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Development and Characterization of Niosomal Drug Delivery of Vildagliptin

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Abstract:

Niosomes have been considered as promising nano carriers for vildagliptin, since they have been shown to sustain the drug release up to 13 hours. The main objective of this study was to prepare and characterize niosomes of vildagliptin. Niosomes were prepared using surfactant span 60 and cholesterol, using the probe sonication method. Scanning electron microscopy and HORIBA scientific SZ-100 instrument was used to assess the morphology, size and size distribution patterns of prepared niosomes. After 4 weeks of storage at 4 °C the vildagliptin-loaded niosomes remained physically stable in terms of encapsulation efficiency, particle size and PDI. Taken together our findings indicate that niosomes could be considered as a plausible drug delivery platform for antidiabetic application of vildagliptin.

Keywords: Niosomes, Vildagliptin, Encapsulation efficiency

1. Introduction:

Type 2 diabetes (T2D), formerly known as adult-onset diabetes, is a form of diabetes that is characterized by high blood sugar, insulin resistance, and relative lack of insulin due to dysfunctioning of islet cells (α & β). Rates of type 2 diabetes have increased markedly since 1960 in parallel with obesity. As of 2015 there were approximately 392 million people diagnosed with the disease compared to around 30 million in 1985. [1]

Several hypoglycemic drugs are available for the treatment of type 2 diabetes which works by different mechanisms for example, the biguanides, thiazolidinediones, and sulfonylureas. Despite the availability of large varieties of hypoglycemic agents, the treatment of type 2 diabetes remains elusive [2, 3].

Among the most encouraging new classes of medications for sort 2 diabetes are those that influence the incretin hormone glucagon-like peptide-1 (GLP-1) [4]. The studies have shown that incretin analogs/regulators have a characteristic role in the successful management of glycemic control. Previous studies have reported that the incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) have association with pancreatic islet α and β cells for their responsiveness against glucose level in the body [5]. Moreover, it has been reported that dipeptidyl peptidase-4 (DPP-4) has vital role in the degradation of GLP-1 and GIP. Thus, leading to the decreased responsiveness of pancreatic islet α and β cells against glucose and dwindled secretion of insulin. Vildagliptin is one of the very effective incretin enhancers that functions as a potent inhibitor of DPP-4. The inhibition of DPP-4 conversely restrict the rapid degradation of GLP-1 and GIP thus improve the insulin secretion through enhancement of sensitivity of pancreatic α and β cells against inappropriate glucose levels [6].

The drug has not been approved by FDA till date as it is still in clinical trials for some of the features. However, based on its clinical importance, it has been approved for clinical and therapeutic use by European Medicine Agency (EMA) and Australian TGA (Therapeutic Goods Administration) and Australian PBS (Pharmaceutical Benefit Scheme) [6, 7]

Vildagliptin is reported to have rapid metabolism and short elimination half-life of 90 minutes. Despite the current use of vildagliptin to treat hyperglycemia, its multiple administration is needed to attain optimal therapeutic concentration which has the potential to cause severe side effects. Therefore, it is of great importance the development of new approaches with higher specificity and effectiveness to deliver as antihyperglycemic agent to T2DM. Certainly, nanoparticulate drug delivery system containing vildagliptin might be a powerful tool to overcome the shortcomings associated with conventional drug delivery. Nanoparticulate formulation with sustained drug release property might result in enhanced anti-hyperglycaemic activity [8, 9]. Among various nanomaterials, developing drug nanocarriers have been received tremendous interest due to their enhancement in controlled, targeted drug delivery. The ideal drug delivery system (DDS) should be biocompatible, inert, mechanically stable, and have drug loading [10]. Among these characteristics, most of the developed colloidal drug delivery systems suffer from toxicity at high concentrations, where does not allow to deliver the high dosage of the drug at once shot administration [11, 12]. Hence, developing nanocarriers with high biocompatibility even at their high concentrations with high drug loading capability is of importance for some medications, where high dosage of the drug is required for successful treatment [13, 14, 15].

In the pharmaceutical field, drug delivery systems (DDS) using vesicular carriers have attracted great interest in recent years because these carriers can provide high encapsulation efficiency, controlled release, can carry both hydrophilic and hydrophobic drugs, biocompatibility, biodegradation, prolonged circulation in blood and ability to target a specific area. Since the composition of vesicles affects their physicochemical characteristics such as their size, charge, lamellarity, elasticity and thermodynamic phase, vesicular carriers with novel functionalization and architecture are being continuously explored.

Among many reported vesicular carriers, carriers such as liposomes, transferosomes, ethosomes and niosomes have proved to possess distinct advantages over other dosage forms [16, 17].

To overcome the drawbacks associated with conventional drug delivery systems of vildagliptin, the present investigation aimed to explore niosomes as carriers of vildagliptin. The developed formulations were optimized using Response surface methodology. The aim of using the experimental design methods was to investigate the effect of independent variables on dependent variables [18].

2. Material and Methods:

2.1. Materials

Vildagliptin (Precise Chemipharma ltd. Mumbai) was used as an API in the formulation. Cholesterol, Span 60 (Sorbitan monostearate), Potassium Dihydrogen Phosphate and sodium hydroxide were obtained from Loba Chemie ltd. Mumbai. The dialysis bag (MW 12-14 kDa) was obtained from Serva. Distilled water was used for all the experiments.

2.2. Optimization of vildagliptin loaded niosomes by experimental design

The optimal design was applied using Design-Expert 13.0.5.0 software to study the effect of independent variables (amount of cholesterol, sonication time) on physicochemical properties of vildagliptin loaded niosomes. These factors and their levels are illustrated in Table 1.

Table 1: Levels of Independent variables

Sr. No.	Independent Variables	Levels		
		Low (-1)	Medium (0)	High (+1)
1.	Amount of Cholesterol	50 mg	75 mg	100 mg
2.	Sonication Time	3 min	5 min	7 min

Also, the effects of these variables were investigated on the particle size, Polydispersity index (PDI), and entrapment efficiency (EE). The optimum formulation was selected regarding the minimum size and PDI range of the niosomes and maximum range of entrapment efficiency. Furthermore, the percentage of error between the expected and the observed results were calculated. Finally, the optimized formulation was selected for further investigation. [18]

2.3 Preparation of niosomes [19]

Probe sonication method was used to prepare niosomes. Vildagliptin was mixed with 15 ml of water with the aid of magnetic stirrer. Weighed amount of cholesterol and span 60 was added & Mixture was then subjected to probe sonication. Probe temperature at 50-60°C in a pulsatile manner (50 s sonication with 10 s pause) at an amplitude of 30%. Niosome formulations were collected and stored at 4 °C for further purification and characterization.

The amount of cholesterol & sonication time were the variables in the optimization of niosome formulations. The exact compositions of studied niosomal formulations are shown in Table 2.

Table 2: Formulation composition of niosomal batches

Batch	Vildagliptin	Span 60	Cholesterol	Sonication time
F 1	50 mg	100 mg	-1	-1
F 2	50 mg	100 mg	0	-1
F 3	50 mg	100 mg	+1	-1
F 4	50 mg	100 mg	-1	0
F 5	50 mg	100 mg	0	0
F 6	50 mg	100 mg	+1	0
F 7	50 mg	100 mg	-1	+1
F 8	50 mg	100 mg	0	+1
F 9	50 mg	100 mg	+1	+1

2.4. Characterization of niosomes

The particle size, zeta potential, and polydispersity index (PDI) of all niosomal formulations were measured by dynamic light scattering (HORIBA scientific SZ-100 instrument). The particle morphology of the optimized niosomes was observed using SEM. FTIR spectroscopy was used to analyse the molecular interactions between drug and niosomal components for ex. cholesterol, Span 60, vildagliptin, physical mixture and also optimised niosomal formulation. [20]

2.4.1. Vesicle size analysis & zeta potential determination

Mean vesicle sizes of vildagliptin loaded niosomes were determined by dynamic light scattering using Zetasizer (HORIBA scientific SZ-100 instrument) at 25 ± 1 °C and at a scattering angle of 90°. Niosomes were suitably diluted (1:100) with distilled water. [18, 21]

The zeta potential (ZP) of niosomes represents the overall charge of vesicles and stability of formulation. The electrophoretic mobility measurement was carried out using HORIBA scientific SZ-100 instrument. The sample were dispersed in appropriate distilled water. All measurements were carried out in triplicates at 25°C for 120s.

2.4.2. Entrapment efficiency

Vildagliptin niosomes formulations were centrifuged at 15,000 rpm for 30 min at 4 °C using a refrigerated centrifuge (C-24BL, Remi instruments, India) to separate niosomes from un-entrapped drug. Concentration of the free drug in the supernatant was determined by measuring absorbance at 222 nm with a UV–Visible spectrophotometer (LABINDIA® ANALYTICAL UV 3000+). The percentage of

drug entrapment in niosomes was calculated using the following formula. This process was repeated twice to ensure that free drug was completely removed.

$\% EE = (C_t - C_f)* 100$

Where,

C_t = Total amount of drug added

C_f = Unentrapped drug

[21]

2.4.3. Optimization of batch

Data obtained from particle size, PDI, zeta potential, entrapment efficiency were used to find the optimized batch. This optimized batch was further subjected to invitro drug release and release kinetics, IR, SEM characterisation.

2.4.4. Fourier transformation infrared spectroscopy (FTIR)

The spectra were recorded for pure drug, and optimized batch using FTIR. FTIR spectra was obtained using a Schimadzu FTIR spectrometer (model). KBr-press was used to make drug and KBr pellets. The sample was scanned in the 4000-450 cm-1 range [18, 22].

2.4.5. In Vitro Drug Release Studies

The in vitro drug release of the F1 to F9 batches were performed by using dialysis bag method against 0.1N HCl pH 1.2 for first two hours followed by phosphate buffer pH 6.8 for next six hours and lastly in phosphate buffer pH 7.4 up to 13 hour. The dissolution mediums were maintained at 37 ± 0.5°C in an incubator shaker at a constant speed (50rpm).

1ml of vildagliptin niosomal suspension was filled in the dialysis bag which was hydrated overnight and then immersed in the dissolution medium. At certain time intervals of 1, 2, 3, up to 13 hour, aliquots of 5ml of dissolution medium was taken and replaced with same volume of fresh medium. The sample was analysed by UV spectrophotometer. All experiments were performed in triplicate [13, 22, and 23].

2.4.6. Scanning electron microscope (SEM) [18]

SEM was used to examine the morphology of the optimised batch. The samples were adhered on a gold-sputtered double-faced adhesive tape. Scanning electron photos were taken at a 15kV accelerating voltage, and the resulting micrographs were studied at magnifications of X500, X1000, and X2000.

2.4.7. Stability Study

The stability of the optimized formulation was determined by storing it at 4 °C in a sealed glass vial. The size, PDI, zeta-potential and % EE values were recorded before and after 4 weeks of storage [19, 22]

2.4.8. Statistical analysis of data

Results are expressed as mean ± standard deviation. Statistical analysis of obtained results was carried out using ANOVA and Design Expert software. Differences were considered statistically significant at the < 0.05 level of probability (P).

3. Results and Discussion:

3.1 Effect of Variables

Central composite design of design expert software (design expert software version 13) was used to study effect of variables on the physicochemical properties of the antidiabetic niosomes. X1 and X2 are the independent variables while Y1, Y2 and Y3 are the response variables. The analysis of variance (ANOVA) is performed to identify the significant factor, better fit and the best formulation possible (Table 4). Value of "Prob > F" less than 0.05 indicate model terms are significant. Value greater than 0.1 indicate the model terms are not significant.

In present study, responses studied are particle size, PDI and % EE while amount of cholesterol and sonication time is considered as independent variables as shown in table 3.

The optimum formulation was selected considering minimum particle size of the niosomes and maximum range of entrapment efficiency. The desirability index was used in the data optimization of D-optimal design. Furthermore, the percentage of error between the expected and the observed results were calculated. Finally, the optimized formulation was selected for further investigation.

Table 3: Particle Size (nm), PDI & Zeta potential for Formulation Batches

Batch No. & Variables	Particle Size (nm)	Polydispersity Index (PDI)	Zeta Potential	% EE
F 1 [C50:S3]	220.3	0.314	-40.0	86.82
F 2 [C75:S3]	225.2	0.339	-42.1	87.81
F 3 [C100:S3]	250.9	0.335	-34.2	88.32
F 4 [C50:S5]	209.2	0.311	-43.3	89.72
F 5 [C75:S5]	214	0.263	-48.3	90.18
F 6 [C100:S5]	219.7	0.283	-43.4	92.32
F 7 [C50:S7]	179	0.200	-42.7	87.72
F 8 [C75:S7]	190	0.316	-33.5	87.98
F 9 [C100:S7]	194.5	0.351	-50.4	88.43

Table 4: Fit Summary table of response variables

Response	Source	R^2	Sequential p-value	Adjusted R^2	Predicted R^2	Std. Dev.	
Particle size	Linear	0.9409	0.0009	0.9172	0.8457	6.61	Suggested
PDI	Linear	0.8414	0.0040	0.7885	0.5704	0.0215	Suggested
% Entrapment efficiency	Quadratic	0.9611	0.0492	0.8640	0.3007	0.6255	Suggested

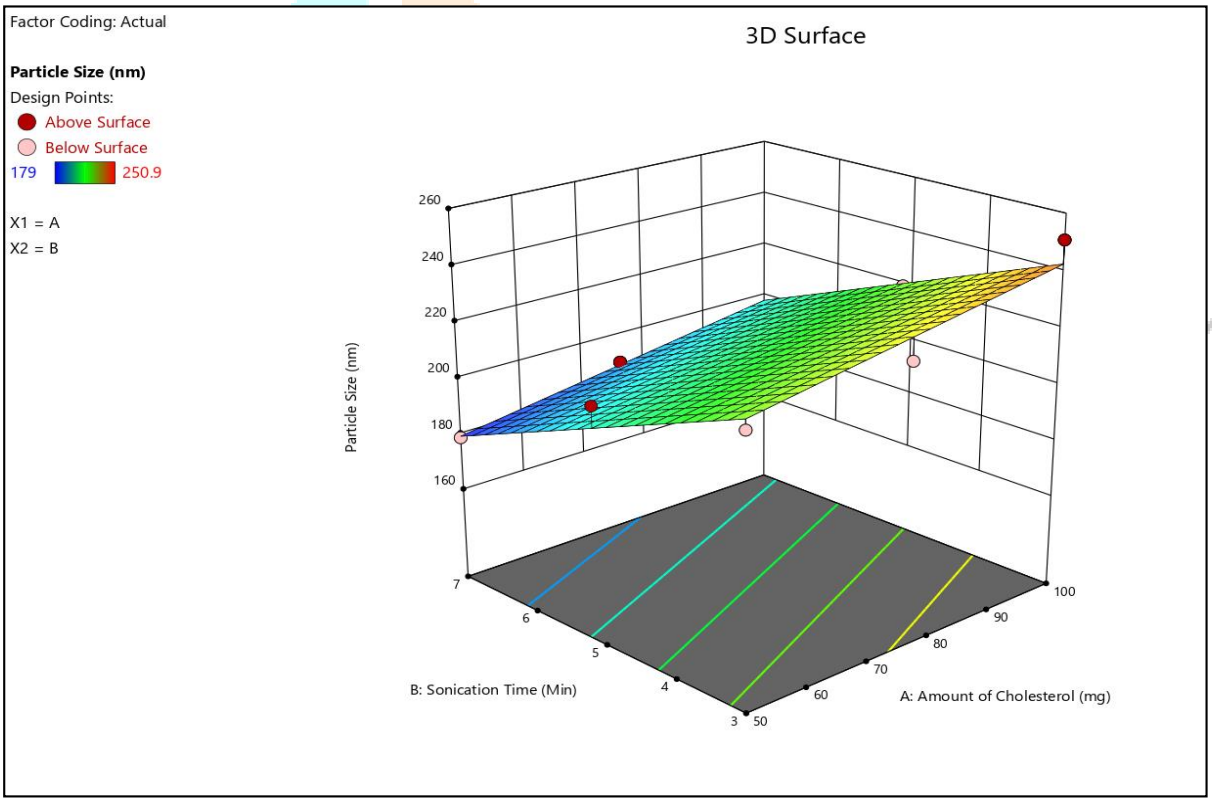

Figure 1: Response surface graph of particle size

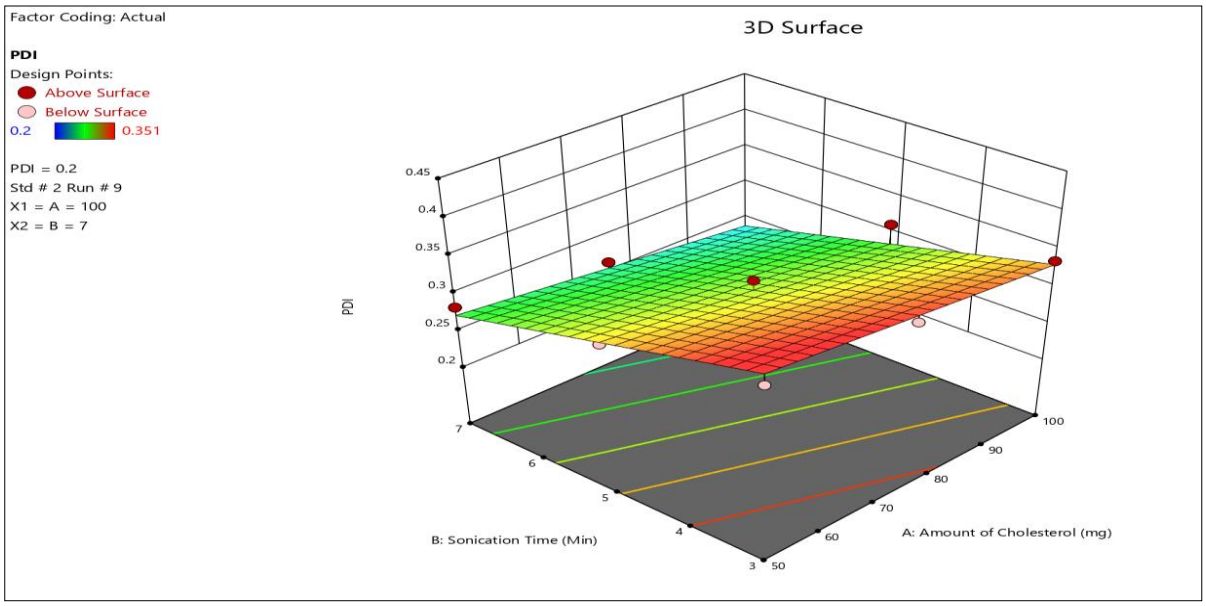

Figure 2: Response surface graph of PDI

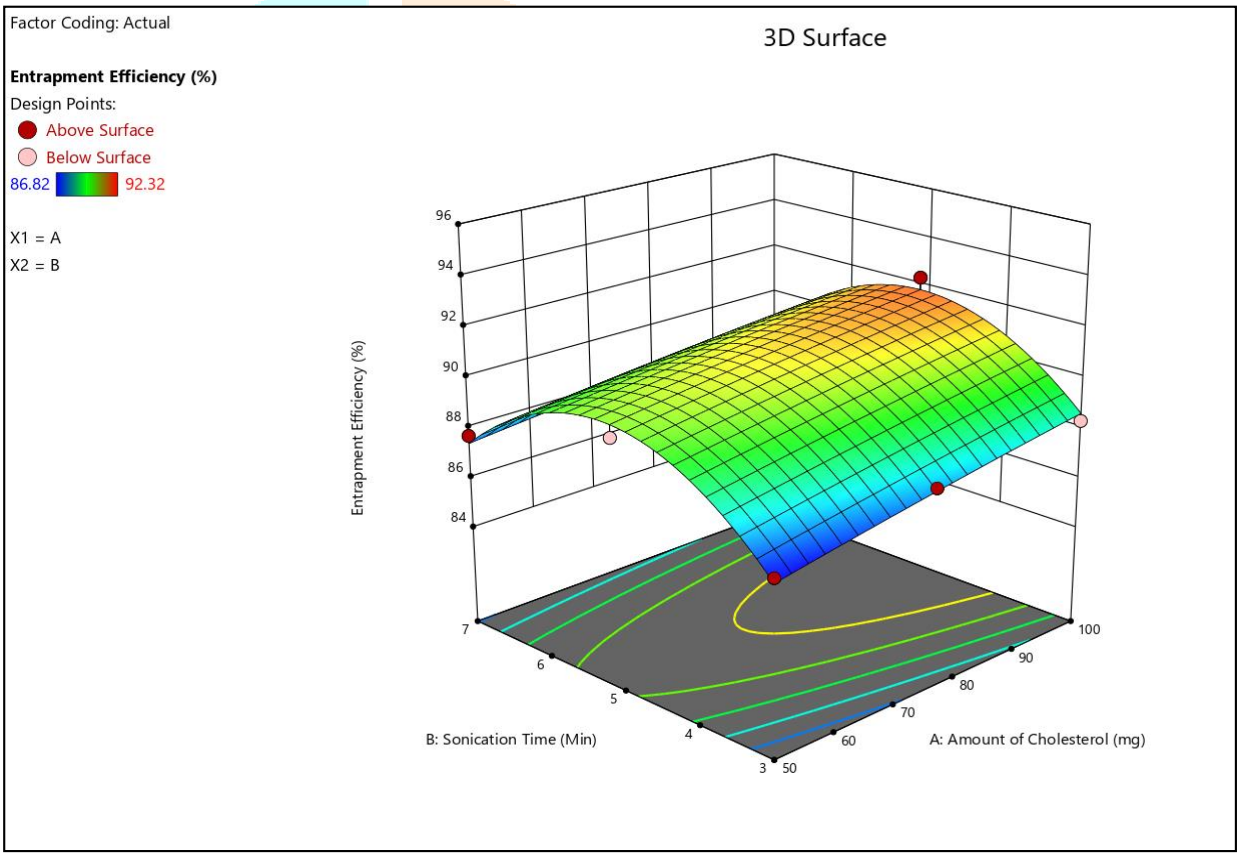

Figure 3: Response surface graph of entrapment efficiency

3.2 Particle Size Analysis

Particle sizes of niosome batches F1 to F9 are shown in table 3. From results of particle size analysis, it was observed that the niosomes have nanometric particle size ranging from 179 to 250.9 nm. The formulation batch F7 showed the smallest particle size i.e. 179 nm.

- Effect of amount of cholesterol

From Fig. 1 it was analysed that as the amount of cholesterol increases, particle size of niosomes also increases. It might be due to widening of bilayers on addition of cholesterol. To explain this, it is important to understand the mechanism by which cholesterol is incorporated in the bilayer membrane. Being amphipathic, cholesterol can imbibe itself into the bilayer membrane with its hydrophilic head oriented towards the aqueous surface and aliphatic chain line up parallel to the hydrocarbon chains in the centre of the bilayer. It is known that cholesterol increases the chain order of the liquid-state bilayer and strengthen the nonpolar tail of the non-ionic surfactant. At low cholesterol concentration, it is feasible to expect that cholesterol would have resulted in close packing of surfactant monomers with increasing curvature and reducing size. However, increasing cholesterol content, with its known lipophilic nature (log P of 7.02), would have resulted in increased hydrophobicity of the bilayer membrane and may have imparted disturbance in the vesicular membrane, thus, increasing vesicles radius in a way to establish a more thermodynamic stable form. Similar results were obtained in earlier articles [20, 21].

- Effect of sonication time

As the sonication time increases, particle size of niosomes found to be decreasing.

3.3 Polydispersity Index

Polydispersity index indicates the homogeneity of the niosomal dispersion. A PDI value < 0.3 indicates a homogenous dispersion. As the PDI value decreases, uniformity of vesicle size in the formulation increases. The PDI of niosomal formulations were obtained in the range 0.20 to 0.35 as given in table 3.

- Effect of amount of cholesterol & Sonication time

From 3D surface response graph of Polydispersity index (Fig 2), it was analysed that as the amount of cholesterol & sonication time increases, PDI value of niosomes also decreases, reflecting improvement in the homogeneity of niosomes population with increasing cholesterol content as well as sonication of niosomes.

3.4 Zeta potential analysis

The zeta potential (ZP) of a vesicle represents the overall charge of niosomes and stability of formulation. Zeta potential predicts the stability of the niosomal system. Higher the zeta potential value, the more repulsion between charged particles which prevents aggregation of vesicles. Thus, it results in the formation of a stable niosomal system. Niosomes with -30 mV > zeta potential values > +30 mV are considered stable. Zeta potential values of vildagliptin loaded niosomes were found to be ranging from -33.5mV to -50.4mV as per table 3. Thus results indicate that all niosomal formulations were electro statistically stable.

3.5 Percent Entrapment Efficiency

Percentage entrapment efficiency is expressed as proportion of drug encapsulated into niosomes relative to total amount of drug added. Percentage entrapment efficiency (%EE) of nine batches F1 to F9 depicted in table 3. % Entrapment efficiency of vildagliptin in different formulations is found to be ranging from 86.82 % to 92.32 %. Formulation F 6 was found to have maximum %EE of 92.32.

- Effect of amount of cholesterol

Cholesterol has been widely employed as an additive agent in niosomal formation, due to its ability to impart rigidity of the membrane and conversely to improve their vesicular integrity and stability of niosomes. Cholesterol has been noted to stabilize bilayers by modulating their cohesion and mechanical strength, to prevent leakage and retard permeation of solutes enclosed in the central aqueous cavity of the vesicles. In this study, highest entrapment efficiency was achieved by batch F6 [C100: S5]. Thus obtained results from fig. 3 indicate that increasing amount of cholesterol causes increase in entrapment efficiency of drug into niosomes.

- Effect of Sonication time

From above results, it is seen that as the sonication time increases from 3 min to 5 min, entrapment efficiency of niosomal formulation increases. However, further increase in sonication time (7min) resulted in decrease in entrapment efficacy of niosomes, which might be due to leakage of drug on excess sonication. Similar results were obtained in earlier articles [20, 21].

Table 5: Optimized batch suggested by design expert software

Factor	Optimized level
Amount of Cholesterol	58.705
Sonication Time	5.70835

Table 6: Expected and Observed results of optimized batch

Response	Expected	Observed	Residual
Particle Size	183.000	182.3	0.700
Polydispersity Index	0.284	0.297	- 0.013
% Entrapment efficiency	88.705	87.74	0.965

3.6 Fourier Transform Infrared Spectroscopy

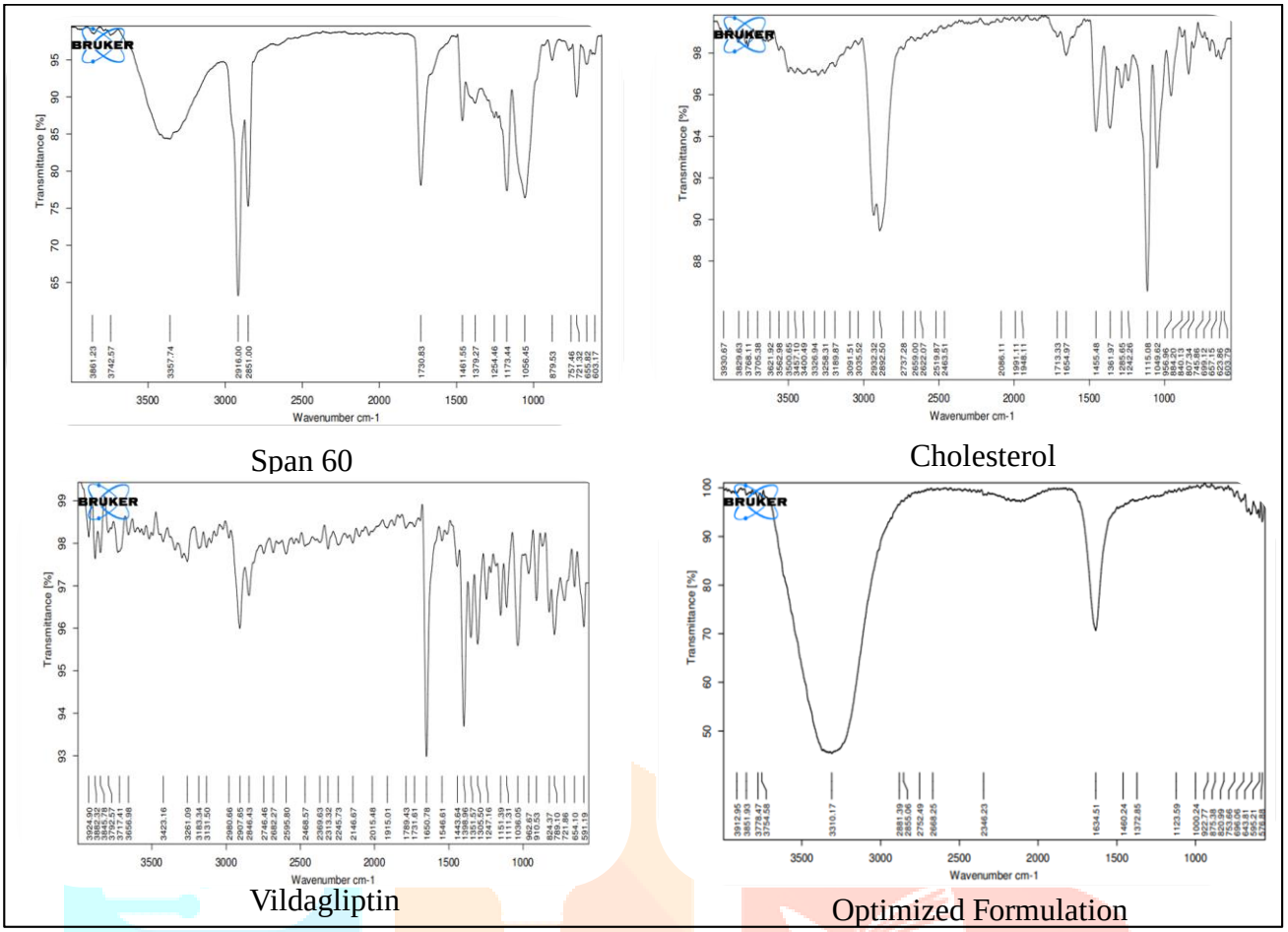

Figure 4: FTIR result of drug, excipients and optimized formulation

Table 7: The characteristic peaks for FT-IR spectra of different samples

Bonds	Functional Group	Peak observed	Peak obtained
1) Span 60			
-CH stretch	Alkyl group	2916.00 cm-1 2851 cm-1	3000 – 2840 cm -1
C = O stretch	Ester group	1730.83 cm-1	1725 – 1750 cm-1
-OH stretch	Hydroxyl group	3357.74 cm-1	3400 – 3200 cm-1
C – O stretch	Ester group	1056.45 cm-1 1173.44 cm-1	1300 – 1000 cm-1
2) Cholesterol			
C – H stretch	Aromatics	2932.32 cm^{-1} 2892.50 cm^{-1}	2900 – 2880 cm^{-1}
O – H bend	phenol	1361.97 cm^{-1}	1390 – 1310 cm^{-1}
C = C	Alkene	1654.97 cm^{-1}	1670 – 1600 cm^{-1}
OH stretch	Hydroxyl group	3400.49 cm^{-1}	3200 – 3600 cm^{-1}

3) Vildagliptin			
O – H stretch	Alcohol	3261.09 cm-1	3600 – 3200 cm-1
C = O	Amide	1650.78 cm-1	1680 – 1630 cm-1
C – O stretch	phenol	1247.16 cm-1	~ 1200 cm-1
−C≡N	Nitrile	2245.73 cm-1	2260 – 2220 cm-1
N – H	Secondary amine	3423.16 cm-1	~ 3450 cm-1
C – N stretch	Aromatic secondary amine	1305.50cm-1	1350 – 1380 cm-1
4) Optimized formulation			
-OH stretch	Alcohol	3310.17 cm^{-1}	3600 - 3200 cm^{-1}
-CH stretch	Alkyl group	2881.39 cm^{-1} 2855.06 cm^{-1}	3000 - 2800 cm^{-1}
C = O	Amide	1634.51 cm^{-1}	1680 - 1620 cm^{-1}

3.7 In-Vitro Drug Release and kinetics study of optimized batch

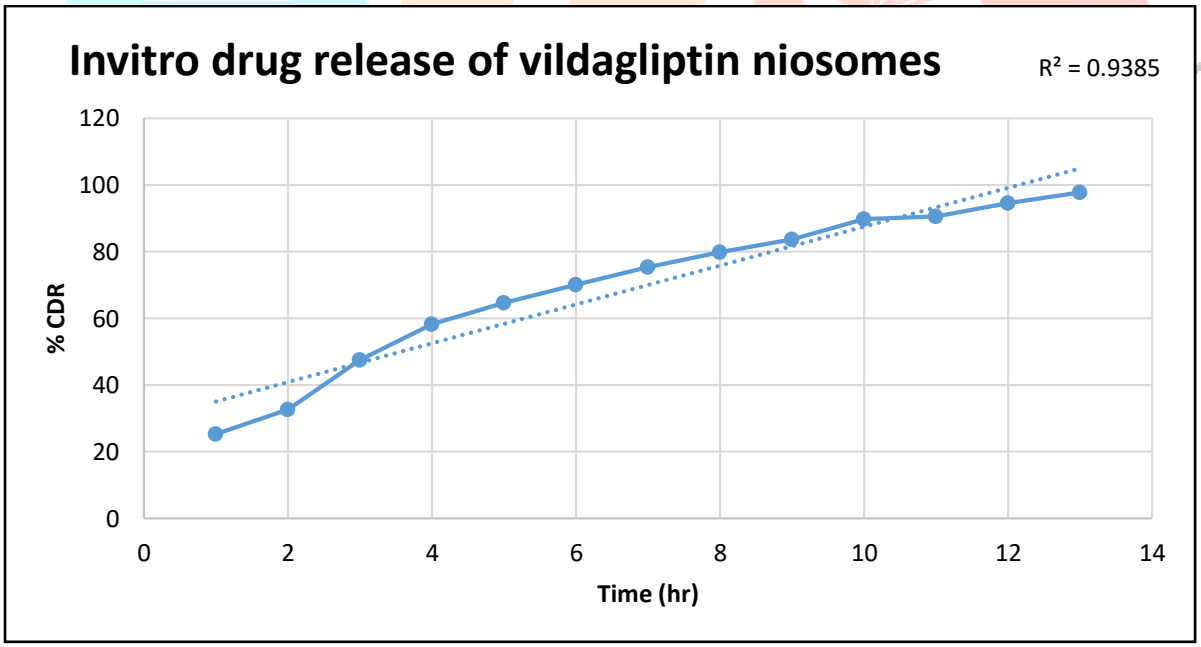

Figure 5: In-vitro drug release of vildagliptin niosomes

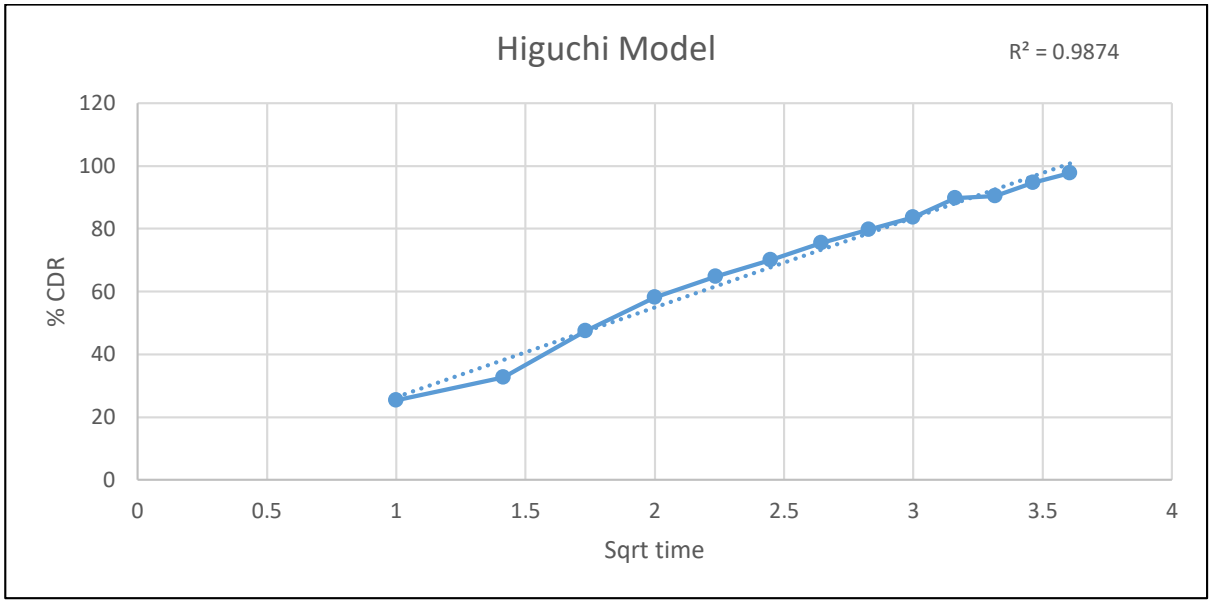

Figure 6: Higuchi Model of release kinetics

A linear form of various kinetic models was plotted based on drug release data for realizing the mechanism of drug release. Some of the most important release kinetic models are as follows: zero-order (cumulative percent drug release vs time), first-order (log cumulative percent drug remaining vs. time), Higuchi (cumulative percent drug release vs. square root of time), Hixon crowells (cube root of cumulative drug release vs. time) and Korsmeyer Peppas (log percent cumulative drug release vs. log time). The R2 calculated for the linear curve was obtained by regression analysis to determine the release kinetics of the optimum formulation. A kinetic model with a regression coefficient near to one; is a desirable model for the release profile of that formulation. Here, the drug release mechanism for optimum formulation can be best fitted by the higuchi model.

3.8 SEM

From the SEM morphology image in figure 7, prepared niosomes were found to be spherical in shape with smooth surface & vesicles were discrete & separate with no aggregation or agglomeration.

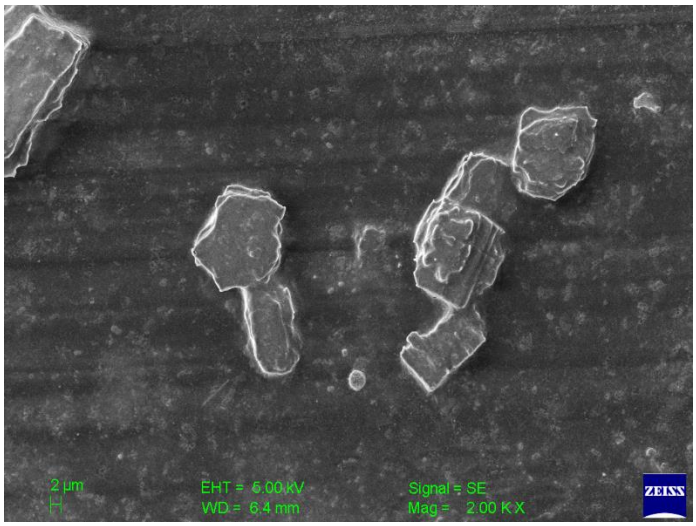

Figure 7: SEM image of optimized niosome formulation

3.8 Stability study

Investigation on the physical stability of optimum niosomal formulation were assessed by measuring vesicle particle size, polydispersity index, and % entrapment efficiency before and after 4 weeks of storage at refrigerator (4°C) as given in table 8.

There is no significant change in particle size, PDI i.e. the formulation still has particle size in nanometric range and PDI indicates homogenous dispersion. The amount of drug retained in niosomal formulation shows drug leakage of less than 10 %.

At the end of the stability study period, investigated niosomal formulation remained visually unchanged without any manifested gross physical instability signs such as creaming, flocculation or sedimentation.

These findings show the physical stability of tested niosomes and indicate that proposed niosomes may act as an effective formulation protecting against drug leakage.

Table 8: Stability study of optimized batch

Evaluation Test	Initial formulation	After 4 weeks formulation
Particle Size	182.3 nm	204.5 nm
PDI	0.297	0.341
Zeta Potential	-43.1 mV	-35.2 mV
% EE	87.74 %	83.4 %

4. Conclusion:

Our findings indicate that niosomal system may be a promising approach for vildagliptin delivery. The stable niosomes prepared by probe sonication method was optimized to obtain acceptable vesicle size, PDI and % drug EE and was evaluated for, IR spectroscopy, in vitro drug release, stability studies and scanning electron microscopy. Results suggest that drug release from niosomes was sustained up to 13 hours. Niosomes also showed acceptable particle size, PDI, zeta potential and high entrapment of drug. Further, the developed vildagliptin niosomal formulations did not produce any remarkable changes with respect to size, PDI, entrapment of drug. These results put together convincingly prove that vildagliptin niosomes can be a safe and promising alternative to conventional delivery systems displaying superior drug release.

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