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Original Research Article

Mupirocin Loaded Niosomal Gel for Topical Wound Healing Applications

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ABSTRACT

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. A lipid hydration technique was employed to formulate niosome with polymers Carbopol and Chitosan at various concentrations. 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 formulation.FTIR and 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. The post-evaluation study was further subjected to an in-vitro diffusion study. The formulation F5 has shown a better sustained release of active drug (98% at 12hr) which contains a higher ratio of carbopol and tween 80. A higher concentration of tween 80 increases the entrapment efficiency of mupirocin in the niosome and carbopol helps to sustain the release rate to an optimum period as a swellable gelling agent.

***Keywords*:** Wound healing, Nanomedicine, Niosomes, Mupirocin gel.

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 structure [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 it. [7-9] The drug was loaded to the vesicle at a minimum concentration to produce fewer side effects and stability and modified the release pattern.[10]

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The non–ionic surfactants and the additive cholesterol together help to form a bilayer membrane and improve drug permeability and solubility.[11-13] Niosome as a carrier protects the drug from unwanted immunological effects, rapid degradation, and instability.[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, pasteurellamultocida*, etc.) can be controlled by mupirocin.[16] Resistance gradually increases by the bacteria towards the active drugs which is a major concern for researcher.[17-21] 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.[22-24] Mupirocin with unique mechanism action is converted to monic acid20 and excreted through urine once it reached systemic circulation. Also, mupirocin can kill antibiotic-resistant bacterial strains such as methicillin-resistant Staphylococcus aureus (MRSA),[25] and the wound healing ability is also related to its capacity to promote re-epithelialization and angiogenesis and stimulate skin and immune cells.[26]

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.

Materials and Methods

Materials

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.

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

Preparation of mupirocin-loaded niosome

The lipid hydration method is used for the preparation of multilamellar vesicles of niosome represent in Table.1.[27] 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.

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 gel.[28]

Evaluation of mupirocin-loaded niosomal gel

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 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 formula 1

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

Yield percentage

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 2.

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

Drug content

Niosomal gel 1 gm dissolved in 50mL volume of 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 spectrophotometer at 226 nm.

Determination of pH

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.

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.

Spreadability

Spreadability is determined for all the formulations. 1 gm of niosomal gel was weight and applied in between the glass plates.[29] After a minute the diameter of the circle formed between two glass plates was measured and the average is taken into consideration.

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.

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 (Mınıpore white cellulose nitrate membrane filter paper, pore size: 0.45µm & 0.22µm). 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±0.5^{O}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.

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 R^2 value also known as the correlation coefficient value indicates the best fitting of the release kinetics of any of the models.

Table 1: Formulation of mupirocin-loaded niosomal gel 2% (Net Weight 15g)

Formulation	Drug	CP	CH	TWEEN 80
F1	2	5	-	4
F2	2	-	5	4
F3	2	2	3	5
F4	2	1	4	6
F5	2	4	1	6
F6	2	2	3	3
F7	2	3	2	3
F8	2	2.5	2.5	5

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

*all formulation contained Cholesterol 8%w/w, Glycerin 5%w/w, methyl paraben 0.22%w/w and distilled water q.s.

Stability studies
The best formulation F5 was taken for the stability test. The stability test was carried out as per ICH guidelines at 25ºC with 60% RH and 40ºC with 75% RH for 90 days.[30] Any changes in physical appearance, pH, viscosity, Spreadability, and drug release profile.

Results and Discussion

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.

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 and 4.

Evaluation study of mupirocin-loaded niosomal gel
The 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 of cholesterol makes the niosomes leak proof [31] and the lipid hydration method enhances the entrapment efficiency of the aqueous phase and permeability. Nonionic surfactants also played an important role in increasing the entrapment efficiency of the drug in the current formulation of niosome.[32]

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.

Drug content
The drug content was estimated for all the formulations 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.

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.

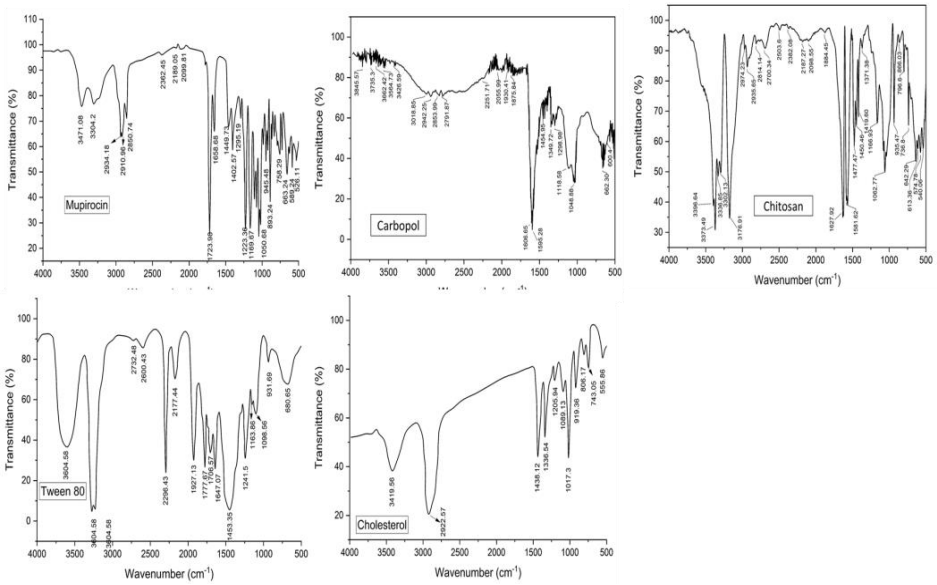

Figure 1: FTIR spectra of pure drug and excipients

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.

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.

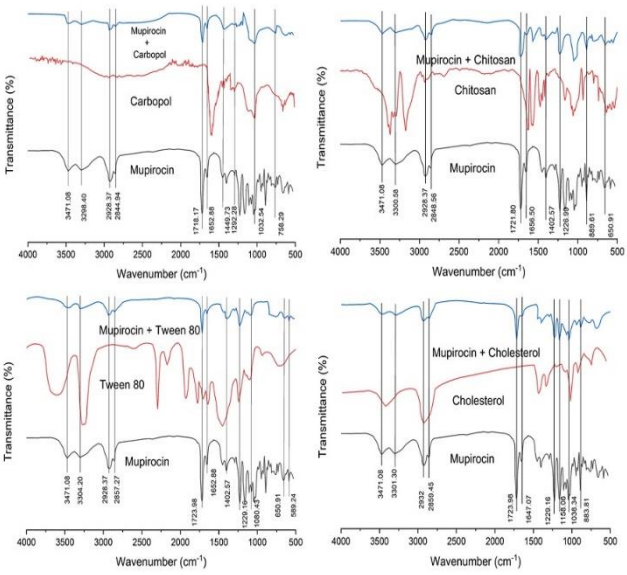

Figure 2: FTIR Spectra of mupirocin with excipients

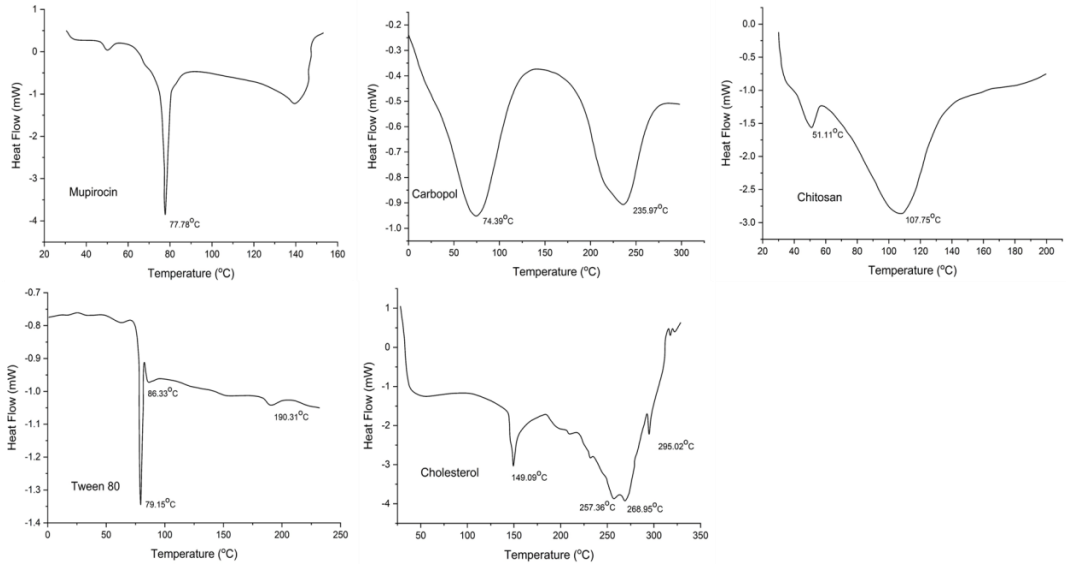

Figure 3: DSC spectra of pure drug and excipients

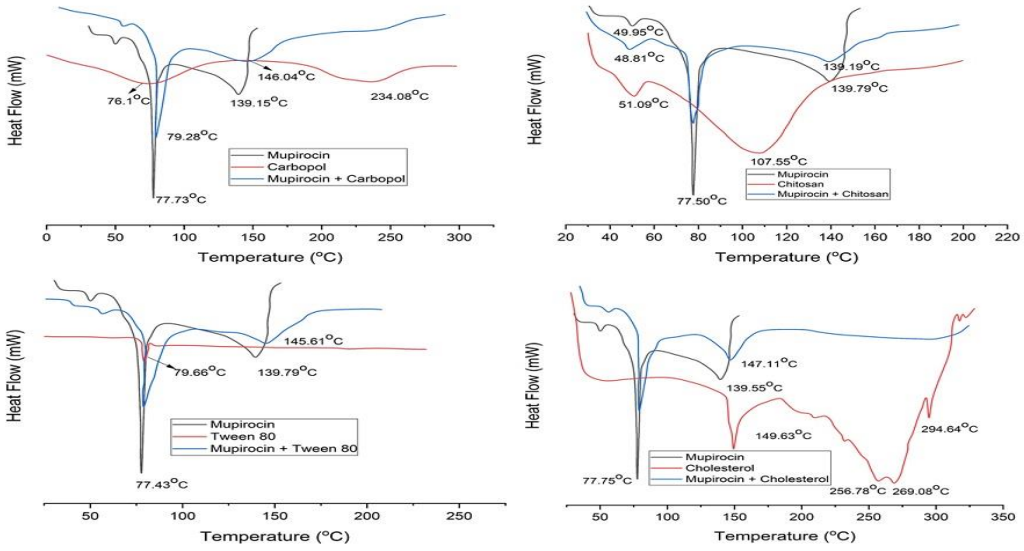

Figure 4: DSC Spectra of mupirocin with excipients

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 ±SD (n=3)

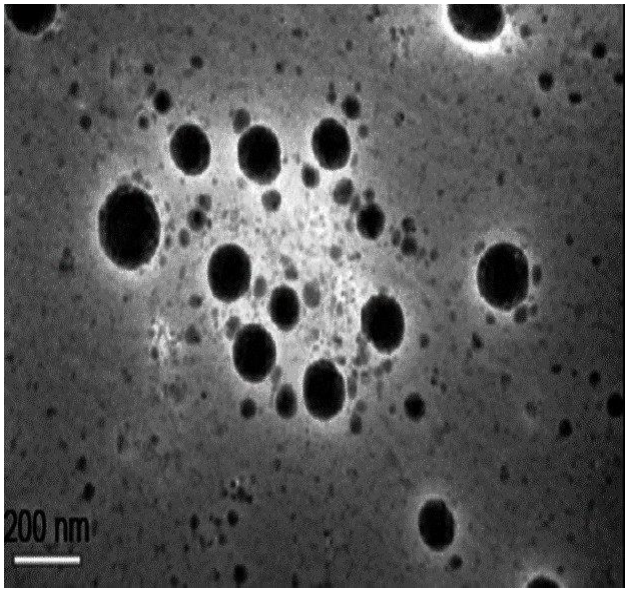

Figure 5: SEM Image of mupirocin-loaded niosomal gel for formulation F5

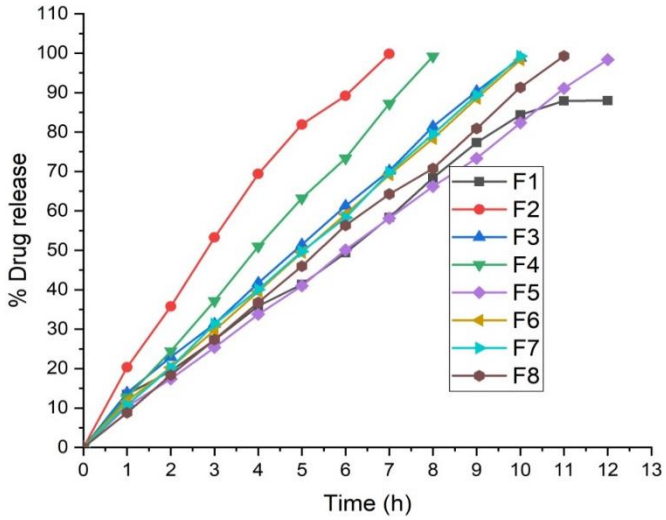

Figure 6: *In-vitro* diffusion study of mupirocin-loaded niosomal gel formulation (F1-F8)

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 spherical shape, as shown in Figure 5.

In-vitro diffusion study

The dissolving study was carried out in triplicate using the diffusion medium phosphate buffer with a 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 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. Figure 6 demonstrates the mupirocin drug release from all niosome-based gel formulations (F1 to F8).

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

The in-vitro dissolving investigations were evaluated using zero-order, first-order, Higuchi, and Peppa'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 3 displays the results, the drug release followed by zero-order kinetics, independent of concentration. The illustration data fit into Peppa's equation, which depicted non-fickian release, implying diffusion release and a 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.

Stability study

The best formulation F5 was subjected to stability at two different temperatures and related 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 4. Obtained results show no change or minor variation in formulation F5, confirming the stability of the mupirocin-loaded niosomal gel.

Conclusion

Treatment of persistent, non-healing ulcerative 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. 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. 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 niosome-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.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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Table 3: Release kinetics of mupirocin-loaded niosomal gel formulation (F1-F8)

Formulation	R^2 Values					
	Zero-order plots	First-order plots	Higuchi plots	Korsmeyer-peppas plots		Order of release
				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

Table 4: Stability study for Formulation F5

Storage condition	Days	Evaluated parameters				
		Physical appearance	pH	Viscosity	Spreadability	Drug release profile (12h)
25ºC/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%
40ºC/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)

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