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Formulation Development and Optimization of Nanoemulsion for Topical Delivery of Sertaconazole Drug to Treat Ecezema

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A B S T R A C T
This study investigates the physical and chemical characteristics of Sertaconazole, focusing on its solubility, melting point, and analytical properties. Sertaconazole is a pure white substance with solubility varying by pH, being soluble in DMSO and DMF, but insoluble in water. The melting point was established at 166°C, aligning with established standards. FTIR and DSC analyses confirmed the drug's purity and crystalline nature, while PXRD showed a highly crystalline structure, indicating no polymorphic changes from milling and lyophilization. The developed analytical method exhibited strong linearity (R^2 = 0.999), high precision (RSD <1.1%), and near 100% accuracy in rat plasma. Robustness was validated across different solvent compositions. The QTPP analysis identified critical quality parameters, and risk analysis revealed significant factors affecting particle size and drug content in nanoformulations. Central Composite Design (CCD) optimization demonstrated enhanced drug delivery characteristics, validating the method's effectiveness for Sertaconazole formulation optimization.
Keywords: Sertaconazole, DMSO and DMF, Ecezema

A R T I C L E I N F O

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Contents

1. Introduction. 18
2. Methodology. 19
3. Results and Discussion. 20
4. Conclusion. 24
5. References. 25

1. Introduction

Preformulation studies:
Preformulation studies are a crucial and necessary phase for formulation scientists. These studies ensure the optimal use of ingredients and the avoidance of any potential interactions, aiding in the selection of appropriate excipients. Some commonly conducted studies include:

Drug identification
The drug or API can be identified using various physical and chemical parameters like solubility, FTIR, DSC etc

Physical characteristics
The physical appearance of the drug like color order shape etc can be determined which forms a preliminary identification.

Solubility testing
Saturation solubility was determined based on the Higuchi and Connors method. This involved using a series of flasks with the drug kept on a rotary shaker to achieve saturation solubility, with concentrations measured using a previously

validated method. Various solvents and buffers, including water, ethanol, chloroform, ether, 0.1 N HCl, acetate buffer at pH 4.5, and phosphate buffer at pH 6.8, were tested. The solubility characteristics of the drug were then tabulated.

Melting point

The melting point is crucial in characterizing the nature of the drug. It is determined using the capillary method, where the drug is loaded into a capillary tube sealed on one end and inserted into the apparatus. The melting point is recorded when the drug begins to melt.

FTIR

The FTIR spectrum was obtained using the KBr pellet technique (Alfa, Bruker, Germany). In this method, an appropriate quantity of the drug is mixed with KBr and compressed into a tablet. The readings are then recorded. FTIR measurements provide insights into the functional groups and interactions among the ingredients.

DSC

DSC analysis was carried out using a 5 mg sample with a thermal analyzer (EVO 131, France). Temperature calibration was done with in medium as the std. An empty pan, sealed in the same manner as the sample, served as the reference. scanning rate of 10˚C/min from 25˚C to 300˚C.

Analytical method development

An initial stock solution of the drug was prepared in methanol. From this stocksolution, secondary dilutions with known concentrations were created, and the absorption maxima were determined. After identifying the lambda max, a series of dilutions were prepared, and a standard plot was constructed to estimate the Beer-Lambert range.

Preparation of Nanoparticles

The solvent-antisolvent precipitation method was used for preparation. In this process, 10 mg of the drug was dissld in 2mL of acetone, serving as the solvent. This solution was then gradually added at a rate of 0.2mL/min or 0.6mL/min into an anti solvent mixture (water and poloxamer 188 as a stabilizer)

2. Methodology

Experimental design

A Design Expert was employed to implement a Quality by Design approach. Parameters were chosen based on preliminary studies and past experience. The statistical design assesses key parameters. Each factor was examined at 2levels according to preliminary laboratory data. The parameters and their respective levels are presented in the table.

Statistical analysis

It was analyzed statistically and mathematically using methods such as regression & ANOVA. The software-generated polynomialexpression was recorded, and its effects were analyzed.

Lyophilization

The nanoparticles were lyophilized using mannitol as a cryoprotectant. They were loaded into vials & frozen at-80°C for 4hours. Subsequently, the vials were transferred to a freeze dryer and dried at apressure of 0.098Mbar for 24 hours at -80±0.5°C.

Evaluation of nano particles

Size and surface morphology

SEM and TEM was employed to assess surface characteristics, such as smoothness or roughness, which impact solubility.

Zeta potential, Poly Dispersibility Index

The surface potential of the particles, measured using a Zeta Sizer (Malvern), is crucial for maintaining stability. Achieving the optimum potential is vital for ensuring uniform dispersion and preventing caking and other adverse effects. Generally, a zeta potential value between 5 to 15 mV indicates a stable formulation. The particle size distribution provides an indication of the range of particle sizes.

Dissolution studies

Dissolution testing of the nanoparticles was performed using a type II paddle dissolution apparatus at 50RPM and a temperature of 37 ± 1.0°C. The dissolution medium utilized was 0.1N HCl with a pH of 1.2. Drug release was measured by sampling and analyzing using a previously validated method. To maintain sink conditions, the sampled volume was replaced with fresh medium.

Study of release kinetics

The dissolution data was fitted into the following various mathematical models, Zero order equation118

$$Q = Q_0 - k_0 t$$

Where Q is the concentration at time t, Q_0 is the initial concentration and K_0 is zero order rate constant.

First order equation

$$\ln Q = \ln Q_0 - kt$$

Preparation of aloevera carbopol gel

Preparation of aloevera extract

Thick, succulent aloevera leaves are taken and placed in an inverted position to drain the yellow liquid, which is then discarded. The thick, white pulp is carefully separated using a spoon and placed in a bowl. The pulp is neutralized with 0.1 N NaOH and repeatedly washed with hot water. The mucilage is then subjected to centrif to remove any suspended leafy particles. The extract is stored in a container and kept refrigerated for future use.

Preparation of aloe-carbopol gel

50 mL of viscous aloe extract was combined with 1% w/w carbopol 974 (gelling agent) and allowed to swell for 24 hours. The mixture was then thoroughly mixed and filtered through muslin cloth to remove any suspended particles. Next, 0.2% w/w methylparaben was added to the gel and blended until a homogeneous viscous solution was formed. The gel was treated with triethanolamine (TEA) under continuous stirring to adjust the pH to 5.5-6.0. The resulting gel was transferred into a container and stored in the refrigerator for next use.

Pre paration of nano loaded gel

The optimized nano formulation, obtained through statistical processes, is mixed with the aloe-carbopol gel to create a homogeneous gel. The nanoparticles, prepared with a predetermined drug concentration, are incorporated into the gel.

Physiochemical characterization of nano gel

Transparency, smoothness and relative density

The transparency and smoothness is determined by visual observation and rubbing the gel between fingers.

pH: The pH of the gel is measured by using pH meter

Moisture content

Equal quantities of the gel and commercial preparation were weighed and placed in a dessicator till a constant weight is obtained.

$$\%\, MoistureLoss = \frac{Initialweight - Finalweight}{Finalweight} X\ 100$$

Rheology

Over the course of the investigation, the sample temperature was continuously kept at 25°C. By contrasting the system's dynamic viscosity, the gel's flow properties were ascertained.

Spreadability

A 1 mL syringe was used to deposit a 250 mg sample of the nanoformulation (aloecarbopol gel, blank/AZA-loaded nanogel, and commercial preparation) on a glass slab, and the diameter of the sample was measured. and to get consistent thickness, a 500 g weight was applied for five minutes. The preparation's diameter growth (measured in centimeters) served as a benchmark for spread ability (Bachhav and Patravale, 2010).

Uniformity of drug content: Three nanogel samples, each eq. to 5 mg of the drug, were taken from different locations within the in the meoh. The emulsion was gently warmed over a water bath to facilitate complete drug extraction, then centrifuged at 7000 rpm for 10 minutes.

***Ex-vivo* permeation studies**

Rat skin was used for ex vivo permeation studies. After collection, the underlying adipose tissue was removed using a scalpel. The skin was then washed in phosphate buffer (pH 7.4) to maintain hydration. The prepared skin was mounted onto a Franz diffusion cell, with the gel applied to the donor compartment and covered to prevent any loss. A 500 µL sample was collected at intervals for analysis, replacing it with fresh buffer to maintain sink conditions. Samples were collected up to 48 hours, and drug estimation was performed spectrophotometrically using a validated method.

Stability studies

The optimized formulation was packed into its final container, sealed, and subjected to stability studies in a stability chamber for 3 months at a temperature of 40°C ± 2°C and a relative humidity of 75% ± 5%. The results were analyzed statistically using one-way ANOVA.

3. Results and Discussion

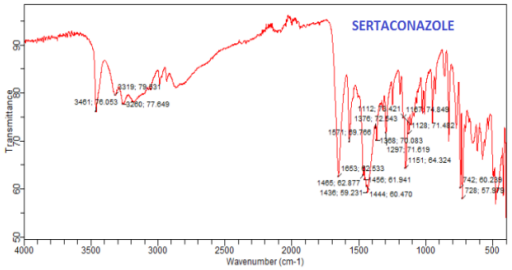

Fig.1 FTIR spectrum of pure Sertaconazole

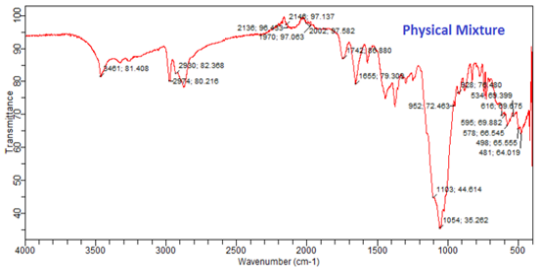

Fig.2 FTIR spectrum of physical mixture of Sertaconazole along with excipients

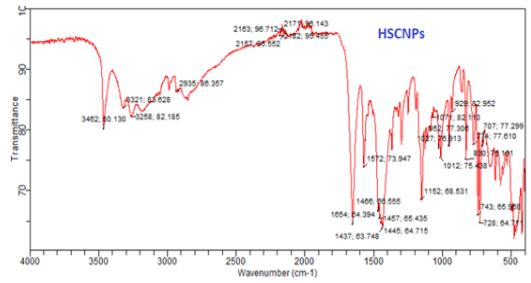

Fig.3 FTIR spectrum of Sertaconazole Nanoparticles

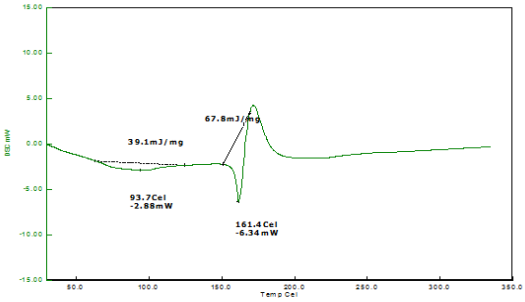

Fig.4 DSC Thermogram of pure Sertaconazole

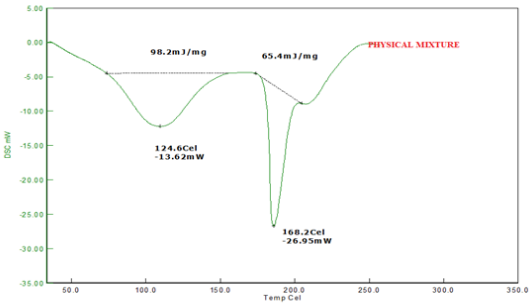

Fig.5 DSC Thermogram of physical mixture of Sertaconazole along with excipients

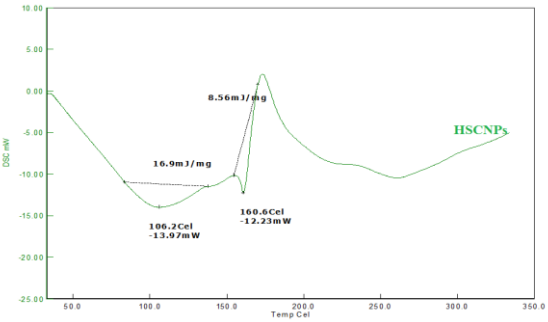

Fig.6 DSC Thermogram of Sertaconazole nanoparticles

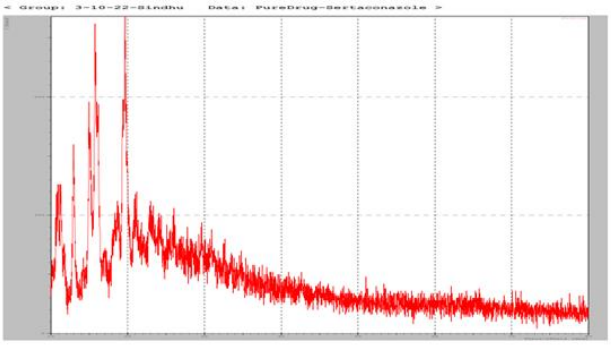

Fig.7 PXRD of Sertaconazole along with excipients

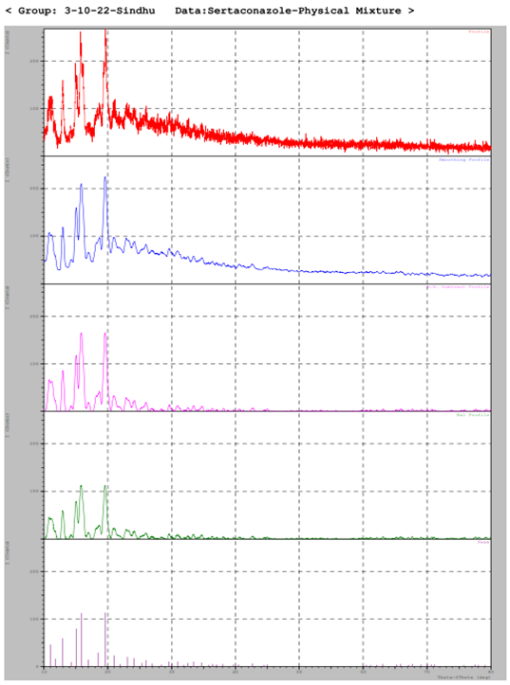

Fig.8 PXRD of Sertaconazole physical mixture

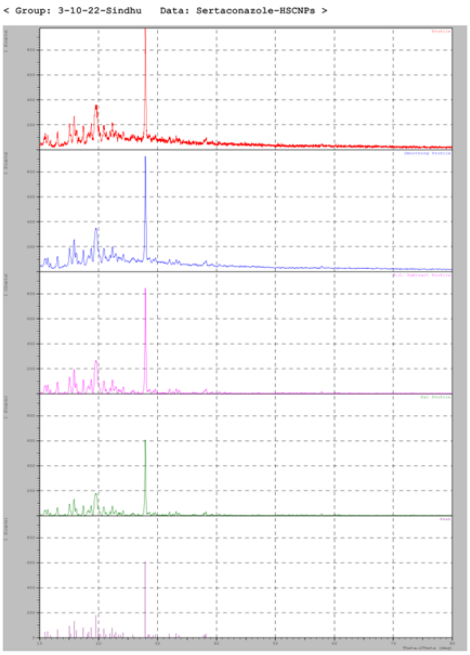

Fig.9 PXRD of Sertaconazole nanoparticles

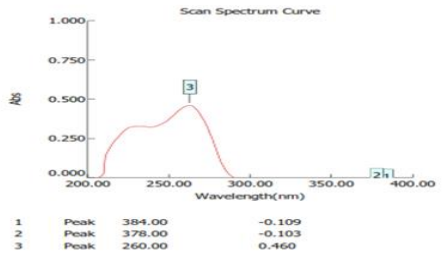

Fig.10 Graph showing absorption maxima of Sertaconazole in 0.1N HCl of pH 1.2

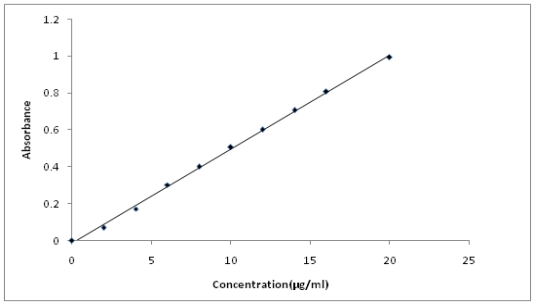

Fig.11 Calibration plot of Sertaconazole in 0.1N HCl of pH 1.2

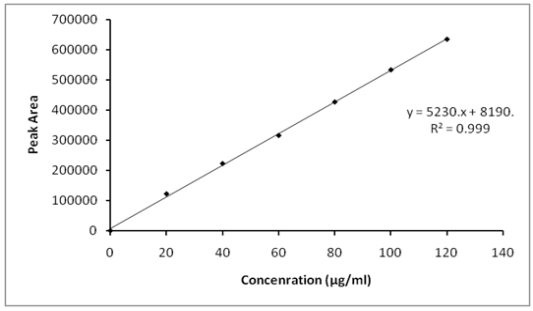

Fig.12 Calibration plot of Sertaconazole in rat plasma

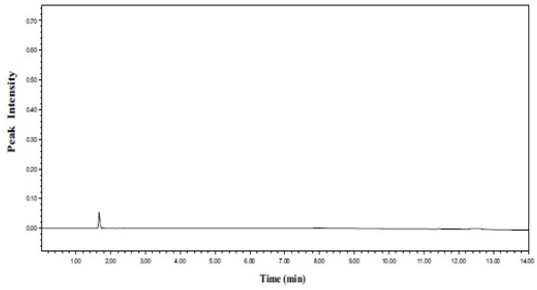

Fig.13 Blank plasma sample chromatogram

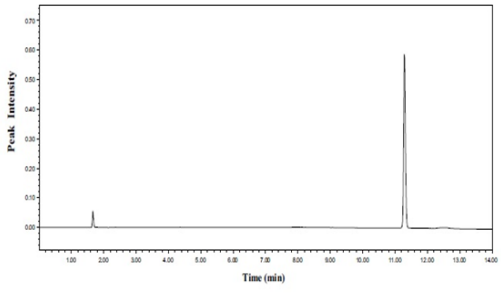

Fig.14 Chromatogram of Sertaconazole in Drug spiked rat plasma

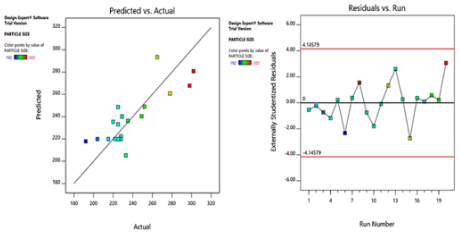

Fig.15 Residual and Predicted Plots Displaying the effect of Independent Factors onY1 Response (Particle Size)

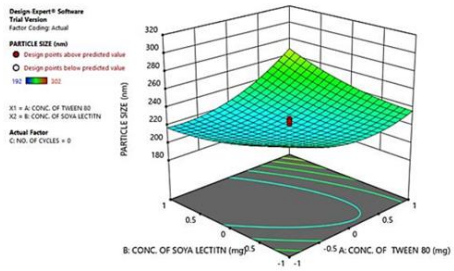

Fig.16 3D Surface Response Plot Displaying the effect of Independent Factors onY1 Response (Particle Size)

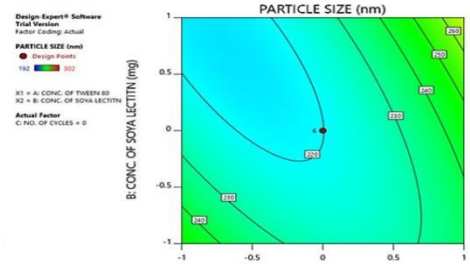

Fig.17 Contour Plot Displaying the effect of Independent Factors onY1 Response (Particle Size)

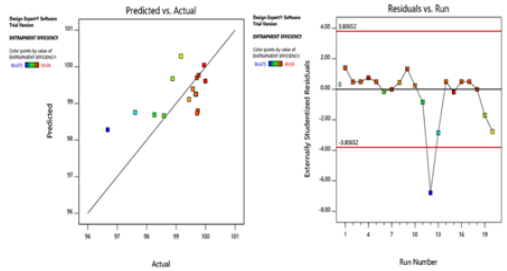

Fig.18 Residual and Predicted Plots Displaying the Impact of Independent Factors onY3 Response (Entrapment Efficiency).

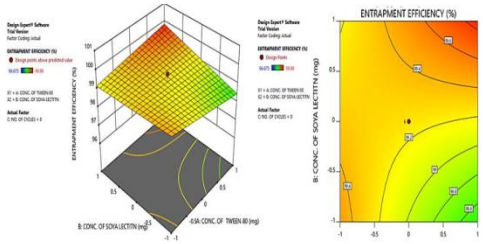

Fig.19 3DSurfaceResponsePlot and Contour Plot Displaying the Impact of Independent Factors onY3 Response (Entrapment Efficiency).

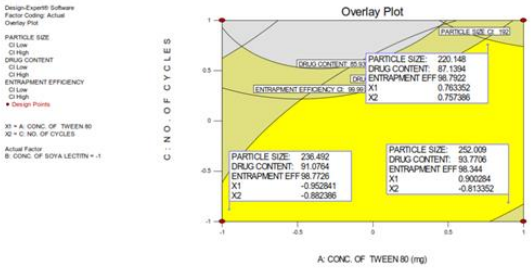

Fig.20 The Design Expert Software's suggested overlay plot shows the design space in yellow along with the compositions of a few chosen optimized formulations and the responses.

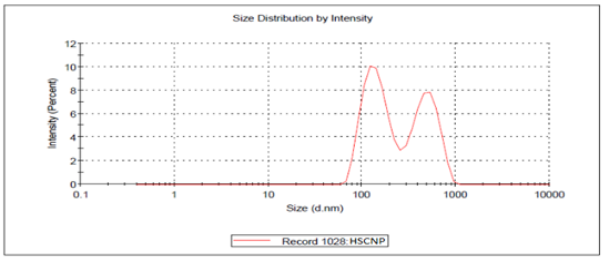

Fig.21 Graph showing the size distribution of the particles by intensity

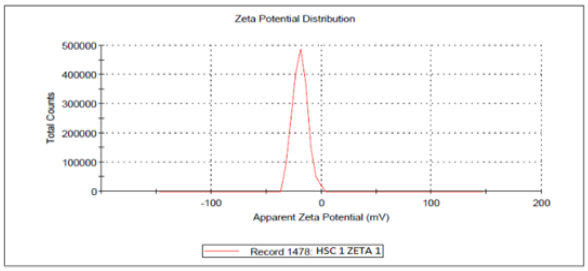

Fig.22 Zetapotential graph of Sertaconazole Nanoemulsion

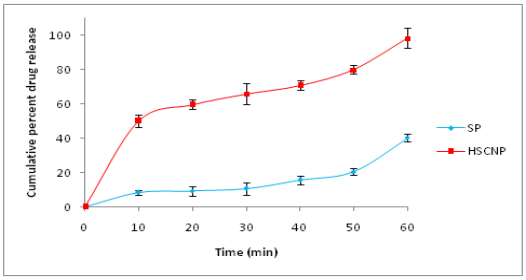

Fig.23 Drug release plot of Sertaconazole Nanoemulsion

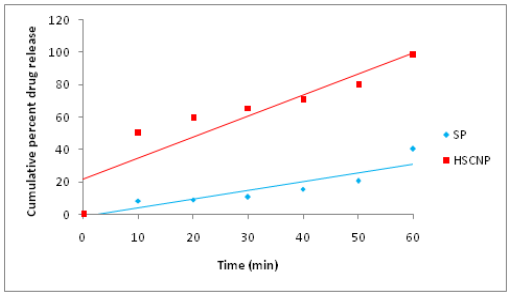

Fig.24 Zero order drug release profile of Sertaconazole Nanoemulsion

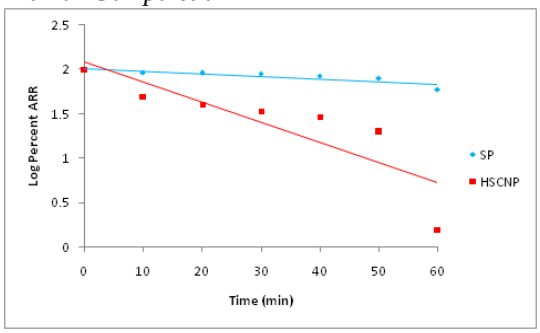

Fig.25 First order drug release profile of Sertaconazole Nanoemulsion

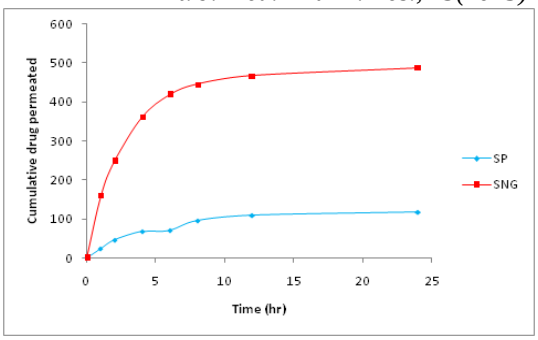

Fig.26 Ex-vivo permeation studies of SNG

Table.1 Solubility profile of Sertaconazole

Solvent	Solubility
H20	Insoluble
Ethanol	Slightly Sol.
DMSO	Soluble
DMF	Soluble
1.2pH	Soluble
4.5pH	Slightly soluble
6.8pH	Soluble

Table.2 Characteristic peaks observed in FTIR spectrum

peak type	Characteristic value	Pure	Formulation
-C-Cl stretching	785-540	Yes	Yes
-SH bending	2550	Yes	Yes
-C=O symmetric	1485	Yes	yes
- C-O	1436	Yes	Yes

Table.3 Optical characteristics of Sertaconazole in 0.1N HCl of pH 1.2

Conc. (µg/ml)	Abs. ± SD	%CV
0	**0**	**0**
2	0.0693±0.0006	0.8327
4	0.1730±0.0046	2.6489
6	0.3020±0.0075	2.4999
8	0.4013±0.0050	1.2541
10	0.5053±0.0055	1.0899
12	0.6016±0.0045	0.7495
14	0.7063±0.0064	0.9102
16	0.807±0.0053	0.6557
20	0.9930±0.0036	0.3631

Table.4 Optical characteristics of Sertaconazole in 0.1N HCl of pH 1.2

Parameter	Value
Absorption maxima	260 nm
Beers law range	2-20 µg/ml
Regression equation	Y = 0.051X -0.013
Correlation coefficient (R^2)	0.998

Table.5 Findings from the regression analysis of response variables Y1, Y2, and Y3 using the quadratic and 2FI models

Quadratic model	R2	Adjusted R2	Predicted R2	SD	%CV
Y1	0.6539	0.3419	-1.7409	23.21	9.8
Y2	0.9418	0.8903	0.5582	0.8719	0.9728
2FI	R2	Adj.R2	PredictedR2	S.D	%CV
Y3	0.3449	0.0438	.-2.815	0.8382	0.846

Table 6. Results of optimized batches obtained from anoverlay plot of Design expert software

Optimized batch	Independent variables			Dependent variables					
				Observed value			Predicted value		
	A	B	C	Y1	Y2	Y3	Y1	Y2	Y3
HSCNP1	0.152	16	28	218±0.24	93.51±0.53	99.02±0.43	221.148	87.139	98.79
HSCNP2	0.141	15	29	235±0.31	91.41±0.54	98.68±0.48	236.492	91.076	98.77
HSCNP3	0.159	15	31	250±0.37	92.23±0.45	98.52±0.52	252.009	93.77	98.79

Table.7 Release kinetics of Sertaconazole Nanoemulsion

Time (min)	SP	HSCNP
0	0	0
10	8.41±1.22	50.22±3.58
20	9.19±2.63	59.63±2.81
30	10.56±3.68	65.91±5.96
40	15.62±2.49	70.76±2.73
50	20.54±1.92	80.11±2.38
60	40.27±2.37	98.42±5.89

Table.8 Drug release kinetics of Sertaconazole Nanoemulsion

Formulation	Zer Order		First Order	
	Eq.	R^2	Eq.	R^2
SP (Dapsone Pure)	y = 0.541x - 1.290	0.826	y = -0.003x + 2.013	0.773
HSCNP (Sertaconazole Nano Emulsion)	y = 1.307x + 21.48	0.6234	y = -0.022x + 2.079	0.730

Table.9 Stability testing of Sertaconazole Nanoemulsion

Time of sample	Particle Size(nm)	Zetapotential(mv)	%Drug entrapment
Initial (0 month)	113.25 ±1.31	-22.47 ± 0.18	92.48 ± 2.12
1st month	128.53 ±2.42	-26.24 ± 0.87	90.37 ±3.22
2nd month	115.84 ±1.29	-23.39 ± 2.51	90.66 ± 1.43
3rd month	119.61 ±2.95	-20.61 ± 1.56	90.79 ± 2.40

Table. 10 Cumulative drug permeated studies of SNG

Time (hr)	Cumulative drug permeated(µg/cm^2)	
	SP	SNG
0	0	0
1	24±1	161±6
2	46±2	248±11
4	68±3	362±14
6	71±6	419±28
8	96±2	446±11
12	109±9	468±29
24	117±2	489±33

Table.11 Stability testing of SNG

Time of sample	pH	Drug content	% Drug permeated at 24 hours
Initial (0 month)	6.2 ± 0.2	96.3 ± 1.8	489 ± 33
1st month	6.5 ± 0.4	96.8 ± 1.9	496 ± 11
2nd month	6.2 ± 0.3	94.6 ± 1.2	479 ± 65
3rd month	6.5 ± 1.8	95.3 ± 1.9	459 ± 56

4. Conclusion

Fungal infections of the skin are common and often treated topically with antifungal agents. Sertaconazole, a poorly water-soluble drug from BCS Class II, was selected for formulation as a nanoemulsion to enhance solubility and bioavailability for the treatment of fungal infections like eczema. Nanoemulsion technology is advantageous for improving dissolution, bioavailability, and drug permeation, making it a promising approach for transdermal drug delivery. The study aimed to develop and optimize a nanoemulsion of Sertaconazole using statistical design methods. A full factorial design (2^4) was employed using Design of Experiments (DoE) to minimize trials and

optimize the formulation based on parameters such as rate of injection, stirring time, solvent-to-anti-solvent ratio, and stabilizer-to-drug ratio. The responses observed were particle size and polydispersity index (PDI). After optimization, the nanoemulsion was lyophilized and incorporated into an Aloe vera gel, which was then evaluated for viscosity, flow properties, stability, and ex-vivo skin permeability. The optimized nanoemulsion-based Aloe vera gel passed all the regulatory and quality control tests, demonstrating successful drug delivery and enhanced skin penetration. In conclusion, nanoemulsion-loaded Aloe vera gel of Sertaconazole was successfully formulated using a quality-by-design approach, offering an effective transdermal delivery system for treating fungal infections like eczema.

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