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A REVIEW: DEVELOPMENT AND EVALUATION OF TRANSDERMAL PATCHES WITH *CONVOLVULUS NERVOSUS BURM* LEAVES EXTRACT

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ABSTRACT

Argyreia nervosa (Convolvulaceae) plant is an example of hallucinogenic plant. The antiseptic, anti-infl ammatory, antispasmodic, antibacterial, antiviral, antifungal, anticonvulsant, nootropic, antifertility and aphrodisiac properties have already been reported for this plant. Transdermal drug delivery system (TDDS) established itself as an integral part of novel drug delivery systems. In a broad sense, the term transdermal delivery system includes all topically administered drug formulations intended to deliver the active ingredient into the general circulation. Transdermal drug delivery systems are polymeric formulations which when applied to skin deliver the drug at a predetermined rate across dermis to achieve systemic effects. This review article describes the methods of preparation of different types of transdermal patches, evaluation parameters.

KEYWORDS: Transdermal drug delivery system, Transdermal patches, Argyreia Nervosa, Covolvulaceae, Wound healing.

INTRODUCTION

Transdermal therapeutic systems have been designed to provide controlled continuous delivery of drugs via the skin to the systemic circulation. The relative impermeability of skin is well known, and this is associated with its functions as a dual protective barrier against invasion by micro-organisms and the prevention of the loss of physiologically essential substances such as water. Elucidation of factors that contribute to this impermeability has made the use of skin as a route for controlled systemic drug delivery possible. Basically, four systems are available that allow for effective absorption of drugs across the skin. The

microsealed system is a partition-controlled delivery system that contains a drug reservoir with a saturated suspension of drug in a water-miscible solvent homogeneously dispersed in a silicone elastomer matrix. A second system is the matrix-diffusion controlled system. The third and most widely used system for transdermal drug delivery is the membrane-permeation controlled system. A fourth system, recently made available, is the gradient charged system. Transdermal drug delivery system is topicaly administered medicamentsin the form of patches that deliver drugs for systemic effects at a predeterminedand controlled rate. A transdermal drug delivery device, which may be of an active or a passive design, is a device which provides an alternative route for administering medication. These devices allow for pharmaceuticals to be delivered across the skin barrier.

ARGYREIA NERVOSA

The Argyreia nervosa plant, belonging to the Convolvulaceae family, is also referred to as woolly morning glory or elephant creeper. This plant grows as undergrowth in semi-deciduous forests, along riverbanks, and along lakeshores. The primary constituents of A. nervosa leaves are quercetin, 1-tricontanol, and α-sitosterol. Due to the plant's numerous therapeutic benefits, including its antiviral, antibacterial, antifungal, and anti-inflammatory qualities, it has long been utilized in medicine. It also possesses spermatogenic, age-maintaining, and rejuvenating properties.[1] Of all the parts of the plant, the seeds have the highest concentration of psychoactive compounds. In India, the plant's leaves and roots are typically used as antiseptic and anti-inflammatory medications. Its leaves are antiphlogestic, emollient, local stimulant, rubifacient, and vesicant, while its roots are known to have aphrodisiac and diuretic qualities and have been used to treat gonorrhea in the Unani medical system. The leaves of A. nervosa have been used internally to treat swellings and boils. It is applied externally to skin conditions, ringworm infections, eczema, and scratches. Its seeds have tonic, spasmolytic, and hypotensive properties.[2] In an initial biological screening, a 50% ethanolic extract of the seeds exhibited antibacterial activity against Staphylococcus aureus and antispasmodic activity in the isolated guinea pig ileum.[3] In albino rats, the root's alcoholic extract demonstrated statistically significant anti-inflammatory activity against granuloma technique.[4] The seed oil exhibited antifungal properties against Alternaria solani and Aspergillius fl avus.[5] Stomach abscesses are treated externally with a paste made from its tubers. There have been reports of the anticonvulsant[6] and nootropic properties of A. nervosa Burm.[7]

MORPHOLOGY OF ARGYREIA NERVOSA

Convolvulaceae is the family to which Argyreia nervosa belongs. It is a climbing shrub with a woody tomentose stem. In English-speaking nations, it is frequently referred to as elephant creeper, while among Hindi-speaking Indians, it is called samundar-ka-pat.[8] It is widely found throughout the world's tropical regions. It is commonly grown natively in India, from Assam and Bengal to Karnataka, and has been observed up to 900 meters above sea level.[9,10] Typically, it grows as undergrowth in semidecidous forests and along riverbanks, lakeshores, and other slightly damp areas.[11] It is a twining, woody climber that can grow to a height of at least 10 meters. Simple, alternating leaves range in length from 5 to 15 cm. Large, showy, funnel-shaped flowers with a distinct odour and slightly bitter taste are borne on stout, whitish, and tomentose peduncles. The flowers are tinted purple or pale to deep rose and are regular, with short pedicels in axillary bracteates cymes.[12] The smooth, globose, indehiscent, irregularly crumbling berries have a diameter of 1.2–1.8 cm and are yellowish brown in color. They contain one or two seeds encased in a mealy pulp. The seeds are roughly triangular in shape, with two flat or slightly concave sides and a convex third. They range in length from 0.5 to 0.75 cm and width from 5 mm. When the stem is young, it is tomentose and white. The older stem (25 mm) is so thick that many lenticels, most of which are transversely elongated, are visible along with vertical ridges. Both in size and thickness, Argyreia nervosa roots vary in size. The thin roots have a smooth, brownish exterior and typically have a diameter of 2-4 mm. When they are cut transversely, a thin periderm and cambium can be seen, which appears as a dark line that divides the inner central wood from the outer phloem almost halfway between the two. Due to the abundance of lenticels, the thicker roots, which have a diameter of 5 to 25 mm or more, have a rough exterior. The plant is multiplied by seeds as well as stem cuttings.[13]

Table 1.1: Taxonomical Classification.

Kingdom	**Plantae**
Division	Tracheophytes
Order	Solanales
Family	Convolvulaceae
Genus	Argyreia
Species	A nervosa

1.2. COMPONENTS OF TRANSDERMAL DRUG DELIVERY SYSTEMS[14,18]

- Polymer matrix or matrices.
- The drug
- Permeation enhancers
- Other excipients.

1.2.1. Polymer Matrix

The Polymer controls the release of the drug from the device. Possible useful polymers for transdermal devices are.

Natural Polymers

E.g. Cellulose derivatives, Zein, Gelatin, Shellac, Waxes, Proteins, Gums and their derivatives, Natural rubber, Starch etc.

Synthetic Elastomers

E.g. Polybutadieine, Hydrin rubber, Polysiloxane, Silicone rubber, Nitrile, Acrylonitrile, Butyl rubber, Styrenebutadieine rubber, Neoprene etc.

Synthetic Polymers

E.g. Polyvinyl alcohol, Polyvinyl chloride, Polyethylene, Polypropylene, Polyacrylate, Polyamide, Polyurea, Polyvinylpyrrolidone, Polymethylmethacrylate, Epoxy etc.

1.2.2. The Drug

For successfully developing a transdermal drug delivery system, the drug should be chosen with great care. The desirableproperties of a drug for transdermal delivery.

Physicochemical properties

- The drug should have a molecular weight less than approximately 1000 daltons.

- The drug should have affinity for both – lipophilic and hydrophilic phases. Extreme partitioning characteristics are not conductive to successful drug delivery via the skin.
- The drug should have low melting point.

1.2.3. Enhancers

These are compounds which promote skin permeability by alteringthe skin as a barrier to the flux of a desired penetrant.

Solvents

These compounds increase penetration possibly by swallowing the polar pathway and/or by fluidizing lipids. Examples include water alcohols – methanol and ethanol; alkyl methyl sulfoxides – dimethyl sulfoxide, alkyl homologs of methyl sulfoxide dimethyl acetamide and dimethyl formamide; pyrrolidones – 2 pyrrolidone, N-methyl, 2-purrolidone; laurocapram (Azone), miscellaneous solvents – propylene glycol, glycerol, silicone fluids, isopropyl palmitate.

1.2.4. Other Excipients

Adhesives

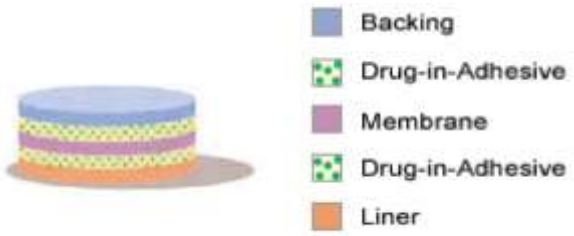
The fastening of all transdermal devices to the skin has so far been done byusinga pressure sensitive adhesive which can be positioned on the face of the device or in the back of the device and extending peripherally.

1.3. TRANSDERMAL PATCHES

1.3.1. Single-layer Drug-in-Adhesive

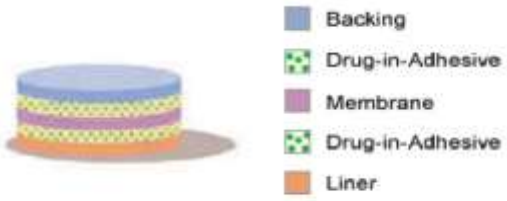
The Single-layer Drug-in-Adhesive system is characterized by the inclusion ofthe drug directly within the skin-contacting adhesive. In this transdermal systemdesign, the adhesive not only serves to affix the system to the skin, but alsoserves as the formulation foundation, containing the drug and all the excipientsunder a single backing film. The rate of release of drug from this type of systemis dependent on the diffusion across the skin.

1.3.2. Multi-layer Drug-in-Adhesive



The Multi-layer Drug-in-Adhesive is similar to the Single layer Drug-in-Adhesive in that the drug is incorporated directly into the adhesive. However, the multi-layer encompasses either the addition of a membrane between two distinct drug-in-adhesive layers or the addition of multiple drug-in-adhesive layers under a single backing film.

1.3.3. Drug Reservoir-in-Adhesive



The Reservoir transdermal system design is characterized by the inclusion of a liquid compartment containing a drug solution or suspension separated from the release liner by a semi-permeable membrane and adhesive. The adhesive component of the product responsible for skin adhesion can either be incorporated as a continuous layer between the membrane and the release liner or in a concentric configuration around the membrane.

1.3.4. Drug Matrix-in-Adhesive

The Matrix system design is characterized by the inclusion of a semisolid matrix containing a drug solution or suspension which is in direct contact with the release liner. The component responsible for skin adhesion is incorporated in an overlay and forms a concentric configuration around the semisolid matrix.

1. MATERIALS AND METHODS

1.1. Collection and identification

The plant leaves of A. nervosa were collected locally from Kapoor Chand Kulish Smriti Van, Jaipur, Rajasthan, and identifi ed in the Botanical Survey of India/Arid Zone Circle, Jodhpur. The voucher specimen of the same was also deposited at the above-mentioned herbarium (specimen number JNU/JPR/PC/ HG-1). Alloxan monohydrate was purchased from Spectrchem Pvt. Ltd. Company, Mumbai, India.

1.2. Preparation of the extract

The freshly collected leaves were shade-dried and pulverized using a mechanical grinder. The powdered leaves were macerated with 90% ethanol for 3 days, with occasional shaking. The extract was subjected to preliminary phytochemical tests and percentage yield was calculated in the extract after drying.[19]

PHYTOCHEMICAL CONSTITUENTS

According to[20], fatty oil derived from Argyreia nervosa seeds contained the glycosides of palmitic, oleic, stearic, behenic, linoleic, and linolenic acid. Myristoleic, myristic, palmitic, linoleic, linolenic, oleic, stearic, nonadecanoic, eicosenoic, heneicosanoic, and behenic acids were identified in the seed oil by gas layer chromatography (GLC). It was also noted that there were two branched fatty acids present: 12-methylmyristic acid and 15-methylstearic acid.[21] Three different alkaloids were identified in the ethanolic extract of the seeds, but only one of them was identified as ergometrine. According to[22], caffeic acid and ethyl caffeate were the other components that were isolated. According to[23], ergoline alkaloids were also present. The ergoline alkaloids comprise the following: agroclavine, chanoclavine-I, chanoclavine-II, festuclavine, lysergene, lysergol, isolysergol, setoclavine, iso-setoclavine, ergine, and isoergine .the free amino acids found in the seeds included glutamic acid, glycine, isoleucine, leucine, lysine, phenylalanine, tyrosine, praline, and α-aminobutyric acid. The seeds contained 30.6% crude protein overall, with 10.4%, 8.8%, and 10.6% of albumin, globulin, and glutelin, respectively. These results recommended using seeds for food purposes.[24] A significant glycoside known as argyroside (24R)-ergost-5-en-11- oxo-3β-ol-α-D-glucopyranoside has been extracted from the seeds. The primary psychoactive ingredient in the seeds that gives rise to the plant's hallucinogenic effects is lysergamide. reported the presence of triacontanol, β-sitosterol, p-hydroxycinnamoyl octadecanolate, and caffeic acid in the fruits of Argyreia speciosa. Argyreia speciosa leaves were extracted with petroleum ether

to produce β-sitosterol, 1-triacontanol, and epifriedelinol acetate.[25] Flavonoids, quercetin, kaempferol, and kaempferol 3-O-Lrhamnopyranoside were discovered to be present in the leaves. Two flavone glycosides were identified from leaves and named 7,8,3',4',5'-pentahydroxyflavone-5-O-β-D glucopyranoside and 7,8,3',4',5'-pentahydroxyflavone, 5-O-α-L-rhamnopyranoside.[26] Friedelanol, 5-O-β-Dglucopyranoside, was a triterpene that was identified from leaves. Tetradecanyl palmitate, 5,8-oxidotetracosan-10-one, was obtained from the hexane extract of Argyreia speciosa roots. The root was used to isolate two aryl esters, coumarin scopoletin and stigma steryl-p-hydroxycinnamate and hexadecanyl-phydroxycinnamate.[27] Additionally, a coumarin glycoside known as 6-methoxy7-o-alpha-D-glu, or L-ester coumarin, was identified from the root.[28]

PHARMACOLOGICAL ACTIVITIES

Antimicrobial activity

While the aqueous extract of the leaves was ineffective against these two organisms, the alcoholic extract of the leaves demonstrated antibacterial activity against Staphylococcus aureus but was inactive against Escherichia coli.[29] Both gram positive and gram negative bacteria were found to be susceptible to the antibacterial properties of argyreia seed oil.[30], but the oil had no effect on S. aureus. Numerous fungal species, including Aspergillus flavus, Colletotrichum capsici, Cryptococcus neoformans, Alternaria solani, Helminthosporium sp., Colletotrichum dematium, Aspergillus niger, A. sydowi, and Fusarium oxysporum, were found to be susceptible to the antifungal activity of the seed oil. It was discovered that Penicillium sp. was resistant to the oil.

Analgesic activity

At doses ranging from 30-300 mg/kg, the methanolic extract of A. speciosa roots demonstrated notable analgesic activity.

Anti-inflammatory activity

Using carrageenan-induced paw edema, the anti-inflammatory properties of an ethyl acetate and methanol extract of the entire aerial part of Argyreia nervosa were investigated in healthy wistar strain albino rats weighing between 140 and 250 g. Significant anti-inflammatory activity was produced by both extracts.[31]

Antipyretic activity

Investigated the antipyretic activity of a methanol and ethyl acetate extract of the whole aerial part of Argyreia nervosa. Using brewer's yeast-induced pyrexia for antipyretic research, the investigation was conducted on healthy wistar rats weighing between 150 and 200 g. which demonstrated the plant's potent antipyretic properties.

Hypoglycemic activity

500 mg/kg of an alcoholic extract of Argyreia nervosa roots was used to test the hypoglycemic effect in normal, glucose-loaded, and streptozotocin (STZ)-induced diabetic rats. In rats that were normoglycemic, oral glucose-loaded, and STZ diabetic, the extract resulted in a drop in blood glucose levels.[32]

Antiviral activity

According to[33], the plant and fruit extract had antiviral activity against the vaccinia virus but was ineffective against the Ranikhet disease virus.

Anticonvulsant activity

The plant Argyreia Nervosa exhibits anticonvulsant properties in its root.

Nootropic activity

A. speciosa roots' aqueous extract was found to have nootropic and anticholinesterase properties.[34]

Anthelmintic activity

The leaves of A. nervosa exhibited anthelmintic activity in both alcoholic and aqueous extract.[35]

Aphrodisiac activity

The mice exhibited aphrodisiac activity towards the leaf, flower, and root extracts. Additionally, the plant promotes male sex.[36] It has been reported that mice treated with the product "Speman," which contains various plant materials, including this species, show anabolic-cum androgen-like activity. it also enhances sperm motility, release of follicle-stimulating hormone, and synthesis of the hormone.

Antidiarrheal activity

Significant antidiarrheal activity was demonstrated by the ethanolic extract of A.nervosa flower.[37]

Antiulcer activity

Rats protected against ulcers by an ethanolic extract of A. speciosa flower. Using aspirin, indomethacin, and ethanol-induced ulcer models, researchers examined the antiulcer properties of Argyreia speciosa root extract at doses of 25, 50, and 100 mg/kg in rats. The results demonstrated the ethanolic root extract's significant and dose-dependent antiulcer activity.

Treatment of Skin Diseases

The entire plant was used as a paste to treat various skin conditions, including smallpox.[38]

Wound healing activity

Through oral and topical administration, the wound-healing properties of Argyreia nervosa leaves extract were investigated in both normal and diabetic animals. As compared to oral administration, the results indicated that topical application of the extract significantly promoted healing.[39]

Immunomodulatory activity

When given orally to rats, an ethanolic extract of the dried root of A. speciosa stimulates humoral immunity as well as cellular immunity.[40]

Central nervous system depressant activity

Different root solvent extracts, including chloroform, nhexane, and ethyl acetate, showed central nervous system depressant activity, reducing spontaneous motor activity and intensifying pentobarbital-induced hypnosis in mice.[41]

Hallucinogenic effect

Plant-derived ergot alkaloids exhibited hallucinogenic properties.[42]

Action on obesity

The effects of A. speciosa root ethanolic extract on rats given a cafeteria diet were assessed. According to[43], the extract dramatically lowered the levels of triglycerides, low density

lipoprotein, total cholesterol, and leptin in the serum, which resulted in a decrease in obesity in the test animals.

EVALUATION OF TRANSDERMAL PATCHES[44,49]

Transdermal patches have been developed to improve clinical efficacy of the drug and to enhance patient compliance by delivering smaller amount of drug at a predetermined rate. This makes evaluation studies even more important in order to ensure their desired performance and reproducibility under the specified environmental conditions.

Physicochemical Evaluation

Thickness

The thickness of transdermal film is determined by traveling microscope, dial gauge, screw gauge or micrometer at different points of the film.

Uniformity of weight

Weight variation is studied by individually weighing 10 randomly selected patches and calculating the average weight. The individual weight should not deviate significantly from the average weight.

Drug content determination

An accurately weighed portion of film (about 100 mg) is dissolved in 100 mL of suitable solvent in which drug is soluble and then the solution is shaken continuously for 24 h in shaker incubator. Then the whole solution is sonicated. After sonication and subsequent filtration, drug in solution is estimated spectrophotometrically by appropriate dilution.

Content uniformity test

10 patches are selected and content is determined for individual patches. If 9 out of 10 patches have content between 85% to 115% of the specified value and one has content not less than 75% to 125% of the specified value, then transdermal patches pass the test of content uniformity. But if 3 patches have content in the range of 75% to 125%, then additional 20 patches are tested for drug content. If these 20 patches have range from 85% to 115%, then the transdermal patches pass the test.

Moisture content

The prepared films are weighed individually and kept in a desiccators containing calcium chloride at room temperature for 24 h. The films are weighed again after a specified interval

until they show a constant weight. The percent moisture content is calculated using following formula.

% Moisture content = Initial weight – Final weight X 100

Folding Endurance

Evaluation of folding endurance involves determining the folding capacity of the films subjected to frequent extreme conditions of folding. Folding endurance is determined by repeatedly folding the film at the same place until it break. The number of times the films could be folded at the same place without breaking is folding endurance value.

Tensile Strength

To determine tensile strength, polymeric films are sandwiched separately by corked linear iron plates. One end of the films is kept fixed with the help of an iron screen and other end is connected to a freely movable thread over a pulley. The weights are added gradually to the pan attached with the hanging end of the thread. A pointer on the thread is used to measure the elongation of the film. The weight just sufficient to break the film is noted. The tensile strength can be calculated using the following equation.

Tensile strength= F/a.b (1+L/l)

Where, F is the force required to break;
a is width of film;
b is thickness of film;
L is length of film;
l is elongation.

Thumb tack test

The force required to remove thumb from adhesive is a measure of tack.

CONCLUSION

Throughout the world, traditional medical systems have included a significant amount of herbal drugs and remedies. Many different herbs have been used in one form or another. or another for the improvement of health and treatment of different diseases. The morphology, traditional uses, phytochemistry, and pharmacological characteristics of A. nervosa (synonym: A. speciosa), a medicinal plant that grows in tropical and subtropical regions, have all been attempted to be covered in this review. This plant has been utilized since ancient

times and has a wide range of pharmacological potential. The plant should be widely grown because it has a bright future in the field of herbal medicine, especially in abandoned and waste land that will beneficial to the advancement of research in the field of herbal medicine as well as the financial well-being of farmers. In addition, systemic and scientific research is needed to investigate the plant's full pharmacological potential. Researchers will undoubtedly benefit from this review as they examine the various characteristics of argyreia nervosa.

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