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Innovative Formulation of Dual Drug Release Tablets: Itraconazole and Omeprazole via FDM 3D Printer

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Abstract - This study used the potential of fused deposition modelling (FDM) 3D printing to formulate a bi-compartmental tablet of Itraconazole and Omeprazole. The aim of this study was to incorporate both drugs into spatial and temporal compartments within a single dosage unit to reduce pharmacokinetic interactions. The shell of the tablet was created using itraconazole-loaded filaments of PVA and sorbitol made by hot-melt extrusion. Due to its heat sensitivity, omeprazole was manually placed into the protected compartment. Drug compatibility and thermal stability were assessed using FT-IR and DSC, while standard physicochemical tests, including weight variation, hardness, thickness, friability, and drug content, were evaluated. In vitro dissolution study was performed using a two-step pH shift method to mimic gastrointestinal conditions. The result demonstrated the potential of the FDM 3D printer to develop a customized dual drug delivery system for improved patient outcomes.

Keywords: Fused Deposition Modelling, 3D Printer, Bi-compartmental tablet, Hot melt extrusion, dual drug delivery.

INTRODUCTION:

Additive manufacturing technology, also known as 3D Printing, is widely recognized as a potential platform for fabricating customized drug delivery. This technology has gained a lot of attention in the pharmaceutical field due to its ability to create complex structures, modify drug release kinetics, adjust dose and combine multiple drugs into a single dosage form (1).

Various 3D printing technologies like Fused deposition modelling, Semi-solid extrusion, Inkjet printing and selective laser sintering have shown a lot of potential in the formulation of personalized medicines. Among these techniques, FDM emerged as the most advanced and cost-effective method for the development of personalized medicines and can be used with most of the Pharmaceutically approved polymers (2). When compared with traditional methods, 3D printing enables flexible designs and complex structures within the rapid manufacturing and prototyping of drugs, precision in drug release to meet a variety of clinical needs and reduction in formulation development time, changing the way we manufacture, design and use the drugs (3).

3D printing has many advantages, a high production rate, precise drug loading even for potent drugs, minimum material wastage that reduces the cost and accepts more classes of API's, including poorly soluble drugs (4).

Polyvinyl alcohol (PVA) is the most preferred polymer to formulate pharmaceutical dosage forms using an FDM 3D printer (5). It offers excellent thermoplasticity, biocompatibility and is generally recognised as safe (GRAS) with its long history of safety in drug delivery. Furthermore, it guarantees various drug release profiles from Immediate to modified release using FDM 3D printing (6).

Goyanes et al. introduced innovative dosage forms: multilayer and duo-caplet using PVA filaments, combining either paracetamol or caffeine and the multilayer contains alternate layers of both drugs. He altered the release profile of this drug combination using various structures and shapes made with a 3D printer (7).

A triazole antifungal agent Itraconazole, has a broad-spectrum activity against several fungal pathogens in both in vitro and in vivo studies. It exhibits more effect and has a wider range than ketoconazole. Being a weak base, itraconazole ionizes only in low pH levels like those found in gastric fluid. Because itraconazole is pH-dependent, its dissolution and absorption require a stomach pH less than 3.0 (8).

Omeprazole is a proton pump inhibitor used to treat acid-related disorders like GRED, peptic ulcer and dyspepsia (9). Omeprazole acts by inhibiting the enzyme H+ K+ ATPase which is responsible for acid secretion by the gastric parietal cells (10).

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Co-administration of omeprazole can significantly interact with the pharmacokinetics of itraconazole. Many years ago, a study conducted by S. Jaruratanasirikul on a few healthy volunteers concluded that omeprazole reduces the maximum plasma concentration (Cmax) of itraconazole by 66%. It's due to the suppression of gastric acid by omeprazole, which leads to reduced itraconazole absorption (11).

In this research, an FDM 3D printer is used to create a novel bi-compartment tablet that physically separates itraconazole and omeprazole into the same dosage unit. This approach aims to design a spatial and temporal separation of drug release.

Materials and Methods:

Itraconazole and Omeprazole were selected as a model drug and purchased from Labware India; Polyvinyl alcohol (PVA) (Parteck 4-88) is a biocompatible and biodegradable polymer were used as a filament-forming polymer and Sorbitol (Parteck SI 200) was used as a plasticizer to improve the extrusion process, which was gifted by Merk Life Science Pvt. Ltd., New Mumbai.

Every other chemical and solvent that was used was of analytical grade.

Preparation of drug-loaded filaments:

Itraconazole-loaded PVA filaments were extruded by the Hot Melt Extruder (Pharma mini HME Thermo Fisher) equipped with counter-rotating screws consisting of conveying elements and a heated barrel (Merk Life Science Pvt Ltd., New Mumbai). Itraconazole, PVA and Sorbitol were weighed and sifted through sieve no. 40 and mixed properly in a polybag and added to the hopper of hot melt extruder, gradually having extrusion temperature 180°C Screw speed 50 rpm and torque 15-18 rpm. The composition of filaments is shown in table no 1. (Omeprazole is a heat-sensitive drug, so there are chances of degradation if it is incorporated into the filament.) The mixture was extruded through a nozzle having a diameter of 1.75mm and parameters were optimized until a filament of uniform diameter was obtained. A desiccator was used to protect the filaments from light until printing.

Table no. 1: Composition of drug-loaded filaments

Sr. No.	Ingredients	F1	F2	F3
1	Itraconazole (%)	10	10	10
2	Sorbitol (Parateck SI 200) (%)	10	15	20
3	PVA (Parateck MXP 4-88) (%)	80	75	70

Design and Printing of tablets:

Simplify 3D software was used to design the tablets, which have a length of 12 mm, a Width of 7 mm, and a Height of 5mm, and were exported into a STL format. FDM 3D printer (Thin CR Technologies, Pune) was used to print the tablets. To print a 400 mg tablet, the dimensions were kept accordingly. Tablets were printed in a two-step procedure. Firstly, a tablet was fabricated until both the compartments are fully printed, keeping extrusion temperature 175°C, bed temperature 50°C, infill density 100% and infill pattern in Line. The fan inside the printer was kept on until printing. After completing the compartments fan was turned off and the compartments were filled with the respective drugs (Itraconazole 60 mg and Omeprazole 10 mg) In the second step, the tablet was sealed by changing the extrusion temperature to 180°C. (other parameters kept the same). the tablets were allowed to cool before undergoing quality control checks to confirm their integrity and dosage accuracy.

FT-IR Compatibility Study:

Compatibility study of the tablet was carried out by FT-IR (PerkinElmer Spectrum Two). A background scan was conducted after cleaning the crystal with acetone. The tablet was crushed and 10-15 mg of powder was placed on a crystal of FT-IR and the scan. Peaks were compared with the pure Itraconazole.

Thermal Analysis:

Differential Scanning Calorimetry (PerkinElmer DSC 4000, IPER, Wardha) was used for the thermal analysis. Drug loaded filament were cut into a small piece (2-3 mg) and placed into the DSC pan. 10°C/min was the heat rate in the temperature range 40°C to 400°C. the peaks were compared with the standard.

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Characterization of tablets:

A Vernier calliper was used to measure the tablet's dimensions, and average values were calculated. A weight variation test was performed on 20 tablets using a digital weighing balance (CX200 Citizen scale, India). Hardness of the tablet was calculated using the Monsanto hardness tester.

Friability of tablets:

Friability of the tablets was evaluated by Friability Tester (Roche Electrolab). Ten pre-weighed tablets were placed inside a plastic chamber that rotates at a speed of 25rpm, with the tablet falling with each rotation. After 4 minutes (100 revolutions), tablets were dusted and re-weighed. The tablet's friability was measured in terms of weight loss and represented as a percentage.

Drug Content:

Drug content of 3D printed bi-compartmental tablet was determined individually for each compartment (n=3). The inner compartment containing Omeprazole was manually opened and the filled powder was collected separately, while the outer capsule shell printed using Itraconazole-loaded filaments was carefully crushed using a mortar and pestle. An accurately weighed amount of each sample was transferred to 100mL volumetric flasks, dissolved in appropriate media (Itraconazole in 0.1 N HCl and Omeprazole in 6.8 pH Phosphate buffer). The samples were sonicated for 10-15 min and filtered. Absorbance of Itraconazole and Omeprazole was measured at 261 nm and 304 nm respectively in a UV-Spectrophotometer (Shimadzu UV 1800). Drug content was calculated using respective calibration curves.

In Vitro Dissolution Testing:

USP Type II apparatus (DS8000 Lab India) was used at 50 rpm and 37 ± 0.5°C to study in vitro dissolution of tablets (n=3). Two step pH shift method was employed to stimulate gastrointestinal conditions. At first tablets were kept in 900 mL of 0.1 N HCl for 2 hours to assess the quick release of Itraconazole and the sample was withdrawn at defined intervals and analysed using a UV Spectrophotometer at 261 nm. Two hours later, the dissolution media was swapped to a 6.8 pH Phosphate buffer to initiate the delayed release of Omeprazole. The samples were injected out at defined time intervals and analysed using a UV-Spectrophotometer at 304 nm (12).

Result and Discussion:

Selection of Filament:

Among the above batches, batch F1 has a slightly yellowish colour and good mechanical strength and batch F2 have clear white colour and good mechanical strength. while batch F3 has slightly reduced mechanical strength. From the above batches, F2 was optimized and selected for printing of the tablets because of having constant thickness, colour and good mechanical strength.

Printing of the tablets:

Tablets printed using an FDM 3D printer (ThinCR Technologies, Pune) were slightly yellowish in colour and oval in shape. The tablet is designed for 400 mg and the filament contain 10 % Itraconazole. This means the porous tablet without filling the drug contains 40 mg Itraconazole, 60 mg Itraconazole was manually filled in the quick-release compartment and 10 mg Omeprazole in delayed release protected compartment. The tablet was sealed using the same Itraconazole-loaded filament. The printing parameters for compartments and sealing of the tablet are shown in the table no 2.

Table No 2: Compartments

Printing Temperature	175°C
Bed Temperature	50°C
Infill Density	100%
Infill Pattern	Line
Fan Speed	100%

Sealing of the Compartments

Printing Temperature	180°C
Bed Temperature	50°C
Infill Density	100%
Infill Pattern	Line
Fan Speed	00%

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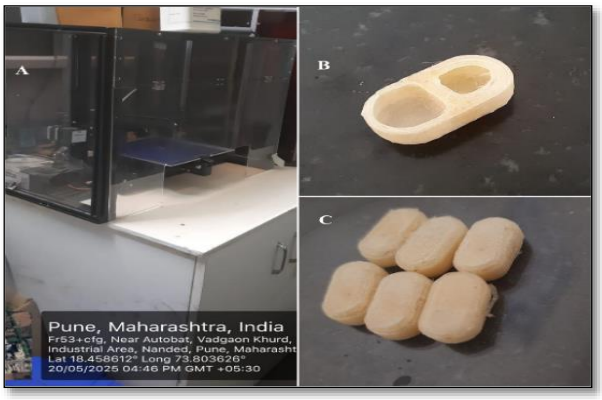

Fig 1: (A) FDM 3D Printer ThinCR Technologies, Pune **(B)** Bi-compartment Model **(C)** 3D Printed Tablets

FT-IR Compatibility study:

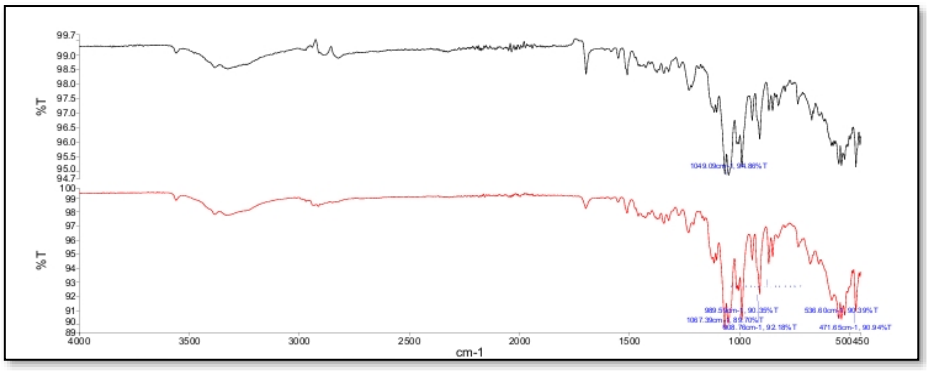

Fig 2: FTIR Spectra of pure Itraconazole and Formulation

The FT-IR spectra of pure itraconazole showed characteristic peaks at 1067.51 cm^{-1}, 989.57 cm^{-1} and 908.68 cm^{-1}. These peaks were retained in the tablet with PVA and sorbitol, with no major shifts or disappearance. New peaks around 3228.07 cm^{-1} and 2764.20 cm^{-1} were due to excipients. The absence of significant spectral changes indicates no chemical interaction, confirming compatibility of the tablet.

Thermal Analysis:

DSC Thermogram of pure itraconazole showed a sharp melting peak at 162.31°C, confirming its crystalline nature. In formulation, this peak became broader and less intense, which means itraconazole was partially converted to an amorphous form and was well mixed with excipients (PVA and Sorbitol). No new peaks were observed, so there was no chemical interaction. Omeprazole was not loaded in the filament because it is heat-sensitive and may degrade at high temperatures. The DSC study confirms that itraconazole is thermally stable and compatible with the excipients used.

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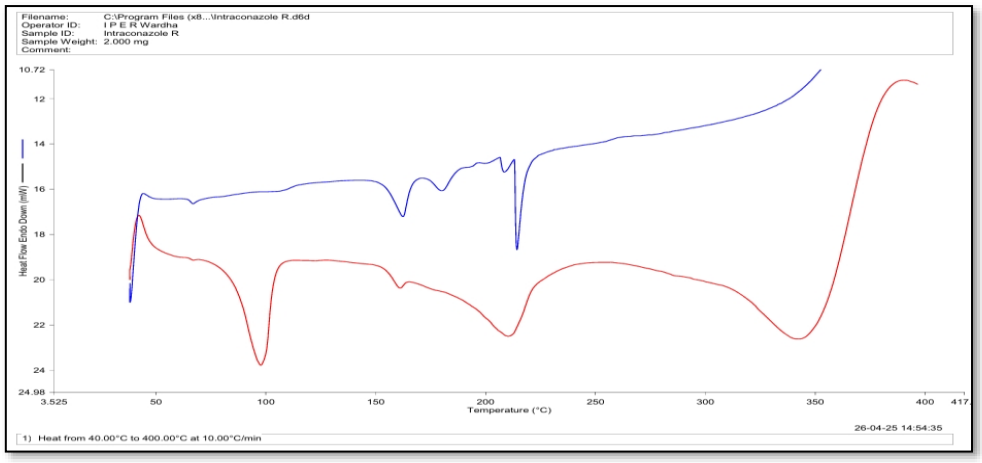

Fig 3: DSC Thermograms of pure Itraconazole and Formulation

Characterization of 3D Printed tablets:

Table no 3: Characterization of 3D Printed Tablets

Weight Variation	Hardness	Thickness
470.25 ± 2.5 mg	5.5 ± 5.5 Kg/cm^2	5.0 ± 00 mm

Friability Test:

Total Initial weight of 10 tablets was 4702 mg and final weight was 4693 mg. total weight loss was 8 mg

$$\% F = \{(W_I - W_F)/W_I\} * 100$$

Where, % F = Friability in percentage

W_I = Initial weight of tablets (4702 mg)

W_F = Final Weight of tablets (after the revolution) (4693 mg)

Friability percentage of the 3D printed tablets was found to be 0.19%, which is within the limit.

Drug Content:

Three 3D printed tablets were used to calculate drug content and the mean S.D. was taken.

Table no 4: Drug content of 3D printed tablets

Drug	Itraconazole	Omeprazole
Content	101.6 ± 0.2 mg	9.7 ± 0.4 mg

In Vitro Dissolution Study:

The in vitro dissolution profile shows successful dual-compartmental release behaviour of the 3D printed tablet. Itraconazole exhibited a rapid release phase from the outer shell followed by sustained release from an internal compartment, reaching 88.83% within 60 minutes and gradually increasing to 101.13% by 240 minutes, indicating complete drug release. Under acidic conditions, the pH-sensitive compartment containing omeprazole released 13.74% of its content in 120 minutes, confirming

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acidic protection. A sharp increase in release was observed upon exposure to phosphate buffer (pH 6.8), with 98.41% released by 240 minutes.

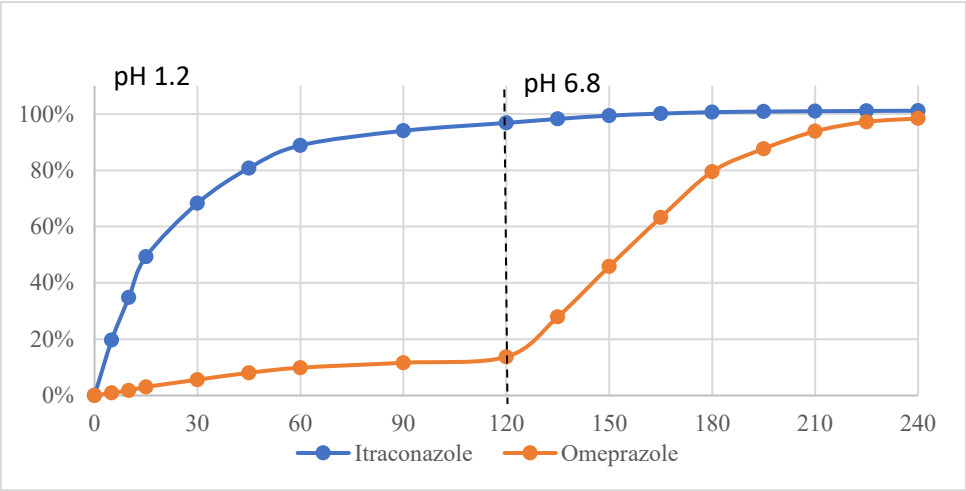

Fig 4: In vitro dissolution study of 3D printed tablet

Conclusion:

A bi-compartment itraconazole and omeprazole tablet of dual release profile was created using an FDM 3D printer. Itraconazole was incorporated into a PVA and sorbitol filament for immediate release and compartments were manually filled with Itraconazole and Omeprazole for sustained and delayed release. As a result, itraconazole showed an initial rapid release reaching 88.83% within 60 minutes and then gradually increased up to 101.13% by 240 minutes in acidic conditions. Omeprazole, which was manually filled into a protected compartment, remained stable in acidic media with only 13.74% release in 120 minutes and exhibited a sharp increase to 98.41% in alkaline pH. Drug polymer compatibility was confirmed by FT-IR study, and thermal stability by DSC. Physical evaluation of the validated integrity of the tablet. In conclusion, the study highlights the potential of the FDM 3D printer in formulating personalized dual drug delivery systems with precise control over sequential drug release.

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Conflict of Interest:

The author declares no conflict of interest.

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Tehre R. conducted the experimental work and data analysis and Dr. Sakhare R. supervised and guided the research.

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