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Original Article

Formulation and Characterization of Mouth Dissolving Tablet for Controlled Delivery of Ketoconazole

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ABSTRACT

Recent advances in Novel Drug Delivery System (NDDS) aim for designing forms, convenient to be manufactured and administered free side effects, offering immediate release and enhanced bioavailability. So as to achieve better patient compliance, mouth dissolving tablet is one of such delivery system. Ketoconazole was used the treatment of oral thrushes and systemic infections. A total of eight formulations were prepared using sodium starch glycolate and microcrystalline cellulose as quick breaking agents for mouth dissolving tablet. The prepared tablet was evaluated for dissolution studies, which showed 99.9 % drug release at the end of 1 hrs.

Keywords: Ketoconazole, sodium starch glycolate, mouth dissolving

1. INTRODUCTION

The drug delivery system "Solid Dosage Form" consists of mainly capsules, sachets, tablets, pills, mass or unit-dose powders and granules. Oral dosage form is the most popular route for drug therapy. Over 80% of the drugs formulated to produce systemic effects in the United States are produced as oral dosage forms [1,2,5]. Tablets and capsules are currently accounted for the highest proportion of all drug presentations. This is because of several reasons like, Ease of administration, Accurate dosage, Self- medication, Pain avoidance, Patient compliance.

Scientist have introduced a creative new drug delivery system known as mouth dissolving drug delivery or fast dissolving drug delivery system to get rid of these situations.

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The moment we put Mouth Dissolving Tablets or Fast Dissolving Tablets on tongue, they start dissolving rapidly [1,3,5]. The drug which dissolves or breaks-up in the saliva. As drug goes faster into solution, absorption and onset of clinical effect of the drug is quicker.

The orally disintegrating tablets as "A solid dosage form which dissolves rapidly within seconds when placed under the tongue". The time taken by tablet for orally disintegrating varies from seconds to minutes. It also depends upon the size of tablet and formulation. Ketoconazole is the first orally active azole convenient for the treatment of systemic mycoses. Solubility of ketoconazole is that it is soluble in methanol acids, ethanol (slightly) and insoluble in water [5,6,7]Azoles are potentially fungistatic. They inhibit C-14 demethylase (a cytochrome P450 enzyme), resulting in blockage of demethylation of lanosterol to ergosterol.[9-12]

2. MATERIALS AND METHOD

Table 1: Material and source

S. NO	MATERIALS	SOURCE
1.	Ketoconazole	HAB Pharmaceutical limited, Dehradun.
2.	Lactose monohydrate	Central Drug House (p) Ltd, New Delhi
3.	Magnesium sterate	Molychem , Mumbai
4.	Sodium saccharin	Central Drug House (p) Ltd, New Delhi
5.	Sodium alginate	Molychem , Mumbai
6.	MCC	Molychem , Mumbai
7.	Mannitol	Molychem , Mumbai
8.	Talc	Central Drug House (p) Ltd, New Delhi
9.	Sodium Starch Glycolate	HAB Pharmaceutical limited Dehradun.
10	PVP K30	Central Drug House (p) Ltd, New Delhi

Procedure For Manufacturing:

Wet Granulation

Wet granulation is the process simply involves which a liquid is added to a massing of the powder in a vessel blend with any type of agitation which produce granules, wet sizing and drying. These granules after drying are compressed to form tablets.[13-20]

Table 2: Formulation parameters

Formulation code	API (mg)	Manitol (mg)	Lactose (mg)	SSG (mg)	Sodium alginate	HPMC (mg)	MCC (mg)	Sodium Saccharine (mg)	Magnesium stearate (mg)	Talc (mg)
F1	200	140	_	25	_	_	25	40	10	10
F2	200	140	_	_	25	_	25	40	10	10
F3	200	_	140	25	_	_	25	40	10	10
F4	200	_	140	_	25	_	25	40	10	10
F5	200	140	_	25	_	25	_	40	10	10
F6	200	_	140	25	_	25	_	40	10	10
F7	200	_	140	_	25	25	_	40	10	10
F8	200	140	_	_	25	25	_	40	10	10

Evaluation:

Water Absorption Ratio

For water absorption ratio test a Petri dish is used which has internal diameter 5.5cm containing 6ml of purified water was taken. A slice of tissue paper bend twice was then kept in the Petri dish. Then the tablet was then plot on the tissue paper until it gets wet completely. The wetted tablet was removed and again weighted. Water absorption ratio, R was determined by using following equation.

$$R = \frac{wa - wb}{wb} \times 100$$

Where Wb and Wa are the weight before and after the water absorption, respectively. [21-27]

Content Uniformity Test

For this test we take 20 tablets of every formulations were weighed and crushed in mortar. Then powder equivalent to 200mg of Ketoconazole was weighed and dissolved in 100 ml of pH 6.8 phosphate buffer. From the stock solution 1ml sample was withdrawn and diluted to 10ml with pH 6.8 phosphate buffer, Then we checked the absorbance was measured at wavelength 225 nm using double beam UV-Visible spectrophotometer (IP, 2007). Uniformity of the Content was calculated using formula [28-37]

$$\% \text{ Purity} = 10\ C \times \frac{\text{Absorbance of unknown (Au)}}{\text{Absorbance of Standard (As)}}$$

Where C = Concentration.

Disintegration Time

At first, the disintegration time for mouth dissolving tablets was measured using the conventional test for tablets as described in the Pharmacopoeia. Tablets were then placed in the disintegration tubes and time required for complete disintegration without leaving any residues on the screen was recorded as disintegration time.[38-42]

In-Vitro Dissolution

Using six basket dissolution apparatus, Dissolution study was done for all the formulations. The dissolution test was implemented using 900ml of phosphate buffer (PH 6.8) was taken as the dissolution medium at 50 rpm and 37°C±0.5°C. 10 ml of sample were withdrawn in different time interval and the sample volume was replaced with fresh dissolution medium of equal volume. The samples were analyzed spectrophotometrically at 225 nm.[43-47]

In the preformulation study, identification of drug by UV spectroscopy and FTIR spectroscopy. The λ max of drug was found to be 225 nm and the FTIR absorption spectrum of Ketoconazole was obtained using Agilent technology The FTIR spectra observed the good compatibility of Ketoconazole and with other polymers. [48-53]

Table 3: Absorbance of Ketoconazole at different concentration

Concentration (µg/ml)	Absorbance
1	0.102
2	0.126
4	0.197
6	0.245
8	0.303
10	0.364

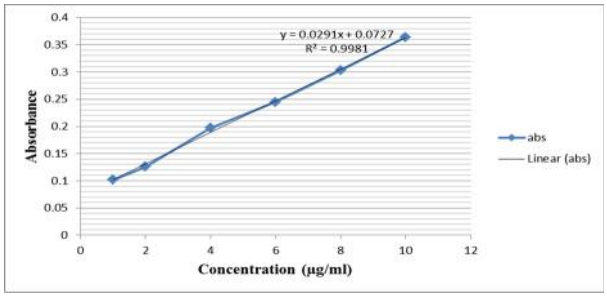

Fig 1: Standard curve of Ketoconazole

Table 4: Sample no 1 of Ketoconazole only

Sample ID: 1	**Sample Scans: 32**
System Status: Good	**Resolution: 8 cm-1**
Background Scans: 32	**Range: 4,000.00 - 650.00**
Apodization: Happ-Genzel	

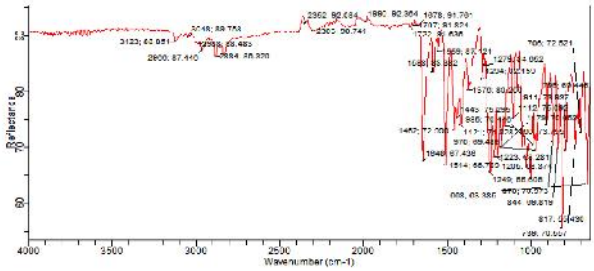

Fig 2: FTIR of Ketoconazole

Table 5: Sample no 2 of Ketoconazole & excipients

Sample ID: 2	**Sample Scans: 32**
System Status: Good	**Resolution: 8 cm-1**
Background Scans: 32	**Range: 4,000.00 - 650.00**
Apodization: Happ-Genzel	

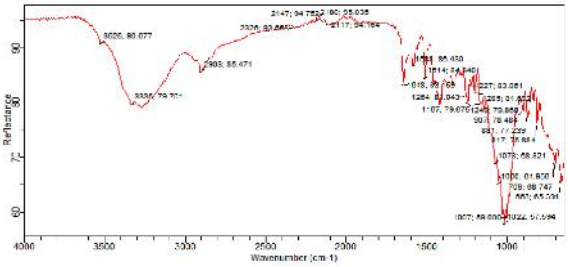

Fig 3: FTIR of Ketoconazole + Excipients

- The physical properties showed white in colour, crystalline powder and bitter in taste. The solubility having freely soluble in methanol and slightly soluble in ethanol and insoluble in water. The melting range was found to be 145-148^{0}C **(Table 6)**.

Table 6: Physical properties of Ketoconazole

S. No	Parameters	Inferences
(1)	Appearance (colour, nature and taste)	White, crystalline powder and bitter test.
2)	Melting Point	145^{0}C-148^{0}C.
3)	Solubility	Freely soluble in methanol, very slightly soluble in ethanol and insoluble in water.

- The pre-compression evaluation parameters were angle of repose (27.55^0-30.79^0), it shows better range, bulk density (0.40-0.45 gm/ml), tapped density (0.52-0.55 gm/ml), Carr's index (16-20%), it shows that the drug had good flowability and Hausner ratio (1.20-1.26), it shows good flowability (**Table 7)**.

Table 7: Pre-compression evaluation parameters

Parameters	F1	F2	F3	F4	F5	F6
Angle of Repose(θ)	28·34	28·79	27·55	29·34	30·79	29·55
Bulk Density(g/ml)	0.45	0.43	0.44	0.44	0.44	0.41
Tapped Density (g/ml)	0.55	0.53	0.55	0.53	0.54	0.52
Carr's index (%)	18.18	18.86	20	16.98	18.51	21.15
Hausner ratio	1.25	1.23	1.25	1.20	1.22	1.26

- The post compression evaluation parameters were found as thickness (4-6 mm), hardness (3-4 kg/cm^2), and friability (0.50-0.70%). The water absorption ration were also found as F1 (91.68%), F2 (89.27%), F3 (90.34%), F4 (90.65%), F5 (88.36%), F6 (95.28%), F7 (90.91%), and F8 (83.69%) (**Table 8**).

Table 8: Post comprsession evaluation parameters

S. No	Thickness	Hardness	Friability	Water Absorption Ratio (%)
F1	4.71	3.30	0.52	91.68
F2	4.55	3.40	0.60	89.27
F3	4.56	3.40	0.52	90.34
F4	4.87	3.30	0.58	90.65
F5	5.01	3.40	0.59	88.36
F6	4.83	3.40	0.60	95.28
F7	4.87	3.40	0.67	90.91
F8	4.53	3.50	0.61	83.69

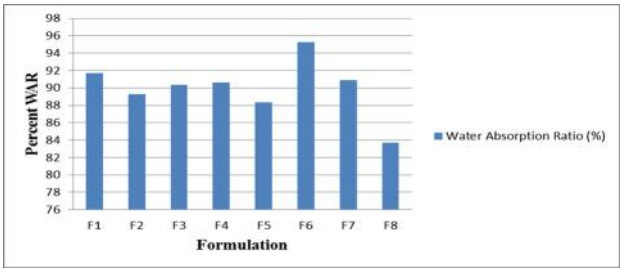

Fig 4: Water absorption ratio of ketoconazole tablets

- The drug content of different formulation was determined by using double beam spectrophotometer (Shimadzu 1800) of different formulations. Drug content were found as F1 (98.7%), F2 (99.2%) F3 (99.6%), F4 (99.9%), F5 (100.1%), F6 (98.2%), F7 (100.0%) and F8 (101.0%). The disintegration time was found to be within 1 min (T**able 9**).

Table 9: Percent drug content

Formulation	Drug content (%)	Disintegration time (min)
F1	98.7	0.35
F2	99.2	0.42
F3	99.6	0.30
F4	99.9	0.24
F5	100.1	0.34
F6	98.2	0.39
F7	100.0	0.46
F8	101.0	0.52

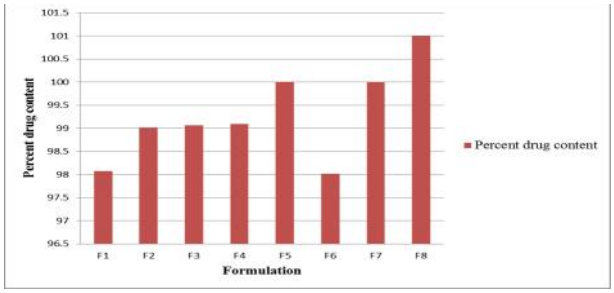

Fig 5: Drug content of Ketoconazole tablet

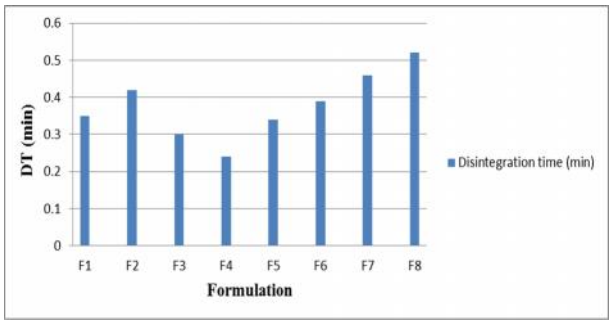

Fig 6: Disintegration time of ketoconazole tablets

Table 10: *In-vitro* drug release rate

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8
5	17.24	22.27	19.23	14.72	21.98	21.11	16.23	18.23
10	26.84	31.98	33.45	23.67	33.12	33.77	30.12	32.35
20	38.83	37.13	47.98	38.43	45.56	40.32	41.56	46.48
30	57.54	59.11	65.55	59.88	61.19	48.89	58.23	70.35
40	82.43	76.98	79.12	79.91	76.37	72.98	80.45	81.12
50	92.44	88.17	91.78	86.55	89.94	88.98	90	91.78
60	99.02	98.12	99.23	98.76	99.94	99.11	98.78	99.67

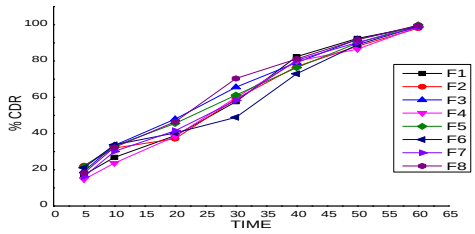

Fig 7: Percent cumulative drug release

4. RESULT AND DISCUSSION

The prepared mouth dissolving tablets were evaluated for various parameters like hardness, friability, weight variation and dissolution. Prepared tablet met all the parmacopieal requirements as discussed in above table. F8 formulation sowed 99.9 % drug release at the end 1hrs.

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