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FORMULATION DEVELOPMENT AND CHARACTERIZATION OF TRANSDERMAL DRUG DELIVERY SYSTEMS WITH ANTIHYPERTENSIVE DRUG.

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ABSTRACT

Transdermal therapeutic systems were studied applying different ratios of polymer HPMCK_{15}M, (PVPK_{30}) polyvinyl pyrrolidone and ethyl cellulose was added in the formulation as pore creating agent for improvement of bioavailability of drug and reducing toxic effects. Dibutyl phthalate and PEG-400 were used as plasticizer and tween 80 and DMSO were used as penetration enhancer. Solvent evaporation method was used for the formulation of patches. The patches showed satisfactory folding endurance and tensile strength and it indicated good physical stability. The drug-excipients compatibility studies were performed by Infrared spectrophotometer (IR). Transdermal permeation of carvedilol through rat abdominal skin was determined by using modified Franz diffusion cells and formulation F4 and F5 showed 93.00%, 92.05% drug release at the end of 24 hours. Release kinetics studies revealed that the drug release from formulation F4 and F5 followed Higuchi kinetics with release exponent value n=0.2, 0.28 which shows that release pattern of patches follows diffusion mechanism.

KEYWORDS: Carvedilol, Matrix type transdermal patch, PVPK_{30}, Ethyl cellulose, HPMCK_{15}M, PEG-400, Release kinetics.

INTRODUCTION

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 body. A closely monitored intravenous infusion can provide the advantages of both direct entry of drug into the systemic circulations and control of circulating drug levels. 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 and its subsequent permeation through the skin tissue. Historically, developments in transdermal drug delivery have been incremental, focusing on overcoming problems associated with the barrier properties of the skin, reducing skin irritation rates and improving the aesthetics associated with passive patch systems. Transdermal drug delivery system (TDDS) are defined as self-contained, discrete dosage form which, when applied to the intact skin, deliver the drug(s), through skin at controlled rate to the systemic circulation. Transdermal delivery of drugs through the skin to the systemic circulation provides a convenient route of administration for a variety of clinical indications. Pharmaceutical scientists have accepted the challenge of transdermal drug delivery over the last 25 years. The skin offers a large (1-2 cm^2) and very accessible surface for drug delivery. Transdermal applications, relative to other routes are quite non-invasive, requiring the simple adhesion of a "Patch" much like the application of a Band-Aid. A transdermal patch is used to deliver a specific dose of medication through the skin and into bloodstream.[1] Hypertension, a cardiovascular diseases account for a large proportion of all deaths and disability worldwide. Global Burden of Disease study reported that there were 5.2 million deaths from cardiovascular diseases in economically developed countries and 9.1 million deaths from the same causes in developing countries. Worldwide prevalence estimates for hypertension may be as much as 1 billion individuals and approximately 7.1 million deaths per year may be attributable to hypertension. Hypertension is directly responsible for 57% of all stroke deaths and 24% of all coronary heart disease deaths in India. Pooling of Indian epidemiological studies shows that hypertension is present in 25% urban and 10% rural subjects. Therefore cost effective approaches to optimally control blood pressure among Indians are very much needed. Transdermal systems are ideally suited for diseases that demand chronic treatment. Despite the suitability of TDDS in the treatment of chronic disease like hypertension, the high cost of antihypertensive patches than conventional products made the target patients to think twice. In spite of the high cost of transdermal patches for hypertension treatment, antihypertensive patches with the established dosage forms reduced the occurrence of hospitalization and diagnostic costs. For instance, from a study based on Medicaid claims in two American states, Florida and South Carolina, it have been revealed that though the prescription expenditure of the patients using the patch was significantly higher, it saved them from hospitalization and diagnostic costs. These advantages prepared the target consumers to accept antihypertensive patches as a costlier alternative to the conventional therapy. This acceptability factor had encouraged both academicians and research scientists

to take up various challenging projects in this particular area. Further, the possibility of achieving controlled zero order absorption, simple mode of administration and the option of easy withdrawal of dose in case of adverse manifestations make them desirable in antihypertensive therapy. Clonidine was the first antihypertensive drug developed in the transdermal form. Currently a number of antihypertensive transdermal patches are introduced in to the pharmaceutical market.[2]

MATERIALS AND METHODS

Materials

Carvedilol was received as a gift sample from Astra IDL Limited, Bangalore. Polyvinyl Pyrrolidone K_{30}, Polyethylene Glycol 400, obtained from S.D. Fine Chemicals, Mumbai. All other materials and chemicals used were of either pharmaceutical or analytical grade.

Method

Preparation of patches[3]

The transdermal patches of composition listed in Table were prepared by solvent evaporation technique employing a glass substrate (Bangles wrapped with aluminium foil. Membrane type transdermal patches containing carvedilol prepared using HPMC alone and by using different ratio of $HPMCK_{15}M$, $PVPK_{30}$ and ethyl cellulose. The polymers were dissolved in suitable solvent mixed well by using magnetic stirrer. Carvedilol was added slowly to the polymer solution and mixed thoroughly to obtain uniform solution. PEG-400 and dibutyl phthalate used as a plasticizer. DMSO and tween-80 were used as a penetration enhancer. The polymeric solution was poured into bangles placed in a level, hard rigid surface. and dried at room temperature in a dust free environment for 24 hrs. An inverted funnel was placed over the mould to prevent fast evaporation of the solvent. Patches of 2.0 cm diameter were prepared by cutting and packed in an aluminium foil and stored in a dessicator.

Table 1: Composition of various formulation of carvedilol patches.

Formulation	F1	F2	F3	F4	F5	F6	F7
Drug (%w/w)	13	13	13	13	13	13	13
$HPMCK_{15}M$ (parts)	500	450	400	300	-	-	-
$PVPK_{30}$ (parts)	-	50	100	200	400	300	200
EC (parts)	-	-	-	-	100	200	300
PEG-400(%w/w)*	40	40	40	40	-	-	-
Dibutyl pthalate((%w/w)*	-	-	-	-	40	40	40
Tween 80(%w/w)*	30	30	30	30	-	-	-
DMSO (%w/w)*	-	-	-	-	25	25	25
DCM/Methanol(ml)	12	12	12	12	-	-	-
Chloroform(ml)	-	-	-	-	5	5	5

***Based on polymer weight**

Evaluations of Transdermal Patches[4,5,6,7,8]

Weight variation

Weight variation was studied by taking individual weight of ten randomly selected patches for each formulation prepared in different batches. The weights were taken in electronic digital balance.

Folding Endurance

A strip of specific area (2 cm*2 cm) was cut evenly and repeatedly folded at the same place till it broke. The number of times the film was folded at the same place without breaking gave the value of the folding endurance.

Thickness Uniformity

The thickness of each film was measured by using screw gauze. The thickness was measured at three different places on each film and the average thickness of the film was taken as the thickness of the patches.

Percentage Moisture content

The prepared films were weighed individually and to be kept in a desiccators containing fused calcium chloride at room temperature for 24 hrs. After 24hrs the films are to be reweighed and determine the percentage moisture content from the below mentioned formula.

$$\text{Percentage moisture content} = \frac{\text{Initial weight- Final weight}}{\text{Final weight}} \times 100$$

Percentage Moisture uptake

The weighed films were kept in desiccators at room temperature for 24hrs containing saturated solution of potassium chloride in order to maintain 84% RH. After 24hrs the films are to be reweighed and determine the percentage moisture uptake from the below mentioned formula.

$$\text{Percentage moisture uptake} = \frac{\text{Final weight- Initial weight}}{\text{Initial weight}} \times 100$$

Tensile strength

Mechanical properties of the polymeric patches were conveniently determined by measuring their tensile strength. The tensile strength of the patches was determined by using a tensile strength instrument (Fig. 1). Average reading of three patches was taken as the tensile strength. The transdermal patch was fixed to the assembly, the weights required to break the patch was noted, and simultaneously elongation was measured with the help of a pointer mounted on the assembly and calculated the tensile strength of the patch using the following formula.

Tensile Strength = break force/ a.b (1+ΔL/L)

Where a, b and L are width, thickness and length of the patch respectively.

ΔL is the elongation of patch at break point.

Break force = Weight required to break the patch (Kg).

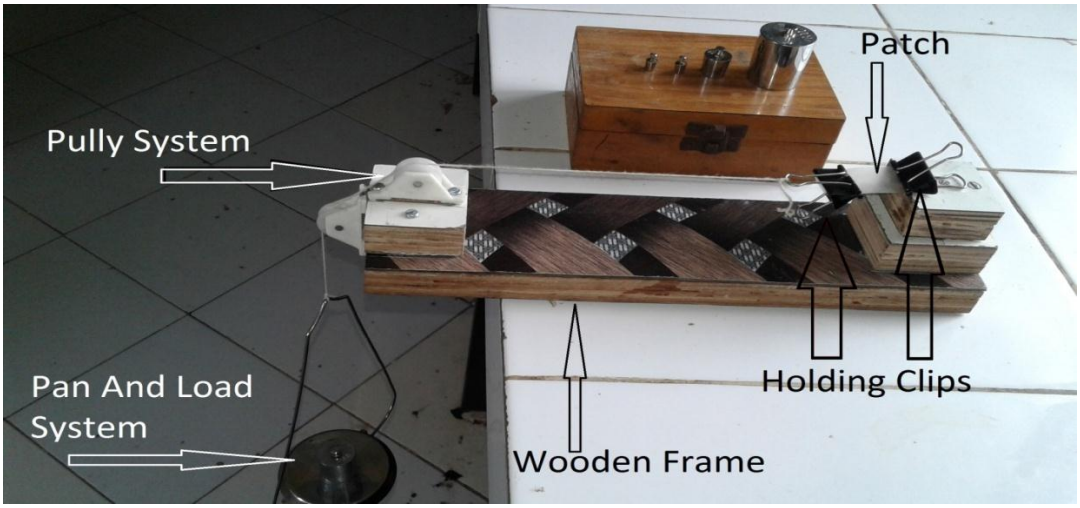

Fig. 1: Tensile Strength apparatus.

Drug content uniformity

The patch (1 cm) was transferred into a graduated glass stopper flask containing 100 ml of phosphate buffer saline 7.4 P^H. The flask was shaken for 4hr in a mechanical shaker. Then the solution was filtered and 1 ml diluted to 10 ml with of phosphate buffer and the absorbance was measured at 243 nm using the placebo patch solution as blank and the drug content was calculated.

In-vitro permeation studies

A Franz diffusion cell was used in this experiment. The Franz diffusion cell was fabricated from borosilicate glass and consisted of two compartments i.e. receptor and donor. The cell had lower jacketed halve through which water maintained at 37°± 5°C was circulated and this lower halve had an effective receptor volume of 50ml and skin surface area of 3.14 cm^2. The two halves of the cell were secured in place with the help of strong metallic clips. The receptor solution was stirred by a Teflon bead of 12 mm length on a magnetic stirrer.

Selection of animal

The experiment was conducted according to the protocol approved by the institutional animal ethics committee (IAEC NO: NIPS/05/29/2016). For in-vitro evaluation of TDDS, albino rat was selected because of its easy availability and suitability. Animal was sacrificed and skin was excised from the abdomen. The rat abdominal skin was immersed in 0.32N ammonium hydroxide solution to facilitate removal of hairs. The dermal side of the skin was thoroughly cleaned of any adhering tissues or blood vessels and washed with distilled water before running the experiment. The skin was trimmed into a circular section of about 2cm diameter.

Procedure for In-vitro permeation studies

The in-vitro permeation study of transdermal patches of carvedilol was carried out by using excised rat abdominal skin and Franz diffusion cell. The skin was sandwiched between donor and receptor compartments of the diffusion cell, so that the epidermis faces the donor compartment. A 2.0cm diameter patch was placed in intimate contact with the stratum corneum side of the skin; the top side was covered with Aluminium foil as a backing membrane. Teflon bead was placed in the receptor compartment filled with 25ml of phosphate buffer saline p^H 7.4. The cell contents were stirred with a magnetic stirrer and a temperature of 37°±5°C was maintained throughout the experiment. Samples of 1ml were withdrawn through the sampling port at different time intervals for a period of 24 hours. Withdrawal of samples were done at 2^{nd} hr., 4^{th} hr., 6^{th} hr., 8^{th} hr., 12^{th} hr., 16^{th} hr., 20^{th} hr., and 24^{th} hr., simultaneously replacing equal volume by normal saline after each withdrawal. The samples were analyzed spectrophotometrically.

Characterization of API and Polymer

IR spectroscopy study was carried out to determine the physical or chemical interaction between drug and polymers.

RESULT AND DISCUSSION

Table 2: Physico-Chemical Evaluation of Transdermal patches.

Formulation Code	Thickness (mm)	Weight variation (mg)	% Drug Content	Folding endurance	Tensile strength Kg/mm^2
F_1	0.12±0.01	0.150±0.01	95.92±3.32	57±12.04	2.45±0.81
F_2	0.19±0.02	0.148±0.005	96.59±3.14	36.6±21.0	2.80±0.80
F_3	0.14±0.004	0.155±0.021	97.51±2.17	38±18.20	2.40±0.70
F_4	0.17±0.008	0.160±0.011	99.65±2.42	60±24.33	3.85±1.80
F_5	0.35±0.09	0.149±0.017	98.36±2.02	58±22.03	3.92 ±1.84
F_6	0.37±0.003	0.156±0.014	97.71±1.42	57±10.41	2.81±1.84
F7	0.35±0.003	0.153±0.015	98.71±1.42	59±10.41	2.93 ±1.78

Formulation Code	% Elongation	% Moisture Content	% Moisture uptake	Swelling index
F_1	24.43±2.51	1.85±0.35	4.87±3.13	24.17±1.38
F_2	23.80±2.12	2.6±0.77	3.6±3.7	25.75±0.72
F_3	25.75±2.61	3.1±1.29	5.3±1.22	25.50±2.12
F_4	26.25±4.12	3.2±1.82	4.7±0.85	23.41±0.74
F_5	28.04±4.71	2.7±0.98	5.7±1.45	22.82±1.25
F_6	25.26±4.19	2.8±0.97	4.76±1.06	24.18±1.37
F7	24.25±4.18	3.23±2.78	4.77±1.05	25.19±1.36

Table 3: Kinetic Release of Dissolution Data.

Sr. No	Zero Order	First Order	Higuchi	Korsmeyer-Peppas		Best Fit Model
	(r^2)	(r^2)	(r^2)	(r^2)	(n)	—
F_1	0.926	0.991	0.941	0.893	0.11	Zero order
F_2	0.985	0.973	0.989	0.890	0.12	Higuchi matrix
F_3	0.995	0.909	0.995	0.927	0.12	Zero order
F_4	0.994	0.852	0.995	0.926	0.12	Higuchi matrix
F_5	0.916	0.882	0.988	0.906	0.28	Higuchi matrix
F_6	0.992	0.974	0.990	0.981	0.22	Zero order
F7	0.988	0.933	0.983	0.870	0.11	Zero order

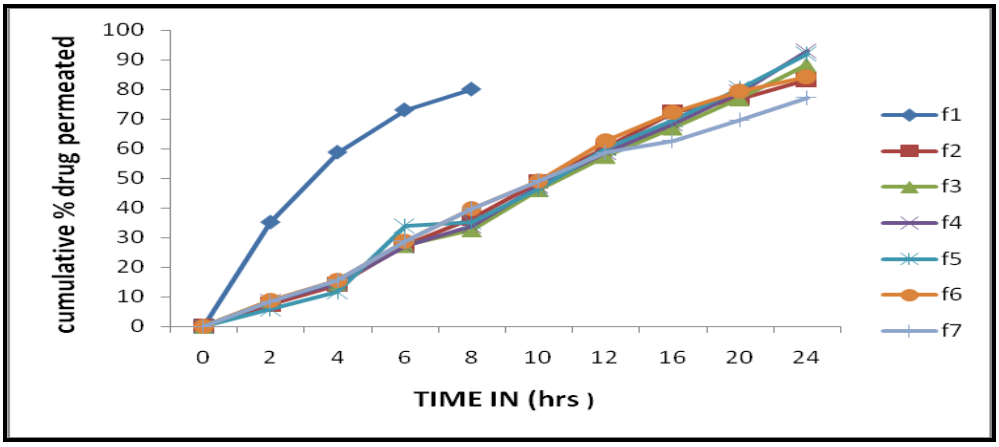

Fig. No.2: Zero Order Release Kinetic Profile of Carvedilol TDDS.

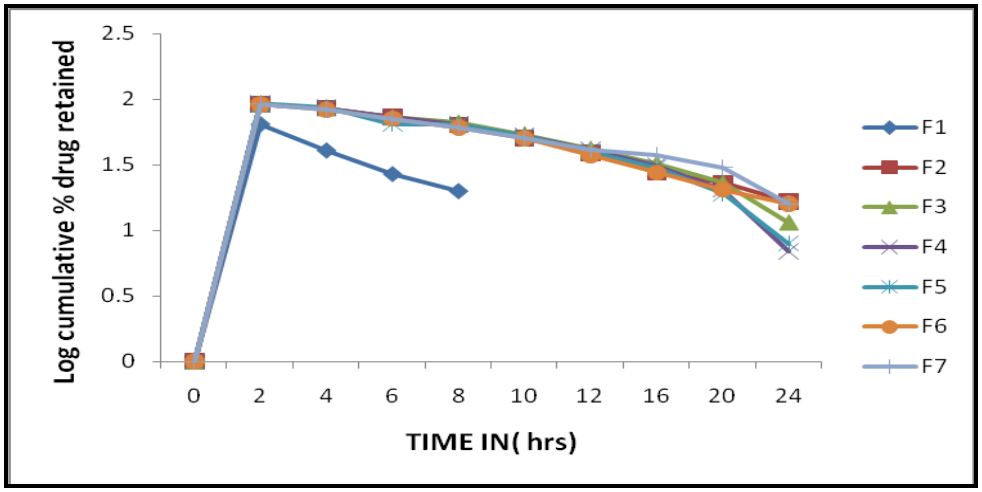

Fig. No. 3: First Order Release Kinetic Profile of Carvedilol TDDS.

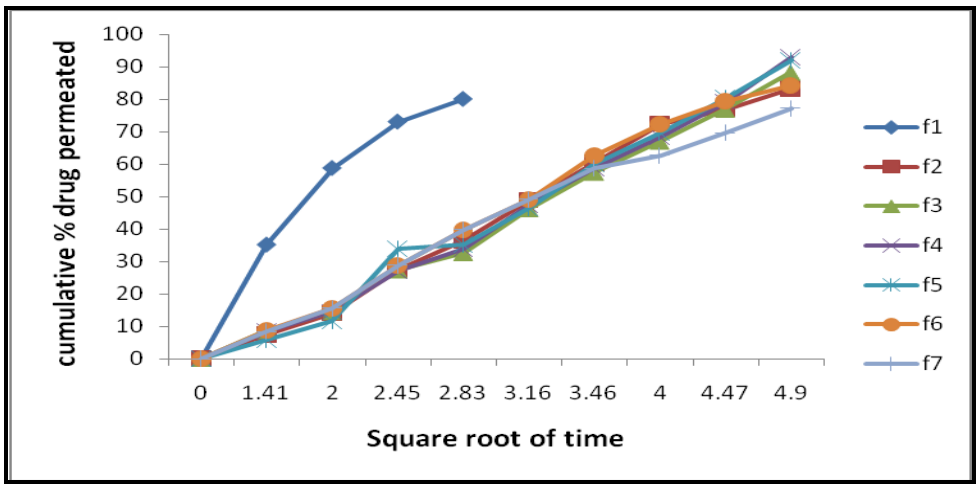

Fig. No. 4: Higuchi Release Kinetic Profile of Carvedilol TDDS.

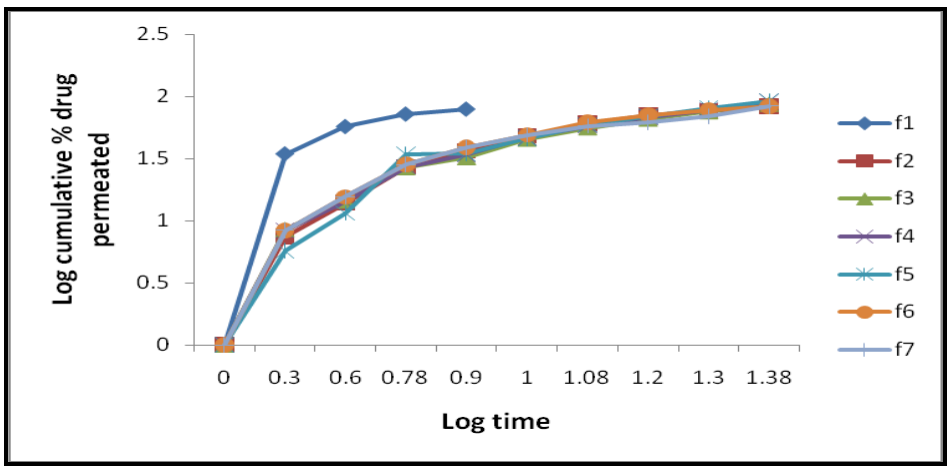

Fig. No. 5: Korsmeyer-peppas Release Kinetic Profile of Carvedilol TDDS.

DISCUSSION

The selection of polymer combinations produces clear, smooth, uniform, flexible and desired thickness film for the transdermal patches of carvedilol. The prepared patches were evaluated for different physicochemical characteristics such as thickness, folding endurance, drug content and weight uniformity. The release characteristics also studied. After 24 hour 93% drug was permeated through skin. The thickness of the patches varied from 0.12±0.01mm to 0.37±0.003mm. As the concentration of PVP and ethyl cellulose increase, moisture content of patches was also increase. The folding endurance was measured manually all the formulation shows good folding endurance.

Stability Study of batch F4

Sr. no	Evaluation Parameter	At o day	After 90 days
1	Thickness (mm)	0.17±0.008	0.16 ± 0.06
2	Weight variation	0.328±0.011	0.326 ± 0.010
3	% Drug Content	99.65±2.42	98.63 ± 1.25
4	Folding endurance	39±24.33	38 ± 23.32
5	Tensile Strength Kg/mm^2	2.45±2.18	1.43 ± 1.64
6	% Elongation	26.25±4.12	24.41 ± 4.3
7	% Moisture content	3.2±1.82	3.1 ± 0.94
8	% Moisture uptake	4.7±0.85	4.5 ± 3.03
9	Swelling index	23.41±0.74	22.40 ± 0.71
10	% drug permeated	93	92.38

The selected optimized formulation F4 had a residual drug content of more than 90% after weekly checking upto 3 month when stored at room temperature 0^0c, 25^0c at 60% RH & 40^0c at 75% RH. These results indicate that the selected formulation exhibited good stability during storage & they were stable.

CONCLUSION

Transdermal drug delivery systems are ideally suited for drugs that undergo hepatic first pass metabolism. Hypertension being a very common disorders leading to preventable death & been treated with different classes of drugs in form of several dosages. On the basis of good mechanical properties like tensile strength, thickness elongation at break, better compatibility and stability. The matrix type transdermal drug delivery system of Carvedilol was successfully designed & developed by trial and error method. The transdermal patches were prepared using combination of $HPMCK_{15}M$, PVPK30 and ethyl cellulose in various ratios. From the result it was conclude that the highest release i.e. F4 and F6 gave 93.00%, 92.05% with suitable polymer ratio and penetration enhancer.

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