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Research Article

Formulation and evaluation of microspheres loaded topical gel for fungal infections

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Abstract

Fluconazole is a derivative of the imidazole and is used for the management of both local and systemic fungus infections. The Fluconazole should not be used orally as it has several negative impacts. fluconazole topical sold commercially, since there are no commercially available gel preparations, these formulations are developed to improve patient compliance and medicine dosage should be decreased in order to prevent negative effects like both renal and liver damage. It was a gel, altered by altering the polymer ratio. FT-IR analysis identified no interactions and verified the drug's purity. Between excipients and the medication. Gel formulas were used to characteristics for drug content, pH measurement, antifungal, in vitro diffusion, and viscosity measurement skin discomfort and activity. Some studies indicated that the oils from medicinal plants could be used as potential anti FLU-resistant C. albicans agents.

Keywords: Fluconazole, Topical gel, Microspheres, Fungus infection

INTRODUCTION

A long-lasting inflammatory condition called psoriasis is marked by distinct, erythematous plaques covered in thick, silver-white scale.1 1% to 2% of the North are impacted. Similar to diseases like cancer, diabetes, and depression in terms of how it affects quality of life in the American population, psoriasis is both a physically and mentally crippling condition.2Although psoriasis can manifest at any age, the largest peaks of occurrence are between the ages of 20 and 60.3 Up to 5% of the body surface area of persons with psoriasis who have mild-to-moderate illness is affected.4Importantly, psoriasis typically has remissions and flare-ups during its chronic duration. Education of the patient, the selection of medicines, and adherence to the prescribed course of therapy are only a few of the variables that influence management success. Up to 80% of psoriasis patients will experience scalp involvement. 5Scalp psoriasis can develop on its own or in combination with other psoriatic conditions. Scalp psoriasis is characterized by silver-white scales on red, thicker plaques that may be contained inside the hairline or may spread over the forehead, ears, and back of the neck. 6In addition, up to 97% of those with scalp psoriasis state that the illness interferes with their everyday lives, making it important to note that it can cause significant physical and social misery.7In many cases, scalp psoriasis is accompanied by severe itching, and scale is frequently shed as dandruff, causing serious social shame for those who are affected (Bhalaria, Naik, 2009). These índices take into consideration the erythema, induration, and desquamation of illness affecting the scalp solely, unlike the PASI, which assesses disease severity on four different body surface regions8,9. Other devices are available, although they are used less frequently.10,11,Additionally, methods for patient self-evaluation have been created, such as the Dermatology Life Quality Index and the Scalpdex, a tool for measuring

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quality of life that takes into account both symptoms and the effect of the condition.12-14 Together, these techniques may be used to evaluate patient response on a range of indicators and guide treatment decisions in addition to symptomatology assessment (Chalmers, 2015). Even with the wide range of psoriasis treatments available, treating the condition on the scalp is still challenging. Hair not only affects how drugs are applied and reach the damaged regions, but it also has a significant impact on how well patients follow their treatment plans. Patients frequently lament how oily their drugs make them feel in this region as well as how difficult it is to get things out of their hair. At the moment, topical drugs are suggested as a first line of treatment for mild to severe psoriasis, while they can also be employed. Pharmacological or biological treatments for moderate-to-severe psoriasis should be used together with phototherapy. The most effective treatment for scalp psoriasis is topical corticosteroids, either alone or in combination with the vitamin D analogue calcipotriol.Importantly, a variety of fresh formulas (such as foams, shampoos, and sprays) have recently entered the market and improved aesthetic acceptance and adherence. Systemic therapy should be taken into consideration in severe or stubborn instances (Chan, Van Voorhees et al., 2009).

Microsphere

Microspheres are tiny, spherical particles that generally have sizes in the micrometer range (between 1 and 1000 m). A microsphere is occasionally known as microparticles. Different natural and artificial materials can be used to make microspheres (Chen et al., 2002). Commercially accessible microspheres include those made of glass, polymer, and ceramic. Microspheres that are both solid and hollow have vastly varying densities, making them suitable for various uses. In order to reduce a material's density, hollow microspheres are frequently employed as additives. Depending on their size and construction material, solid microspheres can be used in a wide range of applications.14 Microspheres made of polyethylene and polystyrene are the two most popular forms. The capacity of polystyrene microspheres to simplify processes like cell sorting and antibody precipitation makes them a common choice for biomedical applications **Table 1**. Polystyrene microspheres are useful for medical research and biological laboratory studies because proteins and ligands easily and permanently adhere to the material (Crowley, 2010).

Table 1. Standard curve of Fluconazole at 260nm in methanol.

CONCENTRATION (µg/ml)	ABSORBANCE (nm)
0	0
10	0.262
20	0.456
30	0.513
40	0.567
50	0.61

Microspheres made of polyethylene are frequently employed as temporary or permanent fillers. Polyethylene microspheres enable porous shapes to be produced in ceramics and other materials at lower melting temperatures. For flow visualization and fluid flow analysis, microscopy methods, health sciences, and other fields, polyethylene microspheres are extremely attractive because to their high sphericity and availability of colorful and fluorescent microspheres (DeMuria et al., 1993). multiple research applications and process troubleshooting. In electronic paper digital displays, charged polyethylene microspheres are also utilized. Glass microspheres have a limited number of uses in medical technology but are largely employed as filler to reduce weight, as a retro-reflector for road safety, as an ingredient for cosmetics, and in adhesives (Finlay, Khan, 1994). Microspheres made of ceramic are mostly utilized as grinding medium. The quality, sphericity, particle homogeneity, and particle size distribution of microspheres vary greatly (Fredriksson, 1978). Each single application requires a different microsphere to be selected5 A number of chances to manage drug delivery processes are provided by the wide range of microsphere production procedures.15.

METHOD OF PREPARATION

Solvent Evaporation Method

A liquid manufacturing vehicle is used to carry out the procedures. A volatile solvent that is immiscible with the liquid production vehicle phase is used to disseminate the microcapsule coating. The coating polymer solution contains dissolved or scattered core material that will be microencapsulated (Gerry Fink, 2005). The mixture of the core materials is disseminated in the liquid production vehicle phase with agitation to produce the proper size microcapsule. The solvent is then removed from the mixture, if necessary, so that the core material's polymer can dissolve in the polymer solution and shrink around the core. Microcapsules of the matrix kind are created when the core material is dissolved in the coated polymer solution. **Figure 1** illustrates the solvent evaporation method. Water soluble or water in soluble materials might make up the fundamental components. A polymer solution and an immiscible continuous phase, whether aqueous (o/w) or non-aqueous, must first form an emulsion in order for the solvent to evaporate. The comparison of gelating hyaluronic acid microcapsules with mucoadhesive hyaluronic acid microspheres, chitosan glutamate, and a combination of the two.16.

Fluconazole

Fluconazole is an antifungal medication that treats severe

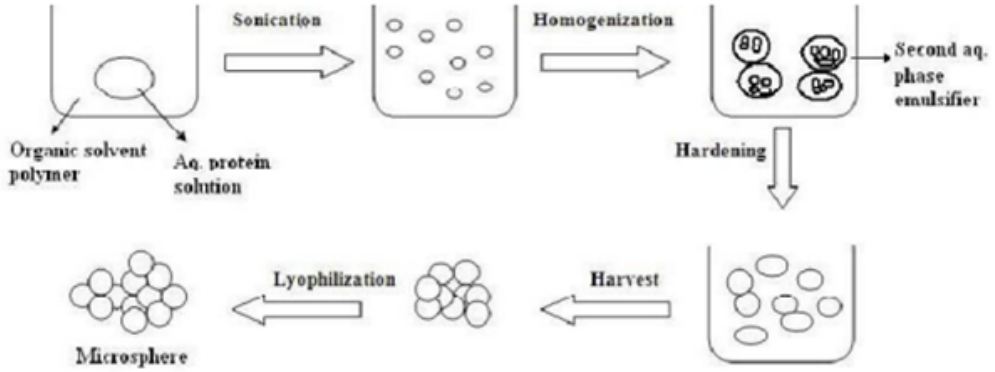

Figure 1. Solvent evaporation method for preparation of microsphere.

fungal infections in HIV-positive patients as well as opportunistic infections. Fluconazole is a novel medicine that belongs to the triazole class of antifungal agents and has none of the adverse effects associated with other antifungal medications such as ketoconazole, amphotericin B, clotrimazole, and miconazole (Gholap, 2010). Despite some of the negative effects being present in the oral and intravenous dosing forms. Due to its good absorption, tolerance, and side-effect profile, fluconazole continues to be one of the most frequently prescribed triazoles. More than 80% of the medicine taken in is discovered in the bloodstream, and 60 to 70% of it is eliminated in the urine (Henseler, 1985). Fluconazole is only 10% protein bound (1). The tissue penetration of fluconazole is likewise quite good. Penetration. The levels found in saliva, sputum, and other places are well within therapeutic limits and correspond to matching serum levels in CSF to a 70% level. If the kidneys are functioning normally, the half-life is between 27 and 34 hours, enabling once-daily dosage . The usual dose has to be cut in half for people with a decreased creatinine clearance. Rarely are serum levels of fluconazole required (Parmar, 2010). At the moment, 50, 100, 150, and 200 mg pills as well as 200 or 400 mg IV formulations are offered (18, 19).

Available Dosage Forms

Tablets and capsules: However, this antifungal agent's dose for gel has not been developed. The topical treatment of superficial fungal infections uses a variety of dose forms, including creams, liquids, gels, ointments, lacquers, and others. Creams, liquids, gels, and ointments provide effective treatments for ringworm and athlete's foot (Jain, 2007). Fluconazole has certain adverse effects in the oral and parenteral dose forms when it passes through the first pass metabolism through the liver and excretion through the kidneys, which it does after other antifungal drugs that have side effects have been defeated by it (Lowes, 2014).

- A change in how food tastes
- Nausea
- Diarrhea
- Dizziness
- Nausea

Damage to the liver and kidneys: Due to these side effects of tablet dosage of fluconazole drug the gel dosage form was formulated which was not yet marketed in India.

Gels: Gels are defined as “semisolid system in which a liquid phase is constrained within a polymeric matrix in which a high degree of physical and chemical cross-linking introduced” (Menter et al., 2008).

Gels can be classified based on colloidal phases, nature of solvent used, physical nature and rheological properties.

Based On Colloidal Phases: They are classified into

- Inorganic (two phase system)
- Organic (single phase system)

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-forming semisolids on standing and become liquid on agitation (Papp et al., 2007).

Single-phase system: These consist of large organic molecules existing on 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 walls forces (Pavia et al., 2014).

METERIALS AND METHODOLOGY

Drug-Excipients Compatibility Studies: (20) Drug-excipients compatibility studies were carried out using FT-

IR infrared spectrum of pure drug was seen in between 600 to 3800 cm-1. The study was carried out on individual pure drug and its physical mixture with the excipients used in the study (Rapp, 1999). UV Spectrum analysis of Fluconazole: The solution was scanned in the range of 200 to 400 nm to fix the maximum wavelength and UV spectrum was obtained.

Preparation of standard graph: (20) Standard 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 100 ml volumetric flask. Volume was made with methanol in order to get standard stock solution containing 100 µg/ ml. Standard Graph of Fluconazole: Form this standard stock solution, a series of dilution (10, 20, 30, 40, 50 µg/ml) were prepared using methanol. The absorbance of these solutions was measured spectrophotometrically against blank of methanol at 260 nm for fluconazole.

Preparation of gel base: (21) Carbopol 934p (1, 2, 3, 4, 5% w/w) and purified water were taken in a beaker and allowed to soak for 24 h. To this required amount of drug (2 gm) was dispersed in water and then Carbopol 934p was then neutralized with sufficient quantity of Triethanolamine. Glycerine as moistening agent, methyl paraben and Propyl paraben as preservatives were added slowly with contineous gently stirring untill the homogenous gel was formed (Sera, 2006).

EVALUATION OF FLUCONAZOLE GEL

Percentage yield: The empty container was Weighed in which the gel formulation was stored then again, the container was weighed with gel formulation. Then substracted the empty container weighed with the container with gel formulation then it gives the practical yield. Then the percentage yield was calculated by the formula (Spuls et al., 2010).

Percentage yield = × 100

Drug content: (22) Weighed 10 gm of each gel formulation were transfered in 250 ml of volumetric flask containing 20 ml of alcohol and stirred for 30 min. The volume was made up to 100 ml and filtered. 1 ml of 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 spectrophotometrically at 260 nm. Drug content was calculated by the following formula (Thanoo et al., 1992).

Drug content = × Dilution factor ×1/ 100

pH: Weighed 50 gm of each gel formulation were transferred in 10 ml of beaker and measured it by using the digital pH meter (Dubey et al., 2007). pH of the topical gel formulation should be between 3 – 9 to treat the skin infections.

Spreadability: (23-24) The Spreadability of the gel formulation was determined, by measuring diameter of 1 gm gel between horizontal plates (20×20 cm2) after 1 minute (van de Kerkhof, 200). The standardized weight tied on the upper plate was 125.

Viscosity studies: The viscosity of FZG1, FZG2, FZG3, FZG4, FZG5, and FZG6 formulations shows that the concentration of polymer increases, viscosity of gel formulation also increases. However, at the higher concentration of polymer may affect the spread ability of gel formulation. From the results, it was concluded that the formulation FZG4 showed maximum viscosity, that is, 560 cps and formulation FZG1 showed minimum viscosity, that is, 100 cps. The value of viscosity is shown in **Table 2**.

Gel strength: Gel strength is important because strong gels will support a much higher pressure than weak gels before they are washed out of the targeted site. It is calculated in time (s) and found within the range of 18–56 s. The values of gel strength are shown in **Table 3**.

Spreadability: About 1 g of gel was placed at the center of glass slide, the weight of 1000 g was carefully applied on the upper side of the slide after 5 min. Weight of 150 g is gradually added to pan to the upper slide by means of string and hook. The time at which the upper slide moves little over the lower slide was noted and this was taken as a measurement of Spreadability which can be calculated using formula:

S=ML/T

Homogeneity: All developed gels showed good homogeneity with the absence of lumps. The developed preparations were much clear and transparent [13]. The results are shown in **Table 4**.

RESULT AND DISCUSSION

Preformulation studies

Organoleptic properties of the drug:

- Physical Description – Solid
- Color - White crystalline powder

Table 2. Viscosity, gel strength, homogeneity, and pH of formulation code of FZG1–FZG6 Formulation code Viscosity (cps) Gel strength (s) Homogeneity pH.

Concentration(µg/ml)	Absorbance(nm)
4	0.204
6	0.339
8	0.443
10	0.598
12	0.670
14	0.834

Table 3. The drug release was increased with decreased due to increase in polymer concentration.

Formulation code	Angle of repose (°)	Bulk density (g/mL)	Tapped density (g/mL)	Carr index	Hausner ratio
FZMS-1	21.22 ± 0.55	0.55 ± 0.02	0.65 ± 0.02	15.15 ± 0.21	1.20 ± 0.01
FZMS-2	24.43 ± 0.93	0.59 ± 0.04	0.68 ± 0.02	19.28 ± 0.9	1.92 ± 0.03
FZMS-3	27.19 ± 0.91	0.51 ± 0.02	0.59 ± 0.01	18.52 ± 0.8	1.31 ± 0.02
FZMS-4	19.45 ± 0.33	0.59± 0.01	0.69 ± 0.03	16.23 ± 0.95	1.11± 0.05
FZMS-5	24.23 ± 0.82	0.37 ± 0.05	0.45 ± 0.04	15.5 ± 1.3	1.10 ± 0.02
FZMS-6	29.89 ± 0.40	0.49 ± 0.03	0.59 ± 0.02	16.4 ± 1.01	1. ± 0.03

Table 4. Formulation of fluconazole microsphere loaded gel.

FORMULATION CODE	Fluconazole loaded microsphers Eqv to 1gm	CARBOPOL (% W/V) (10ml)	SOD. BENZOATE (%)	PURIFIED WATER (Q.S)
FZG1	FZMS 1	2%	0.2	20ml
FZG2	FZMS 2	3%	0.2	20ml
FZG3	FZMS 3	2%	0.2	20ml
FZG4	FZMS 4	3%	0.2	20ml
FZG5	FZMS 5	2%	0.2	20ml
FZG6	FZMS 6	3%	0.2	20ml

- Odour – Characteristics
- Melting point of fluconazole**:** 138-140°C
- Solubility **-** slightly soluble in water, soluble in chloroform, Ethanol, propylene glycol

STANDARD CURVE OF FLUCONAZOLE

Preparation standard calibration curve of Fluconazole: Accurately weighed 10mg of pure drug of fluconazole and dissolved with methanol in 10ml volumetric flask to prepare 1000µg/ml solution. Label it as stock A solution **Table 5**. From stock a solution pipette out 1ml and dilute with methanol up to 50ml in volumetric flask to form 20µg/ml solution. Label this as stock B solution **Figure 2**. Prepare the aliquotes by pipetting out 2ml, 3ml, 4ml, 5ml, 6ml, 7ml from stock B solution, dilute up to 10ml with methanol in 10ml volumetric flask to prepare 4µg/ml, 6µg/ml, 8µg/ml, 10µg/ml, 12µg/ml, 14µg/ml solution. Then analyzed the highest concentration solution in UV spectrophotometer to determine the λ max i.e. found to be 260nm. Set the wavelength at 261nm and note the absorbance of all the concentration.

Preparation standard calibration curve of Fluconazole in pH 6.8: Accurately weighed 10mg of pure drug of fluconazole and dissolved with pH 6.8 in 10ml volumetric flask to prepare 1000µg/ml solution. Label it as stock A solution. From stock a solution pipette out 1ml and dilute with methanol up to 50ml in volumetric flask to form 20µg/ml solution. Label this as stock B solution. Prepare the aliquoted by pipetting out 2ml, 3ml, 4ml, 5ml, 6ml, 7ml from stock B solution, dilute up to 10ml with methanol in 10ml volumetric flask to prepare 4µg/ml, 6µg/ml, 8µg/ml, 10µg/ml, 12µg/ml, 14µg/ml solution. Then analyzed the highest concentration solution in UV spectrophotometer to determine the λ max i.e. found to be 231 nm. Set the wavelength at 261nm and note the absorbance of all the concentration **Figure 3**.

a) Solubility of fluconazole in water

Dissolve 260 mg of pure drug fluconazole in 10 ml of water by continuous stirring in sonicate for 4 hours. Filter the solution through filter paper and dry it in room temperature until it become completely dry and weight the residue. By using amount of residue left in the filter paper determine the amount of drug dissolve in water and calculate solubility of fluconazole in water **Figure 4.**

b) Solubility in 0.1N HCl (pH1.2±0.2)

Dissolve 260 mg of pure drug fluconazole in 10 ml of 0.1N HCl (1.2±0.2pH) by continuous stirring in sonicate for 4 hours. Filter the solution through filter paper and dry it in room temperature until it become completely dry and weight the residue. By using amount of residue left in the filter paper determine the amount of drug dissolve in water and calculate solubility of fluconazole in 0.1N HCl **Figure 5**.

***In vitro* diffusion studies**: The diffusion studies were carried out using cellophane membrane using phosphate buffer (pH 6.8) as a dissolution medium for 10 h. The drug release was increased with decreased due to increase in polymer concentration **(Table 4)**. Compared all formulations FZG4 formulation shows best drug release at 10 h. For every hour, 5 ml was withdrawn with aliquots, and it is going to be filled with equal volume of receptor medium. The sample was diluted and measured using UV spectrophotometer at 260 nm.

Preparation of microsphere loaded gel: 2% w/v Carbopol was taken and water was added to it by continuous stirring

Table 5. Formulation of fluconazole microsphere loaded gel.

S.NO	FORMU-LATION CODE	VISCOSITY (CPS)	SPREAD-ABILITY (g.cm/s)	GEL STRENGTH (s)	HOMO-GENITY	pH	DRUG CONTENT(%)
1.	FZG1	134	2.16±0.3	20	Good	5.43±0.3	77±0.5
2.	FZG2	235	3.95±0.3	24	Good	6.24±0.3	82±0.5
3.	FZG3	387	4.77±0.3	35	Satisfactory	6.78±0.3	87±0.5
4.	FZG4	598	5.69±0.3	59	Excellent	6.89±0.3	90±0.5
5.	FZG5	437	4.99±0.3	49	Satisfactory	7.02±0.3	89±0.5
6.	FZG6	356	4.83±0.3	47	Good	7.5±03	85±0.5
7.	MKT GEL	298	5.80±0.3	52	Good	6.9±0.3	89±0.5

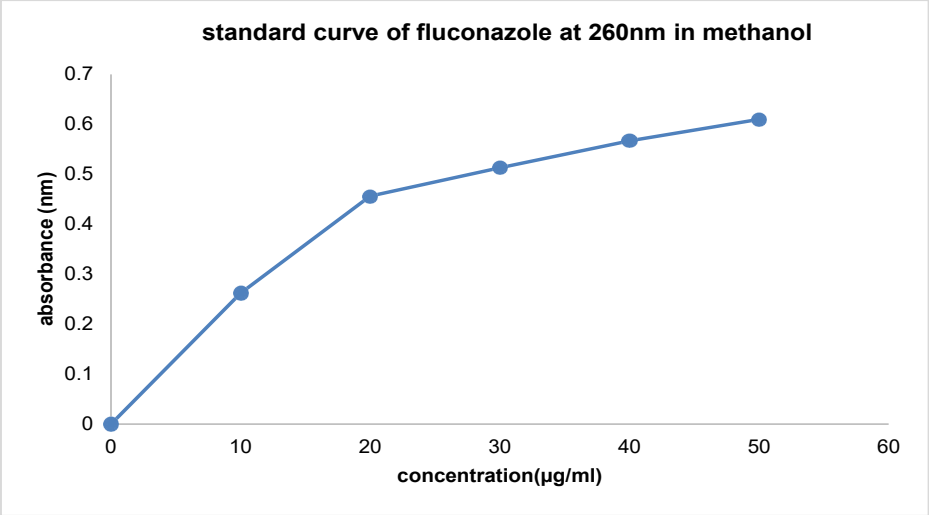

Figure 2. Standard curve of fluconazole at 260nm in methanol.

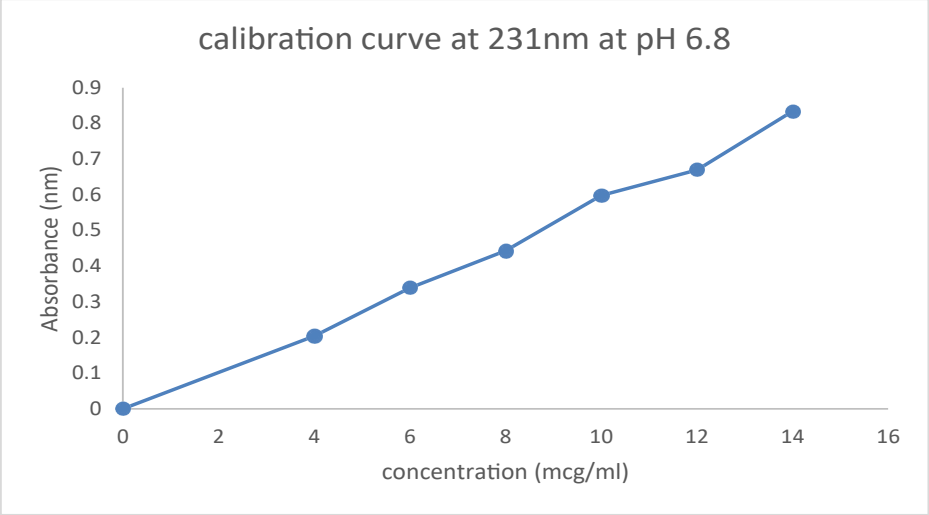

Figure 3. Calibration curve at 232nm at pH 6.8.

at 1000–1200 rpm. The resultant mixture was mixed thoroughly. In this carbopol gel prepared microspheres were added to get uniformly dispersion using magnetic stirring for 10 min to form gel loaded with microspheres **Figure 6**. The detailed composition of various formulations was prepared and mentioned in **Table 4&5.**

Stability studies: Stability testing of drug product being as a part of drug discovery and ends with the commercial product, to assess the drug and formulation stability, stability

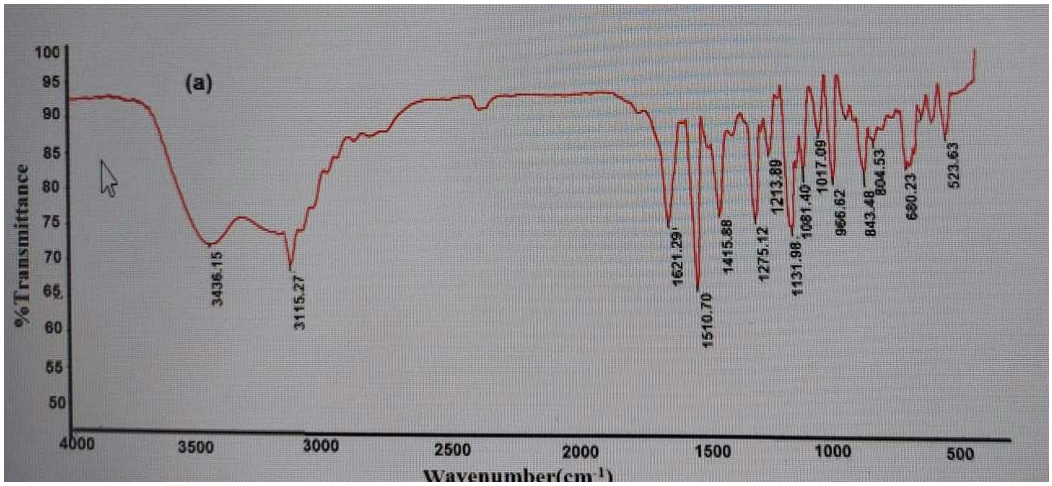

Figure 4. Ftir spectra of fluconazole.

Figure 5. Preparation of microspheres.

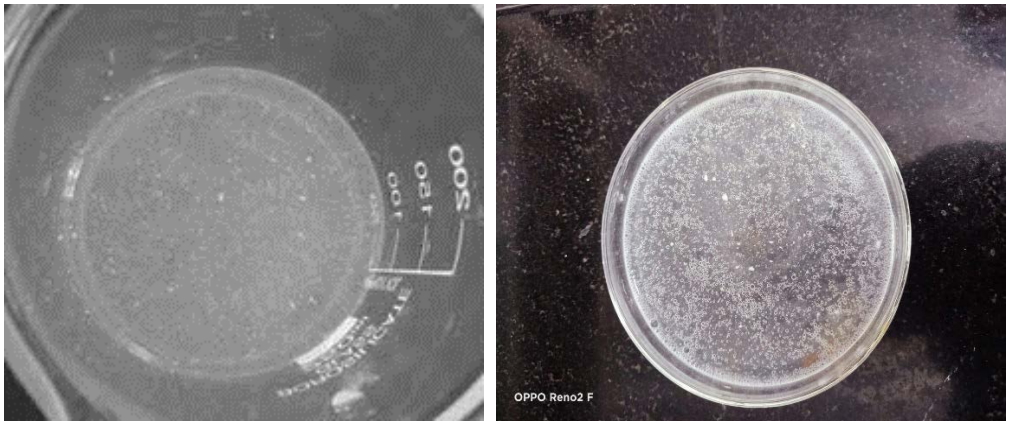

Figure 6. Prepared gel loaded with microspheres.

studies were done. The stability study will be carried out for the most satisfactory formulation. The most satisfactory formulation will be sealed in a glass vial and kept at 30 ± 2°C and 40 ± 2°C at RH 65 ± 5 and 75 ± 5 RH for 2 months. At the end of 1 and 2 months, the samples were analyzed for the drug content and in vitro diffusion study. The antimicrobial properties of volatile aromatic oils from plants have been recognized since antiquity **Table 6**.

Table 6. *In Vitro* diffusion study.

TIME (H)	FZG1	FZG2	FZG3	FZG4	FZG5	FZG6
0	9.8±0.5	16.1±0.5	23.3±0.5	32.7±0.5	22.04±0.5	13.1±0.5
1	11.5±0.5	20.34±0.5	34.7±0.5	44.6±0.5	23.4±0.5	15.5±0.5
2	14.2±0.5	27.3±0.5	46.6±0.5	50.7±0.5	35.8±0.5	16.9±0.5
3	15.9±0.5	39.7±0.5	58.7±0.5	62.3±0.5	42.5±0.5	29.8±0.5
4	16.3±0.5	43.6±0.5	60.3±0.5	70.2±0.5	52.7±0.5	39.4±0.5
5	27.8±0.5	56.7±0.5	74.2±0.5	78.3±0.5	58.3±0.5	43.3±0.5
6	34.4±0.5	62.3±0.5	77.3±0.5	81.3±0.5	61.2±0.5	52.3±0.5
7	45.3±0.5	70.2±0.5	67.3±0.5	84.2±0.5	63.3±0.5	58.3±0.5
8	56.3±0.5	72.3±0.5	63.2±0.5	89.1±0.5	58.2±0.5	61.5±0.5
10	67.6±0.5	63.2±0.5	60.1±0.5	90.2±0.5	56.3±0.5	64.8±0.5

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