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Formulation and Evaluation of Immediate Release Fluconazole Tablets for the Treatment of Fungal Infections

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A B S T R A C T

In the present study immediate release tablets of fluconazole have been developed which is used for the treatment of various fungal infections. Fluconazole is having longer half life thus a delivery system is designed to release the drug in short period of time, thereby enhancing the dissolution and bioavailability. Formulations have been developed using different concentration of various disintegrants by direct compression method. Initially the powder blend was evaluated for micromeritic properties and found to have good flow properties. The results of post compression studies were satisfactory. Formulation containing Ac-di-sol was found to be better in terms of wetting time, disintegration time and dissolution time when compared to other formulations and is thus optimized.

Keywords: Immediate release tablets, Fluconazole, Disintegrants, Ac-di-sol.

A R T I C L E I N F O

CONTENTS

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1. Introduction

Over the last hundred years tablet manufacturers have developed materials and processes that can produce compressed tablet containing precise amount of an active pharmaceutical ingredient (API) at high speed and at relatively low cost. The development in the field of API, excipients, and tableting machinery during the past decade has made tablet manufacturing a science and tablets the most commonly used dosage form [1].

The development of enhanced oral protein delivery technology by immediate release tablets which may release the drugs at an enhanced rate are very promising for the delivery of poorly soluble drugs high molecular weight protein and peptide. The oral route remains the perfect route for the administration of therapeutic agents because the low cost of therapy, manufacturing and ease of administration lead to high levels of patient compliance [2].

Many patients require quick onset of action in particular therapeutic condition and consequently immediate release of medicament is required. It is estimated that 50% of the population is affected by this problem, which results in a high incidence of ineffective therapy. However, in many cases immediate onset of action is required than conventional therapy such as analgesia, cardio-vascular disorders, sedation/hypnosis and many other conditions. To overcome these drawbacks, immediate release pharmaceutical dosage form has emerged as alternative oral dosage forms [3].

The term "immediate release" pharmaceutical formulation includes any formulation in which the rate of release of drug from the formulation and/or the absorption of drug, is neither appreciably, nor intentionally, retarded by galenic manipulations. In the present case, immediate release may be provided for by way of an appropriate pharmaceutically acceptable diluent or carrier, which diluent or carrier does not prolong, to an appreciable extent, the rate of drug release and/or absorption. Immediate release drug delivery system is a conventional type of drug delivery. It is designed to disintegrate and release their medicaments with no special rate controlling features. These are the dosage forms in which ≥ 85% of labeled amount dissolves with in 30 min [4, 5].

Fluconazole is a non- Pharmacopoeial bis-triazole antifungal drug, and highly effective against a variety of fungal pathogens that led to systemic mycoses. It has the bioavailability greater than 90% when given orally and half life is 30 hours [6], so the present work is aimed to prepare immediate release tablets.

2. Materials and Methods

Materials:

Fluconazole is obtained from Arene Life Sciences Limited, Hyderabad. Crospovidone, Sodium starch glycolate, crosscarmellose sodium were purchased from FMC Biopolymer Mumbai. Mannitol and MCC were purchased from Merk Specialities Pvt Ltd, Mumbai, India. Magnesium stearate was purchased from S D Fine chemicals limited, Mumbai.

Methods:

Preparation of tablets:

All ingredients were weighed accurately as given in the table-1. Drug and diluent are passed through mesh #20**.** Remaining lubricants were passed through the mesh #60. After passing through the mesh, the ingredients are mixed thoroughly and blended for 20 mins and finally compressed to obtain tablets.

Evaluation:

Precompression evaluation:

The powder blend of the formulations prepared are subjected to evaluation for bulk density, tapped density, compressibility index (carr's index), Hausner's ratio and angle of repose to determine their flow and compressibility nature.

Post compression evaluation:

Hardness test:

This is the force required to break a tablet in a diametric compression. Hardness of the tablet is determined by Monsanto hardness tester. It is expressed in kg/cm^2.

Tablet Thickness:

The thickness of tablet is measured by Vernier Callipers scale. Tablet thickness should be controlled within a ±5%. In addition thickness must be controlled to facilitate packaging.

Friability:

This test is performed to evaluate the ability of tablets to withstand abrasion in packing, handling and transporting. Initial weight of 20 tablets is taken and these are placed in the friabilator, rotating at 25rpm for 4min. The difference in the weight is noted and expressed as percentage. It should be preferably between 0.5 to 1.0%.

% Friability = $(W_1-W_2)/W_1$ X 100

Where,

W_1= weight o f tablets before test, W_2 = weight of tablets after test

Weight variation of Tablets:

It is desirable that all the tablets of a particular batch should be uniform in weight. Twenty tablets were taken randomly and weighed accurately. The average weight was calculated. If any weight variation is there, that should fall within the prescribed limits as given in the table-2. Ten tablets were weighed and average weight is calculated. All the ten tablets were crushed in mortar. Powder equivalent to 10mg of fluconazole was dissolved in 50ml of pH 6.8 phosphate buffer solution and shaken for 20 mins. Volume was made upto the mark with pH 6.8 phosphate buffer solution and filtered and 1 ml filtrate was diluted to the 100ml using pH 6.8 phosphate buffer solution. Absorbance of resultant solution was measured at 261 nm [7].

Wetting Time:

A piece of tissue paper folded double was placed in clean and dry petri plates containing 6 ml of water. The tablet was placed on the paper and the time for complete wetting of the tablet was measured in seconds [8].

Disintegration Time:

The disintegration test is carried out in an apparatus containing a basket rack assembly with six glass tubes of 7.75 cm in length and 2.15 mm in diameter, the bottom of which consists of a #10 mesh sieve. The basket is raised and lowered 28-32 times per minute in a medium of 900 ml which is maintained at 37±2^{0}C. Six tablets were placed in each of the tubes and the time required for complete passage of tablet fragments through the mesh (#10) was considered as the disintegration time of the tablet [9].

***In-vitro* Dissolution study:**

The in vitro dissolution study was carried out using USP Type II dissolution apparatus. The study was carried out in 900 ml of pH6.8 phosphate buffer solution for 1 hour. The medium was allowed to equilibrate to a temperature of 37±0.5°C. Tablet were placed in the vessel and operated at 50 rpm. At definite time intervals, 5 ml of the fluid was withdrawn, filtered and again 5ml of the fluid was replaced. Suitable dilutions were done with the dissolution fluid and the samples were analyzed using UV spectrophotometer at 261nm [10].

Table 1: Composition for immediate release tablets of fluconazole

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Fluconazole	150	150	150	150	150	150	150	150	150
Crospovidone	3.9	5.2	6.5	-	-	-	-	-	-
Crosscarmellose sodium(Ac-di-sol)	-	-	-	3.9	5.2	6.5	-	-	-
Sodium starch glycolate	-	-	-	-	-	-	3.9	5.2	6.5
Mannitol	10	10	10	10	10	10	10	10	10
Magnesium stearate	9	9	9	9	9	9	9	9	9
MCC	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s
Total weight (mg)	250	250	250	250	250	250	250	250	250

Table 2: Acceptance criteria for tablet weight variation

Average weight of tablet (mg)	Maximum % difference allowed
130 or Less than	± 10
130-324	± 7.5
More than 324	± 5

3. Results and Discussion

Precompression evaluation of powder blend:

The results of the evaluation tests are represented in the table-3. Angle of repose values were in the range of 22.96 ± 1.49 to 24.78±0.742. Bulk density was in the range of 0.626±0.01 to 0.637±0.003. Tapped density was in the range of 0.721±0.009 to 0.733±0.005. Percentage compressibility (Carr's index) was in the range of 12.23±1.633 to 14.44±1.031. Hausner's ratio was in the range of 1.136±0.021 to 1.30±0.014. From the above results it was observed that powder has good flow properties.

Table 3: Precompression results for the formulations

Formulation	Bulk density (gm /ml)	Tapped density (gm/ml)	Hausner's ratio	Carr's index	Angle of repose (θ)
F1	0.633±0.007	0.721±0.009	1.136±0.22	12.23±1.033	24.55±1.052
F2	0.626±0.010	0.731±0.006	1.30±0.014	14.44±1.031	24.58±0.921
F3	0.635±0.007	0.727±0.011	1.14±0.021	14.29±1.123	23.92±1.435
F4	0.633±0.002	0.733±0.005	1.15±0.021	13.58±1.632	24.38±0.722
F5	0.633±0.006	0.728±0.012	1.14±0.014	12.98±1.102	22.96±1.495
F6	0.629±0.002	0.724±0.008	1.14±0.025	13.18±1.851	24.55±0.868
F7	0.637±0.003	0.728±0.013	1.15±0.020	14.38±1.125	23.82±0.769
F8	0.635±0.004	0.733±0.004	1.14±0.019	13.58±1.623	24.78±0.742
F9	0.637±0.005	0.729±0.014	1.14±0.015	12.98±1.105	23.96±1.495

Post compression evaluation:

The results of post compression studies are given in the table-4. Weight variation was in range of 246.3 to 254.3mg, Hardness was in range of 4.0±0.05 to 5.1±0.05 kg/cm^2. Weight variation and hardness of fluconazole tablets were within range. Percentage friability of tablet was evaluated in 100rpm and tablet passed the friability test. Content uniformity was done as per IP and the values were satisfactory. Wetting time was in the range of 26 to 37sec as wetting time increases disintegration time of tablet also increases. Formulations containing of Ac-di-sol (crosscarmellose sodium) showed somewhat lower wetting time than other batches hence showed satisfactory disintegration time. Formulations containing of crospovidone showed very low wetting time compared to other formulations hence showed more disintegration time than other formulations. Disintegration Time of tablets was evaluated and was found to be in the range of 27 to 39 sec. Formulations containing of Ac-di-sol (crosscarmellose

sodium) in higher quantity showed good disintegration time.

Table 4: Post compression evaluation results of the prepared tablets

Formulation	Weight Variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Wetting Time(sec)	Disintegration Time(sec)	Content uniformity (%)
F1	248.3±0.15	4.0±0.05	3.1± 0.85	0.25±0.21	37±0.4	39±0.4	100.08±0.01
F2	246.3±0.15	4.9±0.10	3.3±1.04	0.30±0.25	31±0.5	32±0.5	99.38±0.23
F3	252±0.2	4.1±0.10	3.1±0.86	0.27±0.02	30±0.5	31±0.3	99.32±0.15
F4	250±0.3	5.1±0.10	3±0.85	0.28±0.01	32±0.3	34±0.2	100.82±0.4
F5	248.3±0.5	4.2±0.05	3.2±0.74	0.29±0.16	30±0.6	30±0.4	99.48±0.2
F6	249.3±0.2	4.1±0.05	3.4±0.90	0.5 ± 0.11	26±0.5	27±0.4	99.58±0.6
F7	254.3±0.3	4.9±0.33	3.5 ±0.33	0.5 ± 0.10	30±0.4	32±0.3	98.58±0.5
F8	253.3±0.10	5.0±0.31	3.1 ±0.30	0.5 ± 0.21	29.1±0.3	30±0.2	99.58±0.3
F9	246.0±0.3	4.9±0.35	3.2 ±0.33	0.29 ± 0.23	28±0.3	29±0.2	99.85±0.6

***In-vitro* dissolution studies:**

Super disintegrants has a dominant role in disintegration as well as drug release form IR tablets. Super disintegrants chosen in the present work have showed better and satisfactory drug release profile. Due to the swelling and wicking action of the superdisintegrants the tablets showed better disintegration time which in turn showed good drug release from tablet formulations. The results are represented in table-5. The Dissolution study of various batches from F1- F9 shows that fluconazole release from tablets containing Ac–di-sol at higher concentrations showed higher drug release. As concentration of Ac- di-sol decreased it showed lower drug release. Further we can say that as concentration of superdisintegrants increases it causes higher % of drug release. The dissolution results show that there was an increase in the dissolution velocity of the tablets. The maximum drug release of 100.4% was observed at 20 min in formulation F6 having higher concentration of Ac-di-sol and is thus optimized.

Table 5: *In-vitro* dissolution studies for formulation F1-F9

Time (mins)	Cumulative percentage drug release								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
5	49±0.4	44±0.1	44±0.2	50±0.3	56±0.6	62±0.1	51±0.3	54±0.4	61±0.2
10	68±0.3	58±0.1	69±0.4	69±0.4	74±0.5	80±0.2	58±0.5	74±0.3	64±0.4
15	79±0.3	71±0.2	79±0.3	76±0.5	89±0.2	89±0.2	71±0.5	78±0.3	76±0.2
20	85±0.2	86±0.4	88±0.4	89±0.2	95±0.2	100.6±0.2	83±0.4	86±0.4	89±0.2
25	94±0.5	96±0.6	97±0.2	98±0.2	100.4±0.3	100.6±0.4	92±0.5	97±0.2	99±0.4
30	96±0.4	97±0.2	100.1±0.2	101.2±0.4	101.3±0.2	100.8±0.2	99±0.1	100.1±0.2	100±0.5

4. Conclusion

Different formulations were prepared varying the super disintegrant concentration. Preformulation study of the tablet blend was carried out, the tablet blends showed good flowing properties directing for the further course of formulation. The tablets were prepared by direct compression method by 3.5 mm, round shaped, B tooling punch. Tablet blend was evaluated for post formulation studies like hardness, weight variation, friability, wetting time, *in-vitro* disintegration time and *in-vitro* dissolution and were satisfactory.

It was concluded that, the formulations containing Ac-di-sol as super disintegrants can be proved to be ideal formulation considering all the evaluation parameters mainly wetting time, in vitro disintegration time and in-vitro dissolution studies. From the above results Formulation F6 having better characteristics than compared to remaining formulations. This formulation contain only 6.5 mg of Ac-di-sol showed 100.62% of drug release within 20mins and is thus optimized.

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