

# *In the Name of God*

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evaluation of fluconazole suspension**

***By:***

**Samaneh Aslannejad**

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***Supervisor:***

**Dr. Payam Khazaeli**

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خدایا همانطور که در تمام دوران زندگی فقط از تو کمک خواستم،  
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به پاس قدردانی از محبت‌ها و زحمات ایشان.

کلیه اساتیدم

در دانشکده داروسازی کرمان

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به ویژه سرکار خانم مهربابان

و جناب آقای دانش پژوه

## Abstract

Dr. Payam khazaeli<sup>1</sup>, Samaneh Aslannejad<sup>2</sup>

**Introduction:** Fluconazole is a triazole antifungal, used for superficial mucosal candidiasis and fungal skin infections. Because the required dosage in children is lower than the drug content of capsule dosage form. Therefore, in this study tried to prepare a fluconazole suspension as dosage form.

**Material & methods:** The first step in formulation of a suspension was to choose a suitable wetting agent. Therefore, different series of HLB between 5 and 9 were prepared with Tween 60 and Span 60. By using a cathetometer like apparatus, drop height of surfactant solutions on a disc of fluconazole powder was measured and then, contact angle was calculated by paddy equation. The best surfactant was selected.

Next step was the selection of a suitable flocculant. Several formulations were prepared three electrolyte ( $\text{AlCl}_3$ ,  $\text{KH}_2\text{PO}_4$ ,  $\text{K}_2\text{HPO}_4$ ), F value and degree of flocculation ( $\beta$ ) were also measured. The suitable electrolyte was selected. The sedimentation rate should be decreased. Two thickening agent (Na-CMC and Carbapol 934) were used with different concentrations. The F and  $\beta$  values were measured and suitable thickening agent was selected. Standard curve of

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1- Assistant Professor of Pharmaceutical, School of Pharmacy, Kerman University of Medical Science & Health Services. Email: [payam.khazaeli@gmail.com](mailto:payam.khazaeli@gmail.com)

2- Student of Pharmacy. Email: [samaneh\\_aslannejad@yahoo.com](mailto:samaneh_aslannejad@yahoo.com)

fluconazole was drawn and fluconazole in suspension was assayed. Chemical stability of the formulated suspension was studied and the expiration date was determined. Changes in shape and particle size were studied by using light microscopy. Rheological studies with Brookfield rheometer and the dissolution study with USP II dissolution apparatus were carried out.

**Results:** The suitable surfactant had a HLB value equal to 7 and the best flocculant was  $\text{KH}_2\text{PO}_4$  at concentration of 1.5%. The best rheological property was achieved with CMC at concentration of 0.5%. The fluconazole was assayed in the suspension with 98% accuracy. The expiration date of formulated suspension was 13.6 months with no changes in shape and particle size during three months. The formulated suspension shows a plastic flow with suitable thixotropy.

**Conclusion:** The results at this study show that fluconazole can be formulated in a suspension dosage form with suitable properties like as viscosity, particle size, stability and dissolution rate.

**Key words:** Suspension – Fluconazole - Formulation

## خلاصه

دکتر پیام خزانلی<sup>1</sup>، سمانه اصلان نژاد<sup>2</sup>

مقدمه: فلوکونازول یک ضدقارچ تری آزول است که برای عفونت‌های قارچی پوست و کاندیدیاز سطحی کاربرد دارد. از آنجا که دوزاژ مورد استفاده در کودکان کمتر از محتوای شکل دارویی کپسول فلوکونازول می‌باشد. هدف این تحقیق ارائه فرمولاسیون سوسپانسیون فلوکونازول قرار گرفت.

روش کار: اولین مرحله در فرمولاسیون سوسپانسیون، انتخاب یک سورفاکتانت مناسب است. لذا به این منظور درصدهای مختلف توپین ۶۰ و اسپان ۶۰ استفاده گردید و سری HLB بین ۵ تا ۹ تهیه، به کمک معادله Paddy زاویه تماس اندازه‌گیری گردید و بهترین سورفاکتانت با HLB=7 انتخاب شد. مرحله بعدی کار انتخاب یک عامل فلوکوله‌کننده مناسب بود. بنابراین از درصدهای مختلف دو الکترولیت معمولی یعنی  $AlCl_3$  و  $KH_2PO_4$  استفاده و با محاسبه پارامترهای  $F$  و  $\beta$ ،  $KH_2PO_4$  با غلظت مناسب به عنوان فلوکولانت انتخاب گردید.

برای کاهش سرعت ته‌نشینی از دو عامل قوام‌دهنده 'Na-CMC' و کاربویل ۹۳۴ استفاده شد و با محاسبه پارامترهای  $F$  و  $\beta$  برای غلظت‌های مختلف، 'Na-CMC' با غلظت مناسب به عنوان عامل قوام‌دهنده انتخاب گردید.

از روی منحنی استاندارد فلوکونازول نمونه سوسپانسیون تهیه شده آن مورد آنالیز قرار گرفت و صحت آن تعیین گردید.

پایداری شیمیایی سوسپانسیون تهیه شده بررسی و تاریخ انقضاء تعیین گردید.

1- استادیار گروه فارماسیوتیکس، دانشکده داروسازی، دانشگاه علوم پزشکی و خدمات بهداشتی - درمانی کرمان، آدرس پست

الکترونیک: [pavam.khazacli@gmail.com](mailto:pavam.khazacli@gmail.com)

2- دانشجوی داروسازی، آدرس پست الکترونیک: [samaneh\\_aslannajad@yahoo.com](mailto:samaneh_aslannajad@yahoo.com)



تعیین اندازه ذره‌ای، تغییرات شکل و اندازه ذره‌ای برای فرمولاسیون سوسپانسیون تهیه شده با نمونه خارجی به کمک میکروسکوپ نوری مقایسه گردید.

مطالعات رئولوژیک سوسپانسیون تهیه شده و نمونه خارجی توسط ویسکومتر بروکفیلد و روند انحلال سوسپانسیون تهیه شده و نمونه خارجی مورد بررسی قرار گرفت و نمودارهای مربوطه رسم گردید.

**نتایج:** در این مطالعه بهترین سورفاکتانت با HLB=7 و  $KH_2PO_4$  با غلظت ۱.۵٪ به عنوان فلوکولانت و CMC با غلظت ۰.۵٪ به عنوان عامل قوام‌دهنده مناسب انتخاب گردید. صحت آنالیز نمونه سوسپانسیون تهیه شده معادل ۹۸٪ بود و تاریخ انقضاء برابر ۱۳/۶ ماه تعیین گردید. تغییر شکل و اندازه ذره‌ای و رشد کریستالی بعد از سه ماه نگهداری مشاهده نشد. سوسپانسیون تهیه شده رفتاری پلاستیک با تیکسوتروپی مناسب داشت.

**نتیجه‌گیری:** نتایج این مطالعه نشان داد که فلوکونازول به شکل سوسپانسیون با خواص مناسبی از قبیل ویسکوزیتی، اندازه ذره‌ای، پایداری و سرعت انحلال قابل فرموله کردن می‌باشد.

**لغات کلیدی:** سوسپانسیون، فلوکونازول، فرمولاسیون

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# **Chapter 1**

***Introduction***

## **1-1- Aims and Introduction**

Fluconazole is a triazole antifungal drug which in sensitive fungi inhibits cytochrom P450-dependent enzyme, resulting in impairment of ergostrol synthesis in fungal cell membranes. Fluconazole is suitable for both oral and intravenous administration as the free base (1,2,3).

According to advantages of fluconazole in the treatment of fungal administration and because the required dosage in children is lower than the drug content of capsule dosage form presented in Iranian market and also because of the capsule dosage form is not suitable for children usage, then we tried to present a formulation of fluconazole in a suspension dosage form for better use in children and also old persons.

## **1-2- Principles**

### **1-2-1- Fluconazole**

#### **1-2-1-1- Dosage form (1,2,3)**

Capsule: 50, 100, 150mg

Suspension: 10mg/ml, 40mg/ml

Injection: 200 mg/100 ml, 400 mg/200 ml

#### **1-2-1-2- Antimicrobial action**

Fluconazole inhibits cytochrome P450 reductore enzyme in some kinds of fungus, resulting in impairment of ergostrol synthesis in fungal cell membranes (1,2,3).



### 1-2-1-3- Uses

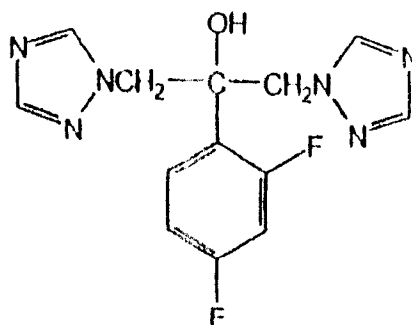
Fluconazole is a triazole antifungal used for superficial mucosal (oropharyngeal, esophageal, or vaginal) candidiasis and for fungal skin infections. It is also administered for treatment of systemic infections including systemic candidiasis, and cryptococcosis and has been tried in blastomycosis, chromoblastomycosis, histoplasmosis and sporotrichosis (1,2,3,4,5,6,7).

### 1-2-1-4- Brand Names

Diflucan, Biozolene, Elazor, Fungata, Lavisia, Solacap, Triflucan (1,2,3).

### 1-2-1-5- Chemical Name and Structure (3,8)

2-(2,4-Difluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-yl)propan-2-ol



Fluconazole

### 1-2-1-6- Pharmacology

Fluconazole, a synthetic broad-spectrum bis-triazole antifungal agent, is a highly selective inhibitor of fungal cytochrome P450 and sterol C-14 alpha-demethylation. Mammalian cell demethylation is much less sensitive to

fluconazole inhibition. The subsequent loss of normal sterols in fungi may be responsible for the fungistatic activity of fluconazole (1, 2, 3).

#### **1-2-1-7- Pharmacokinetic**

The pharmacokinetic properties of fluconazole are similar following administration by the IV or oral routes.

In healthy volunteers, the bioavailability of oral fluconazole is more than 90%. Compared with IV administration, bioequivalency was established between the 100mg tablet and both suspension strengths when administered as a single 200mg dose. Peak plasma concentration ( $C_{max}$ ) in fasting healthy volunteers occurs between 1 and 2 hours with a terminal plasma elimination half-life of 30 hours (range, 20 to 50 hours) after oral administration. Steady state concentration is reached within 5 to 10 days following oral doses of 50 to 400mg given once daily. The apparent volume of distribution approximates that of total body water. Plasma protein binding is low (11% to 12%).

In healthy volunteers fluconazole is cleared primarily by renal excretion. The pharmacokinetics of fluconazole are markedly affected by reduction in renal function. The dose may need to be reduced in patient with impaired renal function (1,2,3,9,10,11).

#### **1-2-1-8- Side effects**

The side effects reported with fluconazole were the following:

Gastrointestinal: nausea, abdominal pain, diarrhea, dyspepsia.

CNS: Dizziness, seizures, headache

Skin: Angioedema, exfoliative, skin disorder (including Stevens Johnson syndrome), alopecia, toxic epidermal necrolysis.

Blood: Leukopenia, thrombocytopenia

Others: Hypertriglyceridemia, hepatic reaction, hypercholesterolemia and anaphylactic reaction (rare) (1,2,3).

#### **1-2-1-9- Contraindication**

Any hypersensitivity to fluconazole or any excipients in the product (1,2,3).

#### **1-2-1-10- Precautions**

Fluconazole should be used with caution in patients with impaired renal or hepatic function. It is not recommended in pregnancy and breast-feeding because of distribution into breast milk and achieving concentrations similar to those found in plasma (1,2,3).

#### **1-2-1-11- Drug interactions**

- Cimetidine resulted in a reduction in fluconazole AUC and C<sub>max</sub>.
- Hydrochlorothiazide causes significant increase in fluconazole C<sub>max</sub> and AUC, which can be attributed to reduced renal clearance.
- Rifampin causes a decrease in AUC and increase clearance in the level of oral contraceptive component.

- Fluconazole resulted in significant increase in C<sub>max</sub> of cyclosporine, phenytoin, theophylline, sulfonylureas, warfarin and zidovudine with inhibition of the cytochrome P450 3A4 enzyme system (1,2,3,12).

#### **1-2-1-12- Physical description**

Fluconazole is a white crystalline solid that is slightly soluble in water and saline. Molecular weight is 306.27 and melting point is 137 to 140° C (2,8,13).

#### **1-2-1-13- Storage**

Fluconazole injection has been used safely for up to 14 days of intravenous therapy. The oral suspension should be shaken well before using and stored between 5 to 30°C (41°F to 86°F). Unused Portions should be discarded after 2 weeks (14,15,16).

#### **1-2-1-14- Solubility**

Fluconazole is slightly soluble in water (aqueous solubility of 8mg/ml at 37°C). Solubility in alcohol is 25mg/ml at room temperature (17).

#### **1-2-1-15- Assay**

Several assay methods are:

- Gas Chromatography. Column: 5% methyl phenyl, 95% dimethyl polysiloxan. Column temperature: 230°C. Carrier gas: hydrogen, 25ml/min flow rate. Retention time of fluconazol, 1.5min.