RESEARCH ARTICLE

Formulation and Evaluation of Transdermal Patches for Antianxiety Drug

Himabindu Peddapalli[1], Rajendra Prasad Ganta[2], Narender Boggula[1]

[1]Department of Pharmaceutical Chemistry, School of Pharmacy, Anurag Group of Institutions, Ghatkesar, Telangana, India, [2]Department of Pharmaceutics, Karnataka College of Pharmacy, Bengaluru, Karnataka, India

Abstract

Aim: The aim of the present study was to design, develop, and evaluate a matrix-type transdermal formulation containing buspirone hydrochloride (HCL) for treatment of anxiety with a goal to increase the bioavailability and improve the patient compliance. **Materials and Methods:** In the present research work, the different concentrations of hydroxypropyl methylcellulose (HPMC) E50, HPMC E15, and Eudragit RS100 were used in combination to optimize the concentration of HPMC E15 and Eudragit RS100 in the formulation of transdermal patches. These different ratios of hydrophilic and hydrophobic polymeric combinations plasticized with dibutyl phthalate by the solvent evaporation technique. The prepared patches were evaluated for their physicochemical characteristics such as thickness, weight and drug content uniformity, moisture content, moisture uptake and folding endurance, and *in vitro* drug release studies. Optimized formulation was further evaluated by *in vivo* release study, drug-excipient compatibility, and stability study. **Results and Discussion:** Effect of permeation enhancers such as oleic acid was studied. The interference of the polymers was ruled out by Fourier transform infrared and ultraviolet-spectroscopic methods. *In vitro* release studies of buspirone HCL-loaded patches in phosphate buffer (pH, 7.4) were performed using a modified diffusion cell and showed first-order release rate. Skin studies for the transdermal patches were assessed and were found to be free of irritation. *In vivo* drug release studies had shown release up to 24 h with the release of 73.82% and it was correlated with *in vitro* studies. The patches were subjected to short-term stability studies and were found stable. **Conclusion:** It is concluded from the present studies that the transdermal patches of buspirone HCL were capable of exhibiting controlled release with the stability. Studies had shown promising results, and there was a scope for further pharmacodynamic and pharmacokinetic evaluation.

Key words: Buspirone hydrochloride, Eudragit RS100, hydroxypropyl methylcellulose, *in vitro* permeation, transdermal patches

INTRODUCTION

Over the last two decades, transdermal drug delivery had become an appealing and patience acceptance technology as it minimizes and avoids the limitations allied with conventional as well as parenteral route of drug administration such as fluctuation in plasma drug concentration level, pain and inconvenience of injections, and the limited controlled release options of both.[1] Transdermal drug delivery system (TDDS) is widely recognized as one of the most reliable, appealing as well as effective techniques. Delivery of drugs through the skin has been an attractive as well as a challenging area for research.[2] Controlled drug release can be achieved by TDDS which can deliver medicines through the skin portal to systemic circulation at a predetermined rate over a prolonged period of time.[3,4]

TDDS was defined as self-contained, discrete dosage forms which, when applied to intact skin, deliver the drug(s), through the skin, at a controlled rate to systemic circulation.[5,6] The transdermal route of administration is recognized as one of the potential routes for the local and systemic delivery of drugs. TDDS, also known as "patches," is dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin.[7,8] Transdermal medication provides safe, convenient, and pain-free self-administration for patients.[9]

Address for correspondence:
Narender Boggula, Department of Pharmaceutical Chemistry, School of Pharmacy, Anurag Group of Institutions, Venkatapur, Ghatkesar – 500 088, Telangana, India. Mobile: +91-9666552211.
E-mail: narender.b987@gmail.com

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In comparison to conventional pharmaceutical dosage forms, TDDS offers many advantages[10] such as elimination of first-pass metabolism, enhancement of therapeutic efficiency, and maintenance of steady plasma level of the drug sustained drug delivery, reduced frequency of administration, reduced gastrointestinal side effects, and improved patient compliance.[6,11] The drug input can be terminated at any point of time by removing transdermal system. When compared with other therapies on a cost basis, transdermal systems are generally inexpensive and economical. An ideal features of drug to be formulated as transdermal drug delivery should possess several physicochemical properties[12,13] such as short half-life, small molecular size, low dose, and low oral bioavailability.

Buspirone hydrochloride (HCL) is an antianxiety drug and used to treat generalized anxiety disorder. It undergoes extensive hepatic first-pass metabolism and its low oral bioavailability 5%. It has a biological half-life of only 2–3 h. A daily dose is 20 mg or less is preferable. Hence, it can be conveniently loaded onto a patch. The molecular weight of drug is 421.97 g/mol. Hence, the drug gets easily absorbed across the stratum corneum of skin. Based on the above reasons, it was considered as an attractive alternative to formulate TDDS for delivery of buspirone HCL, which can improve its bioavailability by avoiding hepatic first-pass metabolism. Hence, it is suitable for formulation as a transdermal patch.

MATERIALS AND METHODS

Materials

The pure drug buspirone HCL was obtained as a gift sample from Dr. Reddys Laboratories (Hyderabad, India). Hydroxypropyl methylcellulose (HPMC) E50 and HPMC E15 were purchased from Central Drug House (P) Ltd. (New Delhi, India). Eudragit Rs. 100 was purchased from Hetero Drugs Ltd. (Hyderabad, India). Dibutyl Phthalate and oleic acid were purchased from Karnataka Fine Chem Laboratory Chemicals (Bengaluru, India).

Methods

Preformulation studies of the selected drug

Solubility determination

The solubility of the selected drug was determined in distilled water and phosphate buffer of pH 7.4 using standard method.[14]

Procedure

Excess amount of the selected drug was taken and dissolved in a measured amount of above solvents separately in a glass beaker to get a saturated solution. The solution was shaken intermittently to assist the attainment of equilibrium with the undissolved drug particles. Then, measured quantity of the filtered drug solution was withdrawn after 24 h and successively diluted with respective solvents, and the concentration was measured spectrophotometrically. Average of triplicate readings was taken.

Melting point determination

Melting point of the drug was determined by taking a small amount of the drug in a capillary tube closed at one end and was placed in Thiel's melting point apparatus and the temperature at which the drug melts was noted.[15] Average of triplicate readings was taken.

Partition coefficient determination

A drug solution of 1 mg/ml was prepared in n-octanol, 25 ml of this solution was taken in a separating funnel and shaken with an equal volume of phosphate buffer of pH 7.4 (aqueous phase) for 10 min and allowed to stand for 2 h. Then, aqueous phase 50 and organic phase were collected separately and centrifuged at 2000 rpm. Both the phases were analyzed for the drug concentration using ultraviolet spectrophotometer. Partition coefficient was calculated by taking the ratio of the drug concentration in n-octanol to drug concentration in aqueous phase.[15,16] Triplicate readings were taken.

Permeability coefficient determination

The permeability coefficient of drug was calculated by "Potts and Guy equation,"[16]

$$\text{Log Kp} = -2.7 + 0.71 \times \log \text{Ko/w} - 0.0061 \times \text{Molecular weight}$$

Where,
Log Kp = Permeability coefficient
Ko/w = Partition coefficient

Fourier transform infrared (FTIR) absorption spectroscopy

To investigate any possible interaction between the drug and the utilized polymers (HPMC, Eudragit), IR spectrum of pure drug (Buspirone HCL) and its physical mixture was carried using FTIR; the range selected was from 400/cm to 4000/cm.

Preparation of transdermal patches

The matrix-type transdermal films containing buspirone were prepared by solvent casting method. HPMC E50, HPMC E15, and Eudragit RS100 were used as polymers in the preparation of transdermal films. Dibutyl phthalate was used as a plasticizer, oleic acid was used as a permeation enhancer, and aluminum foil was used as backing membrane.[17,18]

Weighed required quantity of polymers and dissolved in 25 ml of solvent mixture consisting of 1:1 ratio of dichloromethane and methanol [Table 1]. The polymeric solutions were kept a side for swelling for 5 h. Then,

required quantity of plasticizer and drug solution are added and vortexed for 10 min. Further, it is set-a side for some time to exclude any entrapped air and is then poured on to the mercury surface in a Petri plate and this was kept a side for solvent evaporation. The rate of solvent evaporation was controlled by inverting a glass funnel over the Petri plate. After overnight, the dried films were cut into a 2 cm^2 piece and stored in desiccators until further use.

Evaluation of transdermal patches

Physical appearance

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

Weight variation

Ten patches from each batch were randomly selected and individually weighed on digital balance.[19] The average weight and standard deviation were calculated. The percent deviation was calculated using the following formula.

$$\%\ \text{Deviation} = \frac{\text{Individual weight} - \text{Average weight}}{\text{Average weight}} \times 100$$

Film thickness

The thickness of films was measured at three different places using a screw gauge and mean values were calculated.[3,19]

Folding endurance

Folding endurance was determined by repeatedly folding the film at the same place until it broke. The number of times the film could be folded at the same place without breaking was the folding endurance value.[20]

Uniformity of drug content in the patch

The uniformity of drug distribution was evaluated by determining drug content of the film by a spectrophotometric method. A known weight of film was dissolved and diluted subsequently with ethyl alcohol and the concentration of buspirone HCL was spectrophotometrically measured at 240 nm against the blank ethyl alcohol solution containing the same amount of polymer and plasticizer without drug.[21]

Percentage of moisture content

The films were weighed individually and kept in desiccator containing activated silica at room temperature for 24 h. Individual films were weighed repeatedly until they showed a constant weight. The percentage of moisture content was calculated as the difference between initial and final weight with respect to final weight.[3,22]

$$\%\ \text{Moisture cotent} = \frac{\text{initial weight} - \text{final weight}}{\text{final weight}} \times 100$$

Percentage of moisture uptake

A weighed film kept in a desiccator at room temperature for 24 h was taken out and exposed to 84% relative humidity (a saturated solution of aluminum chloride) in a desiccator until a constant weight for the film was obtained. The percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight.[16,23]

$$\%\ \text{Moisture uptake} = \frac{\text{Final weight} - \text{initial weight}}{\text{initial weight}} \times 100$$

In vitro drug diffusion studies

In vitro diffusion studies were performed using a Franz diffusion cell with a receptor compartment capacity of 140 ml. The dialysis membrane was mounted between the donor and receptor compartment of the diffusion cell [Figure 1]. The film was placed on cellulose acetate membrane and covered with aluminum foil. The receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4. The whole assembly was fixed on a hot plate magnetic stirrer, and solution in the receptor compartment was constantly and continuously stirred using magnetic beads and the temperature was mentioned at 37 ± 0.5°C. The samples were withdrawn at different time intervals and analyzed for drug content spectrophotometrically. The receptor phase was replenished with an equal volume of phosphate buffer at each sample withdrawal.[12,24]

In-vivo studies

Skin irritation test using rabbits

A primary skin irritation test was performed since skin is a vital organ through which drug is transported. The test was carried out on three healthy rabbits weighing 2–3 kg. Formulation F5 (Eudragit Rs. 100 1%, HPMC E -15 9%), which was subjected to the study, and plain polymer films were used as control. The dorsal surface of rabbits was cleared well and the hair was removed using a depilatory preparation. The skin was cleared with rectified spirit. The patches were placed over skin with the help of adhesive tape. The patches were removed after 24 h and the skin was examined for erythema and edema.[25]

In vivo drug release study

Selection of animals

Rabbit's *Oryctolagus cuniculus* of male sex 10-12 weeks old weighing 2-3 kg were selected [Figure 2]. They were kept with husk bedding and were fed with standard rodent pellet diet and water. Light and dark cycles with 12 h light and 12 h dark were maintained. The temperature and relative humidity conditions were 28°C ± 2% and 60°C ± 15% respectively.[26]

Figure 1: *In vitro* studies by using Franz diffusion cell

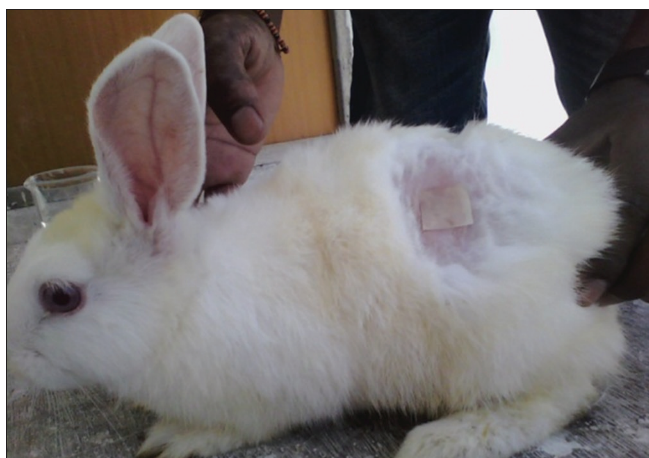
Figure 2: *In-vivo* studies on the rabbit skin

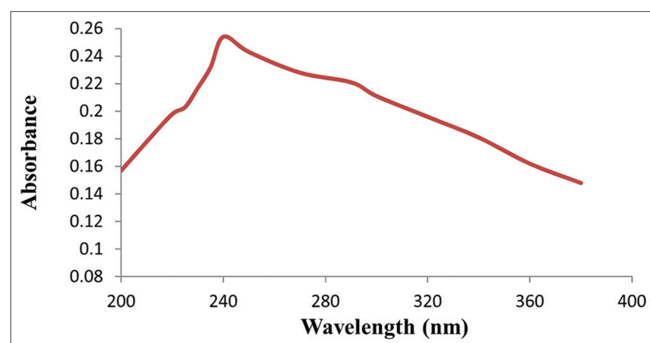

Figure 3: Ultraviolet absorption spectrum of buspirone hydrochloride in phosphate buffer pH 7.4

Method

A set of healthy rabbits were selected. They were checked to ensure that they were free from disease. The dorsal surface of the selected rabbits was cleaned and hair was removed. The dose of buspirone was calculated according to the body weight, i.e. 5 mg. The patch F5 (Eudragit Rs. 100- 1%, HPMC E 15- 9%) was placed on the dorsal surface. The experiment protocol was approved by an Institutional Animal Ethical Committee of Karnataka College of Pharmacy, Yelahanka, Bengaluru and care of the animals was taken as per guidance of the Committee for the Process of Control and Supervision of Experiments on Animals (Reg No: IAEC/KCP/PC/96a/1).

At specific interval, the patch was removed from the rabbit carefully and analyzed for remaining drug content. Initial drug content was determined before placing the film. The remaining drug content was subtracted from the initial drug content of the film. The value obtained denotes the amount of drug in diffused from the patch into the body.

Amount of drug released at any time interval = Initial drug content before placing the film - Remaining drug content after removal of the film.

In vitro in vivo correlation between cumulative % drug released in vitro and % drug release in vivo of optimized formulation of transdermal patch (F5)

In vitro and *in vivo* correlation was carried out for the therapeutic efficacy of a pharmaceutical formulation. It was governed by the factors related to both *in vitro* and *in vivo* characteristics of the drug. Percent *in vivo* release on X-axis was plotted against *in vitro* drug release on Y-axis for the same period of time.[26]

Stability studies

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light and to establish a re-test period for the drug substance or a shelf life for the drug product and recommended storage conditions. To assess the drug and formulation stability, stability studies were done according to ICH guidelines Q1C.

Stability studies were carried out on the films of most satisfactory as per ICH Guidelines Q1C. The most satisfactory formulation stored in sealed in aluminum foil. These were stored at room temperature for 2 months. Films were evaluated for *in vitro* drug release, *in vivo* diffusion study, and various physical characteristics.[15]

RESULTS

Preformulation studies

The Preformulation studies are prerequisite for any formulation development and various parameters namely solubility, melting point, partition coefficient (aqueous & octanol), permeability coefficient are and found to be within the range.

Determination of absorption maxima (λmax)

The λ_{max} of the selected drug was determined in phosphate buffer pH 7.4 and it was found to be 240nm

Table 1: Formulation chart of buspirone HCL transdermal patches

Formulation code	Amount of drug (mg)	% of Eudragit RS-100: HPMC-E50	% of Eudragit RS-100: HPMC-E15	% of oleic acid	% of dibutyl phthalate	Amount of solvent (ml)
F1	5	1:9	-	20	30	25
F2	5	2:8	-	20	30	25
F3	5	3:7	-	20	30	25
F4	5	4:6	-	20	30	25
F5	5	-	1:9	20	30	25
F6	5	-	2:8	20	30	25
F7	5	-	3:7	20	30	25
F8	5	-	4:6	20	30	25

HCL: Hydrochloride

FTIR absorption spectroscopy

FTIR spectrum of pure drug and various polymers with drug were studied and the results were optimum without any drug interaction.

In vitro diffusion study

In vitro diffusion studies of buspirone HCL transdermal films were carried out using dialysis membrane and diffusion cell in phosphate buffer saline pH 7.4 solution. The release data were given in Figure 5, respectively, for formulation F1–F8.

In-vitro release kinetic parameters of buspirone HCL from transdermal patches

Mathematical models used for study of release phenomenon of drug from dosage forms. This models helps in designing of new drug delivery system based upon the general release expression and accurate prediction of drug release profile and improve overall therapeutic efficacy and safety of these drug. *In-vitro* drug release data were fitted to kinetic models like zero order, first order, Higuchi and Korsmeyer-Peppas equations to ascertain the pattern of drug release of buspirone hydrochloride from transdermal patches.

In vivo drug release studies of optimized formulation (F5)

In-vivo studies were carried out for optimum formulation in rabbit and showed drug release approximately more than 70% and results were satisfactory.

In vitro and in vivo correlation between cumulative % drug released in vitro and % drug release in vivo of optimized formulation of transdermal patch (F5)

The main goal of correlating in vitro drug release information of various drug formulations to the in vivo drug profiles was shortens the drug development period, economizes the resources and leads to improved product quality. The *in vitro* and *in vivo* correlation was performed for optimize formulation and showed good correlation coefficient.

Stability study of most satisfactory formulation

Stability studies were carried out on most satisfactory formulation for 2 months as per ICH Guidelines Q1C. The results were satisfactory without any physical changes.

DISCUSSION

The pure drug buspirone HCL was obtained as a gift sample from Dr. Reddy's laboratories, Hyderabad, was used in the present investigation. In the first phase of our study, the drug was subjected to various preformulation parameters, namely, solubility, melting point, partition coefficient (aqueous and octanol), and permeability coefficient. The results were shown in Table 2. The solubility of drug in water and buffer of pH 7.4, melting point, partition coefficient, and permeability coefficients were found to be 0.588 mg/ml, 0.125 mg/ml, 201.5°C, 61.42 mg/ml, 39.88 mg/ml, and 0.29 respectively. The λ_{max} of the selected drug found to be 240 nm as shown in the Figure 3, and it was used throughout the study for the estimation of drug in the formulations.

The peaks observed in Table 3 can be considered as characteristic peaks of buspirone. These peaks were not affected and prominently observed in FTIR spectra of buspirone HCL along with polymers as shown in Figures 4-7. This indicates that there is no interaction between buspirone and polymers.

Transdermal patches of buspirone HCL were prepared successfully by solvent casting method using different polymers (HPMC E 50, HPMC E 15, and Eudragit RS-100) in different combinations and proportions, dibutyl phthalate used as a plasticizer, and oleic acid used as permeation enhancer.

Table 2: Preformulation studies of buspirone HCL

S. No	Drug	Melting point (°C)	Solubility (mg/ml)		Partition coefficient (P)		Log *P*
			Water	Buffer pH 7.4	Amount in aqueous phase (mg/ml)	Amount in octanol (mg/ml)	
1	Buspirone HCL	201.5	0.588	0.125	61.42	39.88	0.29

HCL: Hydrochloride

Table 3: FTIR study of pure buspirone hydrochloride

Bond	Wave number (cm^{-1}) pure drug	Drug with HPMC E15	Drug with HPMC E50	Drug with Eudragit Rs. 100
Sp^3 C-H (stretching) (2850–3000)	2962	2961	2964	2961
C=C- (Ar. stretching) (1475–1600)	1594	1598	1594	1592
C-H (Bending) (1450–1375)	1464	1465	1463	1468
C-N (1350–1000)	1327	1331	1327	1326
C-H (Ar. Out plane bending) (900–690)	814	813	813	815

FTIR: Fourier transform infrared, HPMC: Hydroxylpropyl methylcellulose

Table 4: Physicochemical parameters of prepared buspirone formulations F1–F8

Formulation code	Weight variation* (mg)	Thickness* (mm)	Folding endurance*	% Content uniformity	% Moisture content*	% Moisture uptake*
F1	82±0.043	0.29±0.01	106±9	94.6±0.52	4.67±0.42	4.03±0.58
F2	85±0.026	0.21±0.03	95±2.1	90.5±0.61	4.17±0.42	3.49±1.01
F3	88±0.068	0.24±0.06	115±10	91.6±2.93	3.47±0.53	3.66±0.44
F4	82±0.005	0.21±0.01	116±4	95.7±0.64	3.45±0.31	3.30±1.07
F5	84±0.01	0.27±0.04	113±2	99.0±0.92	3.84±1.25	4.01±0.96
F6	84±0.047	0.20±0.04	113±7	97.1±0.8	3.66±0.37	3.81±0.29
F7	81±0.015	0.17±0.01	106±1.5	96.8±0.63	3.45±1.27	3.60±0.42
F8	85±0.030	0.21±0.01	123±3	98.3±0.82	3.42±0.61	3.39±0.91

*n=3 studies were repeated in triplicate, and the mean was calculated

Table 5: Kinetic parameters for the *in-vitro* release of buspirone HCL from different formulations

Formulation	Zero-order	First-order	Higuchi	Korsmeyer-Peppas
		R^2		n
F1	0.8075	0.9663	0.9241	0.8376
F2	0.8279	0.9678	0.9379	0.7893
F3	0.8453	0.9557	0.9289	0.8321
F4	0.8519	0.9248	0.9002	0.8458
F5	0.8473	0.9797	0.9521	0.7392
F6	0.8604	0.9602	0.9314	0.7954
F7	0.8567	0.9624	0.9321	0.7982
F8	0.8542	0.9643	0.9271	0.832

HCL: Hydrochloride

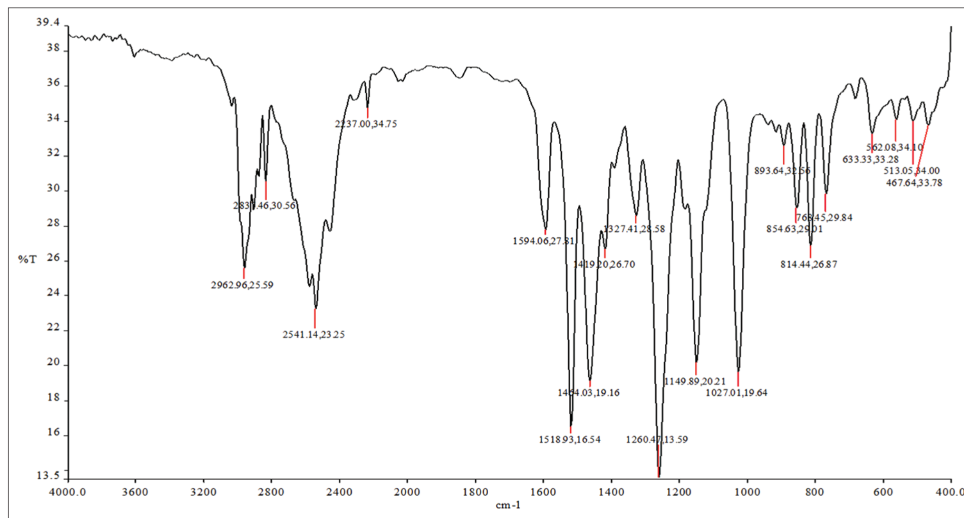

Figure 4: Fourier transform infrared spectrum of buspirone hydrochloride

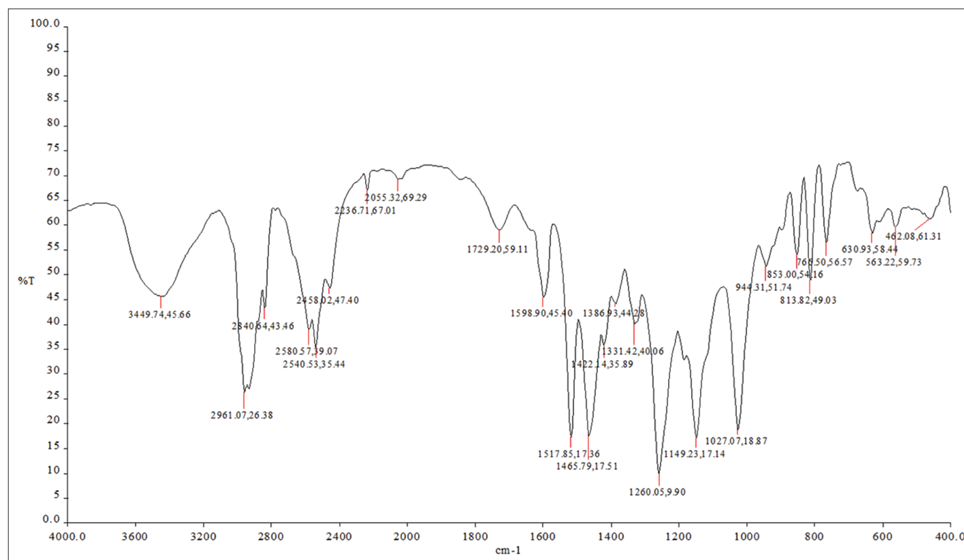

Figure 5: Fourier transform infrared spectrum of physical mixture of drug with HPMC E15

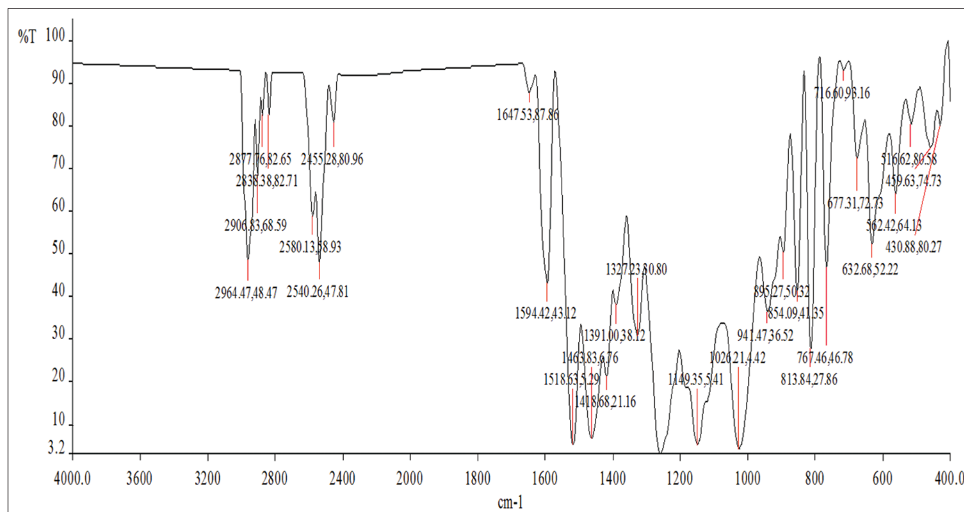

Figure 6: Fourier transform infrared spectrum of physical mixture of drug with hydroxylpropyl methylcellulose E50

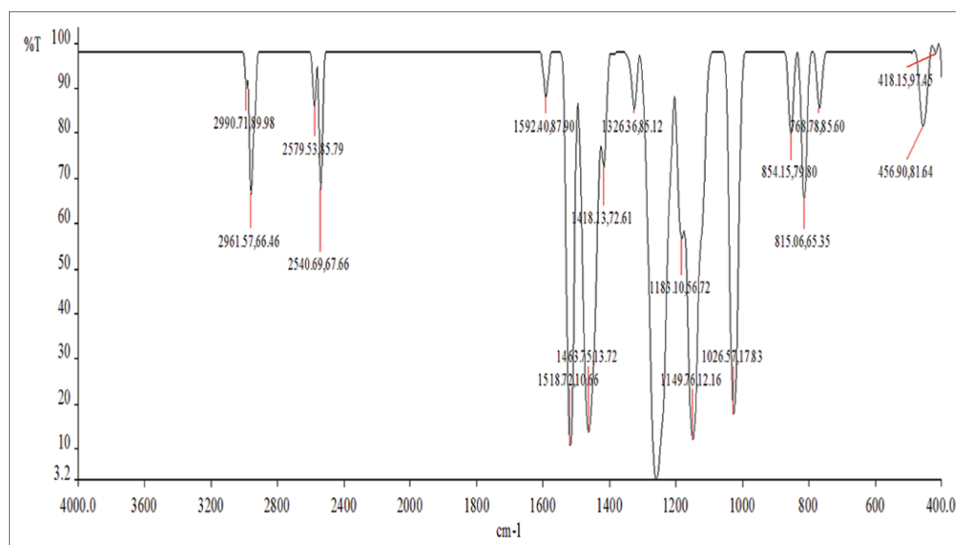

Figure 7: Fourier transform infrared Spectrum of physical mixture of drug with eudragit RS-100

Evaluation of the developed transdermal patches

Weight, thickness, and drug content uniformity

The prepared patches were smooth, elegant in appearance, uniform in weight, thickness, and drug content and showed no visible cracks and showing good folding endurance. Table 4 shows the important physicochemical parameters of transdermal patches of buspirone HCL. The weight of the patches ranged from 81.33 to 88.66 mg. The thickness ranged from 0.17 to 0.29 mm and was found to be increased with increase in polymer concentration. The drug content in the patches was uniform showed that the drug was dispersed uniformly throughout the patches. The drug content of transdermal patches was found to be in the range of 90.53 to 99.03%. From the results obtained, it was clear that there was proper distribution of drug in all formulations. The mean and standard deviations were calculated. All these parameters were within acceptable limits.

Moisture content test

Moisture content of the developed formulations F1–F8 varied from 3.42 to 4.67%. The formulations F1 which is having high moisture absorption was found to be 4.67%. The formulations F8 which is having less moisture absorption was found to be 3.42%. The results revealed that the moisture content was found to increase with increasing concentration of hydrophilic polymer (HPMC). The moisture content of the prepared formulations was low, which could help the formulations remain stable and reduce brittleness during long-term storage.

Moisture uptake test

Moisture uptake of the developed formulations F1–F8 varied from 3.30 to 4.03%. The formulations F1 which is having high moisture content was found to be 4.03%. The formulations F4 which is having less moisture absorption was found to be 3.30%. The results revealed that the moisture uptake was found to increase with increasing concentration of hydrophilic polymer (HPMC). The moisture uptake of the formulations was also low, which could protect the formulations from microbial contamination and reduce bulkiness.

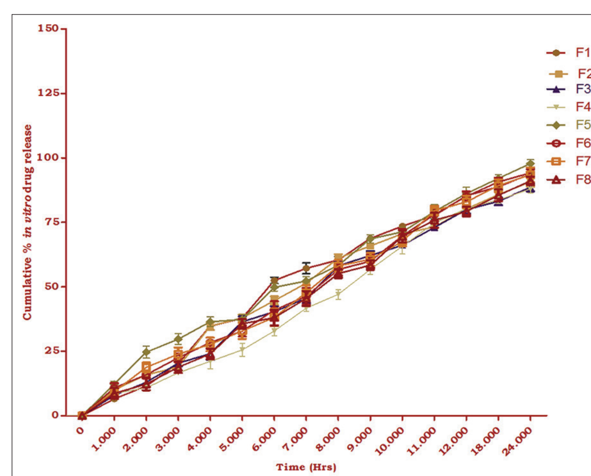

Figure 8: Comparative *in vitro* diffusion study of all formulations. *n=3, studies were repeated in triplicate, and the mean was calculated

In vitro drug release studies from transdermal patches

The drug release profiles of buspirone HCL from transdermal patches are shown in Figure 8. Formulations F1, F5, and F6 exhibited greatest (93.70%, 97.80%, and 94.16%, respectively) percentage of drug release values, which are significantly different compared to the lowest values observed with the formulations containing Eudragit RS-100 in higher concentration (F3–F4 and F7–F8 formulations).

In vitro drug release data were fitted to zero order, first order, Higuchi, and Korsmeyer-Peppas equations to ascertain the

Table 6: Physicochemical properties of most satisfactory formulations (after stability)

Formulation code		F5	
Time (days)		30 days	60 days
Folding endurance*	A	111.66±7.6	112±11.01
% Content uniformity*	A	96.04±0.15	94.19±2.92
% Moisture content*	A	4.09±1.47	3.42±0.91
% Moisture uptake*	A	3.99±0.77	3.47±0.54

Where A: 40°C±2°C/75%±5% RH. *n=3

pattern of drug release of buspirone HCL from transdermal patches [Table 5]. In the present study, it was observed that as the concentrations of hydrophilic polymer (HPMC) increased in the formulations, the drug release rate increased substantially. The description of drug release profiles by a model function has been attempted using different kinetics (zero order, first order, and Higuchi square-root model, peppas). Higuchi square root seemed to be the most appropriate model describing kinetics from all patches. On the other hand, "n" values ($0.721 \leq n \geq 1.012$) indicated that amount of released drug was by non-Fickian diffusion.

In vivo studies

In vivo studies were carried out in rabbit revealed that the consistence *in vitro* pattern of the matrix F5 was reproducible even in biological environment. The *in vivo* drug release shows 73.82% release as shown in the Figure 9.

Skin irritancy test

Skin irritation studies revealed that the batch F5 (HPMC E50 1%, Eudragit RS-100 9%) had no erythema and edema.

In vitro and in vivo correlation between cumulative % drug released in vitro and % drug permeated in vivo of optimized formulation of transdermal patch

Cumulative percentage of *in vivo* buspirone HCL release through the rabbit was correlated against cumulative percentage of drug released using *in vitro* release tests for optimized formulation F5. Figure 10 shows the relationship between the percentage of buspirone HCL released *in vivo* and percentage of drug released *in vitro*. The straight line and the high correlation coefficient of 0.984 proved the good correlation between *in vitro* drug release and *in vivo* drug release studies. Hence, by considering the complete difference in the test conditions of *in vitro* and *in vivo* release studies, the high correlation, and coincidence of *in vitro* and *in vivo* release profiles, it can be concluded that transdermal patches could be a useful carrier in improving the bioavailability.

Stability studies

Stability studies were carried out on most satisfactory formulation as per ICH Guidelines Q1C. The most satisfactory formulation was sealed in aluminum foil and stored in stability chamber. These were stored at room temperature for 2 months; after 2 months, drug content of most satisfactory formulation was determined by method discussed previously in entrapment efficiency section. Table 6 and Figure 11 show that there were no significant changes found in physicochemical parameters and *in vitro* diffusion of the most satisfactory formulations (F5) after stability studies.

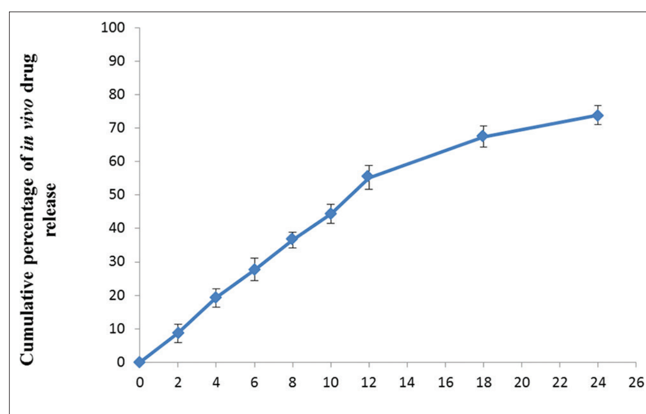

Figure 9: *In-vivo* drug release of the optimized formulation F5. *n=3, studies were repeated in triplicate, and the mean was calculated

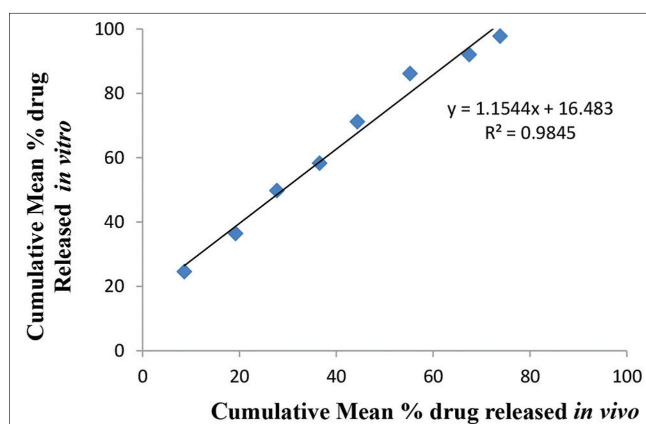

Figure 10: Correlation between *in vitro* and *in vivo* drug release of the optimized formulation F5

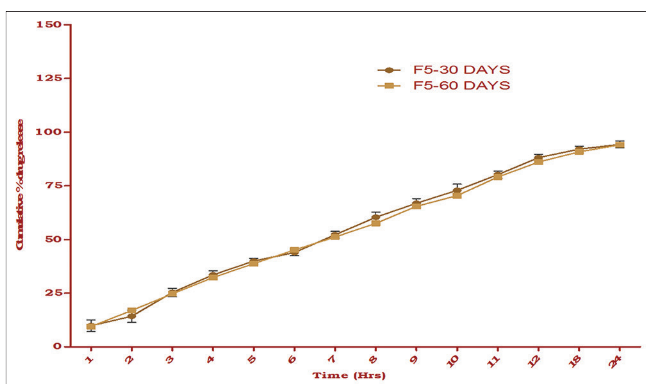

Figure 11: *In vitro* cumulative % of drug permeation studies of most satisfactory formulations (after stability). n=3, studies were repeated in triplicate, and the mean was calculated

CONCLUSION

It was concluded from the present studies that the transdermal patches of buspirone HCL are capable of exhibiting controlled release with the stability. Stability study of the formulations showed no significant changes in the drug content as well as physical characteristics of the film. The formulation (F5) HPMC E15: Eudragit RS-100 (1:9%) has fulfilled the objectives of the present study such as increasing the bioavailability, reduction in the frequency of administration, and improved patient compliance. Studies have shown promising results, and there is a scope for further pharmacodynamics and pharmacokinetic evaluation. There is a need to conduct toxicity studies using various experimental animals and evaluate the safety and efficacy of selected formulations.

REFERENCES

1. Sharma S. Topical preparations are used for the localized effects at the site of their application by virtue of drug penetration into the underlying layers of skin or mucous membranes. Pharma Rev 2008;6:1.
2. 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.
3. Gupta JR, Tripathi P, Irchhiaya R, Garud N, Dubey P, Patel JR. Formulation and evaluation of matrix type transdermal patches of glibenclamide. Int J Pharm Sci Drug Res 2009;1:46-50.
4. Sanap GS, Dama GY, Hande AS, Karpe SP, Nalawade SV, Kakade RS. Preparation of transdermal monolithic systems of indapamide by solvent casting method and the use of vegetable oils as permeation enhancer. Int J Green Pharm 2008;2:129-33.
5. Divya A, Rao MK, Gnanprakash K, Sowjanya A, Vidyasagar N, Gobinath M. A review on current scenario of transdermal drug delivery system. Int J Res Pharm Sci 2012;3:494-502.
6. Selvam RP, Singh AK, Sivakumar T. Transdermal drug delivery systems for antihypertensive drugs-a review. Int J Pharm Biol Res 2010;1:1-8.
7. Kumar JA, Pullakandam N, Prabu SL, Gopal V. Transdermal drug delivery system: An overview. Int J Pharm Sci Rev Res 2010;3:49-53.
8. Jain NK. Advances in Controlled and Novel Drug Delivery. 1st ed. New Delhi: CBS Publishers and Distributors; 2001. p. 108-10.
9. Gaur PK, Mishra S, Purohit S, Dave K. Transdermal drug delivery system: Review. Asian J Pharm Clin Res 2009;2:14-20.
10. Patel D, Patel N. Transdermal drug delivery system-review. Int J Biopharm Toxicol Res 2011;1:61-80.
11. Hadgraft J, Lane ME. Skin permeation: The years of enlightenment. Int J Pharm 2005;305:2-12.
12. Gannu R, Vishnu YV, Kishan V, Rao YM. Development of nitrendipine transdermal patches: *In vitro* and *ex vivo* characterization. Curr Drug Deliv 2007;4:69-76.
13. Darwhekar G, Jain DK, Patidar VK. Formulation and evaluation of transdermal drug delivery system of clopidogrel bisulfate. Asian J Pharm Life Sci 2011;1:270-8.
14. Desai BG, Annamalai AR, Divya B, Dinesh BM. Effect of enhancers on permeation kinetics of captopril for transdermal system. Asian J Pharm 2008;2:35-7.
15. Kelvin CG, Anil JS, Prathik HS. Formulation and *In vitro* characterization of monolithic matrix transdermal system using HPMC/Eudragit S100 polymer blends. Int J Pharm Sci 2009;1:108-20.
16. Sadashivaiah R, Dinesh BM, Uma AP, Desai BG, Raghu KS. Design and *in vitro* evaluation of haloperidol lactate transdermal patches containing ethyl cellulose povidone as film formers. Asian J Pharm 2008;2:43-9.
17. Honeywell-Nguyen PL, Bouwstra JA. Vesicles as a tool for transdermal and dermal delivery. Drug Discov Today Technol 2005;2:67-74.
18. Sateesh K, Vinod N, Ramesh P. Polymers in transdermal drug delivery systems. Pharm Tech 2002;62-80.
19. Anil J, Kevin C, Harinoth N. Development and characterization of transdermal therapeutics system of Tramadol hydrochloride. Asian J Pharm 2008;2:265-9.
20. Peddapalli H, Chinnala KM, Banala N. Design and *in vitro* characterization of mucoadhesive buccal patches of duloxetine hydrochloride. Int J Pharm Pharm Sci 2017;9:52-9.
21. Raju RT, Krodhi GM, Harigopal SS. Formulation and evaluation of transdermal drug delivery system for lercanidipine hydrochloride. Int J PharmTech Res 2010;2:253-8.
22. Sivakumar T, Shivaraj A, Panner S, Tamiz M. Design and evaluation of transdermal drug delivery of ketotifen fumarate. Int J Pharm Biomed Res 2010;2:42-7.
23. Guru S, Biplab K, Nagarajan K. Effect of permeation enhancers on propranolol hydrochloride formulated patches. Int J Pharm Pharm Sci 2010;2:21-31.
24. Jamakandi G, Mulla JS, Vinay BL, Shivakumar HN. Formulation, characterization, and evaluation of matrix-type transdermal patches of a model antihypertensive drug. Asian J Pharm 2009;3:59-65.
25. Jadhav RT, Kasture PV, Gattani SG, Surana SJ. Formulation and evaluation of transderal films of diclofenac sodium. Int J Chem Tech Res 2010;2:354-60.
26. Jayaprakash S, Mohamed HS, Firthouse PU. Preparation and evaluation of celecoxib transdermal patches. Pak J Pharm Sci 2010;23:279-83.

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