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In Vitro Skin Permeability Studies Of Transdermal Patches

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ABSTRACT

This article is prepared to continue the Transdermal patches of pantoprazole studies which was covered in our earlier article published in International Journal for Multidisciplinary Research (IJFMR), Volume 6, Issue 6, November-December 2024, IJFMR240631777. The aim of this study is to evaluate the in vitro drug release characteristics of the transdermal patches of proton pump inhibitor (PPI). An in vitro permeation study was carried out by using Franz diffusion cell using full-thickness abdominal skin of male Wistar rat weighing 200 to 250 g [26]. Pantoprazole is extensively metabolized in the liver, and to overcome these problems the current study was aimed as In-Vitro skin permeability studies of Transdermal patches. In this study different polymers (HPMCE5 with PVPK30 and HPMCE5 with EudragitL100) used in different ratios. Solvent evaporation methods were used to fabricate the transdermal patches [1]. Patches were assessed for In vitro permeation study. The in vitro drug release characteristics of the formulated transdermal patches were studied by using a cellulose acetate membrane. The *in vitro* skin permeability studies showed that 96.26 % of drug Pantoprazole sodium permeated through the rat abdominal skin in 24h. The kinetic studies were carried out and it was found that all the formulations follow zero-order and the release mechanism of drugs was found to be diffusion rate-limited, Non-Fickian mechanism which was confirmed by Korsmeyer–Peppas model.

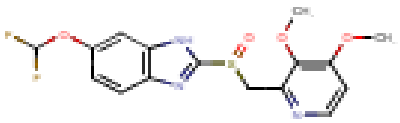
Keywords: *Peptic ulcer*; Proton pump inhibitor (PPI); Pantoprazole sodium, Invitro study

SIGNIFICANCE OF TDDS

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 to its requirement in various diseases like hypertension, angina pectoris, motionsickness, female menopause, and male hypogonadism [8].

The transdermal drug delivery system is used to maximize the skin flux into systemic circulation while reducing the retention and metabolism of the drug in the skin at the same time[3–5]. These therapeutic benefits reflect the higher marketing potential of TDDS [6]. Most of the drug molecules penetrate through the skin through the intercellular micro route and therefore the role of permeation or penetration enhancers in TDDS is vital as they reversibly reduce the barrier resistance of the stratum corneum without damaging viable cells [7].

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

Materials Used:

Pantoprazole
Eudragit L100
PVA
Potassium dihydrogen phosphate
Sodium hydroxide
HPMCE5
PVP
Ethanol & Methanol
Chloroform
N-Dibutyl phthalate
Propylene Glycol
1% DMSO

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

Table1: Formulation details of pantoprazole sodium transdermal films

Ingredients	Formulations in mg/ml)			(All quantities are		
	F1	F2	F3	F4	F5	F6
Pantoprazole Sodium(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].

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

In vitro permeation study

An in vitro permeation study was carried out by using Franz diffusion cell using full-thickness abdominal skin of male Wistar rat weighing 200 to 250 g [26]. Hair was carefully removed from the region of the abdominals with an electrical clipper; the dermal side of the skin was thoroughly cleansed with distilled water to remove any adhesion of tissues or blood vessels. It was equilibrated for an hour in Phosphate buffer saline, pH 7, before beginning the experiment. A thermostatically controlled heater maintained the cell temperature at 37±0.5 °C [27, 28]. The piece of rat skin was mounted between the diffusion cell compartments, and the epidermis faced up into the donor compartment [29]. At regular intervals, the 1 ml sample volume was removed from the receptor compartment at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24 h, and an equal volume of fresh medium was replaced.

The samples have been filtered through the Whatman filter and analyzed in Shimadzu UV 1800 double-beam sodium (Shimadzu, KYOTO/Japan) at 292 nm for pantoprazole sodium.

Drug release kinetics

The data obtained from in vitro release of drug was plotted in various kinetic models such as zero-order (cumulative amount of drug released vs time), first-order (log cumulative percentage of drug remaining vs time), and Higuchi's model (cumulative percentage of drug released vs square root of time) to know the release kinetics [30–32].

Mechanism of drug release

The mechanism of drug release of the prepared transdermal patches of Pantoprazole was calculated by using the Korsmeyer equation (log cumulative percentage of drug released vs log time), and the exponent 'n' was calculated through the slope of the straight line [33].

Statistical analysis

Each experiment was repeated at least three times. The results are expressed as mean ± SD. One-way analysis of variance was used to test the statistical significance of differences among groups. Statistical significance of the differences of the means was determined by Student's t-test.

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	8.02±1.8

				.54	1
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

The in vitro drug release characteristics of the formulated transdermal patches were studied by using a cellulose acetate membrane. The transdermal patches F1-F6 showed the % release of 98.99 % at 24 h, 97.95 % at 20 h, 99.57 % at 12 h, 99.58 % at 24 h, 99.10 % at 20 h, and 101.68 % at 10 h, respectively (fig. 1). The formulation F3 and F6 showed the release up to 10 and 12 h, and that may be due to low viscosity and also the higher concentration of HPMC E5 polymer. The formulations F2 and F5 showed the release of 97.95 % and 99.10 % of drug release at 20 h. But the formulations F1 and F4 showed the release of drug pantoprazole 98.99 % and 99.58 % at 24 h respectively. In these two formulations, the polymer to polymer ratio was maintained at 1:1 which results in a good sustained action for the 24 h period. But in the view of other factors such as the formation of smooth, transparent, uniform, and flexible film, the formulation F1 was taken for the in vitro permeation studies

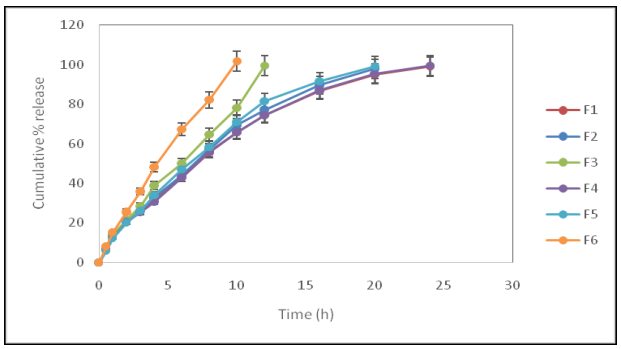


Fig. 1: In vitro release profile of pantoprazole sodium transdermal patches (mean±SD; n=3)

The formulation F1 showed a permeation of 96.26 % of the drug Pantoprazole sodium through the rat abdominal skin in 24 h. It showed that the permeation profiles of the drug Pantoprazole sodium might follow zero-order kinetics as it was evident by correlation coefficients r=0.9714, better fit than first order (r2=0.9383) and Higuchi model (r2=0.9946). The results were similar to that of the study conducted by the various authors [38-40]. According to the Korsmeyer-Peppas model, a value of slope for F1 was between 0.5 and 0.85 (0.7672) which indicates that the release mechanism was non-Fickian diffusion.

It was found that the in vitro drug release of transdermal patches of Pantoprazole sodium followed the zero-order release, as the plot showed the highest linearity (r2=0.9385, 0.9584, 0.9936, 0.9398, 0.9552, and 0.994 for the formulations, F1, F2, F3, F4, F5, and F6 respectively), which indicates the release rate-independent, and the drug release from all batches follow diffusion rate-controlled mechanism (table 5). According to the Korsmeyer-Peppas model, a value of slope for all the six formulations of transdermal patches showed between 0.5 and 0.85 which indicates that the release mechanism was non-Fickian diffusion.

Table 5: Release kinetics of transdermal patches of pantoprazole sodium

Formulations	First-order		Zero-order		Higuchi		Peppas	
	Slope	R2	Slope	R2	Slope	R2	Slope	R2
F1	0.0745	0.934	4.2436	0.9385	23.717	0.9909	0.6963	0.9929
F2	0.0755	0.9269	5.0132	0.9584	25.589	0.9917	0.7278	0.9945
F3	0.0625	0.9736	7.7296	0.9936	31.656	0.9647	0.7767	0.9956
F4	0.0845	0.8926	4.294	0.9398	24.03	0.9899	0.7078	0.9935
F5	0.0881	0.9065	5.2119	0.9552	26.749	0.9918	0.7704	0.9939
F6	0.0935	0.9775	9.9666	0.994	38.036	0.9834	0.8376	0.9992

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, and in vitro release of the drug for a period of 24 h, 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. The results of drug permeation from transdermal patches of Pantoprazole sodium through the rat abdominal skin confirmed that Pantoprazole sodium was released from the formulation and permeated through the rat skin and, hence, could permeate through the human skin.

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