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Formulation and Evaluation of Transdermal Patches of Ondansetron Hydrochloride Using Various Polymers in Different Ratios

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Abstract

This paper describes the formulation and evaluation of transdermal patches of Ondansetron Hydrochloride. The films were formulated using different hydrophilic and lipophilic polymers combination of hydrophilic-lipophlic polymers, ethyl cellulose : poly vinyl pyrrolidine. The polymeric films of Ondansetron Hydrochloride were prepared using film casting technique on mercury substrate. The study is also extended to investigate the effect of plasticizer such as dibutyl phthalate and propylene glycol and effect of penetration enhancer oleic acid by using keshary-chein diffusion cell. The films were evaluated for physico-chemical properties. In vitro drug diffusion study through rat skin indicates hydrophilic polymer showed higher release than the liphophilic and hydrophilic-lipophilic combination. The release rate was found to follow first order kinetics. Also permeation enhancer was found to give favourable permeation enhancement.

Key words: Transdermal film, Ondansetron Hydrochloride, polymers, In vitro drug release, permeation enhancer.

Introduction

Ondansetron is an antinauseant and antiemetic agent indicated for the prevention of nausea and vomiting associated with moderately-emetogenic cancer chemotherapy and for the prevention of postoperative nausea and vomiting.

The chemotherapeutic agents produce nausea and vomiting by releasing serotonin from the enterochromaffin cells of the small intestine, and that the released serotonin then activates 5-HT_3 receptors located on vagal efferents to initiate the vomiting reflex. Therefore Ondansetron HCl works by blocking the reception of serotonin at these 5-HT_3 receptors. Ondansetron HCl has the half-life of 5-6 hours. It's total bioavailability in the body is 60% due to first pass metabolism (1).

Materials and Methods

Ondansetron HCl was procured as a gift sample from Sun Rise pharma Ltd., ethyl cellulose pharm grade (colorcon Goa), eudragit LR (Evonik pharma Germany), Dibutyl phthalate LR (Ranbaxy fine chemicals Ltd., New Delhi.), oleic acid (Ranbaxy fine chemicals Ltd., New Delhi), Chloroform LR (Merck Ltd., Mumbai), Methanol LR (Rankem, fine chemicals limited, Mumbai), poly vinyl pyrrolidine, poly vinyl alcohol (Hi-media), backing membrane gift sample from Hi-media.

Preparation of Matrix- Type Transdermal Films containing Ondansetron HCl : The transdermal films were prepared by solvent evaporation method using different ratio of polymers like PVA, PVP, EC, and EUDRAGIT RS and RL . The polymers in different ratio were dissolved in different solvents such as methanol, water and chloroform respectively. Solutions were prepared at room temperature using plasticizer PG(10%) for PVP:PVA combination, DBP(5%) for Eudragit RS:RL and EC:PVP combination respectively. The drug was added to polymeric solution and stirred on the magnetic stirrer to obtain uniform solution (Table. 1). Oleic acid (10%) was used as penetration enhancer. The total volume of the solution was 20 ml. Then solution was poured with help of volumetric pipette in a petri dish having surface area of 78.5 cm^2 . The rate of evaporation of solvent was controlled by inverting cup funnel. The dried films were stored in desiccators. Since the drug is slightly soluble in chloroform, drug was added in small portions to the solvent with continuous and vigorous stirring (2, 3).

Characterization of Transdermal films : The films were evaluated for physical appearance, moisture content, thickness, folding endurance, tensile strength and drug content.

Thickness : The thickness of films was measured by digital Vernier caliper with least count 0.001mm (Table. 2). The thickness uniformity was measured at five different sites and average of five readings was taken with standard deviation (4).

Tensile strength : The drug matrix film was fixed to assembly the weights required to break the film was noticed, and simultaneously film elongation was measured with help of a pointer mounted on assembly and calculated tensile strength of drug reservoir film using following formula (5).

$$TS = \text{break force} / a.b(1+L / I)$$

Where a, b and L are the width, thickness, and length of the film and I is the elongation of film at breaking point (Table. 3).

Folding endurance : This was determined by repeatedly folding on film at the same place till it broke (Table. 2). The number of times the film could be folded at same place without breaking/ cracking (6).

Weight variation : The three disks of 2X2 cm^2 was cut and weighed on electronic balance for weight variation test (Table. 2). The test was done to check the uniformity of weight and thus check the batch- to- batch variation (7).

Moisture uptake : The percent moisture absorption test was carried out to check the physical stability and integrity of the films at high humid conditions (2).

The films were placed in the dessicator containing saturated solution of aluminium chloride, keeping the humidity inside the dessicator at 79.5 % R.H. After 3 days the films were taken and weighed the percentage moisture absorption of the films was found (Table. 3).

Drug content : The patch of area 2X2 cm^2 was cut and dissolved in the mixture of methanol and 0.1N HCl and then the distilled water was added to make the volume upto 100 ml. Then 1 ml was withdrawn from the solution and diluted to 10 ml(Table. 2). The absorbance of the solution was taken at 303.5nm and concentration was calculated. By correcting dilution factor, the drug content was calculated (8).

In Vitro Skin Permeation Studies : *In vitro* skin permeation studies were performed by using a Keshary - Chein diffusion cell with a receptor

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compartment capacity of 20 ml. The excised rat abdominal skin was mounted between the donor and receptor compartment of the diffusion cell (9). The formulated patches were placed over the skin and covered with paraffin film. The receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4. The whole assembly was fixed on a magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred using magnetic beads at 50 rpm; the temperature was maintained at 32 ± 0.5°C. The samples were withdrawn at different time intervals and analyzed for drug content by U V spectrophotometer. The receptor compartment volume was replenished with an equal volume of phosphate buffer at each sample withdrawal. The cumulative amounts of drug permeated per square centimeter of patches were plotted against time (7).

Results and Discussion

In the view of low permeability of Ondansetron HCl, monolithic device of drug has been attempted. The films were studied for the thickness, weight variation, tensile strength, drug content, in-vitro drug diffusion (Table. 2).

Study shows that for PVA: PVP, Eudragit RS: RL and EC : PVP along with the plasticizer PG 10% w/w, DBP 5% w/w of polymer weight was suitable for good flexibility, clarity and elasticity. The weight of all the six formulations was found to be in the range of 65.24 to 67.05 mg. Thickness variation was found to be 0.025 to 0.48 mm, tensile strength was found to be between 0.58 - 0.75 (Table. 3).

The formulation F1 comprising of PVA:PVP (5:5), oleic acid 10% and propylene glycol 10% showed tensile strength of 0.75 and % elongation upto 15.25%. The moisture absorption for formulation F1 was 4.5%, whereas for the formulation F5 it was 3.5%. The % drug content for all the formulations was found to be in the range of 92.41 ± 0.1% – 95.9± 0.4 %.

On studying the in-vitro diffusion of drug through the rat skin using keshary chein cell, the drug diffused for formulation F1 was maximum. The drug diffused was 76.69%. The permeability coefficient for the formulations F1 to F6 was 50.75, 43.85, 29.84, 29.17, 32.48, 31.97 μg/cm^2/h respectively (Table. 4).

In order to understand mechanism of release, in vitro release data were treated to the models and linearity was observed with respect to Higuchi equation. The correlation coefficient obtained from Higuchi plot was found to be 0.960 to 0.984 (Fig. 2). This indicates that mechanism of drug release was diffusion type (Fig. 1). The

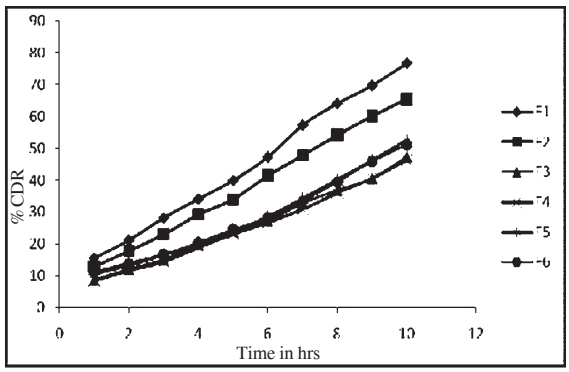

Fig. 1. Plot of time v/s % CDR for all six formulations

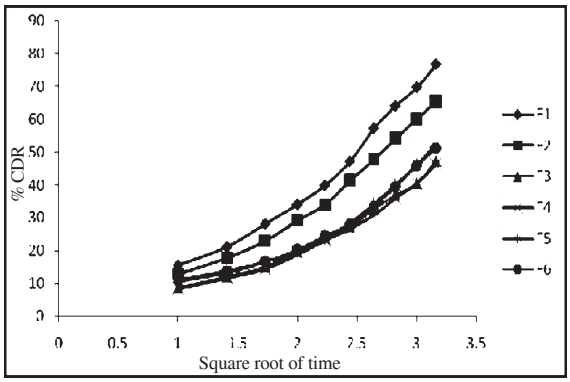

Fig. 2. Higuchi plot for all six formulations

Table 1. Formulation table

Formulation	Polymer PVA:PVP	Polymer RLPM:RSPM	Polymer EC:PVP	Plasticizer	Oleic acid	Solvent
F1	5:5	-	-	PG (10%)	10%	Water
F2	3:7	-	-	PG (10%)	10%	Water
F3	-	5:5	-	DBP (5%)	10%	Acetone
F4	-	7:3	-	DBP (5%)	10%	Acetone
F5	-	-	8:2	DBP (5%)	10%	Chloroform
F6	-	-	5:5	DBP (5%)	10%	Chloroform

Table 2. Thickness, Weight Variation, Drug Content, Folding endurance values

Formulation code ± SD	**Thickness (mm) (mg)**	**Weight variation ± SD**	**% Drug content ± SD**	**Folding endurance ± SD**
OND 1	0.036 ± 1.2	65.24 ± 1.2	92.41 ± 0.1	78 ± 2
OND 2	0.032 ± 1.5	62.50 ± 1.8	94.28 ± 0.5	76 ±1
OND 3	0.045 ± 1.8	67.05 ± 1.8	95.03 ± 0.2	79 ± 2
OND 4	0.048 ± 1.3	66.55 ±1.8	95.9 ± 0.4	77 ± 1
OND 5	0.025 ± 1.4	66.89 ±1.9	93.66 ± 0.5	72 ± 1
OND 6	0.029 ± 1.6	65.05 ±1.6	94.16 ± 0.6	71 ± 0.9

Table 3. Tensile Strength, % elongation, %moisture absorption values

Formulation	**Tensile Strength**	**% Elongation**	**% moisture absorption**
F1	0.75	15.25 %	4.5 %
F2	0.73	20.54 %	4.8 %
F3	0.68	22.89 %	5.07 %
F4	0.70	23.86 %	5.18 %
F5	0.61	30.5 %	3.5 %
F6	0.58	29.56 %	3.9 %

drug diffusion was non-fickian. On plotting square root of time v/s % CDR the regression co-efficient value obtained for the formulation F1 was 0.983.

Conclusion

The Ondansetron HCl transdermal patches developed in this study have great utility and are viable option for effective and controlled

Table 4. Cumulative % Drug release

Time in hrs	Formulations					
	F1	F2	F3	F4	F5	F6
1	15.46	12.70	8.74	8.40	10.53	11.20
2	21.10	17.74	12.11	11.76	13.24	13.91
3	28.10	22.88	15.07	14.55	16.46	16.71
4	34.02	29.18	19.88	18.92	19.88	20.34
5	39.85	33.99	23.96	23.17	23.89	24.50
6	47.21	41.40	27.24	26.78	28.67	28.17
7	57.23	47.78	32.74	30.95	34.35	33.37
8	64.04	54.20	36.90	36.13	40.24	39.46
9	69.71	60.21	40.57	40.65	46.34	45.85
10	76.69	65.52	47.40	46.46	52.69	51.13

management nausea and ometing. However, pharmacodynamic and pharmacokinetic evaluation of these systems in human volunteers is necessary to confirm these findings.

Acknowledgements

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References

1. http://medical-dictionary. thefreedictionary.com/ondansetron+ hydrochloride.
2. Ubaidulla, U., Reddy, M.V. and Ruckmani, K. (2007). Transdermal therapeutic system of Carvedilol: effect of hydrophilic and hydrophobic matrix on in vitro and in Vivo characteristics. AAPS PharmSciTech. 8(1)Article 2: E1-E8.
3. Patra, S., Choudhury, A.A., Khar, R.K. and Barik B.B. (2007). Spectrophotometric method Ondansetron HCl. Ind J. Pharm. Sci. 69(6): 840-841.
4. Murthy, S.N. and Hiremath, S.R. (2001). Formulation and evaluation of controlled release transdermal patches of theophylline-salbutamol sulphate. Drug Dev. Ind. Pharm.27(10):1057-1062.
5. Seth, A.K., Agarwal, G.P. and Saini, T.R. (1985). Evaluation of free films. Indian Drugs.23 (1):45-47.
6. www.priory.com/pharmmol/transdermal/pdf.
7. Saxena, M., Mutalik, S. and Reddy, M.S. (2006). Formulation and evaluation of transdermal patches of metoclopramide hydrochloride. Ind. Drugs. 43(9):740-745.
8. Sadashivaiah, R., Dinesh, B.M., Patil, U.A., Desai, B.G and Raghu, K.S. (2008). Design and *in vitro* evaluation of haloperidol lactate transdermal patches containing ethyl cellulose-povidone as film formers. Asian J. of Pharma. 2(1):43-49.
9. Carmelo Puglia and Francesco Bonina. (2008). Effect of Polyunsaturated Fatty Acids and some conventional Penetration Enhancers on Transdermal Delivery of Atenolol. Drug Delivery. 15:107–112.