RESEARCH PAPER

DEVELOPMENT AND OPTIMIZATION OF REPAGLINIDE-LOADED LIPOSPHERES FOR ENHANCED DRUG DELIVERY AND ANTIDIABETIC ACTIVITY

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Abstract
The present study was undertaken to formulate and characterize repaglinide-loaded lipospheres using the melt dispersion technique with the objective of achieving improved drug entrapment and sustained drug release. Six formulations (F1–F6) were prepared using stearic acid and cetyl alcohol as the lipid core, Tween 80 as a surfactant, and gelatin as a stabilizer. The prepared lipospheres were evaluated for percentage yield, drug entrapment efficiency, particle size, zeta potential, surface morphology, and flow properties. The percentage yield of the formulations ranged from 73.32 ± 0.25% to 84.65 ± 0.25%, while drug entrapment efficiency ranged from 72.65 ± 0.42% to 85.72 ± 0.35%. Among the prepared formulations, F3 was selected as the optimized formulation, exhibiting the highest percentage yield (84.65 ± 0.25%) and drug entrapment efficiency (85.72 ± 0.35%). Particle size, zeta potential, and SEM analysis confirmed the formation of discrete and relatively spherical lipospheres with satisfactory physical characteristics. The flow properties indicated acceptable handling characteristics, with Carr's index values ranging from 15.424% to 20.802% and Hausner's ratio from 1.182 to 1.263. The optimized formulation F3 demonstrated sustained drug release, with cumulative drug release increasing from 19.98% at 0.5 h to 97.85% at 12 h. Release kinetic analysis showed the highest correlation with the first-order model ($R^2 = 0.9967$), followed by the Korsmeyer–Peppas model ($R^2 = 0.9657$), indicating concentration-dependent release with a significant diffusion component. The α-glucosidase inhibitory study demonstrated concentration-dependent activity, with the optimized liposphere formulation exhibiting 87.96% inhibition at 500 µg/mL and an IC_{50} value of 149.80 µg/mL. Thus, the developed repaglinide-loaded lipospheres, particularly formulation F3, demonstrated satisfactory formulation characteristics, high drug entrapment, and prolonged drug release, suggesting their potential as a promising lipid-based delivery system for sustained therapeutic delivery of repaglinide.

Keywords: Repaglinide, Lipospheres, Melt dispersion technique, Stearic acid, Cetyl alcohol, Tween 80, Drug entrapment efficiency, Sustained drug release, First-order kinetics, α-Glucosidase inhibition.
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Introduction

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from impaired insulin secretion, impaired insulin action, or a combination of both (American Diabetes Association, 2012). It has become a major global health concern and is associated with several long-term complications affecting the cardiovascular system, kidneys, eyes, nerves, and other organs. Effective control of postprandial blood glucose levels is an important component of diabetes management, particularly in patients with type 2 diabetes mellitus (Lu et al., 2023). Oral antidiabetic therapy remains an important approach for glycemic control; however, limitations associated with conventional drug delivery systems can affect therapeutic outcomes and patient compliance (Souto et al., 2019).

Repaglinide is a short-acting insulin secretagogue belonging to the meglitinide class of oral antidiabetic agents. It lowers blood glucose primarily by stimulating pancreatic β-cells to release insulin and is particularly effective in controlling postprandial hyperglycemia (Ambavane et al., 2002). Repaglinide has a rapid onset of action and a relatively short duration of action, which makes it suitable for administration before meals. However, its short biological half-life necessitates frequent administration and may result in fluctuations in drug concentration. Such limitations may reduce patient convenience and compliance during long-term therapy. Therefore, development of an appropriate modified drug delivery system capable of prolonging drug release may provide advantages over conventional immediate-release administration (Hatorp, 2002).

Lipid-based drug delivery systems have received considerable attention because of their ability to improve drug incorporation, protect incorporated drug from environmental degradation, and modify drug-release characteristics (Samimi et al., 2019). Lipospheres are particulate lipid-based delivery

systems in which the drug is incorporated or entrapped within a solid or semisolid lipid matrix. They generally consist of a hydrophobic lipid core stabilized by suitable surfactants and stabilizers. Depending on the composition of the lipid matrix and preparation method, lipospheres can provide controlled drug release and may improve the physicochemical and biopharmaceutical properties of incorporated drugs (Chime and Onyishi, 2013).

The melt dispersion technique is a relatively simple and reproducible method for preparing lipid-based particulate systems. In this technique, the lipid components are melted above their melting temperature, followed by incorporation of the drug into the molten lipid phase. The drug-containing lipid phase is subsequently dispersed into a heated aqueous phase containing a suitable surfactant and stabilizer. On controlled cooling, the lipid phase solidifies and forms drug-loaded lipospheres. The characteristics of the resulting system are influenced by several formulation variables, including the type and concentration of lipid, drug-to-lipid ratio, surfactant concentration, stabilizer concentration, stirring conditions, and cooling rate (Khairnar et al., 2022).

Stearic acid and cetyl alcohol are commonly used lipid excipients for the development of lipid-based drug delivery systems because of their suitable physicochemical characteristics and ability to form a solid lipid matrix. Tween 80 can facilitate emulsification and stabilization of the dispersed lipid phase, whereas gelatin can contribute to stabilization of the formed particles. Appropriate selection and optimization of these components can influence particle size, drug entrapment efficiency, surface characteristics, physical stability, and drug-release behavior (Chauhan and Singh, 2023).

The performance of lipospheres depends on their physicochemical and pharmaceutical characteristics. Parameters such as percentage yield, drug entrapment efficiency, particle size, zeta potential, surface morphology, and flow properties provide important information regarding the quality and suitability of the developed formulation (Chauhan and Singh, 2023). In-vitro drug release studies are particularly important for determining the ability of the lipid matrix to provide prolonged drug release, while mathematical kinetic models can help establish the release kinetics and mechanism.

Therefore, the development of repaglinide-loaded lipospheres may provide a promising approach for modifying the release characteristics of repaglinide and potentially improving dosing convenience. The present study was undertaken to formulate and characterize repaglinide-loaded lipospheres using the melt dispersion technique. Different formulations were prepared using varying concentrations of stearic acid and cetyl alcohol and were evaluated for percentage yield, drug entrapment efficiency, particle characteristics, morphology, flow properties, in-vitro drug release, release kinetics, and biological activity. The study aimed to identify an optimized liposphere formulation exhibiting satisfactory physicochemical properties and prolonged drug release for potential application in the management of type 2 diabetes mellitus.

Material and Methods

Material

Repaglinide was obtained as a gift sample from Glenmark Pharmaceuticals Ltd., Mumbai, India. Stearic acid, cetyl alcohol, Tween 80, and gelatin were procured from Loba Chemie Pvt. Ltd., Mumbai, India. All other chemicals and reagents used in the study were of analytical grade and obtained from Sisco Research Laboratories Pvt. Ltd. (SRL), Mumbai, India. Double-distilled water was used throughout the formulation and evaluation studies.

Methods

Formulation Development of Liposphere

Repaglinide-loaded lipospheres were prepared by the melt dispersion technique (Elgart *et al.,* 2012). The composition of the different formulations (F1–F6) is presented in Table 6.6. The formulations contained 50 mg of repaglinide with different quantities of lipid core (100, 150 and 200 mg), Tween 80 (1.5 mL) as surfactant**,** 2 mg gelatin as stabilizer, and 98 mL water**.** The lipid core consisted of stearic acid and cetyl alcohol**.**

Briefly, the required quantity of stearic acid and cetyl alcohol was accurately weighed according to the respective formulation and transferred into a suitable vessel. The lipid mixture was melted on a water bath at 70–72°C**.** After complete melting, 50 mg of finely powdered repaglinide was incorporated into the molten lipid phase and mixed thoroughly to obtain a uniform drug-lipid dispersion.

Separately, 98 mL of water containing 1.5 mL of Tween 80 and 2 mg of gelatin or pectin as stabilizer was heated to 70–72°C**.** The hot aqueous phase was maintained at approximately the same temperature as the molten lipid phase. The drug-containing molten lipid phase was then slowly added to the hot aqueous phase with continuous stirring to form an oil-in-water (o/w) emulsion**.** The dispersion was further subjected to continuous agitation to facilitate emulsification and obtain a uniform dispersion of the lipid phase.

The resulting milky dispersion was rapidly cooled to approximately 20°C using an ice bath while maintaining continuous agitation**.** Rapid cooling caused solidification of the lipid phase, resulting in the formation of repaglinide-loaded lipospheres. The prepared lipospheres were subsequently washed with distilled water to remove excess surfactant and

stabilizer and were isolated by filtration. The obtained lipospheres were collected and subjected to further evaluation and characterization.

Table 1: Preparation of Liposphere of Repaglinide

F. Code	Drug (mg)	Lipid core (mg)		Tween 80 as Surfactant (ml)	Gelatin as Stabilizer (mg)	Water (ml)
		Stearic acid (mg)	Cetyl alcohol (mg)			
F1	50	100	100	1.5ml	2	98
F2	50	150	200	1.5ml	2	98
F3	50	200	300	1.5ml	2	98
F4	50	100	100	1.5ml	2	98
F5	50	150	200	1.5ml	2	98
F6	50	200	300	1.5ml	2	98

Characterization of Repaglinide encapsulated lipospheres

Percentage yield of Lipospheres

Percent Yield of Lipospheres was calculated according to the following formula:

$$\% \text{ Yield} = \frac{\text{Weight of lipospheres}}{\text{Wt. of drug} + \text{Wt. of excipients}} \text{X } 100$$

Drug loading and entrapment efficiency

The amount of Repaglinide present in lipospheres was determined by taking the known amount of lipospheres in which 10mg of drug should be present theoretically. Then the lipospheres were crushed and the powdered microspheres was taken and dissolved in 10 ml of methanol and stirred for 15 minutes with an interval of 5 minutes and allowed to keep for 24 hours. Then the solution was filtered through whatmann filter paper. Then the absorbance after appropriate dilution was measured spectrophotometrically at 244nm by UV-visible spectrophotometer (Brown *et al.,* 2013).

$$\text{Drug entrapment efficiency (\%)} = \frac{\text{Experimental drug content}}{\text{Initial drug content in the formulation}} \text{X} 100$$

Measurement of mean particle size

The mean size of the lipospheres was determined by Photo Correlation Spectroscopy (PCS) on a submicron particle size analyzer (Malvern Instruments) at a scattering angle of 90°. A sample (0.5mg) of the lipospheres suspended in 5 ml of distilled water was used for the measurement (Shivakumar *et al.,* 2007; Khulbe and Manjal, 2012).

Determination of zeta potential

The zeta potential of the drug-loaded lipospheres was measured on a zeta sizer (Malvern zetasizer instruments) by determining the electrophoretic mobility in a micro electrophoresis flow cell. All the samples were measured in water (Nasr *et al.,* 2008).

Surface morphology (Scanning electron microscopy)

Morphology and surface topography of the lipospheres were examined by scanning electron microscopy. The lipospheres from the optimized batch were mounted on the SEM sample stab using a double-sided sticking tape and coated with gold (~200 nm) under reduced pressure (0.133 Pa) for 5 min using an Ion sputtering device. The gold coated lipospheres were observed under the scanning electron microscope and photomicrographs of suitable magnifications were obtained.

Flow property determination of the Lipospheres

Bulk density: Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. Accurately weighed amount of granules taken in a 50 ml capacity measuring cylinder was tapped for 100 times on a plane hard wooden surface and estimated the LBD and TBD, calculated by using following formulas:

$$\textbf{LBD (Loose bulk density)} = \frac{\text{Mass of powder}}{\text{Volume of Packing}}$$

$$\textbf{TBD (Tapped bulk density)} = \frac{\text{Mass of powder}}{\text{Tapped Volume of Packing}}$$

Compressibility index: Percent compressibility of powder mix was determined by Carr's compressibility index, calculated by using following formula:-

$$\textbf{Carr's Index} = \frac{\text{TBD} - \text{LBD}}{\text{TBD}} \text{X} 100$$

Hausners ratio: It is determined by comparing tapped density to the bulk density by using following equation:-

$$\textbf{Housner's ratio} = \frac{\text{Tapped bulk density}}{\text{Loose Bulk density}}$$

***In-vitro* drug release studies**

The dissolution of Repaglinide from the prepared lipospheres was monitored using USP XXV paddle II apparatus. The Amount of the lipospheres equivalent to 10mg of Repaglinide was dispersed into the dissolution medium. The dissolution media was 900 ml of pH 1.2 buffers maintained at 37 ±0.5ºC and rotating at 50 ±1 rpm. The 5ml aliquots were withdrawn at pre-determined time intervals and the withdrawn samples were replaced with fresh dissolution medium. The samples were then analyzed spectrophotometrically at 244 nm for Repaglinide content.

Results and Discussion

Repaglinide-loaded lipospheres were successfully prepared by the melt dispersion technique using stearic acid and cetyl alcohol as the lipid core, Tween 80 as surfactant, and gelatin as stabilizer. The formulations F1–F6 were prepared by varying the quantity of lipid components while maintaining the drug concentration, surfactant, stabilizer, and aqueous phase. The detailed composition of the prepared formulations is presented in Table 1. The use of a lipid matrix was intended to facilitate incorporation of repaglinide and provide a controlled-release carrier system.

The percentage yield of the prepared lipospheres ranged from 73.32 ± 0.25% to 84.65 ± 0.25%, as shown in Table 2. Formulation F3 exhibited the highest percentage yield (84.65 ± 0.25%), whereas F1 showed the lowest yield (73.32 ± 0.25%). The increase in yield with increasing lipid concentration may be attributed to the greater amount of solid lipid available for formation and recovery of the lipospheres. The relatively high percentage yield obtained for all formulations indicates that the preparation method was suitable for producing repaglinide-loaded lipospheres with acceptable recovery.

The drug entrapment efficiency of the prepared formulations is presented in Table 3. The entrapment efficiency ranged from 72.65 ± 0.42% to 85.72 ± 0.35%. Among all formulations, F3 demonstrated the highest drug entrapment efficiency (85.72 ± 0.35%), followed by F5 (82.36 ± 0.32%) and F6 (80.15 ± 0.37%). The improved entrapment observed with higher lipid content may be attributed to the increased availability of the lipid matrix for incorporation of the drug. The lower entrapment efficiency observed in formulations containing relatively lower amounts of lipid may be due to limited accommodation of repaglinide within the lipid phase. Based on percentage yield and drug entrapment efficiency, F3 was selected as the optimized formulation for further characterization.

The particle size distribution of the optimized formulation F3 was determined and is depicted in Figure 7.6. Particle size is an important parameter because it can influence the surface area, drug release characteristics, physical stability, and performance of lipid-based delivery systems. The particle size distribution obtained for F3 indicated the formation of a relatively uniform liposphere dispersion, supporting the suitability of the melt dispersion technique for preparation of the formulation.

The zeta potential of the optimized F3 formulation was determined to assess the surface charge and physical stability of the prepared lipospheres. The corresponding zeta potential data are presented in Figure 1. The observed surface charge indicates the electrostatic characteristics of the lipospheres and provides information regarding their tendency toward aggregation. A suitable zeta potential contributes to maintaining dispersion stability by reducing particle–particle interaction.

The surface morphology of the optimized lipospheres was examined using scanning electron microscopy (SEM), and the representative SEM image is shown in Figure 2. The SEM image demonstrated the formation of discrete and relatively spherical particles with a well-defined surface morphology. The observed morphology further confirmed successful formation of the lipid-based carrier system. The spherical structure of the particles may provide a relatively large surface area and facilitate controlled interaction of the formulation with the dissolution medium.

The flow properties of the prepared liposphere formulations were evaluated using loose bulk density, tapped bulk density, Carr's compressibility index, and Hausner's ratio. The results are presented in Table 4. The Carr's index values ranged from 15.424% to 20.802%, while Hausner's ratio ranged from 1.182 to 1.263. The results indicated acceptable to moderate flow characteristics among the different formulations. F1 showed a Carr's index of 15.424% and Hausner's ratio of 1.182, whereas F5 showed values of 16.407% and 1.196, respectively. The results suggest that the prepared lipospheres possessed satisfactory flow characteristics and could be handled appropriately during subsequent processing.

The in-vitro drug release study of the optimized formulation F3 was conducted for 12 h, and the results are presented in Table 5. The formulation exhibited a gradual and sustained release of repaglinide throughout the study period. The cumulative drug release increased from 19.98% at 0.5 h to 48.85% at 2 h, followed by 73.32% at 4 h, 83.32% at 6 h, 91.12% at 8 h, and 97.85% at 12 h. The initial release may be attributed to the diffusion of drug present near or on the surface of the lipospheres, whereas the subsequent prolonged release may have resulted from diffusion of the drug through the lipid matrix. The sustained release profile demonstrates the ability of the lipid matrix to control the release of repaglinide over an extended period.

To determine the mechanism of drug release, the release data of formulation F3 were fitted to different mathematical models, including zero-order, first-order, Higuchi, and Korsmeyer–Peppas models. The regression coefficients are summarized in Table 6. The highest correlation coefficient was obtained for the first-order model (R^2 = 0.9967), indicating that the release rate was concentration dependent. The Higuchi model showed an R^2 value of 0.9459, suggesting that diffusion contributed substantially to

drug release from the lipid matrix. The Korsmeyer–Peppas model exhibited an R^2 value of 0.9657, further supporting the involvement of diffusion-based release mechanisms. The release kinetics indicated that drug release from the optimized liposphere was predominantly governed by diffusion from the lipid matrix.

The α-glucosidase inhibitory activity of acarbose and the optimized repaglinide liposphere formulation was also evaluated, and the results are presented in Table 7. Both formulations demonstrated concentration-dependent inhibition, with the percentage inhibition increasing progressively with concentration. At 100µg/mL, acarbose showed 48.65% inhibition, whereas the liposphere formulation showed 46.58% inhibition. At 500µg/mL, the inhibition increased to 89.89% for acarbose and 87.96% for the liposphere formulation. The IC_{50} values were found to be 127.57µg/mL for acarbose and 149.80µg/mL for the liposphere formulation. Although the liposphere formulation showed slightly lower inhibitory activity than acarbose, the concentration-dependent response demonstrates its biological activity.

Table 2: Percentage yields of lipospheres

S. No.	Formulation Code	% Yield*
1	F1	73.32 ± 0.25
2	F2	79.98 ± 0.36
3	F3	84.65 ± 0.25
4	F4	75.26 ± 0.31
5	F5	82.45 ± 0.28
6	F6	80.72 ± 0.22

Table 3: % Drug entrapment efficiency of lipospheres

S. No.	Formulation Code	% Drug entrapment efficiency
1.	F1	72.65 ± 0.42
2.	F2	78.84 ± 0.38
3.	F3	85.72 ± 0.35
4.	F4	74.56 ± 0.41
5.	F5	82.36 ± 0.32
6.	F6	80.15 ± 0.37

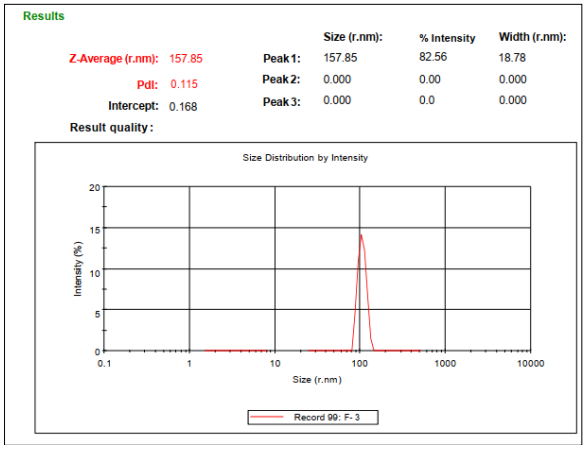


Figure 7.6: Particle size data of optimized lipospheres formulation F3

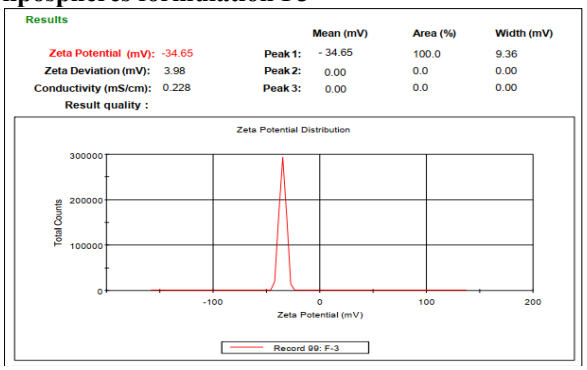


Figure 7.7: Zeta potential data of lipospheres formulation F3

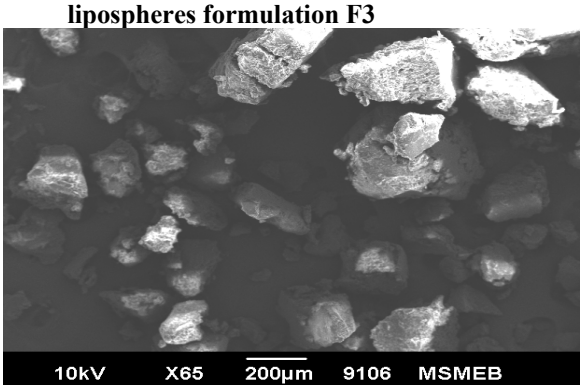


Figure 7.8: SEM Image of Optimized Formulation

Table 4: Result of Flow Properties of different liposphere formulation

Formulation code	Parameters			
	Loose Bulk density(gm/ml)	Tapped bulk density(gm/ml)	Carr's Index (%)	Hausner's Ratio

F1	0.658	0.778	15.424	1.182
F2	0.632	0.798	20.802	1.263
F3	0.674	0.845	20.237	1.254
F4	0.712	0.889	19.910	1.249
F5	0.698	0.835	16.407	1.196
F6	0.615	0.732	15.984	1.190

Table 5: Release study of Formulation F3

Time (h)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative* % Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
0.5	0.707	-0.301	19.98	1.301	80.02	1.903
1	1	0	28.85	1.460	71.15	1.852
1.5	1.225	0.176	33.36	1.523	66.64	1.824
2	1.414	0.301	48.85	1.689	51.15	1.709
3	1.732	0.477	59.95	1.778	40.05	1.603
4	2	0.602	73.32	1.865	26.68	1.426
6	2.449	0.778	83.32	1.921	16.68	1.222
8	2.828	0.903	91.12	1.960	8.88	0.948
12	3.464	1.079	97.85	1.991	2.15	0.332

Table 6: Comparative study of regression coefficient for selection of optimized batch

	Zero order	First order	Higuchi	Peppas model
r^2	0.8389	0.9967	0.9459	0.9657

Table 7: % Inhibition of Acarbose and liposphere formulation

Concentration (µg/ml)	% Inhibition	
	Acarbose	Liposphere formulation
100	48.65	46.58
200	55.63	53.32
300	68.85	66.65
400	73.32	70.65
500	89.89	87.96
IC_{50} value	**127.57**	**149.80**

Conclusion

The present study successfully developed and characterized repaglinide-loaded lipospheres using the melt dispersion technique with stearic acid and cetyl alcohol as the lipid matrix, Tween 80 as surfactant, and gelatin as stabilizer. Among the six formulations, F3 was identified as the optimized formulation based on its superior percentage yield (84.65 ± 0.25%) and drug entrapment efficiency (85.72 ± 0.35%). The optimized lipospheres exhibited satisfactory flow properties, appropriate particle characteristics, and a relatively spherical morphology as confirmed by SEM analysis. The in-vitro drug release study demonstrated a prolonged release profile, with 97.85% drug release over 12 h, indicating the ability of the lipid matrix to control repaglinide release. Kinetic analysis showed that drug release followed first-order kinetics (R^2 = 0.9967)

with a substantial diffusion-controlled component. Furthermore, the optimized formulation demonstrated concentration-dependent α-glucosidase inhibitory activity, showing 87.96% inhibition at 500µg/mL. The findings indicate that repaglinide-loaded lipospheres, particularly formulation F3, possess desirable physicochemical and drug-release characteristics and may represent a promising approach for sustained delivery of repaglinide, potentially improving therapeutic performance and dosing convenience.

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