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Development of Improved Dissolution Profile of Pellets by Micro environmental pH Modification of itraconazole

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ABSTRACT:

Present study is focused on the formulation and characterization of itraconazole-tartaric acid loaded pellets showed a promising approach to enhance the dissolution profile and therapeutic efficacy of itraconazole. The outcomes of this research have the potential to contribute significantly to the development of advanced drug delivery systems for antifungal drugs, ultimately improving patient outcomes in the treatment of fungal infection.

Introduction:

Pellets: Pelletization refers to the process of agglomerating fine powders of drugs and excipients into small, free-flowing, spherical or semi-spherical beads known as pellets. Although the use of sugar seeds (also called nonpareils) as starter cores for creating layered or coated pellet dosage forms has been recognized since 1949, multiparticulate dosage forms offer several advantages over single-unit forms. These include extended release, delayed release, pulsatile release, bi-phasic release, and even site-specific drug delivery. To administer the complete dose of a drug, these pellets are typically filled into a capsule or compressed into a tablet (Shyam, Rao et al. 2019).

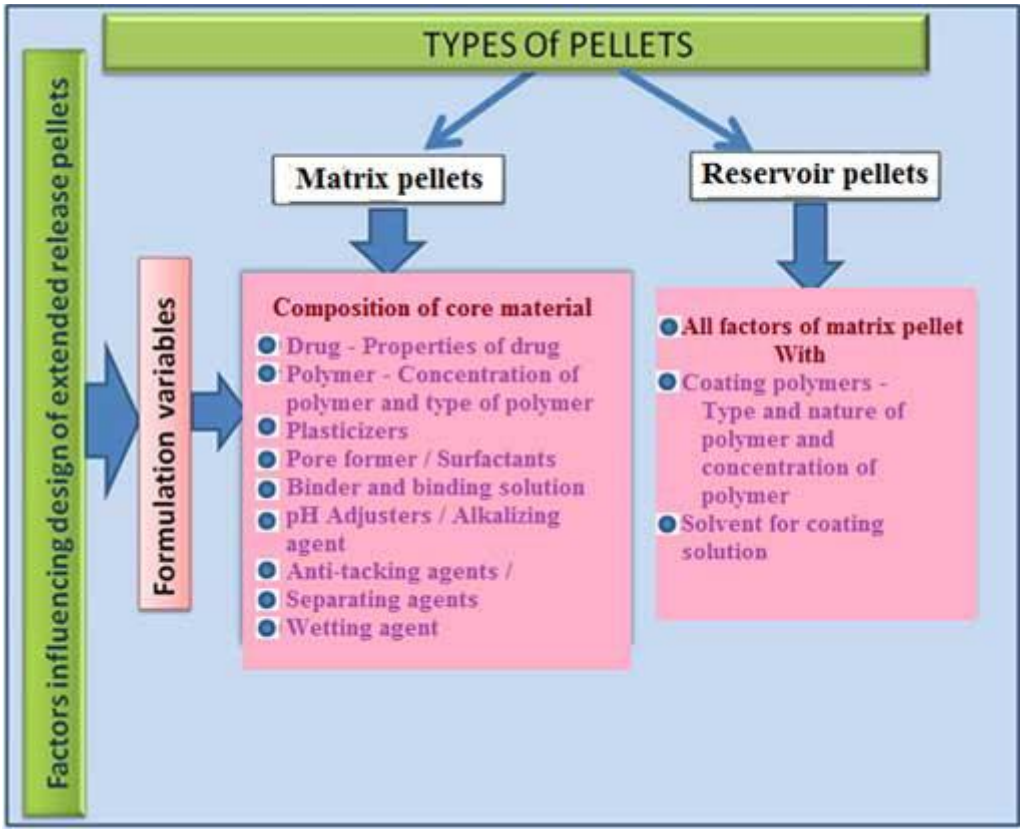

Figure 2: Types of pellets (Sonawane and Patil 2016)

2. Pellet–matrix systems

The pellet–matrix systems can be prepared by a number of techniques such as extrusion–spheronization, spherical shape crystal agglomeration, and melt solidification (Kühl and Mielck 2002).

2.1 Advantages of pellets–matrix systems

- The production of pellet–matrix systems is easier than that of the reservoir systems. The extent of retardation of reservoir–pellets is limited because of pellet geometry (Singh, Mandal et al. 2021).
- One-step manufacturing process and low cost.
- Chances of improvement of aqueous drug solubility.
- Benefit in mechanical properties such as plasticizing effect, due to drug–polymer interactions.

2.2 Disadvantages of pellets–matrix systems

- Initial burst release and in-complete release in a specified time.
- Probability of dose dumping (Pai and Kohli 2011).

3. Pellet–reservoir systems

A pellet–reservoir system consists of either on pellet (nonpareil seed) drug-layered core provided then enclosed by a polymer or matrix pellets coated with polymer. Pellets can be covered with a dispersion of aqueous polymer or an organic solution to achieve controlled drug release (Ghebre-Sellassie 2022).

3.1 Advantages of pellets–reservoir systems

- The major advantage of this system is very high drug loadings and erratic drug release pattern can be archived, by just using various types of polymeric membrane and varying their concentration.
- One can avoid initial burst release and partial release of a drug in a predetermined time by covering sugar cores by special drug–polymer ratios, in which the drug was more intense in deeper layers of the matrix and so counteracting for the increased diffusion pathway (Agrawal, Jain et al.).
- Reservoir systems are appropriate to control drug release of a highly water soluble drug.
- Dose dumping can be avoided by providing proper coating of polymer (Bendas, Christensen et al. 2010).

3.2 Disadvantages of pellets–reservoir systems

- It is very critical to design pellet–reservoir system.
- Manufacturing of pellet–reservoir systems is time consuming.

4. Materials and Methods

4.1 Physicochemical characterization and identification of Itraconazole

4.1.1 Physical appearance test:

Itraconazole was classified based on several organoleptic qualities such as color, odor and appearance. The results were compared to the manufacturer's certificate of authenticity.

4.1.2 Melting point:

Itraconazole's melting point was determined using the capillary technique (Vasilev, Surov et al. 2021). In this procedure, a closed capillary tube is filled to a height of 3 mm with the medication and put in the melting point equipment. Along with the thermometer comes a should take notice of the temperature. The temperature at which the medication begins to dissolve is recorded until the temperature at which the entire medication melts (Chivate, Garkal et al. 2021).

4.1.3 Fourier transform infrared spectral analysis

Itraconazole's FTIR spectrum was detected by making potassium bromide pellets. Itraconazole powder was finely milled and combined with powdered potassium bromide before being pressed using a specified hydraulic compression (Liu, Vanderwyk et al. 2024). The spectra of the manufactured KBr

pellet was obtained using a Fourier transform infrared spectrometer (FTIR). The resulting FTIR spectrum was compared to the spectrum obtained with the Itraconazole standard.

UV standard-plot calibration curve

Methanolic HCL water was chosen as the best solvent for Itraconazole spectrophotometric analysis.

Preparation of standard stock solution (1000µg/ml)

A precisely weighed amount of 100 mg Itraconazole reference standard was put into a 100 ml volumetric flask , dissolved and diluted up to the mark with methanol to yield a stock solution with a strength of 1000µg/ml. Diluting 1 ml of stock solution to 10 ml with Methanol yielded a 100µg/ml working standard solution (Chavan, Bandgar et al. 2021).

Sample stock solution (100µg/ml) preparation

Twenty capsules were weighed and the mean weight was used to establish the ITZ content (label claim 100 mg ITZ per capsule, ILASTAR-100 capsules). A weight of 100 mg ITZ powder was added to a 100 ml volumetric flask containing 50 ml methanol, and the combination was sonicated for 30 minutes before being diluted to 100 ml with methanol (1000 µg/ml) (Agarwal, Muthu et al. 2022). The solution was filtered, then 1 ml of the filtered solution was diluted tenfold to yield a concentration of 100µg/ml.

4.1.4 Determination of absorbance maxima (λ max)

The stock solution, i.e., 100 µg/ml was further diluted to get the concentrations (4,6,8,20 µg/ml) with 0.1 N hydrochloric acid (pH=1.5). The sample of prepared stock solution was subjected to UV-visible radiation between the wavelength range of 200-800 nm to determine the absorption maxima of the given sample. Each sample was determined thrice and absorbance readings were taken. The values are then expressed in mean values (Khurana, Agarwal et al. 2021) (Tumati and W/W 2024).

4.2 pH-determination of dissolution media:

pH solubility study carried out using three concentrations of citric acid (0.25, 0.5 and 1.0g/ml) in methanolic HCL water. Further, PH meter was used to determine the pH and the readings were taken in triplicate for each concentration (Mármol, Fischer et al. 2022).

4.3 Preparation of pellets

The process of pellet formation proceeds in 4 Steps

4.3.1 Feeding the solid material into the extruder and melting or plasticizing it in a thermal carrier, usually a low melting point wax or polymers (starting from high molecular weight polymers to low molecular weight polymers), such as vinyl polymers, co- povidone, polyethylene glycol, acrylates, and cellulose derivatives. Diffusion (ethyl cellulose, carnauba wax) and erosion (HPMC) are the drug release methods (Muley, Nandgude et al. 2016).

4.3.2 Extruder conveys mass, flows through the die, and shapes molten substance into uniform cylindrical segments.

4.3.3 Extrude spheronization at high temperatures to deform by softening and aid in the formation of uniform spheroids.

4.3.4 Solidifying spheroids to achieve the appropriate form, die exit, and downstream processing. The form of extruded items is determined by the endplate die linked to the end of the barrel (Ye, Wang et al. 2007; Swaminathan, Sangwai et al. 2013).

4.3.1 Preparation of mass:

For the present study, Citric acid , methyl cellulose (MCC), lactose and carboxymethylcellulose were used taken initially to form the mass. Three different batches were prepared to form the mass, as shown in table. The concenetrations of citric acid and MCC were varied to prepare the batches. The total batch size prepared was 5g for each batch (Theismann, K. Keppler et al. 2019).

Table - Different batches prepared using varied concentrations of citric acid and MCC.

S.no	Ingredients	F1	F2	F3
1	ITZ	1g	1g	1g
2	Citric acid	0.25g	0.5g	1g
3	MCC	2.5g	2.25g	1.75g
4	Lactose	0.75g	0.75g	0.75g
5	Carboxy methyl cellulose	0.5g	0.5g	0.5g
6	Total weight	5g	5g	5g

4.3.2 Extrusion of the mass

Each batch of the prepared mass (F1-F3) was then passed from the extruder, so as to obtain extrudes by applying a uniform pressure. On the basis of this, final batch of the prepared mass was then selected, and further spheronization process was performed on the selected batch. F1 and F2 could not form the extrudes well and hence was rejected. The F3 batch exhibited the cylindrical extrudes (Sardana, Khurana et al. 2021).

4.3.3 Spheronization of the extrudes: The selected batch, F3, was then subjected to process of spheronization. The cylindrical extrudes obtained were then spheronized, so as to obtain the round spheres by applying heat and softening the extrudes (Chen, Xin et al. 2024).

4.4 EVALUATION OF PELLETS

4.4.1 Bulk density and tapped density

The specified amount of formulation is transferred to the measurement cylinder, and the cylinder volume is measured. The following formula is used to compute tapped density (Kapalatiya, Patel et al. 2022).

Bulk density = weight of sample in g /volume occupied by the sample in Ml

A certain amount of the formulation is delivered to the measuring cylinder and physically tapped, either manually or with a mechanical instrument, until a consistent volume is attained.

Tapped density = Wt. of sample in g / Tapped volume in mL

It is easily determined by the USP density equipment. An automated tapper can be used to estimate the bulk density of pellets, while an air-comparison pycnometer or the solvent displacement technique can be used to determine the real density of pellets. The packing features of pellets or spherical seeds that produce greater bulk densities due to tiny intraparticle porosities are shown by bulk density. The amount of densification or compactness of pellets is indicated by true density (D, Shrestha et al. 2012).

4.4.2 The compressibility index of Carr: The compressibility index (C.I.) or Carr's index value of micro particles was calculated using the equation:

$$\text{Carr's index} = [\text{Tapped density} - \text{Bulk density}/\text{Tapped density}] \times 100$$

A score less than 15% suggests a powder with good flow properties, whereas a value more than 25% indicates a powder with poor flow capabilities (Mohanthi, Ramya et al. 2022).

4.4.3 Haussner's coefficient : Hausner's micro particle ratio was calculated by comparing the tapped density to the bulk density using the following equation:

$$\text{Hausner ratio} = \text{Tapped density}/\text{Bulk density}$$

4.4.4 Angle of Repose : Solid flow qualities have been described using the angle of repose. Angle of repose is a property linked to interparticle friction or resistance to particle movement. This is the greatest possible angle between the surface of a pile of powder or grains and the horizontal plane. The fixed funnel and free standing cone techniques use a funnel with its tip fastened at a set height, h, which was held 2 cm above graph paper on a level horizontal surface. The angle of repose may be calculated using the following equation, where r is the radius of the base of the conical pile:

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

Where, θ is the angle of repose, *h* is the height and *r* is the radius (Dhumal, Treffer et al. 2024).

4.4.5 Drug content : Drug content was determined in both the drug-containing core and the final functioning coated pellets. The drug content was calculated using a calibration curve.

4.4.6 Surface morphology:The cross section of pellets are examined by examination of the microstructure of the pellet surface using optical microscopy with camera and LED.

4.4.7 Particle Size Distribution: The process of determining the size of pellets using Vernier callipers. The produced pellets were estimated using the sieving technique. Weight distribution is obtained directly from the sieving process. The sieves were stacked in a nest, coarsest at the top. A sample (5 gramm) of dry pellets was deposited on the top filter and mechanically agitated. For a predetermined amount of time (10 minutes), the sieve set was

fastened and shook. Each sieve's retained pellets were weighed. Pellets were frequently designated the mesh number of the screen through which they travelled or on which they were held. It was calculated using the Arithmetic mean of the two sieves (Chang, Yang et al. 2024).

$$\text{Mean particle size} = \Sigma XiFi / \Sigma Fi$$

Where, $\Sigma XiFi$ = Weight size ; ΣFi = Percent weight retained.

4.4.8 Friability : Friability is a measure of the ability of a material to tolerate attrition during production, transportation, and storage. A friability of less than 0.8% is commonly acceptable for tablets, however this value may be greater for pellets because to the larger surface area/unit and consequent frictional force involvement. Pellet friability was tested in the same equipment with the equal amount of sample (10 g) and 200 total number of revolutions. the weights of the formulations were accurately recorded, and the friability ratios were calculated. The results were expressed in terms of the percentage of weight lost during the process.

4.9 Physicochemical Characterization of ITZ-organic acid pellets

4.9.1 Particle size and shape distribution: Microscopic approaches are fundamental for studying size distribution. Pellets were evaluated for size and shape determination using optical microscopy with Led and camera.

4.9.2 Dissolution studies :

The dissolution investigations were conducted in two stages. Dissolution in acidic condition, 0.1N HCl, for 2 hours with volume 250 mL, USP apparatus I (Basket), and temperature 37±0.5°C, followed by dissolution in pH 5.5, simulated intestinal condition by 0.1N NaOH, for Another 2 hours with volume 250 mL, total of 500 mL in USP apparatus I (Basket), and temperature 37±0.5°C (Jakhar, Kaur et al. 2023).

Preliminary investigations revealed that pellets made with citric acid might increase the rate of ITZ disintegration. The ITZ-organic acid combinations were synthesised as previously described. Combined with 20% weight/weight super disintegrant, and capsule have been compacted. Dissolution tests were carried out. The USP dissolving equipment 1 was used.at a temperature of in 250 mL of 0.1 N HCl (pH 1.1) solution 37°C±0.5°C. The disintegration apparatus's paddle speed was maintained at 75 revolutions per minute . Using 1-mL syringes, aliquots from dissolution vessels were collected after 10, 20, 30, 45, 60, 90, and 120 minutes and filtered through 0.45 mPTFE membrane filters pre-saturated with drug solution before being analysed using UV- spectrophotometer.

The step dissolution as a function of pH and the possibility for ITZ precipitation owing to pH changes in the GI tract were investigated. The pH of the dissolving media was then raised to 5.5 using 0.1 N NaOH to replicate the duodenal pH condition and to look for drug precipitation at higher pH . Because the drug particles that precipitated out after the pH shift to 5.5 had a propensity to settle at the bottom of the dissolving vessel when the rotation speed of the paddle was 75 RPM (Sardana, Khurana et al. 2019).

Result and Discussion

Physicochemical characterization and identification of Itraconazole

Physical appearance test:

Itraconazole was classified based on several organoleptic qualities such as color, odor, and appearance. The results were compared to the manufacturer's certificate of authenticity.

Identification and characterization of Itraconazole

Physical description: The Itraconazole sample was identified and characterized in accordance with the requirements of the manufacturer's COA (certificate of analysis) (Handattu, Thirumaleshwar et al. 2021).

Table 8: Certificate of analysis of ITZ parameters

Parameter	Specifications as per COA	Observations
Physical state	Solid	Solid
Color	White	White
Odor	Odor less	Odor less

Melting point:

Itraconazole's melting point was determined using the capillary technique . In this procedure, a closed capillary tube is filled to a height of 3mm with the medication and put in the melting point equipment. Along with the thermometer comes a should take notice of the temperature. The temperature at which the medication begins to dissolve is recorded until the temperature at which the entire medication melts.

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Melting point analysis

The observed experimental melting point by capillary method complies with the reported melting point as shown in table

Table : Certificate of analysis of ITZ parameter melting range.

Parameter	Specification as per COA	Observation
Melting range	165°C	164-169°C

5.3 UV Standard plot of Itraconazole:

The results of UV standard plot are shown in table . Five different concentartions of itraconazole were taken (4, 6, 8, 12, 20 mcg/ml). The readings for each concentration were taken in triplicate and the mean absorbance was calculated. The absorbance readings were plotted for each concentration and regression line was obtained by setting zero intercept .

Table : Standard plot of Itraconazole

S. No.	Concenetration (mcg/ml)	Mean Absorbance
1.	4	0.141
2.	6	0.31
3.	8	0.457
4.	12	0.733
5.	20	0.901

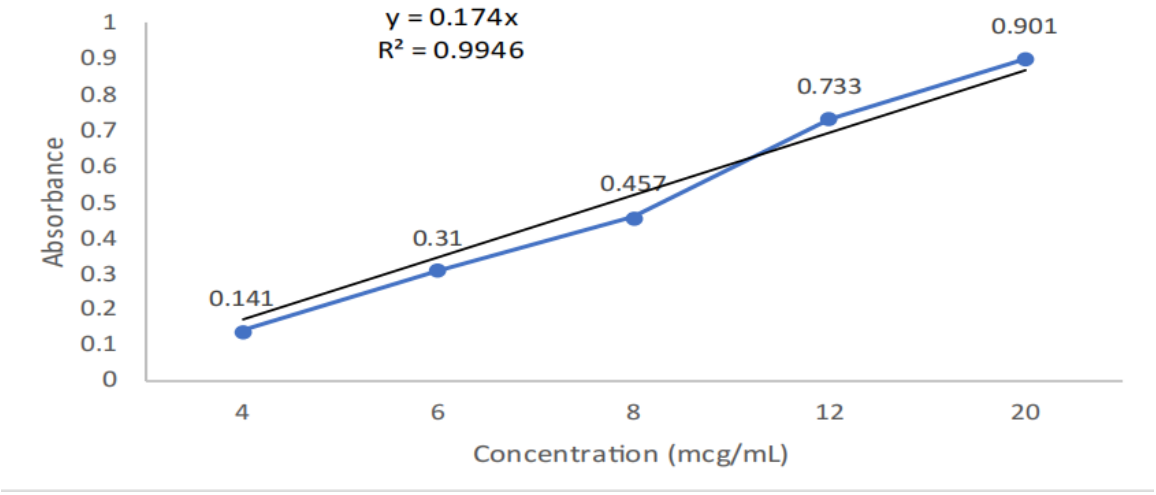


Figure : Calibration curve of Itraconazole by UV spectroscopy

FTIR Identification and Analysis –

Fourier transformed infrared spectroscopy (FTIR) studies were conducted . Samples were placed on the sample holder and the distance between the sample holder screw was adjusted to obtain cumulative results of 64 scans after background correction. The spectra were recorded over the range of 4000 to 400 cm−1 at the resolution of 4 cm−1

The FTIR spectra of pure drugs, physical mixture and Co-precipitation of Itraconazole and organic acids are shown in the spectra exhibited presence of characteristic peaks of drugs in physical mixture indicating that there was chemical absorption interaction between the Itraconazole and Organic acids.

The FTIR spectra of the given sample showed comparable major absorption bands with that of reference standard of Itraconazole. The structure of Itraconazole is presented in (Fig. The similarity in the characteristic peaks of obtained drug with that of reference standard confirmed the identity of the drug. The characteristic peaks represented the functional groups present along with the wave numbers associated with the structure.

Data analysis, interpretation and comparison:

The FTIR spectrum of Itraconazole presented the characteristic peaks at 2821.95-3130.57 cm-1 due to –C-H- stretching vibrations. the stretching due to aromatic ring was absorbed by rare pick at wave number at 3066.92 cm-1, –C-O stretching was characterized at 1224.84-1045.45 cm-1, -C-N- stretch of amine group was observed at 1045.45-1330.93 cm-1, peak at 1699.34 cm-1 was due to stretching of –C=O- and spectrum from 538.16-

734.90 cm-1 indicating C-Cl stretching respectively (Triboandas, Bezerra et al. 2024).
N-H Stretching: The N-H stretching vibrations of the amine groups typically appear as a broad peak in the range of 3300-3500 cm^-1.

C=O Stretching: The carbonyl (C=O) stretching vibrations of the ketone and amide groups are usually observed in the range of 1650-1750 cm^-1.

C-H Stretching: C-H stretching vibrations in aliphatic groups can appear in the region of 2800-3000 cm^-1.

C-N Stretching: Stretching vibrations of the C-N bonds in the molecule may be observed around 1200-1300 cm^-1.

Fingerprint Region: This region, typically below 1500 cm^-1, contains a complex pattern of peaks related to bending vibrations and other molecular motions. It provides unique information about the specific molecular structure.

Other Functional Groups: Depending on the specific structural isomers of itraconazole and any modifications or impurities, you may observe additional peaks associated with other functional groups, such as aromatic C=C bonds or O-H bonds if present.

Citric Acid:
Carboxylic Acid (COOH) Stretching: Citric acid will exhibit peaks around 1700-1750 cm^-1 due to C=O stretching of the carboxylic acid groups. O-H Stretching: Broad peaks in the range of 3200-3500 cm^-1 are associated with O-H stretching vibrations in the hydroxyl groups of citric acid.

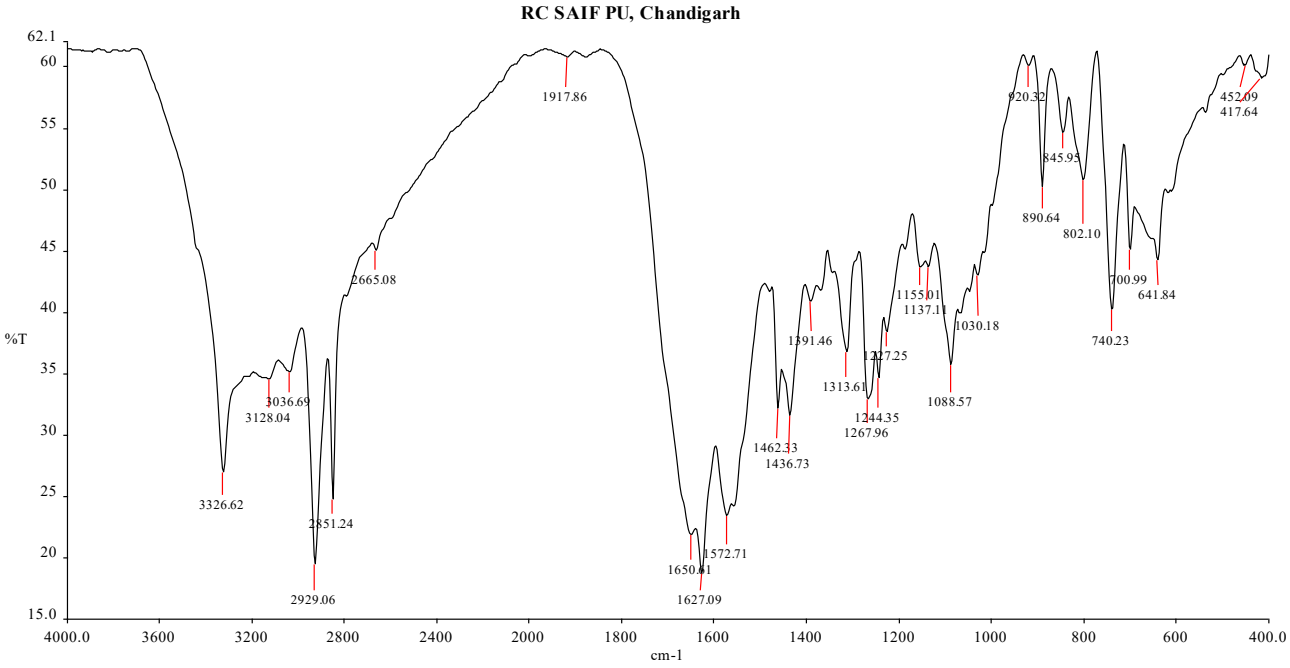


Fig 21. FTIR of ITZ reference standard.

pH-solubility Study :

The solubility of ITZ as a function of pH was evaluated in 10% 0.1 N HCl solution by adding solid acids to aqueous solutions of ITZ and pH was determined using the apparatus pH meter. However, it was discovered that the pH remained virtually constant. After the addition of particular levels of acids, the substance remains unaltered. As a result, the approach was updated to determine pH and acid concentrations affect solubility. Solutions with known concentrations of tartaric, succinic and citric acids were prepared first based on their solubility in water, then excess amounts of ITZ were added to the acid solutions, the suspensions were shaken at 25±1°C for predetermined periods of time using vortex mixture, and the pH values were measured. To generate acid solutions containing 250, 500, and 1000 mg of acid per gramme of solution . Following ITZ equilibration and pH measurement, the whole content of each solution was filtered through a 0.45 m pore size polytetrafluoroethylene (PTFE) membrane syringe filter and an aliquot was analyzed for drug concentration (Parmentier, Tan et al. 2017).

pH determination of citric acid:

Table 11. pH solubility study with different conc of citric acid

S.no	Name of salt	Conc.ug/ml	pH
1	Citric acid	0.25g/ml	2.12
2	Citric acid	0.5g/ml	1.94
3	Citric acid	1.0g/ml	1.75

Selection of the batch

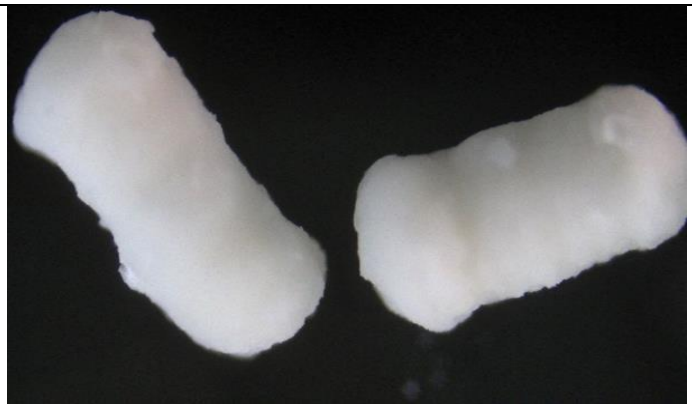
Out of the three batches of the mass prepared, with different concentrations of citric acid, F3 (having 1g of citric acid), was finalised, the extrudes made from these were cylindrical, non-sticky and uniform. F1 batch was slightly hard and extrudes could not be formed easily. The extrudes of the F2 batch were slightly sticky as compared to that of F3. So therefore, F3 batch was finalised and the extrudes were formed. Figure shows the extrudes. These extrudes were then subjected to the process of spheronization. Figure shows the spheronized product thus obtained.

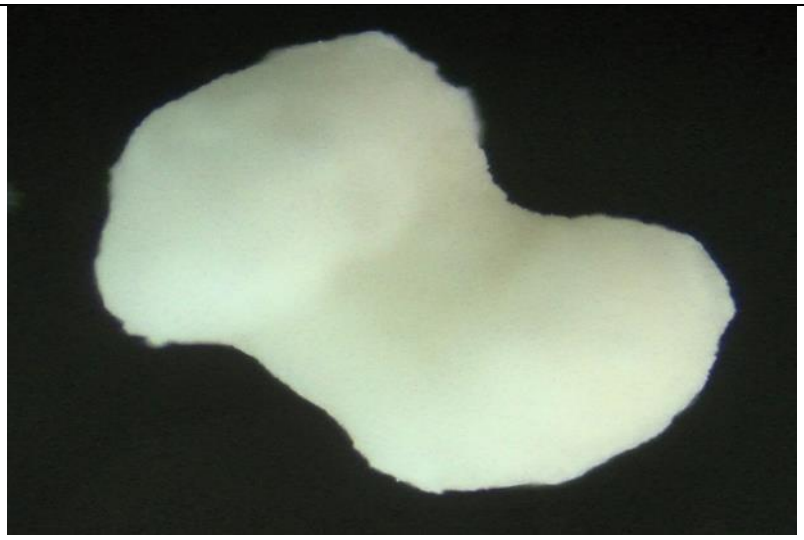
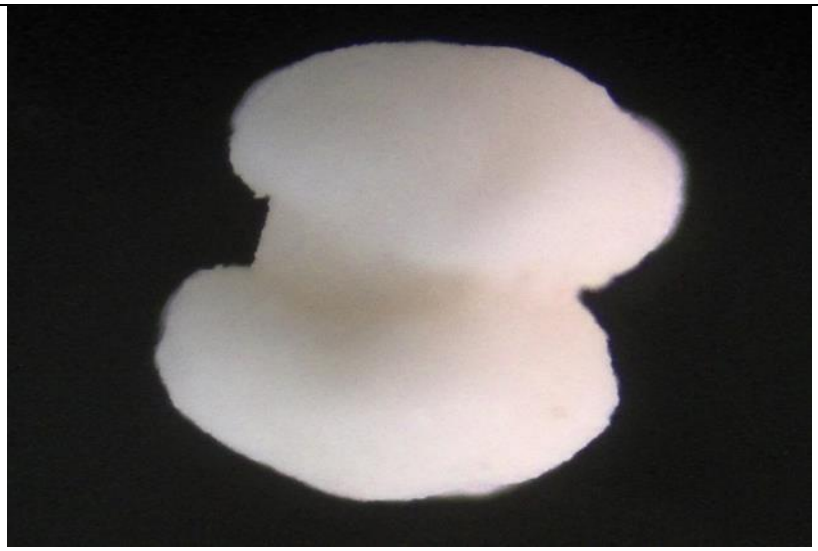
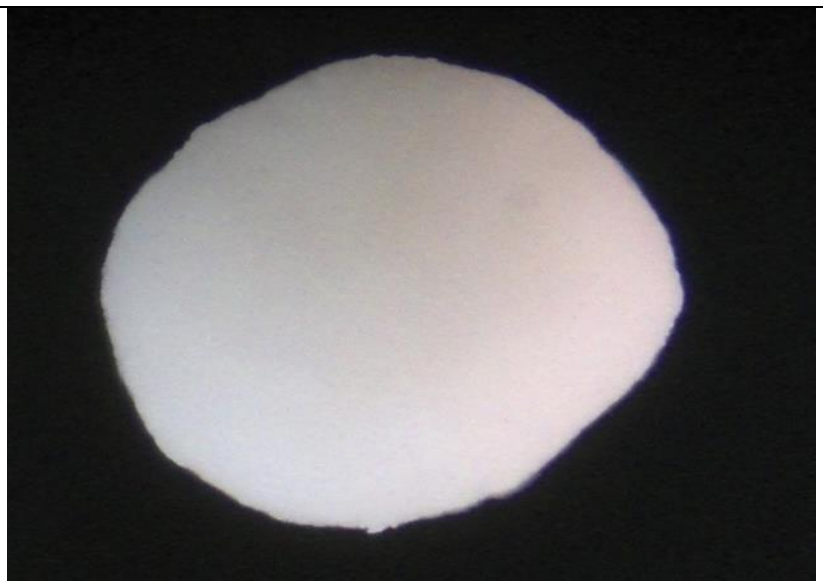
Fig.12. (A) shows the extrude product (B) shows the spheronized product

5.7 Optimization of pellet -Extruder spherionzer

Result :

Table 15 : Citric Formulation -pictures has been taken on different intervals of time during spherionizing process for total of 120 seconds.

Time (sec)		Remarks
30		Longitudnal cylindrical

60		Size reduced but still longitudnal cylindrical
90		Dumbell shaped
120		Spherical

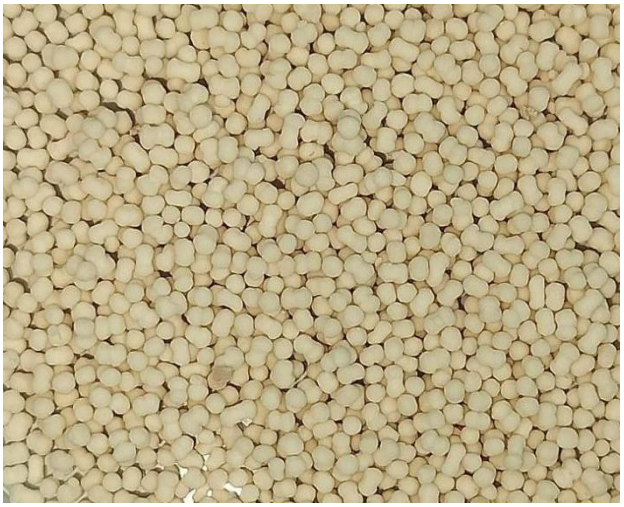


Fig. Final pellet form of Citric acid pellets.

5.8 Characterization of the prepared pellets:

5.8.1 Bulk Density and Tapped Density: The bulk density and tapped density are the necessary parameters for determining the flow properties of the given material. Hence it becomes essential part to estimate the bulk and tapped densities for the prepared pellets. The results are given in the following table.

Table: Results of bulk density and tapped density

	Observed Bulk Density (g/ml)	Mean Bulk density (g/ml)	Observed Tapped density (g/ml)	Mean Tapped density (g/ml)
Pellets of itraconazole	0.73	0.76	0.81	0.823
	0.77		0.82	
	0.76		0.84	

5.8.2 Carr's Index: Carr's index is an indirect measure of the interparticulate forces within the particles and hence their flow ability. Both of them were calculated using the bulk and tap densities of the pellets batch and hence the Carr's index was calculated.

5.8.3 Haussner's ratio: the ratio of the tapped and the bulk density gives the Haussner's Ratio, which is an indirect measure for the ability of the particles to make a good flow. Ideally, the 1-1.11 ratio, signifies excellent flowability. The results observed are shown in the table. As the pellets had the good potential to flow.

	Carr's Index	Mean Carr's Index	Haussner's Ratio	Mean Haussner's Ratio
Pellets of itraconazole	9.88	7.69	1.10	1.08
	6.09		1.06	
	7.14		1.07	

5.8.4 Angle of repose: The flow properties of developed pellets was ranged in excellent micromeritic properties as evident from angle of repose test. The mean value (n=3) of angle of repose for developed pellets was observed to be 22° (less than 25°) which indicates the pellets fall under excellent category of powder flow. The observed values also conforms to the findings of VR Sinha et al. (2005) who reported the angle of repose value less than 25° and suggested good flow potential for developed pellets (Sinha, Agrawal et al. 2005).

5.8.5 Particle size distribution: The particle size of pellets has an impact over rate of dissolution and uniformity in drug content (Priese and Wolf 2013). Therefore, uniformity in size distribution is important to define rate of dissolution and uniformity in drug content. From the results, it was observed that the pellet size was found to be 1500 ± 297 µ (Kállai-Szabó, Farkas et al. 2024) .

5.8.6 Friability: The results for the friability-i.e., the percentage loss in weight during the friability testing-are presented in Table . If these results are compared to those which can be found in the literature and which were obtained by comparable methods, the pellets seem to be strong enough to withstand rough handling. In literature, it is reported that pellets ranging in size around 600 µ showed less percentage weight loss i.e. between less than 1.8% as compared to the pellets with size range around 300 µ i.e. between 0.3 to 2.7%. Hence, concluding that pellets larger in size were having strong mechanical strength as compared to smaller size pellets. In our results the pellets with size range of 1500 ± 297 µ showed approximately 0.45% percentage weight loss and thereby comparing with literature reports the developed pellets seem to have strong physical and mechanical strength

5.8 Dissolution Study:

The ITZ-weak organic acid and its pellets showed very high dissolving rates when powdered and sieved (# 40 mesh). In the current study, pellets were employed for dissolving since the final dose form of the drug was effective.

The binary combination of ITZ with organic acid (20% drug load) was combined with a super disintegrant (10% w/w) and compressed into pellets. 100 mg ITZ (total capsule weight=500 g). The dissolving was started in 250 mL of 0.1 N HCL. (pH 1.5) for 120 minutes at 75 RPM and 37°C, and then the vol. of dissolution media was made up to 500mL with pH adjustment to 5.5 using 0.1N NaOH. The formulation with citric acid were subjected to dissolution study and was compared with marketed formulation.

Absorbance of drug take place 0-120 min in acidic medium and after maintaining pH 5.5 as per duodenal intestinal pH drug dissolution was decreased in all formulations but comparatively Tartaric has more drug release among all formulations and marketed preparation after 120 min. of maintaining pH (Chang, Yang et al. 2024).

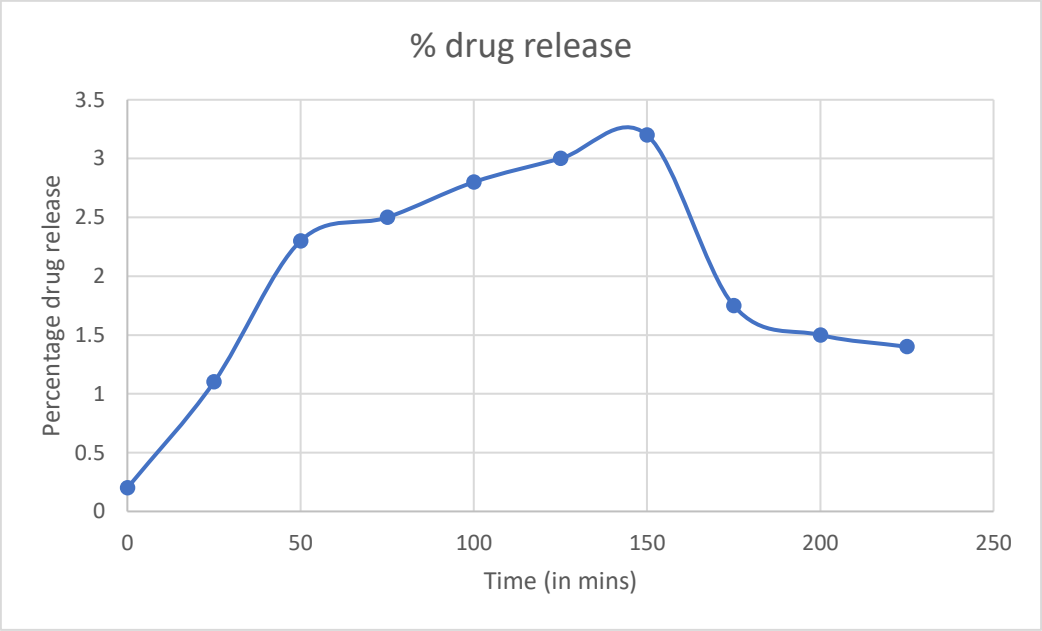


Fig. 27 . Percentage drug release from dissolution studies

Summary and conclusion:

Itraconazole is a broad-spectrum antifungal drug commonly used for the treatment of various fungal infections. However, its clinical effectiveness is limited by its poor aqueous solubility, leading to inadequate dissolution and bioavailability. This thesis aims to explore the potential of pellets as a formulation strategy to enhance the dissolution profile of itraconazole, thereby improving its therapeutic efficacy Itraconazole belongs to the class of triazole antifungal agents and is widely used for the treatment of fungal infections. However, its therapeutic benefits are hindered by its limited solubility in aqueous media, resulting in poor oral absorption and reduced bioavailability. The development of an optimized drug delivery system that improves the dissolution profile of itraconazole is crucial to overcome these challenges. The primary objective of this thesis is to investigate the formulation and characterization of itraconazole-loaded pellets as a means to enhance its dissolution profile. The specific goals include:

Selection of suitable excipients and optimization of formulation parameters for pellets.

Evaluation of physicochemical properties, such as particle size, surface morphology, and drug loading efficiency of itraconazole-Tartaric F3 loaded pellets.

Assessment of in vitro dissolution behaviour of itraconazole- tartaric pellets and comparison with conventional formulations were carried out very effectively and drug absorbance of ITZ-tartaric increased accordingly even after duodenal pH 5.5 .

This thesis employed a systematic approach, including formulation development, characterization, and evaluation of itraconazole-pellets. Various excipients will be selected and optimized using suitable techniques such as pH stability, UV spectra, FTIR, extrusion-spheronization or dissolution. The prepared pellets were thereafter evaluated for their physicochemical properties, such as particle size, drug content, and surface morphology. The in vitro dissolution behaviour of itraconazole from pellets were assessed using dissolution apparatus, and the results will be compared with conventional formulations. It is anticipated that the formulation of itraconazole-tartaric acid pellets significantly enhance the dissolution profile of the drug

compared to conventional formulations. This improved dissolution profile is expected to translate into enhanced systemic availability, bioavailability, and therapeutic efficacy of itraconazole. The successful development of itraconazole-loaded pellets could lead to the establishment of a novel drug delivery system for antifungal therapy, providing improved treatment options for fungal infections and potentially reducing the dose and frequency of drug administration.

Dissolution study carried out and we can conclude that the prepared formulations shows better drug release till about 120 mins and even after that, when the pH was changed.

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