IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

Formulation, Development And Evaluation Of Immediate Release Fluconazole Capsules

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Abstract : Fluconazole capsule with rapid release, which are used to treat a variety of fungal infections, have been created in the current study. Due to the extended half-life of fluconazole, delivery systems are made to release the medication quickly, improving both bioavailability and dissolution. formulations have been created with varying concentrations of different disintegrants. When the powder blend's micromeritic characteristics were first assessed, it was discovered to have good flow characteristics. The formulation containing optimum since it performed better than other formulations in terms of Flow property, Blend uniformity, Assay,disintegration time, and dissolving time.

keywords **-** Immediate Release capsule, Antifungal ,In-vitro drug release , Hard gelatin capsule

I. INTRODUCTION

Capsules are defined as unit solid dosage form of medicaments available as small containers (shells) made up of gelatin enclosing accurately measured drug substances. The term capsule is derived from the Latin word capsula, meaning a small container. Capsule occupy a significant position in the drug development. They are often believed as the primary oral dosage form because of their manufacturing process compared to other dosage forms. Gelatin has the property of disintegrating when it comes in contact with water, thereby releasing the medicament completely. Instead, of gelatin, denatured gelatin, methyl cellulose and polyvinyl alcohol can also be used to make the capsule shells.[7Hard-shelled capsules containing dry, powdered contents or tiny pellets formed utilizing spheronization or extrusion methods, for example. These are constructed from two parts: a larger-diameter "cap" that is sealed after being filled with a smaller-diameter "body." Aqueous solutions of gelling agents, such as plant polysaccharides or their derivatives (such as carrageenans and modified forms of starch and cellulose) or animal protein (mostly gelatin) are used to make both of these groups of capsules. To lessen the hardness of the capsule, additional components can be added to the gelling agent solution, such as plasticizers like sorbitol or glycerin.

Types of capsules

1. Soft gelatin capsule
2. Hard gelatin capsule

1.Soft gelatin capsule

Soft gelatin capsules (sometimes called soft gel or soft elastic) are made up of softer shells that are hermetically sealed in a single piece. To make soft gelatin capsules, plasticizers such glycerine or polyhydric alcohol (like sorbitol) can be added to the gelatin.

2. Hard gelatin capsule

The main ingredient in the capsule goods is hard gelatin capsules. A hard gelatin capsule consists of the capsule body and a shorter cap. The cap fits snugly over the open end of the capsule body. The basic hard gelatin capsule shell is made from mixtures of gelatin, sugar, and water. In essence, they are translucent, colorless, and tasteless. To make gelatin, collagen from bones, white connective tissue, and animal skin is partially hydrolyzed.

FLUCONAZOLE

An antifungal drug called fluconazole is used to treat a variety of fungal infections. Both intravenously and orally are utilized with the medication. Fluconazole is extensively absorbed by the body and can be found in tissues, nails, saliva, sputum, vaginal secretions, and other bodily organs such as the heart, brain, or lungs.

Fluconazole capsules with improved release

The goal of the development is to create capsules containing fluconazole that release the active ingredient more successfully. According to the invention, the fluconazole capsules dissolve and absorb in vivo more rapidly and reliably than fluconazole-containing compositions that are currently on the market. It is predicated on the finding that when lactose or another material capable of giving fluconazole particles a hydrophilic surface is added to the particles during granulation, the active ingredient releases steadily and rapidly. This, according to the idea, makes capsules suitable for enhancing the active component's absorption.

Fungal Infection

Histoplasmosis. Your brain, lungs, or other regions of your body may become infected with the fungus Histoplasma, which is the cause of histoplasmosis. The valleys of the Mississippi and Mississippi rivers are typical locations for it.
Coccidiomycosis is often known as valley fever. Coccidioidomycosis, which is brought about by a mold called Coccidioides, is a lung infection that sometimes spreads to other areas of the body. Arizona and California are where it's most prevalent. The disease is blastomycosis. The fungus Blastomyces, which causes blastomycosis, frequently infects your skin, lungs, and bones. It can very rarely infect your spinal cord and brain as well.
Aspergillosis. Several lung illnesses, notably acute bronchopulmonary a condition called (ABPA) and persistent pulmonary aspergillosis, can be brought on by the mold Aspergillus, which is the source of aspergillosis. It may also develop into a mold-like ball (aspergilloma) or spread to other areas of your body.
Urinary tract infection in a candidate. Infections of the urinary tract (UTIs) are caused by bacteria, but some are also brought on by yeasts like Candida.
Deep-seated candidiasis. Invasive candidiasis is caused by several species of Candida. It can infect your brain, eyes (endophthalmitis), bones, heart, blood (candidemia), or other parts of your body. PJP, or pneumocystis pneumonia. pneumonia jirovecii pneumonia (PJP) is a fungal infection that can affect your lungs.

MATERIALS AND METHOD:

Materials

The material used in the present research was obtained from a range in sources. The Antiarrhythmic drug and all other reagent obtained from investigational laboratory. Ingredients were all of analytical quality, and all chemical reagents were of conventional pharmaceutical standard.

Formulation and Development:

1. **Procedure of Drug and Excipient compatibility study:**

the IR spectra of Fluconazole the IR spectra of a physical combination of a medicine and an excipient. For the formulation's excipients and fluconazole interactions between them, FT-IR investigations were carried out. Indicating the drug's stability, the same peaks were seen in the formulation as well. Insignificant alterations in real peaks can be seen in all physical combinations of the drug and various excipients. The formulation showed the same maxima with little variation, demonstrating the drug's stability. The fact that the medicine's peak did not alter suggests that the excipients utilized to formulate the immediate-release capsules did not interact with the drug in any way.

2.Procedure of Geometric mixing:

1. Geometric shifting

Step I - API+ Lactose monohydrate was shifted through a 40# ASTM sieve using a spatula.

2.Step II- Mixing - Maize starch 'colloidal anhydrous silica 'was shifted through a 40#ASTM Sieve using a spatula.

This blender was transferred into a suitable DCB and mixed for 5 Min.

3.Step III - Prelubrication - sodium lauryl sulphate was shifted through 40# ASTM using a spatula and added in the above step- II blend.

This blend was added into the blender and mixed for 15 Min.

4.Step IV- Lubrication - Magnesium stearate was shifted through a 40# ASTM sieve from transfer into step - III and mixed for 5 Min.

5. Mixing blend powder

Product Name: Fluconazole Capsule 200 mg IP Assay

Stage: Process Validation 25 Min Mixing T1, T2, M1, M2, B1, B2, C1

Table 1. Mixing blend powder

Stage	**T-1**	**T-2**	**M-1**	**M-2**	**B-1**	**B-2**	**C-1**
Assay	**98.87**	**98.30**	**98.31**	**98.61**	**99.06**	**99.40**	**100.87**
Average	**NA**						**9.06**
SD							**0.89**
RSD							**0.90**

6.Capsules filling

The powder blend was manually put into size "2"capsules.

COMPLETED QUALITY CONTROL TEST OF THE PRODUCT FOR CAPSULE:

1. **Appearance:** Regardless of their production size, capsules must to have a consistent appearance.
2. **Size and Shape:** There is a range of sizes available for hard capsules; the most common industrial sizes used for human medications are 000, which is the largest, and 5, which is the smallest. These capsules are sold commercially. Size and form inspections are required.

Table 2 Identification test of Fluconazole

Parameter	**Reported value**	**Observed value**
Appearance	crystalline	crystalline
Colour	White	White
Odour	odourless	odourless

3.Uniformity of content: Supplements with less than 10 mg or less than 10% w/w of active ingredient are suitable for this test. Analyse the active component content of ten randomly selected capsules using the monograph's method or any other appropriate analytical technique with comparable precision and accuracy.

4.Content uniformity of drug: Thirty capsules are taken as a sample, and ten are tested separately. A capsule's drug content shall not exceed the average drug content of ±15%, and none of the capsules' drug contents should be higher than ±25%.

5. Disintegration test

Fill the water and maintaining the temperature 37°C ± 2 °C introduce one capsule into each tube and if directed in the appropriate general monograph, add a tube suspend the assembly in the beaker containing the specified liquid and operate the apparatus for the specified time. Remove the assembly from the liquid. the capsule passes the test if all of them have disintegrated. note down the time of disintegration.

6. **Dissolution test**

Preparation of media :01N HCL Take a 500 ml water in a beaker add 0.82ml of 37% hydrochloric acid and add water to make up the volume 1Litre.

Solvent: A mixture of 60 volumes of buffer solution prepared by dissolving 1.36g potassium dihydrogen orthophosphate in 1000 ml water and 40 volumes of methanol adjusted PH 3.6 orthophosphoric acid.

Table No : 3 In vitro dissolution studies

Drug name	**Dosage form**	**USP Apparatus**	**Speed (RPM)**	**Medium**	**Volume (ml)**	**Recommended sampling times (hrs)**	**Remark**
Model API	**Capsule**	**II Paddle**	**50**	**0.1N HCL**	**900**	**45 minutes**	**As per USP**

RESULT:

1. **Characterization of the API**

According to the procedure outlined in the preceding section, quantitative API characteristics including bulk density and tapped density were calculated contains the information for these variables.

Table No.4: Physical Evaluation of API

Sr.no	**Physical property**	**Result**
1	Angle of repose	26.56 °
2	Bulk density (g/ml)	0.41 gm/ml
3	Tapped density(g/ml)	0.50 gm/ml
4	Compressibility index (%)	18 (%)
5	Hausner ratio	1.21
6	LOD	0.34%

2.Capsule (Blend) in process results:

Table 5: Capsule (Blend) in process results of all trials

Batches Code	**Bulk density (gm/ml)**	**Tapped density (gm/ml)**	**%Compressibility Index**	**Hausner's ratio**	**Angle of Repose (^{0})**
F1	0.413	0.501	18.4	1.21	26.56
F2	0.416	0.512	17.3	1.22	26.21
F3	0.421	0.503	17.4	1.21	28.45
F4	0.412	0.505	18.5	1.20	25.12
F5	0.416	0.501	18.6	1.22	28.14
F6	0.411	0.504	17.4	1.21	28.26

F7	0.412	0.491	17.5	1.22	24.68
F8	0.416	0.501	18.6	1.21	26.56

Observation: As per USP Criteria for Bulk Density, Tapped Density, Compressibility Index, Hausner's ratio above trail formulation show theacceptable results.

3.Disintegration test-

For the fluconazole capsule, the disintegration period for all batches F1–F8 was determined to be between 7.35-5.31min. Less than 10 minutes is the usual immediate-release limit.

Table No. 6: Disintegration test

Trial batch	F1	F2	F3	F4	F5	F6	F7	F8
DT	7.35	7.42	6.40	6.38	5.46	6.12	5.31	5.31

4.Dissolution test-

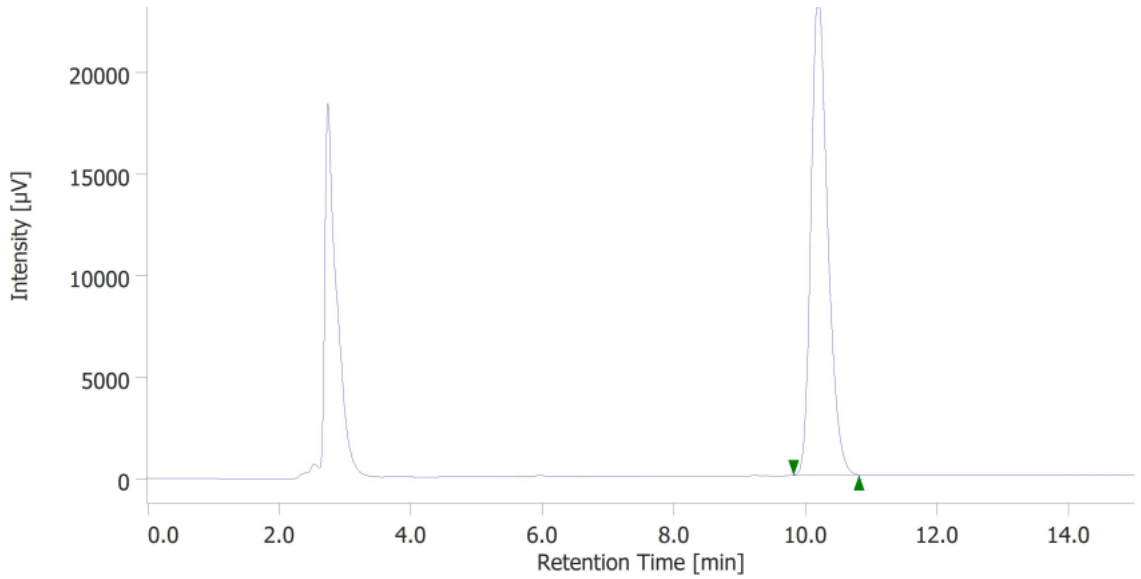
Table No. 7: Dissolution Test

Stage	**F 1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
Assay	**95.32**	**97.34**	**96.21**	**91.02**	**96.95**	**98.04**	**100.3**	**100.3**
Average	**NA**							**96.14**
Minimum								**91.02**
Maximum								**100.3**

F8 Batch (Optimized batch)

Figure 1. Dissolution of RLD & Trial 8 batch graphical representation

chromatogram



Peak information

Peak Name	**CH**	**tR (min)**	**Area Uv.sec**	**Height(%)**	**Area**	**Height (%)**	**Quantity**	**NTP**	**Resolution**	**Symmetry factor**	**warning**
Fluconazole	**1**	**10.192**	**431500**	**22725**	**100.000**	**100.000**	**NA**	**8142**	**NA**	**1.279**	

Observation: Drug release profile of Trail 8 was comparable with reference product.

5. Evaluation of powder blend

Evaluation of powder blends such as Bulk density and Drug content of all formulations from (F1-F8) Batch.

Table No. 8: Evaluation of powder blend

Batches	Drug Content (%)
F1	100.3±0.055
F2	99.1±0.004
F3	99.8±0.006
F4	99.1±0.007
F5	100.1 ±0.004
F6	99.0±0.002
F7	101.2±0.004
F8	100±0.006

Each formulation the amount of drug was found to be in the range of 99.0 to 101.2 for all formulations.

6.Stability studies

In stability study the optimize formulation has to be kept at temperature condition 40^{o}C and 75% relative humidity for a minimum 3-month period as per the standard ICH guideline.In stability study after 1 month the final formulation visual appearance is White and Colour blend powder. Disintegration of Immediate release part-time is 30min and Immediate release % Drug release is 100.2% In terms of appearance, disintegration time, drug content, Assay, Dissolution rate nothing significantly changed.

Table No.9: Stability study of optimized formulation

Time	**Evaluation parameters**			
	Colour	**Disintegration time**	**Dissolution time**	**Drug content uniformity**
0 Month	White colour	6.12	98.04	100±0.006
1 Month	White Colour	5.46	100.3	101.2±0.004

Summary & Conclusion

Over the recent past, fluconazole capsule is becoming increasingly popular. substitute for the traditional oral dose form because of numerous advantages like administration with the becoming immediate preparation accuracy of dosage, easy portability, with a prolonged release action and a quick beginning of effect, it is appropriate for paediatric and geriatric patients. The goal of the study was to formulate and evaluate a Capsule containing Fluconazole as the active ingredient for immediate release. The active pharmaceutical ingredient, Fluconazole was selected and formulate as immediate release offers many advantages including reduced side effects, improved patient compliance.

The present investigation deals with the formulation, optimization and evaluation of immediate release capsule for the fungal infection difference excipient like Maize starch, lactose monohydrate, colloidal silicon dioxide, sodium lauryl sulphate, magnesium stearate. The result of different optimized batches shows the desire result. The method used here sample are collect to proper sieving the powder. powder proper mixed to use in equipment V cone blender drug is uniformly distributed in excipients. Blend powder collect to polythene bags, then capsule filling result was compared with the innovator. Evaluated Bulk density, tapped density, Drug content, loss on drying. bulk density obtained for all formulation in the range of 99.0 to 101.2

% and loss on drying 0.34%w/w. Blend powder F7 & F8 Assay of batch 99.18 to 101%. Disintegration time of fluconazole capsule 6 to 8min. In vitro – dissolution studies of formulation F7 & F8 shows 99.10 to 103% in vitro drug release of formulated product shows as similar as that of the innovator product. Assay of fluconazole capsule F7 & F8 100.87% stability of fluconazole capsule 100.60%

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