Design and Optimization of Posaconazole-Loaded Solid Lipid Nanoparticles for Enhanced Topical Antifungal Therapy

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Abstract
The purpose of this study was to production and characterization of Posaconazole based solid lipid nano-carrier system for topical administration into the skin. Solid lipid nanoparticles have colloidal carrier system made up of solid lipid and surfactant in which drug encapsulated in carrier system. Posaconazole is the structural derivatives of itraconazole related drug. It contain BCS category of Class II (low solubility/high permeability) and lipophilic in nature. Posaconazole-loaded solid lipid nanoparticles were synthesized by high-speed homogenization/ultrasonication method utilizing 2^3 factorial designs. The independent variables were Glyceryl mono stearate, tween 80 and homogenization time. On the basis of responses, these data obtained 170 nm particle size, 88% entrapment efficiency and 64% cumulative drug release, Posa-SLNs optimized on it. According to this report, Posa-SLNs are best carrier system for conveying the posaconazole drug at transdermal delivery for fungal infection.

Keywords- Posaconazole, Solid lipid nanoparticles, Particle size, entrapment efficiency, *in-vitro* drug release

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1. Introduction

Dermatomycoses, which are the most common type of mycotic infections, are widespread across the globe. Fungal infections affecting the skin are prevalent worldwide, impacting 20-25% of the global population. The likelihood of developing a dermatophytic infection over a lifetime is estimated to be between 10-20%. A study conducted in Nepal indicated that superficial infections of the skin, nails, and hair accounted for 13.5% of all outpatient visits related to skin issues.[1] The frequency of these visits increases during the spring and summer months. Climatic factors, along with cultural and socioeconomic influences, not only heighten the occurrence of fungal diseases in tropical areas but also dictate the specific types of infections found in particular geographic regions. These infections are particularly common in tropical countries due to the warm and humid climate, crowded living conditions, and various socioeconomic factors. While dermatomycoses is not considered a life-threatening condition, it can lead to significant discomfort that affects an individual's quality of life. The main challenge associated with these infections is their tendency to recur. A wide range of medications is available for the treatment of fungal infections, including both topical and systemic options. Various antifungal agents, such as triazole and imidazole derivatives, are utilized to address these infections. In tropical climates, fungal infections represent the most prevalent disease among humans.[2]

Posaconazole is a structural derivative of the itraconazole drug. It is a triazole antifungal agent that interacts with heme in the cytochrome P-450 enzyme sterol 14-demethylase found within fungal cells. Ergosterol is one type of component that is inhibited by this drug, leading to the accumulation of methylated sterol precursors. Posaconazole is inherently lipophilic and has a log P value of 5.5. It exhibits low solubility in water. This medication is effective against various types of fungi, including Cryptococcus, Aspergillus, Candida albicans, endemic mycoses, and filamentous fungi such as coccidioidomycosis and histoplasmosis. According to the US FDA, this drug has been approved for the treatment of oro-pharyngeal candidiasis.[3]

However, in contemporary times, the alteration of development and manufacturing processes has led to improved treatment efficacy, extended duration, and cost-effectiveness, establishing it as a significant and attractive scientific field. Recently, nanocarrier systems have been developed.[4]

The nano-particulate carrier system has attracted interest for the localized treatment of membrane infections due to its capacity to improve the penetration of encapsulated active substances through the stratum corneum. As a result, several unique characteristics have been linked to solid lipid nanoparticles (SLNs), such as their small size, large apparent surface area, high drug loading capacity and the interaction of phases at the interfaces, which enhance the effectiveness of medications and nutraceuticals.[5]

It may offer numerous advantages over traditional dosage forms, including enhanced bioavailability, reduced toxicity, improved bio-distribution, and increased patient adherence.[3]

The effectiveness of drug delivery methods is greatly affected by the carriers used; thus, the carrier must be suitable for transdermal or topical drug delivery. Colloidal systems represent a highly promising strategy for drug delivery, improving both the bioavailability and therapeutic effectiveness of pharmaceuticals. This includes micelles, vesicles, liposomes, liquid crystals, nanocrystals, nanoparticles and others. The particle size of the specified nano-carriers varies from 10 to 800 nm.[5] Nanoparticles are solid colloidal entities ranging from 10 to 1000 nm (1.0 μm), in which the active pharmaceutical ingredient is dissolved, encapsulated, or adsorbed. The benefits of nanoparticles include effective therapy with minimal side effects due to controlled and targeted drug delivery.[4] For enhance the solubility and bioavailability of poorly water-soluble pharmaceuticals, Lipid-based delivery systems comprise carriers syatem.[6] They were initially employed in drug delivery, and significant research has been conducted in this area.[7] SLN is a proficient method for including non-biodegradability and instability linked to traditional colloidal drug delivery approaches.[8]

Solid lipid nanoparticles represent an advanced drug technology in which the lipid remains in a solid state at both ambient and physiological temperatures. This technology comprises solid lipids such as stearic acid, glyceryl mono-stearate, triglycerides and an emulsifying agent. These nanoparticles encapsulate drugs within their internal phase while surfactants act as stabilizers in the external aqueous phase.[9]

SLNs are lipid-based submicron colloidal carriers that remain solid at room temperature as well as body temperature, exhibiting minimal drug release.[10,11] Various technologies, including high shear homogenization/ultrasonic methods, solvent emulsification/evaporation, and the micro-emulsion process, are employed in the production of solid lipid nanoparticles (SLNs). The components used in the formation of SLNs, such as fatty acids, mono-, di-, and triglycerides, phospholipids, and other excipients, are part of the physiological constitution, thus demonstrating biocompatibility with the human body.[12,13]

C. Carbonea et al. formulated a combination drug delivery system targeting the treatment of skin infections caused by Candida albicans.[14] Shaimaa El-Housinya et al. prepared and evaluated solid lipid nanoparticles based on a Fluconazole-loaded gel for topical application in pityriasis versicolor.it were prepared by lipid content and surfactant by high speed homogenization as well as ultrasonication method.[15]

The creation of drug delivery carriers is frequently arduous, owing to the physicochemical characteristics of the medication, including inadequate solubility, limited permeability, brief half-life, and elevated molecular weight.[16]

The purpose of study to developed and characterized Posaconazole SLN dispersion system increases the permeation of drug into the skin. Posa-SLN based formulations were prepared by design of expert (DOE) method for transdermal administration can offer advantages by sustain the release pattern.

2. Material and Method-

Material-Posaconazole (standard) was procured from Dhamtec Pharma and Consultants (Navi Mumbai, india), glyceryl mono stearate, from central drug house (P) Ltd. (Delhi) tween 80, chloroform and methanol purchased for science emporium, Najibabad. All chemicals used as analytical grade.

2.1. Experiment project-

The 2^3 factorial designs were utilized to assess the impact of 3 parameters and their inferences for the physical chemical properties of lipid nanoparticles. The best formulation of Solid Lipid Nanoparticles involved selecting the proportions of Glyceryl mono stearate, Tween 80 and homogenization time as independent variables. Each element was established with its lowest and highest levels as depicted (Table 2). Factorial design methodology was applied were to developed 8 creations. The responses were established such as particle size, entrapment efficiency and cumulative percentage drug release. [17,18]

2.2 Characterization of solid lipid nano-particles (SLNs)-

2.2.1. Determination of particle size (PS)

SLNs were evaluated using dynamic light scattering on a Zetasizer Nano, utilizing a 5 mW helium-neon laser. Samples were maintained in cuvettes and diluted 100-fold with purified water.[19]

2.2.2. Entrapment efficiency

Entrapment efficiency was assessed by centrifuging the solid lipid nanoparticles dispersion at 17,000 rpm for 1 hrs. 1 ml of supernatant was diluted with 10 ml with methanol and evaluated by Ultraviolet spectroscopy at 260 nm. The entrapment capabilities of each formulation of solid lipid nanoparticle dispersion were attained. The entrapment efficiency (EE %) of drug in solid lipid nanoparticles was determined using the following formula. Each experiment was conducted in triplicate.[20]

% EE = Quantity of posa mixed in Posa-SLNs – the Quantity of posa in supernatant.

Amount of posa added in posa-SLNs

2.2.3. Statistical investigation

In this project, results were described through mean ± standard deviation. In this, t-test and one way-Anova at $P<0.05$ used to assessed the significance of difference.

3. Result and Discussion

3.1. Characterization of Solid lipid nanoparticles-

Table 1- Eight Posa-SLNs formulations (F_1- F_8) were prepared and their compositions

Formulation code	Factor 1 (A: GMS, gm)	Factor 2 (B: Tween 80, gm)	Factor 3 (C: Homogenization, min)	Response 1: Particle Size (nm)	Response 2: EE (%)	Response 3: Drug Released (%)
F_1	3	6	20	140	80	72
F_2	5	6	20	170	88	64
F_3	5	5	20	180	86	60
F_4	5	6	15	175	86	62
F_5	3	5	20	160	76	70
F_6	3	6	15	150	78	71
F_7	5	5	15	190	84	58
F_8	3	5	15	170	74	69

Response 1: Particle size (nm)- The effect of the independent variables such as Glyceryl monostearate, tween 80 and homogenization time on particles size were studied table 1.

Table 2: ANOVA for Linear model

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	1809.37	3	603.12	64.33	0.0008	significant
A-GMS	1128.12	1	1128.12	120.33	0.0004	
B-Tween	528.80	1	528.80	56.41	0.0017	
C-Homogenization speed	153.13	1	153.13	16.33	0.0156	
Residual	37.50	4	9.38			
Core Total	1846.88	7				

Particle size- Table 2 indicate that the linear model is highly significant, All three factors GMS, Tween 80, and Homogenization speed are statistically significant. Specifically, GMS has the strongest effect followed by Tween 80 and Homogenization speed. The residual error is relatively low, indicating that this model was appropriate the investigational facts well. This analysis confirms that all included factors influence particle size and that the model is reliable for prediction and optimization within the studied range.[21]

Contour Plot Interpretation

The contour plot provides a two-dimensional map of particle size as a function of GMS and Tween 80, with each line representing an iso-response contour. This plot is particularly useful for identifying factor combinations that achieve a desired particle size range.

3D Surface Plot Interpretation

The 3D response surface demonstrates the correlation between GMS and Tween 80 concerning particle size, while maintaining the homogenization speed at its midpoint. The surface inclines towards higher levels of GMS and lower levels of Tween 80, thereby confirming the contrasting effects of these two variables.[22,23]

The 3D response graphs clarified that particle size increases with a rise in lipid content. This phenomenon is primarily due to the elongation of lipid chains, which significantly enhances particle adherence and gradually decreases the mono-dispersity of the formulation. The dimensions of solid lipid nanoparticles (SLN) are also affected by the viscosity of the lipids, which increases with the length of the lipid chains. A rise in viscosity leads to larger lipid droplets, resulting in greater sizes of SLNs. For effective topical delivery, a nanosized solid lipid nanoparticle is essential. Therefore, surfactant (Tween 80) was employed to improve the stability of the smaller lipid droplets. The particle size decreased with an increase in Tween 80 content.[24,25]

Particle size is a critical characteristic of nanoparticles, as it directly influences the drug release pattern and its absorption. By utilizing the high-pressure homogenization method followed by sonication, smaller particles (below 200 nm) proved to be highly beneficial for topical preparations as well as for cutaneous applications.[26]

The minimum mean particle size was recorded with a high concentration of Tween 80 and extended homogenization time, coupled with a low concentration of glyceryl mono-stearate (solid lipid). However, particle size was largest when increase the concentration of Glyceryl Mono Stearate.[27]

Moreover, with the increase in the homogenization time as well as sonication time are increases, The reduction in particle size is accompanied by surfactants that stabilize the newly formed surfaces and inhibit particle aggregation.[28]Moreover, with the increase in the homogenization time as well as sonication time are increases, the size of particle size decreases.[29]

ANOVA for Linear model

Table 3: Response 2: Entrapment efficiency (%EE)

Table 3-A quantitative assessment to evaluate the quantity of medication encapsulated inside the lipid matrix.

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	188.00	3	62.67	125.33	0.0002	significant
A-GMS	162.00	1	162.00	324.00	< 0.0001	
B-Tween 80	18.00	1	18.00	36.00	0.0039	
C-Homogenization speed	8.00	1	8.00	16.00	0.0161	
Residual	2.00	4	0.5000			
Cor Total	190.00	7				

The ANOVA results for Response 2, Entrapment Efficiency (EE %), demonstrate that the linear model was significant, All three factors in the model GMS (A), Tween 80 (B), and Homogenization speed (C) are statistically significant contributors to the variability in EE%. This analysis validates that adjustments in GMS, Tween 80, and Homogenization speed are all effective levers for controlling and optimizing the entrapment efficiency in this formulation process.[28,29] This analysis highlights that, unlike for particle size where Tween 80 and homogenization speed had negative effects all three factors positively contribute to EE%, with GMS being the most influential. This information is essential for optimizing EE% while considering potential trade-offs with other responses such as particle size and drug release.[30]

3D Surface Plot Interpretation

The surface slopes upward toward the high levels of both A and B, demonstrating that increasing either factor enhances EE%. The upward trend is more pronounced along the GMS axis, visually emphasizing its stronger effect.

Contour Plot Interpretation

The contour plot provides a two-dimensional map of EE% as a function of GMS and Tween 80. The contour lines, representing constant EE% levels, run diagonally, showing that similar EE% values can be achieved by different combinations of A and B. a slightly lower GMS level can be compensated for by a higher Tween 80 level to maintain the same EE%. All possible factor combinations that achieved a specific EE% target, offered flexibility in formulation design. According to graph, %EE increase with an enhance in lipid concentration as higher the amount of core matrix greater will be the drug entrapped.[31]

These figures represented that, variation in the concentrations of GMS, Tween 80 resulting That elevation of stabilizer concentration (tween 80) significantly influenced the SLN.

% EE, as the lipid matrix can fully wrap the drug molecules to their maximum loading capacity. The report indicates that an increase in the concentration of solid lipids (Glyceryl mono-stearate) led to a higher percentage of encapsulation efficiency (%EE) of the drug. The %EE of posaconazole-loaded SLNs was 88%, indicating that the SLN system efficiently integrated with posaconazole.[32]

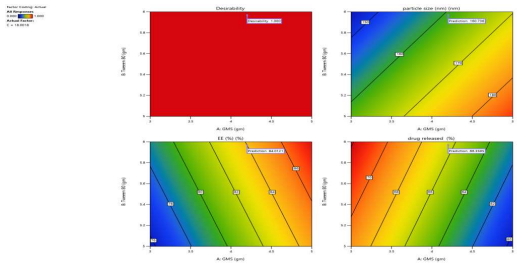
ANOVA for Linear model

Table 4: Response 3: % Cumulative drug release

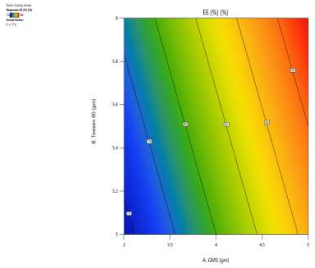
Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	203.00	3	67.67	108.27	0.0003	significant
A-GMS	180.50	1	180.50	288.80	< 0.0001	
B-Tween 80	18.00	1	18.00	28.80	0.0058	
C-Homogenization speed	4.50	1	4.50	7.20	0.0550	
Residual	2.50	4	0.6250			
Cor Total	205.50	7				

The ANOVA results for Response 3, drug released (%), indicate that linear representation is extremely significant, through a Model F-value of 108.27 and 0.0003(p-value), demonstrating that the factors must a strong and statistically influence on drug release. Among the factors, A (GMS) is the most

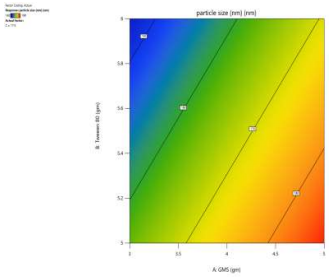
dominant, with an exceptionally high 288.80 (F-value) and a less than 0.0001(p-value), contributing the largest portion of the explained variation. B (Tween 80) is also a significant factor, with an F-value of 28.80 and a p-value of 0.0058, demonstrating a clear but more limited effect. C (Homogenization speed), however, shows a borderline p-value of 0.0550. The residual error is small (Sum of Squares = 2.50), confirming a good model fit with low unexplained variability. This analysis directs focus toward GMS and Tween 80 as the primary factors for sustain/controlling drug release, while homogenization speed appears to play a less critical role in this response. The model highlights a key trade-off: while GMS strongly increases entrapment efficiency (EE%), it concurrently reduces the percentage of drug released. Therefore, formulation strategies aiming to maximize drug release may need to prioritize lower GMS levels, compensated by higher Tween 80 content, while homogenization speed can be adjusted with minimal impact on this particular response.



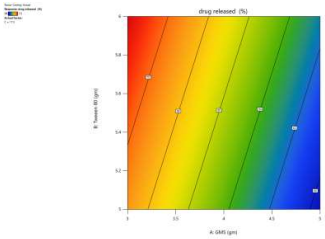
Figures 1: contour plots of the optimized formulation



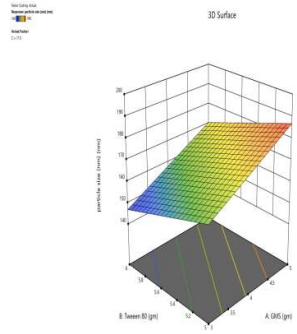
2(a)



2(b)



2(c)



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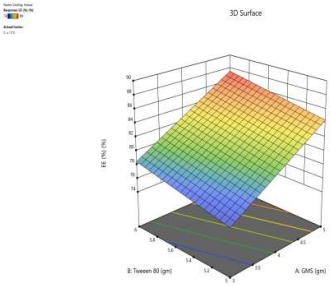
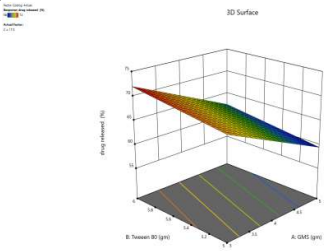


2(e)



2(f)

Figures 1: Contour Plot of response of SLNs formulation and Figures 2 (a,b,c,d,e,f) - 3D Surface Plot of response of SLNs formulation.

4. Conclusion

The present study successfully developed and characterized a Posaconazole-loaded solid lipid nanoparticle (Posa-SLN) dispersion system using a Design of Expert (DOE)-based optimization approach for enhanced topical/transdermal antifungal delivery. The prepared formulations demonstrated desirable physicochemical properties, including nanoscale particle size, high entrapment efficiency, and sustained drug release behavior. Among the evaluated formulation variables,

glyceryl monostearate (GMS), Tween 80 concentration, and homogenization time significantly influenced particle size, entrapment efficiency, and cumulative drug release. The optimized formulation (F_2) exhibited a particle size of approximately 170 nm, 88% entrapment efficiency, and 64% cumulative drug release, indicating effective drug incorporation and controlled release characteristics. Overall, the developed Posa-SLN system represents a promising and effective carrier for improving the topical delivery and therapeutic efficacy of Posaconazole in fungal skin infections.

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Conflicts of Interest-The writers assert the absence of any disagreement of interest. The company was not involved in the study's project, data gathering, explanation, drafting or the result to publish the judgments.

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