

DEVELOPMENT AND CHARACTERIZATION OF TRANSDERMAL PATCHES OF ONDANSETRON HYDROCHLORIDE

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ABSTRACT

The purpose of this research was to develop a matrix-type Transdermal therapeutic system containing drug Ondansetron hydrochloride (OSH) with different ratio of hydrophilic and hydrophobic polymeric systems by the film casting techniques on mercury by using 10 % w/w of propylene glycol to the polymer weight, incorporated as plasticizer and 5% oleic acid was used to enhance the Transdermal permeation of OSH. Formulated transdermal patches were physically evaluated with regard to thickness, moisture content, moisture uptake, tensile strength, folding endurance, flatness, drug content, and water vapor transmission rate. All prepared formulations indicated good physical stability. The mercury substrate method was found to give thin uniform patches. *Ex vivo* permeation studies of formulations were performed by using Franz diffusion cells. It was observed that the formulation B3 shows better extended release up to 12 hrs and followed Korsmeyers–Peppas model in dissolution study. The release rate found to follow first order rate kinetic. Primary irritation study shows that the prepared transdermal films are nonirritant. Transdermal delivery is a potential route for the administration of Ondansetron hydrochloride.

Keywords: Ondansetron hydrochloride, Hydrophilic and hydrophobic polymers, Sustained release, Transdermal patches.

INTRODUCTION

In the advent of modern era of pharmaceutical dosage forms, transdermal drug delivery system (TDDS) established itself as an integral part of novel drug delivery system¹. Transdermal patches are polymeric formulations which when applied to skin deliver the drug at a predetermined rate across dermis to achieve systemic effects. Transdermal dosage forms, though a costly alternative to conventional formulations, are becoming popular because of their unique advantages. Controlled absorption, more uniform plasma levels, improved bioavailability, reduced side effects, painless and simple application and flexibility of terminating drug administration by simply removing the patch from the skin are some of the potential advantages of transdermal drug delivery².

Ondansetron is a potent antagonist of Serotonin (5 HT₃) receptor which has been proved effective in prevention of chemotherapy and radiotherapy-induced nausea and vomiting. Ondansetron hydrochloride has been used by oral and injectable administration. Ondansetron hydrochloride is rapidly absorbed orally, but extensively metabolized by the liver. It should be administered 30 min before chemotherapy, and the orally administered antiemetic drug tends to be discharged by vomiting. On the contrary, intravenous administration renders rapid effect to a patient, but the onset of effect is too rapid to cause undesirable effects. In addition, it gives a local pain, and may cause an unexpected accident when it is not perfectly prepared³. In this work an attempt was made to formulate and evaluate TDDS for sustained release OSH by solvent casting method. Low molecular weight, good permeability, poor bioavailability (60%) and shorter half-life (5-6 h) of OSH made it a suitable drug candidate for the development of Transdermal patches⁴. The main objective of formulating the Transdermal system was to prolong the drug release time, reduce the frequency of administration and to improve patient compliance.

MATERIALS AND METHODS

Ondansetron Hydrochloride was obtained as a gift sample from Pranami Drug Pvt. Ltd, Ahemadabad. Eudragit RL100 was obtained as a gift sample from Vikram Thermo India Ltd, Gandhinagar. Chitosan was obtained from Marine Chemicals (Cochin, India). HPMC, Oleic acid and Propylene glycol were obtained from Research Lab Fine Chem (Mumbai, India). All other chemicals used were of analytical grade.

FTIR- spectroscopy

In order to investigate the possible interaction between drug and selected polymers, FT-IR spectroscopy studies were carried out. IR

spectrum for pure drug and physical mixture of drug-polymers were compared. Then it was characterized for any change in the finger print-region of drug in the presence of polymer.

Formulation of transdermal patches

The transdermal patches were prepared by film casting techniques on mercury⁵. A 2² fractional factorial design were applied to formulate the matrix type transdermal film of Ondansetron HCl. Hydrophilic materials i.e. HPMC and chitosan (in 2% Glacial acetic acid) were dissolved in 10 ml distilled water and hydrophobic materials i.e. Eudragit RL 100 and Ondansetron HCl were dissolved in 10 ml ethanol. Then both the solutions were mixed and stirred on magnetic stirrer to accomplish a homogeneous mixture. Known volume of Propylene Glycol was mixed thoroughly in the solution and stirred for 30min. The resulting whole solution was poured in a petri dish containing mercury. Mercury is used to avoid the adherence of film to dish. The solvent was allowed to evaporate for 24 hr. at 35° C. The prepared transdermal Ondansetron HCl patches were store in a dessicator until further use. In the formulations the concentration of Drug (OND), Chitosan (50) mg, 5% Oleic Acid and 10% Propylene Glycol were kept as constant.

Table 1: Fractional factorial experimental design layout

Batch	X1	X2	Batch	X1	X2	Batch	X1	X2
B1	-1	-1	B4	0	-1	B7	1	-1
B2	-1	0	B5	0	0	B8	1	0
B3	-1	1	B6	0	1	B9	1	1

Table 2: Amount of variable in 2² factorial design

Coded level	-1	0	1
HPMC (X1) mg	400	450	500
Eudragit RL 100 (X2) mg	300	350	400

Evaluation of Transdermal formulation

Thickness

The thickness of transdermal patches was measured at three different places using digital Vernier caliper and the average values were calculated⁶.

Moisture content

The patches were weighed individually and kept in a dessicator containing calcium chloride at 37°C for 24 hrs. The final weight was

noted when there was no change in the weight of individual patch. The percentage of moisture content was calculated as a difference between initial and final weight with respect to final weight^{7,8}.

$$\% \text{ MC} = \frac{(X - Y)}{Y} \times 100$$

Where, X = initial weight, Y = final weight

Moisture uptake

A weighed film kept in desiccator at 40°C for 24h was taken out and exposed to relative humidity of 93%RH (saturated solution of Potassium bromide) in a desiccator at room temperature then the weights were measured periodically to constant weights^{9,10}.

$$\% \text{ MU} = \frac{(X - Y)}{Y} \times 100$$

Where, X = initial weight, Y = final weight

Determination of tensile strength

The tensile strength was determined by using a modified pulley system. It contains two clamps, one was fixed and other was movable. The strip of the patch (2 x 1 cm²) was cut and set between these two clamps. Weight was gradually increased on the pan, so as to increase the pulling force till the patch broke. The force required to break the film was considered as a tensile strength and it was calculated as kg/cm²^{11,12}.

$$\text{Tensile strength} = (\text{break force}/a \times b)$$

Where, a, and b are the width & thickness, of the films respectively.

Folding Endurance

Folding endurance was measured to determine the ability of patch withstand to rupture. Folding endurance of films was determined by continually 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 of that prepared transdermal film¹³.

Flatness

The construction of a film strip cut out from a drug-loaded matrix film is an indicator of its flatness. Longitudinal strips (1.5cm x 0.75 cm) were cut out from the prepared medicated matrix films. The initial length of films was measured, and then it was kept at room temperature for 30 min. The variations in the length due to non-uniformity in flatness were measured. Flatness was calculated by measuring constriction of strips and a zero percent of constriction was considered to be equal to 100% flatness^{14,15}.

$$\% \text{ constriction} = \frac{L_1 - L_2}{L_2} \times 100$$

Where, L₁ = initial length of each strip (cm).

L₂ = final length of each strip (cm).

Drug content determination

To determine drug content, a 2 cm² film was cut into small pieces, placed into a 100 ml of isotonic phosphate buffer of pH 7.4 and ultrasonicated for 30 min, then the solutions were stirred with a magnetic bead continuously for 5 h. After filtration, 1 ml was withdrawn from the solution and diluted to 10ml. The absorbance of the solution was taken at 309 nm and concentration was calculated. By correcting dilution factor, the drug content was calculated^{16,17}.

Water vapor transmission (WVT) rate

The water vapor transmission is defined as the quantity of moisture transmitted through unit area of a patch in unit time. The water vapor transmission data through transdermal patches are important in knowing the permeation characteristics. The film was fixed over the brim of a glass vial, containing 3 g of fused calcium chloride as

desiccant, with an adhesive tape. The vial was weighed and kept in desiccator containing saturated solution of potassium chloride to provide relative humidity of 84%. The vial was taken out and weighed at every 24 hrs intervals for a period of 72 hrs. The WVT was calculated by taking the difference in the weight of the patches before and at regular intervals of 24 hrs^{18,19}.

The water vapor transmission was calculated using the equation:-

$$\text{WVT rate} = \text{WL/S}$$

Where, W = g of water transmitted.

L = thickness of the patch

S = exposed surface area of the patch.

In-vitro drug Permeation Studies

The in vitro study of drug permeation through the semi permeable membrane was performed using a modified Keshary-Chien type glass diffusion cell. The modified cell having higher capacity (25 ml) is used to maintain sink condition. This membrane was mounted between the donor and receptor compartment of a diffusion cell. The transdermal patch was placed on the membrane and covered with aluminum foil. The receptor compartment of the diffusion cell was filled with isotonic phosphate buffer of pH 7.4. The hydrodynamics in the receptor compartment were maintained by stirring with a magnetic bead at constant rpm and the temperature was maintained at 37±0.5°C. The diffusion was carried out for 12 h and 1 ml sample was withdrawn at an interval of 1 h. The receptor phase was replenished with an equal volume of phosphate buffer at each sample withdrawal. The samples were analyzed for drug content spectrophotometrically at 309 nm^{20,21}.

Kinetic Modeling of Drug Release

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model²².

Skin Irritation Study

The patches were tested for their potential to cause skin irritation /sensitization in rats. Skin irritation studies were performed on healthy rat (CPCSEA approval Number GNCP/IAEC/2011-2012/QA-1). The dorsal surface of the rats was cleaned, and the hair were removed by depilatories. The skin was cleaned with rectified spirit. Treated skin areas were then evaluated according to a modified Draize scoring method and the irritation index was evaluated. The rats were divided into two groups. Group I received prepared transdermal patch and Group II received 0.8% v/v aqueous solution of formalin as a standard irritant. After 24 h & 72 h after test article application, the test sites were examined for dermal reactions in accordance with the Draize scoring criteria^{23,24}.

Table 3: Draize evaluation of dermal reaction

Score	Reaction	
	Erythematic	Edema
1	No erythema	No edema
2	Very slight erythema	Very slight edema
3	Well-defined erythema	Slight edema
4	Moderate to severe erythema	Moderate edema
5	Severe erythema	Severe edema

RESULTS AND DISCUSSION

Table 4: Characteristic peaks of group

cm ⁻¹	Group
3245	-NH (STR)
3200-3180	-NCH ₃
1635-1612	C=O (ketonic)
2720-2662	-CH ₃
750-760	Aromatic Stretching

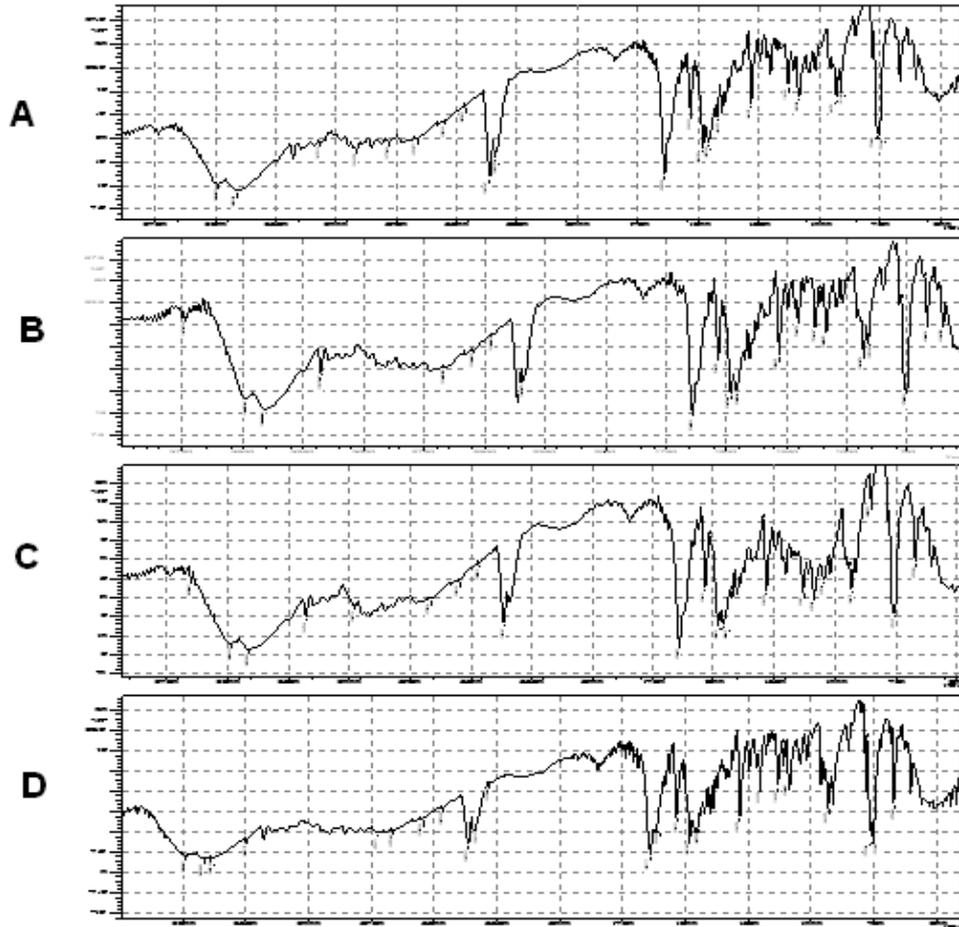


Fig. 1: (A) IR Spectrum of Ondansetron HCl (B) IR Spectrum of Ondansetron HCl + Chitosan (C) IR Spectrum of Ondansetron HCl + Eudragit RL 100 (D) IR Spectrum of Ondansetron HCl + HPMC

The IR spectrum of pure drug was found to be similar to the standard spectrum of Ondansetron HCl. The spectrum of Ondansetron HCl shown following functional group in their frequency

Table 5: Evaluation data of Ondansetron HCl Transdermal patches

Formulation Code	Thickness (mm)	% Moisture Content	% Moisture Uptake	Tensile Strength (Kg/cm ²)
B1	0.2987 ± 0.02	5.26 ± 0.12	10.61 ± 0.43	0.536 ± 0.002
B2	0.2256 ± 0.04	5.30 ± 0.09	10.43 ± 0.14	0.557 ± 0.023
B3	0.1982 ± 0.02	4.14 ± 0.08	9.52 ± 0.58	0.576 ± 0.021
B4	0.3491 ± 0.03	5.04 ± 0.14	10.56 ± 0.21	0.527 ± 0.025
B5	0.2536 ± 0.01	4.86 ± 0.13	10.12 ± 0.13	0.541 ± 0.032
B6	0.2143 ± 0.01	4.91 ± 0.14	9.58 ± 0.29	0.545 ± 0.030
B7	0.3572 ± 0.05	5.41 ± 0.18	11.02 ± 0.46	0.513 ± 0.032
B8	0.3402 ± 0.02	5.04 ± 0.19	10.43 ± 0.35	0.530 ± 0.010
B9	0.241 ± 0.05	4.96 ± 0.13	9.76 ± 0.41	0.544 ± 0.013

Mean ± SD, (n=3)

Table 6: Evaluation data of Ondansetron HCl Transdermal patches

Formulation Code	Folding Endurance	% Flatness	Drug Content %	Water vapour Transmission rate(gm/cm ² /hr)X10 ⁻⁴
B1	94 ± 2	100	97.68 ± 0.2	3.91 ± 0.16
B2	98 ± 1	100	98.46 ± 0.3	3.48 ± 0.18
B3	110 ± 0.15	100	98.81 ± 0.2	2.15 ± 0.14
B4	92 ± 2	100	97.15 ± 0.4	4.34 ± 0.15
B5	96 ± 1	100	98.16 ± 0.7	3.26 ± 0.16
B6	100 ± 1	100	96.64 ± 0.5	2.57 ± 0.17
B7	90 ± 2	100	98.79 ± 0.3	4.61 ± 0.18
B8	94 ± 0.46	100	98.45 ± 0.2	3.52 ± 0.14
B9	97 ± 2	100	97.94 ± 0.3	2.84 ± 0.17

Mean ± SD, (n=3)

Nine formulations of Ondansetron HCl transdermal patches were prepared using different polymer concentrations. These formulated transdermal patches were transparent, smooth, uniform and flexible. The addition of plasticizer was found to be essential to improve mechanical properties of patches & easily removed from mercury surface without any rupture. These formulations are subjected to evaluation parameters like thickness, moisture content, moisture uptake, tensile strength, folding endurance, flatness, drug content, water vapor, IR studies, in-vitro drug release studies.

From the IR spectra, it was clear that there was no change in peak positions of Ondansetron HCL, when mixed with the polymers. Thus, there was no interaction between Ondansetron HCL and polymers. The physical evaluation of Transdermal patches for all formulations was performed. Thickness of Transdermal patches varies from 0.1982 to 0.3572 mm. Moisture content of Transdermal patches varies from 4.14 % to 5.41%. Moisture content studies indicate that the increase in the concentration of hydrophilic polymer i.e. HPMC was directly proportional to the increase in moisture content of the patches. The moisture content of the prepared transdermal film was low, which maintains suppleness, thus preventing drying and brittleness. Moisture uptake studies also indicate that the increase in the concentration of hydrophilic polymer i.e. HPMC was directly proportional to the increase and moisture uptake of the patches. The moisture uptake of the transdermal formulations was also low, which protects the film from microbial contamination as well as bulkiness of transdermal patch. The prepared transdermal films showed good tensile strength and there was no sign of cracking in prepared transdermal film. There was an increase in tensile strength with an increase in Eudragit RL 100 in the polymer blend. Folding endurance test results indicates that all the patches will withstand to rupture and would maintain their integrity with general skin folding when used. All the patches were showed near to 100% flatness, which indicates negligible amount of constriction of the prepared transdermal patches. Thus, a patch does not constrict, when it is applied on the skin.

Drug content was found to be in the range of 96.64% to 98.81% indicating that the drug was uniformly distributed throughout the patches and evidenced by the low values of SD.

Patches containing higher amount of HPMC showed good water vapor transmission (4.61 ± 0.18) than that of Eudragit RL 100. The enhancement of water vapor permeation with increase of HPMC is due to the irregular arrangement of molecules in the amorphous state, which causes the molecules to be spaced further apart than in crystal. Hence the specific volume is increased and the density decreased compared to that of crystal, which leads to the absorption of vapor into their interstices. All the formulations were permeable to water vapor.

In-Vitro Dissolution Studies

The maximum release of the drug from transdermal patches was controlled by the chemical properties of the drug and delivery form. The matrix allows one to control the overall release of the drug via

an appropriate choice of polymers and their blends. The blends of polymers create several diffusion pathways to generate overall desired steady and sustained drug release from the patches. 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 into the diffusion medium and hence, to cause higher release rate. The cumulative percentage of drug permeated from B1 to B9 formulations was given in the following order B7> B8 > B9 > B4 > B5 > B6 > B1 > B2 > B3.

The Batch B7 containing highest amount of HPMC showed maximum release 67.52 %. While The Batch B3 containing the higher proportion of the Eudragit RL100 shows only 50.73 % drug release within 12 hr, which was the lowest amount of the drug release among the all 9 batches.

Kinetic Modeling of Drug Release

The *in vitro* permeation data were fit to different equations and kinetic models to explain permeation profiles. The coefficient of correlation of each of the kinetics was calculated and compared. The *in vitro* permeation profiles of all the different formulations of transdermal patches did not fit to zero order behavior truly and they could be best expressed by first order kinetics for the release of drug from a homogeneous polymer matrix type delivery system that depends mostly on diffusion characteristic. The drug release kinetics studies showed that the all the formulations were governed by Peppas model and mechanism of release was non-Fickian mediated.

Skin irritation study

Dermal observation of skin irritation test of Optimized B3 Patch shown in Table A 72 hour skin irritation study was conducted on healthy adult male rat. There was not any trace of edema, erythema or any skin irritation on site of application of the patch hence these formulations are non irritable to the skin tissue and can be considered as the safe therapeutic transdermal patches. In Group II, which contain formalin as a standard irritant, showed the slight to sever skin irritation reaction.

Table 7: Dermal observation of skin irritation test of Optimized B3 Patch

Rat No.	Reaction	Group - I (test patch)		Group - II Standard (0.8% Formalin)	
		24Hour	72 Hour	24Hour	72Hour
1	Erythema	0	0	1	1
	Edema	0	0	2	1
2	Erythema	0	0	1	2
	Edema	0	0	1	1

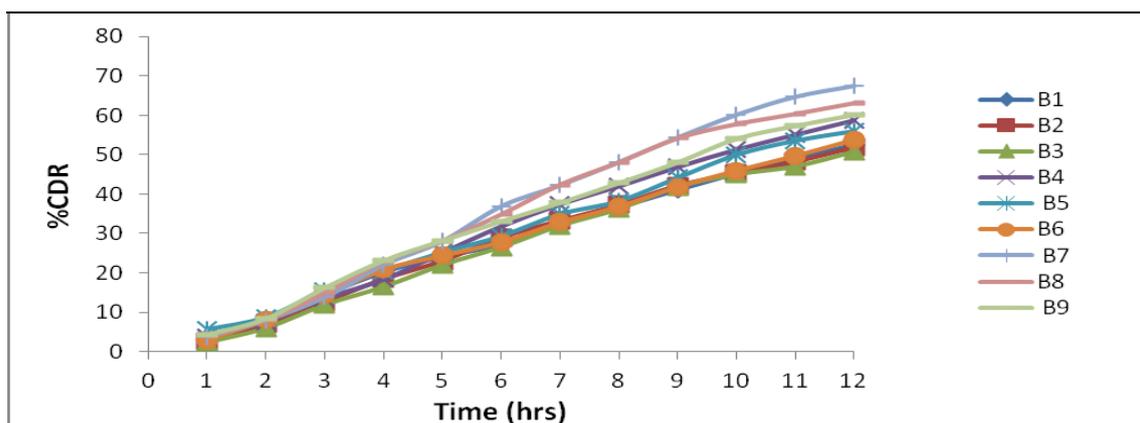


Fig. 2: In-vitro release profile of Ondansetron HCl transdermal patches (B1-B9)

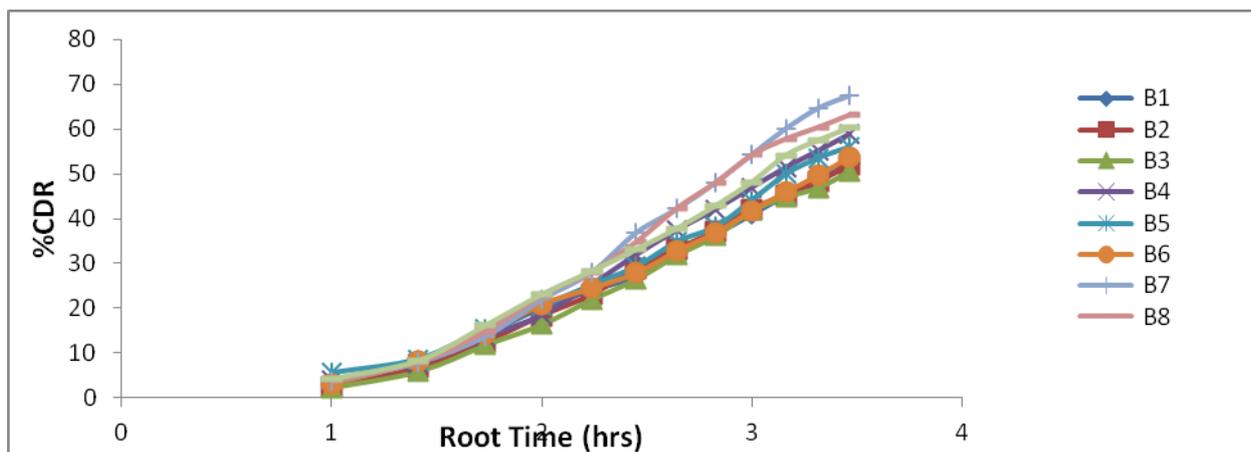


Fig. 3: Higuchi release kinetic profile of Ondansetron HCl transdermal patches

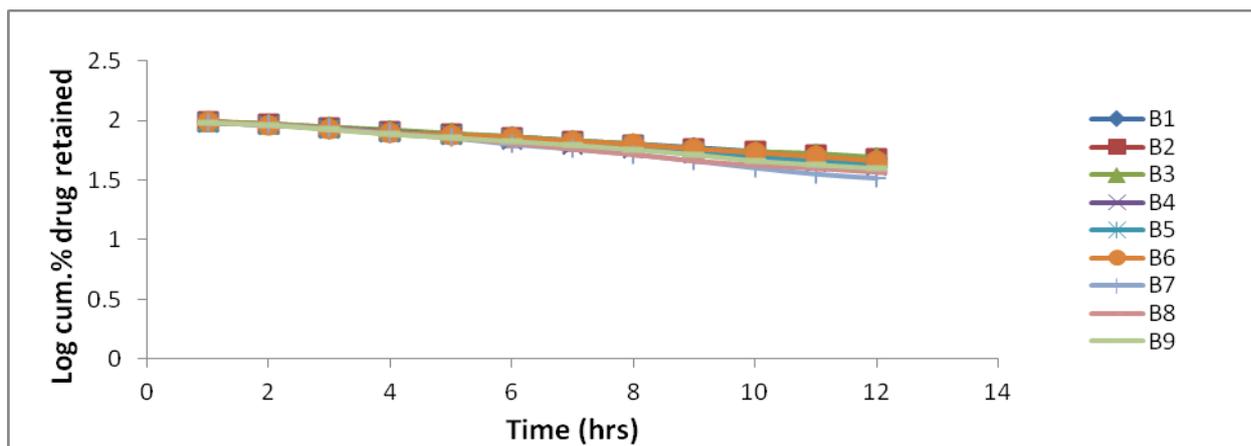


Fig. 4: First order release kinetic profile of Ondansetron HCl transdermal patches

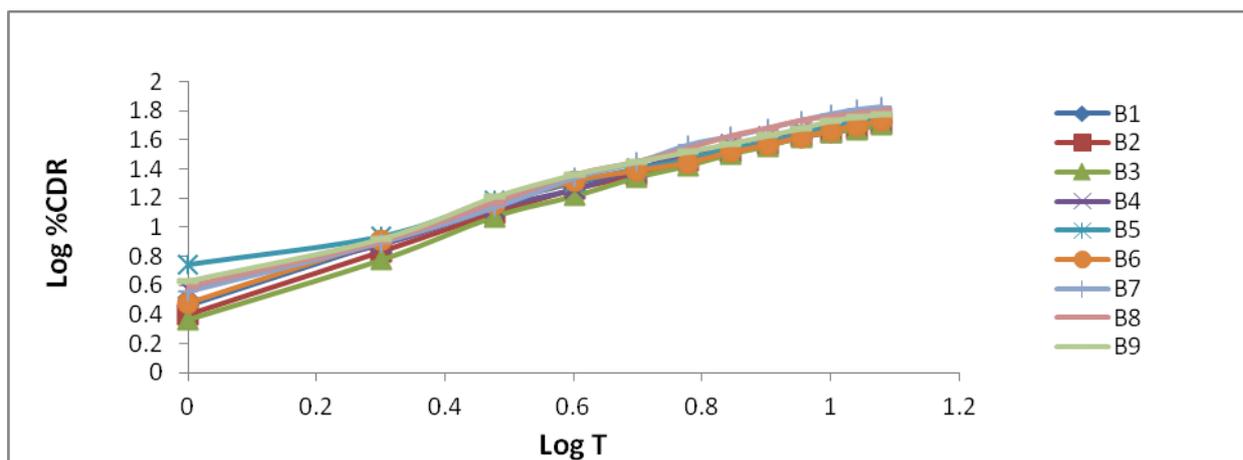


Fig. 5: Peppas release kinetic profile of Ondansetron HCl transdermal patches

CONCLUSIONS

In conclusion, it may be concluded that formulation of Ondansetron HCl transdermal patches with suitable and optimum concentration of excipients in form of polymers, plasticizers, & permeation enhancers etc. may be used to get the effective rate of release of drug from the patches. Among all the prepared films, B3 would be better formulation based on the *in vitro* permeation studies as it sustained the release of drug for longer duration without significantly releasing the drug in a burst manner in the initial hours.

The drug release kinetics of all fabricated patches follows first order kinetics except B5 & B7 showing zero order release kinetics,

whereas, the mechanism of drug release of all formulations were non-Fickian. Further, *in vivo* studies have to be performed to correlate with *in vitro* release data for the development of suitable controlled release patches for Ondansetron HCl.

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