



Feasibility Assessment of Ondansetron Hydrochloride Transdermal Systems: Physicochemical Characterization and *In vitro* Permeation Studies

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SUMMARY. The present investigation aims at feasibility assessment of ethyl cellulose (EC) and polyvinylpyrrolidone (PVP) based ondansetron hydrochloride matrix type transdermal systems. The effects of polymeric concentration, its blend and drug loading dose on the *in vitro* drug permeation from the transdermal patches has been investigated. Ratio of EC: PVP and drug loading dose were selected as independent variables and their influence on the amount drug permeated at 24 h, permeation flux and steady state permeability coefficient were studied using experimental design. Various physicochemical parameters were studied to assess the feasibility of the transdermal systems. Ratio of EC: 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 evaluated and found satisfactory. Fourier transform infrared spectroscopy, scanning electron microscopy and X-ray diffraction studies confirmed amorphous state of ondansetron in the transdermal system. The study indicated the need for permeation enhancement techniques to meet the clinical requirement.

INTRODUCTION

Ondansetron is a serotonin (5-hydroxytryptamine) subtype 3 (5-HT₃) receptor antagonist used in the management of nausea and vomiting ¹⁻³. 5-HT₃ receptors, located centrally in the chemoreceptor trigger zone of the area postrema as well as peripherally on vagal nerve terminals, are key receptors in the nausea and vomiting response ⁴. Ondansetron has been used to prevent and control nausea and vomiting after cancer chemotherapy, radiotherapy and surgery ¹⁻⁴. The most commonly reported adverse events with ondansetron are headache, constipation and diarrhea, which are mild to moderate in severity and rarely necessitate treatment withdrawal ⁵. Ondansetron hydrochloride has been used by oral and injectable administration. It is rapidly absorbed orally, but extensively metabolized by the liver ⁶. In any situation where a patient is suffering from nausea and vomiting, oral administration of an antiemetic

agent is challenging and creates more discomfort for the patient. The orally administered antiemetic drug tends to be discharged by vomiting ⁷. On the contrary, intravenous administration renders rapid effects to a patient, but the onset of effects is too rapid to cause undesirable effects. Due to its short half-life and low bioavailability, it is administered orally 3 to 4 times a day, wherein the patient compliance is low ⁸. Alternative route of drug administration like rectal and nasal administrations of ondansetron are also considered to have low patient compliance ^{9,10}. Drug in adhesive type transdermal delivery systems of ondansetron hydrochloride were developed by Gwak *et al.* ¹¹ but the flux achieved was significantly less than the desired flux. Hence, in the present study, an attempt has been made to assess the feasibility of ondansetron hydrochloride delivery through transdermal route using ethyl cellulose and

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polyvinyl pyrrolidone as release modulating polymeric system.

MATERIALS AND METHODS

Materials

Ondansetron 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.

Response surface design

A hexagon response surface design was used in development of dosage form and two factors were evaluated, one (X_1) at five levels and the other (X_2) 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 cumulative amount of ondansetron hydrochloride permeated per cm^2 of human cadaver skin at 24 h (Q_{24}), permeation flux (J) and steady state permeability coefficient (P_{ss}) were chosen as dependent variables. Ratio of EC and PVP was evaluated at 10:90 (-1.00), 30:70 (-0.50), 50:50 (0.00), 70:30 (+0.50) and 90:10 (+1.00); while ondansetron loading dose was evaluated at 30% (-0.87), 40% (0) and 50% (+0.87) 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 composed of different ratios of EC and PVP (Table 1) containing ondansetron hydrochloride 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. Total dry weight of polymer blend was fixed at 100 mg. Ondansetron 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 membrane in a flat bottomed petridish and dried at 40 °C for 12h. The dried patches were removed and stored 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 100 ml 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 weight¹². 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 weight¹².

Runs	Factors		Observed Responses ^c		
	X_1^a (EC:PVP)	X_2^b (Drug loading)	Q_{24} ($\mu\text{g}/\text{cm}^2$)	J ($\mu\text{g}/\text{cm}^2.\text{h}$)	P_{ss} (cm/h)
1	-1.00	0.00	33.49 (± 1.87)	1.41 (± 0.13)	1.35 (± 0.07)
2	-0.50	0.87	29.32 (± 1.52)	1.19 (± 0.02)	0.91 (± 0.11)
3	-0.50	-0.87	21.42 (± 0.93)	0.90 (± 0.03)	1.14 (± 0.03)
4	0.00	0.00	17.25 (± 0.73)	0.72 (± 0.06)	0.68 (± 0.05)
5	0.50	0.87	15.48 (± 0.890)	0.62 (± 0.03)	0.47 (± 0.06)
6	0.50	-0.87	14.38 (± 1.47)	0.44 (± 0.02)	0.56 (± 0.02)
7	1.00	0.00	7.28 (± 0.21)	0.29 (± 0.09)	0.27 (± 0.04)

Table 1. Composition and observed responses from runs in Hexagon design. ^a Levels of ratio of EC: PVP (X_1) as 10:90(-1.00), 30:70(-0.50), 50:50(0.00), 70:30(+0.50) and 90:10(+1.00). ^b Levels of drug loading (X_2) as 30% (0.87), 40% (0) and 50% (+0.87). ^c Data shown are mean of three determinations and figure in the parantheses indicates standard deviation.

Flatness

Longitudinal strips were cut out from the prepared patches. The length of each strip was measured, and then 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% flatness¹².

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.

Fourier transform infra red (FTIR) spectroscopy

The pure drug, ondansetron hydrochloride 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 (FT-IR 8400S, Shimadzu Corporation, Japan).

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 Pentax Camera of 35 mm film.

X-ray diffraction (XRD) studies

Samples of ondansetron hydrochloride in its pure crystalline state and the transdermal patches were assessed for crystallinity using X-Ray diffractometer (Model: SEIFERT, C-3000, Germany) using Nickel – filtered CuK α radiation ($\lambda = 1.54\text{\AA}$). The voltage and current were 30 kv and 15 mA, respectively. Measurements were carried out in the angular scan range from 5° to 40° (2 θ) at a scan speed of 1°/min.

In vitro drug permeation studies

The extent and rate of skin permeation of ondansetron hydrochloride through the defatted full thickness human cadaver skin (obtained

from Forensic Medicine and Toxicology Department of M.K.C.G. Medical College and Hospital) were carried out using Keshary-Chein diffusion cell (cell capacity 20 ml, cross sectional area 1.766 cm²). The receptor compartment was filled with 20 ml normal saline (0.9%w/v of Na-Cl) and its temperature was maintained at 37 \pm 5 °C during the experiment. The receptor fluid is constantly agitated at 100 rpm by a teflon coated magnetic bead. The patch was applied under occlusion on the epidermal surface of the human cadaver skin fitted between the donor and receptor compartments of the diffusion cell. The whole of the receptor fluid was collected from the sampling port at predetermined time interval and replaced immediately with fresh normal saline. A similar set was run simultaneously using the patch (without drug) at the donor compartment as a skin patch control system to avoid the influence of inherent extracts from the skin or leaching of any material from the patch without drug on the absorbance at 248 nm, at which the sample aliquots were analyzed spectrophotometrically. The amount of drug permeated per square cm at each time interval was estimated and subjected to further data analysis.

Permeation data analysis and statistics

The flux ($\mu\text{g}/\text{cm}^2\cdot\text{h}$) of ondansetron hydrochloride was calculated from the slope of the plot of the cumulative amount of ondansetron hydrochloride permeated per cm² of human cadaver skin at steady state against the time using linear regression analysis. The steady state permeability coefficient (P_{ss}) of the drug through human cadaver skin was calculated by using the equation [1]:

$$P_{ss} = J/C \quad [1]$$

where J is the flux and C is the initial concentration of ondansetron hydrochloride in the patch. The observed difference in the permeation parameters of ondansetron hydrochloride in different formulations were compared by using one way analysis of variance (ANOVA) followed by all pair wise multiple comparison procedure such as Holm-Sidak test at overall significance level of 0.05 using SigmaStat software (SigmaStat 3.5, SPSS Inc, Chicago, IL, USA).

RESULTS

A summary of the results of physicochemical studies has been presented in Table 2. The moisture content (%) and moisture uptake (%) was found to increase with increase in PVP con-

Runs	Moisture uptake ^a (%)		Moisture content ^a (%)	Flatness ^a (%)	Folding endurance ^a
	RH 64%	RH 84%			
1	5.44 (±1.73)	8.07 (±1.17)	5.12 (±1.68)	100	38.666 (± 0.577)
2	5.33 (±0.91)	7.75 (±1.08)	4.82 (±0.67)	100	37.66 (± 0.57)
3	4.86 (±0.89)	6.85 (±1.14)	3.98 (±1.17)	100	36.333 (± 1.154)
4	4.32 (±0.77)	6.25 (±0.91)	3.32 (±0.58)	100	37 (± 1.000)
5	3.96 (±1.19)	5.89 (±0.86)	3.28 (±0.75)	100	37 (± 1.000)
6	3.91 (±0.88)	5.27 (±0.62)	3.11 (±0.83)	100	35.66 (± 0.57)
7	3.17 (±0.89)	4.96 (±0.95)	3.08 (±0.97)	100	35 (± 1.000)

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

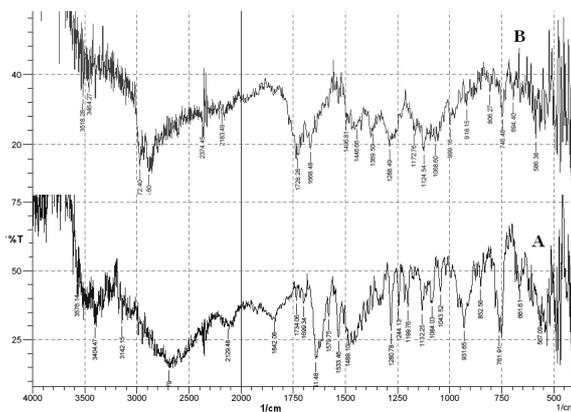


Figure 1. FT IR spectra of ondansetron hydrochloride (A) and transdermal film containing drug and polymers (B).

centration and the moisture uptake was higher at high humidity condition. Flatness study indicated absence of any constriction in the prepared patches. A higher value of folding endurance was identified in all the patches. The FT IR spectra of the active pharmaceutical ingredient and the developed patches have been presented in Figure 1. The FT IR spectra indicated amorphisation of ondansetron in the formulation. Figures 2 and 3 explains the SEM and XRD behavior of the formulations. They also confirmed the amorphous state of the drug in the patches. Experimental outputs pertaining to *in vitro* drug permeation studies are presented in Table 1 and the results of statistical analysis are presented in Tables 3 and 4. Figure 4 shows the permeation pattern of the transdermal patches and Figs. 5-10 indicates the influence of the independent variables on the measured responses. The permeation parameters were affected both by levels of EC: PVP and loading dose. Though the value of Q₂₄ increased when drug loading was increased from 30% to 50%, the re-

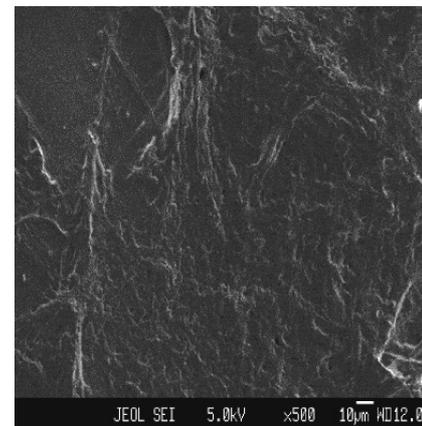


Figure 2. Scanning electron micrographs of the transdermal patch showing uniform distribution of drug in polymeric system.

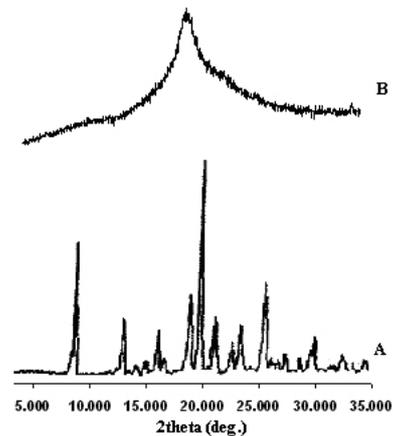


Figure 3. X-Ray diffraction pattern of ondansetron hydrochloride (A) and transdermal formulation (B) containing drug and polymers.

sponse was affected more by the levels of fraction of PVP. Steady state permeation flux (J) was found to increase linearly when the independent variables were raised from lower level to higher level. The ratio of EC: PVP was the main influential factor on P_{SS}.

DISCUSSION

Evaluation of physicochemical parameters

Results of the physicochemical studies have been summarized 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 percentage moisture uptake at laboratory ambient condition (3.17 ± 0.89 to 5.44 ± 1.73) protects the material from microbial contamination and bulkiness of the patches. Again a small percentage moisture content (3.08 ± 0.97 to 5.12 ± 1.68) in the formulations helps them to remain stable and from being a 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 of its flexibility.

Fourier transform infra red (FTIR) spectroscopy

The IR spectra of the pure drug and the patch (with EC and PVP) prepared by casting and solvent evaporation method were scanned over a wave number range of $4000-400\text{ cm}^{-1}$ in FT-IR (FT-IR 8400S, Shimadzu Corporation, Japan), showed all the characteristic bands of ondansetron hydrochloride. The shoulder at $1600-1700\text{ cm}^{-1}$ is due to the presence of C–O–C stretching (Fig. 1). Basically no change of frequency and shape of ondansetron hydrochloride bands were noticed, which leads to the conclusion that there is no significant redistribution of electronic density in the structure of organic molecule. The characteristic carbonyl peak at 1641 cm^{-1} with low intensity in the patch prepared by solvent evaporation and casting method, indicates amorphisation of the drug in the patch. This indicates no strong interaction between the drug and the polymers, in the transdermal films prepared by 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 ondansetron hydrochloride

in the polymeric system, homogeneously distributed drug particles were observed. No drug crystals were observed indicating relative amorphous state of ondansetron in the patch which is also confirmed by X-Ray diffraction studies.

X-ray diffraction (XRD) studies

X-ray diffraction studies were undertaken to confirm the physicochemical characteristics of ondansetron hydrochloride in the polymeric matrix of transdermal patches (Fig. 3). The pure ondansetron hydrochloride exhibited the diffraction peaks at 2θ value of 16.84° , 20.20° , 23.96° , 24.36° , 25.72° , 27.88° , 30.84° , etc., indicating the presence of crystalline ondansetron hydrochloride. Interestingly, there were no crystalline peaks of ondansetron hydrochloride in the polymeric matrix. Therefore, it is presumed that the drug molecule was dispersed at the molecular level and the crystallinity of the drug was not shown by X-ray diffraction study. This result implies that ondansetron hydrochloride is present as an amorphous form in the polymer system.

In vitro drug permeation studies

Effects of the variables on the *in vitro* drug permeation from the transdermal patches were studied by statistical experimental design. Experimental design has been widely used in pharmaceutical field to study the effect of formulation variables and their interactions on response variables¹³⁻¹⁶. In this study, a hexagon response surface 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 Table 3, the quadratic model was selected as a suitable statistical model for optimized formulations because it had the smallest value of PRESS and highest value of adjusted R^2 . 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 points¹⁷. Cubic model has terms that are aliased and hence that model was not selected. 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 quadratic model generated by the design is given below.

Source	Q ₂₄		J		P _{ss}	
	Adjusted R-Squared	PRESS	Adjusted R-Squared	PRESS	Adjusted R-Squared	PRESS
Linear	0.9042	93.24	0.9621	0.068	0.9570	0.068
2FI ^a	0.9226	112.95	0.9611	0.071	0.9584	0.073
Quadratic	0.9790	169.75	0.9969	0.048	0.9989	0.016
Cubic ^b	1.0000	Not defined	1.0000	Not defined	1.0000	Not defined

Table 3. Response model summary statistics. ^a Two factor interaction. ^b Aliased model not to be selected.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1X_1 + b_{22}X_2X_2$$

Where, Y is the dependent variable, b₀ is the arithmetic mean response of the 7 runs, and b_i (b₁, b₂, b₁₂, b₁₁ and b₂₂) is the estimated coefficient for the corresponding factor X_i (X₁, X₂, X₁X₂, X₁X₁ and X₂X₂), which represents the average result of changing one factor at a time from its low to high value. The interaction term (X₁X₂) shows how the response changes when two factors are changed simultaneously. The polynomial terms (X₁X₁, X₂X₂) are included to investigate nonlinearity.

Final equation in terms of coded factors

$$Q_{24} = +17.25 -12.22 * A +2.60 * B -3.93 * A * B +3.13 * A^2 +2.83 * B^2$$

$$J = +0.72 -0.55 * A +0.13 * B -0.068 * A * B +0.13 * A^2 +0.051 * B^2$$

$$P_{ss} = +0.69 -0.53 * A -0.093 * B +0.083 * A * B +0.12 * A^2 +0.073 * B^2$$

Final equation in terms of actual factors

$$Q_{24} = +17.25100 -12.21750 * \text{Ratio of EC:PVP} +2.59844 * \text{Loading Dose} -3.92552 * \text{Ratio of}$$

$$\text{EC:PVP} * \text{Loading Dose} +3.13400 * \text{Ratio of EC:PVP}^2 +2.82717 * \text{Loading Dose}^2$$

$$J = +0.72020 -0.54810 * \text{Ratio of EC:PVP} +0.13458 * \text{Loading Dose} -0.068476 * \text{Ratio of EC:PVP} * \text{Loading Dose} +0.12965 * \text{Ratio of EC:PVP}^2 +0.050520 * \text{Loading Dose}^2$$

$$P_{ss} = +0.68600 -0.52883 * \text{Ratio of EC:PVP} -0.093245 * \text{Loading Dose} +0.082564 * \text{Ratio of EC:PVP} * \text{Loading Dose} +0.12150 * \text{Ratio of EC:PVP}^2 +0.072504 * \text{Loading Dose}^2$$

The permeation profile of all the experimental batches is shown in Figure 4. The coefficient estimate and standardized main effects (SME) values for the responses are listed in Table 4. 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. 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 4).

The influence of ratio of EC: PVP (fraction of PVP) and drug loading dose on Q₂₄ is evident from the contour plot and three-dimensional response surface plot (Figs. 5 and 6). Regarding the overall effect of both factors, it appeared that the Q₂₄ value was affected more by the levels of fraction of PVP, which was cleared from the response surface plot (Fig. 6), as the decline of the Q₂₄ 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 Q₂₄ from the transdermal patches in the whole stage permeation. Less or negligible curvature on both axes in response surface plot indicates little contribution of interaction terms along with linearity of responses. It was found that the Q₂₄ value increased with increase in

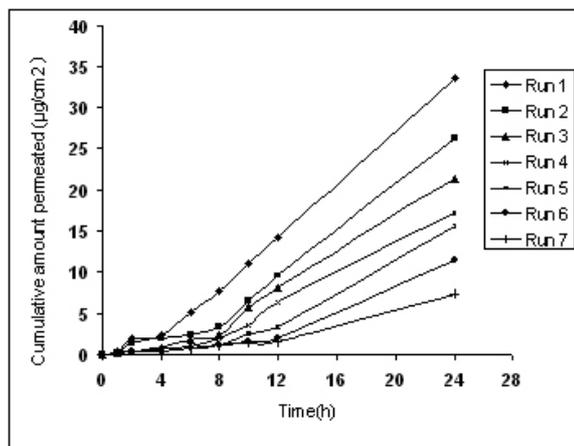


Figure 4. In-vitro dissolution profile of the experimental batches of ondansetron hydrochloride transdermal films in normal saline as receptor media.

Coefficient of regression parameter	Measured Responses								
	Q ₂₄			J			P _{ss}		
	Coeff. estimate	P-value	SME	Coeff. estimate	P-value	SME	Coeff. estimate	P-value	SME
b ₀	17.25	0.0004	31.94	0.72	< 0.0001	79.12	0.69	< 0.0001	130.18
b ₁	-12.22	<0.0001	-19.39	-0.55	< 0.0001	-50.00	0.53	< 0.0001	-86.6
b ₂	2.60	0.0143	4.42	0.13	0.0002	11.82	0.093	0.0001	-15.19
b ₁₂	-3.93	0.0351	-3.14	0.068	0.0317	-3.24	0.083	0.0025	6.92
b ₁₁	3.13	0.0290	3.33	0.13	0.0012	8.12	0.12	0.0002	13.05
b ₂₂	2.83	0.0397	3.01	0.051	0.0334	3.19	0.073	0.0014	7.94

Table 4. 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.

fraction of PVP and drug loading. The addition of hydrophilic component to an insoluble film former (EC) tends to enhance the release rates, as reported by Arora *et al.*¹⁸. 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 patches¹⁹. One of the rate limiting factors for drug permeation from transdermal patches is the rate and extent of drug dissolution 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^{20,21}. 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 patches²².

It was also observed that the value of Q₂₄ increased 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.*²³. Such linearity of effect has also been reported by El-Arini *et al.*²⁴. The drug release was high from the formulations in the initial hours. One way ANOVA followed by Holm-Sidak test confirmed significant difference among the Q₂₄ values of different runs except between run 4 vs 5 and run 5 vs 6.

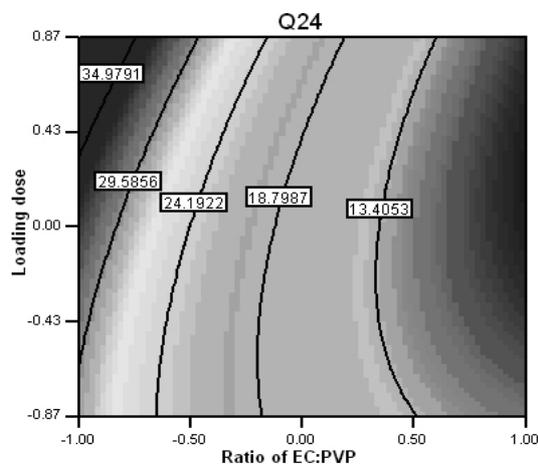


Figure 5. Contour plot for cumulative amount drug permeated at 24 h (Q₂₄) indicating the effect of the ratio of EC: PVP and drug loading on Q₂₄.

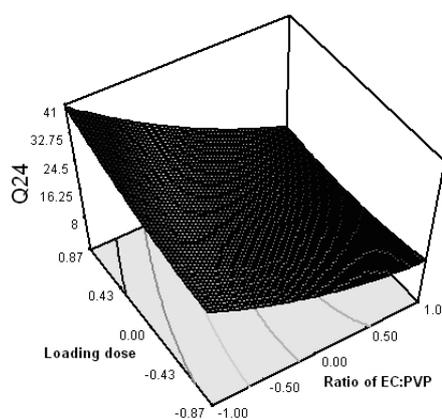


Figure 6. Response surface plot for cumulative amount drug permeated at 24 h (Q₂₄) indicating the effect of the ratio of EC: PVP and drug loading on Q₂₄.

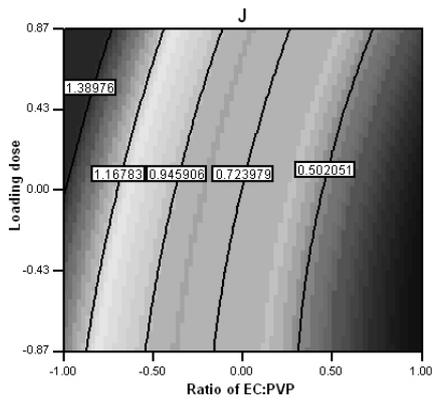


Figure 7. Contour plot for permeation flux (J) indicating the effect of the ratio of EC: PVP and drug loading on J.

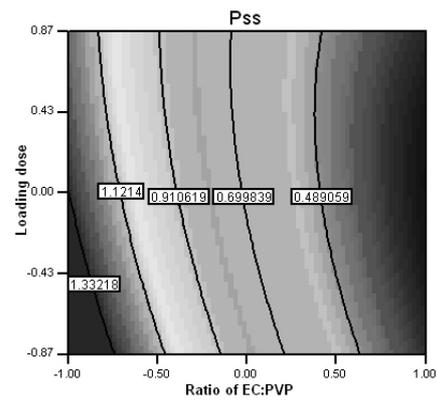


Figure 9. Contour plot for permeability coefficient (P_{ss}) indicating the effect of the ratio of EC: PVP and drug loading on P_{ss} .

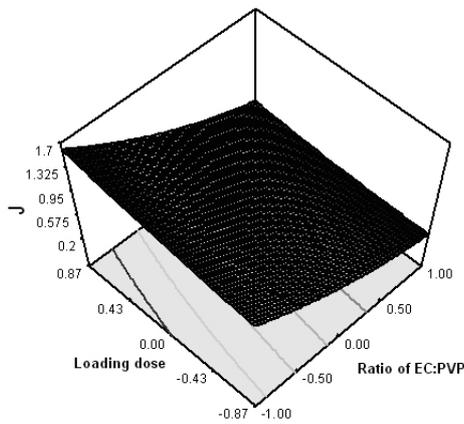


Figure 8. Response surface plot for permeation flux (J) indicating the effect of the ratio of EC: PVP and drug loading on J.

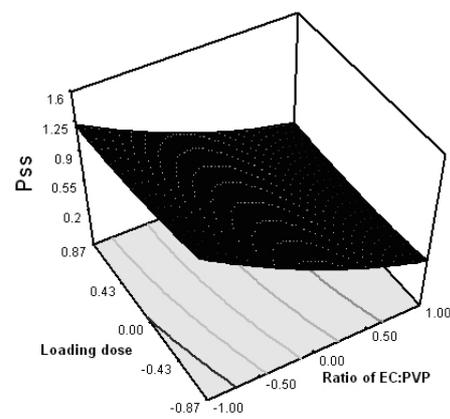


Figure 10. Response surface plot for permeability coefficient (P_{ss}) indicating the effect of the ratio of EC: PVP and drug loading on P_{ss} .

The influence of ratio of EC: PVP (fraction of PVP) and drug loading on J is evident from the contour plot and three-dimensional response surface plot (Figs. 7 and 8). The larger SME value 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 J. J was found to increase linearly when the independent variables were raised from lower level to higher level. A statistically significant difference was observed among all the runs except between run 4 vs 5, when subjected to one way ANOVA followed by Holm-Sidak test. However, the maximum flux achieved with the experimental batch is $1.41 (\pm 0.13) \mu\text{g}/\text{cm}^2$, which is well below the desired flux for effective transdermal delivery of ondansetron hydrochloride. Hence, there is a vital need for use of active permeation enhancement techniques.

Figures 9 and 10 are the contour plot and response surface plot, respectively indicating influence of the independent variables on P_{ss} . It is cleared from the results of multiple regression analysis that the ratio of EC: PVP was the main influential factor on P_{ss} . A statistically significant difference was observed among all the runs except between run 4 vs 6 and run 6 vs 5, when subjected to one way ANOVA followed by Holm-Sidak test.

CONCLUSION

The principle of statistical experiment designing has been effectively employed to estimate the effects of the independent formulation variables on the dependent responses. It is found that that both the independent factors, ratio of EC: PVP and drug loading dose, influence the response parameters like Q_{24} , J and P_{ss} . The

main influential factor for all the measured responses is found to be the ratio of EC: PVP. The physicochemical parameters of the experimental trial batches were evaluated and found fairly satisfactory for further development. The XRD and SEM along with FTIR studies confirmed the existence of ondansetron in its amorphous state. The experimental trial batches failed to meet the clinical requirement of desired flux and hence it can be concluded that matrix type transdermal patches of ondansetron hydrochloride may be attempted using either chemical or other physical permeation enhancement methods.

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