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Research Article

Development and characterization of Luliconazole ethogel for topical use in the treatment of athlete's foot infection

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Abstract

Luliconazole is an imidazole antifungal agent with a unique structure, as the imidazole moiety is incorporated into the ketene dithioacetate structure. To develop and optimize the ethosomal formulation of luliconazole for Athlete's foot infection. Characterization of optimized formulation in vitro. To develop and characterize luliconazole ethosomes loaded topical gel (Ethogel). Anti–fungal study of the optimized ethogel formulation. That ethosomes can become a promising drug carrier in future for not only the topical treatment of local and systemic disorders, but also for the cosmetic and cosmeceutical fields. The present study focused on the development and characterization of LCZ-loaded ethogel and they're in incorporation in the topical gel to increase the permeation through stratum corneum, imparting controlled release as well as enhancing the hydration of the skin. Therefore, LCZ-loaded ethosomes were prepared by the Cold method with high-speed homogenization combined with ultrasonication. The particle size was found to be in the range of 185 to 289 nm, and a maximum of 93 % EE and -24.49 mV Zeta potential. ATR and XRD data ruled out any possible incompatibility among the excipients. Release studies confirmed the sustained-release nature of ethosomes.

Keywords: Luliconazole, Etheosome, Ethogel, Method of Preparation.

1. Introduction

Athlete's foot or Tinea Pedi's is a superficial inflammatory infection of the skin of the feet caused by dermatophyte fungi. Mainly, the fungi responsible for athlete's foot are Trichophyton rubrum, Trichophyton mentagrophytes (var. Interdigitale) and Epidermophyton floccosum [1]. Ethosomes: Unlike classic liposomes, which are known mainly to deliver drugs to the outer layers of skin. The ethosomes can enhance permeation through the stratum corneum barrier. Ethosomes permeate through the skin layers more rapidly and possess significantly higher transdermal flux in comparison to conventional liposomes. [2] The ethosomes are vesicular carriers consisting of hydro alcoholic or hydro/alcoholic/glycolic phospholipids in which the concentration of alcohols or their combination is relatively high. The ethosomes may contain phospholipids with various chemical structures like phosphatidylcholine (PC), hydrogenated PC, phosphatidic acid (PA), phosphatidylserine (PS), phosphatidylethanolamine (PE), phosphatidylglycerol (PPG), phosphatidylinositol (PI), hydrogenated PC, alcohol (ethanol or isopropyl alcohol), water and propylene glycol (or other glycols). Such a composition enables the delivery of a high concentration of active ingredients through the skin. A change in alcohol: water or alcohol polyol: water ratio alters drug delivery. The phospholipids generally used are soya phospholipids such as Phospholipon 90 (PL-90) in the concentration range of 0.5- 10% w/w. Cholesterol at concentrations.[3]

2. Materials and methods

2.1 Preparation methods of Ethosomes

Ethosomes may be prepared by the cold or hot method as described follows. Both methods are convenient, do not require any sophisticated equipment.

2.1.1 Cold Method

It is the most common method for preparing ethosomes. In this process, drug, phospholipid, polyglycol and other lipid materials are dissolved in alcohol (mainly ethanol) in a covered vessel at 30oc by continuous stirring with the use of a magnetic stirrer. Polyglycol and other lipid materials are added after dissolving of drug and phospholipid in the organic phase during stirring. This mixture is allowed to heat at 30 °C in a water bath. The aqueous phase (water) was heated to 30°C in a separate

vessel. The aqueous phase is added to the organic phase with continuous stirring and a flow rate. After completion of the addition, stirring is continued for 5 min. The ethosomal vesicles were formed, and the size of the ethosomal formulation can be decreased to the desired extent using probe sonication or the extrusion method. Finally, the formulation is stored under refrigeration.[4]

2.1.2 Hot Method

In the hot method, firstly weighed the amount of water taken with the Phospholipid was weighed. Dispersion is made by continuous stirring and providing constant temperature, i.e., 40oc by heating in the water bath until a colloidal solution is obtained. In a separate vessel, ethanol, other lipid materials and propylene glycol are mixed and heated to 40 °C. After reaching both solution temperatures of 40 °C, the organic phase is added to the aqueous dispersion of phospholipid with continuous stirring and constant temperature. The drug dissolved in water or ethanol, depending on its hydrophilic or hydrophobic properties. The vesicle size of formed ethosomes can be decreased by using probe sonication or the extrusion method [4]

2.2 Drug excipient compatibility

2.2.1. Attenuated total reflection (ATR) Spectra

ATR spectra of Drug (LCZ), phosphatidylcholine, Cholesterol, Tween 20, a Physical mixture of solid ingredients and selected lyophilised LCZ-loaded ethosomes were obtained by placing the sample on the stage of the ATR instrument. (Bruker ALPHA). The sample was prepared by grinding it to make a fine powder for solids and also to make a homogeneous mixture for compatibility study. The infrared (IR) spectra were recorded in the wavelength region between 4000 and 400 cm−1. The spectra obtained for LCZ, lipid materials, and physical mixtures of LCZ with polymers were compared.

2.2.2. XRD Studies

XRD pattern of lyophilised ethosomes and pure drug was obtained by employing an X-ray diffractometer, using Ni-filtered Cu-K radiation, a voltage of 45 kV, a current of 40 mA radiation scattered in the crystalline regions of the sample, which was measured with a vertical goniometer. Patterns were obtained by using a step size of 0.001°C with a detector resolution in 2ɵ (diffraction angle) between 3° to 50° at 25°C temperature.

2.3 Analytical method development: Calibration curve of Luliconazole in water

The stock solution (100 µg/ml) of the drug was prepared by dissolving 10 mg, accurately weighed, of LCZ in 20 ml of methanol, then the volume was made up to 100 ml with water. The working solution of 10 µg/ml was prepared by taking 10 ml of stock solution in a 100ml volumetric flask, and the volume was made up to 100 ml with water. Aliquots were prepared as 2 to 10 µg/ml solutions.

The absorbance of these solutions was recorded at 298 nm using a UV-Visible spectrophotometer (SHIMADZU (1700), Double beam, Japan). The standard curve was constructed between absorbance and concentration. This standard curve was linearly regressed, and statistical parameters related to it were derived.

2.3.1 Calibration curve of LCZ in ethanol

The stock solution (100 µg/ml) of the drug was prepared by dissolving 10 mg, accurately weighed, of luliconazole in 100 ml of ethanol. The working solution of 10 µg/ml was prepared by taking 10 ml of stock solution in a 100 ml volumetric flask, and the volume was made up to 100 ml with ethanol. Aliquots were prepared as 2 to 10 µg/ml solutions. The absorbance of these solutions was recorded at 298 nm using a UV-Visible spectrophotometer (SHIMADZU (1700), Double beam, Japan). The standard curve was constructed between absorbance and concentration. This standard curve was linearly regressed, and statistical parameters related to it were derived.

2.3.2 Calibration curve of Luliconazole in buffer 7.4

The stock solution (100 µg/ml) of the drug was prepared by dissolving 10 mg, accurately weighed, of LCZ in 20 ml of methanol, then the volume was made up to 100 ml with buffer 7.4. The working solution of 10 µg/ml was prepared by taking 10 ml of stock solution in a 100ml volumetric flask, and the volume was made up to 100 ml with buffer 7.4. Aliquots were prepared from 2- 10 µg/ml solutions. The absorbance of these solutions was recorded at 298 nm using a visible spectrophotometer (SHIMADZU (1700), Double beam, Japan). The standard curve was constructed between absorbance and concentration. This standard curve was linearly regressed, and statistical parameters related to it were derived.

2.4 Preparation of ethosomes

Luliconazole (LZ) ethosomes are prepared by the cold method. Luliconazole (1%) taken in ethanol (30-50%). Cholesterol, soya phosphatidylcholine (SPC) and propylene glycol (PG) were added to this mixture. This mixture was allowed to stir in a closed vessel till a clear solution formed. In a separate vessel, water (qs 100%) was taken with tween80 with constant stirring (700 RPM) and temperature (30oc). Then aqueous phase containing surfactant was added in a drop-wise manner with constant flow in the organic phase containing LCZ, SPC, and PG with constant stirring (700RPM) and constant temperature. While the whole process is stirring, and temperature should be maintained constant. After completion of adding the stirring is allowed for 5 more minutes. The prepared formulation was sonicated by a probe sonicator for 5 min for 3 cycles, with a 5-minute gap in between cycles at 4°C.[5]

2.5. Characterisation of the prepared ethosomes: Particle size and zeta potential (ZP) analysis

Mean particle size, Polydispersity index (PDI) and Zeta Potential of the formulations were determined by using a particle size analyser, Delsa Nano-C (Beckman Coulter, USA). The instrument measures the fluctuation rate of laser light due to the particle diffusion in fluid and interprets it as size. All particle size measurements were performed using a scattering angle of 165°C, and at 25°C. PDI is a dimensionless number indicating the width of the size distribution, having a value between 0 and 1 (0 being for monodispersed particles). Samples were diluted approximately with the aqueous phase of the formulation, and the made at a 165-degree fixed angle every time. The Zeta Potential of the suspension was measured by Electrophoretic Light Scattering (ELS). The measured value is then converted into zeta potential using the Helmholtz–Smoluchowski equation that is built into the software. The zeta potential was measured using an appropriately diluted nanoparticle solution with an applied electric field of 16 V/cm.

3. Results and discussion

3.1 ATR studies

Drug-polymer interaction studies were carried out by Attenuated total reflection (ATR) spectra. ATR spectra of LCZ, Phosphatidylcholine, Cholesterol, ethosomes, and a physical mixture were taken. The peak of LCZ in the fingerprint was well correlated with the physical mixture and ethosomes. Therefore, ATR results indicated that there was no physical and chemical interaction between the drug and the excipient used in the formulation.

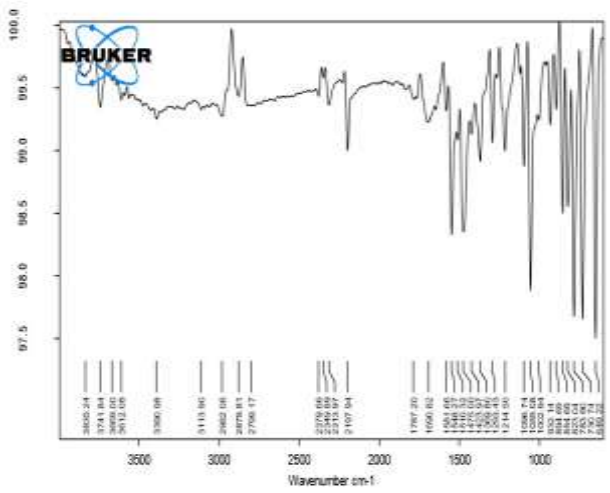


Fig. 1: ATR spectra of luliconazole.

Name of vibrations	Range	Available in spectra
Aromatic C-H Stretching	3050-3150	3139 cm^{-1}
C=N Stretching	1690-1640	1680 cm^{-1}
C-N Stretching	1350-1000	1293 cm^{-1}
C≡N Stretching	2260-2200	2197 cm^{-1}
C-Cl Stretching	785-540	730 cm^{-1}

3.2 X-Ray Diffraction (XRD)

XRD studies were performed to indicate the reduction of the crystallinity of LCZ in the ethosomes drug carrier. Therefore, the X-RD of pure LCZ, Phosphatidylcholine, a physical mixture of drug and excipient and LCZ-loaded Ethosomes were obtained. The diffraction spectrum of pure LCZ showed that the drug was very little in crystalline nature, with characteristic peaks observed in the range of 3 to 50 at 2θ, of a small peak at 32 and a broad peak at 13.

The XRD patterns of the drug Ethosomes show that characteristic peaks of LCZ were absent, which suggests a change in the crystallinity of the drug within Ethosomes. Thus, the relative reduction of diffraction intensity may be attributed to a reduction in the crystal quality, a change in the crystal orientation and the presence of some crystalline form of the amorphous drug. The XRD spectra of pure drug, phosphatidylcholine, physical Mixture and LCZ-loaded Ethosomes are shown in Figure 1.

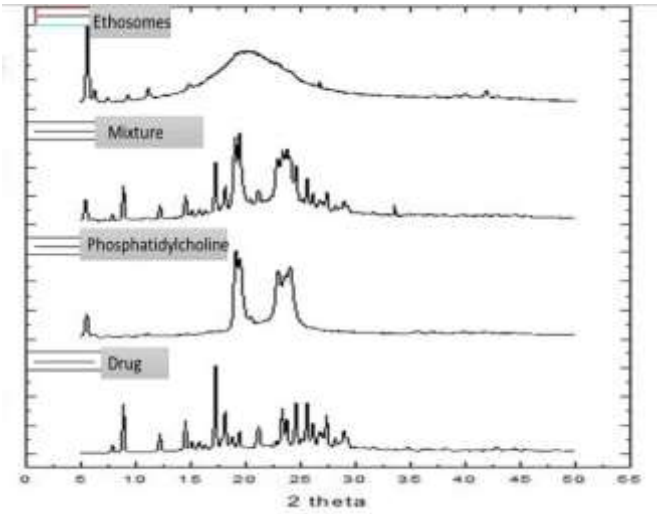


Fig 2: X-ray diffraction pattern of (a) pure drug, (b) Phosphatidylcholine, (c) physical mixture, (d) Ethosomes.

3.3 Analytical Method Development

Accurately weighed 100 mg of CUR and dissolved in 100 mL of ethanol, to the prepared stock solution of 1000 µg/ml. From, above stock, solution aliquots were prepared in a range of 2- 10µg/ml by dilution with distilled water, phosphate buffer (pH 7.4 and 6.8). Then the absorbance was measured at their respective λmax (298 nm) in a double beam UV- UV-UV-Spectrophotometer (UV 1700 SHIMADZU). Figures 3 to 5 show the calibration curve of LCZ in different media.

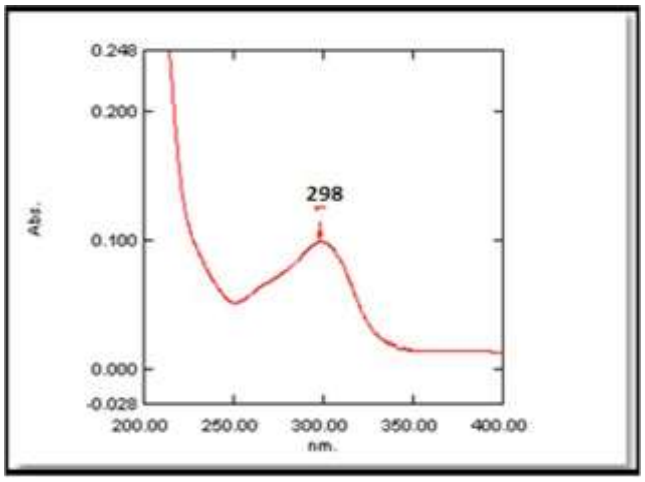


Fig 3: Scanning spectra of luliconazole.

Calibration curve of luliconazole in water

Table 1: Calibration curve of luliconazole in water.

Concentration (µg/ml)	Absorbance in water
0	0
2	0.144
4	0.25
6	0.342
8	0.453
10	0.561

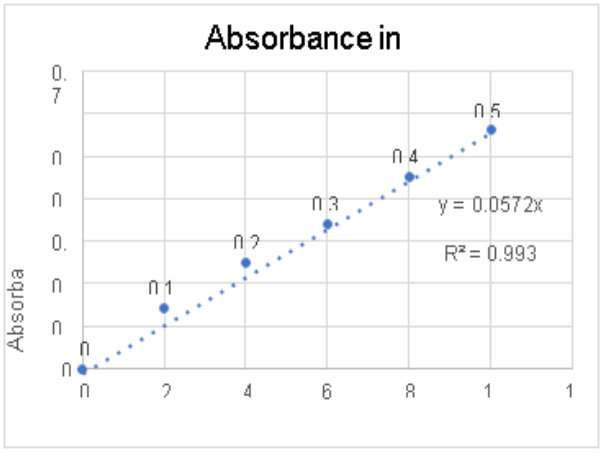


Fig. 4: Calibration curve of luliconazole in water

Table 2: Absorbance of luliconazole on a pH 7.4 buffer.

Concentration (µg/ml)	Absorbance in water
0	0
2	0.099
4	0.175
6	0.24
8	0.319
10	0.411

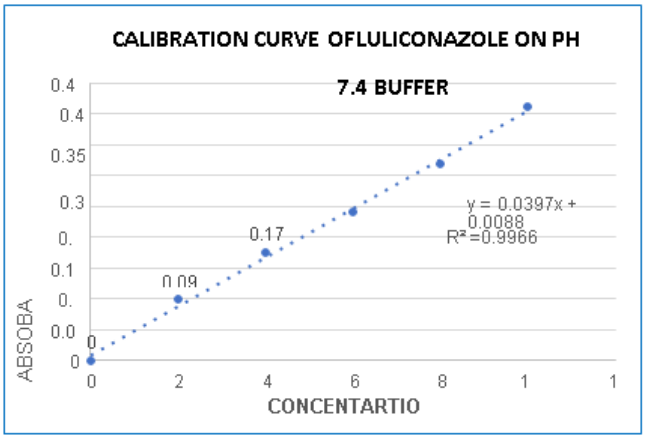


Figure 5: Calibration curve in pH 7.4 buffer

3.4 Characterisation of ethosomes Particle Size and Polydispersity Index Analysis

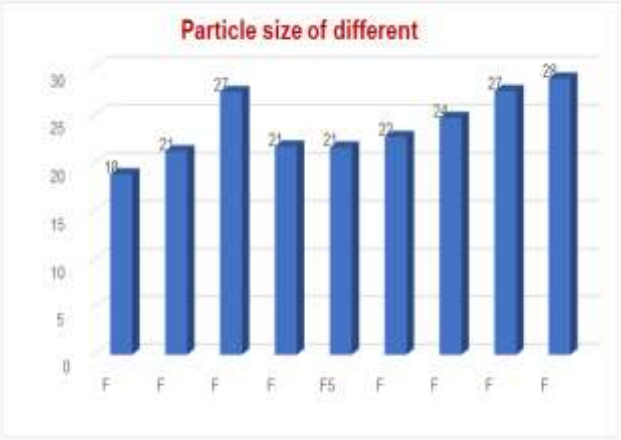
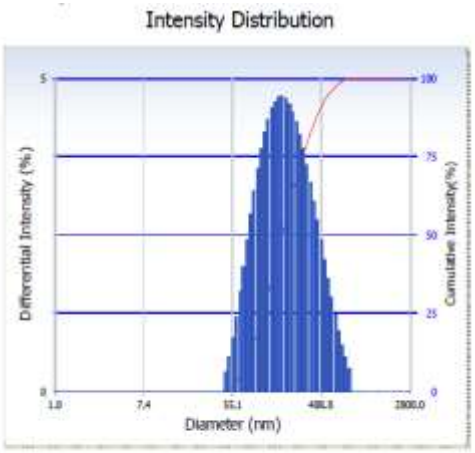
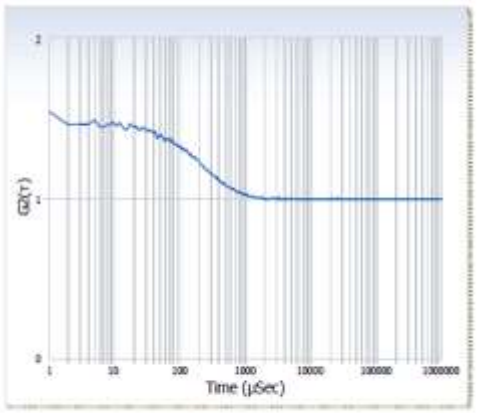


Figure 6: Polydispersity Index Analysis

The particle size, polydispersity index and zeta potential of ethosomes were measured by photon correlation spectroscopy (PCS) Delsa Nano-C (Beckman Coulter Counter, USA) particle size analyser. The particle size of different batches was found in the range of 189 to 295 nm. The particle size range of 50 to 1000 nm is generally considered as ethosomes. This indicates the particle size was in the nano range.





Distribution Results (Contin)

Peak	Diameter (nm)	Std. Dev.
1	217.7	139.3
2	0.0	0.0
3	0.0	0.0
4	0.0	0.0
5	0.0	0.0
Average	217.7	139.3

Residual : 7.609e-003 (O.K)

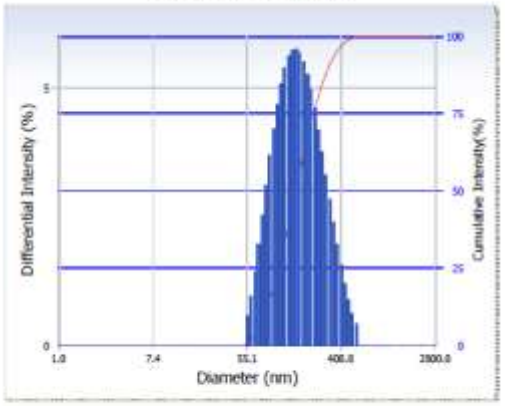
Cumulants Results

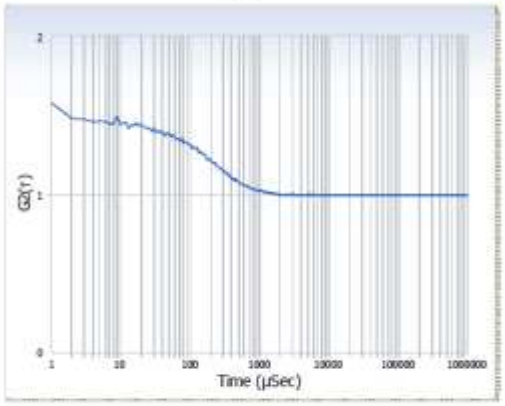
Diameter	(d)	: 156.0	(nm)
Polydispersity Index	(P.I.)	: 0.244	
Diffusion Const.	(D)	: 3.154e-008	(cm^2/sec)

Measurement Condition

Temperature	: 25.0	(°C)
Diluent Name	: WATER	
Refractive Index	: 1.3328	
Viscosity	: 0.8878	(cP)
Scattering Intensity	: 8249	(cps)

Fig 7: Particle size of different batches.





Distribution Results (Contin)

Peak	Diameter (nm)	Std. Dev.
1	185.9	98.6
2	0.0	0.0
3	0.0	0.0
4	0.0	0.0
5	0.0	0.0
Average	185.9	98.6

Residual : 1.059e-002 (O.K)

Cumulants Results

Diameter	(d)	: 148.5	(nm)
Polydispersity Index	(P.I.)	: 0.267	
Diffusion Const.	(D)	: 3.312e-008	(cm^2/sec)

Measurement Condition

Temperature	: 25.0	(°C)
Diluent Name	: WATER	
Refractive Index	: 1.3328	
Viscosity	: 0.8878	(cP)
Scattering Intensity	: 7812	(cps)

Figure 8: Particle size of blank formulation.

4. Conclusion

Athlete's foot or tinea pedis is an inflammatory skin disease caused mainly by Trichophyton species of fungi belonging to the class dermatophytes. It occurs mainly on the feet. It can be characterised by Itching, which gets worse as the infection spreads, Scaling, Dry skin, Redness, Cracking, A white, wet surface, Blisters, which may open and become painful. Various types of medications are available for the treatment of athlete's foot by oral and topical routes. Oral therapy is used in chronic conditions. Topical therapy, whether it is conventional or novel, is always a choice of delivery system for pharmaceutical technocrats.[6] Luliconazole is highly efficacious and potent towards dermatophyte infections. Its topical 1% cream is already available in the market. For increasing its penetration and for releasing the drug in a controlled manner for a longer duration, a novel approach is needed.[7]

As mentioned above, numerous studies have been published showing that ethosomes can substantially improve the permeation of drugs through the stratum corneum and thereby their efficacy. The versatility of ethosomes for transdermal as well as topical drug delivery is evident from the research reports of enhanced delivery of quite a few drugs like minoxidil, testosterone, trihexyphenidyl hydrochloride, bacitracin, indinavir, salbutamol sulfate, azelaic acid, and insulin. Delivery of Hepatitis B surface antigen (HBsAg) and DNA via ethosomes opens new opportunities to transcutaneous immunisation (TCI) and gene therapy. [8,9] Several excellent phytochemicals and herbal extracts have been successfully delivered via ethosomes and showed some distinct advantages over conventional drug delivery systems. As an alternative to conventional transdermal permeation enhancement techniques, ethosomes are superior by offering safety, efficiency, long-term stability, simplified industrial manufacture, as well as better patient compliance. Thus, it can be a logical conclusion that ethosomes can become a promising drug carrier in future for not only the topical treatment of local and systemic disorders, but also for the cosmetic and cosmeceutical fields.[10-12]

The present study focused on the development and characterization of LCZ-loaded ethogel and they're in incorporation in the topical gel to increase the permeation through stratum corneum, imparting controlled release as well as enhancing the hydration of the skin. [13] Therefore, LCZ-loaded ethosomes were prepared by the Cold method with high-speed homogenization combined with ultrasonication. The particle size was found to be in the range of 185 to 289 nm, and a maximum of 93 % EE and -24.49 mV Zeta potential. ATR and XRD data ruled out any possible incompatibility among excipients. Release studies confirmed the sustained-release nature of ethosomes.

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