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Formulation Development and In Vitro Evaluation of Itraconazole Layered Granules

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Abstract

With a wide range of action against several fungal species, including candidiasis and aspergillosis, itraconazole is an efficient and well-tolerated synthetic triazole antifungal. HPMC E5 and HPC were used as formulation factors in the fluid-bed layering process to effectively generate itraconazole-layered granules. To determine how they affected granule properties and medication release, researchers used a factorial experimental design. The drug-excipient compatibility was validated by DSC analysis, and the formulations exhibited acceptable physicochemical features and sufficient drug content. The correlation between most answers and the regression models was excellent, and the range of itraconazole release after 45 minutes was 76.4–98.4 percent. The drug release was decreased as the polymer concentration increased, with HPMC E5 having a stronger effect than HPC. The results showed that factorial design is a good fit for improving controlled-release itraconazole-layered granules.

Keywords: Itraconazole, Granules, Fluid-bed, Antifungal, Solubility

I.INTRODUCTION

Itraconazole (ICZ) is a trizole group member and a broad-spectrum antifungal medication used to treat both systemic and localised fungal infections. Itraconazole has a very low pKa value (3.7) and is very hydrophobic. Due to its low water solubility and slow digestion, ICZ is considered a Biopharmaceutical Classification System II medicine. low bioavailability and inter-individual variability in plasma drug concentrations are consequences of oral delivery of ICZ due to its low water solubility. The solubility of ICZ is more concentrated at acidic pH (4µg/ml) than basic pH (1ng/ml), indicating that its solubility is pH dependant. In contrast, ICZ has a very lipophilic nature (log P=6.2), which allows it to readily cross the intestinal barrier. This points to the major cause of decreased plasma concentrations, which is the poor aqueous solubility.

Many recent studies have detailed various ways for improving the water solubility and oral bioavailability of ICZ. These efforts include preparing amorphous ICZ, cyclodextrin complexations, solid dispersions with eudragits, and particle tailored compositions. To increase the oral bioavailability of lipophilic medications, solid dispersions have shown to be an effective method. "The dispersion of one or more active ingredients in an inert excipient or matrix" describes solid dispersions, which can contain active compounds in amorphous, solubilised, or finely crystalline forms. Solid dispersions prepared using inert matrix made from various polymers have encountered difficulties with method, stability, and other issues. These difficulties paved the way for the use of lipids and other non-traditional ingredients in the preparation of solid dispersions. There is a wide variety of lipid formulations available, from those that simply use dietary triglycerides to dissolve the medications to those that employ complicated mixes of triglycerides, partial glycerides, surfactants, cosurfactants, and solvents.

Nevertheless, research into lipid-mediated solid dispersions has focused on filling hard or soft gelatin capsules with a mixture of melted lipids and a medication. The produced solid dispersions need to have the right flow properties to be turned into a solid oral dose form. The development of free-flowing powders from suspensions and solutions, whether aqueous or non-aqueous, is a common use of the spray drying process.

II.REVIEW OF LITERATURE

Kaoud, Rashad et al., (2025) Although itraconazole is an efficient antifungal medication, its short duration of action and poor skin penetration make it an inadequate topical treatment. The current research is focused on creating and evaluating a formulation of itraconazole (TCZ) in a prolonged-release niosomal gel (NSM-Gel) with the goal of making antifungal treatments for skin infections more effective. A thin film hydration approach was used to manufacture TCZ-loaded NSM-Gel, which made use of a variety of non-ionic surfactants, including tweens and spans. Polydispersity Index (PDI), particle size (PS), entrapment efficiency (EE%), pH, and TCZ

niosomal gel formulations were evaluated. Finally, the best-selected formula (TN4) underwent further testing for antifungal activity in vitro, physical stability, scanning electron microscopy (SEM), in-vitro release, and zeta potential (ZP). The created NSM-Gel has an acceptable EE% ranging from 86.41 to 98.44%, a PS ranging from 4.12 to 8.17 µm, and a PDI ranging from 0.22 to 0.39. The NSM-Gel effectively produced a delayed release effect when it released TCZ. TN4 exhibited a delayed release profile with an increased EE% (100.00% ± 1.25% after 18 hours). The findings showed that spherical-shaped vesicles do in fact exist. Research on the chemical formula TN4's physical stability revealed promising results. In addition, TN4 outperformed the commercial product Venzole® gel 1% in terms of antifungal efficacy against Candida albicans, with an inhibition zone that was 2.40 cm greater than 1.50 cm. This study proved that the NSM-Gel may be used to treat fungal infections by transdermal TCZ delivery, as anticipated, with a delayed release effect.

Patil, Manisha & Kshirsagar, Sanjay. (2024) This study compared nine different itraconazole (ITZ) liquid self-micro-emulsifying drug delivery system (L-SMEDDS) formulations. Clove oil(40%), Kolliphor CS 20(40%), and polyethylene glycol (PEG) 400 (20%) made up the most effective formulation (ILS6). With a polydispersity index (PDI) value ranging from 0.47 to 0.73 and a droplet size ranging from 130 to 165 nm—far smaller than 200 nm—ILS6 demonstrated the formation of an emulsion with nanosized droplets and even spreading. With its ultimate drug loading capacity and remarkable stability across a wide range of circumstances, the final formulation was ready for use. The optimised L-SMEDDS was transformed into S-SMEDDS, a free-flowing powder devoid of medication interactions, by solidifying it with sylloid 244 FP. Combining S-SMEDDS with various excipients allowed for the effective formulation of the effervescent system. Both the stability and quality control tests were successful for the chosen effervescent system. The release profile of the effervescent system was fast and not affected by pH. The effervescent system and SMEDDS worked together to make itraconazole more soluble and easier to dissolve.

Kumar, Ashish et al., (2022) Among the many widely used formulation techniques in the cosmetics and pharmaceutical industries, nanoemulsions stand out. Nanoemulsions typically include an oil phase that is scattered inside a continuous water phase. A variety of fungal infections may be effectively treated with the antifungal medicine itraconazole. It belongs to the class of medicines known as triazoles. Because of its limited aqueous solubility, the antifungal drug itraconazole has a low bioavailability. For the purpose of this research preformulation study, we examined compatibility using Fourier transform infrared (FTIR) analysis. The wide area was used to optimise the surfactant-to-co-surfactant ratio (Smix) in the manufacture of istraconazole-loaded nanoemulsions based on the ternary phase diagram. The Smix preparation process begins with precisely weighing the optimised surfactant and co surfactant, followed by vortexing the mixture for 5-10 minutes. A zeta potential of -15.9 mV and a particle size and PDI value of 159.21 nm were used to illustrate the stability of the produced nanoparticles.A uniform distribution of tiny, spherical optimised nanoemulsion formulations filled with itraconazole was shown by the transmission electron microscope. The purpose of these investigations was to determine if nanoemulsions might increase the oral bioavailability of itraconazole.

Singh, Yogesh & Bhardwaj, Anjana. (2021) Ophthalmic, rectal, vaginal, and cutaneous channels are all part of the topical drug administration system, which allows for localised medication delivery to any part of the body. Topical medication delivery systems mostly use the skin since it is one of the most permeable organs on the human body. Fungus may cause a wide range of skin illnesses. Mycoses like candidiasis, athlete's foot, and ringworm may be effectively treated with antifungal medicine, a pharmaceutical fungicide. In order to eliminate the fungal organism without causing harm to the host, antifungals take use of the fact that fungal cells are different from mammalian cells. Treatments for fungal infections often include the use of itraconazole (ITZ). The first pass effect and poor water solubility contribute to its low bioavailability of 55%. So, we set out to create a hydrogel that would be invasives-free and filled with itraconazole. Using ethanol, terpene (limonene), and Phospholipon 90H, the traditional thin layer evaporation process was used to create invasives loaded with ITZ. A hydrogel was created by combining the optimised ITZ-loaded invasives with a carbopol 934p solution ranging from 0.5% to 2%. This hydrogel is designed to enhance the ease of superficial application. There was no evidence of drug-excipient interaction in FT-IR investigations. Parameters such as pH, gel strength, drug content, spread ability, extrudability, washability, and stability tests were used to assess the hydrogel formulation. The OIGF4 formulation, which comprises 2%w/w carbopol 934p, exhibited a 99.12% drug content and a 99.78% drug release after 72 hours. Making the formulation more pharmaceutically acceptable is also a focus of the current effort.

Basher, Taha & Jasim, Entidhar. (2020) For both local and systemic fungal infections, doctors use itraconazole (ITZ), an antifungal medicine (BCSII). Antifungal prophylaxis with ITZ is also used to individuals with impaired immune systems. By manufacturing ITZ as floating microparticles, the work aims to solve the two difficulties of its poor solubility and pH dependence. To begin, oil-in-water solvent evaporation was used to create pH-dependent floating microparticles. Out of all the formulas tested, the one with the optimal pH-dependent composition (F7) was chosen. This formula included 200 mg of ITZ, 800 mg of EC, 200 mg of HPMC 15cps, and 2 ml of safflower oil.Next, F7 was compared to a preferred formula for pH-independent ITZ floating microparticles. This formula included 200 mg of ITZ, 200 mg of HPMC15cps in the first coat, 800 mg of EC, 200 mg of HPMC 15cps in the second coat, and 2 millilitres of safflower oil. It was prepared using a dual coating solvent evaporation method, with the first coat providing relatively pH-independent solubility and the second coat acting as a bouncy producing agent. The surfactant in both instances was polyvinyl alcohol (PVA). A number of evaluation parameters were applied to the prepared floating microparticles, including yield percent, drug loading and drug entrapment efficiency (EE), particle size analysis, in vitro bouncy, drug release, FTIR, DSC, and XRD studies.

Thakkar, Hetal et al., (2020). Itraconazole is a class II medicine with limited bioavailability; thus, it is important to develop and test liquisolid compacts of this medication. Aerosil 200 served as the coating material, Alfacel PH 200 as the carrier, and PEG 600 as the non-volatile solvent. Compressed tablets were made from a dry powder that was formed by combining an itraconazole solution with a coating substance and a carrier. When compared to both standard tablets and commercially available capsules, the optimised formulation showed a much greater rate of drug dissolution (90.73% in 90 minutes). In this version, the antifungal action is still there. Oral bioavailability was improved by the formulation, as seen by higher Cmax and AUC0-24 values compared to the plain medication. Both at ambient temperature and under accelerated circumstances, the formulation maintained its stability.

Ghurghure, Shrishail et al., (2019). For both systemic and localised fungal infections, doctors use itraconazole, a product of the imidazole class of drugs. The medication belongs to BCS Class II and has a very poor water solubility (1-4ng/ml). Itraconazole has various negative effects, hence it is not suggested to be used orally. This study set out to solve the problem of itraconazole's poor solubility, permeability, and stability by creating a topical hydrogel formulation of nano sponges loaded with the drug. Utilising varying amounts of ethyl cellulose, polyvinyl alcohol, and dichloromethane, an itraconazole-loaded nano sponge was created utilising the emulsion solvent diffusion technique. Research into the nano sponges' physical properties, drug entrapment efficiency, drug content %, yield percentage, drug polymer compatibility, and solubility was undertaken. Nano sponges' surface morphology and particle size characterisation were carried out. Scanning electron microscopy revealed that nano sponges were round and spongy. A range of 42.75% to 73.10% was determined for the drug entrapment efficiency. We examined the pH, viscosity, and in vitro drug release of the optimised nano sponge formulation after loading it into hydrogel using Carbopol 940. F4 had a medication release rate of 70.62% among the produced nano sponge formulations. Itraconazole nano sponge hydrogel was shown to potentially enhance solubility and medication release.

III.MATERIALS AND METHODS

Materials

Metrochem API Pvt. Ltd. of Hyderabad, India, supplied the itraconazole. The pharmaceutical-grade hydroxypropyl methylcellulose (HPMC E5) and hydroxypropyl cellulose (HPC) were sourced from reliable vendors in India. Loba Chemie Pvt. Ltd. of Mumbai, India, supplied the crospovidone and calcium carbonate. The following chemicals were procured from S.D. Fine-Chem Ltd. of Mumbai, India: dichloromethane, isopropyl alcohol, sodium lauryl sulphate, Tween 80, diethyl phthalate. Without further purification, all chemicals, reagents, and solvents utilised in the investigation were of analytical grade.

Preparation of Granules

The inert sugar granules served as initial cores for the fluid-bed layering process, which was used to generate itraconazole-layered granules. Some of the ingredients were sodium lauryl sulphate, calcium carbonate, crospovidone, isopropyl alcohol, and dichloromethane. The amount of mannitol used to alter the batch size was 2000 g. A fluid-bed processor was used to coat 700 g of 30/40-mesh sugar granules with the medication solution,

with the help of a peristaltic pump. An atomizing pressure of 2 bar, a pump speed of 2 rpm, and an inlet temperature of 45°C were all used to conduct the operation. After that, the granules were dried for 10 minutes at 45°C.

Drug–Excipient Compatibility

Differential scanning calorimetry was used to evaluate the drug-excipient compatibility. A volume of 50 mL of nitrogen was used to heat the sample, which weighed around 5 mg, from 50 to 300°C at a rate of 10°C per minute. For changes in thermal behaviour, the thermograms of pure itraconazole and the granules that were formed were compared.

Factorial Design

Researchers used a factorial design to examine the effects of HPMC E5 (X_1) and HPC (X_2) at three different concentration levels. We used the polynomial equation to assess the answers:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2$$

where Y is the response, b_0 is the intercept, b_1 and b_2 are the linear coefficients, b_{12} is the interaction coefficient, and b_{11} and b_{22} are the quadratic coefficients.

Characterization of Granules

The distribution of granule sizes was discovered using sieve analysis. The morphology and surface texture were assessed by microscopic analysis and rated on a scale from 1 to 10. The bulk density was calculated based on the mass and the volume occupied by the granules. The moisture content was determined using the Karl Fischer technique.

Assay of Itraconazole

The concentration of Itraconazole was assessed using UV-visible spectrophotometry with a Shimadzu UV-1800 spectrophotometer at a wavelength of 258 nm. Standard and sample solutions were formulated utilising methanol in a ratio of 99:1. The analytical technique was assessed for linearity, accuracy, and precision.

In Vitro Drug Release

The in vitro drug release was assessed utilising a USP Type II dissolving device at a temperature of 37 ± 2°C and a rotation speed of 100 rpm. Granules corresponding to 100 mg of itraconazole were immersed in 900 mL of the chosen pH 1.2 dissolving medium. Five-milliliter samples were extracted at specified intervals and substituted with an equivalent volume of new media. The concentration of the drug was assessed using spectrophotometry, and the cumulative percentage of drug release was computed.

IV.RESULTS AND DISCUSSION

Investigation of Physicochemical Compatibility of Drug and Excipients

Differential scanning calorimetry is an effective thermal analysis method for detecting endothermic and exothermic transitions linked to physical or chemical alterations in medicinal substances. The DSC thermograms for pure itraconazole (A) and itraconazole-loaded granules (B) are illustrated in Figure 1.

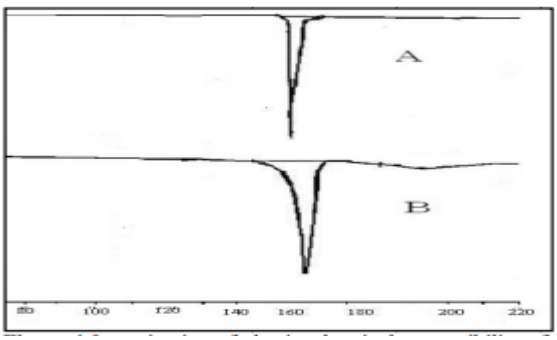

Figure 1. DSC thermograms showing the physicochemical compatibility of itraconazole with the formulation excipients

The thermograms indicated no significant change in the distinctive melting properties of itraconazole after its integration into the granules. The lack of notable alterations in the thermal properties indicated that there was no considerable physicochemical incompatibility between itraconazole and the formulation's excipients. These results demonstrated an acceptable compatibility of the medication with the chosen formulation elements.

Regression Analysis

The regression coefficients derived for the various answers are displayed in Table 1. The elevated coefficients of determination (R^2) achieved for size distribution, surface roughness, bulk density, test, and drug release demonstrated a robust correlation between the chosen formulation factors and their respective outcomes. The somewhat diminished R^2 value for moisture content suggested that the chosen formulation factors insufficiently accounted for the fluctuations in this response.

Table 1. Results of regression analysis

Response	b_0	b_1	b_2	b_{12}	b_{11}	b_{22}	R^2
Size distribution	94.5434	3.8349	0.8067	−0.9850	−2.6550	0.0800	0.9979
Surface roughness	8.8889	1.8333	0.1667	−0.2500	−1.8333	0.1667	0.9932
Bulk density	0.7889	−0.1167	−0.0167	0.0250	0.1167	0.0167	0.9829
Moisture content	1.5322	−0.0083	0.0233	0.0575	0.0217	0.0267	0.4695
Assay	22.0267	0.2983	0.1433	−0.2325	−0.2550	0.0900	0.9528
Drug release	94.0944	−10.0067	−1.2417	−0.9725	−5.2667	−0.6317	0.9970

Size Distribution

The granule size distribution, ascertained using sieve analysis, varied from 86.14% to 95.95% within the established size parameters. The regression model demonstrated a remarkable connection with the experimental data, yielding a R^2 value of 0.9979.

The regression analysis demonstrated that both formulation factors had a substantial impact on the size distribution ($p < 0.05$). HPMC E5 (X_1) demonstrated a more significant effect than HPC (X_2), as seen by its higher regression coefficient. The affirmative coefficients for the linear variables indicated that elevating the polymer concentrations from 2% to 6% enhances the fraction of granules within the targeted size range. This phenomenon may be ascribed to the adhesive characteristics of the polymers, which facilitated particle clustering and diminished the occurrence of suboptimal particles.

The fitted regression equation was:

$$\text{Size Distribution} = 94.5434 + 3.835X_1 + 0.8067X_2 - 0.985X_1X_2 - 2.655X_1^2 + 0.08X_2^2$$

Shape and Surface Roughness

The morphology and surface texture ratings of the synthesised granules varied between 5 and 9, signifying substantial differences among the formulations. The regression model exhibited a robust association between the formulation factors and the answer, yielding a R^2 value of 0.9932.

HPMC E5 (X_1) had a more significant impact on the morphology and surface properties compared to HPC (X_2). Elevating the HPMC E5 concentration from 2% to 6% enhanced the morphology and surface properties of the granules. The enhancement can be ascribed to the enhanced adhesive properties of HPMC E5, which facilitated a more consistent application of the drug-polymer layer and minimised surface imperfections.

The fitted regression equation was:

$$\text{Shape and Surface Roughness} = 8.8889 + 1.8333X_1 + 0.1667X_2 - 0.25X_1X_2 - 1.8333X_1^2 + 0.1667X_2^2$$

Bulk Density

Bulk density is a significant micromeritic characteristic since it can affect capsule filling, coating, blending, segregation, and estimations of batch size. The mass density of the synthesised granules varied between 0.8 and 1.1 g/mL, and the regression analysis demonstrated a strong connection with the empirical data ($R^2 = 0.9829$).

The regression analysis demonstrated that HPMC E5 (X_1) exerted a more significant impact on bulk density compared to HPC (X_2). The adverse linear coefficient of X_1 suggested that raising the concentration of HPMC E5 led to a decrease in bulk density. This conduct could be linked to alterations in granule composition and the development of bigger, less densely arranged granules with less fines.

The fitted regression equation was:

$$\text{Bulk Density} = 0.7889 - 0.1167X_1 - 0.0167X_2 + 0.025X_1X_2 + 0.1167X_1^2 + 0.0167X_2^2$$

Moisture Content

The moisture level of the produced granules was assessed with the Karl Fischer technique. The regression analysis yielded a R^2 value of 0.4695, signifying a somewhat feeble correlation between the chosen polymer concentrations and moisture content. The statistical evaluation revealed that variations in HPMC E5 and HPC concentrations did not markedly influence the moisture content of the granules ($p > 0.05$). Consequently, throughout the examined concentration ranges, the chosen formulation factors did not significantly influence the moisture content.

Assay of Itraconazole

The test findings indicated that fluctuations in the levels of HPMC E5 and HPC did not markedly influence the itraconazole concentration in the granules ($p > 0.05$). The regression model had a R^2 value of 0.9528, signifying a robust overall fit. Nonetheless, the lack of statistical significance for the specific formulation factors indicated that the fluctuations in polymer concentration did not substantially affect medication content. This discovery demonstrated that itraconazole was consistently integrated into the granules throughout the examined formulations.

In Vitro Drug Release Study

The in vitro drug-release characteristics of itraconazole granules are illustrated in Figure 2. The proportion of itraconazole released after 45 minutes varied between 76.45% and 98.45% among the various formulations. The regression model demonstrated a remarkable connection with the experimental data, yielding a R^2 value of 0.9970.

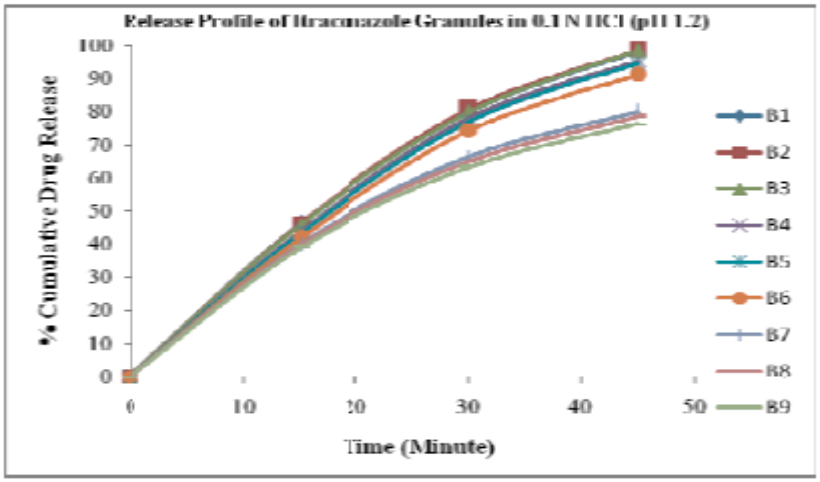

Figure 2. In vitro release profile of itraconazole granules in 0.1 N HCl (pH 1.2)

The findings demonstrated that both HPMC E5 (X_1) and HPC (X_2) had a substantial impact on medication release ($p < 0.05$). HPMC E5 demonstrated a more significant impact compared to HPC, as seen by the higher absolute value of its regression coefficient. The negative coefficients for the linear variables suggested that elevating the polymer concentrations led to a decrease in medication release.

The reduction in drug release as polymer concentration rises may be due to the development of a denser and more viscous polymeric coating surrounding the drug-encapsulated granules. This layer can extend the diffusional

pathway and impede the ingress of the dissolving medium into the granules, thereby diminishing the rate of drug disintegration and release.

The fitted regression equation for drug release at 45 min was:

Drug Release at 45 min = $94.0944 - 10.0067X_1 - 1.2417X_2 - 0.9725X_1X_2 - 5.2667X_1^2 - 0.6317X_2^2$

V.CONCLUSION

The study showed that HPMC E5 and HPC considerably affected the formulations' physicochemical characteristics and in vitro drug-release behaviour, and itraconazole-layered granules were effectively generated utilising the fluid-bed layering approach. The itraconazole and the chosen excipients were found to be satisfactorily compatible according to the DSC analysis. Thanks to the factorial design, we were able to reliably evaluate the impacts of the formulation variables, and the generated granules showed appropriate size distribution, surface properties, bulk density, moisture content, and drug assay. With HPMC E5 having a bigger impact than HPC, increasing the polymer concentration increased the distribution of granule sizes but gradually lowered the release of itraconazole.

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