American Scientific Research Journal for Engineering, Technology, and Sciences (ASRJETS)

ISSN (Print) 2313-4410, ISSN (Online) 2313-4402

http://asrjetsjournal.org/

Formulation & Evaluation of Fluconazole Gel for Topical Drug Delivery System

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Abstract

Fluconazole is a recent triazole antifungal drug that is used in the treatment of superficial and systemic fungal infection. The oral use of fluconazole is not much recommended as it has many side effects. Thus this formulation is made for better patient compliance and to reduce the dose of the drug and to avoid the side effects like liver damage and kidney damage. This research was designed to formulate & evaluate different formulation of a topical gel containing fluconazole by using a polymer with different concentration as Carbopol 940 & NaCMC. Methanol was used as a penetration enhancer.

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The evaluation of formulated fluconazole topical gel was carried out for a physical appearance, pH-value, spreadability, homogeneity, drug content. The formulated gel showed good physical characteristics. The formulation F3 (101.18%) & F6 (105.4%) show good drug content as the polymer concentration in them was higher. The percentage yield of F4 (98.26%) was the highest. The spreadability of gel decreases with an increase in polymer concentration. The pH of the formulation was in the range of 5-8 which is considered acceptable to avoid the risk of irritation upon application to the skin.

Keyword: Fluconazole; Carbopol 940; Sodium Carboxy Methyl Cellulose; Topical Drug delivery system.

1. Introduction

In the past few years, topical delivery of drugs has caused more and more attention: this has the additional benefit that a high concentration of drugs can be localized at the site of action by reducing the systemic side effects as compared to parenteral or oral drug administration [1]. Topical drug administration means, a localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal, and skin as topical routes. Skin is one of the most readily accessible organs of the human body for topical administration of medicament in which the number of medicated products is applied that either enhances or restores a fundamental function of the skin or pharmacologically alters an action in the underlined tissues. Such products are termed as topical or dermatological products [2]. In the formulation of topical dosage forms, they are targeted to utilize drug carriers that ensure adequate localization or penetration of the drug within or through the skin to enhance the local and minimize the systemic effects or to ensure adequate percutaneous absorption [3]. Topical preparation helps to avoid GI- irritation, prevent the metabolism of the drug in the liver, and increase the bioavailability of the drug. Topical preparation medicament directly acts on the site of actions [4]. Fluconazole is a polar bis-triazole antifungal drug that exhibits specificity as an inhibitor of the fungal as opposed to mammalian cytochrome P-450 mediated reactions, including those involved in steroid biosynthesis and drug metabolism. Fluconazole is frequently prescribed triazoles for the treatment of candidiasis and it is used in opportunistic infections in people with HIV, severe fungal infection, because of its excellent bioavailability, tolerability, and side-effect profile [5, 6] Fluconazole is available commercially as oral and parenteral dosage forms which can be associated with serious adverse effects as nausea, vomiting, bloating, diarrhea, rash, reduction in red blood cells, and abdominal discomfort. The bioavailability of conventional forms is less in comparison with topical forms. Oral formulations require high dosage formulations, which may be expensive and unrealistic and it has a less localized effect but more side effects, which needs to be overcome as well as it has altered gastrointestinal drug absorption caused by gastrointestinal pH and enzymatic activity and drug interaction with food and drinks[6, 7]. More than 80 % of the orally ingested drug has been found in the circulation, and 60 to 70% is excreted in the urine and only 10% of fluconazole is protein bound. Thus, it is metabolized in the liver there is an incidence of hepatotoxicity[8]. Topical preparations are applied directly to an external body surface by spreading, rubbing, and spraying**.** Within the major group of semisolid preparations, the use of transparent gels has expanded both in cosmetics and in pharmaceutical preparation due to ease of application and better percutaneous absorption. It can resist the physiological stress caused by the skin flexion, blinking, and mucociliary movement, adopting the shape of the applied area and controlling drug release [9, 10]. Gels are typically formed from a liquid phase that has been thickened with other components. The continuous

liquid phase allows free diffusion of molecules through the polymers scaffold and hence release should be equivalent to that from a simple solution[11]. They are less greasy in nature and provide a faster release of drug substance independent of water solubility of drugs, as compared to creams and ointments, and can be easily removed from the skin [7] . For the reason that the ingredients may not be completely molecularly dispersed (soluble or insoluble), the several gel systems are as clear as water, and others are turbid or they may form aggregates, which disperse light. Most of the concentration of the gelling agents is less than 10%, usually in the 0.5% to 2.0% range, with some exceptions [12]**.** For topical administration, Hydroxy Propyl Methyl Cellulose (HPMC), Sodium Carboxy Methyl Cellulose (NaCMC), and Carbopol 940 are used as hydrophilic polymers. According to the series of grades and based on molecular fractions, these polymers are used at a concentration between 1 to 5% in topical gel formulation [13].

Classification of gels [13]:

A. Gels can be classified depending upon colloidal phases and nature of the solvent used, physical nature, and rheological properties.

B. Based on colloidal phase

1. ***Two phase system (Inorganic)***: In this type, the particle size of the dispersed phase is relatively large and forms the three-dimensional structure through the gel. They must be thixotropic-forming semisolids on standing and become liquid on agitation.
2. ***Single phase system (organic)*****:** Single-phase gels comprise of large organic molecules existing on the twisted strands dissolved in a continuous phase. These larger organic molecules uniformly circulated within a liquid in such a way that no visible boundaries and the liquid.
3. **Based on nature of solvent used**:

    1. ***Hydro gels (water based)***: In hydrogels, water acts a continuous liquid phase E.g.: bentonite magma, Gelatin, cellulose derivatives, carpooler, and poloxamer gel.
    2. ***Organic Gels*** (with a non-aqueous solvent): They have a non-aqueous solvent on their continuous phase. E.g. plastic base (low molecular wt polyethylene dissolved in mineral oil & short Cooled) Olag (aerosol) gel and dispersion of metallic stearate in oils.
    3. ***Xerogels****:* Xerogels represent solid gels with lesser solvent concentration. They are produced by evaporation of the solvent, leaving the gel framework behind on contact with fresh fluid. E.g. Tragacanth ribbons, acacia tear β-cyclodextrin, dry cellulose, and polystyrene.

4. **Based on rheological properties:** Usually gels exhibit non-Newtonian flow. They are classified into:

    1. ***Plastic gel*** - The plot of rheogram gives the yield value of the gels above which the elastic gel distorts and begins to flow E.g., Bingham bodies, flocculated suspensions of Aluminum hydroxide exhibit a plastic flow.
    2. ***Pseudo plastic gel*** – There is a decrease in the viscosity of this type of gel with an increase in the rate of shear with no yield value E.g., Liquid dispersion of tragacanth, sodium alginate, Na CMC, etc.

exhibits pseudo-plastic flow.

3. ***Thixotropic gels*** – In this type of gel, the bonds between particles are very weak and can be broken down by shaking. The resultant solution will reform gel due to the particle collision and linking together again (the reversible isothermal gel-sol-gel transformation), E.g.: Kaolin, bentonite, and agar.

5. **Based on physical nature:**

1. ***Elastic gels***: The fibrous molecules are joined together at the point of the junction by relatively weak bonds, such as hydrogen bonds and dipole attraction. E.g.: gels of agar, guar gum, and alginates.
2. ***Rigid gels*****:** These represent gel macromolecules in which the framework is bonded by a primary valance bond. E.g.: In silica gel, silica acid molecules are held by Si-O-Si-O bond to give a polymer structure possessing a network of pores.

6. **Bases or gel forming polymers**

It can be classified as follows:

1. **Natural polymers –** These polymers are found naturally and can be synthesized by living organisms e.g. Protein like collagen, gelatin, etc and polysaccharides like agar, tragacanth, pectin, and gum, etc.
2. **Semi synthetic polymers –** These types of polymers are mostly formed from natural polymers by chemical modification e.g. cellulose derivatives like carboxymethylcellulose, methylcellulose, hydroxyethyl cellulose.
3. **Synthetic polyners –** The polymers which are prepared under in-vitro conditions are called synthetic polymers. E.g. carbomer carbopol 940, carbopol 934, poloxamer, polyacrylamide, polyvinyl alcohol, and polyethylene.
4. **Inorganic substances –** Aluminum hydroxide and Benitoite.
5. **Surfactants –** Sebrotearyl alcohol and Brij-96.

Preparation of Gels [14] : Generally, the gels on the industrial scale are manufactured at room temperature. Nevertheless, some polymers require unique treatment before processing. Gels are manufactured by the given below methods:

1. **Thermal changes:** Solvated polymers (lipophilic colloids) when subjected to thermal changes cause gelation. If the temperature is lowered, the degree of hydration of lipophilic colloids is reduced and gelation occurs, e.g. gelatin, agar sodium oleate, guar gummed and cellulose derivatives, etc. On the other hand, increasing the temperature of solutions like cellulose ether will disrupt the hydrogen bonding and decrease solubility, which will cause gelation
2. **Flocculation:** In flocculation, gelation is produced by adding just enough quantity of salt to precipitate to produce an aging state but insufficient to bring about complete precipitation. It is essential and ensures rapid mixing to avoid local high concentration of precipitant. e.g.: Solution of ethyl cellulose, polystyrene in benzene can be gelled by rapid mixing with suitable amounts of a non-solvent such as petroleum ether.

3. **Chemical reaction:** In this method, the gel is prepared by a chemical reaction between the solute and solvent. e.g.: aluminum hydroxide gel is precipitated by interaction in an aqueous solution of aluminum salt and sodium carbonate. An increased concentration of reactants will produce a gel structure.

2. Materials and Methods

Active drug Fluconazole, Carbopol 940, NaCMC was provided by Times Pharmaceutical Pvt. Ltd. & other ingredients like glycerine, alcohol, triethanolamine methyl paraben sodium, propyl paraben sodium was available in Shree Medical & Technical College. Similarly, the instruments for the research were also provided by the Shree Medical & Technical College.

Table 1: List of materials used

S.N.	Ingredients	Intended For Use
1	Fluconazole	Active Pharmaceutical Ingredient
2	Carbopol 940	Preparation of Gel base
3	NaCMC	Preparation of Gel base
4	Glycerin	Moistening agent
5	Triethanolamine	Buffer
6	Methyl paraben sodium	Preservatives
7	Propyl paraben sodium	Preservatives
8	Alcohol(methanol)	Diluent/Penetration enhancer

Table 2: List of Equipment used

S.N	Equipment	Specifications
1	Electron balance	Excell ,model BH
2	UV spectrophotometer	Double beam LT-2900
3	Mechanical stirrer	DICA, India
4	PH meter	HANNA instrument
5	Hot air oven	SHIV, India

3. Method of Preparation

Six formulations of fluconazole topical gel (F1-F6) were prepared using different concentrations of polymers. Carbopol 940 & NaCMC of different concentrations and purified water were taken in a beaker and allowed to

soak for 24 h. To this required amount of drug was dispersed in water and then Carbopol 940 was then neutralized with a sufficient quantity of Triethanolamine. Glycerine is a moistening agent & alcohol (methanol) as a penetration enhancer was used. Methyl paraben soduim and Propyl paraben sodium as preservatives were added slowly with continuous gently stirring until the homogenous gel was formed [10, 13]

PROCESS FLOW CHART FOR DEVELOPMENT OF FLUCONAZOLE GEL

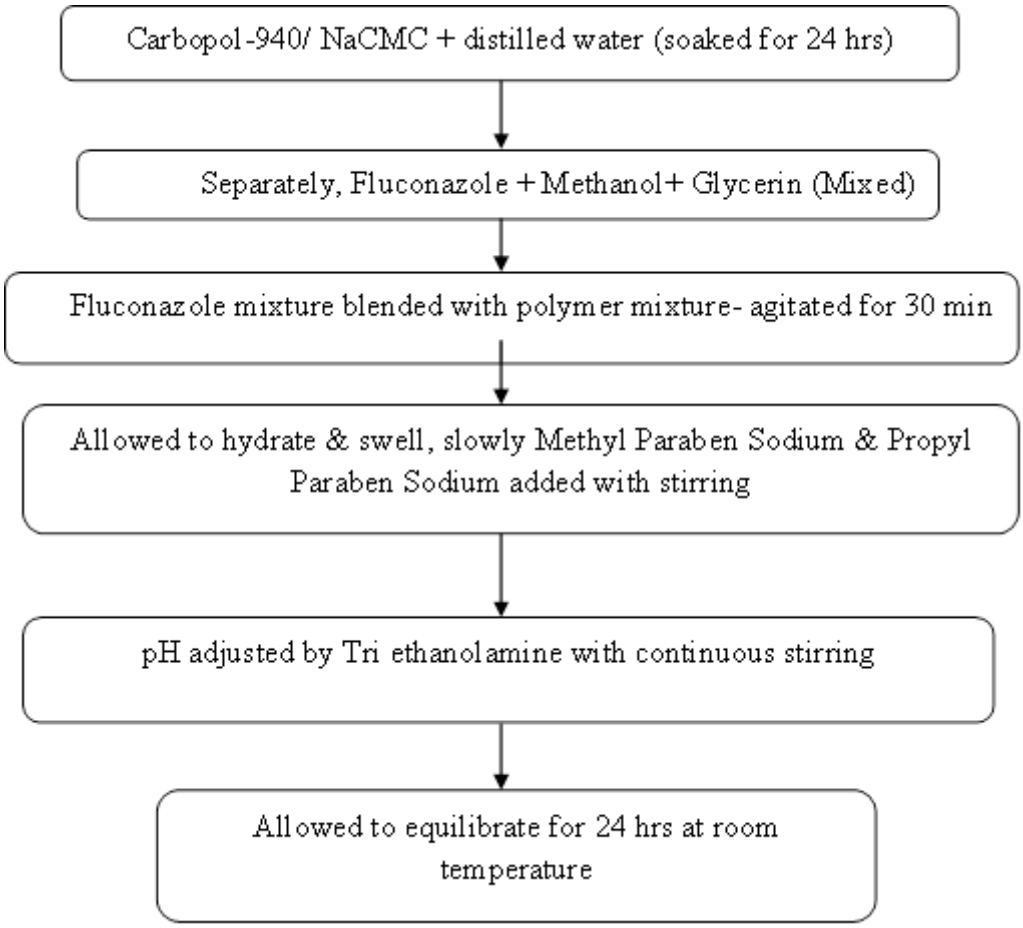

Figure 2

Table 3: constituents of different formulations (f1-f6)

S.N.	Formulation(w/w)	F1	F2	F3	F4	F5	F6
1	**Fluconazole**	**0.4**	**0.4**	**0.4**	**0.4**	**0.4**	**0.4**
2	**Carbopol-940**	**0.5**	**1**	**1.5**	**-**	**-**	**-**
3	**NaCMC**	**-**	**-**	**-**	**0.5**	**1**	**1.5**
4	**Methanol**	**4**	**4**	**4**	**4**	**4**	**4**
5	**Glycerin**	**10**	**10**	**10**	**10**	**10**	**10**
6	**Tri Ethanolamine**	**0.3**	**0.3**	**0.3**	**0.3**	**0.3**	**0.3**
7	**Methylparaben sodium**	**0.1**	**0.1**	**0.1**	**0.1**	**0.1**	**0.1**
8	**Propylparaben Sodium**	**0.05**	**0.05**	**0.05**	**0.05**	**0.05**	**0.05**
9	**Water**	**60**	**60**	**60**	**60**	**60**	**60**
	Total Weight (gm)	**77.046**	**77.546**	**78.046**	**77.046**	**77.546**	**78.046**

4. UV spectrum analysis of Fluconazole

The solution was scanned in the range of 200-400 nm to fix the maximum wavelength and the UV spectrum was obtained.

5. Preparation of Standard Graph [15]

5.1 Standar Stock solution of Fluconazole

Accurately weighed 100 mg of fluconazole and was dissolved in 100 ml of methanol, from this stock solution 10 ml was withdrawn and transferred into a 100 ml volumetric flask. Volume was made with methanol to get a standard stock solution containing 100µg/ml.

5.2 Standard Graph of Fluconazole

From this standard stock solution, a series of dilution (40, 50, 60, 70, and 80µg/ml) were prepared using methanol. The absorbance of these solutions was measured spectrophotometrically against the blank of methanol at 260 nm for fluconazole.'

6. Physiochemical Evaluation of Prepared Fluconazole Gels

6.1 Percentage Yield

The empty container was weighed in which the gel formulation was stored & again the container was weighed with gel formulation. The difference in weight was used to calculate the practical yield then the percentage yield was calculated by using the formula [15]. The results are shown in table no.7.

Percentage yield = (practical yield / theoretical yield) × 100

6.2 Drug Content

10 grams of each gel formulation was transferred in a 250 ml volumetric flask containing 20 ml of alcohol and stirred for 30 min. by using a magnetic stirrer. 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 at 260 nm after suitable dilution [15]. Drug content was determined by using the equation obtained from the calibration curve. The results are shown in table no.8.

6.3 Determination of pH

50 grams of each gel formulation was transferred in a beaker and measured it by using the calibrated digital pH meter. The pH of the topical gel formulation should be between 3 – 9 to treat skin infections [15]. The results are shown in table no.9.

6.4 Spreadability

The spreadability of the gel formulation was determined, by placing 1gm of the gel between horizontal plates (20×20 cm^2). Above the plates, the standardized weight of 125 gm was placed & left for 1 min. Then the diameter was measured by using the scale [15]. The results are shown in table no.10.

6.5 Homogeneity & Grittiness

All developed gels were tested for homogeneity by visual inspection after the gels have been set in the container. They were tested for their appearance and presence of any aggregates. Similarly, it was applied in the skin & observed for the presence of grittiness or all the gel formulation is checked microscopically for the presence of any particulate matter [16]. The results are shown in table no.6.

7. Result

7.1 Calibration Curve

The technique for the estimation for the drug Fluconazole confirmed maximum absorption at wavelength 260

nm in methanol and all obtained values given in the table 4 Standard curve obeyed Beer's law at given concentration of 10 mcg/ml and when subjected to regression analysis, the cost of regression coefficient was discovered to be 0.9969 which showed linear relationship between concentration and absorbance and regression equation of

y = 0.0024x + 0.0594.

Table 4: Table of Absorbance at Various Concentration of Fluconazole Gel

S.N.	Concentration(µg/ml)	Absorbance (260nm)
1	40	0.156
2	50	0.182
3	60	0.201
4	70	0.227
5	80	0.254

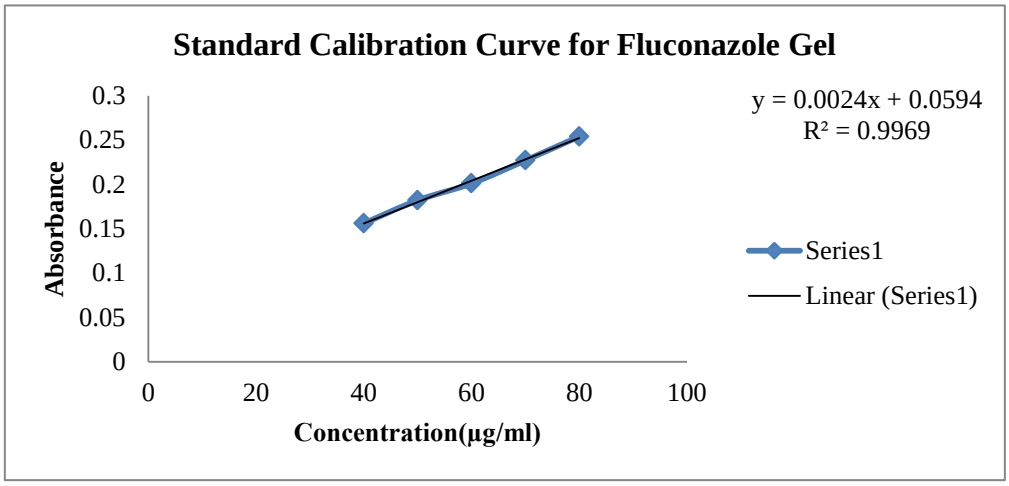

Figure 1: Standard Calibration Curve of Fluconazole Gel in Methanol

7.2 Evaluation of Physiochemical Properties of Different Formulation

The percentage yield, drug content, pH, spreadability, color, homogeneity, grittiness of the different formulations was determined which have been summarized as follows.

Table 5: physico-chemical properties of fluconazole gel

S.N.		**Physicochemical properties of drug**
1	IUPAC NAME	2-(2,4-Difluorophenyl)-1,3-bis(1H-1,2,4-triazole-1-yl)propan-2-ol
2	Molecular formula	$C_{13}H_{12}F_2N_6O$
3	Molecular weight	306.271g/mol
	Pharmacokinetic properties	
4	Bioavailability	>90% (oral)
5	Metabolism	Liver 11%
6	Half life	30hrs (oral)
7	Excretion	Kidney 61-81%
8	Storage & moisture	Store at room temperature away from light

The following properties of drug were evaluated and results are obtained as:

Table 6: characterization *of* fluconazole gel

S.N.	**Parameters**	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
1	**Color**	Colorless	White	White	Color less	Pale yellow	Pale yellow
2	**Homogeneity**	+++	++	+	+++	+++	+++
3	**Grittiness**	-	-	-	-	-	-

Excellent +++, Good ++, Satisfactory +, No grittiness –

The observations mentioned were in contrast to the specifications given in the pharmacopoeia to confirm the identification of the drug and it was found that observations stated complied with the specifications and the Fluconazole gel was found to be homogeneous and no grittiness was noted. The percentage yield of all formulation batches was calculated with the aid of using the following formula,

Percentage yield = (practical yield / theoretical yield) × 100

The minimum percentage yield was once found in F2 formulation (93.63%) and maximum percentage yield was once observed in the F4 formulation (98.27%). The obtained values are tabulated in table 7.

Table 7: percentage yield of different formulations (f1-f6)

Percentage yield (%)	**1**	**2**	**3**	**Average**	**S.D.**
F1	95.72	94.74	94.17	94.8767	0.78399
F2	93.8	93.6	93.49	93.63	0.15716
F3	93.98	93.85	93.8	93.8767	0.09292
F4	98.31	97.9	98.6	98.27	0.35171
F5	95.39	95.45	96.71	95.85	0.74539
F6	97.61	96.7	96.41	96.9067	0.62613

After various formulation batches of Fluconazole gel the drug content of the formulated gel was estimated by means of UV Spectrophotometer at wavelength 260 nm in alcohol. The results had been given in the table 8 , the minimal drug content was once determined in F1 batch (93.58%) and maximum drug content discovered in the F3 & F4 batch (101.25% &105.41%) respectively. All the formulations were in the limits (90-110) %.

Table 8: drug content of different formulations (f1-f6)

Drug content (%)	**1**	**2**	**3**	**Average**	**S.D**
F1	93.26	92.3	95.19	93.5833	1.471881
F2	91.3	94.23	97.11	94.2133	2.905036
F3	102.8	104.8	96.15	101.25	4.528521
F4	94.23	99.03	97.11	96.79	2.415947
F5	96.1	92.3	94.23	94.21	1.900079
F6	106.73	103.8	105.7	105.41	1.486371

The pH determination of all the formulation batches was accomplished via using the digital pH meter (HANNA instrument). The obtained results are given in the table 9. The pH of all the formulation batches were found within the range that is 4-*7* but formulation F1 & F4 has found to be suitable pH of 5.53 & 7.2 respectively.

Table 9: ph of different formulations (f1-f6)

pH	1	2	3	Average	S.D
F1	5.9	5	5.7	5.53333	0.47258
F2	5.1	5	5.6	5.23333	0.32146
F3	4.6	5.1	5.5	5.06667	0.45092
F4	6.9	7.5	7.2	7.2	0.3
F5	7.5	7.2	7.8	7.5	0.3
F6	7.2	7.8	7.9	7.63333	0.37859

The spreadability of Fluconazole gel was found to be most effective in which the formulation F4 was highest i.e. 12.63 cm .The lowest spreadability observed was of the formulation F3 i.e. 4.46 cm. The obtained results are given in table 10.

Table 10: spreadability of different formulations (f1-f6)

Spreadability(cm)	**1**	**2**	**3**	**Average**	**S.D.**
F1	5.6	5.8	5.9	5.766667	0.124722
F2	4.5	5.1	4.9	4.833333	0.249444
F3	4.6	4	4.8	4.466667	0.339935
F4	13.2	11.8	12.9	12.63333	0.601849
F5	12.1	12.5	11.9	12.16667	0.249444
F6	11.1	11.7	12	11.6	0.374166

8. Discussion

Topical, and transdermal drug delivery systems offer several advantages over oral delivery systems. It has been found so many side-effects were proved by the oral delivery of fluconazole and here to overcome the side-effects of the oral dosage form Fluconazole gel was prepared using different polymers. In the present study, an attempt was made to formulate fluconazole gel for the efficient delivery of a drug to the skin. Fluconazole gel was prepared by using Carbopol 940, NaCMC, alcohol, methyl paraben sodium, propyl paraben sodium, triethanolamine, and distilled water. They are less greasy in nature and provide a faster release of drug substance independent of water solubility of drugs, as compared to creams and ointments, and can be easily removed from the skin. A total number of 6 formulation were prepared. The data obtained from percentage yield, drug content, pH, spreadabilty gave satisfactory results. The percentage yield of formulation F4 was highest 98.26% . The formulations prepared were all in the drug content limit (90-110) %. Formulation F3 & F6 shows highest drug content i.e. 101.18 & 105.4 respectively & F1 shows lowest content 93.53. There was an increase in drug content with an increase in polymer concentration. All formulations were within the pH range [4-7], but formulation F2 & F3 has suitable pH of 5.2 & 5.06 respectively & it cooperates with skin pH. The pH of the formulation was in the range of 5-7.5 which is considered acceptable to avoid the risk of irritation upon application to the skin [17]. The spreadability of gel decreases with an increase in polymer concentration [15]. The spreadability of NaCMC gel formulation F4 was highest i.e. 12.63 cm & lowest spreadability observed was of Carbopol gel formulation F3 i.e. 4.46 cm. The prepared formulations shared a smooth and homogeneous appearance. Among two gelling agents, Carbopol gives solid like appearance & NaCMC gives a liquid-like appearance. The Carbopol & NaCMC gels were transparent and gels were white viscous with a smooth and homogeneous appearance. The grittiness was not observed in all of the formulations. The viscosity increases upon increasing the polymer concentration [18], From the above result, we can conclude that gel formulation prepared with carbopol 940& Na CMC showed acceptable physiochemical properties.

9. Conclusion

Various formulation (F1, F2, F3, F4, F5, F6) were developed by using suitable polymer, synthetic & semi-synthetic respectively (Carbopol 940 and NaCMC). Developed formulations of Fluconazole were evaluated for the physiochemical parameters such as percentage yield, drug content, pH, spreadability, grittiness. The data obtained from drug content, pH, spreadability test studies gave satisfactory results. The physical evaluation of various formulations was successfully carried out. Most of the formulations were easily spreadable and easily washable. The color of formulations was white transparent and few of them were pale. All the formulations were odorless. The pH of the formulation was sufficient enough to treat skin infections (4-7 range). The viscosity of NaCMC gels was very less as compared to Carbopol-940 gels, but both gels showed different gelling properties with an increase/decrease in polymer concentration. The drug content was within the limit & acceptable. The spreadability of the formulations was varied with different polymer concentrations. Because gels offer numerous advantages, targeted drug delivery, and easily washable, thereby gels are becoming increasingly popular, day by day.

10. Recommendations

On the basis of this finding, we can conclude that fluconazole was successfully incorporated into the different topical gel preparation & suitable for topical application. The majority of pharmaceutical gels available in the market are used either for analgesic or anti-inflammatory purposes. Others are mostly antimicrobial. For treating bacterial or fungal infections of the skin, antiseptic creams, ointments, or solutions are commonly used but in near future, more antimicrobial gels are expected to be launched in the market. As a result, we have an opportunity to get an increasing number of gels patented. Transdermal prodrugs could also emerge in the market in the coming years. Due to the ever-increasing use of novel penetration enhancement techniques, indications of gels for the treatment of systemic diseases are expected to rise up in the future. The present study deals with the usefulness of gels in comparison to other pharmaceutical preparation used as topical drug delivery for various treating skin problems

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