

Research Article

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Formulation and in –Vitro Evaluation of Glimepiride Encapsulated Niosomes to Enhance its Oral Bioavailability and as Sustained Release Drug Delivery System

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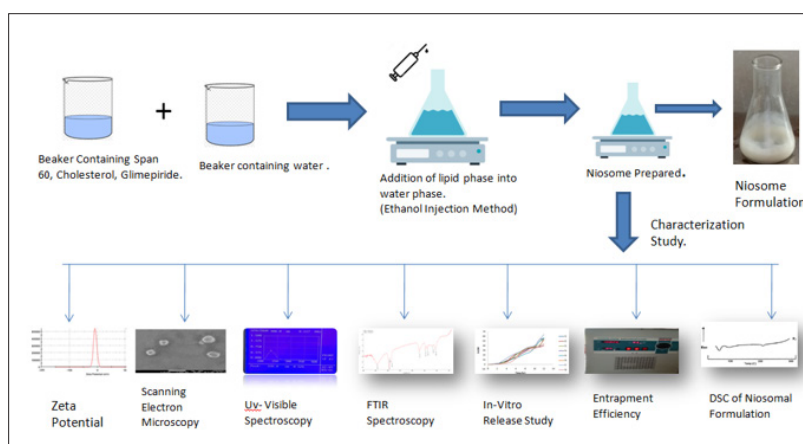
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ABSTRACT

Niosomes are a non-ionic spherical surfactant vesicle (NIS) effective drug carriers that are biodegradable, non-toxic, more durable, and cost-effective than liposomes. The NISs were prepared by the modified ethanol injection method in this work. This study was designed to provide information related to the preparations niosomes composite (GLM-NIS). Aiming to enhance its oral bioavailability, minimize side effects, and solve the swallowing problem in geriatric patients. In-vitro and in vivo release studies were performed by dialysis technique and formulation (Span60:Cholesterol 0.5:1.0), respectively. As synthesized, GLM-NIS exhibited high entrapment efficiency percentages 86.66 % and particle size diameter with -22. Mv zeta potential (ZP) reveals high stability. These findings encourage the further study of niosomes to enhance oral bioavailability, extended for its in vivo studies for in vitro-in vivo correlation and various in vivo studies of GLM.

Graphical Abstract



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Keywords: Glimepiride, Niosomes, Nonionic Surfactant Vesicles, Formulation, Targeted Drug Delivery, Stability

Introduction

Metabolic disease such as Diabetes mellitus (DM) is of pancreatic insulin insufficiency, a global health issue in the 21st century that increases the economic burden globally [1]. Insulin-dependent diabetes (T1DM) and insulin-independent diabetes (T2DM) are the two types of DM in which ~90% were diagnosed under T2DM [2]. The limitation of insulin is known as insulin resistance means insulin cannot be utilized by target organs; therefore later study showed that various types sulfonylureas are introduced to maintain

appropriate blood glucose level [3]. Among them, glimepiride (GLM), a third-generation sulfonylurea, reported Hamaguchi et al [4], which was used for the management of T2DM. Despite having the advantage of GLM, such as stimulating the release of insulin from pancreatic β -cells could overcome the cardiovascular complications as other sulfonylureas showed, its poor aqueous solubility (acidic and neutral aqueous media), biocompatibility problems, adverse effects (dizziness, hypoglycemia, and headache), oral treatment (nausea, gastric disturbances, heartburn, and diarrhea) lead to maintain the blood level of a drug causing an irreproducible clinical response [5]. Therefore, these serious issues could be solved by formulations of GLM has potency to improve

the clinical efficacy, minimize the side effects, and increase patient compliance [6].

In general, in the targeted drug delivery systems, the drug molecules are directly targeted at the targeted site of action without any interaction with other tissues. With this concern, the niosome vesicle non-ionic surfactant (NIS) has been widely used as effective drug carrier which have delivered both amphiphilic and lipophilic drugs in advanced drug delivery systems [7]. Therefore, to achieve the targeted delivery drug, bind the receptor site and then get the therapeutic action without attaching other sites to prevent the undesirable effect the niosome is a beneficial drug delivery system [1-2].

In this study, we have formulated an In-Vitro evaluation niosomes for GLM targeting to enhance the oral bioavailability of glimepiride, prolong its action, and attain a stabilized blood glucose level. Moreover, dose frequency, drug side effects, and increased patient compliance have also been studied. These findings could provide valuable insights toward solving the swallowing problem in geriatric patients and further for tablet formulation.

Material and Methods

The raw materials like drugs, excipients, and chemicals required for the present work were procured from different sources. Following materials were used for the formulation and evaluation of Glimepiride containing niosome.

Table 1: List of Drug and Excipients

Particulars	Material	Manufacturer / supplier
Drug	Glimepiride IP micronized	USV Private Limited, Baddi, India
Surfactants	Tween 60	Research –Lab Fine Chem. Industries, Mumbai, India
	Span 60	
Vehicle	Methanol	Research –Lab Fine Chem. Industries, Mumbai, India
	Distilled water	Satara College of Pharmacy, Satara, India
Membrane stabilizer	Cholesterol	SD Fine Chemicals Pvt. Ltd. Mumbai.India

All the other chemicals used were of analytical grade and were used as a procedure

Preparation of Niosome

- Ethanol Injection Method: Niosomes were prepared by the modified ethanol injection method. Glimepiride, Span60, and Cholesterol (were dissolved in methanol.
- The resulting solution was slowly injected using a microsyringe at a rate of 0.25 ml/min into water
- The solution was stirred continuously on a magnetic stirrer and temperature was maintained above 60°C.
- As the lipid solution was injected slowly into the aqueous phase, stirring continuously. Vaporization of solvent takes place, resulting in spontaneous vesiculation and the formation of unilamellar spherical niosomes.
- The Prepared Niosome suspension is stored in a well-closed container [3-5].

Table 2: Formulation Table

Formulation	Drug	Span 60	Methanol	Cholesterol	Distilled water
Blank	-	100 MG	10 ML	150 MG	10 ML
F1	10 MG	100 MG	10 ML	-	10 ML
F2	10 MG	100 MG	10 ML	50 MG	10 ML
F3	10 MG	100 MG	10 ML	100 MG	10 ML
F4	10 MG	100 MG	10 ML	150 MG	10 ML
F5	10 MG	100 MG	10 ML	-	10 ML
F6	10 MG	100 MG	10 ML	50 MG	10 ML
F7	10 MG	100 MG	10 ML	100 MG	10 ML
F8	10 MG	100 MG	10 ML	150 MG	10 ML

Evaluation of Niosomes

Entrapment Efficiency

The enhanced Niosomes percent entrapment efficiency (percent EE) was calculated using the ultracentrifugation method. A precise amount of 5 ML dispersion was measured and centrifuged at 10,000 RPM for 30 minutes at 4 °C using the premier tabletop ultracentrifuge to obtain supernatant (REMI). A little amount of the supernatant was diluted with methanol (1:10). The amount of drug in the supernatant was determined spectrophotometrically at 227 nm and was referred to as free drug (UV-1700, Shimadzu, and Tokyo, Japan) [6-8].

Infrared spectroscopy

It was determined by Fourier Transform infrared spectrophotometer (FTIR-410, Jasco, Japan) using the KBr pellet technique. FTIR spectra of individual drugs and excipients and Niosomes formulation were put down within the wavelength range of 4000 to 400 cm⁻¹ [9-11].

- Differential Scanning Calorimetry (DSC)**
 Thermal analysis is a crucial evaluation technique to seek out any possible interaction between the drug and excipient. Such interaction is often identified by any change in the thermogram. Thermograms of pure drug and finished niosomes formulations were obtained using a DSC instrument (Mettler Toledo DSC 821Ce, Switzerland) equipped with an intercooler. Indium standard was wont to calibrate the DSC temperature and enthalpy scale. The powder sample of niosomes was kept within the aluminum pan and heated at a constant rate of 5°C/min up to 300°C. The inert atmosphere was maintained by purging nitrogen at the flow of 10ml/min [4, 12,13].
- Scanning microscopy (SEM)**
 Scanning microscopy was wont to study the microscopic aspects of the niosomes. The morphology of niosomes was estimated by using SEM [4-14]
- Particle Size Analysis**
 Particle size analysis of prepared niosomes was administered by using a zeta sizer (Particulate system nano plus) [13-15].
- Zeta Potential**
 The Zeta potential of optimized niosomes was measured by using a zeta sizer at 25°C (Particulate system nano plus) [12-14].
- Stability Study**
 Based on the findings of the in-vitro evaluation of the produced niosomal formulation, the F2 (1:0.5 cholesterol and surfactant ratio) formulation was chosen for further stability testing. The capacity of vesicles to retain the medication was tested as part of the stability investigation of the F2 formulation. The F2 niosomal formulation was kept at two different temperatures: refrigerated and at room temperature (RT). Throughout the study, niosomal formulations were maintained in aluminum foil-sealed glass vials. On the 7th, 14th, 21st, 28th, and 30th days, samples were obtained and analyzed using a spectrophotometer set to 226 nm for things like Entrapment Efficiency and drug release [15,16].
- In vitro Release of glimepiride from Niosomes**
 In vitro, drug release studies on the generated niosomal formulations were carried out using a dialysis technique. To maintain sink conditions, the dialysis bag was filled with niosomes corresponding to 2 mg of GLM (molecular weight cutoff 12,000–14,000Da) and placed in a beaker containing 50 ml PBS as a solvent with physiological pH 6.8 and 30% methanol (v/v). The temperature was maintained at 37±1°C, and the beaker was stirred at 100 revolutions per minute. After 24 hours, samples (2 ml) were collected at regular intervals and replaced with 2 ml of fresh buffer. After that, the drug content in the removed samples was determined using a spectrophotometric method at 226 nm [4-15].

Result and Discussion

Preformulation Studies

Determination of Melting Point of Glimepiride

Glimepiride melting point was established between 205°C- 207°C, while as per literature standard it is 206°C-207°C.

Ultraviolet Spectroscopy

Uv Spectrum in Methanol

Determination of λ_{max} - In Figure 4.1 the UV spectrum obtained in methanol is presented. The wavelength of maximum absorption (λ_{max}) was observed at 226. nm.

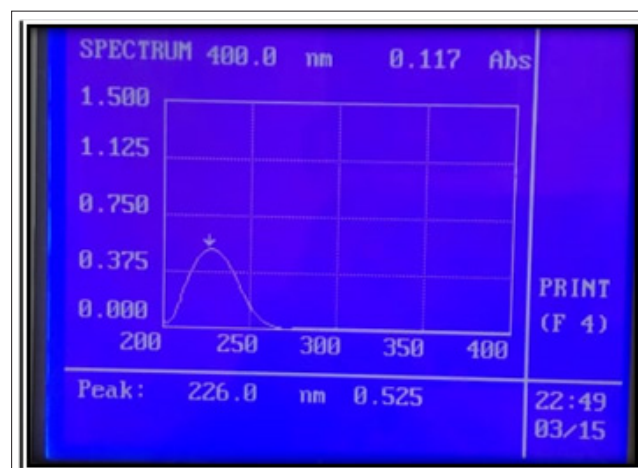


Figure 1: UV Spectrum of Glimepiride in Methanol

Calibration Curve of Glimepiride in Methanol

The calibration curve for Glimepiride in methanol was plotted by using the following results of absorbance at various concentrations taken at 226 nm. Calibration curve as concentration versus absorbance was constructed to study Beer- Lambert's law and regression equation of Glimepiride. The high value of R2 (0.997) denotes linearity.

The obtained Data of concentration and absorbance at 226 nm showing in Table No 3: Data of Concentration and Absorbance at 226 nm

Table 3: Calibration Curve Reading

Concentration	Absorbance
0	0.00
6	0.304
8	0.422
10	0.576
12	0.687
14	0.808

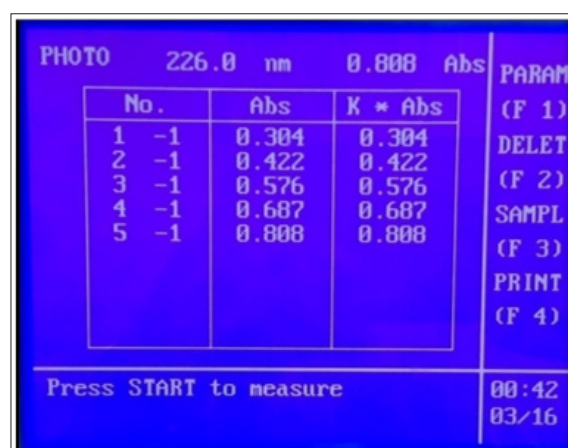


Figure 2: Calibration Curve Reading

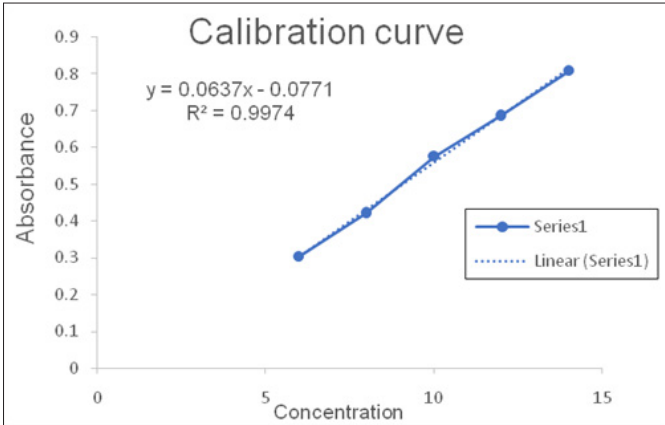


Figure 3: Calibration Curve of Glimepiride in Methanol

IR Spectroscopy

FTIR spectra of pure drug show characteristics’ peak at 3369 cm⁻¹ and 3288 cm⁻¹ Corresponding to N-H stretching 1707 cm⁻¹ and 1674 cm⁻¹ due to carbonyl stretching 1345 cm⁻¹ showing C-N stretching 1153 cm⁻¹ Showing S=O stretching vibration showing in Figure 4.

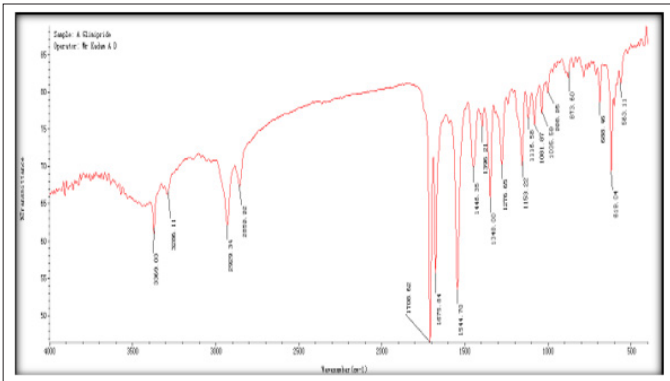


Figure 4: FTIR Spectra of Glimepiride

In-Vitro Dissolution Study

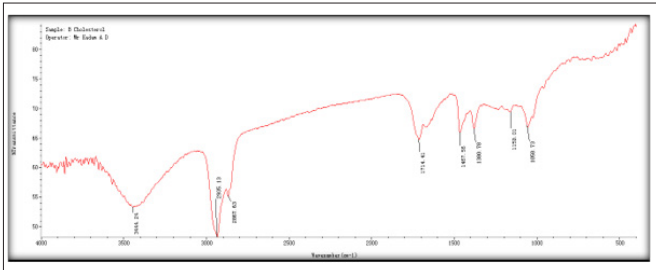


Figure 5: Cholesterol FTIR Spectra

Table 4: Inference Table of Cholesterol Spectra

Wave number	Observed Range	Functional group
3420	3444.24	Hydroxy group
2929	2935.13	Carboxylic acids
2360	2867.13	Primary and secondary amines
1459	1467.56	Alkanes, Aromatic ring stretch

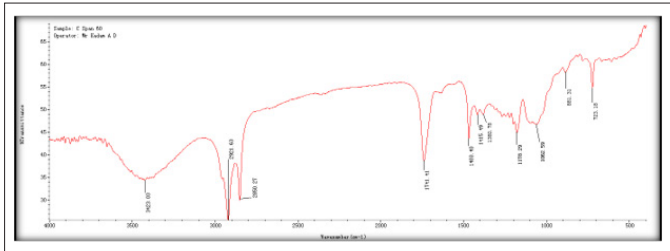


Figure 6: Ftir Spectra of Span 60

IR spectra of span 60

Table 5: Inference Table of Span 60- Spectra

Wave number	Observed Range	Functional group
3310	3423.03	Amines or hydroxyl group
2926	2921.63	Carboxylic acids
2360	2850.27	Primary and secondary amines
1733	1741.41	Aldehyde
1459	1469.49	Alkanes, Aromatic ring stretch
1052	1062	Cyclohexane ring vibrations, Alkyl substituted ether

Drug and Excipient Compatibility Study
FTIR of Glimepiride and Cholesterol

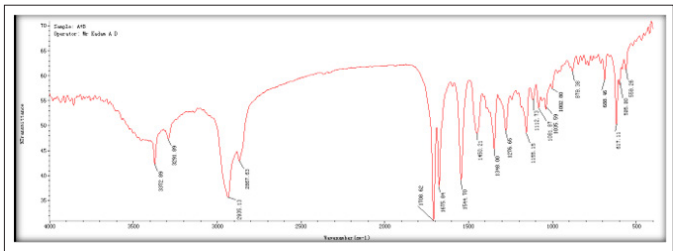


Figure 7: FTIR Spectra of Glimepiride and Cholesterol

FTIR spectra of drug show characteristics peak at 3369 cm^{-1} and 3288 cm^{-1} Corresponding to N-H stretching 1707 cm^{-1} and 1674 cm^{-1} due to carbonyl stretching 1345 cm^{-1} showing C-N stretching 1153 cm^{-1} Showing S=O stretching vibration. Showing in figure 7. There is no interaction done.

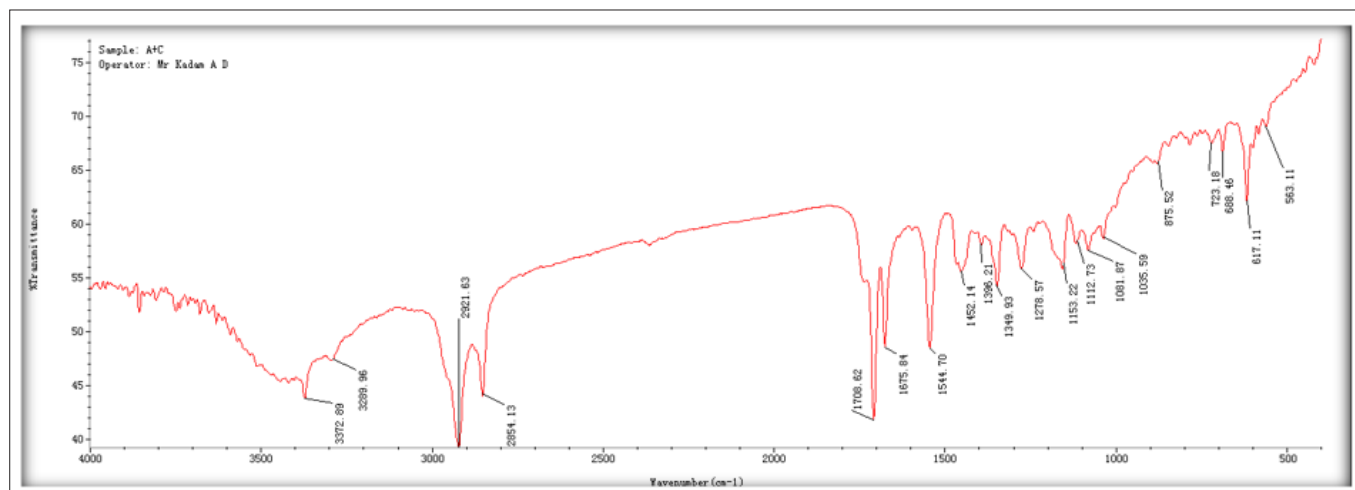


Figure 8: FTIR Spectra of Glimepiride and Span 60

FTIR spectra of drug show characteristics peak at 3369 cm^{-1} and 3288 cm^{-1} Corresponding to N-H stretching 1707 cm^{-1} and 1674 cm^{-1} due to carbonyl stretching 1345 cm^{-1} showing C-N stretching 1153 cm^{-1} showing S=O stretching vibration. Showing in figure 8. There is no interaction done.

FTIR of Blank Niosome

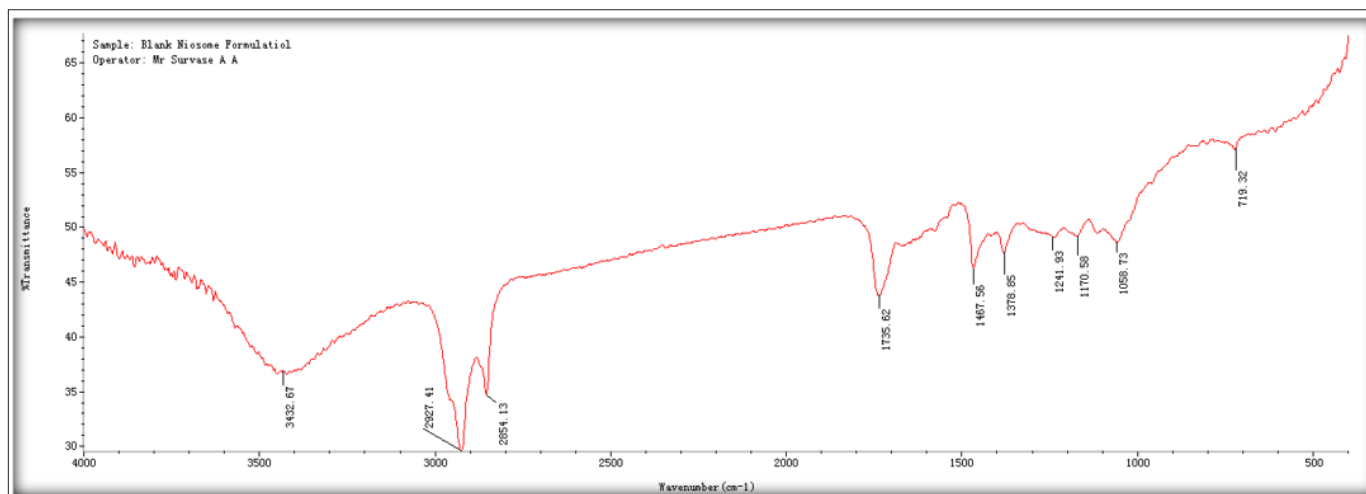


Figure 9: FTIR Spectra of Blank Niosomes

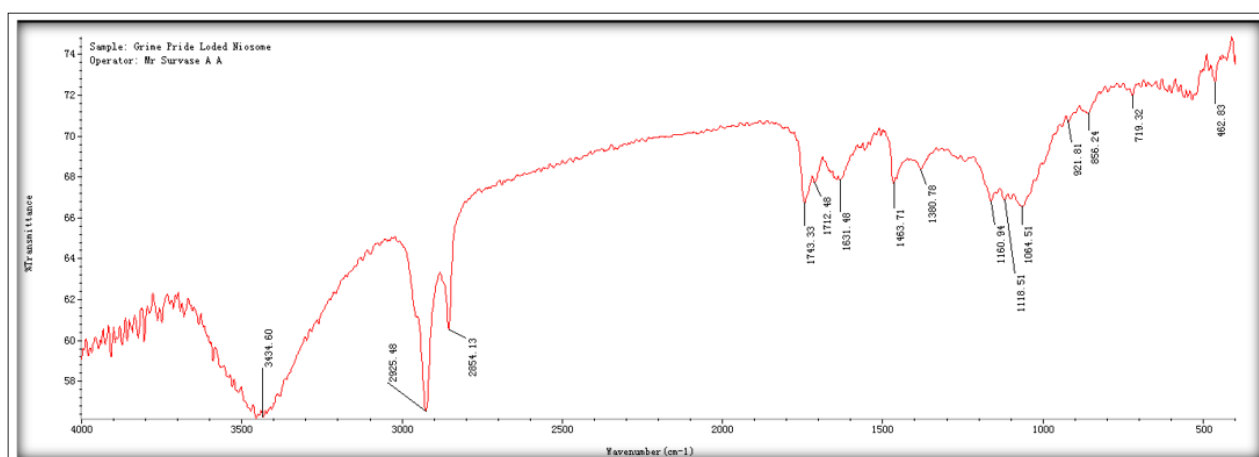


Figure 10: FTIR Spectra Glimepiride Loaded Niosome

FTIR spectra of drug show characteristics peak at 3369 cm^{-1} and 3288 cm^{-1} Corresponding to N-H stretching 1707 cm^{-1} and 1674 cm^{-1} due to carbonyl stretching 1345 cm^{-1} showing C-N stretching 1153 cm^{-1} showing S=O stretching vibration showing in figure 10. This peak is shown in the glimepiride-loaded niosome therefore it is glimepiride-loaded niosome.

Scanning Electron Microscopy

The scanning electron microscopy SEM shows that the niosome formed in spherical form with having a size of $10\text{ }\mu\text{m} - 100\text{ }\mu\text{m}$ which is showing in figure 11.

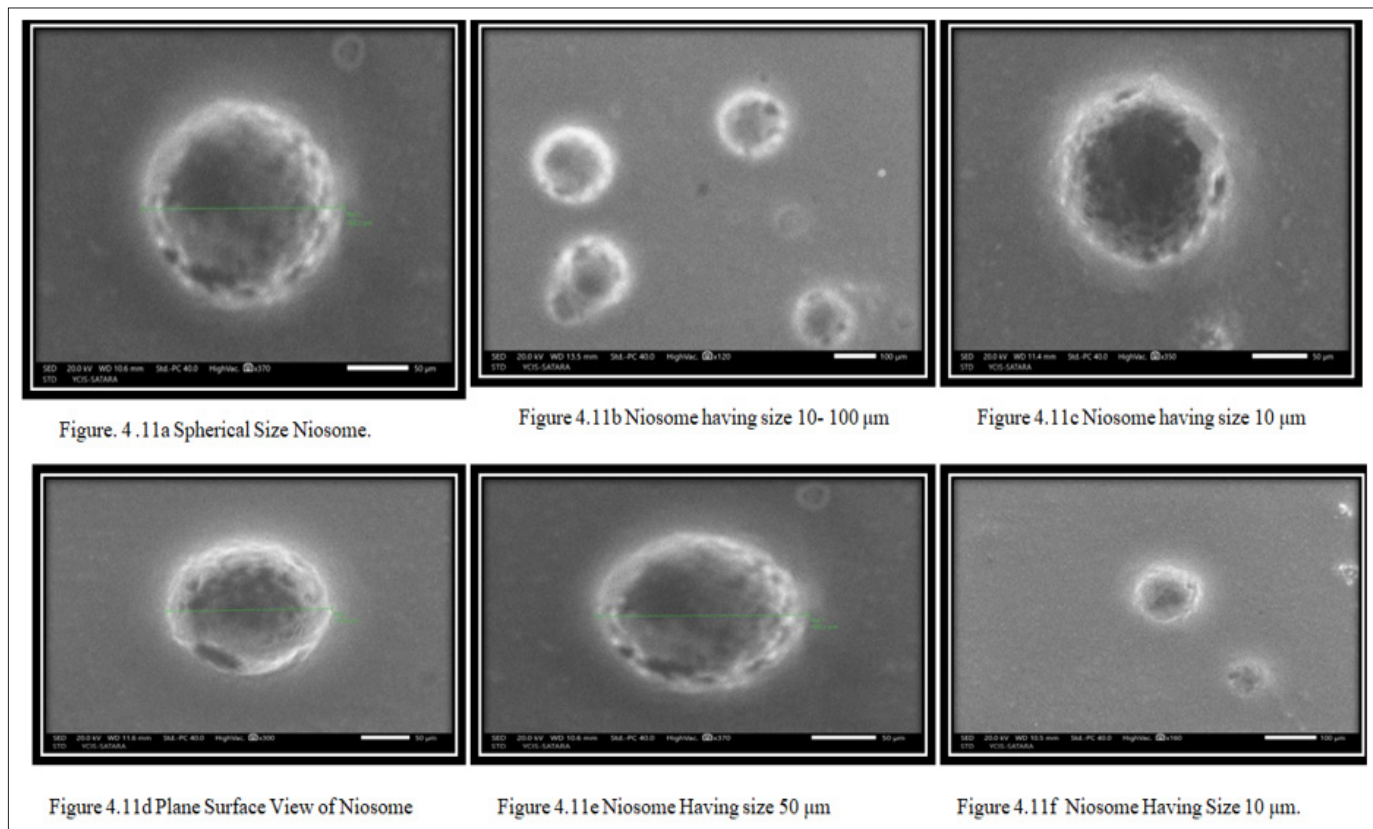


Figure 11: Scanning Electron Microscopy



Figure 12: In-Vitro Dissolution Study

The In-vitro release study reveals that the F2 formulation which is made of the Span60:Cholesterol 0.5:1 having 40% release at 12 hr. compared to other formulations it is very low means it indicating that the F2 formulation batch release pattern is a sustained release pattern which showing in Table 6 and Table 7.

Table 6: Cumulative Drug Release F1-F3 Batch

Time	F1	F2	F3
0	0	0	0
1	0.51± 0.04	0.11± 0.02	0.12± 0.06
2	1.3± 0.05	1.70± 0.01	1.7± 0.04
3	4.4± 0.06	3.6± 0.03	4.0± 0.02
4	6.0± 0.02	5.6± 0.04	8.4± 0.05
5	11.2± 0.03	15.5± 0.05	12.0± 0.03
6	20.3± 0.04	21.9± 0.06	21.1± 0.01
7	26.3± 0.03	25.5± 0.02	26.30± 0.06
8	30.4± 0.01	31.0± 0.05	33.0± 0.04
9	35.0± 0.04	34.2± 0.06	35.4± 0.02
10	36.2± 0.06	35.8± 0.04	37.4± 0.06
11	38.6± 0.02	37.02± 0.01	48.5± 0.05
12	56.4± 0.05	40.5± 0.04	54.4± 0.04

Table 7: Cumulative Drug Release F4-F8 Batch

Time	F4	F5	F6	F7	F8
0	0	0	0	0	0
1	0.51 ± 0.03	0.91 ± 0.04	0.51 ± 0.03	0.51 ± 0.02	0.11 ± 0.03
2	2.1 ± 0.03	1.7 ± 0.04	0.91 ± 0.04	0.91 ± 0.05	0.51 ± 0.04
3	2.8 ± 0.04	3.6 ± 0.05	2.89 ± 0.03	6.46 ± 0.04	1.3 ± 0.05
4	7.2 ± 0.05	5.2± 0.06	5.27 ± 0.02	12.8 ± 0.04	2.5 ± 0.01
5	12.4 ± 0.05	10.4 ± 0.02	12.0 ± 0.06	19.1 ± 0.02	5.67 ± 0.03
6	15.9 ± 0.04	13.6 ± 0.04	15.5 ± 0.05	23.5 ± 0.06	12.8 ± 0.05
7	22.7 ± 0.06	17.9 ± 0.03	25.1 ± 0.04	27.8 ± 0.04	20.7 ± 0.02
8	28.2 ± 0.04	22.7 ± 0.04	33.4 ± 0.01	33.8 ± 0.03	27.1 ± 0.04
9	34.2 ± 0.04	26.3 ± 0.05	35.8 ± 0.03	37.8 ± 0.01	30.2 ± 0.01
10	39.0 ± 0.06	35.4 ± 0.01	37.8 ± 0.05	40.1 ± 0.03	34.2 ± 0.06
11	52.5± 0.06	48.5± 0.03	40.5 ± 0.02	52.5 ± 0.04	37.8 ± 0.07
12	55.6 ± 0.06	56.4 ± 0.04	52.5 ± 0.01	64.4 ± 0.05	44.5 ± 0.04

The cumulative drug release of f1 to f8 formulation showing in Table 13

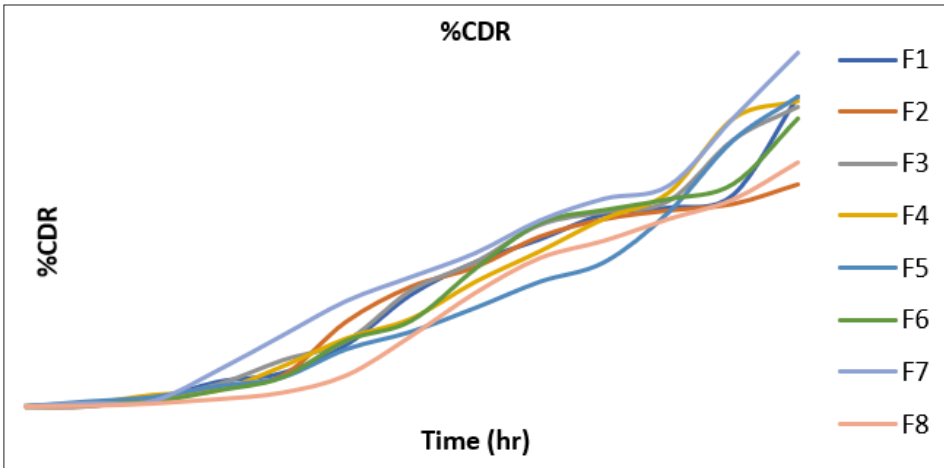


Figure 13: Cumulative Drug Release

Entrapment Efficiency

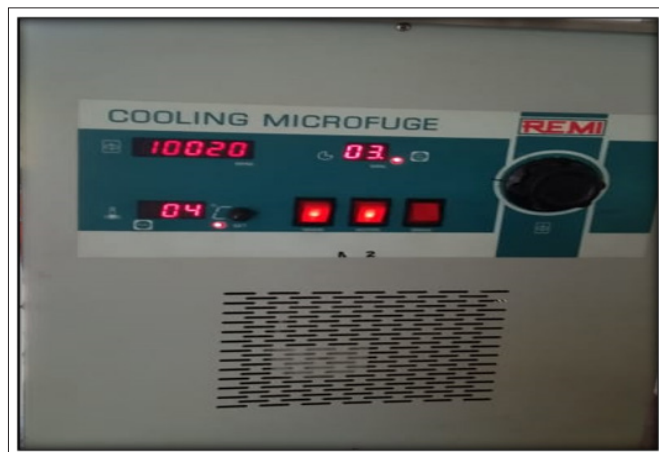


Figure 14: Entrapment Efficiency

The span 60, F2 formulation having the greatest entrapment efficiency because it has a C16 carbons chain it is having a low HLB value therefore high entrapment efficiency. F5 formulation having the lowest entrapment efficiency because it is having tween surfactant and absence of cholesterol content in it the entrapment efficiency was found between 33.3% - 86.66 % Shown in Table

Table 8: % Entrapment Efficiency

Formulation	Entrapment Efficiency
F1	40 % $\pm$ 0.16
F2	86.66% $\pm$ 0.07
F3	73.3% $\pm$ 0.09
F4	80 % $\pm$ 0.12
F5	33.3% $\pm$ 0.11
F6	66.6% $\pm$ 0.10
F7	60% $\pm$ 0.09
F8	72% $\pm$ 0.11

Zeta Potential

The zeta potential of the F2 Formulation is -22 mv showing in Figure 8.16 it indicating that the formulation is stable. Zeta potential predicts the stability of the carrier system. The higher the ZP values, the more the repulsion between the charged particles and hence the more stability against aggregation. The particle with ZP values more than (+30 mv) less than (-30 mv) is considered stable.

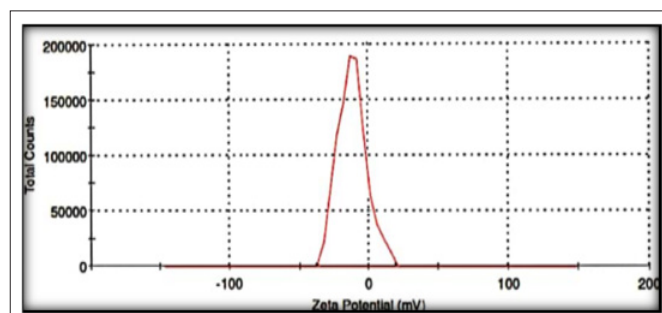


Figure 15: Zeta Potential

Particles Size of F2 Formulation

The particles size of F2 Formulation is 5-100 μ m showing in figure 8.17. The Particle Size of the F2 Formulation is checked by the zeta sizer it gives the size range for the prepared niosome vesicle is 10 – 100 μ m. it is the ideal size for the niosome formulation.

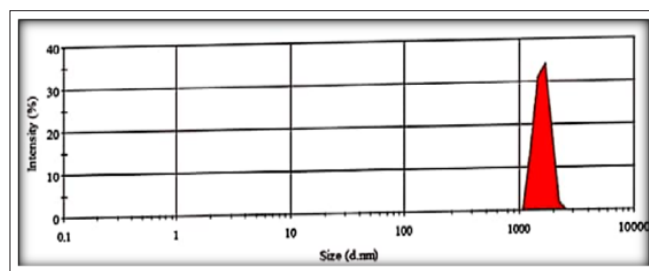


Figure 16: Particle Size Analysis

Differential Scanning Calorimetry

The Differential Scanning Calorimetry of pure drug and Formulation reveals that the niosome containing Glimepiride is bounded by the niosome vesicles.

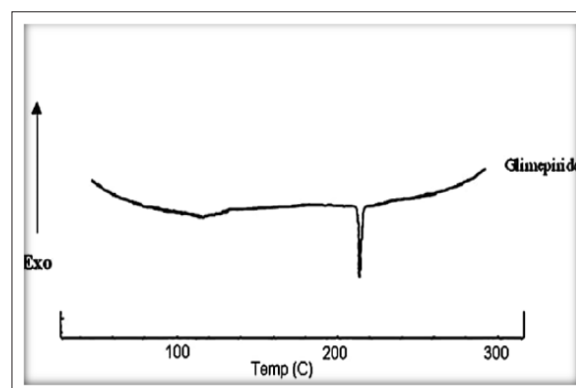


Figure 17: DSC of Glimepiride Drug

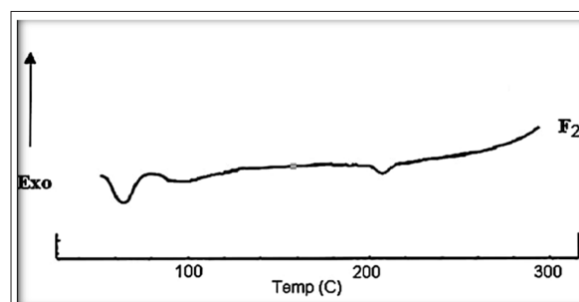


Figure 18: DSC of Niosome Formulations

The Thermogram of glimepiride demonstrates a sharp endothermic peak at 218.8 oC which is corresponding to its melting point. DSC thermogram of Glimepiride loaded niosome molar ration Span 60: Cholesterol (1:0.5), we can notice that the melting endotherm of glimepiride disappears. This suggests probable interaction of drug with a compound of the bilayer and may explain the improved entrapment of the drug into this niosomal formulation.

Stability Study

The F2 formulation Batch was optimized therefore this batch was selected for the stability study. Samples were withdrawn on the 7th, 14th, 21st, 28th, and 30th days and there were no changes in entrapment Efficiency and drug release.

Stability study of f2 optimized batch formulation carried out their entrapment efficiency between the 86.05- 86.66 % and cumulative drug release found between 40.29% - 40.59% showing in Table 9.

Table 9: Stability Study of F2 Formulation Batch

Time	%Entrapment Efficiency		% Cumulative drug release.	
7 days	86.66% ± 0.11	86.60% ± 0.12	40.59% ± 0.06	40.57% ± 0.05
14 days	86.53% ± 0.13	86.54% ± 0.14	40.51% ± 0.04	40.53% ± 0.03
21 days	86.51% ± 0.12	86.52% ± 0.13	40.47% ± 0.05	40.41% ± 0.04
28 days	86.37% ± 0.14	86.49% ± 0.12	40.41% ± 0.03	40.34% ± 0.06
30 days	86.05% ± 0.12	86.42% ± 0.14	40.39% ± 0.04	40.29% ± 0.05

Comparison Study of Sustained Release Glimepiride Tablet and Niosome Formulation

The comparison study shows between tablet and niosome formulation shows that the niosome formulation show more sustained release as compared to the tablet formulation [17].

TIME (hr)	In vitro Release of tablet formulation	In vitro release of F2 Formulation
0	0	0
1	21.46	0.11
2	43.40	1.70
3	57.24	3.6
4	69.16	5.6
6	81.09	21.9
8	85.38	31.0
10	93.02	35.8
12	98.26	40.5

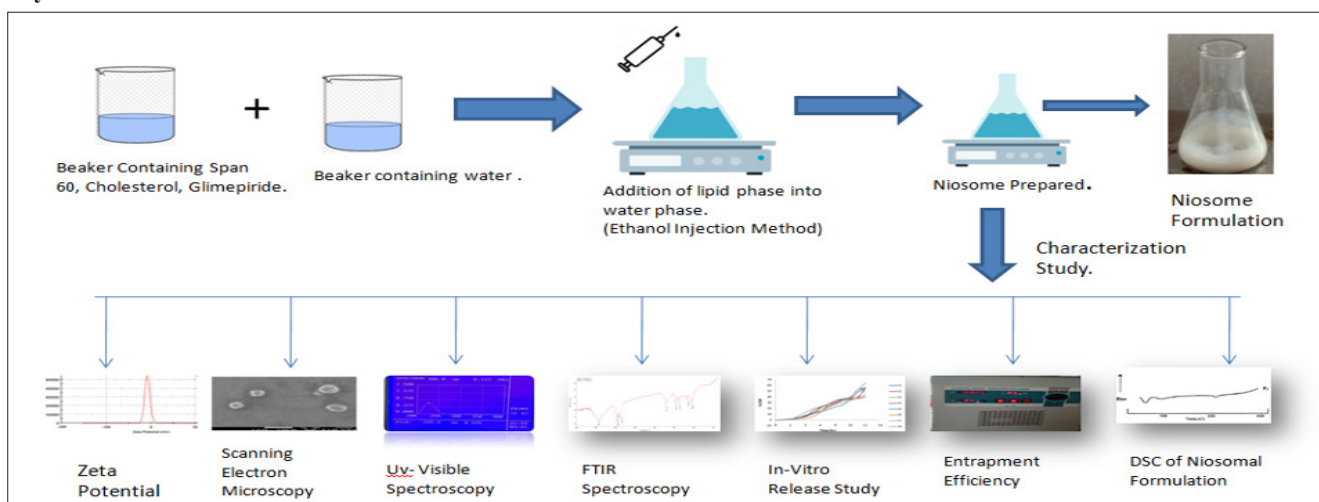
Conclusion

- After the study of the result, it concluded that glimepiride-loaded niosome prepared have a sustained-release effect. This helps the geriatric patient to minimize repeated taking of doses.
- The F2 Formulation which having 40.59% release. It reveals that this formulation attending sustained-release effect. This formulation also having 86.66 % entrapment efficiency.
- The zeta potential value is -22. Mv is indicating the niosomal suspension having high stability.
- The study of Particle size shows the niosomal vesicle size is 10µm – 100µm. The DSC study reveals that the glimepiride was successfully entrapped inside the niosome.

Future Perspective

- The work can be extended for its in vivo studies for in vitro-in vivo correlation and various in vivo studies.
- The formulation of the Niosome drug delivery system can be tried with other Surfactants, to enhance its availability.
- After Niosome Formulation converted into the powder by liophilization technique it can be incorporate into tablet formulation. Tablet formulation can be develop.

Summary



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