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Fabrication of Transdermal Patches

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ABSTRACT

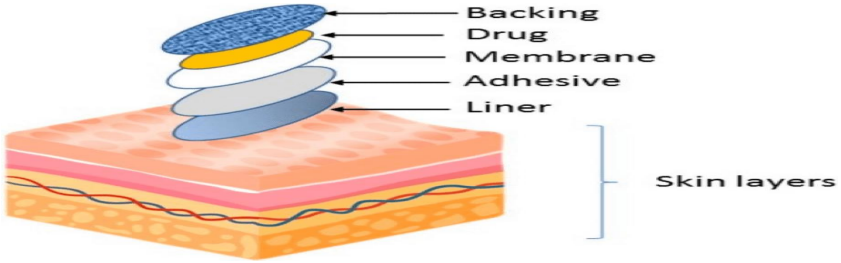
Transdermal delivery leads to over-injectable and oral routes by increasing patient compliance and avoiding the first-pass metabolism, respectively. The aim of this study is to fabricate & evaluate the transdermal patches of proton pump inhibitor (PPI) for treatment of peptic ulcer. Pantoprazole is extensively metabolized in the liver, and to overcome these problems the current study was aimed to formulate a transdermal drug delivery system for it. In this study different polymers (HPMCE5 with PVPK30 and HPMCE5 with EudragitL100) used in different ratios. Solvent evaporation method were used to fabricate the transdermal patches. Patches were assessed for their thickness, folding endurance, weight uniformity, content uniformity, swelling index, percentage moisture content, moisture uptake, surface pH. Fabrication of TDDS patches was performed at laboratory of Sardar Patel University, Balaghat (Department of Pharmacy). Fabricated patches complies all the QC paramenter's like integrity, flexibility, dispersion of drug. In this study 6 formulation batch were prepared in which F1 showed the prolonged release of drug (98.99 %) for 24 h, which indicates the maximum availability of the drug. This study shows the transdermal application of Pantoprazole sodium follow controlled release of the drug for an extended period of time.

Keywords: Peptic ulcer; Proton pump inhibitor (PPI); Pantoprazole sodium

SIGNIFICANCE OF TDDS

Definition of peptic ulcer/ TDDS, meachnism of PPI, Diagram

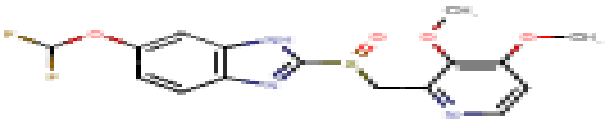
Transdermal patches are devised to treat various diseases[15]. They can even prevent drug-related gastrointestinal problems and low absorption [16].



The market share for transdermal delivery is increasing every year due ti its requirement in various diseases like hypertension, angina pectoris, motionsickness, female menopause, and male hypogonadism [8].

Pantoprazole is a proton pump inhibitor used to treat erosive esophagitis, gastric acid hypersecretion,

and to promote healing of tissue damage caused by gastric acid. Pantoprazole is a first-generation proton pump inhibitor (PPI) used for the management of gastroesophageal reflux disease (GERD), for gastric protection to prevent recurrence of stomach ulcers or gastric damage from chronic use of NSAIDs, and for the treatment of pathological hypersecretory conditions including Zollinger-Ellison (ZE) Syndrome



Chemical formula: $C_{16}H_{15}F_2N_3O_4S$

Pantoprazole exerts its stomach acid-suppressing effects by preventing the final step in gastric acid production by covalently binding to sulfhydryl groups of cysteines found on the (H+, K+)-ATPase enzyme at the secretory surface of gastric parietal cell. This effect leads to inhibition of both basal and stimulated gastric acid secretion, irrespective of the stimulus. As the binding of pantoprazole to the (H+, K+)-ATPase enzyme is irreversible and new enzyme needs to be expressed in order to resume acid secretion, pantoprazole's duration of antisecretory effect persists longer than 24 hours.

MATERIALS & METHODS

(A)Materials & their manufacturer

Material	Manufacture
Pantoprazole	Dr. Reddy's Lab, Hyderabad.
Eudragit L100	Rohm Pharma, Germany
PVA	Thomas Baker (Chemicals) Pvt. Ltd,Mumbai
Potassium dihydrogen phosphate	
Sodium hydroxide	
HPMCE5	Loba Chemie Pvt. Ltd, Mumbai
PVP	Research-Lab Fine Chem Industries, Mumbai
Ethanol & Methanol	
Chloroform	
N-Dibutyl phthalate	
Propylene Glycol	
1% DMSO	

(B) Instrument, Apparatus, Equipment used

Tensiometer
Digital micrometer screw gauge
Sonicator
Shimadzu UV 1800 double-beam
Desiccator
Analytical balance
Agar gel (2%) plate
Petri dish

Filter paper
Hot plate magnetic stirrer
Magnetic beads

Preparation of backing membrane

The backing membrane was prepared with an aqueous solution of 4%w/v polyvinyl alcohol (PVA). 4 gm of PVA was added to 100 ml of warm, distilled water and a homogenous solution was made by constant stirring and intermittent heating at 60°C for a few sec. Then 15 ml of the homogenous solution was poured into glass Petri dishes of 63.5 cm^2 and was allowed to dry in a hot air oven at 60°C for 6 h [10, 11].

Preparation of placebo films

The different placebo films were prepared using various combinations of hydrophilic and hydrophobic polymers by the hit and trial method [12]. Those polymeric combinations that exhibited smooth and flexible films were selected for preparing the drug incorporated matrix systems. All the films were prepared by the Solvent Evaporation technique. The matrix-type transdermal patches containing Pantoprazole Sodium were prepared using different ratios of Hydroxy Propyl Methyl Cellulose (HPMC E5) with Polyvinyl pyrrolidone (PVP), Ethyl cellulose, Eudragit L 100, and Eudragit S100.

Formulation of transdermal patches

Transdermal films containing Pantoprazole sodium were cast on a petridish by a solvent evaporation method using different polymers (HPMC E5:PVP K30 and HPMC E5: Eudragit L 100) [13]. Three different concentrations (200,300 & 400mg) of HPMC E5 were used in all six formulation and another two polymers PVPK30 (used in F1,F2 & F3) and Eudragit L100 (F4,F5 & F6) were used in every three formulations at varying concentrations (200,300 & 400mg shown in table 1).

Drug-Polymer Ratio

Drug to Polymer	1:1
Polymer to Polymer	1:1
	1:2
	2:1
Solvent to Solvent	1:1

Table1: Formulation details of pantoprazole sodium transdermal films

Ingredients	Formulations (All quantities are in mg/ml)					
	F1	F2	F3	F4	F5	F6
PantoprazoleSodium(mg)	635	635	635	635	635	635
HPMC(E5)(mg)	300	200	400	300	200	400
PVPK30(mg)	300	400	200	-	-	-
EudragitL100 (mg)	-	-	-	300	400	200
Ethanol(ml)	10	10	10	10	10	10
Chloroform:Methanol(1:1)(ml)	-	-	-	6	6	6

n-Dibutyl Phthalate(ml)	8.5	8.5	8.5	8.5	8.5	8.5
Propylene *.369glycol(ml)	0.5	0.5	0.5	0.5	0.5	0.5
DMSO(ml)	0.1	0.1	0.1	0.1	0.1	0.1

The polymers were accurately weighed and dissolved in 10ml of ethanol and in the case of Eudragit L100 the chloroform: methanol(1:1) solution was also used and kept a side to form a clear solution. Drug pantoprazole sodium was dissolved in the above solution and mixed until the formation of clear solution. Then the plasticizer and the permeation enhancers were added to the formulation step by step and mixed uniformly. The resulted uniform solution was cast on the petridish , which was lubricated with glycerin and dried at room temperature for 24h. An inverted funnel was placed over the petridish to prevent fast evaporation of the solvent. After 24 h, the dried patches were taken out and stored in a desiccators for further studies [15].

Assessment of transdermal patches

Folding endurance
Tensile strength
Percentage elongation break test
Thickness
Drug content
Percentage moisture content
Percentage moisture uptake
Swelling study

- **Folding endurance**

A Particular area of the strip (2x2 cm) was cut uniformly and folded over and over until it broke. The value of the folding endurance was determined by the number of times the film was folded at the same location either to break the film or to develop visible cracks [16,17].

- **Tensile strength**

The patch's tensile strength was determined using a tensiometer (Erection and instrumentation, Ahmedabad). It is made up of two grips for load cells. The lower one was fixed, while the upper one could be moved. Film strips measuring 2x2 cm were placed between the cell grips, and force was applied progressively until the film broke. The tensile strength was calculated using the dial reading in kilograms [15].

- **Percentage elongation break test**

The percentage elongation break was calculated by noting the length just before the breaking point and the following formula was used to calculate the percentage elongation [18,19].

$$\text{Percentage Elongation} = \frac{\text{Final length of strip} - \text{Intial length of strip}}{\text{Intial length of strip}} \text{x100}$$

- **Thickness**

The thickness of the transdermal patches was measured using a digital micrometer screw gauge at three different places, and the mean value along with SD was calculated [16,20].

- **Drug content**

A 2x2 cm size transdermal patch was dissolved in 100 ml methanol and shaken continuously for 24 h. The

whole solution was then ultra sonicated for 15 min. After filtration, the drug's content was measured using spectrophotometry at a wavelength of 292 nm [21].

- **Percentage moisture content**

The prepared transdermal films were individually weighed and stored in a desiccator containing fused calcium chloride at room temperature for 24 h. After 24 h, the films were reweighed and the percentage moisture content was determined from the following formula [16].

$$\text{Percentage Moisture Content} = \frac{\text{Inital weight} - \text{Final weight}}{\text{Final weight}} \text{x100}$$

- **Percentage moisture uptake**

The prepared transdermal films were individually weighed and stored in a desiccator containing a fused saturated solution of potassium chloride to maintain 84% RH for 24 h at room temperature. After 24 h, the films were reweighed and the percentage moisture uptake was calculated using the following formula [16].

$$\text{Percentage Moisture Uptake} = \frac{\text{Final weight} - \text{Inital weight}}{\text{Inital weight}} \text{x100}$$

- **Swelling study**

The formulated transdermal patches were weighed (W1) individually and incubated at 37±0.5 ° C separately in agar gel (2%) plate. The patches were removed from the petri dish at regular time intervals of every 15 min up to 1 h and the excess water on the surface was removed carefully with filter paper. The swollen patches were reweighed (W2) and the swelling index was calculated by using the formula [22,23].

$$\text{Swelling index} = \frac{W2 - W1}{W1} \text{ x } 100$$

In vitro drug release studies

A Franz diffusion cell with a receptor compartment capacity of 60 ml was used for the in vitro drug release tests [24]. The drug was determined using a cellulose acetate membrane from the prepared transdermal matrix-type patches. The diffusion cell's donor and receptor compartments were separated by a 0.45 µ pore size cellulose acetate membrane. The prepared transdermal patch was and mounted on the cellulose acetate membrane, which was then sealed with aluminum foil. The diffusion cell's receptor compartment was filled with phosphate buffer pH 7.4.

The entire assembly was mounted on a hot plate magnetic stirrer, and the solution was constantly and continuously stirred at 50 rpm during the experiments using magnetic beads, as described by Simon et al. [25] in the receptor compartment, while the temperature was maintained at 37±0.5 °C, which corresponds to normal human body temperature. The samples were taken at various intervals and spectrophotometrically analyzed for drug content. During the experiment, the manual sampling requires constant careful attention since air bubbles are easily entered in the receiver compartment when the samples are taken. At each sample removal, the receptor step was replenished with an equal volume of phosphate buffer.

RESULTS AND DISCUSSION

In the placebo batches, various combinations and concentrations of both hydrophilic and hydrophobic polymers were used. But based on the formation of smooth, transparent, uniform, and flexible film, the HPMC E5:PVP K 30and HPMC E5:Eudragit L 100 were selected for the further formulations with 1:1, 1: 2, and 2:1. Transdermal patches of Pantoprazole sodium were prepared by solvent evaporation method to achieve a controlled release and improved bioavailability of the therapeutic drug.

All the drug-loaded transdermal patches were found to be quite uniform in thickness. All the transdermal patches showed a thickness variation range from 0.322±0.008 to 0.484±0.012 mm as shown in table 2. The high thickness of batch was found in F5 and low thickness was in formulation F1. From these values, it was observed that the thickness of the polymer depends on the solubility and concentration of the polymer. As the solubility decreases and concentration increases would increase the thickness of the patch [5]. It infers that usage of the competent polymer is the prerequisite step to prepare a patch of optimum thickness, which can retard the release of the drug from the patch. All the transdermal batches vary in the weight of 84.3±2.36 to 93.3±2 mg, but the content uniformity in all these batches was found to be 98.86±4.08 % to 101.67±4.78 % of Pantoprazole sodium. Low SD values in the film ensure uniformity of the patches prepared by solvent evaporation technique. The drug content of all the formulations indicated that the process employed to prepare patches in this study was capable of producing patches with uniform drug content and minimal patch variability. All the results showed that the patches were uniform, as was evidenced by the SD value. The batches were evaluated for folding endurance. It varies from 141.6±15.39 to 179±9.48. The folding endurance was found to be>140 revealed that the prepared patches were having the capability to withstand the mechanical pressure along with good flexibility. The formulations prepared with Eudragit L100 were found to have the highest value of folding endurance when compared with the formulations made of PVP and also the concentrations of polymers play a vital role in the folding endurance.

Table 2: Physicochemical evaluation of transdermal patches of pantoprazole sodium

Formulation	Thickness (mm)	Folding endurance	Content uniformity (%)	Weight (mg)
F1	0.322±0.008	175.5±11.65	99.96±4.30	84.3±2.36
F2	0.360±0.022	157.2±16.69	99.49±3.95	87.8±3.12
F3	0.464±0.011	141.6±15.39	101.67±4.78	85.3±2.06
F4	0.442±0.007	179.0±9.48	99.98±4.38	90.2±3.77
F5	0.484±0.012	160.8±15.08	98.86±4.08	92.3±2.06
F6	0.479±0.015	162.2±14.94	100.67±2.61	93.3±2.00

(All values are mean±SD; Thickness n=3; Folding Endurance, Content uniformity and weight n=10) The percent flatness of the transdermal patches was ideal (table 3). The percentage of flatness was found to be 96.67±2.89 to 99.67±0.58%. All films showed an increase in moisture uptake of from 7.67±3.05 to 11.32±6.5 %. The increase in moisture uptake may be attributed to the hygroscopic nature of the polymer. All the films were showed increased weight with time. The surface pH of the formulated patches was tested and found to be uniform between 5.1 to 5.2. The % elongation was found to be 38.33±2.89 to 80.83±2.89 for the formulations F1 to F6 respectively and the formulation F6 showed the highest percent elongation

Table 3: Evaluation of transdermal patches

Formulation	Surface pH	% Flatness	% Elongation	Moisture content (%)	Moisture uptake (%)
F1	5.13±0.06	97.67±2.08	38.33±2.89	7.58±0.66	8.2±0.76
F2	5.17±0.06	97.33±2.31	53.33±1.44	7.61±1.09	8.25±1.27
F3	5.23±0.06	97.67±2.52	58.33±1.44	7.78±1.11	8.44±1.31
F4	5.27±0.06	98.67±1.15	61.67±1.44	9.97±5.08	11.32±6.5

F5	5.2±0.1	96.67±2.89	66.67±1.44	7.41±1.54	8.02±1.81
F6	5.23±0.06	99.67±0.58	80.83±2.89	7.07±2.67	7.67±3.05

(All values are mean±SD; n=3)

The swelling index studies were performed on the transdermal films and the results were shown in table 4. The swelling studies showed an increase in the swelling index of the transdermal films with an increase in time and also it varies based on the polymers and the concentration of polymers [37].

Table 4: Swelling studies of transdermal patches of pantoprazole sodium

Swelling index				
Formulation	15 min	30 min	45 min	60 min
F1	60.05±4.68	67.63±2.11	71.06±3.3	76.58±2.4
F2	48.59±3.79	56.5±3.68	60.62±1.6	66.02±3.08
F3	61.67±3.43	64.34±3.26	67.58±2.35	72.72±2.19
F4	61.76±2.84	64.7±2.44	68.85±1.68	74.88±2.52
F5	50.57±5.37	56.37±1.85	59.85±0.37	66.03±1.94
F6	49.28±7.76	66.63±1.86	70.35±2.37	75.96±3.4

CONCLUSION

The prepared transdermal drug delivery system of Pantoprazole sodium using different polymers HPMC E5, PVP K30, and Eudragit L100 had shown good promising results for all the evaluated parameters. Based on the results of various evaluation parameters such as minimum film thickness, film weight and % elongation, higher folding endurance, it was concluded that HPMC E5: PVP K30 and HPMC E5: Eudragit L 100 in the ratio of 1:1 may useful for the preparation of sustained-release matrix transdermal patch formulation. This study will be continue for evaluation of drug permeation & release of drug from transdermal patches .

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