International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 2006-2017 www.ijprajournal.com ISSN: 2456-4494

Formulation and Evaluation of Delafloxacin Loaded Niosomal Gel for the Treatment of Acute Bacterial Skin and Skin Structure Infection.

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Submitted: 18-04-2024 Accepted: 28-04-2024

ABSTARCT: For the last 30 years, acute bacterial skin and skin structure infection (ABSSSI) has caused 2% of all hospitalizations and 14.2 million visits per year in the US and in India is about 29-32%. For the treatment of ABSSSI, many marketed Formulations are available like tablets and injections with many lacunas like first-pass metabolism, less patient compliance, and dosing frequency. So, in this study, a niosomal gel that contained Delafloxacin was produced to aid patients treat ABSSSI.This study focuses on developing a topical gel Formulation that will help the patients with the application of the medication. Non-ionic surfactant vesicles were used for the transport of the drug considering the capabilities of the carrier it can improve the permeability of the drug through the skin and it can carry both hydrophilic and hydrophobic drugs. 12 Batches of niosomes were prepared using various surfactants and cholesterol combinations with different ratios. % Entrapment efficiency, Vesicle size, PDI, and other parameters are checked. All formulations produced satisfactory results for tested parameters. The result indicates that the formulation DL 2 (Span 60) was better than other batches. The optimized formulation % entrapment efficiency was found to be 87.98 ± 1.895, Vesicle size 576nm, and PDI 0.346. The niosomes gel was preparedwith the help of Carbopol 934 and Triethanolamine. Carbopol 934 was selected as the suitable gelling agent. Different evaluation parameter of niosomal gel was evaluated in which viscosity was found to be 9476(±0.08) and Spreadability was found to be 8.16 gm.cm/sec. After examining these parameters, it was concluded that niosomal gel can effectively cure ABSSI.

Keywords: Niosomal gel, Delafloxacin, ABSSSI, Topical drug delivery, Non-ionic surfactant.

I. INTRODUCTION:

Acute Bacterial Skin and Skin Structure Infection:

For the last 30 years, complicated skin and skin structure infections (cSSSIs) and more recently acute bacterial skin and skin structure infections (ABSSSIs) have placed an increasing burden on healthcare systems globally. Acute bacterial skin and skin structure infections (ABSSSI), formally referred to as complicated skin and soft tissue infections, include infections with resistance to previously effective antimicrobials. [1] Infections due to bacteria with resistance to previously effective antimicrobials such as methicillin-resistant Staphylococcus aureus (MRSA) are increasing in incidence and have led to higher rates of complications and hospitalization. [2]

Symptoms of ABSSSI may depend on the type of infection but can include swelling, inflammation, tender or sore skin, skin that is warm to the touch, crusting, and blisters. Symptoms of ABSSSI may depend on the type of infection but can include swelling, inflammation, tender or sore skin, skin that is warm to the touch, crusting, and blisters. Diagnosis is based on clinical presentation, the bacterial etiology of cSSSIs and ABSSSIs is confirmed in over 60% of cases, and the evidence suggests the predominance of Gram-positive bacteria. The selection of antibiotics is primarily empirical for ABSSSI patients which subsequently can be adjusted based on culture results, which is rarely available in outpatient management. [3]

II. MECHANISM OF ACTION:

Beta-lactam antibiotics inhibit bacterial peptidoglycan synthesis by binding the penicillin-binding proteins (PBPs) in the bacterial cell wall. Inhibition of PBPs leads to irregularities in cell wall structures, such as elongation, lesions, loss of selective permeability, and eventual cell death and lysis.

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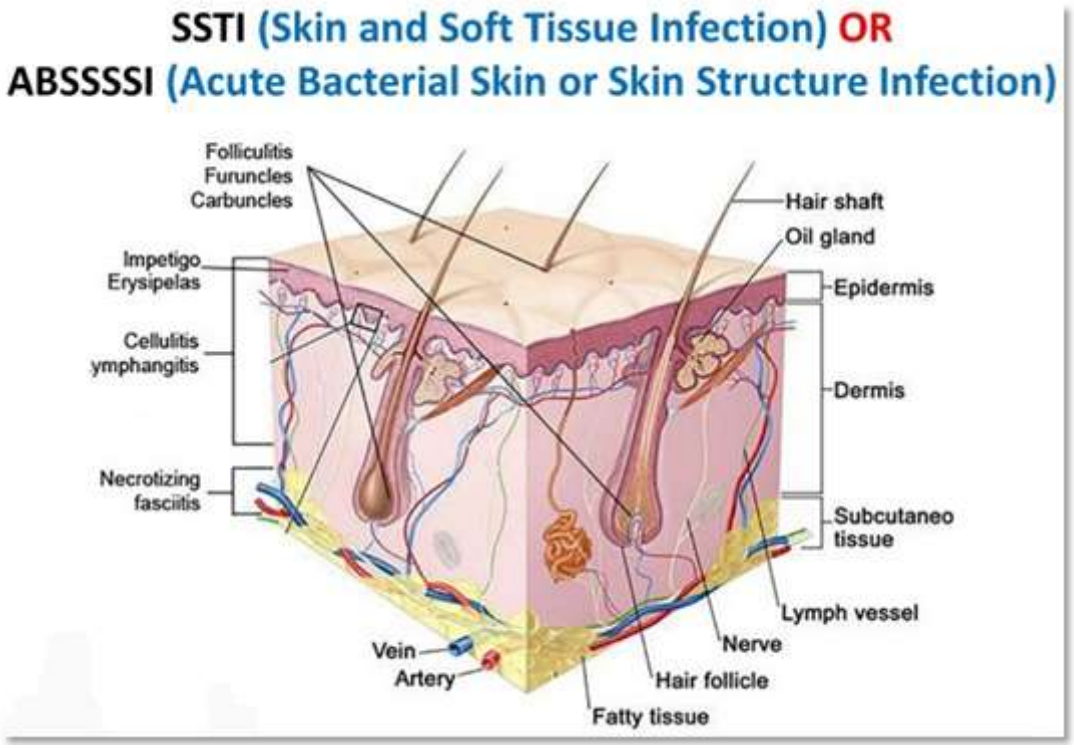

Fig 1. Necroinflammation in gout

III. CLASSIFICARION OF NEW DRUGS FOR THE TREATMENT OF ABSSSI:

FDA approval of serval newer antibiotics for the treatment of ABSSSIs, including dalbavancin, oritavancin, tedizolid, delafloxacin. Vancomycin, linezolid, tigecycline, daptomycin, ceftaroline and telavancin are all are considered appropriate antimicrobial agents for treatment of serve purulent infection. While trimethoprim-sulfamethoxazole and doxycycline are recommended for moderate purulent infections.

IV. Antibiotic treatment option for ABSSSI:

[1] BETA-LACTAMS: Ceftaroline, a beta-lactam, is an initial treatment option for patients with ABSSIs, providing broad-spectrum activity against gram-positive and some gram-negative bacteria, and demonstrating low potential for in vitro resistance. [4]

[2] CYCLIC LIPOPEPTIDES: Daptomycin, a daily cyclic lipopeptide, has a rapid, concentration-dependent bactericidal activity against gram-positive pathogens like MRSA and vancomycin-resistant pathogens, with a clinical success rate of 83.4%. [5]

[3] FLUOROQUINOLONES:

Fluoroquinolones like ciprofloxacin, levofloxacin, and moxifloxacin aren't commonly used for MRSA-induced ABSSSIs due to their decreased susceptibility. Delafloxacin, a non-zwitterionic fluoroquinolone approved by the FDA in 2017, offers broad-spectrum activity for gram-positive infections. [6]

[4] GLYCOPEPTIDES: The IDSA guidelines recommend vancomycin as a first-line treatment for MRSA-induced ABSSSIs, with nephrotoxicity being the most serious adverse event, and the combination with piperacillin-tazobactam has been linked to acute kidney injury. [7]

[5] GLYCYLCYCLINES: Tigecycline is an IV broad-spectrum glycylcycline with in vitro activity against various organisms and multidrug-resistant pathogens, showing no cross-resistance with other antibiotic classes. [8]

[6] LIPOGLYCOPEPTIDES: Dalbavancin and oritavancin are lipoglycopeptide class IV options, with dalbavancin being noninferior to vancomycin and oral linezolid for treating ABSSSI with less frequent adverse events. [9]

[7] OXAZOLIDINONES: Linezolid, available in IV and oral forms, is effective against resistant gram-positive organisms like MRSA, VRE, and macrolide-resistant streptococci, with higher clinical and microbiological success rates in patients with renal insufficiency. [10]

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[8] TRIMETHOPRIM SULFAMETHOXAZOLE AND CLINDAMYCIN: Recent trials show trimethoprim-sulfamethoxazole and clindamycin are effective in treating uncomplicated ABSSSIs, with higher cure rates and comparable effectiveness in cutaneous abscesses and wound infections. [11]

V. STRUCTURE OF NIOSOMES:

Niosome are spherical and consist of microscopic lamellar structure. The vesicles consist of bilayer amphiphilic molecules that surround an aqueous compartment. [12] Niosomes are vesicles of non-ionic surfactant and cholesterol that act as a carrier for amphiphilic and lipophilic drugs. [13]

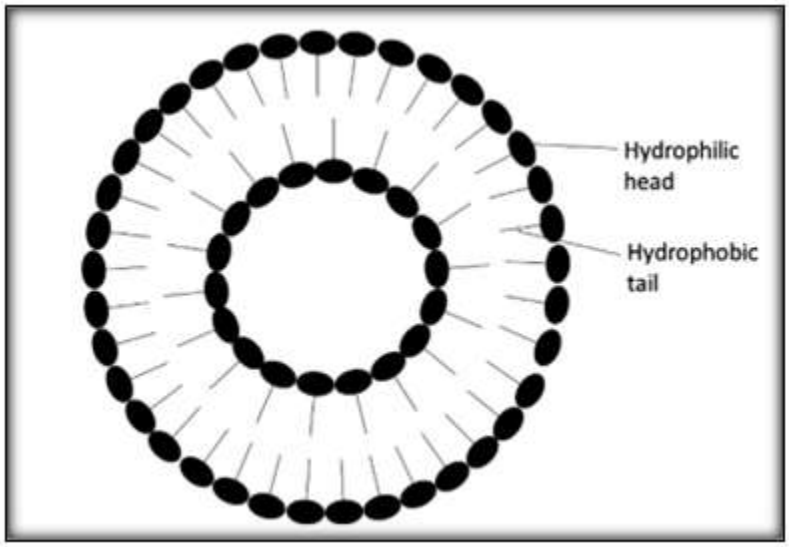

Fig 2. Structure of Niosome

VI. METHOD OF PREPARATION:

Preparation of niosomes begins with the hydration of a surfactant and lipid mixture at elevated temperatures, followed by optional niosome size reduction to obtain a colloidal suspension [14]

(A) Preparation of small unilamellar vesicles:
- I. Sonication
- II. Micro fluidization

(B) Preparation of multilamellar vesicles:
- I. Hand shaking method
- II. Trans-membrane pH gradient drug uptake process

(C) Preparation of large Unilamellar Vesicles:
- I. Reverse phase evaporation technique
- II. Ether injection method

(D) Miscellaneous:
- I. Multiple membrane extrusion method
- II. The “bubble” method
- III. Formation of niosomes from proniosomes
- IV. Emulsion method
- V. Lipid injection method
- VI. Niosome preparation using Micelle
- VII. Niosome preparation using polyoxyethylene alkyl ether

VII.TOPICAL GEL:

Topical drug delivery are dosage formthat involves drug transport to viable epidermal and or dermal tissues of the skin for local therapeutic effect while a very major fraction of the drug is transported into the systemic blood circulation. [15]

Topical administration of therapeutic agents offers many advantages over conventional oral drug delivery.Several important advantages of topical drug delivery are the limitation of hepatic first-pass metabolism, enhancement of therapeutic efficiency, and maintenance of steady plasma level of the drug.Topical gel preparations are intended for superficial skin application or to some mucosal surfaces for local action or skin penetration of medicament or for their soothing or protective action. [16]

METHOD AND MATERILAS:

Preparation for Delafloxacin loaded noisome:

Step 1: Dissolve Ingredients like drug, surfactant, and Cholesterol in selected organic solvent

Step 2: By using a vacuum rotary evaporator, organic solvent was removed at room temperature

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Step 3: Formation of dry thin film on the surface of the flask wall
Step 4: The vesicles were formed by rehydrating the dry surfactant film with the help
of a rotary evaporator without vacuum with 15 ml phosphate buffer saline pH 7.4 which contained the drug and was kept at 60°C to eliminate any traces of organic solvent
Step 5: The finished niosomal suspension was kept in the refrigerator for further investigation.

VIII.TRAIL BATCHES OF NOISOME :

Table 1 Trail Batches of Niosomes

Sr. No.	Record	Surfactant	Molar ratio	Amount of Drug (mg)
1	NG1	Span 60	1:1	100
2	NG 2	Span 80	1:1	100
3	NG 3	Tween 60	1:1	100
4	NG 4	Tween 80	1:1	100

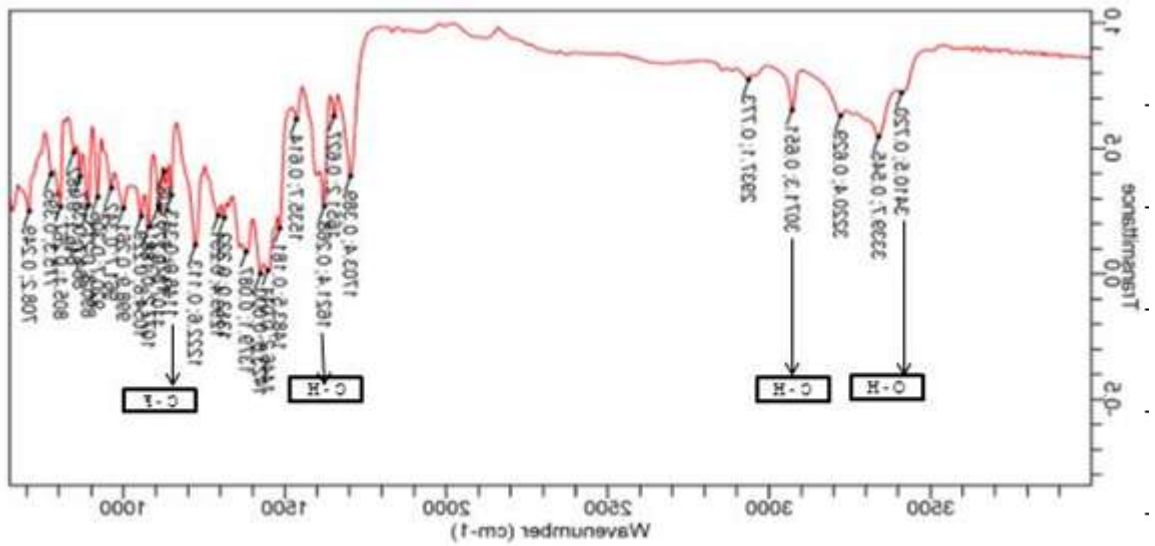

Fig 3. Identification of Drug by FT-IR study

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IX.ORGANOLEPTIC PROPERTIES OF DELAFLOXACIN:

Table 2 Organole[ptic properties of Delafloxacin

Properties	Standard	Result
State	Solid	Solid
Color	Yellow	Yellow
Odor	Odourless	Odourless

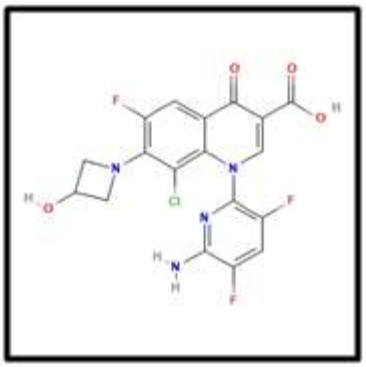

Fig 3. Chemical structure of Delafloxacin

Melting point delafloxacin

Table 3 Melting point Delafloxacin

Drug	Reported value	Observed values n=3; Mean (±SD)
Delafloxacin	225-229 °C	227.57 ± 0.84 °C

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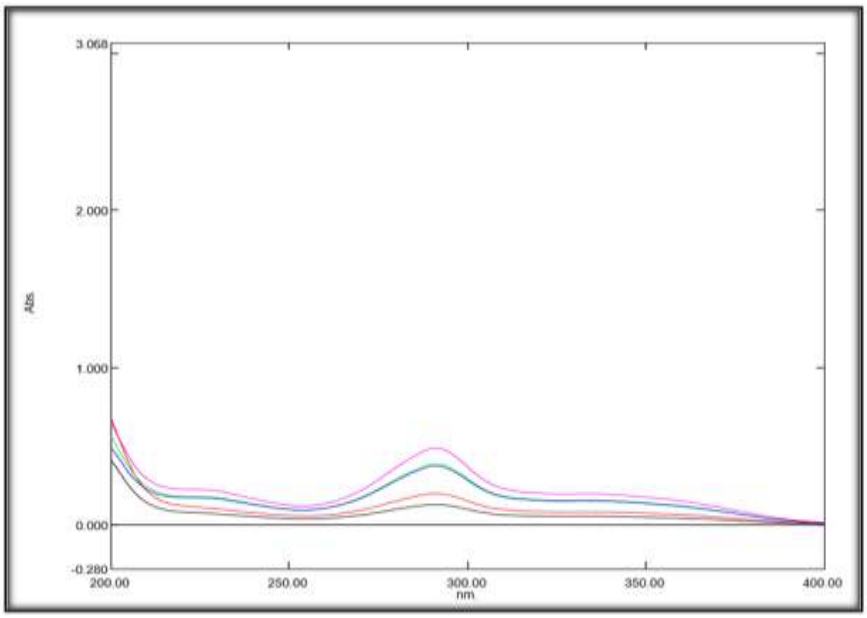

Fig 4. Linearity plot of Delafloxacin

Linearity plot of delafloxacin

Table 4 Standard calibration curve of Delafloxacin

	(µg/ml)	(Mean ± SD) (n=3)
1.	2	0.245 ± 0.003
2.	4	0.368 ± 0.004
3.	6	0.478 ± 0.006
4.	8	0.582 ± 0.007
5.	10	0.692 ± 0.064

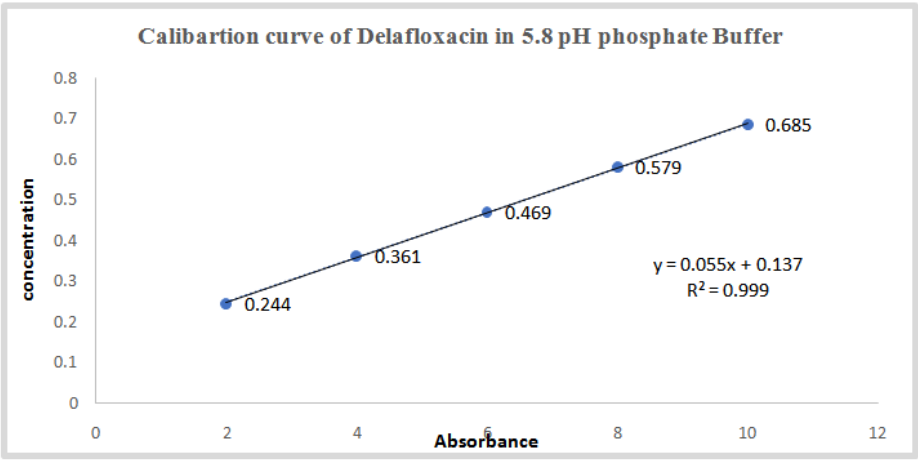

Fig 5. Standard Calibration Curve of Delafloxacin summary

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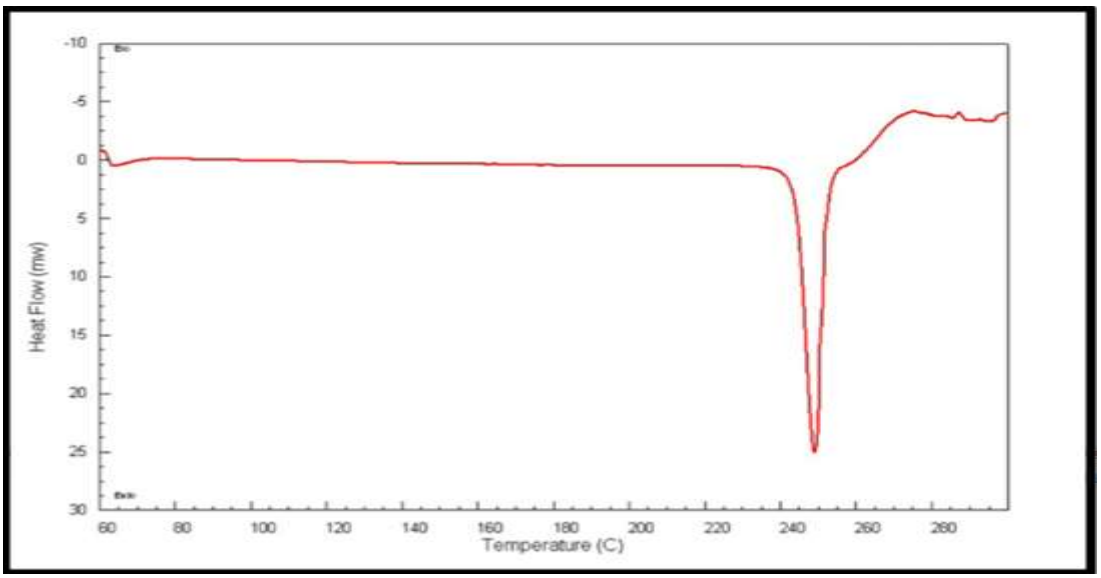

Fig 6. DSC Thermal analysis results of Delafloxacin

Table 5 Niosomes batches

Ingredients	DL 1	Dl 2	DL 3	DL 4	Dl 5	Dl 6	Dl 7	Dl 8	Dl 9	Dl 10	Dl 11	Dl 12
Delafloxacin	250	205	205	250	250	250	250	250	250	250	250	250
Cholesterol: Surfactant ratio	1:1	1:1.5	1:2	1:1	1:1.5	1:2	1:1	1:1.5	1:2	1:1	1:1.5	1:2
Cholesterol (mg)	100	100	100	100	100	100	100	100	100	100	100	100
Span 60 (mg)	100	150	200	-	-	-	-	-	-	-	-	-
Span 80 (mg)	-	-	-	100	150	200	-	-	-	-	-	-
Tween 60 (mg)	-	-	-	-	-	-	100	150	200	-	-	-
Tween 80 (mg)	-	-	-	-	-	-	-	-	-	100	150	200
PBS(ml)	10	10	10	10	10	10	10	10	10	10	10	10

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Table 6 Preliminary Trail batches for screening of surfactant

Sr. no.	Formulation code	Surfactant	Entrapment Efficiency (%)	Vesicle Size (nm)	PDI
1.	NG 1	Tween 80	87.98 ± 1.895	370	0.456
2.	NG 2	Tween 60	85.2 ± 1.181	359	0.664
3.	NG 3	Span 60	89.89 ± 1.895	576	0.346
4	NG 4	Span 80	81.81 ± 0.925	523	0.675

Fig 6. Niosomes Bacthes

X. EVALUATION OF DL 2 BATCH OF NOISOME:

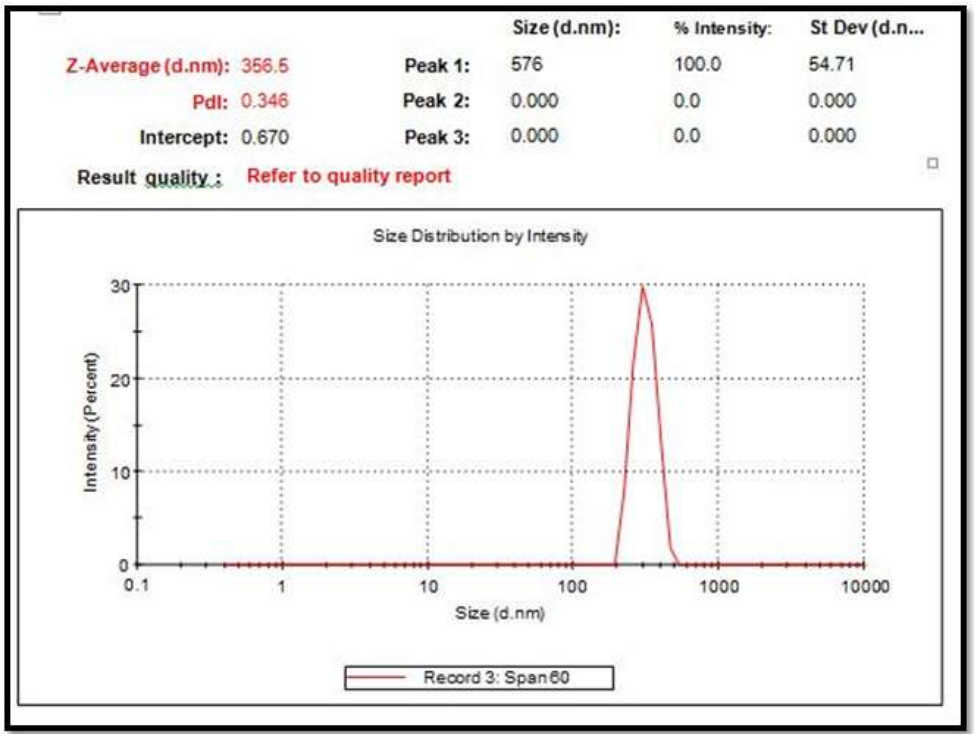

Fig 7. Dl 2 Batch DLS report

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Particle size

Batch no.	Particle Size (nm)	% Intensity
NG 8	187.2	100

Table 7 Determination of Particle Size

Entrapment Efficiency of DL 2 Batch

Batch No.	Entrapment Efficiency (%)
DL 2	87.98 ± 1.895

Table 8Entrapment efficiency

Surface Morphology of Niosomes

Fig 9. Niosomal Gel

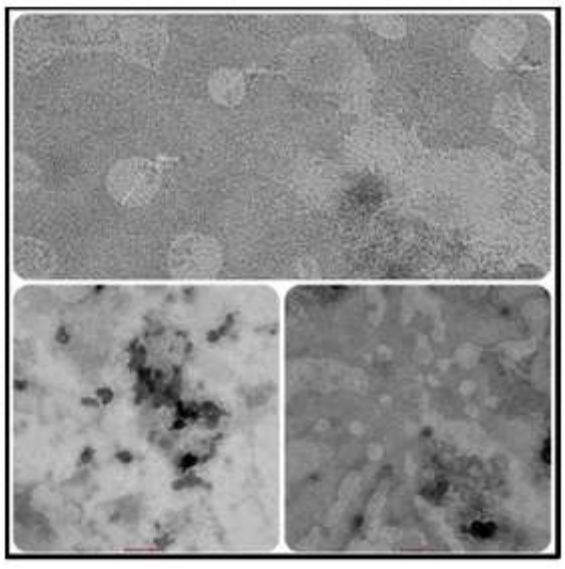

Fig 8. Images of niosomes by TEM

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DISCUSSION

The morphological characteristics of a dispersed system can be examined using TEM analysis. As seen in the TEM images of the representative spherical shape in the figure, the particle size was similar to the results of the particle size analysis

XI. EVALUATION OF TOPICAL NIOSOMAL GEL:

Physical Appearances

The optimized niosomal gel was found to be white, homogenous, and smooth in texture and no phase separation was observed

Measurement of pH

The pH of the formulated niosomal gel was measured. It was found to be 6.94±0.1464.

Table 9 Measurement of pH

Sr. No	Formulation	pH	Mean	SD
1	NG 1	7.1		
2	NG 2	6.81	6.943	0.1464
3	NG 3	6.92		

Viscosity

The viscosity of the optimized niosomal gel was tested with a digital Brookfield viscometer. The viscosity of niosomal gel formulations was found to be 9476(±0.08) cps

Spreadability

The Spreadability of niosomal gel is determined by placing 0.5 g of respective gel within a circle of diameter 1 cm, pre marked on a glass plate over which a second glass plate is placed a weight of 500 g is allowed to rest on the upper glass for about 5 min

The Spreadability was found to be **8.16 gm.cm/sec**

In-Vitro % Drug Release Study

Sr. No.	Time (hr)	Absorbance
1.	1	15.67
2.	2	32.53
3.	3	51.34
4.	4	71.86
5.	5	74.04
6.	6	76.25

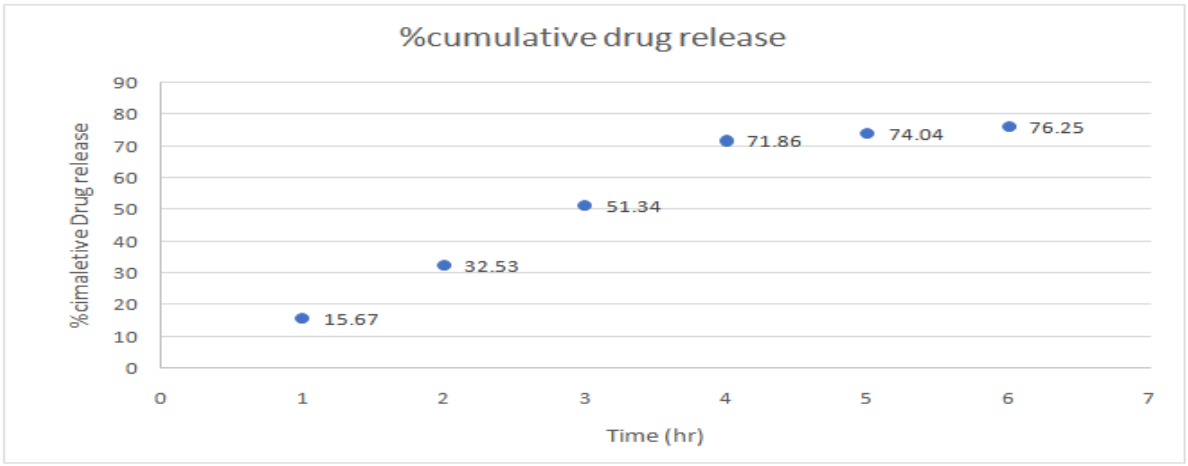

Fig 10. In-vitro Drug release

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Stability studies

Sr. No.	Time (hr)	Absorbance
1.	1	15.67
2.	2	32.53
3.	3	51.34
4.	4	71.86
5.	5	74.04
6.	6	76.25

XII. CONCLUSION:

The present study successfully developed a Niosomal Gel using Delafloxacin for ABSSSI. Niosomal Gel formulas containing Cholesterol and non-ionic surfactant were successfully prepared with the different ratios and Physical parameters, pH, Stability, and Spreadability, were evaluated. Total 12 Formulations (DL 1 –DL 12) Demonstrate among them formulation DL 2 Showed more significant and promising results along with a good cure rate against ABSSSI. Hence, the topical Niosomal Gel of Delafloxacin would have to be a better alternative as a topical drug delivery system for the treatment of ABSSSI.

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