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Research Article

FORMULATION AND EVALUATION OF TRANSDERMAL PATCH OF PROCHLORPERAZINE MALEATE FOR *HYPEREMESIS GRAVIDARUM*

Ganju Eisha*, Ganju Kuldeep and Pathak A.K

Department of Pharmacy, Barkatullah University, Bhopal, Madhya Pradesh, India.

***Corresponding Author: eisha_shukla@yahoo.com**

ABSTRACT

Hyperemesis gravidarum induced nausea and vomiting occurs both acutely and over a prolonged period of time during pregnancy. Prochlorperazine maleate is the drug of choice for the treatment with long dosage regimen of 5-10 mg, 3-4 times daily, orally.Transdermal drug delivery systems of of varying concentration of the polymer containing 2.5mg drug were prepared and analysed. It was found that the film made of 0.05% PVA was found to be the most effective due to the physicochemical studies as performed and irritation tests. The formulated film is expected to give the maximum patient compliance, avoiding first pass hepatic metabolism.

INTRODUCTION

Transdermal drug delivery involves the administration of an active agent through the skin for either local or systemic distribution to affected tissue. Transdermal application of active agents avoids first pass metabolism and can alleviate some of the problems associated with oral delivery of an active agent to the gastrointestinal (GI) tract. Orally administered non-steroidal anti-inflammatory drugs, for instance, can cause significant adverse gastro-intestinal (GI) side effects. By avoiding or reducing delivery of an active to the GI tract, a topical dosage form can reduce the incidence of adverse GI events. A topical dosage form also offers a simple means of administration.

MATERIAL AND METHODS

The solvent-casting technique[1] was used to formulate the PVA patches containing different concentrations of PVA polymer, poly ethylene glycol (PEG 400) as plasticizer, and prochlorperazine maleate. The drug polymer (5 mg/ml) solution was transferred into a glass petridish. The petridish was then kept in an air circulation drier and maintained at a temperature of 45-50^{o}C for 6 hours. A backing film (aluminium foil) and a release liner (wax paper) on either side of the film were applied to complete the TDDS. This served as a matrix-type transdermal delivery system.

CHARACTERIZATION OF TDDS

1. Solubility Measurement

The solubility of prochlorperazine maleate was determined according to the method adopted by Krishnaiah[2].An excess amount of drug was taken and dissolved in a measured volume of distilled water in a glass vial to get a saturated solution. The solution was kept at room temperature for the attainment of equilibrium. The concentration of prochlorperazine maleate in the filtrate was determined spectrophotometrically by measuring at 258 nm after 24 hours.

2. Partition Coefficient (Kp)
The partition coefficient of the drug was determined by shaking equal volumes of oil and the aqueous phase in a separating funnel[3]. A drug solution of 1 mg/ml was prepared in distilled water and 50 ml of this solution was taken in a separating funnel and shaken with an equal volume of octanol for 10 minutes and allowed to stand for 24 hours with intermittent shaking. Then, the aqueous phase was assayed before and after partitioning using a UV spectrophotometer to get the partition coefficient values.

3. Spectrophotometric UV/VIS Analysis
Prochlorperazine maleate was determined using a Jasco UV spectrophotometer at 258 nm. A correlation coefficient of 0.9933 was obtained with a slope value of 0.0474.

4. Physical appearance
All the transdermal patches were visually inspected for color, clarity, flexibility, and smoothness.

5. Folding endurance
A strip of film (2× 2 cm) was cut evenly and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of the folding endurance[4,5].

6. Thickness of the films
The average and standard deviation of five readings were calculated for each batch of the drug-loaded films.

7. Weight uniformity
The films of different batches were dried at 60°C for 4 hours before testing. Five patches from each batch were accurately weighed in a digital balance[5]. The average weight and the standard deviation values were calculated from the individual weights.

8. Percentage moisture uptake
The weighed films were kept in a desiccator at room temperature for 24 hours and then exposed to 84% relative humidity using a saturated solution of potassium chloride[6]. Finally, the films were weighed and the percent moisture uptake was calculated using the formula:

Percentage moisture uptake = [Final weight - Initial weight/Initial weight] × 100

9. Percentage moisture content
The prepared films were weighed individually and kept in a desiccator containing fused calcium chloride at room temperature for 24 hours[6]. The films were again weighed and the percentage moisture content was calculated using the formula:
Percentage moisture content = [Initial weight - Final weight/Final weight] × 100

10. Water vapor transmission
The film was fixed over the glass vial with an adhesive containing 3 g of fused calcium chloride as a desiccant[4]. Then, the vial was placed in a desiccator containing saturated solution of potassium chloride (relative humidity 84%). The vial was taken out periodically and weighed.

11. Skin irritation test
Skin irritation test was performed on seven healthy albino rabbits weighing between 2.0 and 3.5 kg.[8,4,7] Aqueous solution of formalin 0.8% was used as the standard irritant. Drug-free polymeric patches of 4.874 cm^2 were used as test patches. Standard irritant was applied on the left dorsal surface of each rabbit and drug-free patches were applied on the right dorsal surface of the rabbit. The patches were removed after a period of 24 hours with the help of an alcohol swab. The skin was examined for erythema/edema.

12. Drug content
Transdermal system of specified area (2.9865 cm^2) was cut into small pieces and taken into a 50 ml volumetric flask and 25 ml of phosphate buffer pH 7.4 was added,[9] gently heated to 45°C for 15 minutes, and kept for 24 hours with occasional shaking. Then, the volume was made up to 50 ml with phosphate buffer of pH 7.4. Similarly, a blank was carried out using a drug-free patch. The solutions were filtered and the absorbance was measured at 258 nm.

13. *In vitro* drug releasestudies
A Paddle over disc assembly (USP 23, Apparatus 2) was used for the assessment of release of drug[8]. The TDDS patch was mounted on the disc and placed at the bottom of the dissolution vessel. The

dissolution medium was 900 ml phosphate buffer of pH 7.4. The apparatus was equilibrated to 37 ± 0.5°C and operated at 50 rpm. The samples (5 ml aliquots) were withdrawn at appropriate time intervals up to 8 hours and analyzed on a UV spectrophotometer at 258 nm.

14. *In vitro* skin permeation studies

Preparation of the skin barrier: Fresh full-thickness (75-80 mcm) goat skin was used for the study. The skin was immersed in water at 60°C for a period of 5 minutes. The epidermis was peeled from the dermis. The isolated epidermis (25 ± 5 mcm thick) was rapidly rinsed with hexane to remove surface lipids and then rinsed with water and used immediately.The *in vitro* skin permeation[10,11,12] from the prepared polymeric patches across the goat skin barrier was studied using diffusion cell. Fifty-four milliliters of phosphate buffer of pH 7.4 was used as an elution medium. The patches to be studied were placed in between the donor and the receptor compartment in such a way that the drug releasing surface faced toward the receptor compartment.

The elution medium was magnetically stirred for uniform drug distribution at a speed of 60 rpm. The temperature of the whole assembly was maintained at 37 ± 1°C by thermostatic arrangements. An aliquot of 1 ml was withdrawn at a suitable interval and an equivalent volume of fresh buffer was replaced. The amount of drug permeated across the skin was determined on a UV spectrophotometer at 258 nm. The cumulative amount of drug permeated per cm^2 of skin values are tabulated in [Table1].

Table 1: *In vitro* skin permeation

Parameter	0.05%PVA	0.5%PVA	5%PVA
Cumulative Percentage Drug Release	20.2	13.6	11.0

Table 2: Characterization of Transdermal patches of various polymer concentrations

S.No.	Parameter	0.05%PVA	0.5%PVA	5%PVA
1	Folding endurance	16.2±0.75	14.3±0.55	12.7±1.08
2	Thickness(mm)	0.024±0.002	0.046±0.003	0.051±0.004
3	Weight uniformity (g)	0.320±0.018	0.351±0.024	0.427±0.02
4	Moisture uptake(%)	1.35±0.01	2.65±0.03	3.80±0.07
5	Moisture content(%)	0.98±0.031	1.65±0.024	1.72±0.021
6	Water vapour transmission	0.025±0.008	0.068±0.006	0.098±0.005
7	Tensile strength (N)	2.23±0.032	1.65±0.062	1.24±0.040
8	Drug content	2.5±0.002	2.48±0.0021	2.51±0.003
9	Dissolution profile	93.2±1.54	89.5±1.98	84.0±1.95

All values are expressed as Mean±SD

RESULTS AND DISCUSSION

Matrix-type transdermal patches of prochlorperazine maleate were prepared using three different concentrations of PVA (0.05%,0.5%&5%) to get the desired drug release profile. The prepared patches were characterized for their folding endurance, thickness of the film, weight uniformity, drug content, percentage moisture uptake, percentage moisture content, water vapor transmission, and skin irritation test and their values are shown in [Table 2].

Partition coefficient of prochlorperazine maleate in the octanol/water system was found to be 0.05312.

All the polymers used for the fabrication of the transdermal system showed good film forming properties. 0.05% PVA films were found to be most elegant, thin, flexible, smooth, and transparent. All the patches showed satisfactory folding endurance properties, but it was most pronounced in 0.05% PVA film. The 0.05% PVA film was found to be of least thickness as compared to all.

The drug content was nearly the same as the dose of the drug in all the patches. The results of moisture content have indicated that all transdermal systems have a specific amount of moisture content in them. All the formulations were permeable to water vapor.The water vapour transmission and dissolution profiles of the 0.05%PVA patch were found to be most encouraging.

All the formulations were selected for stability studies and observed for changes in color, appe0arance, flexibility, and drug content. The mean (*n* = 3) cumulative amounts of drug released (*in vitro* dissolution) and permeated (*in vitro* skin permeation) from different concentrations of PVA after 8 hours were analyzed and their values are shown in Table 1&2. Studies revealed that 0.05% PVA film gave the maximum release.

CONCLUSION

Prochlorperazine maleate is an antiemetic specifically used in hyperemesis gravidarum with long dosage regimen and first pass hepatic metabolism.Among the three different PVA formulations,transdermal patch with 0.05% showed maximum release and offered least resistance to the movement of the drug molecule due to its high hydrophilic nature and high water vapour transmission.

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