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Nanostructured Lipid Carrier: Optimization, In-vitro, In-vivo Evaluation of Nanocarrier Gel

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ABSTRACT
Pharmaceutical gels are semisolid dosage form designed for application on to the skin mucus membrane and wounds. They are versatile patient friendly formulations that can deliver drugs systemically and locally. Nanostructured lipid carriers loaded gel was prepared for making the topical delivery more effective. Optimized formulation of nanostructured lipid carriers loaded gel exhibits higher *in-vitro* controlled release pattern as compared to marketed formulation and nanocarrier suspension. *In vivo* pharmacodynamic studies shows good results of wound contraction studies. These findings suggest that nanostructured lipid carriers loaded gel can serve as a promising drug delivery system to overcome the limitations of conventional formulations and provides better therapeutic outcomes.

Keywords: *Nanostructured lipid carriers, Gel, In-vitro release, In-vivo.*

1. INTRODUCTION

Skin diseases are the most common problem worldwide. Most of the skin conditions are not life threatening but they have major impact on the life of patient. Lamberth study suggested 55% of the population have some skin diseases but only 22.5% actually had received medical attention [1]. Sanclemente G. et.al. conduct a study to evaluate the impact of skin diseases on quality of life. Occupations associated with an increased risk of skin diseases. Most risks are related to irritants and allergy-inducing materials present at the workplace. Sometimes water also work as an irritant for those working in wet conditions. Skin contact with organic solvents always poses a risk to the skin. Contact dermatitis developed as a result of the combination of occupational exposure and individual predisposition to diseases [2]. Viral replication is slow and is closely dependent on the differentiation of the host cells. Viral DNA is present in the basal cells, but the viral antigens and the infecting virus are produced only when the cells start to become squamous and keratinized once they reach the surface [3]. Viral diseases are observed as viral infection on mouth, foot and, hand. Bacterial skin flora in humans is composed of gram positive and gram negative bacilli. The Gram-positive bacilli are represented by four genera of coryneform bacteria: Brevibacterium, Corynebacterium, Dermabacter and Propionibacterium. Dermabacter spp. are not associated with skin infection, whereas Propionibacterium spp. are associated with skin infection and have an important role. There are many skin fungal infections and superficial fungal infections were reported. Tinea capitis, a communicable fungal infection of the scalp and hair shaft. It is the most common fungal infection in children. Tinea corporis is a dermatophyte infection of the body, often referred to as ringworm. It can be caused by any dermatophyte that infects humans. It is most commonly caused by Trichophyton species, especially Epidermophyton, Microsporum, and Trichophyton [4, 5]. Dermatophytes grow aerobically over a wide range of temperatures and pH. Dermatophytosis is an infection of skin hair and nail. Dermatophytes have been shown to have keratinolytic, general proteolytic and lipolytic activity. Serine proteinase which are involved in extracellular protein catabolism, have been found in dermatophytes which play a major role in the invasion of skin [6]. Tines pedis is the infection of feet associated with fissuring of toeweb. Tinea unguium, or onychomycosis, may be caused by a number of dermatophytes and other molds like Candida sp., T mentagrophytes and T rubrum, E floccosum, T tonsurans, and T verrucosum involved in infection of nails [7, 8]. Predominently these infections are caused by T rubrum. Biofilms have recently been recognized to play an important role in the pathogenesis of onychomycosis [7]. Lotions, topical suspensions, solutions and emulsions intended for application to the skin [9]. A gel is a semisolid dosage form contains a gelling agent to form solution and colloidal dispersion. Gels are classified on the basis of colloidal system (Inorganic gels and organic gels), based on the nature of solvent (hydrogels, organic gel and xerogel), based on rheological properties (plastic, pseudoplastic and thixotropic gel), based on physical nature (elastic and rigid gel) [79]. Gels that consist of an aqueous dispersion medium that is gelled with a suitable hydrophilic gelling agent are known as hydrogels. Gels containing oil or non-polar liquids as a dispersion medium are known as organogels. Bigels are topical formulations that are obtained by combining an aqueous (hydrogels) and lipophilic (organogels) system [10]. Silica xerogels evaluated as drug delivery implants and as a drug delivery device. Xerogels are expensive and associated with biodegradation of pure silica [11]. When gels and emulsions are used in combined form the dosage forms referred as emulgel. Major objective of this formulation is delivery of hydrophobic drugs [12].

Mekkawy A. et. al. prepared and evaluate fluconazole topical gel. Bachhav Y. G. et. al. performed in vitro and in vivo evaluation of meloxicam topical gel. Singh M. P. et. al. prepared the topical gel with different gelling agent and compare it with marketed formulation. Currently, gels are the most demanded semi-solid dosage forms due to their optimal consumer characteristics. However, a significant problem for the development and production of gels is the search for reproducible and relevant ways to evaluate their characteristics. Regulatory documentation contains a narrow list of gel requirements and methods for their determination. Present work emphasizes the development of nanocarrier loaded topical gel for the treatment of fungal infections.

2. MATERIALS AND METHODS

Materials

Piroctone olamine was generously gifted. Seasame oil of RSG herbal house was purchased. Polyoxyethylene (20) oleyl ether, Ethanol and Polyethylene glycol 4000 was purchased from Sigma-Aldrich. Stearic alcohol (lanette 18) and Cetyl alcohol (lanette 16) was gifted by Sunshine India. Monosterol and Capryol 90 was gifted by Gattefosse. Glycerol monostearate was purchased by Loba chemie. Polysorbate 80 was purchased by Spectrochem Pvt. Ltd.. Phosphste buffer was purchased from Himedia. Captex was purchased from Abitec corporation. Carbopol 980 was gifted by Lubrizol. Hydroxyethyl cellulose was purchased from Ashland. Sodium hyaluronate was purchased from Bloomage freda biopharma. Sepineo P 600 was purchased from Seppic. Sodium hydroxide was purchased from Merck. All the reagents were utilized in the experimentation were of analytical grade.

3. METHODS

Preparation of Nanostructured lipid carrierss

Nanostructured lipid carrierss were prepared by hot homogenization technique. Temperatures 75°C was selected for the process which is higher than the melting point of the glycerol monostearate which is 65°C. Lipidic phase having mixture of oil, solid lipid, surfactant and piroctone olamine was heated at 75°C. Similarly, at the same temperature aqueous phase of the formulation was heated. Aqueous phase was added dropwise to the lipid phase. Mixture was homogenized for 15 minutes by using high shear homogenizer. Formulation was prepared at 15000 rpm using high shear homogenizer resulting in an emulsion of oil in water type.

Preparation and optimization of nanostructured lipid carrierss loaded gel

Gelling agent like Carbopol 980 NF, hydroxyethyl cellulose, sodium hyaluronate and sepineo P 600 were used in gel preparation. Rheological parameters were tested by preparing the gel with 0.5% concentration of gelling agent. A method of preparation of nanostructured lipid carriers loaded gel includes dispersion of glycerin and butylated hydroxytoluene in purified water for 20 minutes at 100 rpm by using overhead stirrer. Carbopol 980 NF was dispersed at 250 rpm and stirring was performed for 1 hour. After complete hydration of gelling agent pH was maintained around slightly basic using sodium hydroxide. nanostructured lipid carrierss were added to the prepared gel and mixing was performed for 20 minutes by using overhead stirrer at 250 rpm.

Characterization of nanostructured lipid carriers loaded gel

Determination of pH

The pH value of gel was determined by using pH meter.

Rheological properties

Rheological properties of gel were determined by using cone and plate viscometer (MCR 32 Anton Paar). Temperature of system was set to 25°C. System was optimised by setting zero gap between the plates then, 2g of sample was applied for analysis between cone and plate. Viscosity and yield point was determined at shear rate of 1/32sec. Amplitude sweep was performed to determine the storage modulus of the sample. It helps in understanding of elastic behaviour of sample.

Spreadability

Spreadability of nanostructured lipid carriers loaded gel was determined by using plate method.1g of sample was placed between the plates. An increase in the diameter was observed after applying 50g of weight for 5 minutes. Spreadability area was calculated by using formula.

Spreadability Area (mm2)=S=d2*∏/4

Swelling Index

Swelling Index of the nanostructured lipid carriers loaded topical gel was determined by placing the1 gm of gel on the porous aluminium foil which was then placed in a petri dish containing 5 ml of phosphate buffer of pH 6.8. The sample was removed from petri dish at different time intervals i.e. 10, 20, 30, 40, 50 minutes respectively and put on a dry place for some time, then it is re-weighed. The swelling Index was calculated by using the following formula:

Swelling Index (SW%) = $[(W_t-W_0)/W_0 \times 100]$

Where,

SW% = Percentage of Swelling Index

W_t= Weight of Swollen gel after time t

W_0= Initial weight of gel at zero time

***In-vitro* Release Study**

The *in-vitro* drug release of nanostructured lipid carriers loaded gel was carried out using cellulose acetate membrane (GE Healthcare Limited). Phosphate buffer (pH 7.4), was used to maintain sink condition throughout the study in the receptor chamber that facilitates the diffusion rate. The membrane was placed between the donor and receptor compartments of franz diffusion cells (FDC-06, Logan instrument corporation) (diffusion area 7.07 cm^2, receptor volume of 20 ml). A weighed amount nanostructured lipid carriers loaded gel (approximately to 2g) was loaded over the membrane along with API suspension (approximately equivalent to 5mg of drug) and allowed to release in a receptor chamber containing phosphate buffer media (pH 7.4) at 32±0.5°C with constant stirring for 6 h. Samples (1 ml) were withdrawn at 0.5, 1, 2, 3, 4, 5 and 6 h time intervals, replaced with same volume of fresh buffer solution. Analysis of drug content was carried out in the sample.

Skin Permeation and Retention Study

To evaluate transdermal permeation of a drug, the most relevant membrane of human skin is porcine ear skin. Pig ear skin was used in Franz diffusion cells (FDC-06, Logan instrument corporation) (diffusion area 7.07 cm^2, receptor volume of 20 ml) to evaluate the percutaneous permeation from the developed formulations. Initially pig ears were processed and dorsal portion of pig ear skin was shaved using animal hair clipper. Skin was mounted on vertical Franz-type diffusion cells with the dermis facing the receptor compartment. The temperature was accurately controlled at 32 ± 0.5°C. The receptor compartment was filled with 5 ml of medium consisting of phosphate buffer saline (pH 5.8) and ethanol (85:15). Nanostructured lipid carriers loaded topical gel was applied in the donor compartment and spread over exposed pig ear skin surface. At specific time intervals 0.5, 1, 2, 3, 4, 5 and 6 h, aliquots (500µg) were withdrawn from receptor compartment and immediately replaced with equal volume of fresh buffer to maintain the sink conditions. Permeated amount of the drugs was determined in the collected receptor samples. Moreover, the skin retention study was carried out at the end of the permeation experiment. Skin samples were removed, cleaned with cotton soaked in phosphate buffer to remove any formulations remaining and homogenized in absolute ethanol to extract all the retained gel formulation. Samples were then centrifuged to remove any skin debris, and supernatant was separated for analysis of content. Similarily drug content in the skin was analysed. Skin was chopped for drug extraction and kept in a water shaker bath for 12h in selected ethanol and phosphate buffer medium. Resultant samples were centrifuged to remove skin debris. Then samples were analyzed for cumulative permeated amounts of drug.

Antifungal Activity of the formulation

Antimicrobial assay of samples was performed by agar well diffusion method in Sabouraud Dextrose agar (SDA) plates. Sabouraud Dextrose agar media was autoclaved at 121°C and 15 psi for 15 minutes. Subsequently, the media was poured into plates and allowed to solidify in a laminar air flow. The test organisms were inoculated in sabouraud dextrose broth and incubated overnight at 37°C to adjust the turbidity to 0.5 McFarland standards giving a final inoculum of 1.5 × 108 CFU/ml. Well with a diameter of 5-6 mm was created on the agar plate using a cork borer. Next, 100µl of the inoculum was transferred to a fresh sterile solidified Agar Media Plate. The agar plate was inoculated by spreading the inoculum with a sterile spreader. Each well was then filled with samples. After 30 minutes of diffusion at room temperature, the plates were incubated at 27°C for 24 hours. The antimicrobial activity was determined by measuring the diameter (mm) of the clear zone of growth inhibition.

In-vivo evaluation of anti-candida activity

Three groups of healthy Wistar rats (six in each group) of the same age group, weighing about 150 ± 20 g, were acclimatized. Experimental rats were immunosuppressed by the administration of hydrocortisone at a dose of 2 mg/kg body weight for 3 consecutive days. Suspension of C. albicans contains 10^4 CFU/ml was prepared in the saline. A 0.5 ml volume of this suspension was applied topically to the wound. Wound of approximately 1 cm radius was created using sterile surgical blades on the posterior mid-dorsal side of the animal. Marketed formulation and NLC loaded gel was applied twice a day, for 8 consecutive days. Quantitative evaluation of wound healing and the efficacy of treatment in promoting wound closure was

determined by the percentage of wound closure. Percentage of wound contraction is calculated by the following formula.

$$\textbf{Percentage of wound contraction} = \frac{\textbf{Initial wound area} - \textbf{Specific day wound area}}{\textbf{Initial wound area}} \times \mathbf{100}$$

Rats were randomly divided into three groups:

Group-I served as the negative control (without treatment)

Group-II was treated with a marketed drug

Group-III was treated with the formulated gel

4. RESULTS

Preparation and optimization of nanostructured lipid carriers loaded gel

Gelling agent like Carbopol 980 NF, hydroxyethyl cellulose, sodium hyaluronate and sepineo P 600 were screened for gel preparation. Rheological parameters of thickening agents were tested by preparing the gel. Viscosity and storage modulus of Carbopol 980 were observed satisfactory for the preparation of nanostructured lipid carriers loaded gel.

Excipients in gel preparation were glycerine (2%w/w) as humectant, butylated hydroxytoluene (0.1% w/w) as preservative. pH of the formulation was adjusted by using sodium hydroxide (18%w/w). Concentration of gelling agent was optimized by preparing the gel at 0.3, 0.4, 0.5, 0.6 and 0.7%w/w and testing of these formulations was carried out for the rheological parameters. Concentration of Carbopol 980 0.6% w/w was selected for gel preparation. Carbopol 980 at 0.6% shows the optimum rheological properties.

Table 1: Optimization of gelling agent concentration

Optimization of gelling agent concentration		
Concentration of Carbopol 980 (% w/w)	**Viscosity (mPa.s)**	**G` (storage modulus)**
0.3	560.35	77.7
0.4	2542.9	320
0.5	3452.8	331
0.6	7447.4	608
0.7	10679	1023

Characterization of nanostructured lipid carriers loaded gel

Determination of pH

The pH value of nanostructured lipid carriers loaded gel was of 6.8 range (6.5-7.5).

Rheological properties

Rheological properties of gel were determined by using cone and plate viscometer (MCR 92 Anton Paar). Viscosity of nanostructured lipid carriers loaded gel was observed 8682.8 mPa.s. Amplitude sweep was performed, storage modulus of gel was found to be 859 Pa.

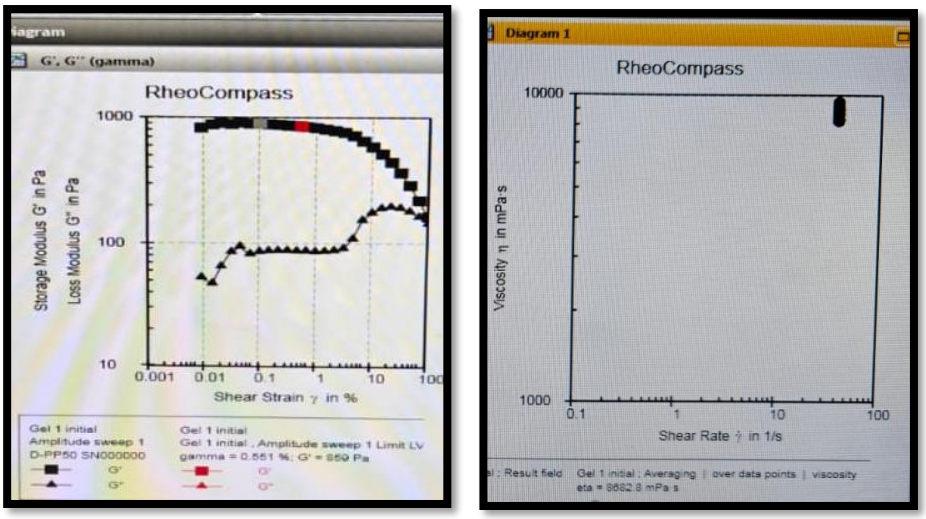


Figure 1: Rheological properties of solid lipid particle loaded gel

Spreadability

Spreadability of nanostructured lipid carriers loaded gel was determined by using plate method. Spreadability of a gel was increased on applying the weight. It indicates that on rubbing the formulation spreadability increases which helps in the application of gel on the skin. Initial viscosity of gel was 6084.57 mPa.s and after applying weight viscosity was increased to 12873.14 mPa.s.

Table 2: Spreadability study results of solid lipid particle loaded gel

Radius (mm)	N=1	N=2	N=3	Average radius (mm)	Spreadability area (mm^2)
Initial	21	22	23	22	6084.57
Time (after 5 minutes)	31	31	34	32	12873.14

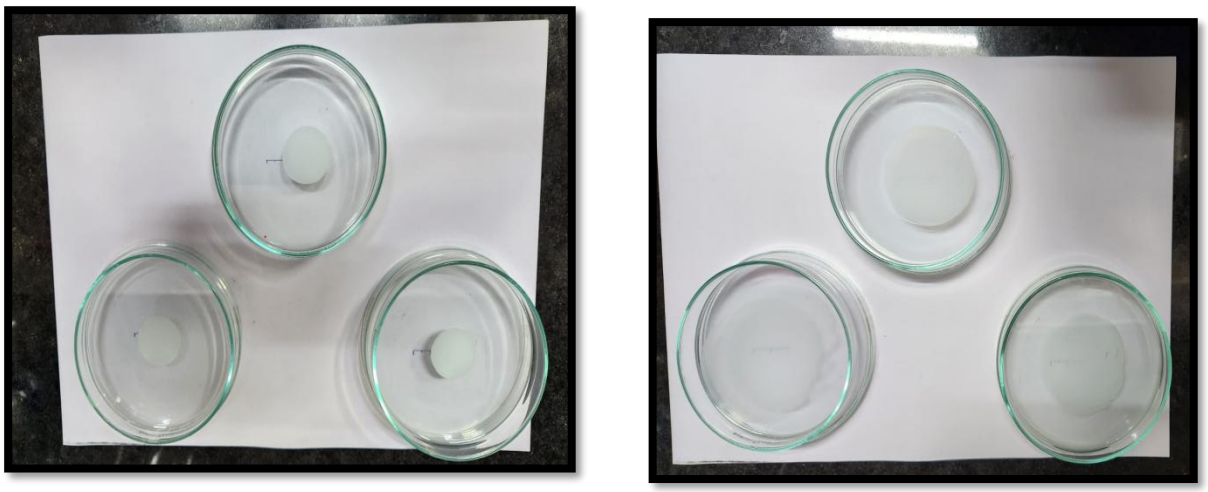


Figure 2: Spreadability study results of solid lipid particle loaded gel

Swelling Index

Prepared formulation comes in to an equilibrium stage after 20 minutes. No marked weight gain percent was observed after 20 minutes of swelling time in all three sets of experiments. table 3 indicates the results of equilibrium swelling percentage

Table 3: Swelling index of solid lipid particle loaded gel

	Weight gain			Equilibrium swelling percentage		
Time Interval	**N=1**	**N=2**	**N=3**	**SW% (N1)**	**SW% (N2)**	**SW% (N3)**
Initial	1.44	1.38	1.48			
10 minutes	1.86	1.74	1.7	29.16666667	26.08695652	14.86486
20 minutes	2.064	1.7489	1.746	10.96774194	0.511494253	2.705882
30 minutes	2.286	1.92	1.852	10.75581395	9.783292355	6.071019
40 minutes	2.4222	1.9402	1.8376	5.958005249	1.052083333	-0.77754
50 minutes	2.4196	1.9422	2	-0.107340434	0.103082156	5.893557

***In-vitro* Release Study**

The *In vitro* drug release profile of nanostructured lipid carriers loaded gel was determined. Release profile of free drug, nanocarrier suspension, nanocarrier gel and marketed formulation was compared. Amount of drug release was least in case of free drug. Drug release profiles of nanocarrier suspension and marketed formulation were observed comparable. Amount of drug release from the nanocarrier loaded gel was observed more as compare to the nanocarrier suspension and marketed formulation. Release pattern of marketed formulation and nanocarrier loaded gel was observed same. Amount of drug release from the system was observed more at certain extent then it decreases to certain amount.

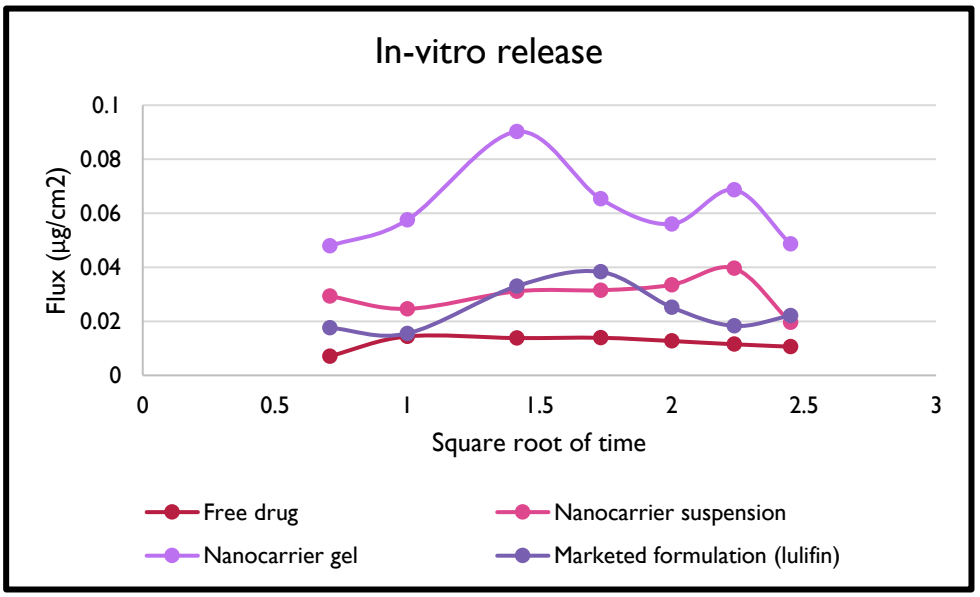


Figure 3: In-vitro release study results

Skin Permeation and Retention Study

Skin permeation and retention study helps in understanding of the amount of the drug that permeated to viable dermis and the amount present in the stratum corneum. From the figure it can be understand that nanostructured lipid carriers shows penetration in the deeper layers of skin.

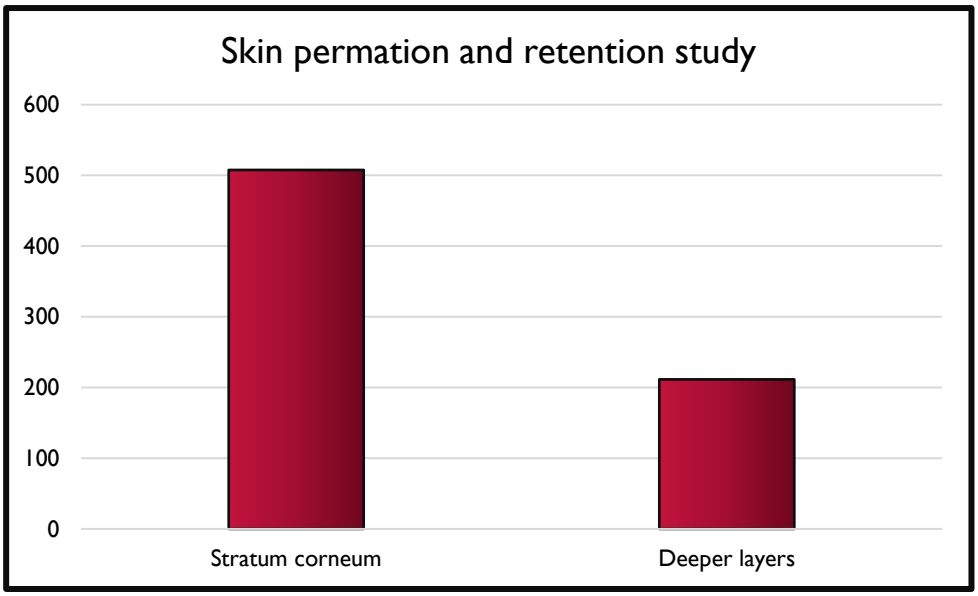


Figure 4: Permeation and retention study results

Antifungal activity of the formulation

The antifungal activity of different samples against *Candida albicans* was evaluated by measuring the zone of inhibition in millimeters. The results indicate significant variations in antifungal efficacy among the tested samples. The blank gel exhibited no antifungal activity, as demonstrated by a complete absence of inhibition zones (0 ± 0 mm) across all plates. In contrast, the oil formulation showed moderate antifungal activity, with a mean inhibition zone of 9 ± 1 mm. The gel formulation exhibited the highest antifungal effect, with a mean zone of inhibition of 20.666 ± 2.081 mm, indicating its strong potential in inhibiting *C. albicans* growth. The API (active pharmaceutical ingredient) displayed mean inhibition zone of 15.666 ± 5.131 mm. Overall, the gel formulation demonstrated superior antifungal activity compared to the oil and API, indicating its potential as an effective formulation for *C. albicans* inhibition.

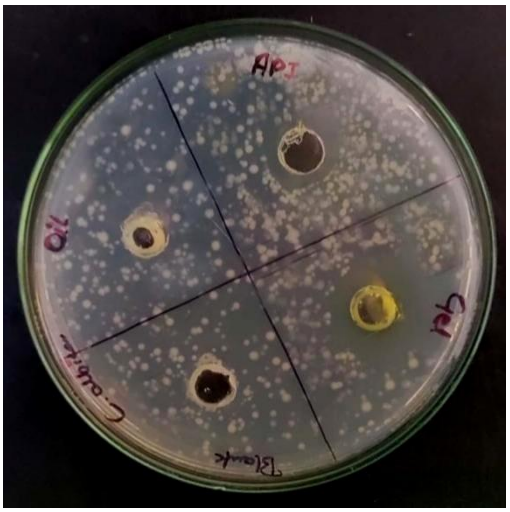


Figure 5: Antifungal activity by zone of inhibition method

***In vivo* evaluation of anti-candida activity**

Wound of animals infected with *Candida albicans* were treated with Marketed formulation and NLC loaded topical gel. Samples were collected from the dry wounds of the rats and spread onto the SDA plates. After 24–48 hours of incubation, creamy to white, yeast-like colonies with smooth surfaces were observed.

Figure 6: SDA Plate of group I

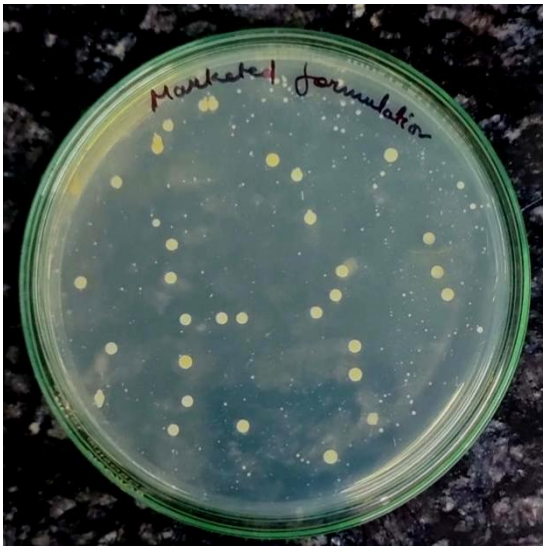


Figure 7: SDA Plate of group II

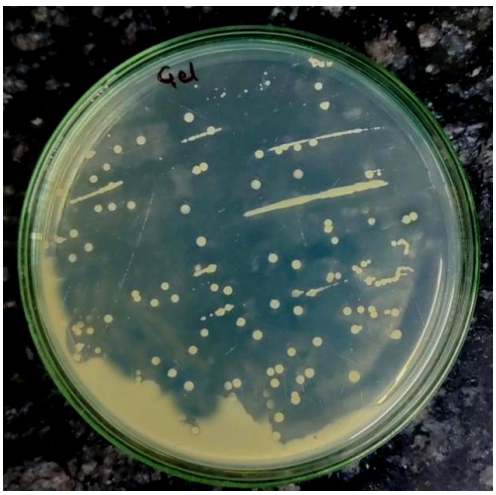


Figure 8: SDA Plate of group III

According to the microbial analysis, the swab collected from the healing wound region showed the presence of *Candida albicans*, which was confirmed by the Lacto Phenol Cotton Blue (LPCB) staining method. Less infection was observed in Groups II and III. Group I showed a high level of infection with *C. albicans*.

Results of Body Weight (gm) and Wound Contraction (%)

Table 4 Changes in Body Weight (gm)

Groups	Body weight in gms								
	Day 0	Day 2	Day5	Day 7	Day 9	Day 12	Day 15	Day 18	Day 20
Negative control	216.666±12.096	181.666 ±7.736	175.666 ±1.527	174±4.101	176.333 ±5.686	178±7	177.333± 10.692	179.333 ±3.152	180.666 ±4.686
Marketed formulation	200.666±12.662	202±1.732	205.666 ±5.507	208.333 ±2.516	209.333 ±0.577	211.666± 3.214	213.666± 3.785	214.666 ±2.516	216.333 ±3.426
Formulated gel	191.666±12.096	187.333 ±5.686	193.666 ±1.527	195.333 ±4.041	196.666 ±5.854	199.333± 4.725	201.333± 2.081	202.333 ±4.236	203.666 ±3.521

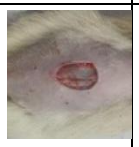
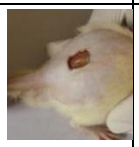
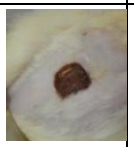
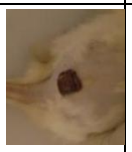
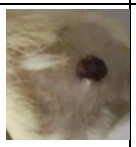
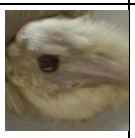
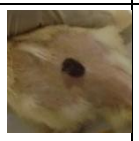
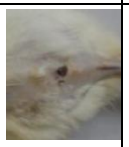
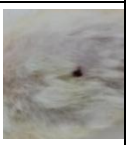
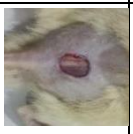
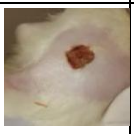
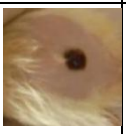
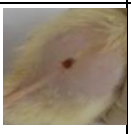
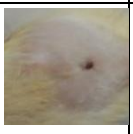
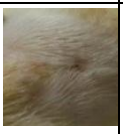
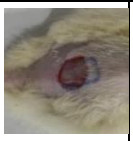
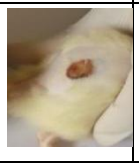
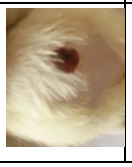
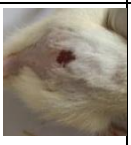
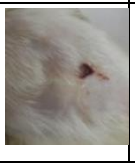
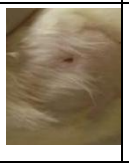
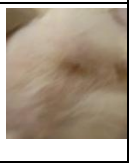
The data suggest that while the negative control group continued to show reduced or stagnant body weight it indicates the poor health status. The treated groups marketed formulation and NLC`s loaded topical gel groups, demonstrated progressive improvements.

Table 5 Wound Contraction study

Groups	Wound contraction in percentage (%)								
	Day 0	Day 2	Day5	Day 7	Day 9	Day 12	Day 15	Day 18	Day 20
Negative control	0±0	3.65±1.254	13.24±3.485	24.36±4.298	32.87± 3.493	48.32±2.896	64.74±5.461	73.56±3.285	82.45±3.769
Marketed formulation	0±0	9.01±2.410	29.12±4.055	51.89±5.247	65.10± 4.852	78.43±5.127	85.71±4.12	99.25±5.24	-
Formulated gel	0±0	6.414±1.856	19.84±.2.559	34.01±3.21	51.04± 3.856	64.57±3.483	76.65±4.964	84.61±6.423	99.12±4.759

Wound contraction is a key parameter in evaluating the efficacy of a topical formulation in the wound healing process. The **Negative Control group** showed a slow and gradual increase in wound contraction, reaching only 82.45 ± 3.77% by Day 20. The marketed formulation demonstrated rapid wound contraction by Day 18 (99.25%). The NLC`s loaded topical gel group also showed wound contraction 99.12% by Day 20, suggesting sustained healing. The formulated gel exhibited antifungal activity and promoted significant wound contraction comparable to the marketed formulation. The results suggest it may serve as a promising candidate for topical treatment of infected wounds, offering both antimicrobial and wound-healing benefits.

Table 6 Pictotial presentation of wound healing

Groups	Day 0	Day 2	Day5	Day 7	Day 9	Day 12	Day 15	Day 18	Day 20
Group I									
Group II									
Group III									

Summary and Conclusion

Topical fungal skin infections are skin conditions where fungi invades the skin surface and subsequently invades the deeper layers also. Antifungal treatment requires effective and targeted treatment property to the skin. Nanostructured lipid carriers were prepared by using hot homogenization technique. Incorporation of antifungal agents into nanocarriers enhances drug penetration, stability, and targeted delivery to infected areas. NLC`s loaded gel was prepared by using Carbopol as a thickening agent. Nanocarrier loaded gel is non-greasy and easy in application. Topical gel shows acceptable pH range of (6.5-7.5). Rheological properties shows the good elastic nature of the topical gel. Viscosity of the gel was observed 8682.8 mPa.s. Spreadability of a gel increased on applying the weight. It indicates that on rubbing the formulation spreadability increases which helps in the application of gel on the skin. In vitro drug release pattern is same as observed with marketed formulation. The amount of drug release in significantly more in the NLC`s loaded gel. A skin permeation and retention study was conducted to evaluate the performance of the nanocarrier-loaded topical antifungal gel. A good skin penetration was observed in the topical gel, suggesting a good candidate for localized delivery and prolonged therapeutic effect. To demonstrate the antifungal efficacy of the prepared NLC`s loaded gel, antimicrobial efficacy test was carried out by measuring the zone of inhibition in the cultured agar plates. In this study NLC`s loaded gel shows higher inhibition of colonies that is 20.666 ± 2.081 mm of ZOI. NLC`s loaded topical gel demonstrates comparable antifungal activity to existing marketed formulations in the in vivo studies, making it a promising candidate in managing dermal fungal infections.

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