



# FORMULATION AND EVALUATION OF NATURAL PENETRATION ENHANCER MEDIATED GEL FOR TOPICAL DELIVERY OF HERBAL APPLICATIONS

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## Abstract:

Given the possible therapeutic benefits coming from natural sources, herbal gels have received interest. The purpose of this study was to create and assess an herbal gel using firebush (*Hamelia patens*), turmeric (*Curcuma longa*), and neem (*Azadirachta indica*), all of which are found locally. These plants are excellent choices for topical applications because of their well-known antibacterial, anti-inflammatory, and wound-healing qualities. The formulation process involved extracting active constituents from neem leaves, turmeric rhizomes, and firebush leaves using suitable solvents. These extracts were then incorporated into a gel base composed of natural polymers to enhance stability and skin penetration. The formulated gels were evaluated for their physicochemical properties including pH, viscosity, spreadability, and drug content. Further evaluation included assessing the *in vitro* antimicrobial activity against common skin pathogens such as *Staphylococcus aureus* and *Escherichia coli* using agar diffusion method. Additionally, the anti-inflammatory potential was evaluated through *in vitro* assays measuring inhibition of pro-inflammatory cytokines.

**Keywords:** *Azadirachta indica*, Antibacterial and anti-inflammatory activity.

## Introduction:

Herbal formulations have been integral to traditional medicine systems worldwide for centuries, offering natural alternatives to synthetic pharmaceuticals. In recent years, there has been a resurgence of interest in herbal products due to their perceived safety, efficacy, and minimal adverse effects compared to conventional treatments. Among herbal preparations, topical formulations such as gels hold particular promise for treating various dermatological conditions.

In recent years, there has been a growing interest in herbal formulations as alternatives or complements to conventional pharmaceuticals. This trend is driven by the perceived safety, efficacy, and holistic benefits of

natural products derived from plants. Herbal gels, specifically, have garnered attention due to their topical application, which allows for targeted delivery of bioactive compounds to the skin, thereby potentially enhancing therapeutic outcomes while minimizing systemic side effects. The use of locally available plants in herbal formulations is particularly appealing for several reasons. Firstly, it promotes sustainable practices by utilizing indigenous flora, often abundant in specific regions and adapted to local environmental conditions.

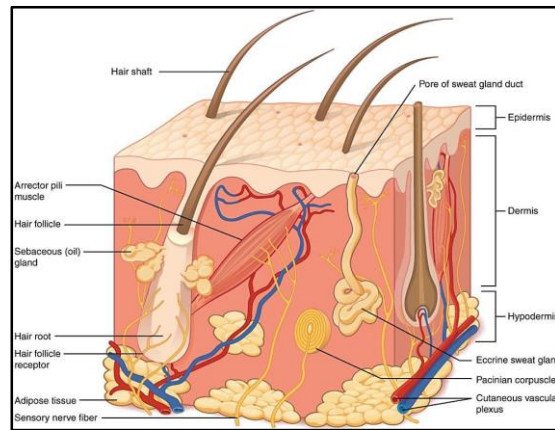
Herbal gel formulation involves the art and science of incorporating natural plant extracts into a gel base to create skincare products that harness the therapeutic properties of botanicals. These formulations blend traditional knowledge with modern scientific techniques to deliver effective solutions for various dermatological concerns. By carefully selecting and extracting bioactive compounds from plants like neem, turmeric, and firebush, herbal gels offer a natural alternative to synthetic skincare products, promoting skin health through their anti-inflammatory, antioxidant, and antimicrobial properties. The process includes rigorous quality control to ensure stability, safety, and efficacy, catering to the growing consumer preference for sustainable and skin-friendly skincare options.

### **TOPICAL DRUG DELIVERY SYSTEM**

To treat disease, drugs are administered to people's bodies by various routes, including oral, vaginal, rectal, parenteral, topical, and inhalation. Topical delivery involves applying a drug-containing formulation to the skin. It is used to treat skin conditions such as acne as well as skin manifestations of more widespread diseases such as psoriasis. The primary goal of this form of drug delivery is to place the pharmacological or other activity of the drug on or under the skin. Varieties of formulations are frequently used in topical regimens, including foams, sprays, medicated powders, solutions, and others. The primary objective of topical medication delivery systems is local drug delivery. They are frequently used to treat localised skin infections because they were intended to address cutaneous problems. The formulations are accessible in a variety of forms, including solid, semisolid, and liquid. If the drug's component in the solution has a favourable liquid water partition coefficient and if it is a non-electrolyte, medication absorption by way of the skin is boosted. The most popular types of derma Production are available in a range of formulations for dermatological drugs. When creating an efficient and successful topical treatment, the primary considerations are the drugs' sites of action and their effects. Topical therapies may lead to:

#### **1. Structure of skin**

The skin is a complex organ that protects the organism from chemical, physical, and biological possible hazards by acting as a crucial barrier. In addition, it takes part in metabolic and sensory processes and supports homeostasis. The three skin layers (epidermis, dermis, and hypodermis) are consists of the extracellular matrix (ECM), which is formed from a variety of cells and proteins. Additionally, each layer has characteristics that are specific to it, such as nerves, blood vessels, hairs, and glands.

**Figure No 1 : Structure of Skin**

## 1. EPIDERMIS

The stratified keratinized squamous epithelium that makes up the epidermis close to the skin's surface is composed of multiple layers. 90% of the cells in this layer are keratinocytes, one of the four main cell types that make up the epidermis. Melanocytes, which are in charge of producing the pigment melanin, make up 8% of epidermal cells. Merkel cells and Langerhans cells are also found in the epidermis. While Langerhans cells are involved in the immune response, Merkel cells are involved in touch perception. The dermis's blood vessels provide the epidermis with oxygenation, the supply of metabolites, and the disposal of metabolic waste products because the epidermis lacks blood vessels. Different types of layers that make up the epidermis, including: Stratum Basale, most substantial layer, is so named (also called the stratum germinativum), the stratum spinosum, it is made up of prickle cells, granular stratum, or layer of granules.

Stratum Lucidum (finger tips, palms and soles). The outermost layer is known scientifically as the Stratum Corneum (SC). These strata show the movement of cells as they are shed from the stratum basale to the SC. The epidermis renews itself by cell division in its deepest layer.

## 1. DERMIS

Its thickness ranges from 3 to 5 millimetres. It is mostly formed of connective tissues, which are essential for controlling body temperature, supplying the skin, and eliminating contaminants. Above the subcutaneous layer and below the epidermis lies the dermis. The dermis contains glands, lymphatic veins, nerve endings, hair follicles, and glands. Its anchors to the epidermis are reti ridges, which are furrows. This movement of nutrients between the skin's dermis and epidermis is made possible by the furrows, which also stabilise the skin. The epidermis and dermis could, however, separate due to friction or shearing forces, resulting in fluid accumulation that would eventually form a blister. The reticular and papillary layers together with other cells form the dermis.

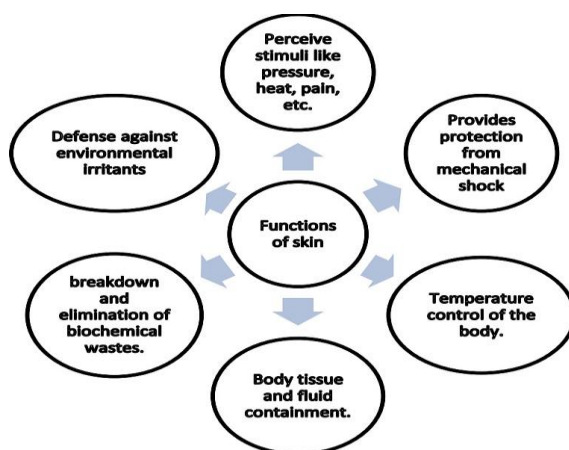
## C. SUBCUTANEOUS TISSUE

The components of this layer is superficial fascia, a film of fatty areolar tissue that connects the dermis to the underlying anatomy. Large arteries and veins are only that are in the surface area.

## D. SKIN APPENDAGES

Both eccrine and apocrine sweat glands, as well as associated hair follicles and sebaceous gland- like regions, are present in skin. All of these are collectively known to as skin appendages.

## Functions of skin :



**Figure No 2. Functions of skin**

## FACTORS AFFECTING SKIN PERMEATION

### Physiological Factor

Numerous physiological factors can influence skin permeability. Age, anatomical location, race, gender, and several skin conditions fall under this category. Although it has been demonstrated that the SC thickness does not considerably change as a result of intrinsic ageing, the epidermis thins and the corneocytes become less adherent to one another. Reports state that as people age, their lipid composition changes and all of the major lipid species, but especially ceramides, decrease in their levels. The dermis also deteriorates and becomes similarly acellular and avascular. The skin has demonstrated a tendency to become less permeable to hydrophilic substances as it ages, which might be connected to declines in hydration and lipid content.

Additionally, young children have much less cutaneous barrier action than adults, which could result in greater permeability. Additionally, the anatomical location may affect skin permeability. Numerous studies have revealed that different anatomic skin areas have different morphologic as well as functional properties. First are the genitalia (more permeable), then the head and neck, the trunk, the arm, and the leg (less permeability). The described modifications to the skin's protective barrier are caused by regional variances. The permeation may also be impacted by the condition of your skin, including whether it is healthy, sick, or injured. Barrier function may be hampered by a number of common skin conditions, including eczema (dermatitis), psoriasis, ichthyosis, and acne vulgaris. Further, skin conditions that result in rashes on the skin's surface might temporarily impair the barrier.

When creating a transdermal system, all of these aspects should be taken into account because physiological changes may generate security concerns and the system at the application site affects the pace of medicine delivery. These include the skin's surface areas, which affect things like membrane thickness, temperature, and penetration rate, along with blood flow, which affects how efficiently drugs are cleared within the body.

### Features of the Drug

The degree to which a drug can permeate this capability determines the hydrophobic and also hydrophilic domains of skin. A molecule's ideal physicochemical characteristics for permeating and penetrating the SC. Among these is], a partition coefficient that is both high and balanced( $K$ ). Since medications that are

excessively hydrophilic may partition from the carrier into the SC, a log  $P(o/w)$  included between 1 and 3 is advised as the best. High lipophilicity drugs, contrasted with, will not partition to the more fluid viable epidermis and will instead stay in the intercellular SC lipids, hence slowing the rate of skin penetration. Ionized species also have permeation coefficient that is less than their unionised counterparts because the former's log  $P$  is smaller than the latter's.

Since the size of the permeant would affect the diffusivity ( $D$ ) within the SC, a low molecular weight is also preferred. Permeability of skin and permeant size have been found to be inversely related. When  $D$  is high, permeants chosen for transdermal administration typically have a molecular weight of less than 500 Da. It should therefore be sufficiently lipid-soluble (high diffusion coefficient,  $D$ ), acceptable in terms of its aqueous solubility ( $>1\text{mg/mL}$ ), and possess a large concentration gradient, which is what drives diffusion (high donor concentration,  $C_v$ ). The intercellular SC lipid area is where medications are best soluble, so having a low melting point ( $200^\circ\text{C}$ ) is also a benefit. To fully benefit from transdermal delivery, drug candidates should have these unique physical and chemical features in addition to a high medicinal strength (deliverable dose ideally  $< 20\text{ mg/day}$ ), poor oral bioavailability, and short biological half-life. Furthermore, the drug should not irritate or cause an immune reaction in the skin.

### **PENETRATION ENHANCEMENT**

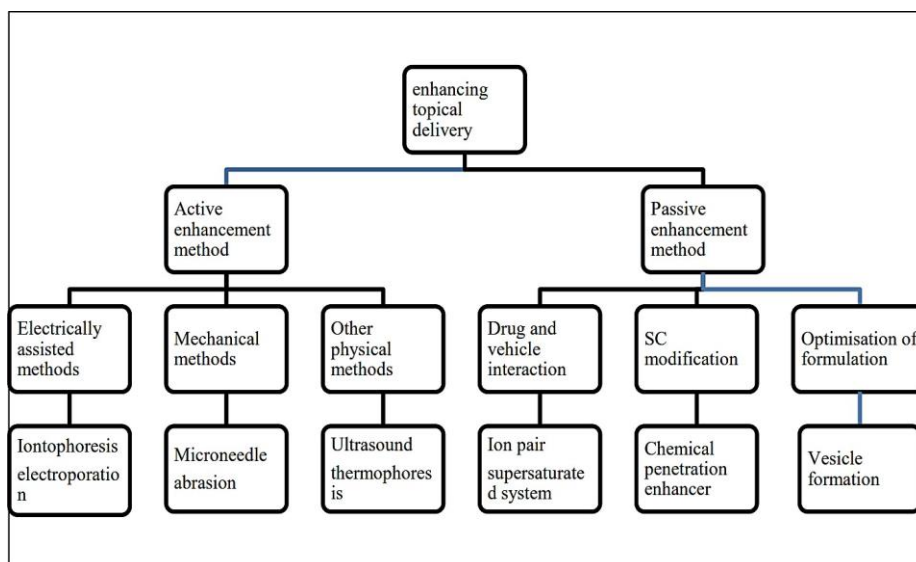
Because of the skin's barrier limitations, transport by simple carriers is often insufficient to achieve therapeutic medication concentrations at the site of action under normal conditions. There are numerous ways to circumvent this limitation, including increasing the range of penetrants and the speed of transdermal distribution. Simple occlusion, formulation augmentation, and the employment of chemical, physical, or hybrid approaches are all passive and active methods for increasing penetration. The two major ways employed in these are increasing skin permeability and/or delivering a driving force that works on the drug.

### **PASSIVE METHODS**

Chemical penetration enhancers (CPE) can change the formulation, increase the drug's thermodynamic activity in formulations (such as supersaturated and nanocarrier systems), change the substance, or even change the drug itself to increase passive permeability. To encourage drug flux, CPE interacts with skin-related substances.

### **ACTIVE STRATEGIES**

Active approaches increase the variety of substances that can be administered via the skin by lowering the SC's barrier function or using external energy as a driving factor. Mechanical techniques and a number of energy sources can be used to penetrate, decrease, or weaken the SC barrier (such as heat, electricity, and magnetism). Mechanical and electrically assisted techniques will be the main focus. A number of other techniques have also been researched, such as thermal ablation to increase the "permeabilization" of the SC, photomechanical waves, and magnetophoresis, which makes use of an applied magnetic field to boost the driving force on a penetrant.



**Figure No 3: Penetration enhancement methods**

### **PENETRATION ENHANCEMENT BY USING NATURAL PENETRATION ENHANCERS:**

The usage of skin penetration agents to medication formulations is one method for improving drug absorption through the skin. Because some skin penetration enhancers are hazardous, it is necessary to find safe and efficient alternatives. This led to the screening of natural chemicals for this purpose.

Numerous chemical substances that were isolated from natural sources demonstrated promise as skin penetration boosters. It was further noted that the physico-chemical properties of the medicine to be delivered through/into the epidermal layers, as well as their concentration in the formulation, affect the effectiveness of the penetration enhancers.

### **PLANT PROFILE**

#### **1. NEEM (*Azadirachta indica*)**

### **PLANT PROFILE**



**Fig 4. Neem (*Azadirachta indica*)**

### Chemical Constituent:

- 1) Neem leaf and its constituents have been demonstrated to exhibit immunomodulatory, anti-inflammatory, anti-ulcer, anti-malarial, antifungal, antibacterial, antiviral properties.
- 2) This review summarizes the wide range of pharmacological activities of neem leaf.
- 3) Leaves contain ingredients such as nimbin, nimbanene, 6-desacetylnimbinene, nimbandiol, nimbolide, ascorbic acid etc.

### Uses:

- 1) Ayurveda medicine for controlling blood sugar level, cleansing blood and strengthening the immune system.
- 2) The extracts of the leaves are widely used in skincare and hair care products.
- 3) Its medicinal properties is an effective herb to treat hair loss.
- 4) It has antifungal properties that may help within the treatment of dandruff [22].

## 2. TURMERIC (*Curcuma longa*)



**Fig 5. Turmeric powder**

### Chemical Constituent:

1. **Curcuminoids:** Curcuminoids are a group of polyphenolic compounds, with curcumin being the most studied and abundant. Curcuminoids are known for their antioxidant, anti-inflammatory, and antimicrobial properties.
2. **Curcumin:** Curcumin is the principal curcuminoid in turmeric and is responsible for its characteristic yellow color. It has been extensively studied for its anti-inflammatory, antioxidant, anti-cancer, and wound healing properties.
3. **Turmerones:** Turmerones are a group of volatile oils found in turmeric. They contribute to its aroma and also possess anti-inflammatory and antioxidant properties.
4. **Gingerols:** Although more commonly associated with ginger (*Zingiber officinale*), some turmeric varieties may also contain gingerols, which are bioactive compounds with anti-inflammatory and antioxidant effects.
5. **Polysaccharides:** Turmeric contains polysaccharides, which are complex carbohydrates that may

contribute to its immunomodulatory and antitumor activities.

6. **Essential oils:** Turmeric contains small amounts of essential oils, including sesquiterpenes such as atlantones and zingiberene, which contribute to its aroma and potential therapeutic effects.

7. **Proteins and amino acids:** Turmeric also contains proteins and amino acids, although they are present in smaller quantities compared to other constituents.

#### USES :

1. In Ayurveda, turmeric is used as a key ingredient in various formulations (called churnas, rasayanas, etc.) to treat a wide range of ailments, including respiratory issues, liver disorders, skin diseases, and digestive problems.

2. It is also considered beneficial for balancing the doshas, particularly for pacifying excess pitta and kapha.

3. **FIREBUSH (*Hamelia patens*) :**



**Fig 6. Firebush (*Hamelia patens*)**

#### Chemical constituents:

**Anthocyanins:** Firebush is known for its vibrant red-orange flowers, which contain anthocyanins, a group of flavonoid pigments responsible for the coloration. Anthocyanins have antioxidant properties and are beneficial for human health.

1. **Flavonoids:** Firebush contains various flavonoids such as quercitrin, kaempferol, and rutin. Flavonoids are known for their antioxidant, anti-inflammatory, and vasodilatory effects.

2. **Triterpenes:** Certain species of the Rubiaceae family, to which Firebush belongs, may contain triterpenes. Triterpenes have diverse pharmacological activities, including anti-inflammatory, antimicrobial, and anticancer properties.

3. **Alkaloids:** Some plants in the Rubiaceae family, not specifically documented for Firebush, may contain alkaloids. Alkaloids can have diverse biological activities, including antimicrobial and analgesic effects.

4. **Polyphenols:** Firebush likely contains various polyphenolic compounds, including phenolic acids and tannins. Polyphenols are known for their antioxidant and anti-inflammatory properties.

**USES :****1. Traditional Medicine :**

**Antioxidant Properties :** Firebush contains anthocyanins and flavonoids, which have antioxidant effects. Traditionally, infusions or extracts of Firebush have been used to protect against oxidative stress and support overall health.

**Anti-inflammatory Benefits :**Compounds like flavonoids and triterpenes found in Firebush may possess anti-inflammatory properties. It has been used in traditional medicine to alleviate inflammation, relieve pain, and treat inflammatory conditions.

**2. Skin Care:**

Firebush extracts are sometimes included in topical formulations for their potential benefits to skin health. They may help soothe irritated skin, reduce inflammation, and protect against oxidative damage.

The antioxidant properties of Firebush can contribute to its potential role in anti-aging skincare products, helping to combat free radicals and promote skin rejuvenation.

**EXPERIMENTAL WORK :****PLANT MATERIAL:**

1. **Neem** is chosen for its potent antimicrobial and anti-inflammatory properties, ideal for addressing skin issues such as acne and eczema.
2. **Firebush** is valued for its antioxidant capabilities and ability to promote wound healing, making it beneficial for soothing skin irritations and treating burns.
3. **Turmeric**, containing curcumin, is renowned for its strong anti-inflammatory properties, effective in managing acne and supporting overall skin health.

**PROCEDURE OF PLANT MATERIAL:**

A gel formulation comprising nanospheres was created in this experiment for efficient skin application and improved penetration hydrophilic gels made of carbopol and HPMCK were tested for their ability to disperse these nanospheres a topical gel containing carbon dots made of geranium oil was created utilizing a dispersion swelling methodology .Following the weighing of all excipients as per table,carbopol 934 and HPMC K4M were concurrently dissolved in water and let to stand for 4hours in order to appropriately swell the polymer .in order to prevent air bubbles,cd powder (equal to 0.5 mg/g) was then continuously agitated in one direction while being added to the polymer gel. At the same time the geranium oil is also added in the formulation. The crosslinking of the carbopol 934 polymer and HPMC K4M to create a gel required the addition of triethanolamine to the gel mixture the gel viscosity was then balanced by the addition of propylene glycol and its permeability was increased by the addition of azone and methyl paraben as preservative. Finally the pH was brought down to 7.4,0.1 the skin pH , by the addition of 0.1 N NaOH.



**Fig 7. Carbapol + HPMC K + water Herbal Gel**

#### **STORAGE CONDITION:**

1. Store herbal gel formulations in tightly sealed containers to prevent exposure to air and contaminants.
2. Keep the containers in a cool, dry place away from direct sunlight and heat sources to maintain stability.

#### **PREPARATION OF EXTRACT BY USING MACERATION METHOD:**

Preparing extracts using the maceration method for herbal gel formulation involves the following steps:

1. **Selection of Plant Material:** Choose high-quality neem, firebush, or turmeric plant parts (leaves, roots, or rhizomes) known for their medicinal properties.
2. **Cleaning and Drying:** Clean the plant material thoroughly to remove dirt and contaminants. Allow it to dry completely to prevent microbial growth during extraction.
3. **Cutting or Grinding:** Cut or grind the dried plant material into small pieces or powder to increase the surface area for extraction.
4. **Solvent Selection:** Choose a suitable solvent based on the polarity of the desired active compounds. Common solvents include ethanol, methanol, or water, depending on the constituents being extracted.
5. **Extraction Process:**
  - Place the cut or ground plant material into a clean, airtight container.
  - Add enough solvent to cover the plant material completely.
  - Seal the container and shake gently to ensure thorough mixing of the solvent and plant material.
6. **Maceration Period:** Allow the mixture to stand at room temperature for a specified period (typically several days to weeks), periodically shaking or stirring to facilitate extraction.
7. **Filtration:** After the maceration period, filter the extract using a fine mesh or filter paper to remove solid plant material and obtain a clear liquid extract.
8. **Concentration (Optional):** Concentrate the extract using methods such as rotary evaporation under reduced pressure to remove the solvent and obtain a more concentrated extract.
9. **Quality Control:** Test the extract for potency, purity, and stability parameters to ensure it meets quality standards for incorporation into herbal gel formulations.
10. **Incorporation into Gel:** Blend the concentrated extract with a suitable gel base (e.g., Carbopol) along with other excipients like preservatives, emollients, and stabilizers to formulate the herbal gel.

11. Packaging: Transfer the finished herbal gel into appropriate containers, ensuring they are tightly sealed and stored under recommended conditions to maintain stability and efficacy.



**Fig 8. Extract of firebush ,neem and curcumin**

### **EVALUATION OF HERBAL GEL:**

#### **1. Solubility:**

- Solubility testing involves determining how well the herbal gel dissolves in different solvents such as water, ethanol, or oils.
- It assesses the compatibility of the gel with various media, which is crucial for ingredient delivery and stability.
- Results are recorded based on observations of complete dissolution, partial solubility, or insolubility in different solvents.

#### **2. Viscosity:**

- Viscosity measurement evaluates the thickness and flow behavior of the herbal gel.
- Conducted using a viscometer, viscosity values indicate how easily the gel spreads and adheres to the skin.
- It influences product application, user experience, and can be adjusted through formulation changes to achieve desired consistency.

#### **3. pH Determination:**

- pH determination involves measuring the acidity or alkalinity of the herbal gel.
- Essential for assessing skin compatibility and ensuring the formulation's effectiveness and stability.
- pH levels are typically monitored using a pH meter and should fall within a suitable range for skincare products, often between pH 4.5 to 7.0.

### **RESULTS AND DISCUSSION:**

#### **1. Formulation Development:**

Successfully formulated herbal gels incorporating extracts of neem, firebush, and turmeric.

- Experimented with different concentrations and combinations to optimize efficacy and stability.

#### **2. Physical Characteristics:**

- Observed that herbal gels containing turmeric had a characteristic yellow-orange color due to curcuminoids.

- Viscosity measurements indicated that gels with neem and firebush extracts exhibited suitable consistency for topical application.

### 3. Antimicrobial Activity:

- Conducted antimicrobial tests revealing significant inhibition zones against *Staphylococcus aureus* and *Escherichia coli*.

- Neem extract showed broad-spectrum antimicrobial properties, while firebush exhibited specific activity against certain strains.

### 4. Anti-inflammatory Properties:

- Tested gel formulations for anti-inflammatory effects using in vitro models.

- Turmeric extract demonstrated potent anti-inflammatory activity, attributed to curcumin's effects on inflammatory markers.

### 5. Stability Studies:

- Conducted stability testing over 3 months under various storage conditions (temperature and light exposure).

- Found that gels with added antioxidants maintained color stability and preserved active compound efficacy.

### 6. Skin Compatibility:

- Evaluated skin irritation potential using a human patch test.

- Majority of participants showed no adverse reactions, indicating good skin compatibility of the herbal gel formulations.

- Synergistic Effects: Combination of neem, firebush, and turmeric extracts potentially enhanced therapeutic benefits due to their complementary actions.

- Formulation Challenges: Addressed challenges such as color stability with turmeric and ensuring consistent viscosity across batches.

- Future Directions: Suggested further research into enhancing bioavailability of active compounds and exploring additional herbal combinations for broader efficacy.



**Fig. no. 9 Preparation of herbal gel**

**CONCLUSION:**

In conclusion, the development of herbal gel formulations incorporating neem, turmeric, and firebush extracts demonstrates promising results for skincare applications. The synergistic effects of these botanical ingredients provide a multifaceted approach to treating various dermatological concerns, including microbial infections, inflammation, and skin aging.

The antimicrobial properties of neem, coupled with the anti-inflammatory and antioxidant effects of turmeric and firebush, offer a comprehensive solution for promoting skin health and vitality. Through systematic formulation optimization and comprehensive quality testing, the herbal gels exhibit stability, efficacy, and skin compatibility essential for consumer acceptance and therapeutic effectiveness.

Future research directions may focus on enhancing the bioavailability of active compounds, exploring novel extraction techniques, and investigating additional botanical synergies to broaden the therapeutic spectrum of herbal gel formulations. By continuing to innovate and refine these formulations, herbal gels have the potential to emerge as preferred choices in natural skincare, catering to the growing demand for effective and safe botanical-based products in the global market.

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