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Research Paper

Review on Phytoconstituents Loaded Transdermal Patches for Management of Herpes Simplex Virus Type-1 Infection.

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Abstract
Herpes simplex virus type-1 (HSV-1) is a prevalent viral infection that primarily affects the oral and facial regions, causing recurrent lesions and discomfort. Conventional antiviral therapies such as acyclovir are limited by poor patient compliance, drug resistance, and low bioavailability upon oral administration. Therefore, development of alternative natural and effective formulations is of growing interest. Melissa officinalis (lemon balm), a medicinal herb rich in rosmarinic acid and other polyphenolic compounds, has been reported to possess potent antiviral, anti-inflammatory, and antioxidant properties against HSV-1.
This review aims to study phytoconstituents loaded transdermal patches for sustained and localized delivery in the management of HSV-1 infection. The patches will be prepared using various polymeric combinations such as hydroxypropyl methylcellulose (HPMC), polyvinyl alcohol (PVA), and Eudragit RL100 by solvent casting technique.

Keywords- *Herpes simplex virus type-1 (HSV-1), Phytoconstituents, Transdermal Patches, Solvent Casting Technique*

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I. INTRODUCTION

Around the world, traditional medicine uses the medicinal herb Melissa officinalis L. It is a fragrant perennial that is widely grown in Western Asia and the Mediterranean region. It is extensively grown in Europe and is the subject of extensive research because of its many pharmacological effects and chemical makeup. This plant, which belongs to the mint family Lamiaceae and the subfamily Nepetoideae, is also known as lemon balm, honey balm, or balm mint. It is an edible therapeutic herb.

The upper portions of Melissa officinalis fade out in early winter and return in early spring, but the hairy root structure helps the plant adapt to many weather circumstances. One of the simplest herbs to cultivate, it spreads so quickly that some gardeners view it as a weed[1,2]

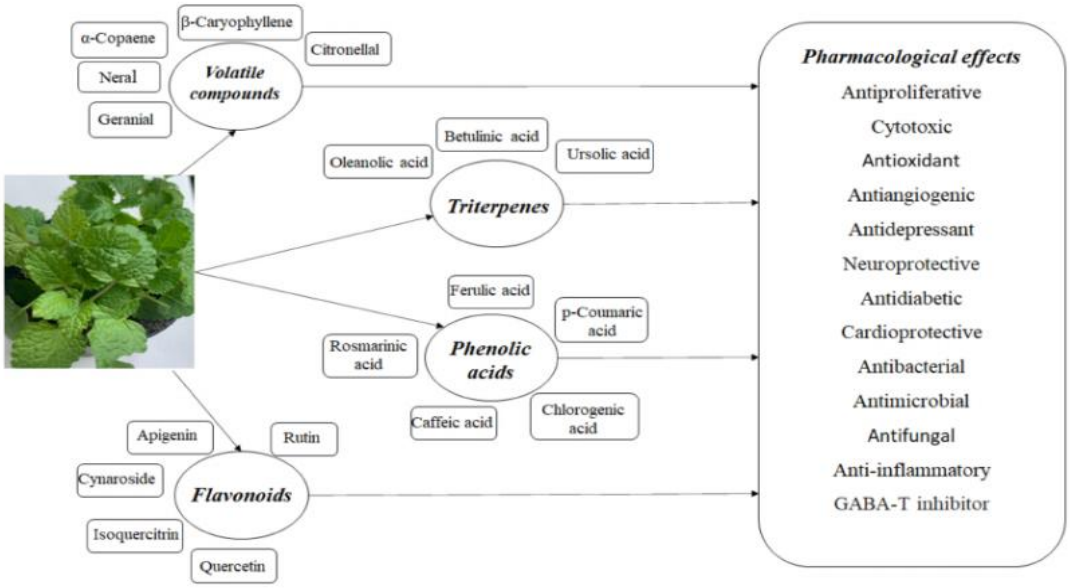

Figure 1. The composition of Melissa officinalis and its pharmacological effects

Herpes Simplex Virus Type 1 (HSV-1) is a nuclear replicating enveloped virus, usually acquired through direct contact with infected lesions or body fluids (typically saliva). The prevalence of HSV-1 infection increases progressively from childhood, the seroprevalence being inversely related to socioeconomic background. Primary HSV-1 infections in children are either asymptomatic or following an incubation period of about 1 week gives rise to mucocutaneous vesicular eruptions.[3] Herpetic gingivostomatitis typically affects the tongue, lips, gingival, buccal mucosa and the hard and soft palate. Most primary oro-facial HSV infection is caused by HSV-1, infection by HSV-2 is increasingly common. Recurrent infections, which occur at variable intervals, typically give rise to vesiculo-ulcerative lesions at mucocutaneous junctions particularly the lips[4]

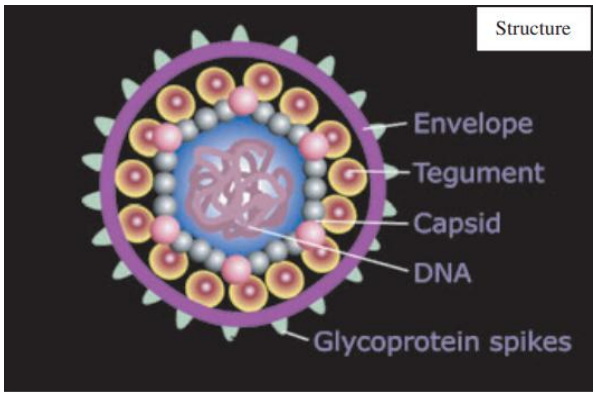

Fig 2. Herpes Simplex Virus Type 1

1.2 PATHOPHYSIOLOGY OF HSV-1

Exposure to HSV at mucosal surfaces or abraded skin sites permits entry of the virus and initiation of its replication in cells of the epidermis and dermis .Initial HSV infection is often subclinical, without apparent lesions. In animal models and human subjects, both clinical acquisition and subclinical acquisition are associated with sufficient viral replication to permit infection of either sensory or autonomic nerve endings[5].

Most primary infections are acquired through direct contact with a lesion or with infected body fluids (saliva, genital fluids, exudates of active lesions). Asymptomatic individuals periodically shed infectious HSV in saliva, observed in 2–9% of total cases. Viral shedding is usually greater in immunocompromised patients (approximately 38%) or in those undergoing.[6]

1.3 Herpes Simplex Virus-Type -1 Symptoms and Signs-

Incubation period: For HSV-1, the amount of time between contact with the virus and the appearance of symptoms, the incubation period, is two to twelve days. Most people average about three to six days.[7]

Duration of illness: Signs and symptoms will last two to three weeks. Fever, tiredness, muscle aches, and irritability may occur. Pain, burning, tingling, or itching occurs at the infection site before the sores appear. Sometimes these symptoms happen prior to the appearance of sores, bumps, pimple like lesions, or blisters (herpes or herpetic stomatitis). Thereafter, clusters of painful blisters or vesicles erupt or ooze with a clear to yellowish fluid that may develop into a yellowish crust. These blisters break down rapidly and appear as tiny, shallow gray ulcers on a red base. A few days later, they become crusted or scabbed and appear drier and more yellow.[8,9]

Oral sores: The most intense pain caused by these sores occurs at the onset and can make eating and drinking difficult. The sores can occur on the lips, gums, throat, the front of the tongue, the inside of the cheeks, and the roof of the mouth. They can also extend down the chin and neck. The gums can become mildly swollen, red-colored, and may bleed.[10,11]

1.4 NEED FOR TRANSDERMAL PATCHES IN HSV-1-

Herpes Simplex Virus Type-1 (HSV-1) is a highly contagious viral infection that primarily affects the oral and facial regions, leading to recurrent cold sores, blisters, and inflammation. Conventional treatments for HSV-1 mainly rely on oral or topical antiviral agents such as acyclovir and penciclovir. However, these dosage forms often face several challenges including low bioavailability, poor skin penetration, short duration of action, and the requirement for frequent administration to maintain effective drug levels. Topical creams or gels are easily removed by saliva, wiping, or washing, which reduces their therapeutic effect, while oral formulations are subjected to hepatic first-pass metabolism, leading to fluctuating plasma concentrations and potential systemic side effects.[12]
To overcome these limitations, transdermal drug delivery systems (TDDS) have emerged as a promising and patient-friendly alternative. Transdermal patches allow the controlled and sustained release of therapeutic agents through the skin into systemic circulation, thereby maintaining steady-state plasma levels for extended periods. This approach improves drug efficacy, reduces dosing frequency, and enhances patient compliance, especially in chronic or recurrent infections like HSV-1. Moreover, transdermal systems bypass gastrointestinal degradation and first-pass metabolism, resulting in better drug utilization and reduced side effects.[13,14]

TDDS in controlling viral infectious diseases-

1. Avoid first pass effect of liver and the effluence of enzyme digestion, gastric emptying time, and pH of gastrointestinal tract
2. Applying to patients who are nauseous or unconscious
3. Prevent discomfort, bruises, and bleeding
4. Improved patient acceptance and adherence to immunization or therapy
5. Enhanced immunogenicity of immunization
6. Increased safety and reduced needle-related illness transmission
7. Reduced sharp medical waste and increased efficiency
8. Potential self-administration could boost immunization rates
9. Direct administration of medication to the areas of skin infection
10. Minimize related adverse effects or systemic toxicity
11. Extended and regulated medication release
12. Termination flexibility
13. Examination using transdermal extraction, particularly for direct collection of cutaneous viral infections[15,16,17]

A transdermal patch is used to deliver a specific dose of medication through the skin and into bloodstream. Transdermal patches products were first approved in 1981 by FDA. Transdermal delivery systems are currently available containing scopolamine (hyoscine) for motion sickness, clonidine and nitroglycerin for cardiovascular disease, fentanyl for chronic pain, nicotine to aid smoking cessation. Transdermal delivery provides controlled, constant administration of the drug, and allows continuous input of drugs with short biological half-lives and eliminates pulsed entry into systemic circulation. TDDS offers many advantages over conventional injection and

oral methods. It reduces the load that the oral route commonly places on the digestive tract and liver. It enhances patient compliance and minimizes harmful side effects of a drug caused from temporary overdose. It is convenient, especially notable in patches which require only once weekly application. Such a simple dosing regimen aids in patient adherence to drug therapy.[18,19]

1.5 The main components to a transdermal patch are:

• **Polymer matrix–** backbone of TDDS, which control the release of the drug. Polymer should be chemically non-reactive, should not decompose on storage, should be non toxic, cost should not be high. E.g.- cellulose derivatives, zein, gelatin, shellac, waxes, gums, Polybutadiene, hydrin rubber, polyisobutylene, silicon rubber, nitrile, acrylonitrile, neoprene, Polyvinyl alcohol, polyvinylchloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinylpyrrolidone, polymethylmethacrylate.[20]

• Drug- The transdermal route is an extremely attractive option for the drugs with appropriate pharmacology and physical chemistry. Transdermal patches offer much to drugs which undergo extensive first pass metabolism, drugs with narrow therapeutic window, or drugs with short half life.eg fenatyl, nitroglyceriene etc.[21]

• **Permeation enhancers-** increase permeability of stratum corneum so as to attain higher therapeutic levels of the drug. These are of three types-lipophilic solvent, surface active agents and two component systems. E.g. DMSO[22]

• **Adhesive-** increase permeability of stratum corneum so as to attain higher therapeutic levels of the drug that increase permeability of stratum corneum so as to attain higher therapeutic levels of the drug.[23]

• **Backing laminates-** should have low modulus or high flexibility. Eg-vinyl, polyethylene
.
• **Release liner-** Protects the patch during storage. The liner is removed prior to use.

• Other excipients like plasticizers and solvent

Advantages:

1. It is convenient method and requires only once weekly application. Such a simple dosing regimen can aid in patient adherence to drug therapy.

2. Transdermal drug delivery can be used as an alternative route of administration to accommodate patients who cannot tolerate oral dosage forms.

3. It is of great advantage in patients who are nauseated or unconscious.

4. Drugs that cause gastrointestinal upset can be good candidates for transdermal delivery because this method avoids direct effects on the stomach and intestine.

5. Drugs that are degraded by the enzymes and acids in the gastrointestinal system may also be good targets. 3 6. First pass metabolism, an additional limitation to oral drug delivery, can be avoided with transdermal administration[24,16,26]

Disadvantages:

1. Possibility of local irritation at the site of application.

2. Erythema, itching, and local edema can be caused by the drug, the adhesive, or other excipients in the patch formulation.

3. May cause allergic reactions.

4. A molecular weight less than 500 Da is essential.

5. Sufficient aqueous and lipid solubility, a log P (octanol/water) between 1 and 3 is required for permeate to transverse SC and underlying aqueous layers.[27,28]

1.6 Various methods for preparation of TDDS

1. **Circular teflon mould method -**Solutions containing polymers in various ratios are used in an organic solvent. Calculated amount of drug is dissolved in half the quantity of same organic solvent. Enhancers in different concentrations are dissolved in the other half of the organic solvent and then added. Plasticizer (e.g., Di-N-butylphthalate) is added into the drug polymer solution. The total contents are to be stirred for 12 hrs and then poured into a circular teflon mould. The moulds are to be placed on a levelled surface and covered with inverted funnel to control solvent vaporization in a laminar flow hood model with an air speed of 0.5 m/s. The solvent is allowed to evaporate for 24 h. The dried films are to be stored for another 24 h at 25±0.5°C in a desiccators containing silica gel before evaluation to eliminate aging effects. These types of films are to be evaluated within one week of their preparation.It have studied about bioadhesive film containing ketorolac. Films were cast from organic and aqueous solvents using various bioadhesive polymers namely: sodium carboxymethyl cellulose (Na-CMC), hydroxypropyl cellulose (HPC), hydroxypropylmethyl cellulose (HPMC) and Carbopol 934. The prepared films were subjected to investigations for their physical and mechanical properties, swelling behaviours, in-vitro bioadhesion, drug permeation via bovine buccal mucosa and in-vitro drug release. These properties were found to vary significantly depending on the preparation methods, the type of the polymers and the ratio of addition of both plasticizer (i.e. polyethylene glycol) and film forming agent (ethyl cellulose and polyvinylpyrolidene). The obtained results indicated that the concentration of ketorolac in the oral cavity was maintained above 4.0 µg/mL for a period of at least 6 h. This film showed promising results for using the ketrolac buccoadhesive route of administration topically and systemically[30].

2. **Asymmetric TPX membrane method (Berner and John 1994)** A prototype patch can be fabricated for this a heat sealable polyester film (type 1009, 3m) with a concave of 1cm diameter will be used as the backing membrane. Drug sample is dispensed into the concave membrane, covered by a TPX {poly (4-methyl-1-pentene)} asymmetric membrane, and sealed by an adhesive. These are fabricated by using the dry/wet inversion process. TPX is dissolved in a mixture of solvent (cyclohexane) and nonsolvent additives at 60°C to form a polymer solution. The polymer solution is kept at 40°C for 24 hrs and cast on a glass plate to a pre-determined thickness with a gardner knife. After that the casting film is evaporated at 50°C for 30 sec, then the glass plate is to be immersed immediately in coagulation bath (maintained the temperature at 25°C). After 10 minutes of immersion, the membrane can be removed, air dried in a circulation oven at 50°C for 12 h. [31]

3. **Mercury substrate method** The drug is dissolved in polymer solution along with plasticizer. It is followed by stirring for 10- 15 minutes to produce a homogenous dispersion and poured into a levelled mercury surface, covered with inverted funnel to control solvent evaporation (Wiechers 1992). Rathore et al., (2006) have studied that transdermal matrix type patches of terbutaline sulphate were fabricated using ethyl cellulose and cellulose acetate polymer. The transdermal patches of terbutaline sulphate were prepared by solvent casting technique employing a mercury substrate. In the present investigation various polymeric transdermal patches of terbutaline sulphate were prepared. The effect of permeability enhancer on the permeability of drug from cellulose acetate and ethyl cellulose patches was studies. The polymeric combinations showed good film forming properties and the method of casting on mercury substrate was found to give good films. Patel et al., (2009) have studied transdermal patches containing glibenclamide (1.06 % w/v, i.e. 13.5 mg/cm2) were prepared by solvent casting technique employing mercury as substrate to formulate transdermal patches using Eudragit RL 100, Eudragit RS 100, Polyvinyl pyrollidone (PVP) as polymers, glycerol and propylene glycol as a plasticizers and Span 80 as a permeation enhancer by solvent casting method. The formulation containing Eudragit RL 100 with propylene glycol as plasticizer showed complete and prolonged release with 98.02 % at the end of 24 h.[32,33]

4. **"EVAC membranes" method**In order to prepare the target transdermal therapeutic system, 1% carbopol reservoir gel, polyethelene (PE), ethylene vinyl acetate copolymer (EVAC) membranes can be used as rate control membranes. If the drug is not soluble in water, propylene glycol is used for the preparation of gel. Drug is dissolved in propylene glycol; carbopol resin will be added to the above solution and neutralized by using 5% w/w sodium hydroxide solution. The drug (in gel form) is placed on a sheet of backing layer covering the specified area. A rate controlling membrane will be placed over the gel and the edges will be sealed by heat to obtain a leak proof device. Friend et al., (1991) have studied the irritation of transdermal devices delivering levonorgestrel and the permeation enhancer ethyl acetate with or without ethanol were evaluated in rabbits. Erythema and oedema were assessed 24, 48 and 72 h and 7 days after application of the 24-h delivery system. The devices were found to be mild to moderately irritating, with erythema the primary manifestation. No

differences were observed between devices using pure ethyl acetate or ethyl acetate-ethanol (7:3 v/v) as enhancers. Devices using pure ethanol as an enhancer gave levels of irritation similar to those using ethyl acetateethanol or pure ethyl acetate.[34]

1.7 Evaluation of Transdermal Patches

Development of controlled release transdermal dosage form is a complex process involving extensive research. 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. These studies are predictive of transdermal dosage forms and can be classified into different types including physicochemical evaluation, in-vitro evaluation, and in-vivo evaluation. After the successful evaluation of physicochemical and in-vitro studies, in-vivo evaluations may be conducted.[35,36]

Thickness: The thickness of transdermal film is determined by travelling 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.[37]

Drug content determination: It can be determined by completely dissolving a small area (1 cm 2) of polymeric film in suitable solvent of definite volume. The solvent is selected in which the drug is freely soluble. The selected area is weighed before dissolving in the solvent. The whole content is shaken continuously for 24 h in a shaker incubator followed by sonication and filtration. The drug in solution is assessed by appropriate analytical method.[38]

Content uniformity test: The test is applied as the gold standard to determine chemically the content of active constituent for each unit dose. The test is completed by performing assay to find out the content of drug material contained in polymeric film of the patch. According to USP the procedure consists of two stages. First stage consists of assaying the randomlyselected ten units. It is followed by second stage to be performed on twenty more units when the first stage fails. Initially ten patches are selected and content is determined for individual patches. Test passes when all 10 unit doses have content ≥ 85 % and ≤ 115 % (RSD < 6%). 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 RSD of all the 30 units is < 7.8%, not more than one value is outside 85–115%, and no value is outside75–125%, the batch passes the test if not fails the test.[39,40]

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.[41]

Moisture Uptake: Weighed films are kept in a desiccator at room temperature for 24 h. These are then taken out and exposed to 84% relative humidity using saturated solution of Potassium chloride in a desiccator until a constant weight is achieved.[42]

Flatness: A transdermal patch should possess a smooth surface and should not constrict withtime. This can be demonstrated with flatness study. For flatness determination, one strip iscut from the centre and two from each side of patches. The length of each strip is measuredand variation in length is measured by determining percent constriction. Zero percentconstriction is equivalent to 100 percent flatness.[43]

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 gives the folding endurance value.[44]

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.[45]

Adhesive studies: The therapeutic performance of TDDS can be affected by the quality of contact between the patch and the skin. The adhesion of a TDDS to the skin is obtained by using PSAs, which are defined as adhesives capable of bonding to surfaces with the application of light pressure.[47,49]

In-vivo Studies

In-vivo evaluations are the true depiction of the drug performance. The variables which cannot be taken into account during in-vitro studies can be fully explored during invivo studies. In-vivo evaluation of TDDS may be carried out using either animal models or human volunteers or both [50]

A. **Animal models** Considerable time and resources are required to carry out human studies, so animal studies are preferred at small scale. The most common animal species used for evaluating transdermal drug delivery systems are mouse, hairless rat, hairless dog, hairless rhesus monkey, rabbit, guinea pig etc. Based on the experiments conducted so far it is concluded that hairless animals are preferred over hairy animals in both in-vitro and in-vivo experiments. Rhesus monkey is one of the most reliable models for invivo evaluation of transdermal drug delivery[50]

B. **Human models** The final stage of the development of a transdermal device involves collection of pharmacokinetic and pharmacodynamic data following application of the patch to human volunteers. Clinical trials are conducted to assess the transdermal systems including the efficacy, risk involved, side effects, and patient compliance. Phase-I clinical trials are conducted to determine mainly safety in volunteers and phase-II clinical trials determine short term safety and mainly effectiveness in patients. Phase-III trials indicate the safety and effectiveness in large number of patient population and phase-IV trials at post marketing surveillance are done for marketed patches to detect adverse drug reactions. Though human studies require considerable resources but they are the best to assess the performance of the drug.[51]

II. CONCLUSION

Transdermal drug delivery represents one of the most rapidly advancing areas of novel drug delivery. Due to recent advances in technology and the ability to deliver the drug systemically without rupturing the skin membrane, transdermal route is becoming a widely accepted route of drug administration. TDDS are designed for controlled release of drug through the skin into systemic circulation maintaining consistent efficacy. It offers the delivery of drug at lowered dose that can save the recipient from the harm of large doses with improved bioavailability. This may be achieved by by-passing the hepatic first metabolism. Almost all major and minor pharmaceutical companies are developing TDDS

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