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Original Article

Natural and Synthetic Polymer-Based Transdermal Patch Formulation for Bosentan: Development and *in vitro* Evaluation

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ABSTRACT

Introduction: The goal of this study was to develop and evaluate Bosentan transdermal patches for the treatment of Pulmonary Arterial Hypertension (PAH), which is defined as an abnormally high blood pressure in the arteries that supply blood to the lungs, in patients aged three and up. Patients with PAH may find that bosentan aids their exercise performance and slows the worsening of their symptoms. **Materials and Methods:** Using the solvent casting method, Bosentan transdermal patches were made with karaya gum and polyethylene oxide as polymers, PEG 600 as plasticizers and propylene glycol as a permeation enhancer. Folding endurance values for the manufactured Bosentan transdermal patches ranged from 95 to 100, indicating that the patches exhibited good elasticity and flexibility. -p f. **Results and Discussion:** The optimized formulation B-10 released 94.77% of the drug for up to 12 hr, according to the drug release trial. Studies using Fourier infrared spectroscopy and differential scanning calorimetry were carried out on the pure drug, polymers and optimised formulation B-10. The results showed that the drug and polymers did not interact with one another. There were no surface cracks or defects in the patches when SEM examination was performed on the pure drug and optimised formulation B-10.

Keywords: Bosentan, Plasticizers and Permeation enhancer, Polymers, Solvent casting method, Transdermal patches.

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INTRODUCTION

Since a very long time ago, the topical administration of active constituents through the skin has been selected as the site of administration. The significance of this method in systemic drug delivery over the past three to four decades has been recognized and taken into consideration for the delivery of drug administration, which is referred to as Transdermal Drug Delivery Systems (TDDS). On the other hand, everyone believed that the function of the skin barrier is to prevent the loss of water and to permit the intake of substances from the outside world into the body. There are some active pharmaceutical components that are capable of passing through the skin in sufficient quantities and producing systemic activity. There is a possibility that medications with a short half-life would undergo substantial metabolism and this route of administration is one that can be utilized (Gupta *et al*., 2009; (Vyas, 2002; Sanap *et al*., 2008). In order to alleviate symptoms of nausea, vomiting and angina, transdermal patches were developed to maintain over the prolonged period of time. Within the past few years, a multitude of transdermal patches have become commercially accessible for the delivery of hormones and analgesic tablets (Patel *et al*., 2009; Devi *et al*., 2003). The main objective of the present investigation was to design and development of transdermal patches of bosentan using natural and synthetic polymers to treat pulmonary arterial hypertension in adults and children up to aged 1-3 years. It is possible for the components of medications to enter the body through the skin through three different paths, including the sweat duct, the sebaceous glands and the hair follicles. In addition to its widespread application in the treatment of a variety of skin conditions, this method of drug delivery is also utilised in the management of angina pectoris, aches, smoking cessation and neurological illnesses such as Parkinson disease (Irfani *et al*., 2001; Jain, 2001). Skin patches are adhesive patches that are medicated and applied on the skin in order to provide a specified dose of

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medication to the skin through the blood stream (Tanner and Marks, 2008). Skin patches are also known as topical patches. For the purpose of this investigation, transdermal patches containing bosentan were manufactured by the process of solvent casting. Bosentan is the name of the endothelin receptor antagonist that was the first to be used successfully in the treatment of Pulmonary Arterial Hypertension (PAH). The oral bioavailability of bosentan is fifty percent in healthy individuals and this bioavailability is not dependent on the consumption of meals (Flynn, 1996).

MATERIALS AND METHODS

Bosentan gift sample from M/S Aurobindo Pharma Ltd, Hyderabad. Karaya Gum and Polyethylene oxide were procured from M/S Aurobindo Pharma Ltd., Hyderabad. PEG 400 and Propylene oxide were obtained from SD Fine Chem., Ltd., and Mumbai.

Preparation of Bosentan transdermal patches

Solvent casting is the method employed to prepare Bosentan transdermal patches. A mixture of drug and polymer was dissolved in ethanol and subjected to sonication for 30 min until a uniform semisolid consistency was achieved. PEG 600 and Propylene glycol were introduced and thoroughly blended. An ethanolic solution was poured onto a petridish containing mercury as a substrate and left to desiccate at ambient temperature for 48 hr. The desiccated patches were collected and kept in a desiccator until they were used for additional experimental analysis (Rastogi and Yadav, 2012). The images and composition of Bosentan transdermal patches were shown in Table 1 And Figure 1 (Hemalatha *et al.*, 2010).

B-1 B-2 B-3

B-4 B-5 B-6

B-7 B-8 B-9 B-10

Figure 1: Transdermal patches of Bosentan.

Table 1: Composition of transdermal patches containing Bosentan.

Ingredients	B-1	B-2	B-3	B-4	B-5	B-6	B-7	B-8	B-9	B-10
Bosentan (mg)	10	10	10	10	10	10	10	10	10	10
Karaya gum(mg)	50	60	70	80	90	-	-	-	-	-
Polyethylene oxide (mg)	-	-	-	-	-	50	60	70	80	90
PEG 600 (mL)	2	2	2	2	2	2	2	2	2	2
Propylene Glycol (mL)	4	4	4	4	4	4	4	4	4	4
Ethanol: Dichloromethane (1:1) (mL)	10	10	10	10	10	10	10	10	10	10

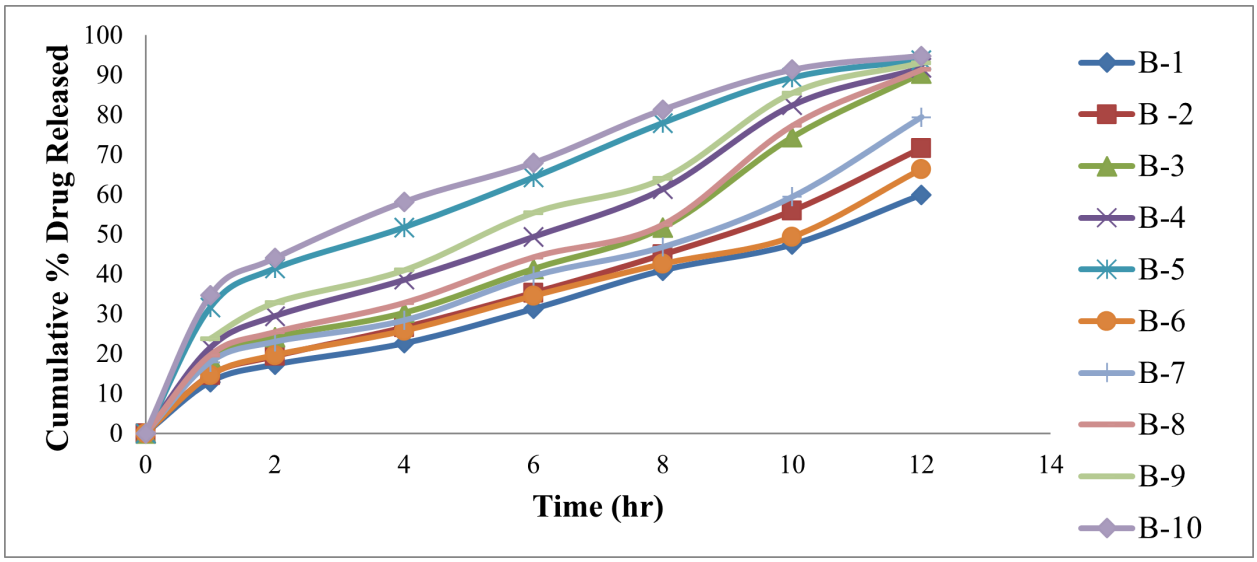

Figure 2: *In vitro* Drug Release Profile of Bosentan transdermal patches.

Evaluation of physical parameters for Bosentan transdermal patches

The Physical parameters for transdermal patches of Bosentan were evaluated (Suganeswari *et l.*, 2011). Each patch measuring 3.14 cm^2 was cut evenly and weighed to ensure consistent weight and reduce differences among all the patches. All the formulations exhibited precise and extremely beneficial content homogeneity.

Weight Variation

For the weight variation test, the three 3.14 cm^2 discs were sliced and weighed using an electronic balance. The purpose of the test was to measure the weight homogeneity and, consequently, the batch-to-batch variance.

Drug Content

The selected patch was cut, and its contents were dissolved in a 6.8 pH phosphate buffer. To make the polymer soluble, it is set aside for a while. After that, 1 mL was taken out of the solution and diluted to 10 mL. After measuring the solution's absorbance at 270 nm and adjusting for the dilution factor, the concentration and drug content were determined.

Patch Thickness

Digital Vernier Callipers with a least count of 0.001 mM were used to measure the thickness of the films. Five distinct locations were used to measure the thickness uniformity and the average of those measurements was calculated using the standard deviation.

Swellability

The 3.14 cm^2 patches were weighed, placed in a petridish with 10 mL of double distilled water and allowed to absorb. The weight of the patch was increased at predetermined time intervals until a consistent weight was achieved.

The degree of swelling (% S) was calculated using the formula:

$$S\ (\%) = Wt\text{-}Wo/Wox100$$

Where S is percent swelling Wt is the weight of patch at time t and Wo is the weight of patch at time zero.

Folding Endurance

A strip of a specified area must be cut uniformly and repeatedly folded at the same location until it breaks. The number of times the film could be folded in the same location without breaking determined the folding endurance.

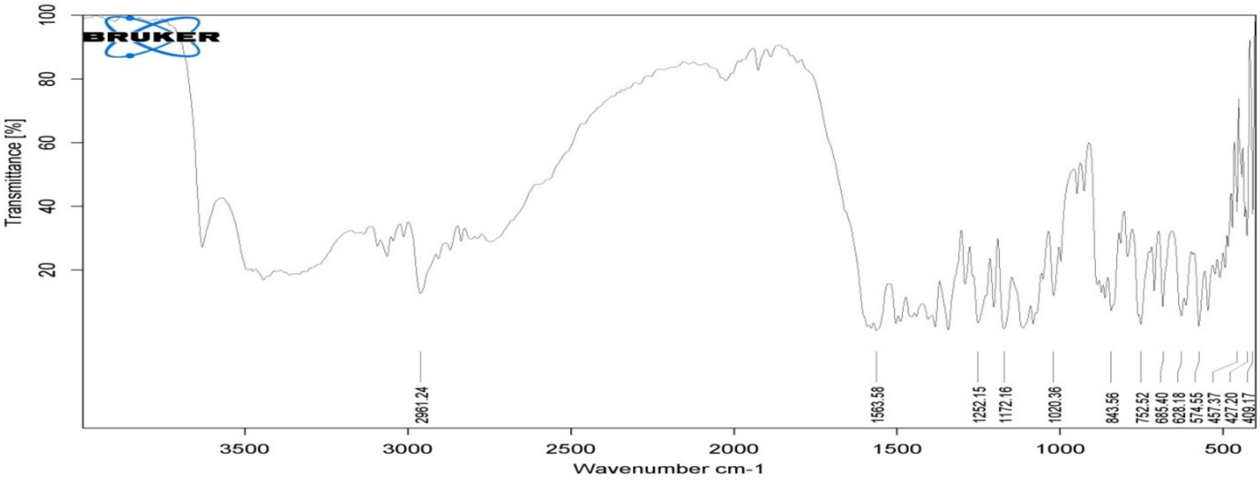

Figure 3: FTIR Spectrum of Bosentan Pure Drug.

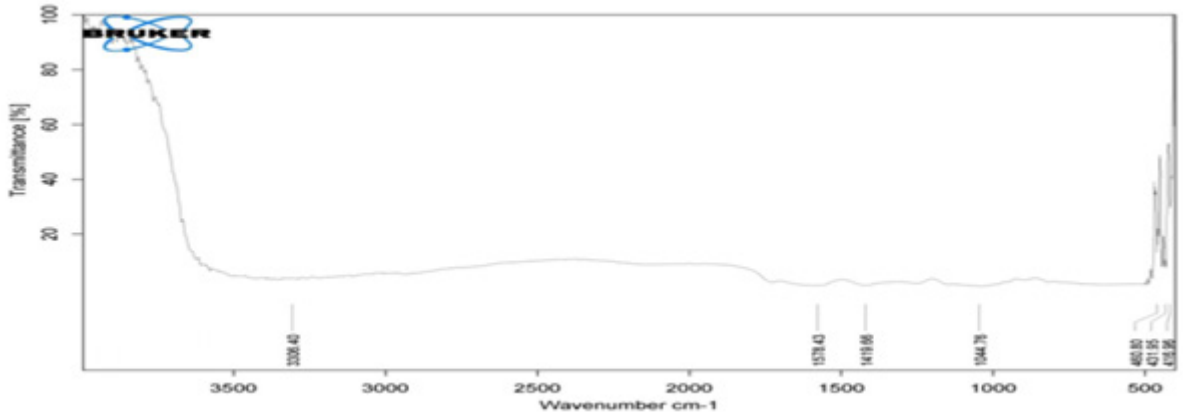

Figure 4: FTIR Spectrum of Gum Karaya.

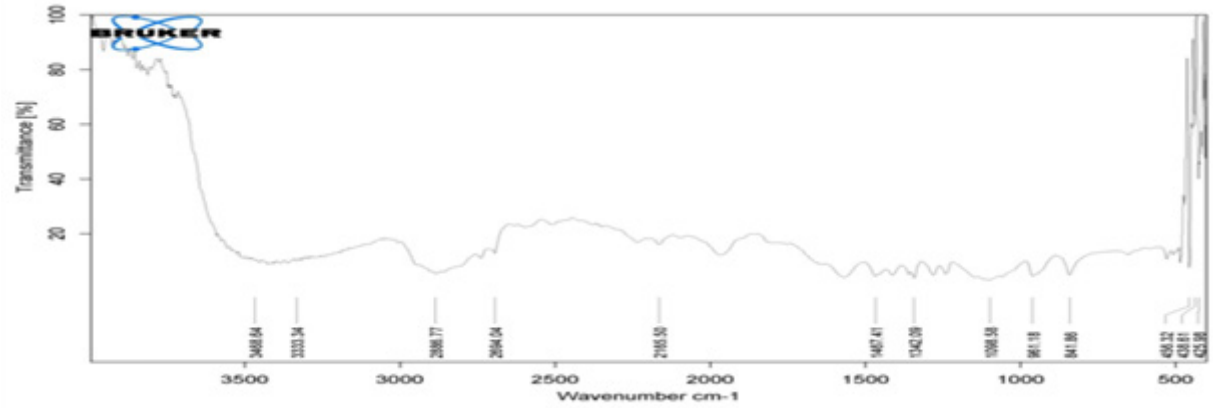

Figure 5: FTIR Spectrum of Polyethylene oxide.

Table 2: Evaluation of physical parameters for Bosentan transdermal patches.

Sl. No.	Formulation	Weight uniformity (mg)	Drug Content (%)	Patch thickness (mm)	Swellability (%)	Folding Endurance (no:)	Flatness (%)
1	B-1	58.26+0.001	92.55+1.0	0.016+0.02	85.14+0.03	95+0.02	100
2	B-2	67.11+0.002	93.74+0.2	0.116+0.04	84.01+0.05	97+0.03	100
3	B-3	79.36+0.009	94.25+0.2	0.134+0.01	83.13+0.08	98+0.04	100
4	B-4	87.55+0.001	95.44+1.1	0.140+0.03	90.11+0.09	98+0.05	100
5	B-5	99.12+0.02	96.35+0.1	0.170+0.01	92.13+0.07	98+0.04	100
6	B-6	59.69+0.002	93.99+0.2	0.100+0.05	86.22+0.04	96 + 0.01	100
7	B-7	68.45+0.004	94.06+0.3	0.120+0.01	85.47+0.06	97 + 0.02	100
8	B-8	80.58+0.005	96.83+0.3	0.118+0.02	88.66+0.05	98+ 0.03	100
9	B-9	89.98+0.005	97.03+0.5	0.115+0.01	89.90+0.09	98+0.04	100
10	B-10	100+0.008	98.06+0.1	0.150+0.03	93.88+0.79	100+0.02	100

Table 3: *In vitro* Drug Release data of Bosentan transdermal patches.

		Cumulative % drug released									
Sl. No.	Time (hr)	B-1	B -2	B-3	B-4	B-5	B-6	B-7	B-8	B-9	B-10
1	1	12.89	14.58	18.96	21.52	31.58	14.55	17.85	19.63	23.69	34.59
2	2	17.25	19.36	24.15	29.44	41.36	19.63	22.99	25.41	32.69	43.96
3	4	22.58	26.58	30.25	38.55	51.69	25.77	28.36	32.74	40.89	58.11
4	6	31.22	35.26	41.28	49.36	64.23	34.52	39.51	44.22	55.33	67.88
5	8	40.87	44.85	51.66	61.36	77.88	42.55	46.78	52.39	63.89	81.25
6	10	47.36	55.86	74.33	82.39	89.25	49.33	59.36	77.22	85.39	91.28
7	12	59.86	71.59	90.36	91.77	93.69	66.36	79.39	91.28	92.99	94.77

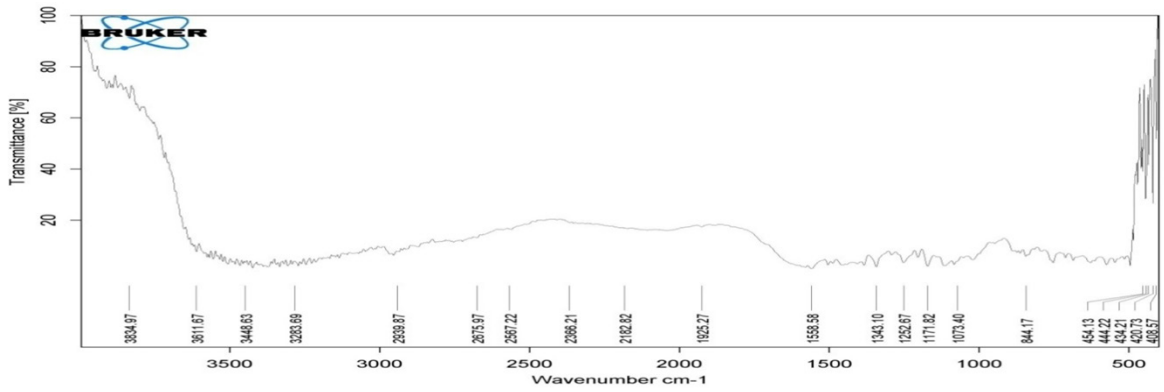

Figure 6: FTIR Spectrum of Optimized Bosentan Formulation (B10).

Flatness

The constriction of patches cut from a drug-loaded matrix patch indicates their flatness. To quantify variation in lengths due to non-uniformity in flatness, longitudinal strips were cut from the produced medicated patch and measured individually. Flatness was measured by measuring strip construction and 0% constriction equals 100% flatness.

$$\text{Constriction (\%)} = L1\text{-}L2/\ L2 \times 100$$

Where L_1=initial length of each strip, L_2=final length of each strip.

In vitro diffusion studies

Analysis of diffusion was performed using a Franz diffusion cell filled with 15 mL of a pH 6.8 phosphate buffer as the diffusion medium. The patch was positioned on the dialysis membrane, wedged between the donor and receptor compartments. The Franz diffusion cell was equipped with a magnetic stirrer and operated at a speed of 50 revolutions per minute. The temperature was

Table 4: Diffusion Parameters of Bosentan transdermal patches.

Formulation	Zero order		First order		Higuchi constant		Peppas constant	
	R^2	K (mg)	R^2	K (hr^{-1})	R^2	K ($mg.h^{1/2}$)	R^2	N
B-1	0.911	2.369	0.922	0.0523	0.933	1.0221	0.963	0.563
B-2	0.932	3.251	0.936	0.0647	0.945	1.1245	0.955	0.611
B-3	0.942	3.641	0.956	0.0772	0.957	1.4112	0.961	0.681
B-4	0.952	3.789	0.967	0.0817	0.966	2.5369	0.977	0.722
B-5	0.966	4.350	0.974	0.0963	0.974	2.7394	0.991	0.800
B-6	0.925	2.457	0.928	0.0525	0.941	1.7112	0.967	0.574
B-7	0.938	3.366	0.940	0.0649	0.951	1.9653	0.978	0.623
B-8	0.944	3.748	0.960	0.0790	0.961	2.0236	0.982	0.700
B-9	0.969	3.874	0.971	0.0884	0.971	2.3693	0.987	0.771
B-10	0.998	4.488	0.981	0.0974	0.988	1.3361	0.991	0.821

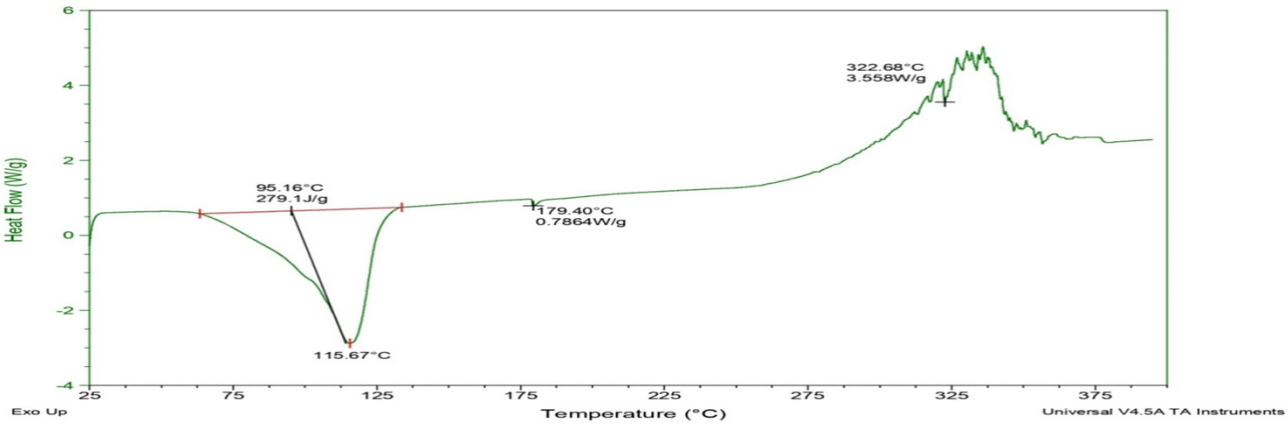

Figure 7: DSC Thermogram of Bosentan Pure Drug.

maintained at 37±2°C for the whole duration of the experiments. Samples were collected at standardized time intervals for up to 12 hr and substituted with an equivalent volume of the same medium. Drug release was quantified using a double-beam UV Spectrophotometer set at 270 nm.

Evaluation of various dissolution parameters

Calculations were made using the dissolution data to determine a number of different types of dissolution parameters, including the Zero order, the first order rate constant, the Higuchi constant and the Korsmeyer-Peppas constant (Bonello *et al.*, 2014; Kuang, 2018). The results were showed in Table 4.

Characterization

After conducting diffusion studies on the formulated patches, we chose formulation B-10 for further analysis. We then performed FTIR, DSC and SEM analysis on this formulation.

Fourier Transform Infrared Spectroscopy

Through the utilization of an FTIR spectrophotometer, the FTIR spectra of Bosentan Karaya Gum, Polyethylene oxide and the optimised formulation B-10 was obtained. This was done in order to examine the incompatibilities that exist between the drug and the polymer in patches. In order to prepare the samples, KBr discs were utilised. The samples were then submitted to a sampling range of 400-4000 cm^{-1}, with a resolution of 4 cm^{-1}. The spectrums of FTIR were showed in Figures 3 to 6.

Differential Scanning Calorimetry

Differential Scanning Calorimetry (DSC) experiments were conducted on Bosentan Karaya Gum, Polyethylene oxide and the optimised formulation B-10 using the eSTAR software from METTLER TOLEDO INDIA. The acquired specimens were placed in an airtight aluminium crucible and exposed to a heating rate of 20°C per minute within the temperature range of 20-2300°C. The results of thermograms were shown in Figures 7-10.

Scanning Electron Microscopy

The samples were coated with a thin gold coating using a sputter coater unit (SPI, Sputter, USA). The SEM pictures were then

acquired using a scanning electron microscope (JSM-6390, Japan) with an accelerated voltage of 15kV.

The obtained results were shown in Figures 11 and 12.

RESULTS AND DISCUSSION

Preparation of Bosentan transdermal patches by Solvent Casting Method

The primary objective of this work is to prepare controlled release transdermal patches of bosentan by using the solvent casting method. The polymers that were chosen were Karaya gum and polyethylene oxide. PEG 600 and propylene glycol were chosen to serve as plasticisers and permeation enhancers, respectively.

Evaluation results of physical parameters for Bosentan transdermal patches

Each Bosentan transdermal patch achieved weight uniformity within the range of 58.26 +0.001 to 100+0.008 mM. The drug uniformity fraction of all the Bosentan transdermal patches was consistently maintained within the range of 98.06% to 98.55%.

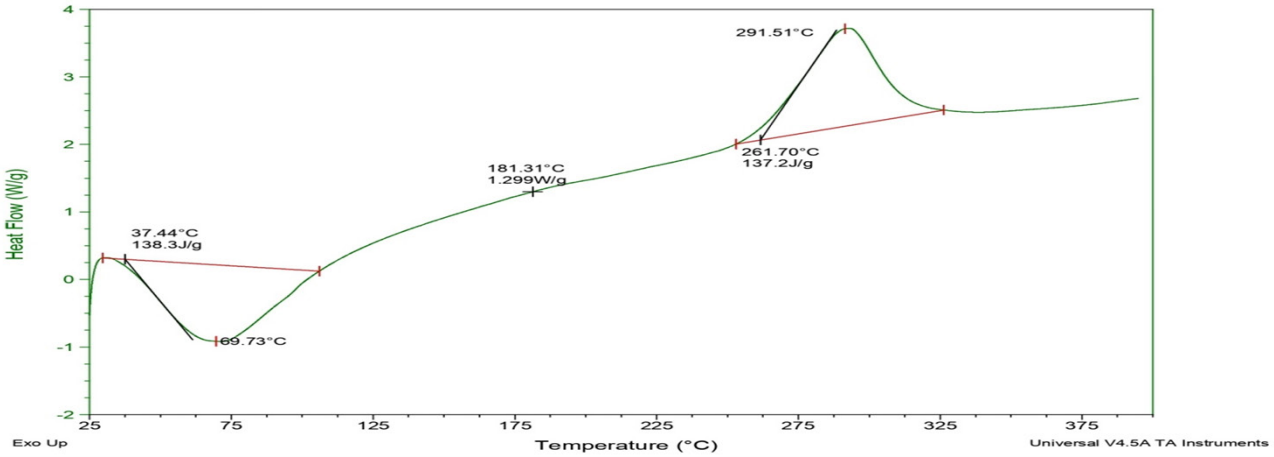

Figure 8: DSC Thermogram of Gum Karaya.

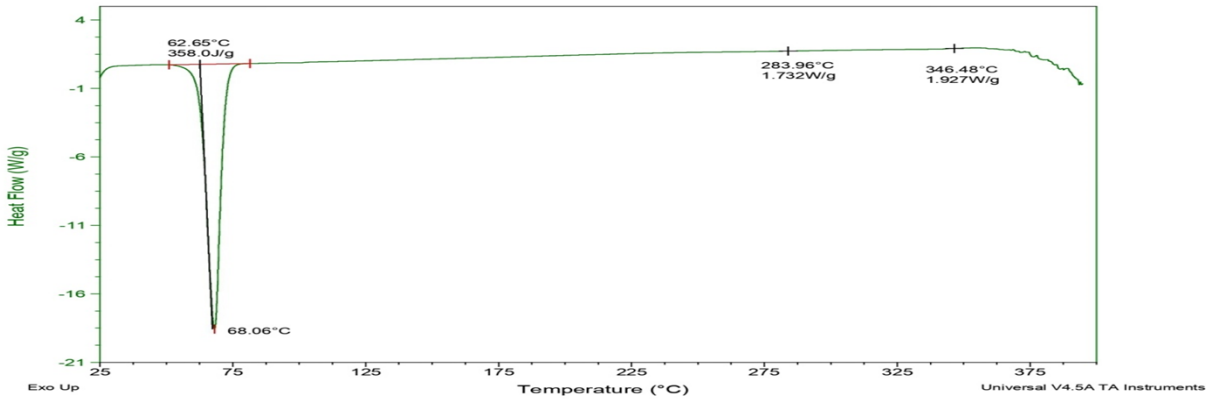

Figure 9: DSC Thermogram of Polyethylene Oxide.

Table 5: Interpretation of FTIR Spectrum.

Functional Group (cm^{-1})	Bosentan	Gum Karaya	Polyethylene oxide	Optimized Formulation (B10)
O-H Stretching	---	---	3366.23	3221.63
C-H Stretching	---	---	---	3112.23
C-H Stretching	2886.23	---	---	2878.11
C=N Stretching	---	---	---	2455.70
C=C Stretching	---	---	2155.23	2012.56
N-H Bending	1533.45	1677.24	---	1544.23
C-H Bending	---	---	1378.57	1330.92

Each Bosentan transdermal formulation maintained a patch thickness ranging from 0.016 to 0.150±0.03 mm. The Bosentan transdermal formulations exhibited a consistent swellability within the range of 85.14% to 93.88%. Every Bosentan transdermal formulation maintained a folding endurance within the range of 95 to 100 numbers. The Optimised formulation B-10 exhibited a commendable folding endurance value of 100.2+2.0, suggesting superior flexibility and tensile strength in comparison to other formulations. The transdermal patches were shown to have a level and uniformly smooth surface. The evaluation studies were showed that the formulations of transdermal patches were quite stable. The results were shown in Table 2.

In vitro diffusion studies of Bosentan transdermal patches

The patches were subjected to diffusion investigations utilising Franz diffusion cell equipment with a pH 6.8 phosphate buffer as the culture medium. Using Karaya Gum, the patch formulations B-1 to B-5 exhibited an average drug release ranging from 59.86% to 93.69% within a 12-hr period. Patch formulations B-6 to B-10, made with Polyethylene oxide, exhibited an average drug release ranging from 66.36% to 94.77%. Out of all the transdermal formulations, the patches made from Polyethylene oxide containing optimized formulation B-10 exhibited superior drug release up to '94.77% within 12 hr. The *in vitro* release data and release profiles were showed in the Table 3 and Figure 2.

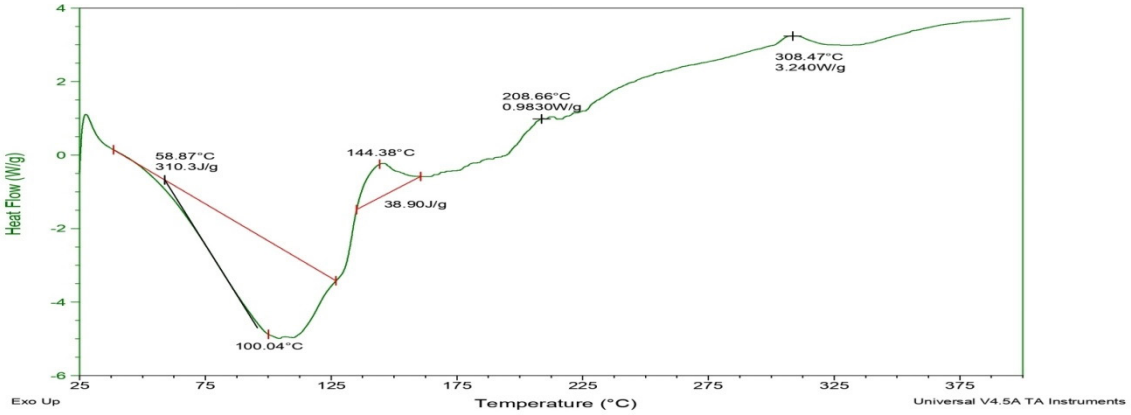

Figure 10: DSC Thermogram of Bosentan Optimized Formulation (B10).

Table 6: DSC Thermogram Interpretations.

Bosentan	Karaya Gum	Polyethylene Oxide	Optimized Formulation (B10)
65.16°C	181.31°C	137.23°C	208.66°C,
Broad Endothermic Peak	Broad Exothermic Peak	Sharp Endothermic Peak	Sharp Exothermic Peak

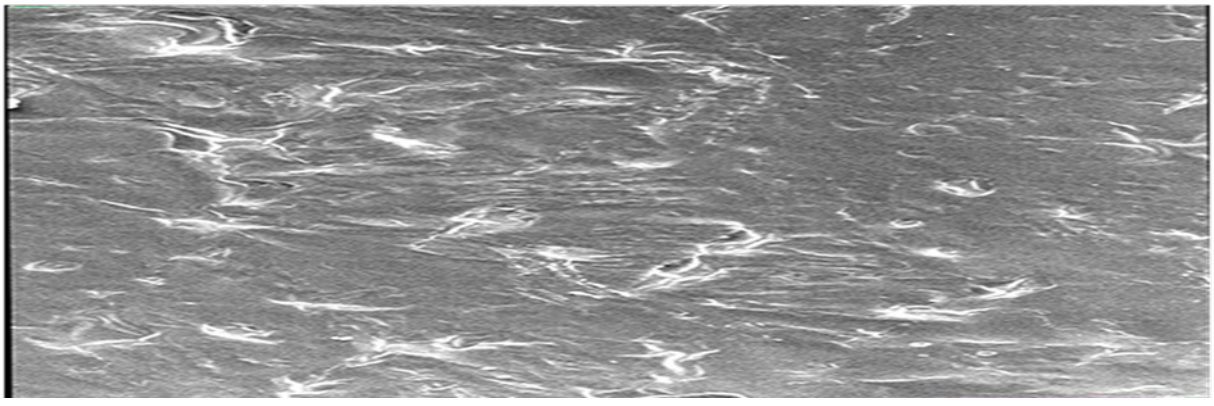

Figure 11: SEM Photograph of Bosentan pure drug.

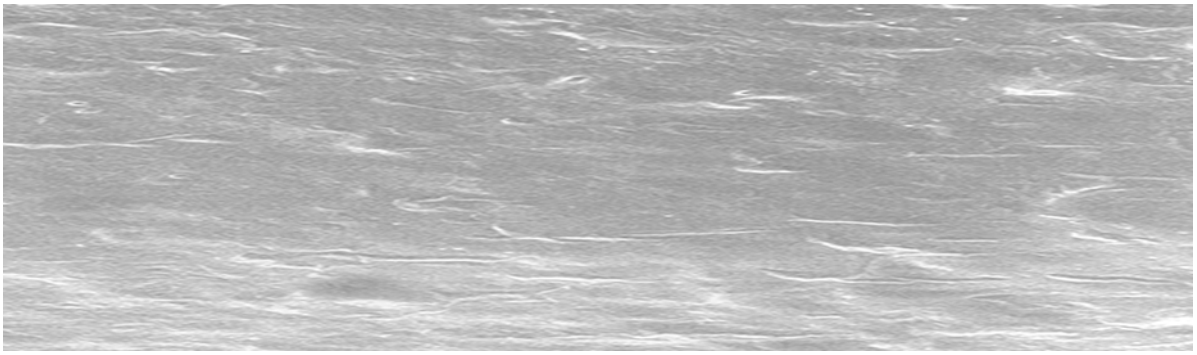

Figure 12: SEM Photograph of optimised formulation (B10).

Diffusion parameters of Bosentan transdermal patches

All transdermal formulations exhibited linearity using a Zero order rate constant are having R^2 values ranging from 0.932 to 0.988. The first-order constant model, with R^2 values ranging from 0.911 to 0.998. Across all transdermal formulations, the Higuchi constants ranged from 1.0221 to 1.3361 and were determined to be linear with R2 values ranging from 0.933 to 0.998. The Korsmeyer -Peppas s constant included values ranging from 0.563 to 0.821. The Mt/M∞ versus log time graphs were shown to be linear, with R2 values ranging from 0.963, to 991. Therefore, the drug was released from all formulations by mean of drug diffusion from the matrix, subsequently followed by polymer erosion. The results of diffusion parameters of Bosentan transdermal patches were showed in the Table 4.

Characterization of Bosentan transdermal patches

Based on the diffusion studies performed on all the formulations, the optimized formulations were selected and following characterization studies were done on pure drug, polymers and optimized formulation.

Fourier-Transform Infra Red (FTIR) Spectroscopic Analysis

The spectra of the optimised transdermal formulation B-10 exhibited all the peaks that are characteristic of the pure drug Bosentan. Thus, there were no incompatibilities seen between the drugs and carriers employed in the transdermal preparations. The spectrums of FTIR and interpretation were shown in the Figures 3-6 and Table 5.

Differential Scanning Calorimetry

It was found that the pure drug had a dominant endothermic peak at 65.16°C. On the other hand, the polymers Karaya Gum and polyethylene oxide exhibited a broad exothermic peak about 181.31°C and a sharp endothermic peak around 137.23°C, respectively. The formulation B-10 displayed at 208.66°C which showed that the optimized formulation should be stable and compatible with drug and polymers. The DSC thermograms were shown in Figures 7-10 and Table 6.

Scanning Electron Microscopy

SEM analysis was performed for Bosentan transdermal patches prepared by solvent casting method. The formulation B-10 with drug showed smooth surface. The photographs were given in the Figures 11 and 12.

CONCLUSION

During the study, transdermal patches were fabricated and observed to possess desirable attributes such as Weight uniformity, thickness, folding endurance, swellability, flatness and drug content, among other properties. The developed patches were shown to possess a very high flexibility and homogeneity. The B-10 formulation, chosen for its enhanced capacity to promote rapid absorption, achieved a release of 94.77% of the compound. Experimental evidence has shown that transdermal patches containing bosentan, produced by the solvent casting technique,

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

PEG: Polyethylene glycol; **FTIR:** Fourier transform spectroscopy; **DSC:** Differential scanning calorimetry.

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