JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

Mathan thailam (a siddha product) Emugel formulation for the treatment of effective diabetic wound healing

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1. INTRODUCTION

1.1 TRADITIONAL SYSTEM OF MEDICINE

Indigenous medicine, commonly referred to as "Traditional Medicine," is a body of knowledge about healing that is practised in a certain location, community, or country. Indigenous medicine is noted for taking a comprehensive approach to ment*al.*,physic*al.*, and spiritual health.(1)

The traditional system of medicine are:

Ayurveda
Siddha
Unani
Homeopathy

1.1.1 Ayurveda:

Ayurveda is a traditional medical system that dates back to the Vedas, which were written roughly 5000 years ago and is now acknowledged and practised in India and many other nations in the Indian subcontinent. It is one of the first healthcare systems to take a holistic approach to human life, health, and disease by considering the physic*al.*,ment*al.*, spiritu*al.*, and social components of human life, health, and disease.

According to Ayurveda, good health is a prerequisite for fulfilling the four life goals of Dharma (obligations), Arth (money), Kama (materialistic desires), and Moksha (liberation) (salvation). All objects and living organisms,

according to Ayurveda's fundamental principles, are made up of five basic components known as the PanchaMahabhootas: Prithvi (earth), Jal (water), Agni (fire), Vayu (air), and Akash (fire) (ether).

The Ayurvedic philosophy is founded on the basic relationship between the universe and man. Ayurveda follows the humeral theory of Tridosha, which consists of three physiological entities in living beings: Vata (ether + air), Pitta (fire), and Kapha (earth + water), which are responsible for all metabolic operations.(2)

1.1.2 Siddha:

The Siddha System is one of India's oldest traditional medical systems. The original founders of this scientific method are the Siddhars, Tamil Land's spiritual scientists. The human body, like food and extracts, is a reproduction of the Universe, according to the Siddha System, regardless of their origin. According to the Siddha System, all items in the Universe, including the human body, are made up of five primal elements: earth, water, fire, air, and space.

The elements of Human Being, according to Siddhars, are 96 Principles. They include a person's physic*al.*,physiologic*al.*, ment*al.*, and intellectual aspects. They are nothing more than a manifestation of the "five fundamental ingredients."

In Siddha Medicine, the following therapeutic method has been used. They use herbal treatments such as surname, Kudineer, Vadagam, and others. Incision, excision, heat application, bloodletting, and leach application, among other surgical methods Physiotherapy- Thokkananm and Varma, the Siddha method of Touch therapy, medicated oil application, fomentation, herbal steam bath, and so on. Using medications such as parpam, chenduram, chuxnam, and others to increase mineral absorption, particularly of metals.(3)

1.1.3 Unani:

The origins of unani medicine can be traced back to Greece. Hippocrates, the famous physician and philosopher, is thought to have founded it (460-377 BC). Galen (130-201 AD) helped to enhance its development. The foundations of anatomy and physiology were laid by Aristotle (384-322 BC). Dioscorides, a famous physician from the first century AD, made substantial contributions to the development of pharmacology, particularly plant extracts. Under the sponsorship of Islamic rulers in numerous Arabian countries, Arabian academics and physicians have played a significant part in the development of this system.

The body, according to Unani's basic principles, is made up of four main elements: Earth, Air, Water, and Fire, all of which have varied Temperaments, such as cold, hot, wet, and dry. They give birth to new beings by mixing and interacting. Organs, both simple and complex, make up the human body. Blood, phlegm, black bile, and yellow bile are the four humours that provide them with nutrition.(4)

1.1.4 Homeopathy:

Physicians have known since Hippocrates' time (about 400 B.C.) that certain chemicals might cause disease symptoms in healthy people that are similar to those seen in sick patients. A German physician, Dr. Christian Friedrich Samuel Hahnemann, studied the phenomenon scientifically and established the core principles of homoeopathy. Homoeopathy was introduced to India by European missionaries about 1810 A.D., and it was given official recognition by the Constituent Assembly in 1948, followed by the Parliament.

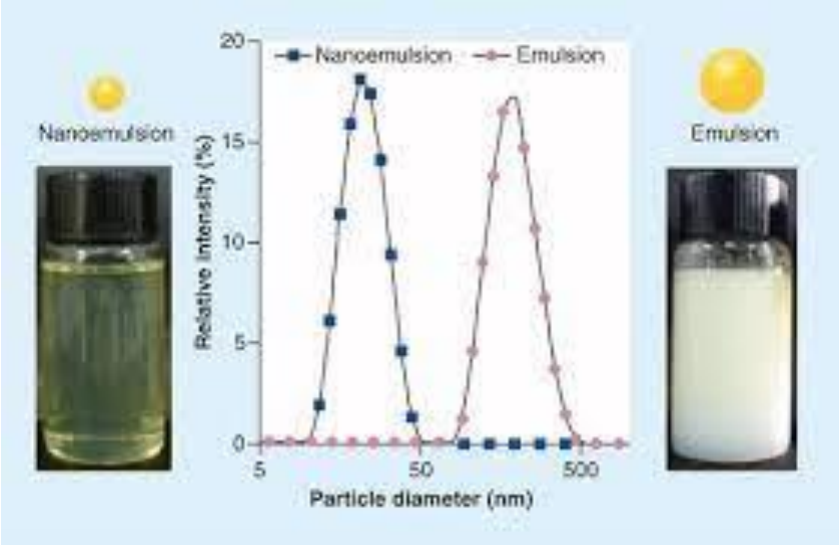
SimilibusCurentur' means that a treatment that can cause a set of symptoms in healthy people can also cure a comparable set of symptoms in people who are sick. The second concept of 'Single Medicine' is that during therapy, just one medicine should be given to a single patient at a time. The third principle of 'Minimal Dose' suggests that the bare minimum dose of an Extract required to generate acurative action without causing any side effects should be used. (5)

1.2 Nano-emulsions

1.2.1. Introduction:

Emulsions with droplet size in the nanometric scale (typically in the range 20–200 nm) are often referred to in the literature as miniemulsions , nano-emulsions , ultrafine emulsions , submicron emulsions , etc. The term nano-emulsion is preferred because in addition to give an idea of the nanoscale size range of the droplets it is concise and it avoids misinterpretation with the term microemulsion (which are thermodynamically stable systems).

Due to their characteristic size, nano-emulsions appear transparent or translucent to the naked eye and possess stability against sedimentation or creaming. These properties make nano-emulsions of interest for fundamental studies and for practical applications (e.g. chemical, pharma pharmaceutical, cosmetic, etc. fields). Oil-in-water (O/W) type nanoemulsions have been investigated since long ago, and have been reviewed thoroughly, specially as nanoreactors for polymerization. In contrast, water in- oil (W/O) nano-emulsions have been described for the first time recently. Both types of nano-emulsions are experiencing a very active development as reflected by the numerous publications and patents. In this review, the attention is mainly focused to nano-emulsion formation, with special emphasis on low-energy emulsification methods. Some recent contributions on nano-emulsion properties and applications are also discussed.(6)



1.2.2 Nano-emulsion formation:

Components of nanoemulsion formulation:

Oils	Emulsifiers
Castor oil, coconut oil, cotton seed oil, fish oil,olive oil, peanut oil ,PEG-vegetable oil,seaseme oil, soybean oil, sunflower oil, wheatgerm oil,jojoba oil.	natural lecithins from plant and animal sources, PEG-phospolipids,poloxamers, polysorbates, polyoxyethylene castor oil derivate
	Additives: Antioxidants,Tonicity modifiers,pH adjustment Agents,preservatives

1.2.3 Significance of smaller droplet size

small droplet size

|

Rapid drug release

|

Increase bioavaiability

|

Reduction in dose

|

Better profile for drug absorption

|

Protection of drugs from the hostile environment of the body

1.2.4 TECHNIQUES OF PREPARTION:

a) High pressure homogenization
b) Micro fluidization
c) Phase inversion technique

a)High pressure homogenization:

This technique makes use of high pressure homogenizer/piston homogenizer to produce NEs of extremlylow particle size(up to 1nm).

b)Microfluidization:

It uses high pressure positive displacement pump of (500-20000)psi ,which forces the product through the interaction chamber, which consist of small chamber called “microchannels”.

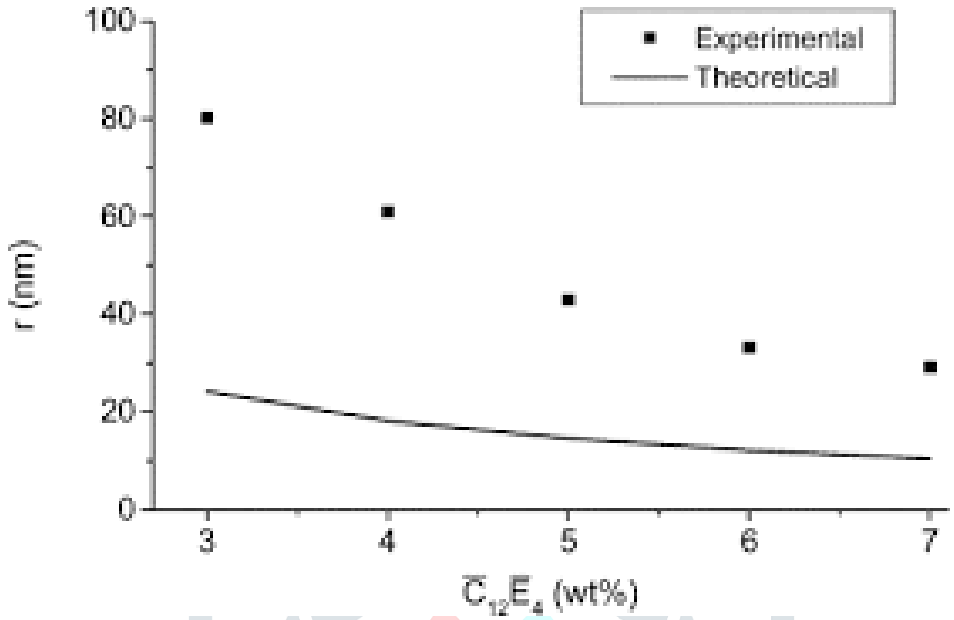
The product flow through the microchannels on to an impingement area resulting in very fine particles of submicron range .the two solution(aq.phase and oily phase) are combined together and processed to obtain a stable nanoemulsion.

c) Phase inversion method:

The temperature range in which an o/w microemulsion inverts to a w/o type or vice versa.

Nano-emulsions, being non-equilibrium systems, cannot be formed spontaneously. Consequently, energy input, generally from mechanical devices or from the chemical potential of the components, is required. Nano-emulsion formation by the so-called dispersion or high-energy emulsification methods is generally achieved using

highshear stirring, high-pressure homogenizers and ultrasound generators. It has been shown that the apparatus supplying the available energy in the shortest time and having the most homogeneous flow produces the smallest sizes. High-pressure homogenizers meet these requirements.Ultrasonic emulsification is also very efficient in reducing droplet size but it is only appropriate for small batches. (6,7)



1.2.5 Stability:

The small droplet size of nano-emulsions confers stability against sedimentation (or creaming) because the Brownian motion and consequently the diffusion rate are higher than the sedimentation (or creaming) rate induced by the gravity force. Ostwald ripening or molecular diffusion, which arises from emulsion polydispersity and the difference in solubility between small and large droplets, is the main mechanism for nano-emulsion destabilization. The Lifshitz–Slezov and Wagner (LSW) theory predicts a linear relationship between the cube of the radius, r3, and time, t, with the slope being the Ostwald ripening rate. The LSW theory assumes that the droplets of the dispersed phase are spherical, the distance between them is higher than the droplet diameter and the kinetics is controlled by molecular diffusion of the dispersed phase in the continuous phase.(8)

According to this theory, the Ostwald ripening rate in O/W emulsions is directly proportional to the solubility of the oil in the aqueous phase. In fact, Taylor has suggested that Ostwald ripening might be used as a tool to estimate the thermodynamics of solution of oils in water. Izquierdo et al. obtained experimental Ostwald ripening rate values higher than the theoretical calculated according to the LSW theory. The discrepancy was attributed to factors not taken into account in this theory such as oil transport due to the presence of micelles and/or microemulsion droplets in the aqueous phase, increase in droplet Brownian motion and lowering of the interfacial Gibbs elasticity. It has been recently reported that, for an ethoxylated nonionic surfactant system, the Ostwald ripening rate can also be decreased by adding a second surfactant with the same alkyl chain length and higher degree of ethoxylation than the primary surfactant .

1.3 DIABETIC FOOT ULCER:

1.3.1 Abstract

Diabetic foot is a serious complication of diabetes which aggravates the patient's condition whilst also having significant socioeconomic impact. The aim of the present review is to summarize the causes and pathogenetic mechanisms leading to diabetic foot, and to focus on the management of this important health issue. Increasing physicians' awareness and hence their ability to identify the "foot at risk," along with proper foot care, may prevent diabetic foot ulceration and thus reduce the risk of amputation.

1.3.2 Introduction

Diabetic foot is one of the most significant and devastating complications of diabetes, and is defined as a foot affected by ulceration that is associated with neuropathy and/or peripheral arterial disease of the lower limb in a patient with diabetes. The prevalence of diabetic foot ulceration in the diabetic population is 4–10%; the condition is more frequent in older patients .It is estimated that about 5% of all patients with diabetes present with a history of foot ulceration, while the lifetime risk of diabetic patients developing this complication is 15% .

The majority (60–80%) of foot ulcers will heal, while 10–15% of them will remain active, and 5–24% of them will finally lead to limb amputation within a period of 6–18 months after the first evaluation. Neuropathic wounds are more likely to heal over a period of 20 weeks, while neuroischemic ulcers take longer and will more often lead to limb amputation. It has been found that 40–70% of all nontraumatic amputations of the lower limbs occur in patients with diabetes. Furthermore, many studies have reported that foot ulcers precede approximately 85% of all amputations performed in diabetic patients .(9)

1.3.3 Pathogenesis

The most significant risk factors for foot ulceration are diabetic neuropathy, peripheral arterial disease, and consequent traumas of the foot.

Diabetic neuropathy is the common factor in almost 90% of diabetic foot ulcers. Nerve damage in diabetes affects the motor, sensory, and autonomic fibers. Motor neuropathy causes muscle weakness, atrophy, and paresis. Sensory neuropathy leads to loss of the protective sensation of pain, pressure, and heat. Autonomic dysfunction causes vasodilation and decreased sweating, resulting in a loss of skin integrity, providing a site vulnerable to microbial infection .

Peripheral arterial disease is 2–8 times more common in patients with diabetes, starting at an earlier age, progressing more rapidly, and usually being more severe than in the general population. It commonly affects the

segments between the knee and the ankle. It has been proven to be an independent risk factor for cardiovascular disease as well as a predictor of the outcome of foot ulceration. Even minor injuries, especially when complicated by infection, increase the demand for blood in the foot, and an inadequate blood supply may result in foot ulceration, potentially leading to limb amputation. The majority of foot ulcers are of mixed etiology (neuroischemic), particularly in older patients.

In patients with peripheral diabetic neuropathy, loss of sensation in the feet leads to repetitive minor injuries from internal (calluses, nails, foot deformities) or external causes (shoes, burns, foreign bodies) that are undetected at the time and may consequently lead to foot ulceration. This may be followed by infection of the ulcer, which may ultimately lead to foot amputation, especially in patients with peripheral arterial disease.(10)

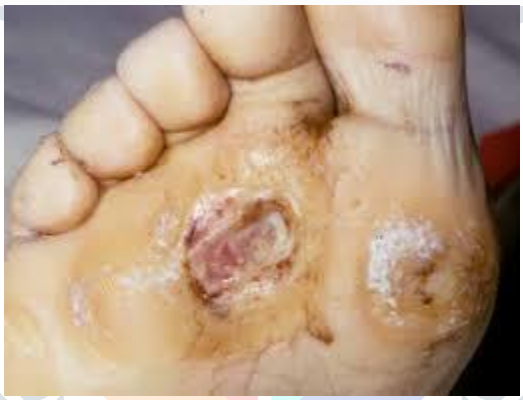


fig no:2 DIABETIC FOOD ULCER

1.3.4 Treatment

The gold standard for diabetic foot ulcer treatment includes debridement of the wound, management of any infection, revascularization procedures when indicated, and off-loading of the ulcer. Other methods have also been suggested to be beneficial as add-on therapies, such as hyperbaric oxygen therapy, use of advanced wound care products, and negative-pressure wound therapy (NPWT). However, data so far have not provided adequate evidence of the efficacy and cost-effectiveness of these add-on treatment methods.(9,10)

1.3.5 Debridement

Debridement should be carried out in all chronic wounds to remove surface debris and necrotic tissues. It improves healing by promoting the production of granulation tissue and can be achieved surgically, enzymatically, biologically, and through autolysis.

Surgical debridement, known also as the “sharp method,” is performed by scalpels, and is rapid and effective in removing hyperkeratosis and dead tissue. Particular care should be taken to protect healthy tissue, which has a red or deep pink (granulation tissue) appearance. Using a scalpel blade with the tip pointed at a 45° angle, all nonviable

tissue must be removed until a healthy bleeding ulcer bed is produced with saucerization of the wound edges. If severe ischemia is suspected, aggressive debridement should be postponed until a vascular examination has been carried out and, if necessary, a revascularization procedure performed.

Enzymatic debridement can be achieved using a variety of enzymatic agents, including crab-derived collagenase, collagen from krill, papain, a combination of streptokinase and streptodornase, and dextrans. These are able to remove necrotic tissue without damaging the healthy tissue. Although expensive, enzymatic debridement is indicated for ischemic ulcers because surgical debridement is extremely painful in these cases.

Biological debridement has been applied recently using sterile maggots. Maggots have the ability to digest surface debris, bacteria, and necrotic tissues only, leaving healthy tissue intact. Recent reports suggest that this method is also effective in the elimination of drug-resistant pathogens, such as methicillin-resistant *Staphylococcus aureus*, from wound surfaces.

Autolytic debridement involves the use of dressings that create a moist wound environment so that host defense mechanisms (neutrophils, macrophages) can clear devitalized tissue using the body's enzymes. Autolysis is enhanced by the use of proper dressings, such as hydrocolloids, hydrogels, and films. Autolysis is highly selective, avoiding damage to the surrounding skin.

1.3.6 Off-loading

Off-loading of the ulcer area is extremely important for the healing of plantar ulcers. Retrospective and prospective studies have shown that elevated plantar pressures significantly contribute to the development of plantar ulcers in diabetic patients . In addition, any existing foot deformities may increase the possibility of ulceration, especially in the presence of diabetic peripheral neuropathy and inadequate off-loading. Furthermore, inadequate off-loading of the ulcer has been proven to be a significant reason for the delay of ulcer healing even in an adequately perfused limb. The value of ulcer off-loading is increasing, as it has been reported that the risk of recurrence of a healed foot ulcer is high if the foot is not properly off-loaded (in the high-pressure areas), even after closure of the ulcer .

1.3.7 Dressings

A wound's exudate is rich in cytokines, platelets, white blood cells, growth factors, matrix metalloproteinases (MMPs), and other enzymes. Most of these factors promote healing via fibroblast and keratinocyte proliferation and angiogenesis, while others, such as leukocytes and toxins produced by bacteria, inhibit the healing process.

The ideal dressing should be free from contaminants, be able to remove excess exudates and toxic components, maintain a moist environment at the wound-dressing interface, be impermeable to microorganisms, allow gaseous

exchange, and, finally, should be easily removed and cost-effective . Various dressings are available that are intended to prevent infection and enhance wound healing, and several studies support their effectiveness for this purpose.

1.4 SKIN

The epidermis and dermis are the two primary layers of skin. Keratinocytes make up the majority of the epidermis, but it also contains melanocytes, Langerhans cells, and Merkel cells. Skin appendages such as pilosebaceous units and sweat glands pass through it, dividing it into four levels or strata. The dermis is separated into two layers: papillary and reticular. The skin's neurovascular supply is located in the dermis. It's usually characterised in terms of three layers oftissues (Figure 1). Skin serves as an anatomical barrier between the body and its surroundings, accounting for 16-18% of typical body weight.

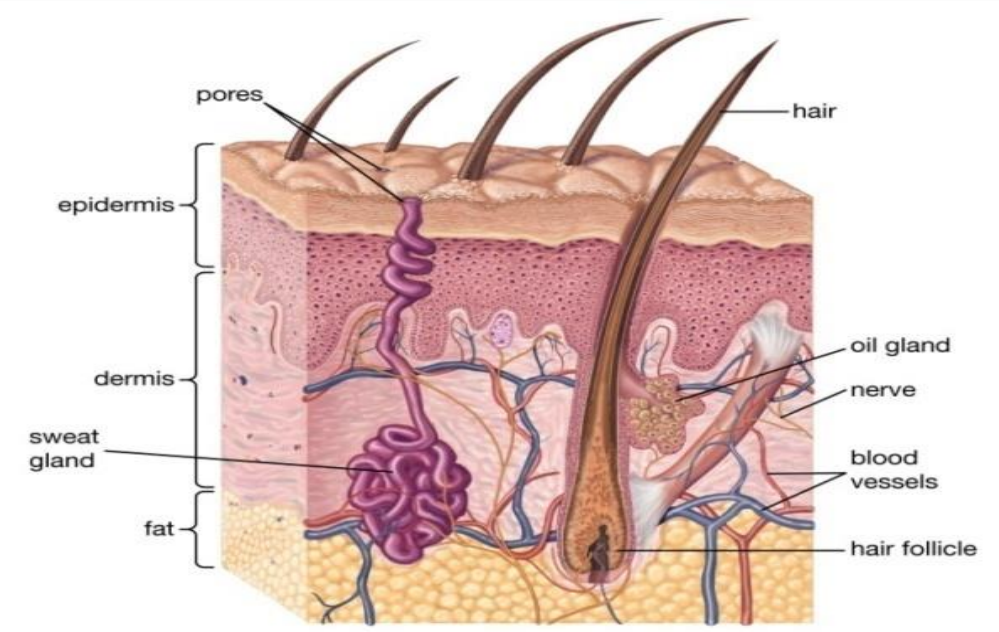


Fig No: 3 Structure of human skin

1.4.1 Epidermis

The epidermis is the skin's outermost layer. It is in charge of the colour, texture, and moisture of the skin. The thickness of the epidermis is rather consistent across the head and neck region. The keratinocyte is the predominant cell type in the epidermis, and the four epidermal layers depict the maturation of keratinocytes from the deep to the superficial layers.. This process of keratinization allows for the development of keratin, a protein filament. The deepest layer of the epidermis is the stratum basale, or basal layer. It is composed of stem cells called basal cells. The basal layer is often 1 cell thick, but can be 2 or 3 cells thick.

1.4.2 Dermis

The dermis lies between the epidermis and subcutaneous tissue and is responsible for the regional variation in skin thickness . It is composed primarily of collagen, but also contains elastin, blood vessels, nerves, and sweat glands. The primary dermal cell type is the fibroblast, and it produces collagen, elastin, and other proteins. The dermis is further divided into the papillary and reticular dermis. The papillary dermis is located beneath the dermal-epidermal junction and contains a loose mixture of fibrocytes, collagen, and blood vessels. Below it lays the much thicker reticular dermis. It contains fewer fibrocytes but a denser collection of collagen. Dermal thickness within the head and neck ranges from less than 1 mm on the eyelids to 2.5 mm on the scalp.

1.4.3 Subcutaneous Tissue

The subcutaneous tissue, or hypodermis, is the tissue bridging the skin with deeper tissues such as muscle and bone. It contains the subcutaneous fat, superficial fascia, perforating blood vessels, and nerves
The relative contribution of the subcutaneous fat and superficial fascia to the overall soft tissue coverage of the facial skeleton varies within each regional unit.

1.4.4 Function of skin

The skin serves a variety of purposes. It acts as a barrier against water, microbial invasion, mechanical and chemical assault, and UV light damage. The cell envelop, a layer of insoluble proteins on the inner surface of the plasma membrane, creates an epidermal water barrier. It is made up of tiny proline-rich proteins and bigger proteins including cystatin, desmoplakin, and filaggrin, and it adds to the barrier's strong mechanics. The lipid envelope is a lipid/hydrophobic layer linked to the plasma membrane's outer surface. Keratinocytes in the stratum spinosum create keratohyalin granules, as well as lamellar bodies (composed of glycosphingolipids, phospholipids, and ceramides) that are assembled within the Golgi. The contents of lamellar bodies are then secreted into extracellular gaps between the stratum granulosum and the stratum granulosum.

1.5 MANTHAN THAILAM

MathanTailam, a herbomineral classical Siddha formulation is used as a remedy for healing suppurative wound and is very useful in healing diabetic ulcers. Medicated oil is prepared by protracted boiling of base oil with juice of prescribed herbal drug and mineral drug till it is dehydrated or near dehydration. This process results in the transfer of some therapeutically active principles of the ingredients into the base oil. Thus, traditional method of *tailam* preparation assures the enrichment of oil with active principles.

MathanTailam is a herbomineral Siddha formulation prescribed widely for several conditions such as eczema, weeping eczema, itches, wounds, chronic ulcers, bed sores, anal fistula, ear infections, carbuncle ulcer of diabetes, per anal abscess, non-healing of external ulcers, folliculitis, alopecia and burn wound *etc*.

Real standard of a drug should be of its therapeutic value, a biological parameter, which varies from individual to individual and species to species. The biological standards can be supplemented and complemented by enhancing the physico-chemical parameters already employed by making use of latest techniques. Information on quality control standards for *MathanTailam* described in CCRAS publication covers only physico-chemical parameters which address mostly the characters of base oil and not about the herbal and mineral portion of the drug . There is a need that as and when more aspects on scientific knowledge are unfolded, new parameters can be included which will make the tests and standards more meaningful

Increasing popularity of this medicated oil for the treatment of diabetic foot ulcer necessitated the improved methods of standardization. Hence the present work was carried out to develop Standardized Operating Procedure (SOP) for the preparation of *MathanTailam* and standardization using suitable analytical techniques namely physico-chemical parameters, qualitative phytochemical parameters, Gas chromatography-mass spectrum (GC–MS) analysis, High performance thin layer chromatographic (HPTLC) and inductively coupled plasma-optical emission spectroscopic (ICP-OES) analysis.

1.5.1 Quality evaluation of MT

1.5.1.a) *Physico-chemical parameters:*

The following physico-chemical parameters namely iodine value, saponification value, acid value, peroxide value, refractive index, specific gravity and rancidity were carried by using standard procedure . Three replicates were prepared and the mean values were computed.

1.5.1b). *Gas chromatography mass spectrum analysis*

Sample was injected into the GC–MS unit (Instrument; Agilent 5975 series, column; DB5 MS 30 m × 0.25 mm × 0.25 mm, single quadrupole detection system with carrier gas of Helium). Oven temperature and injection temperatures were maintained at 280 °C. Injection volume was 10 µl. It was separated into various constituents with different retention times which are detected by mass spectrophotometer. The chromatogram was plot for intensity against retention time and recorded by the software attached to it. From the graph, the compounds were identified comparing the data with the existing software NIST-11.

1.5.1.c) Extractive value:

Extraction of phytochemical constituents from *Mathan Tailam* was done by mixing 5 ml of *Mathan Tailam* with 15 ml of 90% aqueous methanol and subjected to constant stirring by using magnetic stirrer on hot top at 60 °C for 1 h. It was then stored in freezer for solidification. The alcoholic portion was separated and filtered through Whatman filter paper no. 41 and filtrate was used for qualitative phytochemical testing and HPTLC profiling. The extraction was repeated for three times for effective extraction of phytochemicals from the medicated oil. Same procedure was followed for coconut oil.

1.5.1d) Qualitative phytochemical parameters:

Analyses for the following qualitative phytochemical parameters were carried out: steroids, triterpinoids, flavonoids, alkaloids, sugar, coumarine, quinine, saponine, tanic acid, furan, phenol.

1.5.1e). High performance thin layer chromatographic (HPTLC) profile:

HPTLC studies were carried out by following standard methods . The extract prepared for extractive value was utilized for HPTLC fingerprinting of coconut oil and *MathanTailam*. *D. metel* leaf extract was prepared by 4 g shade dried and coarse powdered leaves. The prepared powder was extracted with 40 ml of 90% aqueous methanol. It was then filtered and concentrated to 10 ml. 15 µl of this extract was used for HPTLC fingerprinting. Aliquots of samples were applied on a pre-coated silica gel 60 F254 (E. Merck) of 2 mm thickness aluminum plates to a bandwidth of 6 mm using CAMAG HPTLC system equipped with ATS 4 applicator.

The plate was developed using solvent system of Chloroform: Methanol in the proportion of 9:1 up to 80 mm, removed from the chamber and allowed to dry. The developed plate was visualized under UV 254, 366 nm using deuterium, mercury lamp source, with slit dimensions 5.00 mm × 0.45 mm and scanned using TLC Scanner 4 and analyzed with winCATS software version 1.4.4. The chromatograms were recorded. After scanning, the plate was dipped in vanillin-sulfuric acid reagent and dried at 105 °C in hot air oven till the color of the spots appears. Then the plate was scanned at 520 nm using tungsten lamp. The R_f values and fingerprint data were recorded by winCATS software.

1.5.1f) Inductively coupled plasma-optical emission spectroscopic (ICP-OES) analysis:

Copper and lead estimation was carried out using ICP-OES. 2 g of oil was weighed and treated with 20 ml of 0.1N HNO_3 for 1 h using magnetic stirrer at 60 °C. The aqueous portion was separated by using separating funnel. This aqueous portion was filtered using Whatman filter paper number 40. The volume was made up to 50 ml using de-ionized water. This clear aqueous solution was used for analysis of copper and lead concentration by ICP-OES using the wavelength of copper – 327.393 and lead – 220.353.

Tab

S.No	Physico-chemical parameters	Values	Values as per CCRAS quality check mannual
1	Specific gravity	0.92	-
2	Refractive index	1.3325	1.454
3	Saponification value	252.08	257.2
4	Iodine value	8.02	12.12
5	Acid value	2.99	1.62
6	Peroxide value	0.92	-
7	Rancidity	Nil	-

1.6 EMULGEL

1.6.1 ABSTRACT

In comparison with the other semisolid formulations, the use of gels seems to be more advantageous both in cosmetics and pharmaceutical preparations. When gel and emulsion are used in the combined form, they are referred as emulgel. Emulgel is the promising drug delivery system for the delivery of hydrophobic drugs. Emulgel, an interesting topical drug delivery system, has dual release control system, i.e., gel and emulsion. Emulgel have several merits like greaseless, easily spreadable, easily removable, emollient and transparency. Preparation of emulgel is done by incorporation method. Emulgel are commonly used for the delivery of analgesics, anti-inflammatory, anti-fungal, anti-acne drugs and various cosmetic formulations. Studies on emulgel promises a better future in delivering more numbers of topical drugs as emulgel by their merits over other drug delivery systems.

1.6.2 INTRODUCTION

Topical drug delivery system is the dosage form which is administered on the skin and other routes of drug delivery get failed or for skin disorders. The topical drug delivery system has the advantage of negotiating the first pass metabolism. It also helps to avoid the risk and inconvenience of i.v route therapy. Topical formulations are prepared in different consistency such as solid, semisolid, and liquid. The topical delivery system is failed in the administration of hydrophobic drug. In each formulation with the active ingredients many excipients are used. Sometimes more than one formulation can be combined to enhance the drug delivery; emulgel is such type of combination. It is the combination of emulsion and gel .

Emulgel is prepared both in oil- in- water and water- inoil type emulsion mixed with gel. Oil- in- water type is used for lipophilic drugs and water- in- oil type is used for hydrophobic drugs' delivery. The emulgel have many advantages like thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining, bio-friendly, pleasing appearance, transparent and cosmetically acceptable, which also have a good skin penetration and long shelf-life. The emulsion and gel preparations have their own properties.

But the gels show some limitations as hydrophobic drug delivery. This limitation is overcoming by emulgel. By the use of gelling agent classical emulsion can be converted in to emulgel .Two types of topical delivery products are available. They are external and internal products . As their name indicates, the external products are applied by spreading or spraying, and the internal products are applied orally, vaginally or rectally. The topical preparation can be classified by their consistencies, which are solid preparation, liquid preparation, semi-solid preparation and miscellaneous preparation.

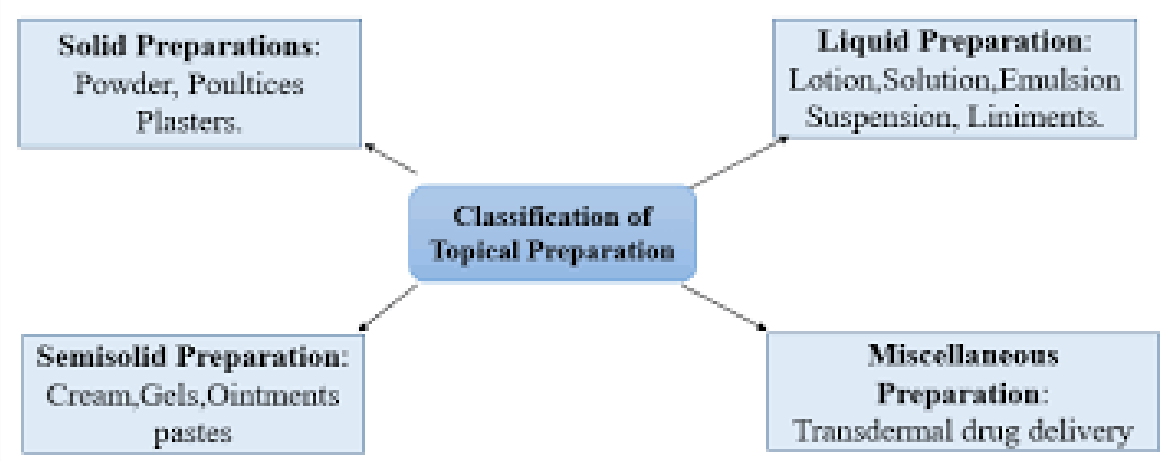


Fig. No. 4 classification Topical preparation

Some factors will affect the absorption of drug through every route. Some factors like skin thickness, skin pH, hydration, inflammation, partition coefficient, molecular weight and other factors affect topical route. The topical delivery system has many advantages and also disadvantages. The main advantage is avoidance of first pass metabolism and gastrointestinal incompatibility. Nearly all topical preparations are applied on the skin. They penetrate through the skin and give the action in right site. The skin is the largest sense organ in our body, which consist of approximately 2 m2 of surface area and pH of skin is 4.0 to 5.6.

The skin contains four layers; non-viable epidermis, viable epidermis, viable dermis and subcutaneous connective tissue. Non- viable epidermis [stratum corneum]: It is the outer layer of skin, which is 10-20 cell thick. The cells are 34- 44 µm long, 25- 36 µm wide, 0.5- 0.20 µm thick with surface area of 750- 1200 µm. Viable epidermis: It lies between stratum corneum and dermis with 10 - 50 µm thickness. The tonofibrils help for joining the cells. Dermis: It is seen under the viable epidermis, and it is a structural fibrin. Thickness of the dermis ranges from 2000 – 3000 µm and contains loose connective tissue. Subcutaneous connective tissue: It is considered as a true connective tissue with loose texture, fibrous connective tissue, blood and lymph vessels.The topical drug absorption is done by three mechanisms; which are transcellular, intercellular, and follicular.

The drugs penetrate the stratum corneum by passive diffusion [11]. For that the rate limiting steps are diffusion and dissolution. Topical drugs are used for three functions; the epidermal formulation, endodermal formulation and transdermal formulation. Transcellular mechanism is the shortest and direct route. Intercellular mechanism is the common route. The follicular mechanism is through hair follicles and sweat glands [12]. The drug penetration is enhanced by chemical (surfactant, water, solvents, etc.), physical (stripping, iontophoresis, ultrasound, etc.), biochemical (peptides and metabolic inhibitors) and super saturation enhancement .

1.6.3 ADVANTAGES:

- Better stability
- Controlled release
- Avoiding first pass metabolism
- Penetration enhancers Penetration enhancers help to absorb drug to the skin
- Avoiding gastrointestinal incompatibility
- More selective for a specific site
- Improved patient compliance
- Convenient and easy to apply

1.6.4 DISADVANTAGES:

- Skin irritation on contact dermatitis
- The possibility of allergenic reactions
- The poor permeability of some drugs through the skin
- Drugs of large particle size are not easy to absorb through the skin
- The occurrence of the bubble during formulation of emulgel.

1.6.5 FORMULATION OF EMULGEL:

For the preparation of emulgel some constituents are used including drug, which are:

- Vehicle: Vehicle should follow the ideal characters given in the Pharmacopeias
- Aqueous material: The aqueous phases used are water, alcohol, etc.
- Oil : Oils are used for preparation of emulsion. Mineral oils and paraffin are used either alone or in combination

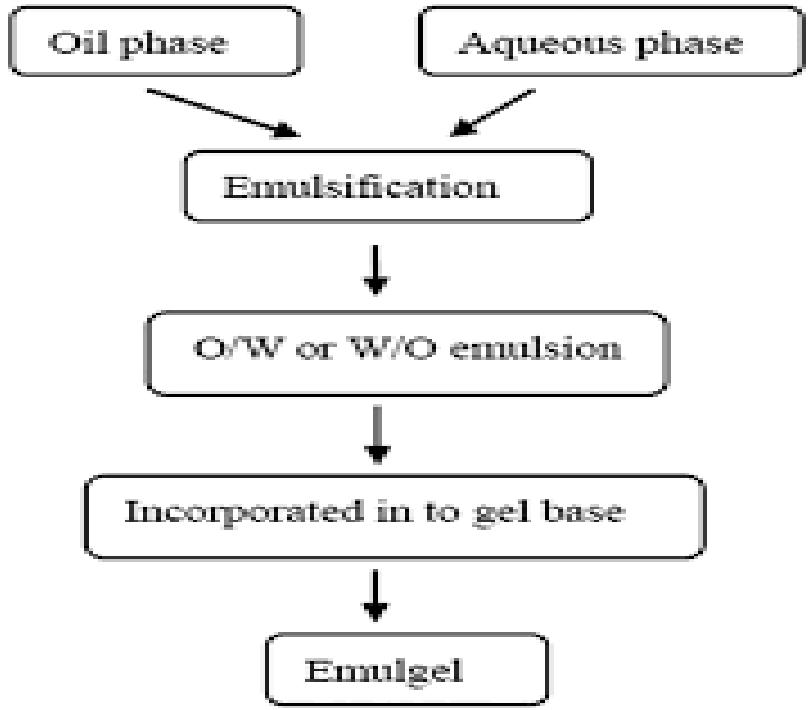
1.6.6 IDEAL PROPERTIES OF ADDITIVES

They should be nontoxic.

- ♣ They should be easily available.
- ♣ They should be cheap
- ♣ They do not be contraindicated.
- ♣ They should chemically and physically be stable.

1.6.7 PREPARATION OF EMLGEL

Emulgel are prepared by incorporating gel and emulsion. The emulsion and gel are prepared separately and mixed together. For preparing emulsion, aqueous phase and oil phase are taken separately and mixed together. Then the gel is prepared by using gelling agent. After preparing gel and emulsion, they are mixed with gentle stirring. The chemicals are used as oil phase are castor oil, clove oil,liquid paraffin, etc. Water and alcohol are used as aqueous phase.



The aqueous phase is prepared by mixing tween 80 and water and also the oil phase prepared by mixing paraben and propylene glycol. The drug is dissolved in ethanol and the two phases are mixed with continuous stirring. Then the polymers are dissolved in water with the pH of 6.0-6.5. After preparing emulsion and gel separately, they are mixed together to get emulgel.

EMULGEL PICTURE

2. LITERATURE REVIEW ON EMULGEL

1. Vermaswati, et al, (2016), formulated the nanoemulgelfor topical delivery of poor water solubledrug ketoconazole which is useful in the treatmentof fungal infection. Formulations were preparedusing different gelling agents i.e. carbopol 934 andcarbopol 940. The highest activity was observedfor the formulation which was based in the carbopol934. The formulated nanoemulgel was found tobe stable for 3 month with no major alterations andglobule size under the range of 200nm indicatesthere is high degree of homogeneity.

2. Khuriah Abdul Hamid, et al (2015) concluded thatthe emulgel represent a solution for incorporatinghydrophobic drugs as benzyl benzoate in watersoluble gel bases. Thus it is recommended for formulationof benzyl benzoate since the release andconsequently the effectiveness and availability ofthe medicament is greatly increased than othertopical formulations and was noticed that additionof 20% of carbopol 934 gel is better than preparationscontaining 10 and 30%.

3. PanwarShailendra, etal, (2015), develops tioconazoleemulgel for the topical delivery system whichis useful in the treatment of vaginal infections usingdifferent polymer ratio. Thus, concluded thatthe formulation using 0.25% carbopol934 showsthe greater release of drug as compared to othersformulations with all aspects.

4. RamakanthAmbala, et al, (2015), formulate theketoprofenemulgels using different viscositygrades of HPMC and carbopol as gelling agentsand concluded that emulgelscontaining HPMCwere poor in clarity when compared to carbopolformulations. The influence of the type of gellingagent on the drug release from the prepared emulgelwas investigated and carbopol showed thegood results not only in the drug release but also inphysical evaluation parameters.

5. Hardenia et al (2014) reviewed that in comparisonto other group of semisolid preparations, the use ofgels has been emerged both in cosmetics and inpharmaceuticals preparations because of its uniquearray of features. Despite of proving several benefits the category gel faces limitations in deliveringhydrophobic drug molecules via skin. So in orderto cover up this lacking a recent emulsion basedapproach is being used so that even a hydrophobictherapeutic moiety can enjoy the unique propertiesof gels. The use of gels and emulsions as combineddosage form results into formation of emulgelshowing dual release.

6. Patil A. Suchita, et al, (2014), investigate the possibilityof the dermal application of the etodolacwith emulgel formulations. Furthermore, the effectof different concentration of oil phase on the drugrelease, viscosity and spreadability was investigatedand emulgel was optimized using 23 factorialdesign. The developed emulgel were efficacious for the delivery of lipophilic and poorly solubledrugs such as Etodolac. Thus results demonstratethe formulation were stable and showed improvedpermeation of the drug from the emulgel comparedto other emulgel formulations.

7. Shah A. Arpan et al (2013) concluded that emulgels the one of the recent technologies in NDDS usedfor dual control release of emulsion and gel fortopical use. In spite of many advantages of gels amajor limitation is the delivery of hydrophobic drugs. So to overcome this limitation emulgels areprepared and with their use even a hydrophobic drug can be used to prepare emulgels.

8. Sonaje et al (2013) surveyed that emulgels havebeen proven as most convenient, better and effectivedelivery systems. Due to its non-greasy, gellike property it provides and lack of oily bases andit provides better release of drug as compared toother topical drug delivery system. Incorporationof emulsions into gel makes it a dual control releasesystem further problem such as phase separation,creaming associated with emulsion gets resolved and its stability improves.

9. Bhatt Preeti et al (2013) concluded that emulgelshows major advantages on novel vesicular systemsas well as on conventional systems in variousaspects. Emulgels for dermatological use have severalfavorable properties such as being thixotrophic,greaseless, easily spreadable, easily removable,emollient, non staining, water soluble, long shelflife, bio-friendly and please appearance. It also concluded that use of various permeation enhancerscan potentiate the effect. So emulgels can beused as better topical drug delivery systems overpresent systems.

10. Kaushal R. Sabu, et al (2013) formulated the terbinafinehydrochloride emulgel using various variablessuch as oil phase and the emulsifyingagents and was further optimized by the factorialdesign. A 22 factorial design was employed toidentify optimal formulations parameters for anemulgel preparation with the minimum value ofspreadability and max value of in-vitro drug release.Hence, the results of the study clearly indicatingpromising potentials of emulgel as sustainedrelease for delivering terbenafine hydrochloridetopically in the treatment of fungal infectionand could be viewed as a potential alternative toconventional dosage forms.

11. SinglaVikas et al (2012) concluded that topicaldrug delivery will be used extensively due to betterpatient compliance. Since emulgel possesses anedge in terms of spreadability, adhesion, viscosityand extrusion and become a popular drug deliverysystem. Moreover, they will become a solution forloading hydrophobic drugs in a water soluble gelbases.

12. RangaPriya M, et al (2012) reports for the developmentof ciprofloxacin emulgel for topical releaseof the drug. The results demonstrate that the releaseof the drug is dependent on viscosity of thepolymer used. It can be conclusively stated that theemulgel formulations appears to be promising systemsfor the topical delivery of ciprofloxacin toavoid the disturbances of the conventional routesof administration.

13. Joshi baibhav, et al, (2012), concluded that Clarithromycinemulgel formulation prepared with eithercarbopol 934, carbopol 940 or HPMC showed acceptablephysical properties, drug release, and antimicrobial activity, which remained unchanged upon storage for 3 months. However, the carbopol934 based emulgel in its low concentration provedto be the formulae of choice, since it showed thehighest drug release and very good antimicrobialactivity when compared to the marketed Azithromycingel. So it can be used as an antimicrobialbroad spectrum medication for topical drug delivery.

14. UpritShubham, et al, (2012), prepared the nanostructuredlipid carrier (NLC) gel, by using minoxidil,which is preferably used in case of alopecia,i.e. baldness pattern as an effective drug. It hasbeen observed that NLC gel produces the gel withgood consistency, homogeneity, spreadability andrheological behavior. They showed faster onset andelicted prolonged activity up to 16 hr. thus, thepresent study concluded that the NLC- based gelcontaining minoxidil dissolved in a mixture of solidlipid and liquid lipid in the nanostructure form helped them to attain the objective of faster onsetyet prolonged actions as evident from in vitro release.

15. MagdyI.Mohamed (2004) develop an Emulgelformulation of chlophenesin (CHL) using twotypes of gelling agents: HPMC and Carbopol 934and studied the influence of the type of gellingagent and concentration of both the oil phase andemulsifying agent on the drug release from theprepared emulgels was investigated using 23 factorialdesign. The prepared emulgels were evaluatedfor their physical appearance, rheologicalbehavior, drug release, stability and other parameters.

3. AIM AND OBJECTIVES

3.1 Aim

To Design and characterize DaturaMatal . L -MathanThailam for the management of diabetic foot ulcer.

3.2 Objectives

- To develop a novel topical formulation of DaturaMatal. L for the management of diabetic foot ulcer.
- It is used in several conditions such as eczema, weeping eczema, itches and wounds.
- It is also used in chronic ulcers, bed sores, and fistula.
- To avoid pain (occur in injectables)
- To release the active principle directly into systemic circulation by passing first pass effect
- To increase the safety & efficacy
- To improve the patient compliance by reducing the pill burden
- Cost effective

4. PLAN OF THE WORK

- Literature survey
- Selection of herb and authentication
- Preparation of Mathanthailam
- Selection of polymers
- Preparation of Emugel formulation
- Phytochemical evaluations
- Trial batches for MathanThailam (extract : different polymer)
- Evaluations
  - Physico chemical evaluation
    - Determination of pH

- Rheological study
- Microbiological assay
- Accelerated stability studies
- Drug content
- In vitro drug release study
- Stability studies
- Result & discussion
- Summary & conclusion

5. PLANT PROFILE

DATURAMETEL.L

5.1 Scientific classification

Kindom **:** plantae

Order **:** Solanales

Family **:** Solanaceae

Genus **:** Datura

Tamil **:** KaruUmaththai

English : Thorn apple

Hindi : KaalaDatura

5.2 Description

Color : Green

Taste : Bitter

Odour : Foul odor similar to rancid peanut butter

Texture : Rough

5.1.3 Synonyms

- Thornapple
- Moon flower
- Hells bells
- Devil`s trumpet
- Devil`s weed
- Tolguacha
- Jamestown weed
- Stinkweed
- Locoweed
- Pricklyburr
- False castor oil plant
- Devil`s cucumber

5.3 Habitat

Daturametel is a shrub like annual (zone 5-7) or short-lived, shrubby perennial (zone 8-10), commonly known in Europe as Indian thorn apple, Hindu Datura, or metel and in the United states as devil`s trumpet or angel`s trumpet. Daturametel is naturalized in all the warmer countries of the world. It is found notably in India. The plant is cultivated world wide, both as an ornamental and for its medicinal properties, the latter being due to its tropane alkaloid content.

5.4 Vernacular names of DaturaMetel

- **English** :Thornapple, Moon flower
- **Hindi** : KaalaDatura, Sadadhattura
- **Bengali** : Dhattura
- **Gujarati** : Gypsum
- **Kanada** : Madulam
- **Malyalam** : Unmatta, Dhattura
- **Telgu** : Ummetta
- **Arabian** : Datur
- **Farsi** :Tatur

5.5 Therapeutic uses

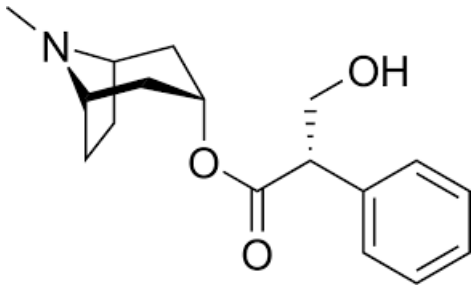
The seeds of Datura are analgesic, anthelmintic and anti-inflammatory and as such, they are used in the treatment of stomach and intestinal pain that results from worm infestation,toothache, **and** fever from inflammation. The juice of its fruit is applied to the scalp, to treat dandruff and falling hair.

5.6 Pharmacological activity

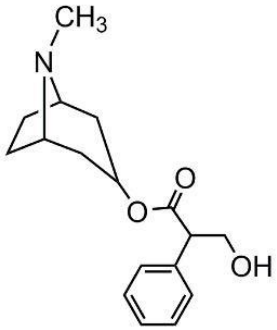
- Anti Asthmatic activity
- Epilepsy
- Organophosphate poisoning
- Anti Microbial activity
- Anti fungal activity
- Anti inflammatory activity

- Acaricivalrepelient and oviposition deterrent propertices

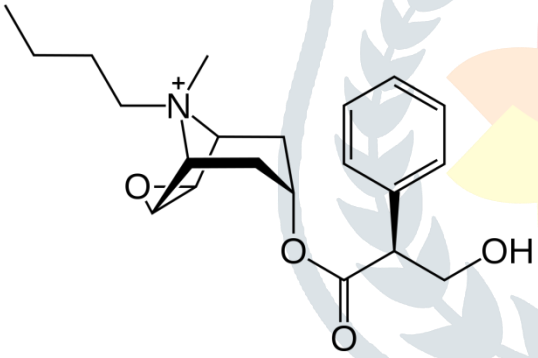
5.7 Chemical constituents



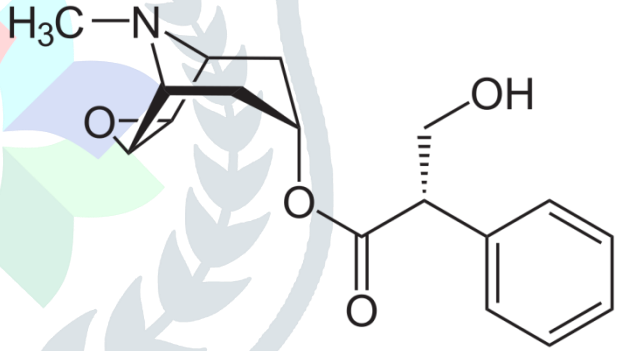
Hyoscyamine



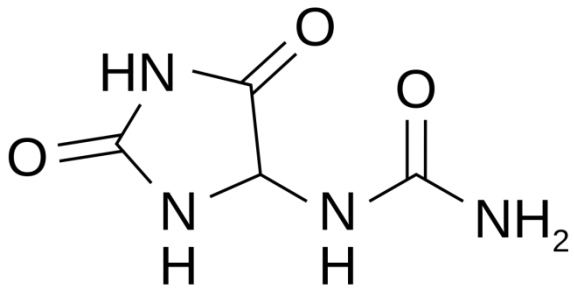
Atropine



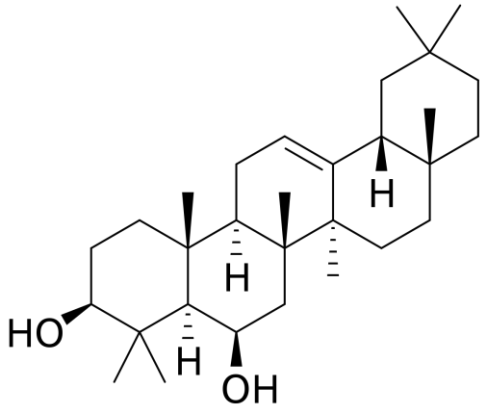
Hyoscine



Scopalamine



Allantoin

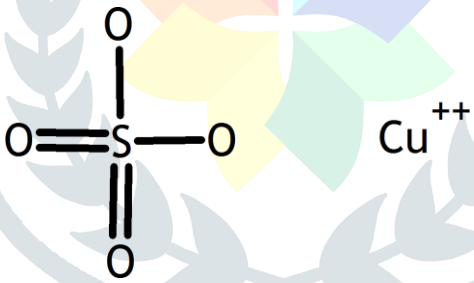


Daturadiol

6. EXCIPIENTS PROFILE

6.1 COPPER SULPHATE :

Chemical Structure:



CAS Number : 7758-99-8

Chemical Name : Copper Sulphate

Formula : Cuso4

Synonyms : Blue Vitriol, Roman Vitriol, Vitriol of copper and Blue Stone

Molecular weight : 159.609 grames/more

Solubility : Dissolve some copper sulfate CuSO4 in hot water. Copper sulfate dissolves much better in hot water than in cold water, so you can obtain a saturated solution much faster using heat and insoulble in ethanol and most organic solvents.

Functional category : Fungicide, algaecide, root killer and herbicide

Specific gravity : 1.186

pH : There is no pH

Pharmaceutical applications :

- Metallic copper is used already for many years in dental fillings and in coper intrauterine Devices.
- Onitments cantaining copper, which release copper ions that are absorbed by the skin in the management of cramps.
- There are also cosmetic facial creams containing copper as their main active imgredient.
- Also used in disturbances of renal function, peripheral, venous hypostatic circulatory disturnances,rheumatic disease and swelling associated with trauma.

Safety:

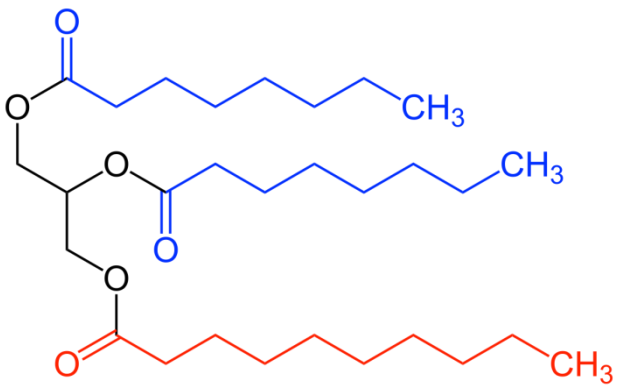
Human and animal feeding studies have shown copper sulphate to be safe.

Solubility and storage:

They are highly soluble in water. Store in a tight container in a cool place.

6.2 COCONUT OIL

Chemical Structure:



CAS Number : 8001- 31-8

Chemical Name : cocos nucifera

Synonmys : Copra oil, cocoa butter, coconut fat, etc.,

Molecular weight : 554.8

Molecular formula : C19H21NO5

Solubility : Practically insoluble in water, freely soluble in methylene chloride and in light petroleum (bp:65-70 C), very slightly soluble in ethanol.

Functional category: Viscosity- increasing agents, tabletbinder, coating agent, adhesive anhydrous ointment.

Specific gravity : 0.925

pH : 7.0-8.0

Pharmacecutical application:

- Protect your skin from UV Rays
- Increase your Metobolsim
- Coconut oil has a long shelf life and is used in baking industries, processed foods, infant formulae, pharmaceuticals, cosmetic and as hair oil.
- It has antibacterial, antioxidant, antifungal, antviral, antiparastic, antidematophytic, hypoglycemic, hepatoprotective, immuostimulant.
- In many industrial uses include the manufacture of soaps and detergents, shampoos, synthetic rubber, and glycerin.

Safety:

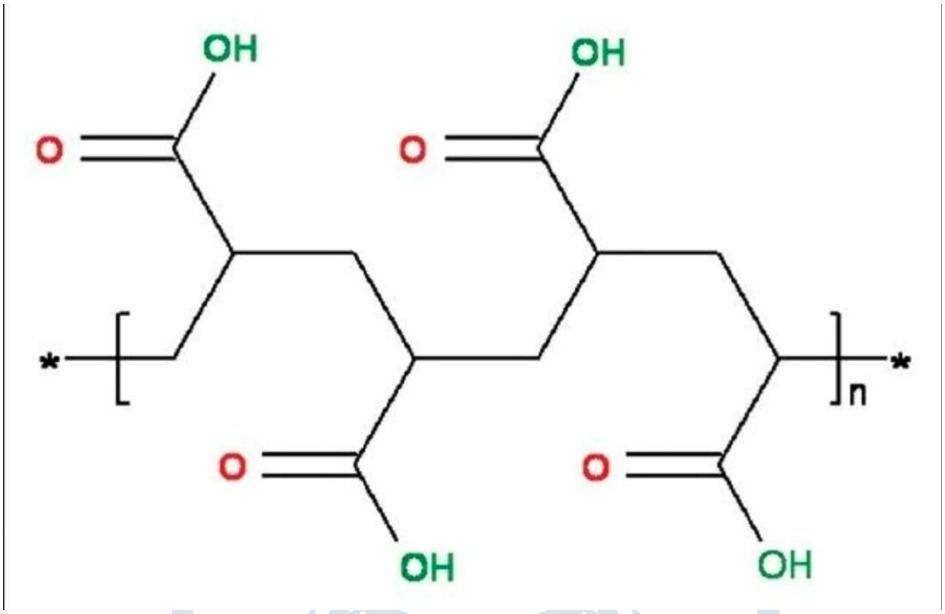
Human and animal feeding studies have shown coconut oil to be safe.

Solubility and storage:

Coconut oil has the best oxidative stability, but this is largely due to its saturated fat content store in a tight container in room temperature.

6.3 CARBAPOL

Chemical structure :



CAS No: 9003-01-4

Synonyms: carbomer, carboxypolmethylene.

Molecular formula: C3 H3 O2.

Solubility : highly water and polar solvent solubale.

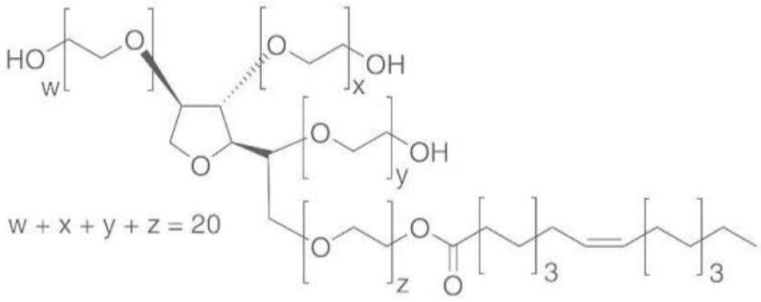
PH: 0.5-1

Functional category: Bioadhesive,emulsifying agent.

Pharmaceutical application: provide controlled release in tablets, biodhesion in buccal,opthalmic,intestinal,nasal,vaginal and ractal application.

Storage: In tightly closed and stpred out of contact with water.

6.4 TWEEN 80



CAS NO: 9005-65-6

Chemical formula : C64 H124 O26

Boilling point: >100 C

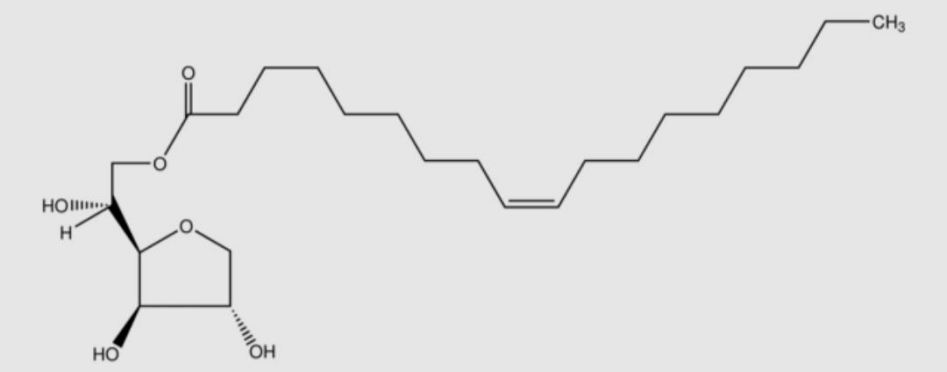
Viscosity : 300-500 centistokes

PH : 5.5-7.2

Pharmaceutical application : Emulsifier in cosmetics, pharamaecuticals and food products.

Storage : +15 C - +25C

6.5 SPAN 80



CAS NO: 1338 – 43 – 8

Chemical formula: C24 H44 O6

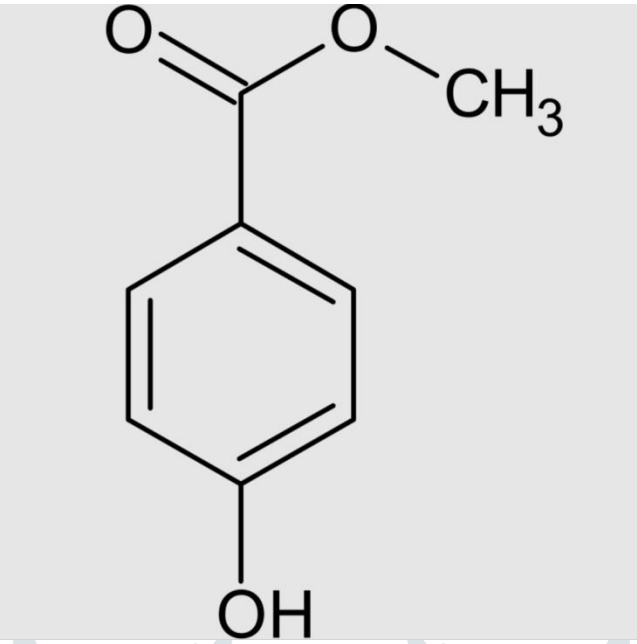
Synonyms: Sorbitan monooleate

Molecular weight: 428.6

Pharmaceutical application: Wetting agent and dispersant

Storage:below +30

6.6 METHYL PARABEN



CAS NO : 99-76-3

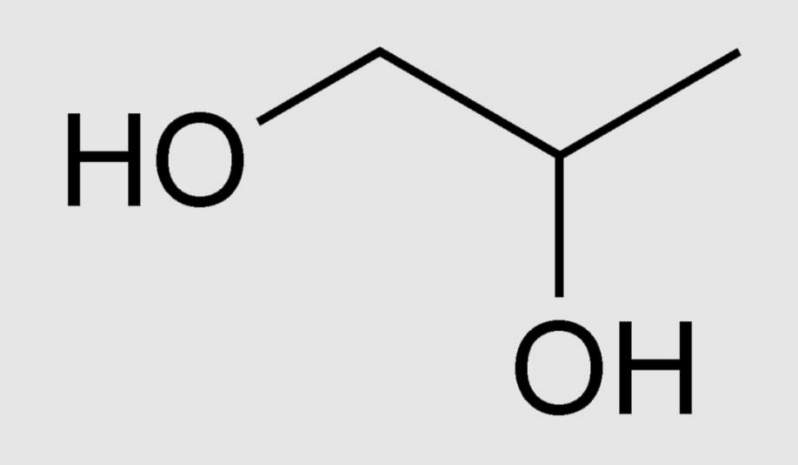
Chemical formula : C8 H8 O3

Molar mass : 152.149 g .mol

Pharmceutical application : Increase shelf life and avoid bacterial and fungal growth.

Storage : Well closed container in a cool dry place.

6.7 PROPYLENE GLYCOL



CAS No: 57-55-6

Synonyms : 1,2-propanediol , 1,2-Dihydroxpropane

Chemical formula : C3 H8 O2

Molar mass : 76.095 g. mol

Viscosity : 0.042 Pas

PH : 9.3 – 10.5

Pharmaceutical application : drug solubilizer , stabilizer for vitamins and water miscible cosolvent.

Storage : Ambient temperatures in closed container.

7. EMULGEL FORMULATION

Formulations with different quantity of ingredient were made as shown in Table 1. The gel portion of the emulgel was made by dissolving carbopol-934 in cold water with constant stirring at a moderate speed until uniform mixture was made. The pH was then adjusted to 6–6.5 using triethanolamine (TEA). Tween 80 was dissolved in distilled water to prepare the aqueous phase of the emulsion while for the preparation of the oil phase of the emulsion; span 80 was dissolved in liquid paraffin. To preserve the emulsion, methyl parabene was dissolved in propylene glycol and the extract was dissolved in ethanol then both solutions were mixed with the aqueous phase. Both the aqueous and the oil phase were heated in a water bath at 70 _C separately. Then the oil phase was added drop wise to the aqueous phase with continuous stirring using homogenizer (WiseStir_ HS-120A, Daihan Scientific, Korea) at speed of 3000 rpm for 10 min then cold to room temperature. At the end the gel and emulsion portions were mixed in 1:1 ratio with moderately stirring to prepare emulgel (Jain et al., 2011).

Table 1:EMULGEL FORMULATION

Ingredient(%w/w)	FB1	FB2	FB3
OB extract	-	5	5
Carbopol 934	0.25	0.50	0.50
Liquid paraffin	3.75	2.50	3.75
Tween 80	0.30	0.50	0.30
Span 80	0.45	0.75	0.45
Propylene glycol	3.50	3.50	3.50
Methyl parabene	0.01	0.01	0.01
Distilled water QS	50.0	50.0	50.0
Triethanolamine few drops	pH=Adjusted to 6-6.5		

*FB1= Formulation 1.

*FB2= Formulation 2

*FB 3= Formulation 3

7.1 CHARACTERIZATION OF EMULGEL

7.1.1 Extraction procedure

Grinded OB leaves (850 g) powder were macerated in 6 L of 70% methanol. The mixture was stirred at an interval of 6–8 hrs for 24 hrs. The mixture was then allowed to keep for 6 days at room temperature. After that, the mixture was coarsely filtered using a muslin cloth followed by a filter paper. The solvent was evaporated in rotary evaporator at 45 _C. The extract was then stored in air-tight bottle. The yield was about 17–19% (Sekar et al., 2009; Amzad et al., 2010).

7.1.2 Physico-chemical parameters

The following physico-chemical parameters namely iodine value, saponification value, acid value, peroxide value, refractive index, specific gravity and rancidity were carried by using standard procedure [7]. Three replicates were prepared and the mean values were computed

Qualitative phytochemical analyses of 90% aqueous methanolic extract of coconut oil, in-house prepared *Mathan Tailam*, and *D. metel* leaf.

Table No 1: Phytochemical test

S. No	Test	*Observation*	*Coconut oil*	*In-lab prepared Mathan thailam*	*In-lab prepared Emugel*
1.	Alkaloids (Dragendorff's reagent)	*Brick red precipitate*	−Absent	+Present	+Present
2.	Flavonoids (Magnesium + Concentrated HCl)	Magenta color	−Absent	−Absent	−Absent
3.	Sugar (Anthrone + Conc. H_2SO_4)	*Green color*	−Absent	−Absent	+Present
4.	Saponins (Frothing test)	*Froth formation*	−Absent	+Present	+Present
5.	Coumarin (10% NaOH)	*Formation of yellow color, Color disappears with the addition of Conc. H_2SO_4*	−Absent	+Present	+Present
6.	Tannins (a) Ferric chloride test	*Green precipitate*	−Absent	−Absent	+Present
7.	Steroids (Conc. H_2SO_4 test)	Reddish brown precipitate at interface	+Present	+Present	+Present
8.	*Triterpenoids (Tin + Thionyl chloride)*	*Red precipitate*	−Absent	+Present	+Present

S.NO	Physio-chemical parameters	Values	Values as per CCRAS quality check manual (9)
1	Specific gravity	0.92	-
2	Refractive index	1.3325	454
3	Saponification value	252.08	257.2
4	Iodine value	8.02	12.12
5	Acid value	2.99	1.62
6	Ranicidity		

Table No : 2 Physiochemical parameters

7.1.3 Lambda max (kmax) determination by UV/Visible spectrophotometer

The lambda max of the plant extract was determined according to the previous studies reported using UV/Visible spectrophotometer (CECIL, CE 2021 Germany) (Bueno et al., 2012; Joseph et al., 2018). For this purpose 20 mg of OB extract was taken and dissolved in 20 ml of methanol (Stock solution). Then one ml of the stock solution prepared was taken and dissolved in volumetric flask. The volume was made up to the mark with methanol. Similarly the stock solution was serially diluted up to three concentrations. Aliquots of various solutions prepared were taken and scanned in UV range from 190 to 400 nm for the determination of wavelength of maximum absorbance for major constituent of Mathan thailam extract. The methanol was used as blank.

7.1.4.Stability study

Eight different formulations (FB1-FB4) were prepared and placed in an incubator at 25 C for three days. Among eight formulations, the formulation FB8 was comparatively stable. FB8 was further selected for stability study. Formulation FB8 was divided into four samples and kept in four different incubators at 8, 25, 40 and 40 C + 75% RH (relative humidity) respectively. These were observed organolaptically with respect of color, homogeneity, phase separation and liquefaction for period of one month at different time interval. The samples were also analyzed for pH

7.1.5 Spreadability study

Spreadabilitywas determined by apparatus suggested by Mutimer et al. It consists of a block of wood at one end of which, a pulley was connected. On the basis of 'drag' and 'sleep' method, spreadability was determined. A ground glass slide was fixed on this block. Test emulgel (2 g) was placed on this slide. The emulgel was then sandwiched between these slides and another glass slide having the same dimension of fixed ground side and provided with hook. Weight (40 g) was then placed on the top of this slide. The time required (in seconds) by the top slide to cover a distance of 6 cm was noted. Then spreadability was calculated using the following formula. S ¼ M:L=T ð1Þ where S = spreadability, M = Weight tied to upper slide, L = Length of glass slides T = Time taken to separate the slides completely from each other.

7.1.6 Viscosity/Rheology

Initially viscosities of freshly prepared eight formulations (FB1- FB4) were determined using brook field viscometer with spindle no 04. The spindle was lowered perpendicular into the center of emulgel formulation placed in a beaker taking care that spindle did not touch the bottom of the beaker and rotated at the speed of 2.5 rpm for 5 min. The viscosity reading was noted (Basha et al., 2011). The stable formulation FB8 was then divided into four samples (i.e. FB4A, FB4B, FB4C and FB4D). The four samples were further subjected to viscosity study and they were checked from time to time for one month time period.

7.1.7 Patch Test/Sensitivity test Human volunteers (n = 3) were selected for patch test.

Formulation (1 g) was applied on the forearm of the volunteers in the form of bandage disc and then covered with surgical dressing. After 24 h, the patches were removed and the areas were washed with saline fluids. The volunteers were asked for any irritation and the areas of application were observed for the presence/absence of edema and erythema (redness of skin) (Rasul and Akhtar, 2011).

7.1.8 Extractive value

Extraction of phytochemical constituents from *Mathan Tailam* was done by mixing 5 ml of *Mathan Tailam* with 15 ml of 90% aqueous methanol and subjected to constant stirring by using magnetic stirrer on hot top at 60 °C for 1 h. It was then stored in freezer for solidification. The alcoholic portion was separated and filtered through Whatman filter paper no. 41 and filtrate was used for qualitative phytochemical testing and HPTLC profiling. The extraction was repeated for three times for effective extraction of phytochemicals from the medicated oil. Same procedure was followed for coconut oil [3].

7.1.9 ZONE OF INHIBITION:

Zone of inhibition is used to determine the suspectibility or resistance of pathogenic bacteria to antibacterial agents.

REQUIREMENT

a) Mueller-hinton agar plate

b) Sterile swab and forceps

c) Pure bacterial culture

d) Sample of antibacterial product(size of 6nm)

TEST METHOD

1.Sterile the culture media and the foreceps and other equipment by using autoclave.After cooling the culture spread evently over mueller-hinton agar plates.

2 .Using a sterile forcep, the treated product sample is placed on the media plate.

3. This petriplate is kept for the incubation for 18-24 hours at 36*c along with other optimal condition for bacterial growth.

4. After the incubation period,a clear area (zone of inhibition) around the antibacterial product sample is observed and measured.

5.Treated products with strong antibacterial activity form a large zone of inhibition or vice versa

LIMITATION :

a) Only suitable for water-soluble antimicrobial agents.

b) A Lack of the zone of inhibition does not mean that the product is ineffective.

8. RESULTS AND DISCUSSION

8.1 *Physico-chemical parameters*

The following physico-chemical parameters namely iodine value, saponification value, acid value, peroxide value, refractive index, specific gravity and rancidity were carried by using standard procedure . Three replicates were prepared and the mean values were computed.

Table No : 3 Physiochemical Parametes

S. no	Physico-chemical parameters	Values	Values as per CCRAS quality check manual
1.	Specific gravity	0.92	–
2.	Refractive index	1.3325	1.454
3.	Saponification value	252.08	257.2
4.	Iodine value	8.02	12.12
5.	Acid value	2.99	1.62
6.	Peroxide value	0.92	–
7.	Rancidity	Nil	–

8.2 Patch Test/Sensitivity test

Human volunteers (n = 3) were selected for patch test**.** Formulation (1 g) was applied on the forearm of the volunteers in the form of bandage disc and then covered with surgical dressing. After 24 h, the patches were removed and the areas were washed with saline fluids. The volunteers were asked for any irritation and the areas of application were observed for the presence/absence of edema and erythema (redness of skin) (Rasul and Akhtar, 2011).

8.3 Qualitative phytochemical parameters

Analyses for the following qualitative phytochemical parameters were carried out: steroids, triterpinoids, flavonoids, alkaloids, sugar, coumarine, quinine, saponine, tanic acid, furan, phenol [11].

Physico-chemical analysis of in-lab prepared *Mathan Tailam* and existing quality standards.

Table No : 4 Phytochemical Test

S. No	Test	*Observation*	*Coconut oil*	*In-lab prepared Mathan Thailam*	*In-lab prepared Emulgel*
1.	Alkaloids (Dragendorff's reagent)	*Brick red precipitate*	−Absent	+Present	+Present
2.	Flavonoids (Magnesium + Concentrated HCl)	Magenta color	−Absent	−Absent	−Absent
3.	Sugar (Anthrone + Conc. H_2SO_4)	*Green color*	−Absent	−Absent	+Present

4.	Saponins (Frothing test)	*Froth formation*	−Absent	+Present	+Present
5.	Coumarin (10% NaOH)	*Formation of yellow color, Color disappears with the addition of Conc.* H_2SO_4	−Absent	+Present	+Present
6.	Tannins (a) Ferric chloride test	*Green precipitate*	−Absent	−Absent	+Present
7.	Steroids (Conc. H_2SO_4 test)	Reddish brown precipitate at interface	+Present	+Present	+Present
8.	*Triterpenoids (Tin + Thionyl Chloride)*	*Red precipitate*	−Absent	+Present	+Present

8.4 Stability study

All four samples of the stable formulation FB8 (i.e. FB8A, FB8B, FB8C and FB8D) were kept at different storage conditions for one month and were examined physically from time to time for color, phase separation, homogeneity, consistency and liquefaction. Initially all formulations were yellowish green in color, viscous in consistency, smooth elegance and phase separation was not seen. pH of freshly prepared formulations was 6.1 which is an accepted value for skin which ranges from 5 to 6 (Helal et al., 2012). All the samples were found stable in respect to the mention parameters. The sample kept at 40 C + 75% RH showed a slight phase separation and its color changed to slightly blackish. This change in color may be due to separation of oily phase promoted at higher temperatures (Khan et al., 2016). The four samples were also analyzed for pH at zero time, after 12, 24 h, one week, two week, three week and four week intervals. All the pH values were subjected to student t test. No significant ($p > 0.05$) change in pH was noted. The average pH of all the four samples of the formulation were in the normal range of 5–6 which is the accepted range to avoid the skin irritation risk upon skin use (Helal et al., 2012). A slight decrease in the pH was observed with the passage of time till one month, but this variation was with in the normal skin pH range. According to (Khan et al), the decrease in pH with the passage of time may be due to diffusion of water (pH 5 to 7) from internal phase to external phase or due to the production of highly acidic by-products from any of the oil ingredients (Khan et al., 2016). The average pH change has been shown in Table 5.

Table No : 5 Stability Study

Formulation codes	Average pH (Mean + SD)
FB4A	6.1 ± 0.57
FB4B	5.39 ± 0.88
FB4C	5.9 ± 0.57
FB4D	5.6 ± 0.48

8.5 Spreadability study

Spreadability indicates that the emulgel is easily spreadable and comes out of containers by small amount of shear (Helal et al., 2012). Average spreadability values of different formulations have been given in Table 3. Larger the value of spreadability coefficient better is its spreadability on the skin. Spreadability values of all sampled formulations were in the following order FB8C > FB8A >- FB8B > FB8D. There was no significant ($p > 0.05$) change in spreadability values among all the formulations. FB8C showed highest average spreadability value that was 34 and the second highest value showed by FB8A that was 31.33. The high value of spreadability is due to low level of gelling agent (Joshi et al).

Table No 6 : Spreadability study

Formulation codes	Average spreadability values (mean + SD)
FB4A	31.33 ± 2.62
FB4B	29.33 ± 0.94
FB4C	34 ± 0.81
FB4D	26.33 ± 1.24

8.6 Viscosity and rheological study

Viscosity is an important parameter to be evaluated because consistency of dosage form and drug content release mainly depend upon viscosity (Ghada et al., 2014). Viscosities of all formulations were performed by using brook field viscometer. Values have been given in Table 4. The most viscous formulation was FB8 (12500 cp). This is due to high level of gelling agent, low level of emulsifying agent and low level of liquid paraffin (Jain et al., 2010). Among the four samples of formulation FB8 that were kept at different temperatures for one month period, the three formulations FB8B (kept at 25 C) FB8C (kept at 40 C), FB8D (kept at 40 C + 74% RH) showed no significant ($p > 0.05$) change in viscosities with respect to each other, but change in viscosities of formulation FB8A with respect to FB8c and FB 8D was significant ($p < 0.05$). Decrease in viscosities was higher at 40 C and 40 C + 75% RH. Such decrease in viscosities is always associated with increase in temperature as mentioned by Li et al. According to his study, decline in viscosities was provoked by increase in temperature (from 25 C to 32 C). It means that when the emulgel was applied at skin surface (application site temperature, 32 C), fluidity and spreadability would increase comparing with the condition of 25 C. Such property of viscosity is important to insure if the formulation is acceptable to patients (Li et al., 2011). Two reasons are mentioned here for inverse relation of viscosities with temperature, first reason is that water molecules defuse from the dispersed aqueous phase to the continuous aqueous phase, the second reason is that the bursting of multiple globules due to osmotic pressure (Khan et al., 2016).

Viscosity of four samples of most stable formulation during storage for 30 days and their SD.

Table No 7 : Viscosity and Rheology study

Time	Viscosities in centipoises			
	FB4A	FB4B	FB4C	FB4D
0 h	12,500	12,500	12,500	12,500
12 h	12490 ± 21.5	12400 ± 16.10	16.10 113 ±17.3	11990 ± 16.1
24 h	12480 ± 21.2	12000 ± 16.20	11370 ± 17.25	11300 ± 16.5
1 week	12400 ± 21.32	11488 ± 16.25	10100 ± 17.10	10000 ± 16.3
2 week	12380 ± 21.15	11400 ± 16.05	9900 ± 17.20	9890 ± 16.10
3 week	12380 ± 21.10	11300 ± 16.07	9890 ± 17.32	9860 ± 16.40
4 week	12350 ± 16.30	11300 ± 17.01	9850 ± 17.	9803 ± 16.25
Average	7480 ± 16.33	12480 ± 21.60	5867 ± 17.02	5020 ± 16.32

FB4A = formulation kept at 8 _C, FB4B = Formulation kept at 25 _C, FB4C = Formulation kept at 40 _C, FB4D = Formulation kept at 40 _C + 75% RH.

PREPARATION OF BACTERIAL CULTURE:RAGASREEEEEEEEEEE

TEST METHOD

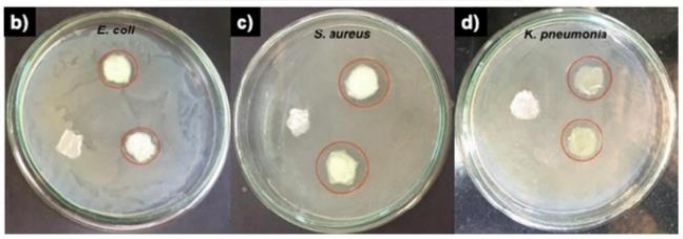
1.Sterile the culture media and the foreceps and other equipment by using autoclave.After cooling the culture spread evently over mueller-hinton agar plates.

2 .Using a sterile forcep, the treated product sample is placed on the media plate.

3. This petriplate is kept for the incubation for 18-24 hours at 36*c along with other optimal condition for bacterial growth.

4. After the incubation period,a clear area (zone of inhibition) around the antibacterial product sample is observed and measured.

5.Treated products with strong antibacterial activity form a large zone of inhibition or vice versa



CONCLUSION

Mathan thailam is a siddha proprietory medicine used in the treatment of wound healing particularly diabetic wound healing and also having antifungal activity.

Mathan thailam is prepared by using coconut oil phase.

On making mathan thailam oil phase into nano emulsion phase , gives more penetration power of active medicatement (by using tween and span).

From the mathan thialam nanoemulsion we prepared mathan thailam emulgel formulation.

Mathan thailam emulgel formulation gives good spreading property, good penetration power antimicrobial property and consumes preferable rheology property.

The leaves of D. Stramonium belonging to the family Solaneace is a widely growing plant throughout India. The plant also has many valuable medicinal properties hence. This study deals with the pharmacognostical identification and phytochemical screening of the selected plant

The D. Stramonium Linn leaves was subjected to preliminary identification of phytoconstituents which showed the presence of alkaloids, flavonoids, sugar, saponins, coumarin, Tannins, steroids, Triterpenoids.

The siddha drug traditionally used for the treatment of DFU. The characteristation of the above mat to find out it is suitability as wound dressing releated that, The formulation of emulgel with significant wound healing potential

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