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FABRICATION AND EVALUATION OF *MIKANIA MICRANTHA* EXTRACT LOADED TRANSDERMAL PATCH

Santanu Halder, Moumita Das Kirtania, Sanjay Dey, Rajkumar Ghosh, Sajal Kumar Jha, Anwesha Barik*

Department of Pharmaceutical Technology, School of Medical Sciences, Adamas University, Barasat - Barrackpore Road, 24-Parganas North, Jagannathpur, West Bengal 700126, India.

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Corresponding Author:
† Dr. Anwesha Barik
Assistant Professor
Department of Pharmaceutical Technology
School of Medical Sciences,
Adamas University
Barasat - Barrackpore Road, 24-Parganas North, Jagannathpur, West Bengal 700126, India
Email ID:
anwesha1.barik@adamasuniversity.ac.in

ABSTRACT

Being approved in the year 1981by USFDA, scopolamine loaded transdermal patch (Transderm-Scop), developed by ALZA Corp, USA was the first one to hit the market of transdermal drug delivery systems. Several other drugs including antihypertensives, anti-anginal, menopausal, anti-motion sickness has established its numerous advantages when delivered from commercially available transdermal drug delivery modules including some others which are currently under clinical investigations at different phases. Delivery of therapeutic/ diagnostic molecules via transdermal route not only maximizes flux in to systemic circulation at a reproducible rate but also reduce the risk of pre-systemic metabolism while minimizing the retention of drug in to the dosage form. Literature review suggests the antidiabetic as well as wound healing potential of the plant *Mikania micrantha* especially at the crude extract obtained from the dried leaves which urged us to design the experiment to fabricate drug loaded transdermal patches. These medicinal properties conferred by the aerial parts possibly owe to the presence of beta-caryophyllene in the essential oil due to its unique mechanism to bind to the cannabinoid 2 (CB2) receptors. The patches were found to maintain uniformity in weight which depicts the reproducibility in the formulation procedure while all other evaluation parameters such as surface pH, moisture content, folding endurance were found to be optimum. Overall the formulation turned out to be physically stable, without being dry and brittle.

Keywords: Transdermal Patch, *M. micrantha*, Antibacterial, wound healing, Crude extract.

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INTRODUCTION:

Asteraceae (or Compositae) is one of the largest families of flowering plants which belong to the genus Mikania. This genus has more than 430 species distributed mainly in the tropical regions. *Mikania micrantha* Kunth (Asteraceae) is a perennial creeping vine that can be found in South and North America, Africa, Pacific Islands and Southeast Asia, including Southern China and Malaysia. Several species of this genus are edible and it has been traditionally known to be a part of folklore medicine. *Mikania micrantha* Kunth is a type of weed originated from tropical Central and South America, commonly known as "selaput tunggul" in Malaysia [1]. It is also known as American rope, Chinese creeper, or mile-a-minute and recognized as "sembungrambat" in Indonesia[2]. Since the early twentieth century, this perennial creeping vine has been widespread to the Pacific Islands and Southeast Asia, including Southern China. These plants also have been found in India, Malaysia, Thailand, Indonesia, Nepal, Papua New Guinea, Philippines, and Australia. *M. micrantha* can be commonly found growing along the roadside, swampy woods, bushes of moist places, forest borders, and also along streams and rivers. They grow and spread easily by wind dispersion of the seed and stem fragments that root easily at the nodes. *M. micrantha* can be divided into several anatomical parts, namely seeds, inflorescence, leaves, stems, and roots. The leaves are simple, heart-shaped, opposite, petiolate, cordate or hastate, acuminate, having the size of 11.5 - 6.6 cm × 1.8 - 0.7 cm. Meanwhile, the stems are nearly rounded, hairy, and sometimes inconspicuously five ribbed. *M. micrantha* has distinctive characteristics that differentiate it from other species belonging to the genus Mikania such as *M. scandens* and *M. cordifolia*. Identification of *M. micrantha* from those other similar plants depends either on flowers or inflorescences,

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or on the specific phytochemical components present in the plant. Another vegetative character that differentiates *M. micrantha* from other genus includes colour and shape of the leaves, colour of stem, growth habit, while the structure of the pseudostipules arising between the petiole bases of the leaves being the most reliable and distinctive one. According to Nicollier and Thompson (1981), the major difference between *M. micrantha* and other previously investigated species of the same genus is the absence of aromatic terpenes or coumarin derivatives therein[3, 4]. The below-mentioned Figure 1 shows the aerial parts of *M. micrantha*.

Figure 1: Digital photograph showing aerial parts of Mikania *micrantha*

Previous studies have reported that the phytochemicals extracted from various parts of *M. micrantha* have been linked to beneficial medicinal properties such as antioxidant, antimicrobial, antitumor, anti-inflammatory, anti-stress, and also anti-diabetic activities [2, 5]. Several species of this family also are found to contain polyacetylenic and thiophenic compounds which are used as taxonomic markers. Their phototoxic activity acts in plant defense mechanism as well. Literature though reports the absence of these compounds in the species *Mikania micrantha*. The composition of the volatile oil extracted from the seeds and inflorescence in the species have also been mentioned somewhere else. Linalool and α-pinene were found to be the main components of this essential oil. Literature showed the ability of the extracts of *Mikania micrantha* to inhibit the mouse ear inflammation in response to topical application of 12-O-tetradecanoylphorbol-13-acetate (TPA)[6]. The antibacterial activity of extracts was also evaluated against Bacillus subtilis and Escherichia coli where the Ethyl acetate extracts of this plant exhibited significant antibacterial and anti-inflammatory properties [5]. It may therefore be potentially used as a medicinal plant [7]. The composition, physicochemical and sensory properties of the essential oil obtained from the sources such as *Chromolaena odorata* (L.) R.M. King & H. Rob, *Mikania micrantha Kunth*, and *Ipomoea pes-caprae* (L.) R. Br. of Philippine origins all were evaluated by GC/MS. and also using brine shrimp lethality assay (BSLA). The GC/MS analysis revealed a composition of 58 sesquiterpenes that represented more than 90 percent of the total oil extracted from the dried leaves of *C. odorata* [8]. The major components were found to be caryophyllene oxide (11.41%), β-caryophyllene (10.9%), δ-cadinene (10.59%), germacrene D (9.87%), α-copaene (3.01%), cadinenol (2.30%), α-trans bergamotene (1.99%), and α-humulene (3.18%). Around 56 compounds were detected from the essential oil in the dried leaves of *M. micrantha* in which the chief constituents of essential oil extracted from the plant contained sesquiterpenoids specifically, β-cubenene (6.31%), δ-cadinene (6.16%), caryophyllene oxide (6.71%), e-nuciferol (4.45%), α-muurol (4.13%), α-bisabolol (4.05%), spathulenol (2.98%), β-bisabolene (2.59%), and E-caryophyllene (2.19%)[9, 10]. In comparison with both of those, a total of 32 compounds were detected in the essential oil identified from the dried leaves of *I. pescaprae*. The major compound which could be extracted was β-caryophyllene that comprised 46.30% of the total relative volatile oil percent composition. The other major constituents identified were a-humulene (7.31%), δ-cadinene (6.16%), germacrene D (7.63%) and caryophyllene oxide (9.11%). All the essential oils extracted from *C. odorata*, *M. micrantha*, and *I. pescaprae* showed cytotoxic activity when brine shrimp lethality assay was performed and LD50 was measured to be about 52.16 µg/mL, 101.38 µg/mL and 92.50 µg/mL, respectively[11]. These essential oils could be used as ingredients for the development of novel formulations containing plant based natural ingredients [3].

Due to the abundance of the plant in its natural habitat, traditional treatment was not only feasible since long but also it provides an adequate supply of raw material for the pharmaceutical industry to develop modern medicines till date. *M. micrantha* is, however considered as a weed which reduces the growth and productivity of other several crops such as rubber, oil palm and cocoa plantation in Malaysia where around 8-10 million dollars need to be invested on an average per annum to control its growth. Scientific studies on the medicinal properties of *M. micrantha* might increase the value of the plant from being the weed to plant with active therapeutic constituents. Despite that, limited studies are available on exploration of the nutritional and pharmacological properties of *M. micrantha* collected from varied geographical locations as a scientific evidence to prove its traditional uses. This manuscript will provide information on the therapeutic properties of *M. micrantha* while providing knowledge for further exploratory experiments.

Transdermal patches are one of the most suitable drug delivery modules which can effectively reduce the adverse effects, increase bioavailability while reducing first pass metabolism of drugs, elevate permeability and facilitate sustained release for longer duration of time. A transdermal patch is designed as a medicated adhesive patch to be placed on the skin to deliver a specific dose of medication through the skin and then into the bloodstream[12]. This promotes healing to an injured area of the body. The advantage of a transdermal drug delivery route over other types of medication delivery including oral, topical, intravenous, intramuscular lies on the fact that the patch provides a controlled release of the medication, usually through either a porous membrane covering a reservoir of medication or through melting thin layers of medication embedded in the adhesive at usual physiological temperature[13]. Since skin is a very effective barrier, it also possesses the fact that only the molecules which are small enough to penetrate the skin can be delivered by this method. Several drug molecules having fulfilled the criteria have been developed as transdermal patch and have been commercialized thereafter.

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MATERIALS AND METHODS:

Collection of *M. micrantha* leaves and extraction of the active ingredients:

Aerial parts of Mikania micrantha were collected from its natural habitat during the flowering season from the district of North 24 Parganas, West Bengal, India. Dried specimens of the herbarium were authenticated by Botanical Survey of India and characterized for the leaves which appeared pale or yellow-green in colour, flowers which were white in colour and measured to be 2.5-3 mm in length, phyllaries and inflorescence both of which were nearly glabrous, and the pseudostipules which were observed to be membranous flap with incised lobes. The collected plant material was washed thoroughly in running water followed by drying under shade at room temperature and then the leaves were milled into finely powdered form using a standard kitchen blender. Extraction was further performed from those dried leaves [14]. Samples were macerated with the mixture of 70% ethanol and water (1:1) as shown in the Figure 2, approximately for one week, and filtered through Whatman No.1 filter paper. Concentrated filtrate was obtained on evaporation of the filtered extract at a temperature of 40℃ until a semi-concentrated crude extract was obtained. The resultant crude extract was analyzed by analytical thin layer chromatography according to the standard protocol, and the ethanol extract was stored in refrigerator at 4◦ C until further use.

Figure 2: Digital photograph showing extraction of therapeutic ingredients from the dried leaves of *M. micrantha* in the form of crude extract followed by filtration (taken during the experiment)

Preparation of extract-incorporated transdermal patches:

The *M. micrantha* extract loaded transdermal patches were fabricated by the conventional solvent evaporation technique while utilizing different ratios of Hydroxy propyl methylcellulose (HPMC) K15, ethyl cellulose respectively. During formulation, initially, the polymer (HPMC K15) was taken in a beaker along with a solvent mixture comprising dichloromethane: methanol (2:1) and the polymer-solvent mixture was allowed to completely swell for a duration of about 1 hour. Subsequently, with continuously stirring, ethyl cellulose was added to the swelled content. The other two additives, plasticizer poly-(ethylene glycol) (PEG 400) and permeation enhancer (SLS) were added afterwards and mixed uniformly for a few minutes. The drug (i.e. extract obtained from *M. micrantha*) was incorporated with continuous stirring to blend well with the previously formulated polymer matrix. The resultant homogenous dispersion was spread over a film former with the help of a dragger. The controlled solvent evaporation was employed later by application of heat and the fabricated dried film was then cut into the dimension of about 10 cm^2. The prepared films were wrapped in aluminum foil and stored in the desiccators for further analysis. The following Table 1 summarizes the quantities of the ingredients required for the formulation of the transdermal patches.

Table 1: Representation of the formulation ingredients for the fabrication of two separate batches of transdermal patch (Formulation 1 and Formulation 2)

Ingredients	Formulation 1	Formulation 2
Extract of *M. micrantha* (in mL)	10	10
Hydroxy Propyl Methylcellulose i.e. HPMCK100M (in mg)	3750	3750
Ethyl Cellulose (in mg)	1250	1875
Mixture of Di-chloro Methane and Methanol (1:2) (in mL)	50	50
Poly-(ethylene glycol) i.e. PEG 400 (in mg)	1000	1125
Sodium Lauryl Sulphate i.e. SLS (in mg)	100	112.5

Figure 3: Real digital photograph showing two representative transdermal patches (Top patch belongs to the batch 'Formulation 1' where as the bottom one belongs to the batch 'Formulation 2'.

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Physicochemical characterization of extract-incorporated transdermal patches:
The following characterization experiments were performed to evaluate the performance of the above-mentioned fabricated transdermal patches according to standard procedures[15, 16]. Prior to those studies, the patches were visually observed for their uniformity in colour, clarity, appearance, smoothness and flexibility[17].

Weight uniformity:
The patches were chosen randomly to be subjected to weight uniformity test where the chosen transdermal patches were weighed in an accurate and precise digital balance. The average weight and standard deviation values were then mathematically calculated from the individual weights noted. All the measurements were recorded in triplicate.

Folding endurance:
This particular experiment is usually performed to evaluate the strength of the prepared transdermal patch along as well as the performance of the plasticizer(s) used therewith. A patch on the specific area (2 cm x 2 cm) was cut evenly and was then repeatedly folded at the same place until it was broken as suggested by the standard procedure. The folding endurance was measured by the number of times that particular patch was being able to be folded at the same place without causing cracks or breaks. The results were noted in triplicate for three different patches.

Surface pH determination:
For the determination of surface pH of the fabricated transdermal patches, a measured area (2 cm x 2 cm) of each of the film was cut, and allowed to swell by immersing it in distilled water for about one hour in a glass tube. The surface pH of the swelled surface of the patches was then recorded after the designated period.

Percentage moisture content and Percentage moisture absorption:
Maintenance of the elasticity, physical stability and integrity of the film is pertinent to the storage of transdermal patches especially while keeping under highly dry atmosphere. The prepared transdermal films were weighed individually and kept in desiccators containing fused calcium chloride at room temperature for the duration of 24 hours. After 24 hours, the films were re-weighed and the percentage moisture content was determined by the given mathematical formula:

Percentage moisture content = (□□□□□□□□ □□□□ℎ □−□□□□□□ □□□□ℎ □)/ □□□□□□ □□□□ℎ □ × 100

The similar experiment but in highly humid conditions was performed to check the stability of the patches thereby measuring the percentage moisture absorption. The patches were weighed individually and kept in desiccators along with the solution of calcium chloride at room temperature. After the duration of 24 hours, those were reweighed and percentage moisture absorption was calculated using the below-mentioned formula thereafter.

Percentage moisture absorption = (□□□□□□ □□□□ℎ □−□□□□□□□□ □□□□ℎ □)/ □□□□□□ □□□□ℎ □ × 100

RESULTS AND DISCUSSION:

The films exhibited excellent weight uniformity among the various fabricated batches. The percentage of weight variation has been found to lie in between 0.41- 0.82. The folding endurance was observed to be satisfactory among the entire batches (99–125) %. The percentage moisture content was found to be in the range of 1.32%–2.64% in the formulation while the surface pH was found to be 5.8. The films exhibited excellent weight uniformity among the various fabricated batches.
The uniformity of weight indicates that the polymer solution of the drug is well dispersed on a flat surface. However, a little variation in weight among the formulation F1–F2 was observed in the range of 41–82 mg which may attribute to the variation in polymeric content. An increase in the weight of the fabricated formulation was seen with an increase in the concentration of Ethyl Cellulose (EC). This may be due to the fact that the polymer has low water permeability which further prevents evaporation of water from the surface thereby retaining the mass considerably.
All the formulations exhibited a slight variation in drug content ranging from 89.16% to 95.04%. The formulation F1 shows the highest drug content of 95.04% while the batch F2 presented the lowest drug content of about 89.16%. All the formulations were found to be satisfactory with reference to the drug loading capacity. The percentage moisture content was found to be in the range of 1.23%–3.16% in the formulation F1 and F2. Along with the increase in the concentration of the polymer blend (HPMC, EC, and PEG), the moisture content was observed to be increasing. Presence of small moisture in the formulation helped those to remain physically stable and prevent further from being completely dried and brittle. It has also been observed that the optimized ratio of HPMC: EC /PEG (2:1) led to an increased retention of moisture to the formulation. The high ratios of hydrophilic polymer concentration in the formulation F2 resulted in increased moisture preservation as the rate of moisture uptake was found to be lying in the range of 1.32%–2.64%. A low moisture uptake supposedly protects the material from microbial contamination and bulkiness of the patch.
The folding endurance was found out manually in order to determine the plasticity of the prepared patch. The number of times the film could be folded at the same place without breaking gave the value of folding endurance. The folding endurance was satisfactory in all the batches (99–125). The increased concentration of hydrophilic polymers in the formulation greatly affected the folding endurance as it provided better elasticity. The surface pH was measured to be 5.8, which has been claimed to cause no irritation to the human skin according to literature. Hence, all the prepared formulations passed the surface pH test.

CONCLUSION:

Mikania *micrantha* extract has potential benefits as antibacterial and wound healing agent. However, prolonged effect of the drug cannot be achieved though ointment or gel formulations. Therefore, delivery through transdermal patch would prolong and sustain the effect of the drug and provide better therapeutic effect. Weight

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uniformity, folding endurance, percentage moisture content, primary Hence, the study is facilitating a better judgment and perception of this fundamental homeostatic process of *Mikania micrantha* and broadcasting it as a matrix transdermal patch.

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