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RESEARCH ARTICLE

Formulation and Evaluation of Hair Gel for the Treatment of Chronic Inflammatory Disorder Seborrheic Dermatitis

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ABSTRACT

Dandruff is a condition in which dead skin cells from the scalp come off in scales that are visible on the hair. The scales are dry, white or greyish and appear as small patches, especially at the top of the head. Dandruff may be a symptom of a more serious problem, such as seborrheic dermatitis. Various Antifungal agents are widely used in hair shampoos for the treatment of dandruff. These products show temporary effect for span of hours in a day on the scalp. Therefore, an attempt has been made for formulation of Ketoconazole Anti-dandruff hair gels which may give antidandruff action for number of hours. All the formulations were evaluated Active Content, Physical appearance, PH, Viscosity, Extrudability, Antifungal activity, Drug release Profile and Stability study. The formulation HG3 shows superior drug release than other formulations. In carbopol gel formulations, the drug release was decrease with increase in carbopol concentration Antimicrobial activity shows that formulation HG3 shows higher efficacy without any dermal irritancy. Moreover the optimized formulation showed no signs of irritation or inflammation.

KEYWORDS

Dandruff, Ketoconazole, Anti-dandruff hair gel.

INTRODUCTION

Dandruff, a common scalp disorder called seborrhoeic dermatitis caused by Pityrosporum ovale. It is the shedding of dead skin cells from the scalp. Ordinarily, dandruff results from excessive drying of skin and over- activity of the oil glands, known as seborrhea. Although many products containing therapeutic agents were reported to control dandruff, no substantial progress has been made in achieving a permanent suitable product. There is a hope of finding out new products from existing antifungal agents.

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Several fungistatic compounds have been shown to improve dandruff condition. These products show temporary effect for span of hours in a day on the scalp. Therefore, an attempt has been made for formulation of Ketoconazole Anti-dandruff hair gels which may give antidandruff action for number of hours. Ketoconazole is an imidazole compound which exerts its antifungal activity through inhibition of lanosterol demethylation. This blocks the synthesis of ergosterol, the major sterol component of the fungal cell membrane. In mammalian cells, ketoconazole also inhibits lanosterol demethylation, with a subsequent decrease in the biosynthesis of cholesterol, the major sterol component of mammalian cell membranes. In addition, ketoconazole interferes with cellular fatty acid and phospholipids biosynthesis.

MATERIALS AND METHODS

Materials

Ketoconazole was obtained as gift sample from Micro Lab. Hosur; Methyl Paraben and Carbapol were obtained from Bioplus Life Science Banglore; Ethanol, Concentrated Hydrochloric Acid and Disodium Hydrogen Phosphate were obtained from Merck Pvt. Ltd, Mumbai; Sodium Hydroxide and N-Hexane were obtained from S.D.Fine Chemical Ltd, Mumbai

Methods

Formulation Development

Measured quantity of Methyl Paraben, Glycerin and weighed quantity of Polyethylene glycol were dissolved in about 35 ml of water in beaker and were stirred at high speed using mechanical stirrer (or sonicator). Then Carbopol 940 was added slowly to the beaker containing above liquid while stirring. In another beaker, Ketoconazole drug was dissolved in ethanol and added to the above solution by stirring, Neutralized the solution by slowly adding triethanolamine solution with constant stirring until the gel was formed

Evaluation of Anti-Dandruff Hair Gels

Psychorheological Characteristic: The Psychorheological Characteristic was checked for hair gel formulations (colour, clogging, homogeneity and texture).

Washability: Formulations were applied on the skin and then ease and extent of washing with water were checked manually.

Extrudability Study: The hair gel formulations were filled into collapsible metal tubes or aluminium collapsible tubes. The tubes were pressed to extrude the material and the extrudability of the formulation was checked.

Spreadability: An important criterion for hair gels is that it must possess good spreadability. Spreadability is a term expressed to denote the extent of area to which the gel readily spreads on application to hairs. The therapeutic efficacy of a formulation also depends on its spreading value. A special apparatus has been designed to study the spreadability of the formulations. Spreadability is expressed in terms of time in seconds taken by two slides to slip of from formulation, placed between, under the application of a certain load. Lesser the time taken for the separation of two slides,

Table 1: Formulation Development of Ketoconazole Hair Gel

Ingredients	HG1	HG2	HG3	HG4	HG5	HG6
Ketoconazole(gm)	1.0	1.0	1.0	1.0	1.0	1.0
Carbopol 940(gm)	0.25	0.30	0.35	0.40	0.45	0.5
Polyethylene Glycol(gm)	10	10	10	10	10	10
Methyl Paraben(gm)	0.08	0.08	0.08	0.08	0.08	0.08
Triethanolamine (ml)	1.2	1.2	1.2	1.2	1.2	1.2
Glycerin(ml)	5	5	5	5	5	5
Ethanol(ml)	10	10	10	10	10	10
Distilled Water(ml) (q.s)	50	50	50	50	50	50

better the spreadability. Two glass slides of standard dimensions (6×2) were selected. The hair gel formulation whose spreadability had to be determined was placed over one of the slides. The second slide was placed over the slide in such a way that the formulation was sandwiched between them across a length of 6 cms along the slide. 100 grams of weight was placed up on the upper slide so that the hair gel formulation between the two slides was traced uniformly to form a thin layer. The weight was removed and the excess of the hair gel formulation adhering to the slides was scrapped off. The lower slide was fixed on the board of the apparatus and one end of the upper slide was tied to a string to which 20 gram load could be applied 50with the help of a simple pulley. The time taken for the upper slide to travel the distance of 6 cms and separate away from lower slide under the direction of the weight was noted. The experiment was repeated and the average of 6 such determinations was calculated for each hair gel formulation.

$$\text{Spreadability} = \frac{m.l}{t}$$

Where, S=Spreadability (gcm/sec)

m = weight tied to the upper slide (20 grams)

l= length of glass slide (6cms).

t = time taken is seconds.

Determination of pH: The pH of the hair gels were determined by digital pH meter. One gram of gel was dissolved in 25 ml of distilled water and the electrode was then dipped in to gel formulation for 30 min until constant reading obtained. And constant reading was noted. The measurements of pH of each formulation were replicated two times.

Viscosity: The measurement of viscosity of the prepared gel was done using Brookfield digital Viscometer. The viscosity was measured using spindle no. 6 at 10 rpm and 25^0C. The sufficient quantity of gel was filled in appropriate wide mouth container. The gel was filled in the wide mouth container in such way that it should sufficiently allow to dip the spindle of the Viscometer. Samples of the gels were allowed to settle over 30 min at the constant temperature (25 $\pm/1^0$C) before the measurements.

Drug Content: The drug content was determined by taking 1 g of gel (equivalent to 10 mg of Ketokonazole) in 10 ml volumetric flask diluted with methanol. The above solution was suitably diluted and determined using UV – Vis spectrophotometer at 257 nm.

***In-vitro* Drug Release Studies Using the Pre-hydrated Cellophane Membrane**

Preparation of Cellophane Membrane for the Diffusion Studies: The cellophane membrane approximately 25 cm x 2cm was taken and washed in the running water. It was then soaked in distilled water for 24 hours, before used for diffusion studies to remove glycerin present on it and was mounted on the diffusion cell for further studies.

Diffusion Studies: The *in-vitro* diffusion of drug from the different gel preparations were studied using the classical standard cylindrical tube fabricated in the laboratory; a simple modification of the cell is a glass tube of 15mm internal diameter and 100mm height. The diffusion cell membrane was applied with one gram of the formulation and was tied securely to one end of the tube, the other end kept open to ambient conditions which acted as donor compartment. The cell was inverted and immersed slightly in 250 ml of beaker containing phosphate buffer pH 7.4as a receptor base and the system was maintained for 2 hrs at 37± 0.5^o C. The media was stirred using magnetic stirrer. Aliquots, each of 5 ml volume were withdrawn periodically at predetermined time interval of 15, 30, 45, 60, 90, 120 min and replaced by an equal volume of the receptor medium. The aliquots were suitably diluted with the receptor medium and analyzed by UV-Vis spectrophotometer at 243.0 nm using phosphate buffer pH 7.4 as blank.

Data Analysis via Drug Release Kinetics Study

The results of in-vitro release profile obtained for all the formulations were plotted in kinetic models as follows,

1. Cumulative of drug released versus time (zero order kinetic model).
2. Log cumulative percent drug remaining to be absorbed versus time (First order model)
3. Cumulative amount of drug release versus square root of time (Higuchi model)
4. Log cumulative drug released versus log time (Korsmeyer-Peppas model)

Anti-fungal Activity: The inhibition of fungal growth under standardized conditions may be utilized for demonstrating the therapeutic efficacy of antifungal drugs. The microbiological evaluation of gels was done using cup-plate method, which depends upon diffusion of the drug from the gel contained in the cup through a solidified agar layer in the petridish to an extent such growth of the added microorganism is prevented entirely in a zone around the cup. Wider zone of inhibition is an indicative of better release of the drug from the base.

Medium Used: Sabouraud dextrose broth

Test Organism: Candida albicans species

The low pH and high sugar content of this media make them particularly selective for fungi and inhibitory to bacteria.

Table 2: Composition of Sabouraud Dextrose Broth Medium

S.No.	Content	Quantity
1.	Glucose	40 gm
2.	Peptone	10 gm
3.	Agar	20 gm
4.	Water	1 liter

Dissolve the ingredients with heat and filtered through cotton gauze and adjust to pH 5.4 autoclave at 121^0 C for 2 hrs.

Test Procedure: The antifungal studies were carried out to ascertain the biological activity of hair gel formulation prepared against fungi. This was determined by sabouraud dextrose diffusion test employing "cup plate technique" using previously sterilized petri-dish. Solution of gel prepared formulation and pure ketoconazole as a standard 1mg/ml was poured into cups bored of size 8 mm in to wells of sabouraud dextrose plate previously seeded with test organism (Candida albicans). After allowing diffusion of solution for 2 h, the plates were incubated at 27^0 for 48 h. The zone of inhibition measured around each cup was compared with that of the standard.

Stability Study: Stability of a drug has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specifications. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, and enables recommended storage conditions, re-test periods and shelf lives to be established. In the present work selected formulations were stored at refrigerator, (0-8ºC), room temperature (25–30ºC) and accelerated temperature (45ºC) for 4 weeks and observed for any changes in their physical characteristics and drug content.

Skin Irritation Test: Gels should not produce skin irritation when applied topical drug delivery system. Hence, skin irritation study was performed. The skin irritation test was performed on healthy white rabbit of average weight 1.75 to 2.25 Kg. About 9 cm^2 area on the dorsal surface of the rabbits in each group was shaved and cleaned with spirit. Rabbits were divided into three groups (n=3) as follows: **Group-I (control):** There was no application on the surface of the rabbit skin. **Group-II (negative control):** An aqueous solution of 1 ml containing 0.8% formalin soaked in 9 cm^2 cotton wool (standard irritant) was placed in the back of the rabbit as negative control. The cotton wool was secured firmly in the place with

adhesive plaster. **Group-III (test):** 1 ml of gel containing 10 mg of Tazarotene was applied to 9 cm^2 area on the dorsal surface of the rabbit. The visual inspection was observed for 3 days to check any evidence of skin irritation (sign of edema and erythrema). The scoring system of Draize et al was followed ingrading the severity of the effect.

RESULTS AND DISCCUSION

Evaluation of Gel Formulation

Psychorheological Characteristic

All the formulations except HG5 & HG6 show good Psychorheological Characteristic. The carbopol quantity above 4.5gm affects the Psychorheological Characteristic such as presence of clogging and decrease of homogeneity.

Table 3: Psychorheological Characteristic

Form	Colour	Cloggi-ng	Homo genity	Texture
HG1	Turbid	Absent	++	Smooth
HG2	Off white	Absent	++	Smooth
HG3	White	Absent	++	Smooth
HG4	Off white	Absent	++	Smooth
HG5	Off white	Present	+	Smooth
HG6	White	Present	+	Smooth

Excellent: (+++) Good: (++) Average: + Poor (-)

Washability: All the formulations except HG5 & HG6 showed good washability.

Table.4: Washability

Formulation	Washability
HG1	++
HG2	++
HG3	++
HG4	++
HG5	+
HG6	+

Excellent: (+++) Good: (++) Average: + Poor (-)

Extrudability Study: All the formulations showed good to satisfactory extrudability. The extrusion of gel from the tube is an important during application and for the patient compliance. Gel with high consistency may not extrude from the tube easily, whereas low viscous gels may flow quickly, extrudability of gel formulation with less concentration of gelling agent was found to be good and with high concentration of gelling agent, it was satisfactory

Table.5: Extrudability

Formulation	Extrudability
HG1	++
HG2	++
HG3	++
HG4	++
HG5	+
HG6	+

Excellent: (+++) Good: (++) Average: + Poor (-)

Spreadability: Spreadability plays an important role in patient compliance and help in uniform application of gel to the skin. A good gel takes less time to spread and will have high spreadability. The spreadability of formulated gel was decreased as the concentration of gelling agent increased.

Table.6: Spreadability

Formulation	Spreadability (gcm/sec)
HG1	13.61
HG2	13.11
HG3	12.65
HG4	12.55
HG5	11.67
HG6	10.15

Determination of pH: The pH of all gel formulation was found between 6.9 to 7.5 which lies in normal pH range of the skin.

Table 7: Determination of pH

Formulation	pH
HG1	6.9
HG2	7.1
HG3	7.2
HG4	7.1
HG5	7.5
HG6	7.3

Viscosity: Viscosity is an important parameters for characterizing the gels as it effect the spreadability, extrudability and release of the drug, all formulated gels showed in increased viscosity as the concentration of the gelling agent was increased.

Table 8: Viscosity

Formulation	Viscosity (cps)
HG1	3352
HG2	3571
HG3	3962
HG4	4325
HG5	4866
HG6	5210

Drug Content: All the prepared gel formulations showed uniformity in drug content and were within permissible range indicating the uniform drug dispersion in the gels.

Table.9: Drug content

Formulation	% Drug content
HG1	98.50
HG2	97.25
HG3	99.25
HG4	99.45
HG5	98.26
HG6	95.23

***In-vitro* Drug Release Profile of Hair Gel:** The in vitro percent release of drug from gel was in the order of decreasing as the concentration of gelling agent was increased. The decrease in vitro-release of drug may be due to the increased viscosity of the gels.

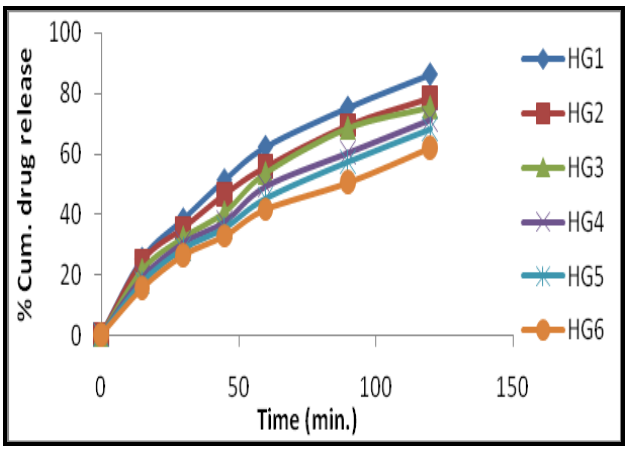

Figure 1: Zero Order Kinetics

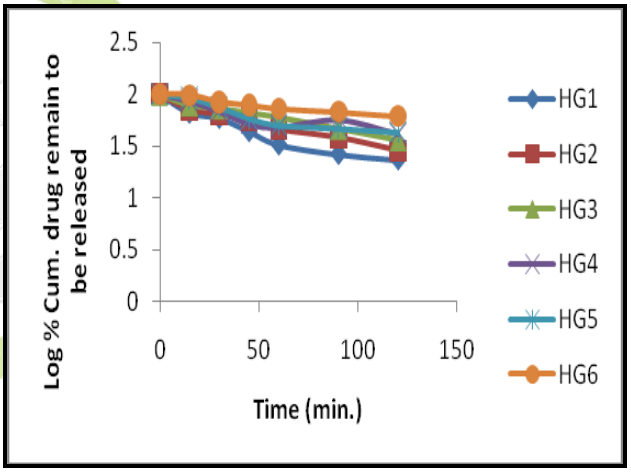

Figure 2: First Order Kinetics

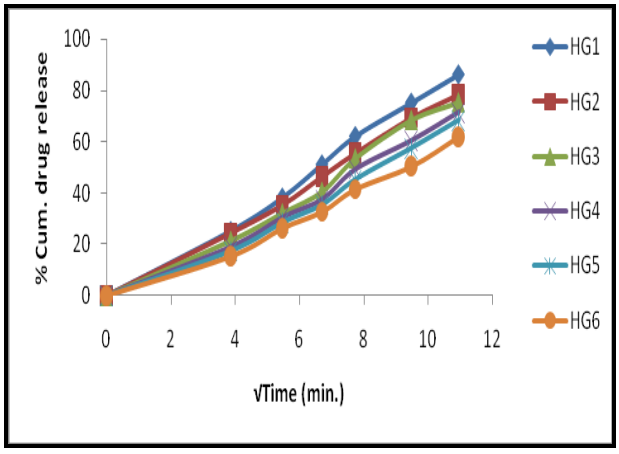

Figure 3: Higuchi Kinetics

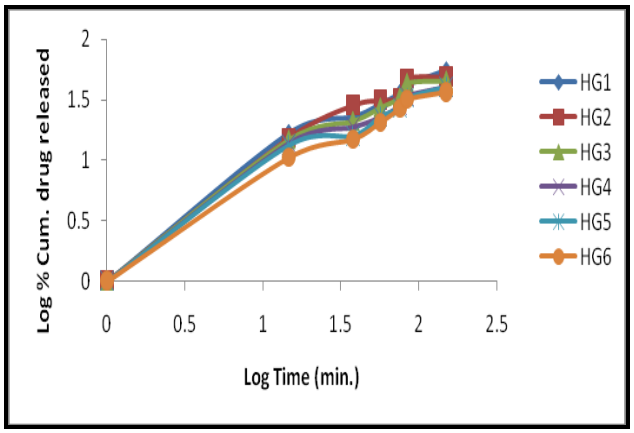

Figure 4: Peppas Kinetics

Table 11: Anti-fungal Activity

Formulation	Zone of Inhibition (mm)
HG1	18.3 mm
HG2	19.5 mm
HG3	21 mm
HG4	15.5 mm
HG5	16.3mm
HG6	18.0mm

Drug Release Kinetics with Model Fitting

Table 10: Drug Release Kinetics with Model Fitting

Formulation code	Correlation coefficient of Model fitting (R^2)				'n' values for - Peppas	Best fit model
	Zero order	First order	Higuchi matrix	Peppas kinetics		
HG3 (Optimized formulation)	0.953	0.881	0.915	0.994	2.613	Peppas kinetics

Anti-fungal Activity: Among the formulations, HG3 showed better release and maximum zone of inhibition than other formulation. Hence, Hair gel formulation HG3 was considered as best formulation.

Stability Study: The hair gel formulation HG3 was subjected to stability performance as it was exhibited good drug release and exhibited maximum zone of inhibition when compared to other formulations.

Table 12: Stability Study of optimized formulation

Temperature	Refrigerator temperature room (0-8^{0}C)			Room temperature (25–30ºC)			Accelerated temperature (45ºC)		
Period	10 days	20 days	30 days	10 days	20 days	30 days	10 days	20 days	30 days
Viscosity (cps)	3960	3960	3959	3962	3962	3961	3959	3959	3958
pH	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2
Spreadability (gcm/sec)	12.64	12.63	12.64	12.65	12.65	12.66	12.65	12.67	12.67
Drug content (%)	75.36	75.36	75.36	75.36	75.36	75.35	75.36	75.36	75.34

* Each reading is an average of three determinations

No appreciable changes were found for the tested parameters after the stability studies.

Skin Irritation Test

The Ketokonazole gel formulation did not showed any irritation and erythema after 72 hours. This indicates better skin acceptability of Ketokonazole gel formulation.

Table 13: Primary irritation study of Ketokonazole gel formulation

Formulation code	Irritation Score		
	Time of Application (Hours)		
	24	48	72
HG1	0	0	0
HG2	0	0	0
HG3	0	0	0
HG4	0	0	0
HG5	0	0	0
HG6	0	0	0

CONCLUSION

From the above results it can be concluded that the Hair gel formulation HG3 containing 0.35 gm of Carbopol 940 was suitable for topical application and it shows comparable good results. The formulation HG3 shows superior drug release than others. In carbopol gel formulations, the drug release was decrease with increase in carbopol concentration because polymer concentration increases the viscosity. Viscosity is negatively related to the release of active substance from formulations. Stability studies in all gel formulations showed that, the physical appearance, drug content, pH, rheological properties, and drug release in all gel formulations remain unchanged upon storage for one month. Antimicrobial activity shows that formulation HG3 shows higher efficacy without any dermal irritancy. Moreover the optimized formulation showed no signs of irritation or inflammation.

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