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ANTI-EMETIC POTENTIAL OF PROCHLORPERAZINE TRANSDERMAL PATCH IN MANAGEMENT OF CHEMOTHERAPY INDUCED NAUSEA AND VOMITING

K. Rajesh [*1], N. Upmanyu [1] and Arun Pandey [2]

School of Pharmacy and Research [1], Peoples University, Bhopal - 462037, Madhya Pradesh, India.
Alkem Research Center [2], Taloja, Navi Mumbai - 410208, Maharashtra, India.

Keywords:

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Correspondence to Author:
K. Rajesh

School of Pharmacy and research, Peoples University, Bhopal - 462037, Madhya Pradesh, India.

E-mail: raajesh.k@gmail.com

ABSTRACT: Uncontrolled nausea and vomiting remain one of the greatest fears of patients undergoing therapy for cancer. In patients getting chemotherapy, serious nausea and vomiting may require dose reduction, treatment delay, or even permanent stoppage. Conventional therapy provides temporary relief from symptoms, but it has lots of undesirable side effects. Prochlorperazine is still widely used as an anti-emetic. Oral and parenteral delivery of prochlorperazine is useful in the management of nausea and vomiting, but due to short half-life, frequent dosing is required, which is inconvenient for the patient. The transdermal drug delivery system is a novel approach and substitute for oral drug delivery and parenteral delivery. It is an easy, painless, and convenient way of applying. In this work, an attempt was made to formulate and evaluate prochlorperazine containing transdermal patches by utilizing casting and solvent evaporation method. The main objective of formulating the Transdermal system was to prolong the drug release time, reduce the frequency of administration and to improve patient compliance. Formulated transdermal patches were evaluated for *in-vitro* parameters such as folding endurance, drug content, thickness, tensile strength, *in-vitro* Dissolution, and diffusion studies, which indicated the good efficacy of the prepared formulation. Furthermore, an *in-vivo* study was performed on chicks using a copper sulfate-induced emesis model. The results showed good therapeutic efficacy of prepared formulation, which confirmed the utility of prochlorperazine transdermal patches as a novel approach in the management of chemotherapy-induced nausea and vomiting.

INTRODUCTION: An oral route is a routine form of drug administration presently. Although the oral administration has various noble advantages such as easy administration but the drug delivered *via* the oral route is the candidate for poor bioavailability due to pre-systemic metabolism and ability to cause a rapid level spike, which results in repeated dosing, which can be inconvenient and costly [1]. During the past few years, interest in the development of novel drug delivery systems for existing drug molecules has been renewed.

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The development of a novel delivery system for existing drug molecules not only improves the drug's performance in terms of efficacy and safety but also improves patient compliance and overall therapeutic benefit to a significant extent [2, 3]. Transdermal drug delivery system (TDDS) is a novel approach and substitute for oral drug delivery and parenteral delivery; it is an easy, painless, and convenient mode of application.

For a long time, people were found placing the substances under the skin for the therapeutic actions; in 1979 the first patch delivered *via* transdermal system was a scopolamine patch for the management of motion sickness was approved by USFDA [4]. The TDDS provides many distinct advantages: skin presents a large and accessible surface area (1–2 m^2) for absorption. Application of

transdermal patch also provides a non-invasive, easy way for drug delivery, which increases patient compliance [5]. The further benefit includes the delivery of drugs for a prolonged period, which is helpful for a drug with a short half-life and controlled release of drugs, which is useful for the delivery of narrow therapeutic index drugs [6]. Vomiting can be defined as forceful removal of gastric content out from the mouth by organized contraction of mainly abdominal muscles and diaphragm while the gastric cardia is open and uplifted with contracted pylorus. Nausea is a common symptom seen in many diseases, and their treatment can be harsh and impairing. Profound continuous nausea/vomiting can lead to serious adverse effects including, malnutrition and a significant decline in quality of life [7]. Gastro-intestinal (GI) side effects such as nausea and vomiting are common adverse effects from many cancer chemotherapy regimens. Having un-controlled nausea and vomiting remains one of the greatest fears of patients undergoing therapy for cancer [8]. In patients getting chemotherapy, serious nausea and vomiting may require dose reduction, treatment delay, or even permanent stoppage. Based on its occurrence, CINV can be named acute (within 24 h), delayed (24–120 h after chemotherapy), or anticipatory emesis (hours to days before chemotherapy).

Anticipatory emesis occurs in patients with an earlier episode of chemotherapy-induced acute and delayed emesis [9]. Prochlorperazine 2 - chloro - 10 - (3 - (1 - methyl-piperazinyl) propyl) phenothiazine] (PCZ) was introduced into medical practice in 1956 and is widely used in the prevention and symptomatic control of nausea and vomiting [10]. This subclass of phenothiazine offers superior antiemetic activity with fewer anticholinergic, sedative, and other neurologic side effects compared with other alkylamino and piperidine side-chain compounds [2, 3]. Prochlorperazine is regularly prescribed phenothiazine antiemetic. The usual adult dose of prochlorperazine is 5 to 10 mg, administered *via* the oral or parenteral route [11]. Present research deals with the formulation of the Transdermal system and its pharmaceutical and pharmacological evaluations.

MATERIALS AND METHODS: The drug was obtained from Cipla Pvt ltd. Mumbai. Polyethylene glycol 400, HPMC, Ethyl Cellulose and Chitosan was purchased from Sigma Aldrich, USA, PVA and PVP, purchased from CDH chemical Pvt. Ltd. New Delhi. The dialysis membrane of Mol Wt cutoff 1200 was purchased from Himedia Laboratory, Mumbai. All other ingredients used were of analytical grade.

Analytical Characterization of Drug:

Finding of Absorption Maxima (λ_{max}): 3 ml of the sample was extracted from the stock solution, and the volume was filled up to 10 ml with PBS to get a concentration of 30 mg/ml. Absorption maxima for selected drugs were determined by ultraviolet drug spectroscopy. The pharmacological solution in a solvent that suits and scanning was done from a range of 200 to 400 nm [12].

Preparation of Standard Calibration Curve: Prochlorperazine maleate (100 mg) was dissolved in a modest quantity of Sorenson's buffer (pH 6.8) in 100 ml of a volumetric jar, and the last volume was made with the Sorenson's buffer. 10 ml of this arrangement was diluted to 100 ml with Sorenson's buffer (pH 6.8) in a 100 ml volumetric flask to get a stock solution of 100 µg/ml. Aliquots of 1, 2, 3, 4, 5, 6 and 7 ml were taken from a stock arrangement in 10 ml volumetric jars and volume was made up to 10 ml with buffer (pH 6.8). The absorbance of these arrangements was estimated at 254 nm. A calibration curve was plotted concentration and absorbance [13].

Fourier Transform Infrared Spectroscopy (FTIR): The pellets were made by mixing 10 mg of prochlorperazine and 100 mg of dry potassium bromide powder. The mixture was then compressed at a pressure of 10tons in a hydraulic press to get a transparent pellet. The thin pellet was placed in a pellet disc, and reading was taken by Perkin Elmer FTIR spectrometer [12].

Differential Scanning Calorimetry (DSC) Study: DSC studies for drug and its physical mixture (1:1) were carried out using DSC-60 calorimeter (Shimadzu Corporation, Japan). The instrument was calibrated with an indium and zinc standard. The sample was heated from 10 to 300 °C at a heating rate of 25 °C / min to remove thermal history. The sample was then immediately cooled to 10 °C and reheated from 10 to 300 °C under the flow of nitrogen at a heating rate of 10 °C/min [14].

Particle X-Ray Diffraction (PXRD): The measurement of X-ray diffraction was performed in pure prochlorperazine with the expert Philip PAN (Bruker D8A X-ray diffractometer) using a filtered Cu Ka α (1542) radiation source, the scanning speed was 5 °C/min. The sample was analyzed between an angle of 2 and 50 ° (2θ), the voltage and current used were respectively Kv and 30 Ma [15].

Drug Excipient Interaction Studies:

Preparation of the Physical Mixture: Drug alone or drugs with polymer (HPMC) were mixed in a 1:1 ratio and kept in the stability chamber (Thermo Lab Scientific Equipment's, 90/90/130 liters) for a month at 25 °C ± 2 °C/60% RH ± 5% RH and 40 ± 2 ºC/75 ± 5% RH according to ICH guidelines to determine the stability. Following one month, tests were pulled back and analyzed for compatibility study utilizing FTIR [12].

FTIR: The pellets were made by mixing 10 mg of HPMC and 100 mg of dry potassium bromide powder. The mixture was then compressed at a pressure of 10 tons in a hydraulic press to get a transparent pellet. The thin pellet was placed in a pellet disk to get IR spectra [12].

TABLE 1: DRUG EXCIPIENT COMPATIBILITY STUDY

S. no.	Name of Ingredients	Ratio	Condition
1	Drug	-	For a month at 25 °C ± 2 °C / 60% RH ± 5% RH and 40 ± 2 ºC/75±5% RH according to ICH guidelines.
2	Drug + HPMC	1:1	
3	Drug + PEG	1:1	

Preparation of Matrix Type Transdermal Patches: The matrix-type transdermal patch of prochlorperazine was formulated by utilizing the casting and solvent evaporation method. The common procedure of the patch is given below in **Fig. 1**.

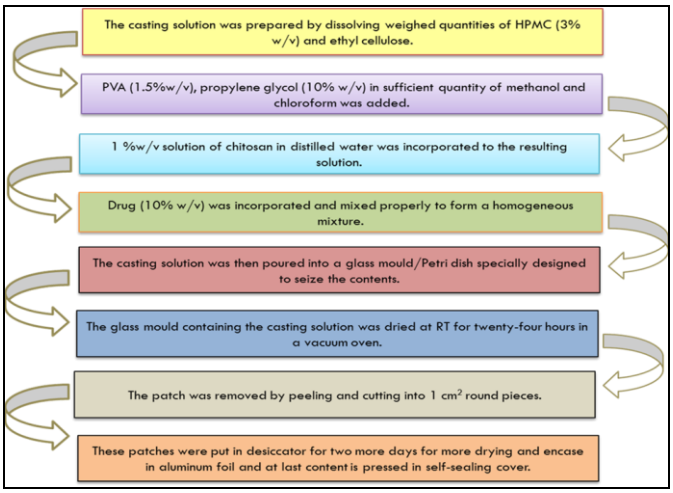

FIG. 1: CASTING AND SOLVENT EVAPORATION METHOD

Optimization and Reproducible batches of prochlorperazine:

Observation: The Best result was found with batch 7 for the prochlorperazine patch, and hence the batch 7 was taken as for the final formulation of the transdermal patch. The optimization and reproducible formulae of transdermal prochlorperazine batch are as follows:

TABLE 2: OPTIMIZATION FACTORS OF PREPARED PATCHES

Factor	Name	Units	Type	Minimum	Maximum	Coded Low	Coded High	Mean	Std. Dev.
A	HPMC	%	Numeric	2.00	4.00	-1 ↔ 2.00	+1 ↔ 4.00	3.00	0.7878
B	Chitosan	%	Numeric	1.0000	3.00	-1 ↔ 1.00	+1 ↔ 3.00	2.00	0.7878
C	Polyethylene Glycol	%	Numeric	5.00	10.00	-1 ↔ 5.00	+1 ↔ 10.00	7.50	1.97

TABLE 3: FORMULAE OF OPTIMIZED BATCH

S. no.	Ingredient	Optimized batch 1	Optimized batch 2
1	Prochlorperazine(w/w)	10 % w/w	8 % w/w
2	Hydroxyl propyl methyl cellulose	3 % w/v	2.5 % w/w
3	Polyethylene Glycol	10 % w/v	8 % w/w
4	Chitosan	1 % w/v	1 % w/w
5	Ethyl cellulose	3% w/v	4 % w/v
6	PVA	1 % w/v	1.5 % w/v
7	Methanol (solvent)	Q.S	Q.S
8	Chloroform (solvent)	Q.S	Q.S

Formulation and Development of Optimized Batch of the Transdermal Patch:

Characterization of Prepared Transdermal patches:

Thickness: Digital micrometer screw gauze was utilized for evaluating patch thickness. The mean of three different places was calculated [16].

Tensile Strength: Evaluation of tensile strength was done by using a tensiometer it consists of two load cell grips. The lower one was fixed, and the upper one was portable.

Film strips with measurements of 2 × 2 cm were fixed between these cell holders, and power was step by step applied till the film broke. The tensile was taken straightforwardly from the dial perusing in kg [17].

Drug Content: A particular portion patch (2 cm × 2 cm) was dissolved in 100 mL methanol, and continuous shaking was done for 24 h. After that total solution was ultrasonicated for 15 minutes [18].

Weight Uniformity: Five films were taken for this experiment. All films were cut, weigh one by one, and the average weight was evaluated [19].

Percent of Moisture Content: The films were prepared and weighed are put in a desiccator where fused calcium chloride is already kept in the room. After 24 h, films are reweighed, and moisture content is determined. [20].

Percentage Moisture Uptake: The films were prepared and weighed are kept at desiccator for 24 h at room temperature. It also contains a saturated KCL solution for maintaining 84% Relative humidity. After 24 h the wright of films is taken again, and the percentage of moisture content is determined [20].

***In-vitro* Release (Dissolution) Studies:** The dissolution study was carried out utilizing the USP basket type apparatus. The patches were put in particular baskets in such a way that the matrix of the drug is presented to the dissolution medium. Entire studies were done at 50 rpm, with every dissolution container having 900 mL of buffer. The samples pulled back at various time interims and were moved through the 0.45 -µm membrane and evaluated for medication content [21].

***In-vitro* Permeation Study:** An *in-vitro* permeation study was performed by utilizing a diffusion cell. Full-thickness stomach skin of a male Westar rat, which is weighing around 200 to 250 g is used. Hair from the stomach area was evacuated cautiously by utilizing electric scissors; the dermis layer of the skin was washed and clean thoroughly with water to remove the adhering tissue or blood vessels, kept in PBS 7.4 for an hour before start-up of the experiment it is kept on a magnetic stirrer with a small magnetic needle for equal dispersion of diffusant. The temperature of the cell was kept up at 32 ± 0.5 °C utilizing a thermostatically controlled heater. The mounting of isolated rat skin was done between the compartments of the diffusion cell, the epidermis was kept in such a way that it is facing up towards the donor compartment. A specific amount of sample is removed from the receptor compartment periodically, and it is replaced by the same volume of fresh medium. Samples are filtered and analyzed by spectrophotometry [22].

***In-vivo* Animal Study:** The *in-vivo* animal study was performed in chicks weighing (50–80 g). The chicks were kept under ideal temperature and humidity and were acclimatized to research facility conditions prior to the trials. Separate groups of animals were utilized for each experiment. The use of laboratory animals was approved by the IAEC of the Institute (CPSCEA Registration No. PJ/DL/11/2019/125), and all experiments were done according to CPCSEA norms.

Induction of Emesis in Chicks: The young chicks (aged 4 days) and weighing from 50-80 g were taken for these experiments. Chicks were set aside for 10 min for stabilization before any treatment was given.

The test area was depilated with a hair remover, and the test patches were applied. Negative control (0.9% saline) and positive control (metoclopramide). 10 min post-administration, $CuSO_4$ was then administered orally (50 mg/kg). The number of retching was calculated for 10 min. The results were compared to the control group. The % inhibition was evaluated by:

$$\text{Inhibition (\%)} = (A-B)/A \times 100$$

A: Freq of retching in the negative control group. B: Freq of retching in the test group [23, 24].

Accelerated Stability Studies Study of Formulated Patches: Stability studies are to be led by the ICH guidelines by keeping the TDDS samples at ambient temperatures of 25 ± 0.5 °C and 60 ± 5% RH for a half year. Samples were also subjected to accelerated stability study at higher temperatures 40 ± 0.5 °C and 75 ± 5% RH for a half year.

The samples were taken back at a different time (0, 30, 60, 90 and 180 days) and based on the product's storage condition. Samples were withdrawn from stability chambers at regular intervals and its physical parameters and drug contents were evaluated [25, 26].

RESULTS AND DISCUSSION:

Analytical Characterization of Drug:

Determination of Absorption Maxima (λ_{max}): Prochlorperazine showed a linear relationship having a correlation coefficient of 0.9964 in the concentration range of 10-60 µg / ml in 0.1 N HCl & PBS pH 7.4, respectively. The absorption maximum of drug prochlorperazine was found to be 254.5 nm, which shows the purity of the drug. **Fig. 2** shows the maximum absorption of the drug.

Fourier Transform Infrared Spectroscopy (FTIR): A sample of pure prochlorperazine showed no alterations in the peaks as seen in the IR spectrum of the sample drug indicated the purity of the drug. The peak values which are characteristics of the drug and the graph are given in **Fig. 3**.

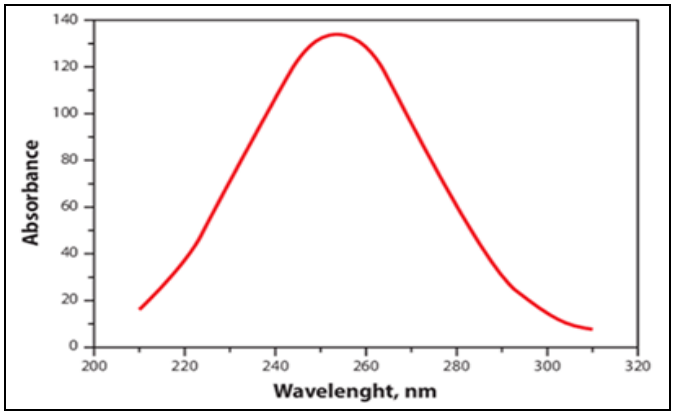

FIG. 2: WAVELENGTH MAXIMA OF PROCHLORPERAZINE

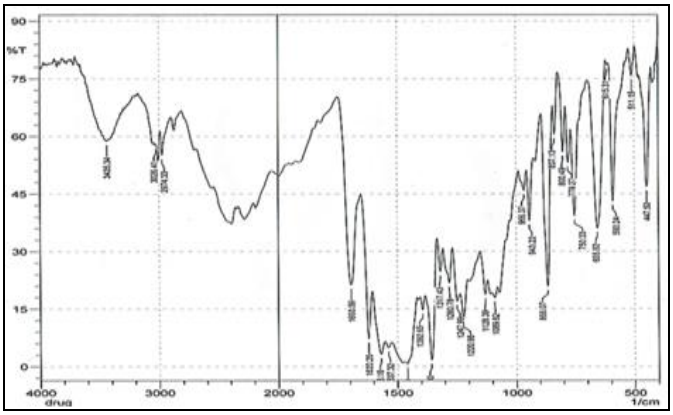

FIG. 3: FTIR OF PURE DRUG

Differential Scanning Calorimetry of Prochlorperazine: The melting of pure Prochlorperazine powder was studied. The melting endotherm was obtained and Prochlorperazine showed sharp peaks at 180 ºC and 225 ºC. The DSC of the drug is seen in **Fig. 4.**

Particle X-Ray Diffraction: In the X-ray diffractogram, prochlorperazine showed intense diffraction peaks of crystallinity at a diffraction angle of 2θ as shown in **Fig. 5** and suggested that the drug is present as a crystalline material.

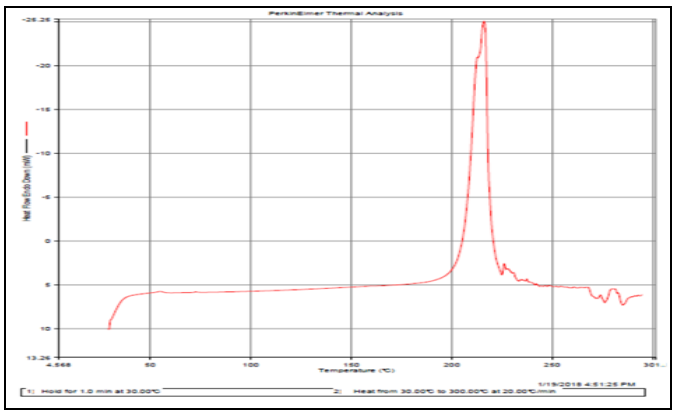

FIG. 4: DIFFERENTIAL SCANNING CALORIMETRY OF PROCHLORPERAZINE

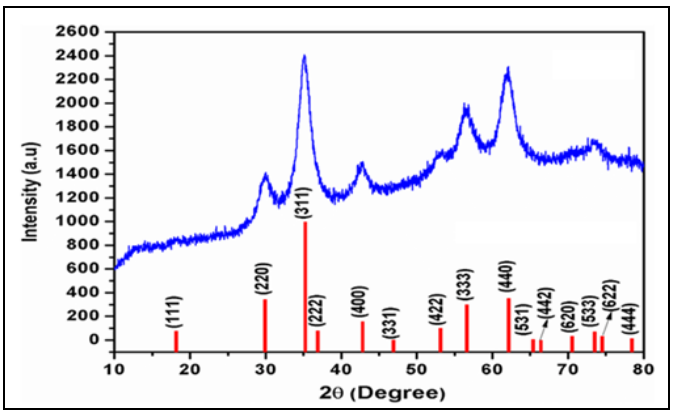

FIG. 5: PARTICLE X-RAY DIFFRACTION OF PROCHLORPERAZINE

Drug-Excipient Compatibility Study:

Physical Examination: The initial color of drug excipient mixtures observed as yellow color powder and white line as shown in FTIR graphs. Off white for HPMC and slightly yellowish for PEG-400. All other excipients along with Prochlorperazine showed yellow to off white color. No characteristic changes were observed in color or physical state for all samples at 15, and 30 days.

The Infrared Spectrum: Showed all the prominent peaks of Prochlorperazine. The IR spectrum of pure Prochlorperazine shows an absorption band observed in the peaks. These peaks were considered characteristic peaks of pro-chlorperazine.

No significant deviations were found between the peaks of prochlorperazine and those of a mixture of drugs and excipients that indicates the stability of the drug in the presence of all the excipients. **Fig. 6A** and **6B** shows the FTIR of a combination of Prochlorperazine with HPMC and PEG respectively.

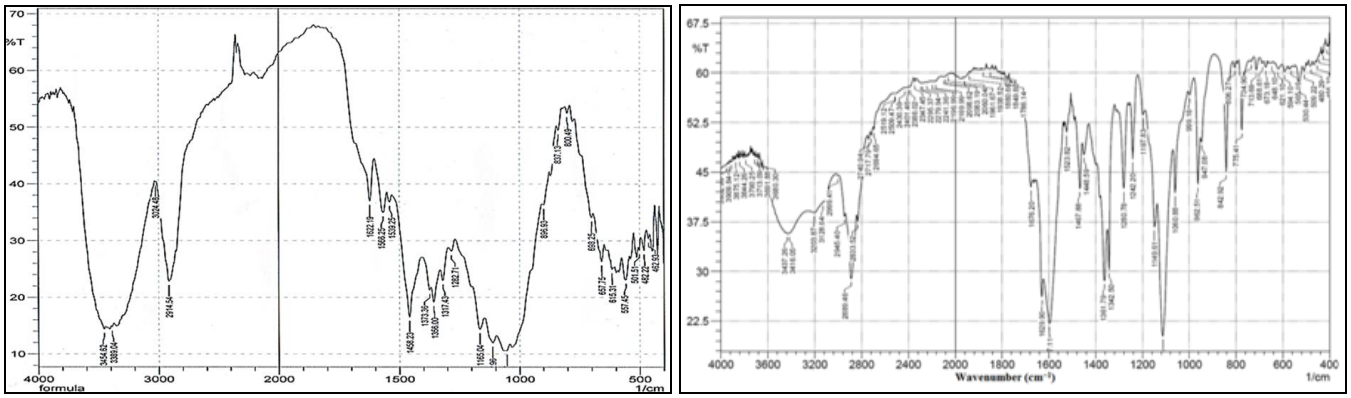

FIG. 6AB: FTIR OF COMBINATION OF PROCHLORPERAZINE AND HPMC

Characterization of Prepared Transdermal Patches: Characterization of prepared patches was done given below are the various parameters which were evaluated for prepared patches.

Thickness: The prepared patches showed uniform thickness. The results indicate that there was no much difference in the thickness of different patches.

The thickness of transdermal patches was calculated using design expert software. The results are shown below in **Fig. 7A** and **7B**.

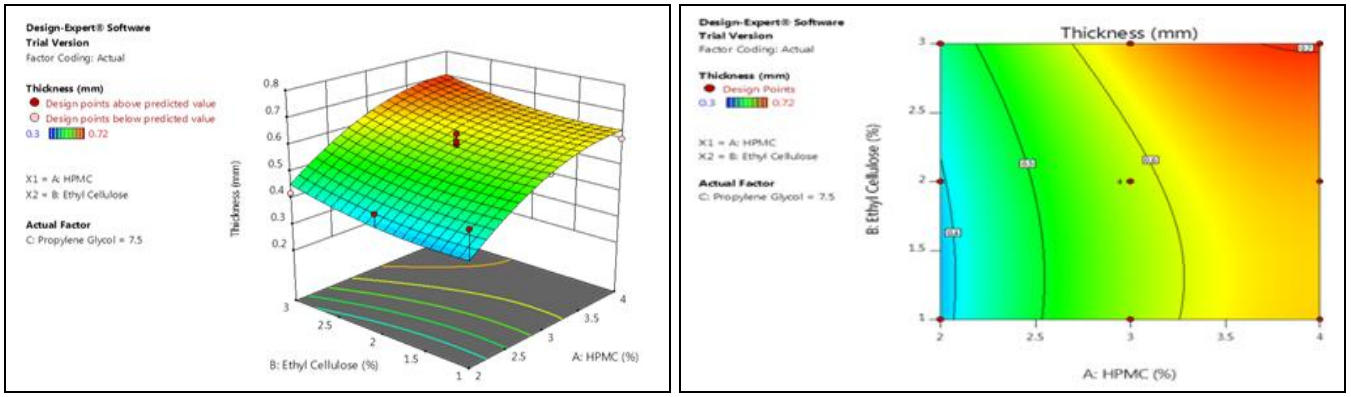

FIG. 7 AB: THICKNESS OF TRANSDERMAL PATCH BY DESIGN EXPERT SOFTWARE

Tensile Strength: The prepared patches were subjected for evaluation to check the tensile strength.

Tensile strength of patch was found to be 6 the formulated patches are having good tensile strength which indicates the patch is having the ability to withstand the pressure in the entire shelf life of it.

Drug Content: The amount of drug present in the formulation was checked by % drug content study in the formulation and the result was found to be

96.52%. These results indicated that the patches were having good content uniformity which is desirable for uniform dosing from the formulation.

Weight Uniformity: The characterization of patches revealed that there were no significant variations in the weights of formulated patches. The formulated patches were having weight uniformity as most of the patches were within the permissible limits as per pharmacopeia standards.

TABLE 4: WEIGHT VARIATION TEST OF PREPARED PATCHES

S. no.	Average Weight of Patch in mg			
	Batch 1	Batch 2	Batch 3	Mean ± S. D.*
1	40	40.2	40.4	40.20 ± 0.200
2	47.0	47.0	47.2	47.06 ± 0.115
3	44.6	44.5	44.4	44.06 ± 0.100
4	51.5	52.0	53.0	52.16 ± 0.763
5	54.0	55.0	54.0	54.33 ±0.577

Standard deviation, n=3

Folding Endurance: The formulated patch was subjected to folding endurance study the results indicated that the folding endurance of the patch was found to be 6 and hence the patches pass this test.

Moisture Content & Moisture Uptake: The moisture content was determined by keeping the drug matrices patches in a desiccator containing activated silica for 24 h. The percentage of moisture content was calculated from the weight differences relative to the final weight. The moisture content and moisture uptake were 3.96 and 2.49 respectively which were well within the permissible limits. Hence, results indicated that the patches pass this test.

***In-vitro* Release (Dissolution) Studies:** The *in-vitro* drug release studies carried out to determine the release of the drug. The cumulative release of the drug (mg/cm^2) and cumulative percentage release of all patches over 24 h.

The diffusion study indicated our formulation was having ideal permeability which is required from the formulation. The results are summarized in **Table 5** and **Fig. 8**.

***In-vitro* Permeation Study:** The *in-vitro* drug release studies carried out to determine the release of the drug. The cumulative release of the drug (mg/cm^2) and cumulative percentage release of all patches over.

In-vitro permeability studies showed the drug prochlorperazine is having good permeation. The % drug release of pro-chlorperazine is shown below in **Table 6** and **Fig. 9.**

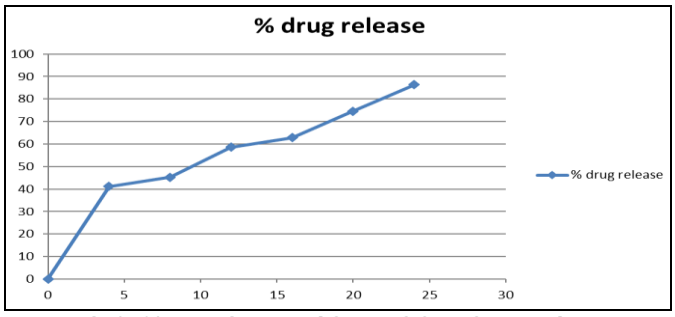

FIG. 8: % DRUG RELEASE PROCHLORPERAZINE TRANSDERMAL PATCH

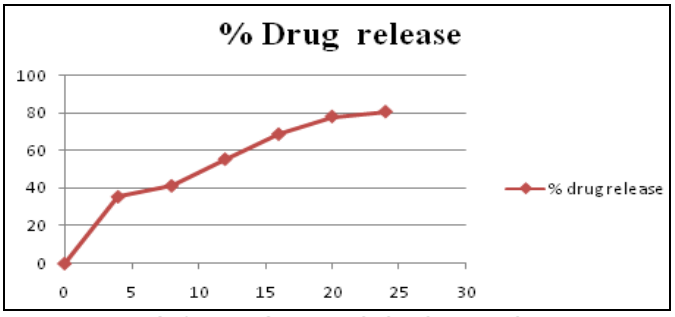

FIG. 9: DRUG DIFFUSION STUDY OF PROCHLORPERAZINE TRANSDERMAL PATCH

TABLE 5: *IN-VITRO* RELEASE OF PROCHLORPERAZINE PATCHES

Time in h	% Drug Release
4	41.08
8	45.25
12	58.53
16	62.86
20	74.60
24	86.33

TABLE 6: DIFFUSION STUDY OF PROCHLO-RPERAZINE TRANSDERMAL PATCH

Time in h	% Drug Release
4	35.47
8	41.27
12	55.40
16	68.67
20	78.03
24	80.61

***In-vivo* Animal Study:** The results of the antiemetic effect of prepared transdermal patches of prochlorperazine are shown in **Table 7** and **Fig. 10**. In a negative control group average of 168.25 retches is taken as 100 %.

Positive control (metoclopramide) showed 4.31% inhibition of retches. The test patch of Prochlorperazine showed 47.40% Inhibition of retches. The result indicates the good anti-emetic activity of test drug prochlorperazine in copper sulfate-induced emesis in the chick model.

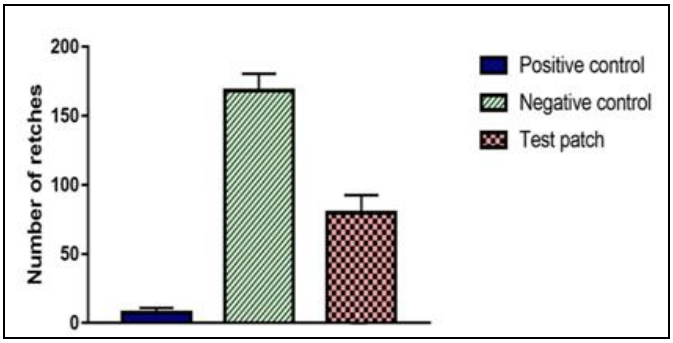

FIG. 10: DATA REPRESENTS % INHIBITION OF RETCHING WITH TREATMENT GROUPS. Error bar represents SD n=4, ** p<0.005.

TABLE 7: RETCHING'S DATA

Groups	1	2	3	4	Average	%Inhibition	STDEV
Positive control	5	4	8	12	7.25	4.31	3.59
Negative control	154	182	174	163	168.25	100.00	12.28
Test patch	75	88	64	92	79.75	47.40	12.76

Retching's Data:

Accelerated Stability Studies Study of Formulated Patches: Further, stability studies were performed as per ICH guidelines by keeping the patches at 25 ± 0.5 °C 60 ± 5% RH and 40 ± 0.5 °C 75 ± 5% RH for 3 months. The samples were taken back at a different time (0, 30, 60, and 90 days) and investigate the medication content.

No significant drug content loss, changes in organoleptic properties, physical appearance and drug diffusion were evaluated were detected over the period of time. The study revealed the patches were stable over the shelf life of the formulation. Stability study Reports of prochlorperazine patches are shown in **Table 8**.

TABLE 8: STABILITY STUDY REPORTS OF PROCHLORPERAZINE PATCHES

Test	Initial	Condition	Time Period		
			1 M	2 M	3 M
Description	_	25±0.5°C 60±5% RH	No change	No change	No change
		40±0.5°C 75±5% RH	No change	No change	No change
% Drug content	99.01± 0.95	25±0.5°C 60±5% RH	98.93± 0.87	98.64± 0.74	97.65± 0.78
		40±0.5°C 75±5% RH	98.71± 0.95	98.04± 0.76	97.04± 0.97
Assay (%)	93.48±1.35	25±0.5°C 60±5% RH	94.42±1.18	94.02±1.05	93.76±1.22
		40±0.5°C 75±5% RH	93.48±1.35	93.48±1.35	93.48±1.35
% drug release in Diffusion study (24 h)	96.52%.±1.65	25±0.5°C 60±5% RH	95.78±1.59	95.34±1.43	95.09±1.14
		40±0.5°C 75±5% RH	94.24±1.65	93.24±1.76	92.24±1.34

CONCLUSION: TDDS is a very useful innovation in the delivery of drugs, particularly in case patients who find it difficult to swallow their medications.

Topical delivery of drugs offers numerous advantages compared to oral and parenteral of drug delivery, such as avoidance of pre-systemic metabolism because of the first-pass effect, steady plasma level of the drug.

From the results, it is clear that the prochlorperazine patches are a good alternative to conventional therapy for the treatment of CINV. The formulated patches showed all the desirable properties for the effective management of CINV. However, further clinical research needs to be carried out to evaluate the clinical safety and effectiveness of the formulation.

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