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Formulation and Evaluation of Herbal Transdermal Patches in Treatment of Wound Healing

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Abstract
According to a current WHO definition, traditional medicine (with herbal medications) includes therapeutic techniques that has been used for hundreds of years or more before modern medicine developed and spread, and that are still in use today. The combination of generation of indigenous medical practitioners' therapeutic experiences is known as Traditional medicine. The transdermal patches with the inclusion of herbal extracts of Psidium guava leaf and piper betle leaf were prepared. As explained previously in the emerging world now the herbal formulation has gained more demand. In the research reviews, it has been found out that there is a vast possibility of introducing new drug delivery systems. It goes without saying that the benefits of novel drug delivery system on the traditional one are overpowering. Innovations in drug delivery mechanism are enabling a broad variety of medicines to be delivered by use of the transdermal drug delivery system. TDDS also benefits from controlled release of drugs for prolonged period of time. More research and innovation bring wide acceptance in the use of various other transdermal drug delivery system like iontophoresis, ultrasound technology, Med Tat, microneedling etc.
Keywords**:** Traditional medicine, Psidium guava leaf, Overpowering, Ultrasound technology.

Introduction

indicators,

1.1 Herbal Medicine

According to a current WHO definition, traditional medicine (with herbal medications) includes therapeutic techniques that has been used for hundreds of years or more before modern medicine developed and spread, and that are still in use today. The combination of generation of indigenous medical practitioners' therapeutic experiences is known as

Traditional medicine. Medicinal plants, minerals, organic material, etc. are used in traditional remedies. Only traditional medicines that predominantly employ preparations of medicinal plants for therapeutic purposes are considered herbal pharmaceutical. (Rastogi, 1990)

1.1.1 Advantages of Herbal Medicine (Harrison, 1998)

- They have been used for a long time, and patients tolerate and accept them better.
- Because medicinal plants have a renewable source, they are the sole sustainable source of reasonably priced drugs for the world's growing population.
- The availability of medicinal plants is unproblematic, especially in developing countries like India, which has a substantial biodiversity of agroclimatic conditions, ethnic groups, and cultures.
- Both in their crude form and as a pure chemical that serves as the foundation for modern medicines, herbal medicine has contributed many of the most powerful medications to the extensive drug science worldwide.
- Prolonged and seemingly inconspicuous use of herbal medicines may provide evidence of their safety and effectiveness.

1.1.2 Limitations of Herbal Medicines (Jonas, 1998)

- Unsuccessful in severe medical care
- Insufficient standardization and lack of quality conditions
- Absence of scientific data

Steps Involve: -

Hemostasis:

Haemostasis is the process by which a wound heals and clots. When blood begins to leak from the body, haemostasis begins. Blood arteries contract to limit blood flow, which is the initial stage of haemostasis. Following this, platelets clump together to close the blood vessel wall crack. In wound healing, the haemostasis stage occurs rapidly. This creates the temporary fibrin matrix for the lesion, and platelets provide the wound its first release of growth factors and cytokines.

Inflammation:

In this stage, the wound area is cleared of germs, pathogens, and damaged cells. Neutrophils and macrophages, mediate this process by eliminating hinder repair. Prolonged inflammation

causes too much reactive oxygen and protease, which slows healing. They eliminate crucial elements.

Proliferation:

New collagen and matrix-based tissue is utilized in the rebuilding of the wound during the proliferative phase of wound healing. There is the need to develop the new blood vessel network. Fibroblasts multiply with the aid of new capillaries and form disordered extra-cellular matrix. Basal epithelial cells proliferate and migrate over the granulation tissue in order to close the wound surface.

Remodelling:

It is also called the maturation period. At this phase, the wound fully heals and collagen transforms type 3 to type 1. To allow the collagen fibres to lay and to cross-link, water is once again reabsorbed and in the process of collagen maturation, collagen is directed along tension lines.

1.2 Wound Healing

The cuts on the skin or the break in skin surface as a result of physical or thermal impact are largely classified as wound (Rastogi, 1990). (Hashemi, 2015)

Skin wounds are of two classifications; acute and chronic. Acute wounds include traumatic or surgical wounds normally heal in a given duration as per the normal healing processes. Acute skin injuries include simple scratches and the deep complex wounds with tissue and blood vessel destruction. In the event that the injury is severe or the wound is large then the body responds to the wound. The process of wound healing is complicated and is bacteriostatic in acute wound healing. I hope to be able to implement that as a technological solution to the issues you have cited because that seems to be the most viable (Nutila, March 2014).

1.3 Transdermal drug delivery system

Transdermal drug administration is painless and allows drugs to be administered systemically simply by placing a drug formulation on healthy skin. The medication enters the stratum corneum before it goes to the deeper layers of the epidermis and dermis without becoming deposited in the dermal layer. Han (2015) (Schoellhammer, Langer, & Blankschtein, 2014) The skin was first utilised as an administration site for long-term drug delivery in the eleventh century, and TDDS is a crucial component of innovative drug delivery systems. One of the most dependable and efficient methods is transdermal medication administration.

1.3.1 Advantages of transdermal drug delivery system (Jain, 1997) (Mathiowitz, Chickering, & Lehr, 1999)

- Frequency of dose may be decreased.
- Improved bioavailability may result in a decrease in drug concentration.
- It can avoid first-pass metabolism by liver.
- They are able to inhibit gastrointestinal medications absorption problems due to stomach Ph, enzymatic functions, and interaction of medication with food, beverage and other pharmaceuticals taken by mouth.
- Less side effects, decreased plasma concentration levels of drugs.
- They also do eliminate the inconvenience of parenteral therapy since they are non-invasive.
- They enhanced adherence over the former dosage forms that necessitated a higher dose rate due to the presence of prolonged therapy with a single application.
- Removal of the application onto the skin surface may terminate drug therapy quickly.
- This system permits self-administration.
- It lowers the drug interactions in the system.
- It has a prolonged action period.

1.4 Transdermal patches

Transdermal patches refer to mediated adhesive patches which are coated with a drug and must be landed on skin to introduce the drug into the blood via skin. Delivery technology such as TDDS can be used to facilitate the convenience of the patients, make them more effective and protect drugs. Transdermal patches are prepared primarily to deliver drugs through the skin, which permeate through the different layers of the skin and arrive in the systemic circulation, i.e., blood stream.

Polymer matrix: -

This mostly helps with the stability of drug release from transdermal patches that use or are controlled by the polymer. A extremely dense matrix is created as the polymer concentration rises, which causes the medication to release more slowly. The backbone of transdermal medication delivery is made of polymers. Drug concentration, as well as the physiochemical properties of the drug and the polymer, influence the rate of drug diffusion and release through a polymer matrix.

Ideal properties of polymer matrix are: -

- It should be inert and should not react with the drug.
- It must not get decomposed in the presence of drugs and excipients.
- It should not interfere in the stability of the drug.
- It should be easily available.
- It should be inexpensive.

It must not lead to any type of antagonistic effect. It should not result in any type of hypersensitivity reactin. Examples of polymer matrix: gelatine, hydroxypropyl methylcellulose, VA (polyvinyl alcohol), PVC (polyvinyl chloride), starch, PVP, polyethylene etc.

Active ingredient: -

The drug reservoir is the most important component of transdermal patches. It should be selected with very much intense care. Drugs that ionize rapidly are not suitable agents for formulating transdermal patches because ionized drug molecules have poor skin permeation and penetration.

Ideal properties for active ingredients: -

- It should be non-irritant to human skin.
- It should have a short biological half -life.
- It should be potent enough to impact the required pharmacological action.
- It should not show any type of hypersensitivity reaction when administered.
- It should have an affinity toward lipophilic and hydrophilic phase.

Penetration enhancers: -

These are the substance that enhance the skin's permeability by enhancing the properties of the skin to the drug. Polar, non-polar, and polar/ nonpolar are 3 pathways for drug penetration through skin. Penetration is enhanced by altering one of these pathways. Polar can be altered by altered the rigidity of the lipids.

Ideal properties of penetration enhancers are:

- It should be non-allergic.
- It should be action specific.
- It should be non-irritant.

Surfactants: -

When a drug exhibits hydrophilic properties, these are added. They improve the drug's polar route transport. There is no use of cationic surfactant. They are said to be the most skin-irritating. Pluronic F127 is an illustration of a non-ionic surfactant. Sodium lauryl sulphate, or SLS, is an example of an anionic surfactant.

Plasticizers: -

The are applied in order to lower the brittleness of polymer film. They are flexible and elastic to the polymeric film. When large volumes of such are used, then the film is sticky and damp.

Ideal properties of plasticizers are: -

- It should be easy to handle.
- It should be non-reactive and non-irritant.
- It should be pharmacologically inert.
- It should not affect the stability of the drug.
- It should be cost-effective.
- It should be easily and readily available. Example of plasticizers are glycerol propylene glycol, dibutyl phthalate, and polyethylene glycol.

Drug reservoir: -

It is one of the components wherein there is a single polymer or a mixture of polymers at different concentrations and ratio.

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Backing laminates: -

The aids in giving and provision of support. They should discourage drug surface release that is not in touch with skin. It must be in suitable compatibility with drugs and excipients. During the process of selection, the flexible nature, strength, and elasticity should be taken into consideration. This gives the transdermal drug delivery system appearance, flexibility and occlusions. Choosing backing laminates, compatibility with the excipients is to be taken into consideration. The best backing laminate should be with high flexibility.

Adhesive laminates: -

This layer adheres the transdermal device on the surface of the skin at the proper site and position.

Ideal properties of the adhesive layer are: -

- It should not interfere with the release rate of the drug.
- It should have the ability to stick with minimum pressure and not affect the solubility of the drug.
- It should be non-irritant to the skin.

Release Liners: -

These are protective layers, which are excluded prior to application of transdermal patches on skin. They will be useful to avoid drug loss in storage and transportation condition. Examples of release liners are Teflon, Silicon, Polyester etc. (Pastore, 2015).

Rationale of the study

Aim: - The aim of the study is to formulate and evaluate an herbal-based transdermal patch for wound healing.

OBJECTIVE: -

- To improve efficacy.
- To reduce systemic side effects.
- Better patients' compliance.
- To maintain a constant, prolonged and therapeutically effective drug levels in the body.
- Easy to apply and to remove.

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Methodology

5.1 Requirements and materials (Singh S. P., 2022)

- Collection of plant sample
- Instruments required- Electric stirrer, Desiccator, pH meter, Weighing balance
- Apparatus: - Beakers, Measuring cylinder, Glass rod, Petri Plate
- Ingredients: - Piper betle extract, Guava leaf extract, Polyethylene glycol-400, Propylene glycol, HPMC, Chloroform and Methanol.

5.2 Procedure for preparation of herbal plant extract: -

5.2.1 Guava Leaf Extract (Porwal, 2012)

The thimble, water cooling system, reservoir, bypass tube, syphon tube, and condenser are among the various components of the Soxhlet extraction that are visible. In a thimble that is placed inside a Soxhlet vessel with extractor solvent, we will add 10 mg of the solid matter of the leaves. The solvent's vapour travels with it and enters the column where the solid thimble is placed. Certain ligands are both soluble and non-volatile. We do this by repeating the procedure multiple times until the flask contains the necessary concentration chemicals. This was accomplished at the solvent's boiling point, and 100 millilitres of ethanol were extracted after 3.5 hours.

Fig. 01 Guava leaf extract

5.2.2 Piper betle leaf Extract (Shivsharan, 2022)

The leaves were freshly dried at room temperature for 7 days and then ground into powder. Cold maceration of piper betel leaf was performed by using acetone at room temperature for 72 hours with occasional stirring of 100g of powered piper betel leaf in 500 ml of acetone for 72 hours.

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5.3 Procedure for formulation of transdermal patches: -

- Initially weigh the required ingredients for the formulation.
- Then add 8 ml of chloroform and 4 ml of methanol to them properly using the electric stirrer or magnetic stirrer.
- Then add 2.5 ml propylene glycol and 2.5 ml polyethylene glycol and again stir it continuously using an electric or magnetic stirrer.
- Each medicinal plant extract, i.e., 5ml guava leaf extract 5ml piper betle leaf extract, was added with constant stirring for 10-15 minutes.
- Now then add HPMC with constant stirring using an electric stirrer. But add 1 gm. HPMC at the time interval minutes.
- After a time period of 10-15 minutes, when the formulation became viscous, it was added to the glass petri plates, which were coated using the aluminum foil.
- Then the petri plate was placed in the Hot Air Oven at 50 degrees for a certain time period for the evaporation of solvent.


FIG. 02 CONTENT IN PETRI PLATE

5.4 Evaluation test

The various evaluation tests will be performed on a laboratory level for the evaluation of transdermal patches.

The following are the tests: -

1. Organoleptic Characteristic
2. Surface Ph determination
3. Phytochemical Screening of Guava Leaf extract
4. Phytochemical Screening of Piper Betle Leaf extract
5. Measurement of thickness of Patches

6. UV Spectroscopy
7. % Moisture content

1. Organoleptic characteristics

In this the organoleptic properties were studied, like color, odor, appearance, etc.

A. Color: - The color of patches was evaluated to be whitish cream.
B. Texture: - The Texture of the formulated patches was evaluated to be smooth and uniform.
C. Appearance: The appearance of the formulated patches was turbid.
D. Odor: The odor of the formulated patches was evaluated to be herbal plant-like.

2. Surface ph. Determination: -

In this evaluation test the Ph of the surface of transdermal patches was evaluated using Ph Meter.

3. Phytochemical screening of guava leaf extract: -

In Phytochemical screening of Tulsi extract the extract the chemical test named Mayer's test, Ferric Chloride test, Killer Kilani test, benedict 'test, Ninhydrin test was performed.

4. Phytochemical screening of piper betle leaf extract: -

In phytochemical screening of Aloe vera Extract the Chemical tests like Ferric Chloride test, Mayer's Chloride test, Steroid test, Lieberman's test, Ninhydrin test was Performed.

5. Measurement of thickness of patches: -

The Thickness of Formulated transdermal patches were evaluated Vernier Calliper.

FIG.9 VERNIER CALIPER

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6. Percentage moisture content: -

The % Moisture content was studied using Desiccator. Initially the individual patches were weighed and then kept in the desiccator containing activated silica at the Room temperature for time period of 24 hours. Then afterwards the Patches were reweighed.

%Moisture Contant = [Initial Wt.-Final Wt.]/ Initial Wt. *100

Results and Discussion

Results of Organoleptic Tests: -

S. No.	Characteristic	Observation
1	Color	Whitish cream
2	Texture	Smooth and Uniform
3	appearance	Turbid
4	Odour	Herbal Extract

Result of Ph determination: - The Ph of Formulated Patches was found to be in Range of 5.9.

Phytochemical screening of guava leaf extract: -

Materials for Phytochemical Analysis-Test-tube, conical flask, spatula, weighing balance, shaker machine

Reagents Used: - 10% NaOH Sodium hydroxide, 5% Ferric Chloride Solution, 5 ml of Fehling's solution, 2 ml of 10% aqueous hydrochloric acid, Wagner's reagent, H_2SO_4, Chloroform, ethanol. Alcoholic ferric chloride solution 5 ml of 10% Ammonia solution, dilute HCl

Test for Flavonoid

To determine whether flavonoids were present, a 3 ml aliquot of the filtrate and 1 ml of 10% NaOH sodium hydroxide were combined.

Test for Tannins

In order to observe the appearance of tannins, a ferric chloride solution + 5% ferric chloride solution will be added drop by drop, 2-3 ml, to the solution of guava extract leaves.

Determination of Saponin

In this test 5 ml of the extract was poured into a test tube, add 5ml of water, and it was then shaken strongly to determine the presence of saponin in the sample.

Determination of Alkaloids

Two millilitres of guava were mixed with around two millilitres of 10% aqueous HCl acid. A second 1 ml sample was treated similarly with Mayer's reagent after 1 ml had been treated with a few drops of Wagner's reagent.

Test for cardiac Glycoside (Keller-Killian's test)

After adding two millilitres of a 3.5% ferric chloride solution to a herb extract solution, the mixture was let to stand for a minute. To create a lower layer, 2 millilitres of concentrated H2SO4 were gently poured down the tube wall.

Determination of Test for Steroids (Salkowski Test)

This was carried out according to the method of J.B Harborne 1973. 2ml of the extract was dissolved in 2ml of chloroform. 2ml of sulfuric acid was carefully added to form the lower layer.

Test for Saponin Glycoside

To 2.5 ml of the extract was added 2.5 ml of Fehling's solution.

Test for Balsams

9.5 ml of the extract was mixed with an equal volume of 90% ethanol, and 2 drops of alcoholic ferric chloride solution were added to the mixture.

Test for Anthraquinones

2ml of each plant extract was shaken with 10 ml benzene, and 5 ml of 10% ammonia solution was added. The mixture was shaken in order to obtained the color of anthraquinones

Test for Volatiles oils

1 ml of the fraction was mixed with dilute HCl, A white precipitate was not formed, this indicated the absence of Volatile oils.

RESULT:- Saponins, alkaloids, volatile oil, steroids, balsams, saponin glycosides, flavonoids, tannins, and anthraquinone were found in the guava extract after phytochemical screening. As the table shows, there are no glycosides or cardiac glycosides present.

Phytochemical test of guava leaf extract

PHYTOCHEMICALS	RESULTS
Tannins	+
Saponins	+
Steroids	+
Saponin glycosides	+
Glycosides	-
Flavonoids	+
Alkaloids	+
Cardiac glycosides	-
Volatiles oil	-
Anthraquinone	+
Balsams	+

4. Phytochemical screening of piper betle leaf: -

Phytochemical analysis:

Alkaloid:

To the extract 1 % HCL and 6 drops of mayer reagent and dragendroff reagent would be added. There was an indication of alkaloids in the sample since an organic precipitate was obtained.

One is a Reagent Test for Flavonoids: -

To a sample of the water filtrate of each plant extract was added drop by drop 5mls of dilute ammonium solution, and as this constitutes De Bari test, conc. H 2SO4 was added. It has a yellow coloration which proves that it contains Flavonoids and which vanishes after standing.

Glycoside test:

Take some of an alcoholic extract of the fresh or dried material in one ml of water; Add a very few drops of aqueous NaOH solution. Yellow colour: It means that it contains glycoside.

Steroids Test

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Two millilitres of acetic anhydride and two millilitres of H 2 SO 4 were added to a 0.5 gramme portion of the corresponding ethanolic extract. The presence of steroids was indicated by this colour shift from violet to blue or green.

Tannins Test:

A few drops of 1 % lead acetate was added to 5 ml of extract. The tannins were detected by a yellow precipitate.

Terpenoids:

Two millilitres of chloroform and three millilitres of concentrated H 2 S04 were added to each five-millilitre extract to create a monolayer, reddish-brown bubble-like interface that showed a positive terpene outcome.

Saponins Test:

In a graduated cylinder 20 ml of distilled water was added to the extract and the mixture agitated during 15 minutes. Saponins were present as indicated by the formulation of 1 cm layer of foam.

Phytochemical screening of piper betle leaf

PHYTOCHEMICAL	RESULTS
Alkaloids	+
Glycosides	+
Cardiac glycosides	+
Anthraquinone glycosides	+
Terpenoids	+
Flavonoids	+
Tannins	+
Saponins	+

+ presence of phytochemical

- absence of phytochemical

5. Result of thickness Measurement: -

The thickness of formulated transdermal patches was evaluated to be **0.22mm** using vernier caliper. This thickness was evaluated by measuring the average thickness from three sites of the patches.

6. Results For % Moisture content: -

Here, Initial weight = 0.6 gm and Final weight = 0.3 gm so by using formula of %MC

% Moisture content = [0.6-0.3]/0.6*100 = 50%. Hence, the % Moisture Content was evaluated to be **50%**

Conclusion

The transdermal patches with the inclusion of herbal extracts of Psidium guava leaf and piper betle leaf were prepared. As explained previously in the emerging world now the herbal formulation has gained more demand. In the research reviews, it has been found out that there is a vast possibility of introducing new drug delivery systems. It goes without saying that the benefits of novel drug delivery system on the traditional one are overpowering. Innovations in drug delivery mechanism are enabling a broad variety of medicines to be delivered by use of the transdermal drug delivery system. TDDS also benefits from controlled release of drugs for prolonged period of time. More research and innovation bring wide acceptance in the use of various other transdermal drug delivery system like iontophoresis, ultrasound technology, Med Tat, microneedling etc.

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