INTRODUCTION

The transdermal drug delivery system (TDDS) is a widely accepted mode of drug delivery, and transdermal patches are designed to treat various diseases [1]. Transdermal delivery leads to over-injectable and oral routes by increasing patient compliance and avoiding the first-pass metabolism, respectively. They can even prevent drug-related gastrointestinal problems and low absorption [2]. The goal of the transdermal drug delivery system is to maximize the skin flux into systemic circulation while reducing the metabolism and retention 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].

FDA approved the first transdermal patch in the year 1981, which was developed by Alza corp, California, for the treatment of motion sickness with the drug scopolamine (Transderm-Scop) and followed by Transderm-nitro for the treatment of angina pectoris. Due to its various diseases like hypertension, angina pectoris, motion sickness, female menopause, and male hypogonadism [8]. The market share of the transdermal drug delivery system is vital as they reversibly reduce the barrier resistance of the stratum corneum without damaging viable cells [7].

The present study was an attempt to develop an alternative dosage form for the existing conventional oral, parenteral proton pump inhibitor (PPI) as transdermal patches for treating peptic ulcers.

Material and Methods

Pantoprazole was obtained as a gift sample from Dr. Reddy's Laboratories Ltd, Hyderabad. PVA, Potassium dihydrogen phosphate, Sodium hydroxide were purchased from Thomas Baker (Chemicals) Pvt Ltd, Mumbai. HPMC E5 was purchased from Loba Chemie Pvt Ltd, Mumbai. PVP, Methanol, Chloroform, Dibutyl phthalate, DMSO were purchased from Research-Lab Fine Chem Industries, Mumbai. Eudragit L100 was purchased from Rohm Pharma, Germany. All the other reagents were all of the analytical grades.

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 cm² 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 E4) with Polyvinyl pyrrolidone (PVP), Ethyl cellulose, Eudragit L 100, and Eudragit S100.

Formulation and evaluation of transdermal patches of Pantoprazole Sodium

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Abstract

Objective: The present study was an attempt to develop an alternative dosage form for the existing conventional oral, parenteral proton pump inhibitor (PPI) as transdermal patches for treating peptic ulcers.

Methods: Transdermal patches of PPI were prepared using HPMC E5 with PVP K 30 and HPMC E5 with Eudragit L100 polymers in different ratios by a solvent evaporation method. 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, surface pH and in vitro release studies.

Results: All patches exhibited satisfactory characteristics regarding integrity, flexibility, dispersion of drug, and other quality control parameters. In vitro release studies of transdermal patches, formulation F1 showed the prolonged release of drug (98.99 %) for 24 h, which indicates the maximum availability of the drug and the in vitro skin permeability studies also showed that 96.26 % of drug Pantoprazole sodium permeated through the rat abdominal skin in 24 h. 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.

Conclusion: This suggests the transdermal application of Pantoprazole sodium holds the promised controlled release of the drug for an extended period of time.

Keywords: Transdermal patches, Pantoprazole sodium, In vitro release, In vitro skin permeability
The polymers were accurately weighed and dissolved in 100 ml of ethanol and in the case of Eudragit L 100 the chloroform: methanol (1:1) solution was also used and kept aside 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 petri dish, which was lubricated with glycerin and dried at room temperature for 24 h. An inverted funnel was placed over the petri dish to prevent fast evaporation of the solvent. After 24 h, the dried patches were taken out and stored in a desiccator for further studies [15].

**Evaluation of transdermal patches**

**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, and force was applied progressively until the film broke. The value of the folding endurance 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 μm pore size cellulose acetate membrane. The prepared transdermal patch was placed 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.

**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].

\[
\text{Percentage Elongation} = \left( \frac{\text{Final length of strip} - \text{Initial length of strip}}{\text{Initial length of strip}} \right) \times 100
\]

**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 ultrasonicated 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].

\[
\text{Percentage Moisture Content} = \left( \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \right) \times 100
\]

**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].

\[
\text{Percentage Moisture Uptake} = \left( \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \right) \times 100
\]

**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].

\[
\text{Swelling index} = \left( \frac{W2 - W1}{W1} \right) \times 100
\]

**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 μm pore size cellulose acetate membrane. The prepared transdermal patch was placed 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.

**Table 1: Formulation details of pantoprazole sodium transdermal films**

| Ingredients                | Formulations |
|---------------------------|--------------|
|                           | F1           | F2           | F3           | F4           | F5           | F6           |
| Pantoprazole Sodium (mg)  | 635          | 635          | 635          | 635          | 635          | 635          |
| HPMC (E5) (mg)            | 300          | 200          | 400          | 300          | 200          | 400          |
| PVP K 30 (mg)             | 300          | 400          | 200          | -            | -            | -            |
| Eudragit L 100 (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 glycol (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          |

(All quantities are in mg/ml)
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 time), first-order (log cumulative percentage of drug remaining vs 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

Oral site-specific drug delivery systems have attracted a great deal of interest recently for the local treatment of a variety of bowel diseases and also for improving systemic absorption of drugs, which are unstable in the stomach [34, 35]. However, the microenvironment in the gastrointestinal tract and varying absorption mechanisms generally causes hindrance for the formulation scientist in the development and optimization of oral drug delivery [36]. 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 K30 and HPMC E5:Eudragit L100 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 0.32±0.008 to 0.48±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±2.7 mg, but the content uniformity in all these batches was found to be 98.86±0.40% to 101.67±4.78% of Pantoprazole sodium.

The surface pH 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±4.48. 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          | 0.32±0.008     | 175.5±11.65       | 99.96±4.30             | 84.3±2.36  |
| F2          | 0.36±0.022     | 157.2±16.69       | 99.49±3.95             | 87.3±1.12  |
| F3          | 0.46±0.011     | 141.6±15.39       | 101.67±4.78            | 85.3±2.06  |
| F4          | 0.44±0.007     | 179.0±9.48        | 99.90±4.98             | 90.2±3.77  |
| F5          | 0.49±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 (%) | Weight 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].

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.

### Table 4: Swelling studies of transdermal patches of pantoprazole sodium

| Formulation | Swelling index |
|-------------|----------------|
|             | 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±2.94 | 64.7±2.44 | 68.05±1.68 | 74.08±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 |

(All values are mean±SD; n=3)

### 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      | 0.9826     | 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     | 9.666   | 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 formulations.
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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AUTHORS CONTRIBUTIONS
All authors have contributed equally.

CONFLICTS OF INTERESTS
All authors have none to declare.

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