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Research Article

DEVELOPMENT AND EVALUATION OF LIPOSOMAL SELEXIPAG: A NOVEL ORAL DELIVERY SYSTEM FOR PULMONARY ARTERIAL HYPERTENSION

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ABSTRACT

Objectives: Pulmonary arterial hypertension (PAH) is a progressive and life-threatening condition characterized by increased pulmonary arterial pressure and vascular resistance. Selexipag, an oral prostacyclin receptor agonist, is effective in symptom management but suffers from poor aqueous solubility and limited bioavailability. This study aimed to develop and optimize a liposomal formulation of Selexipag-loaded liposomes (SLL) to enhance its oral bioavailability and therapeutic efficacy.

Methods: SLL were prepared using the thin film hydration method and optimized through Box–Behnken design with three independent variables: cholesterol, soya lecithin, and sonication time. The dependent variables included particle size (PS), entrapment efficiency (%EE), and zeta potential (ZP). Analysis of variance was used to analyze the experimental design, and the optimized formulation was characterized for compatibility, morphology, and release behavior.

Results: The optimized formulation exhibited a PS of 140.80±1.28 nm, %EE of 85.0±2.5%, and ZP of −25 mV, confirming good colloidal stability. *In vitro* drug release studies demonstrated a sustained release profile, achieving 75% drug release over 12 h compared to 40% from pure drug solution. *Ex vivo* permeation studies revealed a 1.8-fold increase in drug permeability through goat intestinal tissue for the liposomal formulation over the pure drug.

Conclusion: The developed Selexipag liposomal formulation significantly improved drug solubility, stability, and oral bioavailability potential, making it a promising delivery strategy for PAH management. The statistically validated optimization process confirmed the reliability of the formulation, laying a foundation for further clinical evaluation.

Keywords: Pulmonary arterial hypertension, Oral drug delivery, Selexipag, Box–Behnken design, Entrapment efficiency, Zeta potential.

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INTRODUCTION

Pulmonary arterial hypertension (PAH) is a cardiovascular disorder due to raised pulmonary artery pressure and vascular resistance, which causes heart failure and finally fatality. PAH is classified under Group 1 of the World Health Organization's pulmonary hypertension classification and includes idiopathic, heritable, and associated forms of the disease [1]. The prognosis for PAH continues to be harmful despite the fact that numerous therapeutic improvements have been made; hence, the development of novel treatment regimens is required.

An oral selective prostacyclin receptor agonist, i.e., Selexipag is widely used to delay PAH progression and reduce hospitalizations. It mimics the vasodilatory and anti-proliferative actions of endogenous prostacyclin, improving pulmonary hemodynamics and exercise capacity. However, due to its first-pass metabolism, Selexipag exhibits poor aqueous solubility and limited bioavailability (~49%), posing significant challenges for effective oral delivery [2].

Nanotechnology-based drug delivery systems, particularly liposomes, have emerged as promising approaches to overcome the solubility and bioavailability limitations of conventional drug formulations. Liposomes, which are bilayered phospholipids and spherical in nature, are versatile carriers that are able to hold both hydrophilic and lipophilic medicines. Due to the fact that they provide benefits such as better stability, controlled drug release, and improved bioavailability, they are suited for overcoming the problems that are connected with the administration of Selexipag [3].

This research focused its work on Selexipag-loaded liposomes (SLL) development using the thin-film hydration technique for formulation and optimization. A Box–Behnken design (BBD) served to optimize independent variables while producing desirable outcomes such as PS, %EE, and ZP [4]. The optimized SLL underwent *ex vivo* permeability testing and *in vitro* drug release evaluation. The liposomal formulation enhances Selexipag's solubility while improving stability and bioavailability to create a new oral delivery system for PAH management [4].

MATERIALS AND METHODS

Materials

Selexipag was purchased from App Cure Labs. L-α-phosphatidylcholine, cholesterol, chloroform, and methanol were obtained from Sisco Research Laboratories. For the aqueous phase, distilled water was used. All chemicals and reagents used were of analytical grade.

Methods

Preparation of liposomes

The approach of thin-film hydration was used to produce liposomes [5]. The solution of soya lecithin and cholesterol mixture at a 4:1 molar ratio underwent dissolution in a 2:1 chloroform to methanol mixture contained within a round-bottomed flask. The rotary evaporator evaporated solvents to create a thin lipid layer that formed against the flask walls at 60°C under reduced pressure. The formation of multilamellar vesicles was accomplished by hydrating the film with an aqueous solution that contained pre-dissolved Selexipag at a

temperature of 60°C while gently spinning the solution. As a means of reducing the particle size (PS) and obtaining small unilamellar vesicles, the dispersion that was produced was exposed to sonication for 10 min using a probe sonicator.

Optimization using BBD

The optimization process utilized BBD as a response surface methodology. The optimization process focused on three independent variables, including soya lecithin (X_1), cholesterol (X_2), and sonication time (X_3). The experimental design included three levels of independent variables for analysis of three dependent responses, which included PS (Y_1), entrapment efficiency (%EE) (Y_2), and zeta potential (ZP) (Y_3). Table 1 explains the list of independent variables and dependent variables, along with their limits and constraints. BBD given 17 formulation trials, as generated using Design-Expert® software. To identify the main effects and interaction effects, the results were analyzed by analysis of variance (ANOVA). To establish the relationship between all the independent variables, polynomial equations were derived for each response [5]. The optimal levels of all independent variables were determined using the desirability function. Table 1 presents the independent variables and dependent variables together with their boundaries and restrictions. The 17 formulation trials originated from BBD, which Design-Expert® software generated.

The ANOVA method helped identify main effects along with interaction effects from the results. The relationship between all independent variables was established through the derivation of polynomial equations for each response [6]. The desirability function helped determine the optimal levels for all independent variables. Further characterization of the optimized formulation included morphological examination through scanning electron microscopy (SEM) and thermal analysis by differential scanning calorimetry (DSC) and drug-excipient compatibility evaluation by Fourier transform infrared spectroscopy (FTIR). The dialysis bag diffusion method in phosphate buffer (pH 6.8) determined drug concentration, while *ex vivo* permeation studies used goat intestinal tissue in Franz diffusion cells.

Characterization of liposomes

PS and ZP

The DLS method works with a zeta sizer (Malvern Panalytical, Zetasizer lab) to determine this measurement. The liposomal suspension received a 1:10 volume/volume dilution with distilled water to minimize scattering effects. The diluted sample was analyzed for PS measurements through a quartz cuvette [7]. A customized cuvette was used to measure ZP after extracting the sample. The research team recorded the mean PS in nanometers and ZP in millivolts at 25°C during the measurements.

%EE

Determined by centrifugation. The supernatant was analyzed using ultraviolet (UV)-visible spectroscopy (Lab India, UV-3000) to quantify the unentrapped drug [8]. The free drug was separated from the formulated liposomes, and the suspension was placed on the centrifuge for 30 min at 4°C. The supernatant containing unencapsulated drug was collected and analyzed using UV-visible spectroscopy at the drug's maximum absorption wavelength (λmax).

FTIR studies

Drug-excipient compatibility studies were conducted by FTIR (Bruker, Alpha II). The team prepared pure medication and individual excipients, and formulation samples after finalizing the optimal liposomal formulation. The researchers pressed KBr mixtures into pellets before analysis. The FTIR spectrophotometer scanned the pellets within the 4000–400 cm^{-1} wavelength range. The analysis of Selexipag distinctive peaks between pure drug and liposomal formulation helped determine if any interactions existed [9].

Table 1: Variables and constraints in BBD

Factor/independent variables	Level (%)	Constrains
X1=Soya lecithin	100–200	In the range
X2=Cholesterol	100–150	In the range
X3=Sonication time	5–10	In the range
Dependent variables		
Particle size	100–150 nm	In the range
Entrapment efficiency	50–100	In the range
Zeta potential	−35 mv−−10 m	In the range

BBD: Box–Behnken design

Table 2 : Observed responses in Box–Behnken design for formulation

Trails	X1 (mg)	X2 (mg)	X3 (min)	Y1 (nm)*	Y2 (%)*	Y3 (mv)*
1	100	140	5	133.7±1.52	67.4±1.47	−18.5±0.25
2	200	180	7.5	175.2±2.45	87.2±1.38	−30.1±0.14
3	200	140	5	170.2±0.48	89.4±1.24	−32.2±0.36
4	150	100	10	141.6±1.47	83.4±1.18	−25.4±0.68
5	150	140	7.5	140.4±1.28	86.2±1.95	−29.2±0.12
6	150	140	7.5	138.2±1.35	87.1±1.77	−28.2±0.72
7	150	180	10	162.4±1.78	74.2±1.63	−22.1±0.39
8	150	140	7.5	142.3±1.98	88.4±1.98	−27.1±0.87
9	150	100	5	154.2±2.48	80.4±1.47	−27.6±0.87
10	150	180	5	157.9±1.98	76.4±0.58	−24.8±0.99
11	100	140	10	130.5±1.47	68.2±2.41	−17.1±0.13
12	200	140	10	167.2±1.32	90.1±2.78	−31.4±0.46
13	200	100	7.5	159.2±1.58	92.3±1.98	−34.4±0.82
14	150	140	7.5	144.2±2.12	85.2±1.73	−26.3±0.24
15	100	180	7.5	147.6±1.82	65.6±1.49	−15.1±0.36
16	150	140	7.5	145.3±1.87	87.8±1.85	−30.2±0.87
17	100	100	7.5	120.4±1.58	70.2±1.16	−20.3±0.36

*All the values were represented in n=3 (mean±standard deviation)

DSC study

DSC analysis evaluated the drug substance and lipids and liposomal formulation to determine their thermal behavior during heating procedures using the DSC equipment (Shimadzu, 60 plus). A DSC aluminium pan contained 5–10 mg of each sample, containing pure medication and excipients, and liposomes. The pans underwent heating at 10°C/min under nitrogen conditions from 30°C to 300°C. The evaluation of thermograms helped identify any shifts in melting points and endothermic/exothermic events. The results show evidence of drug encapsulation and compatibility between components [10].

SEM study

The research analyzed liposomal morphology and surface characteristics through field emission scanning electron microscope (Jeol, 710HR). A drop of liposomal suspension received placed on a carbon-coated stub. A sputter coater deposited a thin layer of gold onto the dried sample before air-drying. The researchers enhanced copper conductivity through this process. The SEM analysis of the coated sample required an accelerating voltage between 5 and 20 kV. The method enabled researchers to study both the surface features and overall form of the liposomes [11].

***In vitro* drug release studies**

The dialysis bag diffusion method served to evaluate the drug release properties of the liposomal formulation in an *in vitro* dissolution apparatus (Remi Electrotechnik LTD). Inserted a predetermined amount of liposomal formulation into the pre-soaked dialysis bag which had a molecular weight cutoff between 12,000 and 14,000 Da. The bag received continuous stirring at 100 rpm revolutions while submerged in 100 mL of pH 6.8 phosphate buffer solution [12]. The temperature was kept at 37±0.5°C. The experiment followed a pre-established time schedule to exchange buffer solutions with 5 mL medium samples. UV-

visible spectroscopy (Lab India, UV-3000) of aliquots provided data for determining medication concentrations. The evaluation of drug release kinetics required the calculation of cumulative drug release percentages followed by a time-based graphical representation [13].

Ex vivo permeation studies

The permeability of the liposomal formulation was evaluated through *ex vivo* tests using goat intestinal tissue. The Franz diffusion cell contained two separate compartments for donor and receptor solutions after intestinal tissue placement. The receptor compartment received pH 7.4 phosphate buffer solution while the donor compartment contained the liposomal formulation [14]. A spectrophotometric analysis was conducted on the collected samples following the predetermined time points.

RESULTS AND DISCUSSION

Optimization of BBD

A BBD helped improve the formulation to determine how soya lecithin, cholesterol, and sonication time influenced PS, %EE, and ZP displayed in the table 2. ANOVA evaluated seventeen experimental trials that followed the design matrix protocol. The analysis evaluated both individual element significance and their interdependent relationships. The design-exert platform analyzed the observed results from every formulation against all possible models. The linear model provided the most accurate fit for the experimental data. Table 3 displays the ANOVA results together with R2, adjusted R2, anticipated R2, standard deviation, and percentage of confidence interval (%coefficient of variation) values, and the regression equations developed for each response. The model demonstrated excellent fit with response variables because the R^2 values were high. The F values from all response models indicated their usefulness as valid information [15]. The p-value below 0.005 confirmed statistical significance of model terms, thus proving that the mistake likelihood remained below zero. The independent variables A and B have been identified through observations.

The lipid concentration, together with sonication time, showed a direct impact on the PS. The lipid-to-drug ratio increase produced smaller particles because it enhanced lipid bilayer formation, and additional sonication time broke down larger vesicles into smaller uniform structures. The combination of lipid-to-drug ratio and hydration temperature determined the entrapped drug quantity because higher lipid content created larger bilayer spaces, and proper hydration temperatures allowed efficient lipid hydration. The duration of sonication proved most important for ZP because it created a more uniform distribution of surface charges, which led to improved colloidal stability. Fig. 1 presents contour and 3D graphs to demonstrate how ZP changes based on independent variable modifications [16].

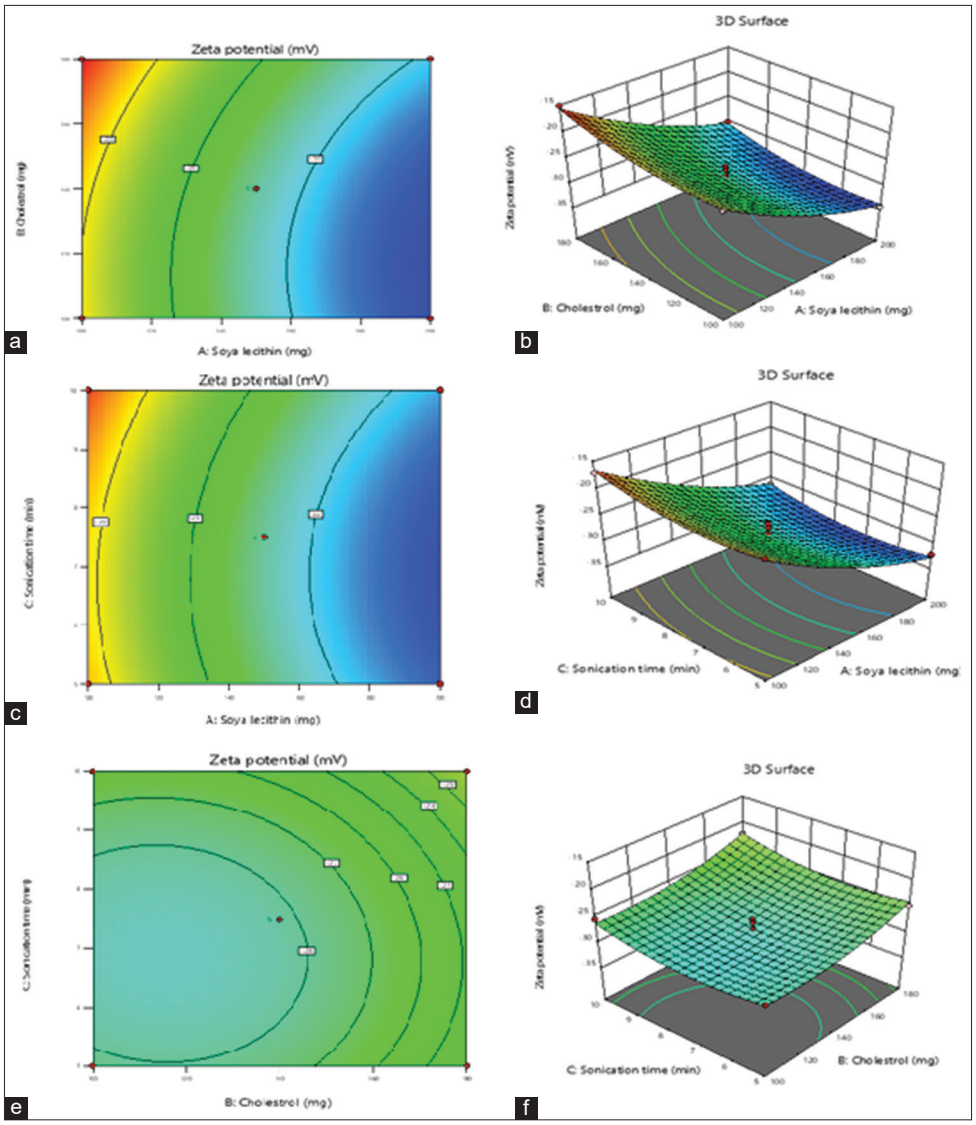

Fig. 1: Representation of influence of X1 and X2 factors at mid-level X3 as (a) contour plot and (b) response surface plot; influence of X1 and X3 factors at mid-level X2 as (c) contour plot and (d) response surface plot; influence of X2 and X3 factors at mid-level X1 as (e) contour plot and (f) response surface plot

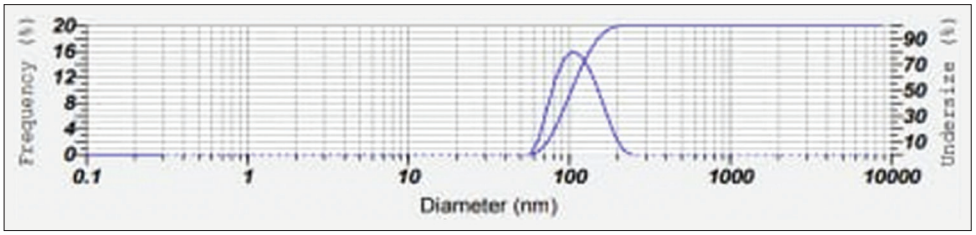

Fig. 2: Particle size analysis of optimized formulation

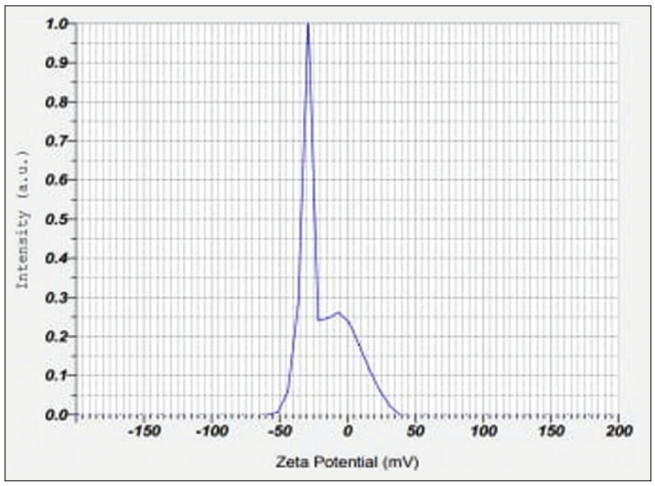

Fig. 3: Zeta potential of optimized formulation

The response surface plots showed important relationships between the independent variables. The production of tiny vesicles became possible using high lipid-to-drug ratios alongside appropriate sonication durations. The combination of elevated lipid content with suitable hydration temperature conditions produced the highest drug encapsulation rate. The extended duration of sonication led to an improvement in ZP, which subsequently strengthened the stability of the liposomal formulation.

The optimal conditions for liposomal preparation emerged from the desired function, which included a 4:1 lipid-to-drug ratio and a 55°C hydration temperature, and 15 min of sonication time. The optimized formulation exhibited a PS of 140.80 nm and achieved 85% entrapment effectiveness and −25 mV ZP, which matched closely with the Box–Behnken model predictions. The optimization procedure achieved its reliability goal through this agreement.

The BBD implemented a systematic method to study formulation variables while minimizing experimental trial numbers. The optimized liposomal formulation met all desired attributes while demonstrating improved solubility alongside enhanced stability and bioavailability, thus qualifying itself for oral delivery.

PS and ZP

The optimized liposomal formulation demonstrated an average particle dimension of 140.80 nm as shown in Fig. 2. The uniform distribution of PSs becomes evident through the polydispersity index (PDI) value of 0.18. The figure 3 described the zeta potential reading as −25 mV ZP reading indicates strong electrostatic repulsion between particles and supports the observed good colloidal stability. The gastrointestinal tract absorbs drugs optimally when particles maintain dimensions below 200 nm. The narrow PDI measurements demonstrate a homogeneous formulation that ensures constant drug release. Stability indicators show a ZP measurement between −10 mV and −30 mV. The ZP range between −10 mV and −30 mV reduces the likelihood of particle aggregation when the formulation is stored or administered.

Table 3: ANOVA data of all three responses

Dependent variable Parameters	Value	F-value	p-value
A) Particle size			
Model	**Quadratic**		
R^2	0.9609	32.88	<0.0001
Adj iR^2	0.9478		
Pred iR^2	0.9099		
Adeq Precision	21.8699		
B) Entrapment efficiency			
Model	**Quadratic**		
R^2	0.8681	122.42	<0.0001
Adj iR^2	0.8242		
Pred iR^2	0.7006		
Adeq precision	10.79		
C) Zeta potential			
Model	**Quadratic**		
R^2	0.9842	231.42	<0.0001
Adj iR^2	0.9628		
Pred iR^2	0.9215		
Adeq precision	24.1258		

ANOVA: Analysis of variance

%EE

The SLL demonstrated an encapsulation efficiency of 85±2.5% which confirms successful incorporation of Selexipag into the liposomal membrane. The combination of optimal lipid-to-drug ratio and cholesterol presence creates rigid membranes that minimize drug leakage, thus resulting in high EE%. The encapsulation method provides sustained drug release capabilities while simultaneously reducing storage-related drug loss.

FTIR study

The FTIR analysis revealed that Selexipag maintained its chemical stability when mixed with the various excipients used in the study. The liposomal formulation maintained the characteristic peaks of Selexipag, including the C=O stretching at 1650 cm^{-1} and the N-H stretching at 3300 cm^{-1} indicating drug stability. The FTIR spectrum analysis in Fig. 4 demonstrates that the medicine remains chemically stable because no new peaks appear and no spectrum changes occur when using excipients in the liposomal formulation.

DSC study

The liposomal formulation of Selexipag displayed a lower melting point than pure Selexipag, as shown by DSC thermograms in Fig. 5. The endothermic peak, which would normally indicate Selexipag, is absent because the drug exists in an amorphous state within the lipid bilayer. Liposomal encapsulation of Selexipag in an amorphous state improves its solubility and dissolution rate, which enhances bioavailability.

SEM study

The SEM images in Fig. 6 displayed spherical liposomes with smooth surfaces and uniform shape. The results from PS analysis matched

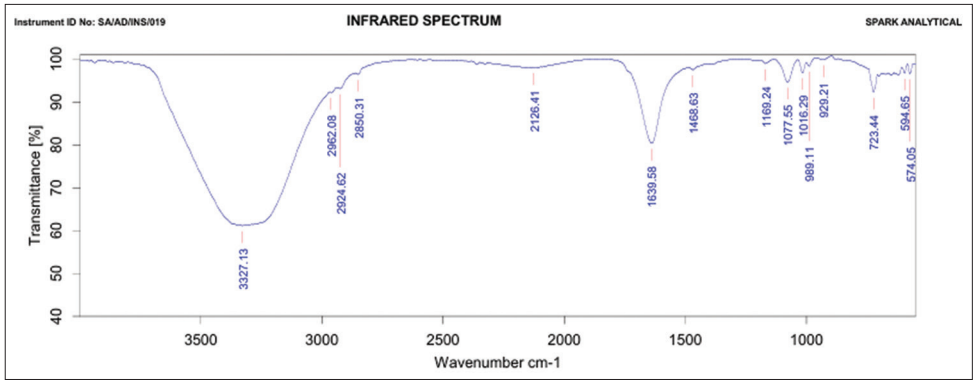

Fig. 4: Fourier transform infrared spectroscopy spectra of optimized formulation

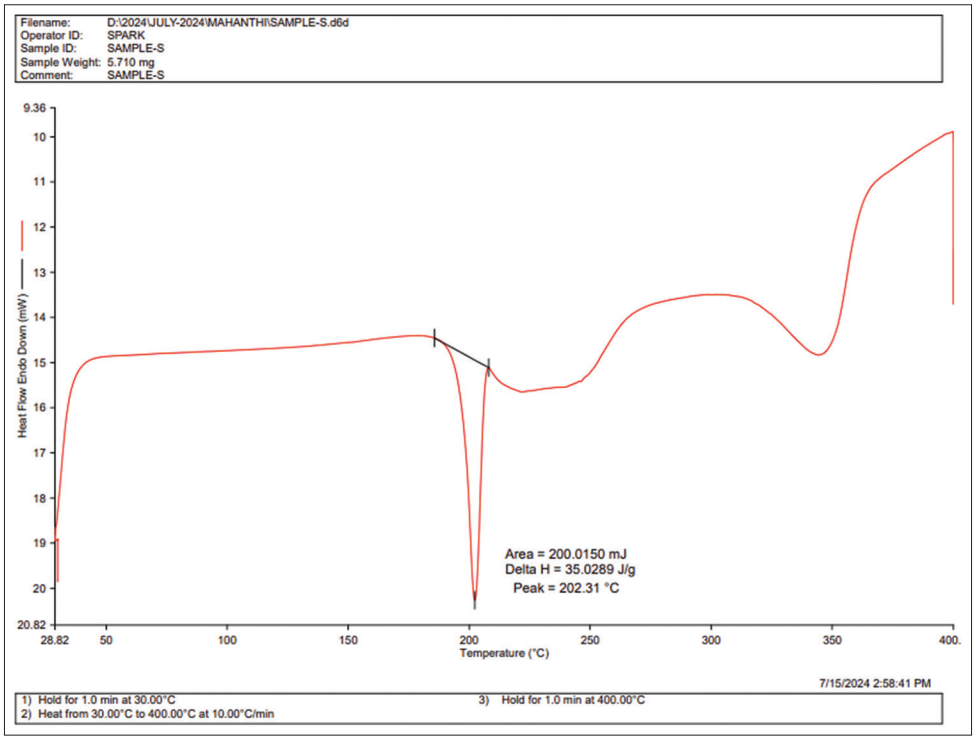

Fig. 5: Differential scanning calorimetry spectra of optimized formulation

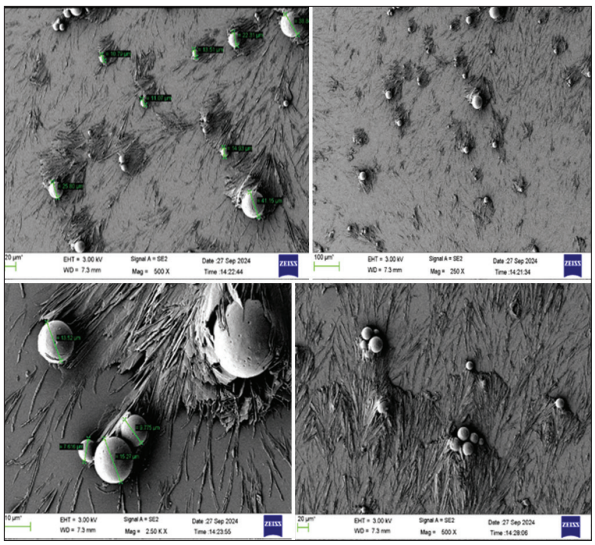

Fig. 6: Scanning electron microscopy studies of optimized formulation

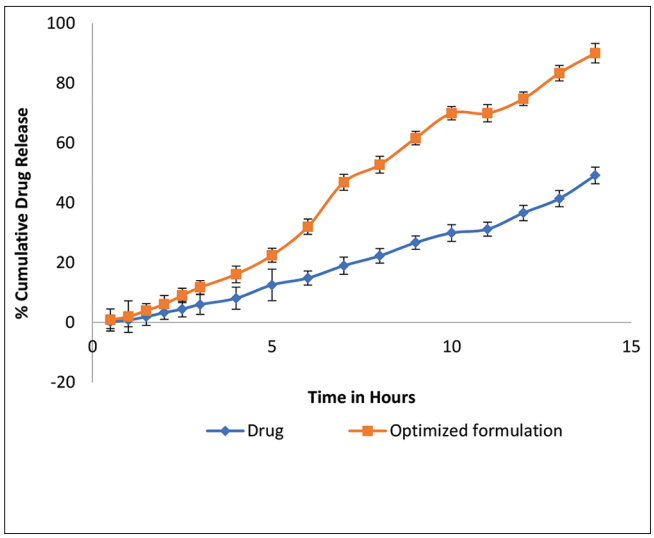

Fig. 7: *In vitro* dissolution studies of the drug and optimized formulation. n=3±standard deviation

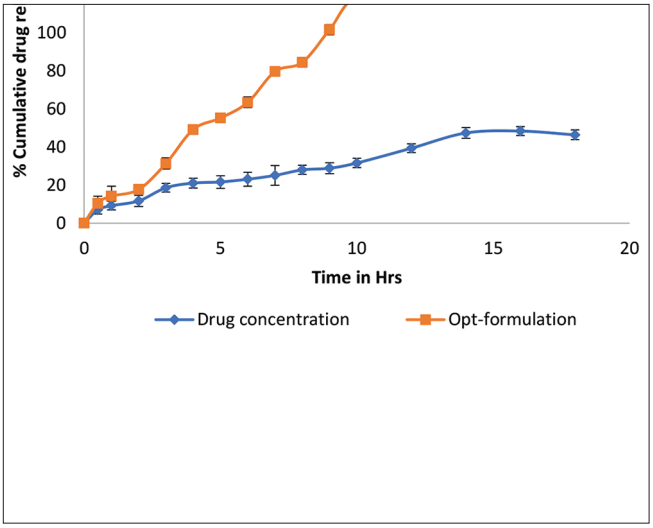

Fig. 8: *Ex vivo* permeation studies of drug and optimized formulation. n=3±standard deviation

the nanometer dimensions of the liposomes. The successful liposome manufacturing process can be verified through both the spherical shape and the smooth surface of the liposomes. The successful drug encapsulation and controlled drug release depend on this fundamental requirement.

In vitro drug release profile

The *in vitro* drug release test demonstrated that the liposomal formulation released 75% of the drug during 12 h, but the pure drug released only 40% of the drug. The release profile showed a biphasic pattern that started with an initial drug burst followed by a steady drug release period. The initial burst release from the liposomes may be attributed to surface-bound drug, while the sustained release results from Selexipag diffusion out of the liposomal core. The drug release pattern is illustrated in Fig. 7 provides extended therapeutic control by maintaining proper drug levels.

Ex vivo permeation studies

The liposomal formulation achieved significantly higher drug penetration through goat intestinal tissue than pure drug administration according to *ex vivo* testing results (Fig. 8). The liposomal formulation of Selexipag achieved a penetration rate that was 1.8 times > the pure drug during the 6-h study period. Liposomes penetrate biological barriers effectively because their nanoscale dimensions and lipid structure enable membrane contact and increase drug transport through biological barriers.

CONCLUSION

The study created and optimized an SLL for PAH treatment by integrating the thin-film hydration technique with BBD optimization methods. The optimized formulation achieved desirable characteristics, which included a PS of 140.80 nm and a ZP of −25 mV, and an EE of 85%. The combination of these properties shows that the system maintains high stability and achieves efficient drug encapsulation while being suitable for oral delivery. The liposomal formulation demonstrated superior drug release performance through its ability to release 75% of the drug content over 12 h compared to the pure drug solution. The *ex vivo* permeability tests showed that drug absorption improved by 1.8 times relative to the pure drug. The study shows that liposomal Selexipag holds promise as a new drug delivery system that overcomes the problems of conventional formulations by enhancing both solubility and bioavailability. The new formulation demonstrates substantial potential to enhance therapy results in PAH management while establishing groundwork for future clinical applications.

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AUTHOR'S CONTRIBUTION

Rajeshwar V: Conceptualization, methodology, writing – original draft preparation, data curation, visualization, and investigation. Kondoju Divya Latha: Investigation, review editing. Bushara Fathima: Validation of data and proofreading of manuscript. Vasudha B mar: Supervised in designing the study, conceptualization, writing – Reviewing and editing.

CONFLICT OF INTREST

Authors don't have any conflict of interest.

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