Journal of Carcinogenesis
Covering Genesis to Therapeutics

Journal of Carcinogenesis, ISSN: 1477-3163
2025; Vol 24: Issue 6s, https://carcinogenesis.com/

Formulation and Invitro Evaluation of Luliconazole Phytosomal Gel for Topical Drug Delivery

Preshita Mehta[1], Komal Soni[2], Mohd. Mustaffa Khan[3], Tanu shree Vyas[3], Abhishek Anand[4]*, Mithul V Mammen[4], Surya Nath Pandey[5]*

[1]Department of Pharmaceutics, School of Pharmacy, Bahra University, Waknaghat, Solan, Himachal Pradesh, India-173234

[2]Department of Pharmaceutics, Quantum University, Roorkee, Uttarakhand, India - 247667

[3]Shri Venkateshwara School of Pharmacy, Shri Venkateshwara University, Rajabpur, Gajraula, Amroha, Uttar Pradesh, India – 244236

[4]Department of Pharmacy Practice, Teerthanker Mahaveer College of Pharmacy, Teerthanker Mahaveer University, Moradabad, Uttar Pradesh, India -244001

[5]Department of Pharmacology, Teerthanker Mahaveer College of Pharmacy, Teerthanker Mahaveer University, Moradabad 244001, Uttar Pradesh, India, Orcid id- 0000-0003-2277-8174

Corresponding author:

Name & Address of Corresponding – Surya Nath Pandey*

E-mail ID: suryanathpandey8@gmail.com

Department of Pharmacology, Teerthanker Mahaveer College of Pharmacy, Teerthanker Mahaveer University, Moradabad 244001, Uttar Pradesh, India, Orcid id- 0000-0003-2277-8174

ABSTRACT

Due to its decreased water solubility, luliconazole a recently produced imidazole molecule with antifungal properties has a reduced cutaneous bioavailability, which hinders its topical distribution. Permeation is further hindered by its poor solubility in the stratum corneum's lipid phase. This work aimed to improve drug entrapment, solubility, permeability, safety, and efficacy by developing a stable phytosomal gel formulation of albendazole. A UV-Spectrophotometric technique was developed with R2 = 0.9944 to accurately estimate the concentration of luliconazole (2–18 µg/ml) at 296 nm. Using a thin layer approach, the formulation included a phospholipid-luclonazole complex that was produced by solvent evaporation and then applied to phytosome vesicles at different molar ratios and concentrations. The phytosome's vesicle diameters were decreased by sonication. With an ideal formulation of 1% silymarin-phospholipid complex and a molar ratio of 1:5 for luliconazole to phospholipid, the phytosomal properties were as desired: the mean vesicle diameter was 117.15 nm, the polidispersity index was 0.268, and the entrapment efficiency was 96.60±0.0131%. The improved Phytosomes were uniformly spherical and free of drug crystals, as proven by TEM pictures. The ideal formulation was used to make gel at different doses, and numerous physicochemical parameters, such as viscosity, pH, and spreadability, as well as drug content and release, were assessed. Because the phytosomal gel F9 has better release characteristics than the pure drug control gel, it was selected as the optimal formulation.

Keywords: *Phospholipid, phytosomes, luliconazole, TEM.*

How to Cite: Preshita Mehta, Komal Soni, Mohd. Mustaffa Khan, Tanu shree Vyas, Abhishek Anand, Mithul V Mammen, Surya Nath Pandey (2025) Formulation and Invitro Evaluation of Luliconazole Phytosomal Gel for Topical Drug Delivery, *Journal of Carcinogenesis*, *Vol.24, No.6s*, 46-59.

1. INTRODUCTION

Phospholipids, whether synthetic or naturally derived, are combined with specific plant-based bioactive compounds in an appropriate solvent to form phytosomes. These innovative phyto-complexes are recognized for their superior chemical and

physical properties, enhancing the bioavailability, stability, and targeted delivery of active compounds (1). Phytosome technology has emerged as a promising strategy in pharmaceutical research, particularly for improving the therapeutic efficacy of drugs with poor solubility or permeability. According to the World Health Organization (2023), fungal infections, particularly superficial mycoses like dermatophytosis, affect approximately 20–25% of the global population, with higher prevalence in tropical and subtropical regions due to favorable climatic conditions (2). This significant global health burden highlights the urgent need for advanced drug delivery systems to optimize antifungal therapy.

The primary objective of this study is to develop and evaluate a phytosomal gel formulation incorporating luliconazole, a potent antifungal agent, for topical drug delivery. The phytosomal gel is designed to enhance luliconazole's permeability across biological membranes, prolong its release profile, improve drug entrapment efficiency, and enhance solubility and dissolution characteristics. (3) By leveraging the unique advantages of phytosome technology, this formulation aims to overcome the limitations of conventional topical antifungal therapies, providing an effective solution to address the global challenge of fungal infections. In vitro evaluations will assess the formulation's performance, focusing on drug release, entrapment efficiency, and skin permeation, to establish its potential for clinical application.

2. MATERIALS AND METHODS

Materials used
Methanol, distilled water, deionized water, Luliconazole (Chemizo Enterprise, Ahmedabad, Gujarat), and soy protein (Lipoid® 90G, Gattefosse) are all included. Every solvent used was at least as good as analytical grade.

3. PREFORMULATION STUDIES:

Preformulation is an important stage in the process of development. The focus of these investigations is on the physicochemical properties of the medicine that may impact its efficacy and the development of a suitable dosage form. A thorough comprehension of these attributes could provide valuable perspectives for formulating formulations or suggest that molecular alterations are required. Preformulation investigations may, in the simplest form, verify that the compound's growth is not appreciably hindered. The technique these research illustrate is essential for creating stable, safe, and effective dosage forms. The drug sample was identified using a variety of analytical techniques, such as melting point analysis, UV spectroscopy, and infrared spectroscopy (3,4).

3.1.1 Organoleptic Characteristics
The appearance, color, and odor of the drug trial's physical components were described. (5)

3.1.2 Melting point
The melting point of a solid material is the temperature at which, for a given total pressure, the solid and liquid phases approach equilibrium. An apparatus called a melting point is used to determine the drug's melting point. A capillary tube with thin walls, typically 10–15 mm long and 1 mm in diameter, is filled with a minute amount of the drug, and one end is sealed. The sample-containing capillary is suspended, and a thermometer is positioned to monitor the temperature, allowing for gradual and even heating. By evaluating the range of temperatures at which the sample is observed to liquefy, the melting point of the medicine is determined. (6)

3.1.3 UV spectrum of Luliconazole
UV-visible spectrophotometry offers unique insights into the chromophoric components of molecules when exposed to light in the visible or ultraviolet spectrum, and is widely used to clarify the structural characteristics of numerous drugs. Certain wavelengths of light are absorbed by molecules based on the type of electrical shift that occurs during absorption. UV spectra are frequently shown as a wavelength vs. absorbance graph.(7)

A double-beam UV-visible spectrophotometer was utilized in this investigation to determine the drug's maximum absorption wavelength (λmax). A solution with 14 µg/ml of Luliconazole in methanol was scanned at 200-800 nm.

3.1.4 Estimation of Luliconazole
3.1.4.1. Estimation of Luliconazole using UV-visible spectrophotometer
A standard stock solution of luliconazole was made through the incorporation of 10 mg of Luliconazole in 10ml of methanol, resulting in a concentration of 1000µg/ml. Subsequently, 10ml of this stock solution was extracted and diluted to a final volume of 100ml using methanol as the solvent, yielding a solution with a concentration of 100µg/ml. Further dilutions were performed to carry out various concentrations ranging from 2-18 µg/ml. A UV-visible spectrophotometer was used to measure the absorbance of these solutions at 296 nm, with methanol serving as the blank. . After that, absorbance and concentration were correlated to create a standard curve. Using the calibration curve (8), parameters including the intercept, slope, straight-line equation, and correlation coefficient were computed.

3.1.5. Solubility Studies

When two or more compounds spontaneously combine to form a homogeneous molecular dispersion, this is referred to as solubility.

In order to assess dissolvability quantitatively, an excess measure of the drug was placed in thoroughly cleaned culture tubes with 1 ml of several solvents, including pH 7.4 mixture of methanol, ethanol, CH3)2CO, chloroform, water, and PBS. After that, these on a water bath shaker, culture tubes were allowed to ferment for a full day at room temperature. Each sample was centrifuged at 15,000 rpm after the 24-hour period, and the resulting the supernatant was carefully discarded. Consequently, the supernatant was filtered, appropriately diluted, and quantitatively resolved using spectrophotometry. (9).

3.1.6 Partition Coefficient of Drug

An indication of a drug's lipophilicity or hydrophilicity and capacity to cross cell membranes is the partition coefficient (oil/water). This is defined as the fraction of the combined drug that separates into the organic and aqueous phases after attaining equilibrium. This coefficient provides information about the drug's lipophilic or hydrophilic characteristics. Drugs classified as lipophilic have partition coefficient values substantially greater than 1.

In contrast, people who have criteria far lower than 1 are considered hydrophilic. Usually, the partition coefficient is calculated using an oil phase that contains water and n-octanol. The ratio of the drug's concentration in n-octanol (Cn-octanol) to that in water (Cwater), commonly expressed in logarithmic form, is known as the partition coefficient (P o/w). The partition coefficient was obtained using the shake flask method. 100 mg of the medication levicole was suspended in 10 ml of a 1:1 mixture of two solvents (n-Octanol: Water) and allowed to sit at room temperature for the entire day. After a day, the two layers were separated, and they were centrifuged for 15 minutes at 15,000 rpm. Using a UV spectrophotometer, the absorbance at the matched λ max was ascertained following the proper dilution. (10)

3.1.7. FTIR of Luliconazole and Excipients

Fourier Transform Infrared (FT-IR) spectroscopy was utilized in this study to examine the structure of lumiconazole. To identify any possible interactions between the drug and the excipients, the FT-IR spectra of a mixture including the drug and excipients was also recorded.(11) The compound's functional groups can be understood by FT-IR spectroscopy.

3.1.8. FTIR Drug-Excipient Compatibility Study

The efficacy of the medication and excipients was evaluated by FT-IR analysis. With FTIR, any chemical or physical interactions between the medication and excipients were found. A 1:1 ratio was used to combine the medicine with several excipients, and they were well mixed. After that, samples were scanned using FTIR between 400 and 4000 cm-1. To look for any indications of physical changes or incompatibility, the medicine's single spectrum and the drug combined with excipients were compared.(11)

3.2 Preparation of Luliconazole-Phospholipid complex phytosomes

The refluxing approach was applied with varying drug to lipid molar ratios (from 1:1 to 1:7) in order to generate the phospholipid complex. Initially, 10 milliliters of methanol were used to dissolve precisely weighed amounts of phospholipid and lumiconazole in a 100 milliliter flask with a circular bottom. Reflux reaction was maintained for two hours at a regulated temperature of 40 °C. The solvent was then allowed to evaporate under vacuum. circumstances to produce a film that sticks to the flask's walls. Overnight, the dehydrated leftovers were kept in desiccators. After that, the cast film was spread at 60°C in phosphate-buffered saline (PBS 7.4). Following around fifteen minutes of hydration, the lipid expanded and separated from the flask wall, vesiculating to create vesicles.Lastly, a probe sonicator with a 60% amplitude and a 5-second on/off period sonicated the phytosomal suspension for 4 minutes. A maximum of 24 hours were allowed for the refrigeration and characterization of each phytosomal solution. Luliconazole-phospholipid molar ratio and complex concentration were adjusted during the optimization phase. (12,13)

Table:1 Phospholipid complex compositions containing Luliconazole

Phytosomal Composition			
Sr.no.	Formulation Code	Drug : Phospholipon 90G (molar ratio)	Methanol (ml)
1	F1	01:01	10ml
2	F2	01:02	10ml
3	F3	01:03	10ml
4	F4	01:04	10ml
5	F5	01:05	10ml

6	F6	01:06	10ml
7	F7	01:07	10ml

3.3. Evaluation of Luliconazole-Phospholipid complex phytosome (12,13)

3.3.1 Visual Appearance

Phytosomes can have a translucent or milky appearance, depending on their composition and size.

3.3.2 Optical Microscopy

Under a microscope, a drop of phospholipid complex phytosome was detected on a glass slide, protected with a glass cover.

3.3.3 pH of phytosomes

We measured the pH of phospholipid phytosomes using a well-known pH meter. A pH meter that had been calibrated with standard buffer solutions at pH 7.4 was used to calculate the pH in each dispersion. The electrode was placed into the sample ten minutes before the reading was taken at room temperature.

3.3.4. Efficiency of Entrapment and Loading Capacity

By counting the amount of liconazole entrapped inside the phytosomes, the efficacy of phytosome entrapment was evaluated. In order to assess the effectiveness of trapping of luconazole within the phytosome, a suitable volume of dispersion was moved into a microcentrifuge tube. Next, the dispersion was centrifuged at 15,000 rpm for 15 minutes. Following centrifugation, the supernatant was collected, and the percentage of free luteconazole was determined using spectrophotometric analysis at λmax= 296 nm. The following formula was used to determine the entrapment efficiency.

$$EE\ \% = \frac{W\ (\text{Added drug}) - W(\text{free drug})}{W\ (\text{Added drug})} \times 100$$

Where W (free drug) is the amount of free drug measured in the lower chamber of the micro centrifuge tube following centrifugation, and W (added drug) is the amount of drug added during the creation of phytosomes.

3.3.5. Morphology of Phytosome Vesicles

Transmission electron microscopy was benefited to visually inspect the morphology of phytosome vesicles. Prior to analysis, the material was divided into a total volume of 10 mL. After swirling the mixture, a drop of the sample was applied to the object. The specimen was covered with a 400 mesh grid, which was left in place for a minute. Using filter paper, any remaining droplets on the grid were eliminated. After adding a dewdrop of uranyl acetate to the grid, surplus solution was smeared off with filter paper. The films were examined under a transmission electron microscope and taken pictures of after the grid was left for half an hour.

3.3.6 Vesicle Size Distribution and Characteristic Determination

Using a particle size analyzer and dynamic light scattering system spectroscopy, the vesicles' dimensions and polydispersity index were investigated. To evaluate the vesicle size and dispersion, the material was placed into a disposable cell, and light intensity readings ranging from 3,000 to 30,000 were recorded.

3.4 Preparation of Luliconazole phytosomal Gel (14)

The Luliconazole-loaded phytosomal gel was formulated by dispersing Carbopol 980 into the phytosome dispersion, while for the control gel, pure Luliconazole was dispersed in Carbopol. The prepared gel was lay by for 24 hours. Triethanolamine was then added to alter the pH to 7.4, and the mixture was totally stirred to achieve a homogeneous gel consistency.

Table: 2 Composition of Luliconazole phytosomal gel

Sr.no.	Ingredients	Formulation Code		
		F8	F9	F10
1	Phytosomal dispersion (ml)	10ml	10ml	10ml
2	Carbopol 980(% w/v)	0.5	1	2
3	Triethanolamine (ml)	q.s	q.s	q.s

3.4.1 Evaluation of Luliconazole phytosomal Gel (15,16)

3.4.1.1 Appearance

Phase separation, homogeneity, texture, color, and physical appearance of the formulations were all evaluated. Visual observation was used to assess these qualities.

3.4.1.2 pH

The pH meter was calibrated using the standard buffer solution, which has a pH of 7.4. The pH of the mixture was measured after weighing and dissolving around 0.1 g of the gel in 10 ml of distilled water.

3.4.1.3 Viscosity
Using a viscometer with a spindle speed of 24 revolutions per minute, the viscosity of the gel (Spindle L4) was measured at 25 °C.

3.4.1.4 Spreadability
The following method was used to assess the gel's spreadability: On a glass plate, a pre-marked circle with a diameter of 2 cm held an amount of 2g gel. The gel was then positioned on top of an additional glass plate. The upper glass plate was weighted down by 500g, and it was left to rest for five minutes. It was measured how much the gel's spreading caused the diameter to increase.

Drug Content
In order to pilot the drug content analysis, 0.1g of gel was dissolved in 10ml of methanol. An adequate volume of the dispersion was transferred to a microcentrifuge tube in order to measure the amount of medication, specifically lindiconazole, present in the phytosome. The dispersion was then centrifuged for 15 minutes at 15,000 rpm. The amount of medication—luliconazole—present was determined by volume-dilution of 1 milliliter of the supernatant, which was collected after centrifugation, with methanol in a 10 milliliter volumetric flask. A UV-visible spectrophotometer was then used to measure the absorbance of the generated solution at 296 nm. This led to the determination of the drug content proportion. (17)

3.4.1.6 FTIR Spectra
The FTIR spectrum of optimized formulation F9 was measured by using FTIR spectroscopy.

3.4.1.7 investigation of drug release in vitro
The study made use of Franz diffusion cells, which have donor and receiver compartments. The donor and receptor cells in the Franz diffusion cells were divided by a suitably sized pre-treated semipermeable barrier.Twenty milliliters of phosphate buffer saline solution at pH 7.4 were kept in the receiver compartment, and the system as a whole was maintained at 37°C ± 0.5°C. One gram of the phytosomal gel formulation and one gram of the control gel formulation, matching the dosage, were applied uniformly to the donor compartments.

One milliliter samples were taken out of the receiver compartment at predetermined intervals throughout the course of a day, and they were quickly replaced with an equivalent volume of saline buffer. After that, the samples were examined at 296 nm for drug content using spectrophotometric analysis. The sink conditions were maintained during the studies. (18)

3.4.1.8 Drug release kinetics (19,20)
Model-dependent approaches use a variety of mathematical functions to characterize the drug release profile. The parameters acquired from the model are used to evaluate the release profiles when a suitable function has been selected. Several data treatment models were employed to examine the ex vivo permeation study data, including:

Zero Order kinetics:
This model explains how medications dissolve in a variety of modified-release pharmaceutical dosage forms, including osmotic tablets, transdermal devices, and matrix tablets that include coated, low-soluble medications. With Qt representing the amount of drug dissolved at time t, Q0 representing the initial drug concentration in the solution (often Q0 = 0), and K0 representing the zero-order release constant given in concentration/time units, the formula for zero-order release is Q0 - Qt = K0t. Researchers were able to investigate the release kinetics by plotting the total amount of drug released against time using information from in vitro drug permeation assays.

First Order kinetics:
This model describes the dissolution of drugs in pharmaceutical dose forms, such as water-soluble drugs in porous matrix. First-order kinetics gives us the following formula to express the medication release: Where t is the time, C0 is the drug's initial concentration, and k is the first-order rate constant, log C is equal to log C0 – K.t / 2.303.
Plotting the gathered data as the log cumulative percentage of medication remaining over time results in a straight line with a slope of K/2.303.

Higuchi's Model:
The elease of medications is predicted by this model using a matrix method. It was first created for planar systems, but it was later expanded to include porous systems and other diverse geometric shapes. It is predicated on multiple theories regarding drug diffusion and system properties. Qt = KH (t) 0.5 is the simplified Higuchi equation, in which Qt is the

dosage delivered at time t and KH is the release rate constant. A straight line with a slope of "KH" is produced when the total amount of medication released is plotted against the square root of time. This illustrates the drug release process by diffusion.

Korsmeyer-Peppas Model:

The drug release from a polymeric structure is explained by this paradigm. The formula below can be used to express the release rates from controlled-release polymeric matrices: The formula is Q = K.t^n, where 'n' is the diffusional exponent that discloses the release mechanism, Q is the amount of medicine released at time 't', and the kinetic constant K accounts for the geometric and structural features of the tablets. For anomalous (non-Fickian) transport, N ranges from 0.45 to 0.89; for zero-order release, n = 0.89; and for Fickian release, n = 0.45. The Korsmeyer-Peppas model plots the log cumulative percentage of drug releases vs log time.

4. RESULT AND DISCUSSION

4.1. Result of Preformulation studies

4.1.2Organoleptic properties (22)

Physical examination was performed to test Luliconazole organoleptic characteristics, including colour (pale yellow), appearance (crystalline powder).

4.1.3 Melting Point (23)

It was revealed that the pure drug's melting point, 123.6±1.52 °C, corresponds to this range. As a result, the medication sample was devoid of all contaminants.

4.1.4 UV Spectroscopy (24)

4.1.5 Determination of Luliconazole Absorption Maxima via UV Spectroscopy

Figure 4.1 displays the Luliconazole UV spectrum result

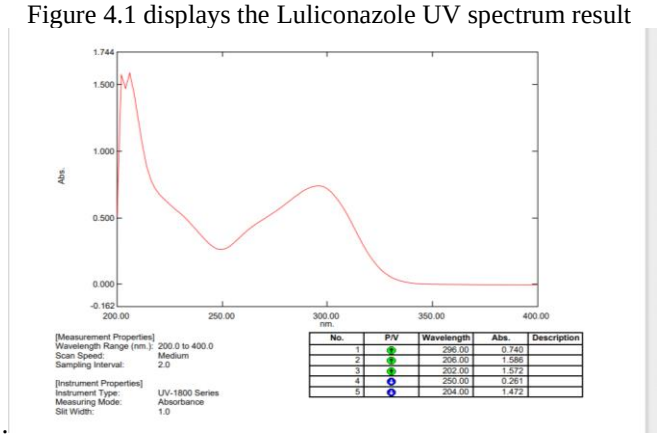

Figure: 1 UV spectrum of Luliconazole

Luliconazole's maximum wavelength was found to be 296 nm.

4.1.6 Luliconazole Standard Calibration Curve Preparation in Methanol

Table: 3 Standard curve data of Luliconazole in methanol

Sr. No.	Concentration (µg/ml)	Absorbance ± SD
1	2	0.123 ± 0.002
2	4	0.232±0.002
3	6	0.336±0.001
4	8	0.422±0.002
5	10	0.537±0.002
6	12	0.652±0.002
7	14	0.756±0.002
8	16	0.858±0.002
9	18	0.972±0.002

Figure: 2 Standard curve of Luliconazole in methanol

The graph depicting the standard curve of leviconzole revealed the regression equation Y = 0.0528X + 0.0147, R^2 = 0.9994, demonstrating strong linearity.

4.1.8 Solubility study

Solubility tests of the drug in diverse solvents were conducted to assess suitable components for formulation development. The drug analysis was performed using a UV Spectrophotometer at 296 nm. It was observed that luliconazole exhibited high solubility in solvents like methanol, chloroform, ethanol, and acetone, while showing poor solubility in water and phosphate buffer (pH=6.8).

4.1.9 Partition coefficient determination (25)

It was discovered that the partition coefficient of luliconzole in n-octanol:water was 4.2614±0.03. This implies that the drug has lipophilic properties.

4.1.10 FTIR of Luliconazole and Excipients

4.1.10.1 FTIR of Luliconazole (24)

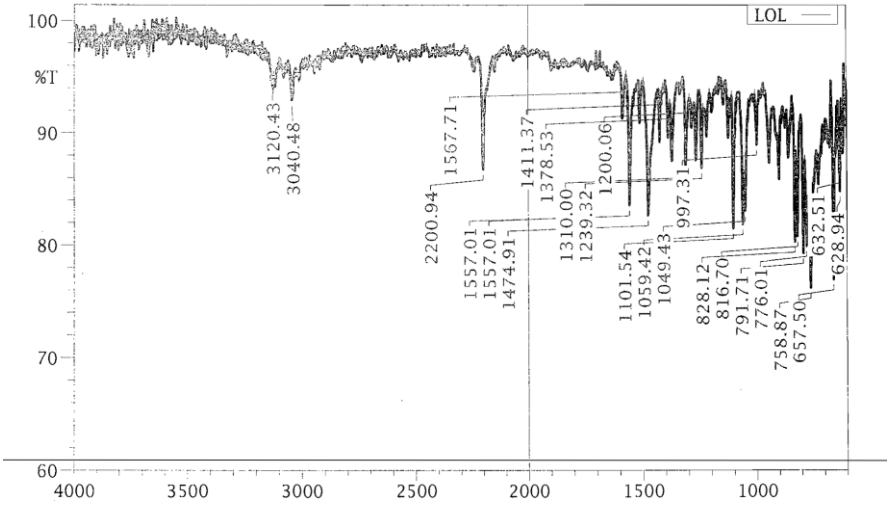

Figure: 3 FTIR interpretation of Luliconazole

The FTIR spectra of Luliconazole showed peak at 3040.48 & 3120.43 cm−1 (Aromatic C-H stretch), at 2200.94 (C=N Stretching), at 1556.01 (C=C Aromatic Stretching), at 758.87&1101.54 (C–Cl Stretching) were all observed in the spectra of Luliconazole. This finding verified the licconazole's authenticity and purity.

4.1.10.2 FTIR spectra of Phospholipon 90G (26)

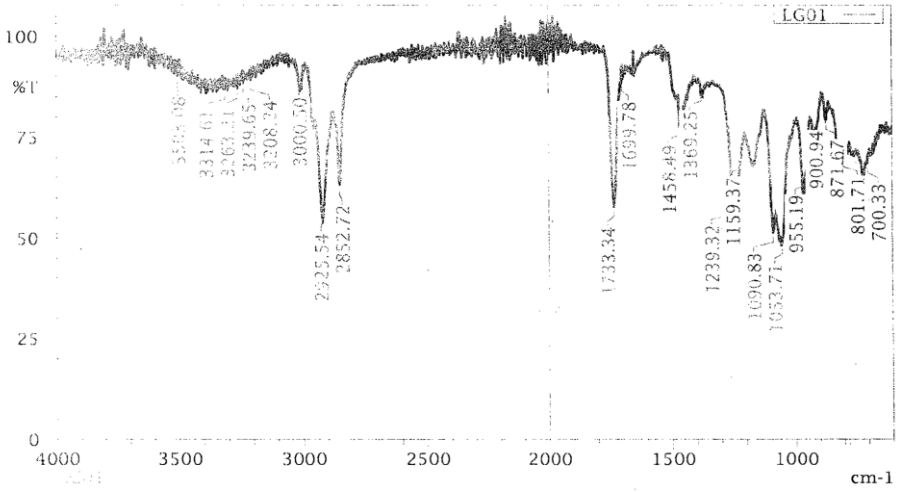

Figure: 4 FTIR spectra of Phospholipon 90G

The FTIR spectra of Lipid 90G showed peaks of Lipid 90G at 1239.25 (P=O stretching), 1733.34 (C=O stretching), 1090.83 at (P–O–C stretching) at 1090.83, −N+(CH3)3 stretching at 954.19 .These were the observed spectra of Lipid 90G. This scrutiny verified the transparency and authenticity of the Lipid 90G.

4.1.10.3 FTIR analysis of the physical mixture

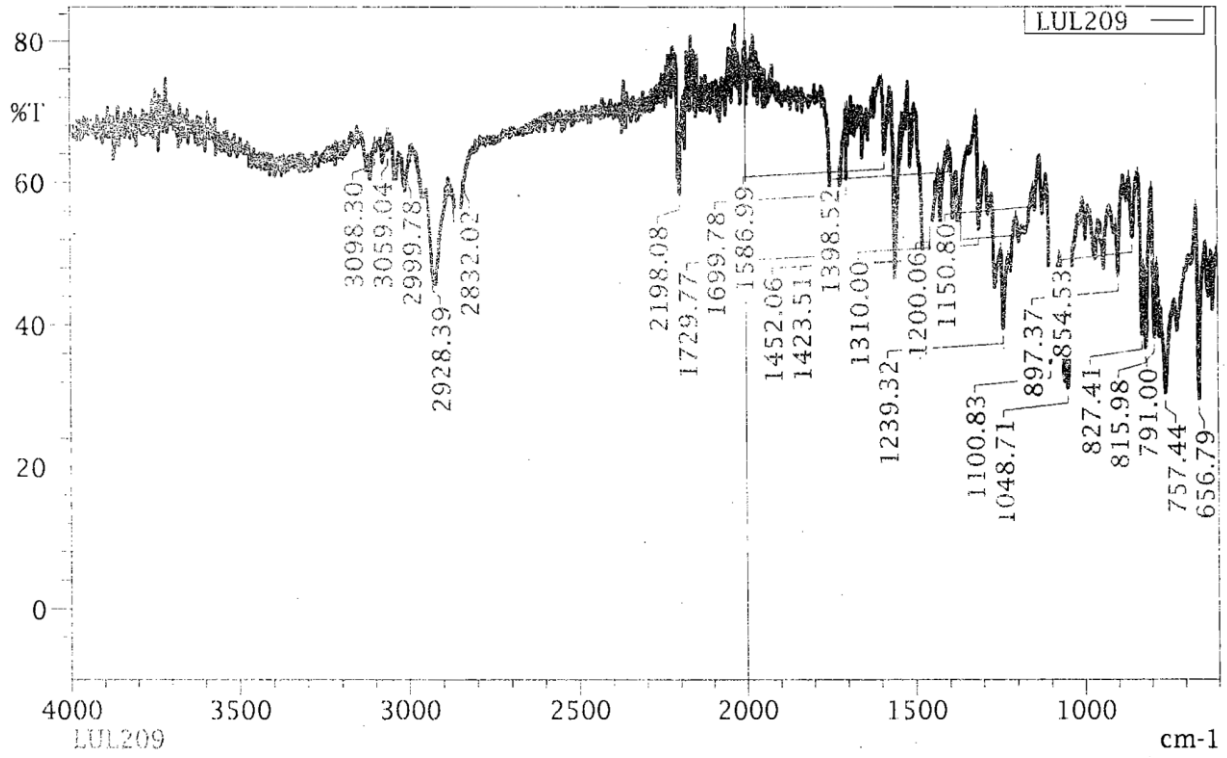

Figure: 5 FTIR interpretation of Physical Mixture

In order to rule out any possible interactions between the drug and the excipients used in the analytical method of drug estimation, FTIR spectra of physical combination investigations were conducted. Analyzing every peak in the spectrum revealed that the drug's corresponding peaks coexisted with excipient peaks in the spectra. As a result, no interaction was found in this combination.

4.2 Evaluation of Phytosome

4.2.1 Appearance of Phytosome

Figure: 6 Luliconazole-phospholipid Complex Phytosome.

Table: 4 Composition of Luliconazole-phospholipid Complex Phytosome.

Visual Appearance		
Sr. No.	**Formulation code**	**Appearance**
1	F1	Milk white homogenous dispersion with no phase separation
2	F2	Milk white homogenous dispersion with no phase separation
3	F3	Milk white homogenous dispersion with no phase separation
4	F4	Milk white homogenous dispersion with no phase separation
5	F5	Milk white homogenous dispersion with no phase separation
6	F6	Milk white homogenous dispersion with no phase separation
7	F7	phase separation

4.2.2 pH of phytosomal dispersion

Formulations F1, F2, F3, F4, F5, and F6 had pH values of 6.81±0.010, 6.83±0.015, 6.82±0.010, 6.84±0.010, 6.83±0.015, and 6.84±0.015, in that order.

4.2.3 Entrapment efficiency

These findings indicate a notable impact on the percent entrapment efficiency of the phytosome as the lipid concentration increased. Based on the percentage of drug entrapment, F5 was chosen as the optimized formulation, and therefore, it was selected for further investigation. Table 5 provided the percentage of drug entrapment for each formulation.

Table: 5 Percentage Entrapment efficiency of different Phytosome formulation containing Luliconazole-phospholipid Complex.

Sr.no.	**Formulation Code**	**Entrapment Efficiency % ±S.D**
1	F1	79.05±0.0860
2	F2	89.50±0.1315
3	F3	91.83±0.0086
4	F4	94.74±0.0086
5	F5	96.60±0.0131
6	F6	96.58±0.0086

4.2.5 Zeta potential and particle size determinations

- **Particle Size**

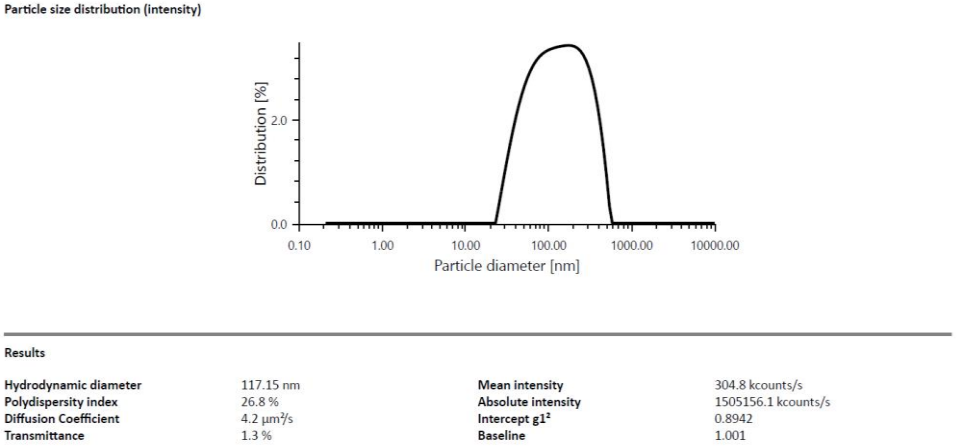

Figure: 7 Particle size of phytosome formulation

- **Particle Size**
  With a PDI of 0.268, the phytosome formulation's particle size was 117.15 nm.
- **Zeta potential determinations**

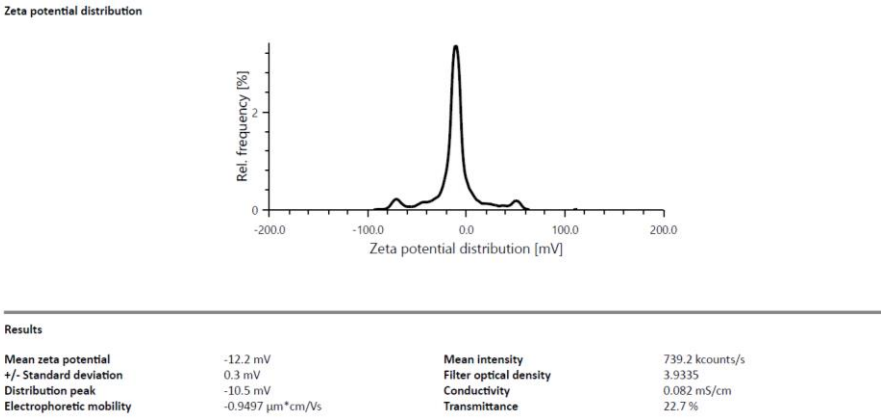

Figure: 8 Zeta potential of phytosome formulation

- **Zeta potential determinations**
  The Zeta potential of phytosome formulation was -12.2mV with SD 0.3 mV

4.2.2 Optical microscopy

Figure 9 displays the results of optical microscopy at 100x magnification used to determine the drug-loaded phytosome composition.

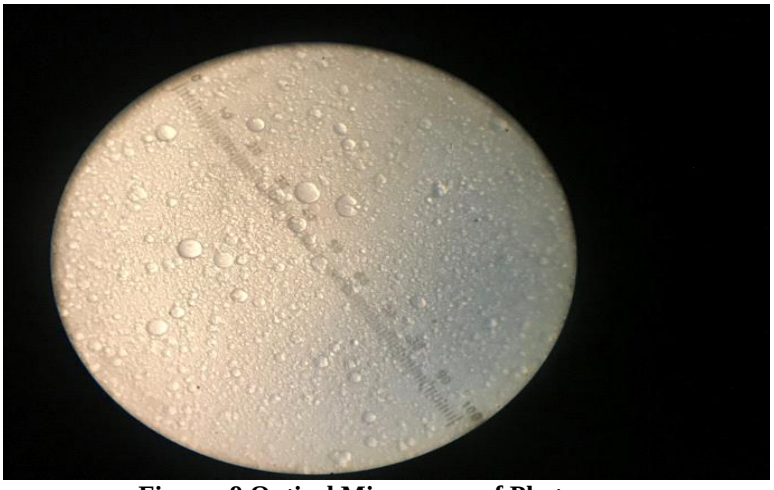

Figure: 9 Optical Microscopy of Phytosome

4.2.5 Transmission Electron Microscope

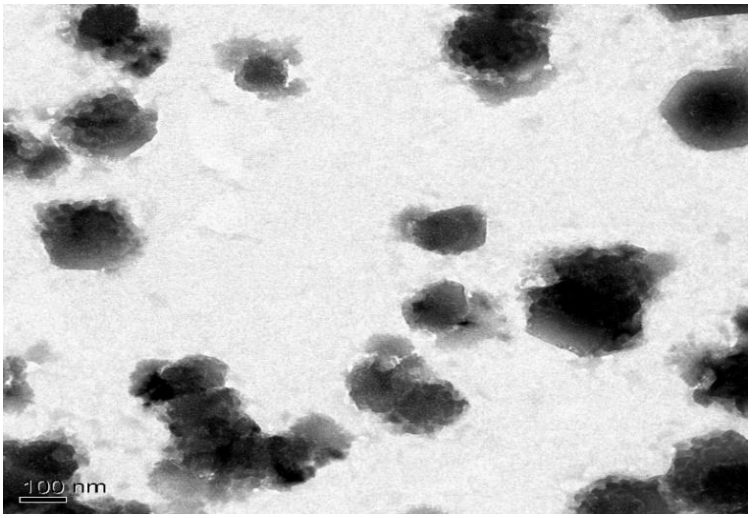

Figure: 10 TEM of Phytosome

TEM was used to confirm the improved phytosomal formulation (F3)'s surface shape. The TEM images depicted dark spherical phytosomes against a light background. The results clearly demonstrate that the prepared phytosomes exhibited a predominantly spherical morphology. The images validated that the phytosomes appeared round, smooth, and devoid of drug crystals.

4.3 Incorporation of phytosome dispersion into Gel

The optimized formulation's phytosomal gel was created by effectively combining formulation 14 into Carbopol 980 at concentrations of 0.5%, 1%, and 2%.

4.4 Evaluation of Phytosomal Gel

4.4.1 Appearance of Phytosomal gel

Freshly prepared drug-loaded phytosome formulations F1 to F7 exhibited a milky white appearance, with no phase separation observed in F1 to F6. However, in F7, phase separation was evident.

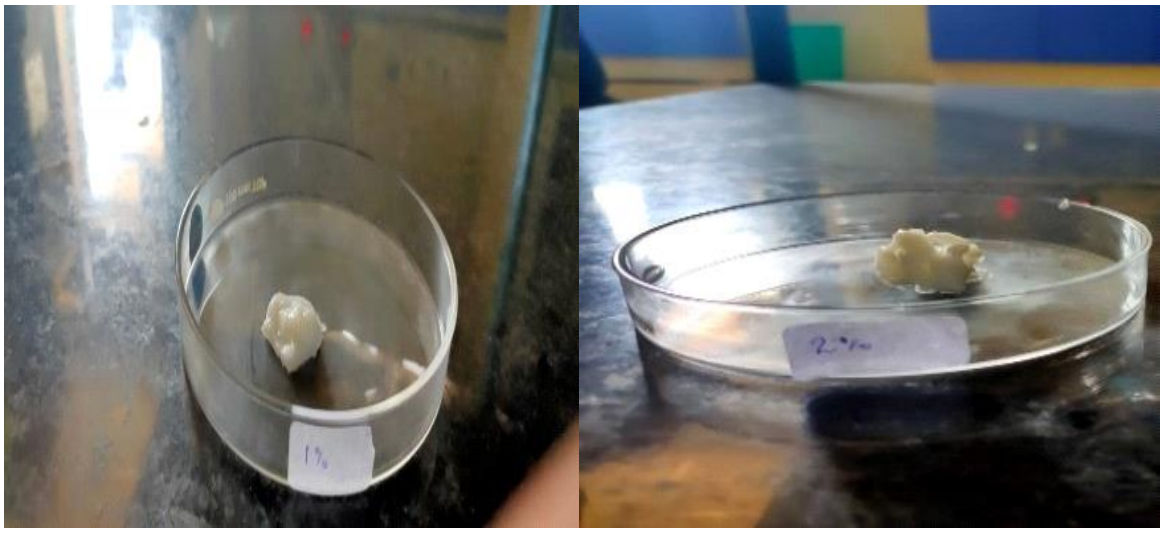

Figure: 10 a,b Photograph of different formulation of Phytosomal gel.

4.4.2 pH of phytosomal gel:

The pH values of formulations F9, F10 were 6.417±0.015, 6.427±0.006 respectively.

4.4.3 Drug content

The findings indicate that the F9 and F10 formulations' percentage medication concentration fell between 98.605±0.219 and 99.236±0.476.

4.4.4 Spreadability of phytosomal gel

The findings indicate that the phytosomal Gel formulation's (F9, F10) spreadability fell between 7.46±0.006 and 7.36±0.010.

4.4.5 Viscosity of phytosomal gel

The gel's viscosity at various formulations (F9, F10) was determined to fall between 10743±1.15 and 12429±0.58.

4.5 FTIR spectral analysis

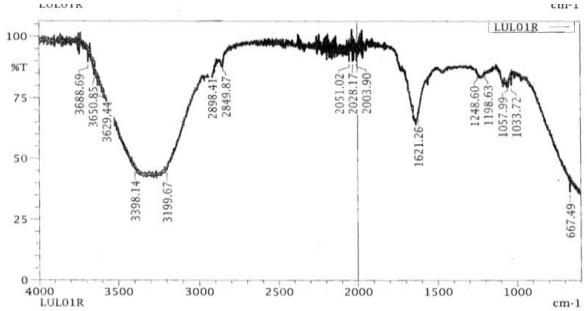

Figure 11: FTIR of formulation (F9)

Spectrum of formulation (F9) peak were obtained at 3199.67 (Aromatic C–H Stretching), at 2051.02 (C=N Stretching), at 1621.26 (C=C Aromatic Stretching), at 1056.99 (C–Cl Stretching). The FTIR spectra of final formulation is maintained with some peaks with slight shifting.

4.6.1 In-vitro Drug release study

Table: 6 In-vitro Drug release study of phytosomal gel

Time (Hr)	% Drug release of F9	% Drug release of F10	% Drug release of Pure drug
0	0	0	0
0.25	4.442±0.068	3.3397 ±0.052	1.817±0.034
0.5	4.146±0.068	4.442±0.068	2.635±0.034
1	9.419±0.034	4.147±0.068	3.420±0.034
2	14.4420±0.034	9.147±0.034	6.033±0.020
3	23.442±0.052	16.942±0.052	4.272±0.020
4	29.647±0.079	23.670±0.239	9.010±0.034
5	33.408±0.052	28.953±0.341	11.499±0.034
6	40.330±0.341	33.317±0.341	16.0784±0.071
8	48.852±0.341	38.625±0.341	21.580±0.341
10	56.375±0.000	46.330±0.521	26.943±0.710
12	62.489±0.341	50.557±0.341	33.170±341
24	64.261±0.341	58.739±0.341	34.239±0.341

Luliconazole release from phytosomal gels F9 and F10 outperformed the pure drug over 24 hours, with F9 reaching 64.261±0.341%, F10 at 58.739±0.341%, and pure drug at 34.239±0.341%. F9 showed faster initial release (4.442±0.068% at 0.25 hours) and sustained release (40.330±0.341% at 6 hours) compared to F10 (3.3397±0.052% and 33.317±0.341%) and pure drug (1.817±0.034% and 16.0784±0.071%). Enhanced solubility and drug entrapment in phytosomes explain F9's superior performance for topical delivery.

4.4.7 In-vitro Drug release kinetic study (27)

Mathematical models are frequently used to compare release qualities and forecast the release mechanism.

Table: 7 Kinetic equation parameter of Formulation F9

Formulation code	Zero order		First order		Higuchi		Peppas	
	R^2	K_o	R^2	K_o	R^2	K_o	R^2	K_o
F9	0.7179	3.362	0.9016	-0.031	0.9284	18.37	0.917	0.5756

For the best formulation, several plots were made: the log of drug release percentage versus time (using the Korsmeyer and Peppas Exponential Equation), the log of drug residue percentage versus time (first order), the log of drug release percentage versus time squared (using the Higuchi plot), and the log of drug release percentage versus time (zero order). The determination coefficients (R2 values) were calculated and recorded from these figures. It was concluded that the Higuchi model (R2=0.9284) provided the best fit to the release data after analyzing the determination coefficients. Thus, the data suggest that a sustained process was used to release the medication from the phytosomal gel containing Luliconazole.

5. CONCLUSION

Through the incorporation of Luliconazole into phytosomes, a successful drug delivery system was formulated, exhibiting sustained release properties that could potentially address the poor bioavailability issues associated with Luliconazole. Preformulation studies were conducted to describe the medicinal material's physical and chemical characteristics before the phytosomes were created. The drug samples' FT-IR spectra matched the reference chemical groups found in the luliconzole structure. Additionally, Luliconazole's UV spectra showed a wide band at 296 nm. The capillary method's melting point was found to be in agreement with the reference melting point.

According to solubility tests, luliconazole dissolves quite well in methanol. The drug's lipophilic character was demonstrated by its solubility profile in several solvents; this discovery was corroborated by the partition coefficient analysis. Luliconazole standard curves were prepared in methanol, and correlation coefficients nearing 0.9994, indicating high linearity, were obtained following linear regression of the absorbance data.

Luliconazole was found to have good purity and quality based on the preformulation study's results (FT-IR spectrum, UV spectrum, and melting point), and the estimation method was considered accurate, reliable, and appropriate for formulation development. The phytosomal formulation of Luliconazole utilized reflux. Various fat levels were employed in the formulations (F1 to F7) in order to optimize the process. Because of its greatest solubility of n-octanol, optimum size, and effective trapping, formulation F5 was determined to be the best formulation. Through microscopy, the optimized F5 formulation's size and shape were verified, and the majority of the particles were easily identifiable.

The formulations of luliconazole phytosomal gel (F8, F9, F10) were prepared by effectively distributing the formulation in Carbopol 980 at concentrations of 0.5%, 1%, and 2%. Formulations F9 and F10 were selected for more research because of their consistent look. Franz diffusion cells were used to test the improved gel formulation's in vitro drug release in phosphate buffer (pH 7.4). The Higuchi, Korsmeyer-Peppas, zero-order, and first-order models were fitted to the in vitro data in order to precisely determine the drug release mechanism and rate. The results demonstrated that the drug release from the F9 formulation followed the Higuchi model, indicating a progressive release of cloconazole from the phytosome.

REFERENCES

[1] Saraf, Ajazuddin S. Novel medication delivery systems applied to herbal compositions. Fitoterapia 81:680–689 (2010)

[2] Semalty, A., Semalty, M., Rawat, M. S. M., & Franceschi, F. (2010). Supramolecular phospholipids–polyphenolics interactions: The phytosome strategy to improve the bioavailability of phytochemicals. Fitoterapia, 81(5), 306-314.

[3] Tripathya S, Barob L. Nair SK, Patel DK. An overview of phytosomes' development, characterisation, and potential for transdermal use. 2013;3(3); 147–152 in Journal of Drug Delivery & Therapeutics.

[4] Ahuja A, Khar R, and Ali J. a dosage form design textbook. Third Edition, Birla Publications Pvt Ltd, Delhi, 2008: 100-107.

[5] Chem Inform. 2012; 43(23):20–5, A Pandey, B. Rath, and A. K. D. Pharmaceutical Preformulation Studies with Particular Emphasis on Excipients Compatibility.

[6] Manikiran SS, Teja D, Ramarao N. A Comprehensive Guide to Preformulation for Drug Excipient Incompatibility Studies and Pharmaceutical Product Development.

[7] USP melting point reference standards: Evaluation of factors influencing the melting point, G. Casay, O. Quattrocchi, W. Hauck, A. Hernandez-Cardoso, J. Belsky, USP Pharmacopeial Forum, PF39(4)

[8] In 2015, Saraf, S., Khan, J., and Saraf, S. Lutein-phospholipid complex preparation and assessment as a potent medication delivery strategy against liver damage caused by GalN/LPS. Development and Technology in Pharmaceuticals, 1–12. doi:10.3109/10837450.2015.1022786

[9] Ahuja A, Khar R, and Ali J. a dosage form design textbook. Third Edition, Birla Publications Pvt Ltd, Delhi, 2008: 100-107.

[10] Baka E, Takacs-Novak K, Comer JE. Examene the saturation shake-flask method for measuring equilibrium solubility with hydrochlorothiazide as a model compound. Biomed Anal J Pharm. 2008 Jan 22;46(2):335–41.

[11] Xia XR, Riviere JE, Baynes RE, and Monteiro-Riviere NA. using a membrane-coated fiber approach to determine the partition coefficients and absorption kinetic characteristics of compounds in a lipophilic membrane/water system. Eur J Pharm Sci. 24(1):15–23; Jan. 2005.

[12] Chatwal GR, Anand SK. techniques for chemical analysis using instruments. Himalaya Publishing House, Delhi. 2002; 2:149–2.159, 5th ed.

[13] The formulation and characterisation of an apigenin-phospholipid phytosome (APLC) for enhanced solubility, in vivo bioavailability, and antioxidant potential was carried out by Telange R. Darshan, Patil TA, Pethe M. Anil, Fegade H, Anand S, and Dave SV. 2017:108; 36–49 in Eur. J. Pharm. Sci.

[14] •Maryana W, Rahma A, Rachmawati H, and Mudhakir D. Formulation and physical assessment of a phytosome containing silymarin for oral administration. Biomaterials and Biomedical Engineering Journal, 2015, 2296-9845(25); 54-65.

[15] Microemulsion based vaginal gel of fluconazole: formulation, in vitro and in vivo evaluation, ELSEVIER International Journal of Pharmaceutics, accepted August 15, 2008, accessible online August 23, 2008. Yogeshwar G. Bachhav, Vandana B. Patravale.

[16] H. Chaudhary, A. Rohilla, P. Rathee, and V. Kumar, Use of innovative penetration enhancers for carbopol-loaded Piroxicam gel formulation optimization and design, Int. J. Biol. Macromol. 55 (2013) 246–253.

[17] Shivhar UD Water soluble polyacrylamide polymer was used in the formulation development and evakuation of Diclofenac sodium gel by Jain KB, Mathur VB, et al. The Digest Journal of Biostructure and Nanomaterials

[18] Ankit Acharya, Diwakar Khadka, and Pramod Dhakal. development, evaluation, and comparison of lornoxicam transdermal gel's impotence and passive delivery systems.International Journal of Pharmaceutical Sciences and Research, 2016;7(2):810–818.

[19] New phytosome-loaded chitosan microsphere system for curcumin delivery: development and evaluation (Zhang J, Tang Q, Xu X, Li N). International Journal of Pharmaceutics, 2013; 448:168–174. Dash S, Chowdhury P, Nath

L, and Murthy PN. Drug release from regulated drug delivery devices using kinetic modeling. 2010; Acta Pol Pharm. 67(3): 217–23.

[20] Islam M, Rahman H, Reza S. In vitro Release Kinetics Study of Diltiazem Hydrochloride from Wax and Kollidon SR Based Matrix Tablets. 2010; 7:101–8; Iranian Journal of Pharmaceutical Research.

[21] Patil JKS, Patil NV, Shreeraj H. A review of gastroretentive medication delivery techniques and possible herbal remedies for the eradication of Helicobacter pylori. 976–82 in J Chinese Integrative Med, 2009; 7(10).

[22] Patel HM, Akbari B, Patel UB, and Gangat A. The creation and evaluation of a topical spray that forms a film of liconazole to treat fungal infections.

[23] Koga H, Yamaguchi H, Miyazako T, Kanai K, Yamadama H, Niwano Y. NND-502, a new optically active imidazole antimycotic drug, inhibits the sterol 14α-demethylation of Candida albicans. 1999; Med Mycol; 37:321–5.

[24] Sanghani G, Keriwala TM, Dedania Z, Jain vc. simultaneous uv spectroscopy method development and validation for beclomethasone and luliconazole dipropionate in combined pharmaceutical dosage form.

[25] Raut, N.A., Dhore, P.W., Saoji, S.D., et al. The Phospholipid-Based Complex of Standardized Centella Extract (SCE) is prepared and evaluated to improve the delivery of phytoconstituents. AAPS J18 (2016), 102–114. The doi:10.1088/s12248-015-2837-8727-2

[26] Kemel K, Laugel C, Faivre V, Baillet-Guffroy A. Part II of ATR-FTIR Characterization of Janus Nanoparticles: Follow-Up Skin Application. Journal of Pharmaceutical Sciences, 108(10), 3366–71, Oct. 1, 2019.

[27] Soni S, Rajnikanth PS, Shanthi N, Mahato AK, Kumar M. Making a hydrogel filled with luliconazole nanocrystals to enhance its solubility and antifungal efficacy. 2019 May 1;5(5):e01688 Heliyon