

# Formulation and Evaluation Emulgel Using Miswak Oil for the Management of Inflammation: Research Paper

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## Abstract:

Inflammation is a significant physiological response to various stimuli, necessitating effective therapeutic interventions. This study focuses on the formulation and evaluation of an emulgel using Miswak oil, known for its potent anti-inflammatory properties. The emulgel was developed by incorporating Miswak oil into a gel base, aiming to enhance its topical delivery and therapeutic efficacy. The formulation process involved optimizing the oil-to-gel ratio to achieve desirable consistency, stability, and skin permeability. The emulgel was subjected to various physicochemical evaluations, including pH, viscosity, spreadability, and stability studies, to ensure its suitability for topical application. In vitro anti-inflammatory activity was assessed using standard assays, demonstrating significant reduction in inflammatory markers. The results suggest that Miswak oil emulgel is a promising topical formulation for managing inflammation, offering a novel and effective alternative to conventional treatments. Further in vivo studies are warranted to corroborate these findings and explore its clinical potential.

**Keywords:** Skin, NSAID, Topical drug delivery system, Emulgel, Polymer, Etc.

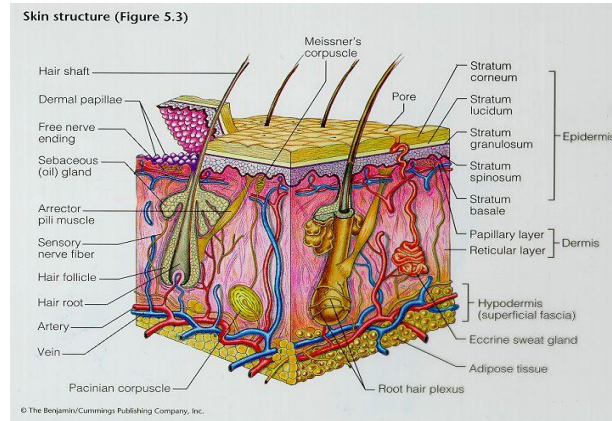
## 1. INTRODUCTION

### 1.1 SKIN<sup>[1]</sup>

The skin is the largest single organ of the body, accounting for about 15% of the total adult body weight. It combines with the mucosal lining of the respiratory, digestive, and urogenital tracks to form a capsule which separates the internal body structure from external environment. For an average 70 kg human with skin surface area of 1.8 m<sup>2</sup>, a typical square covers 10 hair follicle, 12 nerves, and 15 sebaceous glands. 100 sweat glands, and 3 blood vessel with 92 cm total length. The pH of the skin varies from 4 to 5.6 sweat and fatty acid secreted form sebum which influence the pH of the skin surface. Temperature of skin varies in a range of 30 to 40 degree depending of the environmental conditions. It performs many vital functions, including protection against external physical, chemical, and biologic assailants, as well as prevention of excess water loss from the body and a role in thermoregulation. The skin is continuous, with the mucous membrane lining the body's surface.

### 1.1.1 Anatomy and Physiology of skin<sup>[2]</sup>

Skin is the largest organ in the body. It consists of three layers. The epidermis, dermis, and subcutaneous tissue. The outermost layer is called epidermis, consists of a specific constellation of cells known as keratinocytes, which function to synthesize keratin, a long, threadlike protein with a protective role. The middle layer, the dermis, is fundamentally made of collagen and inner most layer is hypodermis.



**Fig 1 : Structure of human skin**

**a) Epidermis :** It is the outermost layer of the skin, which is approximately 150 micrometers thick. It consists of epithelial cells. Among these cells, both living cells and dead cells can be found. These new cells at the bottom of epidermis divide fast and push the older cells upward. The source of energy for lower portions of epidermis is glucose and the end product of metabolism, lactic acid, accumulates in the skin.

**Cell type that exist in the epidermis are :**

- Keratinocyte : these are the main cell type in epidermis ( 95% of cells).
- Melanocytes : these are the pigment producer cells and found in the basal layer of epidermis.
- Langerhans cells : these cells are important immunological cells and can be found in the mid dermis as well Merkel cells these cells are found in the basal layer of epidermis and one part of amine precursor and decarboxylation system.

**The layer of epidermis are as follows<sup>[3,4]</sup>**

- **Stratum Germinativum :** Basal cells are nucleated, columnar. Cells of this layer have high mitotic index and constantly renew the epidermis and this proliferation in healthy skin balance the loss of dead horny cells from the skin surface.
- **Malpighion Layer :** The basal cell also include melanocyte which produce the distribute melanin granule to the keratinocyte required for pigmentation a protective measure against radiation.
- **Stratum Spinosum :** The cells of this layer are produced by morphological and histochemical alteration of the cells basal layer as they move upward. The cells flatten and their nuclei shrink. They are interconnected by fine prickles and form intercellular bridge the desmosomes. These link maintain the integrity of the epidermis.
- **Stratum Granulosum :** This layer is above the keratinocyte the manufacturing basic staining particle, the keratinophylline granules. This keratogenous or transitional zone is a region of intense biochemical activity and morphological change.
- **Stratum Lucidum :** In the palm of hand and sole of the foot , and zone forms a thin, translucent layer immediately above the granule layer. The cells are non – nuclear.

- **Stratum Corneum** : At the final stage of differentiation , epidermal cells construct the most superficial layer of epidermis, Stratum corneum. At friction surface of the body like palms and soles adopt for weight bearing and membranous stratum corneum over the remainder of the body is flexible but impermeable. The horny pads ( soles and palms ) are at least 40 times thicker than the membranous horny layer.

**b) Dermis** :- Dermis is non-descriptive region lying between the epidermis and the subcutaneous fatty region It consist mainly of the dense network of structural protein fiber i.e collagen, reticulum and elastin embedded in the semi gel matrix of mucopolysaccharadic ‘ground substance’ The elasticity of the skin is due to network or gel structure of the cells. Beneath the dermis the fibrous tissue open outs and merges with the fat containing subcutaneous tissue. Protein synthesis is a key factor in dermal metabolism.

**c) Subcutaneous Tissue ( hypodermis )** :- This layer consist of sheet of fat rich areolar tissue known as superficial fascia, attaching the dermis to the underlying structure. Large arteries and vein are present only in the superficial region.

**Skin Appendages** :The skin with hair follicle and associated sebaceous gland like region two types of sweat gland are eccrine and apocrine. Collectively these are referred as skin appendages.

### 1.1.2 Functions of Skin<sup>[5]</sup>

The skin performs various functions as follow ;

- Containment of body fluid and tissues.
- Protection from external stimuli like chemicals, light, heat, cold, and radiation.
- Reception of stimuli like pressure, heat, pain etc.
- Biochemical synthesis.
- Metabolism and disposal of biochemical wastes.
- Regulation of body temperature.
- To control blood pressure.
- Prevent penetration of noxious foreign material and radiation.

### 1.1.3 Permeation through skin<sup>[6]</sup>

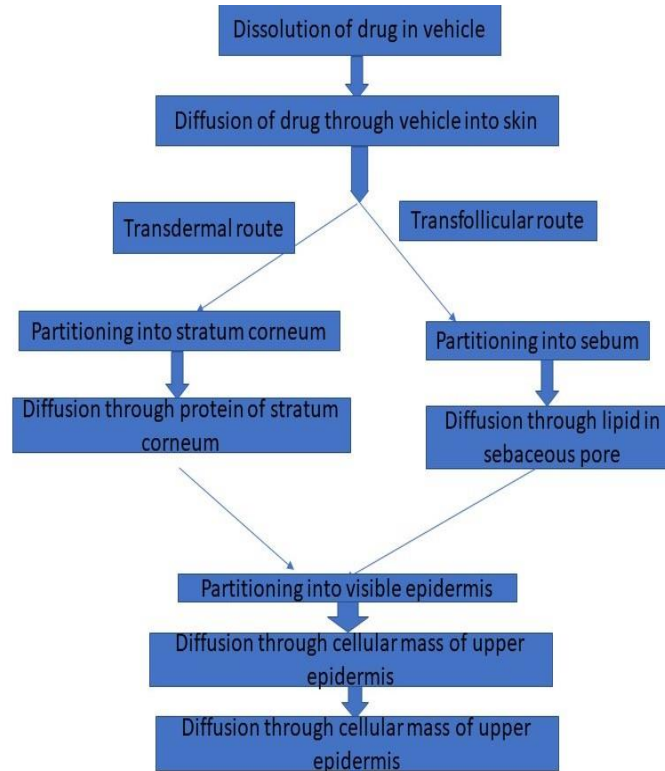
#### a) Trans -epidermal absorption

The trans-epidermal route across the continuous stratum corneum and the epidermis involves two route of entry : via the intercellular spaces which includes passive transport of small molecules, active transport of ionic and polar compound and endocytosis and transcytosis of macromolecule and via intracellular spaces which transport molecule around or between the cells. Tight junctions or similar situations exist between the cells. The partition coefficient (log k) decides the principal pathway for the permeate (0/w log k greater than 2) pass through stratum corenum by both routes. However the indirect intercellular pathway is widely considered to provide the principal route and the major barrier to the permeation of most drugs.

#### b) Trans- follicular absorption

Appendageal route comprises of transport via sweat glands and along hair follicle with their associated sebaceous glands. These route circumvent penetration through the stratum corneum and are therefore known as “shunt” routes This route is considered to be of small importance as it has a small area , approximately 0.1% of the total skin area. In addition, the skin appendages exercise some influence on percutaneous absorption due to their secretions which affect the lipid and the water content of the stratum corneum and so can modify the absorption of molecule. The skin is the largest and the most visible organ the humanbody but, for people with skin diseases, this visibility is often the worst aspect of their conditions. It has been shown that relatively minor skin complaints often cause more anguish to people

than more serious medical problem. Common skin disorders with impaired quality of life are topic eczema, vitiligo, acne urticarial, dermatitis, leg ulcers, skin disease involving the scalp, psoriasis....etc.



**Fig 2. Scheme event for percutaneous absorption**

#### 1.1.4 Physicochemical properties of drug [7,8]

The following physicochemical properties affects the therapeutic of drug, They are ;

- Partition coefficient
- pH condition
- Drug Solubility
- Concentration
- Particle size
- Molecular weight

##### a) Partition Coefficient :-

The partition coefficient is a thermodynamic, time -independent factor and displays the relative preference of a compound to stay either within the vehicle or within the membrane. The degree of partitioning is dependent on the relative solubility of the both lipid and water, whereas, compounds that are largesoluble only in either lipids or water, but not both, are not as good penetrants. The relative solubility of a compound in an organic or water phase can be represented by a partition coefficient. Drug possessing both lipid and water solubility are favorably absorbed through the skin. Topical permeability coefficient shows a linear dependency on partition coefficient a lipid /water partition coefficient of one or greater is generally required

##### b) pH Condition :-

The pH value either very high or very low can be destructive to the skin. With moderate pH values, the flux of ionizable drugs can be effected by changes in pH that alter the ratio of charged and uncharged species and their topical permeability. The pH of topical vehicle affects the extent of dissolution of

ionizable drugs molecule and thus, their thermodynamic activity, partitioning and skin permeation . Normal human skin has a surface pH of 4-6.

#### c) Drug Solubility :-

Solubility is an important physiochemical factor, affecting absorption of drugs and its therapeutic effectiveness. The poor solubility of drug substance in water and their low dissolution rate often leads to insufficient bioavailability.

Solubility of the drug in the vehicle determines the release rate. The mechanism of drug release depends on following factors ;

1. Whether the drug molecule are dissolved or suspended in the delivery system.
2. The interfacial partition coefficient of the drug from the delivery system to skin.

#### d) Concentration

A major determinants of the amount of a compound absorbed across the skin is the concentration or the amount of the compound at the skin surface. Wester and Maibach (2018) demonstrated or the amount of the compound absorbed increases as a function of the applied amount per unit area. Talyor (1%1) estimated that at least 1 mg/cm<sup>2</sup> liquid must be applied to fill the holes in surface of skin. Furthermore, when pick's first law of diffusion applicable, skin penetration at steady state is proportional to the concentration of the penetrant. Pick's first law does not apply when the penetrant damage the skin.

#### e) Molecular weight and particle size

Molecular weight, particle size, degree of ionization, and lipophilicity are important factor determining to partition and diffusion coefficients the molecular weight is inversely proportional to the percutaneous absorption and seems to particularly influence the diffusion coefficient. Molecules larger than 500 Daltons have usually more difficulty to pass through the healthy stratum corenum. It is a common presumption that only non-ionized compounds are able to diffuse through the lipophilic intercellular region of the stratum corenum. Yet, ionized compound have been reported to permeate through human skin through intracellular and trans appendageal pathway, albeit at a slower rate Moreover, the formation of ion pair between compounds ions and ions present in the skin can lead to neutral compounds

#### 1.1.5 Physiochemical properties of topical Route<sup>[9]</sup>

**a) Release Characteristics :-** The mechanism of drug release depends on whether the drug molecules are dissolved or suspended in the delivery system. The interfacial partition coefficient of drug from delivery system into skin pH of the vehicle. Composition of drug delivery system : Example polyethylene glycols of low molecular weight decreases permeation.

**b) Nature of vehicle :-** Liphophilic vehicle increase permeation where as lipophobic vehicle decrease permeation.

#### 1.1.6 Physiological and Pathological Condition of Skin<sup>[10]</sup>

**a) Reservoir effect of horny layer :** The horny layer, depot and modify the transdermal permeation characteristics of some drugs. The reservoir effect is due to irreversible binding of a part of the applied drug with the skin. This binding can be reduced by pretreatment of skin surface with anionic surfactants.

**b) Lipid Flim :** The lipid flim on the skin surface act as protective layer to prevent the removal of moisture from skin and helps in maintaining the barrier function of the stratum corneum.

**c) Skin hydration :** Hydration of stratum corneum can enhance transdermal permeability. Covering or occluding the skin with plastic sheet leading to sweet and condensed water vapor can achieve skin hydration.

**d) Skin Temperature :** Raising skin temperature results in increase in rate of skin permeation This may be due to thermal energy required diffusivity, solubility of drug in skin tissues increased vasodilation of skin vessel.

**e) Regional Variation :** Differences in the nature and thickness of barrier layer of skin cause variation in permeability. Rate of permeation increase in an atomic order. Plantar anterior fore arm, scalp, ventral thigh, scrotum, and posterior articular area.

**f) Pathologic Injuries to the skin :** Injuries that disrupt the continuity of stratum corneum increase permeability.

## 1.2 Inflammation<sup>[11,12]</sup>

Inflammation is part of the complex response of body tissues to harmful stimuli, such as pathogen, damaged cells, or irritants and is protective response involving immune cells, blood vessel. and molecular mediators. The function of inflammation is to eliminate the initial cause of cell injury, clear out necrotic cells and tissue damaged from the original insult and the inflammatory process, and initial tissue repair.

The inflammatory pathway consists of inducers, mediators, and effector and sensors. The inducers can be either infectious organisms or non-infectious stimuli, such as toxins, foreign bodies, signals from necrotic cells, and damaged tissue. Sensor are specialized molecules that are activated by the inducer, which trigger the production of mediator. The mediator are endogenous chemicals that can induce the feeling of pain, can either promote or inhibit inflammation and tissue repair, and can activate the effector -tissue and cells. The conjugation of these multiple players gives rise to many alternative routes in the inflammatory pathway and which path is taken depend on the including stimuli,. For a sterile stimulus, one of the goals is to prevent infection on the injured tissue.

Inducers can be classified as pathogen associated molecular patterns (PAMP) which are molecular pattern from infectious organism and as damaged associated molecular patterns (DAMPs), molecule released from damaged cells of the host. Each of these patterns recognized by different receptors in macrophage and dendritic cells ,pain receptors also sense tissue damaged. Inflammatory cytokines are released after stimulation of those receptors. They include TNF-alpha, IL-10, IL-6 among others, which include changes on the endothelium, allowing the passage of immune cells through the junction between the junctions.

The immune cells that are depend on the inflammatory state of the tissue para-inflammation lead to re, could recruitment of monocyte, while a full – blown inflammation also leads to the translocation of neutrophils to the tissue. These cells will then release enzymes that fight off infectious organisms and clear dead cells. As a consequence of this enzyme release reactive oxygen species (ROS) will accumulate in tissue. These are known as damage healthy cells Endothelial cells also release pro-inflammatory cytokines which further attract inflammatory cells plasma also translocate to adjacent tissues, leading to tissue edema circulating platelets are also activate and aggregate, while anticoagulants protein synthesis is reduced. This can lead to intravascular thrombosis, which in excess, could contribute to organ dysfunction.

### 1.2.1 Causes of inflammation<sup>[13]</sup>

Many different thing that can cause inflammation. These are the most common.

- Pathogen (germs) like bacteria, viruses, or fungi
- External injuries like scrapes or damage through foreign object.
- Effect of chemicals or radiation.

### 1.2.2 Signs of Inflammation<sup>[14]</sup>

There are five symptoms that may be sign of acute inflammation.

- A. Redness :- Redness occurs because blood vessel in the area are filled with more blood than usual.
- B. Heat :- Heat are produced with more blood flow to the affected area, the area becomes warm to the touch.
- C. Pain :- The inflamed area is likely to be painful, especially with touch. This become the chemicals released during the inflammatory process stimulate nerves and make them more sensitive.
- D. Loss of function :- There may be some loss of function in the affected area. Examples include not being able to move an inflamed joint or struggling with breathing if you have a respiratory infection

### 1.2.3 Types of Inflammation<sup>[15]</sup>

There are two types of inflammation

#### a) Acute Inflammation

Acute inflammation is commonly caused by trauma, harmful substances, or microbial invasion (i.e bacteria and viruses ) The healing process starts as the body responds by releasing cytokines – protein that promote inflammation. The acute inflammation process is rapid, may be severe, and occur over a short period of time. Sign and symptoms may be present for a few day but may occur for longer in more serious causes.

Acute inflammation tends to cause five specific symptoms These include :

- A. Redness
- B. Heat
- C. Swelling
- D. Pain
- E. Loss of function

#### b)Chronic Inflammation

Chronic inflammation is long term inflammation lasting for month to years. Chronic inflammation is usually caused by an autoimmune disorder, a disease in which the immune system attacks its own healthy tissues because it think they are diseased. Chronic inflammation can also be caused by low-level exposure to irritants, such as industrial chemicals. Over long periods, or failure to cure whether caused an acute inflammation, such as is the case with illness or infection.

Symptoms of chronic inflammation tend to present differently Than acute cases. Chronic inflammation may follow acute inflammation or be insidious in onset. It is of longer duration and is associated with the presence of lymphocyte and macrophages, the proliferation of blood vessel, fibrosis, and tissue destruction.

Symptoms may include :

- A. Fatigue
- B. Chest pain
- C. Fever
- D. Rash
- E. Muscle pain
- F. Joint pain

### 1.2.4 Nonsteroidal Anti-inflammatory Drugs<sup>[16]</sup>

Nonsteroidal Anti-inflammatory drugs (NSAID'S) have analgesic and antipyretic properties. Although oral NSAID'S are effective in the treatment of variety of acute and chronic pain condition, their use may

be associated with serious adverse effect, particularly gastrointestinal disorder. Transdermal delivery of NSAID’S proved to be a convenient route of administration for a variety of clinical indication. In addition, using of gel as a delivery system. Can increase the residence time of drug on the skin and provide a faster release of drug substance . Extensive preformulation studies are generally necessary in order to optimize both drug release from the topical vehicle and skin permeation.

**1.2.4.1 Mechanism action of NSAID’S<sup>[17]</sup>**

NSAID’S reversibly inhibit the enzyme cyclooxygenase ( prostaglandin endoperoxide synthase or COX), now recognized to consist of two isoforms, COX-1 and COX-2 mediating production of prostaglandins.

**1.2.4.2 Benefits of Topical NSAID’S Formulation <sup>[18]</sup>**

- Avoidance of first pass metabolism and GI tract variability in drug delivery.
- Administration directly to desired site of action.
- Topical administration may be more acceptable to patient and therefore increase adherence.
- Allowance of medication administration when patients are unable to take/tolerate oral formulation.
- May be more cost effective due to ease of administration compared with other route of administration.
- Avoidance of drug-drug interaction.
- Potentially decreased time to efficacy due to elimination of dosage titration.

**1.2.4.3 Treatment for Inflammation<sup>[19]</sup>**

The goal of the treatment is to decrease the size and thickness of the plaques and decreasing pruritus and to prevent infection.

Treatment for inflammation are : Topical therapy include corticosteroids, Vitamin D analogs, diclofenac sodium, pennsaid, Trolamine salicylate, salicylic acid etc., oral therapy include Aspirin, naproxen, ibuprofen, cyclosporin . etc., Herbal treatment and homeopathic treatment.

**Topical Treatment** : Topical treatment is the first line treatment approach prescribed for patients with mild to moderate inflammatory disorders. It include corticosteroid, Arthricam,, soloaze, Icy Hot.

**Table 1 : Marketed topical anti-inflammatory formulation**

Sr no	Marketed topical anti- inflammatory formulation
1	Methyl Salicylate 30% ( Icy Hot)
2	Trolamine salicylate 10% ( Arthricam)
3	Diclofenac epolamine 1.3% patch ( Flector)
4	Diclofenac sodium 1% gel ( voltaren)
5	Diclofenac sodium 2% ( Pennsaid)
6	Diclofenac 3% ( Soloaze)

**1.3 Topical Drug Delivery System<sup>[20,21]</sup>**

Topical drug delivery can be defined as the application of drug containing formulation to the skin to directly treat cutaneous disorders (e.g acne) or the cutaneous manifestations of a general disease ( e.g psoriasis) with the intent of confining the pharmacological or other effect of the drug to the surface of the skin or within the skin. Topical preparation are used for the localized effects at the site of their application by virtue of drug penetration into the underlying layers of skin or mucous membranes. Topical formulation apply a wide spectrum of preparations, both cosmetic and dermatological, to their healthy or diseased skin. The main advantage of topical delivery system is to bypass first pass metabolism. Avoidance of the risks



and inconveniences of intravenous therapy and of the varied condition of absorption, like pH changes, presence of enzymes, gastric emptying time are other advantage of topical preparations. Topical drug delivery system include a large variety of pharmaceutical dosage form like semisolids, liquid preparation, sprays, and solid powders. Most widely used semisolid preparation for topical drug delivery includes gels, creams, and ointments.

Topical delivery include two basic type of product

- A. External topical that are spread, sprayed, or otherwise dispersed on to cutaneous tissues to cover the affected area.
- B. Internal topical that are applied to mucous membrane orally, vaginally for local activity.

For the most part topical preparation are used for the localized effect at the site of their application by virtue of drug penetration into the underlying layers of skin or mucous membrane

#### **Topical formulation have three main functions**

- To help hydrates from external skin because of their emollient properties.
- To protect from external environment or heal an intact or injured area of the skin.
- To deliver medication to the skin.

#### **1.3.1 Advantages of Topical drug Delivery Systems<sup>[22]</sup>**

- Avoids gastrointestinal (GI) drug absorption difficulties caused by GI pH, enzymatic activity and drug interactions with food, drink, and other orally administered drugs.
- A substitute for other route of administration ( e.g oral administration, intravenous injection) when that route is unsuitable, as with vomiting, swallowing problems, resistant children and diarrhoea.
- Patient acceptability is better as this drug delivery system is non-invasive, avoiding the inconvenience of parenteral therapy.
- A relatively large area of application in comparison with buccal or nasal cavity.
- Avoids the first pass effect, possibly avoiding the deactivation by digestive and liver enzymes.
- Reduction of doses as compare to oral dosage forms.
- Ability to dissolve a wide range of medication with different chemical properties, making combination therapy with one transdermal cream possible.
- It Provides extended therapy with as a single application, improving compliance.
- Drug therapy may be terminated rapidly by removal of the application from the skin surface.
- Ability to deliver drug more selectively to a specific site.

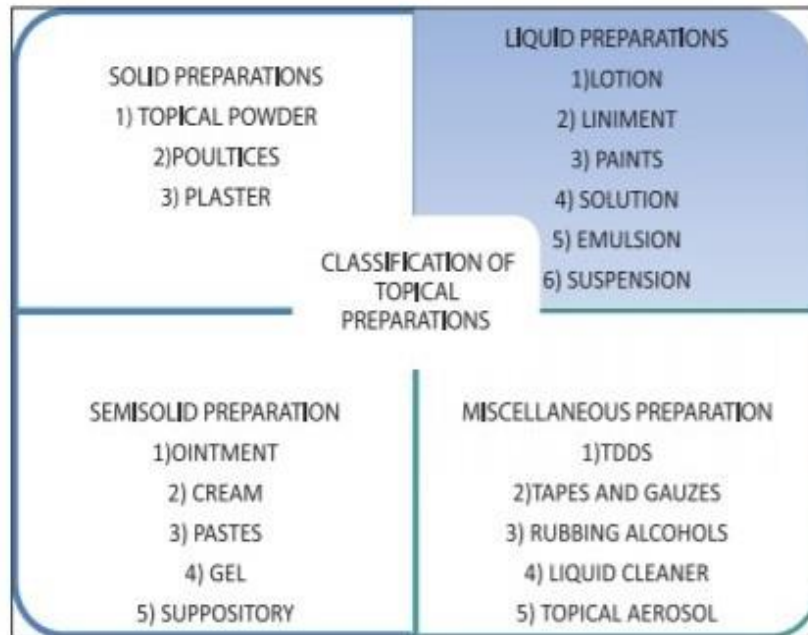
#### **1.3.2 Disadvantage of Topical Drug Delivery Systems<sup>[23]</sup>**

- Skin irritation of contact dermatitis may occur due to the drug and or/excipient.
- Poor permeability of some drug through the skin.
- Possibility of allergic reaction
- It Can be used only for drug which require very small plasma concentration for action.
- Enzyme in epidermis may denature the drug.
- Drug of large particle size not easy to absorb through the skin.

#### **1.3.3 Classification of Topical Drug Delivery System<sup>[24]</sup>**

Classification of Topical Drug Delivery System based on the physical state

- A) **Solid** : Powder, Aerosol, Plaster.
- B) **Liquid** : Lotion, Solution, Emulsion, Suspension, Aerosol.
- C) **Semi-solid** : Ointment, Cream, Paste, Gel, Jelly.



**Fig 3. Classification of Topical Drug Delivery System**

### 1.3.4 Factor affecting Topical absorption of Drug<sup>[25]</sup>

#### A) Physiological Factor

**a) Skin thickness :-** The thickness of horny layer may especially vary. The conventional reduction in permeability due to increased thickness of the stratum corneum is remunerated to some extent by accompanying increase in diffusivity.

**b) Lipid content :-** Skin is made of lipid surface. Lipids are usually defined as those components that are soluble in organic solvents such as ether, hexane, or chloroform but are insoluble in water. This group of substances includes triacylglycerols, free fatty acid, vitamin A and D.

**c) Density of hair follicle :-** A hair follicle is a small pouch in your skin out of which yours hair grow. There are 100,000 hair follicle on your head. an average density of 423 hair follicle per cm<sup>2</sup> was found on the forehead and a mean density of 92 hair follicle on the back.

**d) Density of sweat gland :-** In human, roughly 1.6 to 5 million sweat glands are found in the skin, and the amount varies between individuals as well as anatomic sites. The region with greatest density is the palms and soles of the feet, which contain 600-700 sweat glands /cm<sup>2</sup>

**e) Skin pH :-** Skin maintains its barrier best around 4.5 to 5.5 slightly acidic. The skin is able to maintain a good barrier and, together with natural oils, moisturizers and bacteria, function as a true protective defense organ.

**f) Blood flow :-** when skin temperature rises, cutaneous blood vessel dilate. Maximum skin blood flow is reached when skin temperature is about 42 degree sustained for 30 min. local vasodilation is a biphasic response, with an initial rapid vasodilation followed by sustained blood flow response.

**g) Hydration of Skin :-** Hydration of stratum corneum can enhance transdermal permeability. Covering or occluding the skin with plastic sheet leading to sweet and condensed water vapor can achieve skin hydration.

**h) Inflammation of Skin :-** Skin inflammation can occur due to an immune response. This can be due to a variety of infection like bacterial, fungal, or viral. Variety of factor like immune dysfunction, or allergic

reaction.

### B) Physiochemical Factor

**a) Partition coefficient** :- The partition coefficient is a thermodynamic, time -independent factor and displays the relative preference of a compound to stay either within the vehicle or within the membrane. The degree of partitioning is dependent on the relative solubility of the both lipid and water, whereas, compounds that are largesoluble only in either lipids or water, but not both, are not as good penetrants. The relative solubility of a compound in an organic or water phase can be represented by a partition coefficient. Drug possessing both lipid and water solubility are favorably absorbed through the skin. Topical permeability coefficient shows a linear dependency on partition coefficient a lipid /water partition coefficient of one or greater is generally required

**b) Molecular coefficient** :- Permeation decreases exponentially with molecular weight. Compounds with molecular weight over 500 daltons poorly permeate through normal human skin.

**c) Degree of ionization** :- The effect of ionization on the skin it can be ionized into two parts acidic or basic.

**d) Effect of vehicle** :- A significant vehicle effect was observed for chemical skin permeation and sc absorption. The vehicle effect was consistent between intact SC absorption and total chemical skin absorption and penetration through skin, suggesting intercellular transport as a main pathway of skin penetration for model chemicals.

### 1.4 Emulgels<sup>[26,27]</sup>

Emulgel is a new approach of NDDS for topical drug transport. Emulgel are the one of the of the emulsions, either of the oil in water or water in oil type, which are gelled by mixing with a gelling agent. Bothoil in water and water in oil emulsion. Are extensively used for their therapeutic properties and as vehicle to deliver various drugs to the kin. Emulsion posses a certain degree of elegance and are easily washed off wherever desired. Oil in water emulsion are most useful as water -washable drug bases and for emulsion. Oil in water emulsion are most useful as employed more widely for the treatment of dry skin and emollient application. Gels for dermatological use have several favorable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining, compatible with severable excipient and water soluble or miscible. So emulgels have a high patient acceptability since they possess, previously mentioned advantage of both emulsion and gels. Therefore they have been recently used as vehicles to deliver various drug to the skin. In the market, 2emulgels are available: Voltarenemulgel ( Novartis, Pharma, Basle, Switzerland, ) containing diclofenac diethylamine, and Miconaz-H emulgel ( Medical Union Pharmaceuticals, Egypt ) containing miconazole nitrate and hydrocortisone.

When gel and emulsion are used in combined from the dosage form are referred as Emulgel. In fact, the presence of gelling agent in the water phase converts a classical emulsion into an emulgel. These emulgels are having major advantage on novel vesicular system as well as conventional system in various aspects. Various permeation enhancers can potentiate the effect, so emulgel can be used as better topical drug delivery system over present systems. Emulgel are used for treating for muscle pain, headache, acne, psoriasis, rheumatoid arthritis.

#### 1.4.1 Types of emulgels<sup>[28]</sup>

**a) Macroemulgel** : These are most common type of emulgels in which the particle size of droplets of emulsion is more than 400 nm. They are visually opaque but the individual droplets can be easily observed

in microscope.

**b) Microemulgel:** Micro-emulsion are transparent and thermodynamically stable as their droplet size range from 100 to 400 nm and they do not coalesce. Micro-emulsion are the composed of oil, surfactant, co-surfactant, and water in particular ratios.

**c) Nanoemulgel :** When Nano-emulsion are the incorporated into gel it is called as Nano-emulgel. Nanoemulsion are thermodynamically stable transparent dispersion of oil and water stabilized by an interfacial film of surfactant and cosurfactant molecule having a globule size of less than 100 nm. Nano-emulsion formulation possess development transdermal and dermal delivery properties in vitro as well as in vivo. Nano-emulsion have improved transdermal permeation of drug over the conventional topical formulation such as emulsion and gels.

#### 1.4.2 Ideal properties of Emulgels<sup>[29]</sup>

- It should be greaseless
- It is easily spreadable
- It is easily removable
- It should be Emollient
- It should produce longer self-life.
- It should be Pleasing appearance

#### 1.4.3 Advantage of Emulgels<sup>[30]</sup>

- Avoidance of the first pass metabolism
- It should be Shelf medicated
- It can improved patient compliance
- It is More selective to a specific site
- Incorporation of hydrophobic drugs.
- It should be better loading capacity.
- It should be enhanced stability
- Production probability and low production cost.
- It should be Controlled release
- It is no intensive sonication
- Improve patient compliance and suitability for self medication.
- It is ability to easily terminate medication when needed.

#### 1.4.4 Disadvantage of emulgels<sup>[31]</sup>

- Poor absorption of large particle size through the skin.
- Some drugs have poor permeability through skin.
- Skin irritation or allergic reaction.
- During formation of emulgel bubbles may occur.

#### 1.4.5 Important constituents used in emulgel preparation<sup>[32]</sup>

##### a) Peppermint Essential Oil (*Mentha piperita*)

Peppermint oil generally used as a rubefacient. It is already well known for its medicinal application in the treatment of symptoms of the gastrointestinal tract such as nausea, vomiting, or indigestion. Its antifungal activity has often been proven, for ex. A concentration of this essential oil between 40 and 7000ug/ml and completely inhibit the growth of candida spp. Dermatophytes and *Aspergillus* spp respectively.

**b) MineralOils**

These are the agent forms the oily phase in the emulsion. For externally applied emulsions, mineral oils, either only or combined with soft or hard paraffins, are widely used both as the vehicle for the drug and for their occlusive and sensory characteristic. Widely used oils in oral preparation are non-biodegradable mineral and castor oils that provide a local laxative effect, and fish liver oils or various fixed oils of vegetables origin ( e.garachis, cottonseed, and maize oils ) as nutritional supplements.

**c) Emulsifiers**

Emulsifiers are used both to promote emulsification at the time of manufacture and to control stability during a shelf life for commercial preparation. e.g polyethylene glycol 40 stearate, sorbitan mono-oleate, polyoxyethylenesorbitan mono-oleate, stearic acid, sodium stearate.

**d) Gelling Agent**

These are the used for inhibit the growth of micro-organism and which is added to emulgel to avoid spoilage of the formulation from micro-organism e.g Propylene paraben, methyl paraben, Benzoic acid, Benzyl alcohol etc..

**e) Antioxidants**

The antioxidant are the used for the emulgels to enhance the stability of therapeutic agents. e.g BHA,BHT etc..

**f) Humectants**

The humectants is used for the maintenance of the moist in emulgel formulations. Glycerin, propylene glycol are the commonly used humectants.

**g) Permeation enhancer**

These are agents that partition into and interact with skin constituents to induce a temporary and reversible increase in skin permeability. In order to promote absorption of drugs through skin barrier. Fluidize the lipid channels between corneocytes, modify the partitioning of the drug into skin structures, and increase delivery into the skin. e.g oleic acid, lecithin, urea, Eucalyptus oil, menthol, isopropyl myristate. etc.·

**1.4.6 Application of Emulgels<sup>[33]</sup>**

Emulgels are used for mostly for topical delivery. It deals with the formulator a range of alternatives to develop drug and cosmetic products. These are designed to deliver an active ingredient efficiently at the low dose and also to enhance stability, reduce side effects and modify drug release.<sup>[29]</sup> Various application shown in table 2.

**Table 2. Application of emulgels**

Sr. No	Actives	Application
1	Anti-acne ( Benzoyl peroxide )	Preserved effectiveness with decreased skin irritation and sensitization.
2	Anti-inflammatory (hydrocortisone)	Long lasting activity with reduction of skin allergic response and injuries.
3	Antifungal	Sustained release of actives.
4	Analgesic (diclofenac sodium)	Reduction of muscle pain and to treat disorder.

**1.4.7 Miswak Oil<sup>[34,35, 36,37]</sup>**

Miswak is a traditional chewing stick prepared from the roots, twigs, and stem of *Salvadora persica* has been used as a natural method for tooth cleaning in many parts of the world for the thousands of years. A number of scientific studies have demonstrated that the miswak possesses antibacterial, anti-fungal, anti-

viral, anti-cariogenic, anti-inflammatory properties. Several studies have also claimed that miswak has anti-oxidant, analgesic, and anti-inflammatory effects. The use of a miswak has an immediate effect on the composition of saliva. Miswak contains more than 10 different natural chemical compounds considered essential for good oral and dental hygiene. They are fluorids, silica, tannic acid, resins, alkaloid, saponin and flavonoids.

The literature reviewed that the anti-inflammatory effect of aqueous leaves extract of miswak stick was investigated by carrageenan induced paw edema model. It is evident from literature search that salvodarpersica extract or obtained from oil i.e. miswak have anti-inflammatory properties. The potential efficacy of s.persica oil to treat inflammation is based on hypothesis that it will suppress the proinflammatory cytokines resulting in less odema. so, that miswak oil has been traditionally used for its anti-inflammatory activity by locals for toothache and other topical application.

The present study has been undertaken to incorporate the miswak oil and an anti-inflammatory agent in emulgel using various additives which can proved beneficial for the management of inflammation on by topical route.

## 2. PLANT AND DRUG PROFILE

### 2.1 Miswak oil [62, 63, 64]

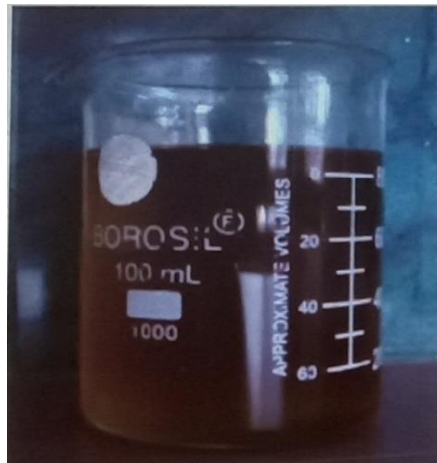


Fig.4 Salvadorapersica leaves



Fig. 5 Miswak oil

**Botanical name** : *Salvadora persica* Linn

**Family** : Salvodaceae

**Synonym** : *Salvadorapaniculatezucc, salvadorawightiiArnn*

**Vernicular name** : Eng – Mustard tree, Arak tree, toothbrush tree

Mar – khakan, Pilu

Hin – Meswak, kharajhal

**Distribution** : It is a small, evergreen shrub or tree having 1 ft in diameter and maximum height of 3m. that grows in hot, dry condition in part of Africa, the middle east, and Arabian peninsula. It widely distributed in arid region of India and often on saline soils. And native to Algeria, Egypt, Nigeria, Saudi Arabia.

**Parts used** : Leaves

**Description** : Organoleptic characters of Miswak oil

Colour : Pale yellowish coloured liquid

Odour : Pungent

Taste : Bitter

Solubility : Insoluble in water, soluble in organic solvent.

**Standards** : Standard value of Miswak oil are as follows ;

Acid value - 7.0125

Saponification value -249.5

Iodine value -15.2

Free fatty acid value - 7.708

Viscosity- 0.9236

Specific gravity - 0.9400

Refractive index - 1.432-1.478

**Chemical Constituents** : Fatty acid composition of Miswak Oil are as follows

Caproic acid ( 1.0-1.5% )

Lauric acid ( 19.6-47.2% )

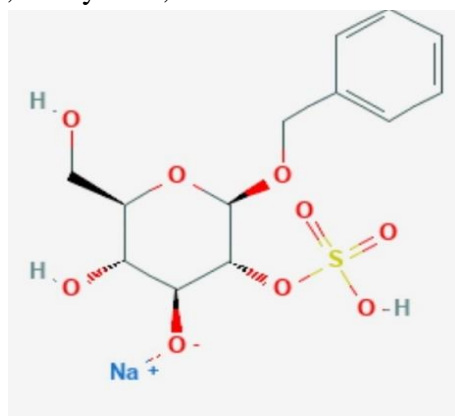
Myristic acid ( 28.4-54.5 % )

Palmitic acid ( 18.9-29.5% )

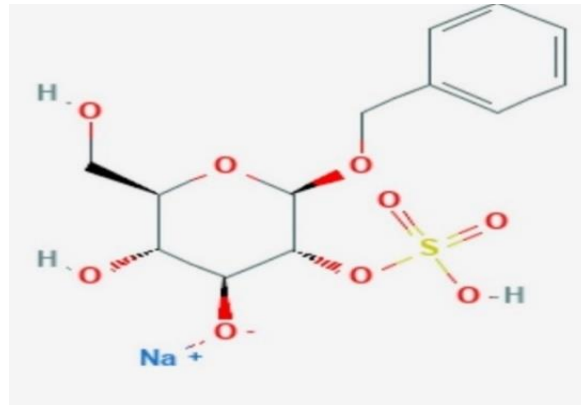
Oleic acid ( 5.5-1.2% )

Linoleic acid ( 0.0-1.2 % )

Unsaponifiable matter of oil contain beta- sitosterol and Nonfatty components , contain Salvoride, Salvadoraside, eucalyptol, eugenol, benzylurea, salvadourea.



**Fig 6. Salvadoraside**



**Fig 7. Syringine**

**Uses** It is used as anti-inflammatory agent.

- The leaves oil have been used for treating various inflammatory and infectious disease such as leukoderma, muscular and articular rheumatism.
- The leaves are hot, digestive, laxative, anthelmintic, and cure piles, wound and other inflammation,
- The contain about 30-40% oil which may be used for tanning leather, for making soap, as a liniment to treat as fuel in diesel engine showing a good thermal efficiency.
- Plants containing alkaloids ( cocaine, morphine, codeine ) are capable to exhibit extensive and well marketed pharmacological activities like analgesic, anti-inflammatory anti-viral, antibacterial, anti-plaque.

## 5.2 Peppermint oil <sup>[65]</sup>



**Fig 8. Peppermint oil**

**Botanical Name:** *Mentha piperita* Linn.

**Family :** Lamiaceae

**Synonym:** Lavandulaeaetheroleum, White peppermint, Menthe piperita

**Vernacular Name:** Marathi – pudina

Hindi – pudina

English – peppermint

**Distribution :** Peppermint is a hybrid mint, a cross between watermint and spearmint. Indigenous to Europe and the Middle east. The plant is now widely spread and cultivated in many region of the world.

**Part used:** Leaves, Flower

**Description:** organoleptic characters of peppermint oil

**Colour :** clear to pale yellow colour

**Odour :** sharp cool and camphor odour

**Taste :** Sweet pungent

taste



**Solubility** : Soluble in oils and alcohol, insoluble in water.

**Specific gravity**: 0.9210-0.9220

**Refractive index** : 0.460-0.465

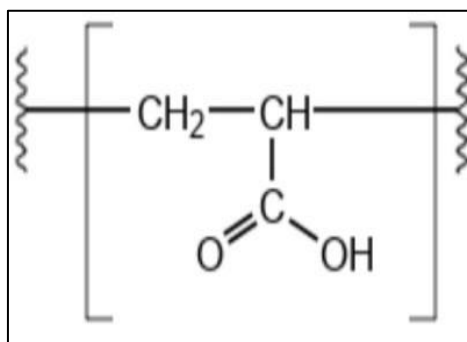
**Chemical constituents** : menthol ( 7-48%), methyl acetate (3-10%), menthone ( 20-46%), 1,8-cieol (3-6%).

**Uses** :

1. Peppermint has traditionally used as rubefacient.
2. Peppermint is used as making oral dentifrices as ti can provide over all freshness in breath and also keep away bad breath .
3. Peppermint is used for treatment of non-obstructive dyspepsia without any known side effect. It improves the gastric emptying rate.

### s3. POLYMER PROFILE

#### 3.1 Carbopol 940 :<sup>[66]</sup>



**Fig 9. Structure of Prop-2-enoic acid**

Carbomer 940 is a polyvinyl carboxy polymer used as a viscosity enhancer, gelling agent, or suspension agent. Carbomer 940 is a cross linked with ethers of pentaerythritol, and is used primarily in system where sparkling clarity or a sharp viscosity response is required.

Synonym : 2 Carboxyethyl acrylate oligomer, Acritamer 940

Non Proprietary names : BP carbomer, USP carbomer

Chemical name : Prop-2-enoic acid Category :Bioadhesive. Emulsifying, suspending agent and viscosity enhancing agent, tablet binder.

nder and release modifying agent.

Description : Carbomer 940 is a polyvinyl carboxy polymer used as a viscosity enhancer, gelling agent, or suspension agent. Carbomer 940 is a cross linked with ethers of pentaerythritol, and is used primarily in system where sparkling clarity or a sharp viscosity response is required.

Carbopol 940 are Fine White Powder, fluffy acidic, hygroscopic powder, with characteristic odour.

Clarity is 80% Minimum ( Neutral solution)

Typical Properties :

pH : 2.7 to 3.5 for a 0.5 % w/v aqueous dispersion 2.5 to 3.0 for 1 % aqueous dispersion.

pKa : 6.0 ±0.5

Bulk density :208 kg/m<sup>3</sup>

Moisture content : 8-10%

Ash content : 0.009 ppm ( average) Solubility : Soluble in water after neutralization in ethanol.

Specific Gravity : 1.41

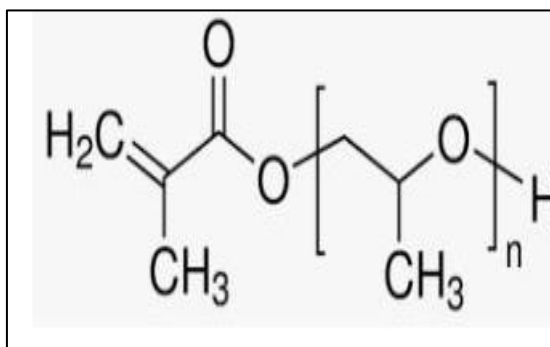
Viscosity : Carbomer disappears in water to form acidic colloidal solution of low viscosity which when neutralized produce highly viscous gel 40,400 to 60,600 cps at 25 degree ( 0.5% neutralized aqueous solution).

Stability and Storage : Store in a tightly closed container. Humidity controlled environment is necessary for storage, as carbomer 940 is very hygroscopic.

Application :It is used as thickening agent, emulsifying, and gelling agent. It is used as tablet binder and matrix forming agent in sustained release formulation affording zero- to near zero order release. It is used as the bioadhesive component in mucoadhesive ointments, gels and tablet

Safety : Carbomer are regarded as non-toxic and non irritant.

### 3.2 Propylene Glycol :<sup>[67]</sup>



**Fig10. structure of 1,2-dihydroxypropane**

Synonym : 1,2-Dihydroxypropane

Nonproprietary names : BP Propylene glycol, USP Propylene glycol JP Propylene glycol

Empirical Formula : C<sub>3</sub>H<sub>8</sub>O<sub>2</sub>

Molecular weight : 76.09

Category : Antimicrobial preservative, disinfectant, humectants, plasticizer, solvent.

Description: Propylene glycol is a clear, colourless, viscous, practically odourless, liquid with a sweet, slightly acid taste resembling that of glycerine..

Typical properties :

Auto ignition temperature : 371 degree

Boling point : 188 degree celceious

Density : 1.038 g/cm<sup>3</sup> at 20 degree

Viscosity : 58.1 mpas ( 58.1 Cp)

Solubility : Miscible with acetone, chloroform, ethanol ( 95%), glycerine and water soluble at 1 in 6 part of ether, not miscible with light mineral oil or fixed oils, but will dissolve some essential oils.

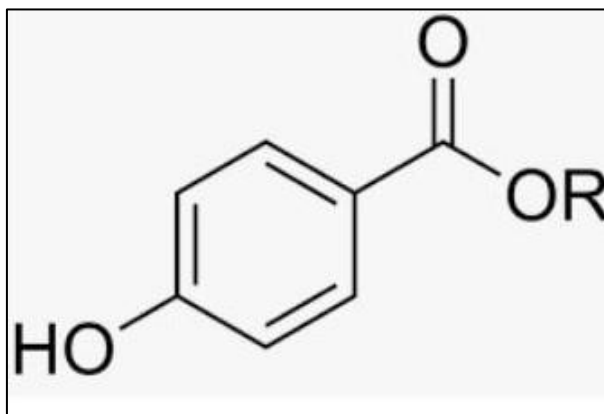
Stability and Storage Condition : At cool temperatures, propylene glycol is stable in a well container, but at high temperatures, in the open, it tends to oxidize, giving rise to products such as propion aldehyde, lactic acid, pyruvic acid, and acetic acid. Propylene glycol is chemically stable when mixed with ethanol ( 95%) glycerine or water aqueous solution may be sterilized by autoclaving.

Incompatibilities : Propylene glycol is incompatible with oxidizing agent such as potassium permanganate.

Safety : Propylene glycol is used in a wide variety of pharmaceutical formulation and is generally regarded as relatively nontoxic material. In topical preparations, propylene glycol is regarded as minimally irritant, although it is more irritant than glycerin

Application : Propylene glycol has become widely used as a solvent, extractant and preservative in a variety of parenteral and non- parenteral pharmaceutical formulation. propylene glycol is commonly used as plasticizer in aqueous flim-coating formulation.

### 3.3 Methyl Paraben : <sup>[68]</sup>



**Fig11. Structure of methyl p- hydroxybenzoate**

Methyl paraben is found in several fruits, in particular blueberries where it acts as an antimicrobial agent.

Synonym :Methyl paraben, Methyl P-hydroxybenzoate, Nipagin M.

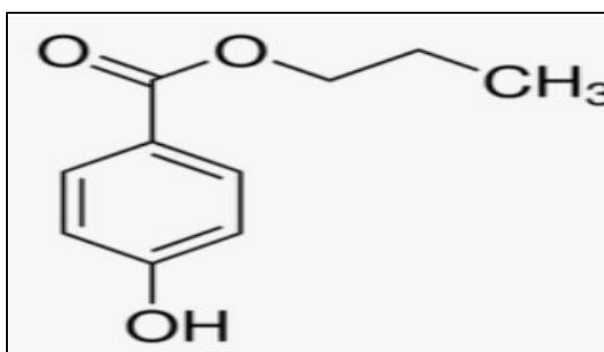
Empirical formula :  $\text{CH}_3(\text{C}_6\text{H}_4(\text{OH})\text{COO})$

Molecular mass : 152.15 g/mol

Molecular Formula :  $\text{C}_9\text{H}_8\text{O}_3$

Application : Methyl paraben is an anti-fungal agent often used in variety of cosmetic and personal care products. It is also used as food preservative. Methyl paraben is commonly used as fungicide in Drosophila food media. Methyl paraben is toxic at higher concentrations, has an estrogenic effect, and slows the growth rate in the larval and pupal stages at lower concentration.

### 3.4 Propylene paraben <sup>[69]</sup>



**Fig 12. structure of Propyl p- hydrobenzoate**

Propylene paraben is an n-propyl ester of hydroxybenzoic acid, occurs as a natural substance found in many plants and some insects.

Synonyms : 4- hydroxybenzoatesaurpropylester, propyl paraben, propyl p-hydroxybenzoate, propyl parahydroxybenzoate, nipasol.

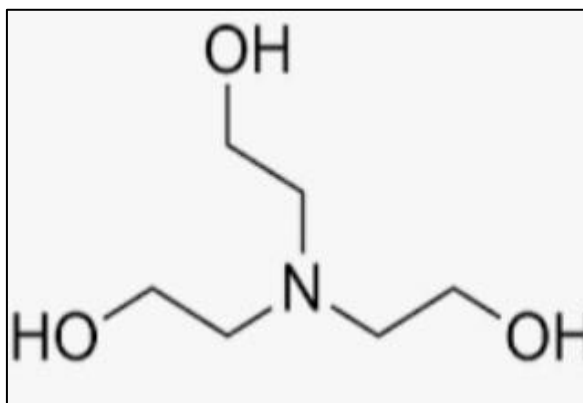
Molecular Formula :  $\text{C}_{10}\text{H}_{12}\text{O}_3$

Molecular mass : 180.2 g/mol

Density : 1.06030 g/cm<sup>3</sup>

Application : It is manufactured synthetically for use in cosmetics, pharmaceuticals and foods. It is a preservative typically found in many water based cosmetics, such as creams, lotions, shampoos, and bath products.

### 3.5 Triethanolamine :<sup>[70]</sup>



**Fig 13. Structure formula of Triethanolamine**

Synonym : TEA, tealan, triethyloamine, trihydroxytriethylamine, tri ( hydroxyethyl ) amine, trolaminum.

IUPAC Name : 2-{ 2-hydroxyethyl } amino] athanol

Molecular Formula :  $C_6H_{15}NO_3$

Molecular weight : 149.19 g/mol

Description : It is mixture of bases, mainly 2,20,200- nitrolotriethanol, although it also contains 2,20-iminobisethanol ( diethanolamine ) and smaller amounts of 2-aminoethanol. Triethanolamine is a clear, colorless to pale yellow-coloured viscous liquid having a slight ammonicalodor.

Typical properties :

pH : 10.5 ( 0.1 N solution )

Melting point : 20-21 degree celcius

Hygroscopicity : Very hygroscopic

Moisture content : 0.09 %

Solubility : It is miscible in water, acetone, methanol and carbon tetrachloride.

Application : i. Triethanolamine is widely used in topical pharmaceutical formulations, primarily in the formation of emulsion and micro emulsion gel.

ii. Triethanolamine is also used in salt formation for injectable solution and in topical analgesic preparation. It is also used in sunscreen preparations.

## 4. EXPERIMENTAL METHODOLOGY

### 4.1 Authentication of Miswak oil ( *Salvodarapersica* )

Miswak oil sample of *salvodarapersica* was provided by Grace Herbals Nagpur and was authenticated by Dr . Ashish shahane, Head Department of Oil, 28.29 Deepkamal society Khapri (Rly) Nagpur-441108. The result are shown in fig 15.

### 4.2 Preformulation studies of Miswak oil

#### 4.2.1 Identification test <sup>[71]</sup>

##### 4.2.1.2 Organoleptic characters

Miswak oil was tested for organoleptic characters such as color, odor, taste, solubility, in organic solvent

and water. The result are given in table 6.

#### 4.2.1.3 Physiochemical parameters<sup>[72]</sup>

Miswak oil was tested for physiochemical parameter like a) Specific gravity, b) Viscosity, c) Acid value, d) Saponification value, e) Iodine value, f) Free fatty acid value. The result are shown in Table 7.

##### a) Specific gravity

Specific gravity of oil was performed by using density bottle. It can be calculated by using formula.

$$G = \frac{W_d}{W_4 - W_3 + W_a}$$

Where,

G = Specific gravity of oil sample

W<sub>d</sub> = Weight of oil

##### b) Viscosity

The Viscosity of oil was determined by using Ostwald's viscometer.

**Procedure** :- The liquid was added to the viscometer, pulled into the upper reservoir by suction, and then allowed to drain by gravity back into the lower reservoir. The time that it takes for the liquid to pass between two etched marks, one above and below the upper reservoir, is measured. It can be calculated by using formula.

$$\eta_L = \eta_w \times \frac{\rho_L t_L}{\rho_w \times t_w}$$

Where,

$\eta_w$  = Absolute viscosity of water

$t_w$  = Time of flow of water

$\rho_w$  = Density of Water

$\eta_L$  = Absolute viscosity of liquid

$\rho_L$  = Density of liquid

$t_L$  = Time of Flow of Water

##### c) Acid Value

The acid value is the number of which express in milligram the amount of potassium hydroxide necessary to neutralise the free acids in 1g of substances.

**Procedure** :- Dissolve about 10g of the substances being examined accurately weighed in 50 ml of a mixture of equal volume of ethanol ( 95%) and ether previously neutralized with 0.1 M of potassium hydroxide to phenolphthalein solutions. If the sample does not dissolve in the cold solvent. Connect the flask with a reflux condenser and warm slowly with frequent shaking until the sample dissolve add 1 ml of phenolphthalein solution and titrate with 0.1 M potassium hydroxide until the solution remains faintly pink after shaking for 30 sec calculate acid value from the expressions.

$$\text{Acid value} = \frac{5.61 n}{w}$$

Where, n = the number of ml of 0.1 KOH required.

W = weight in g of the substances.

##### d) Saponification Value

The saponification value is the number of milligram of potassium hydroxide necessary to neutralise the free acids and to saponify the ester present in 1g of the substances.

**Procedure** :- Introduce about 2g of substances being examined accurately weighed into a 200 ml flask of borosilicate glass fitted with a reflux condenser. Add 25 ml of 0.5 M ethanolic potassium hydroxide add a little pumice powder and boil until reflux on a water bath for 30 min. add 1ml of phenolphthalein

solutions and titrate immediately with 0.5 M hydrochloric acid. Repeat the operation omitting the substance being examined (bml) calculate the saponification value from the expressions.

$$\text{Saponification value} = 28.05 (b-a) / w$$

Where, w = weight in g of substances.

#### e) Iodine value

**Procedure :-** Accurately weigh quantity of the substance being examined in a dry 500ml iodine flask add 10 ml of carbonmonochloride solution insert the stopper and allow to stand in the dark at a temp. between 15degree and 25 degree for 30 min. place 15 ml of potassium iodide solutions. In the cup top, carefully remove the stopper rinse the stopper and the sides of the flask with thiosulphate using starch solutions. Added towards the end of the titration as indicator.

Note : The number of ml required ( a) repeat the operation omitting the sample being examined and note the number of ml required ( b) calculate the iodine value from the expressions.

$$\text{Iodine Value} = 1.269 (b-a) / w$$

Where, w = weight in g of the substances.

#### f) Free fatty acid Value

**Procedure :-** 25 ml of ethanol was added to 1.5 g of each oil sample contained in different conical flask the mixture was brought to boil in a water bath then cooled. Two drops of phenolphthalein indicator was added to the solution. 0.1 M NaOH was used to titrate the mixture with constant shaking for proper mixing.

$$\% \text{ FFA} = v * 0.0282 / \text{wt. of sample} * 100$$

Where, v= titrate value

W = weight of the sample

### 4.3 Phytochemical evaluation <sup>[73]</sup>

The plant was subjected to phytochemical evaluation by various chemical identification test and the result are shown in Table8.

**1.Test for flavonoids :** To 4 ml of extract was added 1.5 ml of 50% methanol solution. 5-6 drops of concentrated HCL was added. Red color indicates flavonoids and orange color indicates flavonoes.

**2.Test for Alkaloids :** To 5.0g of each extract added 5 ml of 1 % aqueous HCL and kept water in bath 1 ml of the filtrates was to be treated with mayer's reagent ( potassium mercuric iodide ). Formation of a yellow coloured precipitated indicates the presence of alkaloids.

**3.Test for Tannins :** To 0.5 ml of extract solution 1 ml of water and 1-2 drops of ferric chloride solution was added. Blue color is observed for gallic tannins and green black forcatecholictannins.

### 4.4 Standard calibration curve of miswak oil

#### 4.4.1 Preparation of standard stock solution (A)

1mg of Miswak oil was accurately weighed and dissolved in methanol and in 100ml Of volumetric flask. This was sonicated for 10 min and volume was made up to the mark with the same solution. The concentration of this standard stock solution (A )was 100ug/ml.

#### 4.4.2 Scanning and Determination wavelength of Maximum Absorption

Scanning for wavelength of maximum absorption was carried out using stock solution of pure Miswak oil using UV-VIS spectrometer within the range of 200-400nm.

**4.4.3 Standard calibration Curve of Miswak oil in methanol**

Serial dilution of stock solution(A) in the Concentration of ( 100ug/ml) with methanol was carried out to prepare the working standard within the range of 2-10 ug/ml. the absorption values of above solutions were measured by using UV spectrophotometer against methanol as blank and the calibration curve was obtained.

**4.4.4 Preparation of standard stock solution (B)**

1mg of Miswak oil was accurately weighed and dissolved in methanol and phosphate buffer (pH 6.8) (60:40) in 100ml of volumetric flask. This was sonicated for 10 min and volume was made up to the mark with the same solution. The concentration of this standard stock solution (B) was 100ug/ml.

**4.4.5 Standard calibration Curve of Miswak oil in methanol and phosphate buffer pH 6.8.**

Serial dilution of stock solution (B) in the ( 100 ug/ml ) with methanol and phosphate buffer (pH 6.8) was carried out to prepare the working standard within the range of 2-10 ug/ml. the absorption values of above solutions were measured by using UV spectrophotometer against combination of methanol and phosphate buffer (pH 6.8) as a blank and the calibration curve was obtained.

**4.5 Formulation of Emulgel**

**4.5.1 Method of Preparation**

**4.5.1.1 Formulation of Emulsion**

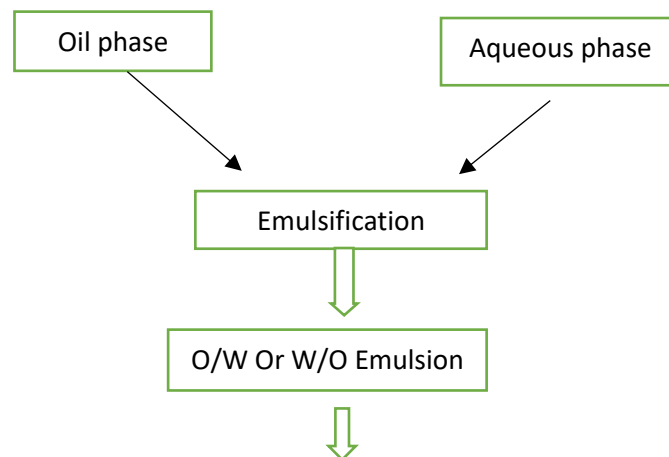
The Emulsion was formulated by using Dry gum method. Miswak oil is a fixed oil thus 4:2:1 ratio was used for preparation of primary emulsion. The accurately weighed quantity of oil (4ml) tween and span was prepared weigh the accurately quantity of Miswak oil ( 4ml), tween and span was weighed in various grade (20,40,60,80) in mortar was triturating them by producing cricking sound and white in colour of emulsion. water is added slowly in small portion mixture by continuous trituration for several min. to get primary emulsion. remaining quantity of water was added to make final volume of emulsion.

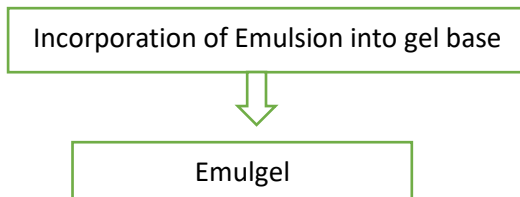
**4.5.1.2 Formulation of gel base**

The accurately weighed quantity of carbopol 940 (1% w/w) was taken in a beaker in sufficient amount of water to soaked overnight. After soaking, gel was stirred on mechanical stirrer for 10- 15 min by adding few drop of triethanolamine for adjusting the pH 6-6.5 to form gel base.

**4.5.1.3 Incorporation of emulsion into gel base to form emulgel**

The prepared emulsion were incorporated into gel base in the ratio of 1:1 on magnetic stirrer at a speed of 1000-1200 rpm for 15 min to form emulgel. Digrametic representation of emulgel formation show in fig. 14.





**Fig 14. Method of preparation of emulgel**

**Table. 5 Formulation table of Emulgel**

Sr. no	Ingredients	F1	F2	F3	F4	F5	F6
1	Miswak oil ( ml )	4	4	4	4	4	4
2	Carbopol 940 (1% w/w)	1	1	1	1	1	1
3	Liquid paraffin (ml)	2	2	2	2	2	2
4	Peppermint oil(ml)	1	1	1	1	1	1
5	Span 20( ml)	1	-	-	-	-	-
6	Span 40 (ml)	-	1	-	-	-	-
7	Tween 20(ml)	-	-	1	-	-	-
8	Tween 40(ml)	-	-	-	1	-	-
9	Tween60(ml)	-	-	-	-	1	-
10	Tween 80(ml)	-	-	-	-	-	1
11	Methyl paraben(gm)	0.00 3	0.003	0.003	0.003	0.003	0.003
12	Propyl paraben(gm)	0.01	0.01	0.01	0.01	0.01	0.01
13	Water (uptoml)	10	10	10	10	10	10

## 4.6 Evaluation Parameter of Emulgel

### 4.6.1 Physical Examination<sup>[74]</sup>

The prepared emulgel formulation was inspected visually by their color, odour, appearance, homogeneity, and consistency, phase separation and texture. Whether, colour is white. Homogeneity and consistency was also good by applying emulgel formulation on thin layer of skin. No phase separation and texture is smooth of emulgel was done.

### 4.6.2 Identification test of Emulsion<sup>[75]</sup>

The type of emulsion was determined by using dilution test. This test is used for the conformation of emulsion type. Take two test tube in one test tube few sample of emulsion can be diluted with sufficient amount of water then it confirm O/W emulsion. And in second test tube take few ml of emulsion add sufficient amount of oil sample then it confirm W/O emulsion type.

### 4.6.3 Determination of pH<sup>[76]</sup>

The pH of all formulated emulgel are determined by using digital (DELUXE) pH meter. 1gm of gel was dissolved in 100 ml of distilled water and stirrer for 5 min then mixed properly. The measurement of pH of each formulation was done in triplicate and average values were noted.

### 4.6.4 Measurement of viscosity<sup>[77]</sup>

The viscosity of all prepared emulgel was measured by using Brookfield viscosimeter (Brookfield DV-E-viscosimeter) using sp-indle No. 96 rotate speed at 6 rpm. For 10 min. Experiment were carried out in



triplicate for each sample, and the results are presented as an average in standard deviation.

#### 4.6.5 Spreadability<sup>[78]</sup>

Two glass slide was used, with same dimension used for determination of the prepared Emulgel formulation. prepared Emulgel was placed over one slide and the other slide was placed over its top. The slide pressed upon each other like sandwich and remove the air bubble. Apply 1 gm of Emulgel is place between the slide and put 125 kg of weight slide. Distance of 6.5 cm can be noted from top slide. Time can be noted to spread the silde from noted distance. A shorter time to reach standard distance show a better Spreadability.

Spreadability ( S ) was calculated as follow :

$$S = M \cdot L / T$$

Where,

S = Spreadability of emulgel

L = Length of slide

T = Time taken to spread the slide.

#### 4.6.6 Drug content<sup>[79]</sup>

Drug content in emulgel was measured by dissolving 1 gm of emulgel in 100 ml of solvent ( a mixture of methanol and phosphate buffer at pH 6.8 ( 60:40 ). After filter this solution to obtain clear solution and subjected to UV spectrophotometric analysis after suitable dilution by using 235 nm.

#### 4.6.7 In-vitro diffusion studies<sup>[80]</sup>

The Release of the salvodarapersica leaves oil from emulgel formulation was measured through standard cellophane. membrane using a franz diffusion cell. Prior to study, cellophane membrane was soaked in diffusion medium for overnight, and then placed on the support screen of the diffusion cell assembly. Methanolic phosphate buffer ( 60:40 ) at pH 6.8 was used as the receptor medium and 1 g of the gel was placed on the donor side. At predetermined time intervals, 2ml of sample was withdrawn from the receptor compartment and replaced with same volume of methanolic phosphate buffer ( 60:40 ) at pH 6.8 The aliquots were analyzed by UV spectrophotometer. At 235nm. Cumulative amount of drug diffused ( CADD ) was calculated as follow.

$$\% \text{ CADD} = [ \text{Concentration ( ug/ml) } * \text{volume of diffusion medium } * \text{Dilution factor } ] / 100$$

Where,

% CADD = Comulative amount of drug release

#### 4.7.8 In-vivo- Anti- inflammatory studies<sup>[81]</sup>

The anti-inflammatory studies of emulgel containing miswak oil were performed using plethysmometer on albino mice of either sex in weighing between 18-22 gm. The selected protocol was approved by IAEC of college and protocol no.was ( P JLCP/2020-21/IAEC/03). The selected mice were kept on healthy diet and were free from other topical infection.

The anti-inflammatory studies, edema was induced on the left hind paw of the mice by sub-plantar injection of 1 % ( w/v ) carrageenan. Marketed Formulation i.e Standard ( diclofenac sodium gel ) were applied 30 min before carrageenan administration. The paw volume was measured at interval of 30, 60, 90, 120 min by mercury displacement method using plethysmometer. ( VJ INSTRUMENTS™ 166/1 at model no. VJDP-01 ) animal are divided into three group. Group 1, group2, group3 respectively.

**Group 1 ( Control group ) :** Group 1 was received Carrageenan ( 1% ) in the plantar surface of mice.

**Group 2 ( Standard group ) :** Group 2 was received topical marketed diclofenac gel + Carrageenan suspension.

**Group 3 ( Test ) :**Group 3 was received formulation ( gel) + Carrageenan suspension.

The % inhibition of paw edema in drug treated group was compared with carrageenan control group and calculated according to the formula

$$\% \text{ Inhibition by test sample} = (V_c - V_t) / V_c * 100$$

Where,

V<sub>c</sub> = Inflammatory increase in paw volume control group.

V<sub>t</sub> = Inflammatory increase in paw volume in ( drug+carrageenan ) treated animals.

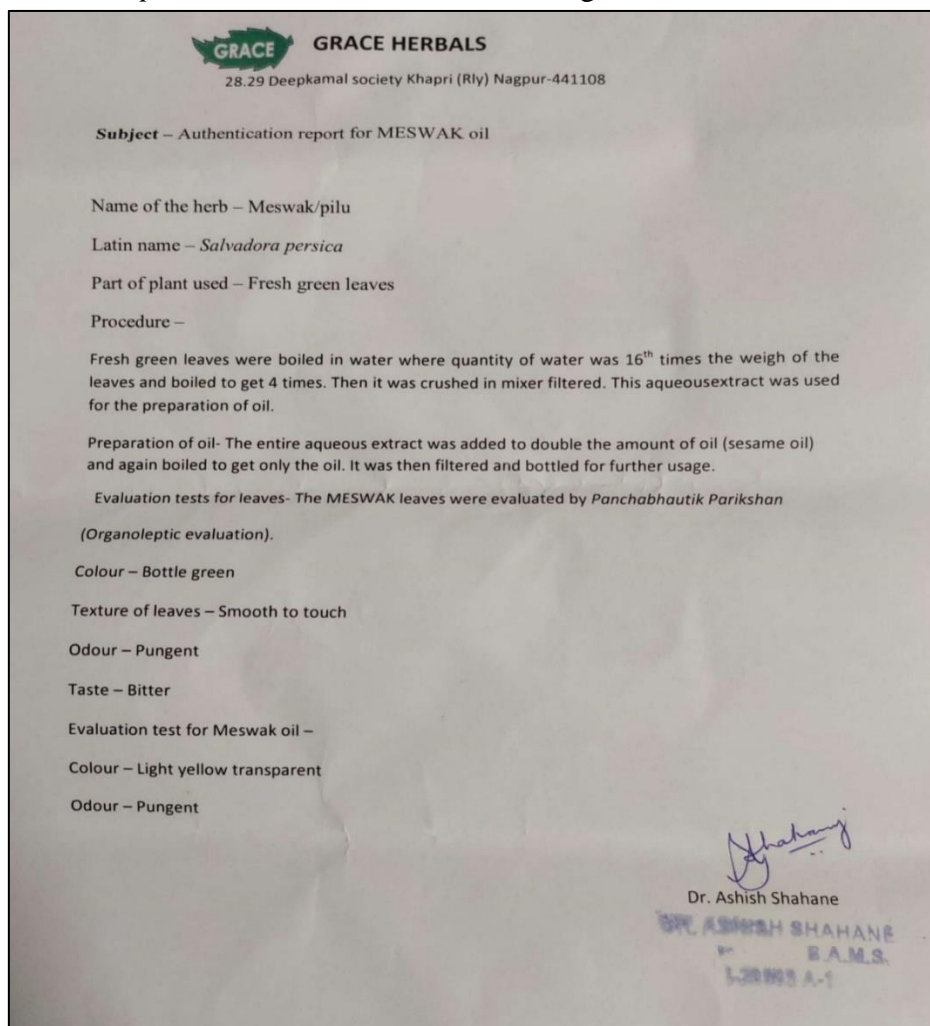
#### 4.5.9 Stability Studies<sup>[82]</sup>

The formulated emulgel were subjected to stability studies at , 40°C, and 75%RH for a period of 45 days. The formulation were checked for 0 and 45 days. The physical appearance, pH, drug content, spreadability and viscosity were determined by taking the samples at predetermined time intervals and have noted the observation.

## 5. RESULT AND DISCUSSION

### 5.1 Authentication of miswak oil ( *SalvodaraPersica* )

Miswak oil sample was procured from Grace Herbal , Nagpur and was authenticated by Dr. Ashishshahane, Head Department of Oil, 28.29 Deepkamal society Khapri (Rly) Nagpur -441108 and authenticated as *salvodarapersica*. The result are shown in fig 15.



**Fig. 15 Authentication of miswak oil**

**5.2 Preformulation studies of Miswak oil<sup>[83]</sup>**

**5.2.1 Identification of Oils.**

**5.2.2 Organoleptic characters :** The organoleptic Characterization of Miswak oil was performed. From the result of organoleptic characterization of Miswak oil, it was observed that all the organoleptic characters like colour, odour, Taste, solubility were found to be pale yellowish, pungent, bitter, soluble in organic solvents and insoluble in water respectively and as per the specification. of standard refrence.( Indian medicinal plants, C.P. Khare *et al*)

**Table. 4 Organoleptic characters of Miswak Oil**

Sr No	Organoleptic characters	Result
1	Colour	Pale yellowish coloured liquid
2	Odor	Pungent
3	Taste	Bitter
4	Solubility in : Organic solvent Water	Soluble Insoluble

**5.2.3 Physiochemical Parameters<sup>[84]</sup> :**The physiochemical parameters of Miswak oil were obtained as given in Table.5

From the above result of physiochemical parameters of miswak oil, it was observed that all the physiochemical parameters like acid value, saponification value, iodine value, free fatty acid value, viscosity, specific gravity, was found within standard limit/range.

**Table. 5 Physiochemical parameters of Miswak oil**

Sr. No	Physiochemical parameters	Standard value	Obtained value
1	Specific gravity	0.9246-0.9240	0.94016±0.00015
2	Viscosity ( cp)	0.9237-0.9230	0.9246±0.0001
3	Acid value	6-7	6.945±0.058
4	Saponification value	251-252	247.26±3.221
5	Iodine value	15.6-15.8	15.166±0.2516
6	Free fatty acid value	7.6-7.8	7.681±0.0413

**5.2.4 Phytochemical Evaluation :**The phytochemical constituents of Miswak oil ( *salvadorapersica* ) were studied and it contained alkaloids, tannins, and flavonoids, the anti-inflammatory activity associated with miswak oil may be due to presence of flavonoids result are showed in table no 6.

**Table. 6 Phytochemical evaluation of miswak oil**

Phytochemical constituent	Test	Oil
Alkaloid	1) Dragendroff’s test	+
	2) Hager’s test	+
	3) Mayer’s test	-
	4) Wagner’s test	+
Tannins	1) Lead acetate	+
	2)Bromine water	+

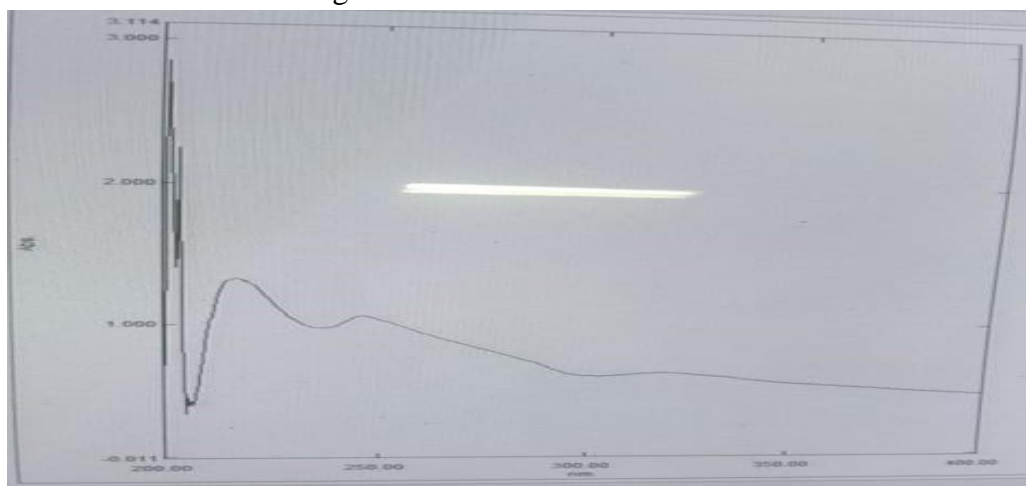
	3)Potassium dichromate	-
	4)Iodine	-
	5)HNO <sub>3</sub>	+
Flavonoids	1)Shinoda test	+
	2)Small quantity of residue add lead acetate solution	+

(+) = Positive      (-) = Negative

### 5.3 Standard calibration curve of miswak oil

#### 5.3.1 Determination of $\lambda_{max}$

A solution of Miswak oil ( 100ug/ml ) was prepared in methanol and UV spectrum was taken using shimadzu ( UV-1601 ) spectrophotometer. The solution was scanned in the range of 200-400 nm. Wavelength of maximum absorption of Miswak oil was found to be 235 nm. Characterized by single sharp peak. The result are shown in fig no. 16.



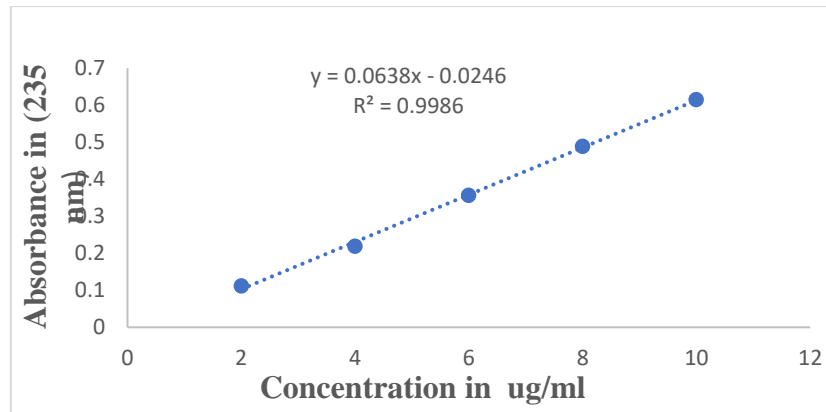
**Fig 16.  $\lambda_{max}$  spectrum of Miswak oil in methanol**

#### 5.3.2 Standard calibration of Miswak oil in methanol

The working standard within the range of 2-10  $\mu\text{g/ml}$  was prepared by serial dilution of stock solution (A) with methanol. The standard calibration curve revealed that Beer's law was obeyed throughout the concentration range 2-10  $\mu\text{g/ml}$ . The linear regression equation of absorbance was found to be  $y = 0.0638x + 0.0246$  with the correlation coefficient of 0.99986. The result are shown in table no.7 and fig. 17.

**Table. 7. Standard calibration of Miswak oil in methanol at 235 nm**

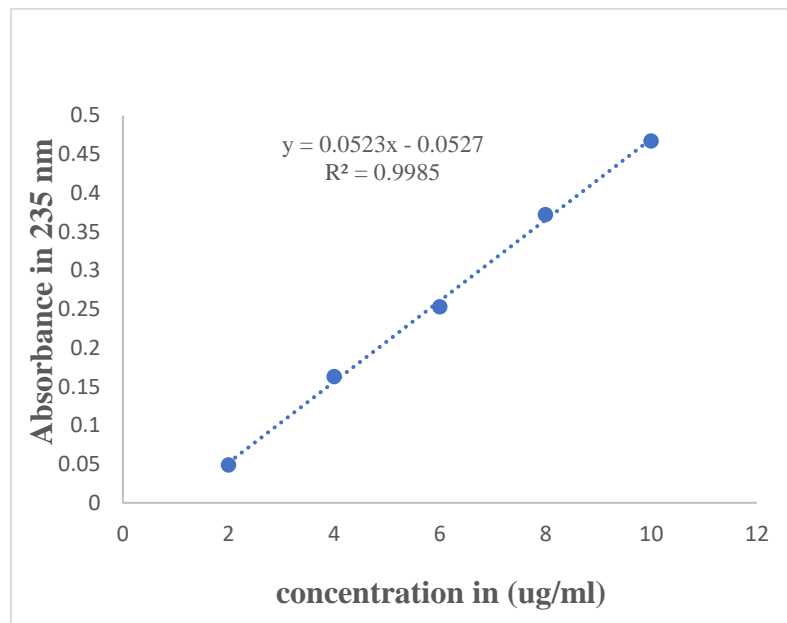
Sr. No	Concentration ( $\mu\text{g/ml}$ )	Absorbance(nm)
1	0	0
2	2	0.112
3	4	0.219
4	6	0.356
5	8	0.489
6	10	0.615



**Fig 17. Calibration curve of Miswak oil in methanol**

### 5.3.3 Standard calibration curve of Miswak oil in methanol and phosphate buffer (pH 6.8) at 235 nm.

The working standard within the range of 2-10  $\mu\text{g/ml}$  was prepared by serial dilution of stock solution (B) with methanol and phosphate buffer (pH 6.8) in 60:40. The standard calibration curve revealed that Beer's law was obeyed throughout the concentration range 2-10  $\mu\text{g/ml}$ . The linear regression equation of absorbance was found to be  $y = 0.0523x + 0.0527$  with the correlation coefficient of 0.99986. The results are shown in table no.8 and fig. 17.



**Fig 18. Calibration curve of Miswak oil in methanol and phosphate buffer pH 6.8**

### 5.3.4 Formulation of Emulgel

The 40 ml of 6 batches of emulgel were prepared (F1-F6). The emulgel was prepared in span 20 and Tween 20 in various grades. The emulsion (Span 40, span 60 and span 80) and ( Tween 40, Tween 60 and Tween 80) separated. Span 20 and Tween 20 was stable usually the emulgel was opaque white in color with characteristic odour due to miswak oil. Emulgel was stored in tightly closed container further. Preparation are shown in fig no.18



**Fig 19. Preparation of Emulgel**

### 5.4 Evaluation of Emulgel

#### 5.4.1 Physical Examination

The formulated emulgel were white in color with no lumps and aggregates indicating good homogeneity and texture was smooth. The results are shown in table no. 9

**Table 9. Physical Examination of Emulgel**

Parameter	F1	F2	F3	F4	F5	F6
Colour	White	White	White	White	White	White
Appearance	Semisolid	Semisolid	Semisolid	Semisolid	Semisolid	Semisolid
Homogeneity	Good	Good	Good	Good	Good	Good
Consistency	Good	Good	Good	Good	Good	Good
Texture	Smooth	Smooth	Smooth	Smooth	Smooth	Smooth

#### 5.4.2 Determination of pH, Viscosity, Spreadability and Drug content

The pH of all prepared emulgel was found to be in the range of  $6.34 \pm 0.04$  to  $6.77 \pm 0.07$ , this value of pH of emulgel are indicated that slightly acidic pH which was found to be compatible compliance with skin pH in the range 4.5 to 6.5.

The viscosity of all prepared emulgel was found to be in the range of  $10883 \pm 02.47$  to  $21376 \pm 280.55$  cps. viscosity was increased with increase in emulsifier concentration. Obtained value of viscosity are indicated as which was optimized result . so, They are easily spreadable on the layer of skin for topical application. The spreadability of emulgel was found to be in the range of  $87.26 \pm 0.32$  to  $96.23 \pm 1.32$  gm.cm/sec. spreadability of emulgel was increased due to presence of surfactant. Obtained value of viscosity are indicated as which was optimized result and they were easily spreadable on the skin layer for topical application.

Drug content of emulgel were found in the range of  $90.25 \pm 0.032\%$  to  $93.56 \pm 0.021\%$ . The obtained value of drug content showed the maximum amount of miswak oil are loaded in F3 formulation as compared to other. Thus, it was optimized for future studies. The results are shown in table no.10.

**Table 10. pH, viscosity, Spreadability and Drug content of Emulgel**

Formulation	pH	Viscosity (cps)	Spreadability (gm.cm/sec)	Drug content %
F1	$6.74 \pm 0.04$	$21376 \pm 280.55$	$95.94 \pm 0.98$	$90.25 \pm 0.021$

F2	6.47±0.04	20015±248.1	90.29±1.05	89.21±0.031
F3	6.77±0.05	12500±201.0	88.98±0.32	94.56±0.024
F4	6.61±0.03	10883±02.47	89.20±0.41	89.79±0.051
F5	6.34±0.04	13248±148.60	87.26±0.32	86.91±0.043
F6	6.61±0.07	13867±501.9	96.23±1.32	93.51±0.041

Data was expressed as Mean ±SD (n=3)

### 5.4.3 In-vitrodifusion studies

At the end of 1.30 hour, the total amount of drug released from the formulation ( F1-F6) was found to be in the range from 70.17±0.01 to 93.10 ±0.05 The result are indicated that miswak oil diffused to desirable extent. The results are shown in table no.11 and fig no. 20.

**Table 11. percentage cumulative drug release of Emulgel**

Sr. No	Formulation	15 min	30 min	45 min	1 hour	1.15 hour	1.30 hour
1	F1	29.05±0.01	49.66±0.20	53.2±0.1	59.63±0.02	73.22±0.01	78.02±0.1
2	F2	34.98±0.01	41.08±0.05	49.88±0.01	56.24±0.01	61.36±0.01	70.17±0.1
3	F4	35.2±0.12	66.43±0.25	66.19±0.01	73.18±0.015	81.25±0.01	93.10±0.05
4	F3	36.45±0.40	46.70±1.05	54.27±0.18	69.2±0.07	75.14±0.02	90.80±0.01
5	F5	41.08±0.01	50.27±0.01	54.85±0.01	62.13±0.01	65.38±0.01	74.2±0.1
6	F6	47.5±0.1	56.02±0.01	59.64±0.01	70.15±0.015	74.15±0.01	79.33±0.01

Data was expressed as Mean ± SD ( n=3)

### 5.4.4 In-vivo Anti-inflammatory Studies

The anti-inflammatory activity of the formulation ( test) was compared with marketed (diclofenac) i.e standard group. The % inhibition of standard and test group were 26.09 and 52.83% respectively. The collected data obtained as Mean ±SEM and was analyzed stastically by means of one way analysis of variance ( ANOVA) values of P< 0.001 are regarded as significant and value indicated in bracket are of % inhibition of edema. Control group showed no paw edema.emulgel containing Miswak oil give significant result of % inhibition of paw volume at 90min and 120 min.

This result indicated the potent anti-inflammatory activity of miswak oil through emulgel and can be used topically for the management of inflammation. The results are shown in table no. 12 and fig no. 21

**Table 12. Mean paw volume and percentage inhibition of the edema in the Mice**

Time ( min)	Group I Induced (Carrageenan)	Group II Treated (Drug)	Group III Standard (Diclofenac gel )	Group IV Control
30	0.808±0.009 <sup>#</sup>	0.733±0.011(9.28%)*	0.640±0.018(20.79%)*	0.498±0.013
60	1.040±0.011**	0.820±0.009(20.33%)*	0.745±0.014(28.36%)*	0.553±0.015
90	1.318±0.009**	1.050±0.015(21.15%)*	0.820±0.009(37.78%)*	0.488±0.026
120	1.533±0.011**	1.133±0.011(26.09%)*	0.723±0.009(52.83%)*	0.478±0.038

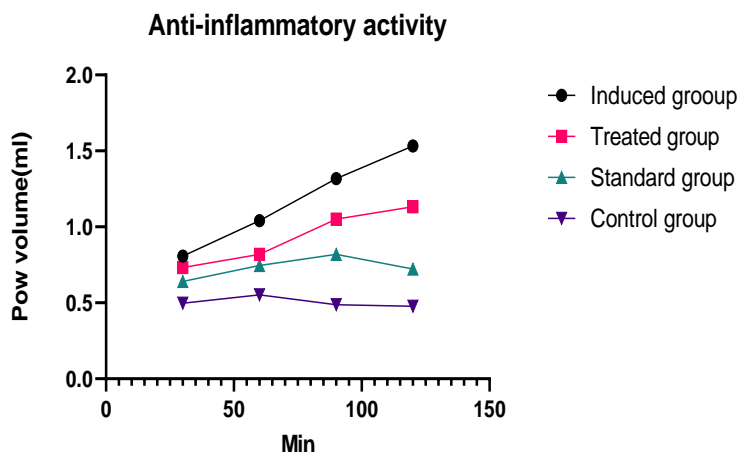


Fig 21. ANOVA for Anti-inflammatory activity of Mice

(Values are expressed in Mean  $\pm$  SEM. Control group compared with #Induction group; and Induction groups are compared with treated group.

The values are analysed in Graph-pad prism followed by one-way ANOVA and  $P < 0.001$  was considered to be statistically significant.)

#### 5.4.5 Stability Studies

Stability studies of prepared emulgel formulation was performed on 45 days. It was observed that the emulgel formulation showed no major alternation in relation to the appearance, pH, spreadability, viscosity and drug content, From Thus, it can be concluded that the prepared emulgel formulation were found to be stable upto 45 days. The result are shown in table no. 13.

Table 13. Stability studies of Emulgel

Period ( Days)	Appearance	Ph	Viscosity	Spreadability	Drug content
0 days	White	6.77 $\pm$ 0.07	12500 $\pm$ 201.0	96.23 $\pm$ 1.32	94.56 $\pm$ 0.024
45 days	White	6.64 $\pm$ 0.06	12499 $\pm$ 201.0	96.20 $\pm$ 1.29	94.54 $\pm$ 0.022

### 6. Summary and Conclusion

In the recent year, topical drug delivery system will be extensively due to better patient compliance since emulgel possesses an edge in terms of spreadability, viscosity they will become a popular drug delivery system moreover they will become a solution for loading hydrophobic drugs in a water soluble gel base. In drug delivery, topical drug administration is a localized drug delivery system where ever, in the body. Drugs are administered topically for their action at the site of application, or for systemic effect.

The literature survey that, the miswak oil is non-edible fixed oil obtained from leaves of salvadorapersica belonging to the family salvadoraceae. It has effective anti-inflammatory activity. Hence Miswak oil was selected for the formulation of emulgel. In present research work attempted were made for the formulation and evaluation of Emulgel containing miswak oil for the management of inflammation

The emulsion containing Miswak oil was used as an oil phase, span 20, 40 and tween 20, 40, 60, and 80 were used as a surfactant, peppermint oil are used as a penetration enhancer and liquid paraffin was used



as a mineral oil for enhancing viscosity of emulgel. carbopol 940 was used as gelling agent. the total 6 batches of emulgel were formulated by using varying the grade of span and tween throughout the batch (F1-F6). the prepared emulgel formulation (F1-F6) was subjected to characterization for physical examination, pH, Spreadability, drug content, in-vitro drug release, anti-inflammatory activity and stability study.

F1 and F3 formulation containing span 20 and tween 20 was stable usually emulgel was white in color with no lumps and aggregates with characteristics odour due to miswak oil indicating good homogeneity and texture was smooth. pH of all prepared emulgel which was found to be compatible with skin pH in the range 4.5 to 6.5. viscosity of all emulgel formulation was optimized. Liquid paraffin may be helpful for enhancing viscosity of emulgel. Spreadability was also good and it is easily to spread the skin surface. Maximum amount of miswak oil are loaded in F3 formulation as compared to other it was optimized for future studies. Then maximum miswak oil was also released in F3 formulation so, it indicated drug are maximum penetrated to the skin surface.

Formulation F3 was optimized for future studies such as anti-inflammatory and stability studies. The anti-inflammatory activity of prepared emulgel containing miswak oil showed significant % inhibition of paw volume at 90 min and 120 min. this result indicated that potent anti-inflammatory activity of miswak oil through emulgel and can be used topically for the management of inflammation.

Formulation (F3) of emulgel were subjected to stability studies on 45 days. It was observed that physical appearance, pH, viscosity, spreadability and drug content. No major alteration was done upto 45 days. From the above result of present work it can be concluded that the miswak oil is an fixed oil obtained from leaves of *salvadarapersica* can be successfully incorporated in topical emulgel. The prepared emulgel containing miswak oil showed promising anti-inflammatory activity. thus, miswak oil emulgel can be used topically for the management of inflammation.

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