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Formulation and liponiosomal hydrid delivery system containing anti-diabetic drug rosiglitazone

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Abstract*— Rosiglitazone is a thiazolidinedione antidiabetic drug used in the management of type 2 diabetes mellitus. The present study aimed to formulate and evaluate a liponiosomal hybrid drug delivery system containing rosiglitazone to improve drug entrapment and provide controlled drug release. The formulation was developed using suitable lipid, non-ionic surfactant, and cholesterol components and optimized based on physicochemical characteristics. The prepared formulations were evaluated for particle size, polydispersity index, zeta potential, drug entrapment efficiency, morphology, drug–excipient compatibility, and in vitro drug release. The developed liponiosomal system is expected to provide enhanced drug encapsulation and sustained release of rosiglitazone, indicating its potential as an advanced delivery approach for antidiabetic therapy.

Keywords*— Rosiglitazone, Liponiosomes, Hybrid drug delivery system, Antidiabetic drug, Nanocarrier, Controlled drug release, Drug entrapment efficiency, Lipid-based drug delivery.

I. INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from impaired insulin secretion, reduced insulin action, or a combination of both. Type 2 diabetes mellitus (T2DM) is the most prevalent form of diabetes and represents a major global health challenge. Long-term uncontrolled hyperglycemia can result in serious microvascular and macrovascular complications, including nephropathy, retinopathy, neuropathy, cardiovascular disease, and impaired wound healing. Consequently, effective pharmacological management of T2DM requires therapeutic strategies that provide adequate glycemic control while minimizing adverse effects and improving patient adherence.

Conventional oral drug delivery remains the most widely accepted route for systemic administration because of its convenience, patient acceptability, and relatively low cost. However, conventional dosage forms may not always provide an ideal drug-release profile. Rapid drug release can produce fluctuations in plasma drug concentration, whereas inadequate control over drug absorption may influence therapeutic response. These limitations have encouraged researchers to investigate novel drug delivery systems capable of modifying drug release, improving drug utilization, and potentially reducing unwanted systemic exposure.

Nanotechnology-based drug delivery systems have emerged as promising platforms for the delivery of therapeutic agents. Nanocarriers can provide several advantages over conventional dosage forms, including improved drug solubilization, enhanced encapsulation, protection of incorporated drugs from degradation, controlled or sustained release, and improved interaction with biological membranes. Among lipid- and vesicle-based systems, liposomes and niosomes have received considerable attention because of their ability to incorporate and transport a variety of therapeutic molecules.

1.1 Liposomes

Liposomes are spherical vesicular systems consisting primarily of phospholipid bilayers surrounding an aqueous core. Their amphiphilic nature enables them to accommodate both hydrophilic and lipophilic compounds, while their biomimetic lipid composition can facilitate interaction with biological membranes. However, conventional liposomal systems may have certain limitations, including physical instability, oxidation of phospholipids, leakage of encapsulated drug, and relatively high production costs.

1.2 Niosomes

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Niosomes are vesicular drug delivery systems composed mainly of non-ionic surfactants, often stabilized with cholesterol. They have been investigated extensively because of their relatively good physical stability, formulation flexibility, ability to encapsulate drugs with different physicochemical properties, and potential for controlled drug release. The incorporation of cholesterol can improve membrane rigidity and reduce leakage of the entrapped drug. However, the performance of niosomal systems is strongly dependent on the type and concentration of surfactant, cholesterol content, preparation conditions, vesicle size, and drug characteristics.

Hybrid drug delivery systems have been developed to combine the desirable characteristics of more than one carrier platform. A liponiosomal hybrid delivery system can be designed by integrating lipidic components with non-ionic surfactant-based vesicular components. Such a system may provide improved vesicular stability, enhanced drug incorporation, controlled release, and favorable interaction with biological membranes. The hybrid approach is particularly attractive for drugs whose therapeutic performance may benefit from modification of release characteristics and improved delivery.

The developed system is intended to provide improved drug entrapment and controlled release characteristics and to explore the potential of liponiosomal hybrid technology as an advanced delivery approach for antidiabetic therapy.

II. MATERIAL & METHODS

2.1 MATERIALS

S. No.	Material	Source
1	Rosiglitazone	Yarrow Pharmaceuticals, Mumbai
2	Potassium di hydrogen phosphate	Oxford Chemicals, Mumbai
3	Disodium hydrogen phosphate	Oxford Chemicals, Mumbai
4	Sodium chloride	Oxford Chemicals, Mumbai
5	Sorbitan mono laurate (span 60)	Oxford Chemicals, Mumbai
6	Polysorbate 80 (tween 80)	Oxford Chemicals, Mumbai
7	Cholesterol	HiMedia
8	Chloroform	Oxford Chemicals, Mumbai
9	Methanol	Oxford Chemicals, Mumbai
10	Dicetyl phosphate	HiMedia
11	Triton X – 100	HiMedia
12	Egg phosphatidylcholine	Sigma

2.2 METHODS

2.2.1 Preformulation Studies

The preformulation studies were carried out for confirming the identity of the drug and to ascertain the compatibility amongst the drug and the excipient (polymers) used in formulation.

2.2.2 Organoleptic Characters

The organoleptic properties of the procured drug sample were examined using sensory organs and include color, odor, taste and appearance. The solubility of the drug in various solvents was also observed.

2.2.3 Partition Coefficient

This study was performed by using octanol as oil phase (30ml) and water as aqueous phase (30ml). The partition coefficient was calculated by following formula.

Ko/w = Concentration of drug in octanol/ Concentration of drug in water

2.2.4 Determination of Absorbance maximum (λmax)

Rosiglitazone was dissolved in methanol solution. Solution with 20 µg/ml concentration was prepared by suitable dilution. The solution was scanned using UV spectrophotometer from 200 to 400 nm using methanol as blank. Absorbance maximum was determined as 249 nm. The drug was later quantified by measuring the absorbance at 249 nm in methanol

2.2.5 Formulation of Rosiglitazone Liponiosomes

The reverse ethanol injection method was used for rosiglitazone-loaded liponiosome formulation. Egg phosphatidylchloline and Span 60 mixture were used to develop a spherical lipid bilayer of the liponiosomes. Cholesterol was used as the membrane stabilizer to improve the rigidity of the vesicular membrane. Accurate quantities of rosiglitazone, phosphatidylcholine, Cholesterol, and Span 60 were dissolved in 2 mL ethanol, as shown in Table 4.1. An appropriate amount of preheated distilled water (60°C), with/without the addition of edge activator (Tween 80), was dropped continuously into the alcoholic lipid solution while being magnetically stirrer. The stirring process was continued at room temperature for 1 h, in order to confirm the total elimination of ethanol. The liponiosomal dispersion was sonicated at room temperature using a bath sonicator for 10 minutes. The liponiosomes were kept overnight in a refrigerator for complete maturation.

Table 1 Composition of rosiglitazone liponiosomes

Formulation Code	Rosiglitazone (mg)	Span 60 (mg)	Egg Phosphatidyl choline (mg)	Tween 80 (mg)	Cholesterol (mg)
F1	10	100	100	50	50
F2	10	100	200	50	50
F3	10	100	300	50	50
F4	10	150	100	50	50
F5	10	200	100	50	50
F6	10	250	100	50	50

2.2.6 Evaluation of rosiglitazone loaded Liponiosomes

2.2.6.1 FTIR spectroscopic analysis

The Fourier transformed infrared spectroscopic analysis of the procured drug sample was performed and the major absorption bands were compared with that of the spectral database of the drug to ascertain its identity. FTIR of physical mixture of the drug and the used polymers was also performed to observe to any possible interaction between the drugs and excipients (cholesterol, phosphatidylcholine, span 60, tween 80).

2.2.6.2 Entrapment Efficiency

The unentrapped drug from the liponiosomal formulation was separated by centrifugation method. The liponiosomal suspension was taken in centrifuge tube. The formulation was centrifuged at 15,000 rpm for 45 min using cooling centrifuge and temperature was maintained at 5°C. The supernatant was separated. The supernatant containing unentrapped drug was carefully separated from the pellet and the

Concentration of the free rosiglitazone in the supernatant was determined spectophotometerically by measuring the absorbance at 249 nm.

$$\mathrm{EE}(\%) = \frac{(\mathrm{Dt} - \mathrm{Ds})}{\mathrm{Dt}} \times 100$$

Where Dt is total drug used, Ds is drug in supernatant

2.2.6.3 *In vitro* release study

The liponiosomal formulation was taken in a dialysis membrane of 5 cm length and suitably suspended in a beaker containing 100 ml diffusion medium of phosphate buffer saline pH 7.4. The temperature of medium was maintained at 37±0.5°C. The medium was stirred by means of magnetic stirrer at a constant speed. 1 ml of sample was withdrawn at every 1 hour and replaced with 1 ml of fresh buffer, so that the volume of diffusion medium was maintained constant at 100 ml. The withdrawn samples were made upto 10 mL using phosphate buffer saline pH 7.4. The samples were measured spectrophotometrically at 212 nm.

III. RESULTS AND DISCUSSION

3.1 Organoleptic characters

The observed organoleptic characteristic of the drug sample is presented in Table 2 and 3.

Table 2 Organoleptic properties of Rosiglitazone

S.No	Test	Observation
1	Color	White
2	Odor	Odorless
3	Appearance	Crystalline powder

The melting point of the procured drug sample was

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found to be 125-127°C which was equivalent to the reported standard for rosiglitazone. Partition coefficient of the procured specimen of rosiglitazone was found to be 2.88.

Table 3 Solubility profile of rosiglitazone

S. No	Solvent	Solubility Observed
1	Water	Partially soluble
2	Ethanol	Soluble
4	DMF	Soluble

3.2 Calibration Curve

The calibration curve of rosiglitazone was prepared according to the reported procedure using methanol as the solvent. The absorbance observed is presented in Table 4 and the calibration curve along with the equation for straight line is presented in Figure 1.

Table 4 UV absorbance of rosiglitazone

Concentration (µg/mL)	Absorbance at 249 nm
5	0.103
10	0.204
15	0.308
20	0.413
25	0.522

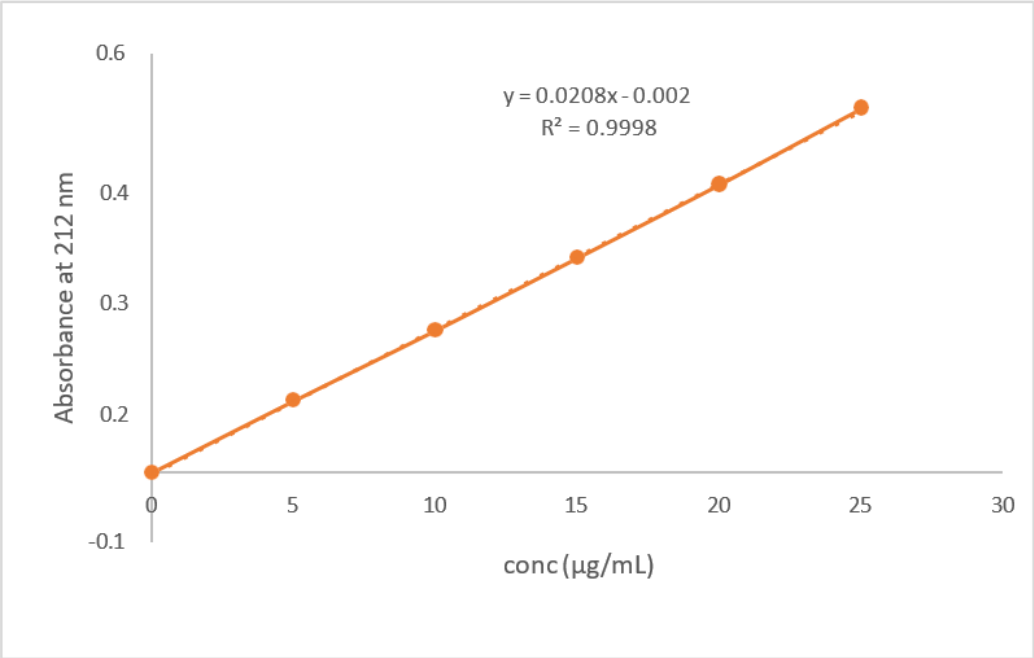

Figure 1 Calibration curve of rosiglitazone

3.3 Development of rosiglitazone proniosomes

In this study, rosiglitazone loaded hybrid liponiosomes were prepared by reverse ethanol injection technique using cholesterol as the membrane stabilizer, phosphatidylcholine as the lipid and non-ionic surfactants such as span 60 with tween 80 as the edge activator. Size of the vesicles in formulation was reduced by sonicating the formulation in bath sonicator.

Formulations with different ratios of surfactant and lipid were prepared. Several physicochemical characteristics of liponiosomes such as morphology, vesicle size determination, drug release profile was investigated.

3.4 Evaluation of rosiglitazone liponiosomes

FTIR and compatibility study

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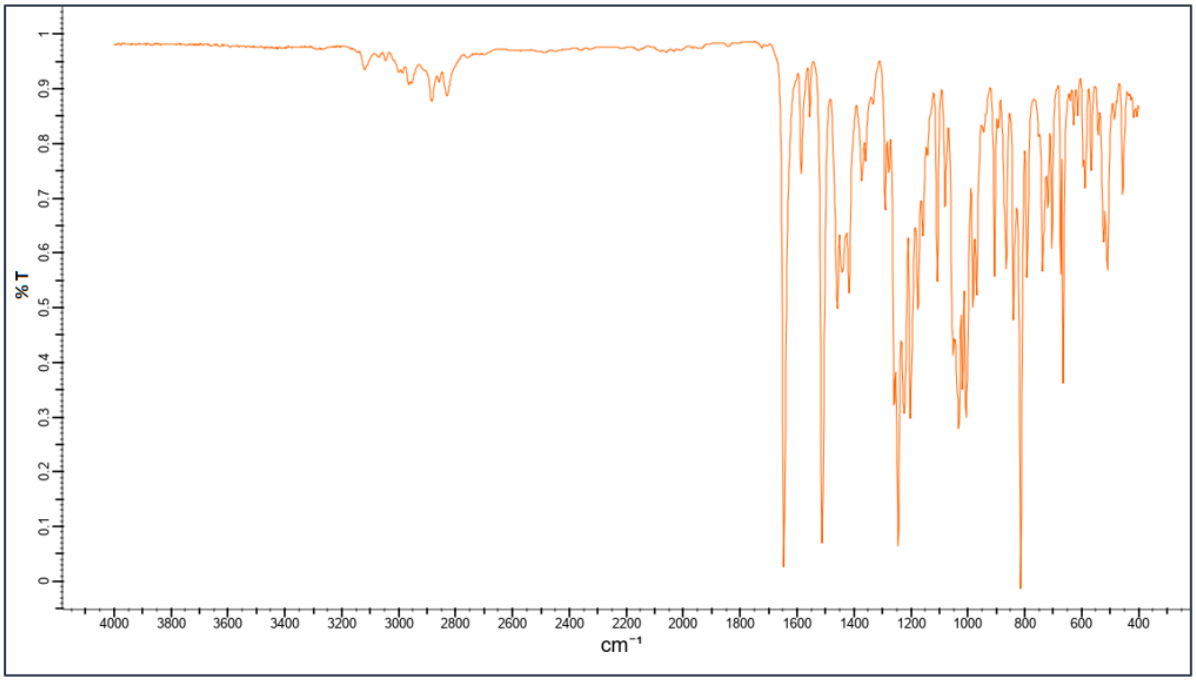

Figure 2 FT-IR spectra of rosiglitazone

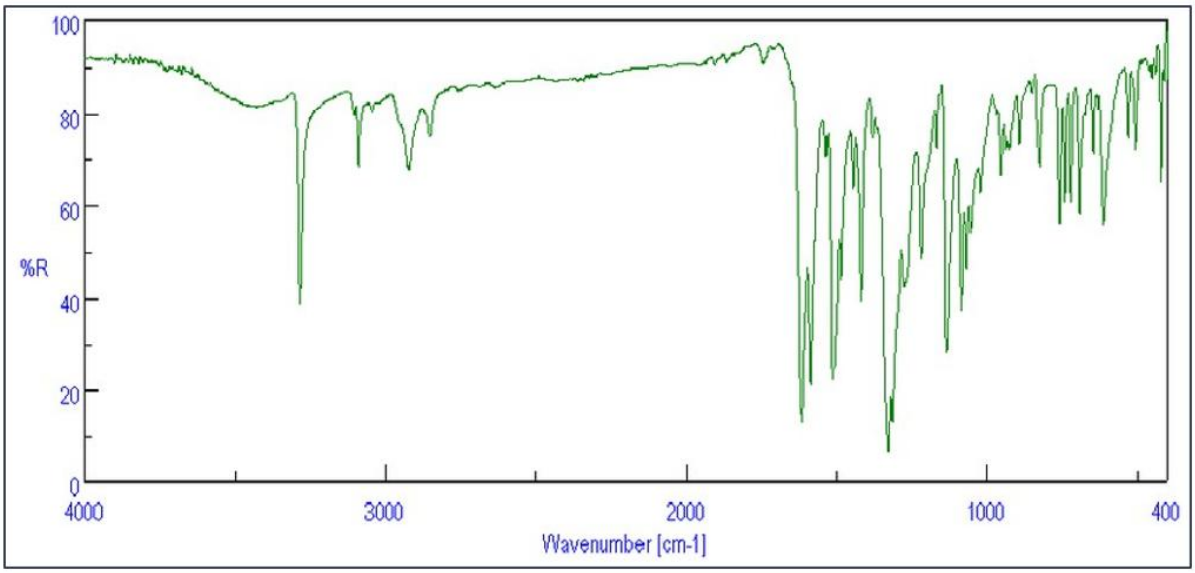

Figure 3 FT-IR spectra of rosiglitazone + cholesterol+ span 60+ tween 80+egg phospatidylcholine

3.5 Percentage drug entrapment efficiency

The entrapment efficiency of the liponiosomes is governed by the ability of formulation to retain drug molecule in aqueous core or in bilayer membrane of vesicles.

Table 5 Entrapment efficiency

Formulation Code	Entrapment Efficiency (%)
F1	68.1
F2	56.8
F3	50.4
F4	71.3
F5	63.9
F6	61.2

The entrapment efficiency using was determined and it was found that a 1.5:1 ratio of the Span 60 and egg phosphatidylcholine resulted in the maximum entrapment of the drug (71.3%) in the liponiosomal bilayer (Figure 4)

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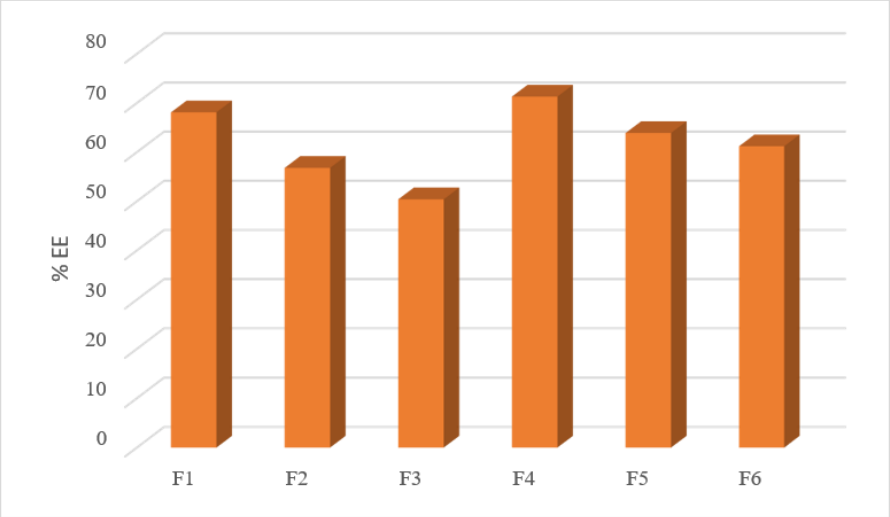

Figure 4 Entrapment efficiency (%)

3.6 In vitro release study

The release of rosgilitazone from the liponiosomes was determined using the membrane diffusion technique. Release study was carried for 12 hours and results are noted in following tables.

Table 6 *In vitro* release of rosiglitazone from liponiosomes

Time (h)	Cumulative percentage of drug released (%)					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	8.3	6.1	4.5	10.8	8.5	6.7
2	21.6	10.9	8.4	24.3	20.9	13.6
3	29.8	17.3	14.9	32.6	28.5	19.9
4	39.5	23.7	20.4	44.4	39.8	31.2
6	52.2	36.2	32.2	55.3	48.1	40.5
8	60.1	43.1	38.7	62.9	56.7	47.3
10	69.5	51.6	46.9	77.8	62.2	52.1
12	83.3	60.9	53.5	89.7	71.9	58.8

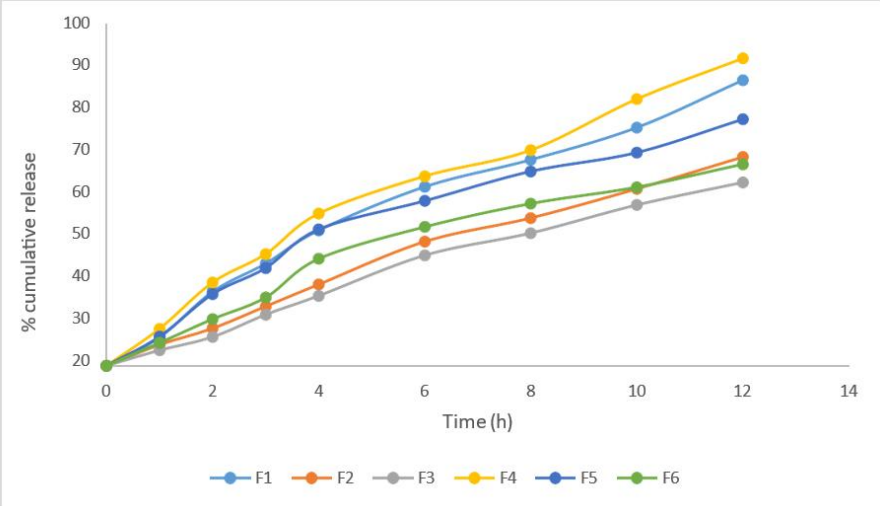

Figure 5 *In vitro* release of rosiglitazone from liponiosomes

From the results of the release studies it was found that the maximum amount of drug was released from formulation F4 (89.7 %) over a period of 12 h at an almost steady rate. The higher amount of drug release along with the higher entrapment efficiency make the formulation F4 containing surfactant to phosphatidyl choline ratio of 1.5:1 the best formulation (Figure 5.5). It was evident from the release data that increasing the non-ionic surfactant aided in increased release whereas increasing the phosphatidylcholine resulted in decrease in release of the drug.

IV. SUMMARY AND CONCLUSION

4.1 Summary

In this study, rosiglitazone loaded hybrid liponiosomes were prepared by reverse ethanol injection technique using cholesterol as the membrane stabilizer, egg phosphatidylcholine as the lipid and non-ionic surfactants such as span 60 with tween 80 as the edge activator. Size of the vesicles in formulation was reduced by sonicating the formulation in bath sonicator.

Formulations with different ratios of surfactant and lipid were prepared. Several physicochemical characteristics of liponiosomes such as morphology, vesicle size determination, drug release profile was investigated.

The entrapment efficiency using was determined and it was found that a 1.5:1 ratio of the non-ionic surfactant and phosphatidyl choline resulted in the maximum entrapment of the drug (71.3%) in the liponiosomal bilayer

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The average size of the F4 liponiosomal hybrid was 276.6 nm and the polydispersity index (PDI) was 0.259 with a zeta potential of −21.7 mv.

The SEM image suggested smooth surface for the liponiosomal hybrid vesicles and spherical shape of the formulation.

The regression coefficients obtained from the graphical models of kinetic reveal that the release of rosiglitazone from the liponiosomes hybrid was primarily due to erosion of the lipid bilayer with time.

4.2 Conclusion

The objective of the present investigation was to develop hybrid lipid-non-ionic surfactant based delivery system for rosiglitazone to improve its half-life for treatment of diabetes. The idea was to increase the half-life by sustaining the release. The results of the study led to conclusion that providing hybrid bilayer resulted in formulations that could be having better permeability across the membrane owing to its better flexibility in comparsion to either liposome or niosome.

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