AN APPLICATION OF NATURAL SOURCES IN FORMULATING KETOCONAZOLE LOADED MICRO DISPERSION GEL

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ABSTRACT

Keywords:

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The objective of the present work was to formulate and characterized micro dispersion gel (MDG) for topical delivery of water insoluble antifungal agent ketoconazole in order to enhance its solubility penetration through the skin and antifungal activity. By the use of an application of natural source like Santalum album in formulation ketoconazole loaded MDG was prepared and then evaluated for different physiochemical parameter like homogeneity, pH, spread ability, drug content, percentage yield, in-vitro diffusion study, skin irritation study. The medical use of this formulation is used to treat a certain skin condition (Seborrheic dermatitis, a type of dandruff) and it is also useful in swelling or patches on skin, inflammation, itching and eczema. This review focus on research till now done an antifungal gel and detailed study over it.

1. Introduction

Fungal infection of the skin is nowadays one of the most common dermatological problems. The physicians have a wide choice for treatment from solid dosage to semisolid dosage form and to liquid dosage formulation. Among the topical formulation, clear transparent gels have widely accepted in both cosmetics and pharmaceuticals.[1] Topical treatment of dermatological disease as well as skin care, a wide variety of vehicles ranging from solids to semisolid and liquid preparations are available to clinicians and patients. Within the major group of semisolid preparations, the use of transparent gels has expanded both in cosmetics and in pharmaceutical preparation.[2] Delivery of drugs to the skin is an effective and targeted therapy for local dermatological disorders. This route of drug delivery has gained popularity because it avoids first-pass effects, gastrointestinal irritation, and metabolic degradation associated with oral administration. Due to the first pass effect, only 25-45% of the orally administered dose reaches the blood circulation. In order to bypass these disadvantages, the gel formulations have been proposed as a topical application.[3]

2. Topical Drug Delivery System

Topical drug delivery systems are localized drug delivery system for local delivery of therapeutic agents via skin to treat the cutaneous disorder. These systems are generally used for local skin infection. The formulations are available in different forms, like from solid through semisolid to liquid. If the drug substance in the solution has a favorable lipid/water partition coefficient and if it is a non-electrolyte, then drug absorption is enhanced via the skin [4].

2.1 Anatomy of Skin [5]

The skin is the largest organ of the body, accounting for about 15% of the total adult body weight. It performs many vital functions, including protection against external physical, chemical, and biologic assailants, as well as prevention of excess water loss from the body and a role in thermoregulation. The skin is continuous, with the mucous membranes lining the body's surface.

The structure of human skin (Fig.1) can be categorized into five main layers

- a) The epidermis
- b) The non-viable epidermis
- c) A viable epidermis (Stratum corneum)
- d) A overlying dermis
- e) The innermost subcutaneous fat layer (Hypodermis)

Fig.1. Anatomy of skin

i) The Epidermis

The epidermis is composed of keratinized, stratified squamous epithelium. It is made of four or five layers of epithelial cells, depending on its location in the body. It does not have any blood vessels within it (i.e., it is avascular).

ii) The Non-Viable Epidermis

The stratum corneum (Latin for ‘horny layer’) is the outermost layer of the epidermis. There has been a long-standing belief in dermatology that the stratum corneum consisted of dead cells (corneocytes), devoid of biological

activity and function. The stratum corneum is now understood to be live tissue that performs protective and adaptive physiological functions including mechanical shear, impact resistance, water flux and hydration regulation, microbial proliferation and invasion regulation, initiation of inflammation through cytokine activation and dendritic cell activity, and selective permeability to exclude toxins, irritants, and allergens. This layer is composed of 15–20 layers of flattened cells with no nuclei or cell organelles.

iii) The Viable Epidermis

Viable epidermis is the layer of the skin situated below the stratum corneum. It is situated, squamous and keratinizing epithelium and is responsible for the barrier properties of the skin. It contains melanocytes, langerhans cells and markel cells. It contains other layers in which the cells are at different stages of differentiation.

iv) Dermis

The dermis or corneum is a layer of skin between the epidermis (with which it makes up the cutis) and subcutaneous tissue, that primarily consist of dense irregular connective tissue and subcutaneous tissues, that primarily consists of dense irregular connective tissue and cushions the body from stress and strain. It is divided into two layers, the superficial area adjacent to the epidermis called the papillary region and a deep thicker area know as the reticular dermis. The dermis is tightly connected to the epidermis through a basement membrane. Structural components of the dermis are collagen, elastic fibres, and thermoreceptors that provide the sense of heat. In addition, hair follicle, sweat glands (oil glands), apocrine glands, lymphatic vessels,

nerves and blood vessels are present in the dermis. Those blood vessels provide nourishment and waste for both dermal epidermal cells.

v) Hypodermis

The hypodermis (subcutaneous layer, or sperfiocial fascia) lies between the dermis and underlying tissues and organs. It consists of mostly adipose tissue and is the storage site of more body fat. It serves to fasten the skin to the underlying surface, provides thermal.

2.2 Rationale For Topical Preparation [6]

With the purpose to formulate an efficient and effective topical preparation, considerations are mainly concerned with the site of action of the drugs and its effect. Topical preparations may be used productively:

i) Effects on Surface Includes

- a) The cleansing effect of removing germs and dirt.
- b) Improves cosmetic appearance.
- c) Protective action against moisture.
- d) Produce an antimicrobial effect.

ii) Effects on Stratum Corneum include

- a) Protectives that penetrate this layer.
- b) Keratolytic action.
- c) Moisturizing effect.
- d) Effects on Viable epidermis and dermis: Anesthetic, anti-inflammatory, antihistamine, antipruritic, etc. are the major classes of drugs that penetrate these layers.

2.3 Factors Affecting Topical drug absorption[7]

i) Physiological factors

- Thickness of skin
- pH of skin
- Temperature of skin
- Lipid content
- Density of sweat gland
- Hydration of skin
- Inflammation of skin
- Blood flow

ii) Physiochemical factors

- Partition coefficient
- Molecular weight of drug
- Degree of ionization
- Vehicle effect

3. Introduction of Natural Resources [8]

The natural resources like Sandalwood (*Santalum album*) is one of the most one of the important tropical trees which is commercially known for its fragrance. It is a member of family *Santalaceae* and being as perfumery material it is commonly known as Chandan. It is a small- to medium-sized hemiparasitic tree, distributed rather widely in India. Sandalwood is mostly confined to the South Indian states, especially Karnataka, Tamil Nadu and Kerala, and is indigenous to Peninsular India

Biological Source

Sandalwood consists of the Heartwood of the stems and roots of *Santalum album* Linn., an evergreen small tree of the family *Santalaceae*.

Chemical Constituent

Sandalwood oil contains more than 90% sesquiterpenic alcohols of which 50-60% is the tricyclic α -santalol. β -Santalol comprises 20-25%. Current ISO standards for *S. album* oil, are 41-55 % α -santalol and 16-24 % β -santalol Sandalwood contains 2 to 5 percent of volatile oil, which contains 90 to 97 percent of sesquiterpene alcohols, called santalols.

Uses of Sandalwood

Sandalwood contains 3 - 6% essential oils (predominantly the sesquiterpenols alpha- and beta-santalol), resin and tannin. It is an aromatic, bittersweet, astringent herb that cools the body, calms the mind, relieves spasms and improves digestion. It has diuretic, analgesic, antiseptic, expectorant and stimulant effect. The wood or essential oil is taken internally in the treatment of genito-urinary disorders, fever, sunstroke, digestive problems and abdominal pain. A paste of the wood is used externally to treat skin complaints. Sandalwood oil is little used in Modern Herbalism, its main application is in aromatherapy.

4. What is gel?[9]

Gels are defined as semi rigid systems in which the movement of the dispersing medium is restricted by an interlacing three-dimensional network of particles or solvated macromolecules of the dispersed phase. The word “gel” is derived from “gelatin,” and both “gel” and “jelly” can be drawn back to the Latin gelu for “frost” and gel are, meaning “freeze” or “congeal.” This origin indicates the essential idea of a liquid setting to a solid-like material that does not flow, but

is elastic and retains some liquid characteristics. Use of the term “gel” as a classification originated during the late 1800s as chemists attempted to classify semisolid substances according to their phenomenological characteristics rather than their molecular compositions. At that time, analytical methods needed to determine chemical structures were lacking. [The USP defines gels (sometimes called jellies) as semisolid systems containing either suspensions made up of small inorganic particles, or large organic molecules interpenetrated by a liquid. In a two-phase system, if the particle size of the dispersed phase is relatively large, the gel mass is sometimes called as a magma. Single-phase gels consist of organic macromolecules uniformly circulated throughout a liquid in such a way that no apparent boundaries occur between the dispersed macromolecules and the liquid.

4.1.Terminology Related To Gel

A number of terms are commonly used in discussing some of the characteristics of gels, including imbibition, swelling, syneresis, thixotropy, and xerogel. [10]

- **Imbibition** is the taking up of a certain amount of liquid without a measurable increase in volume.
- **Swelling** is taking up of a liquid by a gel with a rise in the volume. Only liquids that solvate a gel can cause swelling. The swelling of protein gels is influenced by pH and the presence of electrolytes.
- **Thixotropy** is a reversible gel-sol formation with no change in volume or temperature, a type of non-Newtonian flow.
- **Xerogel** is formed when the liquid is removed from a gel and only the framework remains. E.g., Gelatin sheets, tragacanth ribbons, acacia tears, etc.

4.2 Structure of GEL [11]

Figure 1: Representations of gel structures. (a) Flocculated particles in a two-phase gel structure. (b) Network of elongated particles or rods forming a gel structure. (c) Matted fibers as found in soap gels. (d) Crystalline and amorphous regions in a gel of carboxymethylcellulose.

4.3 Advantages [12], [13]

- Hydrophobic drugs can be easily incorporated into gels using d/o/w emulsions. Most of the hydrophobic drugs cannot be incorporated directly into gel base because solubility act as a barrier and problem arises during the release of the drug. Emulgel helps in the incorporation of hydrophobic drugs into the oil phase and then oily globules are dispersed in an aqueous phase resulting in o/w emulsion. And this emulsion can be mixed into gel base. This may be proving better stability and release of drug than simply incorporating drugs into gel base.
- Better stability: Other transdermal preparations are comparatively less stable than emulgels. Like powders are hygroscopic, creams shows phase

inversion or breaking and ointment shows rancidity due to oily base.

- Better loading capacity: Other novel approaches like micelles and liposomes are about micro size and due to vascular structures may result in leakage and result in lesser entrapment efficiency. But gels due to vast network have comparatively better loading capacity.
- Production feasibility and low preparation cost: Preparation of emulgels comprises of simpler and short steps which increases the feasibility of the production. There are no specialized instruments needed for the production of emulgels. Moreover, materials used are easily available and cheaper. Hence, decreases the production cost of emulgels.
- No intensive sonication: Production of vesicular molecules need intensive sonication which may result in drug degradation and leakage. But this problem is not seen during the production of emulgels as no sonication is needed.

- Controlled release: Emulgels can be used to prolong the effect of drugs having shorter $t_{1/2}$.

4.4 Limitation

- Expensive technique to completely remove the solvents and surfactants at the end of the preparation process.
- Surfactant or monomer traces may remain and can import adverse effects.
- Difficulty in handling.
- Difficulty in loading.

4.5 Properties of gel [10], [11]

- Ideally, the gelling agent must be inert, safe and cannot react with other formulation constituents.
- The gelling agent should produce a sensible solid-like nature at the time of storage, which is easily broken when exposed to shear forces produced by squeezing the tube, trembling the bottle or at the time of topical application.
- It should have suitable anti-microbial agent.
- The topical gel must not be sticky.
- The ophthalmic gel must be sterile.
- They exhibit the mechanical characteristics of the solid state.

- Each component is continuous throughout the system.

4.6 Classification of GEL

Gels can be classified based on colloidal phases, nature of solvent used, physical nature and rheological properties, etc.

i) Based on colloidal phases [10], [14], [15]

a) Inorganic (Two phase system)

If the partition size of dispersed phase is relatively large and form the three-dimensional structure throughout gel, such a system consists of floccules of small particles rather than larger molecules and gel structure, in this, system is not always stable. They must be thixotropic-forming semisolid on standing and become liquid on agitation.

b) Organic (Single phase system)

These consist of large organic molecules existing on the twisted strands dissolved in a continuous phase. This larger organic molecule either natural or synthetic polymers are referred as gel formers, they tend to entangle with each other their random motion or bound together by Vander walls forces.

ii) Based on nature of solvent:- [10], [14], [15]

a) Hydrogels (Water based)

A hydrogel is a network of polymer chains that are hydrophilic, infrequently found as a colloidal gel in which water is dispersion medium. They are highly absorbent natural or synthetic polymeric networks. They also have a degree of flexibility likely of the natural tissue, due to their significant water content.

b) Organogels (With a non-aqueous solvent)

An organogel is a non-crystalline, non-glassy thermoreversible solid material composed of a liquid organic phase trapped in a 3D cross-linked network. The liquid can be, E.g., vegetable oil, an organic solvent or mineral oil. The solubility and particle sizes of the structuring are significant characteristics for the elastic properties and firmness of the organogel. Frequently, these systems are based on self-assembly of the structurant molecules.

c) Xerogels

It is a solid formed from a gel by drying with unrestricted shrinkage. It is frequently retains high porosity (15-50%) and huge surface area

(150-900 m²/g), along with very small pore size (1-10 nm). When solvent removed under supercritical conditions, the network doesn't shrink and a highly porous, low-density material known as an aerogel is produced. Heat treatment of a xerogel at higher temperature produces viscous sintering and efficiently transforms the porous gel into a thick glass. E.g., Tragacanth ribbons, β -cyclodextrin, dry cellulose and polystyrene, gelatin sheets and acacia tears.

iii) **Based On Rheological Properties**
[10-14-15]

a) **Plastic GELS**

E.g., Bingham bodies, flocculated suspensions of Aluminum hydroxide exhibit a plastic flow and the plot of rheogram gives the yield value of the gels above which the elastic gel distorts and begins to flow.

b) **Pseudo-Plastic GELS**

E.g., Liquid dispersion of tragacanth, sodium alginate, Na CMC, etc. exhibits pseudo-plastic flow. Viscosity of these gels decreases with increasing rate of shear, with no yield value. The rheogram results from a shearing action on the long chain molecules of the linear polymers. As the shearing stress is increased

the disarranged molecules begin to align their long axis in the direction of flow with the release of solvent from gel matrix.

c) **Thixotropic Gels**

The bonds between particles in these gels are very weak and can be broken down by shaking. The resulting solution will revert back to gel due to the particles colliding and linking together again (the reversible isothermal gel-sol-gel transformation). This occurs in a colloidal system with non-spherical particles to build up a scaffold like structure. E.g., Kaolin, bentonite, agar, etc.

iv) **Based On Physical Nature [10-14-15]**

a) **Elastic gels**

Gels of agar, pectin, Guar gum and alginates exhibit an elastic behavior. The fibrous molecules being linked at the point of junction by comparatively weak bonds like hydrogen bonds and dipole attraction. If the molecule possesses free -COOH group then additional bonding takes place by a salt bridge of the type -COO-X-COO between two adjacent strand networks. E.g., Alginate and Carbopol.

b) Rigid Gels

This can be formed from macromolecule in which the framework linked by primary valence bonds. E.g., In silica gel, silic acid molecules are held by Si-O-Si-O bond to give a polymer structure possessing a network of pores.

c) Preparation of Gels [15]

Gels are normally in the industrial scale prepared under room temperature. However, few of polymers need special treatment before processing. Gels can be prepared by the following methods:

- **Thermal Changes**

Solvated polymers (lipophilic colloids) when subjected to thermal changes causes gelatin. Many hydrogen formers are more soluble in hotter than cold water. If the temperature is reduced, the degree of hydration is decreased and gelation takes place. (The cooling of a concentrated hot solution will produce a gel). E.g., Gelatin, agar sodium oleate, guar gummed, cellulose derivatives, etc. In contrast to this, some materials like cellulose ether have their water solubility to hydrogen bonding with the water. Raising the

temperature of these solutions will disrupt the hydrogen bonding and reduced solubility, which will cause gelation. Hence this method cannot be adopted to prepare gels as a general method. [15]

- **Flocculation**

Here gelation is produced by adding just sufficient quantity of salt to precipitate to produce age state, but inadequate to bring about complete precipitation. It is essential to ensure quick mixing to avoid local high concentration of precipitant. E.g., A solution of ethyl cellulose, polystyrene in benzene can be gelled by quick mixing with suitable amounts of a non-solvent such as petroleum ether. The adding of salts in hydrophobic solution brings about coagulation, gelation is infrequently observed. The gels formed by flocculation method are Thixotropic in behavior. [15]

- **Chemical Reaction**

In this method gel is produced by chemical interaction between the solute and solvent. E.g., Aluminium hydroxide gel can be prepared by interaction in aqueous solution of

an aluminium salt and sodium carbonate an increased concentration of reactants will produce a gel structure. Few other examples that involve chemical reaction between PVA, cyanoacrylates with glycidol ether (Glycidol), toluene diisocyanates (TDI), methane diphenyl isocyanine (MDI) that cross-links the polymeric chain. [15]

d) Formulation Considerations for Pharmaceutical Gels [16]

- **The choice of vehicle/solvent:**

This forms the aqueous phase of the emulsion. Commonly used agents are water, alcohols. E.g., alcohol, glycerol, PG, PEG 400, etc.

- **Oils:**

These agents form the oily phase if the emulsion. For externally applied emulsions, mineral oils, either alone or combined with soft or hard paraffins, are widely used both as the vehicle for the drug and for their occlusive and sensory characteristics. Widely used oils in oral preparations are nonbiodegradable mineral and castor oils that provide a local laxative effect or various fixed oils of vegetable origin (e.g., arachis, cottonseed,

and maize oils) as nutritional supplements. [16]

- **Emulsifiers:**

Emulsifying agents are used both to promote emulsification at the time of manufacture and to control stability during a shelf life that can

Substance	Gel-forming concentrations (wt%)	Required additives
Gelatin	2-5	
Alginates	0.5-1	Ca ²⁺
Pectins (low methoxy)	0.8-2	Ca ²⁺
Carboxymethylcellulose	4-6	Na ²⁺
Cetostearly alcohol	10	Cetrimide

vary from days for extemporaneously prepared emulsions to months or years for commercial preparations. eg Polyethylene glycol 40 stearate, Sorbitan monooleate (Span 80), Polyoxyethylene sorbitan Monooleate (Tween 80), Stearic acid, Sodium stearate.

- **Gelling Agent**

These are the agents used to increase the consistency of any dosage form can also be used as thickening agent.

- **Permeation Enhancers:**

These are agents that partition into and interact with skin constituents to induce a temporary and reversible increase in skin permeability.

- **Inclusion Of Buffers**

Buffers may be involved in aqueous and hydroalcoholic-based gels to control the pH of the formulation. The solubility of buffer salts is reduced in hydroalcoholic-based vehicles. E.g., Phosphate, citrate, etc.

- **Preservatives**

Certain preservatives cooperate with the hydrophilic polymers used to prepare gels, thereby reducing the concentration of free (antimicrobially active) preservative in the preparation. Therefore, to compensate for this, the initial concentration of these preservatives should be improved. E.g., Parabens, phenolics, etc. [16]

5. Evaluation of ketoconazole micro dispersion gel

i) Globule size and its distribution in Emulgel

Globule size and distribution was determined by Malvern zetasizer. A 1.0 gm sample was dissolved in purified water and agitated to get

homogeneous dispersion. The sample was injected to photocell of zetasizer. Mean globule diameter and distribution was obtained. [16]

ii) Rheological Study

The viscosity of the different emulgel formulations is determined at 25°C using a cone and plate viscometer with spindle 52 (Brookfield Engineering Laboratories,) and connected to a thermostatically controlled circulating water bath. [16]

iii) Swelling Index

To determine the swelling index of prepared topical emulgel, 1 gm of gel is taken on porous aluminum foil and then placed separately in a 50 ml beaker containing 10 ml 0.1 N NaOH. Then samples were removed from beakers at different time intervals and put it on dry place for some time after it reweighed. Swelling index is calculated as follows:
Swelling Index (SW) % = $[(W_t - W_o) / W_o] \times 100$.

Where, (SW) % = Equilibrium percent swelling,

W_o = Original weight of emulgel at zero time

after time t,

Wt = Weight of swollen emulgel

$$\text{Drug content} = \frac{\text{Absorbance}}{\text{Slope}} \times \text{Dilution factor} \times \frac{1}{1000}$$

iv) Percentage Yield

The empty container was Weighed in which the gel formulation was stored, then again the container was weighed with gel formulation. Then subtracted the empty container weighed with the container with gel formulation then it gives the practical yield. Then the percentage yield was calculated by the formula.

$$\text{Percentage yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$$

v) Drug Content

Weighed 10 gm of each gel formulation were transferred in 250 ml of the volumetric flask containing 20 ml of alcohol and stirred for 30 min. The volume was made up to 100 ml and filtered. 1 ml of the above solution was further diluted to 10 ml with alcohol and again 1 ml of the above solution was further diluted to 10 ml with alcohol. The absorbance of the solution was measured spectrophotometrically at >290 nm. Drug content was calculated by the following formula.

vi) Determination of pH

Weighed 50 gm of each gel formulation were transferred in 10 ml of the beaker and measured it by using the digital pH meter. pH of the topical gel formulation should be between 3–9 to treat the skin infections.

vii) Spreadability

It indicates the extent of the area to which gel readily spreads on application to the skin or affected part. The therapeutic potency also depends upon spreading the value. The time in sec taken by two slides to slip off from gel which is placed in between the slides under the direction of certain load is expressed as spreadability. [12], [17] Lesser the time taken for the separation of two slides, better the spreadability. The following formula is used to calculate the spreadability:

$$\text{Spreadability (S)} = M \times L / T$$

Where,

M = weight tied to upper slide

L = length of glass slides

T= time taken to separate the slide

viii) Extrudability

The gel formulations were filled into a

collapsible metal tube or aluminium collapsible tube. The tube was pressed to extrude the material and the extrudability of the formulation was checked. The formulations are fill in the collapsible tubes, after it was set in the container. Extrudability is determined in terms of weight in gm required to extrude a 0.5 cm ribbon of gel in 10 second. [12], [17]

ix) Viscosity Estimation

The viscosity of gel was determined by using a Brookfield viscometer DVII model with a T-Bar spindle in combination with a helipath stand. [12], [17]

a) Selection Of Spindle: Spindle T 95 was used for the measurement of viscosity of all the gels.

b) Sample Container Size: The viscosity was measured using 50 gm of gel filled in a 100 ml beaker.

c) Spindle Immersion: The T-bar spindle (T95) was lowered perpendicular in the centre taking care that spindle does not touch the bottom of the jar.

x) Measurement Of Viscosity

The T-bar spindle (T95) was used for determining the viscosity of the gels. The factors like temperature, pressure and sample size etc. Which affects the viscosity was maintained during the process. The helipath T-bar spindle was moved up and down, giving viscosities at a number of points along the path. The torque reading was always greater than 10%. The average of three readings taken in one minute was noted as the viscosity of gels.

xi) In Vitro Diffusion Study

The abdominal skin of Albino mice, weighing 20–25 gm of 8–10 w old was shaved using hand razor and clean the skin with hot water cotton swab. 5 gm of gel was applied uniformly to the skin. The skin was mounted between the compartments of the Frantz diffusion cell with stratum corneum facing the donor compartment. Reservoir compartment was filled with 100 ml phosphate buffer of pH 6.8. The study was carried out at 37 ± 1 °C and the speed was adjusted until the vortex touches the skin and it carried out for 4½ h. 5 ml of the sample was withdrawn from the reservoir compartment at 30 min interval and absorbance was measured

spectrophotometrically at 260 nm. Each time the reservoir compartment was replenished with the 5 ml volume of phosphate buffer pH 6.8 solution to maintain a constant volume. [12], [17]

xii) Skin Irritation Study

For skin irritation study, Guinea pigs (400-500g; either sex) were used. The animals were maintained on the standard animal feed and had free access to water. The animals were kept under standard conditions. Hair was shaved from the back. Five ml of each sample was withdrawn periodically at 1,2,3,4,5,6,7 and 8h and each sample was replaced with an equal volume of fresh dissolution medium. Then analyzed the samples for drug content by using phosphate buffer as guinea pigs and an area of 4 cm was marked blank on both the sides, one side served as control while the other side was tested. The gel was applied (500 mg/ guinea pig) twice a day for 7 days and the site was observed for any sensitivity and the reaction if any. [12], [17] It was graded as:

0	No reaction
1	Normal patchy erythema
2	Normal but confluent or modest but patchy erythema
3	Severe erythema with or without edema

xiii) Stability

It was carried out by freeze-thaw cycling. Here, the product to a temperature of 4°C for 1 month, then at 25°C for 1 month and then at 40°C for 1 month, syneresis was observed. Then the gel is exposed to ambient room temperature. Note the liquid exudate separated.

xiv) Homogeneity

Set the gel in a container and then it was tested for homogeneity by visual inspection. They were tested for their appearance and presence of any aggregates. [12], [17]

Conclusion

Gels are getting more popular nowadays because they are more stable and also can provide controlled release than other semisolid preparations like creams, ointments, pastes, etc. The gel formulation can provide better absorption characteristics and hence increase the bioavailability of the drug. A thorough investigation into the stability characteristics of the gel formulation over an extended period of time may provide scope for its therapeutic use for patients. The principal advantage of

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topical drug delivery lies in targeting the drug action directly to the site of disorder by allowing the accumulation of high local drug concentration within the tissue and around its vicinity for enhanced drug action this is more effective when drugs with short biological half-life, narrow therapeutic window are applied with topical route. The clinical evidence shows that topical gel is a safe and effective treatment choice for use in the management of skin related diseases. Developed formulations of ketoconazole were evaluated for the physiochemical parameters such as percentage yield, drug content, pH, viscosity, spreadability, extrudability, in vitro drug diffusion. Viscosity studies of various formulations revealed that some formulation was better to compare to others.

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