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Original Research Article

DEVELOPMENT AND EVALUATION HYDROGEL OF KETOCONAZOLE

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Abstract

The main aim of this study was to develop a topical drug delivery (Hydrogel) of Ketoconazole to reduce the dose of the active drug, to improve patient compliance, to avoid the side effects and increase local onset absorption and action. Ketoconazole interfare with 14-α sterol demethylase, a cytochrome P-450 enzyme essential for conversion of lanosterol to ergosterol. These turn in inhibition in synthesis of ergosterol and also enhance cellular permeability of fungus due to reduced amounts of ergosterol present in the fungal cell membrane. **Methods:** Topical Hydrogel formulations development of Ketoconazole was prepared by using Different-different polymers by enhancer stability and viscosity with their different concentrations. Six different formulations of Ketoconazole were prepared and evaluated parameters with respect to their colour, Spreadability, viscosity, determination of pH, drug content of formulations, in vitro drug release studies, and stability studies. **Results:** FT-IR study results that there were not any interaction between the drug, Polymers, and excipients. All the developed formulations of Ketoconazole show acceptable standard physical properties. The drug content and percentage yield were higher for F5 formulation among all formulation. F5 shows better drug release. Stability study of the best formulation F5 with guar gum polymer was found with best results. **Conclusion:** From the above observation results that this F5 formulation may be more effective topical formulation for the healing of fungal infections in the skin.

Keywords: Ketoconazole, Hydrogel, Zeta potential, Lanosterol, Ergosterol, Cell membrane

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INTRODUCTION

A gel may be a two-component, cross linked three-dimensional network consisting of structural materials interspersed by an adequate but proportionally large amount of liquid to make an infinite rigid network structure which immobilizes the liquid continuous phase within formulation. The structural materials that form the gel network are often composed of inorganic particles or organic macromolecules, primarily polymers. Cross links are often formed via chemical or physical interactions. This results in gel classification into chemical and physical gel systems, respectively. Ketoconazole interfare with 14-α sterol demethylase, a cytochrome P-450 enzyme essential for conversion of lanosterol to ergosterol. These turn in inhibition in synthesis of ergosterol and also enhance

cellular permeability of fungus due to reduced amounts of ergosterol present in the fungal cell membrane. As ergosterol is an essential component of the fungal cell membrane, inhibition of its synthesis results in the increased cellular permeability causing leakage of cellular contents responsible for cell death.[1-6]

CLASSIFICATION OF GELS:

Gels may be classified supported colloidal phases, nature of solvent used, physical nature and rheological properties.

1. Based on nature of solvent

Hydro gels (water based)

Here they contain water as their continuous liquid phase E.g. bentonite, derivatives of cellulose, carpooler, and synthetic poloxamer gel. Example-plastibase (low molecular wt. polyethylene dissolved in oil) Olag (aerosol) gel and dispersion of metallic stearate in oils.

Hydrogel

A Hydrogel is a semisolid formulation of gel dosage forms, which has an immobilized external apolar phase. The apolar phase is immobilized within spaces of the 3D network structure formed due to the physical interactions amongst all polymers the self-assembling structures of compounds regarded as gelators.[7]

Xerogels

Solid gels with low solvent concentration are called xerogels. These are produced by evaporation of solvent or freeze drying, leaving the gel framework behind on contact with fresh fluid, they swells and may be reconstituted. E.g. Tragacanth ribbons, acacia tear β1-cyclodextrin, dry cellulose and polystyrene.[8]

2. Based on colloidal phases:

They're classified into Inorganic (two phase system) kind of force that's accountable for the linkages determine the structure of the network and therefore the properties of the gel.[8]

Single-phase system these contain large organic molecules existing on the twisted strands dissolved during a continuous phase.

3. Based on rheological properties:

Usually the gels show non-Newtonian flow properties. They're classified into, a) Plastic gels b) Pseudo plastic gels c) Thixotropic gels. (a) Plastic gels E.g. - Bingham bodies, flocculated suspensions of aluminium hydroxide exhibit a plastic flow and also 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 tragacanth dispersion, sodium alginate, Na Carboxy methyl cellulose etc. exhibits pseudo-plastic flow.[9]

4. Based on physical nature:

(a) Elastic gels Gels of agar, pectin, guar gum and alginates exhibit an elastic behavior. The fibrous molecules being linked at the purpose of junction by relatively weak bonds like hydrogen bonds and dipole attraction. E.g.: Alginate and Carbapol. (b) Rigid gels this may be formed from macromolecule within which the framework linked by primary valance bond. E.g.: In colloid, silic acid molecules are held by Si-O-Si-O bond to provide a polymer structure possessing a network of pores.

PREPARATION OF GELS:

Gels are generally prepared at the industrial scale under room temperature. However, few of polymers such-Synthetic and Natural need special treatment before processing. Gels are also prepared by following methods.[10-11]

1. Thermal changes

2. Flocculation

3. Chemical process/ reaction

MATERIALS AND METHODS

Ketoconazole was received gift sample from Praise Pharma Ltd, Mumbai, India.

All Other Chemicals used in the formulation development were of the standard analytical grade. Ketoconazole formulations Hydrogel were prepared by using different polymers with their different-different concentrations. Polymers are dispersed in distilled water with constant stirring by magnetic stirrer at a medium speed maintaining the temperature at 40^0C. Gels are packed in a wide mouthed glass jar, and it is covered with screw copped plastic lid after covering with aluminium foil. Various preparations of Ketoconazole hydrogel are shown in Table 1. They all were kept in the dark and cool place. Evaluation of physicochemical parameters of prepared hydrogel of Ketoconazole gel Drug-excipients compatibility studies by Fourier transfer infrared spectrophotometer (FTIR). The drug, polymer, and excipients interactions are studied using the FTIR method. In general, drug and excipients must be compatible with each other which produce a stable, safe, and efficacious formulation. IR spectral analysis of pure drug and polymers carried out. Pure drug that gives peak and patterns were compared with the peaks and patterns with the combination of polymer and drug.[11-15]

RESULTS AND DISCUSSION

Drug-excipients compatibility studies

The IR studies of clear Ketoconazole formulation comprises greater proportion of the polymers that are conducted to know about the bond between the used polymers and the drug. The IR spectrum of pure Ketoconazole and Ketoconazole gel formulations that used greater proportion of polymer that gives comparable basic patterns and peaks. Outcome status that no notable drug and polymer interactions.

Visual inspection:

Visual determination is done to examine the physical properties and color of the developed formulation.

Determination of pH:

The pH value of all developed gel was in the range of 6.5–7.4. This is sufficient for appealing to skin and avoid the chances of irritation with local application.

Spreadability

The study has a few major elements that show the gel character that emerges out from the tube. Spreadability test is carried for all the formulations.

Determination of drug content

The drug content of the formulated gel was estimated. The drug content manifests that the drug was distributed equally throughout the gel.

Percentage yield and viscosity

Percentage yield of a topical gel consisting of Ketoconazole was in the range of 94.15–98.55%. This was identified that the percentage yield of F5 formulation showed an increase in percentage yield than the other preparation due to use of guar gum polymer.

In vitro drug release

The drug release profile of Ketoconazole topical gel formulations was accomplished by Franz diffusion cell. As an outcome of the *in vitro* release studies of all formulations are given in Table 3, and the statistically represented is shown in Figure

Table 1: Ketoconazole Formulation

Ingredients (Gm)	F1	F2	F3	F4	F5	F6
Ketoconazole	2	2	2	2	2	2
Ethanol	5	5	5	5	5	5
Carbopol	0.5	1	1.5	-	-	-
Guar Gum	-	-	-	0.5	1	1.5
Propylene Glycol	5	5	5	5	5	5
Benzalkonium Chloride	0.5	0.5	0.5	0.5	0.5	0.5
Methyl Paraben	2	2	2	2	2	2
Propyl Paraben	0.5	0.5	0.5	0.5	0.5	0.5
Purified Water (QS)	100ml	100ml	100ml	100ml	100ml	100ml

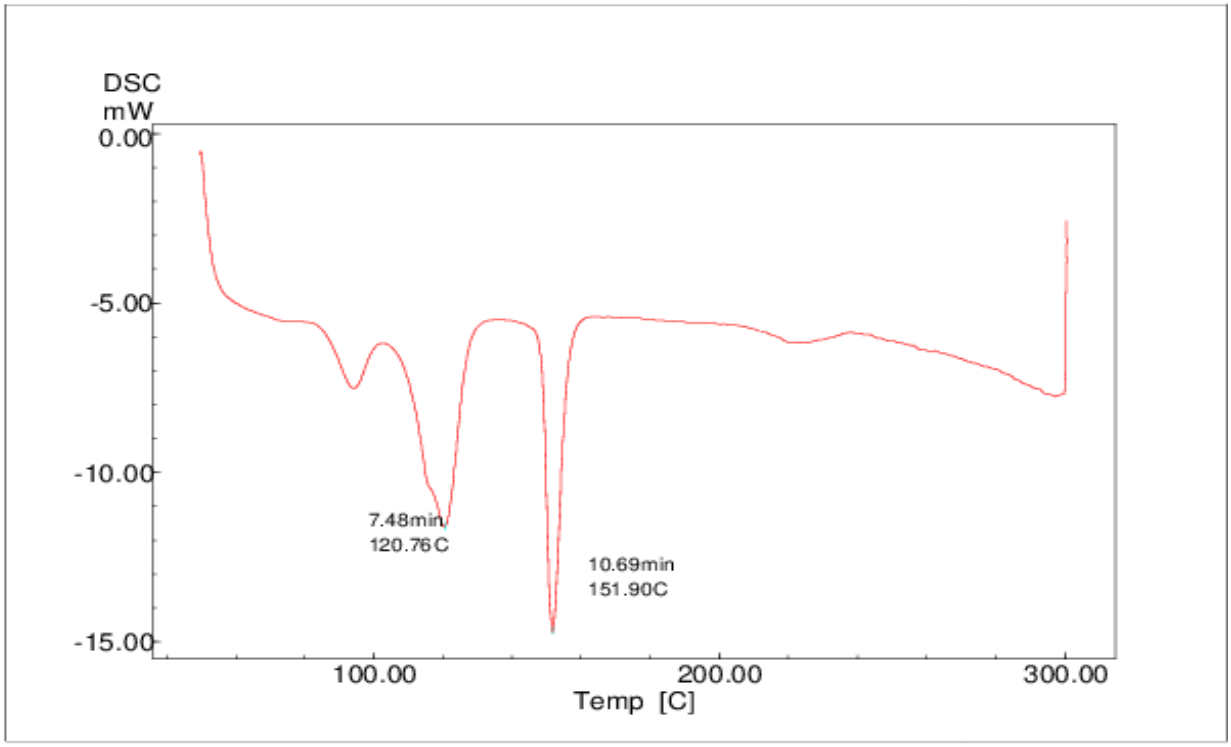


Figure: 1: DSC of Ketoconazole

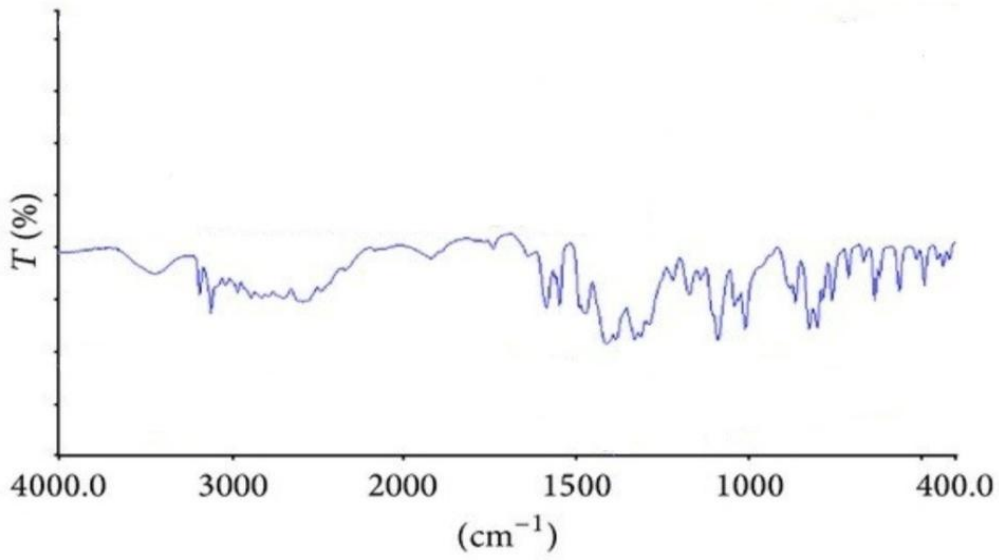


Figure 2: IR Spectra of Ketoconazole

Table 2: Characterization of formulation of Ketoconazole Gel

Characterization	Formulation code					
	F1	F2	F3	F4	F5	F6
pH	7.4	7.2	6.8	7.0	7.1	6.5
Viscosity (CPS)	8811	9221	9198	9255	8854	9152
Visual Appearance	Tanslucent	Tanslucent	Tanslucent	Tanslucent	Tanslucent	Tanslucent
Gelling capacity	++	++	++	+++	++++	+++
Content uniformity	94.15 ±0.02	96.55 ±0.01	95.85 ±0.04	96.20 ±0.02	98.55 ±0.01	98.11 ±0.0 2

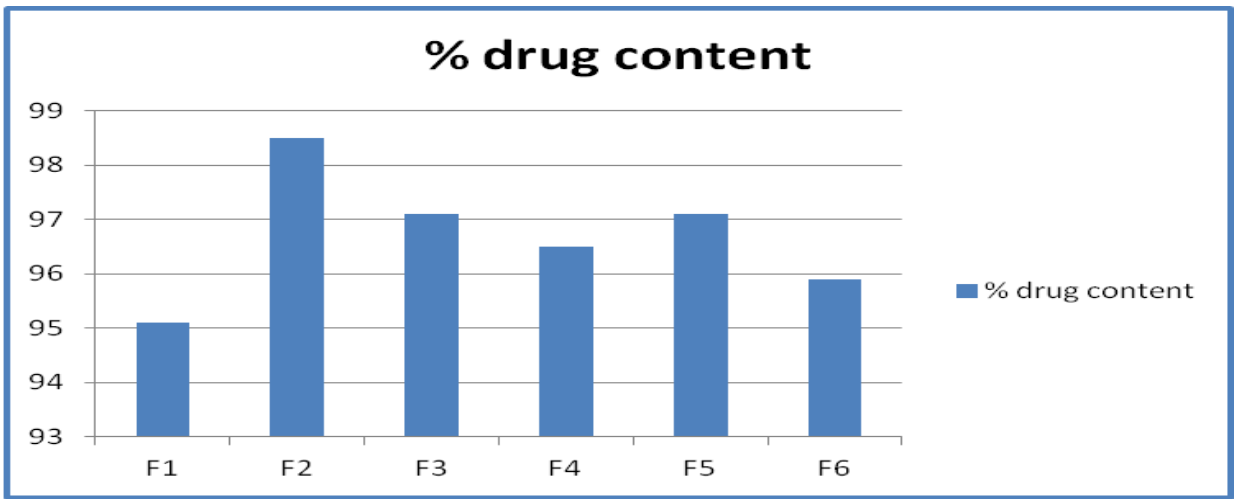


Table 3: Cumulative drug release from various batches

% Cumulative drug release from various batches			
Time (Min.)	F1	F2	F3
0	0	0	0
5	18.44	16.23	22.34
10	26.12	25.24	21.24
15	45.22	47.23	44.28
20	74.23	80.41	81.12
30	71.21	76.16	75.15

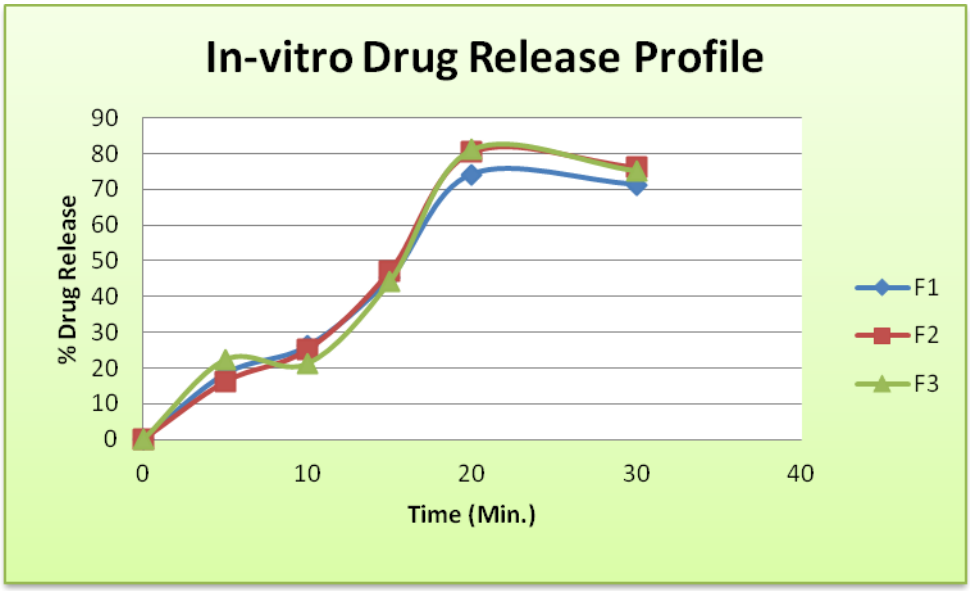
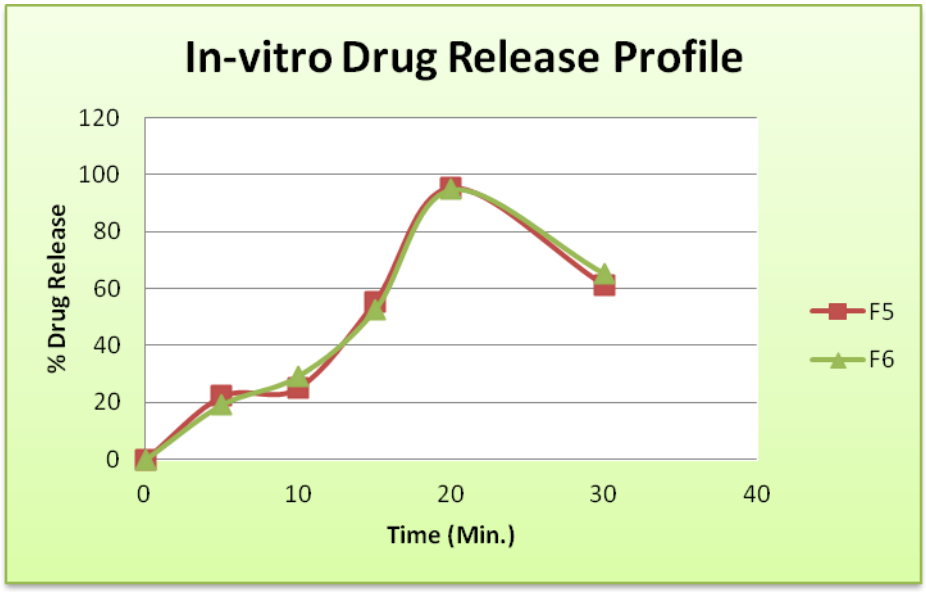


Table 4: Cumulative drug release from various batches

% Cumulative drug release from various batches			
Time (Min.)	F4	F5	F6
0	0	0	0
5	13.32	22.22	19.31
10	14.47	25.21	29.37
15	54.35	55.55	52.56
20	88.29	95.56	94.81
30	55.25	61.25	65.31



DISCUSSION

The imidazole derivative of Ketoconazole is one of the best drugs used for the treatment of fungal infections. In this study, the topical gel preparation of Ketoconazole was formulated for efficient that absorption of the drug across the skin. Advanced formulations of Ketoconazole were analyzed for physiochemical parameters such as viscosity, Spreadability, drug content, and *in vitro* drug release studies.

CONCLUSION

By analysing the above results, concluded that our drug Ketoconazole was incorporated with success into the topical gel development among all the designed formulation, the formulation F2 shows better Spreadability, drug content,

viscosity, and drug release studies. Therefore, this was concluded that our formulation would be very effective and safe topical alternative for the treatment of skin fungal infections.

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