Original Article

PREPARATION AND EVALUATION OF NIOSOMAL HYDROGEL OF AMIKACIN AND ITS BIOLOGICAL EVALUATION

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Abstract

Three different works combine to form a HF-3 dosage form, which is best on the basis of drug diffusion, in-vitro mucoadhesion and viscosity high solubility and, ease to use with adhesive nature over the skin, all three advantages are a must whenever we talk about the dermal formulation. The same happens with the drug amikacin, whose stability with minor solubility enhanced by the solid dispersion formation and encapsulated inside the vesicles called niosomes for sustained release and easy to adhere over the wound surface and finally, niosomes are encapsulated in hydrogels which provides the adhesive nature with easy to apply surety, at the same time it is able to provide a cooling sensation with surety to cure the wound. Also, drug and excipients have no interaction with each other and are quite stable in all dosage forms. Lastly all niosomal and hydrogel formulation compare with each other and proof that NF-8 as niosomal preparation and HF-3 as hydrogel preparation are overall best formulation and selected on the basis of many evaluation parameters. Finally one can conclude that whenever we select an oral route for targeting wound, there is a problem face by patient-related with improper amount of drug reached to the selected area and dose-related side effects and lastly patients non-compliance with tablet, for all this type of problems we can use the drug to be apply over the wound directly and for this prepared formulation NF-3 is best among all other formulation in case when we want to decrease dose frequency, directly applicable procedure and easy to use, and did not want any dose-related side effects as very less amount of drug used which is directly apply over wound and lastly slow or sustained drug release with almost whole drug penetrate from the wound which further help in heal the wound in less time duration.

Keywords: Niosomes, Amikacin, Hydrogel, Characterization.

Introduction

In many cases, just the administration of broad-spectrum systemic antibiotics is necessary to treat a mild postoperative infection. Due to their wide range, ability to penetrate and cure bacterial cells, and limited toxicity to bacteria, these antibiotics are effective against uncomplicated infections while causing minimum harm to the host. Failures in systemic antibiotic treatment are possible, and they may be both costly and harmful [1].

Antibiotics often fail to work because they cannot penetrate poorly vascularized tissues, such as those seen in gaps between joints, diabetic ulcers, irradiated tissues, or abscess holes. In addition, it is far more difficult to eradicate

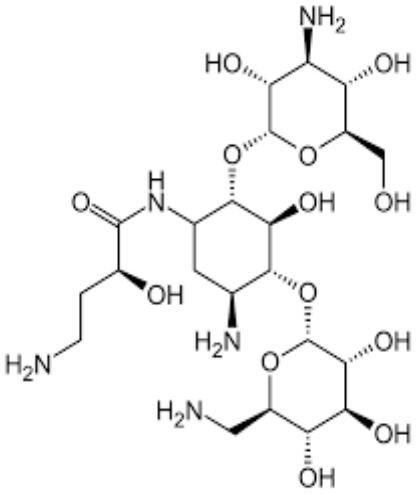
the bacteria that have attached themselves to any foreign bodies (FBs) in the region. Another frequent reason antibiotics don't function is necrotic tissue, which may be caused by injury, cauterization, or fibrin deposits [2].

If therapeutic local antibiotic concentrations could be maintained for sufficient time to kill the organisms, local delivery of an antibiotic could be more successful than the standard systemic therapy in many of these conditions. Nonetheless, standard antibiotics have too short of a half-life, making it impractical to inject or infuse them repeatedly at local sites of illness [3].

With the use of a slow-release antibiotic formulation injected directly into the sites of infection, it is feasible that therapeutic local medicine concentrations might be maintained and systemic exposure to potentially harmful chemicals could be averted. Selection may also be used to stop resistant organisms from travelling to far-flung regions. Slow-release gentamicin-impregnated polymer beads injected locally have shown efficacy in treating infections in a variety of sites, including prosthetic joints, vascular grafts, soft tissues, and contaminated cavities. Unfortunately, they have a number of serious limitations that greatly limit their use. Once the antibiotic has done its job, any residual polymer beads might act as FBs and promote infection if they aren't discarded [4].

They are often removed through surgery performed under general or regional anaesthesia. Since these restrictions exist, gentamicin-impregnated polymer beads cannot be used for prophylactic purposes. DepoFoam is a lipid-based drug delivery technology that we developed, and inside it, amikacin sulphate is encapsulated for sustained release. The foundation of this drug delivery system is microspheres manufactured from amphipathic lipids, which are synthetic, biodegradable analogues of lipid bilayers found in cell membranes [5].

Fig. 1: Structure of Amikacin



Methodology:

Method of preparation of niosomes

Different surfactant-to-cholesterol ratios were used to synthesise niosomes, but the final drug concentration was held constant. The niosome formulations were prepared via thin-film hydration. Five millilitres of a solvent combination containing non-ionic surfactants (span 20, span 40, and span 60) were weighed (Chloroform: Methanol 2:1 ratio). Then, using a graduated cylinder, it was transferred to a 100-milliliter round-bottom flask. The researchers used a revolving flash evaporator spinning at 100rpm and 55°C to generate the ultra-thin layer. After the organic solvent evaporated, a dry coating was left on the sides of the flask. After coating a round-bottom flask with a thin layer of surfactant and cholesterol, 10 ml of phosphate-buffered saline at pH 7.4 was added, and the mixture was vortexed continuously for 45 minutes at 55°C to ensure a uniform dispersion of the components. The niosomal suspension was stored at 2-8 degrees Celsius for 24 hours [6].

Characterization of Niosomes

IR Spectrum Analysis

Here FTIR spectra is used to find out any variation which occur in solid dispersion during niosomal preparation, in which we noticed that in case of solid dispersion in between amikacin and lactose peaks was observed at 3362 cm^{-1} which shows a presence of O-H stretching which also found in lactose and in amikacin, second peak was found at 2954 cm^{-1}, which proved C-H group is present. Last two characteristics peaks was noticed at 1647 cm^{-1} and 1591 cm^{-1} which prove the presence of C=O and N-H and both peaks was also noticed in drug and polymer [7]. Whereas in case of span's and cholesterol peaks was observed at 3250 cm^{-1}, 2917 cm^{-1}, 1736 cm^{-1} and 1490 cm^{-1} due to the presence of C-O, C-H, C=O and N-H. In case of complex B which is a FTIR spectra of prepared niosomes and contains various span's, cholesterol and solid dispersion, proof that all the respective peaks of solid dispersion and span's with cholesterol are observed in complex B, just like 2921 cm^{-1}, 2065 cm^{-1}, 1736 cm^{-1} and 1485 cm^{-1} proving the presence of O-H, C-H, C=O and N-H group at their exact peaks with minor adjustments which occur because of formation of niosomes [8].

Scanning Electron Calorimetry

SEM study was performed to check out the vesicle's size, structure and surface morphology. After seen image given below, one can confirm that the niosomes was prepared with irregular structure and most of the niosomes was reported as a oval structure with uniform size. Niosomes are found in a bunch which proved that they have low polydispersity index or can say that they have charge related issue because of which after few days vesicles may form heavy bunch like structure [9].

Evaluation Parameter of Vesicles

% Entrapment efficiency

Entrapment efficiency denoted to the amount of drug in percent captured by the vesicles which is totally depends on surfactant and cholesterol concentration. when we check out down side from formulation F1 to F9 we notice that the mean entrapment efficiency of formulation containing span 85(N1-N3) and span 85(N4-N6) have lower in comparison with span 60(N7-N9) this is because of the reason that those spans have lower HLB values must have higher number of unsaturated alkyl chains which is generally responsible for the leakage and cause reduction in the entrapment efficiency, that is why span 60 contain by formulations N7—N9 have higher entrapment efficiency than others. Whereas in case of cholesterol first entrapment efficiency increase at the concentration of 0.25% w/v and 0.5 % w/v but further enhancement of the concentration from 0.75% w/v of cholesterol decrease the entrapment efficiency this happen because of the reason that cholesterol is able to enhance the hydrophobic behavior with vesicles bilayers stability which cause reduction in permeability and entrapment efficiency enhanced which is clearly noticeable in case of formulation N1,N2,N4,N5,N7,N8 but when we enhance the concentration of cholesterol beyond the limit of 0.5% found in formulation N3,N6 and N9 then we found reduction in entrapment efficiency as cholesterol concentration enhance inside the vesicles because of which drug have less area to pack themselves [10].

Vesicle Size

After seen the result one can conclude that the size of the niosomes depends on the type and concentration of surfactant and cholesterol. When we checkout the results, we noticed that when we move from formulation N1-N3 to N4-N6 and to N7-N9, a vast enhancement in mean particle size of niosomes was found this is because of the variation in HLB value of different surfactants used to prepare niosomes. Span 60 have highest HLB values (4.7) and obtain with highest mean particle size among all three surfactants this is because of the reason that higher HLB value is responsible to contain a lower hydrocarbon chain and enhance surface free energy which cause size

enlargement [11]. But when we use span 85 and span 80 in formulation F1-F3 and F4-F6 which have lower HLB value then span 60, we notice the mean size reduction because of increment in hydrocarbon chains and cause size reduction by reducing surface free energy. Cholesterol concentration also responsible for size variation, when we increase the amount of cholesterol, we notice the size enlargement of niosomes because cholesterol responsible to impart rigidness and fill in the bilayer part which further enhance the diameter because of which size of niosomes increases but sometimes beyond the limit cholesterol is capable for enhancement in bilayer hydrophobicity which is generally responsible for decrement in surface free energy to cause reduction in size to (22, 24) [12].

Polydispersity index and Zeta potential

PDI value helps to notice homogeneous behavior of distribution of particles as well as their uniformity of size. PDI value range from 0 to 1 and value shifting towards zero is a proof that higher and uniform particles distribution. Here PDI study for all the formulation (F1to F9) are noticed the PDI value range of 0.131-0.422, which signifies that all formulation have uniform size distribution without any aggregation. Secondly in case of zeta potential, which value was noted in the range of 48.7 – 64.6 mv. After analyze all the values one can notice that the concentration of charge inducing agent (steryl amine) and type of surfactant variate the value of zeta potential, in case first when we increase steryl amine concentration zeta potential value also enhanced and in case second when we use span 85 and span 80 we found a higher zeta potential value then the span 60 [13].

% Cumulative drug release

For a accurate prediction of drug release over the skin, % drug release test was performed in which highest and lowest % drug release in 12th hour was recorded in case of formulation NF-8 and NF-3. All three groups (NF-1-NF-3, NF-4 – NF-6, NF7 – NF9) of niosomal formulation follow a similar pattern of drug release because of cholesterol and non-ionic concentration. when cholesterol concentration enhanced drug encapsulation also enhanced but beyond the limit of concentration in noisomes drug encapsulation decreased and this directly relate with the drug release, also decreased the cholesterol concentration support the betterment of drug release because of reduction in membrane permeability but as the lesser amount encapsulated in vesicles that's why reduced drug release was found. Whereas when we change the type of surfactant we also find the variation in drug release this is because those surfactant have a a lower hydrocarbon chain they have recorded with the higher surface free energy which cause size enlargement and help in encapsulation of higher amount of drug which finally support the higher rate of drug release [14].

Preparation of vesicles loaded Hydrogel

The reason behind hydrogel formation is to increase the residential time of gel over the wound which also helps to increase the sustained drug release because of which desire time duration for drug release will obtain for the niosomes containing drug, as discussed earlier NF-8 is incorporated inside the hydrogel for further studies [15].

Evaluation of Hydrogel

Physical Appearance

All prepared hydrogels examined by visual analyzing on the basis of color and clarity, in which all formulation shows a similar level of appearance and found with a thick mass like consistency with full clarity and appeared as transparent like pure water [16].

Grittiness and pH measurement

Gritty appearance of gel was observed with the help of microscope, in which a close view shows a clear transparent network of gel without any presence of solid particles. Whereas pH of the different formulations was observed in range of 5.74± 0.03 – 6.4±0.04 which is a proof that after applying over wound, hydrogels behave like a neutral formulation and will not cause any change over wound like other formulation may cause irritation, redness and itching etc. [17].

Spreading ability of Hydrogel

After seen the result shown in Table 4, one can observe that the result of spreadability is based on the concentration of polymers, as we enhance the concentration of both the polymers (HPMC and Carbopol 940) we notice a decline rate of spreadability, also spreadability is inversely proportional to the viscosity of hydrogels [18].

Extrudability and Viscosity

Viscosity is important factor when a requirement of any formulation to stay over the topical area. Viscosity of hydrogel is totally based on the concentration and type of polymer chosen for hydrogel preparation. Here viscosity of all formulations lies in range of 8945 to 9756 cps shown in given table 5, formulation F6 with highest concentration of carbopol 940 is record with highest viscosity among all six formulations, Final result of viscosity proof that hydrogel based on formulation F6 can be easily retained over the wound for longer time duration. Result of extrudability is totally opposite from viscosity, we recorded highest extrudability with the formulation have minimum viscosity this is due to the reason that when we enhance the viscosity, we require higher pressure over the tube containing drug and patient may face difficulty in extrudation of hydrogels. Highest extrudability recorded for formulation F1 having minimum amount of HPMC in it [19].

Skin irritation test

All Noisome incorporated hydrogels pass the skin irritation test, not any volunteer reported occurrence of any kind of variation over the skin after applying hydrogel for 30 minutes of time duration [20].

***In vitro* mucoadhesion**

Niosomal hydrogel was able to show 2874±2.565 dynes/cm^2 and result based end result proof that hydrogel found with more than average mucoadhesive strength which depend on concentration of HPMC. Higher strength of hydrogel with the skin tissue is because of strong bonding in between the carboxyl group of carbopol present in gel and skin tissue, based on this explanation one can conclude that there is no chance of self detachment of gel until a forcefully removal of gel taken place. So, one can conclude that gel is able to provide desirable time duration of skin adhesive strength for more than 12hrs which help to release desire amount of drug but this strength of hydrogel may variate in presence of blood over bound as in presence of liquid hydrogel viscosity may effect and gel can easily remove at that time [21].

Drug diffusion study

In a drug diffusion study we notice a drastic variation in drug release mechanism and only 4 -7% of drug release was found in first hour whereas only 24.606 to 27.528 % of drug release within 4 hrs, clearly mention in a given figure 5, this is totally based on type and concentration of polymer used to prepare hydrogels, when we enhance the concentration of both the polymer reduction in drug release rate was noticed whereas when we use the carbopol polymer a lower rate of drug release with better sustained release was noticed in comparison with HPMC polymer,

this is because of the reason that carbomer have self crosslinking property which help to make a thick mass that is why support the better sustained release of drug. Also drug release further reduced because of drug encapsulated by niosomes which is much more responsible for delayed the drug release [22].

Antibacterial study

The antibacterial activity of drug amikacin was observed by checkout the zone of inhibition occurred after addition of the hydrogel over the growth of pseudomonas aeruginosa bacterial strains. In this case formulation F3 which was selected as best formulation was able to show the 19 mm area of zone of inhibition, which is a kind of highly active inhibition and provide a satisfactory result which is enough to proof that amikacin based solid dispersion containing hydrogels are able to work against bacteria which commonly grow after wound formation over the skin [23].

Result and Discussion

FORMULATION OF SELECTED DRUG NIOSOMES:

Thin-film hydrolysis of niosome formulations employing various surfactants (Span 20, Span 40, Span 60) and Cholesterol with varying ratios as shown in table 1 resulted in a steady, uniform dispersion of niosomal particles. The formation of niosomal vesicle was confirmed by Transmission Electron Microscopy (TEM).

Table 1: Formulations of niosomes

Form. code	**Drug tolmetin sodium**	**Surfactant Grade (mg)**	**Cholesterol (mg)**	**Ratio (Drug: Surfactant: Cholesterol)**	**Solvent (Chloroform: Methanol**
NF1	100	Span 60	100	1:1:1	6:2
NF2	100	Span 60	100	1:2:1	6:2
NF3	100	Span 60	200	1:.75:2	6:2
NF4	100	Span 40	100	1:1:1	6:2
NF5	100	Span 40	100	1:2:1	6:2
NF6	100	Span 40	200	1:.75:2	6:2
NF7	100	Span 20	100	1:1:1	6:2
NF8	100	Span 20	100	1:2:1	6:2
NF9	100	Span 20	200	1:.75:2	6:2

Characterization of Niosomes

IR Spectrum Analysis

Figure 2: FTIR Images of (A) Complex A denote solid dispersion (B) Span's (C) Cholesterol (C) Solid dispersion, Excipients and niosomes as a complex B

Figure 2 (A)

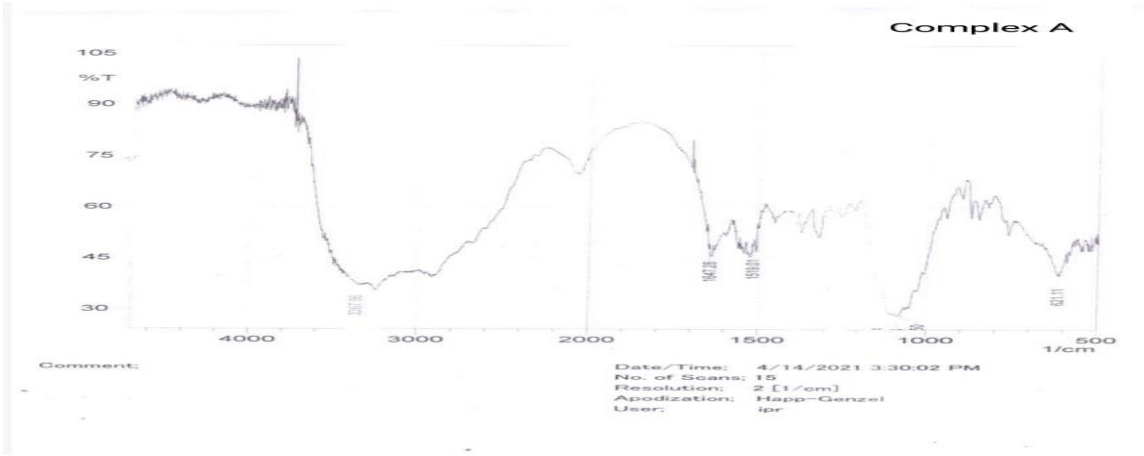


Figure 2 (B)

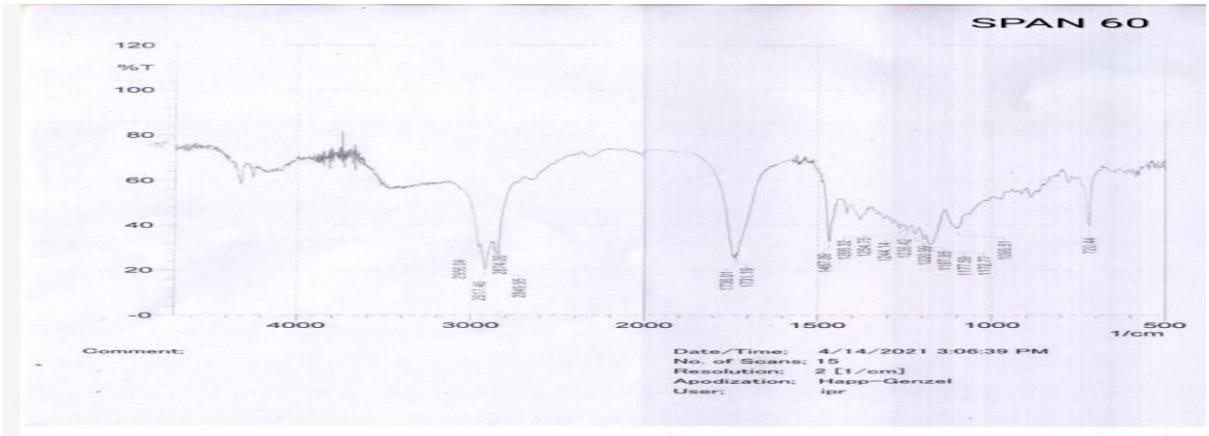


Figure 2 (C)

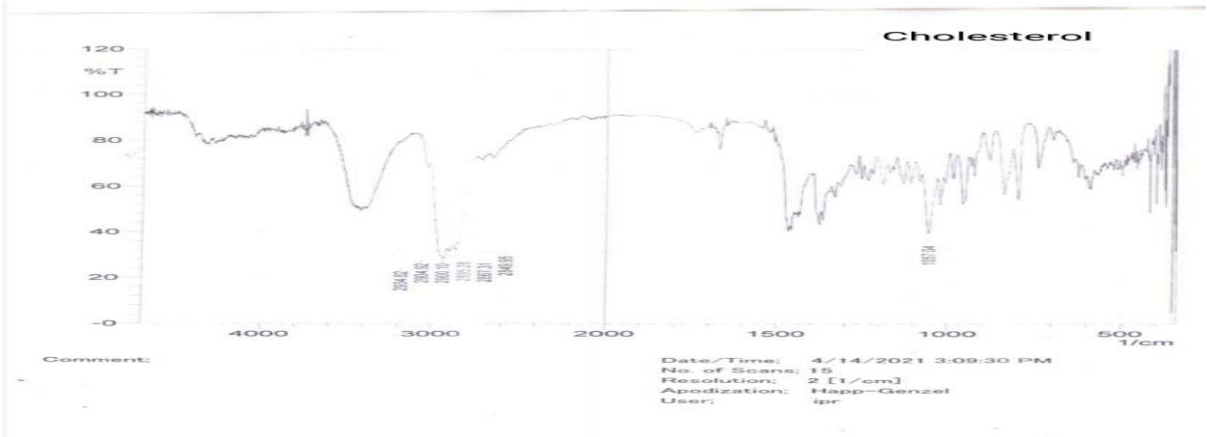
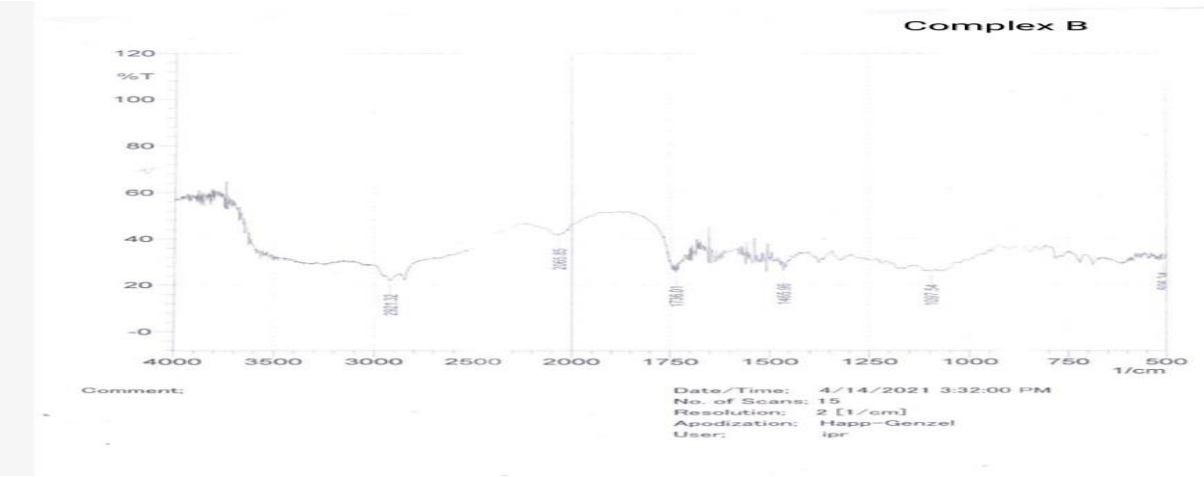
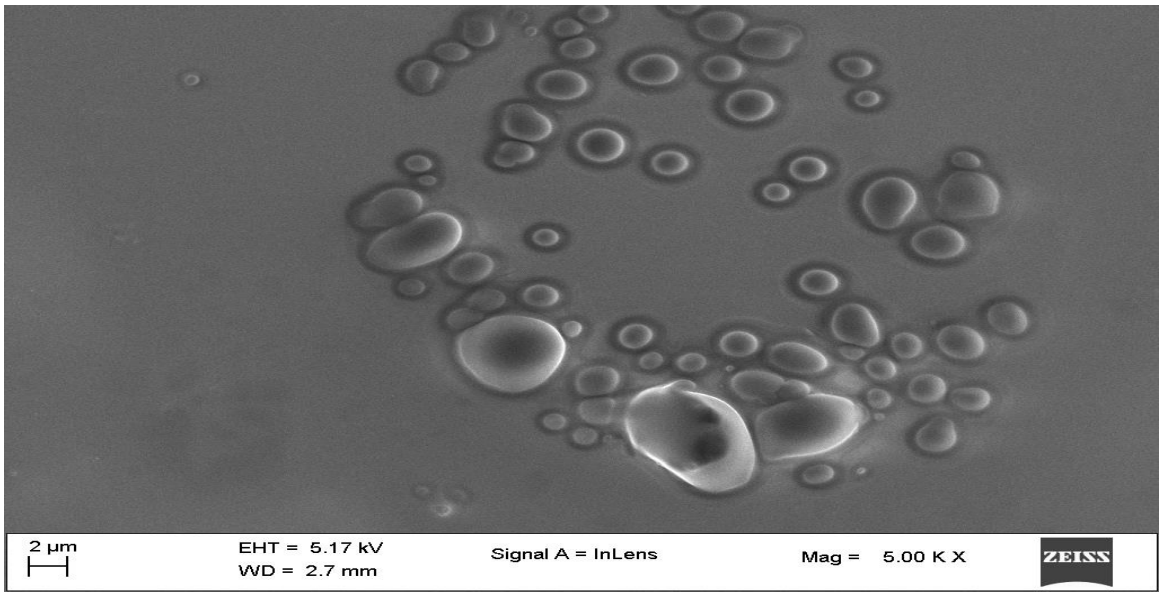


Figure 2 (D)



Scanning Electron Calorimetry

Figure 3: SEM image of Niosomes



Evaluation Parameter of Vesicles

Table 2: Evaluation Parameters for Niosomes

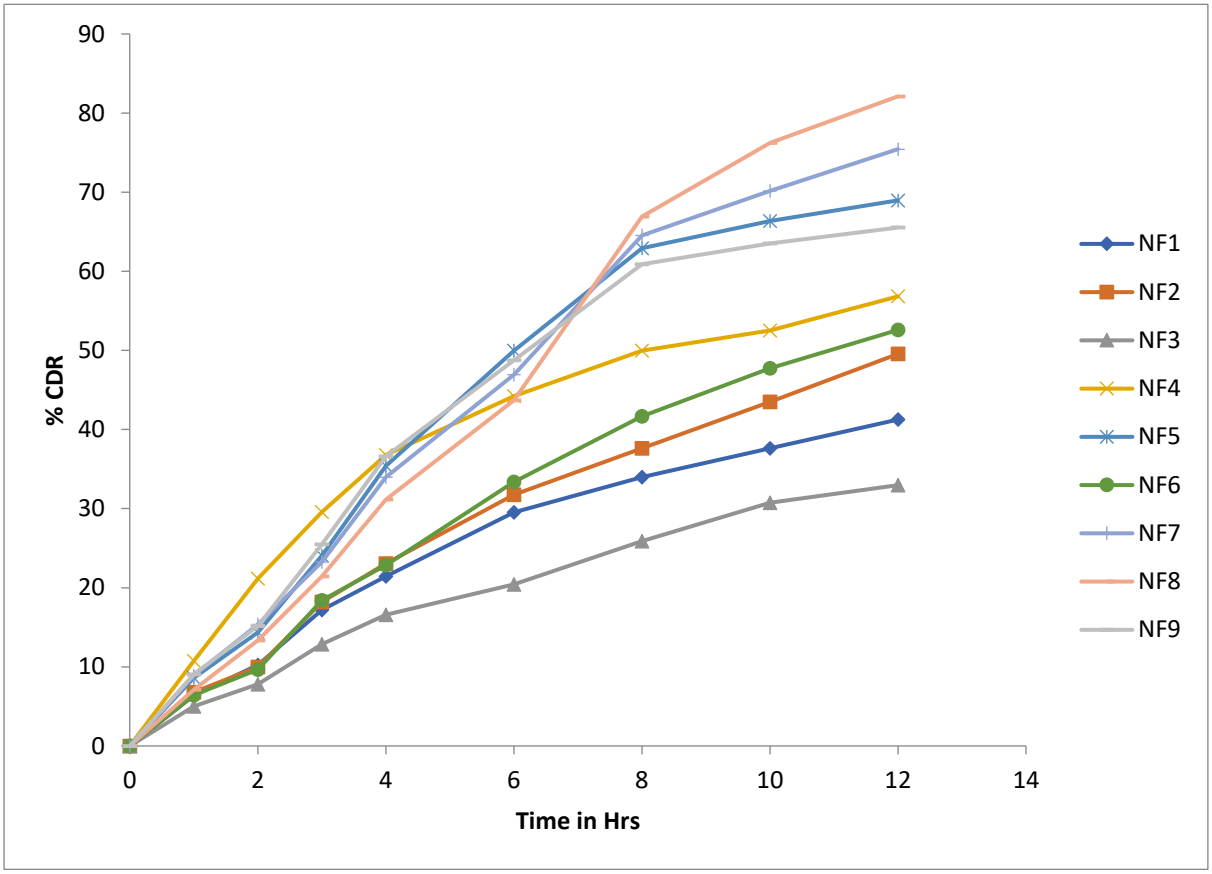
Formulation code	Vesicle Size (nm)	Zeta Potential	Polydispersity index	% Entrapmment Efficiency
NF1	489.7	60.7	0.248	43.876
NF2	509.3	64.4	0.331	51.405
NF3	853.4	64.6	0.422	34.887
NF4	177.96	48.7	0.247	62.752

NF5	1611.6	58.1	0.390	69.835
NF6	1142.7	61.7	0.307	55.730
NF7	203.2	50.6	0.131	77.921
NF8	289.8	50.7	0.271	85.449
NF9	4394.4	51.7	0.319	66.236

Table 3: % Cumulative drug release data for Niosomes

Time in hrs	**% Cumulative Drug Release**								
	NF1	NF2	NF3	NF4	NF5	NF6	NF7	NF8	NF9
0	0	0	0	0	0	0	0	0	0
1	6.391±0.03	6.775± 0.01	4.994± 0.043	10.751± 0.047	8.615± 0.0087	6.471± 0.09	8.898± ±0.03	7.119± 0.04	9.04± 0.036
2	10.213 ±0.034	9.991± 0.031	7.806± 0.013	21.163± 0.021	14.359± 0.086	9.667± 0.08	15.37± ±0.03	13.348± 0.08	15.168± 0.0058
3	17.191 ±0.003	18.202± 0.087	12.862± 0.062	29.58± 0.06	24.067± 0.004	18.404± 0.07	23.258± ±0.007	21.438± 0.03	25.483± 0.0021
4	21.438 ±0.006	23.056± 0.008	16.584± 0.004	36.781± 0.055	35.393± 0.006	22.853± 0.007	33.977± ±0.04	31.146± 0.008	36.606± 0.069
6	29.52 ±0.0043	31.752± 0.004	20.426± 0.086	44.241± 0.026	49.955± 0.005	33.370± 0.06	46.921± ±0.05	43.685± 0.006	48.741± 0.085
8	33.977± 0.052	37.617± 0.076	25.887± 0.026	49.546± 0.028	62.898± 0.065	41.662± 0.05	64.516± 0.007	66.943 ±0.02	60.876± 0.41
10	37.617± 0.054	43.483± 0.0087	30.741± 0.0027	52.519± 0.048	66.337± 0.087	47.730± 0.09	70.179 ±0.03	76.247 ±0.09	63.505± 0.062
12	41.258± 0.01	49.550± 0.066	32.966± 0.72	56.828± 0.031	68.966± 0.042	52.584± 0.41	75.438 ±0.01	82.112 ±0.03	65.528± 0.004

Figure 4: % Cumulative Drug Release profile of all nine niosomal formulation (NF-1 – NF-9).



Preparation of vesicles loaded Hydrogel

The reason behind hydrogel formation is to increase the residential time of gel over the wound which also helps to increase the sustained drug release because of which desire time duration for drug release will obtain for the niosomes containing drug, as discussed earlier NF-8 is incorporated inside the hydrogel for further studies.

Evaluation of Hydrogel

Table 4: Evaluation Parameters based result of Hydrogels

Formulation Code	Physical Appearance	Grittiness	pH	Spreadability
HF1	Transparent	Clear	5.74± 0.03	22.42±0.05
HF2	Transparent	Clear	5.8± 0.06	18.44±0.03
HF3	Transparent	Clear	5.74±0.04	14.98±0.06
HF4	Transparent	Clear	5.9±0.02	19.6±0.1
HF5	Transparent	Clear	6.1±0.02	13.4±0.2
HF6	Transparent	Clear	6.4±0.04	10.6±0.03

Table 5: Evaluation Parameters based result of Hydrogels

Formulation Code	**Extrudability**	**Viscosity (Centipoise)**	**Skin Irritation Test**	**In-vitro Mucoadhesion (dynes/cm^2**
HF1	Excellent	7215±0.08	Pass	2144
HF2	Good	7994±0.2	pass	2312
HF3	Good	8413±0.3	Pass	2704
HF4	Good	7590±0.2	Pass	2208
HF5	Good	8042±0.1	Pass	2637
HF6	Poor	8718±0.07	pass	2998

Drug diffusion study

Figure 5: % Cumulative Drug Diffusion profile of all Five Hydrogel formulation (HF-1 – HF-9).

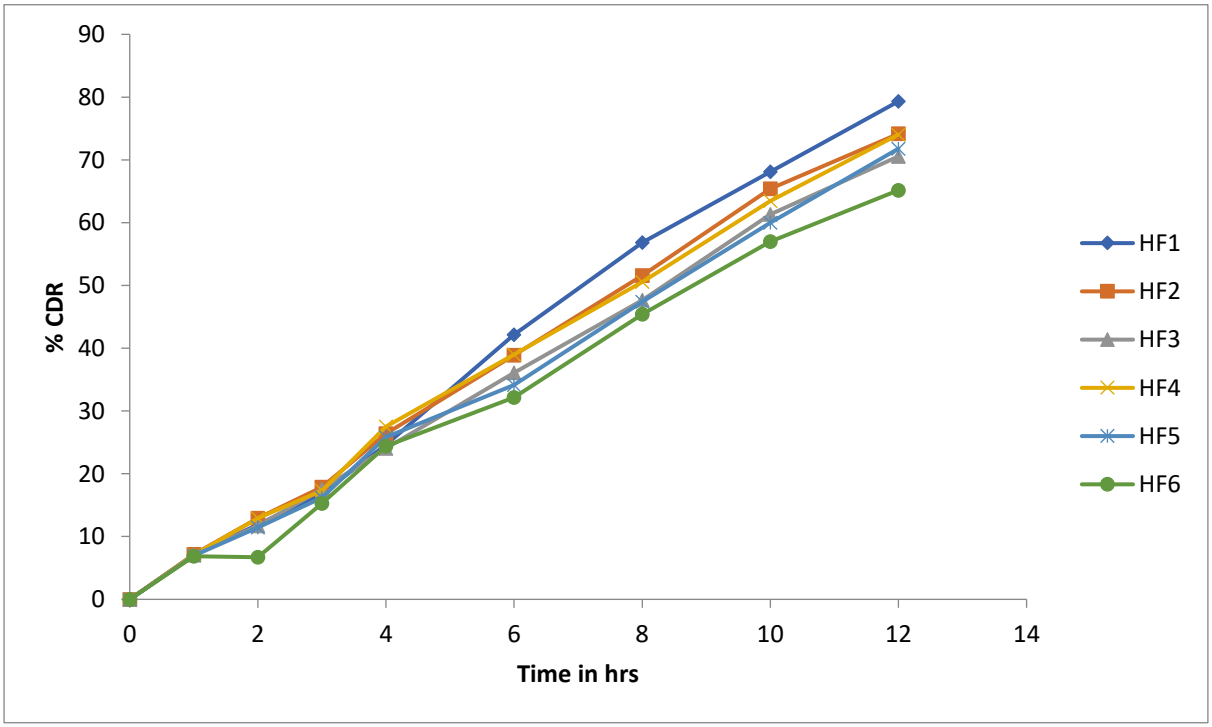


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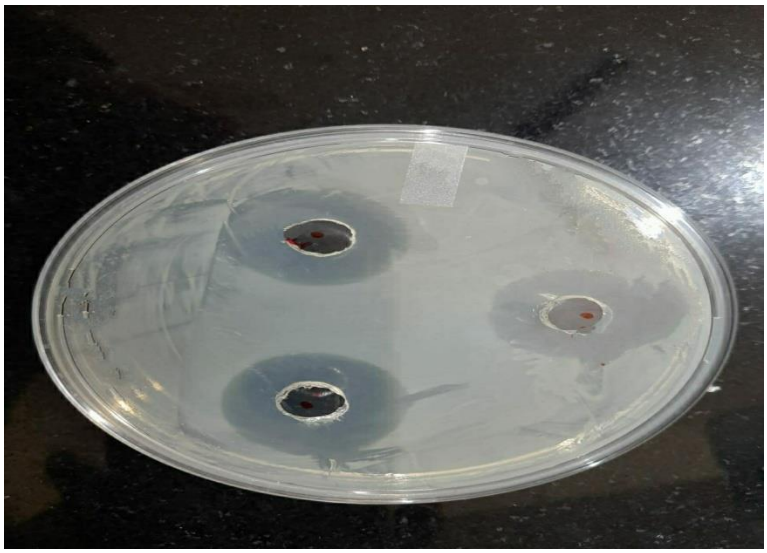
Figure 6: % Shows a Antibacterial activity of hydrogel through Zone of inhibition



Conclusion:

Three different works combine to form a HF-3 dosage form, which is best on the basis of drug diffusion, in-vitro mucoadhesion and viscosity high solubility and, ease to use with adhesive nature over the skin, all three advantages are a must whenever we talk about the dermal formulation. The same happens with the drug amikacin, whose stability with minor solubility enhanced by the solid dispersion formation and encapsulated inside the vesicles called niosomes for sustained release and easy to adhere over the wound surface and finally, niosomes are encapsulated in hydrogels which provides the adhesive nature with easy to apply surety, at the same time it is able to provide a cooling sensation with surety to cure the wound. Also, drug and excipients have no interaction with each other and are quite stable in all dosage forms. Lastly all niosomal and hydrogel formulation compare with each other and proof that NF-8 as niosomal preparation and HF-3 as hydrogel preparation are overall best formulation and selected on the basis of many evaluation parameters. Finally one can conclude that whenever we select an oral route for targeting wound, there is a problem face by patient-related with improper amount of drug reached to the selected area and dose-related side effects and lastly patients non-compliance with tablet, for all this type of problems we can use the drug to be apply over the wound directly and for this prepared formulation NF-3 is best among all other formulation in case when we want to decrease dose frequency, directly applicable procedure and easy to use, and did not want any dose-related side effects as very less amount of drug used which is directly apply over wound and lastly slow or sustained drug release with almost whole drug penetrate from the wound which further help in heal the wound in less time duration.

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