ARTICLE

DESIGN, DEVELOPMENT AND EVALUATION OF BETAXOLOL HYDROCHLORIDE LOADED NIOSOMAL DRUG DELIVERY SYSTEM TO ENHANCE BIOAVAILABILY AND MANAGE HYPERTENSION

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ABSTRACT

Betaxolol Hydrochloride (BH), a selective β1-adrenergic receptor antagonist widely used in the management of hypertension and cardiovascular disorders, suffers from limitations associated with conventional oral dosage forms, including poor mucosal permeation and delayed onset of action. The present study was undertaken to formulate and evaluate niosomes with BH, combining the advantages of vesicular drug delivery with the rapid, with the goal of enhancing bioavailability, patient compliance, and therapeutic performance. It incudes the preformulation studies, confirmed the identity, purity, and suitability of the drug, while drug–excipient compatibility studies verified the absence of significant interactions with cholesterol, Span 60, HPMC E15, and PEG 400. BH-loaded niosomes (BHN),were prepared by the thin-film hydration method and optimized using a Central Composite Design with cholesterol and Span 60 concentrations as independent variables. The nine experimental batches were characterized for vesicle size, polydispersity index, zeta potential, drug content, % Entrapment Efficiency, and drug loading. These findings demonstrate that niosomes represent a promising alternative to conventional oral dosage forms of BH, offering rapid absorption, enhanced drug release, and improved patient convenience, and warrant further evaluation through in vivo and clinical studies.

Keywords: Betaxolol Hydrochloride, Niosomes, Novel Drug Delivery System, Hypertension, Thin Film Hydration Method, Cardiovascular disorders

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INTRODUCTION

High blood pressure, is one of the most common chronic disorders and major public health concern. It affects millions of people globally and is a leading risk factor for cardiovascular diseases such as stoke, heart attack, heart failure, and kidney disease. It is commonly caused by factors including obesity, high salt intake physical inactivity, stress, smoking, alcohol consumption, and genetic predisposition. Effective management through lifestyle modifications and antihypertensive medications is essential to prevent complications and improve quality of life.[1] Conventional oral dosage forms of antihypertensive drug faces major drawbacks. Although BH is commonly administerd as an oral tablet, its therapeutic effectiveness is limited by extensive first-pass metabolism and relatively low bioavailability. The drug also takes time to be absorbed through the gastrointestinal tract, resulting in a slower onset of action. In some cases, higher doses may be needed to achieve the desired therapeutic effect. Increasing the dose can also raise the risk of adverse effects, including bradycardia and hypotension.[2] Novel drug delivery systems have gained considerable attention in recent years owing to their ability to improve therapeutic efficacy, enhance patient compliance, and overcome the limitations associated with conventional dosage forms.[3] Niosomes are vesicular carriers made from non-ionic surfactants that improve drug stability, enhance permeability, and promote better drug delivery. Incorporating niosomes into fast dissolving oral films combines the advantages of both systemic, enabling rapid drug release, improved bioavailability, and enhanced therapeutic effectiveness.[4] Thus, The present study aims to formulate and evaluate BHN using non-ionic surfactant and cholesterol to improve drug entrapment, stability, and drug-release characteristics for enhanced drug delivery[5].

MATERIALS AND METHODS

MATERIALS

BH, was obtained from Indoco Remedies Ltd.,Goa. Span 60, cholesterol, Hydroxypropyl methylcellulose (HPMC E15), polyethylene glycol 400 (PEG 400), Microcrystalline cellulose, saccharin sodium, and menthol were purchased from research lab. Mumbai. Methanol, chloroform, phosphate buffer (pH 7.4) Tablet, and other analytical reagents used for drug estimation were procured from standard suppliers.

METHODS

Preformulation studies

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Organoleptic Properties

BH was observed visually by using watch glass for its physical appearance such as texture, color and odor.

pH determination

It was done using calibrated pH meter after suitable dilution of BH sample.

Melting point

The melting point of BH was determined using capillary tube method. Thieles tube containing liquid paraffin solution and then small amount of pure drug was filled in the capillary tube which is sealed at one end using flame. Sample filled in capillary is tied with thread to the thermometer and suspended into Thieles tube and heated till drug powder melts. The temperature at which the pure drug powder started melting was noted in triplicate.

CALIBRATION CURVE AND ASORPTION MAXIMA

The sample of the standard solution were scanned between 200-400 nm regions on UV spectrophotometer (Jasco V-630) and absorption maxima has been reported.The calibration curve was generated in range of 10 to 60 µg/ml in Phosphate buffer pH 7.4, that demonstrated a linear relationship between concentration (µg/ml) and absorbance. It was evidenced by the equation y =0.0132x + 0.0033 and a strong correlation coefficient of 0.9973.

Solubility studies

The solubility of drug was performed in methanol, ethanol, distilled water, phosphate buffer pH 7.4, phosphate buffer pH 6.8, acidic buffer pH 1.2 and Deionized Water by taken in different 100 ml conical flask & 50 mg of BH were added in it. The conical flask was stirred for 24 h on mechanical shaker at 150 rpm till equilibrium obtained. The flask was removed and solutions were filtered. The absorbance was measured at 223 nm and concentration were reported (n=3).

Drug-excipient compatibility study

Compatibility between BH and the selected excipients was evaluated using FTIR spectroscopy. Physical mixture of Drug:Cholesterol:Span 60 (1:1:1) and Drug:HPMC E15:PEG 400 (1:1:1) were analyzed using a JASCO FTIR spectrophotometer with an ATR accessory. Spectra were recorded over 4000-6500 cm^{-1} at a resolution of 4 cm^{-1} using 32 scans. The obtained spectra werw examined for changes in characteristic peaks to assess possible drug-excipient interactions.[6,7]

Preparation of Niosomes

Experimental design

A Central Composite Design (CCD) was applied using Design-Expert® software (Version 13.0) to optimize the niosomal formulation. The amounts of cholesterol and Span 60 were selected as independent variables, while drug content (%) and entrapment efficiency (%) were considered as responses. The design consisted of factorial, centre, and axial points, giving a total of 9 experimental runs (F1-F9) as shown in Table 1[8, 9].

BHN formulation

Niosomes of each batch F1 to F9 were prepared by the thin-film hydration method using Span 60 as the non-ionic surfactant and cholesterol as a membrane stabilizer. The drug, Span 60, and cholesterol were dissolved in chloroform, and the solvent was evaporated under reduced pressure at 60°C to form a thin lipid film. The film was hydrated with 10 mL deionized water at 60°C, followed by vortex mixing for 10 min. The resulting niosomal suspension was sonicated for 20 min at 25°C and stored at 4–8°C for further evaluation.[10]

Table 1: DOE suggested Formulation composition of BHN

Formulation batch	Betaxolol HCl(mg)	Cholesterol (mg)	Span 60(mg)	Chloroform(ml)	Deionized Water
F1	20	25	125	10	10
F2	20	75	125	10	10
F3	20	125	125	10	10
F4	20	75	50	10	10
F5	20	25	200	10	10
F6	20	125	50	10	10
F7	20	25	50	10	10
F8	20	125	200	10	10
F9	20	75	200	10	10

Evaluation of developed BHN

Determination of Particle size, Zeta potential and Polydispersity index (PDI)

The weighed amount of 10 ml niosomal suspension F1-F9 was taken separately and mixed with distilled water and sonicated for 30 min. The analysis was performed at a temperature of 25°C using molborn zetasizer to determine Particle size, Zeta potential and PDI (n=3) [11].

Determination of % Drug content

The weighed amount of 5ml of niosomal suspension was taken in a volumetric flask of 10 ml and the volume was made up by methanol and sonicated for 15 min., after that 1 ml of this mixture was diluted to 10 ml by methanol, and the percentage drug content was observed at 223 nm using UV method. Drug content for each formulation was calculted by the calibration curve statistically(n=3)[12].

Determination of Entrapment efficiency (% EE)

The EE of all niosomal formulations were determined by centrifugation method, in which 5ml in 10 ml of the prepared niosomal suspension was placed in the Eppendorf for centrifugation
(RM-12) at 1400 rpm for 30min. After centrifugation, the supernatant liquid was separated, containing the un-entrapped drug, diluted with phosphate buffer pH 7.4 and analyzed using UV spectrophotometer at 223 nm[13]. Readings were recorded in triplicate and amount calculated as follows-

EE% = Total amount of drug – Amount of the unentrapped drug / Total amount of drug × 100

Cumulative % In vitro drug release

A dissolution test was performed using dissolution test apparatus USP type II in Phosphate buffer pH 7.4 with all BHN formulations separately, at 37±0.5°C at 50 rpm. 20 mg plain drug was added to the dissolution apparatus containing 900 ml of dissolution media as standard and compared with niasomal formuations. The 2 ml solution was withdrawn at time intervals of 10,20,30,40, 50, 60, 90 and 120 min. The same amount of solvent was replaced to maintained the sink condition. The dissolved amount of the drug was calculated by using UV at 223 nm (n=3).

Physical Stability study

The optimized batch of BHN, on the basis of above parameters was selected for stability study. The sample was stored at refrigeration temperature (4±2)ºC, room temperature (25±2)ºC and 40ºC, 75% RH as per ICH guidelines for 3 months. After every month time interval, % residual drug content and physical appearance was determined and reported (n=3).

RESULT AND DISCUSSION

The drug was observed as a white to off-white crystalline powder, with an odourless nature and a bitter taste. The pH of the drug solution was found to be in the range of 5.0-6.5.The melting point of BH was found to be 117ºC, which was comparable with the reported value, including the purity of the drug. The calibration curve showed the strong correlation indicated that the absorbance values reliably reflect the concentration of the analyte within the tested range of 10 to 60 µg/ml under phosphate buffer pH 7.4 conditions. It showed a consistent increase in absorbance with higher concentrations, highlighting the sensitivity and precision of the method within the specified pH environment. The solubility of drug was evaluated in different media, and significant variations were observed. The highest solubility was found in methanol (52347±45 µg/mL), indicating excellent solubility in this solvent. Moderate solubility was observed in acidic buffer pH 1.2, distilled water and deionized water (Figure 1). Overall, the results indicate that the substance possesses greater solubility in organic solvents, particularly methanol and ethanol, compared to aqueous media. These findings are important for selecting suitable solvents and designing formulations to enhance drug dissolution and bioavailability.

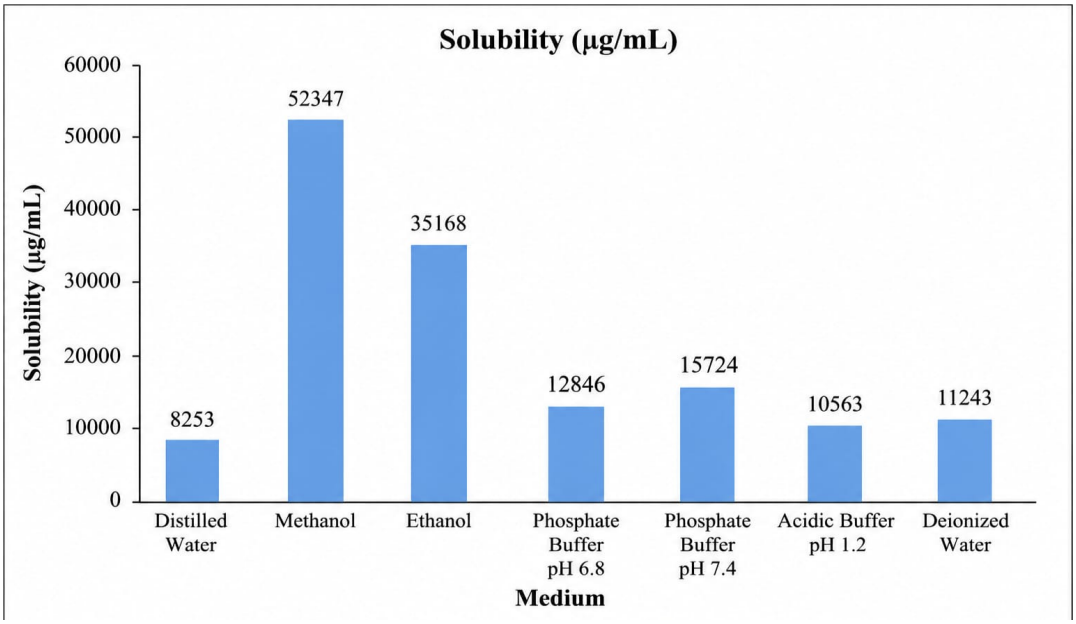


Figure 1: Solubility of BH in different solvents (µg/mL)

The prepared physical mixture were analyzed for compatibility study between BH and the selected excipients using FTIR spectroscopy. The FTIR spectrum of BH: Cholesterol:Span 60 (1:1:1) and BH: HPMC E15: PEG 400 (1:1:1) formulation showed characteristic peaks corresponding to the major functional groups present in the formulation. The broad peak observed at 3239.82 cm^{-1} indicated O–H stretching vibration. Peaks at 2925.48 cm^{-1} and 2850.27 cm^{-1} confirmed C–H stretching vibrations. The absorption peak at 2357.55 cm^{-1} corresponded to atmospheric CO_2 stretching vibration. The characteristic peak at 1732.73 cm^{-1} indicated C=O stretching vibration, while the peak at 1613.16 cm^{-1} represented C=C stretching vibration. Peaks at 1558.2 cm^{-1}, 1512.88 cm^{-1}, and 1472.30 cm^{-1} corresponded to CH_2 bending vibrations. The peaks at 1337.59 cm^{-1} and 1300.75 cm^{-1} indicated C–N stretching vibrations. The peak at 1278.53 cm^{-1} represented C–O stretching vibration, whereas the peak at 1086.69 cm^{-1} corresponded to C–O–C stretching vibration. Furthermore, peaks at 959.412 cm^{-1}, 893.844 cm^{-1}, 850.454 cm^{-1}, and 827.312 cm^{-1} indicated aromatic C–H bending vibrations. These findings confirmed the presence of characteristic functional groups of drug and formulation excipients without any significant shift or disappearance of major peaks. It suggested good compatibility between the drug and excipients.

BHN were developed in nine batches F1-F9 using CCD by Design-Expert® software by thin film hydration method. These were evaluated for physicochemical properties with the drug release profile and therapeutic efficacy to optimize its performance in practical applications. Particle size, zeta potential and PDI for all batches were found in the range of 111.9±0.65 to 179.3±0.07nm; -21.4 to -29.7 and 0.131 to 0.348 respectively. The formulations (F1 to F9) exhibit varying levels of drug content percentages. Formulation F1 stands out with the highest drug content at 97.56±0.74%, followed closely by F7 at 94.36±0.71%. In contrast, formulations F4, F5, and F9 have the lowest drug contents, ranging from 79.96±0.22; 75.23±0.92% and to 80.12±0.14% respectively. The %EE of formulations F1 to F9 was evaluated and showed considerable variation among the prepared batches, having in the range of 78.52±0.93% to 92.57±0.05%. The cumulative % *in vitro* drug release study of formulation F1 to F9 demonstrated increase in drug release over the study period. The cumulative drug release at 120 min. ranged from 76.27±0.16% to 92.17±0.02%, indicating satisfactory release characteristics for all formulations.

Among the tested batches, It was observed that Formulation F1, with a particle size of 166.3±0.65 nm, moderate PDI of 0.170, and a zeta potential of -26.8 mV, shows promising characteristics for pharmaceutical formulations (Fig. 2 & 3). It showed the highest drug content (97.56±0.74%) and highest %EE (92.57±0.05%), indicating superior drug encapsulation and retention within the carrier system. With that it had most favorable release profile, releasing 92.17±0.02% of the drug in 120 min (Table 2). The rapid and efficient drug release from F1 suggests enhanced drug diffusion and dissolution suitable for oral, topical and parenteral delivery in niosomal carrier system and was identified as the optimized formulation.

Table 2: Evaluation of BHN batches

Formulation code	Particle size (nm)	PDI	Zeta potential (mv)	% Drug content	EE(%)	Cumulative % In vitro drug release after 120min.
F1	166.3±0.65	0.170	-26.8	97.56±0.74	92.57±0.05	92.17±0.02
F2	111.9±0.21	0.131	-21.4	89.56±0.63	88.76±0.66	82.32±0.07
F3	179.8±0.07	0.348	-24.7	87.43±0.05	86.49±0.12	76.27±0.16
F4	142.4±0.08	0.139	-24.5	79.96±0.22	83.59±0.62	83.22±0.64
F5	144.2±0.61	0.286	-26.1	75.23±0.92	85.67±0.09	79.68±0.43
F6	145.8±0.98	0.136	-27.8	84.23±0.73	82.48±0.18	80.26±0.55
F7	135.8±0.67	0.142	-29.7	94.36±0.71	86.48±0.63	84.41±0.03
F8	167.8±0.33	0.245	-23.4	91.23±0.08	80.42±0.07	89.56±0.91
F9	118.6±0.71	0.137	-23.6	80.12±0.14	78.52±0.93	86.33±0.04

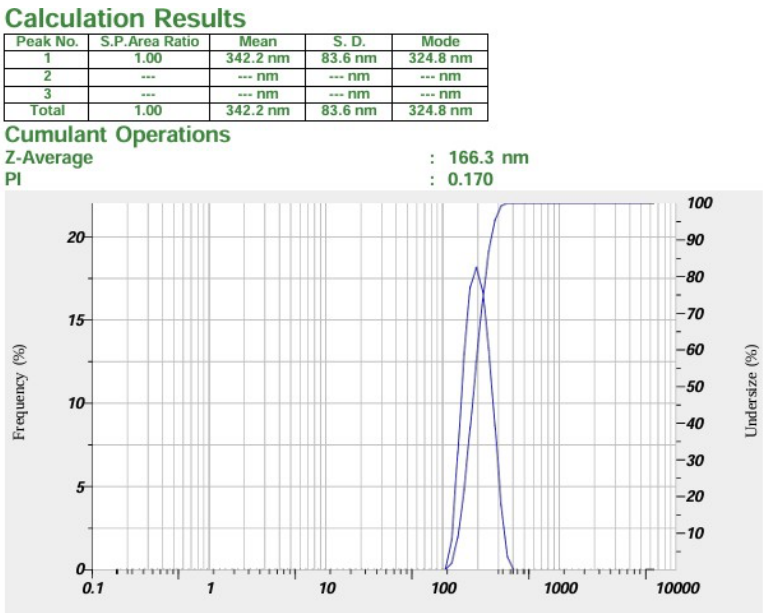
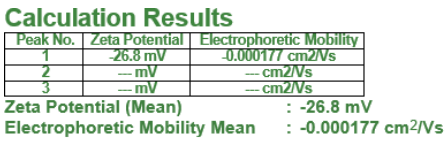


Figure 2: Particle size and PDI of optimized batch (F1)



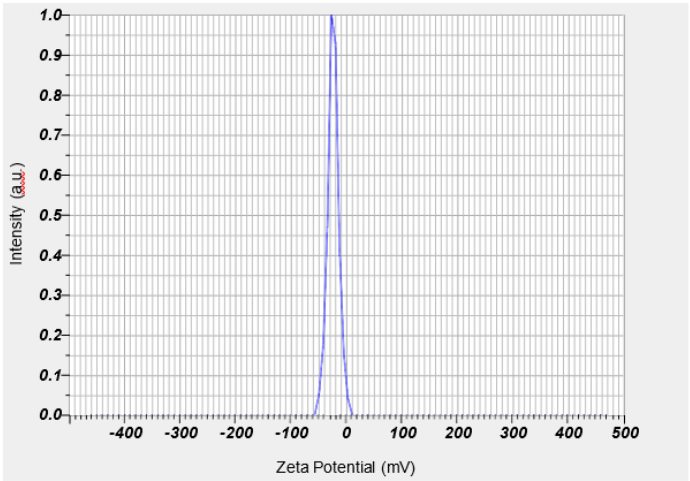


Figure 3: Zeta potential of optimized batch (F1)

The optimized batch F1 of BHN, on the basis of above parameters was selected for stability study. The sample was stored at refrigeration temperature (4±2)ºC, room temperature (25±2)ºC and 40ºC, 75% RH as per ICH guidelines for 3 months. It was observed that No significant changes in appearance, Residual % drug content was found. It indicating the acceptable formulation homogeneity after short term stability study (Table 3).

Table 3: Stability study of optimized batch (F1)

Parameter	Initial	After 1 Month	After 2 Months	After 3 Months
Physical appearance	White	White	white	white
Residual Drug Content (%)	97.12 ± 0.21	96.40 ± 0.12	96.32 ± 0.14	96.23 ± 0.23

ANOVA Analysis of Drug content

The ANOVA results showed that the quadratic model was significant (F-value = 34.84, p-value = 0.0074), Cholesterol(a), Span 60 (B), their interaction (AB), and the quadratic term B^2 significantly affecting drug content ($p < 0.05$). The model showed good fit, with an $R^2 = 0.9831$ and a predicted $R^2 = 0.9143$ (Fig. 4).

Table 4: ANOVA for Quadratic model

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	102.22	5	20.44	34.84	0.0074	Significant
A-Cholesterol	20.65	1	20.65	35.19	0.0096	
B-Span 60	15.49	1	15.49	26.40	0.0143	
AB	6.00	1	6.00	10.23	0.0494	
A^2	1.61	1	1.61	2.75	0.1958	
B^2	58.46	1	58.46	99.64	0.0021	
Residual	1.76	3	0.5867			
Cor Total	103.98	8				

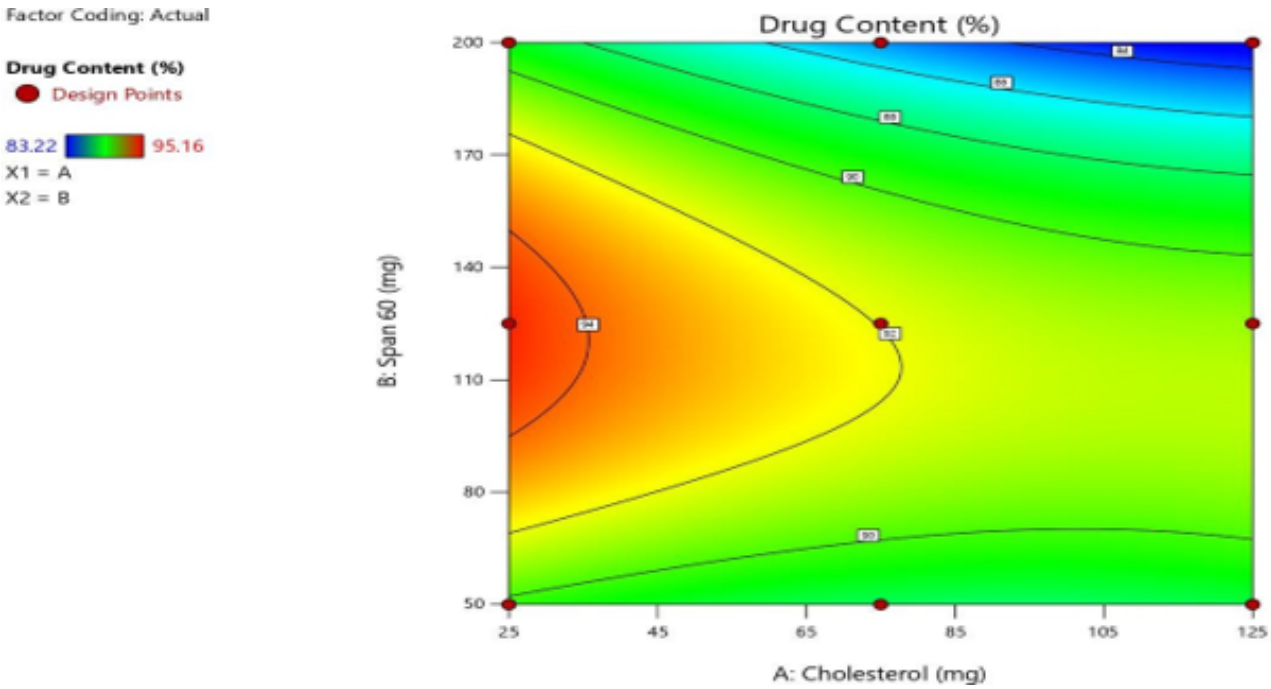


Figure 4: Counter Plot of Drug content

ANOVA Analysis of %EE

The ANOVA results demonstrated that the quadratic model was significant (F-value = 12.47, p-value = 0.0320). Cholesterol (A) and the quadratic term B^2 significantly influenced entrapment efficiency ($p < 0.05$). The model demonstrated a good fit with $R^2 = 0.9541$ and predicted $R^2 = 0.8439$ (Fig. 5) .

Table 5: ANOVA for Quadratic model

Source	Sum of Squares	Df	Mean Square	F-value	p-value	
Model	140.83	5	28.17	12.47	0.0320	Significant
A-Cholesterol	39.17	1	39.17	17.33	0.0252	
B-Span 60	10.51	1	10.51	4.65	0.1200	
AB	0.3906	1	0.3906	0.1729	0.7055	
A^2	8.50	1	8.50	3.76	0.1478	
B^2	82.26	1	82.26	36.41	0.0091	
Residual	6.78	3	2.26			
Cor Total	147.61	8				

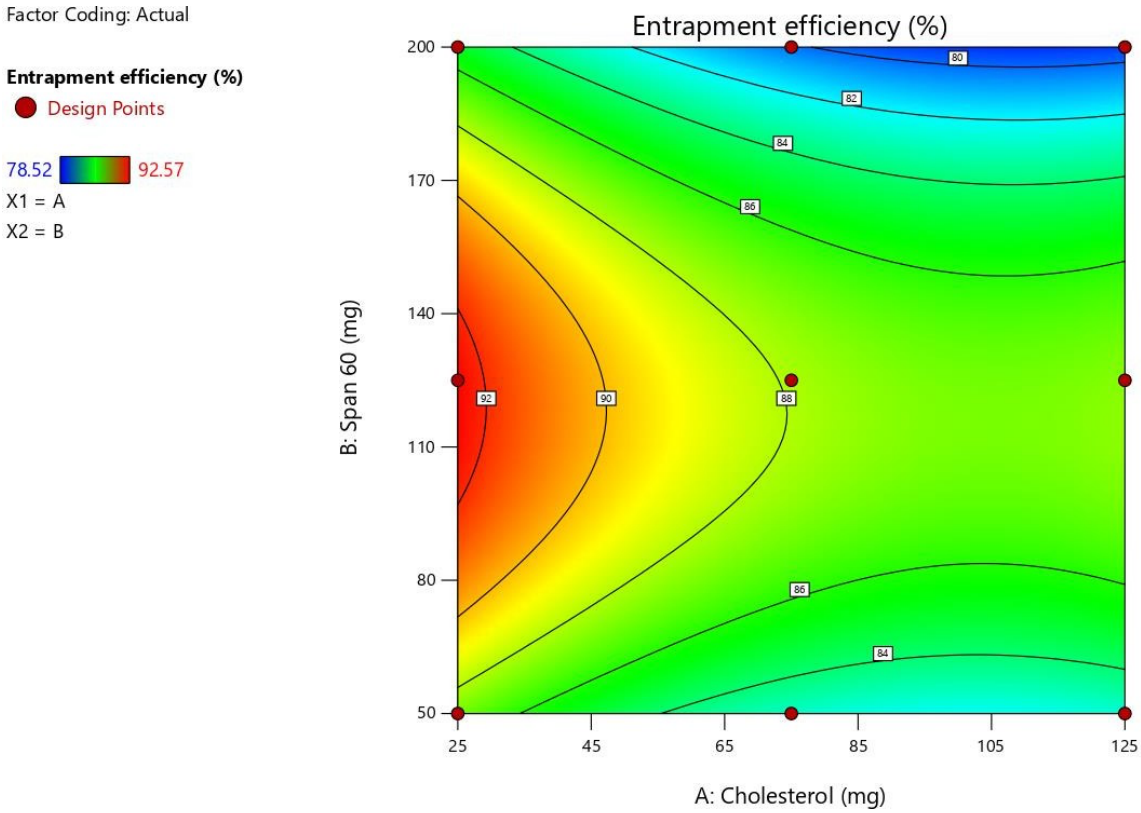


Figure 5: Counter plot for % EE

CONCLUSION

The aim of the study to prepare BHN were successfully developed and evaluated. Preformulation studies confirmed the suitability of the drug for formulation development, while FTIR studies demonstrated compatibility between the drug and selected excipients. The prepared niosomes exhibited satisfactory vesicular properties, including high drug entrapment and efficient drug loading The developed system offers improved drug release, enhanced patient convenience, ease of administration, and the potential for improved therapeutic efficacy. Therefore, BH niosomal carrier may serve as an effective alternative to conventional oral dosage forms and warrant further investigation through in vivo and clinical studies.

CONFLICT OF INTEREST

Nil

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