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Research article

Development and physicochemical evaluation of bilayered transdermal patches of Ondansetron hydrochloride

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Abstract

Bilayered transdermal patches for delivery of ondansetron hydrochloride were developed by-using polymers HPMC E15 (2.5 gm) and Eudragit RLPO (0.35gm) for the treatment of chemotherapy-induced nausea and vomiting. Different formulations were prepared by varying the grades of polymers by solvent casting method. Prepared patches were evaluated for physicochemical characteristics, mechanical properties, ex vivo permeation study, etc. Optimum formulation consisted of drug (0.395gm), HPMC E15 (2.5gm), PEG 400 (0.75 mL) and oleic acid (0.25 mL) in primary layer and Eudragit RLPO (0.35gm) and PEG 400 (0.105 mL) in secondary layer. The optimized formulation containing showed 109.1 µg /hr/cm^2 linear diffusion of drug, 6.33 kg/mm^2 tensile strength and 120.33 folding endurance. Drug and polymers interactions were investigated by FTIR studies. FTIR of ondansetron has shown intense band at 3486.61 cm^{-1}, 2922.38cm^{-1}, and 1651.99 cm^{-1} corresponding to presence of functional groups such as NH group, C-C-Aromatic group and C-C-Aliphatic group. FT-IR of optimized batch had intense bands at 3498.22 cm^{-1}, 2929.13 cm^{-1}, and 1635.88 cm^{-1} which indicate no change in the functional groups such as NH group, C-C-Aromatic group, C-C-Aliphatic and confirmed undisturbed structure of ondansetron, which indicate no drug-excipients interaction. Thus, Ondansetron hydrochloride can be effectively formulated as bilayered transdermal patch, and it is possible to achieve adequate physicochemical parameters and desired drug diffusion profile with the optimum combination of polymers.

Introduction

Transdermal patches generally refer to topical application delivers to healthy intact skin either for localized or for systemic therapy. Transdermal patch has many advantages over the conventional therapy or controlled release oral systems. Transdermal patch imparts constant blood levels, avoids first pass metabolism, increased patient compliance, and avoids dose dumping. The application of transdermal delivery to access of drugs is limited due to the significant barrier to penetration across the skin which is allied primarily with the outermost stratum corneum layer of the epidermis [1-3].

Ondansetron hydrochloride (OND HCl) is a serotonin (5HT-3) receptor inhibitor, widely used in prevention of nausea and vomiting associated with moderately-emetogenic cancer chemotherapy, radiation therapy and for the prevention of postoperative nausea and vomiting [4-6]. After oral administration, drug is rapidly absorbed but undergoes extensive first pass metabolism which leads to poor bioavailability of 60%. Hence, OND HCl was considered to be a suitable candidate for transdermal delivery system [7]. There are various drug delivery system such emulsion,

suspension, mucoadhesive tablets, nasal delivery system, etc available for various drugs [8-16]. In reported work, single layered matrix patches of OND HCl were prepared that may have non linear diffusion pattern [17]. By taking the account of advantages of bi-layer matrix patches over single layer matrix patches, attempts were made to develop bilayered transdermal patches for delivery of same drug.

Materials and methods

Materials

Pure drug OND HCl was obtained as a gift sample from Alpha Pharmaceuticals Pvt. Ltd. Mumbai. Polymers and Polyethylene glycol 400 and Oleic acid were obtained as gift sample from Concept Pharmaceuticals Pvt. Ltd. Aurangabad. All other ingredients were use of analytical grade.

Method

Drug loaded matrix-type transdermal patches of OND HCl were prepared by using solvent casting method. HPMC E15 (0.35gm) (Viscosity 15cP) and Eudragit RLPO (2.5gm) (Viscosity 15cP) in the concentration used as primary and secondary layer polymers, respectively, and polyethylene glycol 400 as plasticizer [18]. HPMC E15 was added to 25 ml of the solvent mixture (dichloromethane and methanol, 1:1 v/v) and allowed to stand for 6 hrs to swell. About 0.395 gm of drug was dissolved in 10 ml of solvent mixture and added to the polymeric solution. Measured quantity of oleic acid (10%v/w) was added as penetration enhancer and 30% v/w of PEG 400 added as a plasticizer. This was set aside for 2 hrs to remove entrapped air, then transferred into a petri plate of diameter 9 cm and dried at room temperature. The secondary polymeric solution was prepared by dissolving weighed Eudragit RLPO and 30% v/w of PEG 400 in 15 ml of solvent mixture and poured on the primary polymer layer and allow to dry at room temperature.

The developed patches were removed carefully, cut to size 2.2×2.2 cm (each having an area of 4.84 cm^2 contain 30mg of OND HCl), and stored during a desiccators. The batches composition is shown in Table 1.

Evaluation of physicochemical properties

Physicochemical and *ex-vivo* drug release study of prepared batches were undertaken [19-22]. The studied parameters are discussed below.

Thickness

Patch thickness was measured using digital micrometer screw gauge at three different places, and therefore the average value was calculated.

Folding endurance

The folding endurance of patches was measured manually. A strip of patch (2.2 x 2.2cm) was cut and repeatedly folded at the identical place till it broke. The patch may well be folded in number of sometime at the identical place without breaking/cracking gave the worth of folding endurance.

Weight uniformity

Randomly selected patches were weighed individually and average weight was calculated.

Moisture absorption

The patches were weighed accurately and placed in a desiccator containing 100 ml of saturated solution of aluminium chloride (60% and 84 % RH). The films were taken out and weighed after 3days. The percentage of moisture uptake was calculated as the difference between the final and initial weight with reference to the initial weight.

$$\% \text{ Moisture absorption} = \frac{\text{Final weight - Initial weight}}{\text{Initial weight}} \times 100$$

Table 1. Composition of batches.

	Primary Layer				Secondary Layer	
Batch	**Drug***	**HPMC [a],***	**PEG 400#**	**Oleic acid #**	**E- RLPO [b],***	**PEG 400 #**
F1	0.395	2.00	0.600	0.200	0.30	0.090
F2	0.395	2.25	0.675	0.225	0.30	0.090
F3	0.395	2.50	0.750	0.250	0.30	0.090
F4	0.395	2.75	0.825	0.275	0.30	0.090
F5	0.395	3.00	0.900	0.300	0.30	0.090
F6	0.395	2.50	0.750	0.250	0.35	0.105
F7	0.395	2.50	0.750	0.250	0.40	0.120
F8	0.395	2.50	0.750	0.250	0.45	0.135
F9	0.395	2.50	0.750	0.250	0.50	0.150

* amount in gm; # amount in mL; [a] HPMC E15; [b] Eudragit RLPO.

Percentage moisture loss

Percentage moisture loss was applied to test the (physical stability) moisture sensitiveness during storage of patch. The films were weighed accurately and kept in an exceedingly desiccators containing anhydrous salt. The films were taken out and weighed after 3 days [21]. The moisture loss was calculated using the formula.

$$\% \text{ Moisture loss} = \frac{\text{Initial weight - Final weight}}{\text{Final weight}} \times 100$$

Water vapour transmission rate

Glass vials of 5 ml capacity were washed thoroughly and dried to a relentless weight in an oven. About 1 gm of fused salt was taken within the vials and thus the polymer films of 4.84 cm2 were fixed over the brim with the assistance of a tape. Then the vials were weighed and stored in a very humidity chamber of 80-90% relative humidity condition for a period until it show constant weight gain (7 days). The vials were removed and weighed at 24hr time intervals to notice down the weight gain.

$$\text{Water vapour transmission rate} = \frac{\text{Final weight - Initial weight}}{\text{Area x Time}} \times 100$$

Flatness of patches

Longitudinal strips were cut from the prepared patch and therefore the lengths of each strips was measured. Variation within the length because of the non-uniformity in flatness was measured. Flatness was calculated by measuring constriction of strips and a zero percent constriction was considered to be adequate 100% flatness.

$$\%\text{Constriction} = \frac{L_1 - L_2}{L2} \times 100$$

Where, L_1 - Initial length; L_2 - Final length

Tensile strength

The tensile strength of the patch was determined by using the tensiometer. It consists of two load cell grips in which lower cell was fixed and upper one was movable. Film strips with dimensions of 2*2 cm were mounted between these cell grips, and force was bit by bit applied until the film broke. The tensile strength was taken directly from the dial reading in kg unit.

$$\text{Tensile stress (S)} = \frac{\text{Applied force}}{\text{Cross section area}} = \frac{m \times g}{b \times t}$$

Where, m - Mass in kg; g- Acceleration due to gravity;
b- Breath of specimen in mm; t - Thickness of specimen in mm.

Determination of drug content

The patch with size 2.2 x 2.2 cm^2 was cut and dissolved in distilled water, methanol and dichloromethane were added to dissolve the patch and volume was made up 100 ml with water. Then 1ml was withdrawn from the solution and diluted to 10ml. The absorbance of the solution The absorbance of the solution was measured using UV-visible spectrophotometer (Simadzu model UV 2401 PC, Shimadzu Corporation, Kyoto, Japan) with spectral width of 2nm, quartz cell (1.0 cm path) at 249 nm and concentration was calculated. By correcting dilution factor, the drug content was calculated.

Ex-vivo drug permeation study

Preparation of skin

A thickness of skin was excised from dorsal site of dead rat and skin was washed with water. The fatty tissue layer was removed by using nails of fingers. The outer portion with hair were applied with depilatory and allowed to dry. With the help of wet cotton the hairs were scrubbed and washed with normal isotonic solution. The skin was kept in normal isotonic solution in refrigerator until skin was used for drug permeation study. Before use, the skin was allowed to equilibrate with room temperature. Then skin were mount between donor and receptor compartment of cell. The skin was clamped in such a way that the dermal side are getting to be in touch with receptor medium.

Diffusion study

In-vitro permeation of drug from transdermal patch through dialysis membrane (Hi–Media) with molecular weight cut off of 12000 was studied. The membrane was mounted over a Franz diffusion cell and then placed the transdermal patch. The receiver compartment of the diffusion cell was filled with 15ml of phosphate buffer pH 7.4 and the setup was placed over a magnetic stirrer at 37°C with the help of hot plate. Samples of 3ml were withdrawn and replenished immediately from the receiver compartment at 1, 2, 3, 4, 6 and 12h. They were stored in refrigerated condition till the analysis was performed. The content of drug in the samples was analyzed by UV–Visible spectrophotometer 249 nm.

Drug-polymer interaction studies

FTIR spectroscopy was used to study the physical and chemical interaction between drug and excipients. FTIR spectrum of OND HCl, HPMC E15 and Eudragit RLPO and a physical mixture of OND HCl: HPMC E15 and Eudragit RLPO was recorded using KBr mixing method on FTIR (FTIR-1700, Shimadzu, Kyoto, Japan).

Accelerated stability study

The accelerated stability studies were applied on optimized formulation i.e. F6. The formulation was stored at 40 ± 2°C/75 ± 5 % RH for 3 months. After 3 months, samples were withdrawn and retested for drug content, enduringness and ex-vivo permeation study.

Result and discussion

Here, we have prepared bilayered transdermal patches of ondansetron hydrochloride in order to prevent the drug

diffusing from the surface of the patches and it act as diffusion controlling membrane. Various batches of bilayered transdermal patches of OND HCl were prepared using HPMC E15 and Eudragit RLPO polymers (see Table 1). All nine batches were evaluated for physicochemical properties. Thickness of all batches were ranged from 500 to 636 µm and folding endurance of all bathes were ranged from 110 to 132. Weight variation amongst different batches were lies in between 252 to 345mg/patch. Percent moisture absorption study was undertaken to check the integrity of patches at extreme humidity condition.

The % moisture absorption was determined at relative humidity (RH) of 60% and 84% level. The % moisture absorption in the formulations was found to be increased by increase in the concentration of HPMC E15 due to its hydrophilic property and also with decreasing the grade of Eudragit RLPO polymer. The moisture absorption in the patches ranged from 3.55 to 5.72%.

The % moisture loss was determined to check the moisture holding capacity which relates the stability of formulation. The range of % moisture loss was found to be 2.26 to 3%. The results are depicted in Table 2.

Water vapour transmission rate was checked in order to get information about optimal moisture at skin. All the prepared patches were 100% flat and uniform. Tensile strength and % drug content in all batches were also measured. With increase in concentration of HPMC E15 and Eudragit RLPO results in increase in tensile strength. Folding endurance of patches was found to be satisfactory. The results ranges from 1.82 to 2.42 (water vapour transmission rate), 110.66 to 132.66 (folding endurance), 5.33 to 7.26 (tensile strength, Kg/mm^2) and 93.78 to 96.13 (% drug content) (Table 3).

Ex- vivo permeation study was undertaken for all batches. Batch F6 showed linear diffusion of drug at rate of 109.1 µg /hr/cm^2. Eudragit layer minimizes the permeation of the drug molecules from the patches. In addition, Eudragit layer could control the release of the drug from the patches. This was evidenced from the release studies of the monolayer patches where the drug release was rapid. Therefore a rate controlling membrane can control the drug release from patches. The batch F6 showed required flux with zero order release kinetics was selected as the optimized formulation (Figure 1).

Table 2. Results of thickness, weight variation, % moisture absorption and % moisture loss.

Batch	Thickness (um)	Weight variation (mg)	%Moisture abs. at RH		% Moisture loss
			60%	84%	
F1	500±0.010	252.66 ± 2.51	3.55 ± 0.19	4.96 ± 0.20	2.26 ± 0.20
F2	530±0.010	287.33 ±4.163	3.82 ± 0.21	5.09 ± 0.31	2.62 ±0.10
F3	556±0.012	300.00 ± 5.29	4.08 ± 0.29	5.27 ± 0.23	2.77 ± 0.052
F4	593±0.015	327.00 ±2.64	4.13 ± 0.24	5.51 ± 0.19	2.96 ± 0.104
F5	636±0.012	345.33 ± 3.51	4.42 ± 0.23	5.72 ± 0.25	3.17 ± 0.062
F6	560±0.017	299.33 ±10.69	4.09 ± o.24	5.41 ± 0.25	2.78 ± 0.10
F7	570±0.010	303.00 ± 7.00	4.12 ± 0.20	5.36 ± 0.23	2.80 ± 0.067
F8	556±0.005	323.33 ± 7.02	4.05 ± 0.17	5.29 ± 0.15	2.83 ± 0.098
F9	576±0.005	313.66 ± 9.29	3.98 ± 0.12	4.92 ± 0.18	2.79 ± 0.078

Table 3. Results of water vapor transmission rate, folding endurance, flatness, tensile strength and % drug content.

Batch	Water vapor transmission rate	Folding endurance	Flatness	Tensile strength (Kg/mm^2)	% Drug content
F1	2.42 ± 0.32	110.66±2.08	100%	5.33±0.058	96.13 ± 0.78
F2	2.12 ± 0.21	111.66±2.08	100%	5.80±0.58	95.55 ± 0.65
F3	2.06 ± 0.19	119.33±1.53	100%	6.26±0.058	95.09 ± 1.87
F4	1.95 ± 0.32	125.33±0.58	100%	6.66±0.15	94.38 ± 0.89
F5	1.82 ± .024	132.66±2.52	100%	7.26±0.057	93.78 ± 0.70
F6	2.11 ± 0.32	120.33±0.58	100%	6.33±0.057	96.04 ± 0.84
F7	2.02 ± 0.25	122.00±1.73	100%	6.36±0.057	95.81 ± 1.06
F8	1.95 ± 0.24	123.33±0.58	100%	6.36±0.15	96.13 ± 0.76
F9	1.89 ± 0.26	123.66±1.15	100%	6.56±0.057	95.86 ± 0.02

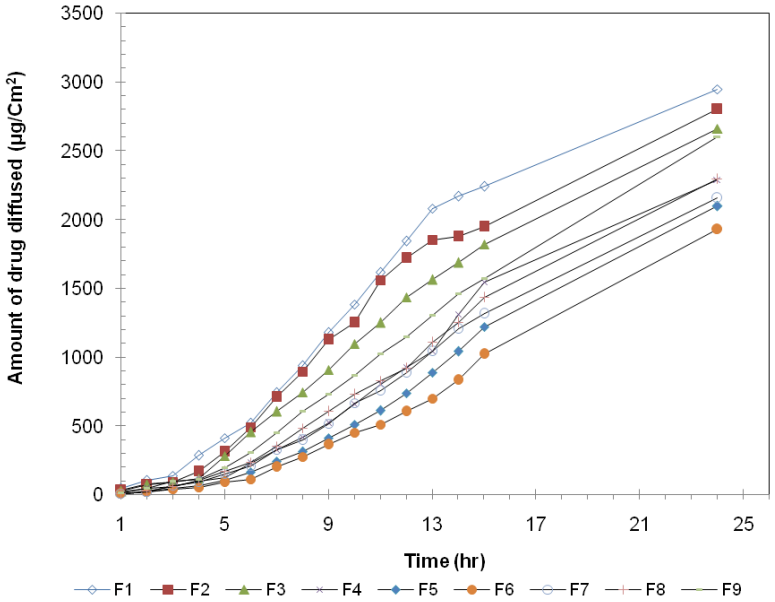

Figure 1. Comparative *in- vitro* drug diffusion profiles from experimental batches using phosphate buffer (PBS, pH 7.4) as a dissolution medium.

Drug-polymer interaction was studied by FTIR spectroscopy. FTIR spectrum of OND HCl with HPMC E15 and Eudragit RLPO were shown all characteristic peaks for drug and polymers, which was suggested lack of significant interaction between drug and selected polymers and which confirm compatibility of drug with polymers. FTIR of ondansetron has shown intense band at 3486.61 cm^{-1}, 2922.38cm^{-1}, and 1651.99 cm^{-1} corresponding to presence of functional groups such as NH group, C-C-Aromatic group and C-C-Aliphatic group. FTIR of optimized batch had intense bands at 3498.22 cm^{-1}, 2929.13 cm^{-1}, and 1635.88 cm^{-1} which indicate no change in the functional groups such as NH group, C-C-Aromatic group, C-C-Aliphatic and confirmed undisturbed structure of ondansetron, which indicate no drug-excipients interaction. FTIR spectrum of optimized formulation composition is shown in Figure 2.

Accelerated stability studies were carried out for optimized batch at temperature 40 ± 2°C and 75 ± 5% RH for 3 months. The results are shows no significant change in drug concentration and patch properties of optimized formulation over the period of three months (Figure 3, Table 4).

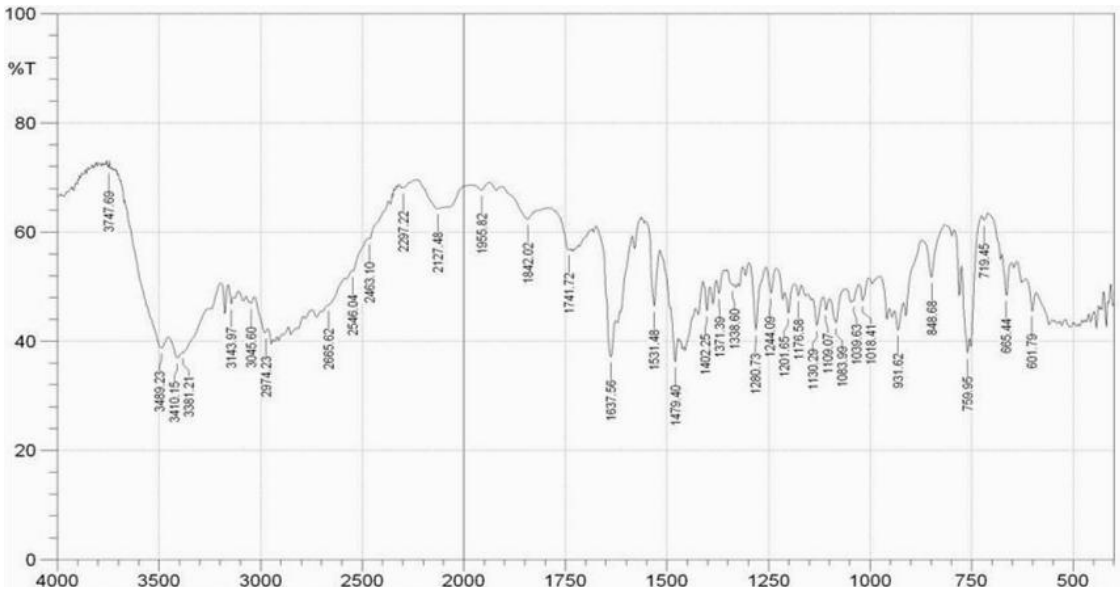

Figure 2. FTIR spectra of optimized formulation (Batch F6).

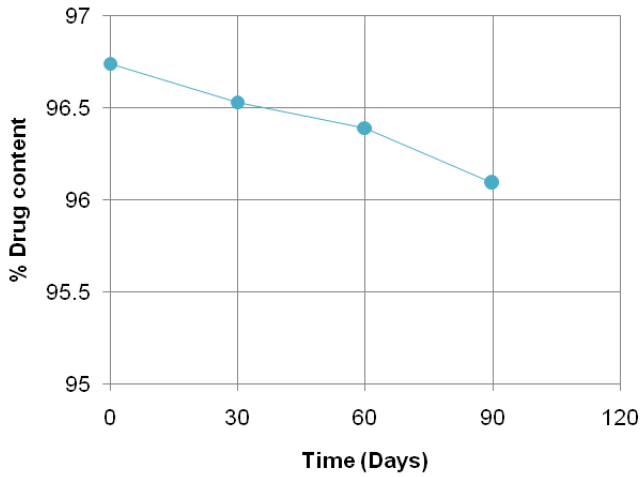

Figure 3. Accelerated stability study of optimized batch (F6).

Table 4. Accelerated stability study of optimized batch (F6).

Time (days)	% Drug content	Tensile strength
0	96.74±0.3	6.59±0.3
30	96.53±0.31	6.54±0.32
60	96.39±0.21	6.04±0.12
90	96.09±0.01	5.90±0.2

Conclusion

In this work, we successfully designed a bilayered patch based on a combination of a HPMC E15 and Eudragit RLPO polymer for the transdermal delivery of ondansetron hydrochloride. Batch F6 showed the potential to retard the drug release and possessed significant tensile strength. Patches were found stable with respect to evaluation of physicochemical properties as per ICH guidelines. Finally, it could conclude that Ondansetron hydrochloride can be effectively formulated as bilayered transdermal patches, and it is possible to achieve adequate physicochemical parameters and desired drug diffusion profile with the optimum combination of polymers.

Disclosure of conflict of interest

The authors declare no conflicts of interest.

Author contributions

All the authors have contributed equally in designing, drafting the manuscript as per the journal submission format. All authors read and approved the final manuscript.

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