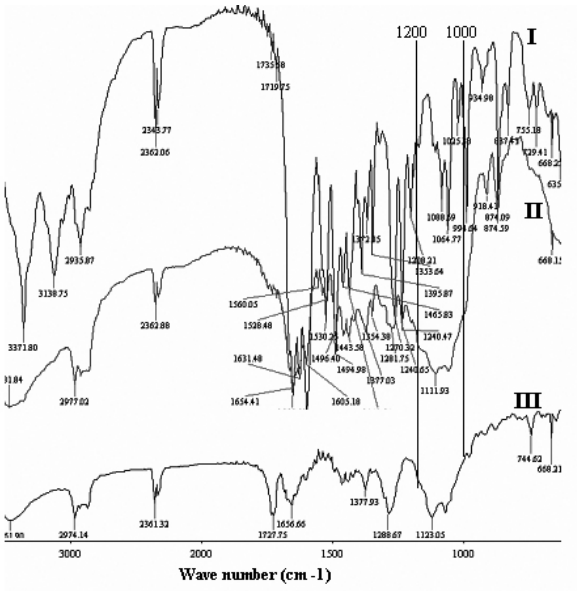

Figure 1. FT IR spectra of alfuzosin hydrochloride (I); physical mixture of drug, ethyl cellulose and PVP (II) and transdermal film containing drug and polymers (III).

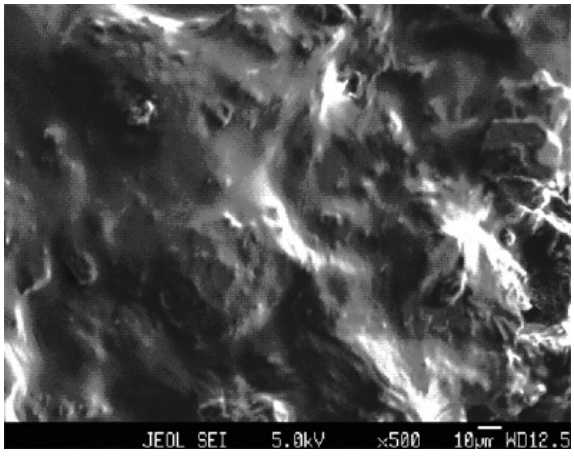

Figure 2. Scanning electron micrographs of the transdermal patch showing uniform distrubition of drug in polymeric system.

Source	Q_{24}		K_H		$t_{50\%}$	
	Sum of Squares	**p-value**	**Sum of Squares**	**p-value**	**Sum of Squares**	**p-value**
Mean *vs.* total	80475.48		3927.18		2067.91	
Linear *vs.* Mean	441.19	< 0.0001	35.97	< 0.0001	44.03	< 0.0001
2FI [a] *vs.* Linear	0.59	0.1990	0.076	0.5312	1.07	0.1266
Quadratic *vs.* 2FI	1.47	0.0721	0.18	0.6644	0.37	0.6693
Cubic *vs.* Quadratic	0.61	0.2064	0.68	0.1995	1.10	0.3248
Residual	0.70	0.75	1.94			
Total	80920.03		3964.84		2116.41	

Table 3. Model analysis by sequential model sum of squares. [a] Two factor interaction.

Source	Q_{24}		K_H		$t_{50\%}$	
	Adjusted R-Squared	**PRESS**	**Adjusted R-Squared**	**PRESS**	**Adjusted R-Squared**	**PRESS**
Linear	0.9909	7.68	0.9464	3.68	0.8893	7.96
2FI	0.9917	11.86	0.9432	6.88	0.9064	8.85
Quadratic	0.9950	10.99	0.9350	12.02	0.8928	22.99
Cubic	0.9962	80.94	0.9522	87.10	0.9042	195.03

Table 4. Model Summary Statistics.

of experiment (DOE) has been widely used in pharmaceutical field to study the effect of formulation variables and their interactions on response variables [12,13]. In this study, a 32 full factorial design (Table 1) was used. A suitable equation involving the main effects was selected based on the estimation of several statistical parameters, such as the multiple correlation coefficient (R^2), adjusted multiple correlation coefficient (adjusted R^2) and the predicted residual sum of squares (PRESS), provided by the Design-Expert software. As presented in Tables 3 and 4, the linear model was selected as a suitable statistical model for optimized formulations because it had the smallest value of PRESS. Predicted residual sum of squares (PRESS) is a measure of the fit of the model to the points in the design. The smaller the PRESS statistic is, the better the model fits to the data points [14].

The adequacy of the model was also confirmed with residual plot tests of regression models. Analysis of variance (ANOVA) was applied to estimate the significance of the model at the 5% significance level. The linear model generated by the design is given by the equation [$Y = b_0 + b_1X_1 + b_2X_2$], where Y is the dependent variable, b_0 is the arithmetic mean response of the 9 runs, and b_i (b_1 and b_2) is the estimated coefficient for the corresponding factor X_i(X_1 and X_2), which represents the average result of changing one factor at a time from its low to high value.

Final Equation in Terms of Coded Factors

Q_{24} = + 78.68 + 8.36*A + 1.91*B

K_H = + 17.38 + 1.87*A + 1.58*B

$t_{50\%}$ = + 12.61 - 2.03*A - 1.79*B

Final Equation in Terms of Actual Factors

Q_{24} = + 78.67923 +8.36000*Ratio of EC:PVP + 1.90833*Drug loading dose

K_H = + 17.38077 + 1.87333*Ratio of EC:PVP + 1.57667 *Drug loading dose

$t_{50\%}$ = + 12.61231 - 2.03167*Ratio of EC:PVP - 1.79167*Drug loading dose

The release-rate determination is one of the most important studies to be conducted for all controlled release delivery systems. Although, for transdermal delivery devices, permeation studies through a suitable animal skin or human cadaver skin is essential to predict its performance, the dissolution studies of the patches are also very crucial because one need to maintain the drug concentration on the surface of stratum corneum consistently and substantially greater

than the drug concentration in the body to achieve a constant rate of drug permeation [15,16]. Hence, in the present study transdermal films were subjected to dissolution testing as a screening method for future in-vitro and in-vivo skin permeation studies.

The Higuchi square-root equation [17] gives the drug release from a planar surface of a heterogeneous matrix by diffusion through the intergranular openings created by the porosity of the matrix:

$$Q = [D\ \varepsilon\ Cs\ t\ (2A - \varepsilon\ Cs)\ \tau]^{\frac{1}{2}}$$

where *Q* is the cumulative amount of drug released per unit area at time *t*; *D* is the diffusion coefficient of the drug in the dissolution medium; ε is the porosity of the matrix; *Cs* is the solubility of the drug in the dissolution medium; τ is the tortuosity of the matrix; *A* is the drug concentration in the dosage form. Higuchi describes drug release as a diffusion process based on the Fick's law, square root time dependent. This relation can be used to describe the drug dissolution from several types of modified release pharmaceutical dosage forms including some transdermal systems [18]. In the present work, dissolution data was subjected to a simple Higuchi-type equation:

$$Q = (K_H \times t^{\frac{1}{2}}) + c$$

where *Q* is the percentage cumulative drug released in time *t*; K_H is the Higuchi-type release rate; *c* is the y-intercept. The equation predicts a straight-line relationship if *Q* is plotted *vs.* $t^{\frac{1}{2}}$.

The dissolution profile of all the factorial batches is shown in Fig. 3. The coefficient estimate and standardized main effects (SME) values for the responses are listed in Table 5.

SME values were calculated by dividing the main effects by the standard error of the main effects. In addition, the contour plots and three-dimensional response surface plots were presented to estimate the effects of the independent variables on each response (Figs. 4 and 3).

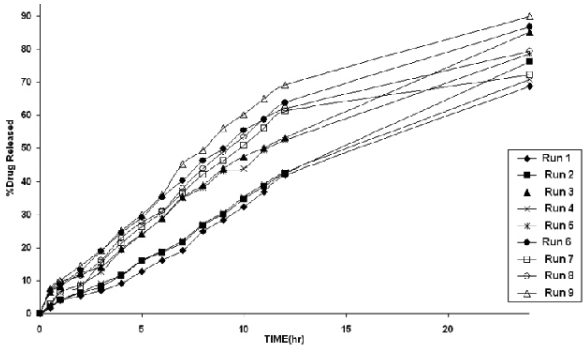

Figure 3. *In-vitro* dissolution profile of the factorial batches of alfuzosin hydrochloride transdermal films in normal saline as dissolution media.

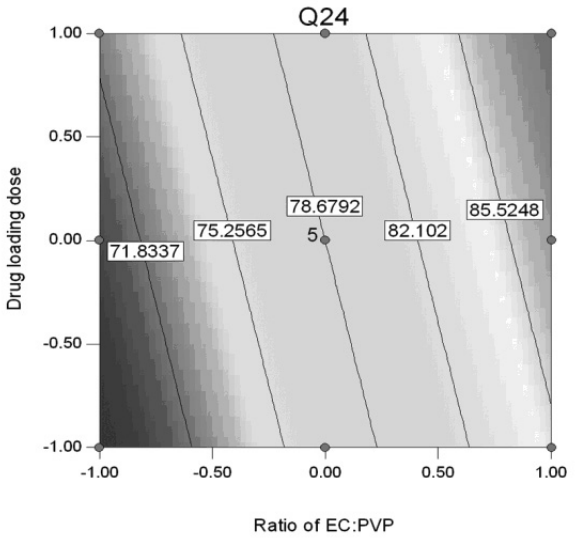

Figure 4. Contour plot for percent drug released at 24 h (Q_{24}) indicating the effect of the ratio of EC: PVP and drug loading on Q_{24}.

Results of multiple regression analysis and standardized main effects (SME) revealed that both ratio of EC: PVP (fraction of PVP) and drug loading had statistically significant influence on all dependent variables (P <0.0001, Table 5). The influence of ratio of EC: PVP (fraction of

Coefficient of regression parameter	Measured Responses								
	Q_{24}			K_H			$t_{50\%}$		
	Coefficient estimate	P-value	SME*	Coefficient	P-value estimate	SME*	Coefficient estimate	P-value	SME*
b0	78.68	<0.0001	491.75	17.38	<0.0001	158	12.61	<0.0001	66.37
b1	8.36	<0.0001	34.83	1.87	<0.0001	11	-2.03	<0.0001	-7.51
b2	1.91	<0.0001	7.96	1.58	<0.0001	9.29	-1.79	<0.0001	-6.63

Table 5. Standardized main effects of the factors on the measured responses. * Standardized main effects (SME) were calculated by dividing the main effect by the standard error of the main effect.

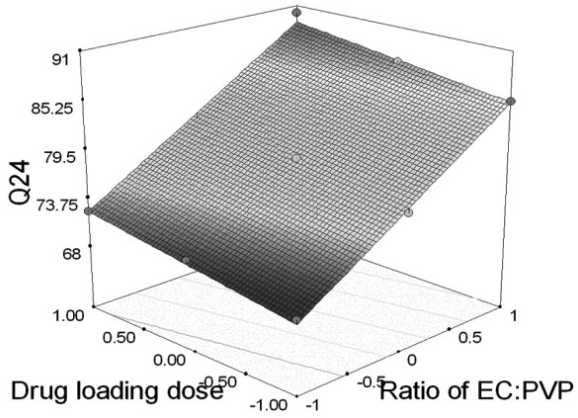

Figure 5. Response surface plot for drug released at 24 h (Q_{24}) indicating the effect of the ratio of EC: PVP and drug loading on Q_{24}.

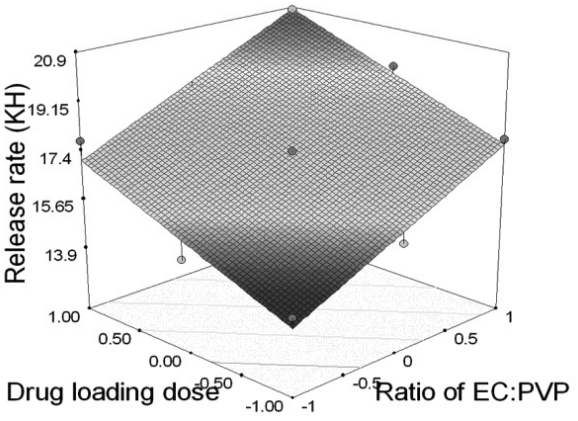

Figure 7. Response surface plot for release rate (K_H) indicating the effect of the ratio of EC: PVP and drug loading on KH.

PVP) and drug loading on Q_{24} is evident from the contour plot and three-dimensional response surface plot (Figs. 4 and 5).

Regarding the overall effect of both factors, it appeared that the Q_{24} value was affected more by the levels of fraction of PVP, which was cleared from the response surface plot (Fig. 4), as the decline of the Q_{24} value was more extreme on the axis of ratio of EC: PVP compared with the drug loading. The higher SME of ratio of EC: PVP level indicated that the effect of ratio of EC: PVP level was found to be the main influential factor on the Q_{24} from the transdermal patches in the whole stage dissolution. Negligible or no curvature on both axes in response surface plot indicates little contribution of interaction terms along with linearity of responses. It was found that the Q_{24} value increased with increase in fraction of PVP and drug loading. The

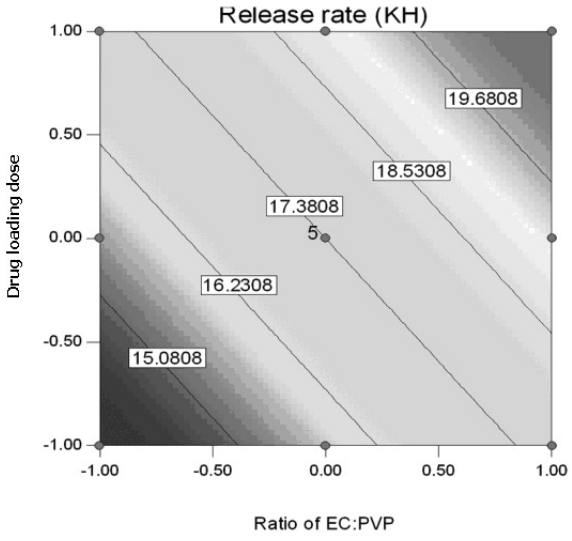

Figure 6. Contour plot for release rate (K_H) indicating the effect of the ratio of EC: PVP and drug loading on K_H.

addition of hydrophilic component to an insoluble film former (EC) tends to enhance the release rates, as reported by Arora *et al.* [19]. The increase in rate of drug release could be explained by the ability of the hydrophilic polymers to absorb water, thereby promoting the dissolution, and hence the release of drug. Moreover, the hydrophilic polymers would leach out and, hence, create more pores and channels for the drug to diffuse out of the patches 20 It has also been reported that PVP decreases the crystallinity of the drug in patch, which accounts for the increased release of drug with an increase in the PVP concentration in the patches [10].

It was also observed that the value of Q_{24} increased linearly when drug loading was increased from 30% to 50%. The increased release rate at high drug loading might partly due to the drug entrapped in the superficial layer of the patch. When the patch comes in contact with dissolution medium, the drug from the surface leaches into the surrounding medium, leaving a more porous polymer structure, which enables faster drug diffusion from the matrix. Similar finding of metronidazole release from chitosan inserts has been reported by Barat *et al.* [21]. Such linearity of effect has also been reported by El-Arini *et al.* [22]. The drug release was high from the formulations in the initial hours. This may be because of the presence of hydrophilic polymers, and their hydrophilic layers might need a very little "lag time" to establish a concentration profile in the patches [23].

The linear influence of ratio of EC: PVP

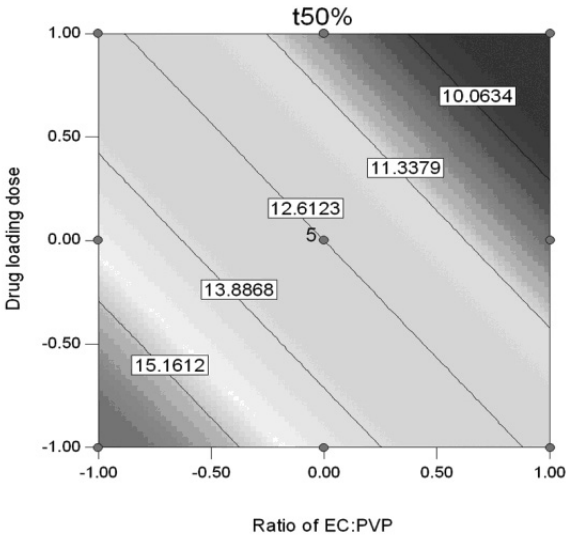

Figure 8. Contour plot for time taken for 50% drug release ($t_{50\%}$) indicating the effect of the ratio of EC: PVP and drug loading on $t_{50\%}$.

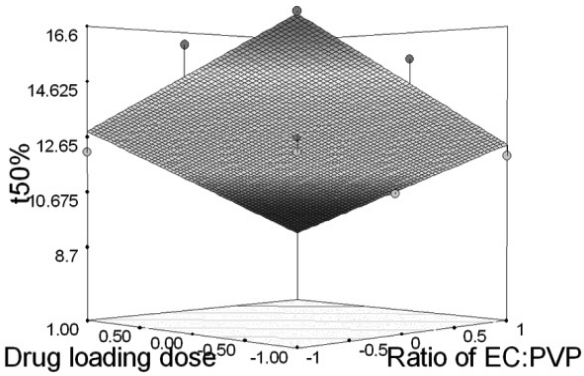

Figure 9. Response surface plot for time taken for50% drug release ($t_{50\%}$) indicating the effect of the ratio of EC: PVP and drug loading on $t_{50\%}$.

(fraction of PVP) and drug loading on K_H is evident from the contour plot and three-dimensional response surface plot (Figs. 6 and 7). The larger SME of ratio of EC: PVP level indicated that the effect of ratio of EC: PVP level was found to be the main influential factor on KH. KH was found to increase linearly when the levels of independent variables were raised from -1 through 0 to +1.

Figures 8 and 9 are the response surface plot and contour plot respectively indicating influence of the independent variables on $t_{50\%}$. It is cleared from the results of multiple regression analysis that the ratio of EC: PVP was the main influential factor on $t_{50\%}$.

Hence it may be concluded that both the independent factors, ratio of EC: PVP and drug loading, influence the response parameters linearly. The method adopted in this work can be used to screen formulation parameters and to selectively choose transdermal films for skin permeation studies. Further, in vitro and in vivo skin permeation studies have to be carried out to optimize the transdermal delivery system for controlled delivery of alfuzosin hydrochloride.

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