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FORMULATION AND EVALUATION OF TRANSDERMAL PATCH FOR ANTIRHEUMATIC AYURVEDIC MEDICINE USING DIFFERENT POLYMER COMPOSITIONS: *INVITRO*

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ABSTRACT

Transdermal delivery system bypass the hepatic first pass metabolism and avoid drug degradation due to gastrointestinal pH, enzymes etc., minimize plasma level fluctuations and extend the drug activity besides improving patient compliance. The present investigation was aimed at formulation of transdermal patches incorporating herbal drug components. The allopathic system of medicine includes two conventional lines of treatment for rheumatoid arthritis, which come along with certain side effects. Hence, turning to safe, effective and time-tested ayurvedic herbal drug formulations would be a preferable option. With this view transdermal patches incorporating herbal drug component such as Boswellic acid (***Boswellia serrata***) was envisaged. The drug is selected on the basis that, it produces action in suppressing inflammation and safer. The transdermal films were prepared using polymers like HPMC, PVP and Ethyl cellulose by solvent casting method. The prepared patches were evaluated for their physical properties like percentage flatness, thickness and drug content, folding endurance and diffusion studies. The average percent release of Boswellic acid was found to be 81.44% for Boswellic acid in the phosphate buffer diffusion medium at the end of 96 hrs. The graphs obtained for the average percent release through transdermal patch indicate drug release occurred at constant rate.

Key words: Boswellic acid, Transdermal Delivery system, HPMC, PVP, herbal drugs and diffusion studies

INTRODUCTION

The polymeric technologies have been honed and refined over the past several years and currently great interest has been focussed on development of novel drug delivery systems [1]. Treatment of deseases such as asthma, rheumatoid arthriti s by transdermal route of druig administration might prove to have several advantages over the other routes of drug administration [2]. Drug delivery through the skin to achieve a systemic effect of a drug is commonly known as transdermal drug delivery and differs from traditional topical drug delivery. Continuous intravenous infusion is recognized as a superior mode of drug administration not only to bypass hepatic "first-pass" metabolism, but also to maintain a constant and prolonged drug level in the body. A closely monitored intravenous infusion can provide the advantages of both direct entry of drug into the systemic circulation and control of circulating drug levels. These advantages offered the development of controlled release transdermal dosage forms. With the advent of new era of pharmaceutical dosage forms, transdermal drug delivery system (TDDS) established itself as an integral part of novel drug delivery systems.Recently, it is becoming evident that the benefits of intravenous drug infusion can be closely duplicated, without its hazards, by using the skin as the port of drug administration to provide continuous transdermal drug infusion into the systemic circulation [1]. Transdermal drug delivery systems (TDDS) are dosage forms involves drug transport to viable epidermal and or dermal tissues of the skin for dermal tissues of the skin for local therapeutic effect while a very major fraction of drug is transported into the systemic blood circulation. To provide continuous drug infusion through an intact skin, several transdermal therapeutic systems have been developed for topical application onto the intact skin surface to control the delivery of drug.

MATERIALS AND METHODS

Materials

Boswellic acid was received as gift sample from Arpan Herbikem, Hyderabad. HPMC and Acetonitrile were gifted by Suven pharmaceuticals Pvt. Ltd., Hyderabad. PEG-6000, PEG-400, Ethyl cellulose, PVP and Di butyl phthalate were purchased from S.d.fine Chemicals, Mumbai. Other chemicals and reagents used in the study were of analytical grade and distilled water is used throughout the experiments.

Method

Boswellic acid was dissolved in a solvent along with dibutylphthalate and menthol {0.3 ml (3% w/v in ethanol)}. This solution was then added to polymer base i.e. casting solution. The casting solutions were prepared by dispersing the polymers (Ethyl Cellulose, PEG-400, PEG-6000 and HPMC) of different ratios in a solvent, using mechanical stirrer operated at 250 rpm speed for 20 min. The resulting solution was added to the mixture of menthol and glycerin and finally making up the volume with the solvent. The resulting solution was stirred well under mechanical stirrer at speed 200 rpm for about 5 minutes and kept aside for sonication. The casting solutions were sonicated in order to remove the air bubbles if any. Then the solutions were casted on 5x5 cm^2 PVC backing membranes and dried at 60^o c in a hot air oven. Then the patches were wrapped in an aluminum foil and stored in a desiccator for further study. The patches were prepared with different polymer ratios.

EVALUATION

Thickness
The thickness of patches was determined by using micrometer vernier callipers. The thickness of each film at 3 different places was determined and the mean value was calculated.

Folding endurance
Folding endurance of patches should be determined by repeatedly folding a small strip of film (2cm x 2cm) at the same place

Weight variation
Weight variation should be studied by individually weighing 10 randomly selected patches. Such determination should be performed for each formulation.

Drug content
Drug content was found out by dissolving four patches each of 2 cm x 2cm in 10 ml of Ethanol. 0.1ml of this solution was diluted to 10 ml with phosphate buffer (p^H- 7.4).
The absorbance of the solution was found out at 270 nm for Boswellic acid and the drug content determined using the standard calibration curves

Flatness
Three longitudinal strips should be cut out from each film: one from the centre, one from the left side, and one from the right side. The length of each strip should be measured and the variation in Length because of non-uniformity in flatness was measured by determining percent

In vitro drug diffusion and skin permeation study

Preparation of skin membrane

Skin was obtained from a local abattoir of freshly slaughtered goat. The abdominal skin hairs were shaved and removed. Then the skin was hydrated in normal saline

till it broke. The number of times the film could be folded at the sample place without breaking was the folding endurance value.

Tensile strength
The tensile strength should be determined by using a modified pulley system. Weight was gradually increased so as to increase the pulling force till the patch broke. The force required to break the film was consider as a tensile strength and it was calculated as $kg/cm^{2.}$

constriction, 0% constriction equivalent to 100% flatness.

Percentage of moisture content
The films should be weighed individually and kept in a desiccators containing activated silica at room temperature for 24 hours. 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.

Percentage of moisture uptake
A weighed film kept in desiccator at room temperature for 24 hrs was taken out and exposed to 85% 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. solution. Adipose tissue layer of skin was removed by rubbing with cotton swabs. Skin was kept in isopropyl alcohol solution and stored at $0\text{-}4^0$c.

Procedure of drug diffusion through skin membrane

The *in vitro* release studies were carried out using a Franz diffusion cell. The

excised skin was mounted between the half-cells with the dermis in contact with receptor fluid, phosphate buffer and was equilibrated for 1 hr. The receiving chamber had a volume of 20 ml and the area available for diffusion was about 1 cm^2. The donor cell was covered with an aluminum foil to prevent the evaporation vehicle. The temperature was maintained at 37 ± 0.5^0 C and receptor compartment was provided with sampling port. Under these conditions, the temperature at the skin surface was 32+0.5^0C the skin sections were initially left in the Franz diffusion cells for 2 hours in order to facilitate the hydration of membranes. A sample of 5 ml was withdrawn at predetermined time intervals and replaced with fresh buffer. The concentration of drug was determined by spectrophotometrically at 270nm.

Stability study

The patches were subjected to stability study by wrapping them with aluminum foil and storing in desiccators for three months. They were then subjected to further evaluation studies and checked for any deterioration, concentration or any change in the physico-chemical parameters.

RESULTS AND DISCUSSION

In this study, various matrix type transdermal films containing Boswellic acid and different combinations of polymers were prepared. In the present work efforts have been made to design a polymer matrix for Boswellic acid by using different polymers in different ratios such as HPMC, Ethyl Cellulose, PEG-6000, PEG 400 and PVP. The study was targeted to prepare once a week delivery system of Boswellic acid by using the plasticizer, solvents. The prepared formulations were examined for various physicochemical characteristics such as percent moisture absorption, percent moisture loss, drug content, thickness, flatness, folding endurance and weight uniformity. The release characteristic of the formulation was studied in vitro diffusion studies by using goat skin. Stability studies were performed using desiccators.

Boswellic acid is lipid soluble so dissolved in chloroform and dispersed uniformly throughout the film. The films were formed within a short period of time and easy to prepare. The film of boswellic acid showed a satisfactory flatness. Average thickness of films was found to be 0.17±0.02mm. Average content of Boswellic acid in films was found to be 49.06mg. For easy penetration of drugs through skin penetration enhancer as menthol (5% w/v in Ethanol) had been selected. The calibration curve of Boswellic acid was prepared in hydro alcoholic medium using U.V-VISIBLE spectrophotometer and the time versus concentration graphs were plotted (Fig.1)

The *in vitro* diffusion profile of films of Boswellic acid was found to be better in buffer medium than either hydro alcoholic medium and surfactant solution (sodium lauryl sulphate) so buffer medium was taken for study. The release of drugs from transdermal patch was found to be linear for the first 4 hours and attained a steady level up to 12 hours (Fig. 3). The average per cent release for Boswellic acid formulations 6, formulations 7 were 71.24% and. 81.44%.The graph obtained for the average per cent release through transdermal film indicates that the drug is released from the film at a constant rate and follows nearly zero order release Kinetics.

Fig. 1: Standard Calibration Curve of Boswellic acid.

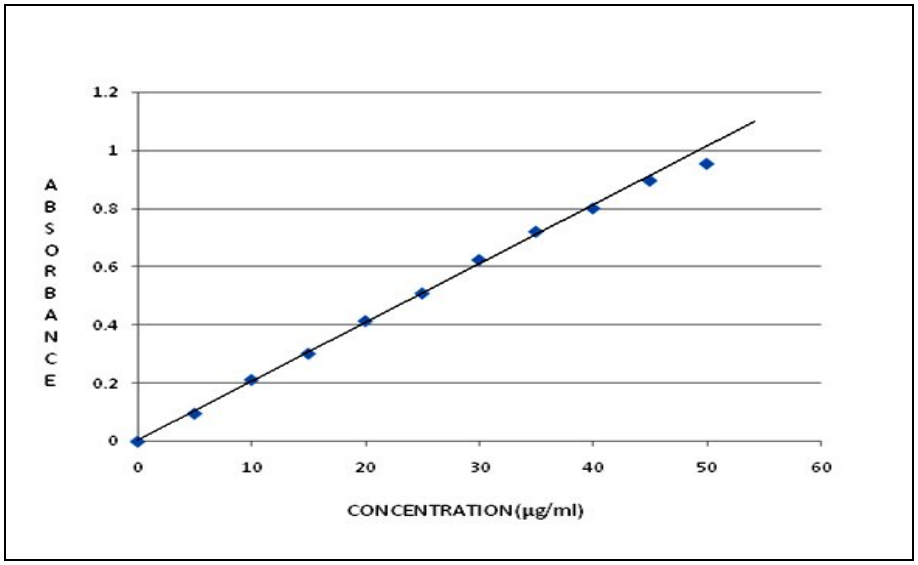


Table 1: Formulation of Boswellic acid Transdermal patches

S.No.	Drug (mg)	Polymers					DBP (ml)	Solvent (ml)		Menthol (ml)	Glycerin (ml)
		EC (mg)	HPMC (mg)	PEG6000 (mg)	PVP (mg)	PEG400 (ml)		$CHCl_3$	ACN		
F_1	200	900	-	90	-	-	1	21	-	0.4	1
F_2	200	-	900	90	-	-	1	21	-	0.4	1
F_3	200	-	900	-	-	0.6	2	21	-	1	1
F_4	200	-	900	90	-	-	2	-	21	1	1
F_5	200	-	-	90	900	0.6	2	21	-	0.5	1
F_6	200	900	900	90	-	-	2	21	-	0.5	1
F_7	200	900	900	90	-	-	0.3	22	-	0.1	1

*HPMC: Hydroxypropyl methyl cellulose *EC: Ethylcellulose *PEG: Polyethylene glycol *ACN: Acetonitrile *PVP: Poly vinyl pyrrolidone *DBP: Dibutyl phthalate * $CHCl_3$: Chloroform

Table 2: Physico-Chemical Evaluation of Formulated Patches of Boswellic Acid

S.No.	Weight(mg)	Thickness(mm)	Drug content(mg)	Tensile strength(kg/cm^2)	% Flatness
F1	310.5 ± 1.5	0.19 ± 0.03	49.18	1.68	99.87
F2	311.3 ± 1.4	0.11 ± 0.02	49.23	1.82	99.99
F3	313.4 ± 1.3	0.18 ± 0.02	48.82	1.50	99.97
F4	328.6 ± 1.7	0.19 ± 0.03	48.91	1.70	99.87
F5	326.3 ± 1.3	0.18 ± 0.02	49.15	1.74	99.88
F6	530.1 ± 1.5	0.19 ± 0.03	48.88	1.60	99.97
F7	604.3 ± 1.4	0.21 ± 0.03	49.29	1.90	99.87
Mean	389.2 ± 1.4	0.17 ± 0.02	49.06	1.71	99.91

Fig. 2: Physico-Chemical Parameters

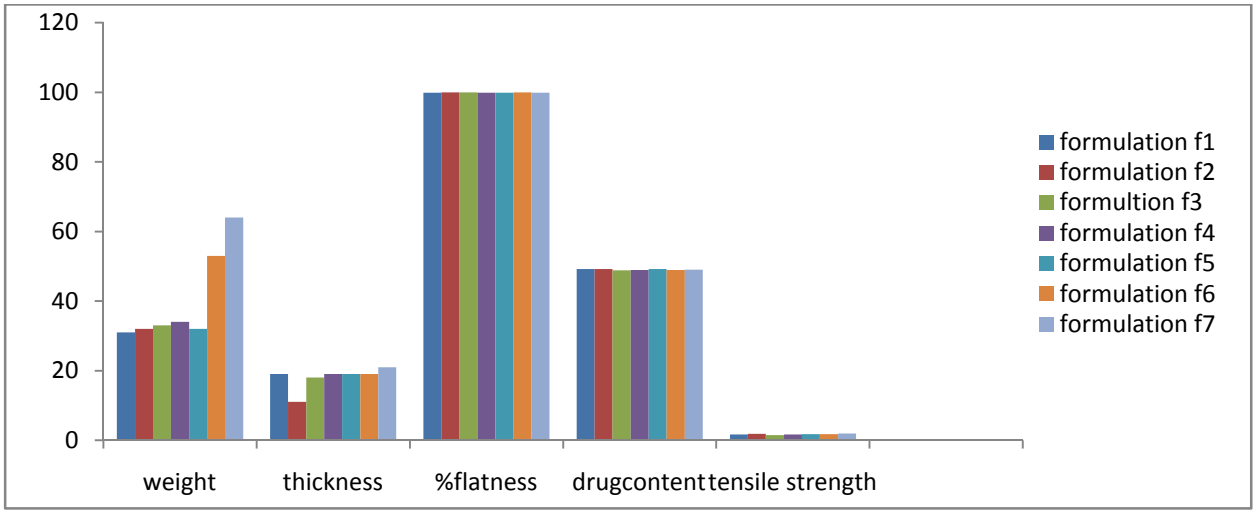
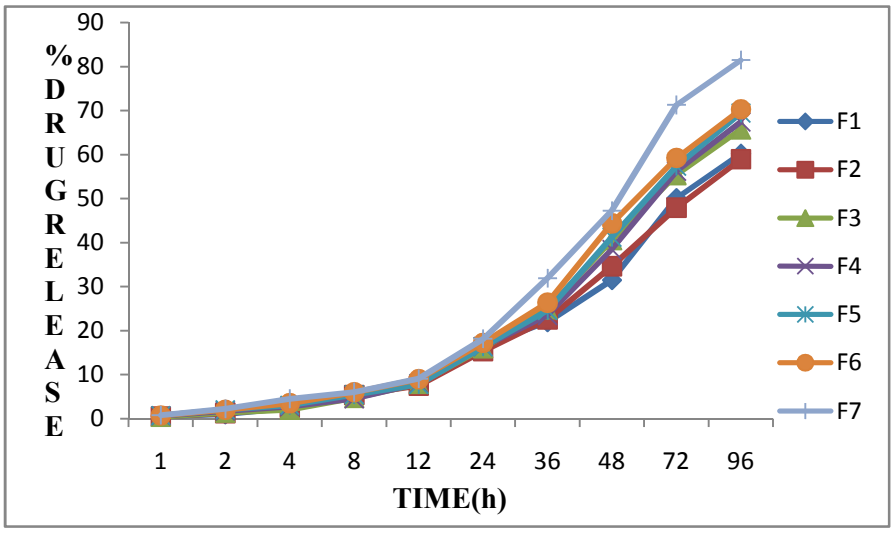


Table 3: *In vitro* Diffusion and Skin Permeation Study

Time(hrs)	% Drug release						
	F1	F2	F3	F4	F5	F6	F7
0	0	0	0	0	0	0	0
1	0.59	0.47	0.41	0.67	0.69	0.71	0.76
2	1.01	1.22	1.38	1.78	1.97	2.01	2.22
4	2.5	2.45	2.01	2.75	3.01	3.50	4.50
8	5.05	5.32	4.71	4.56	5.42	5.98	6.01
12	8.01	7.43	7.88	7.99	7.77	8.95	9.02
24	16.6	15.3	15.99	16.4	16.34	17.20	18.11
36	21.98	22.5	24.83	23.46	24.56	26.33	31.87
48	31.5	34.6	40.51	38.44	41.22	44.34	47.23
72	50.1	47.9	55.33	56.2	57.34	59.22	71.24
96	60.2	58.9	65.67	67.4	69.42	70.24	81.44

Fig. 3: Drug Release Patterns of Seven Formulations



CONCLUSION

Ayurvedic system of medicine has described specific methods and natural drugs. Through the present experimentation, it has found that the drugs of ayurvedic origin can be utilized in a better form with enhanced efficacy by incorporating in modern dosage forms. This experimentation is one of the first few attempts to utilize ayurvedic drugs through TDDS. The drug release patterns of different formulations having different polymer ratios were studied. 4-day skin permeation study shows 81.44% release of drug from the formulation 7 containing polymers HPMC, Ethyl cellulose and PEG-6000 (10:10:1). Hence, this formula was considered to be the optimized formulation with good Physico-chemical properties, skin compatibility, and sustained drug release.

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