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Research article

Formulation and evaluation of pantaprazole transdermal patches for enhanced therapeutic efficacy

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ABSTRACT

The present study was an attempt to develop an alternative dosage form for the existing conventional oral, parenteral PPI in the form of transdermal patches for treating peptic ulcer. Transdermal patches of PPI were prepared using HPMC with PVP and HPMC with Eudragit L100 polymers in different ratios by solvent evaporation method. Drug-excipient compatibility studies were performed using FT-IR and the spectral details indicate that the drug is compatible with the formulation components. All the formulated patches were subjected to various evaluation parameters such as thickness, folding endurance, weight uniformity, content uniformity, swelling index, percentage moisture content, moisture uptake, water vapour transmission rate and surface pH. All patches exhibited satisfactory characteristics regarding to integrity, flexibility, dispersion of drug and other quality control parameters. *In vitro* release studies of transdermal patches PAN1 shows prolonged release of drug (93.14%) which indicates the maximum availability of drug in systemic circulation in turn shows maximum bioavailability to treat the peptic ulcer. The kinetic studies are carried out and it was found that all the formulations follow first order and the release mechanism of drugs was found to be diffusion rate limited, Non-Fickian mechanism which was confirmed by Higuchi's model and Korsemeyer – Peppas model respectively. Short term stability studies were carried out for 3 months and were found to be stable. From the studies it may be concluded that PAN1 is considered as the suitable substitute for conventional and parenteral PPIs which satisfy the need of the patient, physician and pharma industry.

Key words: Peptic ulcer, Conventional and parenteral PPIs, Transdermal patch, Prolonged release.

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1. INTRODUCTION

Peptic ulcer is a major health hazard both in terms of morbidity and mortality. Peptic ulcer is a benign lesion of gastric or duodenal mucosa occurring at a site where the mucosal epithelium is exposed to acid and pepsin. Since peptic ulcer is considered as a complicated disease, various efforts have been made to find suitable remedial measures. Various medications are used for treatment of peptic ulcer like antacids, H_2 blockers and anti-microbial agents. For antacids neutralizing action is short-lived and frequent doses are required, H_2 blockers have a limited neutralising action without antibiotics and antimicrobial agents are effective only in combinations. Among these PPIs are used which are safer and most potent suppressors of gastric acid secretion and also promote healing. Pantoprazole Sodium is a proton pump inhibitor that inhibits gastric acid secretion, used in the treatment of dyspepsia, peptic ulcer disease (PUD), gastro oesophageal reflux disease (GORD/GERD). In peptic ulcer (GERD), conventional tablets of PPIs are prescribed which shows lesser availability of the drug at the site of action thus shows poor bioavailability which in turn does not provide required therapeutic efficacy. In case of post-operative surgeries, multiple therapies of injections are given like

NSAIDs and antibiotics which cause gastric irritation associated with pain. To minimize the gastric irritation caused by these medications; PPIs in the form of only parenterals are used to get maximum bioavailability by avoiding first pass hepatic metabolism.

Thus an attempt was made to formulate a transdermal therapeutic system for pantoprazole sodium which, when applied to the intact skin, deliver the drug, through the skin at a control rate to the systemic circulation and maintain drug concentration within the therapeutic window, thereby reducing the adverse effects of the drug [1].

2. MATERIALS AND METHODS

2.1. Drugs and chemicals

Pantoprazole was purchased from Dr.Reddy's Laboratories Ltd, Hyderabad. PVA, Potassium dihydrogen phosphate, sodium hydroxide are purchased from Thomas Baker (chemicals) Pvt Ltd, Mumbai. HPMC, E_5 were purchased from Loba Chemie Pvt Ltd, Mumbai. PVP, methanol, chloroform, di butyl phthalate, DMSO are purchased from Research-Lab Fine Chem Industries, Mumbai. Eudragit L100 was purchased from Rohm Pharma, Germany. Ethanol was purchased from Jiangsu Huani International trade Co. Ltd., China. All the other reagents are all of analytical reagent grade.

2.2. Preparation of standard curve

From the stock solution 1mL was withdrawn and further diluted to 10mL to obtain a concentration of 100µg/mL. From this solution appropriate aliquots were taken into different volumetric flasks and made up to 10mL with phosphate buffer pH 6.8, so as to get a separate drug concentrations of 2.0 to 10.0µg/mL. Absorbance of pantoprazole sodium solution was measured at 292nm against blank solution i.e., phosphate buffer pH 6.8. The standard calibration curve yields a straight line ($y = 0.0507x + 0.0063$; $R^2 = 0.9993$) which shows drug obeys Beer-Lambert's law in the range of 2 -10 µg/mL.

2.3. Preformulation studies

The pH of pantoprazole sodium was determined using potentiometer for freshly prepared 1% aqueous solution of Pantoprazole sodium. Melting point of pantoprazole sodium was determined by taking small amount of drug in a capillary tube closed at one end. The capillary tube was placed in a melting point apparatus and the temperature at which drug melts was recorded. The solubility of pantaprazole sodium was determined by solubilising it in different solvents. Drug-excipient compatibility studies were performed by Fourier Transform Infrared Spectroscopy. The infrared spectrum of the pure pantoprazole sodium and polymer samples were recorded and the spectral analysis was done. The dry samples of drug and polymers were directly placed after mixing and triturating with dry potassium bromide. The backing membrane was prepared with an aqueous solution of 4%w/v Poly vinyl alcohol (PVA). 4g of PVA was added to 100mL of warm, distilled water and a homogenous solution was made by constant stirring and intermittent heating at 60°C for few seconds. Then 15mL of homogenous solution was poured into glass Petri dishes of 63.5cm^2 and was allowed to dry in hot air oven at 60°C for 6h [2,3].

2.4. Preparation of transdermal patches

The different placebo films were prepared using various combinations of polymers by trial and error method. Those polymeric combinations that exhibited smooth and flexible films were selected for preparing the drug incorporated matrix systems. All the films were prepared by solvent evaporation technique. The matrix-type transdermal patches containing Pantoprazole Sodium was prepared using different ratios of Hydroxy Propyl Methyl Cellulose (HPMC, E_5) with Poly vinyl pryrrolidone (PVP). The polymers in different ratios and drug were dissolved in the solvents and stirred on the magnetic stirrer for 30min to obtain a uniform solution separately in two beakers. Then the drug solution was poured slowly drop by drop into the polymer solution and few drops of Di-n-butyl phthalate and Dimethyl Sulfoxide were added. Di-n-butyl phthalate (DBT) was used as plasticizers. Dimethyl Sulfoxide (DMSO) was used as the penetration enhancer. The whole mixture was mixed thoroughly on the magnetic stirrer to obtain a uniform solution. Then the solution was poured on the Petri dish having surface area of 63.5cm^2 and dried at the room temperature. Then the patches were cut into 2x2cm^2 patches. Drug incorporated for each 2x2cm^2 patch was 40mg (Table 1) [4,5].

Table 1

Formulation of pantoprazole sodium transdermal patches

Ingredients	PAN1	PAN2	PAN3	PAN4	PAN5	PAN6
Pantoprazole sodium (mg)	635	635	635	635	635	635
HPMC,E_5 (mg)	300	150	100	300	450	500
PVP (mg)	300	450	500	*	*	*
Eudragit L100 (mg)	*	*	*	300	150	100
Ethanol in Drug, Polymer (mL)	10, 0	10, 0	10, 0	10, 5	10, 5	10, 5
Methanol (mL)	8	8	8	*	*	*
Chloroform: Methanol 1:1(mL)	*	*	*	6	6	6
Di butyl phthalate (drops)	15	15	15	15	15	15
DMSO (drops)	2	2	2	2	2	2

2.5. Evaluation of transdermal patches

All the transdermal patches were visually inspected for color, clarity, flexibility, smoothness and found that the

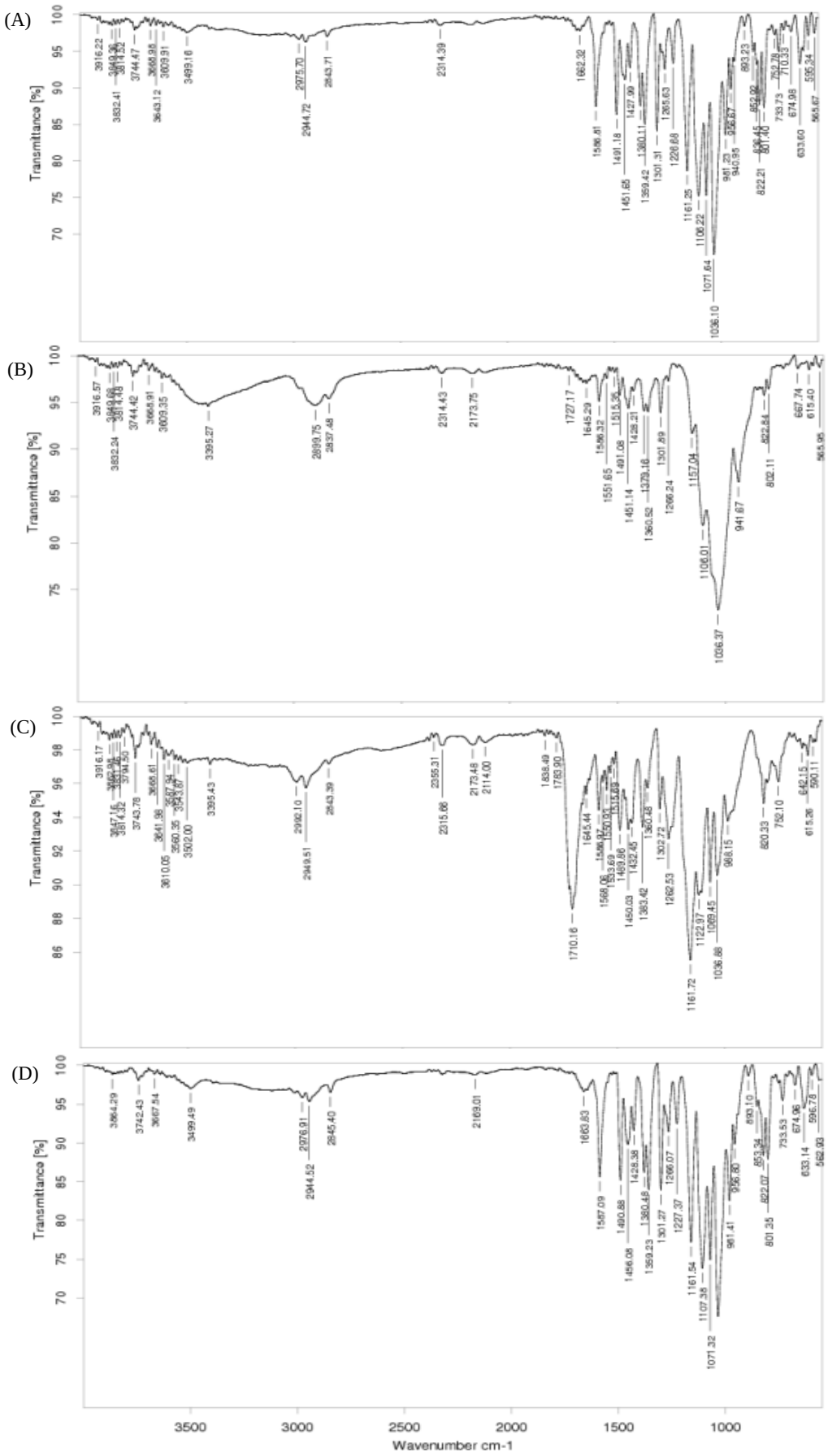

Fig.1.IR Spectrum of (A) pure pantoprazole sodium (B) physical mixture of pantoprazole sodium and HPMC, E5 (C) pantoprazole sodium and PVP (D) pantoprazole sodium and eudragitL100

Table 2
Evaluation of pantoprazole sodium transdermal patches

Formulation code	Thickness uniformity (mm)	Weight uniformity (mg)	Folding endurance	Surface pH	% Flatness	% Moisture content	% Moisture uptake	Water vapour transmission rate ($gm/cm^2/h$)	% Drug content
PAN1	0.031±0.0005	81.67±0.57	80.33±0.57	5.2	100	9.166±1.44	6.90±2.325	0.0044±0.0001	99.21
PAN2	0.035±0.0010	83.33±0.57	77.33±0.57	5.1	100	9.643±1.51	6.34±1.374	0.0025±0.0005	97.23
PAN3	0.045±0.0010	84.67±1.52	75.33±1.52	5.2	100	12.5±2.50	4.50±1.558	0.0032±0.0003	93.25
PAN4	0.042±0.0005	85.67±0.57	79.33±0.57	4.8	100	3.80±1.65	3.63±1.616	0.0036±0.0001	98.36
PAN5	0.046±0.0005	87.00±1.00	75.33±0.57	5.0	100	5.00±2.50	3.243±1.408	0.0026±0.0001	94.02
PAN6	0.047±0.0015	90.33±0.57	74.67±0.57	5.1	100	5.23±0.513	2.51±0.623	0.0024±0.0001	92.65

patches were translucent, having good strength, visually smooth surfaced and the drug and polymer distribution was uniform [6]. The thickness uniformity of the films was measured using micro meter screw gauge and the average thickness of all films was observed [7]. Weight uniformity of prepared films were determined using digital balance and the average weight of all films and the results were recorded [8]. The folding endurance of the formulated patches was determined by folding the centre between the finger and thumb and then opened [9]. Thumb tack test was performed by lightly pressing a thumb on a patch for approximately 5 sec and then quickly removing it [10,11].

Surface pH of the patches was determined by allowing it to swell and by keeping them in contact with 0.5mL of double distilled water for 1 hour in glass tubes [12]. Percentage flatness was determined by cutting one strip from the centre and two from each side of patches. The length of each strip was measured and variation in length was measured by determining % flatness. Zero percent constriction is equivalent to 100% flatness [13,14]. Percentage moisture content of prepared films was carried out in desiccator and determined using digital balance [15]. The % moisture uptake of prepared films was carried out in desiccator and determined using digital balance [16,17]. The swelling of the drug loaded patches of size 1 x $1cm^2$ was studied up to 60 min in case of change in weight. The swelling of the patches were observed in phosphate buffer solution (pH 6.8) [18]. Water vapour transmission rate was calculated by taking the difference in the weight of the patches before and at regular intervals of 24 hrs. The experimental was performed in triplicate and the average values were calculated [19,20]. Drug content was determined for the prepared formulations [21].

In vitro release studies of pantoprazole sodium patches were carried out in phosphate buffer solution, pH 6.8 [22]. The release kinetics was evaluated for zero order, first order, Higuchi's diffusion, Korsemeyer-Peppas equation [23]. Stability study was carried out at normal room conditions. Formulated patches were packed in butter paper followed by aluminium foil and plastic tape. After 3 months, the films were evaluated for the physical appearance, surface pH and drug content and no change was observed [24-26].

3. RESULTS AND DISCUSSIONS

The pH of pantoprazole sodium was found to be 8.6. Due to gradual degradation of pantoprazole sodium during heating, the melting point cannot be determined. Pantoprazole sodium was found to be soluble in ethanol, water, and in phosphate buffer of 6.8 and 7.4. Pantoprazole sodium shows a clear solution in stimulated gastric pH 1.2 but also show a characteristic yellow coloration when PPIs are dissolved in acidic pH. The coloration intensifies as the pH decreases. FT-IR studies were conducted for the drug, polymer and formulated patches. The peaks obtained in the spectra of each formulation correlates with the peaks of drug spectrum. This indicates that the drug is compatible with the formulation components (Fig.1).

All the drug-loaded films have uniform thickness. The thickness of the films varied from 0.031 to 0.048 mm and order of the thickness of films is PAN1 < PAN 2 < PAN 4 < PAN 3 < PAN 5< PAN 6 (Table 2). The weight of all the patches were found to be uniform. The weight of the films varied from 81.67 to 90.33 mg and order of the weight of films is PAN 1 < PAN 2 < PAN 3 < PAN 4 < PAN 5 < PAN 6 (Table 2). The folding endurance was found to be in the range of 74.67 to 80.33. This data revealed that the patches had good mechanical strength along with flexibility and order of the folding endurance is PAN 6 < PAN 5 < PAN 3 < PAN 2 < PAN 4 < PAN 1 (Table 2). This test is important to check the ability of sample to withstand folding, which gives an indication of brittleness; less folding endurance indicates more brittleness. Thumb tack test was performed for all the formulations and it showed optimum tackiness with the thumb and good adherence capacity with human skin. Surface pH study was done and all the formulations show pH in the range of 4.8 to 5.2. So we can expect no irritation. The % flatness in all the patches was found to be 100. This data indicates the smoothness as well as non-constriction nature of the patch. The % moisture content was found to be in the range of 3.80 to 9.166. Patches PAN 1, PAN 2, PAN 3 showed highest loss due to water soluble polymer HPMC and PVP. Patch PAN3 showed maximum moisture content due to low concentration of HPMC compared to other formulations. The order of the percentage moisture loss is PAN 4 < PAN 5 < PAN 6 < PAN 1 < PAN 2 < PAN 3 (Table 2). From the % moisture uptake

study it was found that all the patches showed least % moisture absorption**.** The % moisture content was found to be in the range of 2.51 to 6.90 and order of the % moisture absorption is PAN 6 < PAN 5 < PAN 4 < PAN 3 < PAN 2 < PAN 1 (Table 2). PAN1 showed maximum moisture uptake due to high hydrophilicity of HPMC and PVP. Water vapour transmission rate was found to be in the range of 0.0024 to 0.0044 and order of the percentage moisture absorption is PAN 6< PAN 2< PAN 5< PAN 3< PAN 4< PAN 1. All the formulations showed more than 90% of the drug loading indicating much of the drug is not lost. The drug content was found to be in the range of 92.65 to 99.21 and order of the drug content is PAN 6< PAN 3< PAN 5< PAN 2< PAN 4 < PAN 1 (Table 2). The results indicated that the drug was uniformly dispersed. The swelling index data was found to be in the range of 114.92 to 196.25 and order of the swelling index is PAN 6 < PAN 5 < PAN 3 < PAN 2 < PAN 4 < PAN 1 (Fig.2).

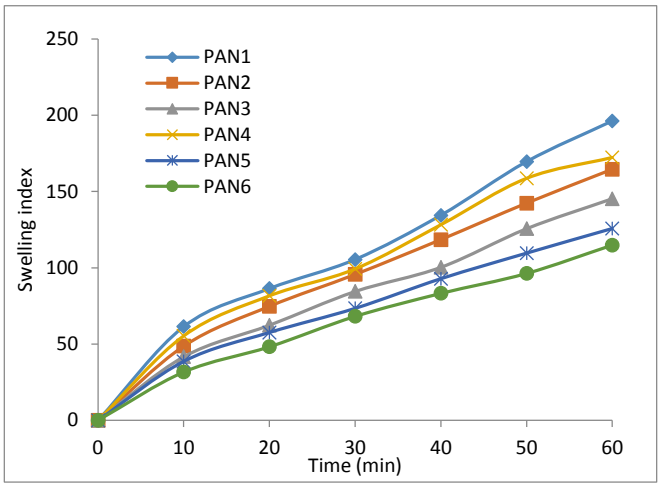

Fig.2.Swelling index of pantoprazole sodium transdermal patches (PAN1 to PAN6)

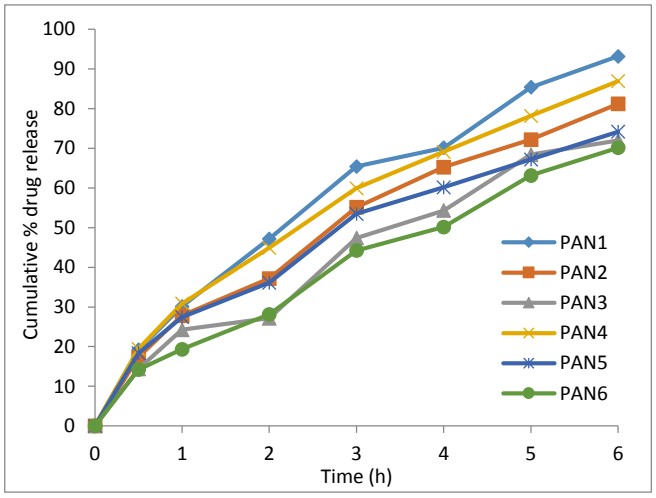

Fig.3.In vitro release of pantoprazole sodium transdermal patches (PAN1 to PAN6)

The percentage of drug release at each time interval was calculated and plotted against time. The drug release from the formulations PAN 1 to PAN 3 which has varying proportion of HPMC and PVP showed release of 71.98 to 93.14 %, the drug release from the formulations PAN 4 to PAN 6 which has varying proportion of HPMC and Eudragit showed release of 70.12 to 86.92 %, F1 showed maximum release of 93.14 % for 6h (Fig.3). It is well known that the addition of hydrophilic component to an insoluble film former leads to enhance its release rate constant. This is due to the fact that dissolution of aqueous soluble fraction of the polymer matrix leads to the formation of gelaneous pores. The formation of such pores leads to decrease the mean diffusion path length of drug molecules to release into the diffusion medium and hence, to cause higher release rate. The results of the kinetic studies were shown in Table 3. Kinetic studies reveals that majority of the formulations were governed by Peppas model and to see whether the drug release is by diffusion, by swelling or by erosion mechanism, the data was plotted according to Higuchi's equation. The co-efficient of determination indicated that the release data for formulation F1 to F6 followed first order release kinetics with diffusion mechanism. Higuchi equation explains the diffusion release mechanism. The diffusion exponent 'n' values were found to be in the range of 0.5 to 1 indicating Non-Fickian mechanism. The stability study was carried out for 3 months and no change was observed in the formulated patches (Table 4).

Table 3
Release kinetics studies

Formulation code	Kinetic models (r^2)				
	Zero order	First order	Higuchi model	Korsmeyer Peppas	
				r^2	n
PAN1	0.9571	0.958	0.9877	0.9968	0.9289
PAN2	0.9606	0.992	0.9861	0.9897	0.8260
PAN3	0.967	0.9799	0.961	0.9977	0.8196
PAN4	0.9518	0.9886	0.9946	0.9978	0.7737
PAN5	0.9443	0.9918	0.9911	0.9955	0.7553
PAN6	0.9813	0.9875	0.9665	0.9964	0.7309

Table 4
Stability studies

Formulation code	Appearance	Surface pH	Drug content
PAN1	No change	5.2	99.21
PAN2	No change	5.1	97.23
PAN3	No change	5.2	93.25
PAN4	No change	4.8	98.36
PAN5	No change	5.0	94.02
PAN6	No change	5.1	92.65

4. CONCLUSIONS

Pantoprazole transdermal patches were formulated and evaluated with the objective of providing maximum therapeutic efficacy, patient compliance by decreasing the dosing frequency and other problems associated with existing conventional and parenteral PPIs. From the various evaluation studies it was found that the all the formulated patches exhibited certain satisfactory characteristics regarding integrity, flexibility, and dispersion of drug. Among these formulations PAN1 was found to satisfy the maximum parameters of transdermal patch. *In vitro* diffusion studies and kinetic studies of PAN1 also shows prolonged release of drug which indicates the maximum availability of drug in systemic circulation to treat the peptic ulcer (GERD) and in Post-operative surgeries that satisfy the need of the patient providing maximum therapeutic efficacy with increased patient compliance. From the studies it may be concluded that PAN1 is considered as the suitable substitute for conventional and parenteral PPIs. PPIs used in this study are safer, not only block the acid production but also promote healing, widely used in treating peptic ulcer. Further studies has to be carried out to develop a new dosage form of pantoprazole in the form of patch to satisfy the need of the patient, physician and pharmaceutical industry.

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