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Formulation and Evaluation of Transdermal Ondansetron Hydrochloride Matrix Patch: *In Vitro* Skin Permeation and Irritation Study

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Subject: Formulation science

Abstract:
In the present study an attempt was made to develop a suitable matrix type transdermal patch of ondansetron hydrochloride using blends of two different type of polymeric combinations viz. PVP and HPMC K4 M and Eudragit L100 with Povidone (PVP). The prepared formulations were subjected to various physiochemical evaluation test like moisture content loss, moisture absorption, flatness to study the stability of the formulations, *in vitro* dissolution was performed to determine the amount of ondansetron hydrochloride present in the patches. Drug-excipient interaction studies were carried out using Fourier transform infrared (FTIR) spectroscopy technique. *In vitro* skin permeation study was conducted in a modified Franz's diffusion cell. The *in vitro* release of the drug from the formulations was studied using commercial semi permeable membrane. All the formulations were found to be suitable for formulating in terms of physiochemical characteristics and there was no notification in significant interaction between the drug and polymer used. *In vitro* dissolution data showed that formulation of PVP: HPMC K4 M showed faster release of drug than the PVP: Eudragit L100 formulations during skin permeation studies. Skin irritation studies revealed that the batch containing PVP-Eudragit L100 has no erythema and oedema. Based on the observation, we can reveal that PVP- eudragit L100 polymers are better suited than PVP-HPMC K4 M polymer for the development of ondansetron hydrochloride transdermal patches.

Keywords: *Ondansetron hydrochloride; Transdermal patches; Eudragit L100; HPMC K4 M; Povidone.*

Introduction:

During the last decade, controlled release concept and technoloty have received increasing attention in the face of growing toxicity and ineffectiveness of drugs when administered or applied by conventional methods [1]. A controlled release drug delivery may be defined as a system that implies a predictability and reproducibility in the drug release kinetics [2]. The findings accumulated over the years have practically revolutionized the old concept of impermeable skin barrier and motivated a number of pharmaceutical scientists to develop patch type drug delivery system for transdermal rate controlled administration of drugs for systemic medications. Transdermal drug delivery system can be defined as the delivery of drug across the epidermis to achieve systemic effects. The success of transdermal patches lies in their commercialization. Transdermal patches control the delivery of drugs at controlled rate by employing an appropriate combination of hydrophilic and lipophilic polymers [3-6].

Ondansetron hydrochloride is5-HT_3 receptor antagonists are the primary drugs used to treat and prevent chemotherapy-induced nausea and vomiting (CINV) [7]. A common use case is to give them intravenously about 30 minutes before commencement of a chemotherapy treatment. Ondansetron is also effective in controlling post-operative nausea and vomiting (PONV) and post-radiation nausea and vomiting, and is a possible therapy for nausea and vomiting due to acute or chronic medical illness or acute gastroenteritis. Although it is highly effective, the high cost of the brand-name version had limited its use to controlling PONV and CINV. It

is also used off-label to treat hyperemesis gravid arum in pregnant women, but there is no conclusive data available on its safety in pregnancy, especially during the first trimester. It is also used to treat cyclic vomiting syndrome; although there have been no formal trials to confirm efficacy, case reports suggests it can be helpful in some cases. The drug is administered 1–3 times daily, depending on the severity of nausea and/or vomiting [7, 8]. The normal oral dose for adults and children over the age of 12 is 8 mg initially, followed by a second dose of 8 mg eight hours later. The drug is then administered once every 12 hours, usually for not more than 2–3 days. Following oral administration, it takes about 1.5 to 2 hours to reach maximum plasma concentrations. This drug is removed from the body by the liver and kidneys[9].

The system designs for transdermal patches include matrix, microreservoir, reservoir, adhesive and membrane matrix type hybrid system. Matrix type transdermal patches remain among the most popular, as they are easy to manufacture [10.11].

In present study, an attempt was made to design to develop suitable matrix patch type transdermal drug delivery system (TDDS) for ondansetron hydrochloride employing various ratios of Povidone (PVP) and HPMC K4 M as well as PVP and Eudragit L100. The aim was to compare the polymeric combinations in terms of in vitro skin permeation of the drug and to find out the best possible ratio of hydrophilic and lipophilic polymeric combinations, which may be chosen for further studies.

Materials and methods

Materials:

Ondansetron hydrochloride (Biological E Ltd, Hyderabad, India) and Hydroxypropyl methyl cellulose (Methocel K4 M, Alex Pharmaceutical Pvt. Ltd, Sanand, India) were obtained as a gift sample. Eudragit RL-100 (Mol. Wt 32,000g/mol, Evonik industries, Sweden), polyvinylpyrrolidone (PVP; k-value 30-45, Biodeal laboratories Pvt. Ltd, Surendranagar, India), di-n-butylpthalate (Zydus healthcare Ltd, Ahmedabad, India), chloroform (Chemdyes Corporation, Rajkot, India) were obtained commercially. Polyvinyl alcohol (PVA; m.w 125,000), polyethylene glycol 400 and sodium chloride were purchased from S.D Fine Chemicals Ltd, Boisar, India. All the chemicals were used as received without any further treatment and purification.

Methods:

Drug-excipient interaction study

The pure drug, ondansetron hydrochloride and mixture of it with polymers, HPMC K4 M and Eudragit L100 were mixed separately with IR grade KBr in ratio of 100:1 and corresponding pellets were prepared by applying 7.5 metric ton of pressure in a hydraulic press. The pellets were scanned over a wave number range of 4000-400 cm^{-1} in Thermo Scientific Series I (Nicolet, USA) FTIR instrument.

Preparation of films

Transdermal patch composed of different ratios of HPMC K4 M and PVP as well as Eudragit L100 and PVP containing ondansetron hydrochloride (approx. 1.2mg/square centimeter patch) were prepared using glass mould solvent evaporation technique [12,13]. Accurately weighed quantities of polymer and drug were dissolved in suitable solvents and mixed thoroughly. To this mixture di-n-butylphthalate was incorporated as a plasticizer at a concentration of 25% w/w of dry weight of polymers and mixed thoroughly. This was poured into a glass ring of 2.8ml capacity on mercury surface. It was dried in hot air if necessary after 24 hours of controlled evaporation at room temperature. The dried film were taken out and packed in an aluminum foil covering [14]. The backing membrane used was aluminum foil. The dry patches were kept in desiccators until use.

Physical characteristics of the prepared films

The following physical studies were conducted:

1. Percentage moisture loss:

The films were weighed accurately and kept in the desiccators containing anhydrous calcium chloride. After 3 days films were taken out and weighed. The moisture loss was the difference between the constant weight taken and the initial weight and was reported in terms of percentage (by weight) moisture loss [15] (Fig I).

2. Percentage moisture absorption:

The percentage moisture absorption was studied by placing reweighed films of six numbers in each formulation in desiccators containing 75% of saturated solution of aluminum chloride, maintained at 79.5% relative humidity (RH). After 3 days, the films were taken out and weighed periodically to constant weights [16].

3. Flatness:

Longitudinal strips were cut out from the prepared medicated patches and the length of each strip were measured and then the variation

in the lengths due to the non –uniformity in flatness was measured (Table I). Flatness was calculated by measuring constriction of strips and a zero percent constriction was considered to be equal to a hundred percent flatness.

Constriction (%) = $(l_1 - l_2) / l_2 \times 100$

Where l_1, initial length of each patch; l_2, final length.

4. Film thickness:

The thickness of the film was measured at three different points using screw-gauge and average thickness was found out.

5. Weight variation:

Each film was weighed individually and average weight of three films was found out.

6. Folding endurance:

It was determined by repeatedly folding a small strip of film at the same place till it break. The number of time the film could be fold at the same place without breaking gave the folding endurance value. The average of three reading was calculated [17].

7. Determination of drug content in the patches:

A fabricated film was cut into small pieces and put in a 100ml of phosphate buffer 7.4 pH solution. This is then stirred in a mechanical stirrer to get a homogenous solution and filtered. The filtrate of 1ml was withdrawn and made up to 100ml, again from this 1ml of solution was pipette out and made up to 10ml with buffer 7.4 pH. The drug content was analyzed at 251nm by UV spectrophotometer (Shimadzu 1800)

8. In vitro skin permeability studies:

The *in vitro* skin permeation of ondansetron hydrochloride from the selected patches through depilated male albino rat abdominal skin was conducted using a modified Franz diffusion cell. The study was conducted in accordance with the Helsinki declaration and Animal care and Facilities in Principles and Method of toxicology [18].

Normal saline containing 20% v/v of polyethylene glycol 400 was used as bathing solution [19], in the receptor compartment of a modified Franz diffusion cell. The selection of the receptor fluid is an important criterion in the in vitro skin permeation studies. Biphasic characteristics of the receptor fluid are desirable as the diffusion of drug molecules in through aqueous and non- aqueous heterogeneous media. PEG 400 and normal saline are commonly chosen to provide the biphasic characteristics to the receptor fluid. Moreover, PEG 400 us a non-interacting fluid for the receptor media [20]. The abdominal skin of male albino rat weighing 100-120gm was used. Hairs on the abdominal area were removed using depilatory agent for 10 min about 12 h before sacrifice. Rats were sacrificed by excessive ether inhalation. An incision was made on the flank of the animal and the skin was separated. The skin was mounted between donor and receiver compartments of the diffusion cell having capacity 300ml with the epidermis facing upward into the donor compartment. The film of area 1 cm^2 to be tested was placed on the skin [21]. The bathing solution in receiver compartment was agitated with a magnetic stirrer at a temperature of 34 ± 1°C maintained thermostatically. Samples (1ml in each case) were withdrawn at regular intervals and fresh receptor fluid was added to maintain a constant volume of receptor fluid. The samples were analyzed spectrophotometrically at 251 nm and the drug content was determined from the calibration curve.

9. Primary skin irritation test:

Primary skin irritation and corrosion were evaluated most often by modification described by Draize and his colleagues in 1994, which based on scoring method. Scores as assigned from 0 to 4 based on the severity of erythema or oedema formation. The safety of the patch decreases with increase in scoring. The following table explains the scoring approach for cutaneous toxicity for a transdermal patch [22].

Result:

The physiochemical properties like % moisture loss, % moisture absorption, weight variation, folding endurance etc. provide information regarding the stability of the formulations. The moisture content and moisture uptake (Fig. I and II) varied to a small extent in all the formulations studied. However, there was an increase in moisture loss and absorption in hydrophilic polymers, PVP and eudragit in matrix patches. The moisture content was found to be greater with increase in hydrophilicity of polymer. All the patches showed one hundred percent flatness (Table 1), which indicates no amount of constriction of the formulated patches.

The thickness of the film was varied from 57 to 66 µm. The minimum standard deviation values assured that the process used for preparing the delivery system is capable of giving reproducible results. This fact is further confirmed by drug content and weight uniformity study. In order to evaluate the flexibility, the films were subjected to folding endurance studies. The values in the range of 68 to 81 were observed in all batches. This revealed that the prepared films were having capacity to withstand the mechanical

pressure along the good flexibility (Table I). The in vitro dissolution studies were carried out for different formulations using modified Franz diffusion cell using phosphate buffer (pH 7.4) as a dissolution medium at 32°C to determine the drug content in the patches. The average of ondansetron hydrochloride contents in the PVP-HPMC transdermal drug delivery system s F1, F3, F5 and F7 were found to be 1.125, 1.498, 1.699 and 1.823 mg/cm^2, respectively (Table 2). The drug content in PVP-eudragit TDDS F2, F4, F6 and F8 was 1.291, 1.282, 1.105 and 1.179 mg/cm^2 (Table 2), respectively. This represents nearly homogeneous distribution of drug. There are some very minor changes in the peaks in the range of 2400 – 3450cm$^-$. This indicates that there may be some physical interactions related to the formation of weak to medium intensity hydrogen bonding between polymers (Figure III, IV and V).

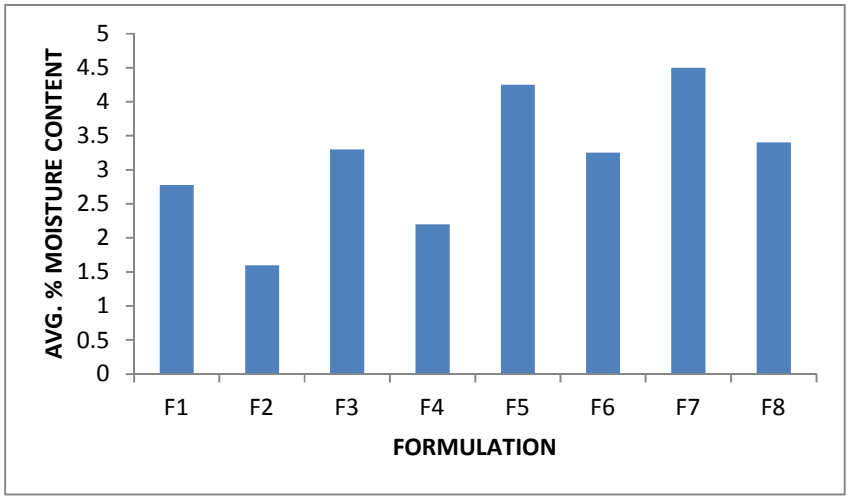

Figure I: Average percentage of moisture content by weight of different formulations. Data shows mean (n= 20) ± SD

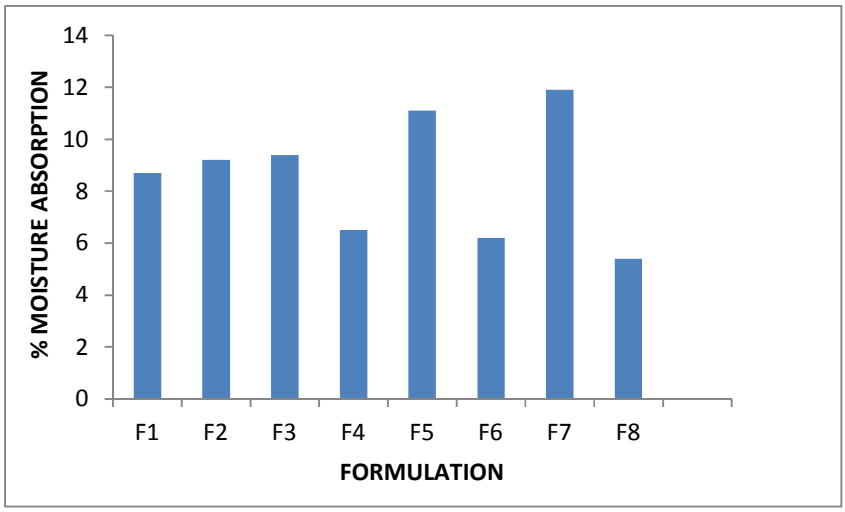

Figure II: Percentage moisture absorption by weight of the different formulation. Data shows mean (n=20) ± SD

Table I: Composition and physiochemical evaluation of transdermal patches of ondansetron hydrochloride

Sr. No.	Formulation code	Polymeric blend	Ratio (w/w)	% Moisture loss ± S.D	% moisture absorption ± S.D	Mean thickness ± S.D (µm)	Weight uniformity ± S.D	Flatness	Constriction of strip	Folding Endurance	Drug content	Strip length (cm)
1	F1	PVP:HPMC	3:2	2.78	8.70	60±0.13[a]	0.251±0.01	100±0.02[a]	0	79±0.51	90.10±0.51	2
2	F2	PVP:Eudragit	3:2	1.60	9.20	58±0.33[a]	0.236±0.18	100±0.11[a]	0	68±0.69	92.36±0.36	2
3	F3	PVP:HPMC	2:3	3.30	9.40	62±0.27[a]	0.198±0.35	100±0.37[a]	0	73±0.25	93.33±0.25	2
4	F4	PVP:Eudragit	2:3	2.20	6.50	57±087[a]	0.215±0.48	100±0.48[a]	0	75±0.87	93.11±0.11	2
5	F5	PVP:HPMC	1:4	4.25	11.10	65±0.92[a]	0.208±0.69	100±0.21[a]	0	81±0.14	94.65±0.66	2
6	F6	PVP:Eudragit	1:4	3.25	6.20	66±0.80[a]	0.185±0.41	100±0.34[a]	0	82±0.36	93.52±0.58	2
7	F7	PVP:HPMC	1:5	4.50	11.90	59±0.62[a]	0.204±0.03	100±0.19[a]	0	71±0.15	95.01±0.48	2
8	F8	PVP:Eudragit	1:5	3.40	5.40	56±0.53[a]	0.232±0.06	100±0.61[a]	0	69±0.22	94.15±0.98	2

[a] Each value indicate the mean ± SD (n=20)

Table II: Drug concentration in the patches by in vitro dissolution study (n=10)

Sr. No.	Formulation code	Average drug concentration (mg/cm^2)
1	F1	1.125 ± 0.055
2	F2	1.291 ± 0.031
3	F3	1.498 ± 0.031
4	F4	1.282 ± 0.081
5	F5	1.699 ± 0.059
6	F6	1.105 ± 0.075
7	F7	1.823 ± 0.019
8	F8	1.179 ± 0.076

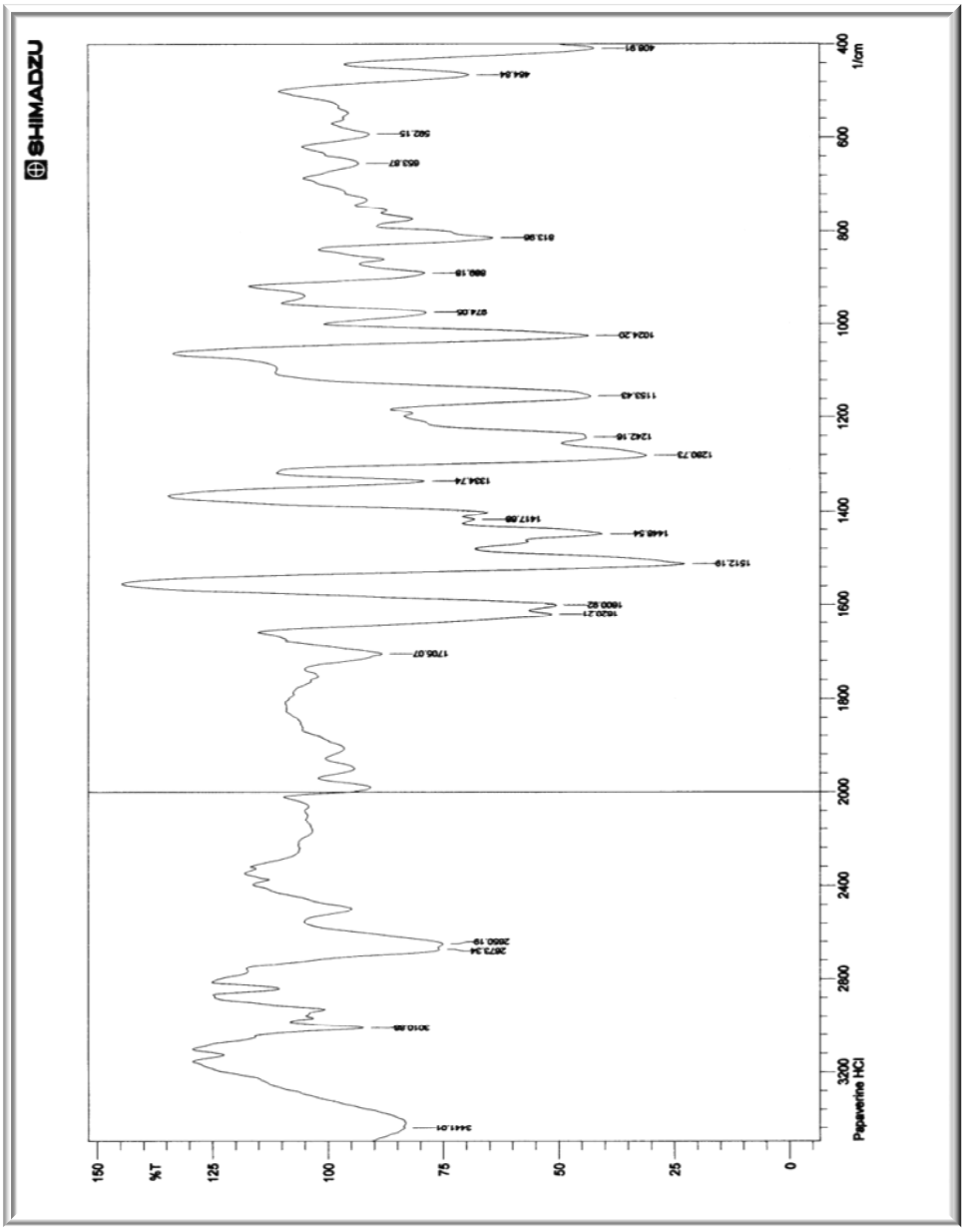

Figure IV: FTIR spectra of ondansetron hydrochloride and eudragit L 100 physical mixture

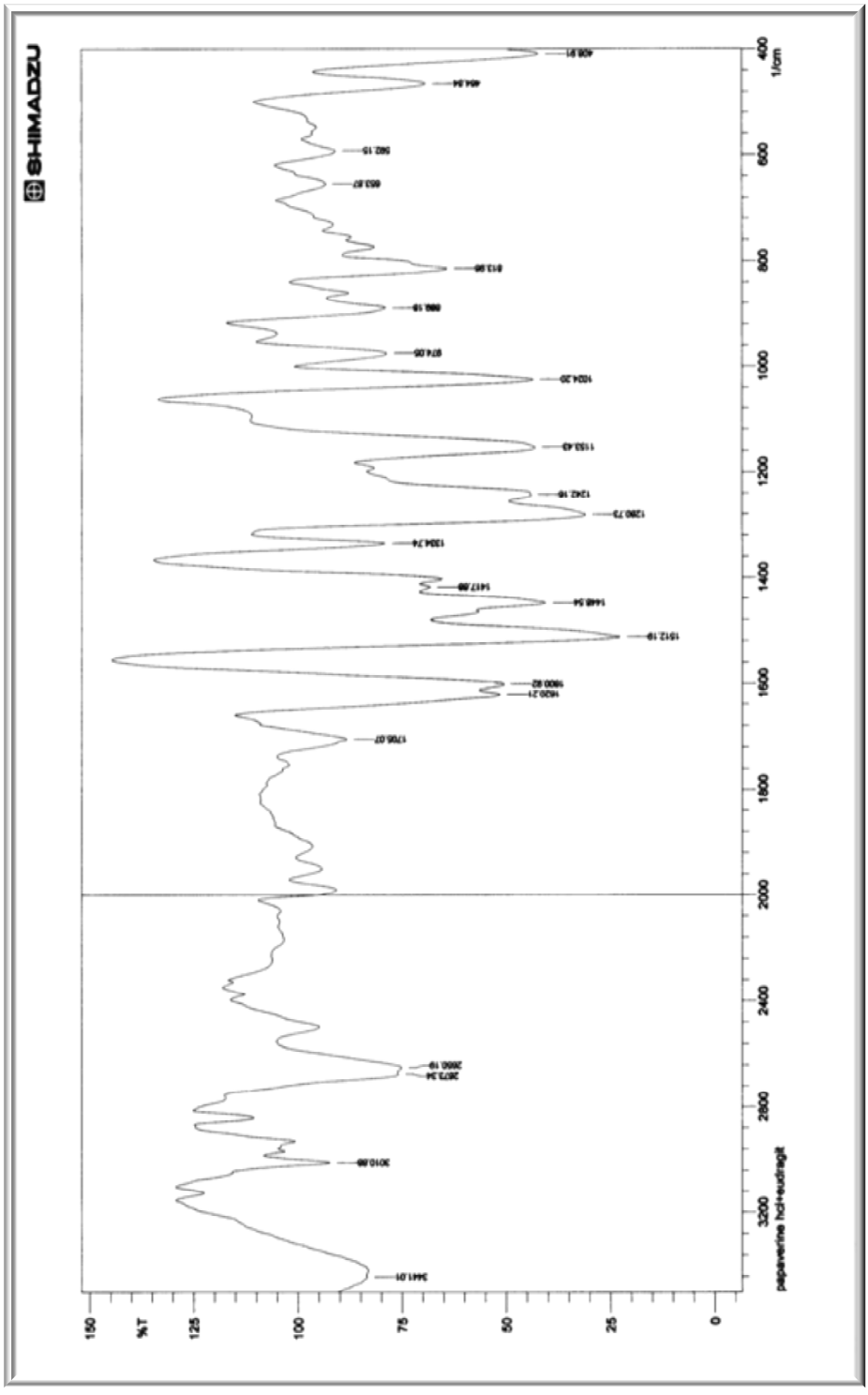

Figure III: FTIR spectra of ondansetron hydrochloride

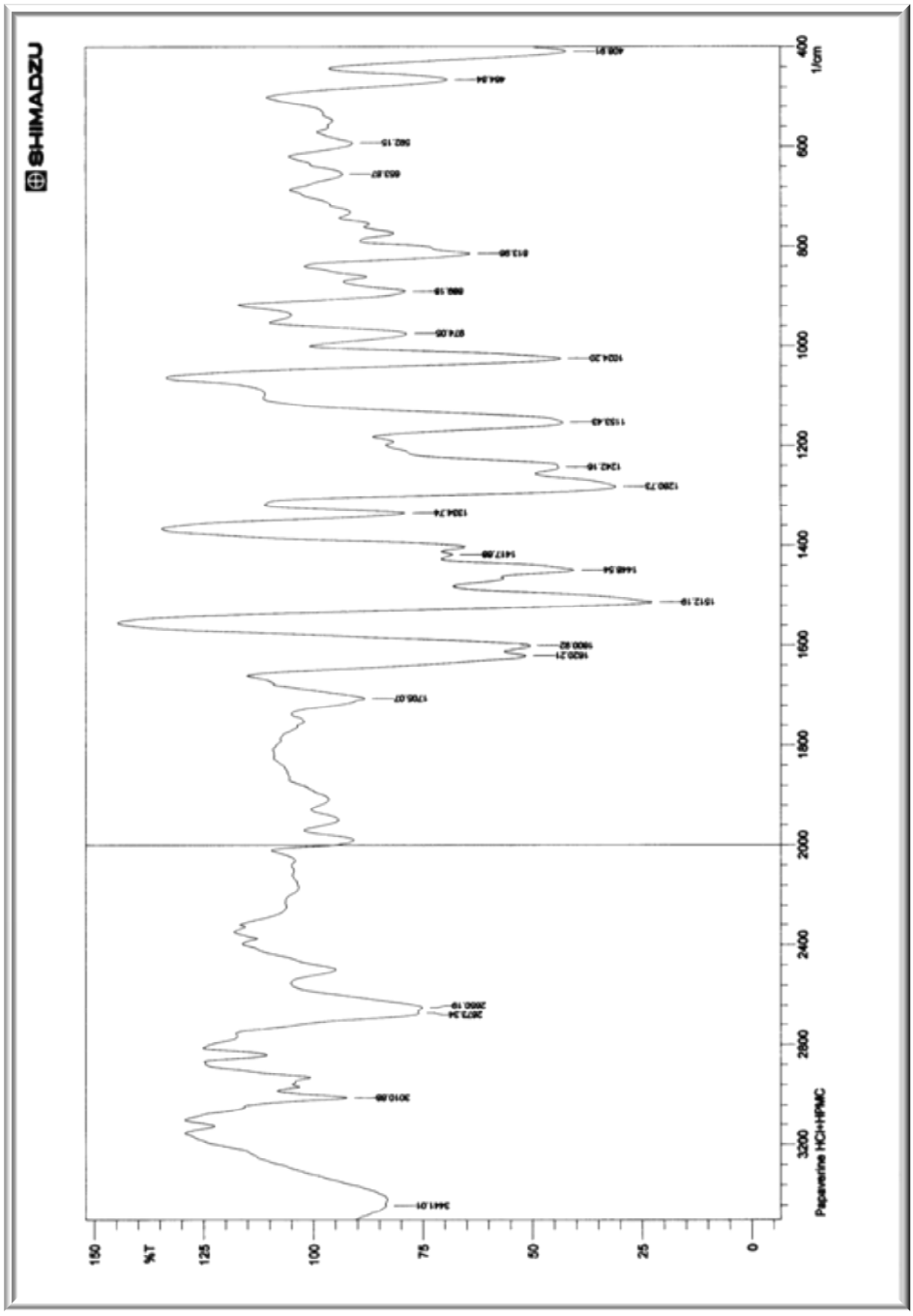

Figure V: FTIR spectra of ondansetron hydrochloride and HPMC K4 M physical mixture

In vitro skin permeability is predictive of *in vivo* performance of a drug. The study was carried out in a modified Franz's diffusion cell. Mean cumulative amounts of drug permeated from the patch after 24 h were found to be 0.588, 0.396, 0.688, 0.480, 0.814, 0.545, 0.891, and 0.436mg/cm^2 in case of the formulation F1, F2, F3, F4, F5, F6, F7 and F8 respectively. (Fig. VI and VII). The permeation rate of drug increase with increase in the amount of HPMC and decrease with increase in eudragit amount. Again, when the rate of drug release was compared in both type of formulations, PVP-HPMC containing matrix patches showed a higher drug permeation rate. Skin irritation studies revealed that the batch containing PVP-HPMC and PVP-Eudragit has no erythema and oedema .

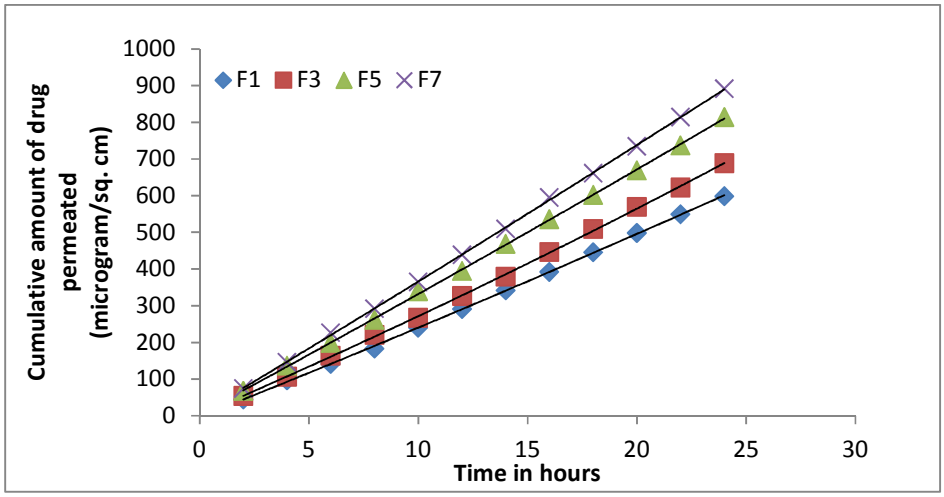

Fig. VI In vitro skin permeation profile of ondansetron hydrochloride incorporated in transdermal patches – F1, F3, F5 and F7. Data shows cumulative amounts of drug release against time, mean (n=6) ± SD

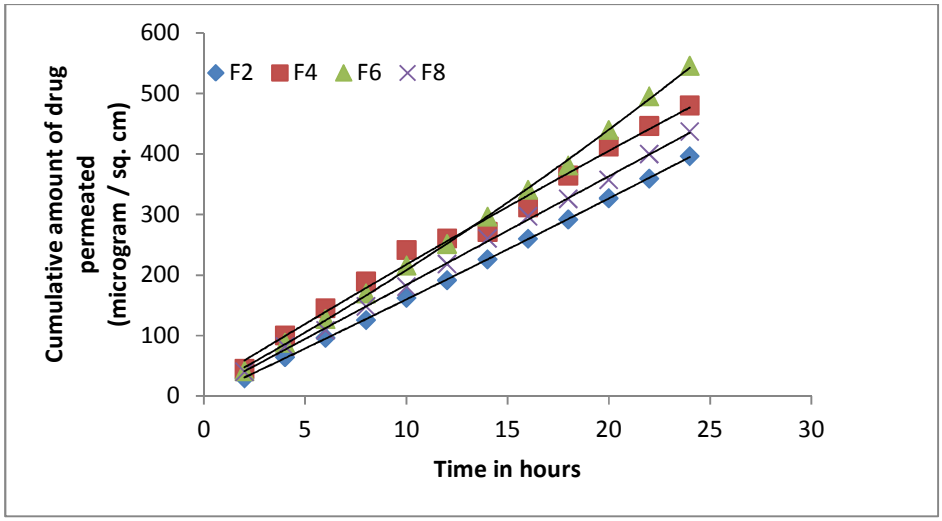

Figure VII: In vitro skin permeation profile of ondansetron hydrochloride incorporated in transdermal patches – F2, F4, F6 and F8. Data shows cumulative amounts of drug release against time, mean (n=6) ± SD

Discussion

In this study, it was desired to design transdermal patches of ondansetron hydrochloride using a polymeric matrix film. Cumulative amount of drug (ondansetron hydrochloride) released per cm^2 from the different patches varied ratio of PVP and HPMC K4 M (F1, F3, F5 and F7) and Eudragit (F2, F4, F6 and F8) showed variable release patterns (Fig VI and VII). The process of drug release in most of the controlled/sustained release devices including transdermal patches is governed by diffusion [23]. When this patch comes in to contact with *in vitro* dissolution fluid, the fluid is absorbed into the polymer matrix and initiates polymer chain dissolution process in the matrix [24]. Dissolution of the polymer chain involves changes in entanglement of individual drug molecules at the matrix surface, which depends upon the rate of hydration and transport of this molecule from the surface across the skin, adjacent to the matrix patch, initially to the surface and then in to the bulk of the dissolution fluid [25]. Molecular diffusion through the polymer is an effective, simple and reliable mean of attaining sustained release of variety of active agents.

The release of drug from a transdermal patch is controlled by the physiochemical properties of the drug and the delivery form along the properties of the biological membrane. Various releases kinetic of ondansetron hydrochloride from the various blends of the two different experimental polymeric combinations – PVP & HPMC K4 M and PVP & Eudragit – through male albino rat skin may help us to consider some assumptions of behavioral changes of patches with respect to drug release due to the variation of polymeric composition in their blends. Diffusion of any molecule in a multi polymeric matrix depends on structural and morphological parameters of the polymeric blend [28]. Diffusion in the polymer occurs through the amorphous polymeric regions and diffusivity of the drug molecule is related to the mobility of polymer chains [29]. Drug-excipient plays a vital role with respect to release of the drug from the formulation amongst others. FTIR technique has been used here to study the physical and chemical interaction between the drug and excipients used. In the present study, it has been observed that there is no chemical interaction between ondansetron hydrochloride and the polymers used. Physical interaction between drug and polymers was observed in the peak range of 2400-3450cm^- which is related to the formation of weak to medium intensity hydrogen bonding between polymers and the drug, but release and permeation studies showed that this type of interaction did not interfere with the release of the drug from the polymer matrix [30].

A 100% flatness of all the formulation indicates (Table. I) no amount of constriction of formulated transdermal membrane strips. Thus this does not constrict when it is applied on to the skin. Percentage moisture absorption (Fig. II) was found to increase with the increase of hydrophilic polymer, PVP in both type of formulations (HPMC and Eudragit). The moisture content was found to be grater with the increase of HPMC as compared to eudragit. Significant changes in properties such as reduced crushing strength, increased total porosity and increased pore diameter of hydrophilic polymer containing polymer matrix due to water uptake were reported [31]. Moisture content loss in the formulations was found to be low and they varied very little in the formulations (Fig. I).

When the release rates of different formulations were studied, it was observed that release rate increased with increase amount of HPMC K4 M in the formulation (Fig. VI). A more or less similar trend was studied in case of PVP: Eudragit formulations (Fig. VII), where increases in amount of eudragit also increase the release rate of drug except the formulation F8. In this formulation we find an abrupt decrease in rate of drug release of drug. When PVP-HPMC formulations were compared against PVP-Eudragit formulations in terms of drug release rate it was observed that rate of drug release was much higher in case of HPMC containing polymer matrix. HPMC is known to have larger cavity size in its polymeric network [31] and thus, it may involve a faster mode of diffusion of ondansetron hydrochloride from the PVP-HPMC formulations as compared to the formulation of PVP-Eudragit combinations.

Conclusion

Based on the drug release data we can concluded that the formulation F2 (PVP-Eudragit, 3:2) and F8 (PVP-Eudragit, 1:5), shows slowest release profile as compared to the other formulations. So it can be reasonably concluded that PVP-Eudragit polymer are better suited over PVP-HPMC polymers for the development of TDDS of ondansetron hydrochloride and the formulation F2 and F8 may be used for the further pharmacokinetic and pharmacodymanic studies in suitable animal models.

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