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Preparation and Evaluation of Repaglinide-Loaded Liposomes via Thin Film Hydration: Impact of Excipients on Formulation Properties

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Abstract

The study was undertaken to formulate and analyze repaglinide loaded liposomes to obtain a sustained release dosage form over an extended period of time. All the formulations were prepared by thin film hydration method one of the suitable methods for preparing liposomes. Different formulations were designed to observe the effect of lecithin, cholesterol, nigella oil, stearylamine, Tween 80, Span 80, and sodium lauryl sulfate on percent of drug entrapment efficiency, cumulative drug release, permeation through the membrane, stability, and uniformed vesicular structure, respectively. Microscopic observation was performed to confirm the presence of liposomal vesicles, *in vitro* dissolution study and *ex vivo* permeability studies were carried out according to USP-II paddle method in phosphate buffer (pH 7.4) for a period of 8 hours. Additionally, comparison between the formulated liposomes was performed to ensure sustained release characteristics of liposomal formulations. Stability study was executed by storing formulations under different environmental conditions for a period of 30 days. Visual observation under optical microscope displayed the presence of unilamellar liposomal vesicles formed by thin film hydration method. The percent drug entrapment efficiency of conventional liposomes was found to be highest for the formulation F-10 (73 .26%) with a ratio of 1:0.44 (phosphatidylcholine: cholesterol). Addition of tween 80 and span 80 to the formulations, stabilized liposomes which exhibited higher entrapment efficiencies for formulations F-24 (81.43%), F-29 (78.98%) and F-34 (89.67%) compared to non-ionic surfactants free liposomes. The drug release of repaglinide from conventional liposomes was found to be 96.23% at the 8^{th} hour. For non-ionic surfactants incorporated liposomes, 84.52% drug release obtained for the formulation F-34 at the 8^{th} hour from which it can be predicted that non-ionic surfactants incorporated liposomes can prolong drug release for more than 10 hours. The best data fitted with the highest correlation coefficient for liposomes was obtained for zero order kinetic models and the drug release was mostly by super class II diffusion transport for most of the formulations. Results from the stability study showed that the drug leakage from the vesicles was least when non-ionic surfactant was incorporated into the formulations and among the three storage conditions, all the liposomal formulations were found to be most stable at refrigeration temperature (2-8°C).

Key words: Repaglinide, liposomes, thin film hydration, drug entrapment efficiency, controlled release.

Introduction

The oral delivery of drugs classified within the biopharmaceutics classification system-II` (BCS-II) category is often characterized by diminished and unpredictable bioavailability due to factors such as inadequate aqueous solubility, active extrusion by intestinal transport proteins, and extensive hepatic first-pass metabolism (Tsume *et al*., 2015). In order to mitigate these challenges, diverse formulation approaches have been devised, encompassing methodologies such as the utilization of polymer and lipid-based nanoparticles, solid dispersion techniques, nano-emulsions and nanosuspensions (Yaghoobian *et al*., 2020).

Liposomes are lipid-based vesicular structures, exhibit a size distribution spanning from 30 nm to the

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micrometer range, characterized by a phospholipid bilayer thickness of approximately 4 to 5 nm (Mazur *et al*., 2017). Currently, it has revealed an extensive research attention for their utility as carriers for the delivery of small-molecule pharmaceuticals, proteins, nucleic acids, and contrast agents in imaging (Mirzavi *et al*., 2021; Wang *et al*., 2021; Rodrigues *et al*., 2019; Man *et al*., 2019). Various routes of administration, including parenteral, pulmonary, oral, transdermal, ophthalmic, and nasal pathways, have been devised to enhance therapeutic effectiveness and foster patient adherence (Han *et al*., 2019; Mirtaleb *et al*., 2021; Mehta *et al*., 2020; Yusuf *et al*., 2017). Furthermore, liposomes have found extensive utilization within the realms of the food (Liu *et al*., 2020) and cosmetics industries (Himeno *et al*., 2017). In recent times, lipid-based formulations designed by the incorporation of lipophilic drugs into inert lipid carriers, in order to enhance the oral bioavailability of poorly water-soluble drug compounds. There are several diverse delivery systems and among them liposomes have several advantages including higher solubilizing capacity, rapid onset of action without additional dispersion time, reduced variability between individuals in terms of gastrointestinal fluid content, extended shelf-life, enhanced toxicological safety, and a substantial lipid phase content (Akhtar *et al.*, 2014; Parveen *et al.*, 2011).

Diabetes is considered one of the major chronic metabolic disorders worldwide resulting from an inadequate supply of insulin or presence of insulin resistance (Arunachalam and Gunasekaran, 2002). Repaglinide is an oral rapid-acting agent for postprandial glucose regulation with low water solubility and high permeability. It was reported that the drug has a low bioavailability due to the extensive hepatic metabolism of the drug. Although being a good drug candidate for the treatment of diabetes mellitus, some of the pharmacokinetic properties of Repaglinide do not support a suitable dosage regimen. The development of a dosage form with improved bioavailability and extended drug delivery is therefore essential to achieving optimized drug therapy (Gumieniczek *et al*., 2009). Considering the advantages of liposomes and the limitations of the drug repaglinide, the study aims to formulate a repaglinide-loaded liposomal drug delivery system and evaluate the effect of various excipients and carriers and thus determining the optimum process variable to develop an effective dosage form.

Materials and Methods

Materials: Different types of materials and solvents were used to prepare repaglinide loaded liposomes. Repaglinide API was collected from Incepta Pharmaceuticals Ltd. as gift sample. Pharmaceutical grade lecithin, cholesterol, stearyl-amine and sodium lauryl sulfate were purchased from Sigma Aldrich, USA. Analytical grade diethyl ether, tween 80, Span 80 was purchased from Merck, Germany. Pure Nigella oil was purchased from Khaas food, Bangladesh. The major ingredients that were used in different ratios and compositions to get desired liposomal formulations.

Formulation design: Repaglinide-loaded liposomal formulations were prepared by varying the ratios of the different excipients and altering the formulation parameters in order to obtain the optimum liposomal formulation. Total 10 mg of repaglinide as active pharmaceutical ingredient was used in each formulation that are summarized in table 1 and 2.

Preparation of repaglinide loaded liposomes by thin film hydration method (TFH): Total 10 mg drug and required quantities of excipients were dissolved in 10 ml of chloroform into a conical flask. The resultant mixture was evaporated within a rotary evaporator at a 60°C temperature for 3 hours at 120 rpm. Then the collected film was subjected to hydration by introducing 15 ml of phosphate buffer into the flask. The mixture was again undergone through a rotary evaporator until all lipid material had been detached from the flask walls and subsequently, the solution was subjected to vortex for preparing uniform suspension of the lipid materials. Then, the solution was sonicated for 15 minutes to reduce vesicle size. It was then left at room temperature for 10 minutes. Finally, the suspension

was refrigerated overnight to facilitate the thorough hydration of the lipid materials (Sagir *et al*., 2023).

Table 1. List of excipients with their range in experimental design.

Name	Minimum amount	Maximum amount
Lecithin (mg)	100	240
Cholesterol (mg)	40	180
Nigella Oil (ml)	2	10
Stearylamine (mg)	0.5	2.5
Tween 80 (ml)	0.5	2.5
Span 80 (ml)	0.5	2.5
Sodium Lauryl Sulfate (mg)	0.5	2.5

Determination of percentage of drug encapsulated in the liposomes: Entrapment efficiency was determined by an indirect methodology employed to quantify the quantity of free drug present within the liposomal dispersion. Total 3 ml liposomal formulation was centrifuged at 6000 rpm for 3 hours. Absorbance of the supernatant was recorded at 281.2 nm to determine the drug content. The % entrapment was determined by the following formula:

$$\text{Entrapment Efficacy} = \frac{\text{Total drug} - \text{Free unentrapped drug}}{\text{Total drug}} x100$$

Table 2. Selected repaglinide loaded liposomal formulations by thin film hydration method.

Formulation Code	Lecithin (mg)	Cholesterol (mg)	Nigella oil (ml)	Stearylamine (mg)	Tween 80 (ml)	Span 80 (ml)	Sodium lauryl Sulfate (mg)
F-3	150	80	-	-	-	-	-
F-10	180	80	-	-	-	-	-
F-16	180	80	6	-	-	-	-
F-20	180	80	-	1	-	-	-
F-24	180	80	-	-	1	-	-
F-29	180	80	-	-	-	1	-
F-34	180	80	-	-	1	1	-
F-40	180	80	-	-	-	-	2

Stability studies: The stability assessments of the optimized liposomal formulation dispersions were aseptically transferred into hermetically sealed glass vials and subjected to storage under refrigeration temperature (2- 8°C), ambient room temperature (25 ± 2°C) and elevated temperature conditions (40 ± 2°C) over 30 days according to the ICH guidelines (Zhang *et al*., 2018). Physical appearance and stability of liposomes was observed at different intervals on the 15th and 30th days. After storage duration, the stability of each formulation was evaluated through the measurement of entrapment efficiency.

Morphology analysis: The formation of vesicles through the specific procedure was verified through optical microscopy at a resolution of 1200x. A suspension of liposomes was applied onto a glass slide and subsequently immobilized through air-drying at room temperature. The resulting dried, thin film of the liposome suspension was scrutinized for the presence of vesicle structures

In vitro dissolution study of liposomal dispersions: The *in vitro* release assessment of repaglinide-loaded liposomes adhered to the USP II paddle method. Liposomal sedimentation was done by centrifugation of 3 ml liposomal suspension for 3 hours at 6000 rpm. These sedimented liposomes were isolated and subsequently diluted with 2 ml of buffer media at a pH of 7.4. Dissolution was performed (triplicate for each sample) of the resulting suspension in 900 ml phosphate buffer at a pH of 7.4 at 75 rpm over the course of 8 hours. The absorbance was recorded using a UV spectrophotometer at 281.2 nm.

Ex-vivo permeability study by using chicken intestinal sac: The *ex-vivo* permeability assessment was conducted utilizing chicken intestinal sacs. Total eight segments of the intestine, each measuring 3 cm in length, were excised using scissors. Each sac was prepared by introducing 2 ml of the liposomal suspension and then sealing both ends securely using cotton thread. These sacs were immersed in vessels containing a dissolution medium comprising 900 ml of phosphate buffer (pH 7.4). The system was constantly agitated at a rate of 75 rpm at 37°C temperature for 8 hours. The permeability study was diligently monitored throughout this duration.

Results and Discussion

Percent drug entrapment efficiency (DEE): Various formulations containing 10 mg of Repaglinide with different ratios of excipients were formulated and their entrapment efficiency was evaluated. Total eight formulations were prepared having a fixed ratio of lecithin (150 mg) and varying amount of cholesterol ranging from 40 to 180 mg. It was observed that percent drug entrapment was gradually increased with the increment of cholesterol at a certain level but it was decreased upon further addition of cholesterol (Figure 1). Thus, based on the results obtained, a ratio of 1:0.53 (lecithin: cholesterol) displayed the highest percentage of repaglinide entrapment efficiency. Again, at a constant level of cholesterol (80 mg) and having different levels of lecithin (100 to 240 mg), eight formulations were prepared. It was observed that with increasing lecithin content, the highest entrapment efficiency was found with the ratio of 1:0.44 (lecithin: cholesterol). Thus, the ratios of 1:0.44 (lecithin: cholesterol) was used as the optimal ratios for further formulation preparation.

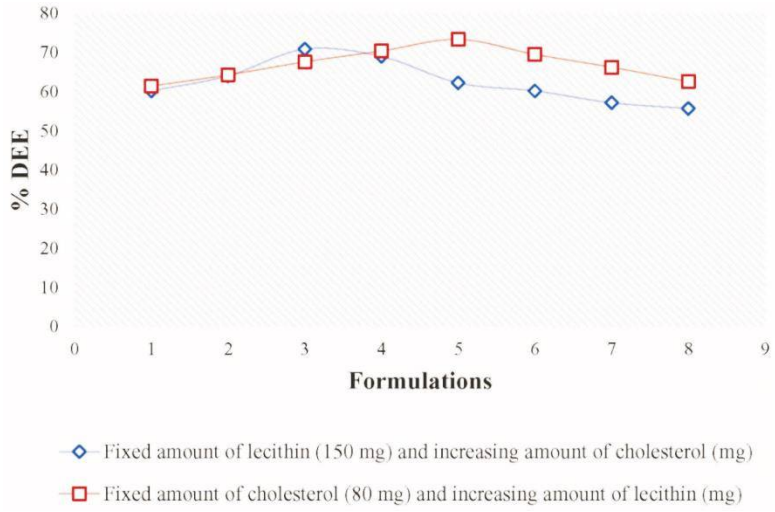

Figure 1. % DEE at constant lecithin and cholesterol level in different formulations.

At a fixed ratio of lecithin and cholesterol (1:0.44), different formulations were developed by adding nigella oil, stearylamine, sodium lauryl sulfate, tween 80 and span 80. In addition to increasing nigella oil content increased the drug entrapment efficiency up to a certain amount and then decreased (Figure 2). The % DEE was increased initially upon adding of stearylamine but showed a decrease in entrapment efficiency after further addition of it (Figure 2). Thus, it was seen that a certain ratio of lecithin, cholesterol and stearylamine (1:0.44:0.006) was responsible for the highest entrapment efficiency. Additionally, sodium lauryl sulfate had no influence on the drug entrapment efficiency of liposomes (Figure 2).

After addition of tween 80 and span 80 separately to the formulation, revealed a decrease in entrapment efficiency (Figure 3). But the combination of tween 80 and span 80, showed higher entrapment efficiency than tween 80 or span 80 alone (figure 3).

Thus, was seen from the above results that a certain ratio (1:0.44:0.006:0.006) of lecithin, cholesterol, tween 80, and span 80 is responsible for the highest entrapment efficiency for the liposomes.

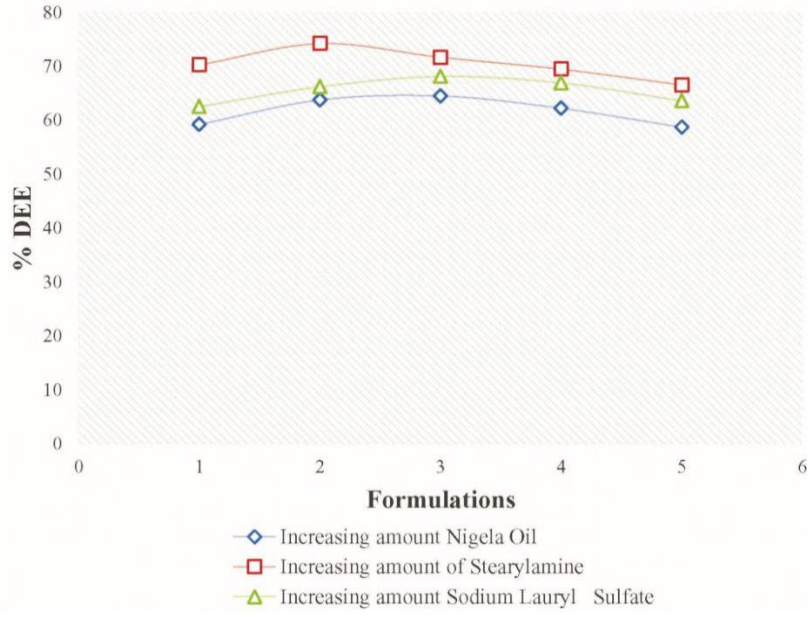

Figure 2. % DEE after addition of nigella oil, stearylamine and sodium lauryl sulfate in different formulations.

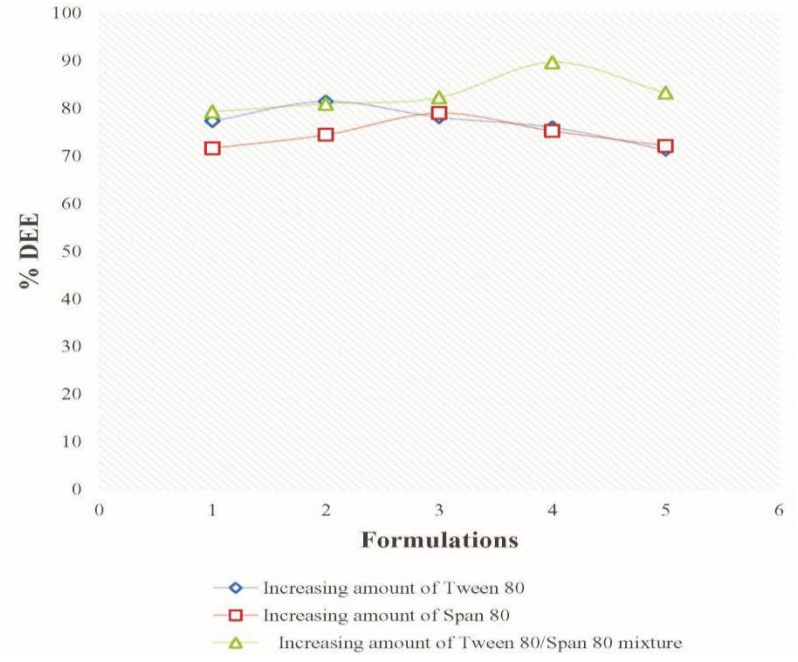

Figure 3. % DEE efficiency after addition of tween 80 and span 80 in different formulations.

In vitro drug release studies of repaglinide loaded best fitted liposomal formulation: In vitro dissolution was performed for the formulations which revealed higher percent of drug entrapment efficiency having different ratios of excipients used. Release kinetics of the selected formulations was studied based on its release rate constant and R^2 values. It was observed that the percent drug release was increased with time consistently but F-24 and F-34 showed least release rate after 8 hours (Figure 4). These formulations contained non-ionic surfactants along with lecithin and cholesterol.

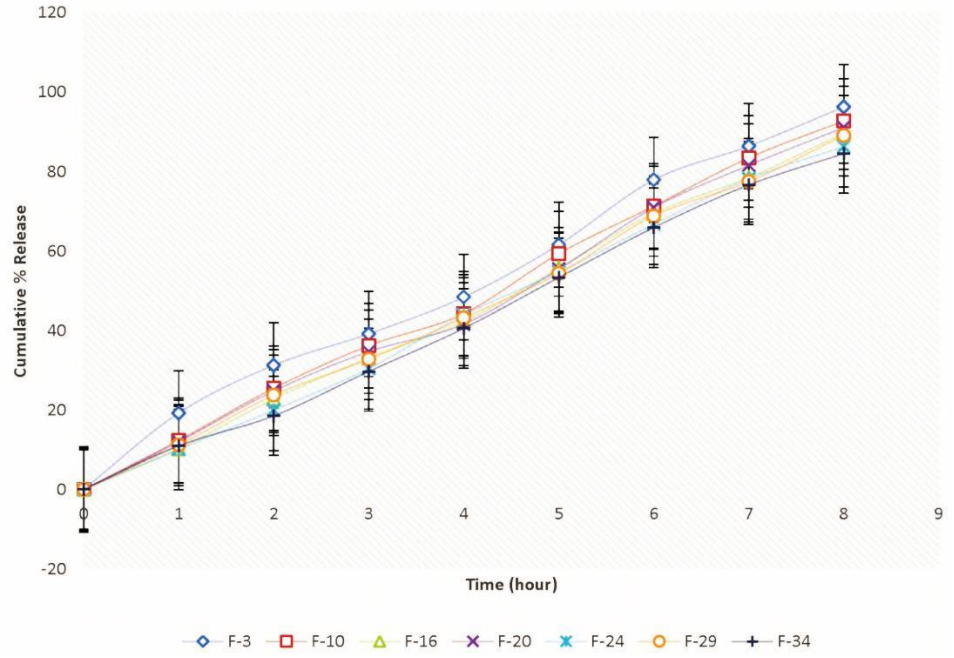

Figure 4. *In-vitro* percent drug release of the best fitted liposomal formulations.

Repaglinide-loaded liposomes were treated in four mathematical models like zero order, first order, Higuchi and Korsmeyer-Peppas. The best release model with the highest correlation coefficient (R^2) was selected. It was seen that all the formulations followed zero order kinetics and followed super class II diffusion transport because the diffusion exponent (n) is greater than 0.85 (Table 3).

Table 3. Release rate constant and R^2 values for different release kinetics of liposomal formulations.

Formulation Code	Zero order		First order		Higuchi		Korsmeyer-peppas	
	K_0	R^2	K_1	R^2	K_H	R^2	N	R^2
F-3	11.704	0.9922	-0.1533	0.8508	36.340	0.9350	0.9780	0.9597
F-10	11.650	0.9981	-0.1292	0.8900	36.654	0.9674	0.9960	0.9208
F-16	11.317	0.9984	-0.1129	0.9085	36.531	0.9771	1.0290	0.9117
F-20	11.432	0.9959	-0.1203	0.8959	36.721	0.9568	1.0230	0.9285
F-24	11.118	0.9984	-0.1040	0.9356	35.322	0.9472	1.0410	0.9191
F-29	11.116	0.9986	-0.1096	0.9088	35.778	0.9765	1.0330	0.9206
F-34	10.890	0.9989	-0.0986	0.9375	34.987	0.9438	1.0490	0.9400
F-40	12.064	0.9988	-0.2430	0.8856	36.778	0.9546	0.9690	0.9520

Ex-vivo drug permeability study: It was observed that the cumulative percent drug release increases with the course of time. The formulation F-40 containing sodium lauryl sulfate had the highest release rate among other formulations after 8 hours of release due to the permeation enhancing ability of sodium lauryl sulfate. The formulation F-3 containing only phosphatidylcholine and cholesterol had the lowest release rate after 8 hours of release (Figure 5).

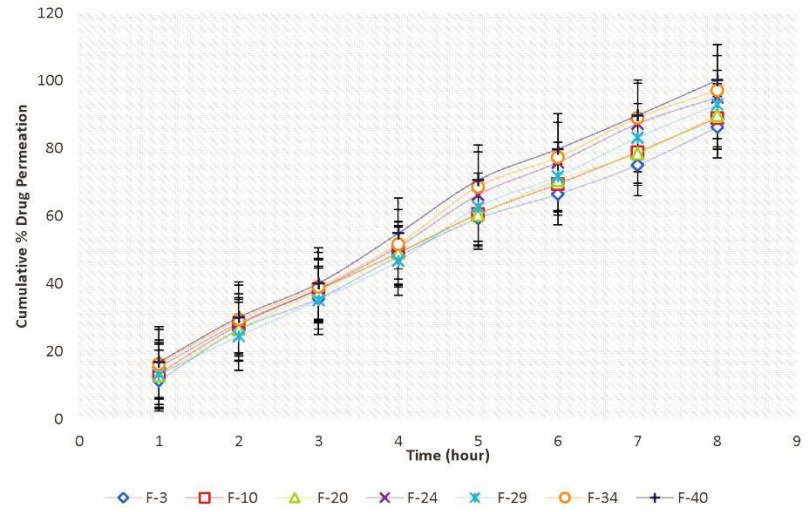

Figure 5. *Ex-vivo* percent drug release of the best fitted liposomal formulations.

Stability Studies of the formulations: Liposomal formulations with the highest entrapment efficiencies were selected and their physical stability were evaluated at three different temperatures for a period of 30 days. It was seen that a noticeable changes in drug entrapment efficiency occurred for all formulations after 15 as well 30 days later (Figure 6). Very little changes were observed for samples when stored at 2-8°C and it can be claimed that refrigeration temperature is suitable to keep liposomal formulations.

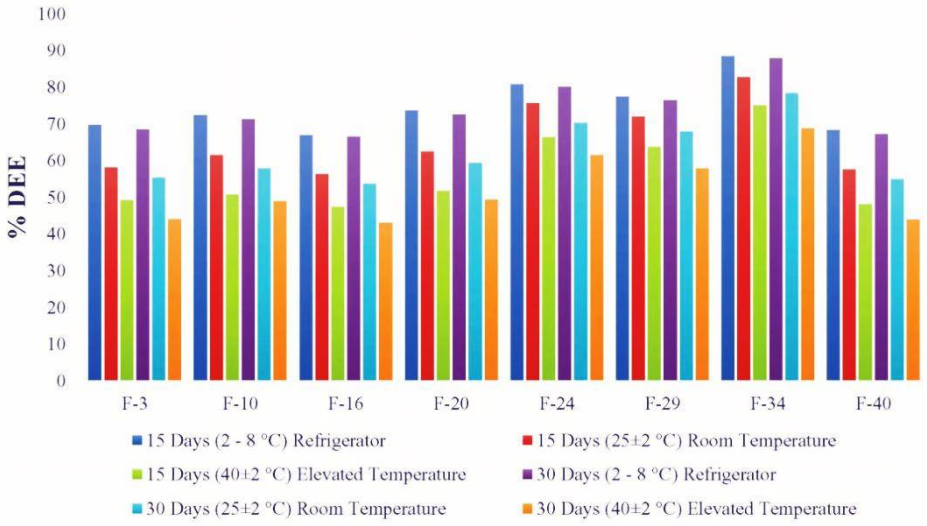

Figure 6. Stability studies of the liposomal formulations.

Morphology analysis of the liposomes: The morphology of the liposomal formulations having higher entrapment efficiencies was determined by an optical microscope equipped with a digital camera. These photomicrographs confirmed the formation of vesicular structures. It was observed that formulation F-16 containing nigella oil produced spherical vesicles that were smaller and thicker when compared to formulations F-3 and F-10. Additionally, F-20 containing stearylamine also produced smaller and thicker spherical vesicles in comparison with others. Formulation F-24 and F-29 containing tween-80 and span-80, respectively, produced spherical vesicles much thicker than formulations containing nigella oil and stearylamine. Formulation F-34 containing an equal amount of tween 80 and span 80 produced spherical vesicles with almost similar size and thickness to those of formulations containing tween 80 or span 80 alone. But the formulation F-40 containing sodium lauryl sulfate produced spherical vesicles that are smaller but not much thicker like liposomes produced by incorporating other excipients like nigella oil, stearylamine, tween 80, span 80 in other formulations (Figure 7).

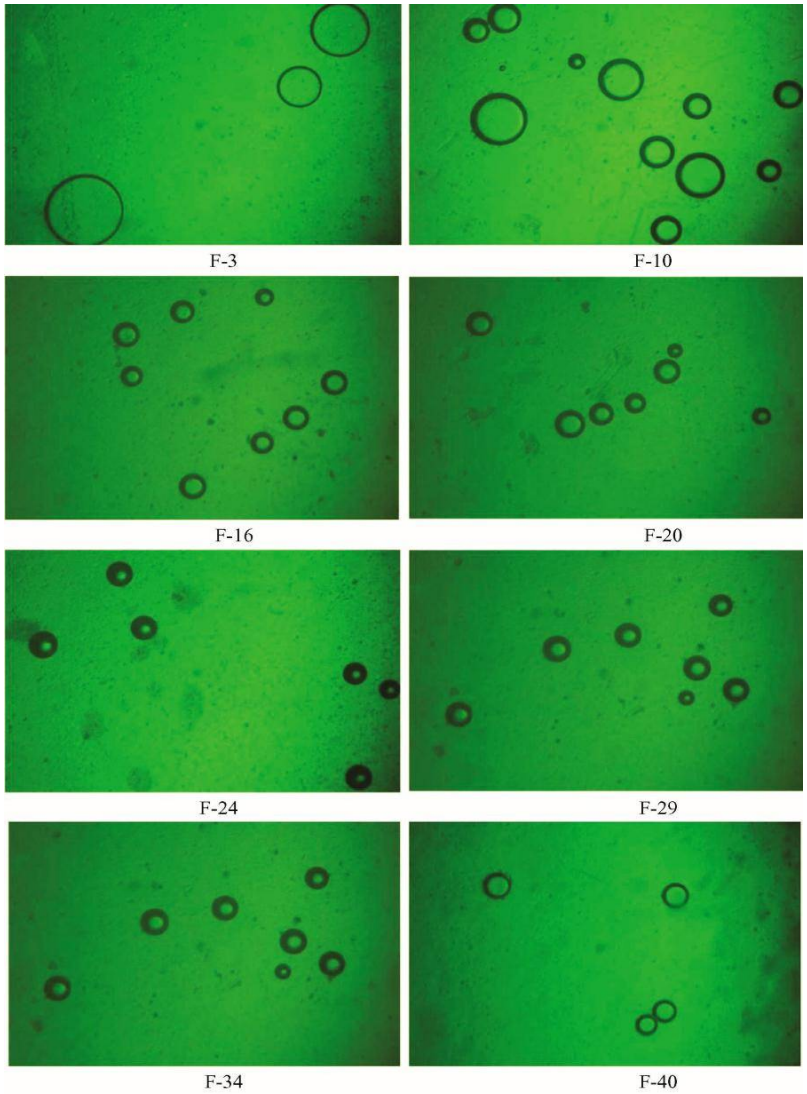

Figure 7. Microscopic images of liposomal formulations.

It has been reported that cholesterol can stabilize the phospholipid bi-layers of liposomes, thus upon increment of cholesterol increased the entrapment efficiency of the formulation. But further addition of cholesterol made the bilayer more rigid and the incorporation of the hydrophobic drug became difficult. On the other hand, due to the lower concentration of cholesterol, a smaller number of the vesicles were formed, resulting in less active drug molecules being incorporated (Nakhaei *et al*., 2019). Nigella Oil, due to its antioxidant properties, may have led to a reduction in the oxidation of phospholipids and the aggregation of liposomes, resulting in smaller liposomes. Thus, less area was available for drug entrapment into smaller liposomes, resulting in decreased entrapment efficiency (Rushmi *et al*., 2016).

As stearylamine acted as a surfactant, it reduced the interfacial tension between two phases and led to a reduction in the aggregation of liposomes, resulting in smaller liposomes. So, upon addition of it, %DEE decreased for the liposomal formulations. Sodium lauryl sulfate is an anionic surfactant having a HLB value of 40, had no significant influence on drug entrapment efficiency, but it could be used in the formulation as a permeation enhancer. Due to the surfactant action, tween 80 and span 80 reduced the interfacial tension between two phases, led to a reduction in the aggregation of liposomes, resulting in smaller liposomes. Thus, less area was available for drug entrapment into smaller liposomes, resulting in decreased entrapment efficiency. But the synergistic effect of combination of tween 80 and span 80 was responsible for the highest entrapment when compared with the entrapments occurred by either tween 80 or span 80 alone (Singh *et al*., 2016).

Sodium lauryl sulfate, an anionic surfactant did not influence the % DEE of the liposomes but nonionic surfactants (tween 80, span 80) greatly influenced the percent drug entrapment efficiency, which has a low HLB value of 15 and 4.3 respectively. So, it can be concluded that nonionic surfactants with low HLB value are superior to anionic surfactants with high HLB value in the case of drug entrapment efficiency. Formulations containing tween and span showed least percent drug release, as non-ionic surfactants retard the drug release from the formulations when incorporated into the liposomal formulations and thus prolong the release rates of the formulations. As a result, sustained release characteristics could be obtained. Due to the oxidation and aggregation of the liposomes, which led to leakage of the drug and ultimately decreased in entrapment efficiency at elevated and room temperatures. Nigella oil and stearylamine containing liposome's spherical structure was thicker and smaller than others. As nigella oil acted as an antioxidant, it might have reduced the oxidation of phospholipids and thus reduced the aggregation of the vesicles produced in that formulation. Additionally, stearylamine has the ability to confer a higher zeta potential that reduces the aggregation of vesicles. Tween 80 and span 80 containing liposomal formulations were smaller due to the stabilizing ability of nonionic surfactants by reducing interfacial tension between two phases, thus reducing the aggregation of vesicles. But it was observed that the synergistic effect of tween 80 and span 80 is much more suitable to produce uniform spherical vesicles (Li *et al*., 2013).

Conclusion

Repaglinide liposomes were prepared by the thin film hydration method and the ratio of 1:0.44 (lecithin: cholesterol) showed the highest drug loading capacity. Further addition of excipients showed significant changes in entrapment efficiencies. The addition of non-ionic surfactants (Tween 80 and Span 80) to formulations showed an increase in the entrapment efficiencies of the liposomes. The addition of non-ionic surfactants showed improved stability of the liposomes compared to other formulations during stability studies, with the least leakage of the entrapped drug. In vitro dissolution study showed the controlled release of drugs from conventional liposomes for 8 hours. The addition of non-ionic surfactants to formulations showed a retardation in drug release

from the liposomes and based on the observation, it can be concluded that drug release from the liposomes can be extended for more than 10 hours in vitro by incorporating non-ionic surfactants. Additionally, ex vivo permeability study displayed an optimized permeation rate through the membrane. Stability study showed that formulations were most stable at a temperature of 2-8°C and the least drug leakage occurred from non-ionic surfactants incorporated liposomal formulations. Optical microscopy showed uniformly smaller and thicker vesicular structures when non-ionic surfactants were incorporated into the liposomal formulations. However, further work is needed to characterize the physicochemical properties of prepared liposomes, such as shape, particle size distribution, and charge through SEM (scanning electron microscopy) and zeta potential tests. These formulations can also be considered a potential candidate for performing *in vivo* studies in animal models to establish an *in-vitro in-vivo* correlation in the future.

Ethical Approval

It is not applicable.

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Competing Interests

The authors have declared that no competing interests exist.

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