

Mupirocin-Loaded Niosomal Gel for Topical Wound Healing Application

Srikrishna Theerdhala^{1,2*}, Narayanaswamy Harikrishnan³

¹Department of Pharmaceutics, Faculty of Pharmacy, Dr. M.G.R. Educational and Research Institute, Deemed to be University, Velappanchavadi, Chennai - 600077, Tamil Nadu, India.

²Department of Pharmaceutics, Ratnam Institute of Pharmacy, Pidathapolur (V&P), Muthukur (M), SPSR Nellore (Dt.) - 524346, Andhra Pradesh, India.

³Department of Pharmaceutical Analysis, Faculty of Pharmacy, Dr. M.G.R. Educational and Research Institute, Deemed to be University, Velappanchavadi, Chennai - 600077, Tamil Nadu, India.

KEYWORDS:

**Wound healing;
Nanomedicine;
Niosomes;
Mupirocin gel;
Niosomal gel**

ARTICLE INFO:

February 12, 2023

Revised: April 23, 2023

Accepted: Apr 6, 2023

Available on line: September 4, 2023

CORRESPONDING

AUTHORS:

Srikrishna Theerdhala

Email: srikrishna.nlr@gmail.com

ABSTRACT

Advanced technology is required to overcome wound healing issues in an improved manner. Mupirocin-loaded niosomal gel has been developed to enhance the drug deposition for a longer period at the targeted site and sustained the rate of release of the drug. Mupirocin is a very efficient antibiotic against a variety of bacteria and pathogens, most often those that cause primary and secondary skin infections. The lipid hydration technique is employed to formulate niosome with polymers (Carbopol and Chitosan) at various concentrations. Those polymers are used in the formulation to sustain the rate of release of the active drug mupirocin and also provide viscosity and non-toxic, biodegradable, and biocompatible properties. Tween 80 is a non-ionic surfactant utilized in the formulation to improve the entrapment efficiency of the drug. Cholesterol is utilized in the formulation to improve vesicle stability and glycerin is a gelling and moistening agent. In addition, to improve the stability of the niosomal gel methylparaben is also added to the current formulation. Fourier transform infrared (FTIR) and differential scanning calorimetry (DSC) studies are used to find out the compatibility study of the drug and other excipients. The post-evaluation studies confirm that yield percentage lies between 85 - 93%, entrapment efficiency 83 - 97%, drug content lies within the limit of 87 - 98%, pH range matches the skin pH and the obtained range is 6.25 - 7.3. Viscosity and Spreadability show the result within the limit of 410 - 560 cps and 3.8 - 5.4 g cm/s respectively. Post-evaluation study further subjected to in-vitro

diffusion study and formulation F5 has shown best formulation sustain the drug release till 98% at 12h. The formulation F5 has shown better-sustained release of active drug which contains a higher ratio of carbopol and tween 80. It was concluded that a higher concentration of tween 80 increases the entrapment efficiency of active drug in the niosome and carbopol helps to sustain the release rate to an optimum period as a swellable gelling agent.

1. Introduction

A general wound can be healed by a natural process of tissue growth but in the case of chronic or non-healing wounds need more attention and effort to heal. In the case of diabetic patients wound healing is very tedious and painful. Wound healing depends upon numerous factors such as blood supply to the wound area, condition of the skin, wounded body parts, types of nutrition intake, etc. Advanced wound care systems replace commercially available medicine and suggest clinicians use nanomedicine for better treatment. In recent years, researchers bring this nano-technology for the improvement of commercially available medicine and bandages. Nano-technology helps to achieve targeted drug delivery, reduce toxicity, and provide better treatment by sustaining the release rate of active drugs^{1,2}. In this regard, a unique technology like niosomes has been considered in this current study.

Similar to liposomes, niosomes are multilamellar vesicular structures^{3,4} containing nonionic surfactants that can entrap together hydrophilic and hydrophobic, antigens and hormonal drugs^{5,6}. Niosome can be prepared by using various types of non-ionic surfactants to form a vesicle to entrap the active drugs in it⁷⁻⁹. The drug was loaded to the vesicle at a minimum concentration to produce fewer side effects and stability and modified the release pattern¹⁰. The non-ionic surfactants and the additive cholesterol together help to form a bilayer membrane and improve drug permeability and solubility¹¹⁻¹³. Niosome as a carrier protects the drug from unwanted immunological effects, rapid degradation, and in-

stability^{14,15}. In addition, it aids in the medication's retention in the targeted location for a longer period and helps the active components' penetration of the skin surface.

Mupirocin is a topical antibiotic used in the treatment of infection. A wide variety of gram-positive and gram-negative bacteria (*Staphylococcus aureus*, *Streptococcus*, *Haemophilus influenza*, *pasteurella-multocida*, etc.) can be controlled by mupirocin¹⁶. Resistance gradually increases by the bacteria toward the active drugs which is a major concern for researchers¹⁷⁻²¹. To increase the therapeutic activity of the active drug nanocarrier has been introduced. Mupirocin-loaded niosomal gels were developed to inhibit the synthesis of RNA and protein of the above-discussed bacteria without any toxic effect on the human body^{22,23}. Mupirocin with unique mechanism action is converted to monic acid²⁰ and excreted through urine once it reached systemic circulation. Also, the mupirocin can kill antibiotic-resistant bacterial strains such as *methicillin-resistant Staphylococcus aureus* (MRSA)²⁴, and the wound healing ability is also related to its capacity to promote re-epithelialization and angiogenesis and stimulate skin and immune cells²⁵.

Excipients play an important role in the preparation of nano-gel formulations. Excipients are inactive ingredients that are added to a formulation to enhance its stability, bioavailability, and other properties. In the case of gel and nano-gel preparations, excipients are used to control the rheological properties, increase the viscosity, and improve the drug release characteristics of the formulation. Carbapol is a water-soluble polymer, used as an emulsifying,

stabilizing, suspending, thickening agent, and gelling agent in many industries. Chitosan, as a cationic natural polymer, has been widely used as a topical dressing in wound management owing to its hemostatic, stimulation of healing, antimicrobial, nontoxic, biocompatible, and biodegradable²⁶ properties. Tween 80 non-ionic surfactants play a major role in the entrapment of drugs and also help stabilize the nanoparticles and improve their dispersion. Cholesterol is used as a membrane additive and acts as a stabilizer as well as a fluidity buffer to improve the stability of the vesicles. Glycerin is used to control the rheological properties of the gel formulations and improve the skin hydration properties of the final product. In addition, preservatives like methylparaben are added to the formulation to prevent bacterial and fungal growth.

In this present study, mupirocin is used as a topical antibiotic loaded with a niosomal carrier for a deeper and better availability of activity to the targeted site. Reports confirm that no study has been reported on the mupirocin-loaded niosomal sustained-release gel. Niosomal gel as a novel formulation enhances patient compliance and acceptance of wound healing treatment.

2. Materials and methods

Mupirocin and Carbopol-934 (102.13g/mol) are obtained from Divya associates, Vijayawada, India. Chitosan (medium molecular weight 200-800cps) is obtained from Nice laboratory, India. Tween 80, Cholesterol, and glycerin are obtained from SD fine chemicals India. All other excipients were of analytical research grade and contain the highest purity.

2.1. Pre-formulation study of the drug:

The significance of the pre-formulation study is to strengthen the formulation under regulatory guidance and gather enough data to develop a chemically stable product containing a better therapeutic effect. This study also helps to enhance product quality, safety, and standard and minimize toxicity. Regarding the same FTIR and DSC studies have been per-

formed. This result helps to determine the chemical composition and physical state of the drug and polymers used in the formulation.

2.2. Preparation of mupirocin-loaded niosome

The lipid hydration method is used for the preparation of multilamellar vesicles of niosome represent in Table.¹²⁷. Weight amounts of polymers such as Carbopol and Chitosan at different concentrations have been mixed with an active drug solution prepared with an organic solvent such as methanol. Tween 80, cholesterol was taken in the prescribed ratio in a 250 ml beaker. The mixture was dissolved in diethyl ether and methanol (8:2) solution. The prepared solution is further added slowly into the drug and polymeric solution during stirring. The centrifugation technique has been used to segregate the organic solvent from the prepared sample at room temperature at 8000 rpm. A thin layer of solid mixture deposited at the bottom of the sample holder was collected and hydrated with an aqueous phase with gentle agitation to remove the residue of the organic solvent. The obtained niosome is stored properly for further use.

2.3. Preparation of mupirocin-loaded niosomal gel

All ingredients used are based on the formulation mentioned in Table 1. The gel base is composed of glycerin 5% w/w, Methylparaben .22% w/w, and distilled water as a quantity sufficient. Mupirocin-loaded niosome 2% w/w was added to the base of the gel in a stirring condition to obtain a clear and transparent gel²⁸.

3. Evaluation of mupirocin-loaded niosomal gel

3.1. Entrapment efficiency

The UV-Visible spectrophotometer is used to determine the entrapment efficiency of the active drug mupirocin present in niosomal gel. Prepared niosomal gel diluted with 10 ml of methanol kept on a magnetic stirrer with continuous agitation. Obtained

Table 1. Formulation of mupirocin-loaded niosomal gel 2% (Net Weight 15g)								
Formulation	Drug	CP	CH	TWEEN 80	CL	Glycerine	Methylparaben	Distilled water
F1	2	5	-	4	8	5	0.22	Q.S
F2	2	-	5	4	8	5	0.22	Q.S
F3	2	2	3	5	8	5	0.22	Q.S
F4	2	1	4	6	8	5	0.22	Q.S
F5	2	4	1	6	8	5	0.22	Q.S
F6	2	2	3	3	8	5	0.22	Q.S
F7	2	3	2	3	8	5	0.22	Q.S
F8	2	2.5	2.5	5	8	5	0.22	Q.S

Drug: Mupirocin, CP: Carbopol, CH: Chitosan, CL: Cholesterol, All Values in Percentage

homogeneous solution subjected to a centrifuge for 30 min at 1200 rpm. The supernatant liquid was analyzed at 226 nm under a UV-Visible spectrophotometer with a suitable dilution. The entrapment efficiency percentage was calculated by the formula given below.

3.2. Yield Percentage

$$\% \text{ Entrapment efficiency} = \frac{\text{Amount of drug entrapped}}{\text{Amount of drug added}} \times 100$$

buffer sample pH 7.4. 1 ml of the above solution was further diluted to 10 ml and the absorbance of the solution was determined by UV-Visible spectro-

The yield percentage is used to determine the product result. It has to compare with the raw materials taken for the formulation of niosomal gel. The yield percentage is calculated by the given formula.

3.3. Drug content

Niosomal gel 1 gm dissolved in 50 ml volume of

tometer at 226 nm.

3.4. Determination of pH

$$\text{Percentage yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$$

A digital pH meter is used to determine the pH of the various niosomal formulations. Calibration should be done before use. Each formulation pH was measured in triplicate to get the average. The pH of the formulated niosomal gel should be in the range of 6-7 to avoid unwanted complications in the patient.

3.5. Determination of viscosity

The formulated niosomal gel was poured into a beaker and rotated with a Brookfield viscometer at 50 rpm. The corresponding reading was noted which was shown on the viscometer. The viscosity is represented in cps. All the samples are done in

triplicate to minimize the error.

3.6. Spreadability

Spreadability is determined for all the formulations. 1 gm of niosomal gel was weight and applied in between the glass plates²⁹. After a minute the diameter of the circle formed between two glass plates was measured and the average is taken into consideration.

3.7. Scanning electron microscope (SEM) analysis

To determine the surface morphology of the formulated niosomal gel subjected to SEM (Model no. JEOL Model JSM - 6390LV). It also gives additional information about the shape and size of the niosome. A small amount of formulated niosome gel spread on a clear glass stub, visualized under SEM after complete drying of the sample.

3.8. In-Vitro release study

An in-vitro drug release study is used to perform to find out the percentage of drug release at a given interval of time. Franz diffusion cell (Model no: KI-2351-6C, volume-20ml) is used to perform the drug release of mupirocin-loaded niosomal gel. From each formulation, 3 mg of freshly prepared niosomal gel was spread on the donor part of the cellulose nitrate membrane (Minipore white cellulose nitrate membrane filter paper, pore size: 0.45 μ & 0.22 μ). The cellulose membrane is soaked with isopropyl alcohol for overnight to open the pores. In a receptor vessel, 20ml of phosphate buffer (pH-7.4) was kept. The temperature was maintained at 37 \pm 0.5 $^{\circ}$ C and the revolution per minute (rpm) was maintained at 400 for 12h. After a regular interval of time, a 5 ml sample was collected and replaced with the same amount of fresh sample to maintain the sink condition. The collected sample after suitable dilution was kept for analysis under a UV Visible spectrophotometer at 226 nm. The obtained result is further used to calculate the percentage of drug release in a particular interval of time.

3.9. Drug release kinetic studies

The drug release kinetic study of mupirocin-loaded niosome has been performed using a dissolution profile. The kinetic study was performed for zero order, first order, Higuchi model, and Korsmeyer-Peppas model. The R² value also known as the correlation coefficient value indicates the best fitting of the release kinetics of any of the models.

3.10. Stability studies

The best formulation F5 was taken for the stability test. The stability test was carried out as per ICH guidelines at 25 $^{\circ}$ C with 60% RH and 40 $^{\circ}$ C with 75% RH for 90 days³⁰. Any changes in physical appearance, pH, viscosity, Spreadability, and drug release profile.

4. Results and Discussion

4.1. Pre-formulation study for all formulations

4.1.1. FTIR study

The drug-polymer combinations were administered, and an agreeableness schedule was followed. This is to ensure that another potentially therapeutically active remedy has not had any physicochemical change after being exposed to the formulation processing processes. This may be used to anticipate the results of subsequent research such as FTIR. Figures 1 and 2 show the FTIR spectra of mupirocin with Carbopol, Chitosan, and other excipients. The characteristic peak of mupirocin bulk appeared at 3471.08, 3304.2 cm⁻¹ corresponding to OH-stretching 2934.18, 2850.74 cm⁻¹ CH-stretching 1723.98, 1658.68 cm⁻¹ belongs to C=O stretching. Similarly, the IR spectrum of mupirocin with carbopol at 3471.08, 3298.04 cm⁻¹ corresponding to OH-stretching 2928.37, 2844.94 cm⁻¹ CH-stretching 1718.17, 1652.88 cm⁻¹ belongs to C=O stretching. Mupirocin with chitosan shows the peak at 3471.08, 3300.58 cm⁻¹ corresponding to OH-stretching 2928.37, 2848.56 cm⁻¹ CH-stretching 1721.80, 1656.50 cm⁻¹ belongs to C=O stretching. Mupirocin with Tween 80 shows the peak at 3471.08, 3304.20 cm⁻¹ corresponding to OH-stretching 2928.37, 2857.27 cm⁻¹

CH-stretching 1723.98 , 1652.88 cm^{-1} belongs to C=O stretching. Similarly, mupirocin with cholesterol composition shows IR frequencies at 3471.08 , 3301.30 , cm^{-1} corresponding to OH- stretching, 2932 , 2859.45 cm^{-1} CH-stretching, 1723.98 , 1647.07 cm^{-1} belongs to C=O stretching. According to the FTIR spectrum analysis report, mupirocin exhibited its distinctive peaks with no shifting or widening when combined with polymers and other excipients. Based on the findings, it is determined that the mupirocin absorption peaks remain unaltered in drug-polymer admixture, indicating that there is no significant interaction.

4.1.2. DSC study

DSC methods had been used to find out about the compatibility of the drug mupirocin, specific polymers (Carbopol, Chitosan), and other excipients. DSC curve of the mupirocin used to be in contrast with 1:1 ratio bodily mixtures. The thermal sphere of the blends i.e. melting point, the absence of an enormous shift in rapid liquefying point, or absence in the result

coming from a new exothermic/endothermic peak in the combination indicated agreeableness in the pure drug and polymers. Moreover, moderate change in the peak shape and width should be an indication of compatibility. DSC curve of pure mupirocin, polymers, excipients, and their mixtures have been represented in Figures 3 & 4.

4.2. Post-formulation study of mupirocin-loaded niosomal gel

4.2.1. Entrapment efficiency of the drug

This study confirms the amount of the drug mupirocin present in the formulated niosomal gel. The main active drug mupirocin concentration should be calculated for each formulation following this study which has shown in Table 2. Obtained results confirm that 83% to 97% of mupirocin is entrapped in various formulations (F1 to F8). The entrapment efficiency and the yield of the niosome depend upon the method chosen and the properties of the drug. The addition

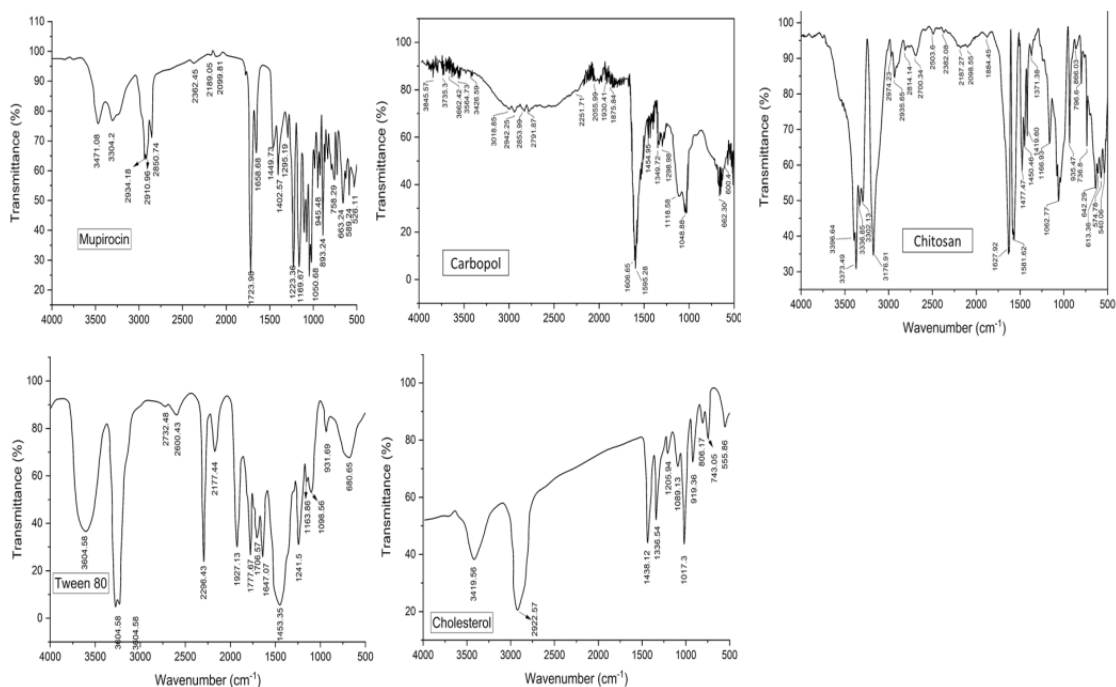


Figure 1. FTIR spectra of pure drug and excipients

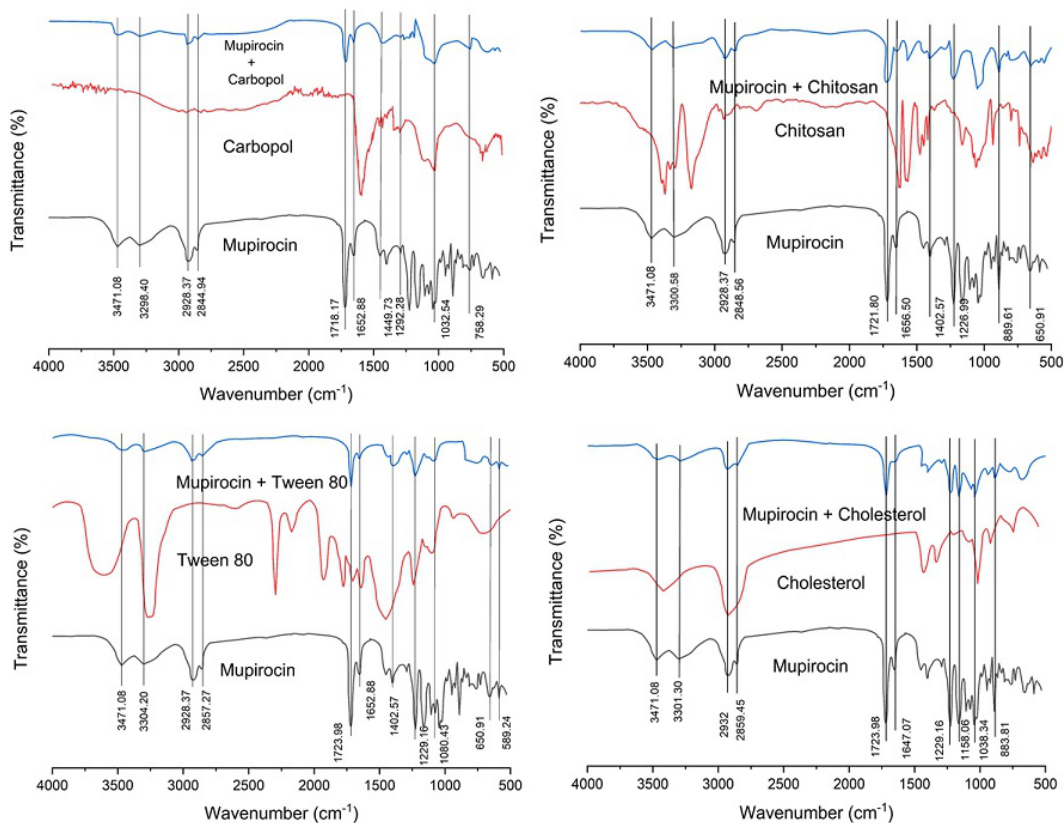


Figure 2. FTIR Spectra of mupirocin with excipients

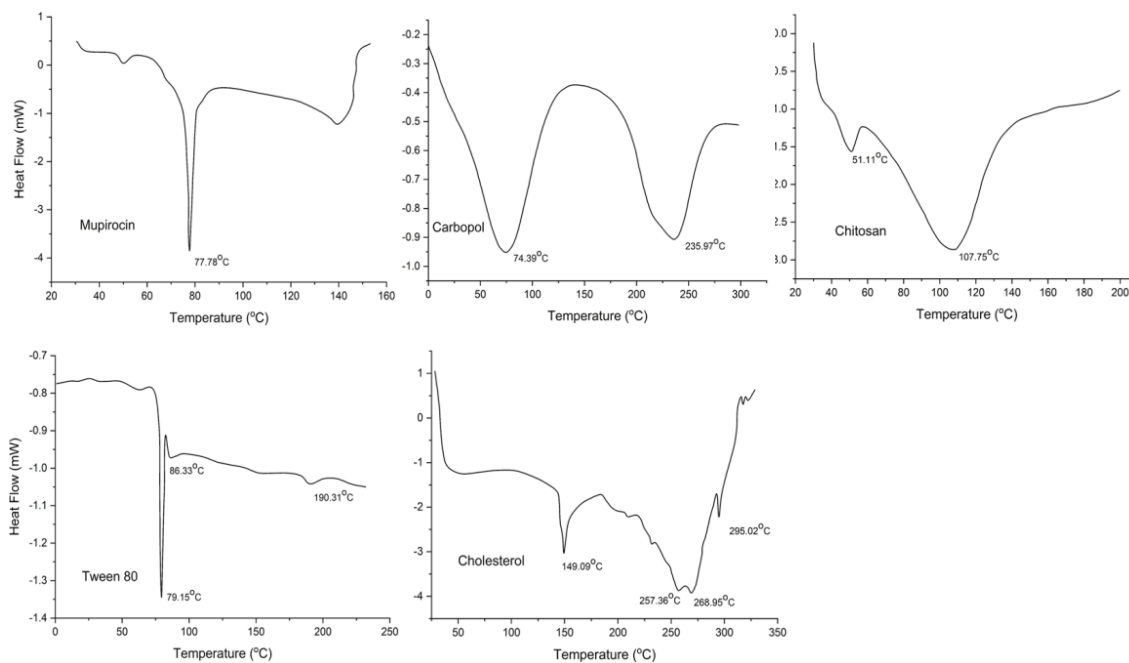


Figure 3. DSC spectra of pure drug and excipients

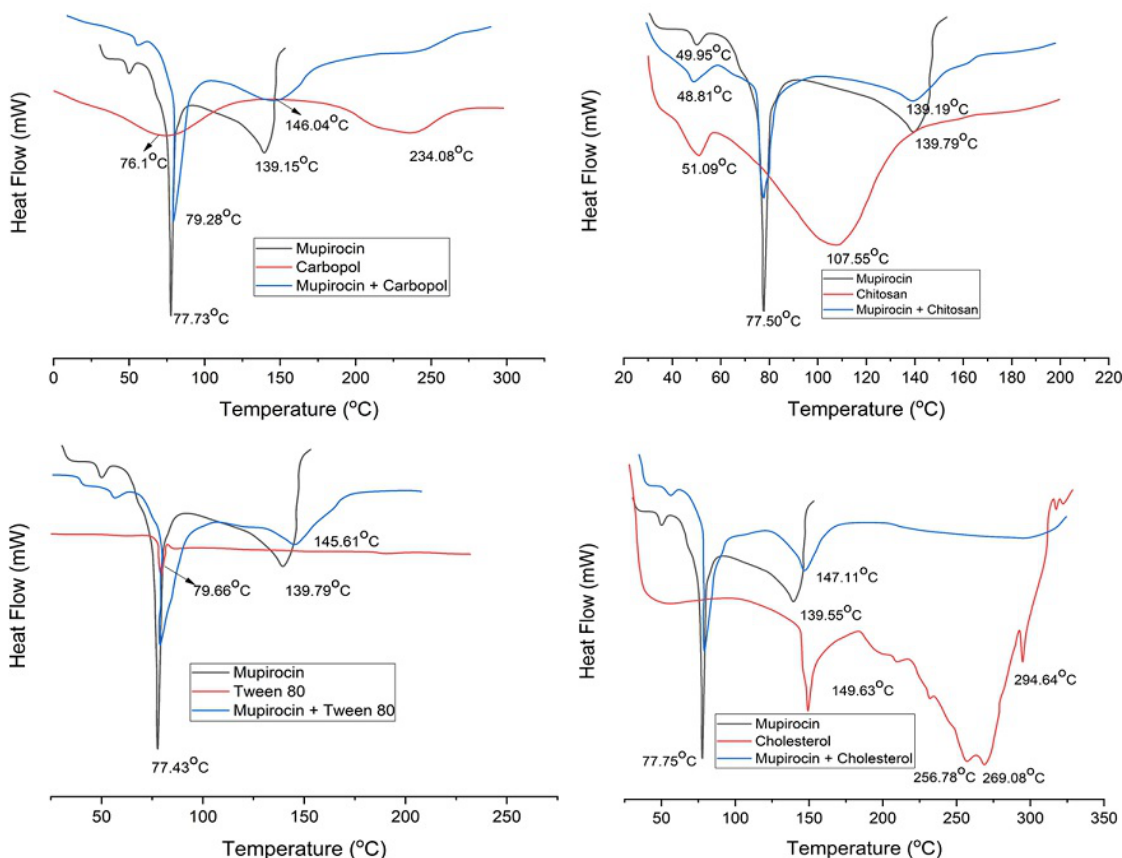


Figure 4. DSC Spectra of mupirocin with excipients

of cholesterol makes the niosomes leak proof³¹ and the lipid hydration method enhances the entrapment efficiency of the aqueous phase and permeability. Non-ionic surfactants also played an important role in increasing the entrapment efficiency of the drug in the current formulation of niosome³².

4.2.2. Yield Percentage

The percentage of yield is fully dependent on practical yield and theoretical yield value. In many cases, it also depends upon the method used in the formulation of niosome. The percentage of yield lies between 85% to 93% represented in Table 2.

4.2.3. Drug content

The drug content was estimated for all the formu-

lations and represented in Table 2. The drug content was found in the range of 87% to 98%. This study confirms that when the concentration of Carbopol and Tween 80 is high it helps to retain more percentage of the drug in the niosomal gel.

4.2.4. Determination of pH

The most important need for a successful topical formulation is skin compatibility. The pH of all formulations of mupirocin-loaded niosome-based gel was determined to be in the range of 6.25–7.3, which corresponds to the skin pH, as indicated in Table 2.

4.2.5. Determination of viscosity

The viscosity for topical drug delivery is very important because with proper viscosity the drug can

remain in the targeted area for a longer time and helps in targeted drug delivery with fewer side effects. Table 2 shows that the viscosity varied between 410 and 560 cps. Formulations F2 and F7 contain low molecular weight and high concentrations of Chitosan. In comparison to other polymers, CH has a low viscosity grade. So the presence of a high concentration of Chitosan brings down the viscosity of the niosomal gel.

4.2.6. Spreadability

The spreading coefficient of a formulation determines its therapeutic efficacy. Table 2 shows that the Spreadability of all formulations containing mupirocin-loaded niosomal gel ranged from 3.8 to 5.4 g. cm/s. The viscosity and gelling properties of the polymers utilized in the formulation influence Spreadability. Formulation F5 has the maximum spreading coefficient of 5.4 g cm/s due

to its viscosity grade of Carbopol polymer, which has shown a viscosity of 560 cps, whereas formulation F2 has a lower spreading coefficient of 3.8 g cm/s due to low viscosity Chitosan polymer such as 410 cps.

4.2.7. SEM analysis

SEM was used to examine the front design and shape of mupirocin-loaded niosomal gel. The smooth surface shown in the photograph confirms the full elimination of the solvent from the formulation, as well as particle sizes ranging from 50 nm to 150 nm. The SEM picture of the best formulation F5 was discovered to be a uniform distribution of niosomes sphere-shaped particles³³, as shown in Figure 5.

4.2.8. In-Vitro diffusion study

The dissolving study was carried out in triplicate using the diffusion medium Phosphate buffer with a

Table 2. An evaluation study of mupirocin containing niosomal gel

Formulation	Entrapment efficiency (%)	Yield (%)	Drug content (%)	pH	Viscosity (cps)	Spreadability (g.cm/s)
F1	91.72+0.92	87.52+1.81	93.92+1.01	7.01+0.08	560.07+1.21	5.4+0.17
F2	88.79+1.33	88.21+1.28	94.11+1.37	6.91+0.05	410.15+10.16	4.51+0.36
F3	95.62+1.31	92.01+1.67	95.84+1.17	6.88+0.51	488.07+11.07	4.01+0.83
F4	97.08+1.42	93.11+1.17	97.82+1.07	6.71+0.11	448.16+12.01	3.8+0.11
F5	97.17+1.32	92.61+1.13	98.21+1.33	6.25+0.31	550.81+10.31	4.78+0.26
F6	83.01+1.32	85.11+0.83	89.63+0.17	6.79+0.17	510.02+11.13	4.23+0.77
F7	85.06+1.71	88.95+1.04	87.71+1.04	6.81+0.06	527.84+10.71	5.13+0.07
F8	95.02+1.01	91.81+1.73	96.71+1.18	7.12+0.11	496.17+11.76	4.97+0.12

*Results are expressed as of mean \pm SD (n=3)

pH of 7.4. At the end of 12 hours, the percentage of mupirocin drug release for all formulations of niosomal gel ranged from 92% to 98%. Formulation F1 and F2 contain pure polymer Carbopol and Chitosan and show drug release of 88% at 12 h and 100% at 7

h respectively. Formulations F3 to F8 contain a mixture of different concentrations of polymers with a variable amount of Tween 80. Formulation F3, F4, and F6 contain a high concentration of chitosan and show 99% at 10h, 99% at 8h, and 98% at 10h

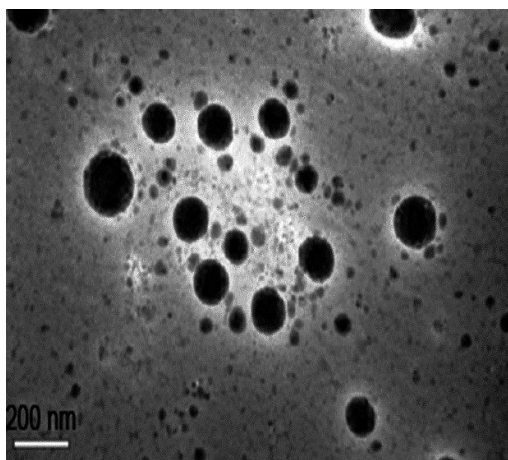


Figure 5. SEM Image of mupirocin loaded niosomal gel for formulation F5

respectively. Formulation F5 and F7 contain a high concentration of Carbopol and show 98% at 12h and 99% at 10h respectively. Formulation F8 contains an equal concentration of Carbopol and Chitosan and shows 99% drug release at 11h. Formulation F5 achieved maximum sustained drug release till 12h. The maximum release might be caused by polymer concentration and viscosity grade and the presence of a nonionic surfactant in the formulation. A high viscosity grade of polymer or a gelling nature of polymer might be a beneficial attribute for topical formulation to keep the drug molecule for a long period and produce a stable plasma drug concentration. Carbopol has gelling properties and demonstrated more regulated release when compared to Chitosan. When comparing Chitosan to Carbopol, Carbopol has a higher viscosity and gelling properties than Chitosan. Because of the greater viscosity grade, Carbopol did not dissolve quickly, which might be a barrier to an aqueous buffer solution, and can readily maintain the active drug release. In some circumstances, the increased viscosity of Carbopol prevents the active medication from being released completely. According to reports, the presence of surfactant Tween 80 in the formulation enhances the entrapment efficiency of the mupirocin drug in the niosome-based gel. Due to the higher concentration of the drug getting entrapped inside the niosome, it

helps Carbopol to sustain the drug and provide better therapeutic efficacy. Chitosan is a natural and low-viscosity grade polymer that cannot regulate the release rate of mupirocin over an extended length of time. As a result, chitosan-based formulations have less control over mupirocin medication release. It was discovered in a few formulations, that when the concentration of Carbopol and Tween 80 increases, drug release decreases. When the mupirocin release is delayed in the formulation that confirms the presence of Carbopol and Tween 80 at higher concentrations. Table 3 & Figure 6 demonstrate the mupirocin drug release from all niosome-based gel formulations (F1 to F8).

4.2.9. Release kinetic study of a mupirocin - loaded niosome-based gel

The in-vitro dissolving investigations were evaluated using zero-order, first-order, Higuchi, and Peppas's equations to determine the correct system of medical discharge from the formulation. The criteria for selecting the best model were based on the highest R^2 value as the best fit. Table 4 displays the results, the drug release followed by zero-order kinetics, independent of concentration. The illustration data fit into Peppas's equation, which depicted non-fickian release, implying diffusion release and a

Table 3. *In-vitro* dissolution of mupirocin-loaded niosomal gel formulations (F1-F8)

Formulation	Time in Hours											
	1hr	2hr	3hr	4hr	5hr	6hr	7hr	8hr	9hr	10hr	11hr	12hr
F1	13.45	19.37	27.31	35.87	41.33	49.37	58.36	68.35	77.31	84.38	87.91	87.98
F2	20.34	35.76	53.26	69.39	81.91	89.21	99.83					
F3	13.83	22.91	31.32	41.72	51.45	61.26	70.18	81.36	90.32	98.81		
F4	12.72	24.41	37.21	50.99	63.21	73.33	87.23	99.21				
F5	10.32	17.37	25.37	33.78	40.98	50.12	58.13	66.17	73.33	82.32	91.09	98.38
F6	11.71	20.31	29.73	39.53	49.45	59.13	69.18	78.36	88.53	98.33		
F7	10.71	20.27	31.32	40.07	49.7	58.26	69.77	79.44	89.34	99.24		
F8	8.82	18.37	27.37	36.78	45.98	56.33	64.29	70.76	80.91	91.32	99.29	

All values in %

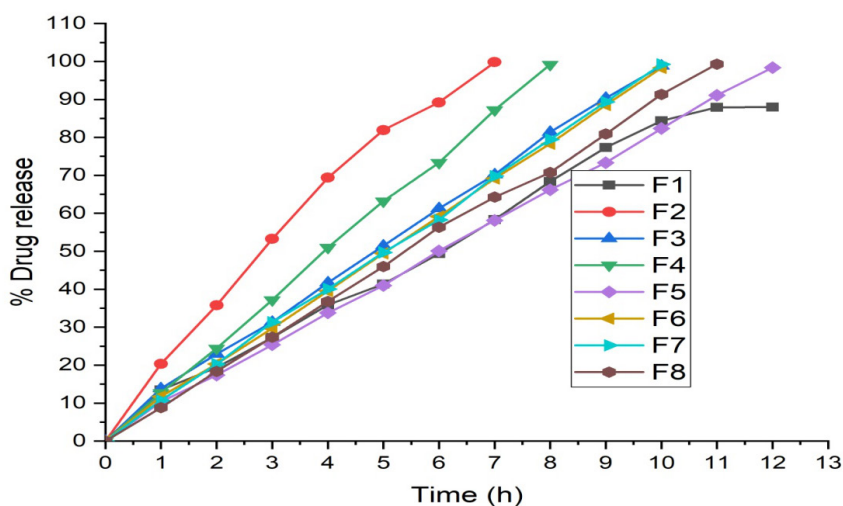


Figure 6. *In-Vitro* diffusion study of mupirocin-loaded niosomal gel formulation (F1-F8)

mixture of diffusion and erosion release of the niosome-based gel. If the diffusional exponent (n) value is less than 0.5, it exhibits fickian diffusion release, and if n is between 0.5 and 0.89, it exhibits nonfickian (anomalous) behavior, i.e., drug release is regulated by both diffusion and erosion, as shown in niosome formulations F1 to F8.

4.2.10. Stability study

The best formulation F5 was subjected to stability at two different temperatures and relat-

ed humidity by keeping the sample in a stability chamber. Every 0, 30, 60, and 90 days interval mupirocin loaded niosomal gel was evaluated for physical appearance, pH, viscosity, Spreadability, and drug release profile shown in Table 5. Obtained results show no change or minor variation in formulation F5, confirming the stability of the mupirocin-loaded niosomal gel.

5. Conclusion

Treatment of persistent, non-healing ulcerative

Table 4. Release kinetics of mupirocin-loaded niosomal gel formulation (F1-F8)

Formulation	R ² Values					Order of release
	Zero-order plots	First-order plots	Higuchi plots	Korsmeyer-peppas plots		
				R ²	Diffusional exponent (n)	
F1	0.988	0.950	0.939	0.773	0.839	Diffusion
F2	0.981	0.700	0.958	0.662	0.895	Diffusion
F3	0.998	0.988	0.991	0.759	0.821	Diffusion
F4	0.999	0.715	0.916	0.763	0.899	Diffusion & Erosion
F5	0.991	0.770	0.925	0.992	0.997	Diffusion & Erosion
F6	0.999	0.764	0.920	0.790	0.89	Diffusion & Erosion
F7	0.999	0.702	0.920	0.800	0.873	Diffusion & Erosion
F8	0.999	0.705	0.923	0.833	0.821	Diffusion & Erosion

wounds presents a significant problem for researchers and physicians. Recently, nanotechnology has drawn attention to improving wound healing by slowing medication release, avoiding degradation, and improving tissue regeneration and retention. In this current research mupirocin gel is a topical skin infection treatment made from niosomes. Niosomes could be a good carrier for targeted drug delivery, protect the drug from rapid degradation, and helps the drug retain the targeted area and ease of penetration. FTIR,

DSC study confirms the compatibility study between drug and other excipients. Carbopol a synthetic polymer and chitosan a natural polymer have been taken at different concentrations to formulate a niosomal gel loaded with mupirocin. Tween 80 significantly enhances drug entrapment efficiency. Obtained results confirm that a high concentration of Carbopol and Tween 80 combined sustained the release rate of mupirocin. Chitosan is a natural polymer unable to sustain the drug release up to an optimum period.

Table 5. Stability study for Formulation F5

Storage condition	Days	Evaluated parameters				
		physical appearance	pH	viscosity	Spreadability	drug release profile (12h)
25°C/60% RH	0	Clear and transparent	6.22	551.3±.11	4.82+0.41	98.16%
	30	Clear and transparent	6.29	550.7±.09	4.79+0.15	97.75%
	60	Clear and transparent	6.3	552.1±.04	4.68+0.8	98.66%
	90	Clear and transparent	6.21	552.11±.11	4.67+0.93	99.1%
40°C/75% RH	0	Clear and transparent	6.3	550.91±.71	4.71+0.82	98.82%
	30	Clear and transparent	6.26	552.61±.77	4.69+0.43	98.42%
	60	Clear and transparent	6.31	553.1±.71	4.66+0.11	97.96%
	90	Clear and transparent	6.24	550.82±.91	4.64+0.52	99.81%

Results are expressed as of mean ±SD (n=3)

Formulation F5 is considered the best formulation by sustaining the release rate of mupirocin 98% at 12 h. The kinetic release data are the best fit for zero-order release kinetics. Obtained data fit for Korsmeyer-Peppas plots and calculate diffusional exponent (n) value and indicate mupirocin drug release following diffusion and erosion mechanism. The noise-based mupirocin-loaded gel is considered a better choice of treatment as per conventional dosage form due to prolonging the release rate of the drug, improving patient compliance, and enhancing penetration properties of the drug.

References

- Priya S.R., Roselin R.B., Karuppiyah A., Sankar V. Formulation of mupirocin adsorbed silver nanoparticle with antibiofilm agents for enhancing antibacterial activity. *Ind. J. Pharm. Edu. Res.* 56(1), 50-7, 2022.
- Mehrarya M., Gharehchelou B., Haghighi Poodeh S., Jamshidifar E., Karimifard S., Farasati Far B., Akbarzadeh I., Seifalian A. Niosomal formulation for antibacterial applications. *J. Drug Targeting.* 30(5), 476-93, 2022.
- Cosco D., Paolino D., Muzzalupo R., Celia C., Citraro R., Caponio D., Picci N., Fresta M. Novel PEG-coated niosomes based on bola-surfactant as drug carriers for 5-fluorouracil. *Biomed. Microdevices.* 11(5), 1115-25, 2009.
- Wu T, Zhu C, Wang X, Kong Q, Guo T, He Z, He Y, Ruan S, Ruan H, Pei L, Zhang Y. Cholesterol and phospholipid-free multilamellar niosomes regulate transdermal permeation of a hydrophobic agent potentially administrated for treating diseases in deep hair follicles. *J. Pharm. Sci.* 111(6), 1785-97, 2022.
- Nikam N.R., Patil P.R., Vakhariya R.R., Magdum C.S. Liposomes: A Novel Drug Delivery System: An Overview. *Asian Pharm. Res.* 10(1), 23-8, 2020.
- Naumov A.A., Shatalin Y.V., Potselueva M.M. Effects of A Nano complex Containing Antioxidant, Lipid, and Amino Acid on Thermal Burn Wound Surface. *Bull. Exp. Biol. Med.* 149(1), 62-70, 2010.
- Abdelkader H., Alani A.W., Alany R.G. Recent advances in non-ionic surfactant vesicles (niosomes): self-assembly, fabrication, characterization, drug delivery applications, and limitations. *Drug delivery.* 21(2), 87-100, 2014.
- Manosroi A., Wongtrakul P., Manosroi J., Sakai H., Sugawara F., Yuasa M, Abe M. Characterization of vesicles prepared with various non-ionic surfactants mixed with cholesterol. *Colloids and Surfaces B: Biointerfaces.* 30, 129-38, 2003.
- Ajrin M., Anjum F. Proniosome: A promising approach for vesicular drug delivery. *Turk. J. Pharm. Sci.* 19(4), 462-475, 2021.
- Rahimpour Y., Hamishehkar H. Niosomes as a carrier in dermal drug delivery. *Recent Adv. Novel Drug Carrier Sys.* 1(1), 141-64, 2012.
- Chen S., Hanning S., Falconer J., Locke M., Wen J. Recent advances in non-ionic surfactant vesicles (niosomes): Fabrication, characterization, pharmaceutical and cosmetic applications. *Eur. J. Pharm. Biopharm.* 144, 18-39, 2019.
- Rajera R., Nagpal K., Singh S.K., Mishra D.N. Niosomes: a controlled and novel drug delivery system. *Biol. Pharm. Bull.* 34(7), 945-53, 2011.
- Yasamineh S., Yasamineh P., Kalajahi H.G., Gholizadeh O., Yekanipour Z., Afkhami H., Eslami M., Kheirkhah A.H., Taghizadeh M., Yazdani Y., Dadashpour M. A state-of-the-art review on the recent advances of niosomes as a targeted drug delivery system. *Int. J. Pharm.* 12(1), 87-98, 2022.
- Barani M., Mirzaei M., Torkzadeh-Mahani M,

Acknowledgments

The authors would like to express their gratitude to the administration and Pharma faculty of Dr. M.G.R. Educational and Research Institute, Deemed to be University, Chennai, Tamilnadu, India, and Ratnam Institute of Pharmacy, Nellore, A.P., India for their motivation and encouragement.

Conflict Of Interest

The authors declared no conflict of interest. □

- Lohrasbi-Nejad A., Nematollahi M.H. A new formulation of hydrophobin-coated niosome as a drug carrier to cancer cells. *Mat. Sci. Eng: C*. 113, 110-122,2020.
15. Mirrezaei N., Yazdian-Robati R., Oroojalian F., Sahabkar A., Hashemi M. Recent developments in nano-drug delivery systems loaded by phytochemicals for wound healing. *Mini Rev. Med. Chem.* 20(18), 1867-78,2020.
 16. Gisby J., Bryant J. Efficacy of a new cream formulation of mupirocin: comparison with oral and topical agents in experimental skin infections. *Antimicrob Agents Chemother.* 44, 255-60, 2000.
 17. Coates A., Hu Y., Bax R., Page C. The future challenges facing the development of new antimicrobial drugs. *Nat. Rev. Drug Discov.* 1(11), 895-910, 2002.
 18. Poovelikunnel T., Gethin G., Humphreys H. Mupirocin resistance: clinical implications and potential alternatives for the eradication of MRSA. *J. Antimicrob. Chemother.* 70(10), 2681-92,2015.
 19. Minhas M.U., Ahmad S., Khan K.U., Sohail M., Abdullah O., Khalid I., Malik N.S. Synthesis and evaluation of polyethylene glycol-4000-co-poly (AMPS) based hydrogel membranes for controlled release of mupirocin for efficient wound healing. *Current drug delivery.* 19(10), 1102-1115,2022.
 20. Sutherland R., Boon R.J., Griffin K.E., Masters P.J., Slocombe B., White A.R. Antibacterial activity of mupirocin (pseudomonic acid), a new antibiotic for topical use. *Antimicrob. Agents Chemother.* 27(4), 495-498,1985.
 21. Thomas C.M., Hothersall J., Willis C.L., Simpson T.J. Resistance to and synthesis of the antibiotic mupirocin. *Nat. Rev. Microbiol.* 8(4), 281-289,2010.
 22. Pappa K.A. The clinical development of mupirocin. *J. Am. Acad. Dermatol.* 22(5), 873-879,1990.
 23. Singh A.P., Gaur P.K., Sharma S.K., Gupta D.K. Formulation and characterization of mupirocin gel and evaluation of *in vitro* antimicrobial activity against staphylococcus aureus. *Eur. J. Mol. Clin. Med.* 7(11), 7491-7501,2020.
 24. Mahalakshmi S., Sankar V. In-vitro antibacterial effect of mupirocin in combination with three essential oils against Staphylococcus aureus. *Int. J. Pharm. Sci. Res.* 11(2), 705-709,2020.
 25. Scepankova H., Combarros-Fuertes P., Fresno J.M., Tornadijo M.E., Dias M.S., Pinto C.A., Saraiva J.A., Estevinho L.M. Role of honey in advanced wound care. *Molecules.* 26(16), 4784-92,2021.
 26. Haque S.E., Sheela A. Miscibility of eudragit/chitosan polymer blend in water determined by physical property measurements. *Int.J. Pharm.* 441,648-53,2013.
 27. Ahmad H., Arya A., Agrawal S., Dwivedi A.K. (2017) Novel lipid nanostructures for delivery of natural agents with antioxidant, anti-inflammatory and antistroke potential: perspectives and outcomes. In: Nanostructures for Oral Medicine. Andronescu E., Grumezescu A.M. (eds) p.p. 577-605. Elsevier Inc.
 28. Singh A.P., Gaur P.K., Sharma S.K., Gupta D.K. Formulation and characterization of mupirocin gel and evaluation of *in vitro* antimicrobial activity against staphylococcus aureus. *Eur. J. Molec. & Clin. Med.* 7(11), 7491-7501,2020.
 29. Sera U.V., Ramana M.V. *In vitro* skin absorption and drug release—a comparison of four commercial hydrophilic gel preparations for topical use. *The Indian Pharmacist.* 73, 356-60,2006.
 30. Acharya A., Dhakal P., Khadka D. Formulation and Evaluation of Transdermal Gel of Lornoxicam and its Delivery by Passive and Inotophoresis Method: A Comparative Study. *Int. J. Pharm. Sci. Res.* 7(2), 810-18, 2016.
 31. Nematollahi M.H., Pardakhty A., Torkzadeh-Mahanai M., Mehrabani M., Asadikaram G. Changes in physical and chemical properties of niosome membrane induced by cholesterol: a promising approach for niosome bilayer intervention. *RSC Adv.* 7(78), 49463-49472, 2017.
 32. Bhattacharya M., Malinen M.M., Lauren P., Lou Y.R., Kuisma S.W., Kanninen L., Lille M., Corlu A., Gu-guen-Guillouzo C., Ikkala O. Nanofibrillar Cellulose Hydrogel Promotes Three-Dimensional Liver Cell Culture. *J. Control Release.* 164(3), 291-298, 2012.
 33. Priprem A., Janpim K., Nualkaew S., Mahakunakorn P. Topical niosome gel of Zingiber cassumunar Roxb. extract for anti-inflammatory activity enhanced skin permeation and stability of compound D. *AAPS Pharmsci Tech.* 17,631-9, 2016.