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DESIGN AND EVALUATION OF FLUCONAZOLE LOADED ANTIDANDRUFF HAIR GEL

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ABSTRACT

Dandruff is a common clinical condition caused by increased growth of fungi and bacteria, it is a flaking of dead skin and over activity of the oil glands, known as seborrhea. Dandruff is a shedding of dead skin cell from the scalp and is suffered by almost 50% of the population and couses significant discomfort. Fluconazole is a imidazole derivative. It is used for the treatment of local and systemic fungal infection. Increased growth of fungi and bacteria on the scalp couse dandruff and seborrheic dermatitis which results in abnormal proliferation, scaling and flaking of scalp epidermis. Dandruff is commonly treated using shampoos or lotions cantaining imidazole, selenium sulphide, salicylic acid and zinc pyrithion. Shampoos or lotions do not use the long duration on the scalp and these cannot prevent reoccurrence. Hair gel last long on the scalp. In persent study was degined to formulate and evaluate different formulae of antidandruff gel containing fluconazole for treatment of dandruff. The fluconazole antidandruff hair gel was formulated by using different polymars with different concentration as carbopol 940, polyethyleneglycol, methyl peraben, glycerine, triethanolamine, polyvinyl pyrrolidone.

KEYWORD: Dandruff, Fluconazole, Antidandruff gel.

1. INTRODUCTION

Dandruff is a common scalp disorder, characterized by presence of corneocytes that form clusters due to their high cohesive power, in the form of flaky white to yellowish scales, accompanied by itching. It has been observed that dandruff occurs mainly between puberty to middle age, the phase when sebaceous glands are most active.[1]

Causes: The cause of dandruff various amoung individuals. Couses can be classified into-[1]

a) Microbial.
b) Non- microbial.

a)Microbial facters

Fungal: *Malassezia furfur* is considered as the leading cause of dandruff by the stimulates the enzyme called lipase on the scalp.

Bacterial: Disequilibrium in the proportion of two main bacterial populations found on scalp propionibacterium acnes and *Staphylococcus* epidermidis may also be a cause of dandruff.

b)Non-microbial factors

1. Damage to the scalp stratum corneum.
2. individual susceptibility to oleic acid.
3. Dry scalp.
4. Oily or irritated skin.
5. Sensitivity to hair cosmetics.
6. Other scalp conditions like psoriasis, eczema etc.

1.1 Dandruff composition

Dandruff scale is a cluster of corneocytes, which have retained a large degree of cohesion with one another and detach as such from the surface of the stratum corneum. The size and abundance of scale are heterogeneous from one site to another and over time. Parokeratotic cells often make up part of dandruff. Their numbers are related to the severity the clinical manifestations, which may also be influenced by seborrhea.[2,3]

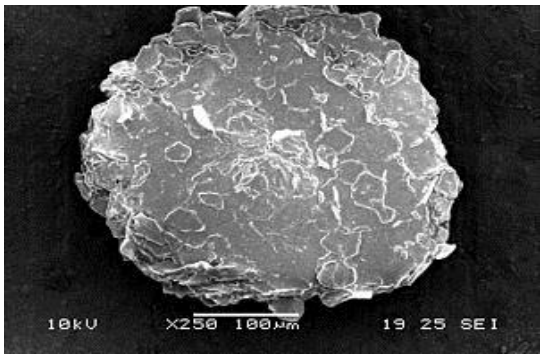


Fig.1: Microscopic image of human dandruff.

1.2 Common sites of dandruff distribution

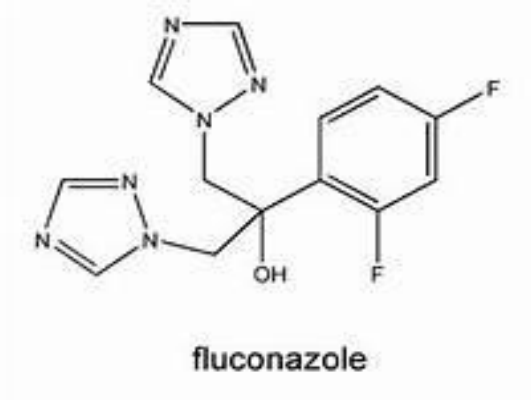
The distribution [Thomas P, et al., 1996] is classically symmetric and common sites of involve ment are as follows[2]

- Hairy areas of head.
- Eyebrows and eyelashes.
- Beard.
- Fore head.
- The external ear cannals.
- Post auricular creases.

2. Antidandruff agent

At present, there are number of antifungal agents use topical application like clotrimazole, fluconazole, griseofulvin, itraconazole its.[4]

Fluconazole is a fluorine-substituted, bis-triazole antifungal agent. Its mechanism of action, like that of other azoles, involves interruption of the conversion of lanosterol to ergosterol via binding to fungal cytochrome P-450 and subsequent disruption of fungal membranes.[5]



fluconazole

3. Gel

Gel are defined as “semisolid system in which a liquid phase is constrained with in polymeric matrix in which a high degree of physical and chemical cross-linking introduced”.[6]

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.[7] 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. Where the gel mass contains a network of small separate particles, the gel is classified as a two-phase system. 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.[7]

3.1 Terminologies Related to Gels

A number of terms are commonly used in discussing some of the characteristics of gels, including imbibition, swelling, syneresis, thixotropy, and xerogel.[7]

- **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.

- **Thixotropyis** a reversible gel-sol formation with no change in volume or temperature, a type of non-Newtonian flow.

- **Xerogelis** formed when the liquid is removed from a gel and only the framework remains. E.g., Gelatin sheets, tragacanth ribbons, acacia tears, etc

3.2 STRUCTURE Of GEL

The rigidity of a gel arises from the presence of a network formed by the interlinking of particles gelling agent. The nature of the particles and the type of force that is responsible for the linkages, which determines the structure of the network and the properties of the gel.[8]

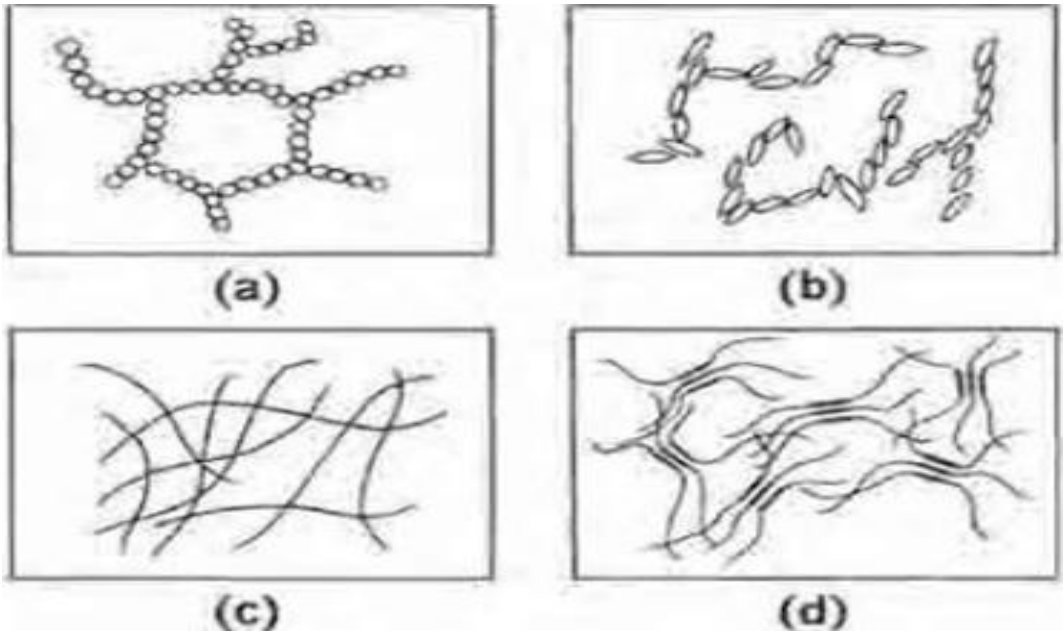


Figure 2: Representations of gel structures. (a) Flocculated particles in a two-phase gel structure. (b) Network of elongated particles or rods forming a gel structure. (c) Matted fibers as found in soap gels. (d) Crystalline and amorphous regions in a gel of carboxymethylcellulose.

3.3 ADVANTGES[10-11]

● 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.

● **Better stability:** Other preparations are comparatively less stable than gels. 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 niosomes and liposomes are of micro size and due to vesicular 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 gels comprises of simpler and short steps which increases the feasibility of the production. There are no specialized instruments needed for the production of gels. Moreover materials used are easily available and cheaper. Hence, decreases the production cost of gels.

● **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 gels as no sonication is needed.

● **Controlled release**: Gels can be used to prolong the effect of drugs having shorter t1/2.

3.4 LIMITATION

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

3.5 PROPERTIES OF GELS

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 apparent viscosity or gel strength increases with an increase the effective crosslink density of the gel. However, a rise in temperature may increase or decrease the apparent viscosity, depending on the molecular interactions between the polymer and solvent.

● They exhibit the mechanical characteristics of the solid state.[7]

4. CLASSIFICATION OF GEL

Gel can be classified based on colloidal phases, nature of solvent used, physical nature and rheological properties.[6-7]

4.1 BASED ON COLLOIDAL PHASE

● They are classified into

1. Inorganic (two phase system)
2. Organic (single phase system)

4.1.1 Two phase system

If partial size of the 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 semisolids on standing and becomes liquid on agitation.

4.1.2 Single –phase system

These consist of large organic molecules existingon 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 wall forces.

4.2. Based on nature of solvent

4.2.1 Hydro gel [water based]

Here they contain water as their continuous liquid phase.
E.g.: bentonite magma, Gelatin, cellulose derivatives, carpooler, and poloxamer gel.

4.2.2 Organic gels [with a non –aqueous solvent]

These contain a non –aqueous solvent on their continuous phase. E.g. plastibase (low moleculer wt poluethylene dissolved in mineral oil and short cooled) Olag (aerosol) gel and dispersion of metallic stearate in oils.

4.2.3. Xerogel

Solid gels with low solvent concentration are known as xerogels. These are produced by evaporation of solvent or freeze drying, leaving the gel framework behind on contact with fresh fluid, they swells and can be reconstituted.
E.g. tragacanth ribbons, acacia tear B- cyclodextrin, dry cellulose and polystyrene.

4.3 BASED ON RHEOLOICAL PROPERIES

Usually gels exhibite non –newtonian flow properties. They are clssifide into,

a) Plastic gels.
b) Pseudo plastic gels.
c) Thixotropic gels.

4.3.1. 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.

4.3.2. Pseudo-plastic gels

E.g., Liquid dispersion of tragacanth, sodium alginate, Na CMC, etc. exhibits pseudo-plastic flow. The 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.

4.3.3. 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.

4.4. Based on physical nature

4.4.1. 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 type -COO-X-COO between two adjacent strand networks.
E.g., Alginate and Carbopol.

4.4.2. 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.

5. Gel forming compounds[2]

A number of polymers are used to provide the structural network that is the essence of a gel system. These include.

1.Natural gum: Alginates, carragenan, tragacanth, pectin etc.

2.Carbomers: Carbopol 934, carbopol 940 and carbopol 941.

3.Cellulose derivatives: Methyl cellulose, sodium carboxy methyl cellulose, hydroxyl ethyle cellulose, hydroxyl propyl cellulose.

4.Polyethylenes: PEG 200 to PEG 8000.

5.Colloidally dispersed solids: Microcrystalline silica, colloidal cellulose.

6. Surfactants: Non –ionic surfactants.

7.Other gellants: Bees wax, carnauba wax, cetyl esters wax, PEGs, etc.

6. Preparation of Gels[6]

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 following methods

1. Thermal changes
2. Flocculation
3. Chemical reaction

6.1. Thermal changes

Solvated polymers (lipophilic colloids) when subjected to thermal changes causes gelatin. Many hydrogen formers are more soluble in hot than cold water. If the temperature is reduced, the degree of hydration is decreased and gelation takes place. (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.[6]

6.2. 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.[6] E.g., 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 to hydrophobic solution brings about coagulation, gelation is infrequently observed. The gels formed by flocculation method are Thixotropic in behavior. Hydrophilic colloids such as gelatin, proteins and acacia are only affected by high concentration of electrolytes, when the effect is to "salt out", the colloidal and gelation doesn't occur.

6.3. 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.

7. Formulation Considerations for Pharmaceutical Gels[9]

7.1. 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.

7.2. 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, and fish liver oils or various fixed oils of vegetable origin (e.g., arachis, cottonseed, and maize oils) as nutritional supplements.[9]

7.3. Emulsifiers

Emulsifying agents are used both to promote emulsification at the time of manufacture and to control stability during a shelf life that can vary from days for extemporaneously prepared emulsions to months or years for commercial preparations.eg Polyethylene glycol 40 stearate, Sorbitanmonooleate (Span 80), PolyoxyethylenesorbitanMonooleate (Tween 80), Stearic acid, Sodium stearate.

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

7.5. Permeation Enhancers

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

7.6. 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.

7.7. 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.[13]

8. EVALUATION OF HAIR GEL[12]

8.1. Psychorheological Characteristic

Psychorehological Characteristic were studied for colour, clogging, sudden viscosity change and feel properties.

8.2. Spreadability

Spreadability is expressed to denote the extent of area to which gel readily spreads on application to skin or affected part. The therapeutic efficacy of a formulation also depends upon its spreading value. Spreadability is expressed in terms of time in seconds taken by two slides to slip off from gel, placed in between the slides under the direction of certain load.

●It is calculated by using the formula

●S = M. L / T
●Where M = weight tied to upper slide, L = length of glass slides, T = time taken to separate the slides.

8.3. Extrudability study
The extrudability of formulations was determined using aluminium collapsible tubes filled with 10 g gel. Tubes were held between two clamps. A tube was compressed and extrudibility of the formulation was determined in terms of weight in grams required to extrude a 0.5 cm ribbon of gel in 10 s.

8.4. Viscosity study
The measurement of viscosity of the prepared gel was done using Brookfield digital Viscometer (Model LV-I+). The viscosity was measured using spindle no. 64 at 10 rpm and 25^0C. Before measurement deaeration of gel was done and the gel was filled in appropriate wide mouth container. Samples of the gels were allowed to settle over 30 min at the assay temperature (25 ±/1^0C) before the measurements.

8.5. Drug content
Taking 1 g of gel (equivalent to 20 mg of Fluconazole) in 10 ml volumetric flask diluted with methanol. The above solution was suitably diluted and determined using UV – Vis spectrophotometer at 262 nm for Fluconazole.

8.6. Determination of pH
The pH of formulations was determined using digital pH meter. One gram of gel was dissolved in 100 ml of demineralised water and stored for two hours. The measurement of pH of each formulation was done in triplicate. Instrument was calibrated before use with standard buffer solutions at pH 4, 7, and 9.[12]

8.7. Turbidimetric measurement
Degree of turbidity of gel was determined by nepheloturbidimeter. Antidandruff hairstyling gel (0.5gm) was added to 150 ml 0.1 N hydrochloric acid under continuous stirring (50 rpm) on magnetic plate at ambient temperature and the increase in turbidity was measured using a turbidimeter.

***8.8. In vitro* release study**
The *in vitro* release study of the prepared gel was carried out using Keshary–Chien (K.C) diffusion cell using a cellophane membrane previously activated in phosphate buffer pH 5.0 for 24 h. The membrane was mounted in K.C cell, kept at 37^0C. The known quantity of gel (1 g gel containing 20 mg of Fluconazole) was spread uniformly on donor side. Phosphate buffer pH 5.0 was used as the acceptor medium, from which samples were collected at regular intervals for 3 hours and replaced with the same amount of buffer. The drug concentration on the receptor fluid was determined spectrophotometrically in triplicate against appropriate blank.

8.9. *Ex vivo*release study
The abdominal hair of albino mice, weighing 22-25 g, was shaved using an electric razor after sacrificing with excess chloroform inhalation. The abdominal skin was surgically removed and adhering subcutaneous fat was carefully cleaned. The epidermis was then separated from dermis by soaking the full thickness skin in 2 M sodium bromide solution in water for 6-8 h. The epidermis was thoroughly washed with water, dried at 25% RH, wrapped in aluminium foil and stored in freeze until further use. For ex-vivorelease study, skin was allowed to hydrate for 1 h before being mounted on the Keshary-Chien diffusion cell with the stratum corneum facing the donor compartment. The gel sample was applied on the skin and then fixed in between donor and receptor compartment of Keshary-Chien diffusion cell. The receptor compartment contain phosphate buffer of pH 5.0. The temperature of the medium was thermostatically controlled at 37±1^0C by surrounding water jacket and the medium was stirred with bar magnet using magnetic stirrer. Aliquots, withdrawn at predetermined intervals of time, were spectrophotometrically estimated at 245 and 262 nm against their respective blank formulation treated in the same manner.

8.10. Stability study
The optimized formulation was subjected to different temperature condition (8^0C± 2°C, 25°C ± 2°C, 45°C ± 2°C) and relative humidity 75 ± 5 % RH during stability studies.Formulation was evaluated for transparency, Viscosity, pH and drug content after every 10 days for one month.

8.11. Skin irritation test
Three healthy male rats, weighed 200-250 g were selected for the study. An area of 1 cm^2 was shaved for each rat to expose sufficient test area. The rats were divided in three group control, standard and test. Formulation was applied on the exposed area of rat labelled test whereas drug solution was applied to standard and control were untreated. The test sites were visually observed for erythema and edema daily upto seven days and compared.[12]

8.12. *In vitro* Antidandruff activity
This activity was determined by Sabouraud dextrose diffusion test employing “cup plate technique” using previously sterilized petridish. Solution of gel formulations HG1, HG7 and HG11 and marketed formulation (as a standard) 1 mg/ml was poured into cups bored of size 8mm in sabouraud dextrose plate previously seeded with test organism (*Candida albicans*). After allowing diffusion of solution for 2 hrs, the plates were incubated at 27^0C for 48 h. The zone of inhibition measured around each cup was compared with that of the standard.

8.13. *In vivo* Antidandruff activity

*In vivo*Antidandruff activity was performed on adult male rabbit weighing 2 to 2.5 kg. Hairs were removed from their flanks with electrical clipper and the area of skin (20mm diameter) was scarified with coarse sandpaper. Scarified skin was infected with few drops of culture of *Candida albicans*. The fungal infection was induced on the rabbit for first 3 days. On the 4th day, treatment was initiated by topical application to the infected sites with gel formulation for another 4 days. The infected skin was analysed for flakes and inflammation.[12]

8. CONCLUTION

Fluconazole is an imidazole derivative used for the topical as well as systemic fungal infection. The formulation of anti-dandruff hair gel provides a method for treating a scalp dandruff or seborrheic dermatitis. Antidandruff hair gel containing fluconazole could be used as an effective in treatment of dandruff on scalp. Gel are getting more popular nowdays because they are more stable and effective than other semi solid preparation like creams, ointments, pastes etc. Developed formulations of fluconazole were evaluated for the physiochemical parameters such as drug content, viscosity, spreadability, in vitro diffusion.

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