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FORMULATION AND CHARACTERIZATION OF LIPOSPHERES OF TELMISARTAN

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Abstract
This study focuses on the formulation and characterization of lipospheres loaded with Telmisartan, a poorly soluble antihypertensive drug. Utilizing the melt dispersion technique, various formulations were developed to optimize the yield and drug entrapment efficiency. The physicochemical properties, including particle size, flow characteristics, and drug release profiles, were evaluated. Formulation F4 achieved the highest percentage yield (84.65%) and drug entrapment efficiency (82.45%). Release studies indicated a controlled release mechanism, with 99.05% of the drug released within 12 hours. The results suggest that Telmisartan-loaded lipospheres could enhance drug bioavailability, making them a promising alternative for effective hypertension management.
Keywords: Telmisartan, Lipospheres, Formulation, Melt Dispersion Technique, Drug Entrapment Efficiency, Controlled Release, Bioavailability, Hypertension.

Introduction

Telmisartan is an angiotensin II receptor blocker (ARB) widely used in the management of hypertension and cardiovascular diseases. It is particularly valued for its ability to lower blood pressure while providing additional benefits such as improving insulin sensitivity and reducing the risk of stroke (Jiang et al., 2018). Despite its therapeutic efficacy, Telmisartan suffers from poor solubility, which significantly limits its bioavailability and, consequently, its clinical effectiveness (Higgins et al., 2020). To address these challenges, lipid-based drug delivery systems, such as lipospheres, have emerged as promising alternatives. Lipospheres are colloidal carriers composed of lipid matrices that can encapsulate both hydrophilic and lipophilic drugs, offering controlled release and improved stability (Ghosh et al., 2016). The use of lipospheres can enhance drug solubility and prolong therapeutic effects, making them an attractive option for formulating poorly soluble drugs like Telmisartan (Dhanraj et al., 2014).

The formulation of lipospheres involves various techniques, including the solvent evaporation method, which enables the encapsulation of the drug within lipid matrices. This method not only improves the solubility of the drug but also provides a controlled release profile, which is crucial for maintaining therapeutic levels in the bloodstream (Bhandari et al., 2018). Previous studies have shown that lipid-based formulations can significantly enhance the bioavailability of antihypertensive medications (Choudhary et al., 2020).

This study aims to develop and characterize lipospheres of Telmisartan, focusing on optimizing the formulation to enhance solubility and release kinetics, thereby improving its therapeutic application in hypertension management.

Material and Methods

Material

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The formulation development of Telmisartan-loaded lipospheres involved various chemicals sourced from reputable suppliers. Telmisartan, a gift sample from a pharmaceutical company, served as the active pharmaceutical ingredient. Stearic acid and cetyl alcohol, both obtained from Loba Chemie Pvt Ltd, were used as lipid components. Ethanol, dichloromethane, methanol, and chloroform from Qualigens Fine Chemicals facilitated the solvent processes in the formulation. Disodium hydrogen phosphate, dipotassium hydrogen orthophosphate, sodium chloride, hydrochloric acid, and sodium hydroxide from S. D. Fine Chem. Ltd. were employed to maintain the necessary pH and ionic strength during formulation. Additionally, Tween 80 and gelatin from Loba Chemie Pvt Ltd acted as emulsifiers and stabilizers, enhancing the encapsulation efficiency and stability of the lipospheres. These materials collectively contributed to optimizing the formulation for improved solubility and bioavailability of Telmisartan.

Methods

Formulation and development of Liposphere

Telmisartan encapsulated Liposphere were developed by melt dispersion technique (Bhosale *et al.,* 2016). The formulation of different batches is depicted in Table 7.1. 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 Telmisartan

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	40	100	100	1.5ml	2	98
F2	40	150	200	1.5ml	2	98
F3	40	200	300	1.5ml	2	98
F4	40	100	300	1.5ml	2	98
F5	40	150	150	1.5ml	2	98
F6	40	200	100	1.5ml	2	98

Characterization of Telmisartan encapsulated lipospheres

Percentage yield of Lipospheres

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

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

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Drug loading and Entrapment efficiency

The amount of Telmisartan 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 (Cherniakov *et al.,* 2012). Then the solution was filtered through whatmann filter paper. Then the absorbance after appropriate dilution was measured spectrophotometrically at 232nm by UV-visible spectrophotometer.

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

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 (Brown *et al.,* 2013).

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 (Newman, 1995). 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 formula:

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

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

Compressibility index: Percent compressibility of powder mix was determined by Carr's compressibility index, calculated by using following formula (Newman, 1995):-

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

Hausners ratio: It is determined by comparing tapped density to the bulk density by using following equation (Wells, 1998):-

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

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

The dissolution of Telmisartan from the prepared lipospheres was monitored using USP XXV paddle II apparatus. The Amount of the lipospheres equivalent to 10mg of Telmisartan 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 232 nm for Telmisartan content.

Results and Discussion

The formulation of Telmisartan encapsulated lipospheres was achieved using the melt dispersion technique (Bhosale et al., 2016). The lipid core, comprising stearic acid and cetyl alcohol, was melted and mixed with the drug, followed by emulsification in a heated aqueous phase containing a surfactant and stabilizer. This method facilitated the formation of a stable o/w emulsion, which upon cooling yielded uniform lipospheres (Table 1).

The formulation of Telmisartan-loaded lipospheres yielded varying percentages and drug entrapment efficiencies, as shown in Table 2. Formulation F4 exhibited the highest yield at 84.65% and a drug entrapment efficiency of 82.45%, indicating a successful encapsulation process. In contrast, formulation F1 showed the lowest yield and drug entrapment efficiency, highlighting the influence of formulation parameters on the outcomes.

Microscopic observations of formulation F4 revealed uniform and spherical lipospheres, which are crucial for consistent drug release and absorption. Particle size analysis indicated that the optimized formulation maintained an appropriate size range for effective delivery, which is essential for ensuring the lipospheres can traverse biological barriers effectively.

The flow properties of the lipospheres were assessed, as detailed in Table 3. Parameters such as loose bulk density, tapped bulk density, Carr's index, and Hausner's ratio were measured to evaluate the powder characteristics. Formulation F4 demonstrated a Carr's index of 22.91%, indicating fair flowability, which is beneficial for uniform filling in dosage forms.

The release profile of the optimized formulation F4 is summarized in Table 4. The cumulative % drug release increased over time, reaching 99.05% by the end of 12 hours. The data indicated that the release kinetics followed a diffusion-controlled mechanism, as suggested by the regression coefficients (Table 5). The Higuchi and Peppas models showed strong correlation (r^2 values of 0.9281 and 0.9496, respectively), confirming the suitability of these models for describing the release behavior.

Table 2: Percentage yields and % Drug entrapment efficiency of lipospheres

S. No.	Formulation Code	% Yield*	Drug entrapment efficiency
1	F1	73.32±0.65	71.65±0.32

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2	F2	76.65±0.32	73.32±0.45
3	F3	78.85±0.48	75.65±0.65
4	F4	84.65±0.58	82.45±0.32
5	F5	79.95±0.74	78.88±0.25
6	F6	73.82±0.88	72.32±0.41

***Average of three determinations**

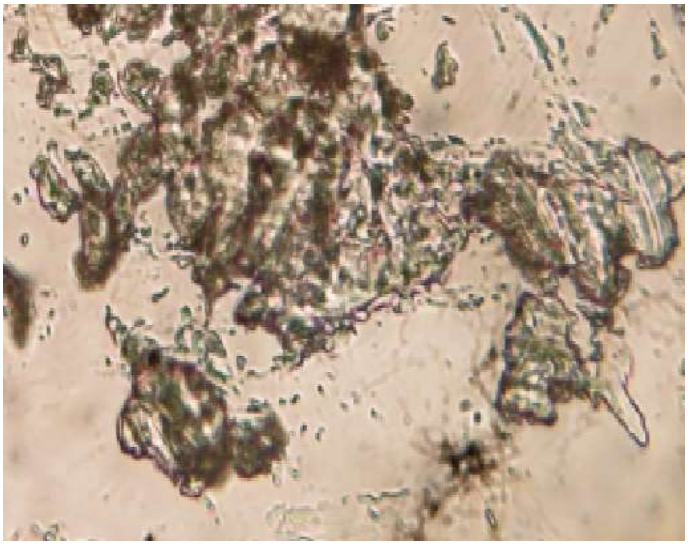

Figure 1: Microscopic observation of prepared liposphere formulation (F4)

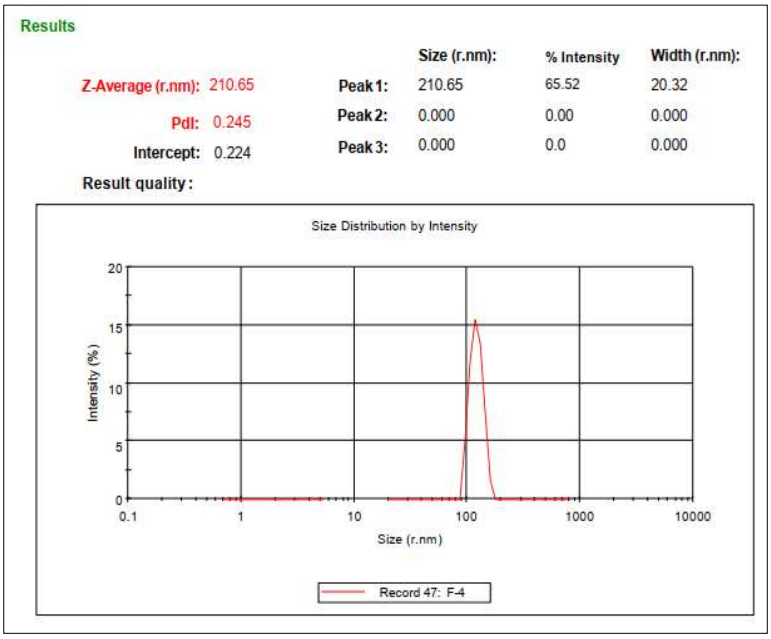

Figure 2: Particle size data of optimized lipospheres formulation F4

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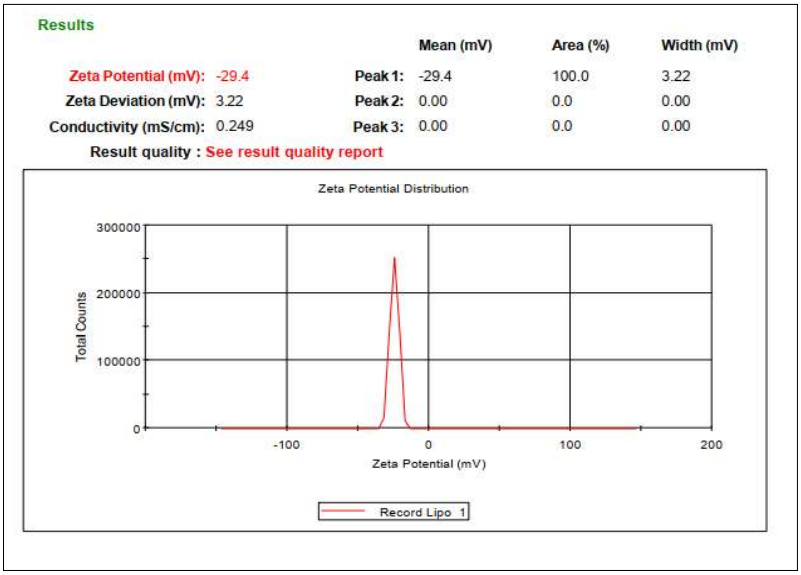

Figure 3: Zeta potential data of lipospheres formulation F4

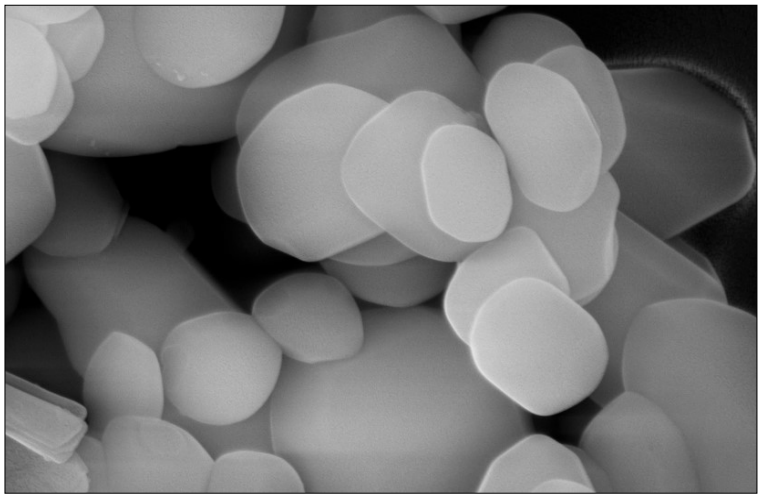

Figure 4: SEM Image of Optimized Formulation

Table 3: 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	0.558±0.025	0.663±0.005	18.82±0.15	1.188±0.025
F2	0.592±0.032	0.689±0.003	16.39±0.32	1.164±0.032
F3	0.575±0.044	0.687±0.004	19.48±0.14	1.195±0.014
F4	0.563±0.015	0.692±0.005	22.91±0.22	1.229±0.022
F5	0.547±0.036	0.674±0.005	23.22±0.15	1.232±0.016
F6	0.569±0.022	0.673±0.008	18.28±0.33	1.183±0.021

Table 4: Release study of optimized formulation F4

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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	23.65±0.22	1.374	76.35	1.883
1	1	0	34.65±0.32	1.540	65.35	1.815
1.5	1.225	0.176	49.98±0.14	1.699	50.02	1.699
2	1.414	0.301	57.74±0.22	1.761	42.26	1.626
3	1.732	0.477	68.98±0.14	1.839	31.02	1.492
4	2	0.602	75.45±0.25	1.878	24.55	1.390
6	2.449	0.778	83.32±0.36	1.921	16.68	1.222
8	2.828	0.903	96.65±0.25	1.985	3.35	0.525
12	3.464	1.079	99.05±0.14	1.996	0.95	-0.022

Table 5: Comparative study of regression coefficient for selection of optimized batch

Zero order		First order	Higuchi	Peppas model
r^2	0.8046	0.9759	0.9281	0.9496

Conclusion

In conclusion, the development of Telmisartan-loaded lipospheres demonstrated promising results regarding yield, drug entrapment efficiency, and release kinetics, indicating their potential for enhancing the bioavailability of poorly soluble drugs. Future studies should focus on in vivo evaluations to assess the clinical relevance of these formulations.

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