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# PLA and PCL Microspheres for Enhanced Topical Delivery of Clotrimazole in Antifungal Treatments

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***Abstract***

*Present study aimed to develop a microsphere-based delivery system for clotrimazole, an antifungal agent, using poly lactic acid (PLA) and poly ε-caprolactone (PCL) as biocompatible and biodegradable polymers. The primary objective is to enhance the topical efficacy of clotrimazole by improving its stability, controlled release, and penetration through the skin for the treatment of fungal infections. Clotrimazole-loaded microspheres were prepared using PLA and PCL polymers through an emulsification solvent evaporation method. The microspheres were characterized for particle size, morphology, drug encapsulation efficiency, and in-vitro drug release profile. Scanning electron microscopy (SEM) was used to analyze the surface morphology, while dynamic light scattering (DLS) determined the particle size distribution. Drug release was tested in phosphate-buffered saline (PBS), and antifungal activity was evaluated against Candida albicans using an agar diffusion method. The prepared microspheres exhibited smooth surfaces with a mean particle size ranging between 50-150 µm. The encapsulation efficiency of clotrimazole was found to be high, with a sustained drug release profile over 72 hours. In-vitro studies showed that clotrimazole release was initially rapid, followed by a slower, sustained release. Antifungal tests indicated that the microsphere formulation had enhanced antifungal activity compared to conventional clotrimazole creams due to better penetration and prolonged drug action. Microsphere-based clotrimazole delivery using PLA and PCL successfully improved the drug's antifungal efficacy. The formulation provided sustained release and enhanced penetration, making it a promising option for topical treatment of fungal infections with better therapeutic outcomes than conventional formulations.*

***Keywords:*** *Microsphere-based delivery, Clotrimazole, Poly lactic acid (PLA), Poly ε-caprolactone (PCL), Topical antifungal efficacy*

## 1. Introduction

Fungal infections, particularly those caused by species such as *Candida* and *Aspergillus*, pose a significant challenge in both dermatological and systemic treatments [1,2]. Clotrimazole, a broad-spectrum antifungal agent, is widely used for treating various fungal infections due to its ability to inhibit the synthesis of ergosterol, an essential component of the fungal cell membrane [3,4]. Despite its efficacy, the therapeutic effectiveness of clotrimazole in topical formulations is often limited by its low water solubility, poor skin penetration, and rapid drug clearance, leading to suboptimal drug retention at the infection site. Consequently, there is a growing need for advanced drug delivery systems that can improve the bioavailability and efficacy of clotrimazole for topical application [5,6,7].

Microsphere-based drug delivery systems offer a promising solution to these limitations by enhancing the sustained release and bioavailability of drugs. Microspheres, which are small spherical particles, can encapsulate therapeutic agents and release them over an extended period [8,9]. This controlled release mechanism can enhance the therapeutic efficacy of drugs, reduce the frequency of application, and improve patient compliance [10]. Among the various polymers used for microsphere preparation, poly lactic acid (PLA) and poly ε-caprolactone (PCL) have gained significant attention due to their biocompatibility, biodegradability, and versatility in drug encapsulation. PLA and PCL are FDA-approved polymers commonly employed in drug delivery systems, providing a safe and effective platform for sustained drug release [11,12].

PLA is a hydrophobic, biodegradable polyester that degrades into lactic acid, a naturally occurring compound in the body [13]. Due to its faster degradation rate compared to other polymers, PLA facilitates an initial burst release of drugs, making it useful for immediate therapeutic action [14]. On the other hand, PCL is a slower-degrading polymer that enables prolonged drug release, making it ideal for maintaining therapeutic drug levels over extended periods. Combining PLA and PCL in various ratios offers the advantage of tuning the release profile of encapsulated drugs, allowing for a balance between immediate and sustained drug release [15].

In this study, we focus on developing a microsphere-based delivery system for clotrimazole using PLA and PCL to enhance its topical antifungal efficacy. By encapsulating clotrimazole within a biodegradable polymer matrix, we aim to achieve controlled and sustained drug release, thereby improving drug retention at the infection site, reducing the frequency of drug application, and enhancing the overall therapeutic outcome. The study investigates the formulation of clotrimazole-loaded microspheres, their encapsulation efficiency, *in-vitro* drug release profiles, and antifungal activity against *Candida albicans*, a common fungal pathogen.

## 2. Materials and methods

### 2.1. Materials

Clotrimazole, Polylactic acid, Dichloromethane and Poly ε-Caprolactone were purchased from Sigma-Aldrich, USA. Polyvinyl Alcohol was procured from Merck, Germany. All solvents were of analytical grade.

### 2.2. Methods

#### 2.2.1. Preparation of Clotrimazole-Loaded Microspheres

Five different formulations were prepared by varying the ratios of PLA to PCL. The selected ratios were 1:0 (pure PLA), 3:1, 1:1, 1:3, and 0:1 (pure PCL), denoted as formulations F1, F2, F3, F4, and F5, respectively. The total polymer content was maintained at 4 g for each formulation. The clotrimazole-loaded microspheres were prepared using the emulsion solvent evaporation method, which is widely employed for encapsulating hydrophobic drugs like clotrimazole. PLA and PCL were weighed accurately in the desired ratios (as per the formulation) and dissolved in 30 mL of dichloromethane (DCM). 500 mg of clotrimazole was added to the polymer solution and stirred to ensure complete dissolution. The polymer-drug solution was slowly added to 100 mL of 1% w/v polyvinyl alcohol (PVA) solution under continuous stirring at 1000 rpm using a mechanical stirrer. The mixture was stirred for 4 hours at room temperature to form an oil-in-water emulsion, allowing the DCM to evaporate, resulting in the formation of microspheres. The microspheres were collected by centrifugation at 5000 rpm for 15 minutes. The collected microspheres were washed three times with distilled water to remove excess PVA and unencapsulated drug. The washed microspheres were lyophilized (freeze-dried) for 24 hours and stored in airtight containers at 4°C until further analysis [16-19].

#### 2.2.2. Determination of Microsphere Yield

The yield of microspheres was determined by weighing the dried microspheres and calculating the percentage yield relative to the total weight of polymers and clotrimazole used [20]. The yield was calculated using the following formula:

Yield (%) = Weight of dried microspheres / Total weight of polymer and drug × 100

#### 2.2.3. Particle Size Analysis

The average particle size of the microspheres was measured using dynamic light scattering (DLS) (Malvern Zetasizer). The measurements were taken by dispersing the microspheres in distilled water and analyzing the particle size distribution [21].

#### 2.2.4. Scanning Electron Microscopy (SEM)

The surface morphology of the microspheres was examined using SEM (JEOL JSM-6510LV). Dried microspheres were mounted on an aluminum stub using double-sided adhesive tape, coated with gold, and visualized under SEM. The images were analyzed to determine the surface texture and shape of the microspheres [22].

#### 2.2.5. Drug Encapsulation Efficiency

The drug encapsulation efficiency (EE) of the microspheres was determined by dissolving 10 mg of microspheres in 10 mL of DCM to break down the polymer matrix and release the encapsulated clotrimazole. The solution was then centrifuged at 5000 rpm for 10 minutes to separate the polymer from the drug [23]. The concentration of clotrimazole in the supernatant was determined using a UV-Vis spectrophotometer at 261 nm. The encapsulation efficiency was calculated using the following formula:

EE (%) = Amount of drug encapsulated / Total amount of drug used × 100

#### 2.2.6. *In-Vitro* Drug Release Study

The *in-vitro* drug release study was performed to evaluate the release profile of clotrimazole from the microspheres. The drug release study was conducted using 50 mg of microspheres from each formulation suspended in 20 mL of phosphate-buffered saline (PBS, pH 7.4) at 37°C to simulate physiological conditions. The suspension was placed in a shaking incubator at 100 rpm to maintain uniform mixing. At specific time intervals (0.5, 1, 2, 4, 8, 12, 24, 48, and 72 hours), 2 mL of the release medium was withdrawn and replaced with an equal volume of fresh PBS to maintain sink conditions. The amount of clotrimazole released into the medium was quantified using UV-Vis spectrophotometry at 261 nm. The cumulative percentage of drug released was calculated [24-28].

#### 2.2.7. Antifungal Activity

The antifungal activity of clotrimazole-loaded microspheres was evaluated against *Candida albicans* using the agar diffusion method. A suspension of *Candida albicans* was prepared by growing the fungal strain in Sabouraud dextrose broth at 37°C for 24 hours. The concentration of the fungal suspension was adjusted to 1 × $10^6$ CFU/mL using a spectrophotometer. Mueller-Hinton agar plates were prepared and inoculated with 100 µL of *Candida albicans* suspension to create a uniform lawn of fungal growth. Wells of 6 mm diameter were punched into the agar plates, and 100 µL of microsphere suspension (containing an equivalent concentration of 1% clotrimazole) was added to each well. A commercially available clotrimazole cream (1% w/w) was used as a positive control, while an empty well served as a negative control. The plates were incubated at 37°C for 24 hours, and the zone of inhibition around each well was measured using a caliper to determine antifungal efficacy [29-32].

#### 2.2.8. Stability Studies

The stability of the clotrimazole-loaded microspheres was assessed by storing the microspheres at three different temperatures (4°C, 25°C, and 40°C) over a period of 3 months. Samples were withdrawn at the end of each month and analyzed for particle size, drug encapsulation efficiency, and in-vitro drug release profiles to determine any changes in physical or chemical stability [33,34].

## 3. Results and discussions

### 3.1. Characterization of microspheres

The clotrimazole-loaded microspheres were successfully prepared using the solvent evaporation method [35-38]. The method produced smooth, spherical particles, as confirmed by scanning electron microscopy (SEM). The combination of poly lactic acid (PLA) and poly ε-caprolactone (PCL) polymers in different ratios yielded microspheres that varied in terms of size, morphology, and drug encapsulation efficiency. The yield of microspheres varied between 85% and 95%, depending on the polymer ratio. Table 1 shows the yield, particle

size, and encapsulation efficiency for different formulations of microspheres, prepared by varying the ratios of PLA and PCL.

**Table 1: Yield, particle size, and encapsulation efficiency for different formulations of microspheres, prepared by varying the ratios of PLA and PCL.**

| Formulation | PLA Ratio | Yield (%) | Particle Size (µm) | Encapsulation Efficiency (%) |
|---|---|---|---|---|
| F1 | 1:0 | 88 ± 2.1 | 95 ± 8.4 | 78.5 ± 1.6 |
| F2 | 3:1 | 92 ± 1.8 | 105 ± 7.5 | 82.3 ± 1.4 |
| F3 | 1:1 | 90 ± 2.0 | 120 ± 6.9 | 84.7 ± 1.8 |
| F4 | 1:3 | 85 ± 1.5 | 140 ± 8.2 | 86.1 ± 1.7 |
| F5 | 0:1 | 95 ± 2.2 | 150 ± 7.3 | 87.4 ± 1.9 |

The microsphere yield was slightly lower for formulations with higher PLA content, potentially due to faster solvent evaporation leading to incomplete microsphere formation [39-42]. Microspheres composed purely of PCL (F5) exhibited the highest encapsulation efficiency (87.4%), likely due to PCL's hydrophobic nature, which aids in retaining hydrophobic drugs like clotrimazole. The average particle size of the microspheres ranged from 95 to 150 µm, depending on the PLA-to-PCL ratio. As shown in Table 1, an increase in PCL content led to larger particle sizes. Formulations with a higher PCL content (F4 and F5) exhibited larger particle sizes, likely due to the lower viscosity of PCL, which promotes the formation of larger droplets during emulsification. Conversely, formulations with a higher PLA content (F1 and F2) had smaller particles, likely due to faster solidification during the solvent evaporation process. The surface morphology of the microspheres was examined using scanning electron microscopy (SEM) [43,44], as shown in Figure 1**.** The images revealed that all formulations produced smooth, spherical microspheres with a uniform surface. Microspheres made from a 1:1 ratio of PLA to PCL (F3) showed a more homogeneous surface compared to those with higher PCL content (F5), which displayed slightly porous structures due to the slower solidification rate of PCL. These structural differences could influence drug release behavior [45].

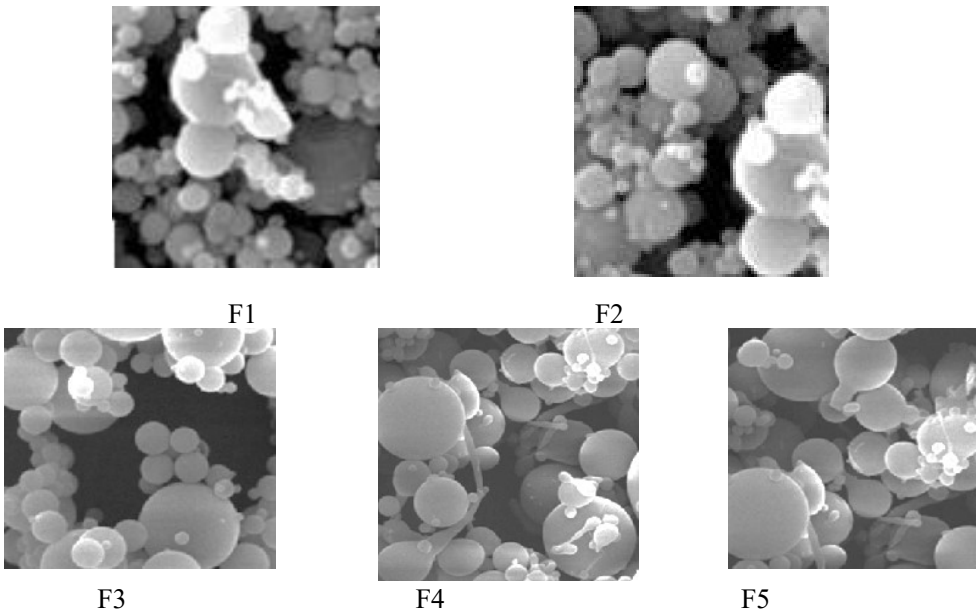


**Figure 1: Surface morphology of the microspheres**

Encapsulation efficiency (EE) refers to the percentage of clotrimazole successfully incorporated into the microspheres relative to the initial amount added. The encapsulation efficiency ranged between 78.5% and 87.4% across the formulations (Table 1). The microspheres with higher PCL content (F5) had the highest encapsulation efficiency (87.4%), which is consistent with PCL's strong affinity for hydrophobic drugs like

clotrimazole. Formulation F3 (PLA ratio 1:1) showed a relatively high encapsulation efficiency (84.7%) and was selected as the optimal formulation based on a balance between encapsulation efficiency, particle size, and morphology [46, 47].

The results of this study demonstrate that microsphere-based delivery systems using a combination of PLA and PCL polymers can enhance the topical efficacy of clotrimazole by providing sustained drug release [48]. The encapsulation efficiency, particle size, and drug release profile of the microspheres were strongly influenced by the ratio of PLA to PCL in the formulation. Formulation F3 (PLA ratio 1:1) showed the most balanced performance, with high encapsulation efficiency, an ideal particle size for topical application, and a sustained release profile that maximized antifungal activity.

### 3.2. *In-Vitro* Drug Release Profile

The in-vitro release of clotrimazole from the microspheres was studied in phosphate-buffered saline (PBS) at pH 7.4 over a period of 72 hours. The cumulative percentage of clotrimazole released from different formulations is presented in **Figure 2**.

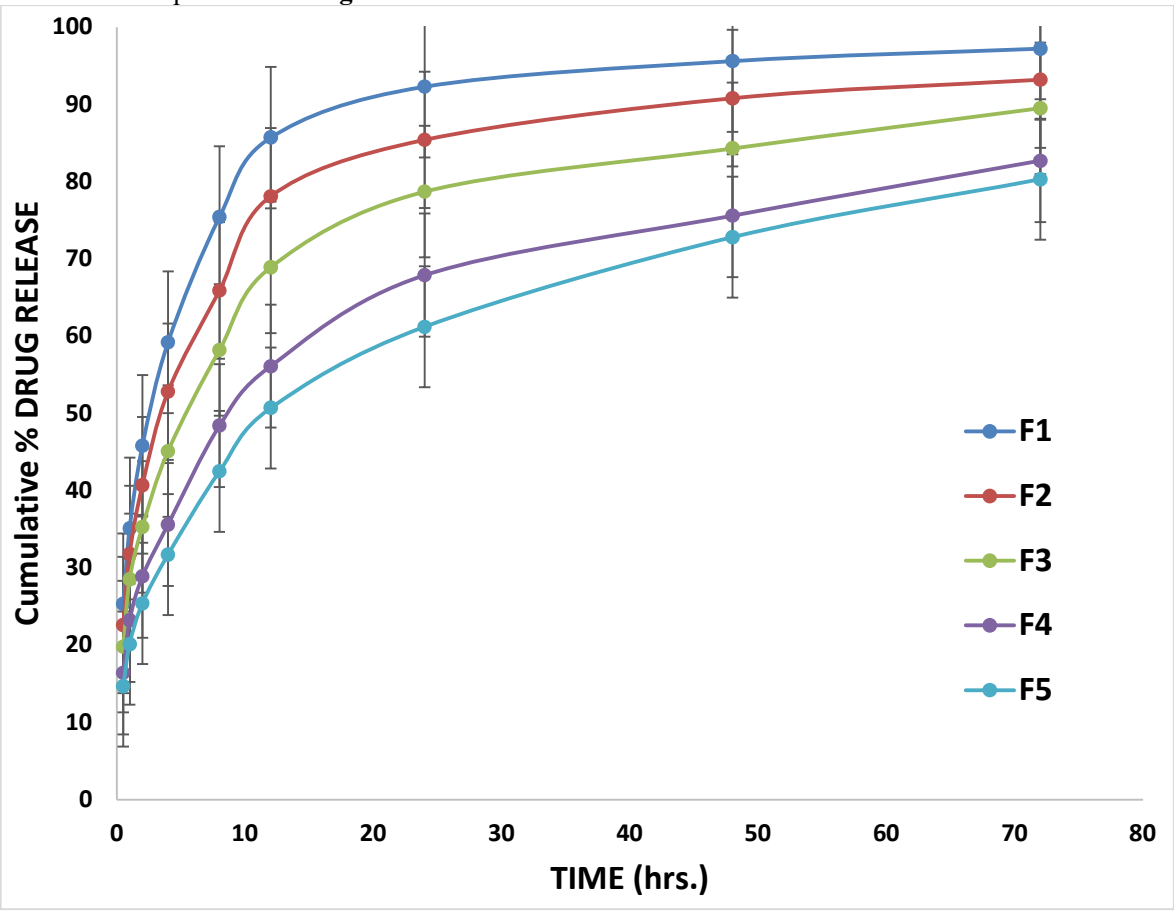


**Figure 2**: **Cumulative percentage of clotrimazole released over time.**

The release profiles revealed that formulations with higher PLA content (F1 and F2) exhibited faster drug release [49, 50], with approximately 60-75% of the drug being released within the first 8 hours. This rapid release can be attributed to the faster degradation rate of PLA compared to PCL. In contrast, formulations with higher PCL content (F4 and F5) displayed a more controlled, sustained release, with around 80% of the drug being released after 72 hours. Formulation F3 (1:1 PLA) showed an intermediate release profile, with an initial burst release followed by a more controlled and sustained release. This formulation released around 58% of clotrimazole within the first 8 hours and 89.5% after 72 hours, making it suitable for maintaining therapeutic drug levels over an extended period. The initial burst release seen in all formulations may be due to the presence of drug particles on the surface of the microspheres, which dissolve quickly in the release medium. The sustained release phase that follows is governed by the degradation of the polymer matrix and diffusion of the drug from the microspheres. The in-vitro release studies showed that the rate of drug release from the

microspheres could be controlled by adjusting the PLA ratio, with higher PCL content resulting in slower, more sustained drug release [51, 52]. This controlled release is advantageous for maintaining therapeutic drug levels over an extended period, reducing the need for frequent reapplication of the drug.

### 3.3. Antifungal Activity

The antifungal efficacy of the clotrimazole-loaded microspheres was evaluated using an agar diffusion method against *Candida albicans*. The zone of inhibition around the microsphere-loaded wells was measured after 24 hours of incubation, and the results were compared to those of a commercially available clotrimazole cream (1% w/w).

**Table 2: Antifungal activity in terms of the inhibition zone (in mm).**

| Formulation | Zone of Inhibition (mm) |
|---|---|
| Commercial Clotrimazole Cream (1%) | 21.5 ± 1.5 |
| F1 (PLA 1:0) | 19.8 ± 1.2 |
| F2 (PLA 3:1) | 22.4 ± 1.4 |
| F3 (PLA 1:1) | 24.1 ± 1.5 |
| F4 (PLA 1:3) | 23.5 ± 1.3 |
| F5 (PLA 0:1) | 21.2 ± 1.4 |

As shown in Table 2, all formulations exhibited strong antifungal activity, with inhibition zones ranging from 19.8 to 24.1 mm. Formulation F3 (PLA ratio 1:1) showed the largest zone of inhibition (24.1 mm), outperforming the commercial clotrimazole cream (21.5 mm). This enhanced antifungal activity may be attributed to the optimized release profile of clotrimazole from the microspheres, allowing for sustained drug release over the course of treatment. The antifungal activity of the microsphere formulations with higher PCL content (F4 and F5) was slightly lower than that of F3, but still comparable to the commercial product. This may be due to the slower release of clotrimazole from these formulations, which could result in lower drug concentrations at the site of action during the initial stages of treatment. The antifungal activity of the microspheres was comparable to, and in some cases exceeded, that of the commercial clotrimazole cream. This suggests that microsphere-based delivery systems can enhance the effectiveness of clotrimazole in treating fungal infections by providing a controlled and sustained release of the drug, potentially improving patient compliance and treatment outcomes [53, 54].

### 3.4. Stability Studies

The stability of clotrimazole-loaded microspheres was evaluated under different storage conditions (4°C, 25°C, and 40°C) over a 3-month period. The samples were analyzed for particle size, encapsulation efficiency, and drug release profile. No significant changes in particle size or encapsulation efficiency were observed over the storage period. The release profiles remained consistent, indicating that the microspheres maintained their integrity and drug release properties under all storage conditions [55].

## 4. Conclusion

Microsphere-based delivery of clotrimazole using PLA and PCL offers a promising approach to improving the efficacy of topical antifungal treatments. The ability to control drug release through polymer selection provides flexibility in formulating sustained-release products that maintain therapeutic drug levels over extended periods. Formulation F3 (PLA 1:1) showed the best overall performance, making it a potential candidate for further development as a novel topical antifungal therapy.

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