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FORMULATION AND EVALUATION OF KETOCONAZOLE SUSTAINED RELEASE TABLET

Mr. Mandar Vijay Sathe[1]*, Ms. Rutuja R. Shah[2]

Anandi Pharmacy College of M. Pharmacy, Tarf Kale Kolhapur.

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***Corresponding Author**
Mr. Mandar Vijay Sathe
Anandi Pharmacy College of M. Pharmacy, Tarf Kale Kolhapur.

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ABSTRACT

Sustained release tablets of ketoconazole were using chitosan polymer. The tablets were evaluated for preformulation studies like angle of repose, bulk density, compressibility index and physical characteristic like hardness, weight variation, friability test, *In-vitro* release of drug in 24-hours. All the physical characteristic of the fabricated tablets were within acceptable limits. The result of drug dissolution studies shown improved drug release, retardation effect of the polymer and could achieve better performance.

KEYWORD: Ketoconazole, *In- vitro*, Bulk density, chitosan, friability.

INTRODUCTION

Ketoconazole is an antifungal medication that is a member of the synthetic imidazole family and has two nitrogen atoms in its five-membered azole ring. Because it can be utilized in a variety of pharmacological formulations and has antifungal properties both topically and systemically, ketoconazole was used as a model medication. Ketoconazole is categorized as a class II drug in the Biopharmaceutics categorization scheme because of its capacity to dissolve and absorb, even if it has a poor solubility in aqueous media that, normally, prevents the entire dose from dissolving in gastrointestinal fluids. The oral route is most commonly used and prepared to control systemic fungal or bacterial infections, which can be chronic and deadly. Many systemic fungal disease mycoses have developed into potentially fatal infections due to clinical drug resistance. New stains that are appearing and the patients who are immunocompromised. Systemic mucocutaneous fungal

infections and nail infections are treated with oral ketoconazole, respectively. Ketoconazole is one potential oral antifungal drug for treating systemic and localized fungal infections. Because it prevents fungus from growing and reproducing, ketoconazole is an excellent treatment for fungal overgrowth. It is used to treat a range of fungal illnesses, such as chromomycosis, histoplasmosis, paracoccidioidimycosis, coccidioidomycosis, candidiasis, and systemic mycosis. Treatment for deep mycoses should continue for at least a week after the infectious infection seems to have been eliminated.

Chitosan, also known as soluble chitin, is a naturally occurring polysaccharide cellulose that is frequently present in the cell walls of crustaceans and fungus. it is non-toxic, biocompatible, and biodegradable. The preparation is from a simple source to rich, and the hydrophilicity is strong. Chitosan can be biodegraded by lysozyme, pepsin, and other enzymes. Chitosan is non-toxic, biocompatible, biodegradable, and has a high charge density.

Chitosan is a nontoxic, biodegradable, and low-immunity polymer. It is a great choice for a long-term drug delivery method. Chitosan particles are excellent, nontoxic, biocompatible, biodegradable, improve drug stability, change how drugs are delivered, and have additional advantages as a novel drug vehicle. As a result, it can perform the controlled medicine release function of the system. Basic characteristics of chitosan include the mass in components, texture, extent of destruction, coefficient of consistency, quantity of monomeric entities, Fountain of energy as well as water keeping value. Pneumonia is the most frequent lung illness caused by Blastomyces, which enters the body through the lungs. Additionally, the fungus can infect the central nervous system, bones, joints, and skin. This rare sickness is more likely to strike those who participate in outdoor activities. Severe symptoms are usually experienced by those with compromised immune systems.

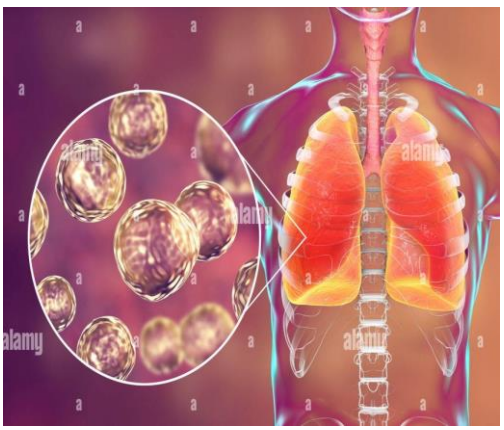

Figure No. 1.1: Blastomyces of Lung Infection.

Direct compression

By compressing tablets directly from a powder mixture process known as "direct compression" produces a solid compact that flows uniformly in the die cavity. Potassium chloride, sodium chloride, and sodium bromide are among the few crystalline materials that can be directly compressed. Additional components are needed if disintegration is a problem, which lowers the method's effectiveness by altering the compressibility of the active agent. Even when a substantial amount of medication is administered, an inert substance that is easily compressed is called a directly compression diluent. Direct compression material must be inexpensive, reworkable, inert, and able to disintegrate in addition to having high flow and compressibility.

Advantage of direct compression method

This method is more cost-effective.

There were fewer steps in the production process.

Labor costs are reduced and there is less process validation as a result of shorter processing times. High compaction pressure, heat, and moisture were not necessary for the production phases. The remaining portion, known as the maintenance dose, is then released gradually to produce a particular type of medication that is pushed yet not ongoing. A drug's progressive release over time is referred to as sustained release. Either the pollution is under control or it is not.

Advantage of sustained release system

The maintenance of drug level within a desire range.

Low dosing and increase patient compliance.

Improving efficacy in treatment. Cure and control of condition.

To reduced night dosing. To reduced patient.

Prevention of side effects.

When compared to conventional therapy, a decrease in overall drug use. It is prevention of side effects.

To reduction of drug toxicity in systematic as well as local route. To improvements of efficacy in treatment.

To reduction in adverse effects.

To effect of cost for patient and healthcare profession.

Disadvantage of dose form with sustained release

Faculty formulation may result in dose dumping.

Less freedom to change the dosage.

To boost first-pass metabolic potential.

Patient education is essential for appropriate medication administration.

potential decrease in systematic accessibility. Poor in-vivo and in-vitro correlations.

They are costly.

MATERIALS AND EQUIPMENT'S

Material List

Table NO. 1.1. Material List.

Sr. No	Name of the material	Manufacturer/supplier
1.	Ketoconazole	Dhamtee pharma Mumbai.
2.	Chitosan	Vishal chemical. Talegaon.
3.	Magnesium stearate	Loba chemical Mumbai
4.	Lactose	Loba chemical Mumbai.
5.	Talc	S.D. fine chemical Mumbai.
6.	Methanol	Loba chemical Mumbai.
7.	Dimethyl sulfoxide	SM pharma chemical Mumbai.

7.2 List of equipment

Table No. 1.2. List of Equipment.

Sr. no.	Name of Equipment	Make and model
1.	Digital weighing balance	UniBloc analytical
2.	Dissolution apparatus type -II	Electro lab
3.	Hardness tester	Dolphin
4.	Friability tester	Dolphin
5.	Vernier calliper	Indiana 2Pcs
6.	FTIR	Bruker Alpha II
7.	UV- visible double beam Spectrophotometer.	Shimadzu UV 1800
8.	Single punching tablet machine	SSTP-12 shakti

EXPERIMENTAL WORK

Preformulation of studies

When a newly created medication exhibits sufficient promise in an animal examination to justify human research, preparation begins. Preparation starts when a newly developed drug shows enough pharmacologic potential in an animal model to support human study.

These studies ought to focus mainly on the physical-chemical properties of the newly

discovered molecule that may affect its curative effectiveness and the creation of an effective medication form.

Drug analysis using (FTIR)

Goal of FTIR spectroscopy is to get over dispersive equipment's drawbacks. The duration scanning procedure was one significant drawback. It is best to measure all infrared frequencies simultaneously. The technique created a single that was embedded with all infrared frequencies using an interferometer, a basic optical device. A single is usually recorded in a few of seconds.

Figure No. 1.2: Instrument of FTIR (FOURIER TRANFORM INFRED RADIATION).

Drug and polymer compatibility analysis (FTIR)

The drug and polymer physical mixture (1:1) was made using a KBr press running at 15 tons of hydraulic pressure, and it was mixed with a suitable amount of IR grade potassium bromide to form pellets. The sample was kept in infrared region and compared to the standard reference and checked for the emergence and disappearance of any characteristic drug peak.

Formation of the standard curve for ketoconazole

A stock solution was made by dissolving ten millilitres of ketoconazole in ten millilitres of methanol. One of the drug's dilutions was scanned between 200 and 400 nm using a UV visibility spectrophotometer.

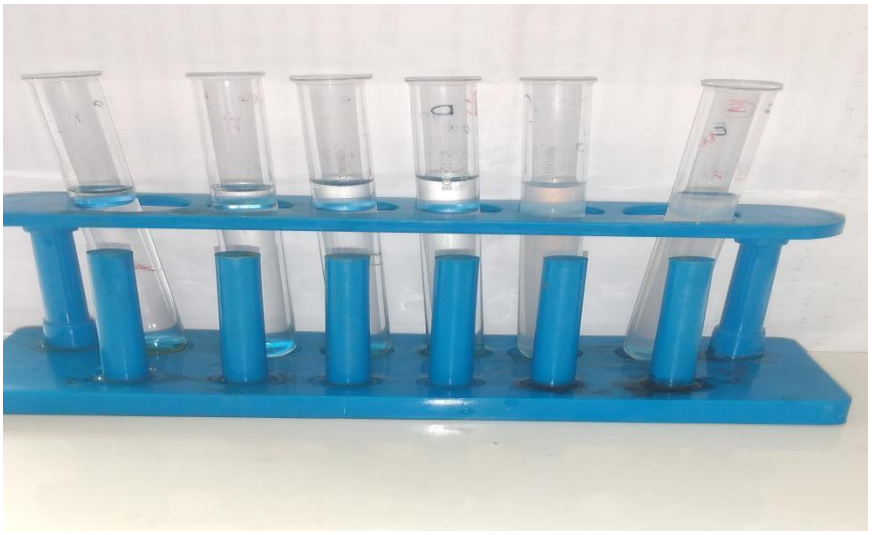

Figure No. 1.3: Calibration of Ketoconazole Dilution Sample.

Physical aprearance of ketoconazole

The physical appearance and pure white color of ketoconazole powder were observed. The provided sample is compared to a standard reference.

Oganoleptic property

Organoleptic characteristics the study of drug organ sense is referred to as evaluate. It refers to analytical techniques such as colour, taste, Odor, size, shape, etc.

Find the ketoconazole's melt point

The point at which things melt of ketoconazole ascertained using vessel coupling technique. The melting point device was fitted with a filled with medication, unilaterally sealed tube. The temperature at which the drug changed from a solid to a liquid was recorded and contrasted with industry norms.

Pre-compression of study

Bulk density determination

The quantity of powder was divided by the bulk volume to determine bulk density, which is given as g/cm3. Particle size distribution, shape, and stickiness all have an impact. The apparatus bulk volume was computed a technique and compared with a standard reference by filling a graduated vessel with the mixture.

The bulk density =

W/V0

Here W represents the weight of the the substance The beginning measured volume is V0.

Tapped density determination

Using weight equipment, the measurement instrument carrying an established quantity of powder mix together was struck evaluated time. It was determined how much area the powder occupied up in the cylindrical container. Determined tapped density is using an equation and compared to a standard reference.

The following formula is used to calculate the density of bulk. W/Vf is the volume of tapped. were W is the weight of substance. Vf stands for tapped volume.

Figure No. 1.4: Instrument of tapper Density.

Calculating the angle of repose (θ)

The angle of lay down was calculated using the funnel method. To put it briefly, a channel that could be elevated straight on was used to pour the powder mixture until the highest cone height was reached. The angle of lay down was computed using the equation and compared with a standard reference once the heap's radius was measured.

$\Theta = \tan^{-1}$ height/ radius is the angle of repose equation.

Figure No. 1.5: Apparatus of Angle of Repose.

Table no. 1.3. Flow Property of Angle of Repose.

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

Calculating Hausner's ratio

Hausner's ratio was an indirect indicator of powder flow ease. The density determination equation was used to calculate the Hausner's ratio, which was then compared to the standard reference.

Formula of Hausner's ratio = $\frac{\text{Tapped density}}{\text{Bulk density}}$

Calculating Carr's index (CI)

Calculating the ability to compress of the substance index was the simplest way to assess its flow properties and compressibility. It is imperative statistic that may be obtained from the amount of densities bulk and tapped.

A material's ability to create flow is shown by its compressibility index, which was calculated using an equation and compared to a standard reference.

CI = (Tapped density -Bulk Density) × 100/Tapped density

Table no. 1.4: Flow Property of Carr's index.

Carr's index	Flow property
≤10	Excellent
11-15	Good
16-20	Fair
21-25	Passible
26-31	Poor
32-37	Very poor
>38	Very very poor

Table no. 1.5: Flow property of Hausner ration.

Hausner's	Flow property
≤10	Excellent
11-15	Good
16-20	Fair
21-25	Passible

26-31	Poor
32-37	Very poor
>38	Very very poor

Preparation of sustained release tablet

Weighing ketoconazole, chitosan, and diluent, we mixed them geometrically in a mortar. This mixture was put through a No. 40 sieve and then aggressively agitated in a polythene bag for 20 minutes.

A single stroke tablet press (SSPT-12) was used to compact the powder into tablets after it had been combined with lubricant, talc, and magnesium stearate for five minutes.

The drug polymer ratio was developed to adjust drug release in line with the anticipated release profile and to maintain a consistent total tablet weight for all made batches under experimental preparation conditions.

The overall weight of the sustained releases was 360 mg, and the drug polymer ratio was 2:3:4:5. The polymer utilized was chitosan.

After being made for extended release using a diluent like lactose, the tablets were recovered.

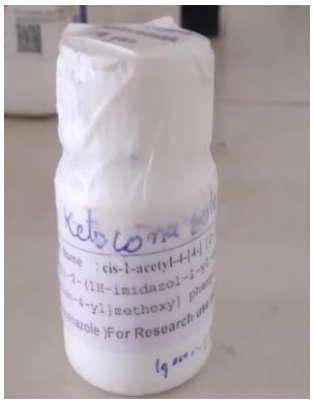

Figure No. 1.6: Ketoconazole Drug.

Figure No. 1.7: Chitosan Polymer.

Figure No. 1.8: Tablet Machine.

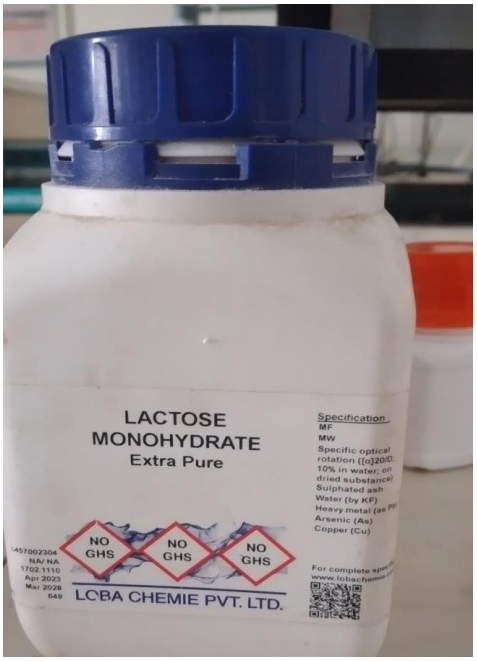

Figure No. 1.9: Lactose Powder.

Table No. 1.6: Composition of the Sustained Release tablets Containing Ketoconazole.

Materials name	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)
KETOCONAZOLE	200	200	200	200
CHITOSAN	04	06	08	10
LACTOSE	148	146	144	142
MAGNESIUM STEARATE	03	03	03	03
TALC	05	05	05	05

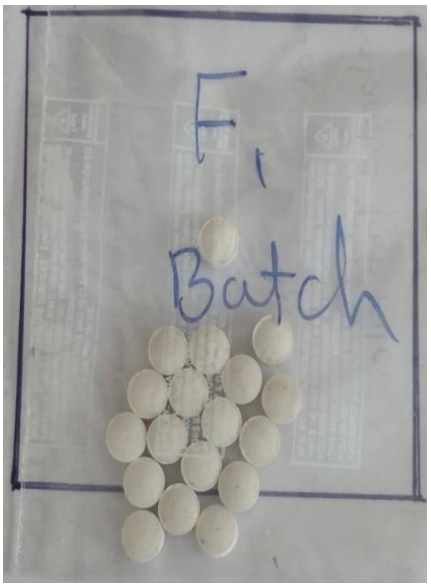

Fig. No.1.10: Batch of F1 Tablet.

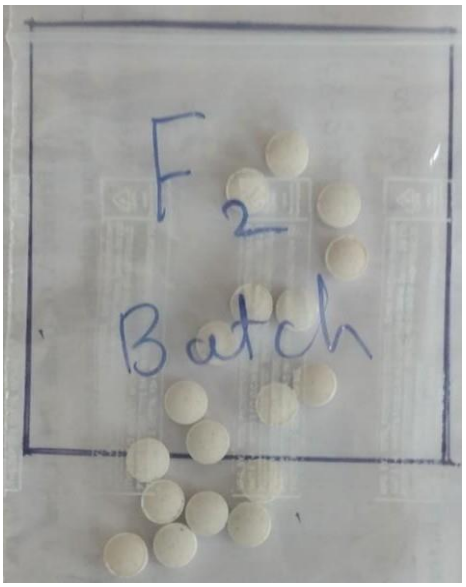

Fig. No. 1.11: Batch of F2 Tablet.

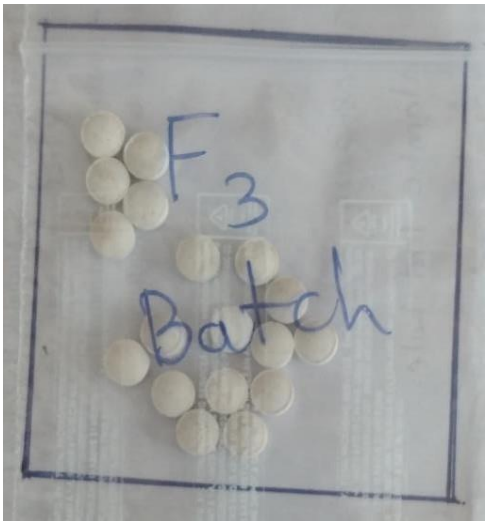

Figure NO.1.12: Batch of F3Tablet.

Figure NO.1.13: Batch of F4 Tablet.

Post-compression study: Analysing the tablet's appearance

Each of these batch of twenty tablets were chosen at random and monitored to be absolutely for any roughness on the outermost layer or in the body.

Calculating the thickness of a tablet

Tablet thickness was an important consideration for both counting with filling machinery and replicating appearance. A lot of tablet refilling receptacles technologies employ the tablets' consistent width as a counting mechanism. Ten pills were selected at random, and their thickness was measured and compared to a standard reference.

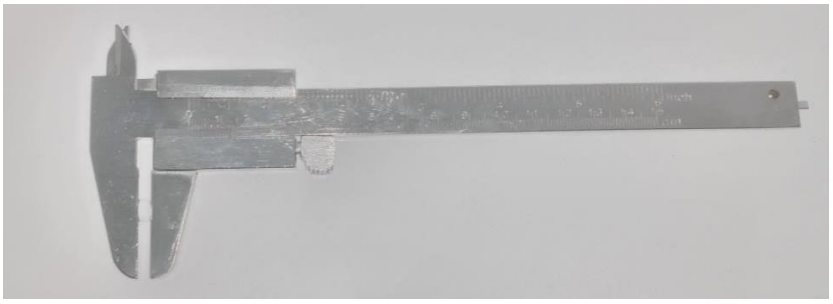

Figure No. 114: Detemination of Thickness By Vernier Calliper.

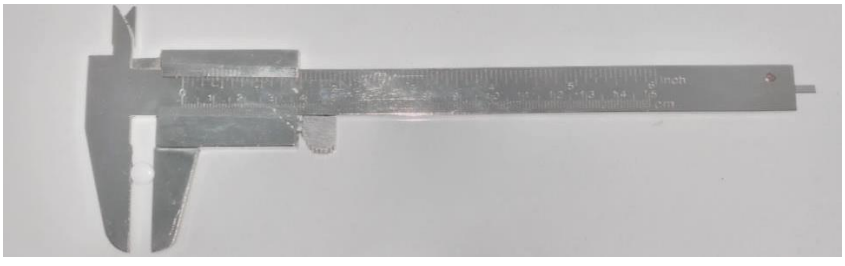

Figure No. 1.15: Measurement of second reading by vernier Calliper.

Determination of weight variation

The uniformity of pharmaceutical content might be ascertained with the weight test. For weight uniformity, the IP or USP procedure was used. The allowed weight fluctuation limitations for tablets weighing 130 mg or less, 130–324 mg, and more exceeding 324 mg were 10%, 7.5%, and 5%, respectively. were, in essence, weighed using a digital analytical balance, both individually and collectively.

Table No. 1.7: % of Standard deviation Allow accordingly to IP as well as BP.

According to IP	% Of deviation allow	As per BP
Less than 80 mg	±10%	Less than 30 mg
80 – 250 mg	±7.5%	30 to 324
More than 250 mg	±5.0%	More than 324

Figure No. 1.16: Instrument of Electronic of Weighing Balance.

Limit

The maximum is average weight plus (average weight percentage previous). Lower limit: Average weight less (previous average weight %)

Each individual weight is compared to the upper limit.

No tablet deviates from the average weight by more than two percent, and no tablet deviates from the average weight by more than twice that**.**

Determination of tablet hardnes

The force exerted across a tablet's circumference was determined to be the force required to shatter it. The tablet's ability to withstand scratching, shattering or fracture during handling, storage, and transportation before use is determined by its hardness or strength. Ten randomly selected tablets were examined for toughness using a Monsanto toughness equipment.

Figure No. 1.17: Instrument of Monsanto Hardnes Tester.

Assessment of tablet friability

The Roche friabilator was used to assess the prepared tablet's friability. In a plastic vessel that rotates at revolution per minute and drops the tablet at a height of 6 inches with each rotation, this device exposes the tablets to the combined effects of abrasion and shock. In the past, weight-20 tablets were put in a friabilator and rotated 100 times. A gentle cotton towel was used to dust the tablets before they were reweighted.

Figure No. 1.18: Instrument of Friabilatter Tester.

Detemination of Dissolution profile

The dissolution studies were conducted using the tablet dissolving test equipment, type 1 (paddle). Using up to 900 ml of 0.1N Hydrochloric acid as the dissolution medium, dissolution studies were carried out over a 24-hour period. The temperature of the dissolving medium was maintained at 370 degrees Celsius. The paddle rotated with ease at 75 rpm. A fixed interval of 12 hours was employed to withdraw the sample (5 ml). To maintain the full sink state, the same volume of fresh dissolving medium was introduced after each sampling. After the sample was situated to the proper volume using phosphate buffer, the absorbance at 273 nm was measured using a UV spectrophotometer.

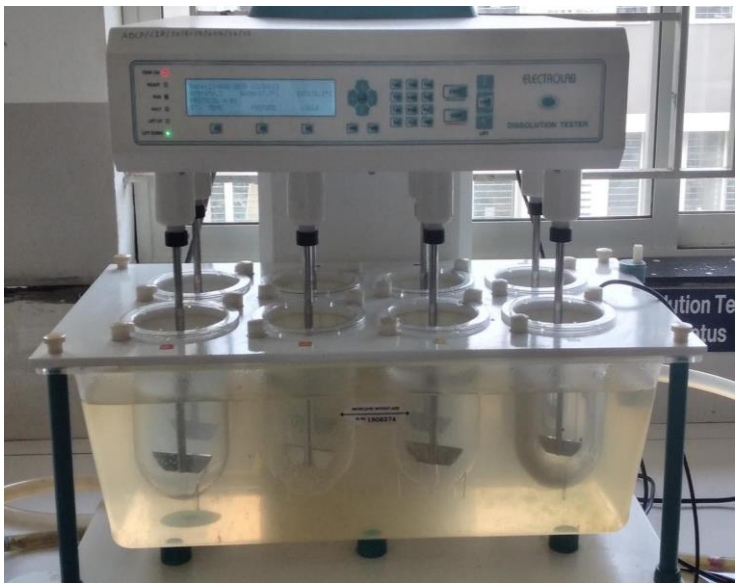

Figure No.1.19: Instrument of Dissolution Apparatus.

RESULT AND DISCUSSION

Pre- formulation study

Calibration of curve of ketoconazole

Table No. 1.8: Calibration Curve of Concentration and Absorption.

Concentration	Absorption
10	0.095
20	0.146
40	0.222
60	0.252
80	0.347
Slope	**0.0046**

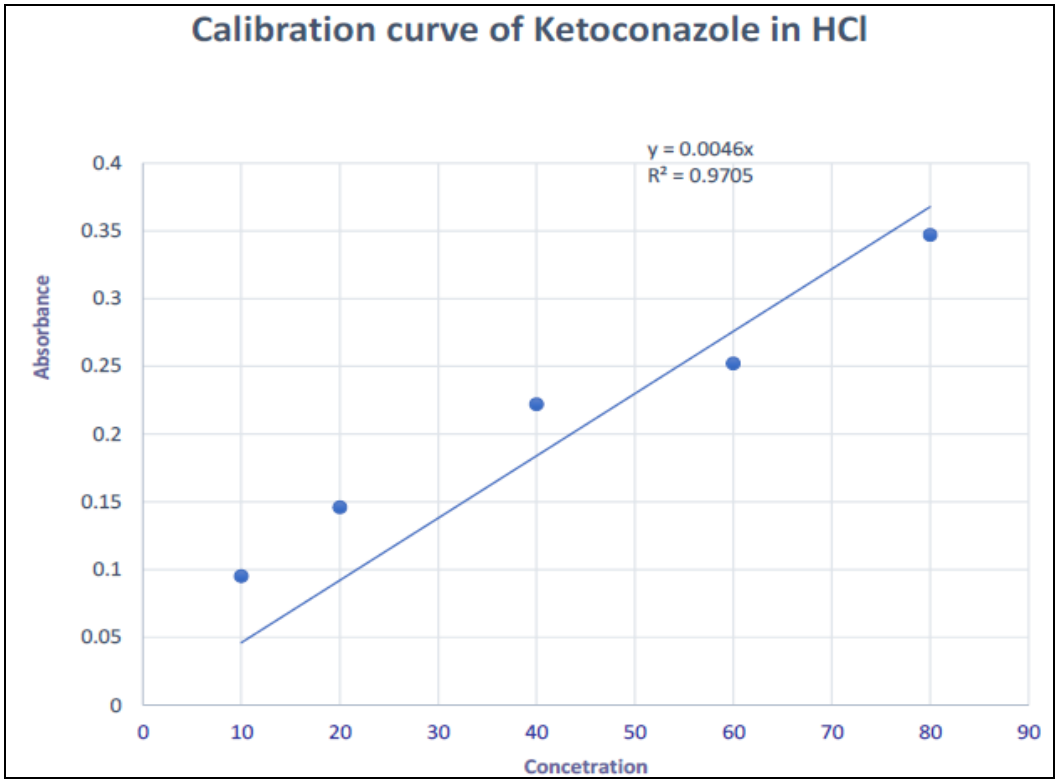

Figure No. 1.20. Calibration Curve of Ketoconazole in HCl.

FTIR (Fourier transform infrared radiation) of Ketoconazole drug

The spectra, which is typical for ketoconazole, contains aromatic and heteroaromatic stretches, C–H and C–N/C–O type stretches, and a distinctive C–Cl out-of-plane band about ~810–830 cm^{-1}. The known ketoconazole structure is consistent with the lack of a strong carbonyl band (~1700 cm^{-1}) and a broad OH/NH band (~3200–3600 cm^{-1}). Overall, the spectrum shows no discernible FT-IR degradation products and is consistent with intact ketoconazole.

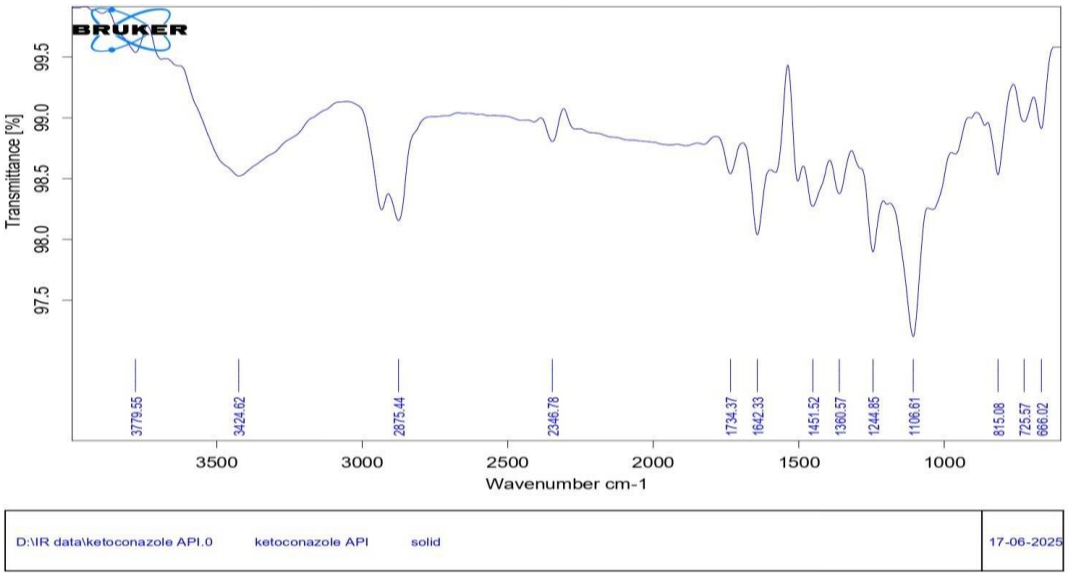

Figure No. 1.21. Ketoconazole of Pure Drug By FTIR.

Table No. 1.9. Frequency Peak of Ketoconazole Drug.

Sr. no.	Frequency peak (cm^{-1})	Assignment
1.	3070 – 3000	C ─ H stretching of aromatic ring.
2.	2950 – 2805	C ─ H stretching of aliphatic ring.
3.	1650 – 1645	C ≡ H stretch of heteroaromatic ring.
4.	1250 -1200	C ─ N, and C ─ o, stretch tertiary amine ketoconazole has ether ring
5.	1100 -1050	C─ O ─C Ethe and C ─N Oxygenated heterocycles ring
6.	820 -810	C ─ Cl Chlorinated aromatic ring

IR Interpretation of Physical mixture of ketoconazole and polymer

If its infrared spectrum shows solely the sum of its peaks and no appreciable changes, it is a physical combination. If you observe peak broadening, shifting, or intensity changes, there might be weak interactions, including hydrogen bonding between ketoconazole and the polymer.

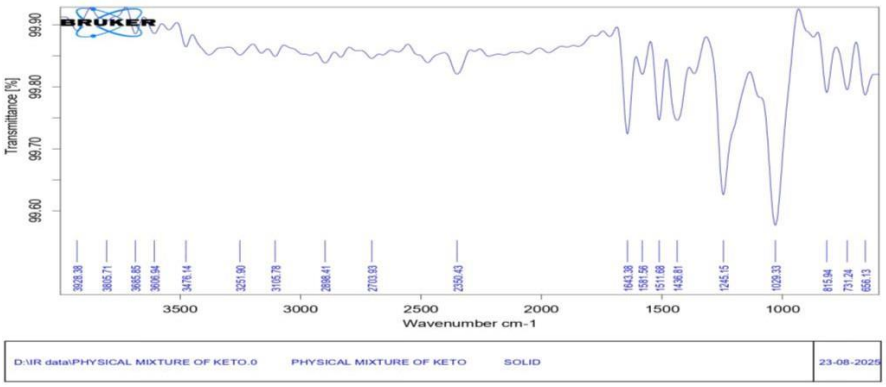

Figure No. 1.22. Physical mixture of Ketoconazole.

Table No. 1.10. Listed the Physical mixture of function Group that was identification along with the typical FTIR wave number range.

Sr. no.	Frequency peak cm^{-1}	Assignment
1.	1580 - 1510	C ═ C aromatic ring.
2.	1225 - 1200	C ─ C tertiary amine ring
3.	830 - 810	C ─ N out of plane.

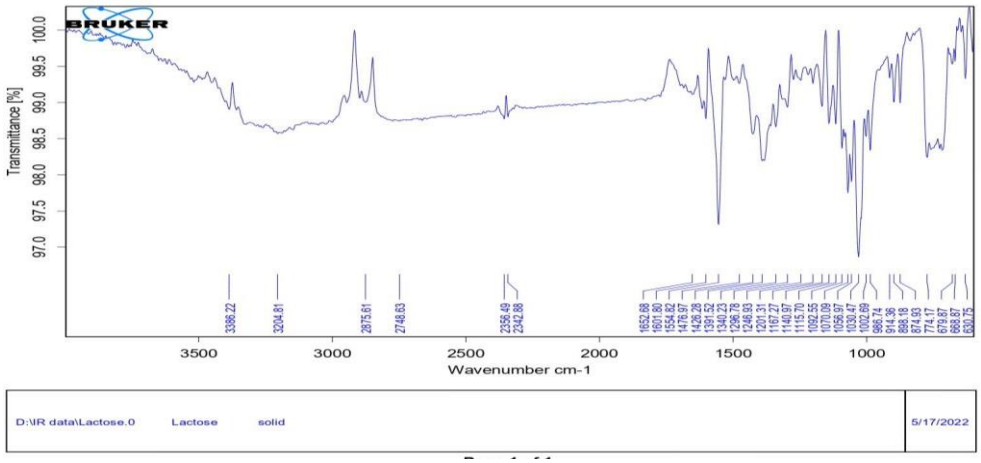

Figure No. 1.23. Lactose By FTIR.

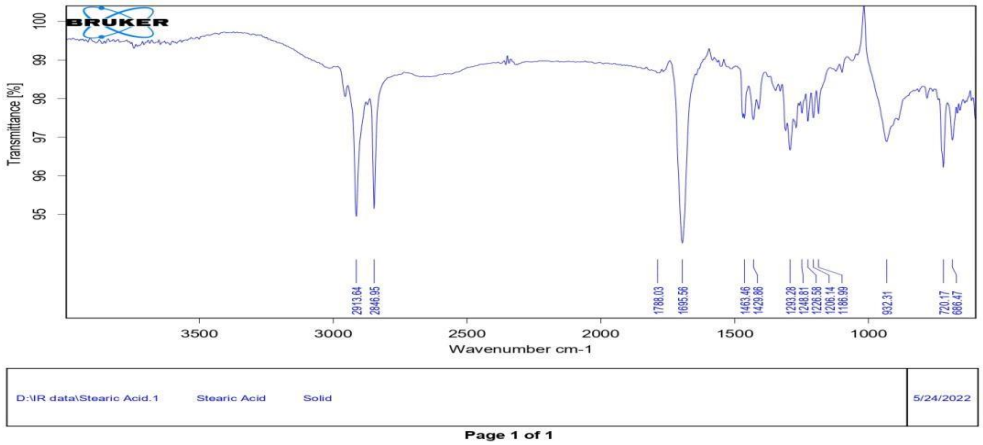

Figure No. 1.24. Stearic acid. By FTIR.

No additional absorptions that might indicate degradation products or covalent interactions are evident in the mixed spectrum, nor are there any new bands that are absent from the API spectrum. Peak locations between API and mixture fall within the typical experimental drift of ±5–10 cm^{-1}; any minor variations and intensity reductions/broadening are more likely to be caused by excipient dilution of the API and minute hydrogen-bonding/packing effects than by chemical incompatibility. A broad band in the 3000–3600 cm^{-1} region, if it exists, is usually brought on by moisture or hydroxyl-bearing excipients and does not always signify contact. (FTIR interpretation in general).

Compatibility of physical mixture

Compatible

The physical mixture reproduces the characteristic ketoconazole bands of the API without the appearance of new peaks and with very little, understandable fluctuations in intensity/width.

Physical appearance of Ketoconazole

The use of pure ketoconazole as a white substance that look was identical to the reference standard, according to the drug sample's physical identification results. These results confirm ketoconazole's.

Organoleptic property

The drug's organoleptic qualities were investigated and determined to be appropriate as an official technique. The table below displays the physicochemical characteristics of ketoconazole. The powder's physical look produced a pleasing outcome.

Table No. 1.11. Organoleptic Property of Ketoconazole.

Sr. no	Parameters	Remark
1.	General appearance	Crystalline powder
2.	Colour	White to slightly beige colour
3.	Taste	Slightly better
4.	Solubility	Sparingly soluble water Free soluble methanol. Free soluble HCL Insoluble chloroform.

Melting point analysis

148^0 C was the measured melting point. These values are consistent with those mentioned in standard reference 148^0–152^0 C, indicating that the drugs employed in this investigation were pure.

Pre- compressibility study

Angle of Repose

$\theta = \tan^{-1}$ height/ radius

$= \tan^{-1}$ 1*0.2

$= 26.28^0$C

Equation of bulk density

Weight of powder/initial volume is the bulk density.

= 15*20

= 0.75g/ml

Tapped density=Weight of powder/tapped volume

= 15 *17

=0.88g/ml Hausner ratio = Tapped density / Bulk density

= 0.88 / 0.75

= 1.25g/ml

Car's index

Car's = Tapped density -Bulk density *100 / Tapped density

= 2%

Post compression study

Thickness of tablet

Table No. 1.12. Thickness of Ketoconazole tablet.

Batches no.	Batches of Thickness mm
F1	6.2
F2	6.1
F3	6.3
F4	6.0

Tablet Hardness of tablet

Table No. 1.13. Hardness of Ketoconazole tablet.

Batches no.	Batches of hardness Kg/cm^2
F1	10.15
F2	10.16
F3	10.14
F4	10.19

Weight variation

Table No. 1.14. Weight Variation of Tablet.

Sr.no	F1	F2	F3	F4
1.	359	358	357	359
2.	357	357	359	358

3.	358	358	360	360
4.	359	359	358	359
5.	357	360	359	358
6.	358	359	358	360
7.	357	357	359	358
8.	359	358	360	360
9.	357	359	357	358
10.	359	357	359	360
11.	360	358	358	360
12.	358	359	359	357
13.	359	360	357	360
14.	358	358	359	358
15.	357	359	360	359
16.	358	357	357	360
17.	359	359	359	359
18.	358	358	358	360
19.	357	359	359	359
20.	359	359	360	360
Total	7163	7168	7172	7182

$$\text{Limit} = \frac{\%\ \text{deviation allow}}{100} \times \text{Average weight}$$

Limit of F1 batch

$$\text{Limit} = \frac{5 \times 358.15}{100} = 17.9075$$

Upper limit = 358.15 + 17.9075 = 376.05.

Lower limit = 358.15 – 17.9075 = 340.24.

F_1 batch of limit is 340.24 to 376.05.

F1 passed by the weight variation test.

Limit of F2 batch

$$\text{Limit} = \frac{5 \times 358.4}{100} = 17.92$$

Upper limit = 358.15 + 17.92 = 376.32.

Lower limit = 358.15 – 17.9075 = 340.48.

F_2 batch of limit is 340.48 to 376.32.

F2 passed by the weight variation test. Limit of F3 batch

$$\text{Limit} = \frac{5 \times 358.4}{100} = 17.92$$

Upper limit = 358.15 + 17.92 = 376.32.

Lower limit = 358.15 – 17.9075 = 340.48.

F_2 batch of limit is 340.48 to 376.32.

F3 passed by the weight variation test.

Limit of F3 batch

Limit = $\frac{5 \times 358.6}{100}$ = 17.93

Upper limit = 358.15 + 17.93 = 376.53.

Lower limit = 358.15 – 17.93 = 340.67.

F_3 batch of limit is 340.53 to 376.53.

F3 passed by the weight variation test. Limit of F4 batch

Limit =5×359.1 = 17.955 ÷ 100

Upper limit = 359.1 + 17.92 = 377.05.

Lower limit = 359.1 – 17.92 = 341.15. F_4 batch of limit is 341.15 to 377.05.

F4 passed by the weight variation test. Friability test of tablets.

Friability test of batch F1

Table No. 1.15. Friability Test of F1 Batch.

Sr. No.	Friability test F1 Batch Before 4-minute weight of tablets.	Friability test F2 Batch After 4-minute weight of tablets.
1.	359	358.7
2.	357	356.5
3.	358	357.7
4.	359	358.4
5.	357	356.5
6.	358	357.6
7.	357	356.4
8.	359	358.6
9.	357	356.5
10.	359	358.6
11.	360	359.6
12.	358	357.5
13.	359	358.6
14.	358	357.4
15.	357	356.6
16.	358	357.7
17.	359	358.4
18.	358	357.8
19.	357	356.6
20.	359	358.5

Friability test of batch F2

Table no. 1.16. Friability Test of F2 Batch.

Sr. No.	Friability test F2 Batch Before 4-minute weight of tablets.	Friability test F2 Batch After 4-minute weight of tablets.
1.	358	357.6
2.	357	356.4
3.	358	357.3
4.	359	358.1
5.	360	359.4
6.	359	358.6
7.	357	356.5
8.	358	357.4
9.	359	358.5
10.	357	356.7
11.	358	357.8
12.	359	358.4
13.	360	359.2
14.	358	357.5
15.	359	358.6
16.	357	356.4
17.	359	358.6
18.	358	357.4
19.	359	358.5
20.	359	358.2

Friability test of batch F3

Table No. 1.17. Friability Test of F3 Batch.

Sr. No.	Weight variation F3 Batch Before 4-minute weight of tablets.	Weight variation F3 Batch After 4-minute weight of tablets.
1.	358	357.5
2.	359	358.6
3.	360	359.3
4.	357	356.4
5.	359	358.5
6.	357	356.6
7.	360	359.3
8.	359	358.4
9.	358	357.2
10.	359	358.5
11.	357	356.2
12.	359	358.3
13.	360	359.7
14.	358	357.4
15.	359	358.6
16.	360	359.3
17.	357	356.2

18.	359	358.4
19.	359	356.6
20.	358	357.2

Friability test of batch F4

Table No. 1.18. Friability Test of F4 Batch.

Sr. No.	Weight variation F4 Batch Before 4-minute weight of tablets.	Weight variation F4 Batch After 4-minute weight of tablets.
1.	358	357.6
2.	359	358.5
3.	360	359.6
4.	359	358.8
5.	358	357.5
6.	360	359.6
7.	358	357.4
8.	360	359.6
9.	358	357.5
10.	360	359.7
11.	357	356.4
12.	360	359.5
13.	358	357.4
14.	360	359.6
15.	359	358.5
16.	360	359.6
17.	359	358.6
18.	360	359.5
19.	359	358.4
20.	360	359.6

Friability calculation of tablet Batches: Formula of % friability

$$\% \text{ of loss} = \frac{\text{Before 4 minute} - \text{After 4 minutes}}{\text{Before 4 minutes}} \times 100$$

Friability of F1 Batch.

$$\% = \frac{7163 - 7154.2}{7163} \times 100$$

$$= \frac{8.8}{7063} \times 100$$

$$= \frac{880}{7163}$$

=0.122%

Friability of F2 Batch

% of loss = Before 4 minute – After 4 minutes ×100 Before 4 minutes

% = 7168-7157.1 ×100

7168

= 10.9 ×100
7168
= 1090
7168
= 0.152%

Friability of F3 Batch

% of loss = Before 4 minute – After 4 minutes ×100

Before 4 minutes

% =7172-7158.2 ×100
7172
= 13.8 ×100
7172
= 1380

7172

= 0.192%

Friability of F4 Batch

% of loss = Before 4 minute – After 4 minutes × 100 Before 4 minutes

% = 7182- 7072.9 ×100

7182

=9.1×100

= 7082

= 910
7182
= 0.126 %

In-vitro dissolution study

According to the dissolving research formulations batches the findings were assessed over a 24-hour period and revealed 97.63%, 97.33%, 97.53%, and 98.63% release.

F1 Batch In- vitro percentage of drug release

Table No. 1.19. %Cumulative of F1 batch.

Time(hrs)	Abs.	Conc.	Conc./ml	%Cumul.
1.	0.245	53.26087	47934.78	23.96
2.	0.258	56.08696	50478.26	25.23
3.	0.262	56.95652	51260.86	25.63
4.	0.267	58.04348	52239.13	26.11
5.	0.272	59.13043	53217.39	26.60
6.	0.275	59.78261	53804.34	26.90
7.	0.392	85.21739	76695.65	38.34
8.	0.435	94.56522	85108.69	42.55
9.	0.456	99.13043	89217.39	44.60
10.	0.485	105.4348	94891.30	47.44
11.	0.515	111.9565	100760.87	50.38
12.	0.565	122.8261	110543.47	55.27
13.	0.595	129.3478	116413.04	58.20
14.	0.655	142.3913	128152.17	64.07
15.	0.695	151.087	135978.26	67.98
16.	0.755	164.1304	147717.39	73.85
17.	0.798	173.4783	156130.43	78.06
18.	0.865	188.0435	169239.13	84.61
19.	0.903	196.3043	176673.91	88.33
20.	0.965	209.7826	188804.34	94.40
21.	0.998	216.9565	195260.87	97.63

F2 Batch In- vitro percentage of drug release

Table No. 1.20. % Cumulative of F2 batch.

Time(hrs)	Abb.	Conc.	Conc./ml	%Cumul.
1.	0.225	55.43478	49891.30	24.94
2.	0.265	57.6087	49891.30	25.92
3.	0.272	59.13043	53217.39	26.60
4.	0.295	64.13043	57717.39	28.85
5.	0.335	72.82609	65543.47	32.77
6.	0.369	80.21739	72195.65	36.09
7.	0.399	86.73913	78065.21	39.03
8.	0.456	99.13043	89217.39	44.60
9.	0.488	106.087	95478.26	47.73
10.	0.515	111.9565	100760.87	50.38
11.	0.565	122.8261	110543.47	55.27
12.	0.589	128.0435	115239.13	57.61
13.	0.635	138.0435	124239.13	62.11
14.	0.665	144.5652	130108.69	65.05
15.	0.699	151.9565	136760.87	68.38
16.	0.756	164.3478	147913.04	73.95
17.	0.795	172.8261	155543.47	77.77
18.	0.835	181.5217	163369.56	81.68

19.	0.865	188.0435	169239.13	84.61
20.	0.899	195.4348	175891.30	87.94
21.	0.965	209.7826	188804.34	94.40
22.	0.995	216.3043	194673.91	97.33

F3 Batch In- vitro percentage of drug release

Table No. 1.21. %Cumulative of F3 batch.

Time(hrs)	Abs.	Conc.	Conc./ ml	% Cumul.
1.	0.245	53.26	47934.78	23.96
2.	0.251	54.56	49108.69	24.55
3.	0.293	63.69	57326.08	28.66
4.	0.309	67.17	60.45652	30.22
5.	0.365	79.34	71.41304	35.70
6.	0.395	85.86	77.28261	38.64
7.	0.443	96.30	86.67391	43.33
8.	0.465	101.08	90.97826	45.48
9.	0.489	106.30	95.67391	47.83
10.	0.525	114.13	102.7174	51.35
11.	0.565	122.82	110.5435	55.27
12.	0.595	129.34	116.4130	58.20
13.	0.645	140.2174	126195.65	63.09
14.	0.695	151.087	135978.26	67.98
15.	0.735	159.7826	143804.34	71.90
16.	0.765	166.3043	149673.91	74.83
17.	0.799	173.6957	156326.08	78.16
18.	0.835	181.5217	163369.56	81.68
19.	0.865	188.0435	169239.13	84.61
20.	0.888	193.0435	173739.13	86.86
21.	0.915	198.913	179021.73	89.51
22.	0.965	209.7826	188804.34	94.40
23.	0.997	216.7391	195065.21	97.53

F4 Batch In- vitro percentage of drug release

Table No. 1.22. %Cumulative of F4 batch.

Time(hrs)	Abs.	Conc.	Conc./ml	% Cumul.
1.	0.254	55.21	49695.65	24.84
2.	0.263	57.17	51456.52	25.72
3.	0.295	64.13	57717.39	28.85
4.	0.335	72.82	65543.47	32.77
5.	0.375	81.52	73369.56	36.68
6.	0.409	88.91	80021.73	40.01
7.	0.456	99.13	89217.39	44.60
8.	0.489	106.30	95673.91	47.83
9.	0.525	114.13	102717.39	51.35
10.	0.565	122.82	110543.47	55.27
11.	0.586	127.39	114652.17	57.32

12.	0.606	131.73	118565.21	59.28
13.	0.645	140.2174	126195.65	63.09
14.	0.675	146.7391	132065.21	66.03
15.	0.699	151.9565	136760.87	68.38
16.	0.735	159.7826	143804.34	71.90
17.	0.765	166.3043	149673.91	74.83
18.	0.798	173.4783	156130.43	78.06
19.	0.839	182.3913	164152.17	82.07
20.	0.878	190.8696	171782.60	85.89
21.	0.915	198.913	179021.73	89.51
22.	0.956	207.8261	187043.47	93.52
23.	0.978	212.6087	191347.82	95.67
24.	0.998	216.9565	195260.87	98.63

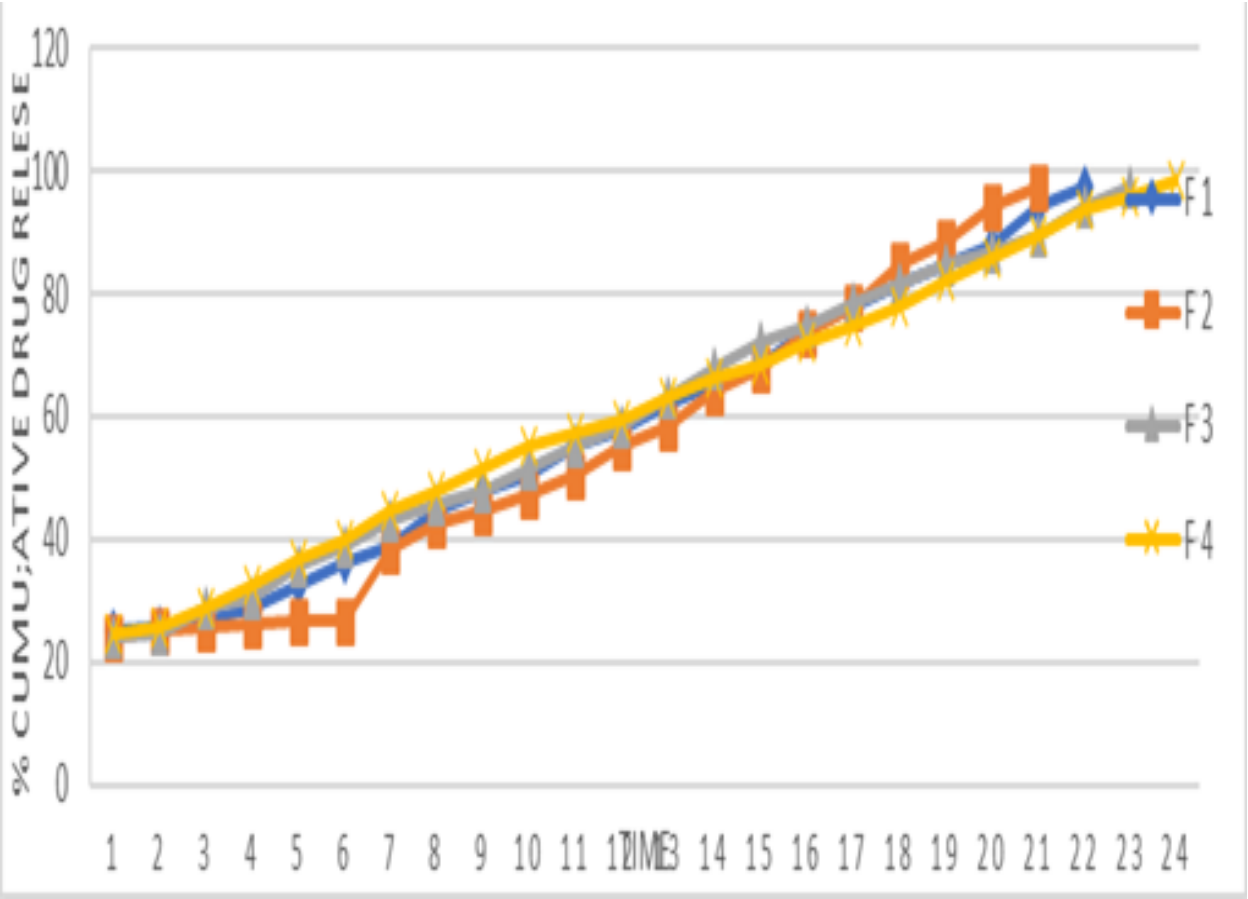

Figure No. 1.25. % Cumulative Release of Ketoconazole tablet.

Zero order drug release

Table No. 1.23.% Drug release of zero order.

Time interval (hrs)	% Drug release
1.	24.84
2.	25.72
3.	28.85
4.	32.77

5.	36.68
6.	40.01
7.	44.6
8.	47.83
9.	51.35
10.	55.27
11.	57.32
12.	59.28
13.	63.09
14.	66.03
15.	68.38
16.	71.9
17.	74.83
18.	78.06
19.	82.07
20.	85.89
21.	89.51
22.	93.52
23.	95.67
24.	98.63

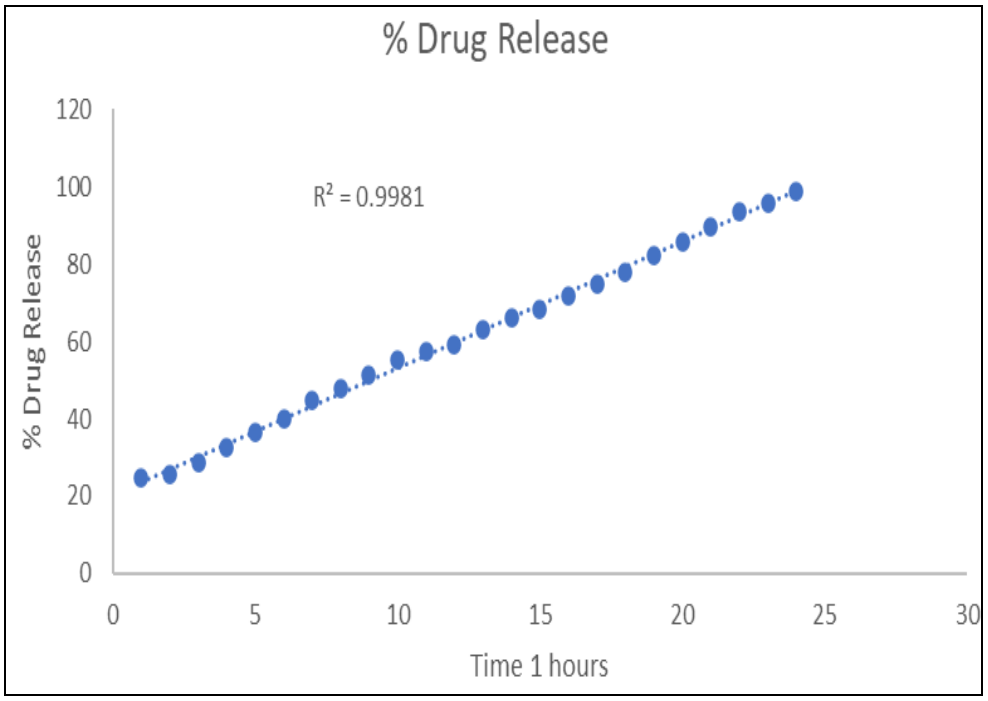

Figure No. 1.26. % Drug release of zero order.

First order drug release

Table No. 1.24. % Drug remaining First Order.

Time intervals(hrs)	% of Drug remaining
1.	2.24
2.	2.24

3.	2.23
4.	2.22
5.	2.21
6.	2.20
7.	2.19
8.	2.18
9.	2.17
10.	2.16
11.	2.15
12.	2.14
13.	2.13
14.	2.12
15.	2.11
16.	2.10
17.	2.09
18.	2.08
19.	2.07
20.	2.05
21.	2.04
22.	2.02
23.	2.01
24.	2.00

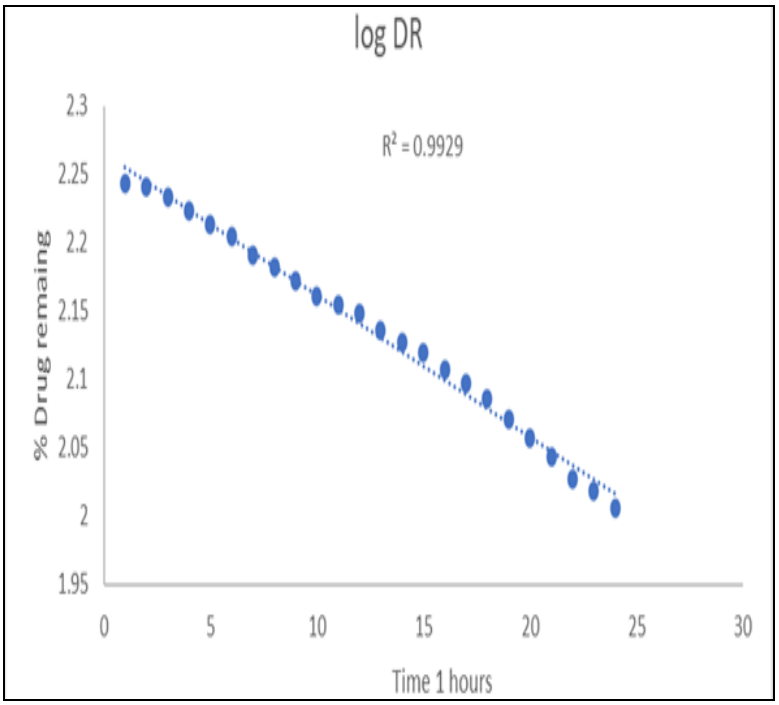

Figure No. 1.27% Drug Remaining of First order.

Higuchi model of Drug release

Table No. 1.25. Higuchi Model of Drug Release.

Time interval(hrs)	Square root of time	% Drug Release
1.	1	24.84
2.	1.41	25.72
3.	1.73	28.85
4.	2.00	32.77
5.	2.23	36.68
6.	2.44	40.01
7.	2.64	44.6
8.	2.82	47.83
9.	3.00	51.35
10.	3.16	55.27
11.	3.31	57.32
12.	3.46	59.28
13.	3.60	63.09
14.	3.74	66.03
15.	3.87	68.38
16.	4.00	71.9
17.	4.12	74.83
18.	4.24	78.06
19.	4.35	82.07
20.	4.47	85.89
21.	4.58	89.51
22.	4.69	93.52
23.	4.79	95.67
24.	4.89	98.63

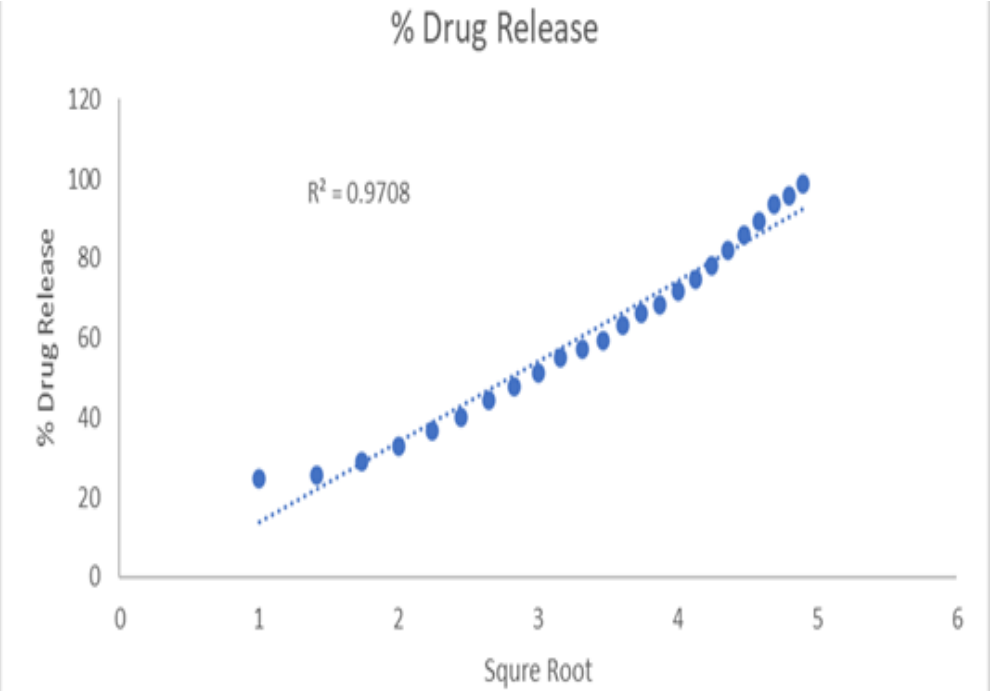

Figure No. 1.28. Higuchi Model of Drug Release.

Kors Mayer Peppas model of drug release

Table No. 1.26. Kors Mayer Peppas Model of drug Release.

Time interval(hrs)	% of drug release	Log of time	Log % of drug release
1.	24.84	0	1.39
2.	25.72	0.30	1.41
3.	28.85	0.47	1.46
4.	32.77	0.60	1.51
5.	36.68	0.69	1.56
6.	40.01	0.77	1.60
7.	44.6	0.84	1.64
8.	47.83	0.90	1.67
9.	51.35	0.95	1.71
10.	55.27	1.00	1.74
11.	57.32	1.041	1.75
12.	59.28	1.07	1.77
13.	63.09	1.11	1.79
14.	66.03	1.14	1.81
15.	68.38	1.17	1.83
16.	71.9	1.20	1.85
17.	74.83	1.23	1.87
18.	78.06	1.25	1.89
19.	82.07	1.27	1.91
20.	85.89	1.30	1.93
21.	89.51	1.32	1.95
22.	93.52	1.34	1.97
23.	95.67	1.36	1.98
24.	98.63	1.38	1.99

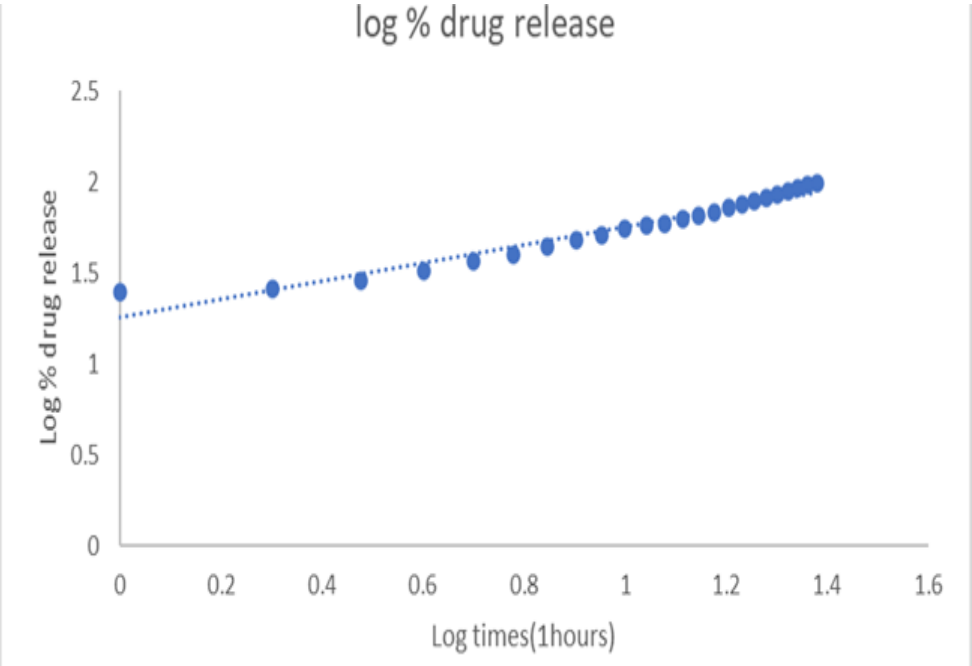

Figure No. 1.29. Kors Mayer Peppas Model of Drug Release.

CHAPTER 10

SUMMARY AND CONCLUSION

Sustained-release tablets are used in polymers with excipients in formulations and are easily compacted. The recent study's findings showed that polymers might be effectively used to create ketoconazole tablets with continuous release. Every formulation with a drug-to-polymer ratio of 2:3:4:5, lactose as a diluent, magnesium stearate and talc has a 24-hour sustained drug release time.

The tablet containing the chitosan polymer demonstrated the rate of drug release. It was discovered that sustained release for a full day was a better option than direct compression. According to the dissolving research formulations of batches the findings were assessed over a 24-hour period and revealed 97.63%, 97.33%, 97.53%, and 98.63% release.

When compared to other formulations, the F4 formulation demonstrated outstanding integrity throughout the research period and a good drug release profile of 98.63%. F4's optimized formulation, which contains polymer, has effectively maintained the drug's release for an hour. This has allowed us to achieve our sustained release tablet goal.

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