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Research Article

Design and *ex-vivo* evaluation of adhesive matrix type transdermal patch of buspirone hydrochloride

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ABSTRACT

The present work was intended to design alternative dosage form to the conventional tablets of the Buspirone hydrochloride (BH); as about 96% drug is metabolized during its first pass by oral route. An adhesive matrix system of BH was prepared by taking different ratios of Polyvinylpyrrolidone K30 (PVP) and Hydroxypropyl methylcellulose LMV (HPMC) with polyethylene glycol 400 (PEG) as plasticizer. Oleic acid was incorporated as penetration enhancer and sodium lauryl sulfate (SLS) as solubilizer in the hydroalcoholic solution. Resultant solution was dried on the Polyvinyl Alcohol EF (PVA) backing membrane to prepare adhesive matrix type transdermal patch. Physical evaluation of the adhesive matrix layers obtained by the various combinations of PVP and HPMC were carried out by performing thickness uniformity, ultimate tensile strength, peel adhesion, ball adhesion and moisture absorption studies. Permeation studies were performed using Keshary-Chien diffusion cell through human cadaver skin in 10% buffered formalin (7.4pH). Approximate zero order release kinetics was observed when a patch containing 4 mg/cm^2 of BH created a flux of 42µg/cm^{2}h^{-1} and penetrated about 1mg/cm^2 of drug in a day. Transdermal patch of BH provides a superior option to conventional tablets and creates reasonable change in the drug therapy of anxiety patients.

Keywords: Buspirone; Polyvinylpyrrolidone; Oleic Acid; Human Cadaver Skin; Transdermal Patch

INTRODUCTION

Currently, transdermal drug delivery is one of the most promising methods for drug application. Increasing numbers of drugs are being added to the list of therapeutic agents that can be delivered to the systemic circulation *via* skin.[Prausnitz MR 2004] Transdermal delivery provides a leading edge over injectables and oral routes by increasing patient compliance and avoiding first pass metabolism respectively.[Jain NK 2001] Drugs can be delivered across the skin to have an effect on the tissues adjacent to the site of application (topical delivery) or to have an effect after distribution through the circulatory system (systemic delivery). While there are many advantages to delivering drugs through the skin, the barrier properties of the skin provide a significant challenge [Bhowmik D 2010].

Transdermal patch or adhesive patch or skin patch used to deliver a controlled dose of a drug through the skin over a period of time. A skin patch uses a special membrane to control the rate at which the liquid drug contained in the reservoir within the patch can pass through the skin and into the bloodstream. Some drugs must be combined with substances, such as alcohol, that increase their ability to penetrate the skin in order to be used in a skin patch. Drugs administered through skin patches include scopolamine (for motion sickness), nicotine (for quitting smoking), estrogen (for menopause and to prevent osteoporosis after menopause), nitroglycerin (for angina), lidocaine to relieve the pain of shingles and many more drugs [Shah S 2008].

Buspirone is the selective anxiolytic drug structurally different from benzodiazepines, acts therapeutically without creating side effects like sedation, muscle relaxation and physical dependence; those commonly observed with Benzodiazepines. Buspirone is widely used in the treatment of generalized anxiety disorder and attention deficit hyperactivity disorder, in children. Recently, buspirone is also found useful in smoking cessation and rehabilitation of alcohol addicts. Though the BH is potent drug; it has a wide therapeutic window making the drug safe for its use in variety of patients. [DeMartinis N 2000, Sachs DP 1991, Farid P 1998]. Approximately 1 to 1.5 mg of drug out of 20-30 mg administered dose per day is actually responsible to create ordinary therapeutic effect. This fact strongly suggests that there is a need of alternative dosage form administrable by other route to avoid oral first pass presystemic metabolism. In addition to this if,

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Table 1: Formulations with different ratios of PVP:HPMC

Formulation Code	PVP:HPMC (total 10% wt/v) (gm:gm)	PEG 400 (0.267% v/v) (ml)	Oleic acid (1.4% v/v) (ml)	SLS (1.3% wt/v) (gm)	BH (2.5% wt/v) (mg)	Ethanol 90% (60% v/v) (ml)	Water sufficient to make (ml)
F1	0.75:0.25	0.267	0.14	0.13	1000	6.6	10
F2	0.76:0.24	0.267	0.14	0.13	1000	6.6	10
F3	0.77:0.23	0.267	0.14	0.13	1000	6.6	10
F4	0.78:0.22	0.267	0.14	0.13	1000	6.6	10
F5	0.79:0.21	0.267	0.14	0.13	1000	6.6	10
F6	0.80:0.20	0.267	0.14	0.13	1000	6.6	10
F7	0.81:0.19	0.267	0.14	0.13	1000	6.6	10
F8	0.82:0.18	0.267	0.14	0.13	1000	6.6	10
F9	0.83:0.17	0.267	0.14	0.13	1000	6.6	10

alternative dosage forms provide steady flux of drug in systemic circulation; avoiding fluctuation commonly observed with oral therapy; will greatly improve the quality of therapy [Barbanoj MJ 1998]. BH tablets are generally taken three to four times a day; but if alternative dosage form provides once a day administration, then it will substantially improve patient compliance.

MATERIALS AND METHODS

Materials

Gift samples of BH USP by NAVKETAN Pharma Pvt. Lt. from Waluj MIDC, Aurangabad; Polyvinylpyrrolidone (K30), Oleic acid, Formalin solution (3.8-4% formaldehyde), monobasic sodium phosphate monohydrate ($NaH_2PO_4H_2O$) dibasic sodium phosphate anhydrate (NA_2HPO_4), bromocresol green and chloroform from Bombay RESEARCH-LAB; Hydroxypropylmethylcellulose LMV (low to medium viscosity i.e. 350±50cps), Polyvinyl alcohol (EF), Polyethylene Glycol (400) and Sodium Lauryl Sulphate from LOBA Chemie Pvt. Ltd. Mumbai; and other chemicals of analytical grade were used.

Formulation Ingredient selection

Formulation development was executed using the simple method of optimizing one variable at time and simultaneously keeping other variables constant to their optimized level. First stage of development initiated with the optimization of different combinations of PVP: HPMC with fixed amount of plasticizer, propylene glycol (30% by weight to the total polymer content) in ethanol: water 50:50 solvent systems [Tsai YH 2011]. Casted blank films were physically evaluated after drying at room temperature for 24 hours and only those selected for the further developments which were having relatively better physical appearance[Udupa N 1995]. The casted films ranging from combination PVP:HPMC, 0.75:0.25 to 0.83:0.17 in 10 ml patch solution were sorted for the further development. The concentration of plasticizer was also altered with 0.8:0.2 combinations of polymers to find the optimum one; but 30% to that of polymer weight was found appropriate.

In the second stage of the development, different penetration enhancers were tried to check the physical compatibility with above casted films; and it was observed that most of them were incompatible with hydroalcoholic system and separated themselves while drying. At the end, oleic acid was found to have reasonable compatibility when composition of solvent system was altered to 60:40 ethanol: water and sodium lauryl sulphate was added as solubilizer. Penetration enhancer, oleic acid was taken as maximum as possible without compromising the quality and physical appearance of the polymer films; while SLS was optimized to have minimum concentration sufficient to keep oleic acid in the system. Final selections of the ingredients in various formulations were depicted in table I.

Preparation of patch

BH & HPMC (LMV) were dissolved in 3.5 ml of distilled water in a test tube. PVP (K30), PEG-400, Oleic acid and SLS were dissolved in 6.6 ml of 90% ethanol in another test tube. Contents of first test tube were added into the second test tube and final volume was adjusted to 10 ml by distilled water to make patch solution. One ml of patch solution poured on backing membrane (PVA sheet); already dried on the bottom of the 2mm deep fabricated stainless steel mold (horizontally leveled) enclosing 25 cm^2 area; for drying at room temperature. Dried adhesive layer was removed from the mold along with the PVA backing membrane and treated as finished patch. One ml of solution containing 100 mg of drug was dried on 25cm^2 surface; therefore, prepared patch was containing 4 mg of drug per square cm. Last eight formulations taken for the permeation study were as shown in the Table I.

Preparation of PVA backing membrane

The backing membrane was prepared by dissolving 4% w/v PVA (EF) in distilled water. A weighed amount of PVA was added in the measured amount of warm dis-

Table 2: Physical evaluation and Mechanical properties (Mean ± S.D. for n=6)

Formulation Code	PVP:HPMC (gm:gm/10ml)	Thickness in mm (Mean± S.D.)	UTS (MPa) (Mean±S.D.)	% Elongation on break	Young's Modulus (MPa) (Mean± S.D.)
F1	0.75:0.25	0.151±0.005	04.11±2.21	043±2.2	09.53±2.43
F2	0.76:0.24	0.150±0.004	06.23±1.94	068±2.4	09.16±1.34
F3	0.77:0.23	0.149±0.005	08.78±1.83	091±2.9	09.64±1.89
F4	0.78:0.22	0.148±0.006	13.20±1.69	136±3.8	09.70±1.45
F5	0.79:0.21	0.147±0.004	32.12±1.52	188±4.8	17.08±1.27
F6	0.80:0.20	0.146±0.003	62.40±1.46	217±5.6	28.75±1.21
F7	0.81:0.19	0.147±0.003	25.44±1.43	239±6.4	10.64±1.18
F8	0.82:0.18	0.148±0.004	04.89±1.48	140±1.5	03.49±1.39
F9	0.83:0.17	0.149±0.005	03.74±1.51	089±1.3	04.20±1.63

tilled water maintained at 70°C to create homogenous solution and stirred for few seconds to get desired consistency. The resultant solution was poured into horizontally leveled stainless steel mould to solidify at room temperature and then dried into the oven (55°C) for 6 hours, forming a smooth, uniform, transparent backing membrane.

Physical Evaluation

Thickness Uniformity

Initially, the thickness of backing membrane (PVA sheet) measured several times using micrometer screw gauge (Surya Lab Expotech, Delhi) having least count 10µm and average thickness was determined. Later, the thickness of prepared patch was measured using same instrument and average thickness of significantly uniform backing membrane subtracted from the thickness of the patch to get thickness of adhesive matrix. Multiple observations were taken and standard deviation was determined.

Measurement of mechanical properties

An instrument was fabricated with hook at one end, a metallic pulley at the other end and a stainless steel scale flush on the surface of the wooden board. A clamp was fitted to the hook and another clamp was tied to the one end of the string. Other end of the same string was running over the pulley and tied firmly to the pan. Strips of adhesive layers (separated from the backing membrane), 4 mm wide and 2 cm long with known thicknesses were taken for the tensile strength studies. Two cm long strips one by one were held into two opposite clamps hanging just over the graduated scale in such a way that, half cm length were held into each clamp and the remaining one cm was held between the clamps for elongation. By this arrangement it was possible to slowly increase and optimize the suitable load by adding weights in the pan; on the adhesive matrix layers to elongate and break within 3-5 seconds. The mechanical properties were calculated according to the following formula. [Udupa N 1995, Jain NK 1997].

$$\% \text{ Elongation at break} = \frac{\text{Increase in length (mm)}}{\text{Original length (mm)}} \text{ X } 100$$

$$\text{Ultimate Tensile strength (MPa)} = \frac{\text{Force at break (N)}}{\text{Initial cross-sectional area of the strip (mm}^2\text{)}}$$

Peel Adhesion Testing

Strips of the finished patches, 1 cm wide and 4 cm long were taken for the peel adhesion studies and 2 cm^2 area stacked on the stainless steel surface such that free end directed away from the pulley fitted at other end of the board. Free end of the strip then folded back and held firmly by clamp tied to the string which was running over the pulley. Other end of the string was tied to the pan, so that different weights can be added to increase the load. Weight in grams required for complete adhesion failure was determined as measure of peel adhesion. [Udupa N 1995, Jain NK 1997]

Ball Adhesion Testing

An instrument was fabricated containing a wooden board with plane surface leveled horizontally and other wooden sheet fitted on to it making 22.5° angle to the first one. Wooden bars were fitted on the inclined surface to guide the running of the stainless steel ball smoothly in the vertical direction. A transdermal patch was fitted on the horizontal platform in such a way that, the running ball could easily continue the motion further on the surface of the adhesive layer. A stainless steel ball of 3 mm diameter and 0.132 g weight taken for the study and altitude of delivery from the inclined surface was optimized by trial and error method. Different patches were studied for their ball adhesion property by using same ball and same altitude on the inclined surface. The inverse of total distance travelled by the ball on the adhesive surface of patch from the point of first contact was determined as measure of adhesiveness of matrix. [Jain NK 2001].

$$\% \text{ Ball Adhesion} = \frac{1}{\text{Distance travelled by the ball away from the point of contact (cm)}} \text{ X } 100$$

Moisture Absorption studies

Saturated solutions of sodium bromide, ammonium chloride and potassium dichromate when stored in the closed glass chamber; creates 58%, 79% and 98% relative humidity, respectively. Patches were cut into three pieces, each enclosing one cm^2 area and stored in tightly closed desiccators with activated silica gel for 24 hours to remove excess of moisture. One piece of every patch was transferred to the different relative humidity conditions in order to study moisture uptake capacity of the adhesive matrix layer. Weight gained by the patches noted after 24 hours and relative moisture absorption were calculated and compared. [Udupa N 1995, Jain NK 2001, Yie WC 1987].

$$\% \text{ Moisture uptake} = \frac{\text{Final Weight - Initial Weight}}{\text{Initial Weight}} \text{ X } 100$$

Preparation of Human Cadaver Skin

Human cadaver hairless skin of neck region procured within 12 hours after the postmortem of the donor's dead body from the hospital. Skin was carefully dermatomed, washed with demineralised water, transferred immediately to 5% wt/v EDTA solution and carried to the laboratory of the present work. After 8 hours of storage in EDTA solution, subcutaneous tissue and dermis were removed using surgical blade and forceps to obtain 0.1 to 0.12 mm thick epidermis. Epidermis was cut into several round pieces of diameter sufficient as per the need of permeation studies and stored at 0 to 4 ^{0}C in formalin solution (3-4 % formaldehyde, in distilled water) till the actual permeation study initiate. Skin pieces were selected for thawing at the room temperature after observing under simple microscope for any possible damage to stratum corneum. Further these pieces were allowed to equilibrate for 15 minutes with sufficient quantity of BF just before mounting them on the diffusion cell for permeation study. [Deepak G 2003, Lalatendu P 2005, Narsimha M 1997]

Skin Irritation Test

Medicated patches were applied on the skin of the healthy subject for 24 hours to observe any possible irritation to the skin. [Yie WC 1987]

Ex-vivo Permeation Study Using Keshary-Chien Diffusion Cell

Keshary-Chien (KC) diffusion cells were used for *ex-vivo* permeation studies. The human cadaver skin was mounted between the two compartments of the diffusion cell with stratum corneum facing the donor compartment. The stratum corneum side of the skin was kept in intimate contact with adhesive matrix of the transdermal patch under test. A cap of donor compartment of KC cell was tightly fitted with clamp to avoid any possible sleep of patch or skin from its expected position. The receptor liquid was 20.3 ml of BFS (prepared by mixing 100 ml of 38-40% formalin with 900 ml distilled water & buffered to 7.4pH by adding approximately 4.2 g monobasic sodium phosphate monohydrate and 6.8 g of dibasic sodium phosphate anhydrate) stirred at 200 rpm on a magnetic stirrer; the whole assembly was kept at 37±0.5°C by circulating constant temperature (38±0.5^{0}C) water through jacket of KC cell. Samples of 1 ml were collected at the 4, 8, 12, 16, 20 and 24th hours since the start of permeation up to the end and replenished every time with an equal volume of BFS (pH 7.4). [Jain NK 2001, Yie WC 1987] The amount of drug permeated was estimated using spectrophotometric method [Amanlou1 M 2009] and concentration was corrected for sampling effects according to Hayton and Chen,

$$C^1n = Cn\ (V_T / V_T - V_S)\ (C^1_{n-1} / C_{n-1})$$

Where, C^1_n is the corrected concentration of the n^{th} sample, C_n is the measured concentration of BH in the n^{th} sample, C_{n-1} is the measured concentration of the BH in the $(n-1)^{th}$ sample, V_T is the total volume of the receiver fluid and V_S is the volume of the sample drawn. All permeation studies were repeated thrice to confirm the results.

The steady state flux (Jss) was calculated from slope of the straight portion of line in the plot of drug amount permeated Vs time for different formulations and compared with theoretical target flux. Permeability coefficient (Kp) was calculated by dividing the flux with the amount of drug in the patch. The lag time was calculated from intercept on time axis in the plot of cumulative amount permeated Vs time. The theoretical target flux was calculated using Equation

$$\text{Target Flux} = C_{SS} \times Cl_T \times \text{B.Wt.} / A$$

Where, C_{SS} is target steady state therapeutic concentration of BH (i.e. 2.5 µg/L), Cl_T is total clearance of BH from human body (i.e. 1.7 L/h), B.Wt. is average body weight of adult human being (i.e. 60 Kg) and A is the area of skin that allowed penetration of the drug into receptor compartment of KC cell (i.e. 6.15 cm^2). Therefore the target flux for BH for given KC cell was 41.46 µg /$cm^2.h^{-1}$.

Spectrophotometric Analysis

A Stock solution of BH was prepared by diluting 10mg of drug in 1 L of BFS (10µg/ml). Suitable amount of solution was withdrawn and diluted with distilled water as per the need. A simple and sensitive spectrophotometric method invented by M. Amanlou et. al. was used for determination of BH dissolved in BFS. The method was based on the reaction of buspirone and bromocresol green. The ion-pair complex was quantitatively extracted into chloroform at pH 2.3 followed by spectrophotometric determination using Double Beam UV-Visible Spectrophotometer (CHIMADZU UV-1800) at 415 nm.

Assay

Table 3: Adhesive strength and moisture uptake evaluation (Mean ± S.D. for n=6)

Formulation code	Peel Adhesion	% Ball Adhesion	% Moisture uptake in closed chamber at different relative humidity's at room temperature (~25°C).		
			(58%)	(79%)	(98%)
F1	[a]	16.33±1.24	08.34±0.86	07.95±0.93	08.32±1.23
F2	[a]	18.08±1.19	09.17±0.76	08.56±1.03	08.88±1.20
F3	00.89±0.053	19.60±1.86	09.89±0.62	09.53±1.06	09.77±1.32
F4	01.10±0.059	22.37±2.15	09.76±0.86	09.23±1.13	09.63±1.24
F5	01.78±0.043	23.92±2.93	11.34±0.94	10.89±1.00	11.10±1.31
F6	02.58±0.059	25.38±3.12	12.03±0.82	11.56±0.98	11.34±1.35
F7	06.13±0.136	39.32±3.65	12.89±0.98	11.94±1.15	12.03±1.45
F8	09.69±2.67	41.12±4.14	13.41±1.02	13.95±1.24	13.22±1.46
F9	12.36±3.24	46.67±4.76	13.34±1.11	13.86±1.20	13.54±1.53

[a] insufficient adhesion to apply any load

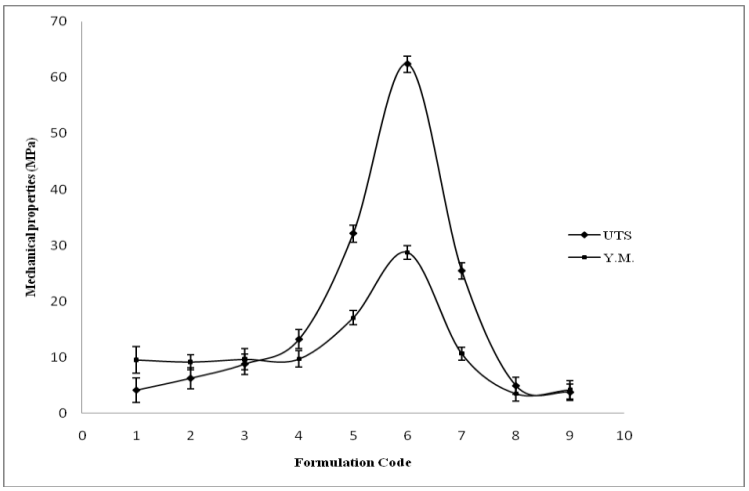

Figure 1: Mechanical properties. (n=6)

Finished transdermal patches were assayed for their drug content in order to know the loading efficiency of the procedure and also to get idea about stability of the drug in the final product at normal conditions. For this purpose, 1 cm^2 patch was dissolved in 1 L of distilled water to obtain matrix solution and filtered to separate backing membrane and insoluble particles, if any. This solution was diluted using distilled water and examined spectrophotometrically at 415 nm to determine unknown concentration of BH.

Stability studies

Stability studies of final product was done as per ICH guidelines for a period of six months at 40^0C temperature and 75% RH in stability chamber (Fourtech, Mumbai) and examined for all parameters.

RESULT AND DISCUSSION

Physical Evaluation

Thickness Uniformity

Measurement of thickness uniformity of backing membrane and finished patch were determined using micrometer screw gauge. Six random samples were evaluated and 5% deviation in the thickness was rarely observed ($p<0.01$) in case of backing membrane; whereas 5% deviation was rarely observed ($p<0.05$) in case of finished patch. (Table II)

Measurement of mechanical properties

Patches containing polymer combination close to 0.8:0.2 (PVP:HPMC) were having large UTS and Young's modulus as depicted in the Table II and Fig II. There were minimum deviation in these parameters close to formulation F6 (0.8:0.2) and large deviation on both sides of this combination.

Adhesion Testing

There was a constant increase in the adhesiveness of the matrix with the increase in PVP concentration shown by both peel adhesion and ball adhesion tests (Table III).

Moisture Absorption studies

Approximately 10% moisture was taken up by the different patches at different humidity conditions and there was slight increase in deviation at large humidity conditions.

Skin Irritation Test

Erythema or edemas like common inflammatory conditions were not created by the patches.

Table 4: Permeation parameters (n=3)

Formulation Code	Total Ex-vivo Permeation per cm^2 in 24 h (Q_{24}) (µg).	Flux (J_{SS}) in µg /cm^2 .h^{-1} (straight portion	Kp – Avg. Permeation coefficient (h^{-1})	Y intercept in (µg /cm^2)	R^2 Zero order plot
TF[b]	0995	41.46(00-24)	0.248	00.00	01.00
F1	0253	13.12(18-16)	0.063	39.05	0.961
F2	0697	33.12(12-20)	0.174	88.75	0.991
F3	0998	42.12(04-12)	0.249	135.5	0.997
F4	0963	37.75(04-12)	0.240	150.3	0.937
F5	1400	37.25(08-16)	0.350	241.4	0.802
F6	1595	13.12(16-24)	0.398	283.1	0.663
F7	1289	15.00(12-20)	0.322	228.7	0.711
F8	1102	17.87(12-20)	0.275	188.0	0.818
F9	0543	03.50(16-24)	0.135	95.53	0.748

[b] Expected theoretical values of different parameters for target formulation.

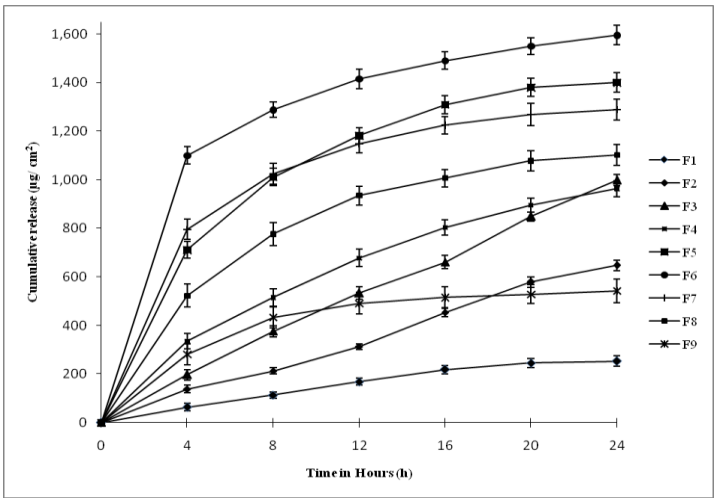

Figure 2: Permeation flux of BH created by various formulations.(n=3)

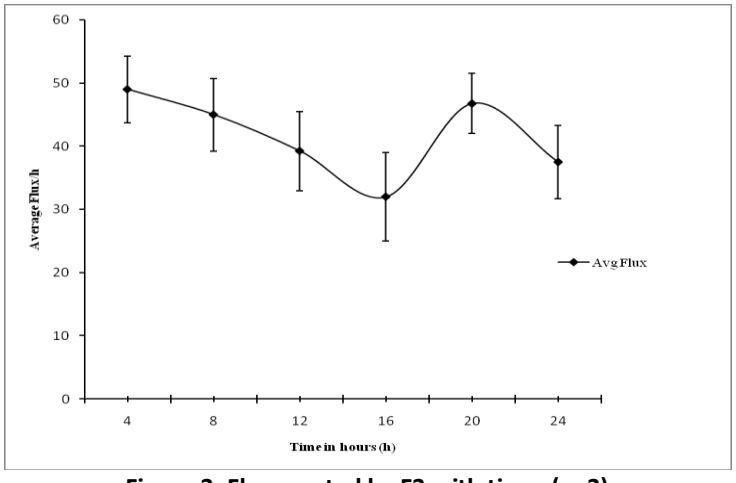

Figure 3: Flux created by F3 with time. (n=3)

Ex-vivo Permeation Study

Different permeation patterns were observed with change in polymer combination; most of them showed mixed order permeation kinetics; faster rate initially and slower rate later, probably indicating diffusion as principal mechanism of permeation (Fig I). Fortunately, F3 and F2 showed approximate zero-order permeation with R^2 values 0.997 and 0.991 respectively. Formulation F3 containing 4 mg/cm^2 of BH created a flux of approximately 42µg/cm^2h^{-1} and permeated about 1mg/cm^2 of drug in a day with less deviation (<7µg on each side) in flux and total amount permeated per day (Fig III and IV). There was no lag phase observed in case of any formulation. Permeation studies were repeated thrice to confirm the results in each case (Table IV, Fig. I).

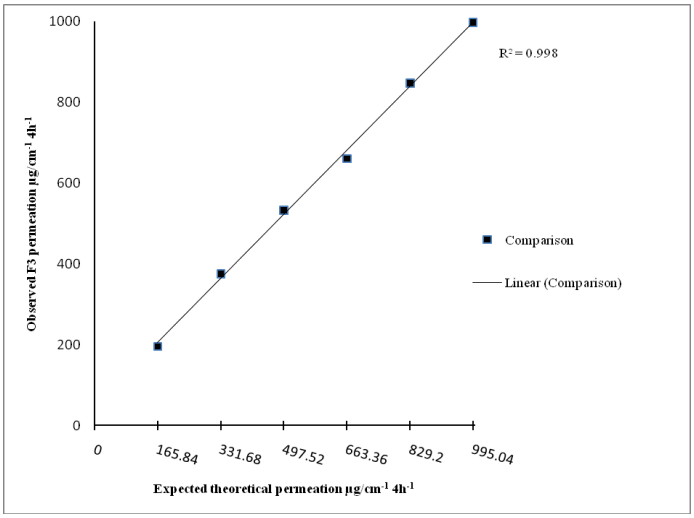

Figure 4: Comparison of permeation between formulation TF and F6

Spectrophotometric Analysis

Spectrophotometric analysis was performed using validated method invented by M. Amanlou et. al. The complex was stable up to 2 days and obeyed Beer's law over the concentration range of 1.5 - 6 µg/ml (R^2= 0.9999).

Assay

Finished transdermal patches were assayed for their drug content in order to know the loading efficiency of the procedure and also to get idea about stability of the drug in the final product at normal conditions. Twenty patches of formulation F3 were assayed and more than 1% deviation was rarely observed ($p<0.05$).

Stability studies

Stability studies were conducted as per ICH guidelines using stability chamber (Fourtech, Mumbai) at 75% RH and 40^0C temperature. There was no significant difference observed in all evaluation parameters after a period of six month.

CONCLUSION

The present study demonstrates the potential of adhesive matrix patch in drug delivery of Buspirone Hydrochloride. This drug can be delivered with low dose and low frequency of dosing by using transdermal route which prevents significant presystemic first pass metabolism. The transdermal adhesive matrix permeates sufficient amount of drug to comply the therapeutic need of BH in ex-vivo model. It is possible to change the dose per cm^2 to achieve different flux values required by different patients like, pediatrics and geriatrics. It was interesting to observe the permeation kinetics of F2 and F3 formulations for 24 hours as it fulfills the therapeutic need.

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