Design and Evaluation of Different Transdermal Therapeutic Systems of Promethazine Hydrochloride

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ABSTRACT

Background: Promethazine Hydrochloride is a water-soluble drug and it suffers from poor bioavailability (25%) when given through oral route due to extensive first-pass metabolism. To overcome hepatic first pass metabolism and to enhance bioavailability, transdermal drug delivery systems (patches and gels) can be exploited. **Objectives:** The present work describes the transdermal permeation of anti-emetic agent promethazine hydrochloride and its transdermal delivery using transdermal patches and gels. For this investigation, HPMC E5, HPMC E50, and HPMC E15 used as a hydrophilic polymer for patch preparation and carbopol and xanthum gum acting as gel forming agent for hydrogel preparation. **Materials and Methods:** Permeability of promethazine hydrochloride was first investigated *ex vivo* using a rat abdominal skin. Then, transdermal gels and patches were developed using various polymers. Matrix diffusion mediated transdermal patches of promethazine can be formulated using polymers HPMC E5, HPMC E50, and HPMC E15 by solvent casting method. Matrix diffusion mediated transdermal gels of promethazine can be formulated using polymer carbopol and xanthan gum. Physicochemical interaction between drug and polymers were examined by Fourier Transform Infrared Spectroscopy (FTIR) and *ex vivo* permeation and *in vitro* drug release studies are conducted with the prepared formulations. **Results:** Transdermal patches of promethazine have reliable mechanical properties measured in terms of tensile strength (formulation F10 and F11 exhibited tensile strength values 0.0788 ± 0.0014 kg/mm^2 and 0.0652 ± 0.0018 kg/mm^2) as well as elongation at break values ($1.1252\pm0.073\%$ mm^{-2} and $0.8749\pm0.059\%$ mm^{-2} respectively) can be generated with HPMC polymers. *In vitro* release trials show the adequacy of formulations formulated for the release of promethazine hydrochloride. The satisfactory percentage drug release was obtained from optimized formulation F1 (87.09 ± 2.9), F7 (75.69 ± 1.65), and F12 (94.69 ± 1.9). Based on *ex vivo* release data menthol when used as a permeation enhancer, the flux 1.4 fold enhanced in transdermal patches and 1.9 folds enhanced in gels. Transdermal gels of carbopol showed the highest flux among all the formulations (F16 showed flux 117.5 µg/cm^2/h). **Conclusion:** The results may be extrapolated to human beings as the permeability and structure of rat skin is identical to that of human beings. With decreased doses of these drugs and consequently reduced side effects, the development of the transdermal patches and gels for promethazine may thus be a promising one.

Keywords: Enhancement ratio, Flux, Promethazine Hydrochloride, Permeation, Transdermal patches, Transdermal gels.

INTRODUCTION

Delivering medicine to the general circulation through the skin is seen as a desirable alternative to taking it by mouth or by oral route. Patients sometimes forget to take their medicines, and they get tired of swallows even the most faithfully compliant, particularly when they need to take a few per day.[1] Furthermore,

bypassing the gastrointestinal tract will prevent frequent GI irritation and prevent partial inactivation in the first pass by the liver. Furthermore, the continuous absorption of the medicine over hours or days is generally preferred to the blood spikes and troughs caused by oral dosage formulations.[2]

The transdermal products give such benefits, but some of the drug candidates are formulated into the transdermal system due to the barrier properties of the skin outermost layer i.e., stratum corneum which is made up of keratinocytes.[3,4] Many approaches are available for increasing the permeation rate of drug molecules through the skin.[5,6] During this present investigation, chemical

permeation enhancers (Terpenes –Menthol) are used for enhancing the permeation.[7,8]

The drug selected for the study is Promethazine Hydrochloride. It is a water-soluble antihistamine, an antiemetic drug that has been chosen as a model drug in the research procedure as it has such characteristics that the medicine ought to be consumed by a transdermal route. The bioavailability is less (25% because of the first-pass metabolism) and the dosage is low, i.e., 10 mg, while taking through oral route.[9] Therefore, it may be loaded into a gel as well as patch easily. Promethazine is efficient to use for avoiding motion sickness if it was taken before traveling; termination of action could be achieved after the purpose is served. It can also be used to reduce postoperative nausea and vomiting, especially in narcotic therapy, migraine episodes, cancer chemotherapy, and so forth.[10] Based on the above reasons it was thought that it might be advantageous to formulate transdermal drug delivery systems of promethazine hydrochloride that may enhance the bioavailability.

MATERIALS AND METHODS

Materials

Promethazine Hydrochloride(PMZ) and HPMC (E5, E15 and E50) were received as gift samples from Dr. Reddy's lab, Hyderabad. Menthol, Carbopol 934P and dialysis membrane purchased from Hi media lab, Mumbai. All other chemicals of analytical grade purchased from S.D fine chemicals, Mumbai.

Methods

Preparation of Rat Abdominal Skin

Albino rats (150 -200g) were sacrificed using anesthetic ether. The hair from the abdominal skin was trimmed carefully using electrical clippers and epidermis was prepared by heat separation technique by soaking in hot water (60°C) for 45 sec. After this, the epidermis was washed with water and then used to do further tests.

Effect of Menthol on PMZ Permeation

Permeation studies were carried out using Franz diffusion cells to know the effect of permeation enhancer (Menthol) on the PMZ permeation through rat abdominal skin. In the donor compartment with varying amounts of Menthol (0, 2.5, 5, 7.5, and 10% w/v) was mixed with the solution of PMZ (5 mg in 5 mL of the 7.4 pH phosphate buffer solution). The 0% Menthol (plain drug solution) served as control. There was a 23 mL phosphate buffer having a 7.4 pH in the receptor cabinet and the content was stirred with a magnetic stirrer at 500 RPM.[3] At standard intervals up to 24 hr. 1 mL of samples were withdrawn and the same phosphate buffer volume was replenished. UV-Visible spectrophotometer has analyzed withdrawn samples at 249 nm.

Drug –Excipients Compatibility Studies

FT-IR ("Fourier transform infrared") spectroscopy was used to verify any physical interference with drugs and excipients. The Non-Thermal Drug-excipient analysis (Binary Drug Mixture: Excipients 1:1 Ratio) compatibility studying has been carried out using FT-IR spectrophotometer ("Spectrum BX series, 51658, Perkin Elmer BX, UK") equipped using spectrum of software v2.19 by the KBr pellet approach. The spectrum was reported with a 4cm⁻¹ resolution for each sample in the 4000-400cm⁻¹ spectral region.

Preparation of Different Transdermal Therapeutic Systems of Promethazine Hydrochloride (PMZ)
For polymeric films

PMZ transdermal matrix films are prepared with a solvent casting process utilizing a different HPMC ("Hydroxy Propyl Methyl Cellulose") polymer proportion. Table 1 illustrates the composition of transdermal films. In a boiling container, weighed quantities of HPMC polymers were taken. The required amount of dichloromethane: methanol (1:1) mixture is added as well as vortexed. Enough precautions should be taken to avoid lump formation. For 6 hr, the boiling tube has been placed aside to swell the polymer. After swelling, to this mixture a required amount of plasticizer (15% of the polymer weight) was added and vortexed. In solvent mixture of 5 mL, the finally weighed PMZ was dissolved and blended well into the polymer solution. It has long been reserved to remove entrapped air and then poured into an anumbra plate that has already been washed. The drying of such patches is taken place overnight at room temperature and then 8 to 12 hr in the vacuum oven at room temperature.[11]

For transdermal gels

Two polymers (Carbopol 934P and Xanthum gum) were selected for the preparation of PMZ gels. Composition of transdermal gels shown in Table 1. Both these polymers are pH-sensitive and anionic polymers. A weighed amount of the drug was dissolved in propylene glycol. Then polymer dispersion in water with glycerol was added to the drug solution. Triethanolamine was added on continuous stirring (100RPM) on a magnetic stirrer for the transparent gel formulation.

Evaluation of Prepared Transdermal Therapeutic Systems
For patches
Weight and thickness variation test

For weight variation test, from each formulation 10 patches (with area 2.89 cm2) were weighed individually and average weight was calculated. The weight was determined with "Shimadzu digital balance". For all formulations, average±SD values were

Table 1: Composition of Transdermal patches and gels.

Formulation Ingredients	Formulation code															
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16
Promethazine hydrochloride (mg)	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
HPMC E15 (mg)	80	100	120	-	-	-	-	-	-	80	-	-	-	-	-	-
HPMC E50 (mg)	-	-	-	80	100	120		-	-	-	80	-	-	-	-	-
HPMC E5 (mg)	-	-	-	-	-	-	80	100	120	-	-	-	-	-	-	-
Carbopol 934(mg)	-	-	-	-	-	-	-	-	-	-	-	10	15	-	-	10
Xanthan gum (mg)	-	-	-	-	-	-	-	-	-	-	-	-	-	10	15	-
Propylene glycol (mL)	-	-	-	-	-	-	-	-	-	-	-	0.2	0.2	0.2	0.2	0.2
Glycerol (µL)	-	-	-	-	-	-	-	-	-	-	-	46	41	31	26	46
Water (mL)	-	-	-	-	-	-	-	-	-	-	-	0.73	0.73	0.73	0.73	0.73
Menthol (%w/w)	-	-	-	-	-	-	-	-	-	7.5	7.5	-	-	-	-	7.5

15% v/w propylene glycol was used as a plasticizer for patches with all polymers. Solvent mixture was approximately 35 mL of dichloromethane and methanol in 1:1 ratio. For transdermal films F1 to F11.

determined. The digital screw gauge was used to measure film thickness (Digimatic outside micrometer, Mituotoyo, Japan). The average±SD values are determined.

Flatness and folding endurance

One patch is cut off from the middle and two from either side of the patch for flatness determination. For all strips length will be determined and the length variation is determined by a determining percent constriction. Zero percent constriction will equate 100% flatness. The folding endurance of formulated polymeric films was determined manually by subjecting to frequent extreme folding conditions. The value of folding endurance is the amount of time the films can be folded in the similar position without splitting. The mean±SD values were calculated.

Moisture absorption studies

Weighed films are held at room temperature in a desiccator with a saturated solution of aluminum chloride of 100 mL, which preserves relative humidity at 79.5%. These films are then withdrawn and weighed after three days. The moisture absorption percentage was evaluated with the formula given below.

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

Moisture loss studies

The prepared films will be individually weighed and stored at room temperature for 24 hr in a desiccator that contains calcium chloride. Until the films give a stable weight the films are weighed

again and again at a given interval. The following formula is used to determine the moisture content percentage.[12]

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

WVTR (Water vapor transmission rate) studies

As transmission cells, glass vials with the same diameter have been used. The cells are thoroughly washed and then dried in the oven. Calcium chloride anhydrous of approximately 1 g was put in the cells and the corresponding polymer film was set over the brim. The cells have now been properly measured and stored in a closed desiccator which contains potassium chloride saturated solution to preserve 84% RH. After storage, the cells were withdrawn as well as weighed. The following formula is used to determine WVTR:

$$\text{WVTR} = (\text{Final Weight-Initial Weight})/(\text{Time} \times \text{Area})$$

WVTR was represented by the number of grams of moisture gained/hr/cm^2.

Mechanical properties

A microprocessor-based advanced force gauze with a motorized measure stand "(Ultra test, Mecmesin, WestSussex, UK")", with a load cell of 25 kg, has been used to evaluate the films' mechanical properties. With 60 ×10 mm dimensions, a film strip was mounted between two clamps with a distance of 3 cm and free from air bubbles and physical limitations. On the clamping surface, cardboard was fitted to avoid the film being cut by clamp grooves. During calculation, the top clamp was dragged to a distance at a 2.0 mm/s speed until the film broken. When

the films were broken, the force and elongations were measured. Observations did not include results of broken film samples at the end and not between the clamps. To measure the mechanical properties of films, the equations given will be used.[13]

$$\text{Tensile strength (kg/mm}^2) = \frac{\text{Force at break (kg)}}{\text{Initial cross-sectional area of sample (mm}^2)}$$

$$\text{Elongation at break (\% mm}^{-2}) = \left[\frac{\text{Increase in length (mm)}}{\text{Original length (mm)} \times \text{Cross sectional area (mm}^2)}\right] \times 100$$

For gels

pH and Viscosity

The gels were evaluated for pH using a combined glass electrode (Remi, India). By putting the electrode into contact with the gel, the pH was observed at room temperature, allowing equilibrating for 1 min. A Brookfield viscometer (model DV-III+Rheometer) was used for checking the viscosity of the gels. The sample holder taken for viscosity measurement was filled with the sample. The spindle was immersed into the sample as per the standard procedure. An optimum speed (25 RPM) was used to measure the viscosity of the preparation. The sample was allowed to settle for 5 min before taking the reading and results are noted.

PMZ estimation in polymeric films and gels

For the drug substance, each formulation of polymeric films as well as gels have been tested. Each formulation was formulated in triplicate and one film from each patch/one gram from each gel was taken and drug content tested. Three patches were taken from the formulation sequence; broken into small pieces or take one gram of gel from each formulation; enabled to dissolve into 7.4 pH phosphate buffer by stirring it 24 hr on a magnetic stirrer. The solution after suitable dilution filtered through a 0.45 μm membrane filter and was analysed in UV-Visible spectrophotometer at 249 nm wavelength against 7.4 pH phosphate buffer as a blank.[14]

In vitro drug release studies

Drug release from PMZ transdermal film and gels have been studied by using Diffusion cells e.g., Franz Diffusion Cell. For transdermal films, patches have been cut with an area of 2.89 cm² and since only patches' one side intended to release the substance, an impermeable backing membrane on one side of the patch was placed. By adhering the patch onto the synthetic membrane with cyanoacrylate adhesive, the diffusion assembly was formed.[15,16] For gels weighed amount (1 g) of the gel was applied to the dialysis membrane. The agitation speed (500 RPM) and temperature (37±0.5°C) should be held stable. The entire assembly is placed on a magnetic stirrer and a pH phosphate buffer solution of 23 mL was continually and consistently stirred

with magnet beads throughout the whole process. For analysis, the samples were obtained at given time slots (i.e., 0.5, 1, 2, 4, 8, 12, or 24 hr) and substituted with a fresh buffer of the same volume. Spectrophotometrically the drug concentration is identified at 249 nm. In three replicates the release studies have been conducted and then average values were considered.[17]

Ex vivo permeation studies

The epidermal membrane was placed over a Franz Diffusion Cell. The patches have been cut with an area of 2.89 cm² and since only one side of the patches intended to release the substance, an impermeable backing membrane on patches' one side was placed. By adhering the patch onto the synthetic membrane with cyanoacrylate adhesive, the diffusion assembly was formed. In the donor compartment, for the gels weighed amount (1 g) of the gel was applied over the skin. To know menthol as a permeation enhancer on *ex vivo* permeability of PMZ from transdermal therapeutic systems, for this purpose menthol at a concentration 7.5 w/w of polymer weight for patches and 7.5 w/w of gel weight was incorporated in the formulation and a permeability study was conducted for the permeability of PMZ from the transdermal patches/gels through rat abdominal skin comparing with plain patch/gel (without permeation enhancer). 23 mL of pH 7.4 phosphate buffer was contained in the receptor fluid.[18] The complete unit was mounted on a magnetic stirrer and it should be held at 37±0.5°C temperature. The samples were obtained at 0.5, 1, 2, 4, 8, 12, and 24 hr intervals and kept until the examination was performed under refrigerator conditions. All the trials have been performed in triplicate.[19,20]

Stability Studies

The optimized formulation (patch and gel) was stored for two months at room temperature; also observe for drug precipitation, the flexibility of patches, drug content, and for gels drug content, pH, viscosity.

RESULTS AND DISCUSSION

Results

Effect of Menthol on PMZ permeation through rat abdominal skin

The effect of different concentrations of permeation enhancer on the overall amount of permeation of promethazine hydrochloride through the rat abdominal skin was observed. 7.5% w/w and 10% w/w menthol having drug solution reported almost the same flux value 96±3.6 and 98.82±1.5 μg/cm²/h. 5% w/w and 7.5% w/w of menthol containing drug solution having flux values were considerably distinct ($p<0.05$) with lower values achieved with 2.5% and 5% w/w of menthol (76.52±3.5 and 86.97±2.6 μg/cm²/h) and control means drug solution without permeation enhancer (56.77±2.1 μg/cm²/h). On the basis of the

findings, a rise of the concentration of permeation enhancer from 7.5% to 10% w/w the permeation of promethazine hydrochloride was not impacted, therefore, transdermal films preparation, 7.5% w/w concentration of menthol was used.

Folding endurance, weight, % constriction, drug content, and thickness variation

Table 2 provides the list of physico-chemical parameters of transdermal films (folding endurance, weight, % constriction, drug content, and thickness variation). The weight levels in the patches ranged from 96.1±3.24 to 118.9±2.82 mg and thickness from 0.29±0.001 to 0.66±0.010 mm. The findings revealed that the films are uniform, as shown by the RSD value that is below 6. The drug content ranged from 9.29±0.034 to 9.84±0.012 mg. Concerning the drug content, all formulations were acceptable. Formulation F10 and F11 containing menthol as penetration enhancer are seen to have the highest number of folding endurances in the range of 142.66±3.79 and 195.33±2.28 respectively. The number of folding endurances provides the mechanical property of the films; a large number of folding endurances show the good mechanical properties of the patches. With increasing polymer content in films, the folding endurance number has been raised. These findings show that the patches will not break and that they would retain consistency when applied to the general skin folding.

Moisture absorption, Moisture content, and WVTR studies

Table 3 lists results of the moisture absorption, moisture content as well as WVTR studies of optimized formulations. The moisture content percentage in the formulation varied between 1.649±2.34 and 2.632±3.47. The moisture absorption percentage in the formulations varied between 4.567±0.54 and 6.233±0.23. The findings show that with an increasing polymeric concentration in patches, the moisture absorption percentage and moisture content percentage are increased. With limited moisture content formulations that allow them to stay constant and not being a dried and broken film. Again, in the case of films that absorb low moisture and prevent the patches from microbial contamination. The WVTR ranged from $0.531 \times 10^{-4} \pm 0.02$ to $1.296 \times 10^{-4} \pm 0.028$ g/cm^2/h. Formulation shows the maximum water permeation, which may be a presence of hydrophilic polymer.

Mechanical properties

The mechanical properties of films shows the film's strength and elasticity, as it was discovered by the parameters of tensile strength (TS), elastic modulus (EM) and elongation at break (E/B). When a polymer is soft and weak indicates a low value of TS, E/B, and EM indicates polymer; a tough and hard polymer is indicated by high values of TS, E/B, and EM. The strain was used as a measure of the overall mechanical

Table 2: Physicochemical parameters of prepared transdermal films and gels.

Formulation code (patches)	Weight (mg)*	Thickness (mm)*	Drug content (mg)**	% Constriction**	Folding endurance**
F1	97.6±2.67	0.29±0.006	9.36±0.042	1.18±0.083	132.45±1.05
F2	108.2±3.06	0.32±0.010	9.53±0.052	2.08±0.011	114.33±2.08
F3	118.9±2.82	0.35±0.005	9.29±0.034	1.56±0.027	251.33±5.56
F4	96.1±3.24	0.49±0.006	9.47±0.039	1.88±0.036	104.67±4.11
F5	107.8±2.97	0.57±0.023	9.33±0.062	2.41±0.022	119.66±2.09
F6	112.4±2.11	0.66±0.010	9.72±0.019	0.84±0.026	130.52±4.28
F7	98.5±3.77	0.34±0.007	9.45±0.035	1.18±0.016	153.66±1.52
F8	106.5±3.23	0.48±0.001	9.81±0.023	0.56±0.013	154.00±4.35
F9	116.2±3.84	0.55±0.004	9.35±0.054	1.85±0.025	92.51±2.65
F10	98.3±6.64	0.29±0.001	9.62±0.025	1.67±0.072	142.66±3.79
F11	97.6±3.94	0.33±0.009	9.84±0.012	2.25±0.017	195.33±2.28
Formulation code (gels)	Gelling	Homogeneity	pH*	Drug content (mg)*	Viscosity (cps)*
F12	†††	†††	6.23±0.29	9.73±0.15	13400±115
F13	†††	†††	6.42±0.26	9.42±0.36	15600±96
F14	†††	†††	7.26±0.31	9.69±0.21	10100±125
F15	††	††	7.81±0.15	9.77±0.25	14600±132
F16	††	†††	6.54±0.32	9.72±0.22	12800±93

*Values are expressed as mean±SD; n=10; **Values are expressed as mean±SD; n=3; †††- Excellent, ††-Good,†-Poor,

Table 3: Moisture studies and mechanical properties of prepared transdermal films.

Formulation code	Moisture studies			Mechanical properties	
	% Moisture absorbed	% Moisture content	WVTR (gm/cm^2/hr)	Tensile strength (kg/mm^2)	Elongation at break (%/mm^2)
F1	4.847±0.95	1.649±2.34	1.296×10^{-4}±0.028	0.0940±0.0022	1.4367±0.187
F7	6.233±0.23	2.103±2.87	0.653×10^{-4}±0.016	0.0793±0.0015	0.9974±0.108
F10	4.567±0.54	1.944±4.99	0.531×10^{-4}±0.029	0.0788±0.0014	1.1252±0.073
F11	5.992±0.61	2.632±3.47	0.782×10^{-4}±0.32	0.0652±0.0018	0.8749±0.059

All values are expressed as mean±SD; n=3

consistency of polymer film as another significant parameter. A high tensile strength, strain as well as elongation at break but a low elastic modulus should apply to an appropriate transdermal patch. Table 3 demonstrates the mechanical properties results (such as E/B and TS). Optimized formulation F10 and F11 exhibited tensile strength values 0.0788±0.0014 kg/mm^2 and 0.0652±0.0018 kg/mm^2 respectively and elongation at break values 1.1252±0.073% mm^{-2} and 0.8749±0.059% mm^{-2} respectively. These findings show that the TS raised but the values of E/B decreased as a consequence of the increased concentration of polymer. The findings are flexible as well as strong but not brittle, based on optimized formulations (F10 and F11).

Physicochemical parameters of transdermal gels

pH, Viscosity, Gelling nature, Drug content and Homogeneity of transdermal gels of PMZ

Gels were formed with low viscosity when the concentration of carbopol934P was below 1% and Xanthum gum at a concentration below 1.5% was used. Initially, when propylene glycol was used in low concentrations, the drug precipitated from the formulation and this problem was solved when higher a concentration of propylene glycol was used. Glycerol was used to give emolliency to the formulation. Polyethylene glycol was also used for the preparation of gels. Propylene glycol when used produced more transparent gels than polyethylene glycol. In formulation F16, menthol was used at 7.5% w/w of the concentration of polymer. Table 2 shows the results for the prepared gels evaluated for pH, viscosity, gelling nature, drug content, and homogeneity. The results demonstrated that F12 and F13 have good gelling nature and homogeneity. All the transdermal PMZ gels observed good uniformity of drug content (9.42±0.36 mg to 9.77±0.25mg). The pH of gels 6.23±0.29 to 7.81±0.15 was in the tolerable range of skin pH (3 to 9). The viscosity was in the range of 10100 cps to 15600 cps at 25 RPM.

In vitro drug release profiles of PMZ transdermal gels and films

In vitro drug release trials were conducted for transdermal films and gels of PMZ by using Franz diffusion cells with gelatin membrane. Formulation F1 to F3 contains HPMC E15 polymer shows the percentage of drug release 87.09±2.9 to 46.55±3.9, for F4 to F6 contains HPMC E50 polymer shows the percentage of drug release 55.47±3.4 to 34.02±2.51, similarly F7 to F9 formulations contains HPMC E5 polymer, percentage of drug release 75.69±1.65 to 37.03±2.45. Based on the results, the drug release percentage decreased as the polymer concentration was increased. When comparing the results of F1, F4 and F7 all the formulations contain the same ratio of drug and polymer but a change in the viscosity. On the finding basis, the drug release percentage was decreased when increasing the viscosity of the polymer. Formulations F1 (87.09±2.9), F7 (75.69±1.65) showed maximum release among their series for 24 hr. For further studies, these two formulations were considered as optimized formulations. All gel formulations obtained were transparent and had good viscosity. They were spreadable onto the skin easily. F12 showed maximum release (94.69±1.9) among all following formulations and it was used for further studies and incorporation of the permeation enhancer. When the polymer concentration was increased, PMZ release was decreased and Xanthum gum showed less release than that of carbopol 934P. The release rate profile was found out by comparing the correlation coefficient (R^2). of First-order equation, Zero-order equation and Higuchi model. Likewise, n value of Korsmeyer- Peppas model was used for mechanism of drug release. The result indicates that as the polymer concentration increases; the Zero-order release profile altered to first order. Formulation F1 and F7 exhibited zero-order release with maximum drug release. The case of gels (F12 to F15) has depicted zero-order and diffusion was the mechanism of release.

Ex vivo permeation studies

Ex vivo permeation studies of promethazine hydrochloride transdermal films and gels were carried out by Franz diffusion cells using rat abdominal skin. All the formulations F1, F7, and F12

Table 4: Effect of chemical penetration enhancers on *ex vivo* permeation of transdermal patches and gels through rat abdominal skin.

Time (hr)	Cumulative amount of Drug Permeated (µg)							
	Drug Solution		Transdermal Patch (Drug: HPMC E15)		Transdermal Patch (Drug: HPMC E5)		Transdermal Gel (Drug: Carbopol)	
	without menthol	with menthol	F1	F10	F7	F11	F12	F16
0	0	0	0	0	0	0	0	0
0.5	62.13±12.3	100.05±15.9	46.12±21	92.36±24	41.45±19	75.9±29	109.2±49	115±46
1	119.41±10.9	267.45±45.8	162.78±59	205.81±49	66.85±25	196.35±35	172.5±92	292.9±59
2	454.11±39.2	638.42±54.3	324.85±98	549.35±95	149.4±51	334.75±103	355.4±74	753.3±78
4	1217.94±128.4	1585.95±178.5	549.33±149	1086.84±105	513.35±95	673.52±174	886.4±69	1573.7±159
8	2463.53±189.2	3911.85±224.7	1629.48±198	2424.94±176	1178.45±152	1654.6±199	2137.2±199	4480.5±269
12	3584.82±201.9	5354.26±269.1	2375.26±261	3493.9±254	1876.88±198	2185.63±203	3182.2±259	5851.7±356
24	4414.37±259.8	6647.39±289.2	4011.49±323	5045.39±351	3093.2±224	3807.81±271	4205.1±301	7889.6±450
Flux (µg/cm²/h)	56.77±2.1	96±3.6	56.6±2.1	73.63±3.6	46.84±1.6	61.22±3.1	60.9±2.6	117.5±3.4
Enhancement ratio	1.69		1.4		1.3		1.92	

showed an increase in flux when menthol was used as permeation enhancer (F10, F11, and F16) as evidenced from Table 4. The skin flux was observed in all optimized formulations of F1 (56.6±2.1 µg/cm²/h), F7 (46.84±1.6 µg/cm²/h) and F12 (60.9±2.6 µg/cm²/h) having the skin flux. Compared to drug solution (56.77±2.1 µg/cm²/h) F12 shows higher flux due to it is in the form of gel, the existence of propylene glycol may also lead to higher transdermal flux. There was an improvement in the rate of permeation of the transdermal systems with menthol which was about 1.3 to 2.0-fold higher as compare to without enhancers. The efficacy of chemical permeation enhancer was measured by evaluating the drug flux in the presence and absence of permeation enhancer. Formulations containing permeation enhancer shows flux F10 (73.63±3.6 µg/cm²/h), F11 (61.22±3.1 µg/cm²/h), and F16 (117.5±3.4 µg/cm²/h) higher than drug solution and all other formulations without permeation enhancer. From all the formulations F16 (Carbopol gel with permeation enhancer) is an optimized formulation due to higher flux compared with other fluxes.

Drug-excipients compatibility studies

Figure 2 shows peaks corresponding to promethazine hydrochloride were present in the IR spectrum of the physical mixture of formulations F10, F11 as well as F16 confirming that there was no change in the structure of promethazine hydrochloride. It was concluded that PMZ is compatible with HPMC E15, HPMC E5, menthol, and carbopol 934P. The major peaks were for out-of-plane -CH bending of disubstituted aromatics at 757 cm⁻¹, for -CH$_2$and -CH$_3$bendingat 1456 cm⁻¹, and for NH⁺ stretching at 2200-2480 cm⁻¹.
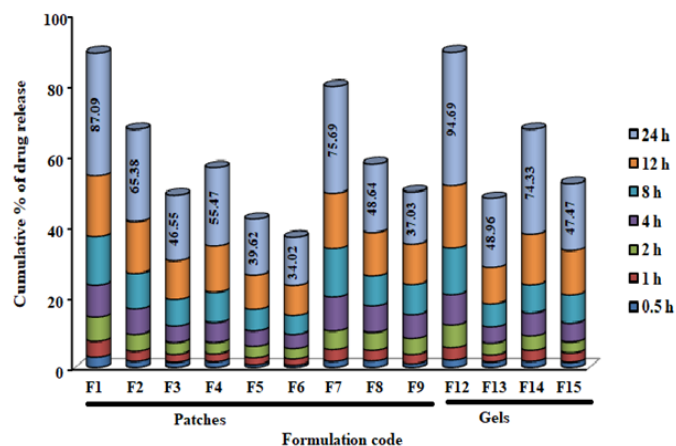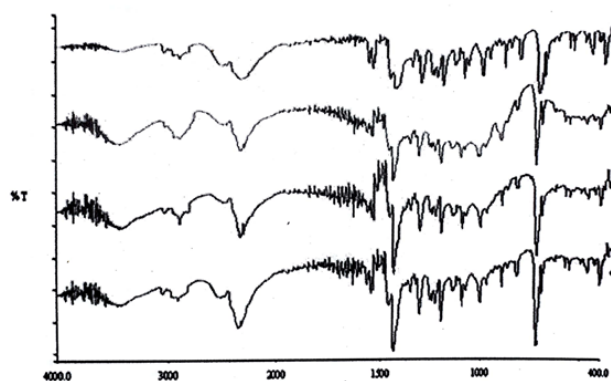

Figure 1: *In vitro* drug release profile of F1 toF15 formulations.

Figure 2: FTIR spectra Promethazine HCl (a), Physical mixture of PMZ, Menthol, Carbopol 934P (b), Physical mixture of PMZ, HPMC E5 and permeation enhancer (c), and Physical mixture of PMZ, HPMC E15 and permeation enhancer (d).

Table 5: Stability studies of Optimized formulations.

Day	Transdermal patch (F10)		Transdermal gel F12 Carbopol gel without penetration enhancer			Transdermal gel F16 Carbopol gel with penetration enhancer		
	Drug content	Folding endurance	Drug content (mg)	pH	Viscosity (cps)	Drug content (mg)	pH	Viscosity (cps)
1	9.81±0.12	190.26±6	9.69±0.09	6.42±0.19	13200±89	9.70±0.19	6.57±0.11	12750±35
30	9.79±0.09	190.52±12	9.68±0.15	6.65±0.31	12600±56	9.65±0.05	6.59±0.08	12600±63
60	9.64±0.05	186.55±14	9.59±0.12	6.79±0.22	12450±72	9.62±0.08	6.63±0.12	12550±85

Stability studies

Stability studies for F10 (transdermal patches) F12 and F16 (transdermal gel) were performed at room temperature and results are depicted in Table 5. Patches concerning drug content were shown to be stable. The drug content was within the limits and no major pH and viscosity variations were observed in transdermal gel formulations after storage for 60 days at room temperature.

DISCUSSION

The work describes transdermal permeation of antiemetic agent PMZ and its transdermal delivery using patches and gels. PMZ is water soluble and suffers from poor bioavailability when given through oral route due to extensive first pass metabolism. Drug delivery through the transdermal route bypasses hepatic first pass metabolism. In a preliminary study, permeability of PMZ was first investigated by *ex vivo* study using rat abdominal skin, then menthol with 7.5%w/w concentration showed a potential enhancement effect on PMZ permeation through rat abdominal skin compared to other concentration. An ideal penetration enhancer should pharmacologically inactive and nonirritant for the skin, potentially and cosmetically acceptable. Menthol is a naturally occurring terpene compound isolated from *Mentha piperita*is free from toxic effects and has been approved as a penetration enhancer in the transdermal delivery of several hydrophilic and lipophilic drugs compared to conventional synthetic permeation enhancers.[21] The interaction of Menthol on stratum corneum lipids at two sites, namely the lipophilic portion of the intercellular lipids and the polar head portion.[22] They can fluidize and extract the stratum corneum lipids to weaken the skin permeability barrier provided by the stratum corneum lipids.

Many experiments were performed for the formulation of transdermal patches of PMZ by varying concentrations of different polymers. Polymer films were formulated with varying concentration of HPMC E15, HPMC E5 and HPMAC E50. The experiment was initiated by taking 50mg of HPMC E15 polymer per each patch and as the polymer concentration increased the patch could accommodate more amount of PMZ. Precipitation of the drug was predominant with 60mg of the polymer and as the polymer concentration was increased to 80mg and above, there

was no precipitation.[23] The films lost their effective mechanical properties when prepared with more than 130mg of the polymer.[24] Therefore, the polymer was taken in amounts 80mg, 100mg and 120mg and patches were prepared. Flexible polymeric films were prepared by varying the concentration of plasticizer. Plasticizer at a concentration of 5% v/w of film former was insufficient to form films. A plasticizer concentration of 5-10%v/w yielded hard and inflexible films. Increasing the concentration to 10-20%v/w yielded more flexible films. Further increase in plasticizer concentration above 20%v/w resulted in enormous in drying time.[25]

Based on the above observation matrix type transdermal patches of PMZ were prepared with 7.5% w/w as a penetration enhancer and PEG 600 v/w as a plasticizer by different ratio with various hydrophilic polymers like HPMC E5, HPMC E15 and HPMC E50 which was found to be transparent, smooth and wrinkle free. Transdermal hydrogel's of PMZ were prepared with carbopol 934P (1%) and xanthum gum (1.5%) which were found to be transparent.[26] By this approach, all cautions related to PMZ conventional dosage form were reduced maximum efficacy of the drug for effective management of motion sickness. The FT-IR spectra of the pure PMZ, physical mixture of PMZ, HPMC E5 and menthol, physical mixture of PMZ, HPMC E15 and menthol and physical mixture of PMZ, Carbopol and menthol are presented in Figure 2. In all the samples, the main peaks of the drug detected indicate no chemical interaction between drug and polymers. In matrix type transdermal patches, the polymers cast off are frequently used and are compatible with a numeral of drugs.[27] The drug release profile of PMZ from transdermal delivery systems is represented in Figure 1. Release of the drug from the formulations governed by polymer concentration and type of polymer viscosity, it is clear from results and plots. Increased concentration and viscosity of polymers were correlated with the reduced drug release rate. This is because HPMC forms a water-swollen gel-type structure that may significantly decrease the dissolution medium's penetration into the patches and thus retarded the drug release.[28] To illustrate the *in vitro* release kinetics of PMZ from transdermal films and gels, *in vitro* release data from formulations of each batch was fitted to various kinetic models. Formulation F1 and F7 exhibited zero-order release pattern with maximum drug release and mechanism of drug release through anomalous diffusion based on 'n' value (0.53 to

0.71). The case of gels (F12 to F15) has depicted zero-order and anomalous diffusion based on 'n' value (0.52 to 0.689) was the mechanism of release.

Polymer (HPMC E15) and drug ratio 1:8, 15% v/w propylene glycol concentration as a plasticizer and 7.5% w/w menthol concentration as a permeation enhancer are the optimal conditions for developing transdermal patches of PMZ. Under the above conditions, 0.0788±0.0014 kg/mm2, 73.63±3.6 µg/cm2/h and 5045.39±351 µg/cm2 were found as the predicted tensile strength, steady state flux and cumulative amount of drug permeated within 24h (Q24) for F10 formulation. Optimal conditions for preparing transdermal gels are polymer (Carbopol 934) and drug ratio 1:1 along with 7.5% w/w of menthol. Based on the above conditions, 12800±93, 7889.6±450 µg/cm^2 and 117.5±3.4 µg/cm^2/h were found as the predicted viscosity, cumulative amount of drug permeated within 24 hr (Q_{24}) for F16 formulation. Permeation enhancers which are obtained from chemical synthesis are typically potent skin irritants and attaining suitable penetration levels requires higher concentration to produce hyperkeratosis and ulcerative eruption of stratum corneum.[29,30] The natural molecules as permeation enhancers which resolve all the above associated problems to a large extent via Lipid-Protein-Partitioning (LPP) mechanism, terpenes can increase skin permeation and solubility of drug into stratum corneum lipids can be increased.[3]

CONCLUSION

Promethazine hydrochloride matrix type transdermal films are successfully made with different concentrations and hydrophilic polymer types (HPMC E5, HPMC E15, and HPMC E50). The films showed good physicochemical and mechanical properties. Matrix diffusion mediated transdermal gels of promethazine hydrochloride can be formulated using polymer carbopol and xanthum gum. In patches and gels during storage, the drug content stays stable. Enhancement in permeation of drug from transdermal delivery system across the rat abdominal skin was achieved by using permeation enhancer (menthol). Transdermal gels of carbopol showed the highest flux among all the formulations (117.5±3.4µg/cm²/hour). The results may be extrapolated to human beings as the permeability and structure of rat skin is identical to that of human beings. With decreased doses of these drugs and consequently reduced side effects, the development of the transdermal patches and gels for promethazine may thus be a promising one.

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Promethazine hydrochloride and different grades of HPMC polymers.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

PMZ: Promethazine Hydrochloride; **HPMC:** Hydroxy Propyl Methyl Cellulose; **RPM:** Rotation per Minute; **WVTR:** Water Vapor Transmission Rate; **RH:** Relative Humidity.

SUMMARY

Promethazine Hydrochloride transdermal gels and patches were developed using various polymers. Matrix diffusion mediated transdermal patches of promethazine were formulated using polymers HPMC E5, HPMC E50, and HPMC E15. Matrix diffusion mediated transdermal gels of promethazine were formulated using polymer carbopol 934P and xanthan gum.

The satisfactory percentage drug release was obtained from optimized formulation F1 (87.09±2.9), F7 (75.69±1.65), and F12 (94.69±1.9). Based on *ex vivo* release data menthol when used as a permeation enhancer, the flux 1.4 folds enhanced in transdermal patches and 1.9 folds enhanced in gels. Transdermal gels of carbopol showed the highest flux among all the formulations (F12 showed flux 117.5 µg/cm²/h).

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