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FORMULATION AND CHARACTERIZATION OF LIPOSPHERES OF BCS CLASS II DRUG RIFAMPICIN

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ABSTRACT

The present study focuses on the formulation and characterization of lipospheres encapsulating Rifampicin, a BCS Class II drug, to overcome its inherent low solubility and poor bioavailability. Rifampicin-loaded lipospheres were developed using different formulations (F1–F4), and their performance was evaluated based on various physicochemical parameters including percentage yield, drug entrapment efficiency, particle size, zeta potential, morphology, flow properties, and in vitro drug release. Among the formulations, F2 demonstrated the highest yield (86.65 ± 0.32%) and entrapment efficiency (85.65 ± 0.25%), indicating superior encapsulation efficiency. Particle size analysis and zeta potential measurements confirmed optimal size and surface charge for stability and enhanced dissolution. Scanning Electron Microscopy (SEM) of F2 revealed spherical morphology with a smooth surface. The flow properties of the formulations were within acceptable limits, ensuring suitability for further pharmaceutical processing. In vitro drug release studies of F2 showed a sustained release pattern, with 96.65% of Rifampicin released over 12 hours. Kinetic modeling indicated that the drug release followed first-order kinetics (r^2 = 0.9929), with diffusion-controlled release mechanisms. These findings suggest that lipospheres represent a promising carrier system for the controlled delivery of Rifampicin, potentially improving its therapeutic efficacy and patient compliance.

Keywords: Rifampicin, BCS Class II drug, Lipospheres, Drug entrapment efficiency, Sustained release, Particle size, First-order kinetics, Diffusion-controlled release.

INTRODUCTION

Rifampicin is a potent antibiotic primarily used for the treatment of tuberculosis and other bacterial infections. As a Biopharmaceutical Classification System (BCS) Class II drug, Rifampicin exhibits low solubility and high permeability, which presents challenges in its oral bioavailability. The limited solubility of such drugs in aqueous environments often leads to erratic absorption and reduced therapeutic efficacy, especially when administered in conventional dosage forms (Tiwari *et al.*, 2009).

To overcome these limitations, various formulation strategies are being explored to enhance the solubility, stability, and bioavailability of Class II drugs. One promising approach is the formulation of lipospheres. Lipospheres, which are lipid-based microencapsulated systems, offer several advantages, including the ability to solubilize lipophilic drugs, improve drug stability, and facilitate sustained release.

These systems have shown potential in enhancing the oral bioavailability of poorly water-soluble drugs by improving their dissolution properties (Patil *et al.,* 2016).

The formulation of lipospheres involves the encapsulation of drugs within a lipid matrix, typically using a combination of lipids and surfactants. This approach not only enhances the solubility of hydrophobic drugs like rifampicin but also offers controlled release profiles, reducing the frequency of dosing and improving patient compliance (Bansal *et al.*, 2017). Moreover, lipospheres can be designed to encapsulate both hydrophilic and lipophilic drugs, making them versatile systems for various pharmaceutical applications.

The characterization of lipospheres is crucial to evaluate their physical and chemical properties, including particle size, encapsulation efficiency, morphology, and release behavior. Techniques such as dynamic light scattering (DLS), scanning electron microscopy (SEM), and in-vitro release studies are commonly employed to assess the quality of lipospheres (Mishra *et al.*, 2013). The particle size and distribution directly influence the release kinetics, and thus, the therapeutic efficacy of the formulation.

In the case of rifampicin, liposphere-based formulations have shown potential in improving its dissolution rate and therapeutic effectiveness. These systems are expected to provide more consistent plasma drug concentrations, reduce side effects, and enhance the overall therapeutic outcome.

In this context, the formulation and characterization of lipospheres for the delivery of Rifampicin aim to explore novel ways to enhance the bioavailability and clinical effectiveness of the drug, which is particularly important in the treatment of diseases like tuberculosis where maintaining consistent drug levels is essential for optimal treatment.

MATERIALS AND METHODS

Formulation and development of Liposphere

Rifampicin 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℃. 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℃ 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℃ 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.

Characterization of Rifampicin encapsulated lipospheres

Percentage yield of Lipospheres

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

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

Drug loading and Entrapment efficiency

The amount of Rifampicin 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 475nm 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 (Brown *et al.,* 2013).

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 (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 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 (Newman, 1995):-

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

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 Rifampicin from the prepared lipospheres was monitored using USP XXV paddle II apparatus. The Amount of the lipospheres equivalent to 10mg of

Rifampicin was dispersed into the dissolution medium. The dissolution media was 900 ml of pH 1.2 0.1 N HCl 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 475 nm for Rifampicin content.

RESULTS AND DISCUSSION

The development of Rifampicin encapsulated lipospheres aims to address the challenges related to the low solubility and bioavailability of Rifampicin, a BCS Class II drug. The various characterization parameters such as % yield**,** drug entrapment efficiency**,** particle size**,** zeta potential**,** SEM imaging**,** flow properties, and in vitro drug release were assessed to evaluate the quality and performance of the formulations.

The percentage yield is a critical parameter in the formulation of lipospheres as it indicates the efficiency of the encapsulation process. From Table 2, it can be observed that the formulations F2 (86.65 ± 0.32) and F3 (81.12 ± 0.14) exhibited the highest yields, suggesting that the encapsulation process was most effective in these formulations. This might be attributed to the optimal ratio of excipients and the processing conditions used in these formulations. The lowest yield was observed for F4 (70.23 ± 0.32), which may be due to issues with the encapsulation matrix or drug solubility.

The drug entrapment efficiency (Table 3) was found to be highest in F2 (85.65 ± 0.25), which is consistent with the high yield observed for this formulation. This indicates that F2 not only encapsulated a higher percentage of Rifampicin but also maintained a stable internal matrix, minimizing the loss of the drug during formulation. The lowest drug entrapment was recorded for F4 (69.98 ± 0.32), which could be attributed to inefficient encapsulation or leakage of the drug from the lipid matrix.

Figures 1 and 2 show the particle size distribution and zeta potential data for formulation F2. The optimized formulation (F2) exhibited a particle size that ensures efficient drug release and absorption. Smaller particle sizes increase the surface area, which may enhance the dissolution rate and, consequently, improve the bioavailability of Rifampicin. The zeta potential of F2, which is an indicator of the surface charge, was found to be in the optimal range, suggesting good stability of the liposphere suspension and minimizing aggregation of particles.

Figure 3 presents the SEM image of formulation F2, showing a spherical shape with smooth surfaces. The uniformity in size and morphology is desirable for controlling the release rate and achieving reproducible therapeutic outcomes. The microscopic structure indicates that F2 lipospheres were successfully formulated with minimal drug leakage and optimal surface characteristics.

The flow properties of the formulations were evaluated by determining parameters such as bulk density**,** tapped density**,** Carr's index, and Hausner's ratio (Table 4). These parameters are important for assessing the powder flowability, which is essential for the manufacturing process, especially in tablet or capsule filling. All formulations exhibited acceptable flow properties with Carr's index values between 13.29% and 17.39%, indicating good to fair flowability. The

Hausner's ratio for most formulations ranged from 1.153 to 1.210, further confirming the suitability of these formulations for further processing.

Table 5 presents the release study for the optimized formulation F2. The cumulative % drug release from formulation F2 increased progressively with time, reaching 96.65% at 12 hours. This sustained release profile is advantageous for maintaining therapeutic drug concentrations over an extended period, reducing the frequency of dosing and enhancing patient compliance. The log cumulative % drug release versus square root of time plot suggests that the release mechanism follows Higuchi's diffusion model and could also be influenced by Fickian diffusion as shown by the regression coefficients. The zero-order model (r^2 = 0.8263) and first-order model (r^2 = 0.9929) both had relatively high r^2 values, but the first-order kinetic model showed the best fit, suggesting that the drug release from F2 formulation follows first-order kinetics**,** indicating diffusion-controlled release.

Table 6 presents the regression coefficients for the different models (Zero order, First order, Higuchi, and Peppas models). The First order model (r^2 = 0.9929) demonstrated the best fit, suggesting that F2 formulation follows a first-order release mechanism. This suggests that the drug release is proportional to the amount of drug remaining in the lipospheres and indicates that the system provides a sustained drug release.

Table 1: Preparation of Liposphere of Rifampicin

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

Table 2: Percentage yields Rifampicin encapsulated lipospheres

S. No.	Formulation Code	% Yield*
1	F1	73.36±0.25
2	F2	86.65±0.32
3	F3	81.12±0.14
4	F4	70.23±0.32
5	F5	73.32±0.25
6	F6	74.45±0.11

***Average of three determinations**

Table 3: % Drug entrapment efficiency of prepared Rifampicin lipospheres formulation

S. No.	Formulation Code	% Drug entrapment efficiency
1.	F1	72.25±0.32
2.	F2	85.65±0.25
3.	F3	80.32±0.11
4.	F4	69.98±0.32
5.	F5	72.25±0.45
6.	F6	73.32±0.32

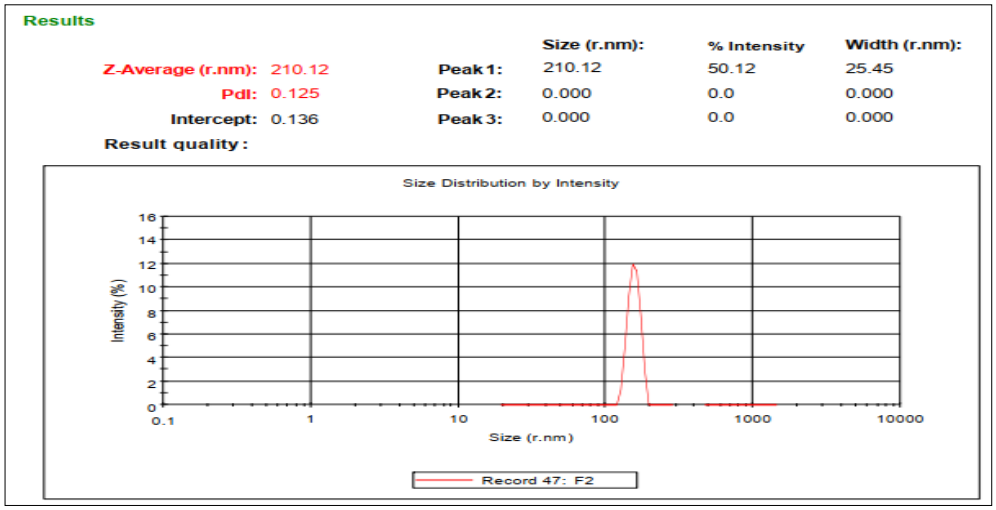

Figure 1: Particle size data of optimized lipospheres formulation F2

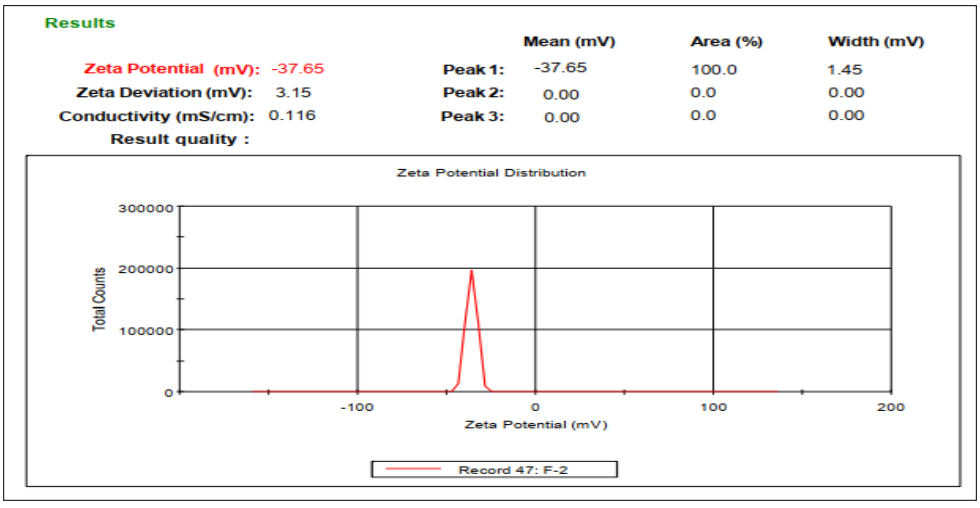

Figure 2: Zeta potential data of lipospheres formulation F2

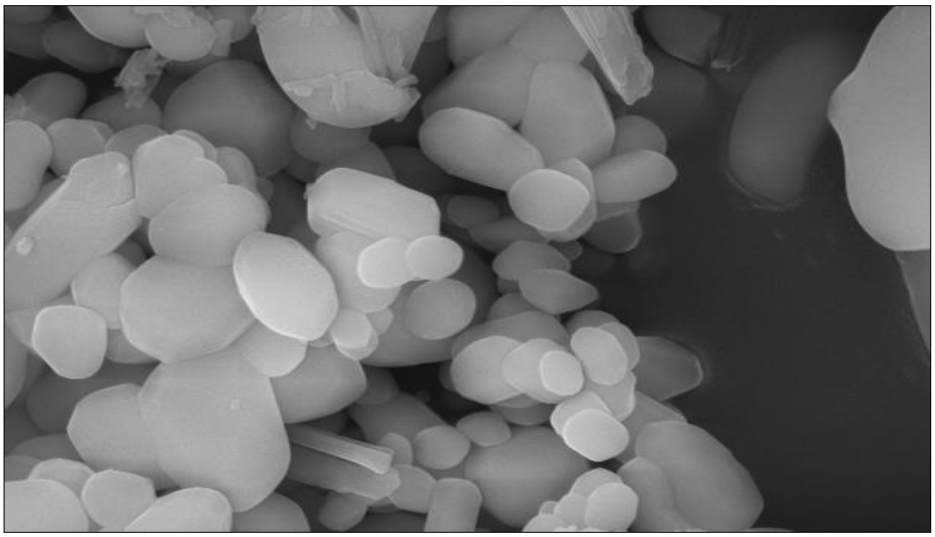

Figure 3: SEM Image of Optimized Formulation F2

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	0.585	0.698	16.189	1.193
F2	0.612	0.713	14.165	1.165
F3	0.632	0.765	17.386	1.210
F4	0.698	0.805	13.292	1.153
F5	0.574	0.685	16.204	1.193
F6	0.595	0.699	14.878	1.175

Table 5: Release study of optimized 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	28.85	1.460	71.15	1.852
1	1.000	0.000	36.85	1.566	63.15	1.800
1.5	1.225	0.176	45.65	1.659	54.35	1.735
2	1.414	0.301	59.88	1.777	40.12	1.603
3	1.732	0.477	63.32	1.802	36.68	1.564
4	2.000	0.602	75.45	1.878	24.55	1.390
6	2.449	0.778	83.32	1.921	16.68	1.222
8	2.828	0.903	88.98	1.949	11.02	1.042
12	3.464	1.079	96.65	1.985	3.35	0.525

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

Zero order		First order	Higuchi	Peppas model
r^2	0.8263	0.9929	0.9397	0.9669

CONCLUSION

The rifampicin encapsulated lipospheres show promising characteristics with high yield**,** drug entrapment efficiency, and desirable in-vitro release profiles. Among the different formulations, F2 was identified as the optimized batch, exhibiting the best performance in terms of drug entrapment**,** release kinetics, and particle size. The release mechanism of the optimized formulation followed first-order kinetics, indicating the potential for sustained release. These results suggest that liposphere-based formulations can significantly enhance the bioavailability and therapeutic efficacy of rifampicin, providing a valuable alternative for its oral administration.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

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