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DEVELOPING A TOPICAL DRUG DELIVERY SYSTEM FOR FLUCONAZOLE GEL

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ABSTRACT

In addition to treating superficial and systemic fungal infections, fluconazole is a triazole antifungal. There are many side effects associated with the oral use of fluconazole. In order to reduce the dose of the drug and avoid side effects such as liver damage and kidney damage, this formulation is made in order to improve patient compliance and reduce the dosage of the drug. By using a polymer with different concentrations, such as Carbopol 945 & NaCMC, this research aimed to formulate & evaluate different formulations of a topical gel containing fluconazole. Penetration was enhanced with methanol. Physical appearance, pH-value, spreadability, and drug content were evaluated for formulated fluconazole topical gel. In terms of physical characteristics, the gel was well formulated. As the polymer concentration in formulations F3 (105.20%) & F6 (110.5%) is higher, they show good drug content. F4 (99.30%) had the highest yield. Polymer concentration decreases the spreadability of gel. In order to prevent the risk of skin irritation, the formulation had a pH of 6-9.

Keywords: Carbopol 945; homogeneity; topical drug delivery system; sodium carboxy methyl cellulose; polymer; Fluconazole; irritation.

INTRODUCTION

A significant amount of attention has been paid to topical delivery of drugs over the past few years: in addition to reducing systemic side effects as compared to parenteral or oral drug administration, this can result in a high concentration of drugs being localized at the site of action [1]. The topical delivery of drugs involves localized drug delivery through the ophthalmic, rectal, vaginal, and skin routes [2]. Medicated products are applied to the skin in a number of ways that either enhance or restore a fundamental function of the skin or alter an action in the tissues underlined, as it is one of the most accessible organs in the human body for topical administration [3].
Topical or dermatological products fall into this category. In making topical dosage forms, the carriers for the drug are selected to ensure that localized and percutaneous absorption of the drug is adequate so that the local effects are enhanced and the systemic effects minimized [4]. A topical preparation minimizes the risk of gastro intestinal irritation, prevents the liver from breaking down the drug, and increases the bioavailability of the drug [5].

Medication that is applied topically directly affects the site of action [7]. The antifungal drug fluconazole inhibits fungal very specifically, unlike mammalian reactions mediated by cytochrome P450, including those involved in the synthesis of steroid hormones and drug metabolism [6, 8]. The excellent bioavailability, tolerability, and side-effect profile of fluconazole makes it an extremely popular triazole treatment for candidiasis [9].

Among the serious adverse reactions associated with fluconazole are nausea, vomiting, bloating, diarrhea, rash, and reduction in red blood cells [10].

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Topical forms have a higher bioavailability than conventional forms [11, 12]. It is expensive and unrealistic to use oral formulations, because they require high dosage formulations, and they have a less localized effect and more side effects [13]. They also alter the absorption of gastrointestinal drugs by altering gastrointestinal pH and enzymatic activity, and by interacting with food and drinks [14]. In addition, more than 85 percent of fluconazole taken orally is found in circulation, 65 to 75% are excreted in urine, and only 15% is bound to proteins [15].

Hepatotoxicity occurs when it is metabolized in the liver. Externally applied topical preparations are spread, rubbed, or sprayed on external body surfaces [16]. A transparent gel is one of the most widely used semisolid preparations in cosmetics and pharmaceuticals due to its ease of application and percutaneous absorption [17]. Physiological stress such as skin flexion, blinking, and mucociliary movement can be absorbed by it, allowing it to conform to the shape of the area and control the release of the medication. Liquids are usually thickened with other ingredients to form gels. By allowing molecules to freely diffuse through the polymer scaffold, the release should be equivalent to that of a simple solution, since molecules can freely diffuse through the continuous liquid phase [18].

Compared to creams and ointments, they offer a faster release of drug substances, independent of their water solubility, and are easy to remove. There are several gel systems that are as clear as water due to their molecular dispersion (soluble or insoluble); others are turbid or form aggregates that disperse light. It is common for gelling agents to have concentrations less than 15%, usually ranging from 1.0% to 2.5%. Hydrophilic polymers are typically used for topical use, such as Hydroxypropyl Methyl Cellulose (HPMC), Sodium Carboxy Methyl Cellulose (NaCMC), and Carbopol 945. They are used in topical gel formulations at a concentration between 2 and 6% based on their grade and molecular fraction [22].

IDENTIFYING GELS BY THEIR CLASSIFICATION:

There are several types of gels, with varying colloidal phases, solvents, physical properties, and rheological characteristics.

On the basis of colloidal phase:

A. two-phase inorganic system consists of:

A dispersed phase of this type consists of relatively large particles that form three-dimensional structures through gels. On standing, they need to form thixotropic semisolids that turn into liquids when agitated.

B. System with one phase (organic):

The twisted strands of single-phase gel are dissolved by large organic molecules. There were no visible boundaries between the larger organic molecules and the liquid in which they circulated.

C. In accordance with the nature of the solvent:

- **Water-based hydrogels:** For example, bentonite magma, gelatin, cellulose derivatives, carpoolers, and poloxamer gels are hydrogels in which water acts as a continuous liquid phase.
- **Gels made from organic substances (with a solvent that is not aqueous):** In their continuous phase, there is a nonaqueous solvent. These include plastic bases, Olag (aerosol) gels, and oils dispersed with metallic stearates.
- **The Xerogelsare:**Solvent concentrations are lower in xerogels than in solid gels. Gels are formed when solvent evaporates and leaves a gel framework behind after it is contacted with fresh fluid. As an example, dragacanth ribbons, cyclodextrin from acacia tears, dry cellulose, and polyethylene are all examples.

D.Gels typically behave non-Newtonian because of their rheological properties. In general, they fall into the following categories:

- **Gel made of plastic -** Rheogram plots indicate the yield value of elastic gels above which they distort and flow. For instance, Bingham bodies and flocculated suspensions of aluminum hydroxide behave plastically.
- **Gel made from pseudoplastic -**Liquid dispersion of tragacanth, sodium alginate, Na CMC, etc., decreases in viscosity with an increase in shear rate without yielding.
- **Gels with thixotropic properties -**There is no bond between particles in this type of gel, so shaking can easily break it down. Due to particle collisions, the resultant solution will reform gel, E.g., Kaolin, bentonite, and agar.

E. On the basis of physical nature:

§ Gels with elastic properties: Hydrogen bonds and dipole attraction bind the fibrous molecules together at the junction, forming relatively weak bonds. Alginates, guar gum, and gels of agar are examples.

§ Gels with rigid properties: There is a primary valance bond between the framework and the macromolecules in these gel macromolecules. As an example, silica gel has pores formed by Si-O-Si-O bonds that hold silica acid molecules together.

F. Polymers that form gels or bases:

The following categories can be used to classify it:

§ Polymers of natural origin - Living organisms can synthesize these polymers, e.g., proteins, like collagen, gelatin, etc., and polysaccharides, such as pectin, gum, tragacanth, and agar.

§ Polymers derived from semi-synthetics: Chemical modification produces these types of polymers e.g. carboxymethylcellulose, methylcellulose, hydroxyethylcellulose from natural polymers.

§ Polymers synthesized from synthetic materials: A synthetic polymer is a polymer which has been synthesized in vitro. Poloxamer, polyacrylamide, polyvinyl alcohol, and polyethylene are some examples of carbomercarbopol 945 and carbopol 935.

§ Substances that have no organic component - Benitoite and aluminum hydroxide.

§ Ingredients in surfactants: A mixture of stearatearyl alcohol and Brij-98:

GELS ARE PREPARED AS FOLLOWS:

A gel is generally manufactured on a larger scale at room temperature. The processing of some polymers requires a unique treatment. In order to manufacture gels, the following methods are used:

§ Changes in thermal properties:

As a result of thermal changes, dissolved polymers (lipophilic colloids) gel. Gelatin, agar sodium oleate, guar gummed derivatives of cellulose, etc., become gelled if the temperature is lowered. When the temperature is increased, hydrogen bonds are disrupted, which decreases solubility and causes gelation.

§ The flocculation process:

Gelation is produced when a sufficient amount of salt is added to produce an aging state but not enough to precipitate fully. It ensures rapid mixing and prevents localized high precipitant concentrations. Using non-solvents such as petroleum ether, it is possible to gelsolutions of ethyl cellulose and polystyrene in benzene.

§ Reaction of chemical compounds:

By chemically reacting the solute with the solvent, the gel is formed. By combining aluminum salt and sodium carbonate in aqueous solution, aluminum hydroxide gel can be precipitated. Reactants with a higher concentration will form gels.

METHODS AND MATERIALS

Carbopol 945, Fluconazole, NaCMC, and other active ingredients were provided by Indian Pharmaceuticals.

The following materials were used

This product contains Fluconazole, Carbopol 945, NaCMC, Glycerin, Triethanolamine, Methyl and Propyl parabens, and Alcohol (Methanol).

The equipment used was

The following are available: Electron balance, Hot air oven, UV spectrophotometer, Mechanical stirrer, PH meter, etc.

Preparation Method

The concentration of polymers used to formulate Fluconazole topical gels (F1-6) varied. NaCMC and Carbopol 945 were taken in separate beakers and allowed to soak for one day in purified water. Afterward, a sufficient quantity of Triethanolamine was added to Carbopol 945 to neutralize it. A moistening agent, glycerine, was used, along with alcohol (methanol) to enhance penetration. It was continued gently stirring until the homogenous gel was formed while methyl paraben sodium and propyl paraben sodium were added slowly as preservatives.

Fluconazole UV spectrum analysis:

To determine the maximum wavelength, the solution was scanned between 250 and 450 nm.

STANDARD GRAPH PREPARATION

Standard Fluconazole Stock Solution:

A concentration of 0.001 grams of fluconazole in a volumetric flask of 0.001 liters of methanol was measured and withdrawn from this solution. A 0.1µg/ml standard stock solution was made with methanol.

An overview of fluconazole's standard graph

The standard stock solution was diluted using methanol into 45, 55, 65, 75, and 85µg/ml solutions. Spectrophophotometric measurements were conducted at 270 nm against a blank of methanol to determine fluconazole's absorbance.

FLUCONAZOLE GELS - PHOSIOCHEMICAL TESTING

Yield in percentage

It was weighed twice: once with an empty container containing the gel formulation, and again with the container containing the gel formulation. We calculated the practical yield by using the weight difference, and then we calculated the percentage yield by using the formula.

Yield as a percentage = Theoretical yield divided by practical yield × 100.0

Ingredients in the drug

An alcohol concentration of 25 ml was added to a 300 ml volum0.001 l of water, the volume was filtered. The solution was further diluted with alcohol to 15 ml twice by adding 1.5 ml to 15 ml of water and 1.5 ml to 15 ml of water. A suitable dilution was used to measure the absorbance at 270 nm of the solution. A calibration curve was used to determine drug content.

pH measurement

A calibrated digital pH meter was used to measure 55 grams of each gel formulation. Skin infections

should be treated with topical gel formulations with a pH range of 4 to 10.

Ability to spread

In order to determine the spreadability of the gel formulation, 1.5g of the gel was placed between two horizontal plates (21 x 21 cm2). The standardized weight of 130 grams was placed above the plates and allowed to sit for 60 seconds. A scale was then used to measure the diameter.

The homogeneity and grittiness of the product:

Upon setting the gels in the container, all developed gels were visually inspected for homogeneity. A visual inspection was conducted to determine whether any aggregates were present. Also, all the gel formulations were microscopically examined for particulates in the skin and observed for grittiness.

RESULT

An overview of the calibration curve

The technique for estimating the maximum absorption at wavelength 270 nm in methanol revealed the maximum absorption for Fluconazole, as shown in table 2. At a concentration of 15 mg/ml, the standard curve obeyed Beer's law. Regression analysis showed a linear relationship between concentration and absorbance and a regression equation of 0.9970 for the regression coefficient.

y = 0.0025x + 0.0599.

An overview of the drug's physicochemical properties is given below

In its molecular formula, the drug has the formula C13H12F2N6O. Its molecular weight is 3110.170g/mol. The IUPAC name of the drug is 2-(2, 4-Difluorophenyl)-1,3-bis(1H-1,2,4-triazole1-yl)propan-2-ol.

Physiochemical evaluation of various formulations

Based on the results of the yield, drug content, pH, spreadability, color, homogeneity, and grittiness of the formulations, the following summary has been provided.

A comparison was made between the observations mentioned and the pharmacopoeia specifications, confirming that the drug was identified and finding that the observations mentioned were in agreement with the specifications and that Fluconazole gel was homogeneous and did not show any grittiness. By applying the following formula to all formulation batches, we were able to calculate the percentage yield for each batch:

Percentage yield = (practical yield / theoretical yield) × 100.0

Earlier, the F2 formulation had the lowest percentage yield (94.70%) and the F4 formulation had the highest percentage yield (99.30%).

An UV Spectrophotometer at wavelength 270 nm in alcohol was used to estimate the drug content of Fluconazole gel after various formulation batches. Table 4 shows the results of the experiment. A minimum drug content of 93.58% was determined in batch F1 and a maximum drug content of 105.30% and 110.50% was found in batches F3 & 4. There was no difference between formulas (95-115) %.

A digital pH meter was used to determine the pH of all formulation batches. Table 5 shows the results obtained. Formulation F1 & 4 were found to be suitable for pH ranges of 6.60 & 7.5, respectively, but formulation F1 was found to be suitable for pH ranges of 4.5-7.5.

A digital pH meter was used to determine the pH of all formulation batches. Table 5 shows the results obtained. Formulation F1 & 4 were found to be suitable for pH ranges of 6.60 & 7.5, respectively, but formulation F1 was found to be suitable for pH ranges of 4.5-7.5.

A formulation F4 had the highest spreadability, i.e. 13.70 cm, while formulation F3 had the lowest spreadability, i.e. 5.50 cm.

Table 1: Formulations (f1-6) and their constituents

Formulation (weight/weight)	1	2	3	4	5	6
Fluconazole	0.5	0.5	0.5	0.5	0.5	0.5
Carbopol-945	0.6	2	2.5	00	00	00
NaCMC	0	00	00	0.6	2	2.5
Methanol	5	5	5	5	5	5
Glycerin	15	15	15	15	15	15
Aqueous solution	70	70	70	70	70	70
Propylparaben Sodium	0.06	0.06	0.06	0.06	0.06	0.06
Methylparaben sodium	0.2	0.2	0.2	0.2	0.2	0.2
Tri Ethanolamine	0.4	0.4	0.4	0.4	0.4	0.4
Amount in grams of the total weight	78.050	78.550	79.050	78.050	78.550	79.050

Table: 2 Fluconazole Gel Absorption at Different Concentrations

Measurement of concentration (µg/ml)	Measurement of absorbance (270nm)
50	0.160
60	0.190
70	0.210
80	0.230
90	0.260

Table: 3 Yield percentages of different formulations (f1-f6)

Percentage yield (%)-F	1	2	3	mean	Standard deviation
1	96.80	95.80	95.20	95.8800	0.79200
2	94.5	94.5	94.50	94.70	0.15800
3	94.00	94.90	94.5	94.8770	0.09595
4	99.40	98.0	99.5	99.30	0.35180
5	96.40	96.50	97.80	96.90	0.74540
6	98.65	97.0	97.45	97.9070	0.63620

Table: 4 Different formulations' drug content (F1-6)

Content of drugs in formulations (%)	1	2	3	Mean	Standard deviation
1	94.30	93.5	96.20	94.5940	1.482090
2	92.5	95.30	98.15	95.3040	2.915140
3	103.5	105.5	97.20	102.50	4.529530
4	95.30	99.50	98.15	97.80	2.426050
5	97.0	93.5	95.30	95.30	1.800080
6	107.80	104.5	106.8	106.50	1.4970375

Table: 5 Formulations with different pH values (f1-6)

pH(formulation)	1	2	3	Mean	Standard deviation
1	6.0	6	6.5	5.60330	0.50200
2	6.5	6	6.5	5.30330	0.32050
3	5.5	6.0	6.5	5.07778	0.46099
4	7.0	8.8	7.5	7.5	0.5
5	8.0	8.0	8.0	8.0	0.5
6	8.5	8.7	8.1	7.74444	0.38860

Table: 6 Formulations (f1-f6) with different spreadability

Measurement of spreadability (cm)	1	2	3	Mean	Standard deviation
F1	6.0	6.0	6.0	6.877778	0.125730
F2	5.0	5.5	5.0	5.944444	0.259555
F3	4.8	5	4.9	5.577778	0.340040
F4	14.0	12.9	13.0	13.74444	0.612950
F5	13.0	13.8	12.0	13.17778	0.358000
F6	12.0	12.8	13	12.5	0.375060

DISCUSSION

Drugs delivered topically or transdermally have several advantages over those delivered orally. It has been discovered that oral delivery of fluconazole has many side-effects, and here fluconazole gel has been prepared by combining different polymers to overcome the side effects of oral delivery [21]. To efficiently deliver fluconazole to the skin, fluconazole gel was developed in the present study. Carbopol 945, NaCMC, methyl paraben sodium, propyl paraben sodium, triethanolamine, and distilled water were used to prepare fluconazole gel [19].

These medications are less greasy than creams and ointments, and they release drugs faster and are easily removed as compared to creams and ointments. Six formulations were prepared in total. Resulting data for percent yield, drug content, pH, and spreadability were satisfactory. Formulation F4 yielded 99.30%. There was

no drug content in any of the formulations prepared (95-115%). The highest and lowest drug content in Formulations F3 & 6 is 105.20 & 110.0, respectively, and 94.60 in Formulation 1

As polymer concentration increased, drug content increased. In all formulations, pH ranges ranged from 4.5 to 7.8, but formulations F2 & 3 have pH values of 6.5 & 6.06, respectively and they cooperate with skin pH. Upon application to the skin, the formulation had a pH between 5.0 and 8.0, which is considered acceptable to prevent irritation. Polymer concentration decreases gel spreadability. Carbopol gel formulation F3 had the lowest spreadability, i.e. 5.50 cm, and the highest spreadability, 13.70 cm, for NaCMC gel formulation F4.

There was a homogeneous and smooth appearance to the prepared formulations. Carbopol and NaCMC are both gelling agents that give a solid like appearance [20]. There was a smooth and homogeneous appearance to the Carbopol &NaCMC gels. The gels were transparent and white viscous. Not all formulations exhibited grittiness. By interpreting the results above, we can conclude that the gel formulation prepared with carbopol 945 & Na CMC showed acceptable properties physiochemically.

CONCLUSION

Different formulations (F-1, 2, 3, 4, 5, 6) have been developed by using suitable polymers, synthetic and semi-synthetic (Carbopol 945 and NaCMC). In order to evaluate the physiochemical properties of Fluconazole formulations, we analyzed their yields, drug content, pH, spreadability, and grittiness. Results of testing for drug content, pH, and spreadability were satisfactory. Different formulations were evaluated physically successfully.

It was easy to spread and wash most of the formulations.

Few formulations were pale in color and the majority were white transparent. There was no odor in any of the formulations. Infections of the skin could be effectively treated with this formulation (pH level 4.5-7.5). However, different polymer concentrations resulted in different gelling properties for NaCMC gels and Carbopol-945 gels. There was an acceptable level of drug content in the sample. With different polymer concentrations, formulation spreadability varied. Gels are becoming increasingly popular day by day due to their numerous advantages, including targeted drug delivery and ease of washing.

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