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FORMULATION AND EVALUATION OF HERBAL TRANSDERMAL PATCHES

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ABSTRACT

Transdermal patch is a medicated adhesive pad that is designed to release the active ingredient at a constant rate over a period of several hours to days after application to the skin. It has been found that drugs from herbal origin can be utilized with enhanced efficacy by incorporating in transdermal drug patches. Transdermal drug delivery system (TDDS) thus offers a better route of delivery, reported to have better patient compliance. In the present work we tried to formulate and evaluate *Nelumbo nucifera herbal patches. Nelumbo nucifera* Gaertn (Nymphaeaceae), a perennial aquatic plant, has been used as a medicinal herb in China and India. It has been recorded in the most famous medicinal book in China for more than 400 years. The pharmacological studies have shown that *N. nucifera* posseses various notable pharmacological activities like anti-ischemic, antioxidant, anticancer, antiviral, antiobesity, lipolytic, hypocholestemic, antipyretic, hepatoprotective, hypoglycaemic, antidiarrhoeal, antifungal, antibacterial, anti-inflammatory and diuretic activities.

KEYWORDS: Transdermal drug delivery, medicated patches, herbal agents, antidiabetic, *Nelumbo nucifera*, transdermal patches.

INTRODUCTION

Plant profile

The indigenous knowledge of many tradition communities has been formulated, been documented and eventually become organized systems of medicine such as ayurveda, siddha, unani and other systems out of India.

The flowers are usually found on thick stems rising several centimeters above the leaves. The plant normally grows up to a height of about 150 cm and a horizontal spread of up to 3 meters, There are two varieties of 'kamala': one has white flowers and is commonly called 'pundarika' or 'sveta kamala'; the other has pink or reddish-pink flowers and is called 'rakta kamala'. The whole plant with flowers is known as 'padmini', the rhizomes as 'kamalkand', the tender leaves as 'sambartika', the peduncle as 'mrinal' or 'visa', the stamens as 'kirijalaka', the torus as 'padmakosa', the seed as 'karnika' or 'padmaksya' and the honey formed in the flowers by the bees feeding.

Uses of Lotus

In Ayurveda this plant is used as a diuretic and anthelmintic and in the treatment of vomiting, leprosy, skin diseases and nervous exhaustion.

A transdermal patch is defined as medicated adhesive patch which is placed above the skin to deliver a specific dose of medication through the skin with a predetermined rate of release to reach into the blood stream.

Transdermal drug delivery system, designed to deliver a variety of drugs to the body through diffusion across the skin layers, is appealing for several reasons including avoidance of the variable absorption and metabolic breakdown associated with oral treatments, drug administration can be continuous and minimal intestinal irritation can be avoided.

The skin is essentially a multilayer configuration with an outer protective layer, the stratum corneum, followed by the epidermis, basal membrane, dermis and fatty tissue. The drug has to be transported to the dermis, where the subpapillary network is located and drugs can diffuse into the vascular system and apply therapy.

ADVANTAGES OF TRANSDERMAL PATCHES

1. It offers constant permeation of drugs through the skin giving constant serum drug level, the goal of therapy.
2. Like intravenous infusion, it also gives constant plasma level.
3. If toxicity develops from TDDS, patch can be removed easily.
4. It is very convenience as application of drug is very easy.
5. It eliminates first pass mechanism.

MECHANISM OF TRANSDERMAL DRUG DELIVERY SYSTEM

Transdermal permeation of a drug moiety involves the following steps:

1. Sorption by stratum corneum
2. Permeation of drug through viable epidermis
3. Uptake of the drug moiety by the capillary network in the dermal papillary layer.
4. The drug must possess some physicochemical properties to reach target site via systemically through stratum corneum.

The rate of permeation of drug moiety across the skin is governed by following equation:

$$\mathbf{dQ/dT = ps(Cd –Cr)}$$

Where, Cd= concentration of penetrate in the donor phase (on the surface of skin);

Cr= concentration of penetrate in the receptor phase (body); and Psis the overall permeability coefficient of the skin which is defined as

$$\mathbf{Ps = ks\ Dss / hs}$$

Where, K = Partition coefficient of the penetrant;

Dss=Apparent diffusivity of penetrant;

hs= Thickness of skin

Method of Preparation

PVA (1 g) and PVP (1g) were weighed in requisite ratios and mixed in 10 ml distilled water, stirred the mixture over a hot water bath until dissolved. After the mixture was cooled down to 25 Ž, added Sinomenine (0.3 g), propylene glycol (0.5 ml), glycerol (0.5 ml) and the pressure sensitive adhesives (2 ml), mixed together using a mechanical stirrer (IKA, RW16, Germany) at 800 rpm for 15min under occluded condition (Paola *et al*., 2003).

The mixture was then cast on the release liner with a micrometer adjustable casting knife (R. K. Coat Instruments, UK) set at 500µm and was dried at 80°C for 25 min. The total area of one formulation is about 300cm^2. The patches were covered with backing laminate.

Main Ingredients Used For the Preparation of Transdermal Drug Delivery System

Liners: It provides the protection of patches during storage and the liner should be removed previous touse.

Adhesive: It serves to adhere the components of the patch together along with adhering the patch to skin.

Membrane- Its controls the drug releases from the multi-layer patches. It's also known as the permeation enhancer.

Drug- Drug reservoir is direct contact with release liner.

Backing- protects the patches from outer environment.

INGREDIENTS USED

Polymer matrix or matrices

Polymers are the foundation of transdermal system. The selection of polymer and design are of prime importance.

The polymers used in transdermal system are:

Natural Polymers: e.g. zein, gelatin cellulose derivatives, gums, natural rubber, shellac, waxes and chitosan *etc*.

Synthetic Elastomers: e.g., Hydrin rubber, polyisobutylene, polybutadiene, silicon rubber, nitrile, neoprene, butylrubber, acrylonitrile *etc*.

Synthetic Polymers: e.g. polyvinylchloride, polyethylene, polyvinyl alcohol, polypropylene, polyamide, polyacrylate, polyurea, polyvinylpyrrolidone, polymethylmethacrylate *etc*.

Plasticizers

Plasticizers have also been used in many formulations ranging from 5 to 20% (w/w, dry basis). Some of its examples are glycerol or sorbitol, at 15%,w/w, dry basis, phosphate, phthalate esters, fatty acid esters and glycol derivatives such as PEG 200 and PEG 400.

Solvents

Various solvents such as methanol, chloroform, acetone, isopropanol and dichloromethane etc. are used to prepare drug reservoir.

Development of Transdermal patches

The patches were prepared by solvent evaporation method. The polymers (total weight: 500 mg) and drug (250 mg) were weighed in requisite polymer ratios (PVP, HPMC K 100LV)

and dissolved in suitable solvent. PEG 4000 was used as plasticizer (46% w/w of polymers). Oleic acid was used as permeation enhancer (12% w/w of polymers) and solvent for a drug. The fixed volume of polymeric solution with drug and plasticizer was poured in to glass petri plate and then dried in by placing funnel over it for 24 hrs. The films were removed by using sharp blade by inserting along the edges of the film.

RESULTS AND DISCUSSION

Table 1: %Moisture Loss and %Moisture Absorption.

S.No	Formulation code	%Moisture Loss ± SDa	%Moisture Absorption ± SDa
1	**F1**	5.778 ± 0.02	8.749 ± 0. 0.02
2	**F2**	5.210 ± 0. 0.02	7.594 ± 0. 0.02
3	**F3**	5.551 ± 0. 0.02	8.694 ± 0. 0.02
4	**F4**	5.421 ± 0. 0.02	8.377 ± 0. 0.02
5	**F5**	6.054 ± 0. 0.02	9.188 ± 0. 0.02
6	**F6**	7.695 ± 0. 0.02	9.923 ± 0. 0.02

a: mean of 3 observation.

Table 2: CHEMICAL EVALUATIONS.

S. No	Test	Methanolic Extract
1.	Molisch's test	-ve
2.	Fehling's test	-ve
3.	Benedict's test	-ve
4.	Lead acetate test	-ve
5.	Ninhydrin test	+ve
6.	Foam test	-ve
7.	Ferric chloride test	-ve
8.	Mayer's test	+ve
9.	Hager's test	+ve
10.	Wagner's test	+ve
11.	Zinc dust test	+ve
12.	Alkaline reagent test	+ve
13.	Baljet test	+ve
14.	Killer-killani test	+ve

Table 3: FORMULATION.

S. No	Formulation	F1	F2	F3	F4	F5	F6
01	Methanolic extract (gm)	0.25	0.25	0.25	0.25	0.25	0.25
02	Methanol (ml)	3	3	3	3	3	3
03	PEG 4000 (%)	40	40	40	40	40	40
04	PVA (%)	5	5	5	5	5	5
05	EC (%)	1	1	1	1	1	1
06	PVP (%)	2	5	10	--	--	--
07	HPMC (%)	--	--	--	2	4	10

Area of patch = $9cm^2$.

Weight of polymers = 500m.

Evaluation of formulated patch: Thickness and Weight Variation

Table 4: Thickness and Weight Variation of F1 to F6.

S. No	Formulation code	Thickness (mm) ± SD[a]	Weight Variation (mg) ±SD[b]
1	F1	0.139 ± 0.0040	39.60 ± 2.7203
2	F2	0.124 ± 0.0021	36.60 ± 2.6711
3	F3	0.142 ± 0.0110	34.30 ± 1.6184
4	F4	0.105 ± 0.0035	33.28 ± 1.8499
5	F5	0.145 ± 0.0030	33.28 ± 2.7167
6	F6	0.120 ± 0.0030	32.26 ± 3.0786

a: mean of 3 observation.

b: mean of 5 observation.

Percentage Drug Content and Folding Endurance

Table 5: Percentage drug content and Folding Endurance of Formulations of F1 to F6.

S. No	Formulation code	% Drug content	Folding Endurance
1	F1	86.604 ± 0.3594	>200
2	F2	86.065 ± 0.1667	>200
3	F3	89.958 ± 0.0868	>200
4	F4	90.047 ± 0.0145	>200
5	F5	86.755 ± 0.0149	>200
6	F6	90.867 ± 0.0059	>200

DISCUSSION

Transdermal drug delivery system is a most suitable system for a long term treatment or for a multi-dose treatment and this system also increases the bioavailability of drug by avoiding the first pass metabolism and increases the therapeutic efficacy of drug by reaching into the systemic circulation. The prepared patches were subjected to thickness, weight variation, folding endurance, drug content uniformity, percent moisture absorption, percent moisture loss and stability studies at different temperature. The result of the finding showed excellent adhering property and controlled release. In this study different matrix type patches were prepared by varying polymer combination and polymer ratios.

Both phytochemical and chemical test for ***Nelumbo nucifera***, flower extract was performed for the selected plant parts. Methonolic extracts were prepared by soxhlation methods.

The prepared patches were subjected to thickness, weight variation, folding endurance, drug content uniformity, percent moisture absorption, percent moisture loss and stability studies at different temperature. Thickness of all patches was ranging from 0.120 to 0.219 and weight variation from 33.28 to 55.79. Folding endurance results indicated that the patches would not break and would maintain their skin integrity with general skin folding when applied.

The moisture loss of the prepared formulations was low (4.23% to 7.695%) which could help the formulations remain stable and reduce brittleness during long term storage.

The moisture uptake of the formulations was within the limits (6.594% to 9.924%) which could protect the formulations from microbial contamination and reduce bulkiness. Small moisture loss in formulation helps them to remain stable and being completely dried and brittle film.

Good uniformity of drug content was observed in all the patches ranging from (86.065% to 95.600%). The results indicated that patches produced uniform drug content and minimal patch variability.

Among different formulations F1- F6, the formulation F6 containing PVA and HPMC in the ratio of (4:1) was selected as the best formulation after considering its low moisture absorbance (7.594%), low moisture loss (6.223%), better drug content, maximum drug permeation (0.1745 mg/cm2 /hr.) through the skin. The formulations were subjected to drug release and permeation studies for 24 hrs. Formulation F6 with higher ratio of HPMC with PVA showed higher drug release and permeation.

CONCLUSION

In this study different matrix type patches were prepared by varying polymer combination and polymer ratios. *Nelumbo nucifera*, flowers were selected for present study. Both phytochemical and chemical test for performed for the selected plant parts. Methonolic extracts were prepared by soxhlation methods. By performing chemical evaluation the extracts showed positive response towards Alkaloids, glycosides, amino acids. The herbal transdermal patches were formulated and the prepared transdermal patches were evaluated and the results were found to be positive. Folding endurance results indicated that the patches would not break and would maintain their skin integrity with general skin folding when applied. The moisture uptake of the formulations was within the limits which could protect

the formulations from microbial contamination and reduce bulkiness. Good uniformity of drug content was observed in all the patches. The formulations were subjected to drug release and permeation studies for 24 hrs. Formulation F6 with higher ratio of HPMC with PVA showed higher drug release and permeation.

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