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FORMULATION OF KETACONAZOLE LOADED FAST DISINTEGRANT TABLET: *IN- VITRO* EVALUATION STUDY

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ABSTRACT

The main objective of the present investigation was to *In- Vitro* evaluation of ketaconazole tablet formulation of fast disintegrant tablet. Ketoconazole was used the treatment of oral thrushes and systemic infections. The tablets of the ketaconazole were prepared by direct compression technique. Among the different routes of administration, the oral route of administration continues to be the most preferred route. Due to various advantages including ease of ingestion, avoidance of pain, versatility and most importantly patient compliance. Recently fast dissolving tablets have started gaining popularity and acceptance as a drug delivery system, mainly because they are easy to administer and lead to better 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. The prepared tablets evaluated in terms of their pre-compression studies, post-compression studies and in vitro study. The Disintegration study and *In-vitro* study showed that formulation of batch F7gives better result than the other batches.

KEYWORDS: Ketoconazole, sodium starch glycolate, enhanced bioavailability, Disintegration study, and *In vitro* study.

INTRODUCTION

Drug delivery refers to approaches, formulations, technologies, and systems for transporting a pharmaceutical compound in the body as needed to safely achieve its desired therapeutic effect. Oral delivery is the gold standard in the pharmaceutical industry where it is safest,

most convenient and most useful method of drug delivery having the major patient fulfillment. Some tablets are intended to melt in saliva remarkably quickly, within a few seconds, and these are fast-dissolving tablets. Fast dissolving tablets dissolve quickly in the mouth saliva without the of water. Others contain agents to improve the rate of disintegration in the oral cavity, and are more properly termed fast disintegrating tablets, as they may take up to a minute to completely fall to pieces.[1]

'Fast Dissolve', 'Quick Dissolve', 'Rapid Melt', 'Quick Disintegrating', 'Mouth Dissolving', 'Orally Disintegrating', 'Oro Dispersible', 'Melt-In-Mouth', etc. are terms that represent the same drug delivery system. Recently orally disintegrating (OD) tablet technology has been approved by United States Pharmacopoeia (USP), Center for Drug Evaluation and Research (CDER). USFDA defined OD tablet as "a solid dosage form containing medical substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue". Recently European pharmacopoeia also adopted the term "oro-dispersible tablets" as a tablet that is to be placed in the mouth where it disperses rapidly before swallowing.[2]

The dosage forms dissolve or disintegrate in the patient's mouth within 15 seconds to 3 minutes without the need of water or chewing. Despite various terminologies used; oro-dispersible tablets are here to offer unique form of drug delivery with many advantages over the conventional oral solid dosage forms.[3] The proper choice of Superdisintegrants and its consistency of performance are of critical importance to the formulation development of such tablets. In more recent years, increasing attention has been paid to formulating not only fast dissolving and/or disintegrating tablets that are swallowed, but also orally disintegrating tablets that are intended to dissolve and/or disintegrate rapidly in water and to be swallowed.[4] Superdisintegrants are more effective at lower concentrations with greater Disintegrating efficiency and mechanical strength. On contact with water the superdisintegrants swell, hydrate, change volume or form and produce a disruptive change in the tablet.[5] Effective superdisintegrants provide improved compatibility and have no negative impact on the mechanical strength of formulations containing high dose drugs, some commonly used superdisintegrants are cross linked carboxyl methyl cellulose (Croscarmellose), sodium starch glycolate, polyvinylpyrroli done etc.[6] In the present investigation prepared tablets evaluated in terms of their pre-compression studies, post-compression studies and in vitro study.

MATERIALS AND METHOD

Materials

Ketaconazole was obtained from Alembic Pvt. Ltd; Vadodara. sodium starch glycolate, microcrystalline cellulose and Avicel PH 102 were a Gift sample from Loba Chemic Mumbai. All other chemicals and ingredients were used for study are of Analytical grade.

Methods[13, 14,15,16,17]

The composition of different formulations of Ketoconazole, fast disintegrant tablets is shown in Table No.1. Different tablet formulations were prepared by direct compression technique. All the powders passed through 40/60 mesh sieve. The required quantity of pure drug, various polymers and other ingredients were mixed thoroughly. Talc and magnesium stearate were finally added as a glidant and lubricant respectively. The blend was directly compressed by KBr Press Each tablet containing 100 mg of pure Ketoconazole.

Evaluation Parameters

Pre-formulation Studies

Fourier Transform Infrared Spectroscopy[18]

The fourier transform infra-red analysis was conducted for the structure characterization. FTIR spectra of the pure drug Ketoconazole, Approximately 5mg of samples were mixed with 50mg of spectroscopic grade KBr, samples were scanned in the IR range from 500 to 3500 cm-1, with a resolution of 4 cm-1.

Pre-compression studies of fast disintegrant tablet granules

Bulk density[19]

It is ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder and volume was noted as bulk density (Db).

It expressed in gm/cc and is given by: **Db =M/Vb**

Where, M= is the mass of powder.

Vb= is the bulk volume of powder.

Tapped Density[19]

It is the ratio of total mass of powdered to the tapped volume of powder. The tapped volume was measured by tapping the powder to a constant volume.

It is expressed in gm/cc and is given by: **Dt =M/Dt**

Where, M= is the mass of powder.

Vt = is the tapped volume of the powder.

Hauser Ratio[20]

Hausner Ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

Hausner Ratio =Dt/Db

Where, Dt = Tapped density.

Db = Bulk density.

Hausner Ratio value of powder show in table.

Swelling index[21]

The study was carried out using a 100 ml stoppered graduated cylinder. The initial bulk volume of 1 gm of starch was noted water was added in sufficient quantity of water to produce 100 ml of a uniform dispersion and was stored at room temperature and the sediment volume of the swollen mass was measured after 24 hour.

Carr's index (I)[21]

It indicates the ease with which a material can be induced to flow. It is expressed as a percentage and is given by.

Carr's index (%) = (Tapped density –Pour density)/Tapped densityX100

Carr's index values of powder show in table.

Angle of repose (θ)[22]

The frictional force in a loose powder can be measured by the angle of repose. It is defined as maximum angle possible between the freely sliding surface of a pile of powder and the horizontal plane.

$\tan\theta = \tan^{-1}(h/r)$

Where, θ = is the angle of repose

h=is the height

r =is the radius

Flow properties and corresponding angle of repose.

Post-compression studies Ketoconazole, fast disintegrant tablets

Hardness or Crushing strength Test[22]

Hardness of the tablet was determined using the Monsanto hardness tester (The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by tuning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force. The force required to break the tablet is measured in kilograms and a crushing strength of 4Kg is usually considered to be the minimum for satisfactory tablets. Oral tablets normally have a hardness of 4 to 10 kg; however, hypodermic and chewable tablets have a hardness of 3 kg and some sustained release tablets have a hardness of 10-20 kg5.

Thickness Test[23]

The thickness of the tablet is mostly related to the tablet hardness can be uses as initial control parameter. Ten tablets were randomly selected from each tablet thickness was determined using a Vernier calliper and the reading was recorded in millimeters.

Friability Test[24]

The pre-weighed tablets were placed in the friabilator (EF-2, Electro lab, Mumbai) which was then operated for 100rpm, then dusted and reweighed. The Conventional compressed tablets that lose less than 0.5-1.0% of their weight are generally considered acceptable.

Friability index =I-F/IX 100.

Where,

I - Initial weight, F - Final weight.

Weight variation test[24]

Weights of 20 individual tablets were noted and their mean weight also calculated. The percentage deviation was calculated by using the following formula,

Percentage deviation = [X-X*/ X] × 100

X - Actual weight of the tablet,

X*- Average weight of the tablet.

Estimation of Drug Content[25]

An accurately weighed amount of powdered Aceclofenac (100 mg) was extracted with water and the solution was filtered through 0.45 µ membrane filter paper. The absorbance was measured at 275 nm after suitable dilution6.

Calculation

The amount of Aceclofenac present in tablet can be calculated using the formula

At/As x Sw/100 x 100.

Where,

At = Absorbance of sample preparation,

As = Absorbance of Standard preparation,

Sw = weight at Aceclofenac working standard (mg)

***In vitro* Drug Release Studies**[26,27,28]

The *in vitro* drug release study was carried out for 24 hours using USP paddle type dissolution test apparatus in phosphate buffer (pH 6.8) at 75 rpm maintaining temperature at 37±0.50c. A 10ml of samples were collected from each vessel at 0, 2, 4, 8, 12, 16 and 24 hours and analyzed by UV spectrophotometer at 275 nm. The withdrawn sample was immediately replaced by equal volume of fresh buffer. The dissolution data obtained were plotted as percentage drug release versus time.

7) In Vitro Disintegration[29, 30, 31, 32]

Six tablets of each formulation were used to determine disintegration time. Phosphate buffer (pH 6.8) was used as a disintegration medium and temperature was maintained 37±0.5 ^{0}C. Average disintegration time of six tablets was determined. Phosphate buffer Media volume 900 ml.

RESULTS AND DISCUSSION

Table No.1: Formulation of different batches of Ketoconazole Fast Disintegrant Tablets. (mg/tab).

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ketoconazole	100	100	100	100	100	100	100	100	100
Sodium starch Glycolate	5	10	15	20	25	30	35	40	45
Microcrystalline cellulose	324	319	314	309	304	299	294	289	284
Talc	3	3	3	3	3	3	3	3	3
Magneshium stearate	5	5	5	5	5	5	5	5	5
Aspartame	3	3	3	3	3	3	3	3	3
Total	450	450	450	450	450	450	450	450	450

Table No.2: Angle of Repose I.P limits.

Angle of repose	Flow property
25-30	Excellent
31-35	God
36-40	Fair
41-45	Passable
46-55	Poor
56-65	Very Poor
>66	Very, Very Poor

Table No.3: Carr's Index I.P limits.

Carr's index (%)	Type of flow
5-15	Excellent
12-18	Good
18-23	Fair to passable
23-35	Poor
35-38	Very poor
>40	Extremely poor

Table No.4: Hausner's Ratio I.P Limits.

Hausner's Ratio	Type of flow
<1.25	Good
1.25-1.5	Moderate
>1.5	Poor

Table No.5: Pre-compression studies of Ketoconazole Fast Disintegrant granules

Properties	F1	F2	F3	F4	F5	F6	F7	F8	F9
Bulk Density	0.576	0.434	0.666	0.476	0..421	0.325	0.525	0.485	5685
Tapped Density	0.425	0.555	0.833	0.625	0.523	0.325	0.425	0.654	0.632
Hausner's Ratio	1.512	1.271	1.250	1.312	1.498	1.458	1.428	1.421	1.625
% Carr's Index	23.520	21.746	20.004	23.824	22.522	25.458	24.231	24.333	25.532
Angle Of Repose	27.580	25.590	28.300	28.750	29.032	27.151	26.120	28.542	29.231

Table No.6: Post-compression studies of Ketoconazole Fast Disintegrant Tablets

CODE	Thickness (mm)	Diameter (mm)	Weight Variation	Hardness (kg/cm)	Friability (%)	Tensile Strength	Water Abs. Ratio	DT* (sec)
F1	0.520	0.826	Complies	2.12	0.8454	3.0756	66.92	47
F2	0.540	0.819	Complies	2.18	0.8528	3.3657	65.89	46
F3	0.530	0.810	Complies	2.16	0.7983	3.4342	67.82	46
F4	0.520	0.814	Complies	2.14	0.8484	3.0476	68.92	48
F5	0.510	0.823	Complies	2.23	0.8658	3.3537	66.89	50
F6	0.530	0.822	Complies	2.22	0.7783	3.4632	67.82	53
F7	0.530	0.823	Complies	2.25	0.8514	3.0746	68.92	57
F8	0.540	0.818	Complies	2.23	0.8458	3.3854	67.89	58
F9	0.520	0.825	Complies	2.24	0.7943	3.4654	66.82	57

Table No.7: Release kinetics.

Release kinetics						
Formulation	**Zero order r2**	**first order r2**	**Higuchi r2**	**Hixsoncrowell r2**	**Korsmeyer -Peppas r2**	**n (Slope)**
F1	0.955	0.934	0.952	0.968	0.957	0.512
F2	0.965	0.966	0.969	0.958	0.988	0.534
F3	0.923	0.971	0.944	0.934	0.925	0.523
F4	0.978	0.988	0.962	0.976	0.934	0.678
F5	0.973	0.986	0.978	0.963	0.957	0.642
F6	0.996	0.997	0.999	0.995	0.992	0.544
F7	0.967	0.989	0.945	0.954	0.967	0.722
F8	0.976	0.969	0.935	0.957	0.981	0.668
F9	0.966	0.978	0.974	0.968	0.967	0.565

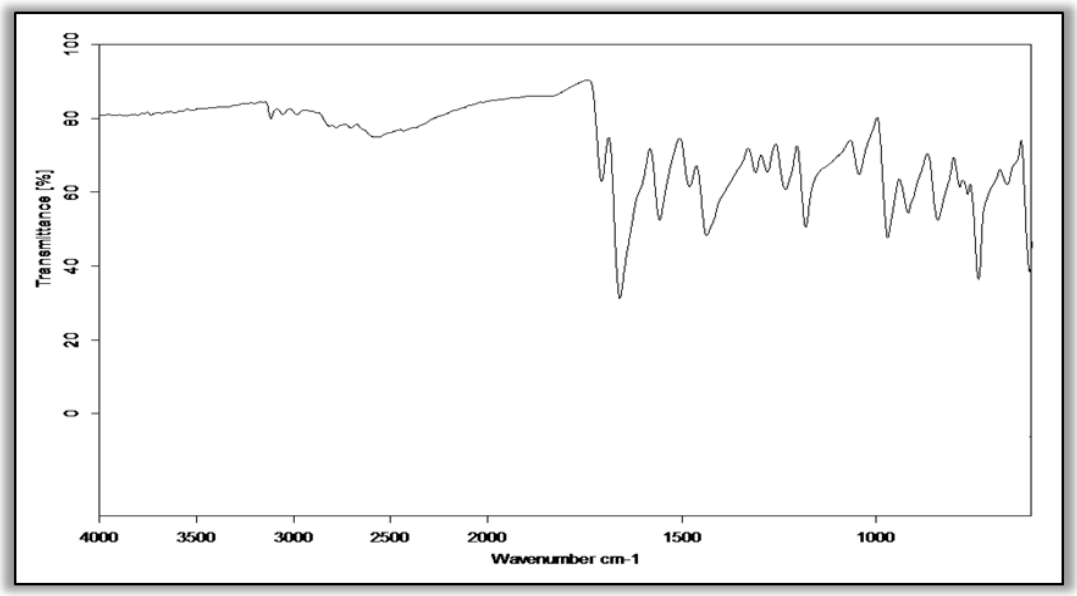

Fig. 1: IR Spectrum of Ketoconazole Pure Drug.

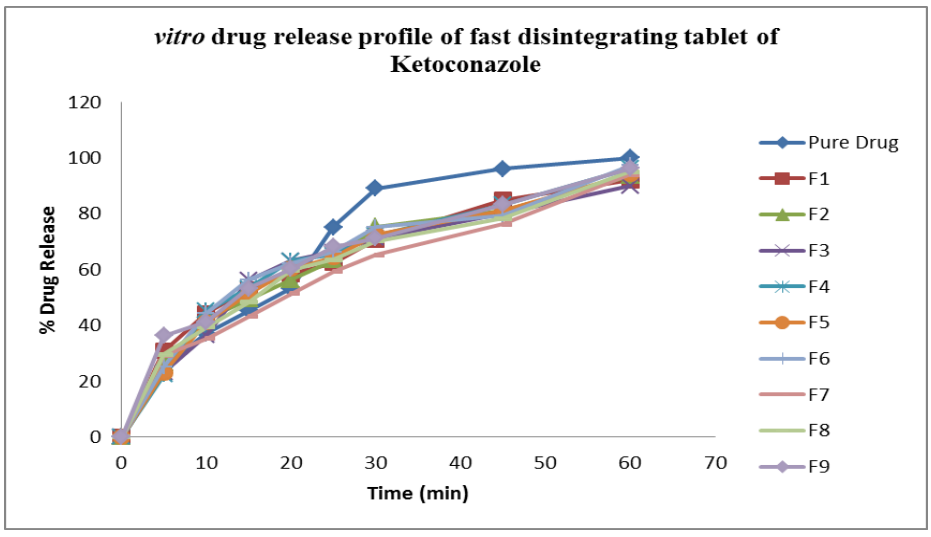

Fig.2: *In-vitro* drug release profile of fast disintegrating tablet of Ketoconazole.

CONCLUSION

The Fast disintegrating tablets of Ketoconazole were successfully formulated by direct compression technique. The Fast disintegrating tablets of Ketoconazole containing synthetic superdisintegrant showed satisfactory results more than 60min and the drug release of sodium starch glycolate has better release of drug when it is compared to other.

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