International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 13, Issue 5, 2021

Original Article

FORMULATION AND EVALUATION OF TRANSDERMAL PATCHES OF PANTOPRAZOLE SODIUM

M. R. SHIVALINGAM, ARUL BALASUBRAMANIAN*, KOTHAI RAMALINGAM

Department of Pharmacy Practice, Vinayaka Mission's College of Pharmacy, Vinayaka Mission's Research Foundation (Deemed to be University), Salem 636008, Tamilnadu, India
Email: arul1971@yahoo.com

Received: 24 May 2021, Revised and Accepted: 29 Jun 2021

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 E_5 with PVP K 30 and HPMC E_5 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 the *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 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.

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

DOI: https://dx.doi.org/10.22159/ijap.2021v13i5.42175. Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

The transdermal drug delivery system (TDDS) is a widely accepted mode of drug delivery, and transdermal patches are devised 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 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].

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 continuous success, currently, 35 TDDS patches are in the market for various diseases like hypertension, angina pectoris, motion sickness, female menopause, and male hypogonadism [8]. The market share for transdermal delivery was $12.7 billion in the year 2005, which rose to $21.5 billion in the year 2010, $31.5 billion in the year 2015, and increasing every year.

The proton pump inhibitor pantoprazole is a substituted benzimidazole sulphoxide for the treatment of acid-related gastrointestinal diseases such as reflux esophagitis, duodenal and gastric ulcers. Pantoprazole, administered as a 40 mg enteric-coated tablet, is quantitatively absorbed. Its absolute bioavailability is 77% and does not change upon multiple dosing [9]. Pantoprazole shows linear pharmacokinetics after both i. v. and oral administration. 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.

MATERIALS AND METHODS

Materials

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 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 E_5) 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 petri dish by a solvent evaporation method using different polymers

(HPMC E_5:PVP K30 and HPMC E_5:Eudragit L 100) [13]. The drug to polymer ratio was fixed as 1:1 and the polymer to polymer ratio was fixed as 1:1, 1:2, and 2:1. Three different concentrations of HPMC E_5 were used in all six formulations and another two polymers PVP K 30 and Eudragit L100 were used in every three formulations at varying concentrations (table 1). N-dibutyl phthalate and propylene glycol were used as a plasticizer. 1% DMSO was used as a permeation enhancer in all the formulations [14].

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 (E_5) (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)

The polymers were accurately weighed and dissolved in 10 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 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].

$$\text{Percentage Elongation} = \frac{\text{Final length of strip} - \text{Intial length of strip}}{\text{Intial length of strip}} \text{x} 100$$

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 24h. After 24 h, the films were reweighed and the percentage moisture content was determined from the following formula [16].

$$\text{Percentage Moisture Content} = \frac{\text{Inital weight} - \text{Final weight}}{\text{Final weight}} \text{x} 100$$

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].

$$\text{Percentage Moisture Uptake} = \frac{\text{Final weight} - \text{Inital weight}}{\text{Inital weight}} \text{x} 100$$

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].

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

***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.

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 ℃ [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

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 E_5:PVP K 30and HPMC E_5: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].

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 E_5 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±2.84	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

(All values are mean±SD; n=3)

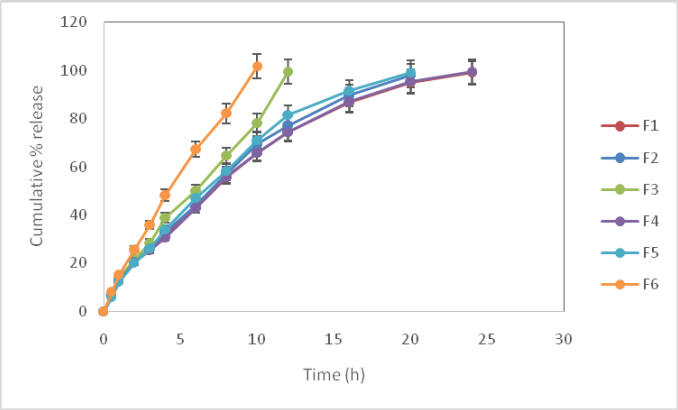

Fig. 1: *In vitro* release profile of pantoprazole sodium transdermal patches (mean±SD; n=3)

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 (r^2=0.9383) and Higuchi model (r^2=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 (r^2=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	R^2	Slope	R^2	Slope	R^2	Slope	R^2
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 E_5, 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 E_5: PVP K30 and HPMC E_5: 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.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICTS OF INTERESTS

All authors have none to declare.

REFERENCES

1. Asbill CS, Michniak BB. Percutaneous penetration enhancers: local versus transdermal activity. Pharm Sci Technol Today 2000;3:36–41.
2. Balaji P, Thirumal M, Gowri R, Divya V, Ramaswamy V. Design and evaluation of matrix type of transdermal patches of methotrexate. Int J Pharm Chem Biol Sci 2012;2:464–71.
3. Das PS, Saha P. Design and characterisation of transdermal patches of Phenformin hydrochloride. Int J Curr Pharm Res 2017;9:90–3.
4. Shivalingam M, Balasubramanian A, Ramalingam K. Non-invasive medicated dermal patch–a review. Int J Pharm Res 2020;12:3018–27.
5. Shivalingam MR, Balasubramanian A, Ramalingam K. Design and evaluation of medicated dermal patches of proton pump inhibitor-esomeprazole. Int J Pharm Res 2020;12:3038–43.
6. Funke AP, Schiller R, Motzkus HW, Gunther C, Muller RH, Lipp R. Transdermal delivery of highly lipophilic drugs: *in vitro* fluxes of antiestrogens, permeation enhancers, and solvents from liquid formulations. Pharm Res 2002;19:661–8.
7. Guy RH. Current status and future prospects of transdermal drug delivery. Pharm Res 1996;13:1765–9.
8. Barry BW. Novel mechanisms and devices to enable successful transdermal drug delivery. Eur J Pharm Sci 2001;14:101–14.
9. Huber R, Hartmann M, Bliesath H, Luhmann R, Steinijans VW, Zech K. Pharmacokinetics of pantoprazole in man. Int J Clin Pharmacol Ther 1996;34:185–94.
10. Mehdizadeh A, Toliate T, Rouini MR, Abashzadeh S, Dorkoosh F. Design and *in vitro* evaluation of new drug-in-adhesive formulations of fentanyl transdermal patches. Acta Pharm 2004;54:301–17.
11. Mukherjee B, Das S, Patra B, Layek B. Nefopam containing transdermal-matrix patches: based on pressure-sensitive adhesive polymers. Pharm Technol 2006;30:146–63.
12. Chandrashekhar SN. Physicochemical and pharmacokinetic parameters in drug selection and loading for transdermal drug delivery. Indian J Pharm Sci 2008;70:94–6.
13. Singh A, Bali A. Formulation and characterization of transdermal patches for controlled delivery of duloxetine hydrochloride. J Anal Sci Technol 2016;7:1–13.
14. Prabhakara P, Koland M, Vijaynarayana K, Harish NM, Shankar G, Ahmed MG, *et al.* Preparation and evaluation of transdermal patches of papaverine hydrochloride. Int J Res Pharm Sci 2010;1:259–66.
15. Shivaraj A, Selvam RP, Mani TT, Sivakumar T. Design and evaluation of transdermal drug delivery of ketotifen fumarate. Int J Pharm Biomed Res 2010;1:42–7.
16. Keleb E, Sharma RK, Mosa EB, Aljahwi A-AZ. Transdermal drug delivery system-design and evaluation. Int J Adv Pharm Sci 2010;1:201–11.
17. Bangale GS, Rathinaraj BS, Rajesh KS, Shinde GV, Umalkar DG, Rajveer CH, *et al.* Design and evaluation of transdermal films of atenolol. J Chem Pharm Res 2010;2:593–604.
18. Lec ST, Yac SH, Kim SW, Berner B. One way membrane for transdermal drug delivery systems/system optimization. Int J Pharm 1991;77:231-7.
19. Venkateswari Y, Jayachandra Babu R, Sampathkumar D, Mittal N, Pandit JK. Development of a low cost tetracycline strip for long term treatment of periodontal disease. Indian Drugs 1995;32:205–10.
20. Pandit V, Khanum A, Bhaskaran S, Banu V. Formulation and evaluation of transdermal films for the treatment of overactive bladder. Int J Pharm Tech Res 2009;1:799–804.
21. Garala KC, Shinde AJ, Shah PH. Formulation and *in vitro* characterization of monolithic matrix transdermal systems using HPMC/Eudragit S 100 polymer blends. Int J Pharm Pharm Sci 2009;1:108–20.
22. Nishad KM, Arul B, Rajasekaran S. Design and comparative evaluation of clarithromycin gastric bioadhesive tablets by ex vivo and *in vivo* methods. Asian J Pharm Clin Res 2018;11:248–56.
23. Pandey S, Shah RR, Gupta A, Arul B. Design and evaluation of buccoadhesive controlled release formulations of prochlorperazine maleate. Int J Pharm Pharm Sci 2016;8:375–9.
24. Suksaeree J, Boonme P, Taweepreda W, Ritthidej GC, Pichayakorn W. Characterization, *in vitro* release and permeation studies of nicotine transdermal patches prepared from deproteinized natural rubber latex blends. Chem Eng Res Des 2012;90:906–14.
25. Simon A, Amaro MI, Healy AM, Cabral LM, de Sousa VP. Comparative evaluation of rivastigmine permeation from a transdermal system in the Franz cell using synthetic membranes and pig ear skin with *in vivo-in vitro* correlation. Int J Pharm 2016;512:234–41.
26. Singh J, Tripathi KP, Sakya TR. Effect of penetration enhancers on the *in vitro* transport of ephedrine through rat skin and human epidermis from matrix based transdermal formulations. Drug Dev Ind Pharm 1993;19:1623–8.
27. Hwang BY, Jung BH, Chung SJ, Lee MH, Shim CK. *In vitro* skin permeation of nicotine from proliposomes. J Controlled Release 1997;49:177–84.
28. Pongjanyakul T, Prakongpan S, Priprem A. Permeation studies comparing cobra skin with human skin using nicotine transdermal patches. Drug Dev Ind Pharm 2000;26:635–42.
29. Hardainiyan S, Kumar K, Nandy BC, Saxena R. Design, formulation and *in vitro* drug release from transdermal patches containing imipramine hydrochloride as model drug. Int J Pharm Pharm Sci 2017;9:220–5.
30. Hadjiioannou TP, Christian GD KMA. Quantitative calculations in pharmaceutical practices and research. New Delhi: NY-VCH publishers Inc; 1993. p. 345–8.
31. Higuchi T. Mechanism of sustained action of medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J Pharm Sci 1963;52:1145–9.
32. DW B. Pharmacokinetics. In: Modern Pharmaceutical. 4th ed. Banker GS, Rhodes CT E. editor. New York: Marcel. Dekker Inc; 2002. p. 67–92.
33. Korsmeyer RW, Gurny R, Doelker E, Buri P PN. Mechanisms of solute release from porous hydrophilic polymers. Int J Pharm 1983;15:25–36.
34. Gnanasekaran J, Arul B, Kothai R. Development of mucoadhesive tablet of pentoxifylline using a natural polymer from Manilkara zapota Linn. Int J Appl Pharm 2019;11:88–91.
35. Selvaraj GJ, Balasubramanian A, Ramalingam K. Application of novel natural mucoadhesive polymer in the development of pentoxifylline mucoadhesive tablets. Int J Appl Pharm 2019;11:37–41.
36. Firoz SG, Kothai R, Arul B. Novel approaches for pulsatile drug delivery system. J Crit Rev 2020;7:2282–9.
37. Cojocariu A, Porfire L, Cheaburu C, Vasile C. Chitosan/montmorillonite composites as matrices for prolonged delivery of some novel nitric oxide donor compounds based on theophylline and paracetamol. Cell Chem Technol 2012;46:35-8.
38. Mishra MK, Ray D, Barik BB. Microcapsules and transdermal patch: a comparative approach for improved delivery of antidiabetic drug. AAPS PharmSciTech 2009;10:928–34.
39. Jain P, Dubey D, Mishra M. Formulation and evaluation of transdermal patch of benazepril hydrochloride using acryl coat L100 and acryl coat S100. Int J Pharm Chem Res 2016;2:167-79.
40. Mutalik S, Udupa N. Formulation development, *in vitro* and *in vivo* evaluation of membrane controlled transdermal systems of glibenclamide. J Pharm Pharm Sci Publ Can Soc Pharm Sci Soc Can des Sci Pharm 2005;8:26–38.