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PREPARATION & EVALUATION OF MICROEMULSION BASED GEL OF LULICONAZOLE

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ABSTRACT

Fungal infection is generally characterized by progressive onsets of species of fungi and causes severe health problems in immune-restricted individuals with high morbidity and mortality. Solid lipid nanoparticles (SLNs) have become an innovative, modern-day pharmaceutical novel drug delivery device (NDDS). Luliconazole has poor water solubility (0.0659 mg/ml) which makes its penetration limited to lipid bilayer of skin. In latest years nano-carriers form topical formulation such as nanoparticles, nanoemulsions, nanocrystals, solid lipid nanoparticles etc. have obtained most importance as likely drug carrier for topical delivery due to their each advantages and great potential as differentiate to normal formulations like higher drug payload capacity, higher permeability, high solubility use of low amount of excipients, high chemical stability, low toxicity and manufacturing. In this study, Luliconazole loaded with solid lipid nanoparticles (SLNs) will develop to increase penetration of drug to skin owing to lipidic nature of SLNs and further drug loaded SLNs were absorb inside gel to enhance skin retention time. Hence, present study is associated with optimization and evaluation of topical gel containing SLN loaded with Luliconazole. Further, prepared best SLN formulation is prepared and evaluated for getting a carbopol based topical gel. The particle size analysis of luliconazole SLN suspension revealed that the particle size measured by laser light method is around to 130-245 nm with low polydispersity index. All the SLN formulation shows particle sizes in the nano range (< 1 µm). The reduced particle size and polydispersity index could be attributed to the stabilization of colloidal system. Zeta potential is one of the important parameters used to forecast the physical stability of nanoparticles. The stability of the nanoparticle system depends on the high zeta potential value which points toward better stability of the nanosystem since it could deliver a deterring force between the nanoparticles. SLN shows a zeta potential -22.2 mV with conductivity 17.6mS/cm and states to the high stability of the nanosystem. The *in vitro* drug diffusion study of the formulated Luliconazole nanoemulgel was conducted for 12 h, during which the formulation showed a release rate of 84.813% to 96.89% . In vitro release investigation of drug-loaded gels demonstrated optimum in vitro drug release up to 12 h. The in vitro release of the drug from the SLN dispersion gel was found to be biphasic, with the initial burst effect followed by steady release of the drug. According to SEM analysis, the Luliconazole containing SLN in the gel had a spherical form and a smooth surface. By using the solvent diffusion approach Luliconazole loaded solid lipid nanoparticle were successfully created. There was determined to have 94.21±0.045entrapment efficiency. 130.5nm was found to be the particle size and 0.265PDI and zeta potential -22.2 mV of the developed formulation LSLN6. The size of the SLN increased along with the amount of lipid. The compatibility of the medicine and excipients is strongly suggested by ATR-FTIR. The Luliconazole loaded SLN LG3 gel formulation with carbopol 934 (1.5% w/v) are best as an optimal formulation and acceptable for topical use according to the findings of the current study.

Keywords: Luliconazole nanoemulgel, topical use, SLNs, carbopol 934.

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1. INTRODUCTION

Fungal infection is generally characterized by progressive onsets of species of fungi and causes severe health problems in immune-restricted individuals with high morbidity and mortality. It is greatly associated with patients having hematologic, prolonged leukopenia and autologous grafts disorders. Fungal infections generally curve whole body's system and lead serious lethality to body's cellular system [1]. The subcutaneous mycosis and is caused by chronic fungal infection which targets dermis and subcutaneous tissue and it is then termed as subcutaneous mycosis [2].

Solid lipid nanoparticles (SLNs) have become an innovative, modern-day pharmaceutical novel drug delivery device (NDDS). SLN discovered in 1991, representing typical colloidal carriers such as polymeric and micro, liposome emulsions, and nanoparticles modern SLN approach is associated with enhancing drug permeation capacity, strong release profile, and targeted drug delivery with excellent physical stability and low degradability etc [3,4]. Nanoparticles sizes from 10 to 1000 nm in size have promising effects in enhancing bioavailability of drug. Formulation hyphenated with SLN is major consideration in era of colloidal drug carrier system which generates an alternative particulate in field of NDDS [5].

Luliconazole is contemporary and wide-spectrum anti-fungal agent that is approved by FDA (USA). Due to bioavailability barrier of Luliconazole, it does not encompass topical delivery system [6]. In fungal infection, cutaneous and subcutaneous encompassment is required to customize drug permeation ability which can situate high drug concentrations at site of therapeutic action. However, many topical pharmaceuticals of Luliconazole are present in markets that have minor skin permeability with shorter skin retention and it leads major patient compliance [7]. In current time, nano-formulation have gained exponential growth in field of pharmaceuticals due to high complexity in drug load capacity, limited excipients quantity, steadiness in drug stability, lesser harmfulness, and easy scale-up and processing. SLNs have strangely wide-ranging properties which mark them beneficial for high permeation ability in topical delivery of drugs and potentiate extended retention at site of contagion [8].

Gels are defined as a "semisolid system where the liquid phase is inhibited in a polymer matrix which induces a high degree of physical and chemical cross-linking." [6, 9-11]

Carbopol, also known as carbomer, is a generic name for a group of synthetic high molecular weight polymers of acrylic acid, typically cross-linked with polyalkenyl ethers or divinyl glycol. They are widely used in various applications, particularly in personal care products, pharmaceuticals, and household products, due to their thickening, suspending, stabilizing, and gelling properties [10-11].

Poloxamers, also known as Pluronics, are a class of nonionic triblock copolymers used extensively in pharmaceutical and cosmetic formulations due to their unique properties. They consist of a central hydrophobic block of poly (propylene oxide) (PPO) flanked by two hydrophilic blocks of poly (ethylene oxide) (PEO). This amphiphilic structure allows them to act as surfactants, solubilizing agents, emulsifiers, and stabilizers [12].

Luliconazole is an approved by USFDA in November 2013. Luliconazole is surface broad-spectrum antifungal drug. Therefore, topical formulation of Luliconazole 1 % cream LUZU is related with poor skin permeation, small skin retention time and has to be applied twice or thrice daily. Further, Luliconazole has poor water solubility (0.0659 mg/ml) which makes its penetration limited to lipid bilayer of skin. In latest years nano-carriers form topical formulation such as nanoparticles, nanoemulsions, nanocrystals, solid lipid nanoparticles etc. have obtained most importance as likely drug carrier for topical delivery due to their each advantages and great potential as differentiate to normal formulations like higher drug payload capacity, higher permeability, high solubility use of low amount of excipients, high chemical stability, low toxicity and manufacturing [13-20]. In this study, Luliconazole loaded with solid lipid nanoparticles (SLNs) will develop to increase penetration of drug to skin owing to lipidic nature of SLNs and further drug loaded SLNs were absorb inside gel to enhance skin retention time.

Hence, present study is associated with optimization and evaluation of topical gel containing SLN loaded with Luliconazole. Further, prepared best SLN formulation is prepared and evaluated for getting a carbopol based topical gel.

2. MATERIALS & METHOD

2.1 Materials & equipment used:

Luliconazole was procured from SMS pharmaceuticals, Hyderabad, Telangana, India, carbopol-934 was purchased from SD Fine-Chem. Ltd, Mumbai, India. Whereas steric acid was purchased from Merck Chemical Company, Mumbai, India and poloxomer 188 was purchased from SD Fine-Chem limited, Mumbai. All other chemicals and solvents were used without further purification and were of analytical grades.

2.2 METHODS

PREFORMULATION STUDIES [6, 13-27]:

The main aim of the preformulation work is to provide relevant data beneficial in formulating more stable and better bioavailable formulations.

CHARACTERIZATION OF DRUG [6, 13-27]:

Physical appearance

Luliconazole was checked visually for Physical appearance.

Melting point

Melting point of Luliconazole was found out using hot stage melting point apparatus. The drug was filled in the one sided fused capillary and placed in to the apparatus. The temperature was noted down when melting of drug started to complete melting temperature.

Differential Scanning Calorimetry (DSC):

DSC was performed using a DSC TA-60 (Shimadzu, Tokyo, Japan) in order to assess the thermal behaviour of the drug. It measured heat flow in and out of both sample and reference during control temperature. About 1 mg of the sample was sealed in the aluminium pan and heated at the rate of 10°C/min, covering a temperature range of 30°C to 350°C under nitrogen atmosphere, at flow rate of 20 ml/min.

Solubility Studies

Solubility studies were carried out in distilled water according to the method reported by Higuchi and Connors. Excess quantity of Luliconazole were introduced in 10 mL of various solvents (purified water, ethanol, n-octanol and PBS pH 7.4)r and shaken for 24 hours at room temperature. After centrifugation, the supernatant was analyzed for solubility. The supernatant content of each flask was then filtered through a Whatmann filter paper. The filtrate was then diluted and assayed spectrophotometrically at respective λ_{max}. Each solubility was determined in triplicate (n=3). The results obtained from saturation solubility studies were statistically analyzed.

Determination of Partition Coefficient:

Additionally ascertain the luliconazole partition coefficient using the water and n-octanol partition systems. A conical flask containing the measured amount of luliconazole was filled with the measured amounts of n-octanol and purified water. To establish equilibrium, the flask was stirred for 48 hours. The resulting mixture was transferred to a separating funnel and left to separate two layers for 45 minutes. Each layer's first component was taken and examined using a UV spectrophotometer set at 298 nm. The resulting value of both phases was determined and $\log_{10}$ P of ration was calculated.

Drug Excipient Interaction Study

This study was carried out to check for any possible interaction between the drug and excipient. Drug and various excipients were mixed separately in a ratio of 1:1 and were stored at room temperature and checked visually after one month interval for 3 months.

If any coulor changes are there, then it may be due to interaction of drug with excipients. Finally it was analysed for quantification of pure drug through UV-visible spectrphotometric methods. Compatibility of drug with carriers was investigated by Fourier Transform Infrared spectroscopy (FT-IR) and DSC studies as mentioned earlier.

Fourier Transform Infrared Spectroscopy (FTIR) Analysis

FTIR spectra were recorded by FTIR-410 spectrophotometer, Jasco, Japan, using the potassium bromide (KBr) disk technique (5 mg samples for 100 mg dry KBr). KBr discs of the compounds were prepared and analyzed at the wavelength range of 4000–400 cm^{-1}.

PREPARATIONS OF LULICONAZOLE LOADED SOLID LIPID NANOPARTICLES (LSLN) [6,18-30]:

The SLN was prepared using a referenced protocol of the solvent diffusion method with some modification. Briefly, a known amount of luliconazole and stearic acid was placed into 5 ml of ethanol and heated at 60±3.0°Con a water bath. The obtained solution was placed into 5 ml of aqueous poloxomer 188 solutions at 4-8°C under magnetic stirring at 2000 rpm with the help of a syringe. The SLN formed instantly and recovered by centrifugation at 2000 rpm for 30 min at 4°C The obtained heterogeneous mixture further proceeded to high- pressure homogenization for 5 min under 8000 rpm. The obtained mixture was placed to be stable at room temperature, which turns to clear nanocrystals by recrystallization of the dispersed lipid. Different formulation of drug loaded SLN were prepared by varying concentration of stearic acid and surfactant. The various formulation trials were formulated using different concentration of stearic acid and surfactant and they were given in **Table 1.**

Table 1: Composition of Different Solid Lipid Nanoparticles

Formulation	Drug (mg)	Steric acid (mg)	Poloxomer 188 (%w/w)
LSLN-1	100	1000	1.0
LSLN-2	100	1250	1.0
LSLN-3	100	1500	1.0
LSLN-4	100	1000	1.5
LSLN-5	100	1250	1.5
LSLN-6	100	1500	1.5

EVALUATION OF SLN [18-30]

Physicochemical property

Physicochemical Properties of SLN dispersions were characterized as colour, odour, pH, and solubility of LSLN-6 in aqueous medium.

Evaluation of entrapment efficiency

Entrapment Efficiency: Entrapment efficiency of solid lipid nanoparticle with Luliconazole (LUL) was

determined by described process with some changes. Solid lipid nanoparticle were prepared at 37°C. Take 5mg dried solid lipid nanoparticle was dissolved in 10 ml ethanol and then filtered by a syringe filter 0.22µm size. Analyzed the concentration of Luliconazole spectrophotometrically at 298nm. Entrapment efficiency was determined by the following equation. % Entrapment Efficency (EE) = (W (initial drug) - W (free drug) / (W (initial drug) Where, W(initial drug) is the mass of drug added initially, W(free drug) is the mass of free drug detected after centrifugation.

Particle size and zeta potential

Particles Size analysis and PDI:

At room temperature, mean particle size and PDI of luliconazole-loaded SLN analysed using a nanoparticle analyser and (DLS). Sample dissolved in water and sonicated for 20 minutes. After that this solution can be diluted and analyse the size of solid lipid nanoparticles.

Zeta Potential:

The charges on the surface of luliconazole-loaded SLN was determine at at 37°C, by using Malvern nanoparticle analyser was determined using solid lipid nanoparticles. The ZP was determined after dilution of sample with phosphate buffer saline solution and maintained the pH of the solution at 7.4 and then analyzed the samples.

Optical Microscopic Analysis:

The optical microscopy analysis of best solid lipid nanoparticle was performed at 100x magnification using a digital optical microscope with a fluorescent lamp (labomed Lx-400). It is used to determine if Luliconazole solid lipid nanoparticles are efficiently localized with uniform texture in solid lipid nanoparticle (SLNs) dispersion.

FTIR spectra of best SLN

FTIR analysis for solid lipid nanoparticle (SLN) of best formulations were determined, each sample mixed with potassium bromide and later proceed for the spectroscopical and observed from 4000 to 400 cm^{-1}.

PREPARATION OF GEL [18-27]

Formulation of Solid lipid nanoparticles loaded topical gel:

The gel developed as per referenced protocol with slight modification. Briefly, Carbopol 934P placed in defined quantity of distilled water while constant stirring at 600 rpm and followed by adding of methylparaben (0.02% w/v) and propylparaben (0.1% w/v) and remained undisturbed with continuous stirring for 30 min. Prepared gel base set aside for 24 hrs. Next, LSLN F6 disseminated with measured quantity of propylene glycol (5% w/w) and 1% ethanol (20% w/w) and far ahead it added to carbopol gel bases with continuous shaking at 1000 rpm and followed by churning for 30min. Tri-ethanol amine (TEA) subjected to the final stage to maintain pH (5.5 - 6.5) for drug stabilization and stirred thoroughly to obtain clear gel.

The same procedure applied to get three formulations having varying amount of carbopol and aim is associated to prepare different forms of gel is to obtain best homogeneous and uniform texture with stable physicochemical reliability in respect of % release of leading moiety. Different formulations of LSLN gel are enlisted as in **Table 2.**

Table 2: Preparation of different formulations of solid lipid nanoparticles containing gel

Formulation code	Carbopol 934 % (w/v)
LG1	0.5%
LG2	1%
LG3	1.5%

CHARACTERIZATION OF GEL [18-27]

Appearance:

The visual appearance, odour, texture, of the LSLN-based topical gels were evaluated upon application, including grittiness, consistency, and uniformity.

Determination of pH :

pH of each LSLN Gel was determined using digital pH meter. Each 50 mg formulation was added in beaker and pH of formulation was determined by using calibrated pH meter.

Determination of viscosity

Viscosity of the gel formulation was calculated using a Brook-field viscometer and a suitable spindle number and RPM.T-bar spindle (Spindle-R/S, S-75) was lower perpendicularly into the gel in a beaker, being careful not to touch the bottom of beaker. The spindle was rotted at 60 rpm, and the readings were taken after 60 seconds, when the gel level had stabilized.

Determination of Entrapment Efficiency:

Entrapment efficiency of each prepared batches of gel was determined by measuring the free mass of drug in diffuse phase of gel solution after centrifugation. Briefly, 1gm gel dispersed with ethanol and stirred for 5min. Then, the resulting mixture was centrifuged at 15000 rpm for 1 hour at 4°C. The supernatant was collected from centrifuged and analyzed spectrophotometrically at 298 nm for quantitative analysis.

Spreadability:

The gel's spreadability was assessed using the previously described methodology, with a few modifications. In short, a second plate was positioned concentrically on top of the 500 mg formulation that had been calculated and placed in the center of the acrylic plate. The primary width was calculated as the diameter of the circle that the gel was applied to. For a few minutes, the plate was subjected to an approximate 500g weight. Gel scattering

caused a rise in diameter, which was used to determine the dispersion of gel.

Drug content

The drug content of SLN loaded gel was determined by diluting 1mL of the formulation with100 mL ethanol, further diluted 10ml to 50ml with ethanol followed by analysis with UV-visible spectrophotometer.

In-vitro drug diffusion and kinetics study [18-27]

***In-Vitro* drug diffusion Study:**

In Vitro drug diffusion study was performed on the Franz diffusion cell using cellulose acetate membrane. 50ml of saline phosphate buffer pH 7.4 was used as diffusion medium and previously put in contact with membrane 30 min before placing the sample. Saline phosphate buffer pH 7.4 was placed in receptor compartment of Franz diffusion cell. The receptor compartment was continuously stirred using magnetic bar and the temperature was kept at 37±0.5 °C using water bath. The experiment was started with the even application of 0.5 gm of LSLN gel on the surface of cellulose acetate membrane from donor compartment side. 1ml sampling was withdrawn after 0.5, 1, 2, 4, 6, 8, and 12 hr and the fresh diffusion 1ml medium was added with each withdrawal of sample. The samples were diluted and analyzed at 296 nm UV Visible spectrophotometrically.

Drug Release and Kinetic Profile [18-27]:

The quantitative analysis of the values obtained in dissolution/release test is easier when mathematical formulae that express the dissolution results as function of some of the dosage forms characteristics are used.

The *in-vitro* drug release profiling approach using dialysis bag techniques was used to assess the drug release and kinetics profiling of the gel with best formulation (LG3).

The Higuchi, Zero order, First order, and Korsemeyer-Peppas models are among the kinetic models that were used to statistically assess the *in-vitro* release profile of the prepared solid lipid nanoparticle gel containing luliconazole. A kinetic model was established to clarify the drug release profile's process. Regression coefficients that are high are seen to be particularly useful for initialization and acceptability.

FTIR Analysis of LG3 [18-27]:

FTIR analysis of LG3 was performed using FTIR spectrophotometer. Individual samples were taken with potassium bromide and then proceed for spectroscopic examination in the range of 4000-400 cm^{-1}.

SEM (Scanning Electron Microscopy) [18-27]:

Morphological analysis of LG3 was determined using scanning electron microscopy according to standard protocols with minor modification. A small quantity of sample of SLN gel was placed on glass slide and dried under vacuum. Then, slide having sample placed in SEM chamber coated with gold-palladium, and after that sample was analyzed under a microscope at an accelerating voltage of 10 Kv 35.

Data analysis

Results are expressed as mean values and standard deviation (±S.D.) and the significance of the difference observed was analyzed by the Student's t-test. In all tests, a probability value of $p < 0.05$ was considered statistically significant.

3. RESULTS AND DISCUSSION [13-16, 18-39]

CHARACTERIZATION OF DRUG

Physical appearance

Physical appearance of the pure drug was studied and it was found a white odorless powder.

Melting point

Melting point of luliconazole was found to be in the range 150 to 152°C, which fully complied with earlier, reported values in literature standard.

Differential Scanning Calorimetry:

DSC thermogram of gift sample is shown in **Figure 1.** In thermogram sharp endothermic peaks was observed at 153.41 ºC, which corresponds to the melting point. Such an endothermic peak was also reported for standard drug material near to the melting range. The thermogram of the drug sample was found to be similar to DSC thermogram of luliconazole as reported earlier. The DSC spectrum of plain luliconazole exhibits a notable strong endothermic peak, demonstrating the crystalline structure of the drug.

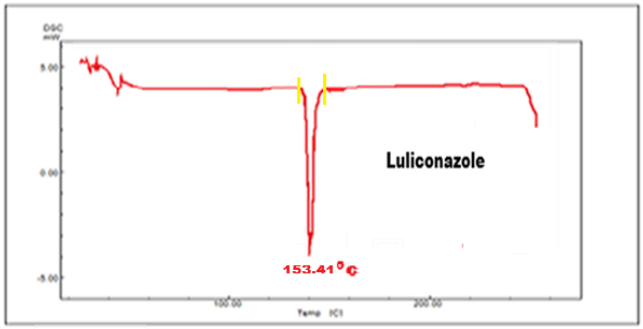

Figure 1: DSC thermogram of Luliconazole solubility of Luliconazole

The solubility (**Table 3)** of the drug in different solvents was studied and a solvent to be used in the final formulation was selected. The solubility was analysed using UV-VIS spectrophotometer at respective maximum wave length.

Table 3: Result of Solubility of luliconazole

Solvent	Solubility in (mg/ml)
Purified water	0.011±0.002
PBS 7.4	0.028±0.005
Ethanol	12.76±0.04 0
n-octanol	17.885±0.53

The solubility of Luliconazole in purified water, PBS 7.4 and ethanol were determined to be 0.0011±0.002, 0.028±0.005 and 12.76±0.04 0mg/ml whereas non-aqueous solubility of Luliconazole in n-octanol obtained 17.885±0.53 mg/ml.

Determination of Partition Coefficient

Partition coefficient is normally used to determine the lipophilic and hydrophilic nature of a substance. Compounds with log p more than 1 are lipophilic in nature whereas those with less than 1 are hydrophilic (**Table 4)**.

Luliconazole had log10 P values of 3.68 in n-octanol. Physicochemical studies of luliconazole were conducted to evaluate the physicochemical properties of the drug. The studies conducted to evaluate luliconazole hydrophilic and lipophilic compatibility.

The result shows that luliconazole having poor solubility potential with water which was found to be 0.011±0.002 mg/ml. Besides, the non-aqueous solubility was obtained 17.885±0.53mg/ml for luliconazole in n-octanol. The log P value of luliconazole in noctanol was obtained as 3.21.

Table 4: Partition coefficient of luliconazole

Partition coefficient of drug	Solvent system	Log P Values
Luliconazole	n-octanol: water	3.21

Drug excipients interaction study:

Table 4: Changes of physio-chemical behaviour of drug with excipients

Sl. No.	Drug: Excipients (1:1)	Color of physical mixtures			Analysed by UV-visible spectrophotometer
		After 1 month	After 2 months	After 3 months	% of drug in physical mixtures
1	Drug: Stearic acid	No change	No change	No change	98.77
2	Drug: Poloxomer 188	No change	No change	No change	98.91
3	Drug: Stearic acid: Poloxomer 188	No change	No change	No change	98.93

This study was carried out to check for any possible interaction between the drug and excipients. Drug and various excipients (**Stearic acid and Poloxomer 188**) were mixed separately in a ratio of 1:1 and were stored at room temperature and checked visually after one month interval for 3 months. If any coulor changes are there, then it may be due to interaction of drug with excipients **(table 4).** Finally it was analysed for quantification of pure drug through UV-visible spectrphotometric methods. Later on it was further confirmed by ATR-FTIR & DSC studies.

ATR-FTIR Spectroscopy:

The FTIR spectrum of drug sample showed sharp peaks at 2986.24 and 3055.75 cm^{-1} for C-H stretching, 2523 & 2647 cm^{-1} for S-H stretching, 2201.52 cm^{-1} for C≡N stretching, 1556.90 cm^{-1} for C=N stretching, 1476.54 cm^{-1} for C=C aromatic ring stretching and 720.33 & 1101.29 cm^{-1} for C-Cl stretching **(Fig. 2)**

Whereas, principal absorption peaks of stearic acid were found at 2926.02 cm^{-1}& 2859.86 cm^{-1} in high-frequency region attributed to -CH_2- band asymmetric and symmetric stretching vibrations, whereas and 1727.79 cm^{-1} for -COOH stretching is attributed in low-frequency region **(Fig. 2 and table 5)** and 1481.52cm^{-1} (C-C stretch), 1305.32 cm^{-1} (C-O stretch, aromatic aster), 946.59cm^{-1}(O-H bend), 730.00 cm^{-1} (C=C bend) and 557.28 cm^{-1} (C-I stretch). The purity and authenticity of stearic acid were confirmed by these identified primary peaks, which were similar to those reported.

Excipient compatibility studies were carried out using ATR-Fourier Transform Infra Red spectroscopy to establish or rules out any possible interaction of stearic acid and Poloxomer 188.

The FT-IR spectra of the co-processed excipient were compared with the FT-IR spectra of pure compound. The results are shown in below figures 6.9, indicating that there is no significant shift in the ATR-FTIR values; hence it may conclude that there is no chemical

interaction between of drug, stearic acid and Poloxomer 188.

The FTIR spectrum (figures 6.9) of Poloxamer 188 showed sharp bands at 3444.70 cm^{-1} (O-H stretching), 2886.54 cm^{-1} (C-H stretching) and 1968.34 and 1667.81 cm^{-1} (C=O stretching).

Spectral analysis of best SLN confirmed that there are no more changes in luliconazole after successful formation of SLN.

Table 5: FTIR interpretation of best LSLN

Functional Group	Observed frequencies cm^{-1}
C-H stretch	2955.75, 2914.97 and 2848.05
C≡N Stretch	2201.52
C=C alkene stretch	1698.03
C=C Aromatic stretch	1463.82
C-Cl stretch	609.29

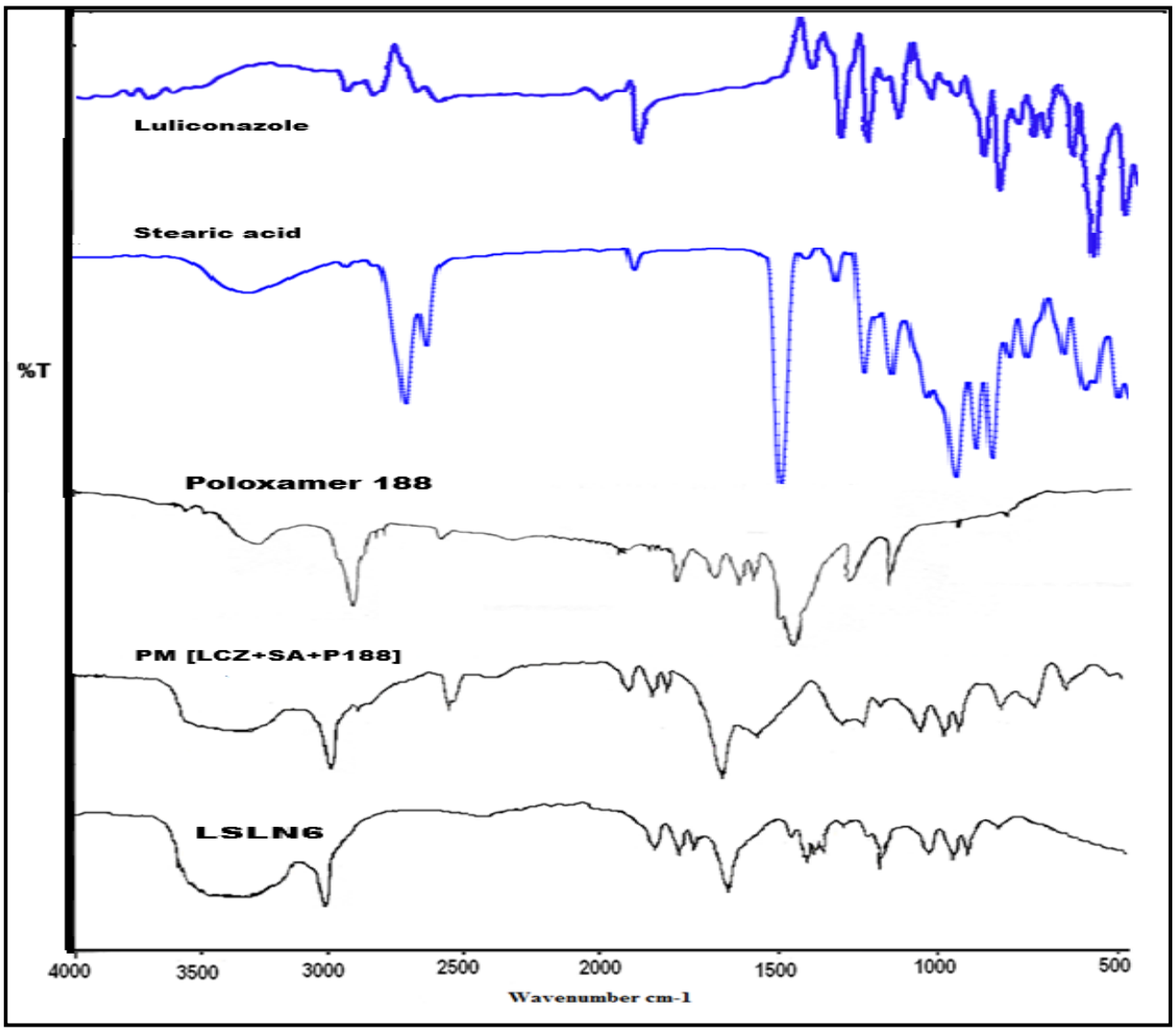

Figure 2: ATR-FTIR Spectra of drug, excipients and its physical mixtures with different excipients and best LSLN formulation

DSC thermogram

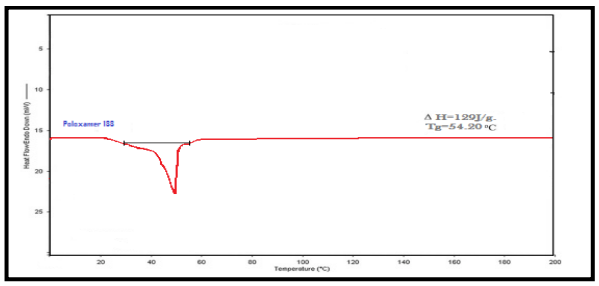

Figure 3: DSC thermogram of Poloxamer 188.

DSC thermogram of gift sample is shown in **Figure 1.** In thermogram sharp endothermic peaks was observed at 153.41 ºC, which corresponds to the melting point. Such an endothermic peak was also reported for standard drug material near to the melting range. The thermogram of the drug sample was found to be similar to DSC thermogram of luliconazole as reported earlier. The DSC spectrum of plain luliconazole exhibits a notable strong endothermic peak, demonstrating the crystalline structure of the drug.

DSC thermogram of Poloxamer 188 sample is shown in **Figure 3.** In thermogram sharp endothermic peaks was observed at 54.2 ºC, which corresponds to the melting point.

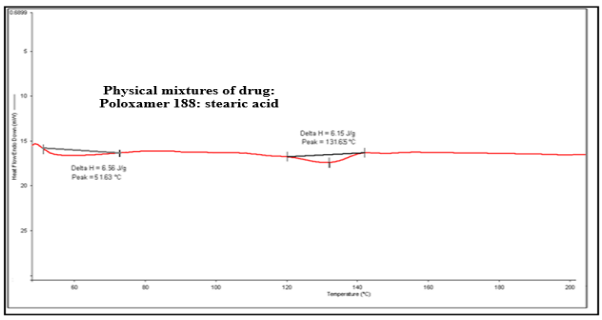

Figure 4: DSC curves of physical mixtures of drug: Poloxamer 188: stearic acid.

DSC thermogram of physical mixtures of drug: Poloxamer 188: stearic acid sample is shown in **Figure 4.** In thermogram sharp endothermic peaks was observed at 51.63 and 131.65ºC, which corresponds to the melting point, suppression of melting point and shifting of that may be due to mixing of all the materials together.

Preparations of Luliconazole loaded solid lipid nanoparticles (LSLN)

The lipid selected was stearic acid according to the solubility of various lipids. The particular concentration of lipid was melted above at a low concentration, resulting in a smaller particle size. Stearic acid was selected for further evaluation. its melting point, and the drug was added to form a clear mixture; this is the oil phase. The aqueous phase was prepared by dissolving the selected surfactant, *i.e.,* poloxomer 188 in the required quantity of distilled water under the same temperature as the oil phase. The aqueous phase is incorporated into the oil-phase drop wise under magnetic stirring while maintaining the temperature constant. This solution was homogenized for 5 min under 8000 rpm and then sonicated for 5 min. This nano-dispersion was allowed to cool to room temperature to yield nanoparticles. Further, in optimization of SLN, method archived step by step with alternate changes in concentration of stearic acid and poloxomer 188 (w/w). All prepared groups of SLN were coded successfully and proceed to quantitate percent entrapment of active moiety spectrophotometrically at 298 nm. Obtained data were evaluated statistically. SLN which deal with high entrapment of luliconazole chosen as best SLN and proceed for further evaluation

The instant adding of the organic phase to the aqueous phase was conserved at 4°C which gives immediate precipitation due to hyphenation with anti-solvent. The temperature was controlled at the initial phase of nano-precipitation which helped to achieve homogeneity. High-pressure homogenization supports to get uniform homogeneity by decreasing larger crystals size and bead milling aggregation. Further, in the optimization of SLN, the method was archived step by step with alternate changes in the concentration of stearic acid and poloxomer 188 (w/v) ranging from 1-1.5 % **(Table 6)**. All the prepared groups of SLN were coded successfully and proceed to quantitative percent entrapment of active moiety spectrophotometrically at 298 nm.

Table 6: Composition of Different Solid Lipid Nanoparticles

Formulation	Drug (mg)	Stearic acid (mg)	Poloxomer 188 (%w/w)
LSLN-1	100	1000	1.0
LSLN-2	100	1250	1.0
LSLN-3	100	1500	1.0
LSLN-4	100	1000	1.5
LSLN-5	100	1250	1.5
LSLN-6	100	1500	1.5

Evaluation of LSLN

Physicochemical property

The LSLN-6 evaluated based on their physicochemical characteristics such as colour, odour and pH. Physicochemical results reveal that SLN has white transparent colour with homogeneous and uniform texture, aromatic odour and water solubility found 0.161 ± 0.014 mg/ml, i.e. much enough than luliconazole solubility.

Evaluation of entrapment efficiency

Initially, in pre-formulation studies, luliconazole characterized physicochemically and spectroscopically. After successful formation of different batches of nanoparticles, percentage EE of luliconazole determined. Percentage of EE evaluated spectrophotometrically at 298 nm. Thereafter results reveal that LSLN6 and LSLN1 have highest and lowest % EE of luliconazole loaded SLN by 94.21% and 84.33% w/w respectively. Similarly, study cited by Ige et al. reported maximum % EE by 90–95% w/w. Therefore, based on percent drug entrapment, LSLN F6 selected as an optimized SLN and proceeds for further evaluation includes physicochemical properties and gel formation (**Table 7)**.

Table 7: Entrapment Efficiency of SLN

Formulation Batch	Drug Entrapment Efficiency (%)
LSLN-1	84.33 ±0.020
LSLN-2	85.42 ±0.014
LSLN-3	86.82±0.015
LSLN-4	90.29 ±0.011
LSLN-5	90.16 ±0.033
LSLN-6	94.21±0.045

Particle size and zeta potential

The particle size, zeta potential and polydispersity index of the best prepared LSLN batches with size of particles 130.5nm and 0.265PDI for LSLN6. The particle size analysis of luliconazole SLN suspension revealed that the particle size measured by laser light method is around to 130-245 nm with low polydispersity index. All the SLN formulation shows particle sizes in the nano range (< 1 µm). The reduced particle size and polydispersity index could be attributed to the stabilization of colloidal system.

Zeta potential is one of the important parameters used to forecast the physical stability of nanoparticles. The stability of the nanoparticle system depends on the high zeta potential value which points toward better stability of the nanosystem since it could deliver a deterring force between the nanoparticles. SLN shows a zeta potential -22.2 mV with conductivity 17.6mS/cm (fig. 6.15) and states to the high stability of the nanosystem. In particle size analysis, SLN unveiled with the mean particle diameter by 130.5 nm, unimodal size distribution, a polydispersity index (PDI) by 0.265, intercept value 0.922 and 100% peak intensity. The PDI is a parameter that represents the dissemination factor with the low aggregation of nanoparticles when PDI value would be < 0.529.

Zeta potential plays a crucial role in the stability of nanoformulations, directly impacting their performance. According to the literature, nanoemulgel systems with higher zeta potential values generally ranging from±20-40 mV tend to be more stable. Greater zeta potential values facilitate the maintenance of globules in Brownian motion by creating repulsive forces between similarly charged particles, preventing their agglomeration.

Zeta Potential, Polydispersity Index (PDI), and particle size measurement: NLC filled with LZ displayed the ideal particle size. This could be the result of the ideal concentration of a lipid and surfactant combination, which works in concert to reduce particle size. Particle size has been found to decrease as surfactant concentration rises; a smaller particle size facilitates drug targeting and enhances drug penetration across biological membranes.

Permeation through the skin is the primary need for a topical drug delivery system loaded with nanoparticles; in the case of NLC, the particle size should be sufficiently tiny to allow for skin penetration. For the creation of NLC formulation, entrapment efficiency can therefore be disregarded or is viewed as less important than particle size. All formulations had zeta potential values between -16.3 and -17.5 mV. Storage stability, or the ability of the dispersion to withstand aggregation, is conferred by a high zeta potential.

The best Luliconazole LSLN exhibited a mean globule size of 130.5 nm and an entrapment efficiency of 94.21±0.045. The actual value for both globule size and % entrapment efficiency in the best LSLN6 was within±5% error. This study showed that the results were statistically significant at 95% confidence interval, which is highly commendable.

Particle size and PDI were characterized for the best formulation (LSLN6) and was found to be 130.5 nm and PDI of 0.265, respectively. A formulation's zeta potential demonstrates the extent of repulsion between similarly charged particles. During storage, repulsive forces prevent particle aggregation. Thus, zeta potential indicates a formulation potential physical stability. The optimum zeta potential range is 30 mV to +30 mV. The optimized formulation zeta potential was determined to be -22.2 mV. Hence, the formulation was found to have good stability.

Optical microscopy of best LSLN

Optical microscopy of optimized preparation, SLN was performed using at a magnification of 100X using a digital light optical microscope, and observations revealed that Luliconazole SLN was effectively localized inside the SLN dispersion with a homogenous and uniform texture. Only particles with an average diameter bigger than 2.5µm could be seen clearly under a microscope, according to the study. Furthermore, there was no assembled structure in the SLN preparation. In optical microscope pictures of LSLN6 containing Luliconazole, the micellar structure was not visible.

SEM Analysis

The SEM image of optimized LSLN6 is shown in Figure 6.17. The SLNs were observed to be spherical in shape, with a smooth surface. It was noticed that particles adhered together, probably due to the nature of the stearic acid used in the formulation.

FTIR spectra of best LSLN

The FTIR spectrum of drug sample showed sharp peaks at 2986.24 and 3055.75 cm^{-1} for C-H stretching, 2523 & 2647 cm^{-1} for S-H stretching, 2201.52 cm^{-1} for C≡N stretching, 1556.90 cm^{-1} for C=N stretching, 1476.54 cm^{-1} for C=C aromatic ring stretching and 720.33 & 1101.29 cm^{-1} for C-Cl stretching. Whereas, principal absorption peaks of stearic acid were found at 2926.02 cm^{-1}& 2859.86 cm^{-1} in high-frequency region attributed to -CH_2- band asymmetric and symmetric stretching vibrations, whereas and 1727.79 cm^{-1} for -COOH stretching is attributed in low-frequency region and 1481.52cm^{-1} (C-C stretch), 1305.32 cm^{-1} (C-O stretch, aromatic aster), 946.59cm^{-1}(O-H bend), 730.00 cm^{-1} (C=C bend) and 557.28 cm^{-1} (C-I stretch). After successful SLN production, spectral analysis of determined SLN indicated that there was no change in Luliconazole.

Preparation of LSLN incorporated gel [LG]

Characterization of LSLN gel [LG]

Table 8: Characterization of LSLN gel [LG]

Formulation	Appearance	pH	Viscosity (cps)	Gel Strength	Spreadability (gm.cm/sec)	% Drug Release After 8 hrs
LG1	White in colour, smooth, no grittiness in nature and good uniformity	5.3- 5.6	2228±34	++	3.6	91.43
LG2		5.4 -5.8	3854±25	++	3.5	87.33
LG3		5.5- 5.8	4021±46	+++	2.7	84.42

+++ if time required is more than 4 hr, ++ if time is 2.5-4 hr and + if time is less than 2.5hr

Appearance

LSLN6 batch was found to be best which is used further for preparation of gel from optimized SLN and evaluated for various physical evaluations like appearance, consistency, grittiness and uniformity and it was found that all the three gel formulations were white in colour, smooth, no grittiness in nature and good uniformity (**Table 8)**.

Determination of pH

pH of luliconazole-SLN based gels was found in range of 5.3-5.8, which is was near to the physiological pH of the skin. Hence it concludes that the gel formulation is safe to use topically.

The pH measurement is an important parameter for topical formulations. The pH of the Luliconazole nanoemulgel was found to be 5.6±0.3 (table 6.14), which indicated that the prepared formulation was compatible with the skin, which was in the acceptable range of 5.5 to 7.4 (**Table 8)**.

Determination of viscosity

The viscosity of luliconazole based SLN gel formulation was found to be in the range of 2228±34to 4021±46cps showing good consistency of the formulation. The results are shown in **Table 8**.The viscosity of the formulation was measured using a Brookfield viscometer, where the viscosity of SLN influenced by the surfactant concentration. According to table 6.14, the viscosity of the best Luliconazole gel was 4021±46 cps, falling within the acceptable range of 50 to 50,000 cps, which is ideal for semisolids. A rheogram was also generated, revealing a shear-thinning behavior in the formulation. The results of the study demonstrated that as the shear rate increases, the viscosity decreases, indicating a pseudoplastic curve and non-Newtonian flow.

Gel Strength:
Gel strength was determined by visually observing and measuring the time required for travel of 5 gm weight up to 2 cm distance through gel. These observations were graded as +++ if time required is more than 4 hr, ++ if time is 2.5 - 4 hr and + if time is less than 2.5 hr. + indicate low gel strength and the gel may get dissolved and cleared off faster from skin surface, ++ and +++ indicate good and very good respectively and will help to hold drug for prolonged period of time. The gel strength for the formulation was found to be ++ indicates good gel strength which will help desired drug release and may get easily cleared off from skin when required. The results are shown in **Table 8**.

Determination of the entrapment efficiency
All the prepared LNZNS loaded batches shows good drug content, the drug content is within the range of 77% - 84.54%.

The drug content
The drug content of Luliconazole gels were found to be 93.54±5.1 %, indicating good content uniformity. The drug content determination also revealed that the drug was distributed uniformly throughout and ensured homogeneity, which is essential for semi-solid preparations.

Spreadability
The value spreadability (**Table 8)** indicates that gel is easily spreadable by applying just a small amount of shear. Spreadability is inversely proportional to the viscosity of prepared gel. Spreadability decreased as the amounts increased. The Spreadability of the prepared carbopol 934 gel formulations was in the range of 2.7-3.6 gm.cm/sec. These values were represented in table 6.14. All the formulations showed good spreadability.

In-vitro drug permeation and kinetics study
All the prepared batches show good drug release. **Table 9** shows the drug release of the SLN based gel batches. The *in vitro* drug diffusion study of the formulated Luliconazole nanoemulgel was conducted for 12 h, during which the formulation showed a release rate of 84.813% to 96.89% **(fig. 5).** Initially, there was a burst release within the first hour, which could be attributed to the presence of free drug adsorbed on the surface of the gel. As time progressed, there was a sustained release, possibly due to the lipophilic membrane entrapped within the gelling system. This led to the confirmation that the drug was released in a sustained manner over an extended period. The drug release mechanism of the optimized formulation was investigated using different kinetic models, with a focus on the significance of the regression coefficients. Analysis of the data revealed good linearity for Luliconazole nanoemulgel, with a release rate regression coefficient (R^2) above 0.95. This indicates that the formulation follows the first order as well as Higuchi release kinetics mechanism, suggesting that the drug release from the formulation is influenced by diffusion and swelling of the polymeric gel.

Table 9: *In vitro* drug diffusion of gel-Avg. % Cumulative drug permeated (n=3)

Time (Min)	LG1	LG2	LG3
0	0	0	0
30	26.19	22.39	17.18
60	41.15	37.26	30.89
120	55.59	49.74	47.09
240	62.33	64.70	57.09
360	78.50	77.18	68.33
480	82.22	78.41	74.57
720	94.70	96.89	84.81

Release mechanisms and comparing release profiles are common applications of statistical modeling. To measure the drug's *in-vitro* release profile in a buffer system for a whole day, the Franz diffusion cell was employed.

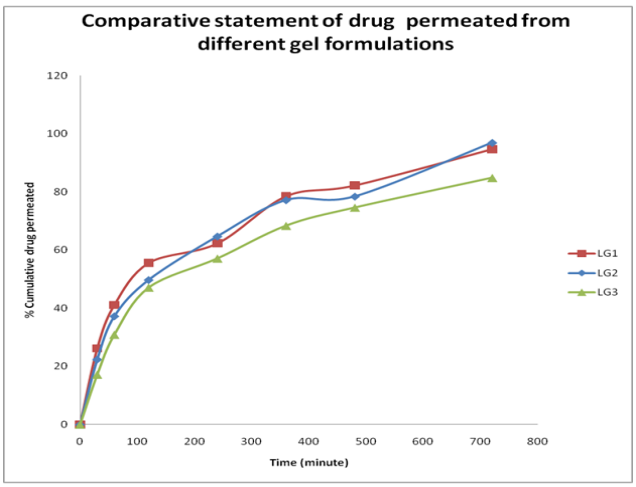

Figure 5: Zero order plots of all three batches of LSLN gel formulations

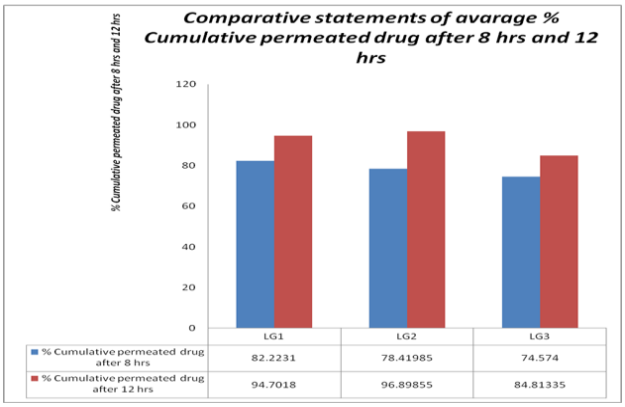

Figure 6: Comparative statements of average % Cumulative permeated drug after 8 hrs and 12 hrs of all three batches of LSLN gel formulations (LG1-LG3)

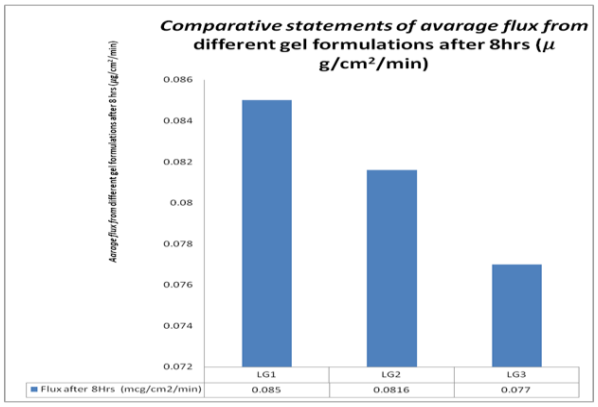

Figure 7: Comparative statements of average flux from different gel formulations after 8hrs (mcg/cm²/min) of all three batches of LSLN gel formulations (LG1-LG3)

Fig. 5, 6 and **Table 10** demonstrate how the percentages of luliconazole that have been desolated from SLN rise over time. Evidence from the release profile demonstrates that the developed SLN is able to release medications under controlled conditions. Because most SLN forms exhibit homogeneous drug trapping throughout the system, the leading moiety can be released gradually.

Mahmoud Ei-badry *et al.* put out a similar idea, asserting that when the drug is evenly dispersed throughout the lipid matrix, a controlled drug desolation profile can be achieved. Poloxomer 407 is significantly more effective than Cremophor RH 40 at preventing drug release from SLN due to its higher HLB value. 20 Poloxomer 407 has a high degree of external spreadability, hence mitigating the impact of interfacial tension that may arise between the dissolving medium and SLN [31-39].

Additionally, it decreases the accumulation of drug particles, hastening the decomposition of medications. Additionally, the lipid mass of SLN can be utilized to modify the size of nanoparticles and enhance the strength of drug delivery. A prolonged time of drug distribution is produced when the lipid surrounding the nanoparticle thickens, extending the period of drug disassociation.

Furthermore, several kinetic models (zero order, first order, Higuchi, and Krosmayer Peppas model) for the ideal formulation made use of an in vitro drug release profile. A statistical analysis was conducted on the obtained data to determine the rate constant and the strongest correlation with the drug release state kinetics profile. In all models, the best-fitted line was discovered, where it was judged to be unsuitable. The results may explain why pharmaceuticals spread more slowly and how they are distributed in a regulated or regular way from homogenous matrix systems.

As a viable topical formulation for long-term pharmaceutical delivery, the results show that SLN LG3 is significantly more efficacious. As evidenced by prior shards of data, this conclusion is essentially identical to the virtuous covenant. **Fig. 5, 6 and 7** provides a graphical representation of the SLN G3 gel's kinetics sequence.

In vitro release investigation of drug-loaded gels demonstrated optimum in vitro drug release up to 12 h. The in vitro release of the drug from the SLN dispersion gel was found to be biphasic, with the initial burst effect followed by steady release of the drug.

Either the unentrapped drug in the SLN dispersion or the location of liquid lipid in the outer shell, which includes lipophilic drug in dissolved form and causes the initial burst release at the initial stage, could be the cause of the initial burst release. Diffusion or matrix erosion can cause release. While sustained release delivers the medication over an extended period of time and maintains therapeutic drug concentration at the site of action, initial burst release gives the drug for rapid therapeutic effect and enhances drug penetration. This suggests that utilizing this formula with a single dose frequency could result in sustained release. Luliconazole was released in a sustained manner from the SLN-based gel.

Table 10: Release kinetics and release mechanism of LG3

Formulation Code	Release kinetics and release mechanism of LG3			
	Zero Order	First Order	Higuchi	Korsmeyer Peppas
Equation	y = 0.1065x + 20.15	y = -0.001x + 1.920	y = 3.235x + 4.073	y = 0.479x + 0.601 n=0.479
(R^2)	R^2 = 0.829	R^2 = 0.971	R^2 = 0.975	R^2 = 0.959

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ATR-Fourier transforms infrared spectroscopy of best gel

The FTIR spectrum analysis of SLN gel LG3 was effective in assessing potential drug-drug additive interactions since it produced spectral data matching stearic acid and luliconazole. Luliconazole's absorption peaks were found at 3340.78 cm^{-1} for N-H stretching, 2971.30 cm-1 for C-H stretching, 2193.49 cm-1 for C-N stretching, and 818.07 & 1053.28 cm-1 for C-CI stretching, according to spectral analysis. The primary absorption peaks of stearic acid were identified at 1639.31 cm-1 in the low frequency zone for –COOH stretching vibrations and 2932.49 cm-1 in the high frequency area for asymmetric and symmetric stretching vibrations in the –CH2-band, respectively. Spectral analysis of improved formulation LG3 revealed no likely interaction between medication and various additives, even after topical gel was produced consecutively. Consequently, the spectra demonstrate the purity and dependability of the SLN LG3 gel.

Scanning Electron Microscopy of best gel (LG3)

SEM shows the shape of the improved formulation as confirmed by SEM analysis. The majority of vesicles are well defined, spherical, and discrete, with plenty of internal aqueous space. SEM analysis reveals a low density of SLN, which could be due to dilution of the nano suspension prior to taking SEM picture. According to SEM analysis, the Luliconazole containing SLN in the gel had a spherical form and a smooth surface.

4. CONCLUSION

The instant adding of the organic phase to the aqueous phase was conserved at 4°C which gives immediate precipitation due to hyphenation with anti-solvent. The temperature was controlled at the initial phase of nano-precipitation which helped to achieve homogeneity. High-pressure homogenization supports to get uniform homogeneity by decreasing larger crystals size and bead milling aggregation. Further, in the optimization of SLN, the method was archived step by step with alternate changes in the concentration of stearic acid and poloxomer 188 (w/v) ranging from 1-1.5 %. All the prepared groups of SLN were coded successfully and proceed to quantitative percent entrapment of active moiety spectrophotometrically at 298 nm.

Initially, in pre-formulation studies, luliconazole characterized physicochemically and spectroscopically. After successful formation of different batches of nanoparticles, percentage EE of luliconazole determined. Percentage of EE evaluated spectrophotometrically at 298 nm. Thereafter results reveal that LSLN6 and LSLN1 have highest and lowest % EE of luliconazole loaded SLN by 94.21% and 84.33% w/w respectively. Similarly, study cited by Ige et al. reported maximum % EE by 90–95% w/w. Therefore, based on percent drug entrapment, LSLN F6 selected as an optimized SLN and proceeds for further evaluation includes physicochemical properties and gel formation.

The particle size analysis of luliconazole SLN suspension revealed that the particle size measured by laser light method is around to 130-245 nm with low polydispersity index. All the SLN formulation shows particle sizes in the nano range (< 1 µm). The reduced particle size and polydispersity index could be attributed to the stabilization of colloidal system.

Zeta potential is one of the important parameters used to forecast the physical stability of nanoparticles. The stability of the nanoparticle system depends on the high zeta potential value which points toward better stability of the nanosystem since it could deliver a deterring force between the nanoparticles. SLN shows a zeta potential -22.2 mV with conductivity 17.6mS/cm and states to the high stability of the nanosystem.

All the prepared batches show good drug release. Table 6.15 shows the drug release of the SLN based gel batches. The *in vitro* drug diffusion study of the formulated Luliconazole nanoemulgel was conducted for 12 h, during which the formulation showed a release rate of 84.813% to 96.89%.

As a viable topical formulation for long-term pharmaceutical delivery, the results show that SLN LG3 is significantly more efficacious. As evidenced by prior shards of data, this conclusion is essentially identical to the virtuous covenant.

In vitro release investigation of drug-loaded gels demonstrated optimum in vitro drug release up to 12 h. The in vitro release of the drug from the SLN dispersion gel was found to be biphasic, with the initial burst effect followed by steady release of the drug.

The majority of vesicles are well defined, spherical, and discrete, with plenty of internal aqueous space. SEM analysis reveals a low density of SLN, which could be due to dilution of the nano suspension prior to taking SEM picture. According to SEM analysis, the Luliconazole containing SLN in the gel had a spherical form and a smooth surface.

By using the solvent diffusion approach Luliconazole loaded solid lipid nanoparticle were successfully created. There was determined to have 94.21±0.045entrapment efficiency. 130.5nm was found to be the particle size and 0.265PDI and zeta potential -22.2 mV of the developed formulation LSLN6. The size of the SLN increased along with the amount of lipid. The compatibility of the medicine and excipients is strongly suggested by ATR-FTIR. The Luliconazole loaded SLN LG3 gel formulation with carbopol 934 (1.5% w/v) are best as an optimal formulation and acceptable for topical use according to the findings of the current study

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