Available online on 15.01.2025 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Copyright © 2025 The Author(s): This is an open-access article distributed under the terms of the CC BY-NC 4.0 which permits unrestricted use, distribution, and reproduction in any medium for non-commercial use provided the original author and source are credited

Open Access Full Text Article

Research Article

Formulation and Evaluation of Liposomal Cream Containing Tolnaftate

Darshini D*[1], Likhita B[1], Mohitha Y B[1], Aruna Kumari V[1], M Hema[1], Ahasanuzzaman [2]

[1] Department of Pharmaceutics, Spurthy College of Pharmacy, Rajiv Gandhi University of Health Sciences, Bangalore, Karnataka

[2] Assistant Professor, Department of Pharmaceutics, Spurthy College of Pharmacy, Rajiv Gandhi University of Health Sciences, Bangalore, Karnataka

Article Info:

Article History:

Received 20 Oct 2024
Reviewed 04 Dec 2024
Accepted 23 Dec 2024
Published 15 Jan 2025

Cite this article as:

Darshini D, Likhita B, Mohitha YB, Aruna Kumari V, Hema M, Ahasanuzzaman, Formulation and Evaluation of Liposomal Cream Containing Tolnaftate, Journal of Drug Delivery and Therapeutics. 2025; 15(1):13-18
DOI:
http://dx.doi.org/10.22270/jddt.v15i1.6944

Abstract

The current study's objective was to formulate and evaluate a liposomal cream containing tolnaftate in order to improve the drug's bioavailability. Tolnaftate is a drug having low permeability which results in decreased drug absorption and so is the bioavailability. To overcome these problems tolnaftate is incorporated in liposomes. Liposome vesicular drug delivery system was preferred due to its greater solubility, permeability and bioavailability. It carries a substantial amount of drug which increased the drug's penetration. The liposomes were prepared using a variety of phospholipids, specifically soy lecithin and egg phosphatidylcholine in varying ratios. Liposomes were prepared by ethanol injection method and evaluated for morphology, percentage practical yield, percentage entrapment efficiency, drug content and in-vitro drug release study. The formulation with the best result according to the evaluation parameters was F2 with greater percentage drug entrapment, drug content and in-vitro drug release was considered to be optimized formulation and this F2 formulation was further evaluated by SEM, DSC and XRD. Liposomal cream was formulated using the optimized formulation. Spreadability, Viscocity, p^H measurement and in-vitro drug release were evaluated for liposomal cream. Formulation F2 and optimized liposomal cream formulation showed in-vitro drug release of 92.44% and 77.48% respectively at the end of 8th hour.

Keywords: Tolnaftate, liposomes, SEM, DSC, XRD

*Address for Correspondence: Darshini D, Department of Pharmaceutics, Spurthy College of Pharmacy, Rajiv Gandhi University of Health Sciences, Bangalore, Karnataka

INTRODUCTION

A thiocarbamate anti-fungal drug named tolnaftate was discovered by Noguchi and co-workers in 1962[1]. It works well against Epidermophyton, Trichophyton species, Microsporum and Malassezia furfur. Several tinea infections which include tinea pedis, tinea cruris, tinea capitis, tinea manuum and tinea corporis can be treated with tolnaftate[2]. However, 10% of the world's population suffers from tinea pedis (affects the foot) and the cure rate was found to be around 80% with tolnaftate. It is marketed in various forms like creams, powders, solutions, sprays and gels at a concentration of 1%[3]. Squalene epoxidase is inhibited by tolnaftate, an essential enzyme in the biosynthesis of ergosterol (a key component of the fungal membrane) in cell walls of fungi. Tolnaftate has an antifungal effect due to squalene buildup and ergosterol insufficiency[4]. Tolnaftate belongs to BCS class IV and has a bioavailability 0.4-0.8%. Half-life is 2-4 days. In some research it was found that tolnaftate was only effective when applied topically and ineffective when taken orally or intraperitoneally. Tolnaftate was designed for topical administration for better permeability, controlled, and localized delivery [5, 6].

British heamatologist, Dr. Alec D Bangham FRS described the liposomes for the first in 1961. The word liposome comes from the words 'lipos' which means fat, and 'soma' which means body[7]. Liposomes are the vesicular structures with two layers, composed of one or more phospholipid bilayers and cholesterol. From the structural standpoint, liposomes are concentric bleeder vesicle in which an aqueous volume is entirely enclosed by a membraneous lipid bilayer[8]. Membranes are molecules containing a hydrophilic head group and a hydrophobic tail group. Drugs are effectively transported to their sites of action via liposomes, a spherical shaped vesicular-based drug delivery system[9]. Liposomes are amphoteric in nature; hence it can entrap both hydrophilic and lipophilic substances there by showing greater accumulation at the site of action[10].Liposomes can penetrate deeper into the skin and provide better absorption due to their affinity to pass through the keratin of the stratum corneum of the skin. Compared to conventional formulation, topical liposomal formulations can be less harmful and more effective.

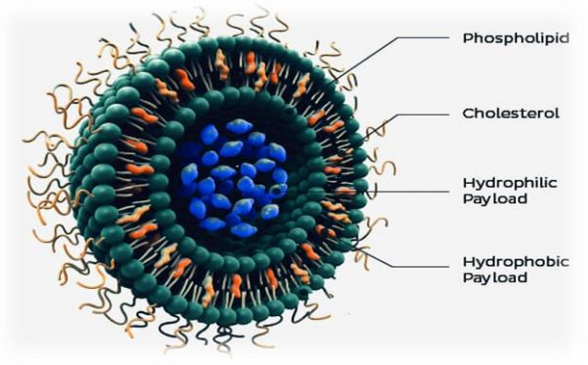


Figure 1: Structure of liposome

Hence, in this study an attempt has made to formulate tolnaftate loaded liposomal cream for potent skin penetration thereby increasing its efficacy.

MATERIALS AND METHODS

Materials:

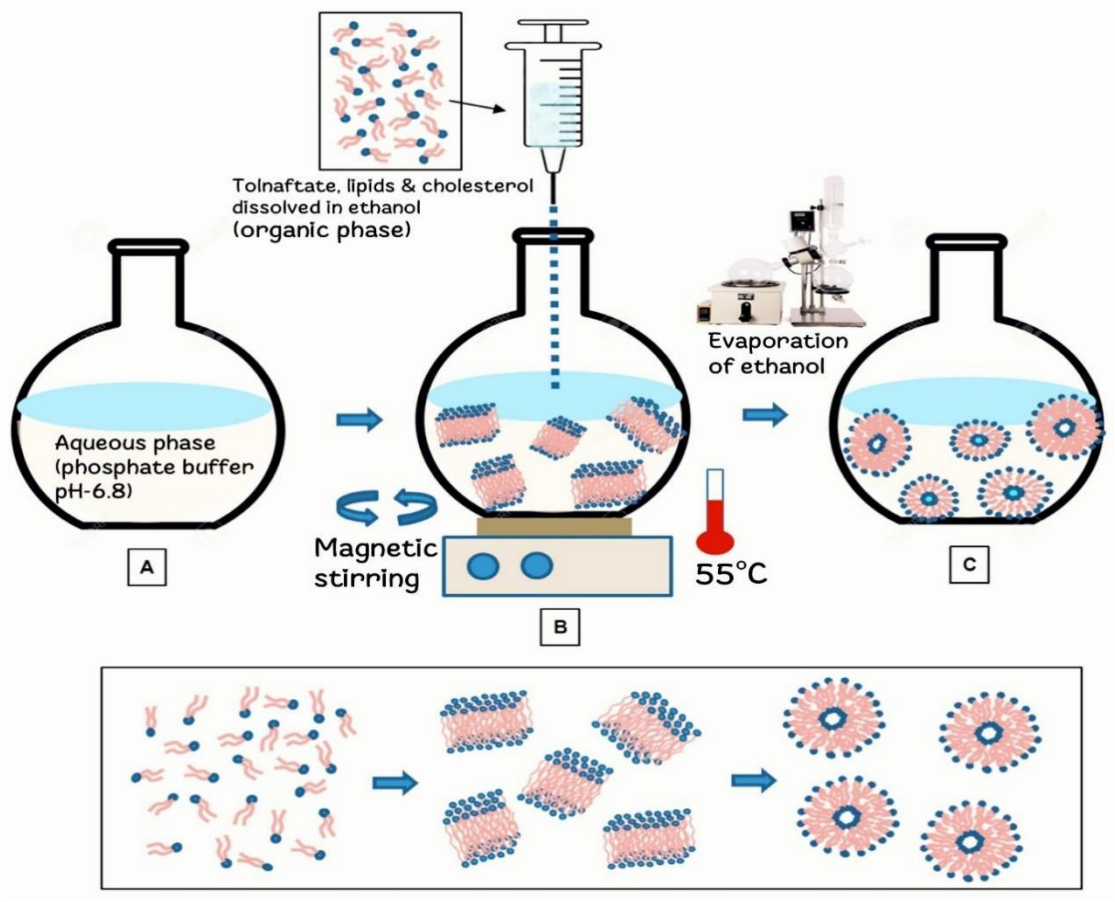
Tolnaftate was procured as gift sample from MOLYCHEM, Bangalore. Egg phosphatidylcholine and soy lecithin was obtained as gift sample from MOLYCHEM, Bangalore. Cholesterol was obtained as gift sample from loba chemi pvt lmt. Analytical grade of other reagents were used.

Table 1: Formulation chart of Tolnaftate liposomes using ethanol injection method (F1-F5)

Formulation	Tolnaftate amount in mg	Eggphosphatidyl choline amount in mg	Soy Lecithin amount in mg	Cholesterol amount in mg
F1	50	175	125	100
F2	50	200	100	100
F3	50	150	150	100
F4	50	125	175	100
F5	50	100	200	100

Methods:

Method of preparation of tolnaftate loaded liposomes:



The method applied for formulation of liposomes was modified ethanol injection method. In this method appropriate quantity of tolnaftate, phospholipids and cholesterol were dissolved in ethanol which acts as the organic phase and phosphate buffer of pH 6.8 will be aqueous phase. Using a syringe the organic phase was introduced into the aqueous phase drop wise while the aqueous phase was kept on magnetic stirrer and maintained the temperature of 55°C. As soon as the ethanolic solution came into contact with the aqueous phase, spontaneous liposome formation occurred. After some time, ethanol is evaporated and liposomal suspension is formed. Further this suspension is dried and incorporated into cream[12, 13].

Formulation of tolnaftate liposomal cream:

Firstly, all the ingredients of oil phase, such as liquid paraffin, cetostearyl alcohol, white beeswax and propyl paraben were accurately weighed and placed in a beaker and in another beaker, borax was taken as aqueous phase. The beakers with various phases were heated to 75°C and at this temperature the oil phase was added to aqueous phase with constant stirring. Stirring continued until the cream base was formed and temperature get reduced. Using a geometric mixing pattern, accurate amount of cream base and prepared liposomes were mixed on tile part by part[14].

METHODOLOGY

Pre-formulation studies of tolnaftate:

Pre-formulation studies were performed for physical appearance, solubility, melting point, λmax of drug, compatibility studies [FTIR and DSC] and XRD. The physical appearance of the drug was observed visually. The solubility was performed in 4 different solvents such as water, ethanol, acetone and DMSO by shake flask method and drug concentration was determined spectrophotometrically. Melting point of tolnaftate was determined by using melting point apparatus. DSC and FTIR spectrophotometer studies were studied to determine the compatibility. XRD was performed to check the crystallinity of the drug[15].

EVALUATION PARAMETER OF TOLNAFTATE LOADED LIPOSOMES:

FTIR studies:

Drug and excipients compatibility was assessed using FTIR spectrophotometer. 1mg of the sample and 100mg of KBr were finely crushed using mortar and pestle. A few mixtures were placed under the hydraulic press for 2 mins to form a pellet. The Shimadzu FTIR spectrophotometer was used to scan the pellet from 4000 cm^{-1} to 400 cm^{-1} while it was in a sample container. The collected spectra were compared and interpreted for the functional groups peaks[16].

Percentage of drug entrapment efficiency:

To measure the entrapment efficiency of liposomes loaded with tolnaftate an ultracentrifuge was used to centrifuge the particles for 30 mins at 1000rpm. The sample supernatant was then pipetted suitably diluted with 6.8 pH and examined at 257nm using a UV spectrophotometer[17].

$$\%DEE = \frac{Total\ drug - drug\ detected\ only\ in\ supernatant}{Total\ drug} * 100$$

Scanning electron microscopy:

Liposomes were scanned in scanning electron microscope at 15 kv to determine the surface morphology (roundness, smoothness and formation of aggregates) of liposomes.

Differential scanning calorimetry:

The physical state of the drug was characterized by DSC (perkin-elmer-4000 series) studies. Formulation samples were placed in aluminum pans and sealed thematically. The heating rate was 20°C per minute using nitrogen as the purge gas. The DSC instrument's temperature was calibrated using indium. Additionally, indium was enclosed in aluminum pans for enthalpy calibration using a reference sealed empty pan[18].

Zeta potential determination:

This method was used to determine the polydispersity index of vesicles using zeta sizer, Nano ZS90, (Malvern instrument) whose working is based on dynamic light scattering. The liposomal vesicle average charge was determined.

Particle size determination:

The particle size of liposome is generally determined by zeta sizer instrument (Malvern).

In-vitro drug release study

Membrane- Egg membrane

Apparatus- 150ml franz diffusion cell

Temperature- 37± 0.5°C

Drug content analysis- UV- spectrophotometer

Medium- 6.8 pH phosphate buffer.

A modified Franz diffusion cell apparatus was used to conduct an invitro diffusion research. As the diffusion medium, a phosphate buffer with a pH of 6.8 was used. On a Franz diffusion cell, the egg membrane was positioned in between the donor and receptor compartments. The donor compartment held the liposomal suspension, whereas the receptor compartment had phosphate buffer (pH 6.8). By using a magnetic stirrer, the diffusion medium temperature was kept at 37±0.5°C with stirring at 500rpm throughout the experiment. 1ml of receptor fluid was withdrawn from the receiving compartment at interval of 30 minutes for the period of 8 hours and replaced with 1ml fresh phosphate buffer pH 6.8 solution. The withdrawn fluid was analyzed by UV spectrophotometer at wavelength of 257nm and utilized a standard calibration curve for calculation[18].

EVALUATION PARAMETERS OF TOLNAFTATE LOADED LIPOSOMAL CREAM:

For cream, FTIR and In-vitro drug release studies were conducted to determine the drug's compatibility with the excipients and the duration of its release respectively.

Spreadability:

The spreadability of cream formulation was determined by using parallel plate method. 2 glass plates were sandwiched by 1g of cream, and the topmost glass plate was topped with 125g of standard weight. Time spent separating the cream from one plate to the other was recorded. The following formula was used to determine the spreadability[19].

$$S=M*L/T$$

Where, S—Spreadability

M—weight tied to the upper slides

L—length of the glass slide

T—time taken

Viscosity measurement:

Viscosity of liposomal cream of tolnaftate was determined by brook field viscometer. After setting the spindle number -21 and the rpm to 100, the liposomal cream was placed under the Brookfield viscometer at room temperature and the results was recorded.

pH:

pH of the formulation was measured using a digital pH meter .The glass electrode was used to measure the pH. Following the glass electrode's immersion in the solution, the reading shown on the screen was noted [18].

RESULTS AND DISCUSSION:

FTIR of tolnaftate loaded liposomes:

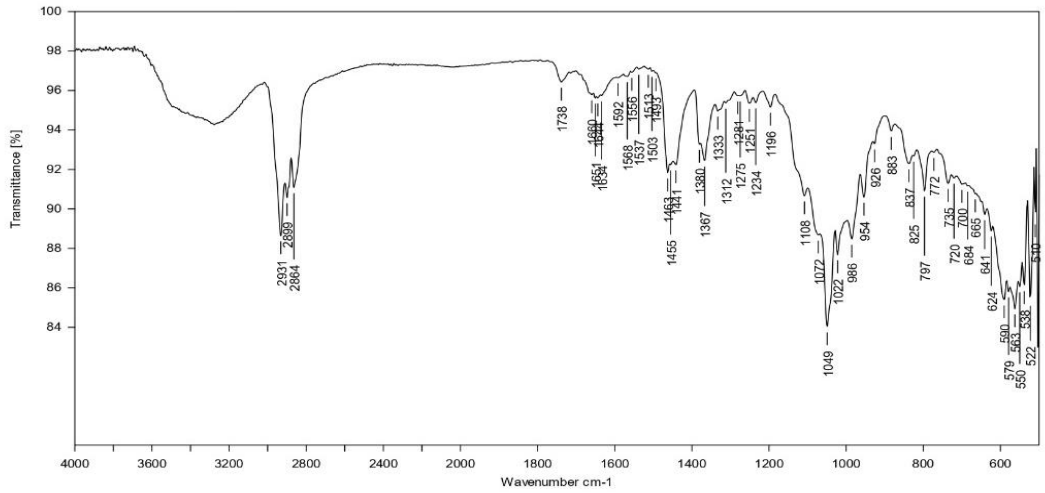


Figure 2: FTIR of tolnaftate liposome

The IR spectrum of tolnaftate loaded liposomes was performed as shown in figure (2) since, all the functional groups were intact, It was found that the drug and excipients were compatible with each other.

Scanning Electron Microscopy:

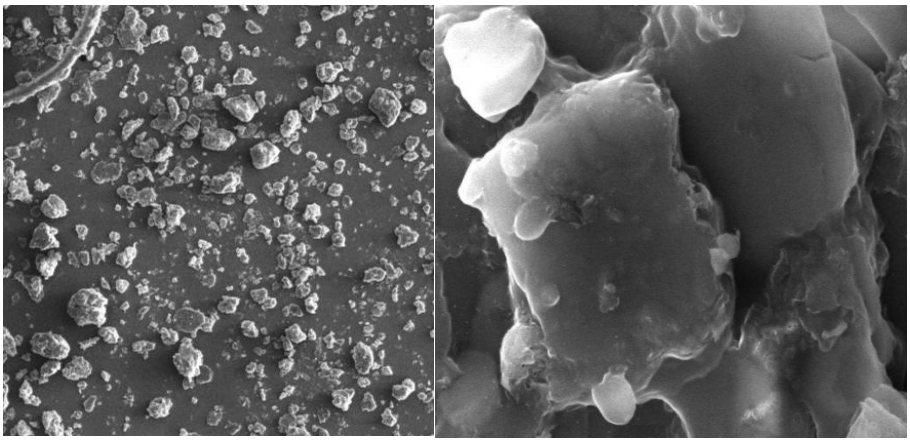


Figure 3: SEM images for Tolnaftate loaded liposome

Scanning electron microscope was used to scan the liposomes loaded with tolnaftate at resolutions of 2500x and 400x. It displays higher surface morphology and indicates particle sizes between 2-100µm. Image 2 displayed liposomes vesicle in individual spherical bulb shape whereas image 1 displayed homogenous spherical bulb shape.

Differential Scanning Calorimetry of tolnaftate loaded liposomes:

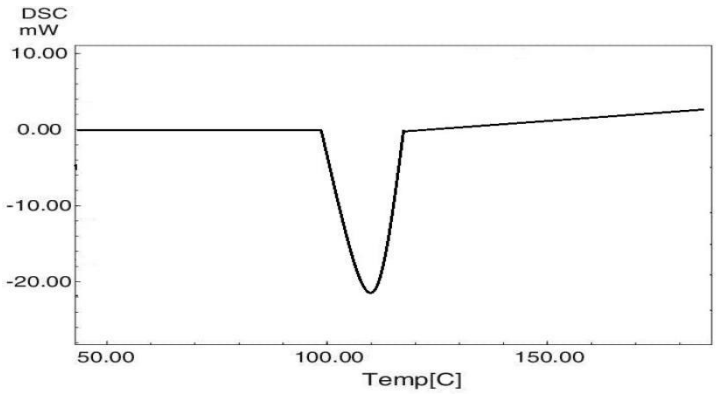


Figure 4: DSC of tolnaftate liposome

A sharp endothermic peak at 110^{0}C that resembled the drug was seen by DSC confirming that the drug's melting point remained unchanged even after the formulation.

Zeta-potential:

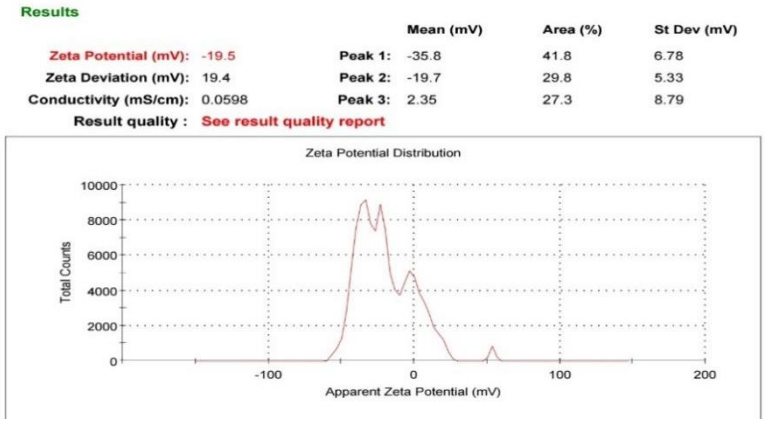


Figure 5: zeta potential of tolnaftate loaded liposome

Zeta potential analysis of the formulation revealed that its value was -19.5mV as shown in the figure (5). The vesicle has a higher surface charge due to its larger negative value. As a result, aggregate formation is less thereby increasing the liposomes stability.

Zeta-sizer:

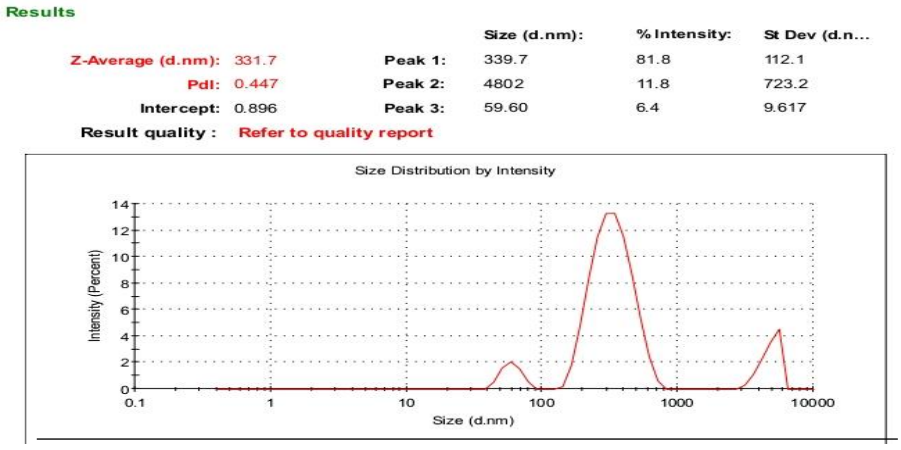


Figure 6: zeta sizer of tolnaftate loaded liposome

Using a zeta sizer technique, the liposome formulation's average particle size was found to be 331.7nm, as illustrated in figure (6) this smaller particle size results from a modifications in the phospholipids ratio.

In-vitro drug release:

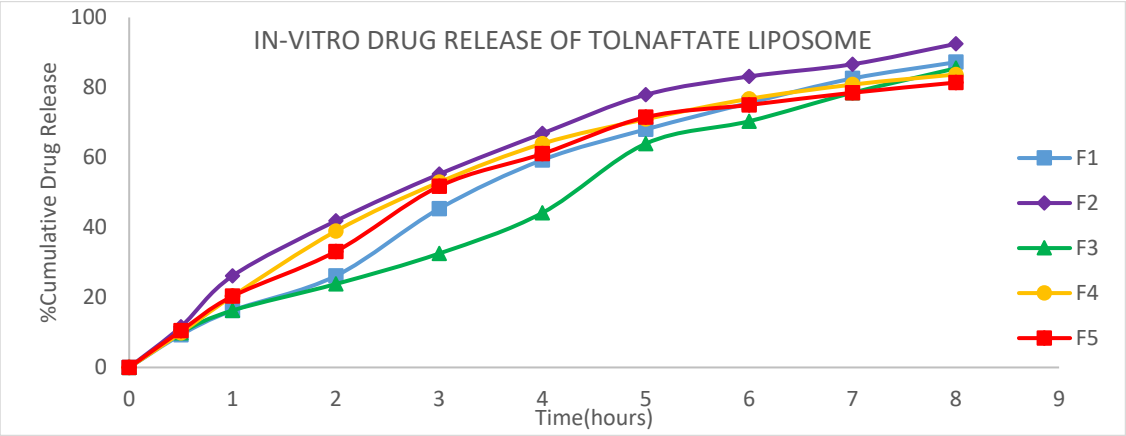


Figure 7: *In-vitro* drug release of formulations F1-F5

As in–vitro drug release investigation was conducted for liposomes loaded with tolnaftate containing varying amounts of phospholipids. The impact on drug release was noted. The observation revealed that F2 had a drug release rate of 11.62% to 92.44%. According to the zeta sizer report, Formulation F2 had improved permeability because of its smaller particle size, and as a result, greater amount of drug release was observed. As indicated in figure 7, the formulation of F1-F5 demonstrated drug release ranges of 87.20%, 92.44%, 85.45%, 83.73% and 81.39% after the eighth hour respectively.

The cream's spreadability, viscosity and pH were determined to be 8.2gcm/s, 12490cp and 5.5 respectively.

CONCLUSION:

A crucial step in enhancing skin permeation and therapeutic outcomes is the incorporation of innovative liposomal-vesicular systems into suitable vehicles such as creams. The present study demonstrated the successful formulation of liposomal cream containing tolnaftate and its evaluation. Formulation 2 showed higher drug entrapment efficiency and drug release over an 8hrs period with smaller particle size. The results of this study further confirms that liposomal creams which are designed to be used topically to address issues with permeability and efficacy, had higher permeation. Thus enhances probable bioavailability and considered to be good liposomal formulation.

REFERENCES:

1. Kezutyte T, Kornysova O, Maruska A and Briedis V. "Assay of Tolnaftate in human skin samples after in-vitro penetration studies using high performance liquid chromatography." Acta Pol. Pharm, 2010; 67(4):327-334.

2. Kumari P, Misra S, and Pandey S. "Formulation and Evaluation of Tolnaftate microsponges loaded gels for treatment of Dermatophytosis." EJPMR, 2017; 4(6), 326-335.

3. Gupta AK, Chow M, Daniel CR, Aly R. "Treatment of tinea pedis." Dermatology Cli, 2003; 21: 431-439. https://doi.org/10.1016/S0733-8635(03)00032-9 PMid:12956197

4. Viswanath V, Roa NB, Prakash KG, Padmini DS, Gouthami B. "Tolnaftate loaded sln for improved transdermal drug delivery: formulation and evaluation." Int J Pharm 2017; 7(2): 43-51.

5. Meghana G, Karri V.V.S.N, Talluri S, Gunda R, Chennareddy S, Ganesh G.N.K. "Formulation and evaluation of Tolnaftate loaded topical liposomal gel for effective skin drug delivery to treat fungal disease." J.Chem.Pharm.Res, 2014; 6(10):856-866.

6. Alpana, and Khatak S. "Formulation developmentand evaluation of nano-structured lipid carriers encapsulated tolnaftate emulgel." Int.Res.J.Pharm.2021; 12(4):37-43. https://doi.org/10.7897/2230-8407.1204132

7. Maurya SD, Prajapati S, Gupta A, Saxena G, Dhakar RC, Formulation Development and Evaluation of Ethosome of Stavudine, Indian J.Pharm. Educ. Res. 2010;44(1)

8. More Samiksha and S.D.Pande. "Development and evaluation of liposomal cream for enhancement of perfume." IJCRT, 2022; 0(7):815-829.

9. Umbarkar M, Thakare S, Surushe T, Giri A, Chopade V. "Formulation and evaluation of Liposome by thin flim hydration method." JDDT, 2021;11(1):72-76. https://doi.org/10.22270/jddt.v11i1.4677

10. Badran M. "Formulation and invitro evaluation of flufenamic acid loaded deformable liposomes for improved skin delivery." Dig. Nanomater.Biostruct,2014;9(1):83-91

11. Singha Roy A, Das S, Arnab S. "Design, formulation and evaluation of liposome comtaining isoniazid." Int J Pharm, 2018; 10(2):52-56. https://doi.org/10.22159/ijap.2018v10i2.24174

12. Akbaezadeh A, Rogaie Razari, Devaran.S, Sang woo joo, Zarghami N, Hanifehpour Y, Saminei M, Kauhi M, Kazem-Nejati-koshki. "Liposome classification preparation and applications." Nanoscale Res Lett, 2013; 8(1):1-9. https://doi.org/10.1186/1556-276X-8-102 PMid:23432972 PMCid:PMC3599573

13. Shehata T, Abdullha M. H, Ibrahim M. M. "Proniosomal oral tablets for controlled delivery and enhanced pharmacokinetics properties of acemetacin." Aaps Pharm Sci Tech, 2014; 72(22):1564-1570.

14. Chadran M.P.S, Pandey V.P. "Formulation and evaluation of gliclazide loaded liposomes." Der Pharmacia Lettre, 2016, 8(11): 60-68.

15. Asthana G. S, Asthana A, Singh D, Sharma P. K. "Etodolac containing topical niosomal gel: formulation development and evaluation." J Drug Deliv. 2016; 16(9):1-8. https://doi.org/10.1155/2016/9324567 PMid:27478643 PMCid:PMC4958486

16. Sahid MS, Dan Chowdeswari A. et al, "A review on nanoparticles." scan J Pharm Sci Res, 2013; 1:6-9.

17. Elagamy H. I, Essa E. A, Nouh A and Maghraby G. M. E. "Development and evaluation of rapidly dissolving buccal films of naftopidil: in-vitro and in-vivo evaluation." Drug Dev Ind Pharm. 2019; 1-32. https://doi.org/10.1080/03639045.2019.1656734 PMid:31418592

18. Abd Elaziz E, Elmowafy M. M, Salman A, Samy A. M, Rashan M. A. "In-vitro and in-vivo evaluation of optimized sustained release of ketoprofen niosomes for once daily administration." Int J Adv Res. 2014; 2(7):807-816.

19. Joshi B, Singh G, Rana AC, Saini S. "Development and Characterization of Clarithromycin Emulgel for topical delivery." Inter J of Drug Develop and Res, 2012; 4(3): 310-323.