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PREPARATION OF SUITABLE TOPICAL DOSAGE FORM USING PLANT BUTTER EXTRACTED FROM *DIPLOKNEMA BUTYRACEA*

Mukul Chakraverti, Neetu Pandey
Department of Applied Chemistry and Basic Sciences
Sardar Bhagwan Singh University Balawala, Dehradun Uttarakhand, India

Address for Correspondence : Neetu Pandey, Department of Applied Chemistry and Basic Sciences, Sardar Bhagwan Singh University , Balawala, Dehradun, Uttarakhand, India, Email ID : neetu_bhtt@yahoo.co.in

ABSTRACT

A medicinal tree namely *Diploknemabutyracea* (Chyuri) is known for its medicinal properties and also the origin of many helpful things. The use of Medicinal plant and Tradition Medicine has been studied in many developing countries. At a height of 300-1500 m, it is distributed throughout the Himalayan belt including Nepal, India and Bhutan. Chyuri is economically beneficial but unknown and underutilized. All parts of this tree have good economic value and are usable. The main product of this tree is Chyuri Ghee. It is a multipurpose tree, which provides food, medicine and plenty products for local people. In Uttarakhand, the population of this species is located especially in the border area of Pithoragarh District. *Diploknemabutyracea* is a medicinal curative tree, mostly found in Nepal, in India it is placed in Pithoragarh district of Uttarakhand, especially areas bordering. The tree reaches a peak of 15-20m and width 1.8m, the fruits are berry type containing 1-3 seed. It is used as multi-functional tree, such as supply food, medicine and much useful stuff for local people. It provides many useful substances like oil, honey, gur, fooder for animals, fuel and timber, being a good source of income. It is frequently cultivated, mainly for the Ghee obtained from the seed. The butter extracted from the seed is known as “Chyuri Ghee” or “Phulwara Butter” is the most used product from the tree. The chyuri ghee is used for many purposes such as for making soap, candles, and cures many diseases like headache, ulcers, itching, rheumatic pains, etc. The prepared formulation was stable, containing butter as oily phase and menthol as penetrating enhancer showed best result. The evaluation test result showed that the plant butter can be used as base in topical formulation and menthol showed good result as penetrating enhancer. The plant butter extracted from *Diploknemabutyracea* has some basic property; it can provide body to any topical formulation.

***KEYWORDS*:** *Diploknemabutyracea* (Chyuri) ; Therapeutic properties ; Phytoconstituents ; Plant butter ; Topical dosage formulation; Diclofenac sodium

INTRODUCTION

1.1 TOPICAL DOSAGE FORMULATION

A dosage form refers to the form of drug in which they are ready to use containing a particular mixture of active constituents and suitable excipients in a specific arrangement (like capsule shell) and dispense into a controlled dose.

A Topical dosage (semi-solid) formulation is one of them; they include creams, ointments, pastes, emulsion gel and rigid form. They are the vehicle for the drug that is topically delivered by means of skin, rectal tissue, cornea, nasal mucosa, vagina and external ear lining. Skin is the main route of drug administration. Topical formulations are intended for the application on the skin to produce and local and systemic effect at the site of application. They contain one or more therapeutic agent uniformly dissolved in a appropriate base and some suitable excipients such as preservatives, antimicrobial agent emulsifier, antioxidant etc.[1] Topical formulation may be mediated or unmedicated. Medicated formulation produces effect of the therapeutic agent, they contain. The unmedicated formulations are used for their physical effect as protectants or lubricants. Topical formulation can be designed for either local effect or systemic absorption. The topical dermatologic formulation is designed to deliver therapeutic agent into the skin as target organ. A transdermal formulation is designed to deliver therapeutic agent by the skin as the way to achieve systemic distribution, with skin not being the target organ. [2] They provide prolong contact at the site of application before they are washed off.

Some topical formulations are directly applicable to the surface of skin and some are applicable to the surface of tissue, it includes eye drops, ear drops, inhalators etc. The application position and pharmacodynamic effect for the topical formulation is local. Eternal route of administration is also a topical formulation, but it has poor absorption and produce local effect.

Examples of topical formulation which are available in market are:

1) Ponds cream, which is used to smoothening the skin.
2) Cataphil moisturizing lotion is an example of topical formulation.
3) Mama earth Aloe vera gel.
4) Vaseline, a body lotion.
5) Sulphur ointment 10% Acne medicament.
6) Hydroquinone USP 4% skin bleaching gel with sunscreen.

1.2 CHOICE OF BASE

The potency of formulation changes with the change of the base, e.g. some steroids are more powerful in

ointment than in cream. The production of topical formulation ensures the amount of base present in it. For topical formulation the choice of base depends upon various factors: the desire therapeutic effect, the nature of the active therapeutic agent, and the condition of environment. The base should be neither sensitize nor irritate the skin and not should delay the healing of wound. It should be smooth, stable, inert and odorless. [3]

According to the Dermatology, in topical formulation the base is important same as the drug. It is the most important same as the drug. It is most important to prepare formulation in the suitable base.

1.3 CLASSES

1.3.1 CREAM

Creams are topical formulation which is usually prepared for the application to the skin and widely accepted in cosmetic. They are used to moisturize the skin in daily life It is a emulsion of oil and water Creams are more dense than lotion and it penetrates the outer surface of skin. Creams can be medicated and unmedicated. Medicated creams contain active therapeutic agent with specific pharmacological activity like antifungal, antimicrobial etc. while unmedicated creams are used for moisturize and beautify the skin. Creams are good in reducing roughness. Medicated creams are mostly used to cure many skin disorders. According to the requirement of the skin condition, creams used can be allopathic, ayurvedic or herbal. [4,5] Creams can be easily applied to everywhere on the skin. It is used by all age group people with ease.

Creams can be classified into two types: one is oil-in-water (O/W) creams which are prepared by small amount of oil dissolved over a large amount of water, they include vanishing creams, foundation cream, or hand cream, and the other is water-in-oil (W/O) creams which are prepared by small amount of water dissolved over large amount of oil, they include cold creams, emollient cream. A Greek doctor, Galen discovered the cold cream in the second century. [6] Oil-in-water creams are easy to manage and comfortable as they are less greasy, easily washable by water and used in cosmetic elegance. Water-in-oil type creams have more tendency of moisturizing dry skin as they provide oily restriction which lowers the loss of water from outer surface of the skin. [7] One or more drug constituents may present in a single cream for different purpose such as baby cream, sunscreen, hair cream, hand cream, cetrimide cream as antiseptic.

Some examples of cream which are available in market are:

1) Ponds moisturizing cold cream are an example of cold cream which are used to smoothening the skin.
2) Cetrimide cream is used as antiseptic.
3) Ponds Vanishing cream.

4) Ayur Herbal cold cream
5) Ring Guard , anti-fungal medicated cream
6) Wow hair vanish cream

USES

1) They provide a restriction to protect the skin.
2) Use as a moisturizing agent.
3) They are the vehicle for the drug constituent like anti-fungal , antiseptic etc.[7]

1.3.2 LOTION

A lotion is a oil-in-water emulsion, having low viscosity, containing active constituents and some other ingredients like fragrances, preservatives, stabilizing agents etc. They are more moisturizable than solution. Generally lotions are prepared for the application to the skin. Lotions may be medicated like lotion for allergies. Preservatives may be present in lotions. Lotions are generally a solid suspension in an aqueous medium. [8]

According to dermatology, the lotions are recommended to cure and prevent skin diseases. [9] Lotions are less viscous and easy to application on hairy area such as scalp. Lotions are the vehicle for the transmission of medicaments into the skin like antiseptic, anti-fungal, antibiotic etc.
Examples of some lotions which are available in market are:

1) Cetaphil moisturizing lotion
2) Base glaxal lotion
3) Aveeno skin Relief moisturizing lotion with cooling menthol
4) Lubriderm daily moisture lotion
5) Vaseline, a body lotion
6) NIVEA nourishing lotion

1.3.3 GEL

Gels are thicker semi-solid emulsion which is a liquid phase constrained within a 3D ploymeric matrix in which cross linking is introduced. According to U.S.P. gels is a semisolid system consisting of dispersion which is either made up of large organic molecule or small inorganic particle enclosed by liquid. They exhibit no flow at stationary state. On the basis of nature of colloid, gels are classified into two type: a) Organic gels b) Inorganic gels. Most organic gels refer as single phase system and inorganic gels are two phase system such as aluminium hydroxide gel. On the basis of nature of solvent gels are classified into two

types: a) Hydrogels b) Organogels. Hydrogels contain water soluble ingredients. Organogels contain hydrocarbons, animal and vegetable fats. [10] They are generally used for the hairy areas and body folds. In some cases the alcohol is used as solvent for dissolving the functional ingredients, so it produces stinging effect when applied on the skin. They carry a notable risk of hypersensitivity because of the fragrance and preservatives present in it. Gel have tendency of self drying and at body temperature some gel get liquefied . Gel have high rate of approval because of its cosmetic elegance.

Examples of some gels which are available in market are:

1) Mamaearth Aloe vera gel
2) OMNIGEL for fast relief from pain, sprain, and strain
3) SET WET hair styling gel
4) WILD STONE EDGE hair gel
5) Benzamycin , Erythromycin-Benzoyl Peroxide Topical Gel

1.3.4 OINTMENT

An ointment is generally a greasy thick oil having high viscosity. It is a homogeneous topical formulation. They are intentionally prepared for external use such as to the skin or mucous membrane. The maximum amount of water that ointment contains is represented by water number. They are used as moisturizing agent for the dry skin, as protective and therapeutic purpose. They are used on various body surface such as skin and mucous membrane of eye, ear, chest, anus etc.. The main constituent of ointment is ointment base which is used to run ointment. Ointment has low risk of irritation and sensitization.

There are two types of ointments: medicated and unmedicated. There is no drug present in non-medicated ointments. They are used as protectants. e.g. Petroleum jelly. [11]

The ointments which contain drugs show local or systemic effect and are known as medicated ointments. They are of sub- types:

1) Dermatologic ointments
2) Opthalmic ointments
3) Rectal ointments
4) Vaginal ointments
5) Nasal ointments

DERMATOLOGIC OINTMENTS

These types of ointments are applied to the surface of the affected area and spread with the help of fingers. The therapeutic agent in a formulation should penetrate in order to treat skin disorder. The penetration of therapeutic agent into the skin depends upon the various factors which are physicochemical properties, the skin condition and the nature of pharmaceutical vehicle These are of three types:

- **Epidermic:** These ointments are not absorbed by the skin and produce local effect when applied to the surface e.g Ketoconazole ointment
- **Endodermic:** These types of ointments partially absorbed by the skin when applied on the skin. They produce their action on the deeper layer of skin.
  e.g Demodex ointment
- **Diadermic:** These types of ointment absorbed by the skin and produce systemic effect. [12]
  e.g Nitroglycerine ointment

OPTHALMIC OINTMENT

This type of formulation intended to application to the eye or conjunctival sac. Due to the penetration of therapeutic agent, the surface of eye and underlying tissue is affected. Simple diffusion via the cornea is a process by which the therapeutic agent enters in the eye. These preparations are free from bacteria or other living organism and applied inside the lower eye lid. For this type of preparation anhydrous base is used. The base should be neither irritating nor contains any bacteria and must allow the diffusion process.e.g. sulfacetamide sodium ointment [13]

RECTAL OINTMENT

These formulations are prepared for the application to the perianal or in the anal canal. Formulation may be absorbed by diffusion into the general circulation . Systemic absorption of therapeutic level is achieved by rectal route of administration of certain drug. A small portion of the formulation is applied on the tissue and spread gently into a thin film. The bases used for preparation are wax, liquid paraffin, acetyl alcohol and white paraffin.e.g. Benzocainointment [13]

VAGINAL OINTMENT

These ointments are intended to application to the vulvo-vaginal area or inside the vagina. Vagina is likely to be harmed by infections, so the ointment should not contain moulds, microorganism etc. e.g. Candicidinointment [13]

NASAL OINTMENT

Nasal ointments are used in the treatment of nasal mucosa. Nasal route of administration primarily produces local effect on the mucous membrane. The absorption of the drug to the general circulation occurs via the high blood supply feeding the nasal lining. Nasal route is also used to achieve systemic absorption. e.g. Ipratropuim bromide ointment [13]

1.3.5 OINTMENT BASES

Ointment bases are the vehicle which carry the therapeutic agent and deliver into the skin. Ointment bases are classified into four types :

1) Absorption bases
2) Water removable bases
3) Oleaginous bases
4) Water soluble bases

Absorption Bases

- An oleaginous base that consists a W/O surfactant is known as Absorption base.
- They are insoluble in water and non-washable,
- Anhydrous but hydrophilic base, water is absorbed into the base to form W/O emulsion.
- Absorption bases are used as emollients, protectants and used as a path for aqueous solution and non-hydrolysable drug.
- e.g. Bees wax, Hydrous wool fat etc. [13]

Water Removal Bases

- They are speedly miscible with water as they contain an emulsifier.
- They are oil-in-water emulsion.
- They make easy contact between skin and medicament.
- They are also called water-washable bases as the easily washed from the skin.
- Water and aqueous solution may be used for dilution.
- e.g. Polybase, Vanishing cream etc.[13]

Oleaginous Bases

- They are non-washable, greasy, anhydrous base. They does not absorb water.
- They are also known as hydrocarbon bases.
- Without drying out, they provide prolong contact with the skin.
- They provide restriction to escape the moisture.
- They are used as vehicle for hydrolysable drug.
- e.g. white petrolatum, Paraffin etc. [13]

Water soluble Base

- They only contain water soluble constituents.
- They are easily washable by water, as they don't contain oleaginous components.
- For incorporation of solid substance, they are mostly used.
- e.g. PEG ointment [13]

SELECTION OF SUITABLE BASE

The selection of the base in the formulation depends upon the following factors:

1) Desired release rate of the therapeutic agent from the base.
2) Desirability of the protection against the escape of moisture.
3) Stability of therapeutic agent in the ointment base. [13]

1.3.6 EMULSION

Emulsion is a thermodynamically unstable two phase system consisting of at least two immiscible liquids, one of which is disperse in the form of small droplets throughout the other and emulsifying agent.

Emulsions are the mixture containing fats, oils, resins, or waxes reduced to a fine state of division and uniformly diffused in aqueous liquids. Subsequent aggregation of the oily particles being prevented by the intervention of viscous chemical substances termed as emulsifying agent.

These dosage forms have several advantages and disadvantages associated with them. The advantages being cost effectiveness, exhibiting improved bioavailability, providing sustained release in the form of multiple emulsions, source of nutritional supplement, providing topical delivery. The disadvantages of emulsion being short shelf life, handling and storage problem.

Depending on the nature of dispersed phase the emulsion can be classified as o/w and w/o. In o/w water forms the continuous or external phase or dispersion medium and oil is the dispersed phase or internal phase.

Benzyl benzoate emulsion, Vit. A in corn oil, liquid paraffin in water are the few marketed products which lies under this class. In w/o emulsion water is dispersed phase and oil is dispersion medium e.g., butter. [14,15]

EMULSIFYING AGENT

Emulsions by nature are physically unstable i.e., they tend to separate into two distinct phases or layers over time. They are stabilized by adding an emulsifier or emulsifying agent in proper quantities. Emulsifying agents have both a hydrophilic and a lipophilic part in their chemical structure and they act by three methods to stabilize the emulsion. The mechanism being reduction of interfacial tension, development of charge on the droplet surface and formation of protective barrier at the oil-water interface.

Emulsifying agents can be classified according to chemical structure and mechanism of action. According to chemical structure they are synthetic, natural, finely dispersed solids and auxiliary agents. According to mechanism of action they are mono-molecular, multi-molecular and solid particle films. Regardless of their classification, all emulsifying agents must be chemically stable in the system, inert and chemically non-reactive with other emulsion components and non-toxic and non-irritant. They should also be reasonably odorless and not cost prohibitive. [14,15]

1.4 ADVANTAGES OF TOPICAL FORMULATION

1) It is used for outer surface of skin.
2) Risk of side effect is lower.
3) First pass metabolism is avoided.
4) More stable than liquid dosage form.
5) Suitable dosage form for bitter drug.
6) Suitable for unconscious patient or patient which are not able to take by oral administration.
7) They provide prolong contact at the site of application.
8) Don't cause any irritation when applied to the skin.
9) They are the vehicle for drug constituents like anti-fungal, antibiotic etc.
10) Easy to handle and comfortable to spread on the skin surface.
11) Convenient for self medication.
12) Drug release selectivity to a particular site. [13]

1.5 DISADVANTAGES OF TOPICAL FORMULATION

1) No accuracy found in this type of dosage form.

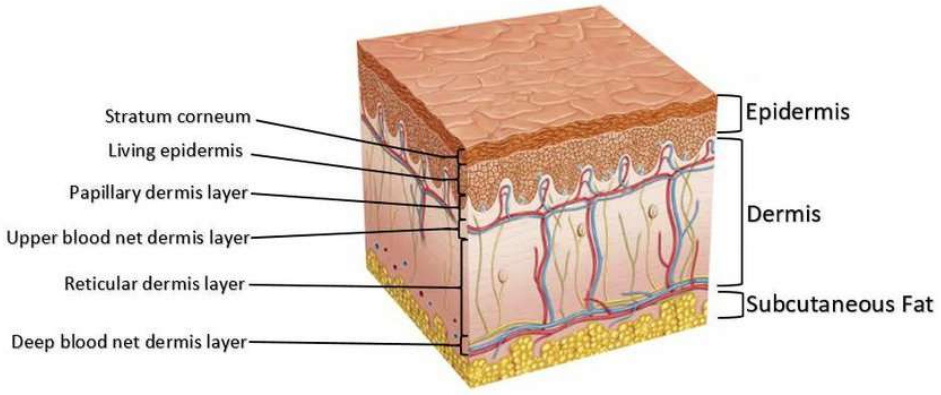
2) Base can be easily oxidized, which is present in formulation.
3) There is possibility of contamination.
4) To some patient, they may cause irritation.
5) They may cause staining.

1.6 SKIN PENETRATION

The skin is a complex organ which is restriction between the inner biological environment and outer environment. For the assistance in body temperature regulation, skin is designed. Without protection against the outside environment, the inner organism would be subject to outside temperature variation, solar radiation and a myriad of toxins. [16] The restriction function of skin, must be selectively overcome, in order to deliver essential component inside the skin cells.

The stratum corneum, outer layer of skin has layer of keratin which is difficult to penetrate. It is the major obstacle for topical absorption of drugs. The penetration of subcutaneous to different depth levels in the skin gives best result. There are four major entries into the skin pores. [17] These are:

a) Stratum corneum
b) Living epidermis
c) Viable dermis
d) Subcutaneus



1.7 PENETRTING ENHANCER

That substance which facilitates the absorption of penetrant through the skin by partially diminishing the impermeability of skin is known as penetrating enhancer. Ideally, they should be pharmacologically inert, non-irritating, non-toxic, non-allergenic, and compatible with the drug and excipients. It should be tasteless, odorless, colourless, and cheap and having good solvent properties. [18] The main function of penetrating enhancer is to reduce restriction of the stratum corneum. The desirable properties of penetrating enhancer are given as :

- ❖ Non-toxic, non-irritant and non-allergic
- ❖ Work rapidly and duration of effect should be predictable and reproducible.
- ❖ No pharmacological activity within the body
- ❖ Should work unidirectionally
- ❖ Cosmetically acceptable with good skin feel

Classification of penetrating enhancer

a) Chemical penetrating enchancer

- Sulphoxides and similar chemicals
- Azone
- Pyrrolidones
- Fatty acids
- Urea
- Oxazolidinones

b) Natural penetrating enhancer

- Linoleic acid
- Essential oil, terpenes and terpenoids
- Cod-liver-oil
- Glycerol derivatives
- Herbal ingredients

1.8 MENTHOL AS A PENETRATING ENHANCER

Terpenes are found in essential oils, and are compounds of only carbon, hydrogen and oxygen atoms, but which are not aromatic. Various terpenes have been used as flavoring agent as well as fragrance agent in many industries since years. [19] Menthol occurs widely in nature. It is derived from the species *mentha* and gives a mint family. Menthol acts as a transdermal delivery agent, it easily crosses the barrier of skin as it is highly soluble in lipids. It does not cause any irritation during enhancing absorption of desired substances. This is unique benefit of menthol. Menthol derivative as potential skin penetration enhancer studies showed that the permeation enhancing effect of 1-menthol is significant high with short lag time. [20]

1.9 INFLAMMATION

The complex biological response of vascular tissue to harmful stimuli like damaged cells, irritants or pathogens is known as inflammation. It is protective attempt shown by the organism to remove the harmful stimuli as well as starts the healing process for tissue. Inflammation caused by infection has two meaning: exogenous caused infection while inflammation is the response of the organism to the pathogen.

There are many allopathic anti-inflammatory drugs to combat inflammation. Non-steroidal anti-inflammatory is the most popular. Non-steroidal anti-inflammatory drugs are abbreviated as NSAIDs. Analgesic and antipyretic effects are shown by NSAIDs. In higher dosage, anti-inflammatory effects are also shown. Aspirin and ibuprofen are the most prominent member of this group of drugs. NSAIDs are most commonly use for various treatment but also has adverse effects. [21]

NSAIDs USES:

NSAID's are commonly used or the symptomatic relief of the following:

- Rheumatoid arthritis
- Osteoarthritis
- Acute goat
- Headache and migraine
- Renal colic
- Metastatic bone pair
- Fever
- Postoperative pain
- Mild to moderate pain due to inflammation and tissue injury

DISADVANTAGES:

The widespread use of NSAIDs has meant that adverse effect of these drug have become increasing prevalent. Gastrointestinal effect and renal effect are the two main adverse drugs reactions associated with NSAIDs. [21]

1) Combination risk
2) Cardiovascular effect
3) Gastrointestinal effect

   Common Gastrointestinal ADRs are

   - Nausea / Vomiting
   - Gastric ulceration
   - Gastric bleeding

4) Inflammatory bowel diseases
5) Renal effect

   Common Renal ADRs include

   - Salt and fluid retention
   - Hypertension (high blood pressure)
   - Acute renal failure

6) Adverse effect during pregnancy

LITERATURE REVIEW

2.1 INTRODUCTION

A medicinal tree namely *Diploknemabutyracea* (Chyuri) is known for its medicinal properties and also the origin of many helpful things. This tree is mostly used in Nepal. The use of Medicinal plant and Tradition Medicine has been studied in many developing countries. At a height of 300-1500 m, it is distributed throughout the Himalayan belt including Nepal, India and Bhutan. Chyuri is economically beneficial but unknown and underutilized. All parts of this tree have good economic value and are usable. The main product of this tree is Chyuri Ghee. It is a multipurpose tree, which provide food, medicine and plenty products for local people. In Uttarakhand, the population of this species is located especially in the border area of Pithoragarh District. [22]

Diploknemabutyracea is a medicinal curative tree, mostly found in Nepal, in India it is placed in Pithoragarh district of Uttarakhand, especially areas bordering. The tree reachs a peak of 15-20m and width 1.8m, the fruits are berry type containing 1-3 seed. It is used as multi-functional tree, such as supply food, medicine and much useful stuff for local people. [22] It provides many useful substances like oil, honey, gur, fooder for

animals, fuel and timber, being a good source of income. It is frequently cultivated , mainly for the Ghee obtained from the seed. The butter extracted from the seed is known as “Chyuri Ghee” or “Phulwara Butter” is the most used product from the tree. The chyuri ghee is used for many purpose such as for making soap, candles, and cure many diseases like headache, ulcers, itching, rheumatic pains, etc.*Diploknemabutyracea* is also known as by Bassia Butyracea (Roxb.) ,MadhucaButyracea (Roxb.) , and commonly known as Chyuri or Indian Butter Tree. In Western Himalayan, it has profitable importance to various cultural groups. The main constituents of butter are Triglycerides and Fatty acids. [22]

2.2 TAXONOMIC CLASSIFICATION

Kingdom : Plantae
Order : Ericales
Class : Dicotyledon
Family : Sapotaceae
Subfamily : Sapotoideae
Genus : Diploknema
Species : D. Butyracea
Division : Phanorogerms
Subdivision : Angiosperms

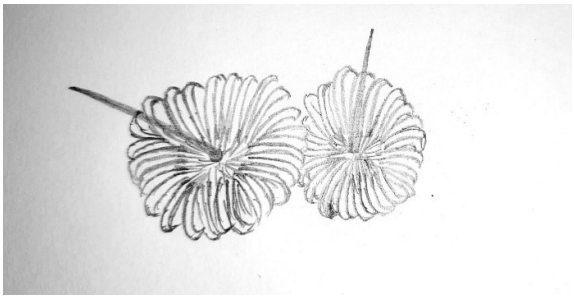
2.3 VERNACULAR NAME

Countries	Synonyms
English	Indian Butter Nut
India	Pulwara
Nepal	Chiuri
China	Zang Lan

2.4 BOTANICAL DESCRIPTION

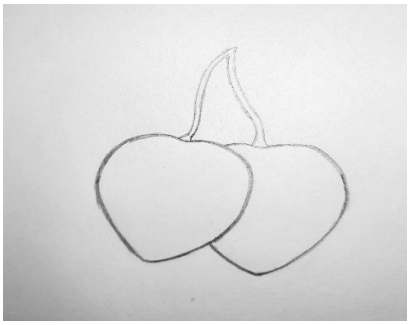
FLOWER:

Flowers are generally come out in bunches below the leaves. The floret is of creamy white in color and have a sweet smell. The flower has a diameter about 2.6cm and 2.3cm long. 2-4.5cm to 5cm of pedical are in the fruit and covered with short soft hair. 4-6 sepals of ovate shape are present in flower. There are 20-40 stamens.



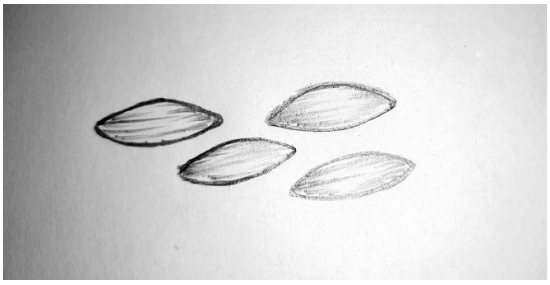
FRUIT:

Berry type fruit looks at the tree, which are ovoid-globose to oblong shaped, 2-2.5×1-1.5cm, having pointed tip and carry 1-5 seed. Mesocarp is fleshy, green and shining. The ripen fruit are yellow in color.



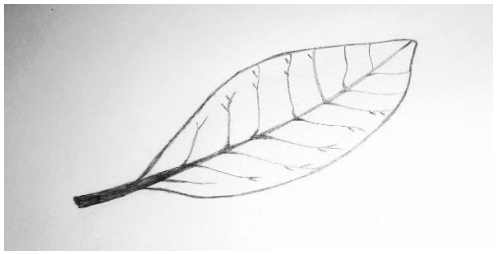
SEED:

Seed of the fruit is brown in color and oblong in shaped. Completely dried seeds are shiny grey in color. The seed have dimension ca. 1.3×1×0.6cm, smooth, shiny scar lanceoate.



LEAVES:

Leaves are elliptic-oblong ovate or ovate oblong in shape, 17-35×8-17cm, leathery, yellowish-brown to brown velvety, base wedge -shaped up, tip blunt. Near ends of the branches, leaves are crowded, tapering to stalk rounded at the apex with prominent veins.



2.5 PHYTO-PHARMACOLOGICAL DESCRIPTION

FLOWER

The phyto-chemicals present in flower are Quercentin 3-O-rhamnoside fig.1(a). Myricetin 3-O-rhamnoside fig.1(b) [23]

FRUIT

The fruit contains phyto-chemicals which are α- spinasterol fig.1(c), β-d-glucoside of β-sitosterol fig.1(d), acetates of α and β amyrins fig.1(e)(f), 3 β-Palmitoxy-olea-12en-28ol, oleanolic acid palmitate. [24]

LEAVES

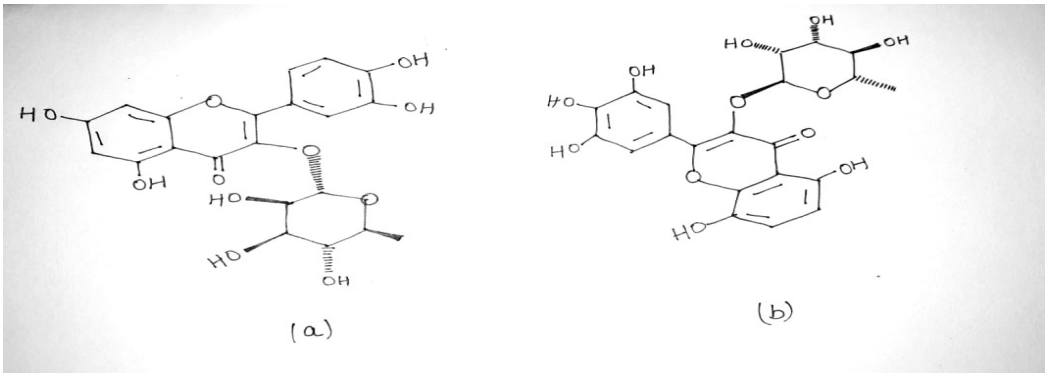
Phyto-chemicals present in leaves are butyracic acid, myricetin-3-O-rhamnoside fig.(b).

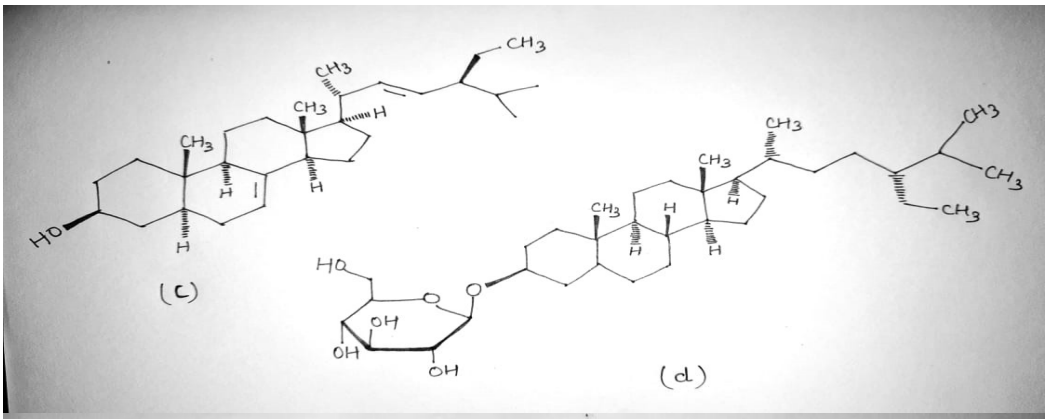
BARK

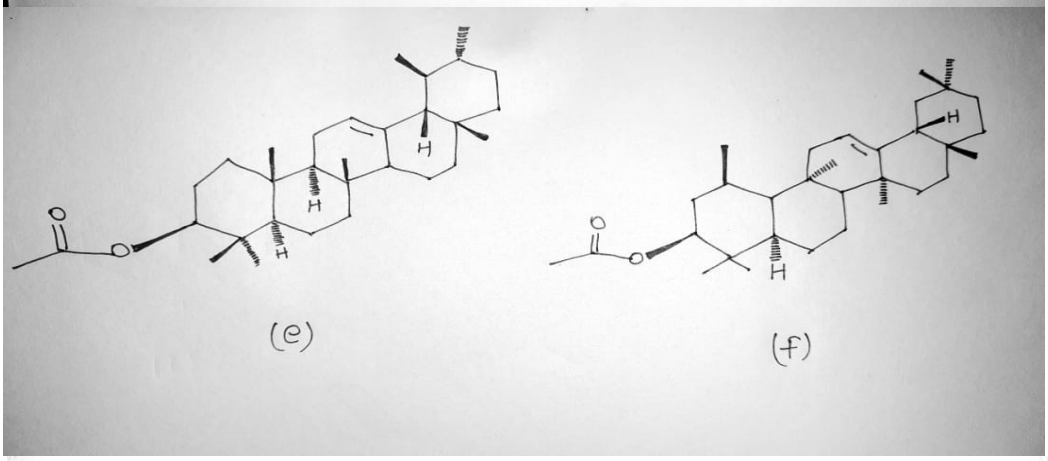
The phyto-chemicals which are present in bark are α- spinasterol fig1.(c), β-d-glucoside of β-sitosterol fig.1(d), acetates of α and β amyrins fig.1(e)(f), 3 β-Palmitoxy-olea-12en-28ol, Betulinic acid palmitate fig.1(g), Friedelin fig.1(h).[23]

SEED

Triterpenoids saponin namely butyrosides A, B fig.1(i), Cfig.1.(j) and D are present in seed. 3-O-Mi- β-D-Glucoside, Mi saponin A, andArganine C (16 α- hydroxy Mi- saponin A) are also present in seed. The nut shell contains flavonoids are Quercetin fig.1 (k) and Dihyro-quercetin . [24,25, 26]




(c)
(d)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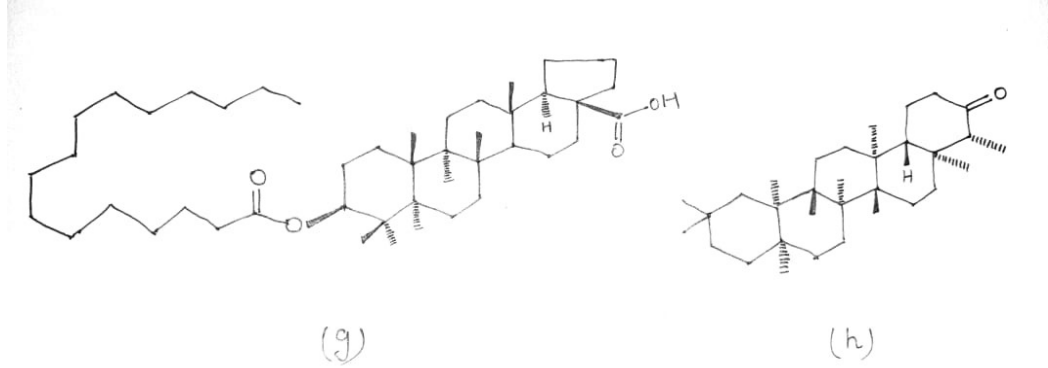
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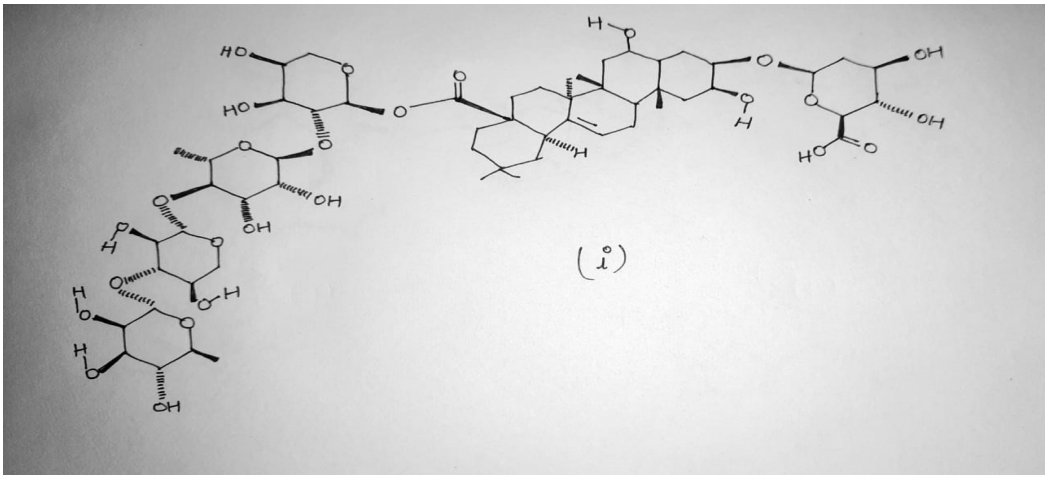
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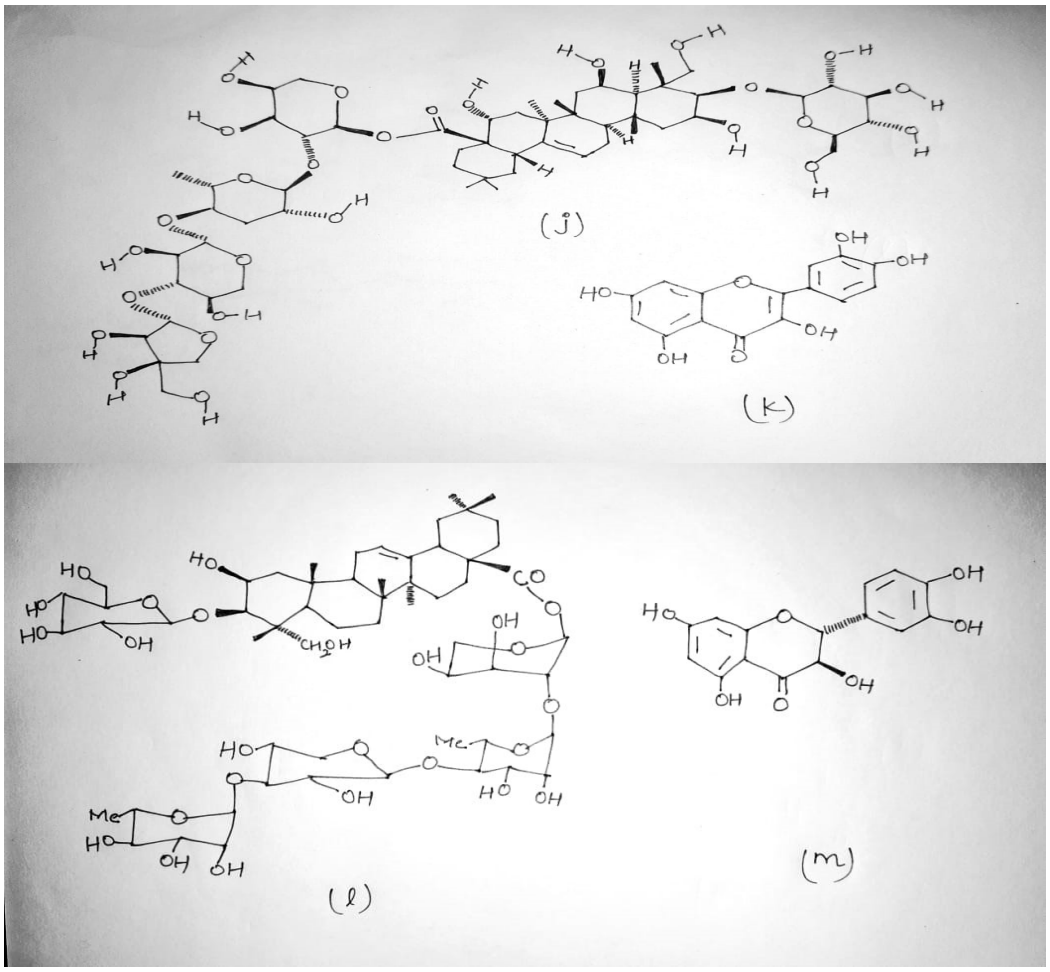


Figure 1 : Structure of Phyto-chemicals.

2.6 SOCIOECONOMIC DESCRIPTION

Diploknemabutyracea (Chyuri) is believed to be socioeconomically more beneficial tree for the local people as it has many productive uses. The fruits are ripen in the month of July-August. The berry type fruit, looks at the tree contain three seeds. The fruit pericarp have thick and squashy pulp which is reported as sweet in taste and sold in the local market in the form of gur at profitable cost. The rest of the product is used for feeding the animals. The leaves of chyuri are grown during summer season and are clumped at the tip of the branchlets. The cattles preferred good to have these leaves being a good source of animal fodder. Plates (Dona/Thali) are also manufactured by the leaves of chyuri. [22] The chyuri tree has excellent blossom during October-November onwards. The chyuri has colored floret and plentiful in sugar and preferred as good for pollinators such as bees etc., for foraging. The honey bees produced honey after foraging is known as chyuri honey as an income source for local people by selling it in local market at good price. The nector of flower is used for making jaggery which is too expensive in Uttarakhand. [22,28] Earlier, the bark of chyuri was used for dyeing as it contains tannins. The need of fuel and timber is managed by the wood of chyuri.

AIM AND OBJECTIVE

3.1 AIM

Preparation of suitable Topical dosage Forms using plant butter extracted from *Diploknemabutyracea.*

3.2 OBJECTIVE

To achieve the above aim of the research project have been divided into following objectives

a) Collection and verification of raw plant material.
b) Extraction of Butter from Plant seeds.
c) Preparation of different topical formulation using plant butter.
d) Evaluation of formulation for

- Homogeneity
- Spreadability
- pH
- Drug release
- Clarity
- Density

4.1 DRUG PROFILE

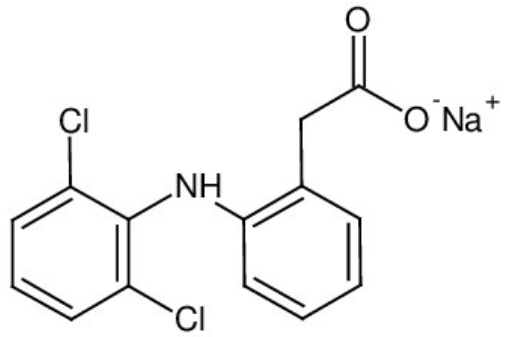
Diclofenac sodium: Non-steroidal anti-inflammatory drug

IUPAC Name: sodium [2-(2,6-Dichloroanilino)phenyl]acetate

Molecular formula: $C_{14}H_{10}Cl_2NNaO_2$

Molecular weight: 318.13gm

Structure:



Melting point: 284.0℃

Solubility: soluble in methanol, ethanol, DMSO
Poor soluble in water

Onset of action: within 4 hour (gel), 30 min. (orally)

Excretion: 60% from urine, 40% from bile duct

Plasma Protein binding: 99%

Therapeutic use: Analgesic, antipyretic and anti-inflammatory agent

4.2 DICLOFENAC SODIUM

Diclofenac sodium is a Non-steroidal anti-inflammatory drug. It is fully absorbed by Gastrointestinal tract. Diclofenac sodium undergoes first pass metabolism when taken orally. Diclofenac shows both analgesic and antipyretic activity. About 1.5 to 2.0 hour, peak plasma concentration occurs after injecting in fasting subjects. Half life in plasma of diclofenac is short, which is about 1.5 hour. The excretion of diclofenac from the body is done by urinary and biliary excretion. In topical absorption of drug like rectal, percutaneous absorption in the form of gel or transdermal system, first pass metabolism is avoided. It can be used topically for the various treatments such as post operative ocular inflammation in cataract extraction. In the management of antipyretic effect (fever), diclofenac sodium has been used orally. [29] In reducing pain and improving function, clinical trials shows that diclofenac is same effective as other NSAIDs like aspirin, ibuprofen, ketoprofen, indomethacin etc. Diclofenac sodium can be administered in various dosage form like orally, rectally or intramuscularly. In acute or chronic pain, inflammation condition, diclofenac could be considered as first NSAIDs choice. [30] Diclofenac sodium inhibits the synthesis of prostaglandins, which gives relief from inflammation. Diclofenac shows good therapeutic index in animals. In comparison to other NSAIDs like aspirin, feprazone, indomethacin and naproxen, diclofenac cause less gastrointestinal damage and is well tolerated.

After 10-30 minutes, peak plasma concentration is attained, when drug is administered intramuscularly.

According to some authorities, the dose of diclofenac should not exceed 100mg daily. Conventional dose for children is 2-3 mg/kg/day. In order to urgent relief of acute pain, 75mg of diclofenac can be administered intramuscularly. Absorption of diclofenac is delayed by antacids but total extent of absorption does not change. [31]

SIDE EFFECT

Diclofenac sodium has come common side effects, few of them are:

- Headache
- Nausea
- Gastrointestinal bleeding
- Dizziness
- Heart disease
- Stroke
- Kidney problem
- Stomach ulceration/bleeding

METHODOLOGY

Experimental work has been conducted as follows:

5.1 MATERIALS:

5.1.1 Chemicals:

Analytical and laboratory grade chemicals were used for the studies which are as follows:

Petroleum ether	LOBA CHEMIE PVT. LTD.
Tween 80	Ranbaxy Fine chemicals Ltd., Faridabad, Hariyana
Ethanol	LR Grade
Menthol	LR Grade
Diclofenac sodium	Yarrow Chem Products Mumbai-400037
pH 7.0 Buffer tablet	Ranbaxy Fine chemicals Ltd., Faridabad, Hariyana
pH 4.0 Buffer tablet	Ranbaxy Fine chemicals Ltd., Faridabad, Hariyana
Distilled water	

5.1.2 Equipment/Glassware:

Soxhlet Assembly	Borosil
Heating Mantle	Perfit India
Magnetic Stirrer	Perfit India
pH meter	Systronics
Water bath	Narang Scientific Works Pvt. Ltd. New Delhi
UV spectrophotometer	Systronics 2101, Delhi

SpreadabilityAppartus	Brookfield TA-SF Spreadability: SKU: V069.TA-SF
Franz diffusion Apparatus	Borosil

5.2 METHODS:

The experimental work carried out in the following sequences

1. Extraction of *Diploknemabutyracea* plant butter
2. Preparation of Diclofenac sodium emulsion
3. Evaluation of formulations

5.2.1 EXTRACTION PROCESS OF *Diploknemabutyracea* PLANTBUTTER

a) SELECTION AND COLLECTION OF PLANT MATERIAL:

It is an important to select and the collect the effective plant material for the isolation of active phyto-constituent. For the plant extraction only healthy and diseases free plant is selected.

b) DRYING OF PLANT MATERIAL:

The active constituent of plant material is produced by active enzymes which is present in fresh plant material. Therefore the drying process has an importance in extraction process.

c) SIZE REDUCTION:

The reduction of size of the plant material is very important in extraction process. Small size particles have high efficiency towards extraction process. Size of plant material is reduced by the hammer mill, grind machine etc.

d) SELECTION OF SUITABLE SOLVENT:

The solvent is selected on the bases of pyto-constituent extraction process. The solvent should be cheap, inert, and easily available. It can be remove easily. Petroleum ether is most commonly used solvent in many extraction process. [32]

e) EXTRACTION PROCESS:

The extraction process is done by soxhlet extractor. It is also known as hot continuous extraction method, and used to extract compounds from solid materials. It is used to determine the crude fat content. Fat is

generally found in the seed and fruit of most plants. This extractor is invented by Franz von Soxhlet in 1879. This method traditionally been used for solid sample. This method requires minimum amount of solvent in complete extraction process. It is a laboratory apparatus. Soxhlet apparatus consist of a round bottom flask, siphon tube, condenser, heat source and thimble. In this method, sample is powdered and enclosed in a thimble. Then thimble is fixed in thimble chamber. The solvent is filled in round bottom flask. Assembled all the setting on a heating mantle. The solvent is heated until it starts boiling. The heat source is adjusted so that the solvent drops from the condenser into the sample chamber. This process is continued for almost 6 hours. In this method the solvent is recycled again and again. [32]

Figure 2.1

5.2.2 PREPARATION OF DICLOFENAC SODIUM EMULSION (o/w)

5.2.2.1 PRE-FORMULATION STUDIES

Pre-formulation involves the application of bio-pharamaceutical principle to the pysicochemical parameters of a drug with the goal of designing an optimum drug delivery system. The various parameters essential for this formulation are as follows:

a) COLOUR:

The colour is an important property as selection of final colour and flavor of the formulation depends on the inherent colour of the drug.

b) pH:

pH is an important fundamental test for pre - formulation drug characterization. The stability of the drug is governed by pH and is important consideration in designing a formulation.

c) MELTING POINT:

Melting point is an important test for pre-formulation drug characterization. It is an important consideration in designing a gel formulation. [30]

d) DRUG EXCIPIENT COMPATIBILITY STUDIES:

Excipients are the components of a finished drug product other than the active therapeutic agent and added during formulation for a specific purpose. In contrast to active therapeutic agent, minor component of an excipient may have significant impact on the pharmaceutical performance thus it worth effective to say that the resultant biological, chemical and physical properties of the drug product are directly affected by the excipient chosen, their concentration and interaction with active therapeutic agent. In topical formulation, the possible type of excipients are:

- Vehicle:

  The dispersion medium which is preferable in a topical dose for dispersion of the drug is known as vehicle.

- Preservatives:

  These are the organic substances that prevent an increased risk of contamination by opportunistic microbial pathogen. It is important that preservative used in a formulation should have broad spectrum of activity because of wide range of the likely contaminants both bacterial and fungal, the impossibility of predicting the kind of contamination that they occur during the life of product.

- Penetration Enhancer:

  Penetration enhancer increases the penetration of drug into the skin. It enhances the diffusion rate

into the skin and allows the drug particles to enter the skin. An ideal penetration enhancer should be chemically stable and inert, non-toxic, non-irritant and non-allergic. It should be cheap, colourless, tasteless, and odorless.

- Emulsifying agent:

  Emulsifying agents have both a hydrophilic and a lipophilic part in their chemical structure and they act by three methods to stabilize the emulsion. The mechanism being reduction of interfacial tension, development of charge on the droplet surface and formation of protective barrier at the oil-water interface. emulsifying agents must be chemically stable in the system, inert and chemically non-reactive with other emulsion components and non-toxic and non-irritant.

5.2.2.2 SELECTION OF PENETRATING ENHACER:

Penetration enhancer increases the penetration of drug into the skin. It enhances the diffusion rate into the skin and allows the drug particles to enterthe skin. Menthol widely occurs in nature, derived from the species *mentha*. Menthol acts as a penetrating enhancer. Menthol functions as a transdermal delivery agent. It is highly lipid soluble and therefore crosses the skin barrier. It has been proven to assist the movement of many molecules, including medicines, from the surface of stratum corneum to the internal layer of the skin. Menthol has a unique benefit that it enhances absorption of desirable molecule without irritating the skin.

5.2.2.3 METHOD

- Weigh 1.5 gm of diclofenac sodium accurately and dissolved in minimum amount of ethanol in a beaker.
- Then 2.5ml of tween 80 is dissolved in sufficient amount of distilled water and pour the all the content in drug solution with constant stirring. This is the aqueous phase or dispersion medium.
- In another beaker 15ml of plant butter is taken and add 0.5ml menthol (penetrating enhancer) is added. This is the oily phase or dispersed phase.
- Now both aqueous phase and oily phase is heated at 50℃ for few minutes, then the oily phase is added slowly into the aqueous phase with constant stirring using magnetic stirrer (fig.2) and makeup the emulsion up to 50ml using distilled water.

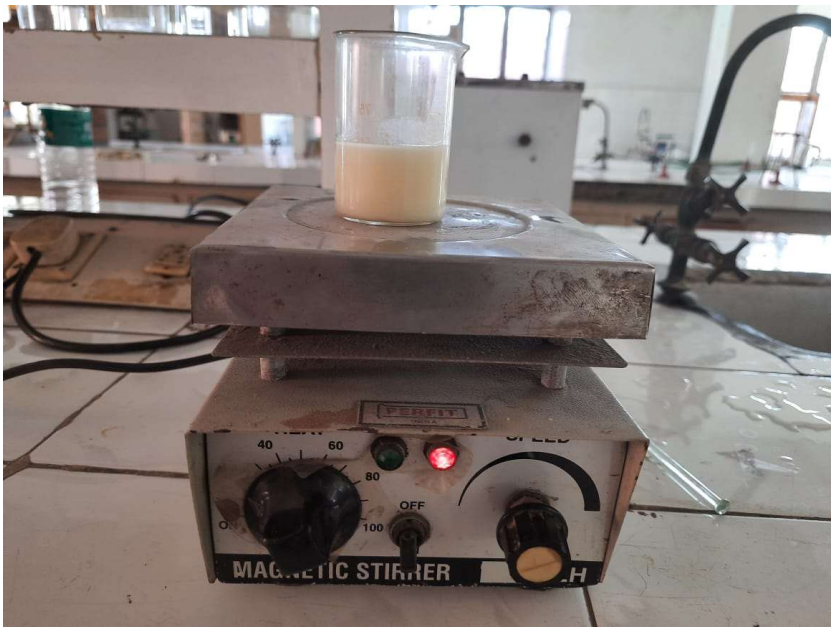


Figure.2.2

5.2.3 EVALUATION TEST

a) HOMOGENEITY:

By visual inspection all formulations are tested for homogeneity. The formulation is set in the container and they are tested for their appearance and formation of aggregates. [33, 34]

b) SPREADABILITY:

Spreadability is defined as the ability of formulation to evenly spread on the skin.. The spreadability value shows the extent at which the formulation is spread on the site of application. The spreadability is measured by the glass slide apparatus. For determination, in between two slides excess of formulation is applied and then compressed by a uniform thickness. The time taken in the separation of two slides is taken as a measure of spreadability. [33, 34, 35, 36]

It is calculated by formulation

$$S = M.L/T$$

Where,

M = weight tied to upper slide
L = length of glass slide
T = time taken to separate slide

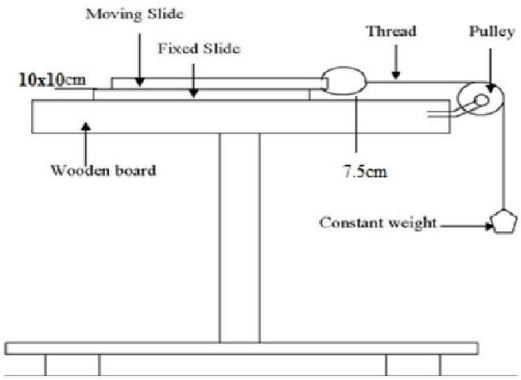


Figure : 2.3

c) pH:

pH is a major determinant of the stability, solubility and other pharmaceutical qualification of drug. Hydrolysis of most drugs depends on the relative concentration of the hydroxyl or hydrogen ions, and the pH at which the drug is optimally stable is therefore important to determine. Limited amount of water of aqueous phase present in topical formulation. The pH of thick formulation can be measured by diluting the formulation with distilled water. Weigh 3.0 gm of formulation and dispersed in 30ml of distilled water. The pH is determined by the digital pH meter. [33, 34]

Figure. 2.4

d) DRUG RELEASE TEST:

Drug release test is important to know the efficacy and quality of nanoparticle based drug delivery system. Franz diffusion cell apparatus was used for the determination of drug release from the formulation (emulsion), where 50ml of dissolution medium was used of pH 6.8 at s37°C. Magnetic stirrer was set at 100 rpm. At a regular time interval , sample (3ml) was withdrawn and filtered by filter paper and same amount of dissolution medium was added. With the help of UV spectrophotometer, drug content in sample was determined.

$$\text{Amt. of drug release mg/ml} = \frac{\text{concentration} \times \text{Dissolution bath vol.} \times \text{dilute factor}}{1000}$$

Figure: 2.5

e) CLARITY:

By visual inspection, the clarity of formulation is determined under white and black background. [33, 34]

f) DENSITY:

Density is defined as mass per unit volume.

Density= mass/volume

RESULTS AND DISCUSSION

The prepared formulation was stable, containing butter as oily phase and menthol as penetrating enhancer showed best result. The evaluation test result showed that the plant butter can be used as base in topical formulation and menthol showed good result as penetrating enhancer. The plant butter extracted from *Diploknemabutyracea* has some basic property; it can provide body to any topical formulation. we have done various tests for the evaluation of formulation which are as follows:

Colour: The colour of the formulation was creamy white.

pH: pH is a major determinant of the stability, solubility and other pharmaceutical qualification of drug. The pH was determined by the digital pH meter. The pH of the formulation was found to be 6.86 i.e., the formulation was slightly acidic in nature.

Spreadability: Spreadability is defined as the ability of formulation to evenly spread on the skin. The spreadability value shows the extent at which the formulation is spread on the site of application. The spreadability was measured by the glass slide apparatus. The spreadability of formulation was found to be 3.04 gcm/sec.

Homogenity: By visual inspection homogeneity was tested. The formulation was set in the container and there were no aggregates formed i.e., homogeneity of formulation was good.

Density: The density of formulation was found to be 1.108 g/ml.

Drug release: Drug release test is important to know the efficacy and quality of the formulation. It was done by Franz diffusion cell apparatus. The maximum percentage drug release was found to be 0.86%.

CONCLUSION

The present study showed that the prepared formulation was stable. The formulation contains plant butter as an oily phase and menthol as penetrating enhancer. The prepared formulation is having pH 6.86, i.e.,

slightly acidic. The drug release percentage was found to be 0.86%. It showed that the plant butter extracted from *Diploknemabutyracea* does not bind drug, it can release drug to the skin, having good base property. It can replace synthetic base such as paraffin etc. in topical formulations including creams, ointments, emulsions. The formulation with menthol penetrating enhancer showed best result. The butter extracted from *Diploknemabutyracea* has its own importance in local people. It provides many useful substances like it can be used as cooking oil, for making soaps, candles, and to cure many diseases like headache, ulcers, itching, rheumatic pains etc. But present study showed that it can also be used in topical dosage formulation, as it has good base property and is inexpensive.

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