Development and Comparative Evaluation of Trans Dermal Therapeutic System for Antiemetic Therapy

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In this work, the membranes of Eudragit RL-100 and Eudragit RS-100 were cast to achieve controlled release of the drug. Transdermal patches are prepared by using different ratios of selected polymers such as Eudragit RL-100 and RS-100 (8:2, 6:4 and 5:5), solvents like chloroform and ethanol (2:0.5) for promethazine formulation (P1). Chloroform, ethanol and diethyl formamide (1:1:0.5) for domperidone formulation (D1). Diethyl phthalate is used as a plasticizer (10 % w/w of the dry polymer). The higher percentage drug released formulation P1 (8:2) was followed the zero order kinetics ($R^2 = 0.0985$) and Higuchi diffusion equation formulation followed the first order kinetics ($R^2 = 0.937$). The D1 (8:2) formulations followed the first order kinetics ($R^2 = 0.969$) and Higuchi diffusion equation ($R^2 = 0.982$). The P1 and D1 formulations are selected as optimized formulation depend on drug release. These formulation release higher percentage of drug (P1-86.62 and D1-87.10 %) at the end of 12 h, compared to P2, P3, D2 and D3 (P2-54.94, P3-39.7, D2-67.12, D3-54.25%) formulations.

Key Words: Promethazine theoclate, Domperidone, Eudragit RL-100, Eudragit RS-100, Diethyl phthalate, Release kinetics.

INTRODUCTION

Transdermal patch or skin patch is a medicated adhesive patch which is placed on the skin to deliver a specific dose of medication through the skin and in to the blood stream. Transdermal patches of promethazine theoclate and domperidone with Eudragit RL-100 and RS-100 were prepared by solvent evaporation technique[1,2].

However, from a drug delivery sand point, its far better that rate control resides with in the delivery devise in order to attain uniform input rates and reduce inter individual variability[3,4]. A transdermal drug delivery is a formulation which is devised to maintain the blood concentration of the drug within the therapeutic window ensuring that drug levels neither fall below the minimum effective concentration nor exceed the minimum toxic dose. Moreover, the administration of the systemic drugs using a transdermal patch represents a noninvasive route, with improved patient compliance. Additionally this route of administration prevents passage through the gastrointestinal track and maintains constant plasma level for prolonged periods of time. Among the different types of dermal and transdermal therapeutic system, the drug in adhesive product (in which the drug is included in the adhesive in contact with the skin) are commonly used, being thin and comfortable[5-7]. The aim of this study is to investigate *in vitro* kinetics of release and the permeation of promethzine theoclate and domperidone from adhesive films.

EXPERIMENTAL

Preparation of promethazine theoclate transdermal patches: The polymers like eudragit-RL-100 and eutragit-RS-100 in the ratio of 8:2, 6:4 and 5:5 were dissolved in chloroform and ethanol (2:0.5) by using magnetic stirrer. Then added accurately weighed amount (50 mg) of promethazine theoclate and add diethyl phthalate as a plasticizer 10 % w/w of the dry polymer and stir well for 20 min. The drug polymeric solution was poured on mercury kept in a petri-dish[8]. The rate of evaporation was controlled by inverting the funnel. After 24 h the films were taken out and stored in a desiccator for further process.

Preparation of domperidone hydrochloride transdermal patches: The polymers like eudragit-RL-100 and eutragit-RS-100 in the ratio of 8:2, 6:4 and 5:5 were dissolved in chloroform, ethanol and N,N-diethyl formamide in the ratio of 1:1:0:5 in magnetic stirrer. Then added accurately weighed amount (20 mg) of domperidone hydrochloride and continue the stirring then added the diethyl phthalate as a plasticizer 10 % w/w of the dry polymer and stir well for 20 min. The drug polymeric solution was poured on mercury kept in a petri-dish[8]. The rate of evaporation was controlled by inverting the

funnel. After 24 h the films were taken out and stored in desiccators for further process. Both the patches were prepared by solvent evaporation technique.

Physico-chemical characterization

Thickness: The thickness of the prepared patches was measured with the help of screw gauge and digital caliper, at three different points of the patches and the average value was determined[9].

Uniformity of weight: Four different patches were weighed individually and the average weight was calculated. The individual weight should not deviate significantly from the average weight. They were performed on a film which was dried at 60 °C for 4 h prior to testing[10].

Flatness and elongation break: Longitudinal strips were cut from the prepared medicated films. The flatness was determined at various points by using vernier calipers[11].

Folding endurance: Folding endurance was determined by repeatedly folding the film at the same place until it broke. The number of times the film could be folding at the same place without breaking was the folding endurance[12].

Moisture content: The films were weighed and kept in a decicator containing calcium chloride at room temperature for 24 h. The films were reweighed after deciccant[13].

Moisture absorption: The weighed films were kept in a decicator at room temperature for 24 h. Then they were taken out and exposed to 75 % relative humidity (saturated solution of sodium chloride)[14].

Fourier transformer infrared spectroscopy: FT-IR spectra of promethazine, domperidone, eudragit RL-100, eutragit RS-100 and trans termal film loaded with drug were using Perkin-Elmer FT-IR spectrophotometer. Sample and KBr was taken in a mortar and triturated. The triturated sample was kept in a holder and scanned between 4000 and 400 cm^{-1}.

X-ray diffraction: X-ray differectometer (Reguku-Miniflex, Japan) consisted of a 30 kV, 15 mA generator with Cu-K$_\alpha$ radiation anode tube. Diffraction pattern of pure drug, polymers and formulated patches were scanned over 2θ range of 0º and 80º at a rate of 2° per min on 0.02°2θ step size.

In vitro diffusion studies

Preparation of skin: Male Wistar rats (150-170 g) were sacrificed by excess chloroform inhalation. Hair from dorsal side of the skin was removed using a razor with blade and a whole skin was excised which is followed by removal of fat adhering to dermis with a scalpel. Any trace of fat adhering to skin was then finally removed by wiping it with cotton swabs soaked in isopropyl alcohol. Finally, skin was rinsed with normal saline and stored at -20 ºC in aluminium foil[15-17].

Skin permeation studies: The fat removed skin was clamped by 'O' ring between the donor and the receptor chambers of vertical modified Franz diffusion cell[6,15] (diffusion area 2.4 cm^2) with the stratum corneum side in contact with the donor phase. pH 7.4 phosphate buffer was used as receptor medium, maintained at 37 ºC and stirred at 100 rpm by a bar magnet. Aliquots (1 mL) were withdrawn from the receptor compartment at scheduled intervals (1 h) for 24 h and same volume of the receptor fluid was replaed and the drug concentration in the aliquots was estimated by UV-spectrophotometrically[18] at 205 and 207nm.

Scanning electron microscopy: SEM analysis was carried out using a Philips XL 30 scanning electron microscope.

Skin irritation studies: Skin irritation studies[6,15,19] were carried out in healthy rats weighing 150-170 g. The dorsal surface of the rats was cleared and hair was removed. The patches were placed over the skin with the help of surgical adhesive tape. An untreated site on the skin of a rat acted as the control site. They were removed after 24 h and the skin was examined for any unwanted reaction.

Stability studies: The formulation was stored at 25 ºC and 65 % relative humidity for 3 months. The samples were taken and analyzed for their physicochemical parameters[20,21] at the end of third month.

RESULTS AND DISCUSSION

Matrix type transdermal patches of promethazine theoclate and domperidone were prepared by solvent evaporation technique using combination of hydrophilic and lipophilic polymers like eudragit-RL-100 and RS-100, in the ratio of 8:2, 6:4 and 5:5. All the physical characteristic results were tabulated in Table-1.

Fourier transforms infrared spectroscopy: The FT-IR analyses of physical mixture of drug polymer showed the major peaks of promethazine theoclate, domperidone, eudragit-RL-100 and RS-100. The characteristic peaks of domperidone and promethazine also appeared in transdermal films. No new peaks were found in the formulated patches. The spectrum of promethazine displays a characteristic absorption at 3427 (NH stretch), 2882 (methyl CH symmetrical stretch), 1684 (aromatic combination bonds), 1636 (NH bonds), 750 (aliphatic chloro compound). Domperidone displays a characteristic absorption at 3442 (NH stretch), 2830 (methyl frequencies), 1619 (NH bonds), 1698 (aromatic combination bonds), 706 (aliphatic chloro compound). Eudragit RL-100 displays peaks at 1646 (ketone and alkyl C-N-C stretch), 2996 (methyl asymmetrical stretch), 848 (1,4 di-substitution).

	TABLE-1						
	CHARACTERISTICS OF PROMETHAZINE AND DOMPERIDONE PATCH						
Formulation code	Thickness (nm)	Uniformity of weight (g)	Flatness and elongtion break (%)	Folding Endurance (no's)	Moisture content (%)	Moisture absorption (%)	Drug content (mg)
P1	0.12 ± 0.014	0.298 ± 0.009	104.0 ± 1.41	102 ± 1.89	4.4210 ± 0.011	1.6806 ± 0.009	49.02 ± 1.22
P2	0.13 ± 0.015	0.295 ± 0.010	96.0 ± 1.26	114 ± 1.67	4.0175 ± 0.008	3.5087 ± 0.011	50.24 ± 0.99
P3	0.12 ± 0.008	0.287 ± 0.011	96.0 ± 1.41	105 ± 1.41	2.4896 ± 0.017	2.9045 ± 0.010	47.94 ± 0.75
D1	0.16 ± 0.014	0.265 ± 0.013	99.6 ± 1.26	124 ± 1.67	4.4897 ± 0.017	2.4489 ± 0.009	19.37 ± 0.93
D2	0.14 ± 0.014	0.249 ± 0.001	102.0 ± 1.26	119 ± 2.19	3.9473 ± 0.018	1.2711 ± 0.008	19.02 ± 0.74
D3	0.15 ± 0.014	0.264 ± 0.001	96.0 ± 1.67	127 ± 1.54	4.0420 ± 0.023	2.9411 ± 0.009	18.03 ± 0.75

The characteristic absorption bands of promethazine loaded patches displays at 3438 (NH stretch), 1674 (aromatic combination bonds), 1622 (secondary amine NH bonds). The characteristic absorption bands of domperidone patch displays at 3453 (NH stretch), 1723 (aliphatic chloro compound). This confirms the domperidone and promethazine were not interacting with polymers during the preparation[18].

X-ray diffractometry: The XRD profile (Fig. 1) of pure drugs illustrates a similar peak to that of the formulated patches. The absence of crystalline peaks of promethazine and domperidone in formulated patches indicates that the drug was molecularly dispersed in the polymeric films[22,23].
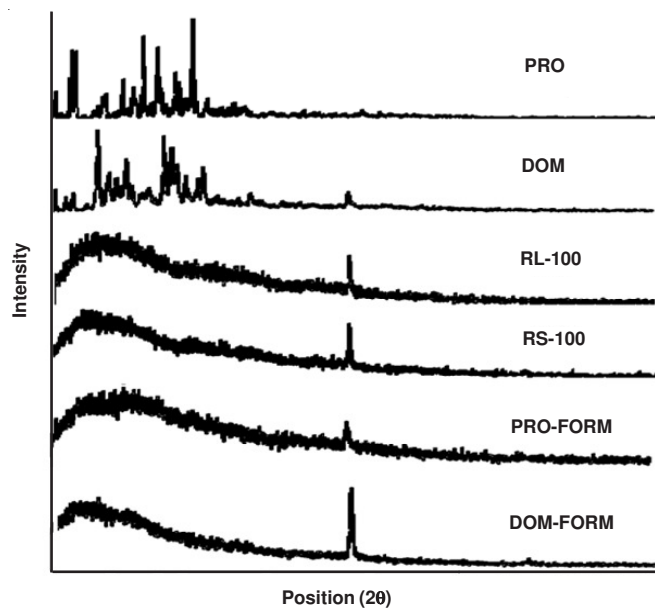

Fig. 1. X-rays diffraction of pure and thier formulated drugs

In vitro **diffusion studies:** The release studies from the formulated patches were studied by modified franz diffusion [6,15,20] cell in pH 7.4 buffer solution using the exercised rat skin[4-6].
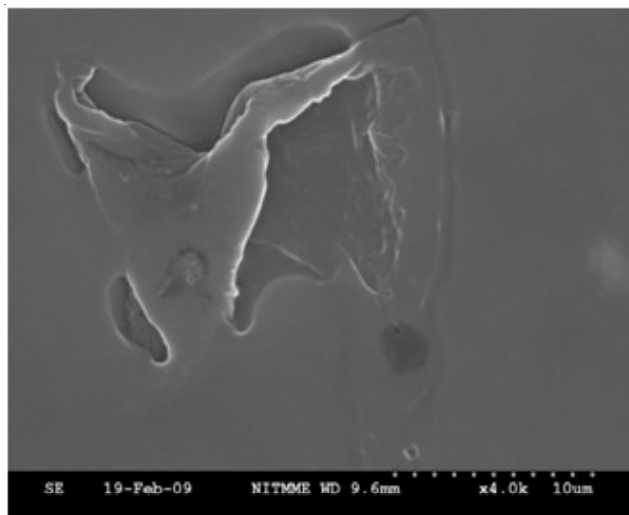
The drug releases from the patches was calculated at the end of 12 h. The formulations P1-86.62, P2-54.94, P3-39.7, D1-87.10, D2-67.12 and D3-54.25 % of drug released at 12 h formulations P1 and D1 released highest percentage of drug compare to the formulations P2, P3, D2 and D3 (Table-2).

Scanning electron microscopy: Results of SEM (Figs. 2 and 3) analysis performed to investigate the surface morphologies and pore size before and after diffusion of patches[22].
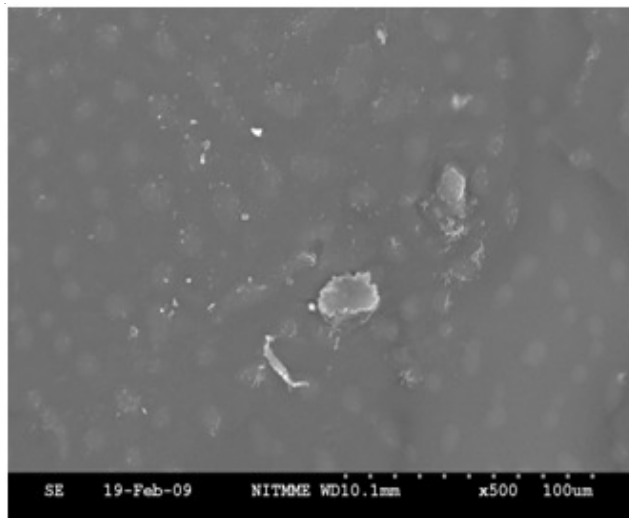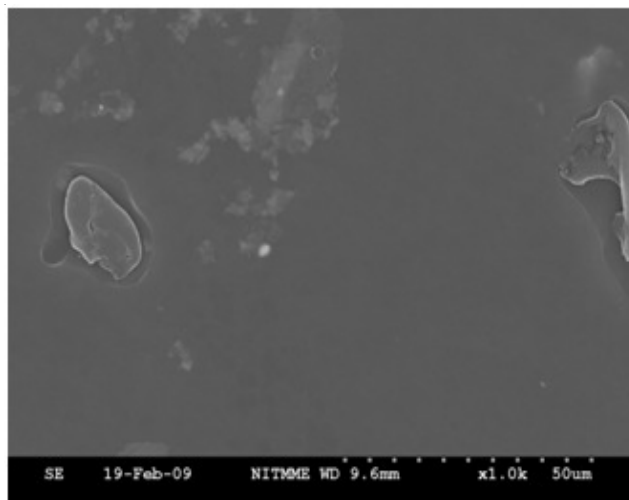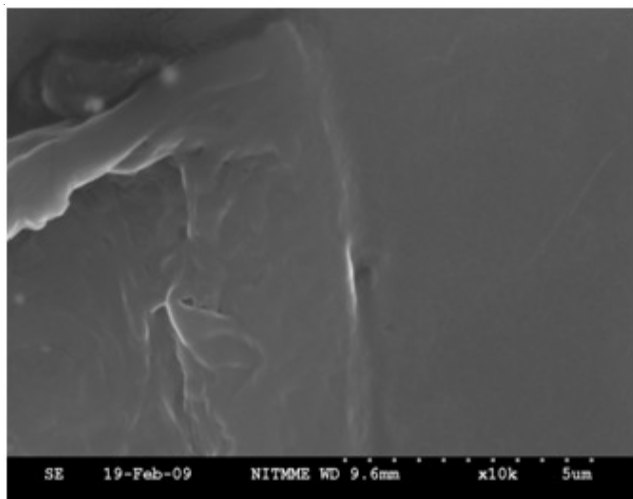

(a)

(b)

Fig. 2. SEM of domperidone formulation (a) before and (b) after diffusion

(a)

TABLE-2 *In vitro* DIFFUSION STUDIES			
	P1		D1
Time	Drug released in		Drug released in
	mg	mg	%	%
0	0	0	0	0
1	5.74	3.288	16.44	11.48
2	9.528	5.246	26.23	19.056
3	13.358	7.25	36.25	26.717
4	16.77	8.716	43.58	33.54
5	20.85	9.942	49.71	41.709
6	25.33	10.87	54.35	50.668
7	29.45	11.926	59.63	58.907
8	34.03	13.642	68.21	68.062
12	43.31	17.42	87.10	86.626

(b)

Fig. 3. SEM of promethazine formulation (a) before and (b) after diffusion

Conclusion

The transdermal patch formulation was found to be efficacious, safe, stable and non irritant to skin. The establishment of steady state levels *in vitro* for 12 h shows the clear advantage of transdermal patches over current modes of administration. Drugs like promethazine and domperidone are formulated into matrix type patches in an attempt to solve the problems associated with oral administration. The drug release was found to be linear and follow the Higuchi diffusion equation. The release kinetics of promethazine and domperidone formulations follows zero order and first order kinetics. Hixon Crowell equation also found to be linear; these indicating that the release from the patches was by both diffusion and erosion methods. In the skin irritation study shows that patches do not produce any noticeable reactions, hence these drugs are suitable for the transdermal delivery system.

The study indicated that either the polymer or drug not caused any noticeable irritation or inflammation on or around the patch area either during the period of study and after removal of the patch.

All the physico-chemical parameters of the transdermal films were found to be satisfactory. No significant changes in physicochemical characteristics including appearance, thickness, weight, moisture absorption, moisture content and drug content *etc.* of patches at the end of third month.

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