

Formulation and Evaluation of Microsphere-Encapsulated Topical Gel

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ABSTRACT

A superficial fungal infection in immunocompromised persons can cause a variety of illnesses and problems. New topical therapeutic options are urgently needed to treat these fungal infections. The current study aimed to create a stable and effective topical formulation containing itraconazole. Itraconazole, abbreviated ITZ, is an antifungal drug used to treat various fungal infections. It is an FDA-approved new azole antifungal medication that combats fungal infections. Fluconazole should not be taken orally because it has various harmful effects. Fluconazole topical is commercially accessible; because there are no commercially available gel preparations, these formulations are designed to increase patient compliance, and medication dosage should be reduced to avoid undesirable effects such as renal and liver damage. It was a gel that was transformed by changing the polymer ratio. The FT-IR analysis revealed no interactions and confirmed the drug's purity. Between excipients and medication. Gel formulas were utilized to determine medication concentration, pH, antifungal activity, in vitro diffusion, and viscosity, as well as skin pain and activity levels. Some research suggested that oils from medicinal plants could be employed as anti-FLU-resistant *C. albicans* drugs.

I. Introduction

Fungal infections have become a major worry around the world, with an estimated 40 million individuals suffering from them in both industrialized and developing countries. The incidence of fungal infections is expanding at an alarming rate, posing a massive challenge to health care

professionals. Drug delivery through the most often used conventional preparations, such as creams, gels, lotions, emulsions, and so on, reduces the efficiency of actives due to barrier qualities, i.e., the skin's epidermis, which prevents drug deposition. As a result, selecting the

appropriate carrier is critical, with the goal of increasing drug deposition through topical formulations. Topical agents are widely used in cosmetics as well as for dermatological problems. Traditional dermatological products provide the active chemicals in relatively high concentrations, but only for a limited time. This may result in a cycle of short-term overmedication and long-term undermedication. Rashes or other potentially dangerous side effects may occur when a more active substance penetrates the skin. Various controlled drug-delivery systems, such as microcapsules, microspheres, emulsions, liposomes, and niosomes, have been investigated to maximize the duration of active ingredients being present either on the epidermis or within the skin layers while minimizing their transdermal penetration. Topical treatment of fungal infections has several advantages, including the ability to target the infection site, lower the danger of systemic side effects, improve treatment efficacy, and ensure high patient compliance. Several topical antifungal medications have been used to treat a variety of dermatological skin infections. This study focuses on the azole class of topical antifungals. When antifungals are given topically, the medication components must pass through the stratum corneum, the skin's outermost layer, to reach the lower layers, specifically the viable epidermis. New carrier systems for approved and investigational drugs are being developed as alternative strategies for topical treatment of skin fungal infections. The goal of this study is to develop and characterize an itraconazole-loaded microsphere gel as a viable topical delivery system. Microspheres are tiny spherical particles with diameters ranging from 1 to 1000 nm. A microsphere is also known as a microparticle. Microspheres can be made from a variety of natural and artificial materials. Glass, polymer, and ceramic microspheres are readily available commercially. Microspheres, both solid and hollow, have widely varied densities, making them useful for a variety of applications.

Superficial Infections and Antifungal Therapy

The delivery of drugs on the skin is recognized as an effective means of therapy for local dermatological diseases. But skin is widely recognized for its barrier properties compared with other biological membranes. The low permeability of skin for drug entry makes it a difficult port for absorption. Superficial fungal infections affect millions of people throughout the world. Dermatophytosis is a superficial fungal infection on the skin, hair, and nails. It is one of the most common diseases caused by dermatophyte fungal species of Epidermophyton, Trichophyton and Microsporum. It is estimated that about 10% to 20% of the world population is affected by mycological infections and sites and severity of infection vary according to geographical location, the organism involved, and environmental and cultural differences. There is a rampant increase in opportunistic fungal infections globally due to long term antimicrobial therapy, organ transplants, immunity compromised HIV cases and cancer chemotherapy. Fungi are eukaryotic and exhibit biochemical resemblance to human hosts. This similarity makes antifungal development process a cumbersome process, as drug should be effective against invading fungus and at the same time safe for the host

Topical delivery system

The term "topical delivery system" refers to a procedure in which the formulation is applied to the skin, eyes, nose, and vagina to treat local conditions. When a treatment is applied topically, it avoids hepatic first-pass metabolism, changes in stomach pH, and fluctuations in plasma levels that occur when a drug is administered orally. The local treatment of these illnesses requires continual study into topical drug distribution to the skin's surface. Most exogenous chemicals (drugs/active moieties) are permeability resistant, which presents a substantial design challenge for topical drug delivery systems. Furthermore, it is difficult to construct an effective topical administration system since disease conditions influence the skin's permeability and barrier properties.

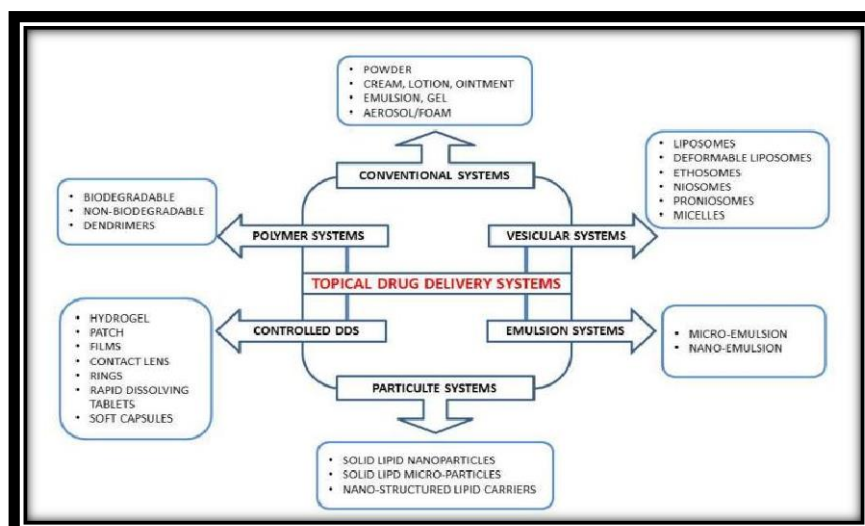


Figure 1: Branches of Topical Drug Delivery System

Microspheres

Sizes range from one meter to one thousand meters. They are spherical, freely moving particles composed of biodegradable synthetic or protein polymers. Micrometrics and microcapsules are two distinct types of microspheres. Microparticles are another term for microspheres. Microspheres can be made from a wide variety of organic and synthetic materials. Microspheres play a significant role in improving the absorption of standard drugs while lowering side effects. Microspheres serve a critical role in increasing the absorption of conventional medications while limiting negative effects. The primary benefit of using microspheres as a medication delivery system is the controlled release of the therapeutic ingredients. Microspheres can be created using a variety of methods, including the emulsification approach with a single or double solvent evaporation system, the spray-dry technique, or the phase separation technique. Microspheres can be formed by dissolving the beginning ingredients in volatile solvents and then dispersing them in another solvent that is not miscible with the first. Later, complete evaporation of the final solvent yields a fine powder known as microspheres, which is soluble in water.

Advantages of microspheres

1. Reduce toxicity and dosage.
2. They are excellent for drug distribution because they prevent enzymatic and photolytic cleavage of the medication.

3. Maintain a steady medication concentration in the blood, boosting the compliance of patients.
4. Offer a consistent and long-lasting therapeutic impact.
5. Reducing the size of the particles to improve a drug's low solubility.

Microspheres versus Microcapsules

Microspheres and microcapsules are two major forms of microparticulate drug delivery systems that differ primarily in terms of internal structure and drug release mechanism. Microspheres are solid, homogeneous matrix systems with the active component uniformly distributed throughout the polymeric material. They do not have a distinct core and shell, and the medication is delivered primarily by matrix diffusion or polymer erosion and degradation. Microspheres are widely employed for long-term or regulated medication delivery due to their simple structure and stability. Microcapsules, on the other hand, have a core-shell structure in which the active ingredient is encased in a distinct central core that is surrounding by a protective covering or wall. The medicine is released from microcapsules via diffusion over the shell, coating disintegration, or capsule rupture under certain conditions. Microcapsules offer superior protection for sensitive or volatile compounds, and they are frequently utilized for taste masking, environmental protection, and targeted or triggered release. To summarize, microspheres work as matrix systems for controlled release, whereas microcapsules act as reservoir systems, providing better protection and precise control over drug release.

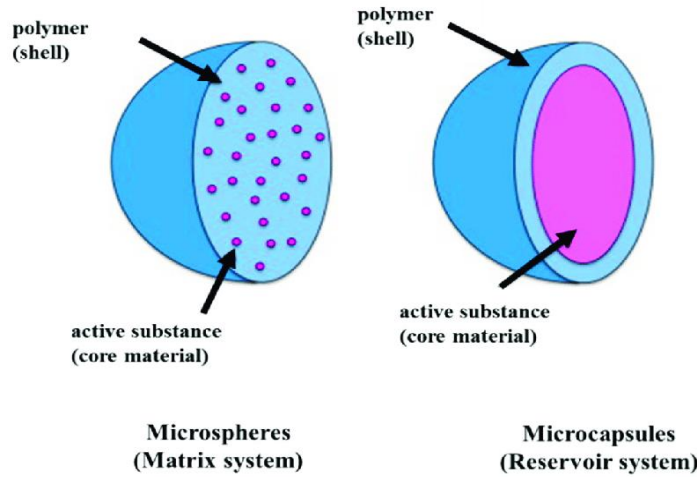


Figure 2: Structural Comparison Between Microspheres and Microcapsules

Future Perspectives of Microspheres in Topical Drug Delivery

The future of microspheres in topical medicine delivery appears bright because of major breakthroughs in polymer science, nanotechnology, dermatopharmacokinetics, and biomedical engineering. Ongoing studies seek to improve skin targeting, therapeutic efficacy, safety, and patient acceptability. The main prospects are presented:

Advanced Polymer Development: Future microspheres will utilize smart and functional polymers with improved biocompatibility and biodegradability, such as:

- Stimuli-responsive polymers (pH, temperature, enzymes, light)
- Natural and bio-inspired polymers

Stimuli-Responsive Microspheres: Microspheres that respond to external or internal stimuli will play a major role in topical therapy:

- pH-sensitive microspheres for infected or inflamed skin
- Temperature-sensitive systems for controlled release
- Enzyme-responsive microspheres for disease-specific targeting

Combination with Novel Delivery Technologies:

Microspheres are expected to be integrated with other advanced delivery systems, including:

- Microneedle
- Hydrogels
- Lipid-based carriers

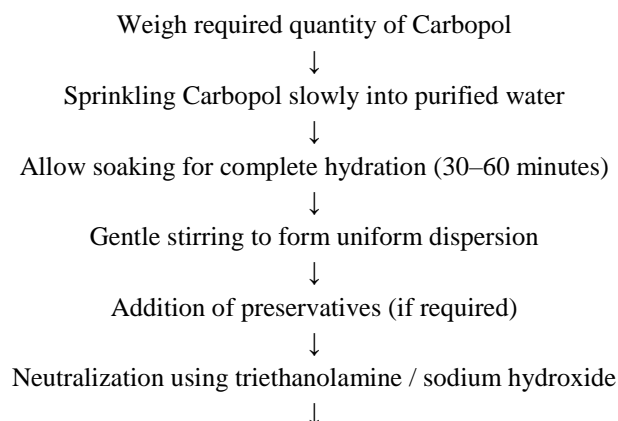
Methodology

Material

The itraconazole sample was obtained from Carbanio: B2B Chemical Marketplace, and other analytical-grade chemicals and reagents were used from the laboratories.

Method

Preparation of gel base: Carbopol 934 and filtered water were placed in a beaker and left to soak for 24 hours. The appropriate amount of medication was disseminated in water, and Carbopol 934p was neutralized with adequate triethanolamine. Glycerine was added slowly as a moistening agent, followed by methyl paraben and propyl paraben as preservatives, and gently stirred until a homogeneous gel formed.



Adjustment of pH (about 6.0–7.0)



Formation of clear, viscous gel

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-sized 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 3: Prepared Microspheres

Table 1: Composition of different formulation codes

Formulation Code	Carbopol W/V (10 ml) (%)	Sod. Benzoate (%)	Purified Water (Q.S.)
F1	2%	0.2	20 ml
F2	3%	0.2	20 ml
F3	2%	0.2	20 ml
F4	3%	0.2	20 ml
F5	2%	0.2	20 ml
F6	3%	0.2	20 ml



EVALUATION

Physical appearance

It is the initial evaluation during preformulation studies that assesses the colour, Odor, and taste of the substance.

pH

Weighed 50 gm of each gel formulation was placed into a 10 ml beaker and tested using a digital pH meter (Dubey et al., 2007). The pH of the topical gel formulation should be between 3 and 9 to treat skin infections.

Viscosity studies

The viscosity of formulations indicates that as the polymer concentration increases, so does the viscosity of the gel

formulation. However, larger polymer concentrations may compromise the gel formulation's spreadability. The results revealed that formulation FZG4 had the highest viscosity (560 cps), whereas formulation FZG1 had the lowest viscosity (100 cps).

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.

Spreadability

About 1 g of gel was placed at the center of the glass slide, and the weight of 1000 g was carefully applied on the upper side of the slide after 5 min. A weight of 150 g is gradually added to the pan on the upper slide by means of a 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 the formula:

$$S=ML/T$$

Homogeneity

All developed gels showed good homogeneity with the absence of lumps. The developed preparations were much clearer and more transparent.

Identification of drug and drug excipient interaction study

By UV Spectroscopy: The identification of pure drug The pre-formulation studies were carried out for the drug using the UV spectrophotometer. The calibration curve was plotted for different concentrations of the drug in 6.8 pH buffer solution using Shimadzu 1800 UV at 255 nm.

Standard Calibration Curve of Itraconazole

To create a 1000 µg/ml solution, accurately weigh 10 mg of pure itraconazole and dissolve it in methanol in a 10 ml volumetric flask. Label it as a stock solution. Table 5. To make a 20 µg/ml solution, pipette 1 ml of the stock solution and dilute it with 50 ml of methanol in a volumetric flask. Label this "stock B solution" (Figure 2). Prepare aliquots by pipetting out 2 ml, 3 ml, 4 ml, 5 ml, 6 ml, and 7 ml from stock B solution. Dilute up to 10 ml with methanol in a 10 ml volumetric flask to prepare 4 µg/ml, 6 µg/ml, 8 µg/ml, 10 µg/ml, 12 µg/ml, and 14 µg/ml solutions. The maximum concentration solution was tested with a UV spectrophotometer to measure the λ max, which was determined to be 255 nm. Set the wavelength to 255 nm and record the absorbance of all concentrations.

Preparation of a standard calibration curve of itraconazole in pH 6.8

To create a 1000 µg/ml solution, accurately weigh 10 mg of pure itraconazole and dissolve it in a 10 ml volumetric flask with pH 6.8. Label it "stock A solution." To make a 20 µg/ml solution, pipette 1 ml of the stock solution and dilute it with 50 ml of methanol in a volumetric flask. Label this as stock B solution. To create 4 4µg/ml, µg/ml, 8 µg/ml, 10 µg/ml, 12 µg/ml, and 14 14µg/ml solutions, pipette out 2 ml, 3 ml, 4 ml, 5 ml, 6 ml, and 7 ml of stock B solution and dilute with methanol in a 10 ml volumetric flask. The maximum concentration solution was examined with a UV spectrophotometer to determine the λ max, which was 231 nm. Set the wavelength to 255 nm and record the absorbance of all concentrations (Figure 3).

In vitro diffusion studies

Cellophane membrane was used in the diffusion investigations, using phosphate buffer (pH 6.8) as the dissolving media for 10 hours. The medication release rate increased as polymer concentration rose (Table 4). Every hour, 5 ml was withdrawn in aliquots and will be replaced with an equal volume of receptor medium. The sample was diluted and analyzed with a UV spectrophotometer at 255 nm.

Stability Studies

Stability testing of drug products begins with drug discovery and ends with commercialization. Stability studies were conducted to examine drug and formulation stability. A stability study will be conducted to determine the most suitable formulation. The optimal formulation will be stored in a glass vial at $30 \pm 2^\circ\text{C}$ and $40 \pm 2^\circ\text{C}$ at RH 65 ± 5 and 75 ± 5 RH for two months. The samples were tested for drug concentration and in vitro diffusion after one and two months. The antibacterial effects of volatile aromatic oils derived from plants have been recognized since antiquity.

RESULT & DISCUSSION

Organoleptic properties of the drug:

Physical Description – Solid

Colour—White crystalline powder

Table 2: Evaluation Parameters

Formulation Code	Viscosity (Cps)	Spreadability (G.Cm/S)	Gel Strength (S)	Homogeneity	pH	Drug Content (%)
F1	134	2.16±0.3	20	Good	5.43±0.3	77±0.5
F2	235	3.95±0.3	24	Good	6.24±0.3	82±0.5
F3	387	4.77±0.3	35	Satisfactory	6.78±0.3	87±0.5
F4	598	5.69±0.3	59	Excellent	6.89±0.3	90±0.5
F5	437	4.99±0.3	49	Satisfactory	7.02±0.3	89±0.5
F6	356	4.83±0.3	47	Good	7.5±0.3	85±0.5

MKT GEL	298	5.80±0.3	52	Good	6.9±0.3	89±0.5
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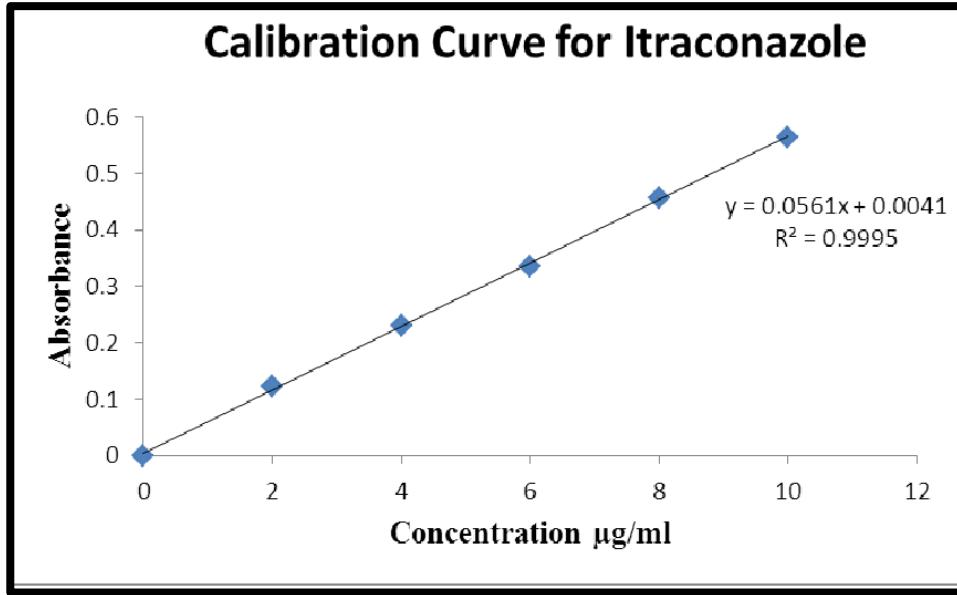


Figure 4: Standard calibration curve at 255 nm

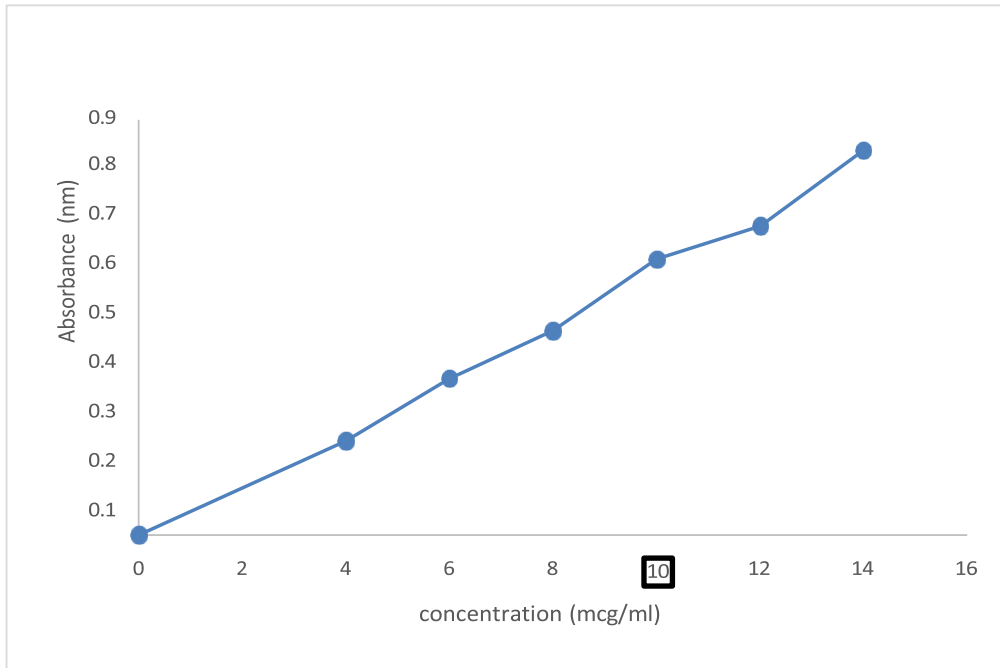


Figure 5: Calibration curve at pH 6.8.

Table 3: In vitro diffusion study

TIME (H)	F1	F2	F3	F4	F5	F6
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

Conclusion

A polymeric porous microparticle-based system was successfully developed for continuous topical delivery over an extended period to reduce application frequency. The implemented method was found to be simple, reproducible, and rapid, resulting in the formation of highly porous, spherical microparticles with good flow. The varied drug-

polymer ratio had a significant impact on drug content, encapsulation efficiency, particle size, and drug release. Gel-based itraconazole microspheres are excellent for topical medication administration. Thus, the microsphere-based delivery method created and evaluated in the current study strategy appears to be promising for the eradication of fungal diseases.

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