Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol.14 , Issue 33s (2025)
https://www.jneonatalsurg.com

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Formulation, And Characterization Of Solid Lipid Nanoparticles (Sln) Of Isavuconazole

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Cite this paper as: Anup Kumar, Pushp Raj Singh (2025) Formulation, And Characterization Of Solid Lipid Nanoparticles (Sln) Of Isavuconazole. Journal of Neonatal Surgery, 14, (33s) 1274-1288

ABSTRACT

Since their introduction in the early 1990s, solid lipid nanoparticles (SLNs) have gained a reputation as the most potent lipid-based colloidal transporters. Isavuconazonium sulfate is the prodrug of the azole antifungal isavuconazole. The present study was based on the formulation, and characterization of solid lipid nanoparticles (SLNs) of isavuconazole. Isavuconazole was purchased from the (Sigma Aldrich, India). Stearic acid, Span 20, Tween 80, and ethanol were purchased from the SD Fine Chemicals, Mumbai. After, preformulation studies, SLNs were prepared using spray drying method. In results, Isavuconazole sample was observed as white, solid powder, with its characteristic odor. Stearic acid was observed as white solid flakes and odorless. Entrapment efficiency was observed in the range of 77.15±0.42 % to 84.34±0.21 %. It exhibits the remarkable and almost identical drug content in different SLNs. These have the efficient drug content's release which represents the better solubility and optimized drug-excipient compatibility. The pH of solid lipid nanoparticles loaded with Isavuconazole was measured and found to be slightly acidic or alkaline. SLNs loaded with Isavuconazole showed almost identical response 120°C when observed with the temperature in range of 50ºC to 300ºC. SLNs loaded with Isavuconazole showed the particle size in the range of 100-300 nm, in SEM analysis. The maximum drug release was seen in 10 hours i.e., 96.45±0.6, 94.31±0.4, 93.19±0.1, 91.10±0.4, 95.14±0.3 and 93.37±0.6 in F1, F2, F3, F4, F5 and F6, respectively. In concluded that SLNs loaded with Isavuconazole showed the significant in all the characterization parameters i.e., droplet size, drug content and in-vitro drug release. Isavuconazole is promising anti-fungal moiety with a wide range of potential health benefits. SLNs loaded with Isavuconazole can be utilized as anti-fungal or anti-microbial agent with sustained action...

Keywords: Solid lipid nanoparticles, formulation, characterization, Isavuconazole, in-vitro drug release..

INTRODUCTION

Since their introduction in the early 1990s, solid lipid nanoparticles (SLNs) have gained a reputation as the most potent lipid-based colloidal transporters. This is one of the most widely used strategies to increase the oral bioavailability of medicines that are poorly water soluble. SLNs are lipid components that are physiologically tolerated and are in a solid form at room temperature. They have a submicron size range of 50-1000 nm. The benefits of fat emulsions, liposomes, and polymeric nanoparticles are all combined in SLNs [1].

Isavuconazonium sulfate is the prodrug of the azole antifungal isavuconazole [2]. Isavuconazonium is available in both oral and intravenous formulations and upon arrival into the systemic circulation is rapidly converted to the active isavuconazole by plasma esterases. The dose of isavuconazonium sulfate is 372 mg (equivalent to 200 mg isavuconazole) administered either intravenously or orally thrice daily for 2 days as loading doses prior to beginning daily therapy with 372 mg. The dose does not need to be adjusted for renal dysfunction or mild to moderate hepatic impairment. Alterations may be required for significant liver impairment. However, clear guidance for patients with severe liver dysfunction is currently lacking. As with all azole antifungals, hepatotoxicity may occur [3].

The pharmacokinetics of isavuconazole differ markedly from the other advanced generation azoles (voriconazole and posaconazole), with a substantially longer terminal half-life (184 h) allowing for once daily dosing after the initial loading doses [4]. The pharmacokinetics of isavuconazole also appear more predictable than those of voriconazole and may be slightly more predictable than the newer delayed-release tablet and intravenous formulations of posaconazole. Oral

..:

bioavailability is greater than 97%, and the volume of distribution is large (~400 L), suggesting distribution into a variety of sites. Although isavuconazole appears to penetrate well into the cerebral spinal fluid (CSF) in animal models, results are limited and mixed in humans. In one case report, central nervous system (CNS) tissue concentrations as high as 1.46 mg/kg were reported in a patient with cerebral aspergillosis following craniectomy [5].

The current research was based on the formulation, and characterization of solid lipid nanoparticles (SLN) of isavuconazole

MATERIALS AND METHODS

Drugs and chemicals

Isavuconazole was purchased from the (Sigma Aldrich, India). Stearic acid, Span 20, Tween 80, and ethanol were purchased from the SD Fine Chemicals, Mumbai.

Digital weighing balance, Digital pH meter, Franz diffusion cell and UV-Spectrophotometer.

Pre-formulation study

Organoleptic properties

Isavuconazole was observed for their physical characteristics like colour, odour, texture of drug and compared with as reported in official monograph.

Solubility

The solubility of Isavuconazole was determined by placing a small quantity of polymers (about 1-2 mg) individually in a test tube, adding 5ml of solvent (water, ethanol, methanol, phosphate buffer), shaking vigorously, and holding for a while. Take note of the product's solubility in various solvents when it is at room temperature.

Drug-excipients compatibility study

To determine whether the drug's chemical makeup has changed after being combined with the excipients or polymers. A mixture of Isavuconazole and potassium bromide was applied, then compressed into a disc form. The Shimadzu FTIR spectroscopy (4000-400cm-1) was used to evaluate the disk.

Preparation of standard calibration curve

100mg of Isavuconazole was accurately weighed and dissolved in methanol (2ml) and volume is made up to 100ml with 0.1N HCl solution thus stock solution is prepared. The 10ml of stock solution is further diluted with 0.1 N HCl (pH 1.2) in 100ml to get 100µg/ml concentration solution. Then 0.2, 0.4, 0.6, 0.8, and 1ml of solution was taken in 10ml standard volumetric flask and made the volume up to 10ml with 0.1N HCl to prepare 2µg, 4µg, 6µg, 8µg, and 10µg/ml solution. Then the absorbance was measured in a UV spectrophotometer at 270 nm against 0.1 N HCl as blank [6].

Preparation of SLN by spray-drying method

For spray drying, *Freitas* and *Mullera* advise using lipids with melting points greater than 70°C. Isavuconazole was added and swirled until completely dissolved after the lipid components- stearic acid & cholesterol melted at 60ºC. Tween 80 and Span 20 were dissolved in distilled water to form aqueous phase. Water that had been deionized was heated to the same temperature with constant stirring. Using homogenizer, the aqueous phase was mixed with the lipid phase for 5 minutes at a speed of 10,000 rpm. After that, a 25 Kw ultrasonicator was used to sonicate the suspension for 5 minutes. The nanosuspension was finally cooled to room temperature [7].

Table 1. List of composition

Formulation	Isavuconazole (mg)	Stearic acid (mg)	Cholesterol (mg)	Tweens 80 (mg)	Span 20 (%)	Deionized water (ml)
F 1	100	400	0.2	3400	2%	100
F 2	100	500	0.2	3400	2%	100
F 3	100	600	0.2	3400	2%	100
F 4	100	700	0.2	3400	2%	100

F 5	100	800	0.2	3400	2%	100
F 6	100	900	0.2	3400	2%	100

Characterization parameters [8][9][10][11]

Entrapment efficiency

The centrifugation technique was used to calculate the Isavuconazole's SLN entrapment efficiency. Methanol was used to make suspension of SLN, which was subsequently centrifuged using a high-speed cooling centrifuge at 10,000 rpm for 30 minutes at -4ºC. The supernatant was taken, and the amount of free SLN was determined using UV visible spectrophotometers at 328 nm and 366 nm, respectively.

Analysis of particle size & Polydispersity index

Zetasizer Nano-ZS was used to measure the average globule size of the Isavuconazole's SLN (Malvern Instrument, UK). measurements were taken at a 90-degree angle at 25ºC. To make sure the light scattering intensity was within the instrument sensitivity range. All measurements were made at 25c. The same instrument was used to calculate the formulation's polydispersity index. The polydispersity index revealed the width of the size distribution.

DSC analysis

Additionally, it provides information on the creation of new substances and medicine excipient compatibility. As a purge gas, dried nitrogen was employed. As per usual practise, the apparatus was calibrated for heat flow and heat capacity using indium. Every sample was heated to a temperature between 25 and 300ºC at a rate of 5ºC per minute. The nitrogen flow was kept at 5ml per minute.

***In-vitro* drug release**

When the pH of the PBS solution is 7.4, a small amount of the SLN is dissolved in it. The residual volume is then brought up to 100ml with PBS after the solvent ethanol is added to make the polymer soluble (pH 7.4). After then, 1ml is taken out of the solution and diluted once more up to 10ml. At a wavelength of 270nm, the solution's absorbance is measured, and concentration is determined.

A modified Franz diffusion cell was used to conduct in vitro diffusion. As a diffusion cell, a glass cylinder of 10cm in height, 3.7cm in outer diameter & 3.1cm in inner diameter was employed. To create a diffusion cell, a sheep mucosa was attached to one end of the cylinder via an. A cell was given 1ml of the nano emulsion, and the cell was then placed in the receptor compartment of a beaker containing 100ml of pH 6.8 phosphate buffer. The receptor compartment was in touch with the whole surface of the cell, and a temperature of 37ºC was maintained while the receptor compartment was being churned magnetically. To keep the sink condition, 10ml of the receptor compartment samples were extracted and refilled with the same volume.

Drug content

To guarantee that the medication was released from its entrapment in the medium, a predetermined amount of SLN dispersion (200 mg) was added to a volumetric flask, suspended in methanol, and continuously shaken for 30 min. This solution was put into a centrifuge tube, spun for 15 minutes at 20°C at 12000 rpm. After being diluted with enough methanol, the supernatant was filtered through a 0.45 um membrane filter. UV-VIS Spectrophotometer, Shimadzu Japan 1601, was used to measure the concentration of the griseofulvin in the supernatant at 299.5 nm and 238 nm, respectively.

pH measurement

Calculating pH is a crucial component of the SLN evaluation process. The pH of the finished preparation and, consequently, the route of administration are determined by the excipients employed in the formulation. A digital pH metre was used to determine the formulation's pH. To decrease mistake, the findings were taken in three copies.

SEM Analysis

A canopy slip made from around 5 L of the griseofulvin's SLN suspension was put onto a specimen tab one by one. At temperature, the samples were allowed to dry. The formulation's particle size was then examined by a photographer using a scanning microscope.

Stability studies

For six months, stability tests on the final optimised SLN dispersion were conducted in sealed lacquered aluminium collapsible tubes at three distinct temperatures-5°C, 25°C, and 40°C while being periodically assessed for percent drug

content, pH, texture, and other physical parameters.

RESULTS AND DISCUSSION

Pre-formulation studies

Organoleptic properties

Isavuconazole sample was observed as white, solid powder, with its characteristic odor. Stearic acid was observed as white solid flakes and odorless. Cholesterol was found as pale-yellow crystalline powder and odorless. While span 20 and Tween 80 were found as liquid.

Table 2. Organoleptic properties of Isavuconazole and excipients

Ingredients	Organoleptic characteristics		
	Appearance	Colour	Odor
Isavuconazole	Solid Powder	White	Characteristics
Stearic acid	Solid flakes	White	Pungent
Cholesterol	Crystalline powder	Pale yellow	Odorless
Span 20	Liquid	Pale yellow	Faint
Tween 80 (ml)	Liquid	Yellow	Characteristics

Solubility

The solubility of Isavuconazole in the different solvents was assessed. Isavuconazole demonstrated free solubility in Tween 80, ethanol and distilled water. It was found soluble in chloroform, and phosphate buffer solution.

Table 3. Solubility of Isavuconazole

Solvent	Isavuconazole
Span 20	Freely Soluble
Tween 80	Freely Soluble
Ethanol	Soluble
Distilled water	Poor soluble
Chloroform	Soluble
Phosphate Buffer Solution (pH 1.2)	Higher soluble

Drug-excipients compatibility studies

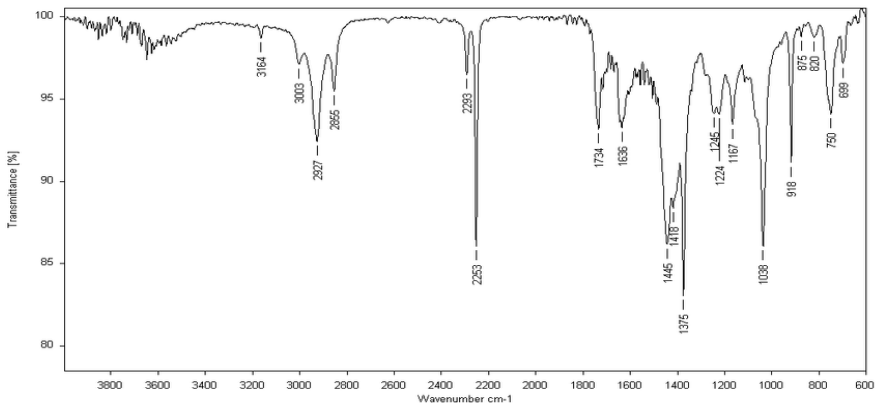


Fig 1. FTIR spectrum of Isavuconazole (API)

Table 4. IR Spectrum interpretation of Isavuconazole (API)

Functional group	**Absorption of Isavuconazole at wavenumber (cm^{-1})**
Aromatic C-H group	3164
Aromatic C-H group	3003
Aliphatic C-H group	2927
Ester C=O group	2666
C≡N and C≡C stretching	2293
C≡N and C≡C stretching	2253
C=O group	1734
C=O group	1636
C=C	1445
CH3-N group	1418
NO2 group	1375
C-N group	1245
C-O-C group	1224
C-O-C group	1167
C-N-H group	1038
C-N bending in aromatic ring	918
NO2 group	875
NO2 group	820
Aromatic C-H bending	750

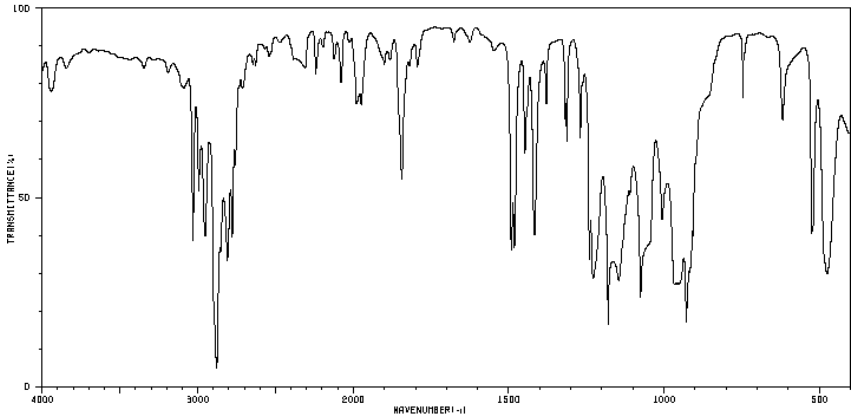


Fig 2. FTIR spectrum of Isavuconazole (API)+ Stearic acid

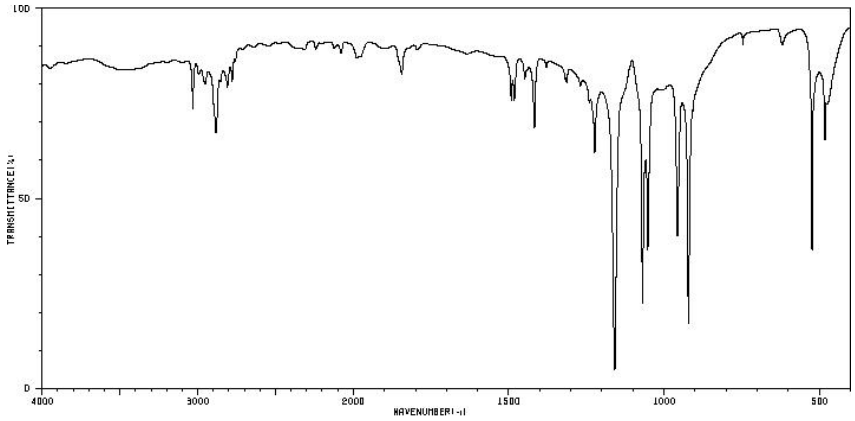


Fig 3. FTIR spectrum of Isavuconazole (API)+ Cholesterol

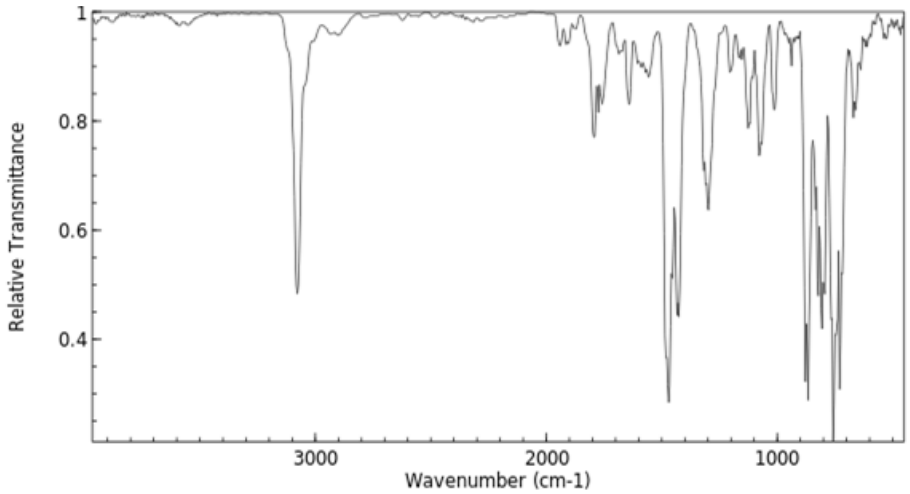


Fig 4. FTIR spectrum of Isavuconazole (API)+ Span 20

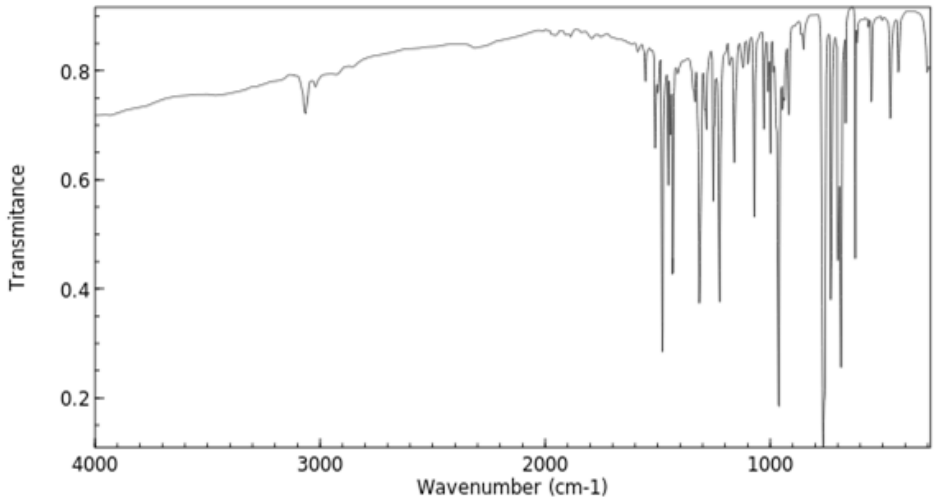


Fig 5. FTIR spectrum of Isavuconazole (API)+ Tween 80

Preparation of Std. Calibration curve of Isavuconazole

Isavuconazole showed the maximum absorption wavelength (λmax) at 285nm when determined in the conc. range of 2 µg/ml- 10 µg/ml.

Table 5.3 Std. Calibration curve of Isavuconazole

Conc. (µg/ml)	Absorption (λmax 285 nm)
2	0.19
4	0.35
6	0.59
8	0.76
10	0.93

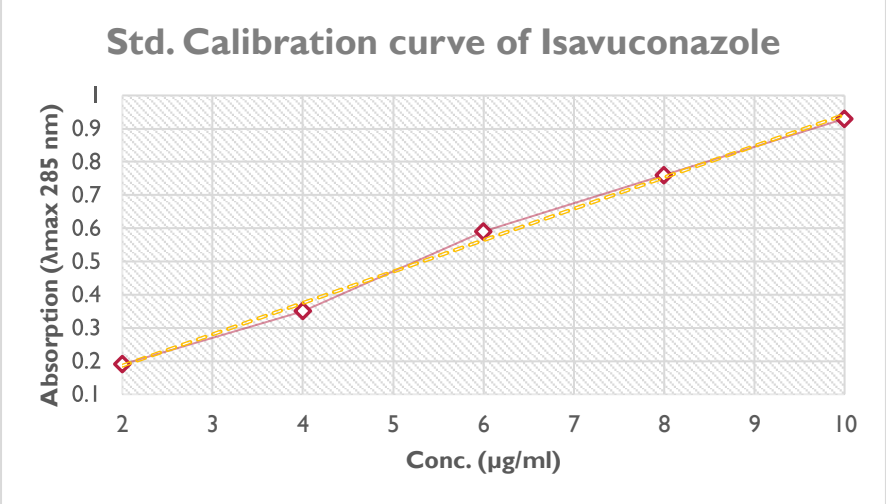


Fig 6. Std. Calibration curve of Isavuconazole

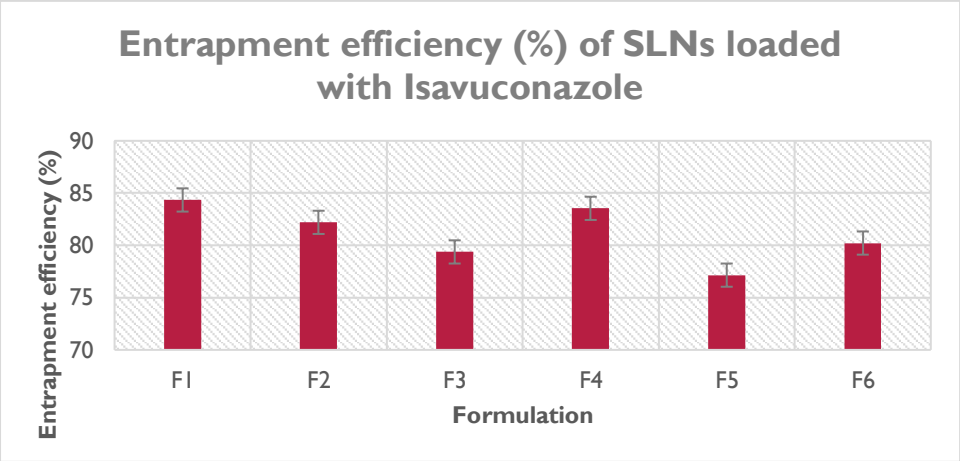
Characterization parameters

Entrapment efficiency

Entrapment efficiency is a distinct feature of solid lipid nanoparticles to characterize for the optimized formulation. It was determined as 84.34±0.21 % which observed maximum among all the formulated SLNs. Entrapment efficiency was observed in the range of 77.15±0.42 % to 84.34±0.21 %. Below table shows the entrapment efficiency of gallic acid- based SLN:

Table 6. Entrapment efficiency (%) of SLNs loaded with Isavuconazole

Formulation	Entrapment efficiency (%)
F1	84.34±0.21
F2	82.20±0.14
F3	79.37±0.11
F4	83.54±0.24
F5	77.15±0.42
F6	80.22±0.10

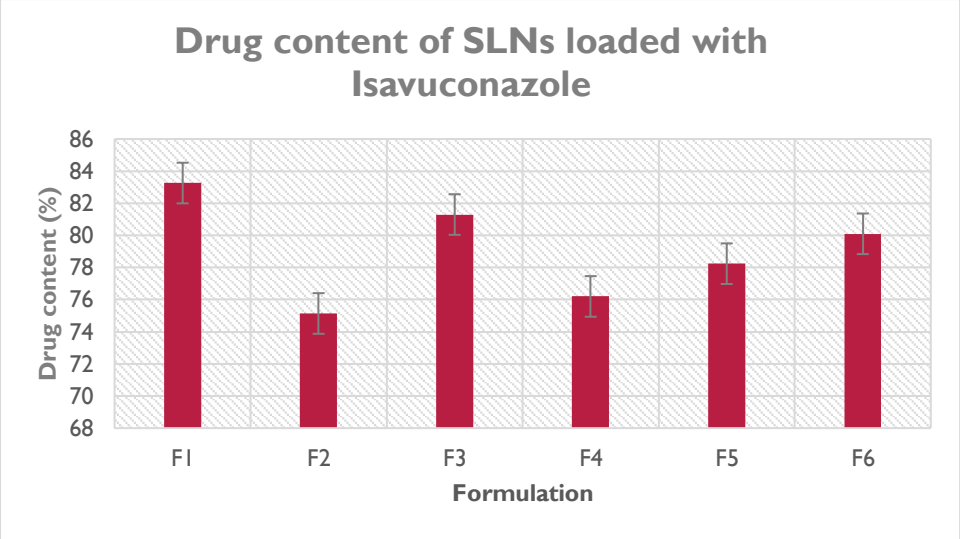


Drug content

In solid lipid nanoparticles loaded with Isavuconazole, the drug content was estimated as 83.26± 0.43 % which observed highest in contrast all the formulations. It exhibits the remarkable and almost identical drug content in different SLNs. These have the efficient drug content's release which represents the better solubility and optimized drug-excipient compatibility. Below table shows the drug content (%) of SLNs loaded with Isavuconazole.

Table 7. Drug content of SLNs loaded with Isavuconazole

Formulation	Drug content (%)
F1	83.26± 0.43
F2	75.14± 0.20
F3	81.30± 0.09
F4	76.20± 0.14
F5	78.24± 0.39
F6	80.10± 0.47

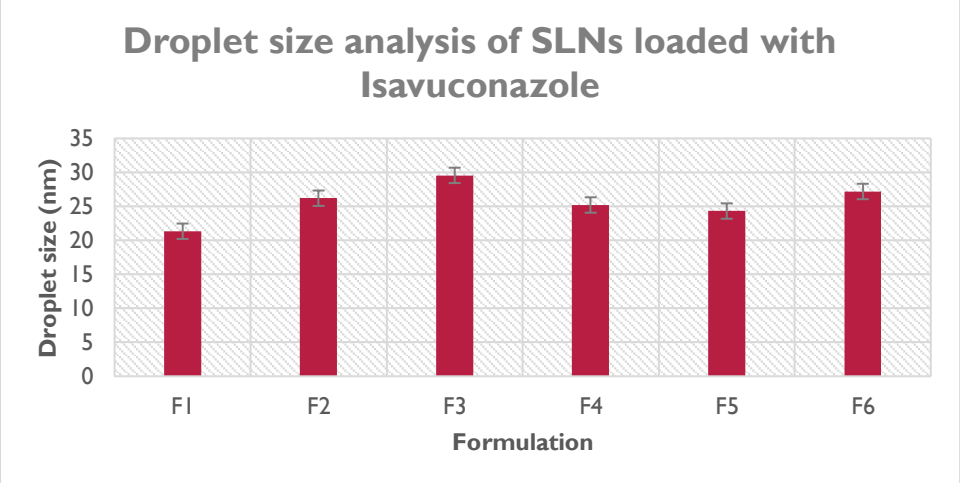


Droplet size analysis

The Nanodroplet analyser was utilized for the droplet size analysis of SLNs loaded with Isavuconazole. It showed almost similar droplet size with represents an identical drug relase and thus enhanced bioavailability. Droplet size was observed in the range of 21.34±0.11 nm to 29.56±0.13 nm.

Table 8. Droplet size analysis of SLNs loaded with Isavuconazole

Formulation	Droplet size (nm)
F1	21.34±0.11
F2	26.20±0.14
F3	29.56±0.13
F4	25.20±0.19
F5	24.31±0.17
F6	27.19±0.42

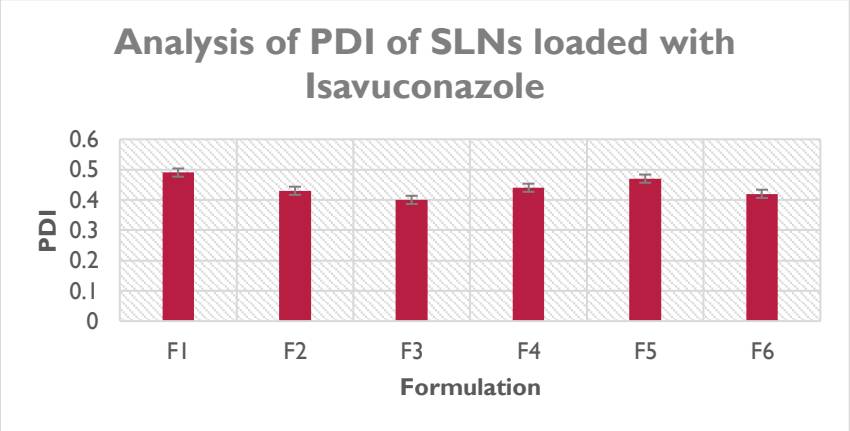


Analysis of PDI

The analysis of polydispersity index (PDI) exhibits the particle homogeneity. The PDI values found in the expected range of 0.40±0.07 to 0.49±0.05. F1 showed the highest PDI as 0.49±0.05. However, all the formulations (F1-F6) showed the PDI below 1.0.

Table 9. Analysis of PDI of SLNs loaded with Isavuconazole

Formulation	PDI
F1	0.49±0.05
F2	0.43±0.09
F3	0.40±0.07
F4	0.44±0.02
F5	0.47±0.06
F6	0.42±0.01

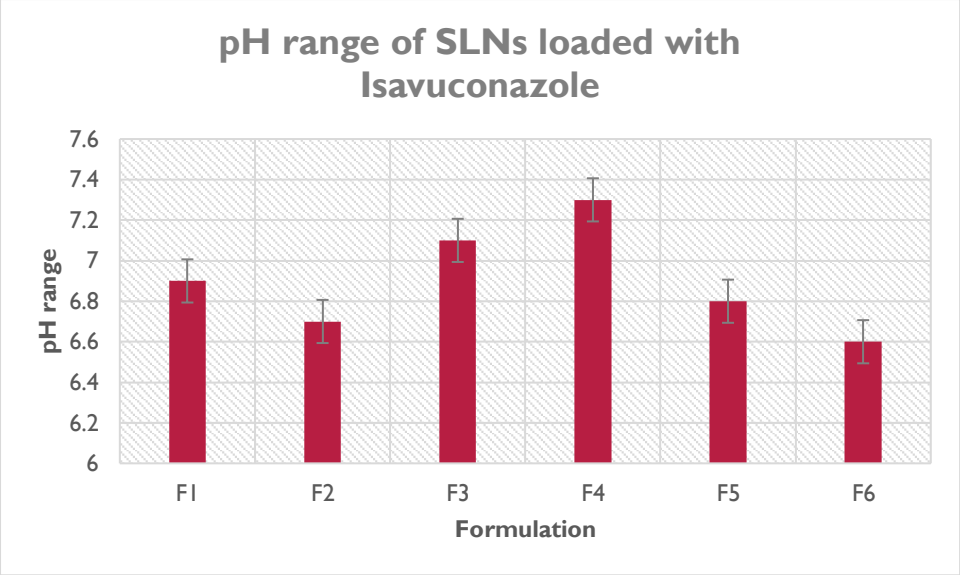


pH measurement

The pH of solid lipid nanoparticles loaded with Isavuconazole was measured and found to be slightly acidic or alkaline. One hour after the preparation of SLNs, the pH was estimated. It assures that the pH range used to manufacture the solid nanoparticles was ideal for their better patient's compliance and solubility in body secretions.

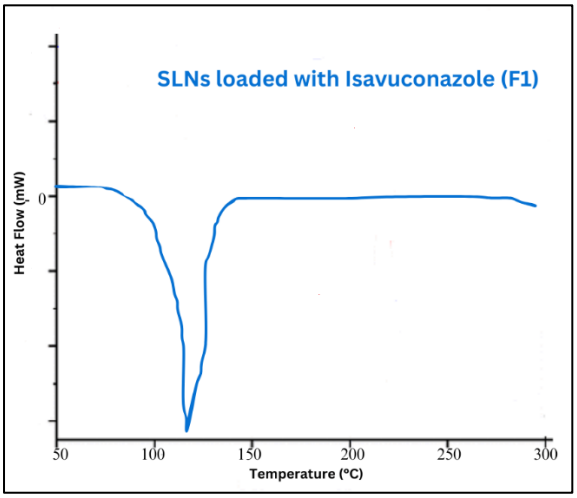
Table 10. pH range of SLNs loaded with Isavuconazole

Formulation	pH range
F1	6.9± 0.14
F2	6.7± 0.23
F3	7.1± 0.15
F4	7.3± 0.27
F5	6.8± 0.20
F6	6.6± 0.12

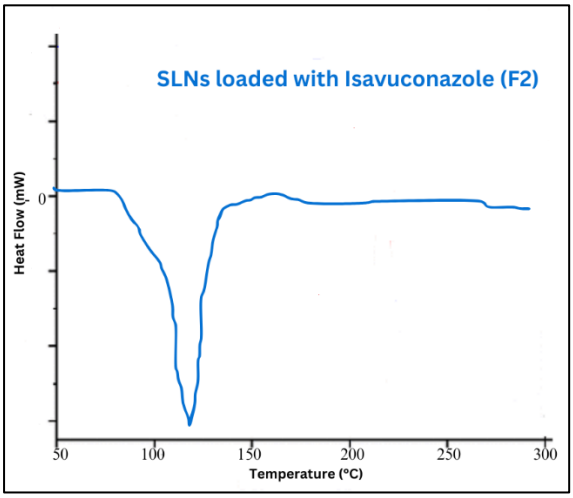


DSC estimation

DSC analysis is done to confirm if the SLNs are resistant to the moisture and increasing temperature. SLNs loaded with Isavuconazole showed almost identical response 120°C when observed with the temperature in range of 50ºC to 300ºC.



F1



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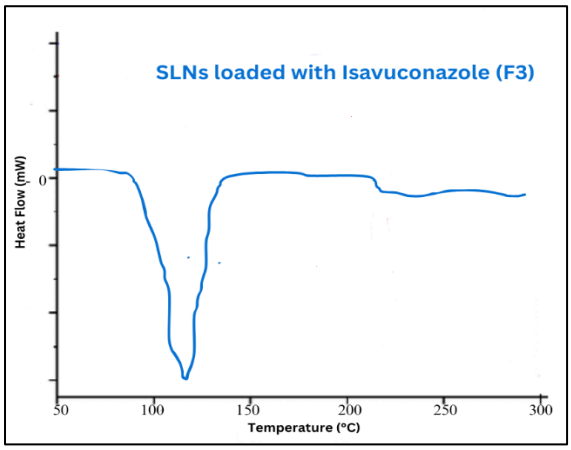

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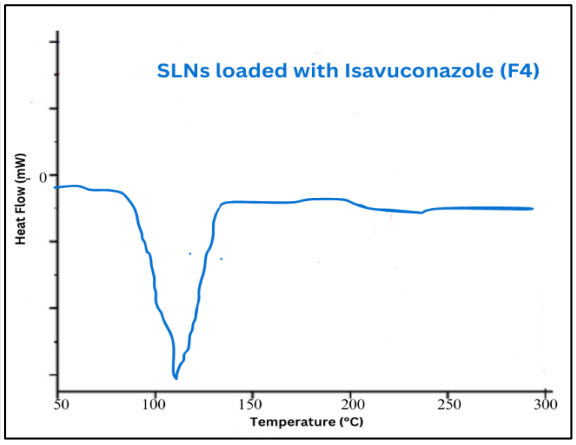

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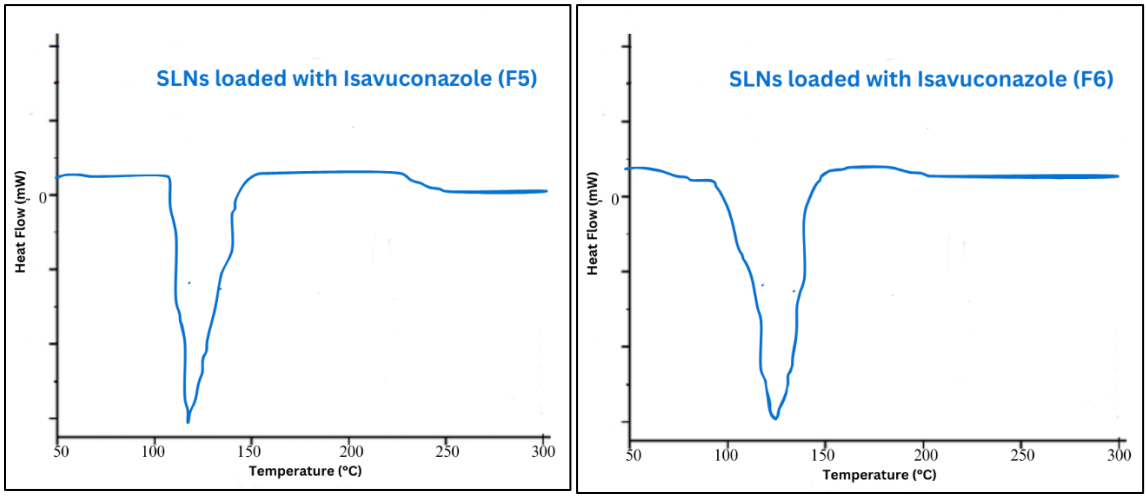
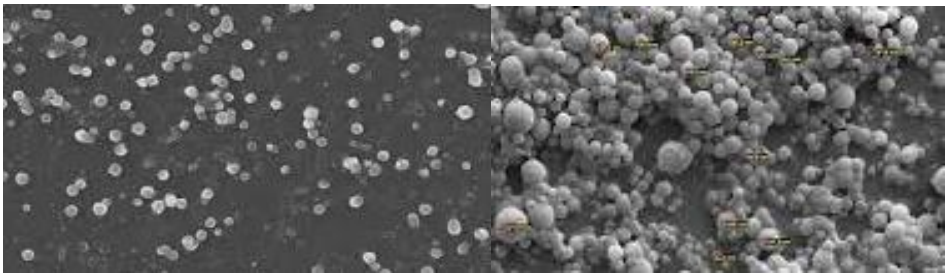


F5 **F6**

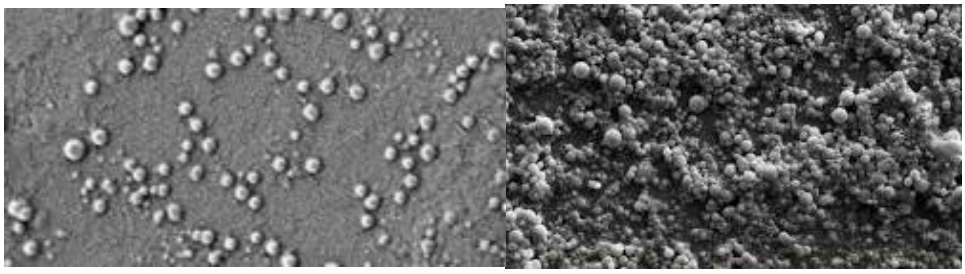
Fig 7. DSC thermographs of SLNs loaded with Isavuconazole

SEM determination

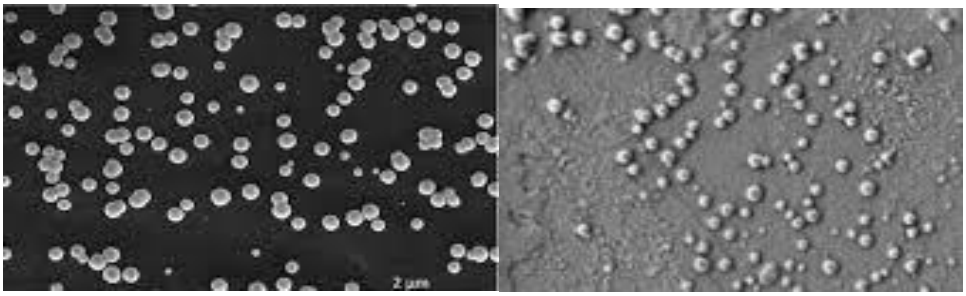
SLNs loaded with Isavuconazole showed the particle size in the range of 100-300 nm, in SEM analysis.



F1 **F2**



F3 **F4**



F5 **F6**

Fig 8. SEM analysis of SLNs loaded with Isavuconazole

***In-vitro* drug release**

The maximum drug release was seen in 10 hours i.e., 96.45±0.6, 94.31±0.4, 93.19±0.1, 91.10±0.4, 95.14±0.3 and 93.37±0.6 in F1, F2, F3, F4, F5 and F6, respectively.

Table 11. *In-vitro* drug release of SLNs loaded with Isavuconazole

Time (hr)	% Drug release ± S.D. F1	F2	F3	F4	F5	F6
0	0.00	0.00	0.00	0	0.00	0
1	10.19±0.2	11.34±0.6	9.72±0.4	9.54±0.2	8.17±0.6	9.78±0.4
2	15.19±0.1	14.52±0.4	13.74±0.2	14.82±0.6	13.79±0.2	15.11±0.6
4	31.24±0.2	29.13±0.4	27.83±0.1	29.17±0.2	29.21±0.4	30.41±0.2
6	53.16±0.3	51.24±0.6	49.18±0.2	50.36±0.4	50.14±0.2	52.34±0.6
8	76.20±0.1	74.16±0.3	72.31±0.4	69.82±0.1	74.59±0.2	73.16±0.4
10	96.45±0.6	94.31±0.4	93.19±0.1	91.10±0.4	95.14±0.3	93.37±0.6

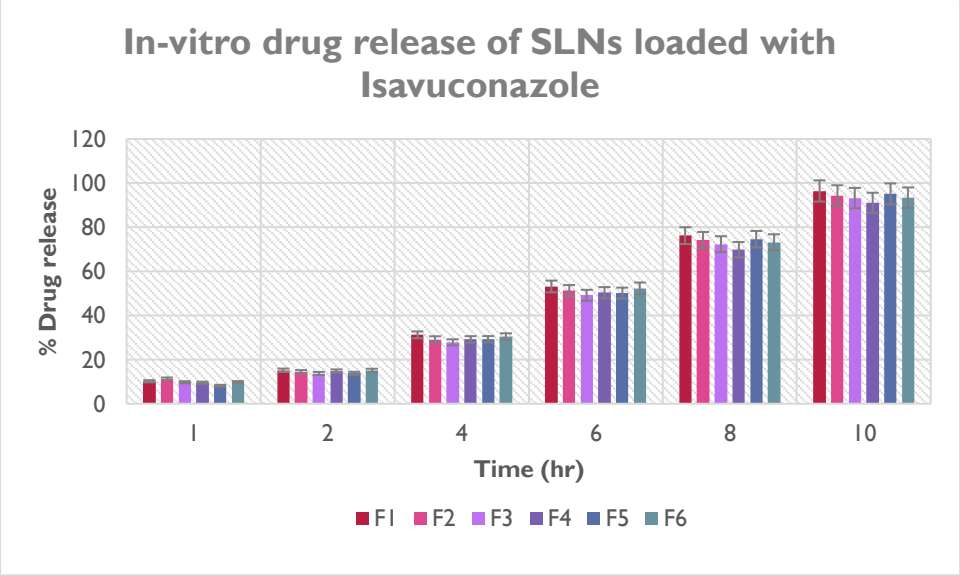


Fig 9. In-vitro drug release of SLNs loaded with Isavuconazole

Stability studies

To confirm the stability of solid liquid nanoparticles, their pH, drug content and *in-vitro* drug release were examined. After 1 month of storage, the physical characteristics of a number of solid liquid nanoparticles were found to be consistent. Therefore, it is feasible to conclude that solid lipid nanoparticles based on Isavuconazole that were made using these excipients were very stable and effective.

Consequently, tests for pH, in-vitro drug release, and physical appearance revealed that the gallic acid-based formulation was stable after a month of storage. One way to improve these insufficient GA PKs is by nanoformulation. Research has shown that using NDDS can lead to better pharmacokinetics and therapeutic advantages [12]. Another objective of nanocarriers was to improve a drug's stability. In order to improve encapsulation efficiency and offer controlled release at the desired site, they must also be built correctly. Nanocarriers can boost a medication's therapeutic effectiveness by

improving its lipophilicity and bioavailability. New GA-derived compounds with substantial pharmacological potential might certainly be produced by advancements in nanoparticles. GA may be useful as a medicinal agent for a variety of human diseases [13].

In this regard, several nanoformulation methods were applied to enhance GA's pharmacokinetic properties. For example, research has demonstrated that phytosomes boost the hepatoprotective effectiveness and bioavailability of GA. Elastic niosomes are highly beneficial for enhancing GA's stability and penetration for topical anti-aging therapies, according to another study [14][15].

As a result, niosomes are very elastic and helpful in boosting the drug's potency and permeability for topical anti-aging uses. Graphene oxide as a nanoparticle to demonstrate the anti-tumor effect of GA. It showed a longer release of GA, which improved therapeutic effectiveness and reduced dosage frequency. Gallic acid's pharmacological action offers a number of health benefits. In order to improve patient compliance in the prevention and treatment of various illnesses, efforts are being made to enhance the therapeutic efficacy and bioavailability of herbal bio-actives, such as gallic acid, with an emphasis on nanotechnology and other NDDS [16].

For better antidandruff treatment, the study effectively created and refined a solid lipid nanoparticle (SLN) formulation loaded with ketoconazole and added to a shampoo base.

The optimal composition showed a desirability value of 0.643 at 20 mg drug, 74.39 mg lipid, and 32.78 ml surfactant. The optimized SLN formulation was achieved by independently varying the amounts of drug, lipid, and surfactant. The produced SLNs showed desirable physicochemical characteristics, such as acceptable polydispersity, high entrapment efficiency, mild negative zeta potential, and particle diameters, suggesting durable and effective ketoconazole encapsulation.

The finished composition remained clear, uniform, smooth, and aesthetically pleasing after being added to the shampoo base. Its viscosity of 1500 cP supported acceptable handling and application qualities, and its pH of 6.02 indicated suitable for scalp application. Additionally, the shampoo demonstrated consistent medication distribution, steady foam retention, and excellent foamability, demonstrating that the SLNs were successfully included into the formulation without sacrificing shampoo quality [17].

Nanoparticles still need to be developed for therapeutic usage, even though they are more bioavailable, efficient, and reactive than traditional drug delivery methods. Immunogenicity and biocompatibility are the primary obstacles to creating and using nanoparticle-based solutions. One explanation for the hazardous response of nanoparticles might be the generation of free radicals, which lead to oxidative stress. Excessive quantities of free radicals can harm DNA, proteins, lipids, and other biological components. Additionally, products based on nanoparticles must pass strict regulatory clearance processes before being utilized in clinical settings [18].

CONCLUSION

In concluded that SLNs loaded with Isavuconazole showed the significant in all the characterization parameters i.e., droplet size, drug content and *in-vitro* drug release. It reported the improved stability when estimated after 1 month of storage, with no significant change in pH, *in-vitro* drug release and drug content.

Isavuconazole is promising anti-fungal moiety with a wide range of potential health benefits. SLNs loaded with Isavuconazole can be utilized as anti-fungal or anti-microbial agent with sustained action. Further studies are suggested to confirm the safety and efficacy of SLNs loaded with Isavuconazole, clinically.

CONFLICT OF INTEREST

Authors declare for none conflict of interest.

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