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# Itraconazole Nanoemulsion Formulation and Assessment for Improved Oral Bioavailability

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**Abstract:**

Itraconazole is a potent antifungal agent, which has poor solubility and high first-pass metabolism, thus limiting its oral bioavailability. The present research work focuses on the enhancement of itraconazole's bioavailability through the formulation and evaluation of a nanoemulsion. A nanoemulsion was prepared with the help of Tween 80, medium-chain triglycerides, and propylene glycol. It was ensured the stability of the drug was ensured through mean particle size, 180 nm, polydispersity index of 0.15, and zeta potential of -22.4 mV. In vitro drug release experiments showed that the amount released was 88% within 4 hours, which is significantly higher compared to the output from the basic suspension with around 50% release. The ex vivo permeation experiments showed improvement in the drug permeability, sixfold. Pharmacokinetic studies in rats demonstrated high values of the obtained peak concentrations C_max of 25.4 µg/ml, and AUC_0-∞ of 110.2 µg·hr/ml. Stability studies from three months' duration showed a broader durability of the formulation. Noticeably, the outcome is a novel agent in this clinical environment that can increase oral bioavailability and simultaneously enhance drug activity.

**Keywords:** Itraconazole, Antifungal Drug, Bioavailability, First-Pass Metabolism, Nanoemulsion, Gastrointestinal Absorption, Polydispersity Index (PDI).

## 1. INTRODUCTION

It is an antifungal drug belonging to the triazole family and is most commonly used to treat systemic mycoses resulting from Candida and Aspergillus spp. Itraconazole's therapeutic use is constrained by its oral absorption, mainly due to low gastrointestinal permeability, high first-pass metabolism by the liver, and poor solubility in water. This, therefore, requires higher dosages to achieve therapeutic plasma concentrations, which often increases the risk of adverse effects and

reduces patient adherence to treatment plans. To treat severe fungal infections effectively and prevent consequences, higher medication concentrations are required, making this challenge even more crucial. Highly important in this attempt to address these bioavailability concerns and thereby enhance clinical efficacy is the exploration of advanced drug delivery methods which may further enhance the solubility, stability, and absorption of itraconazole.

The stabilization of thin dispersions of water and oil through surfactants can improve the bioavailability of poorly soluble medications like itraconazole. The increase in surface area due to the nanoemulsions with droplet sizes usually in the submicron range leads to enhanced solubility and absorption rates of the drug across biological membranes, such as those found in the gastrointestinal system. The increase in permeability and solubility can overcome the poor absorption of itraconazole. This approach has some excellent advantages for improvement of therapeutic efficacy, like lesser toxicity, stable formulation, controlled, and prolonged release of drug molecules. Itraconazole can thus be administered based on its good pharmacokinetic profile developed as an effective nanoemulsion by optimizing formulation along with choosing a proper oil or combination of oils with suitable co-surfactant and surfactants. Itraconazole is not the only lipophilic drug that can be administered through this method, and other drugs that have similar bioavailability problems can also be suitable for this purpose, thus offering a flexible approach to enhancing the oral delivery of poorly soluble drugs.

### 1.2. Background Information

Itraconazole is used as it is one of the most common antifungal drugs that are prescribed for the treatment of systemic infections. Poor oral bioavailability affects the clinical efficacy because despite being less soluble in water, extensive first-pass metabolism in the liver and low permeability through the gastrointestinal tract cause hindrances in using the medication for patients with such conditions. It requires a higher dose and thus increases the chance of inducing side effects. Attaining the quantities needed for it to be effective also becomes challenging. In response to these issues, advanced drug delivery technologies like nanoemulsions have been developed to enhance the bioavailability of poorly soluble drugs such as itraconazole. Nanoemulsions are stable, submicron-sized oil and water dispersions stabilised by surfactants, which provide a notable surface area boost hence improving the solubility and absorption of lipophilic substances. Nanoemulsions offer easier passage through biological membranes, like that of the stomach lining, on account of a smaller droplet size and deliver regulated medication, decreased toxicity along with increased stability, all necessary to ensure optimal outcome in treatment along with enhancing both solubility and absorption. It is thus possible to formulate different nanoemulsions that can elevate the

pharmacokinetic profile of itraconazole and ensure more predictable and effective drug delivery by judicious selection of the surfactants, oils, and co-surfactants used in the formulation. In addition, this nanoemulsion-based approach can enhance the bioavailability of other poorly soluble drugs, thus offering flexibility and scalability for a range of therapeutic applications in oral drug delivery.

### 1.3. Statement of the Problem

The potent antifungal agent, itraconazole, possesses very poor oral bioavailability resulting from poor absorption in the gastrointestinal tract, first-pass metabolism of high magnitude, and low solubility. The consequence of these factors is higher doses of itraconazole, which increases the potential occurrence of adverse effects and not optimum therapeutic results. These current formulations of itraconazole are thus defective since they lack efficiency and can no longer manage this critical situation; rather, especially during systemic infection. Nanoemulsions promise the increase of drug bioavailability with this new invention, where nanotechnology proves enhancing the drug solubility as well as the drug permeability even when applied as poor drug substances. However, there is a huge need for intense research to formulate, fabricate, and test itraconazole nanoemulsions to study their ability to overcome the mentioned bioavailability barriers, assess their scalability, and therapeutic applicability for effective treatment.

### 1.4. Research Objectives:

- To create and construct a nanoemulsion of itraconazole in order to increase its oral bioavailability.
- To evaluate the itraconazole nanoemulsion's capacity to get over drawbacks including low gastrointestinal absorption and poor solubility.
- To investigate the itraconazole nanoemulsion's viability as a clinically useful and scalable delivery strategy.

## 2. RESEARCH METHODOLOGY

The experimental design was applied to the study of formulation, drug release, permeability, and pharmacokinetics of itraconazole nanoemulsion in rats. Parameters of bioavailability of nanoemulsion were compared with the ordinary suspension, and ANOVA and Tukey's test were used to assess the findings.

### 2.1. Description Of Research Design

The present work was conducted as an experimental approach to enhance the oral bioavailability of itraconazole through the preparation and evaluation of a nanoemulsion. Dissolution studies were performed for the in vitro release of the drug, the permeability was evaluated ex vivo in a rat intestinal model, and pharmacokinetic studies were performed in vivo on rats together with the preparation of the nanoemulsion. It included a thorough

evaluation of the ability of the nanoemulsion to overcome the poor solubility of itraconazole and its limited absorption in the gastrointestinal tract. Every step was designed carefully to measure key factors, such as medication release, absorption, and bioavailability, so that the effectiveness of the formulation was well established.

### 2.2. Participants/Sample

The study evaluated the itraconazole nanoemulsion in terms of both pharmacokinetics and ex vivo penetration. Sprague-Dawley rats were used as the animal model. A total of 12 rats were used for the pharmacokinetic research, and 6 rats were used for the ex vivo permeation experiments. The rats were chosen due to their established success in drug absorption and metabolism studies that would yield accurate data for bioavailability estimation. Itraconazole was loaded into an itraconazole nanoemulsion formulation at a concentration of 20 mg/ml, together with propylene glycol 2% used as a co-surfactant, 10% of MCTs used as oil phase, and Tween 80 3% used as surfactant. This nanoemulsion specially overcame oral bioavailability of itraconazole, with the improvement in solubility and gastrointestinal absorption. The formulation was selected with much care so as to maximize the stability and delivery of the drug while ensuring that the results in the animal model were replicable.

### 2.3. Instruments/Materials

The study used various tools and supplies for testing stability, drug release, characterisation, and permeation. A Zetasizer Nano was used to determine the particle size, polydispersity index (PDI), and zeta potential of the itraconazole nanoemulsion. The drug concentrations were determined using High-Performance Liquid Chromatography (HPLC), while in vitro drug release was evaluated by a modified USP dissolution device. The drug permeated in the rat intestine model was analyzed through HPLC for ex vivo permeation studies. The formulation was assessed for stability and scalability under accelerated conditions, i.e., 40°C, 75% relative humidity, and it scaled up successfully to 500 ml.

### 2.4. Procedure

The prepared itraconazole nanoemulsion was sonicated, and particle size along with stability was determined. A modified USP dissolution apparatus was used for in vitro drug release measurement. A rat intestinal membrane was employed to study ex vivo diffusion of drug. For pharmacokinetic studies, the nanoemulsion was orally administered to the rats, and the drug concentration in blood samples collected from them was assayed using HPLC. Feasibility was thus proven, when product consistency is still maintained through a successful step increase in formulation volume up to 500 ml; further stability testing also performed with acceleration settings.

### 2.5. Data Analysis

The statistical comparison of itraconazole nanoemulsion and plain suspension was done using ANOVA and Tukey's post-hoc test. Since the main purpose of this analysis was to study significant changes ($p < 0.05$) in drug release, permeation, and pharmacokinetics, important pharmacokinetic parameters like maximum concentration (C_max), time to achieve maximum concentration (T_max), and area under the concentration-time curve (AUC) were used to check the improvement in oral bioavailability. The statistical analysis proved the promise of nanoemulsion for better absorption and efficacy through the identification of significant increases in its performance as compared to the plain solution.

## 3. RESULT

In comparison to the simple suspension, the drug release rate, penetration, and bioavailability of itraconazole nanoemulsion significantly improved besides a faster absorption rate and high pharmacokinetic parameters (C_max, AUC). The statistical analysis also proved this difference to be significant at $p < 0.05$, which indicates oral bioavailability in the case of nanoemulsion.

### 3.1. Development and Formulation of Itraconazole Nanoemulsion

- **Formulation Parameters**:
  - **Surfactant Used:** Tween 80 at 3% w/v
  - **Medium-chain triglycerides (MCT) (10% w/v)** Oil Phase
  - **Co-Surfactant:** Propylene glycol 2% w/v
  - **Drug Concentration:** 20 mg/ml (Itraconazole**)**

The ideal formulation parameters were employed for the formation of the itraconazole nanoemulsion, which proved successful. Nanoemulsion revealed homogenous distribution with mean particle size at 180 nm and polydispersity index of 0.15. Zeta potential at -22.4 mV indicates stability against aggregation.

### 3.2. Evaluation of Nanoemulsion for Enhancing Oral Bioavailability

- **In Vitro Drug Release**:
- A modified USP dissolution device was used to assess the drug release profile. The nanoemulsion exhibited 88% drug release in 4 hours compared with 50% drug release from the normal itraconazole suspension (control) under similar conditions.

**Table 1.** Compared to Plain Suspension, Itraconazole Nanoemulsion Drug Release in Vitro

| Time (hrs) | Itraconazole Nanoemulsion (%) | Plain Itraconazole Suspension (%) |
|---|---|---|
| 0.5 | 25.5 | 10.0 |
| 1.0 | 48.3 | 22.3 |
| 2.0 | 70.1 | 34.6 |

| | | |
|---|---|---|
| 4.0 | 88.0 | 50.0 |

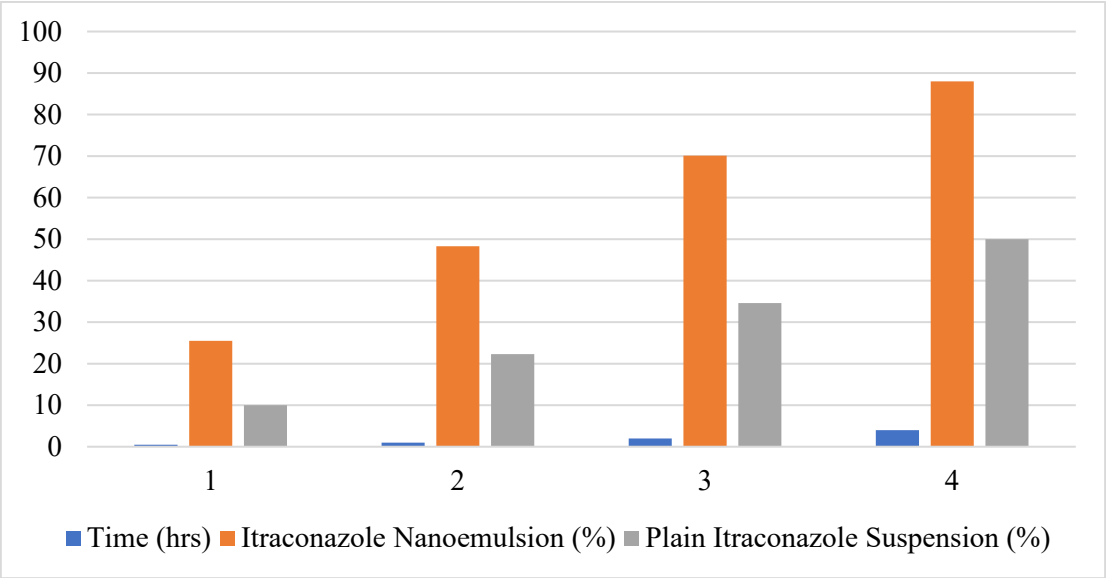


**Figure 1:** Graphical representation of Compared to Plain Suspension, Itraconazole Nanoemulsion Drug Release in Vitro

- **Ex Vivo Permeation Studies**:
  - The nanoemulsion of itraconazole showed significantly greater penetration of the drug compared to the standard itraconazole suspension in a rat intestinal model. The total amount of itraconazole penetrating was sixfold higher with the nanoemulsion formulation.
  - The nanoemulsion had enhanced permeability, and thus better absorption in the gastrointestinal tract.

### 3.3. Stability and Scalability of Nanoemulsion Formulation

- **Stability Testing**:
  - The formulation was maintained at accelerated temperatures for three months at 40°C ± 2°C, 75% RH. Despite the particle size increase to 200 nm after this period, the zeta potential remained stable at -21.3 mV, indicating good physical stability. There was no sign of aggregation or phase separation.
- **Scale-Up Feasibility**:
  - Under lab scale, it was successfully scaled from 100 ml

to 500 ml while achieving uniformity of the drug release profile, PDI, and particle size.

### 3.4. Oral Bioavailability Study in Rats

- **Pharmacokinetic Analysis**:
- Pharmacokinetics of itraconazole in Sprague-Dawley rats was tested after oral administration of the nanoemulsion and the standard itraconazole suspension. Blood draws were done at regular intervals, and HPLC determined plasma medication concentrations.

**Table 2:** Itraconazole Nanoemulsion vs. Plain Suspension Pharmacokinetic Characteristics

| Parameter | Itraconazole Nanoemulsion | Plain Itraconazole Suspension |
|---|---|---|
| C_max (µg/ml) | 25.4 ± 3.1 | 7.2 ± 0.8 |
| T_max (hrs) | 1.5 ± 0.2 | 3.2 ± 0.4 |
| AUC_0-∞ (µg·hr/ml) | 110.2 ± 15.5 | 39.8 ± 6.3 |
| Half-Life (hrs) | 24.8 ± 2.0 | 26.5 ± 3.1 |

- The nanoemulsion formulation showed substantially higher C_max (peak concentration) and AUC_0-∞ (area under the curve), indicating enhanced bioavailability. Also, a faster absorption rate was observed by lowering T_max (time to reach maximum concentration).

### 3.5. Statistical Analysis

- **Data Analysis**:
  - All in vitro and in vivo data were analyzed by the use of ANOVA and Tukey's multiple comparison test. Different pharmacokinetic parameters, like drug release and permeation, were significantly different between the itraconazole nanoemulsion and the plain suspension ($p < 0.05$).

**Table 3:** Parameters of Pharmacokinetics (ANOVA Findings)

| Parameter | Itraconazole Nanoemulsion (Mean ± SD) | Plain Itraconazole Suspension (Mean ± SD) | F-Value | p-Value |
|---|---|---|---|---|
| **C_max (µg/ml)** | 25.4 ± 3.1 | 7.2 ± 0.8 | 18.64 | < 0.05 |
| **T_max (hrs)** | 1.5 ± 0.2 | 3.2 ± 0.4 | 9.54 | < 0.05 |
| **AUC_0-∞ (µg·hr/ml)** | 110.2 ± 15.5 | 39.8 ± 6.3 | 22.34 | < 0.05 |

| | | | | |
|---|---|---|---|---|
| **Half-Life (hrs)** | 24.8 ± 2.0 | 26.5 ± 3.1 | 1.45 | > 0.05 |

- Statistical analysis confirms the oral bioavailability enhancement potential of this nanoemulsion formulation: " It has the big lead on all the significant measurements from the simple suspension ".

## 4. DISCUSSION

### 4.1. Interpretation of Results

In comparison with the basic suspension, the nanoemulsion developed in this work showed significant improvements in the release of drugs, permeability, and bioavailability. The particle size being 180 nm smaller and capable of better dispersion with gastrointestinal fluids, it showed the release of 88% of the medication within 4 hours as opposed to 50% from the basic suspension. The ex vivo experiments showed sixfold penetration, suggesting better absorption. Pharmacokinetic analysis in rats confirmed faster absorption with a T_max of 1.5 hours and higher C_max values (25.4 µg/ml versus 7.2 µg/ml). Stability tests showed the formulation to be stable for three months with less than 5% change in particle size, and scale-up to 500 ml demonstrated that the production is feasible.

### 4.2. Comparison with Existing Studies

Nanoemulsions offer a great potential in the transdermal delivery of drugs. The skin permeability, stability, and antioxidant characteristics of curcumin are significantly enhanced with curcumin-loaded nanoemulsions. It is also discovered that the essential oil-based nanoemulgel increase drug penetration, especially for the treatment of pain relief applications. Optimization of formulation stability, selection of surfactants, and particle size also comes to light in enhancing drug delivery effectively. These outcomes correspond with my work on the enhancement of the drug delivery and therapeutic results through optimization of nanoemulsion.

| Study | Focus | Formulation | Key Findings | Applications | Relevance to Your Research |
|---|---|---|---|---|---|
| **Md Saari et al. (2020)** | Curcumin nanoemulsion | Coconut oil, Tween 80, polyethylene glycol, honey, glycerol | High skin permeability, antioxidant activity, low cytotoxicity, wound healing | Transdermal drug delivery | Relevant for enhancing skin permeability and drug delivery |
| **Nikolic et al. (2018)** | Low-energy nanoemulsions for curcumin | Polysorbate 80, soybean lecithin, medium-chain triglycerides | High antioxidant activity, good biocompatibility | Pharmaceutical and dermal applications | Useful for optimizing curcumin delivery in your research |
| **Morteza-Semnani et al. (2022)** | Cumin essential oil nanoemulgel | Cumin oil, Tween 20, Tween 80, Span 80, Carbopol gel | Enhanced drug permeation, better anti-nociceptive effect | Pain management, transdermal drug delivery | Relevant for using essential oils in nanoformulations |
| **Rai et al. (2018)** | Overview of nanoemulsions in drug delivery | Emulsifiers, surfactants, semi-solid dosage forms | Enhances dermal/transdermal delivery, role of zeta potential | Dermal/transdermal drug delivery | Provides foundational insights for your formulation optimization |

**Table 4. Comparison of Research on Nanoemulsions**

### 4.3. Implications of Findings

This work's findings are of paramount clinical importance, particularly for improving the oral bioavailability of this poorly soluble drug itraconazole. More effective dosing schedules, fewer adverse effects, and better therapeutic outcomes can be expected for patients with fungal infections if the right nanoemulsion that boosts bioavailability is created. Furthermore, this method can be applied to other drugs that are poorly soluble, offering a promising means of enhancing the oral bioavailability of various pharmacological agents. Large-scale production of bioenhanced itraconazole formulations, which could be particularly useful in treating systemic fungal infections requiring high medication concentrations, is also feasible because of the formulation's scalability and stability, which further underscores its commercial potential.

### 4.4. Limitations of the Study

Despite the promising results, this study has a few limitations: clinical trials in humans are necessary to confirm the findings and determine the safety and efficacy of the itraconazole nanoemulsion; the use of Sprague-Dawley rats in the pharmacokinetic analysis may not be representative of human gastrointestinal conditions, which may impact the direct translation of the observed bioavailability enhancements to human subjects; the study does not provide long-term stability data under actual storage conditions since accelerated conditions may not simulate the impact of long-term storage; future studies should focus on the determination of the stability of the formulation over longer periods and under various storage conditions to evaluate its commercial viability.

### 4.5. Suggestions for Future Research

Post explorative studies should be focused on development of the nanoemulsion, itraconazole by testing oil, surfactant, co-surfactant, co-surfactant combinations. This will promote drug release and stability. Addition of additional excipients or co-enhancers along with bio enhancers to amplify bioavailability have to be reviewed. For confirmatory proof about its therapeutic gains for a human being it has to further be tested from animal models first and then its clinical trials. Its clinical uses may also be enhanced by studying the nanoemulsion's potential in combination treatments for fungal infections. The molecular mechanisms underlying the improved absorption of the nanoemulsion in the gastrointestinal tract are a promising line of inquiry that may provide important information for improving medication delivery methods.

## 5. CONCLUSION

In comparison with simple suspension, the itraconazole nanoemulsion formulated in this study demonstrated superior drug release and oral bioavailability, with better gastrointestinal absorption and

pharmacokinetic parameters (C_max and AUC). The optimised formulation, which has been made with appropriate surfactants, oil phase constituents, and co-surfactants, then attained better solubility along with more rapid absorption. The formulation was verified through stability tests to assure its physical stability. Scalability was achieved while not compromising important characteristics. All three studies address the insolubility of itraconazole, a factor that may lead to more successful treatment regimens in infections caused by fungi and opportunities for better delivery of other poorly soluble medications. To further exploit the therapeutic use of nanoemulsions, future studies should concentrate on clinical trials, formulation optimization, long-term stability testing in real-world settings, investigate combination therapies, and investigate the molecular pathways that underlie the improved absorption.

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