DEVELOPMENT AND CHARACTERIZATION OF LULICONAZOLE LOADED NANOSPONGES FOR TOPICAL APPLICATION

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Article History: Received: 18.04.2023 **Revised:**07.05.2023 **Accepted:** 16.06.2023

Abstract: *The aim of this research is to develop nanosponges and determine their appropriateness for delivering Luliconazole to the skin in order to enhance its therapeutic impact and ensure better dispersion and preservation. Because nanosponges are water-soluble, water cannot chemically broken down it into its constituent molecules, but rather the nanosponge particles are combined with water and employed as a carrier fluid. Nanosponges are superior to conventional medication delivery techniques in a number of ways. The emulsion solvent diffusion technique was used to develop a nanosponge using ethyl cellulose as the polymer and polyvinyl alcohol as the surfactant. Nanosponges were evaluated for drug content, entrapment efficiency, etc. Based on the results optimized batch of nanosponge is chosen further to develop as a gel. The produced gel was assessed for pH value, viscosity, spreadability and in vitro diffusion studies. Results showed that NS8 batch was best optimized with highest drug content, entrapment and % yield however NG2 batch of gel showed best performance and followed for stability study.*

Keywords*:* *Nanosponges, Luliconazole, Zeta potential, in vitro drug diffusion.*

DOI: 10.48047/ecb/2023.12.si12.162

INTRODUCTION

Topical drug delivery is challenged by barrier nature of the skin that restricts the entry of most drugs, to increase the therapeutic effectiveness of the existing drug molecules is by formulating them using novel nanocarrier systems and incorporating them into topical preparations. The development of novel treatment modalities as well as the improvement of many current treatments efficacy was made possible by various nano-devices, which had a substantial impact on medical technology. A novel material called a "nanosponge" allows different chemicals to be enclosed inside a chamber that is only a few nanometers in size.

Nanosponges are a novel class of nanoparticles, exhibiting promising potential in controlled drug delivery, especially topical formulations. Nanosponges(NS) as biocompatible porous nanoparticles formulate as nano-sized colloidal carriers having the shape of tiny sponges in nature; with a size of about a virus and the average diameter (250 nm -1μm) which will fill with a variety of materials. These particles have the ability to transport hydrophilic and lipophilic materials and boost the solubility of molecules that aren't very water-soluble. Nanosponge is a scaffold-like material that is naturally biodegradable and virus-sized.

Luliconazole, an optically active R-enantiomer of the dichlorobenzene class of organic compounds, is a topical Broad-spectrum imidazole Antifungal molecule. It was used for treatment of Epidermophyton flocosum fungal infections, specifically Tinea pedis, tinea cruris, and tineacorporis, and was found to be safe and well tolerated by human subject. It is poorly water soluble and high permeable drug. Being BCS class II drug with less than 600 dalton molecular weight it can be easily developed as nanospong gel delivery for topical application.

MATERIALS AND METHODS

Materials

Luliconazole (LNZ) was obtained as gift sample from Swapnroop Drugs and Pharmaceuticals, Aurangabad, Maharashtra. Ethyl cellulose, Polyvinyl Alcohol, Carbopol-940 and Propylene glycol were procured from Sigma Aldrich. All the other chemicals used were of analytical grade.

Methods

Preformulation study

Calibration curve on UV

UV spectrum of luliconazole was carried out in phosphate buffer pH 7.4. luliconazole was weighed 10 mg accurately and transfer in phosphate buffer 7.4 pH in a 100 ml volumetric flask. The solution of 10µg/ml was kept in a fused silica cuvette. The UV spectrum was recorded in the range of 200-800 nm by shimadzu double beam UV visible spectrophotometer against blank buffer solution pH 7.4. And linearity calibration curve was carried out by using standard Luliconazole solutions in the range 2-10µg/ml and the absorbance with respect to 2, 4, 6, 8, 10µg/ml were determine for linearity.

Drug-Excipient Compatibility Study

The compatibility between the drug, chosen polymer and solvent, and other excipients has been checked by using FTIR peak matching method.

Preparation of Luliconazole-loaded Nanosponges

The solvent evaporation method was used to load luliconazole onto ethyl cellulose nanosponges. Acetone and ethanol are employed as solvents. 100 ml of an appropriate solvent (organic phase) should be combined with the ethylcellulosenanosponge. The ratio of the mixture to the extra cross-linking agent should ideally be 4:16. i.e, Mix 100 ml of solvent with 4000 mg of luliconazole medication. The reaction continues at 100 °C for 1–48 hours of solvent reflux. After being cooled to room temperature, distilled water was added to the solution. Purify the mixture. By filtering it, the product was recovered, and it was then dried at 40 °C in an oven.

Table 1: Formulation Batches of Luliconazole Nanosponges

Sr. No.	Name ofingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Luliconazole(gm)	1	1	1	1	1	1	1	1	1
2	Ethyl cellulose(gm)	0.5	0.5	0.5	1	1	1	1.5	1.5	1.5
3	Poly vinylalcohol(gm)	1	1.5	2	1	1.5	2	1	1.5	2
4	DCM (ml)	20	20	20	20	20	20	20	20	20
5	Dist. Water(ml)	100	100	100	100	100	100	100	100	100

Formulation of Topical Gel Containing Luliconazole Loaded Nanosponges

The dried drug-encapsulated nanosponges (optimized batch) were collected and transfer the required amount of drug equivalent to the nanosponges, that is, 0.2 gm, into a 250 ml volumetric flask containing 100 ml of ethanol to remove free unencapsulated drugs by dissolving in ethanol. The drug-encapsulated nanosponge is separated from the free drug by membrane filtration. Collect the remaining drug-loadednanosponges and disperse them in distilled water by ultrasonic treatment to form a nano-suspension. Disperse 250 mg of gelling agent in 5 ml of distilled water and allow for swelling overnight. Use different gelling agents, such as Carbopol940, gum arabic, HPMC, sodium alginate. Stir continuously in a magnetic stirrer for 1-2 h and add the weighed other excipients to the previously soaked

Carbopol940. Triethanolamine was used to adjust the pH. Transfer the gel to a graduated cylinder and makeup to 20 ml with distilled water.

Table 2:Formulation table of LNZNS loaded Gel

Ingredients	**NG1**	**NG2**	**NG3**
LNZNS	250 mg	250 mg	250 mg
Carbapol 940	0.5%	1%	1.5%
Propyleneglycol	10%	10%	10%
Ethanol	10%	10%	10%
Propylparaben	0.02	0.02	0.02
TEA	q.s	q.s	q.s
DistilledWater	Upto q.s.	Uptoq.s.	Uptoq.s.

Evaluation of Nanosponges

Physical appearance

Nanosponges were observed visually to determine its physical appearance.

Percentage Yield

By measuring the prior weight of the raw ingredients (API, polymer) as well as the end weight of the NS produced, the production yield of NS can be reliably estimated.

$$\%Yield = \frac{ActualYield}{TheroticalYield} \times 100$$

Drug Content

In 100 ml of phosphate buffer pH 7.4 solution, a precisely weighed equal amount (10 mg) of the drug-containing nanosponge was constantly swirled for an hour. Next to the blank, further examine the filtered sample at 296 nm using a UV spectrophotometer. Using the following expressions, the drug content of all batches was estimated:

$$\%\ DrugContent = \frac{Actualconcentrationofdruginthe formulation}{Theroticalconccentrationofdrug} \times 100$$

Drug Entrapment Efficiency

The weight of luliconazole put in phosphate buffer 7.4 and diluted with 100 ml of phosphate buffer 7.4 solution can be used to calculate the drug's effective equivalent (EE). And sonicate for 10 minutes, centrifuge at 1000 rpm for 15 minutes, remove the supernatant, further dilute with buffer 7.4 solution, and conduct UV spectroscopic analysis on the luliconazole at its maximum wavelength of 296 nm.Thenthe entrapment efficiency wasdeterminedby-

$$\text{Entrapment Efficiency} = \frac{\text{Total drug concentration} - \text{Free drug concentration}}{\text{Total drug concentration}} \times 100$$

Particle Size

With the aid of a zeta sizer (Malvern), an average particle size study was carried out on optimized batch to determine particle size.

Zeta potential

Optimized nanosponge batch was assessed for its stability by determining its zeta potential using Malvern Zeta sizer.

X-Ray Diffraction

AnXRD was used toobtain X-Ray diffraction patterns of drug as well as optimized batch to assess their

structural arrangement.

Scanning Electron Microscopy
SEM used to examine the surface structure of optimized nanosponge. An SEM image of a nanospongeparticle can also be used to show its structure.

DSC
Optimized batch was subjected to DSC thermoanalysis. DSC study was used to assess its thermal behavior of drug developed as nanosponges.

Evaluation of Nanosponge loaded gel
Appearance
The formulations were observed for the presence of any particulate matter. The appearance and clarity is determined by visual testing.

pH
The pH of nanosponge gel formulation is determined by using digital pH meter.

Drug content
Nanosponge gel, 2 gm from each formulation were taken in 100 ml volumetric flask having 10 ml methanol and stirred by magnetic stirrer for 5 minutes. The solutions were filtered using whatmann filter paper. The absorbance of the solution was estimated spectrophotometrically (UV 1800, Shimadzu) at 272 nm using standard curve against blank.

Determination of viscosity
Viscosity of nanosponge gel was determined by using Brookfield viscometer. 20 gm of nanosponge gel was filled in a 25 ml beaker and the viscosity was measured by using Spindle number 6 at 10 rpm.

Spreadability
It is determined by apparatus which consists of a wooden block, which is provided by a pulley at one end. The spreadability is measured on the basis of 'Slip' and 'Drag' characteristics of nanosponge gel. A ground glass slide is fixed on this block. An excess of nanosponge gel (about 2 g) under study is placed on this ground slide. The nanosponge gel is then sandwiched between this slide and another glass slide. A 1 Kg weight is placed on the top of the two slides for 5 minutes to expel air and to provide a uniform film of the nanosponge gel between the slides. By putting weight of 1kg, the time (in seconds) required by the top slide to cover a distance of 7.5 cm with the help of string attached to the hook is noted.

A shorter interval indicates better spreadability, which is calculated by the formula:

$$S = \frac{ML}{T}$$

Where,
S=Spreadability,
M=Weight tied to upper slide,
L=Length of glass slides,
T=Time taken to separate the slides completely from each other.

In vitro drug diffusion study
The diffusion studies of the prepared nanosponge gel were carried out in Franz diffusion cell through a cellophane membrane. Gel sample (0.5gm) was taken in cellophane membrane and the diffusion studies

were carried out at 37 ± 1 C° using 250 ml of phosphate buffer (pH 7.4) as the dissolution medium. 5ml of each sample was withdrawn periodically at 1, 2, 3, 4, 5, 6, 7 and 8 hrs and each sample was replaced with equal volume of fresh dissolution medium in order to maintain sink condition. Samples were analyzed by UV-visible spectrophotometer at 272 nm for drug content.

Stability study

Formulation of nanosponge gel are placed in collapsible tubes with proper sealing and for a short term accelerated stability study at room temperature and 40±2°C,75±5% RH as per ICH Guidelines. The formulation was withdrawn after particular period of interval; the physical stability was evaluated by visual inspection for physical changes (such as phase separation and drug precipitation) and evaluated for drug content and in vitro drug release.

RESULT AND DISCUSSION

Preformulation results

UV Calibration

The calibration of luliconazole in PBS 7.4 was found to be linear in conc. range at 2, 4, 6, 8,10 µg/ml having a coefficient of regression (R2) value 0.996.

Table 3: Absorbance of Luliconazole in PBS 7.4

Concentration µg/ml	Absorbance
2	0.126
4	0.256
6	0.338
8	0.455
10	0.552

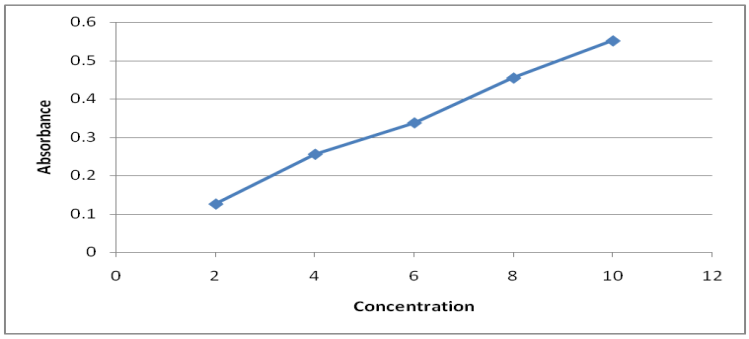

Figure 1: Calibration Curve of Luliconazole in PBS 7.4

FTIR Study

Based on the results obtained of FTIR it can be concluded that drug and excipients are best compatible to each other.

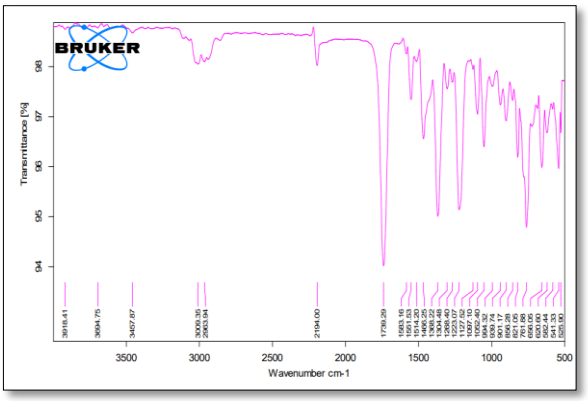

Figure 2: FTIR of Luliconazole API

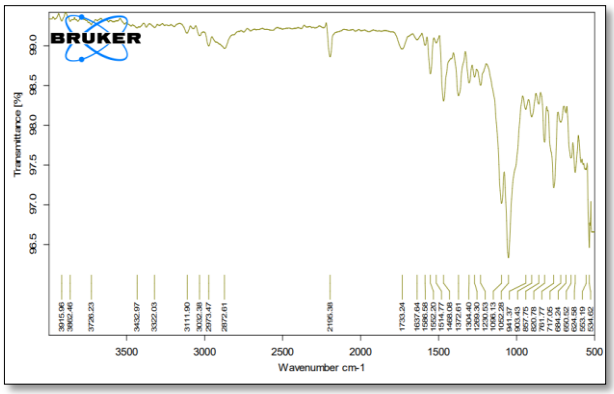

Figure 3: FTIR of Physical Mixture

Evaluation results of Luliconazole Nanosponges

Physical appearance

All the batches were found to as a whitish, spongy powder. The nanosponge's spherical appearance is dependent on the ethyl cellulose solution's viscosity.

Drug Encapsulation Efficiency, Drug Content and Percentage yield

Table 4: Evaluation results of all batches of Nanosponges

Batch	Drug Entrapment Efficiency(%)	Drug Content (%)	Percentage yield (%)
NS1	87.11	88.32	86.66
NS2	81.64	84.88	87.33
NS3	78.65	81.59	86.66
NS4	73.89	78.43	80
NS5	88.66	91.89	75
NS6	85.23	89.26	73.5
NS7	86.16	90.65	84
NS8	91.48	94.11	91.2
NS9	83.24	88.68	88

The range of manufactured nanosponges percentage drug entrapment efficiency was determined to be between 73.89 and 91.48. The dispersed phase's viscosity was marginally increased when the greatest PVA concentration was utilised to make nanosponges with greater drug:polymer ratios.For all of the formulations, the drug content was confirmed to be within permissible limits. It was discovered that the formulation's drug content ranged from 78.43% to 94.11%, indicating that the medication was distributed uniformly.All batches output yields varied from 73 to 91.2%. It was discovered that both the concentration of polyvinyl alcohol and the drug-to-polymer ratio had a significant impact on the production yield.

Particle size and Zetapotential

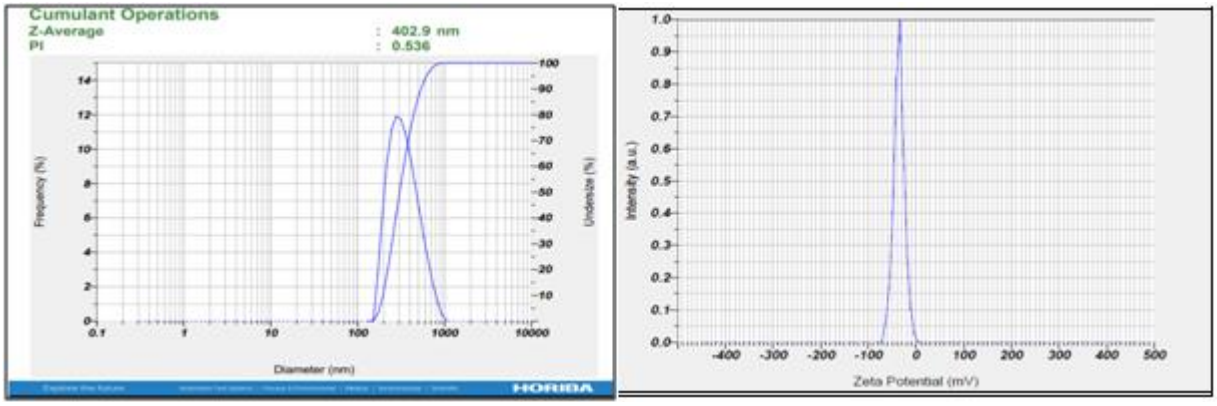

Figure 4: Particle size &Zeta Potential of optimized batch NS8

Particle sizes in the nanosponge (less than 1 μm) are present in every nanosponges formulation. The stabilisation of the colloidal system may be responsible for the smaller particle size and higher polydispersity index. The zeta potential was between -21.4 and -32 mV. The increased magnitude of repulsive forces present in the high zeta potential was discovered to diminish the likelihood of particle aggregation.

XRD

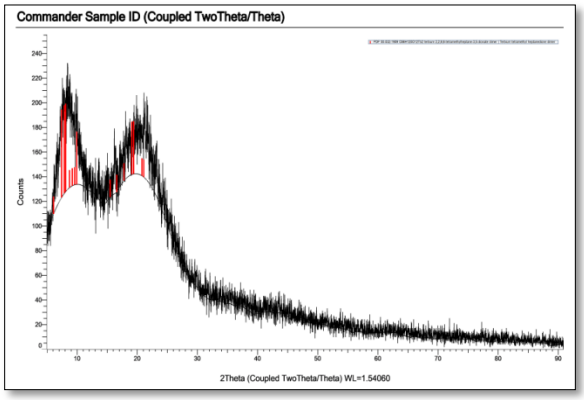

Figure 5: XRD image of NS

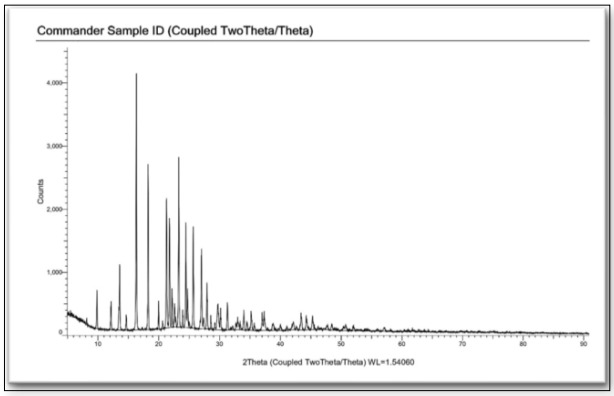

Figure 6: XRD image of Luliconazole

XRD diffractograms reported that drug was amorphous in nature and its nanosponge form get converted it to crystalline structure proving its sustained drug release.

Scanning Electron Microscopy

The morphology of the nanosponges examined using SEM. Despite the fact that there weren't many entire luliconazole crystals to be seen, SEM images showed that the nanosponges were porous and mainly spherical in shape.

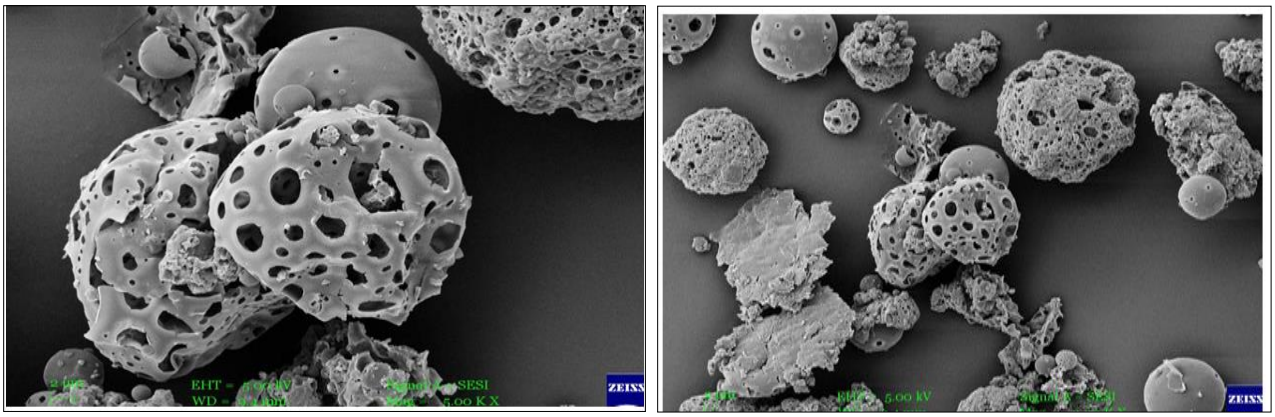

Figure 7: SEM images of Optimized Batch

Differential Scanning Calorimetric (DSC) Studies

DSCisathermoanalyticaltechniquethatmeasuresphysicalandchemicalchanges of amaterial in response to temp. DSC studies indicated a sharp endothermic peak at 151^0ccorrespondingto melting of pureluliconazole as shown in results.

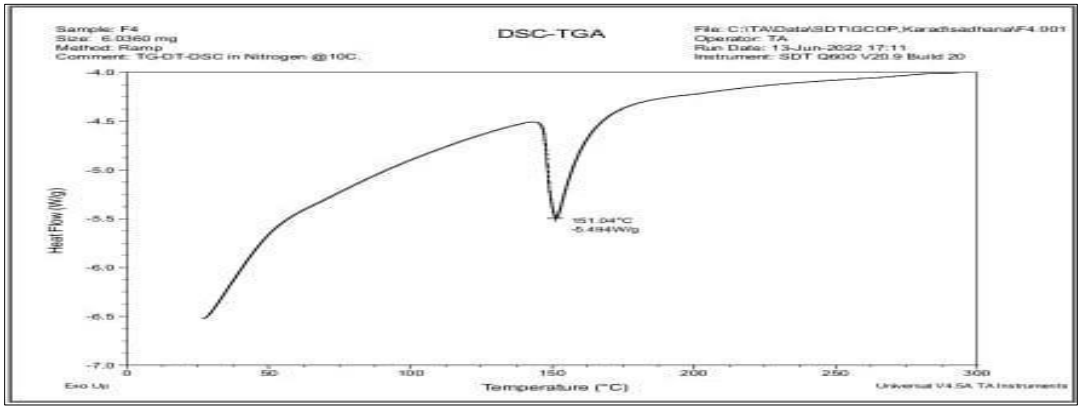

Figure 8: DSC of optimized batch

Evaluation of Topical Nanosponges Loaded Gel

Appearance

All the prepared gels were homogenous in nature and clear without any aggregate.AllpreparedLNZNSloadedgelbatcheshavethegoodconsistency.

pH,Spreadability, Viscosity&Drug Content

All gel formulations pH values were determined to be in the range of 5.4-5.8 which indicates that they were close to skin pH. Skin irritation could result from a rise in pH values.

Spreadability is inversely proportional to the viscosity of the prepared gel. Spreadability decreased as the amounts increased. The spreadability of the prepared carbopol gel formulation was in the range of 12.45–15.22 g/cm^2. All the formulations showed good spreadability.

A Brookfield viscometer was used to measure the viscosity of the gel at a temperature of 25 °C and a spindle speed of 10 rpm. As the polymer concentration rises, the viscosity of the formulations increases. The formulation's viscosity values fall within a certain range 812-938 cps.

All the prepared LNZNS loaded batches shows good drug content, the drug content iswithintherangeof 73% - 85.3%.

Table 5: Evaluation results of all gel batches

Batch	NG1	NG2	NG3
pH	5.7	5.4	5.8
Spreadability (g.cm/sec)	2.3	2.0	2.2
Viscosity (cps)	812	938	874
Drug Content (%)	78.01	86.33	81.50

In vitro drug diffusion study

All the prepared batches show good drug diffusion. The drug release of the nanosponge based gel batches shown in below table. The percentage drug release at 12 hrs is maximum among all the batches i.e. 87.8%. From these it is considered to be best optimized one.

Table 6: In vitro drug diffusion of gel

Time	NG1	NG2	NG3
0	0	0	0
1	7.1	8.2	7.5
2	10.52	12.24	12.02
3	14.62	16.2	15.22
4	16.32	20.32	17.5
5	24.23	26.01	24.83
6	36.4	38.03	37.3
8	52.5	55.25	53.8
10	76.2	75.7	73.33
12	80.2	87.8	84.53

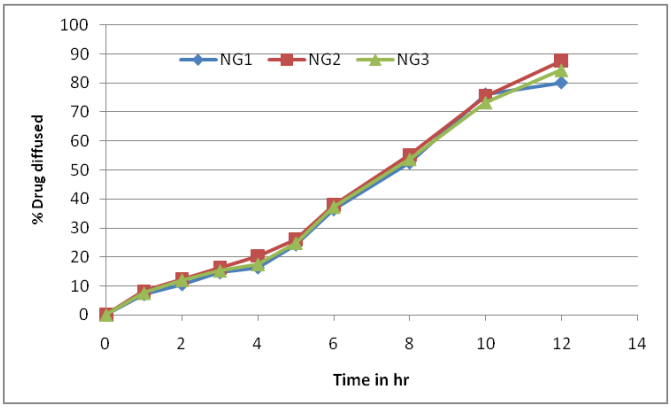

Figure 9: In vitro drug diffusion

Stability Study

As per ICH guidelines, The optimized NG2 topical gel was assessed for stability test for 90 days by exposing the sample at room temperature (25±2°C)and accelerated condition(40±2°C and75± 5% RH) in Stability chamber, after 90 days stability the gel is evaluated for Appearance,pH, viscosity, % drugdiffusion, etc.

Table 7: Stability Study

Month	Temperature	Appearance	pH	Viscosity (cps)	% Drug diffusion
1	R.S.T. Acc. S.T.	No Change No Change	5.7 5.4	840 822	87.7 87.6
2	R.S.T. Acc. S.T.	No Change No Change	5.5 5.6	898 923	87.4 87.2
3	R.S.T. Acc. S.T.	No Change No Change	5.9 5.8	904 956	86.7 86.3

There was a negligible difference in the Appearance, pH, viscosity and % drug diffusion observed after stability study. The physical characteristics also remained unchanged suggesting that the formulation is stable under the given conditions.

CONCLUSION

The prepared nanosponges were successfully in-corporated into topical gel. The nanospongesbased formulation showed better drug release and good stability. The nanosponges system wasfound to have better penetration of drug through the skin and hence we can conclude thatluliconazole NS loaded gel formulation is a good candidate for topical application in thetreatment of skin and soft tissue infection. The overall investigation described luliconazoleNS gel formulation could be an alternative to the current topical formulation available for thetreatmentof fungal infection if properlyoptimized.From the study it can be concluded that the nanosponges topical gel is a viable alternative to conventional topical gels as it enhances bioavailability by prolonging the contact time of the drug with the corneum stratum and its ability to release the drug in a sustained manner. It also results in better patient compliance by reducing the frequency of administration. Hence we can conclude the nanosponges topical gel formulations used as drug carriers to enhance the bioavailability of topical application.

ACKNOWLEDGMENTS

All authors would like to express their sincere gratitude to Channabasweshwar Pharmacy College (Degree), Latur for their support and resources that enabled the successful completion of this research. The facilities provided by Channabasweshwar Pharmacy College (Degree), Latur were instrumental in conducting experiments and gathering data. Authors would also acknowledge Swapnroop Pvt. Ltd Aurangabad, Maharashtra, India for providing Luliconazoleas gift sample.

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