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Research Article

Formulation and Evaluation of Topical Microemulgel Containing Tolnaftate

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ABSTRACT

The current study's goal was to look into the possibilities of a micro-emulgel formulation for tolnaftate topical administration. Among the available oil phases, tolnaftate showed the maximum solubility in propylene glycol. Polyethylene glycol and isopropyl myristate are utilized as co-surfactants and surfactants, respectively. In the Central Composite Design Method Six formulations are created, each with a different range of Smix and oil phase. Transmittance was used to choose the final formulation. According to the optimization plot, the maximum transmittance was produced by Smix at 29.98% and oil phase at 7.56%. The final Tolnaftate microemulgel is then prepared using the optimized formulation. The spreadability, drug content, in-vitro drug release, and rheological study of a six-gel formulation made from different concentrations of carbopol 934, methyl paraben, borax, and triethanolamine were assessed drug content, drug release in vitro, rheological research, and jock itch and athlete's foot in vitro antifungal activities. On the basis of a study on the drug release and penetration through rat skin, formulations with the right consistencies are chosen, and optimization is carried out. Compared to other formulations, the one with the 1:3 ratio of carbopol 934, methyl paraben, borax, and triethanolamine demonstrated better drug release and skin permeability. In vitro release experiments are carried out to ascertain the medication release rate from micro-emugel. In vitro tests on formulation F6 revealed a maximum release of 97.09% after 24 hours. The F2 and F6 formulations are comparable to commercial Itraconazole. As a result, our research shown that the microemulgel formulation of tolnaftate can be applied topically and inhibits the growth of fungi that cause skin illnesses like ringworm, jock itch, and athlete's foot.

Keywords: Tonaftate, Microemulgel, topical formulation.

INTRODUCTION

Transdermal Drug Administration System:

In order for pharmacologically active compounds to exert their effects as efficiently as possible, they must be distributed and released into cells, tissues, and organs in a controlled manner. This is known as a "drug delivery system" (DDS).[1-2] Unlike the traditional direct administration methods that rely on injections with needles. The distribution of numerous therapeutic substances has been greatly impacted by TDDS, particularly in the treatment of disorders of the cardiovascular and central nervous systems, hormone therapy, and pain management.[3-6]

Since TDDS does not enter the digestive tract, first-pass metabolism is not lost, and drugs can be delivered without being impeded by pH, enzymes, or intestinal flora.

Due to the built-in skin barrier, it still does not reach its full potential. The body's outermost organ, the skin, which has many layers, serves to protect us from the outside world by insulating us from toxins, heat, and chemicals.[7-8]

The dermis, which contains blood vessels and produces skin cells, and the epidermis, which acts as a barrier, are two skin layers with elements that prevent transdermal distribution. First, the stratum corneum, the outermost layer, is where the epidermis's stratum barrier effect occurs, is responsible for blocking external substances. When it comes to the movement of compounds with high molecular weights, the barrier effect is crucial. It is widely acknowledged that in TDDS, the intracellular pathway is used for the delivery of drugs with tiny molecular weights. However, approaches and other. In addition to the intercellular pathway, methods involving the intracellular pathway are introduced applied for compounds with a high molecular weight.[9-11]

In the skin the position of both cells and hydrophilic and hydrophobic substances is not totally regular, although has an irregular position but contains cells and both hydrophilic and hydrophobic substances chemicals does occur regularly, this is caused by the structure of the skin.[12]

The concepts of physicochemical properties, which aim to improve medication administration through the skin, can explain these structural characteristics. The dermal layer's vascular system can next prevent transdermal delivery. The interface between the tissues around the skin and the human vasculature is represented by a one cell thick layer of endothelial cells terminating in the papillary loops of the superficial arteriovenous plexus near the dermal epidermal junction in the upper dermis. The endothelium's function in the skin is similar to that of the body as a whole. It reacts promptly

In order to transfer the medicine pass via cellular and vascular, it is necessary to get beyond the stratum corneum's barrier effect in order to reach the target tissue from skin tissue.

In order to overcome this problem, novel TDDS methods have been developed extensively and have gained

popularity as administrative strategies. Such progress might also give it a competitive edge over other drug administration methods in terms of delivered dose, cost-effectiveness, and therapeutic effectiveness.[13-16]

In this article, we cover a number of transdermal medication delivery methods. We list the features of active/passive Transdermal characterisation and delivery techniques. In addition, we go through TDDS's prospects for the future.

TDDS benefits:

- include avoiding preliminary metabolism and gastro intestinal incompatibility
- Wider and more predictable range of motion.
- Reducing undesirable outcomes.
- Offers the using substances with a short biological half-life.
- A little but useful window.
- Enhancing pharmacological and physiological response.
- Preventing fluctuations in drug levels.
- Treatment can be stopped easily at any moment, for more advanced patients.

TDDS's restrictions:

- This course's structure is unsatisfactory for medications that irritate or prick the skin.
- Transdermal delivery cannot be pulsatile in nature.
- Transdermal delivery is not rational nor common sense when large areas of drug skin are involved.
- Transdermal delivery cannot control medications that need high blood levels.
- Can’t reasonable, when medication is mostly utilized within the skin & when atomic size is sufficiently incredible to keep particles from diffusing skin.
- Not reasonable for medication, which doesn't have ideal, O/W segment coefficient.[17]

The Human Skin:

Transdermal is a remarkably effective method of optional transfer. A typical human body's skin has a 2 m^2 surface area and receives approximate33% of the body's blood. It is crucial to understand the skin's transdermal layer, which has an expiration date. The skin is the largest organ in the integumentary system and the outermost layer of the human body. It protects the vital internal organs and major muscles, bones, and ligaments. The average adult's skin is between 1.5 and 2m2 in surface area, with a bigger portion that is between 2.3mm (0.10inch) thick. The typical square inch (6.5cm2) of skin has 1,000 tiny patches, 60,000 melanocytes, 650 sweat glands, and 20 veins. It demonstrates a few significant boundaries.

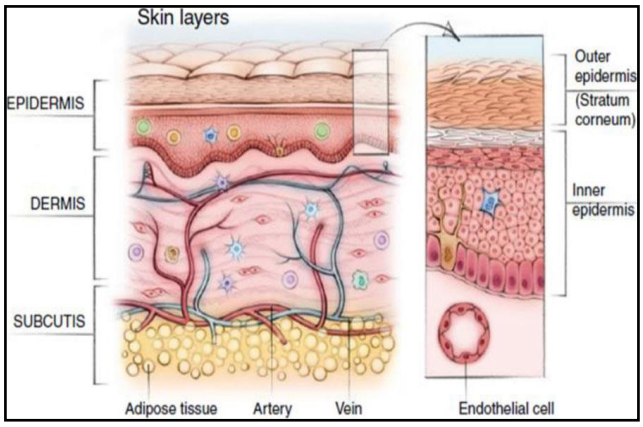


Figure 1: Structure of Skin

Skin's Anatomy:

The skin consists of two basic components. The epidermis is the thinnest, outer layer that is made up of epithelium. The inner, denser, connective tissue layer known as the dermis is connected to the epidermis. There is a subcutaneous layer beneath the dermis. Additionally, this layer is referred to as the shallow belt or hypodermis. Areoles and fat tissues are involved. Dermal fibers that are loosely attached to the skin is attached to it by the subcutaneous layer. Accordingly, the subcutaneous layer connects to vital organs and tissues.[18]

Skin structure:

It is the skin's deepest layer. It forms the protective fold around the body's surface that seals off the water and is made up of distinct squalors epithelium with a fundamental basal lamina. There are no veins in it, and the deepest layer's cells are sustained by blood arteries that extend to the dermis' top layers.

Dermal layer:

The dermis is a connective tissue layer that is 3 to 5 mm thick that is made up of veins, lymphatic vessels, and nerves. The coetaneous blood supply is strictly constrained by the degree of internal heat. In addition to removing toxins and results, it also provides skin with vitamins and oxygen. Most particles that penetrate the skin obstacle settle into capillaries, which extend to within 0.2 mm of the skin surface. The dermal gathering for each inferred is kept low by the blood supply in this way, and the focus contrast across the epidermis that results gives all fixation propensity to transdermal pervasion. contains lymphatic vessels, veins, sweat glands, sebaceous glands, and apocrine organs.

Dermis and epidermis are supported by the subcutaneous fat tissue, hypodermis. It fills in the area where fat is stored. This layer assists in control temperature and provides reliable support and mechanical assurance It provides typical veins for the nerve skin and need to have indisputable crushing organ parts. For transdermal

medication delivery, the drug must pass through all three of these layers and undergo critical dispersion, but if skin drug development occurs, only layer corneum penetration is crucial, and maintenance of the drug in the skin layers is needed shortly after. It contains flexible free connective tissue. The three main cell types are adipocytes, macrophages, and fibroblasts.[19]

Microemulgel:

A topical drug delivery technology with dual release control, microemulgel combines the benefits of gel and microemulsion. To make the drug particles easily pass through the stratum corneum, the emulsion's globule size is reduced to less than 200 nm to create the microemulgel.

The administration of a formulation by means the skin to treat a problem is known as topical drug delivery, which has the advantages of bypassing initial metabolic and enhancing the therapeutic effectiveness of the medicine.[20]

Because topical medications penetrate deeper layers of the skin or mucous membranes to operate, they have localized effects. It allows you flexibility to deliver medications to a spot more successfully. It makes it possible to extend the duration of action for drugs with a constrained therapeutic window and brief biological half-life. The topical drug can be applied topically to any part of the body through the ocular, rectal, vaginal, and cutaneous channels. The method of administration is determined by the type and severity of the illness. Using a drug delivery system, a formulation can be applied directly to the skin to provide the drug's localized effects. As they administer medications more specifically to a particular place, topical drug delivery systems have various benefits. To minimize GI intolerance and metabolic degradation brought on by oral dosing, topical application is used. Additionally, the topical distribution offers a consistent and improved bioavailability of the medicine from the topical dose form, based on the physicochemical features of the carrier and the drug.[21]

Hoar and Schulman developed the idea of a micro-emulsion in the 1940s. A microemulsion is a mixture of liquids that is optically isotropic and thermodynamically stable. It contains water, oil, and amphiphilic. Many medications can be delivered more effectively and have higher bioavailability thanks to the microemulsion. A "microemulsion" is a transparent, thermodynamically stable dispersion of two immiscible liquids that contains oil and water and is stabilized by molecules of surfactant through the formation of an interfacial film. A kinetically stable liquid dispersion of a lipid phase, an aqueous phase, and a surfactant is referred to as a micro-emulsion. The modest oil/water interfacial surface tension and the dispersed particles' size range of 5-200 nm.[22]

Because of their small (less than 25%) globule size, micro-emulsions are transparent. The micro-emulsion can be formed without a lot of energy input. A co-surfactant is frequently used in addition to the aqueous phase, the lipid phase, and the surfactant. Fig. 1 shows the micro-emulsion structure below is described. Depending on their composition, there are three different kinds of microemulsions:

1. Oil in water micro-emulsions in which the water is a continuous aqueous phase and the oil is a scattered phase.

2. Water in oil microemulsions, in which the continuous oil phase is mixed with a water phase;

3. Emulsions that are bi-continuous and contain the system's aqueous and lipid microdomains are interspersed.

Microemulgels, which are created by combining micro-emulsion and gels, display the traits of both. By creating an oil-in-water microemulsion and incorporating it into the gel foundation, Microemulgel aids in the delivery of hydrophobic medications. They offer a wider surface area for drug absorption, and the lipid part increases bioavailability by enhancing drug penetration. Additionally, the micro-emulsion has improved stability because to the gel foundation. Microemulgels are easier to clean if necessary and have a firmer level of elegance than micro-emulsions.[23]

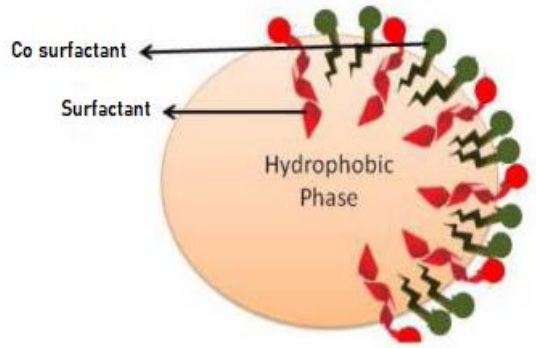


Figure 2: Microemulgel Structure

The use of micro-emulgel as a topical drug delivery system has several benefits

- Using o/w micro-emulsion, hydrophobic medicines can be easily integrated into gels.
- Increased capacity for loading.
- Production viability and inexpensive setup.
- No thorough sonication.
- Controlled ejection.
- The capacity to deliver drugs more precisely to a target spot.
- Preventing gastrointestinal compatibility issues.

Microemulsion Based Gel's Drawbacks

- Medicines with bigger particle sizes are more difficult to absorb through the skin, and some medicines have poor skin permeability.
- Can only be used for medications whose actions depend on very low plasma concentrations.

- The potential for allergic responses.
- The medications could be denatured by an enzyme in the epidermis.
- Drugs or excipients may cause contact dermatitis, which causes skin irritation.[24]

Mechanism of Action:

A topical fungicide is called tolnaftate. It is thought to stop ergosterol manufacture by blocking squalene epoxidase, while the specific mechanism is uncertain. Additionally, it has been observed to alter hyphae and impede mycelial growth in species that are vulnerable to it.

Formulation Considerations:

Selection of Oil Phase:

The lipophilic bioactive molecule may be dissolved in carrier oil, which makes up the oil phase.[25]

Low molecular weight oils, such as triglycerides, are favored in the formulation of micro-emulsions over high molecular weight oils because they can permeate the interfacial film and promote the development of an ideal curvature. Additionally, because micro-emulsions are thermodynamically stable systems, they do not experience Ostwald ripening is an unstable phenomenon, hence it is unnecessary to include oil as ripening inhibitors.[26]

The oil phase for creating a micro-emulsion-based gel is chosen depending on the oil's excess drug solubility. These lipids can range in consistency from mobile liquid to high solids. The lipid phase occasionally acts as a penetration enhancer, therefore a penetration enhancer is not required in a microemulsion delivery system.[27]

A study demonstrates that soybean oil works well in a solution that includes Tween 80, EOs, and water. Soybean oil had a significant impact on the creation of the system, increasing the regimes of microemulsions and reducing the droplet size. It was able to enhance the dilutability of EOs-based microemulsions. It also helped to lessen the volatility of the Eos.[28]

Choosing a surfactant:

The second criterion for surfactant selection was supported by their capacity to create microemulsions with specified lipids that had the best drug solubility.[29]

Surfactants are unit-active molecules with a structural structure that includes both a hydrophilic and a lipotropic region.[30]

Surfactants' amphiphilic nature allows them to disperse two incompatible phases by reducing the surface tension and creating a sufficiently flexible material that can curve to fit the best-curved drops.[31]

They are promptly absorbed by the interface during the emulsification process and prevent the droplets from aggregating.[32]

Such systems are stabilized with Surfactants that are not ionic, zwitterionic, cationic, or anionic. The region of the microemulsion is effective for both ionic and surfactants that lack an ion. Surfactants made of polyoxyethylene, such Brij 35, tween-20/80, like sorbitan monooleate (Span 80), or sugar esters are examples of non-ionic embodied substances.[33]

In contrast to microemulsions, which are thermodynamically unstable, emulsions are stabilized to some extent by the addition of emulsifying agents by lowering their surface tension. Microemulgels, like microemulsion and gel, are a fusion of two dosage forms. A water-in-oil or an oil-in-water mixture that has been gelled by the addition of a gelling agent constitutes a microemulsion. A good surface-active substance strikes a balance between lipotropic and hydrophilic teams and can create stable emulsions. While mineral oils like liquid paraffin have HLB values less than eight and are therefore used. Nonionic surfactants such as spans and tweens are used in the creation of water-in-oil emulsions with the HLB values exceed eight and are used in the formation of o/w emulsions.[34]

Selection of Co-surfactants:

Examples of short- and medium-chain alcohols and polyglycerol derivatives include propylene glycol (PG), ethanol, isopropanol, isopropyl myristate, and isopropyl acetate that are commonly used as cosurfactants. Low irritancy cosurfactants have also been produced using nonionic surfactants.[35]

To temporarily lower the interfacial tension to a negative value, cosurfactants and surfactants are utilized. Fine droplets are produced by the interface expanding at this negative value, and more surfactant and co-surfactant are until the bulk condition is sufficiently depleted to make the interfacial tension positive once more, adsorbed on the surface. Co-surfactant of short-medium chain length alcohols also makes sure that the interfacial layer is flexible enough to deform easily around droplets because the connection between primary surfactant molecules minimizes both the polar head group interaction and the hydrocarbon chain interaction.[36]

Additionally tested as Cosurfectants in microemulsion drug delivery systems were derivatives of ethanol in polyethylene glycol, stearoyl phosphatidyl ethanolamine, propylene glycol fatty acid esters, and polyglycerol, ethyl glycol, and propylene glycol oleic esters.[37]

Choosing a Gelling Agent:

Gel phase is added to formulations to provide the gel structure. Two types of natural and artificial exist. A formulation becomes thixotropic when gel phase is added to it. In O/W microemulsions and nanoemulsions, thickening agents are used to balance the density of the oil portion with the surrounding liquid part. They may therefore delay the occurrence of the deposit or creaming phenomena by focusing on the impact of the attraction

forces.[38] Modifiers for textures are also frequently utilized. In order to prevent the growth of germs, preservative agents must typically be forced into water-based systems. Since EOs are naturally occurring antimicrobials, preservatives are often added on top in the specific situation of EO-based systems. According to the study, EOs-based microemulgel was used to successfully encapsulate the antibacterial compound nisin. Through the synergistic effects of nisin and EOs, rosemary, thyme, oregano, and herbaceous plants were selected to increase the system's overall antibacterial efficacy.[39]

Research demonstrates that carbopol 980 was utilized as a gel base to create an Amophotericin B nano-emulgel that will be an affordable, reliable, and secure carrier for enhanced and sustained topical delivery of Native skin mycosis treated with aminophotericin B.[40]

Diagram of the pseudo-ternary phase:

The phase diagrams are produced using the water titration method, characterize the behavior of mixtures under dilution, and determine the type of structure that occurred in the subsequent emulsification.[41]

An oil, water, and surfactant/co-surfactant combination pseudo-ternary phase diagram is created with a set surfactant/co-surfactant weight ratio. By adding materials to the vial and titrating with water, the emulsification region is created. Visual inspection proves that a mono-phasic and biphasic system has formed. After stirring, clean and transparent mixtures can be seen in monophasic systems, while in biphasic systems, turbidity first emerged, then phase separation. just the area where transparent Microemulsion was taken into consideration. After that, the prepared Microemulsion's particle size and poly-dispersity index (PDI) were examined).[42]

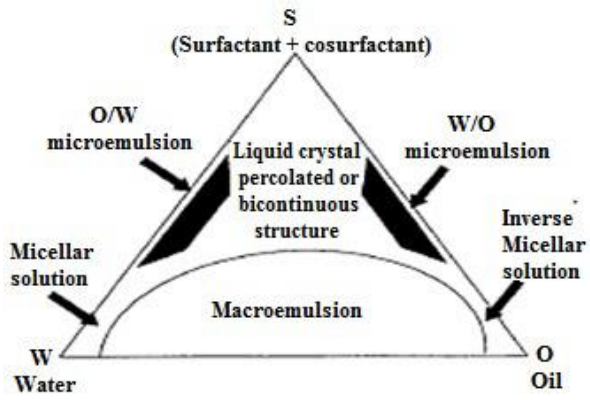


Figure 3: Imaginary phase regions of micro-Oil (O), water (W), and surfactant in an emulsion system + co-surfactant (S)

Formulation Procedures for Micro-emulgel:

Micro-emulgel may be created in three steps.[43]

Step 1: The process of creating an Microemulsions of water in oil or oil in water employing these two phases

Step 2: Gel is made by continuously swirling a gelling chemical and water while optimizing the pH.

Step 3: Micro-emulge is created by mixing micro-emulsion with the gel basis.l.[44-45]

Low energy and high energy emulsification procedures are primarily employed for the manufacture of micro-emulsions

Technique for Emulsification with Low Energy:

For the creation of the micro-emulsion, low energy techniques outperform high energy methods. The phase inversion method and the naturally occurring approach are both part of the low energy technique. When using the phase inversion method, oil, water, and a wetting agent are mixed in a precise ratio. A continuous phase of titration between the oil and aqueous phases results in the creation of nano-sized drops.

The emulsification process is impacted by the presence of wetting agent and co-surfactant. The type of emulsion that forms depend how much wetting agent is used the amount of wetting agent employed in the formulation; temperature also affects emulsion formation.

They are hydrophilic at low temperatures, of the oil in water kind. They are water-in-oil-type lipophilic and higher temperatures. A bi-continuous structure is created by the micro-emulsion of the aqueous phase and oil at an intermediate temperature.

Otherwise, the part inversion approach is utilized to generate a temperature-dependent spontaneous twist of non-ionic material. The spontaneous technique is specifically applied for the unstable element.

The emulsions created at partially inversion temperature will reverse while cooling while being continuously stirred. This method is also confined to include unstable elements, albeit the restriction takes surfactant selection as a way to lower part inversion temperature.[46]

High energy emulsification technique:

By using hard-hitting homogenizers and ultrasonicators, apply strong shear force energy to rupture the interior and inject nano-sized droplets. In this method, the formulation needs to be stabilized by external energy.[47]

MATERIALS AND METHODS

Tolnaftate was obtained as a gift sample from YaxonBiocare Private Limited, Mukherjee Nagar, Sonipat H.R, Soluble Myristate from Delhi's Shiv Ram Park, Swami Enterprises and all other ingredients from TIPER Meerut.

Formulation Method of Tolnaftate Micro-emulgel:

Tolnaftate, Borax (API), Triethanolamine Methyl Paraben, Carbopol-934, Propylene Glycol, (surfactant), and (co-surfactant) & Liquid Paraben (preservative), and Purified H2O (solvent) were used in the manufacture of the microemulgel. The preparation of the microemulgel formulations involved two steps: 1) Micro-emulsion

formation and 2) Micro-emulsion conversion to emulgel. In order to create micro-emulsions, the medication was first dissolved in the oil phase, then water was added while adding the surfactant combination drop by drop on a continuous magnetic stirrer. Using a homogenizer, the resultant transparent, isotropic micro-emulsion was combined with preservatives and pre-swelled gelling polymer to create micro-emulgel. Table lists the ingredients and their quantities 1.[48-49]

Table 1: Composition of Microemulgel formulation

Formulation code	F1	F2	F3	F4	F5	F6
Ingredient	%					
Tolnaftate w/v	1	1	1	1	1	1
Cabopol-934 w/v	10	15	20	10	15	20
Triethanolamine w/v	5	10	15	5	10	15
Isopropyl Myristate	2	4	6	2	4	6
Borax	2	4	6	2	4	6
Propylene glycol w/v	1	1	1	1	1.5	1.5
Methyl Paraben w/v	25	25	25	30	30	30
Liquid Paraben w/v	1	1.2	1	1.1	1.2	1.2
Purified water (v/v)	100	100	100	100	100	100
Speed (RPM)	15000	20000	25000	15000	20000	25000

Evaluation of Formulation:

Physical Appearance:

The clarity of the formulation is one of the crucial characteristics of microemulgels. By visually comparing the prepared anti-fungal microemulgel to a texture in black and white, its clarity was assessed.

Determination of Particle Size (nm):

DLS, or Differential Light Scattering) technology (Austrian inventor Particle Analyzer-Litesizer TM 500, Anton Paar, Graz) was used to determine the mean particle size. Each microemulgel was diluted with water to make it 2% weight per weight. The 2% weight/weight solution was diluted 100 times more. After that, the diluted mixture was put run in triplicate in the glass cuvettes.

Potential Zeta:

the evaluation of a particle's repulsion or attraction is called zeta potential. Its measurement provides information on the electrostatic dispersion measurement mechanism. Pharmaceuticals, brewing, medicine, ceramics, and water treatment are just a few of the many areas where the zeta potential calculation is a significant restriction. The repelling forces between two particles must be dominant for colloidal stability. Zeta potential is a helpful gauge of magnitude for colloidal particle interaction. In general, tests based on zeta potentiometry are used to determine the stability of colloidal systems.

Measurement of pH:

The pH of the created antifungal microemulgel was assessed utilizing a digital pH meter made by Digisun Electronics services.

Determination of Homogeneity:

All produced microemulgels have continued to set in the beaker with homogeneity as determined by visual examination. Physical characteristics and the presence of any particles in the microemulgel were evaluated.

Estimation of % Drug Content Uniformity:

In order to estimate the amount of medication in Microemulgel, 1g of Microemulgel was combined with 50 ml of pH 7.4 phosphate buffer, and the resulting liquid was filtered using a membrane filter. 2 ml of the sample, which was taken out of the mixture and increased to 10 ml, was then examined for its absorbance spectrophotometrically at 262 nm. The calibration curve was used to estimate the amount of tolnaftate in the test sample.

Determination of Microemulgel Spreadability:

To geta test sample's uniform thickness and spreadability, 2gm of Microemulgel was placed in each of the 1 kilogram, two glass slides of weight was placed on each slide for 10 minutes. By retaining two slides, the test sample's ability to spread out microemulgel was assessed in a minute.

Calculation of Viscosity:

Using a Brookfield viscometer (Dv-E, Brookfield), the viscosity of microemulgel was measured. In this technique, the surface of the microemulgel was almost touched by spindle number 4. Viscosity was measured and dial readings on a Brookfield viscometer were recorded at various rpm.

Skin Irritation Study:

The study included 12 rats in total. On the appropriately shaved skin of the rat, the emulgel was applied. Unwanted skin alterations, such as color or morphological changes, were observed for 24 hours.

Antifungal Activity Study:

16.25g ofA 500ml conical flask containing 250ml of filtered water and Sabouraud dextrose agar was heated to a moderate temperature to completely dissolve the agar. around 20 minutes of autoclave sterilization at 121 °C and 15 lb of pressure. The medium was then dissolved in the fungal strain (Tinea pedis) once it had reached room temperature. The three petri dishes were then filled with the medium, which was then allowed to cool and solidify at room temperature. Next, a 6 mm sterile steel bore was used to bore the three cups into each Petridish. The findings were then calculated. The bores were treated with itraconazole concentration and gel formulation (F6), and after that, the petri plates were kept in incubators for 72 hours at 37°C. The radius of the zone of inhibition was calculated following monitoring of the zone of inhibition.

In Vitro Drug Release Studies:

Franzs diffusion cell, which had a cellophane dialysis membrane applied, was used for this research. Phosphate buffer with a pH of 6.8 was poured into the diffusion cell's receptor compartment, which has a capacity of 25 ml. It was soaked to activate the cellophane membrane. For activation, leave it in 50 cc of pH 6.8 phosphate buffer overnight. The membrane, which had a 1 cm2 surface area and was installed between the diffusion cell's donor and receptor compartment, there then trimmed to the necessary size. The assembly was mounted on a hot plate magnetic stirrer, and a magnetic bead was used to continuously agitate the solution in the receptor compartment to maintain a temperature of 37°C and 0.50°C. After applying emulgel to the donor compartment membrane, 1ml of sample was removed at regular intervals. Throughout the experiment, sink conditions must be maintained using the same volume of fresh phosphate buffer was also added to the receptor compartment at the same time. Using a UV spectrophotometer, the samples were examined for drug content at 262 nm.

Studies on stability

The resulting emulgel was placed Features 5g collapsible aluminum tubes and tested for three-month stability tests at 5°C, 25°C with 60% RH, and 30°C with 65% RH, and 40°C with 75% RH. Every so often of 15 days, samples were taken out and tested for pH, viscosity, and drug concentration (Tripartite Guidelines 2003 Harmonized).

RESULTS AND DISCUSSION

Preformulation Study:

Melting Point:

Drug	Melting Point	Normal Range
Tolnaftate	110°C	110-111°C

Solubility:

It was found that tolnaftate has a very low solubility in water and a very low solubility in acetone, ethanol, and methanol. It became soluble in carbon tetrachloride and chloroform. The two main solubilizing solvents were tween-20 and diethyl ether.

Determination of λmax by UV-Spectrophotometer:

Table 2: Calibration data for Analysis of Tolnaftate in methanol at λ262

Concentration (µg/ml)	Absorbance	Standard Deviation
1	0.124	±0.001
2	0.250	±0.001
3	0.390	±0.01
4	0.545	±0.001
5	0.652	±0.00144

FTIR Study:

The IR spectra of the formulation revealed that there was little to no indication of a drug-polymer interaction. Peaks of both medications and their formulation were seen to be identical. Given that there was no change in the positions of the medication's distinctive absorption bands in the formulation, this strongly suggests that the drug did not interact with the polymer there.

Evaluation of Formulation:

Physical properties:

It was assessed visually, and the findings are shown in the table. Every formulated emulgel had excellent homogeneity and was lump-free. Microemulgel has opaque physical characteristics and is often white in color**.**

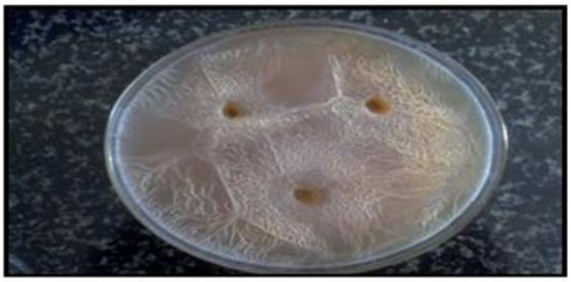
Table 3: Evaluation of Tolnaftate

Formulation Code	Physical appearance	pH	% Drug Content Uniformity	Particle Size (nm)
F1	Clear White	6.1	76.10	126.22
F2	White	5.8	80.42	112.55
F3	White	4.6	82.26	123.50
F4	Clear White	5.8	83.66	140.40
F5	Clear White	6.5	90.46	156.36
F6	Clear White	5.9	92.16	120.14

Table 4: Comparative Viscosity values and Spreadibility

Formulation Code	Viscosity (cps)*	Spreadibility	Homogeneity
F1	78.8±0.5	16.52	+++
F2	87.5±0.2	26.16	++
F3	83.5±0.4	32.13	++
F4	110.2±0.8	38.32	++
F5	135.6±0.2	35.54	+++
F6	139.3±0.9	39.40	++

Zone of Inhibition of F6 micro emulgel formulation



Zone of inhibition of standard microemulgel formulation

Zone of inhibition of Tolnaftate microemulgel formulation

Figure 4: Zone of inhibition of F6 micro emulgel, Standard microemulgel, Tolnaflate microemulgen formulation

Table 5: Zeta Potential and Globule sizes

Formulation Code	Zeta Potential (mv)	Globule Size (nm)
F1	-4.64	56.12
F2	5.08	60.22
F3	4.56	56.48
F4	-10.40	49.71
F5	-3.45	64.36
F6	4.18	48.86

Study on Antifungal Activity:

Tablet 6: Study of Antifungal Activity

Formulation	Zone of Inhibition ($mm^{2)}$
Standard drug	8.9
F6	8.4

In Vitro drug release studies:

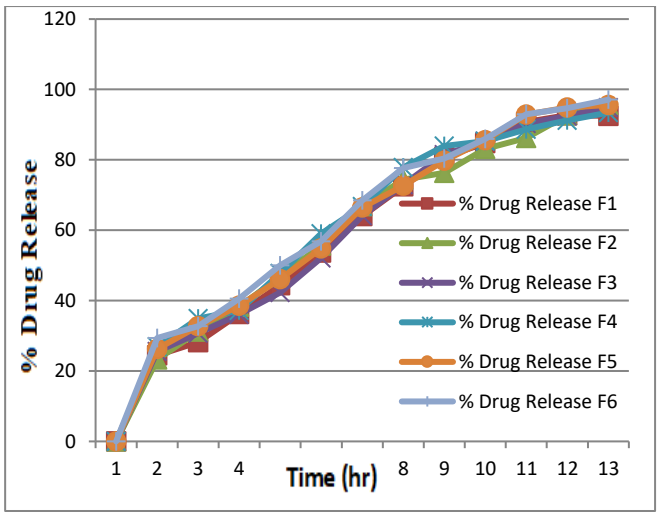


Figure 5: *In-vitro* drug diffusion study of Microemulgel F1-F6

Table 7: *In Vitro* drug release studies

Time (hr)	% Drug Release					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	24.45	23.28	25.54	26.90	26.24	29.34
3	28.22	31.15	30.76	34.88	32.74	32.76
4	36.16	38.31	36.14	37.18	38.58	40.56
7	44.36	46.72	42.26	47.78	46.09	50.01
8	53.68	55.65	52.14	59.03	54.87	56.87
9	64.05	66.86	64.10	66.78	66.52	68.44
10	72.50	74.42	72.94	77.89	72.64	77.64
12	80.72	76.35	81.46	83.90	79.72	80.36
14	84.72	83.15	85.35	85.29	85.62	85.91
16	90.81	86.24	90.34	88.65	92.86	92.95
20	92.70	92.71	92.46	91.18	94.89	94.64
24	92.45	95.58	94.89	93.42	95.61	97.09

Skin Irritation Test:

The test for skin irritability was performed on twelve Wistar rats, either six or twelve. While the test group received treatment with the improved formulation F6, the control group received only a gel base without any medication. After 24 hours, it was noticed that neither group had any evidence of irritation or redness, therefore they were given as the result. This demonstrates the safety of using the created formulation.

Stability Study:

After three months of storage, all of the created microemulgel formulations were discovered to remain intact; however, several changes in pH, viscosity, and drug release had occurred.

CONCLUSION

To ensure more patient compliance, drug delivery via micro-emugel will be employed extensively in the future. Better spreadability and viscosity are provided by microemulgel, which quickly gained popularity. Additionally, they will develop into gel basis for solutions used to load hydrophobic medicines for long-term stability. Similar to this, Tolnaftate micro-emugels were created for the study and put through physiochemical tests such spreading coefficient, rheological, antifungal activity, and in vitro drug release tests. In vitro release assays were carried out to figure out the medication release rate from micro-emugel. In vitro tests on formulation F6 revealed a maximum release of 97.09% after 24 hours. The F2 and F6 formulations were equivalent to commercial Itraconazole. Thus, our research shown that Tolnaftate can be used topically in the microemulgel formulation, which inhibits the development of bacteria.

REFERENCES

1. Vega-Vásquez, Mosier, and Irudayaraj. Nanoscale drug delivery systems: from medicine to agriculture, Front BioengBiotechnol. 2020;8:79-84. Doi: 10.3389/fbioe.2020.00079.
2. Mitragotri S, Anselmo AC, and Vargason AM. the advancement of industrial medication delivery techniques. 2021. Nat Biomed Eng. 10.138/s41 551-021-00698-w.
3. Brambilla DA, Babity S, Laszlo E, and Roohnikan M. An overview of Canadian research in transdermal and tropical medication delivery. Pharmaceutics. 2019;11(6):256-61.
4. Pea-Juárez MC, Guadarrama-Escobar OR, Escobar-Chávez JJ. Transdermal delivery systems for biomolecules. 2021;6:1-14.
5. Leppert W, Malec-Milewska M, Zajaczkowska R, Wordliczek. Transdermal and Topical Drug Administration in the Treatment of Pain. Molecules. 2018; 23(3):681-6.
6. Akhter, N., Singh, V., Yusuf, M., Khan, R.A. Non-invasive drug delivery technology: creation and current status of transdermal drug delivery devices, methodologies, and biomedical applications. Biomed Tech. 2020;65(3): 243-72.
7. Wang M, Luo Y, Wang T, Wan C, Pan L, Pan S, et al. Artificial skin perception. Adv Mater. 2020;33:e2003014.
8. Hutton AR, Donnelly RF, Larraeta E, and McCrudden MT. Influence of molecular weight on hydrogel-forming microneedles-based transdermal distribution of model macromolecules: potential to improve delivery of innovative low-molecular-weight biotherapeutics. J Mater Chem B. 2020;8(19):4202-9.
9. Prausnitz MR, Jeong EH, and Andrews SM. Full epidermis, not just Stratum Corneum, limits the transdermal transport of molecules. Pharm Res. 2013;30(4):1099.
10. Chaulagain B, Jain SK, Tiwari A, Verma A. Transdermal route of passive protein drug administration. Artif Cells NanomedBiotechnol. 2018; 46(1):472-87.
11. Ogbonna J, Attama AA, Uchechi O. Drug delivery via cutaneous and transdermal nanoparticles. In: Drug delivery using nanotechnology. p. 193-235 in Sezer AD, InTech C, 2014.
12. Pradhan S, Shrestha K, Yuan L, Zhou X, Hao Y, and Pradhan O. A review of nanoformulations for transdermal medication delivery. Chin Chem Lett. 2018; 29(12):1713–1724.
13. Mujoriya R and Dhamande KA. An analysis of transdermal medication delivery. Res J Sci Tech. 2011;3(4):227–31.
14. Patel R, Patel A, Prajapati B, Shinde G, and Dharamsi A. A brief review of transdermal medication delivery techniques. International Journal of Advanced Research. 2018;6(5):891-900.
15. Kakar, Singh, and Rani. Transdermal medication delivery examined. Innoriginal Int J Sci. 2016;3(4):1–5.
16. Govil, S.K., and Tyle, P., Drug Delivery: Fundamentals and Application, Marcel Dekker, Inc., New York, 1998: 385–406.
17. Jayaswal SB, Sood R. The Eastern Pharmacist, 1987; 30(357): 47–50
18. Hoar TP, Schulman JH, Transparent Water-In-Oil Dispersions, The Oleopathic Hydro-Micelle, Nature, 1943: 152; 102-103.
19. J.H. Schulman, W. Stoeckenius, and L.M. Prince, Mechanism of Formation and Structure of Microemulsions By Electron Microscopy, J. Phys. Chem., 1959:63:1677–1680.
20. Rajput R., Sharma S., and Kumar V. Microemulsions are a recent discovery in sustained release medicine delivery techniques. Global Journal of Pharmaceutical Research. 2016;7:1326–1332.
21. Mishra A, Panola R, and Rana AC. Microemulsions are a method of medication delivery. J Sci Innov Res. 2014;3: 467-474.
22. Ashara KC, Paun JS, Soniwala MM, Chavda JR, Mendapara VP, and Mori NM. Microemulgel is a useful technique for enhancing the therapeutic efficacy of drug moiety. Pharmacy Journal. 2014; 24: 452-457.
23. Vats S, Saxena C, Easwari TS, and Shukla VK. An innovative method for improving the topical administration of hydrophobic medicines is the emulsion-based gel technique. Int. J. Pharm. Res. 2014;3: 649–660.
24. Patravale VB and Bachhav YG. Clotrimazole vaginal gel made from a microemulsion: formulation, in vitro testing, and stability tests. Aaps Pharm. Sci. Tech. 2019;10:476-481.
25. Flanagan J and Singh H. Microemulsions: A Potential Delivery System for Bioactives in Food. Critical Reviews in Food Science and Nutrition. 2016;46(2):221-237

26. Wani RR, Patil MP, Dhurjad P, Chaudhari CA and Kshirsagar SJ. Microemulsion based gel: A novel approach in delivery of hydrophobic drugs. Int J Pharm Res Sch. 2015; 4:398-410.
27. RB Patel, MR Patel, KK Bhatt, and BG Patel. For the transnasal administration of carbamazepine, formulation consideration and characterisation of microemulsion drug delivery system. Cairo University's Faculty of Pharmacy Bulletin. 2013; 51: 243-253.
28. Sharma PK, Kumar A. Celecoxib microemulsion for topical delivery: development, characterisation, and evaluation. J Dis Sci Tech, 2012;33:1411–1418.
29. Nastiti CM, Ponto T, Abd E, Grice JE, Benson HA, and Roberts MS. Skin delivery with topical nano- and microemulsions. Pharm., 2017;9:37-43.
30. Muhammad AS, Daik R, and Ramli S. Study on the impact of oil phase and co-surfactant on microemulsion. Malasiyan Journal of Anal Science. 2017;21: 1406–41.
31. Fontana MC, Rezer JFP, Coradini K, Leal DBR, and Beck RCR. improved effectiveness of a dermatological nanomedicine containing clobetasol propionate in treating contact dermatitis in rats. Eur. J. Pharma. Biopharm. 2011; 79: 241-249.
32. Xenakis A, Chatzidaki MD, Balkiza F, Gad E, Alexandraki V, Avramiotis S, Georgalaki M, Papadimitriou V, Tsakalidou E, and K. Papadimitriou. Nisin as nano-carriers of reverse micelles for the defense against foodborne bacteria. The case of essential oils in Part II. Food Chemistry.2019; 278: 415–423.
33. Hussain A, Samad A, Singh SK, Ahsan MN, Haque MW, Faruk A, and Ahmed FJ. Topical administration of an antifungal medication using nanoemulsion gel: in vitro activity and in vivo evaluation.2016; 23:642-657.
34. Samson S, Basri M, Masoumi HRF, Karjiban RA, and Malek EA. By using D-optimal mixture design, a nanoemulsion system containing copper peptide was created, and its physicochemical characteristics were assessed. RSC advancements. 2016; 6: 17845–17856.
35. Kesavan K, Kant S, Singh PN, and JK Pandit. Evaluation in vitro and in vivo of a mucoadhesive, cationic microemulsion of dexamethasone for ocular administration. Current eye research.2013; 38:342–352.
36. Nandgude T, Patil S, Syed N, Jadhav A, and Wani M, J Dis Sci Tech, 2016;36:911–917.
37. A Novel Topical Drug Delivery Approach: Phytoconstituent Based Microemulgel. Int J Res Pharma Sci., 2020;11:6595-6605.
38. Kale SN and Deore SL. Emulsion microemulsion and nanoemulsion: a review. Sys Rev Pharma.2017; 8: 39–47.
39. Patel K, Patel R, and Patel M. creation and description of an antifungal drug's microemulsion-based gel. Pharma Tutor.2014; 2:79–89.
40. Lovelyn C and Attama AA. Current medication delivery status of nanoemulsions. J Bio Nanobiotech, 2011;2:626-31.
41. Qian C and McClements DJ. Particle size influences the formation of nanoemulsions stabilized by model food-grade emulsifiers utilizing high pressure homogenization. Food Hydrocolloids. 2011;25:1000-1008.
42. Chincholkar AM, Nandgude TD and Poddar SS. Formulation of in-situ gelling ophthalmic drops of moxifloxacin. W J Pharma Res. 2016; 5:712–725.
43. Purohit DK. Nano-lipid carriers for topical application: The present situation. Asian Journal of Pharmacology. 2016; 10: 1–9.
44. Shah KK, Shiradkar MR, and Bindu VH. Aceclofenac transdermal delivery: The role of piperine and its mechanism of action. Int. J. Pharma Bio Sci.2011; 2: 10–18.
45. Nandgude T, Thube R, Jaiswal N, Deshmukh P, Chatap V, and Hire N. creation and assessment of a salbutamol sulphate pH-induced in-situ nasal gel. Int J Pharm Sci Nanotechnol, 2008;1:177–182.
46. DePillis GD, Wu JC, Matsuda A, and Santi DV. 5-Fluorocytosine in DNA is a mechanism-based inhibitor of HhaI methylase, according to Osterman DG, Biochemistry. 1988 July 12;27(14):5204-10.
47. Waldorf AR, Polak A. Mechanisms of action of 5-fluorocytosineAntimicrob Agents Chemother. 1983 January;23(1):79-85.
48. Sujit Kakade & Amjadkhan Pathan, Naproxen Microemulsion Gel Formulation and Evaluation for Transdermal Delivery, International Journal of Pharmaceutical Research and Applications, 2023;8(1):647–658.
49. Basha BN, Prakasam K, Goli D. Formulation and evaluation of gel containing fluconazole antifungal agent. Int J Drug Dev Res 2011;3(4):109-28.
50. Sabir F, Asad MI, Qindee M, Afza I, Dar MJ, Shah KU., Polymeric nanogel as versatile nano platforms for biomedical applications. J Nanomater. 2019;20(2):1155-71.

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