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FORMULATION & CHARACTERIZATION OF LIPOSPHERE OF LINAGLIPTIN

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Abstract
This study focuses on the formulation and characterization of Linagliptin encapsulated lipospheres for sustained drug release. Linagliptin, an anti-diabetic drug, was encapsulated in lipid-based carriers to enhance bioavailability and provide controlled release. Various formulations were prepared and evaluated for key parameters including % yield, drug entrapment efficiency, particle size, flow properties, and drug release behavior. The results revealed that formulation F3 exhibited the highest drug entrapment efficiency (83.32 ± 0.45%) and optimal particle size, suggesting effective encapsulation. In vitro drug release studies demonstrated a sustained release profile, with formulation F3 releasing 98.15% of the drug over 12 hours. The release kinetics followed the First-order and Peppas models, indicating a diffusion-controlled release mechanism. These findings highlight the potential of Linagliptin-loaded lipospheres as an effective drug delivery system for improving the management of type 2 diabetes.

Keywords: Linagliptin, Lipospheres, Sustained release, Drug entrapment efficiency, Controlled release, Diabetes management, Particle size, Drug delivery system, First-order release, Peppas model.

Introduction

Diabetes mellitus (DM), particularly type 2 diabetes (T2D), is a prevalent chronic metabolic disorder that has become a global health concern. The management of diabetes requires effective glycemic control to prevent complications such as cardiovascular diseases, nephropathy, and neuropathy. Linagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, is widely used in the treatment of type 2 diabetes due to its ability to enhance insulin secretion and suppress glucagon release, thereby improving blood glucose control (Rosenstock et al., 2011) [1]. However, despite its efficacy, Linagliptin has certain limitations including poor solubility and bioavailability, which can affect its therapeutic effectiveness.
To overcome these challenges, drug delivery systems like lipospheres have gained considerable attention. Lipospheres are lipid-based spherical particles designed to improve the solubility, stability, and controlled release of poorly soluble drugs. These particles consist of a lipid core, which may be surrounded by a surfactant or polymer, and offer several advantages such as enhanced drug absorption, prolonged circulation time, and reduced toxicity compared to conventional drug formulations (Patel et al., 2012) [2].
The formulation of **lipospheres** for Linagliptin offers several potential benefits. Firstly, the lipid-based matrix can protect the drug from degradation in the gastrointestinal tract, leading to improved bioavailability. Secondly, by modulating the release rate of Linagliptin, lipospheres can provide a controlled drug delivery profile, reducing the frequency of dosing and enhancing patient compliance. Lastly, liposphere-based formulations can target specific tissues or organs, improving therapeutic outcomes and minimizing side effects (Verma et al., 2015) [3].
This research aims to design, formulate, and characterize **Linagliptin-loaded lipospheres** to improve the solubility, bioavailability, and therapeutic efficacy of Linagliptin. The study will investigate the preparation of lipospheres using different lipid and surfactant combinations, and evaluate their

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physicochemical properties, including particle size, entrapment efficiency, morphology, and in-vitro drug release profiles. The findings will contribute to the development of a more effective drug delivery system for Linagliptin, addressing the challenges faced by conventional oral formulations.

Material and Methods

Material

The materials used for the formulation development of lipospheres include several chemicals and reagents sourced from reliable suppliers. Linagliptin**,** the active pharmaceutical ingredient (API), was obtained as a gift sample from Bioplus Life Sciences Pvt. Ltd., Bangalore. The formulation also involved commonly used excipients such as Disodium hydrogen phosphate**,** Potassium dihydrogen phosphate, and Sodium chloride, all sourced from S.D. Fine Chem. Ltd., Mumbai. Solvents like Methanol**,** Ethanol, and Chloroform were procured from Qualigens Fine Chemicals, Mumbai, which are used for dissolving the API and excipients. The pH of the formulation was adjusted using Sodium hydroxide from Chempure Speciality Chemicals, Mumbai and Hydrochloric acid from Thomas Baker**,** Mumbai. For the preparation of the lipid core of the lipospheres, Stearic acid and Cetyl alcohol, obtained from HiMedia Laboratories Private Limited**,** Mumbai and Lobachemie, Mumbai, respectively, were used as lipophilic components. To stabilize and aid the formulation, Tween 80**,** a surfactant, was used and supplied by Thomas Baker, Mumbai, while Gelatin, sourced from HiMedia Laboratories, was used as a stabilizing agent in the formulation. These materials were carefully selected to optimize the formulation process and achieve the desired properties for the liposphere-based drug delivery system.

Methods

Formulation Development of Liposphere

Drug encapsulated Liposphere were developed by melt dispersion technique (Elgart *et al.,* 2012). The formulation of different batches is depicted in Table 1. Briefly, the lipid core was melted on a water bath maintained at 70-72°C. Finely powdered drug was dispersed into the molten lipidic phase. The aqueous phase was prepared by heating a blend of water and surfactant to 70-72°C with a stabilizer. The molten lipidic phase was slowly transferred to the hot aqueous phase (o/w emulsion) and the emulsification was assisted by stirring the content on a sonicator continuously. The milky dispersion was then rapidly cooled to 20°C by immersing the formulation in an ice bath without stopping the agitation to yield a uniform dispersion of lipospheres. The obtained lipospheres were then washed with water and isolated by filtration

Table 1: Preparation of Liposphere of Linagliptin

F. Code	Drug (mg)	Lipid core (mg)		Tween 80 as Surfactant (ml)	Gelatin or pectin as Stabilizer (mg)	Water (ml)
		Stearic acid (mg)	Cetyl alcohol (mg)			
F1	10	100	100	1.5ml	2	98
F2	10	150	200	1.5ml	2	98
F3	10	200	300	1.5ml	2	98
F4	10	100	100	2.0ml	2	98
F5	10	150	200	2.0ml	2	98
F6	10	200	300	2.0ml	2	98

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Characterization of Linagliptin encapsulated lipospheres

Percentage Yield of Lipospheres

Yield of Lipospheres percent w/w was calculated according to the following formula:

$$\% \text{ Yield } \frac{\text{Weight of lipospheres}}{\text{Wt. of drug } + \text{ Wt. of excipients}} \text{X100}$$

Drug loading and Entrapment efficiency

The amount of Linagliptin 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 226nm by UV-visible spectrophotometer (Brown *et al.,* 2013).

$$\text{Drug entrapment efficiency (\%)} = \frac{\text{Experimental drug content}}{\text{Initial drug content in the formulation}} \text{X100}$$

Microscopic Evaluation

An optical microscope (Cippon-Japan) with a camera attachment (Minolta) was used to observe the shape of the prepared microspheres for each drug: lipid ratio.

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 (Nasr *et al.,* 2008).

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.

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.

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

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

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

$$\textbf{Carr's Index} = \frac{\text{TBD} - \text{LBD}}{\text{TBD}} \text{X100}$$

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 Linagliptin from the prepared lipospheres was monitored using USP XXV paddle II apparatus. The Amount of the lipospheres equivalent to 10mg of Linagliptin 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 226.0 nm for Linagliptin content (Gibaldi and Feldman, 1967).

Results and discussion

The results obtained from the formulation and characterization of Linagliptin encapsulated lipospheres provide valuable insights into the effectiveness of the liposomal system for sustained drug release. The percentage yield data (Table 2) revealed that the formulations F3 (83.35 ± 0.95%) and F2 (80.23 ± 0.89%) exhibited the highest yields, indicating efficient encapsulation and production of lipospheres. In contrast, formulations F5 (74.23 ± 0.45%) and F4 (75.65 ± 0.63%) showed lower yields, which may be attributed to variations in the formulation composition or processing conditions.

The drug entrapment efficiency (Table 3) was found to be highest in formulation F3 (83.32 ± 0.45%), which aligns with the yield data. This suggests that the formulation with the highest yield also exhibited a higher capacity for encapsulating Linagliptin. Formulations F2 and F6 also showed relatively high entrapment efficiencies of 76.44 ± 0.32% and 76.65 ± 0.33%, respectively, while formulations F4 (71.44 ± 0.55%) and F5 (74.45 ± 0.41%) demonstrated somewhat lower efficiencies. These variations can be attributed to differences in lipid composition, surfactant concentration, and other formulation parameters that influence the encapsulation process.

The particle size and zeta potential data (Figure 1 and Figure 2) of the optimized formulation F3 showed favorable results, suggesting that the lipospheres had a relatively small size with a stable surface charge. The smaller particle size is beneficial for improving drug absorption and bioavailability. The zeta potential values indicate that the formulation possesses good stability, which is crucial for preventing aggregation or instability of lipospheres over time.

The SEM images of the optimized formulation (Figure 3) revealed that the lipospheres had a spherical shape with smooth surfaces. This characteristic is indicative of a successful encapsulation process and suggests that the liposomes can potentially provide sustained drug release in the body.

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The flow properties of different liposphere formulations (Table 4) were evaluated using parameters such as loose bulk density, tapped density, Carr's index, and Hausner's ratio. The flowability of lipospheres is important for the ease of formulation processing and uniformity of tablet or capsule filling. Formulation F3 showed the best flow properties with a Carr's index of 3.101%, which suggests excellent flowability. In contrast, formulations F5 and F6 exhibited higher values for Carr's index (16.197% and 16.547%), indicating poorer flow properties, which may complicate the manufacturing process.

The in vitro drug release profile for formulation F2 (Table 5) showed a sustained release pattern over 12 hours, with 98.15% of the drug being released by the end of the study. The drug release was slow and controlled, as demonstrated by the log cumulative % drug remaining values, which were consistent with a sustained release system. The release kinetics were best described by the First Order model (r^2 = 0.993) and Peppas model (r^2 = 0.964), indicating that the release mechanism was both concentration-dependent and diffusion-controlled. The high regression values for these models suggest that the lipospheres are capable of delivering the drug in a controlled manner over time, which is desirable for therapeutic efficacy.

The comparative study of regression models for the release kinetics (Table 6) indicates that the first-order and Peppas models best describe the release behavior of the lipospheres. The Higuchi model (r^2 = 0.927) also showed a good fit, suggesting that diffusion plays a significant role in the release mechanism. The zero-order model (r^2 = 0.801) was the least applicable, indicating that the release was not purely zero-order but rather a combination of different mechanisms, including diffusion and erosion.

Table 2: Percentage yields of Linagliptin encapsulated lipospheres

S. No.	Formulation Code	% Yield*
1	F1	78.35±0.45
2	F2	80.23±0.89
3	F3	83.35±0.95
4	F4	75.65±0.63
5	F5	74.23±0.45
6	F6	76.65±0.25

***Average of three determinations**

Table 3: % Drug entrapment efficiency

S. No.	Formulation Code	% Drug entrapment efficiency
1.	F1	73.25±0.22
2.	F2	76.44±0.32
3.	F3	83.32±0.45
4.	F4	71.44±0.55
5.	F5	74.45±0.41
6.	F6	76.65±0.33

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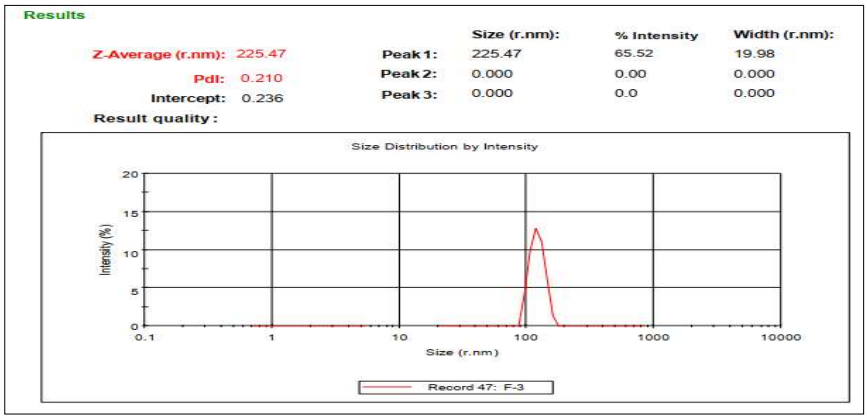

Figure 1: Particle size data of optimized lipospheres formulation F3

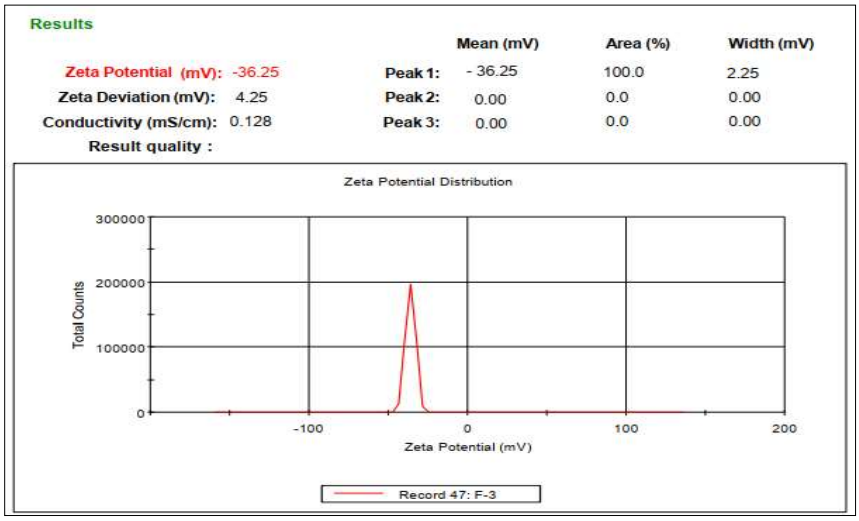

Figure 2: Zeta potential data of lipospheres formulation F3

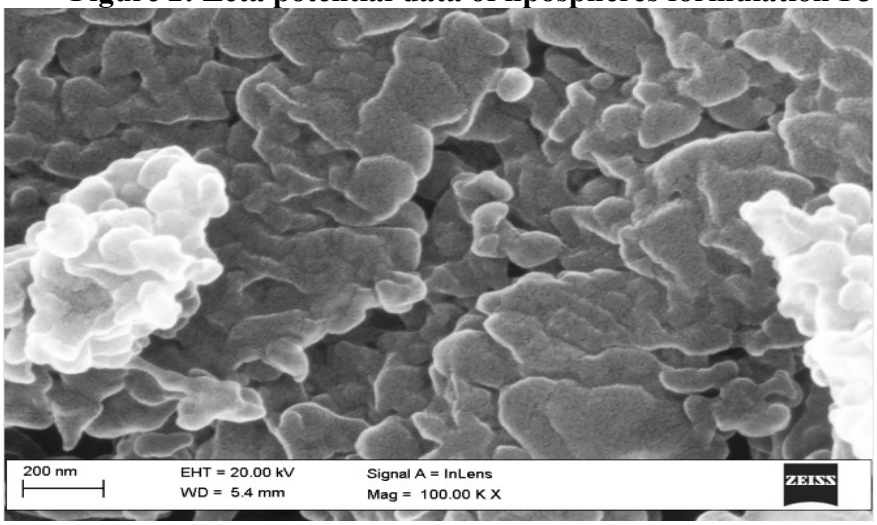

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Figure 3: SEM Image of Optimized Formulation Table 4: Result of Flow Properties of different liposphere formulation

Formulation code	Parameters			
	Loose Bulk density(gm/ml)	Tapped bulk density(gm/ml)	Carr's Index (%)	Hausner's Ratio
F1	1.11	1.38	19.565	1.243
F2	1.15	1.32	12.879	1.148
F3	1.25	1.29	3.101	1.032
F4	1.21	1.35	10.370	1.116
F5	1.19	1.42	16.197	1.193
F6	1.16	1.39	16.547	1.198

Table 5: Release study of Formulation F-2

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	21.45	1.331	78.55	1.895
1	1	0	35.65	1.552	64.35	1.809
1.5	1.225	0.176	46.65	1.669	53.35	1.727
2	1.414	0.301	55.32	1.743	44.68	1.650
3	1.732	0.477	68.98	1.839	31.02	1.492
4	2	0.602	75.65	1.879	24.35	1.386
6	2.449	0.778	83.32	1.921	16.68	1.222
8	2.828	0.903	92.65	1.967	7.35	0.866
12	3.464	1.079	98.15	1.992	1.85	0.267

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

	Zero order	First order	Higuchi	Peppas model
r^2	0.801	0.993	0.927	0.964

Conclusion

In conclusion, the results suggest that Linagliptin encapsulated lipospheres, particularly formulation F3, demonstrate excellent drug encapsulation efficiency, favorable particle size, and controlled drug release properties. These findings support the potential of lipospheres as an effective drug delivery system for Linagliptin, offering sustained drug release and enhanced therapeutic efficacy. Further in vivo studies and clinical evaluations are warranted to confirm the performance and safety of these formulations for potential therapeutic applications.

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