

Formulation and Evaluation of *TDDS* of Indian Medicinal Plant

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Research Article

Abstract

The purpose of the work was to formulate and evaluate the transdermal patches of Indian medicinal . Patches were formulated using various ratios of polymer HPMCK₁₅M, (PVPK₃₀) Polyvinyl Pyrrolidone and Ethyl Cellulose. Transdermal patches were formulated by solvent evaporation method. Transdermal patches were evaluated for various parameters like thickness, folding endurance, percentage moisture loss, percentage moisture absorption, drug content uniformity, stability studies and *in vitro* permeation test. All formulations possess excellent physicochemical properties and exhibited negligible skin irritation with good physical stability. Permeation study was performed by using modified Franz diffusion cells. On the basis of drug release and physicochemical values, formulation F5 was shows higher percentage of drug release at 24 hours. Release kinetics studies revealed that the drug release from formulations followed Higuchi kinetics.

Keywords: Transdermal patches, Polymer, HPMCK₁₅M, *In vitro*,

Introduction Transdermal route is, therefore, a better alternative to achieve constant plasma levels for prolonged periods of time, which additionally could be advantageous because of less frequent dosing regimens. To provide continuous drug infusion through an intact skin, various transdermal systems have been designed for topical application and it control the delivery of drug and its permeation via the skin tissue. Historically, developments related to TDDS have been incremental, concentrating on overcoming issue related with the skin barrier properties, minimizing skin irritation and improving the outlook related with passive patch systems. TDDS defined as self-contained, discrete dosage form applied to the unharmed skin then it deliver the drug, via skin at controlled manner in the systemic circulation. Transdermal drug delivery via the skin provides a suitable route of administration for a various clinical indications. A pharmaceutical scientist focuses the development of transdermal drug delivery over the last 25 years. The skin

offers a large and easily penetrable surface for drug delivery. Transdermal routes, from that of other routes are quite non-invasive, like simple adhesion of a “Patch” similar as that of application of a Band-Aid. A transdermal drug delivery systems transfer a precise dose of drug through the skin and into systemic circulation.¹⁻² Guggul plant commonly known as *Commiphora wightii*. It is belong to family Burseraceae and Class-magnoliopsida. The use of guggul plant in the treatment of diseases occupies an important place in ayurveda, the traditional medicine system of india. The Atharvaveda one of the four well known holy scriptures (Vedas) of the Hindus, the Atharvaveda is the earliest reference for it medicinal and therapeutic properties . Detained description regarding it action, use and induction as well as the varieties of guggul have been described in numerous Ayurvedic treat including Charaka samhita (1000 BC), Sushruta Samhita (600 BC and Vagbhata seventh century AD). In addition, various medical lexicons were return between twelfth and fourteen centuries AD. It responsible for reducing fat, indicated for healing Bone Fracture to inflammation, Arthritis, Atherosclerosis, Obesity, Hyperlipidemia, Rheumatism, Haemorrhoids, Urinary disorder, skin disease high cholesterol, neuro-degeneration, Parkinson's diseases, mongolism and ageing process. Guggul is a gum resin, historically used for antiseptic and deep penetrating action in the treatment of elevated blood cholesterol and Arthritis. Guggul is effective as weight loss and fat burning agent. The guggul plant seed contain 10% oil. The fatty acid composition and chemical properties of the extracted oil were determined. *Commiphora wightii* has become endangered because it slows growth nature poor seed setting and lack of cultivation, poor seed germination rate. The aerial parts of this plant are reported to contain Ketonic steroid compounds, composed of C21 or C27 steroids, named guggulsterone³⁻⁹

Materials and Methods :

Collection and preparation of plant material

The stem barks of *Commiphora wightii* were collected from local market of Bhopal. The plant was washed, chopped in to small pieces and dried under shade then powdered coarsely with a mechanical grinder. The powder was passed through sieve No. 40 and stored in an airtight container for further use.¹⁰

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About 200 gm of coarsely powdered plant material was successively extracted by Soxhlet extraction method using solvents with increasing polarity viz. petroleum ether and methanol. Each time before extracting with next solvent, the powdered material was dried in hot air oven (mentioned temp range). Each extract was then concentrated by distilling off the solvent by evaporation to water bath. All the extracts thus obtained were stored in air-tight bottles at 4°C for further experiments.¹⁰⁻¹¹

Ultra Sonic : After the extraction the extracts were dissolved in minimum quantity of ethanol and placed for 15 mint in ultra sonicator bath machine (Elmasonic S150) for complete dissolution after that this sonicated extract solution used for formulation.

Preparations of Transdermal patches¹²⁻¹⁶

The transdermal patches of composition listed in Table no.2 were prepared by solution casting technique employing a glass substrate (Bangles wrapped with aluminium foil). Membrane type transdermal systems with containing 75 mg Commiphora wightii prepared by employing various proportions of HPMCK₁₅M, PVPK₃₀, and Ethyl Cellulose. The polymers was accurately weight and dissolved in a suitable solvent mixed until clear solution formed with magnetic stirrer then added drugs and placed for 30 mint in ultra sonicator bath machine (Elmasonic S150) for complete dissolution after that this sonicated solution mixed with PEG400 as a plasticizer .The polymer solution was poured into bangles placed in a suitable level, hard rigid surface and patches were dried at a room temperature in a dust free environment for 24 hrs. An inverted funnel was covered over the bangles to avoid fast evaporation of the solvent. Patches of 3.14 cm² were prepared by cutting and packed in an aluminum foil and kept in a desiccator.

Evaluation of Transdermal Patches¹²⁻¹⁹

Thickness of patches

The thickness of Patches were measured by digital vernier calipers with least count 0.001mm at three different sites average of three reading was taken with standard deviation.

Weight variation

The three disks of 3.14 cm² were cut and weighed on electronic balance for weight variation test. The test was done to check the uniformity of weight and thus check the batch- to- batch variation.

Drug content

Accurately weighed patches were individually dissolved in minimum quantity of methanol and made volume up to 100 ml with PBS pH 7.4 solutions; 10 ml was transferred to flask and made volume 100 ml. The absorbance was recorded. The blank solution was

made in the same manner except the patches without drug were used.

Percentage Moisture content

The films were weighed & placed in desiccators containing calcium chloride at 40°C in a dryer for at least 24 hrs or more until it gives a constant weight. The % of moisture content was the difference between constant weight taken and the initial weight and as reported with percentage by weight moisture content.

Percentage Moisture absorption/uptake

The films of which the size 3.14cm² were put in a desiccators with silica gel for 24 hrs and weighed the patches were transferred to another desiccators containing saturated solution of KCL(84% RH) after equilibrium was attained. Patches were taken out and weighed. Moisture uptake was calculated with following formula

Swelling index

The patches of 3.14 cm² were weighed and added into Petri dish which contains 10 ml double distilled water and were permeated to absorb moisture at a fix time interval check the increase weight of the patches. Continue this process till same weight observed until weight remaining the same over a period of time. Swelling index (% S) was determined by applying the formula.

$$S (\text{percentage}) = \frac{W_t - W_o}{W_o} \times 100$$

Where, S percent swelling, W_t patch weight at time t.

W_o patch weight at time zero.

Folding endurance

This was obtained by constantly folding one patch at the same place without breaking gave the value of folding endurance. This test performed to check folding ability of transdermal patches also indicate brittleness of patches, more brittle patch when folding endurance value.

Percentage Elongation

A film strip (4 x 1cm) was cut on a glass plate with a sharp blade. The % elongation break is to be determined by observing the length just before the breaking point with formula by pointer on the graph paper.

$$\% \text{ Elongation} = \frac{[\text{Final length} - \text{Initial length}]}{\text{Initial length}} \times 100$$

Tensile Strength

The tensile strength of the patches was found by the apparatus and the design of instrument such that, it had one wooden frame that horizontally placed having fixed scale. On the top of frame two clips were attached to hold patches that under study. From two clips one clips fixed & other moved. Instrument also has pulley to hold weight a patch, weight applied to one end of pulley and other end attached to the fixed clip. During the test wooden platform not dislocate from the original place so platform was fixed carefully to avoid dislocation. Three patches were cut for study having 3.14 cm² sizes. Thickness and width of patches were noted at three sizes and calculated average value. Rate of stress changes was maintained constant with the addition of 0.5g per 2 minutes. The elongation was observed and the total weights taken were used for calculation. Formula for tensile strength :

$$\text{Tensile strength} = F/a.b (1+L/l)$$

Where,

F is the force required to break; 'a' is width of film; 'b' thickness of film; L is length of the film; l is an elongation of film at break point.

In-vitro permeation studies

Franz diffusion cell (fabricated in our Lab.) with a diameter 3.7 cm was used in in-vitro release studies. A glass tube with both end open, 10 cm height and 3.7 cm outer diameter was used as a permeation cell. A transdermal patch sample was accurately placed on a semipermeable cellophane membrane to occupy a circle of 3.7 cm diameter. The loaded membrane was stretched over the lower open end of a glass tube of 3.7 cm diameter and made water tight by rubber band. The tube (donor compartment) was immersed in a beaker containing 100 ml of phosphate buffer pH 6.8 (receptor compartment). The cell was immersed to a depth of 1 cm below the surface of buffer. The system temperature was maintained at 37^o±1^o and speed was maintained at 30 rpm throughout the experiment by magnetic stirrer. The samples 3 ml were withdrawn at different time intervals and analyzed without dilution or filtration for drug content spectrophotometrically. The receptor phase was replenished with an equal volume of phosphate buffer at each sample withdrawal.

Stability studies

As per ICH Guidelines of Accelerated stability studies were performed at the different storage condition 25^oC±2^oc temp., 60%±5% RH and 40^oC±2^oc temperature, 75%±5% RH, for 90 days on optimized formulation batches (FT5). The parameters studied for stability studies are thickness, drug content, moisture content and uptake, weight variation, folding

endurance, Tensile strength, % elongation and swelling index.

Results and Discussion

Evaluation of Transdermal patches : Physicochemical Evaluation

Table 2 and 3 shows the physicochemical evaluation like the Thickness, Folding endurance, Percentage moisture absorbed, Percentage moisture lost, Drug content uniformity.

Permeation studies and Permeation Kinetics

The drug permeation from the Patches is depends on the polymer type as well used concentration. In- Vitro (permeation) studies were performed with Franz cell in Phosphate Buffer Saline pH 7.4. In drug Permeation study the formulation F1 shows 40.23% at 12 hrs and 52.41 at 24 hrs while F5 containing as the standard permeation enhancer shows maximum drug permeation 65.87 % at 12 hrs and 65.43 at 24 hrs. The drug permeation data of F5 was plotted for Zero order, First order, Higuchi model and Korsmeyer-Peppas model to evaluate the permeation pattern of the dosage form. From these plots, kinetic values of the drug permeation were determined. Drug released from the matrix devices by diffusion studied with first order Model and result suggested that the drug permeation follow first order model. Table 4

Stability Study

Stability is the essential factor for quality, safety and efficacy of product. The drug product is with insufficient stability result in altering of their physical as well as chemical characteristics. The selected formulations namely F5 was subjected for stability studies as per ICH guidelines and observed for all evaluation parameters at a temperature of 25^oC and 60% RH, 40^oC and 75% RH, at an interval of three month. There were no physical changes in flexibility and physicochemical evaluation parameter was slightly changed (Table-5)

Conclusions

TDDS are the ideal delivery system for drugs that undergo hepatic first pass metabolism. In the present study, an attempt was made to prepare, characterize and evaluate of transdermal matrix patches of *Commiphora mukul* plant extract. Based on results of various evaluation parameters like thickness, strength, elongation, better compatibility and stability the transdermal matrix patches was successfully designed and developed by trial and error method. Formulations were prepared by employing combination of HPMCK₁₅M, PVPK₃₀, and EC in various ratios.

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Figure 1 In-vitro Drug Permeation *Commiphora mukul* of F1 to F7

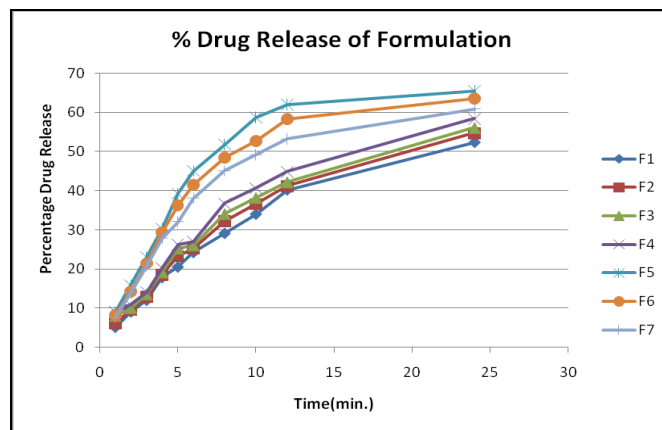


Table: 1 Composition of Transdermal patches

Formulation	F1	F2	F3	F4	F5	F6	F7
<i>Commiphora wightii</i> Extract	100	100	100	100	100	100	100
HPMCK ₁₅ M (mg)	400	350	300	250	-	-	-
PVPK ₃₀ (mg)	-	50	100	150	300	250	200
EC (mg)	-	-	-	-	100	150	200
PEG-400* (ml)	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Tween 80 (*ml)	0.15	0.15	0.15	0.15	0.15	0.15	0.15
Oleic acid	2%	2%	2%	2%	2%	2%	2%
Camphor	2%	2%	2%	2%	2%	2%	2%
DCM/Methanol (ml)	10	10	10	10	10	10	10

Key- *based on polymer weight

Table 2 Physicochemical Evaluation data of *Commiphora mukul* Transdermal Patches

Formulation Code	Thickness (mm)	Weight variation (mg)	% Drug Content	Folding endurance	Tensile strength Kg/mm ²
F1	0.30±0.06	0.159±0.01	97.82±2.02	57.7±12.02	3.31±0.81
F2	0.32±0.004	0.151±0.005	98.15±2.42	058±02.04	2.79±0.80
F3	0.29±0.02	0.150±0.021	97.41±2.17	59±08.20	3.02±0.70
F4	0.31±0.09	0.159±0.011	99.71±1.43	58±14.13	3.41±1.80
F5	0.31±0.29	0.153±0.017	99.12±2.02	57±22.03	3.49 ±1.84
F6	0.31±0.013	0.158±0.014	98.91±1.42	58±11.42	2.94±1.84
F7	32±0.003	0.157±0.015	98.16±2.02	57±59.41	3.16 ±1.78

Table 3 .Physicochemical Evaluation data of Commiphora mukul Patches

Formulation Code	% Elongation	% Moisture Content	% Moisture uptake	Swelling index
F1	33.23±2.51	2.68±0.35	4.37±4.03	25.31±1.28
F2	33.10±2.12	2.53±0.77	4.25±2.7	24.71±0.52
F3	34.65±2.61	2.79±1.29	5.24±1.22	24.49±1.12
F5	35.71±4.12	2.81±1.82	5.16±0.85	24.51±0.74
F5	36.94±4.71	3.35±2.78	5.25±1.25	24.12±0.15
F6	3502±4.19	3.53±0.98	4.35±1.06	25.10±1.37
F7	32.98±4.18	3.27±0.97	4.49±1.05	24.22±1.26

Table 4 *In-vitro* Drug Permeation of Commiphora mukul Kinetics

Time (hrs)	F1	F2	F3	F4	F5	F6	F7
1	5.08	6.03	8.1	9.03	9.03	8.21	7.65
2	9.03	9.49	10.12	10.89	15.89	14.22	13.89
3	11.99	12.81	13.65	14.07	23.07	21.45	20.86
4	17.81	18.52	19.26	20.24	30.24	29.36	27.86
5	20.52	23.24	25.28	26.28	39.28	36.24	32.12
6	24.23	25.23	26.12	27.02	45.02	41.44	38.12
8	29.12	32.21	34.12	36.76	51.76	48.46	45.12
10	34.03	36.56	38.21	40.68	58.68	52.71	49.21
12	40.23	41.21	42.24	44.87	61.87	58.24	53.24
24	52.41	54.77	56.12	58.43	65.43	63.51	60.87

Table 5 Stability Study of batch F5

Sr. No	Evaluation Parameter	At 0 day	After 90 days
1	Thickness (mm)	0.16±0.008	0.16 ± 0.06
2	Weight variation	0.163±0.011	0.161 ± 0.011
3(a)	% Drug Content	99.12±2.02	98±44.13
4	Folding endurance	59±24.33	57 ± 24.33
5	Tensile Strength Kg/mm ²	3.85±1.80	3.55±1.80
6	% Elongation	26.71±4.12	25.99 ± 4.12
7	% Moisture content	3.1±1.82	3.1 ± 0.94
8	% Moisture uptake	4.6±0.85	4.5 ± 3.03
9	Swelling index	23.38±0.74	22.40 ± 0.71