ORIGINAL ARTICLE

Box-Behnken Modeling Served for the Development and Optimization of Nanoparticles Loaded with Perindopril and Erbumine

Gaurav Mude[1], Vedanshu Malviya[2], Sanjay Nagdev[3], Mona Gajbhiye[4], Shantilal Singune[5], Vijay Lambole[1]

[1]Department of Pharmacology, Datta Meghe College of Pharmacy DMIHER (DU), Wardha, Maharashtra, India, [2]Department of Pharmaceutics, P.R. Pote Patil College of Pharmacy, Amravati, Maharashtra, India, [3]Department of Quality Assurance, Shri. Prakashchand Jain College of Pharmacy, Jalgaon, Maharashtra, India, [4]Department of Pharmacology, G. H. Raisoni University Saikheda, Madhya Pradesh, India, [5]Department of Pharmacology, Institute of Pharmaceutical Sciences, SAGE University, Indore, Madhya Pradesh, India

Abstract

Background: The study aimed to optimize and validate a nano-particulate technology for the sustained release of perindopril erbumine, an angiotensin-converting enzyme (ACE) inhibitor, using a box-behnken experimental methodology. **Methods:** The researcher used a Box-behnken experimental methodology to optimize the formulation and assess various characteristics such as particle size, zeta potential, surface shape, encapsulation efficiency and *in vitro* drug release. The nanoparticles characterization findings were recorded included the size, polydispersity index, zeta potential and encapsulation efficiency. **Results:** The nanoparticles had a smooth surface and their size was determined to be 122.38 ± 0.75 nm. The polydispersity index was 0.298, the zeta potential was 38.79 ± 0.05 mv and the encapsulation efficiency was 61.73 ± 0.06%. *In vitro* release was restricted for up to two hours, but at a pH of 7.4, the rate of drug release increased and was maintained. **Conclusion:** The study concluded that the nano-particulate technology for the potential to improve therapeutic efficacy and decrease dosage frequency for drug that need repeated doses such as perindopril erbumine.

Key words: Angiotensin-converting enzyme inhibitor, Box-Behnken design, Nanoprecipitation, Perindopril erbumine

INTRODUCTION

Polymeric nanoparticles (NPs) are one of the drug encapsulation techniques that have received the greatest research attention in contemporary medicine. The fundamental goal of the study is to create a formulation that can deliver medicine precisely where it needs to go. Specifically, we highlight stimulus-responsive NPs due to their superior intracellular drug delivery, lengthy half-lives, and ability to go to the disease location.[1] Enzymes such as pepsin and the stomach's low pH make protein digestion difficult. Intestinal brush-border enzymes and pancreatic enzymes released into the lumen of the gut both play important roles in decreasing drug action. To enter the circulation, a medication must overcome the physical barrier created by gut cells.[2] To sum up the preceding points, a novel NP-based medication delivery technology is now available.

Perindopril erbumine (C23H43N3O5) is a medication that is a medication for treating high blood pressure, congestion, and hypertension. Because perindopril is not well absorbed after oral administration, its availability is quite limited.[3] The immediate oral administration of perindopril is recommended. Due to the short half-life (0.8–1 h) when taken orally, multiple dosing is necessary. Second, excellent absorption and first-pass metabolism in the liver contribute to the drug's

Address for correspondence:
Vedanshu Malviya, Department of Pharmaceutics, P.R. Pote Patil College of Pharmacy, Amravati - 444 602, Maharashtra, India. E-mail: vedanshumlv56@gmail.com

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effectiveness.[4,5] This research sets out to answer the feasibility of developing a controlled-release formulation of perindopril erbumine using a novel polymer to assure a sustained release throughout the course of a lengthier time frame.

The design of experiments method is a systematic analytical methodology that may be used to investigate the impact of response variables and the interplay of independent factors. Response surface approaches, such as Box-Behnken, D-optimal, and central composite, are often used in experimental design. The formulation of polymer NPs was optimized in this work using a Box-Behnken experimental strategy. Studies of stability and *in vitro* drug release profiles were conducted after physicochemical properties were characterized in the NPs.

METHODOLOGY

Samples of perindopril erbumine were generously provided by Lara Drugs Pvt. Ltd. in Hyderabad, India. The Eudragit S100 sample was generously provided by Evonik India, Mumbai. S.D. Fine Chem in Mumbai was where we stocked up on polyvinyl alcohol. No further purification of the materials collected from their different sources was performed. All reagents and substances utilized were of a high enough purity for analytical usage.

Analyzing the convergence of drugs and their excipients

Fourier transform infrared spectroscopy (FTIR)

The manufactured formulation is analyzed by FTIR for signature moieties. Perindopril erbumine and excipients were analyzed for their chemical makeup. FTIR was used to identify and verify the presence of functional moieties in the medication and excipient's physical combination. Weighing and correctly mixing the samples with potassium bromide, a 1:1 ratio of medication and polymer was achieved. A little amount of the powder was squeezed together to form a pellet. To investigate the likelihood of interference, the infrared spectra of the beads were collected from 400 to 4000 cm^{-1} and compared to the reference spectrum.[6]

Thermal study

The drug and excipient heat stability were evaluated using differential scanning calorimetry (DSC). Five mg of pure drug and the physical the aluminum pan mixing of the medication and polymer were scanned at 10°C/min between 50 and 400°C. Nitrogen was sucked out of the sample bottle at a rate of 20 mL per minute.[7,8]

Standard calibration curve

In a standard flask, we mixed 100 mg of perindopril erbumine with 100 mL of phosphate buffer, pH 6.8. Aliquots of 100 g/mL solution were pipetted into 10 mL volumetric flasks at concentrations of 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, and 5 mL. Concentrations of 5, 10, 15, 20, 25, 30, 35, 40, 45, and 50 g/mL were attained by bringing the right quantity of phosphate buffer 6.8 up to the correct level. The absorbance at 215 nm was measured for each concentration.[9,10]

Preparation of perindopril erbumine nanoparticles (PE-ES-NPs)

Perindopril erbumine-laden NPs were synthesized using the nanoprecipitation technique as per the design represented in Table 1. Drug and Eudragit S100 dissolution were accomplished using acetone. After injecting this solution into a warm aqueous PVA solution, we agitated it constantly for 3 h to enable the organic solvent to fully evaporate. After many washing, the fluid containing the NPs was centrifuged at 10,000 rpm for 20 min at 40°C (ELTEK, Refrigerated Centrifuge RC800 S) to collect them.[8,11]

Optimization of PE-ES-NPs

Researchers used a Box-Behnken design (BBD) experimental design using Design-Expert® Software 11's 3-factor, 3-level hierarchy to determine the optimal procedure for producing perindopril erbumine-loaded NPs as shown in Table 2. The polynomial equations and three-dimensional response surface plots for the factor interaction analysis were created using Design-Expert® Software 11. This equation is a representation of the BBDs resulting polynomial:

Y= A0 + A1 * X1 * X2 * X3 * X4 * X5 * X1 * X2 * X4 * X6 * X1 * X3 * X7 * X1 * X4 * X8 * X2 * X3 * X9 * X2 * X4 * X10 * X3 * X4 * X11 * X12 * X12 *.

XaXb (where a and b are 1, 2, 3, 4) = interaction terms and Xi2 (where i is 1, 2, 3, 4) = interaction terms; X1 to X4 = coded values of independent variables; Y = Response value of dependent variables; A0 = intercept; A1 to A14 = regression coefficients; and XaXb Xi2 = interaction terms. The independent variable's additive and subtractive effects on particle size and entrapment efficiency are represented by the positive and negative coefficients, respectively, in the polynomial equation. The ideal batch was determined by maximizing encapsulation efficiency and minimizing particle size.

Characterization of PE-ES-NPs

Drug entrapment

Ten mL of phosphate buffer at pH 7.4 were mixed with 10 mg of PE-ES-NPs. After being centrifuged at 8000 rpm for 5 min, the solvent containing the NPs was removed. The centrifuged and filtered supernatant was then disposed of with great care. Using a UV Spectrophotometer set at 215 nm and room temperature, the drug concentration in the supernatant was calculated.[12]

Determination of particle size

PE-ES-NPs with the desired scattering intensity were produced by dispersing the dried NPs in water. The Malvern zeta size analyzer was used to quantify the particle size.[13]

Determination of zeta potential

The zeta potential was determined by measuring the electrostatic attraction between two gold-plated electrodes in a polycarbonate cell and a sample prepared in water using a zeta sizer manufactured by Malvern Instruments. NPs' stability is linked to their surface potential, which is described by the zeta potential.[13]

Scanning electron microscopy

PE-ES-NPs surface morphology was analyzed using scanning electron microscopy. On create the PE-ES-NPs, the powder was sprinkled over a double-sided sticky tape and then applied on a wooden stub. Then, in an ultra-high vacuum evaporator with a gold sputter module and an argon atmosphere, the tips were coated with platinum. The samples were guaranteed to be moisture-free.

In-vitro drug release study

PE-ES-NPs *in vitro* release kinetics were measured using the dialysis bag diffusion technique. Dialysis membranes-50 (Hi-media) was used with a molecular weight cutoff between 12,000 and 14,000. To prepare the dialysis membrane for use, it was immersed in a 7.4-pH phosphate buffer solution overnight. Dialysis membranes are hermetically sealed on both ends, and the produced NPs were inserted within. After that, we filled the beaker to the top with 100 mL of 7.4-pH phosphate buffer. At maintain a steady sink, the beaker was placed on a magnetic stirrer and the rpm was adjusted at 100. Phosphate buffer at pH 7.4 was used, and 2 mL samples were obtained at regular intervals.[14-16] Following appropriate dilution, materials were examined at a wavelength of 215 nm using a UV-visible spectrophotometer.

Release kinetics

The kinetics of drug release from NPs was evaluated using data from *in vitro* drug release investigations using zero order, first order, Higuchi's model, and the Korsmeyer-Peppas equations.[17,18]

RESULTS AND DISCUSSION

Drug-excipients interaction study

FTIR

The FTIR data were compared to the standard as depicted in Figures 1 and 2, and it was found that the pure medication had the same peaks as the standard. Next, it was made sure that no new peaks arose, vanished, or were mismatched between the optimized formulation and the pure medication by comparing their peaks. C-H stretching at 2931.91 cm^{-1}, C=O stretching at 1736.51 cm^{-1}, N-H bending at 1643.01 cm^{-1}, C=C aromatic at 1566.96 cm^{-1}, and C-H scissoring and bending at 1404.61 cm^{-1} were all seen in the FTIR spectra of the optimized formulation, just as they were in the spectra of the pure medication. That the API and excipients used were chemically and physically compatible with one another was proven here.

Table 1: Box-Behnken design variables and their scales

Variables	Levels			
	Units	−1 (Low)	0 (Medium)	+1 (High)
Independent variables				
X_1				
Volume of organic phase	mL	2.5	5	7.5
X_2				
Drug loading	Percentage	10	20	30
X_3				
Concentration of surfactant	Percentage	0.5	1	1.5
		Constraints		
Dependent variables				
Y_1				
Particle size	nm	Minimize		
Y_2				
Entrapment efficiency	Percentage	Maximize		

Thermal study

DSC thermogram of Perindopril erbumine and its improved formulation shown in Figures 3 and 4 both exhibit an endothermic peak at 161.680°C, although the latter's peak moves somewhat lower, to 159.340°C, suggesting a change in melting point. Chemical and physical stability in the presence of the excipients was demonstrated by the absence of a significant temperature difference between the pure medication and the optimized formulation.

Standard calibration curve

The concentration range of the standard curve from 5 to 50 ng/mL was determined to be linear, with a regression value of R2 = 0.997. Hence, the sample perindopril erbumine at a concentration between 5 and 50 µg/mL obeys the Beer-Lamberts law. The equation can be seen in Figure 5.

Optimization of PE-ES-NPs by experimental design

Table 2 summarizes the results of 17 different NP formulations created using Design Expert® software 11 and the accompanying response factors. Design Expert® Software 11 was used to fit mathematical models to the data seen from 17 different formulations, including linear, first-order, cubic, and quadratic models, to learn more about the interplay between the variables. Based on the data collected, a quadratic model was found to be the most appropriate for analyzing PE-ES-NPs. Each answer was analyzed by plotting it on a three-dimensional graph.

Particle size (Y1)

The quadratic equation generated for the Y_1 response for PE-ES-NPs is as follows:

$$Y_1=+122.59+19.789X_1+1.166X_2 -2.594X_3 -8.42X_1X_2 -3.923 X_1 X_3 +11.35X_2X_3 +21.68 X_1^2+5.303X_2^2+ 19.463X_3^2$$

Based on the results of the ANOVA, we can deduce that the model terms relating to response Y1 are significantly impacted by the independent variables and their interaction effects. Table 3 shows that *P*-value for the Y1 response is <0.0001. Table 4 shows the lack of fit, model F value, *P*-value, modified R2, and projected R2 for particle size (response Y1) and encapsulation efficiency (response Y2).

According to the quadratic equation, particle size is positively influenced by both the volume of the organic phase (X1) and the drug loading (X2). Particle size grows in response to a rise in acetone concentration when the medium capacity is big. As the drug loading in the PE-ES-NPs was raised, so was the particle size. However, the NP particle size was shown to decrease with increasing concentration of surfactant (X3) due to the generation of tiny droplets. As shown in Figure 6a-c, the three-dimensional response graphs look like this:

Table 2: Experimental runs and calculated responses (*n*=3)

Formulation code	Independent variables			Dependent variables	
	Volume of organic phase: X_1 (mL)	Drug loading: X_2 (%)	Concentration of surfactant: X_3 (%)	Particle size (Y_1) (nm±SD)*	Entrapment efficiency (Y_2) (%±SD)*
PENP1	1	1	0	166.14±0.57	59.78±1.45
PENP 2	1	0	−1	188.92±1.23	60.87±2.17
PENP 3	0	0	0	122.46±0.87	64.52±0.15
PENP 4	0	1	−1	136.85±0.42	56.77±1.72
PENP 5	0	0	0	120.68±0.22	62.56±0.14
PENP 6	0	0	0	118.67±0.65	58.91±1.66
PENP 7	−1	−1	0	116.17±0.9	40.84±0.90
PENP 8	−1	0	−1	144.34±0.28	54.92±0.75
PENP 9	0	0	0	128.68±0.31	66.85±1.52
PENP 10	−1	0	1	146.39±0.67	54.21±0.25
PENP 11	−1	1	0	140.56±0.77	56.82±1.62
PENP 12	1	0	1	175.28±0.94	60.35±0.49
PENP 13	0	0	0	122.46±1.21	62.46±0.09
PENP 14	1	−1	0	175.42±1.51	47.76±0.36
PENP 15	0	−1	1	135.16±0.16	38.62±0.06
PENP 16	0	1	1	154.97±0.40	54.72±0.24
PENP 17	0	−1	−1	162.44±1.33	43.25±0.15

SD: Standard deviation, *Utilization of nano-particulate technology

Table 3: ANOVA for quadratic model for particle size (response Y_1)

Source	Sum of squares	df	Mean square	*F*		*P*
Model	8072.59	9	896.95	49.22	<0.0001	Significant
A-Volume of organic phase	3132.36	1	3132.36	171.90	<0.0001	
B-drug loading	10.88	1	10.88	0.5971	0.4650	
C-concentration of surfactant	53.82	1	53.82	2.95	0.1294	
AB	283.42	1	283.42	15.55	0.0056	
AC	61.54	1	61.54	3.38	0.1087	
BC	515.29	1	515.29	28.28	0.0011	
A^2	1979.04	1	1979.04	108.61	<0.0001	
B^2	118.39	1	118.39	6.50	0.0382	
C^2	1594.90	1	1594.90	87.53	<0.0001	
Residual	127.55	7	18.22			
Lack of fit	71.42	3	23.81	1.70	0.3045	Not significant
Pure error	56.14	4	14.03			
Cor total	8200.14	16				

ANOVA: Analysis of variance

Table 4: Summary of various quadratic parameters

Response	Adjusted R^2	Predicted R^2	Lack of fit *F*	Model *F*
Particle size (Y_1)	0.9644	0.8500	1.70	49.22
Encapsulation efficiency (Y_2)	0.9195	0.8843	0.18	21.30

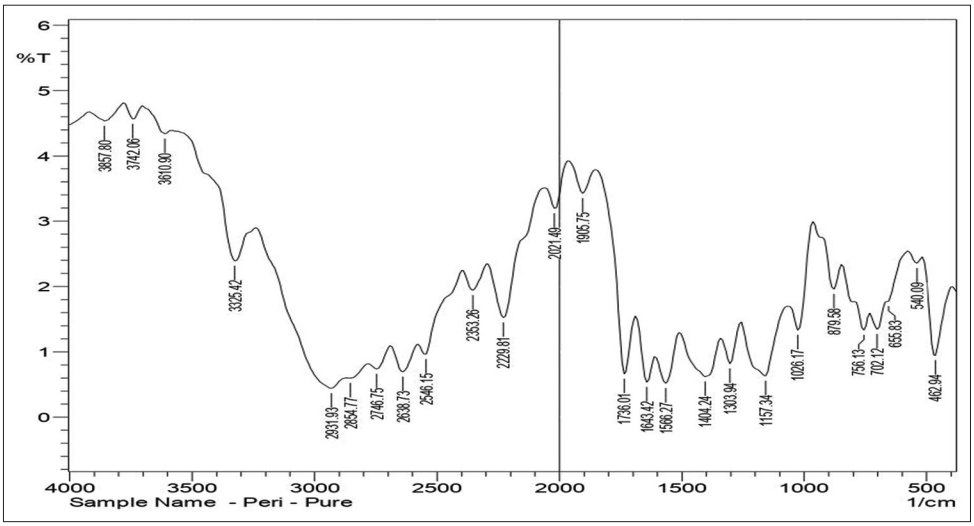

Figure 1: Fourier transform infrared spectroscopy of pure drug

Entrapment efficiency (Y_2)

The quadratic equation generated for the Y_2 response for PE-ES-NPs is as follows:

$$Y_2 = +63.06+2.75X_1+7.203X_2 -0.9888\ X_3-0.99\ X_1X_2 +0.0475\ X_1X_3 +0.645X_2X_3 -1.256X_1^2-10.504X22-4.216X_3^2$$

According to the results of the analysis of variance, there are statistically significant model terms provided by the independent variables and their interaction effects with respect to the Y2 response. A Y2 response had $P = 0.0003$ (Table 5).

As can be seen from the aforementioned quadratic equation, the reaction Y2 is jointly influenced by the organic phase's volume (X1) and the drug loading (X2). However, encapsulation efficiency decreases as surfactant concentration increases. The three-dimensional Y2 response graphs are shown in Figure 7a-c.

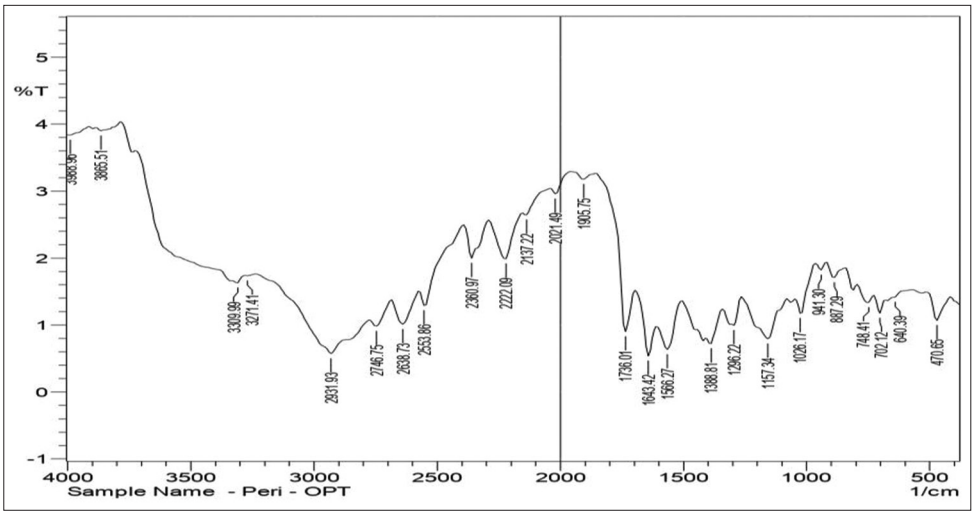

Figure 2: Fourier transform infrared spectroscopy of drug with excipients

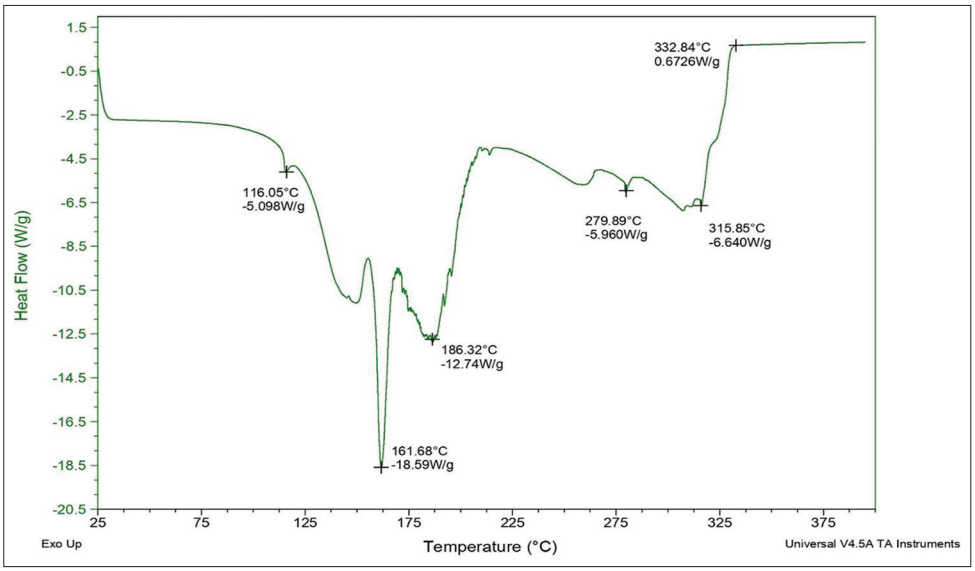

Figure 3: Differential scanning calorimetry of pure drug

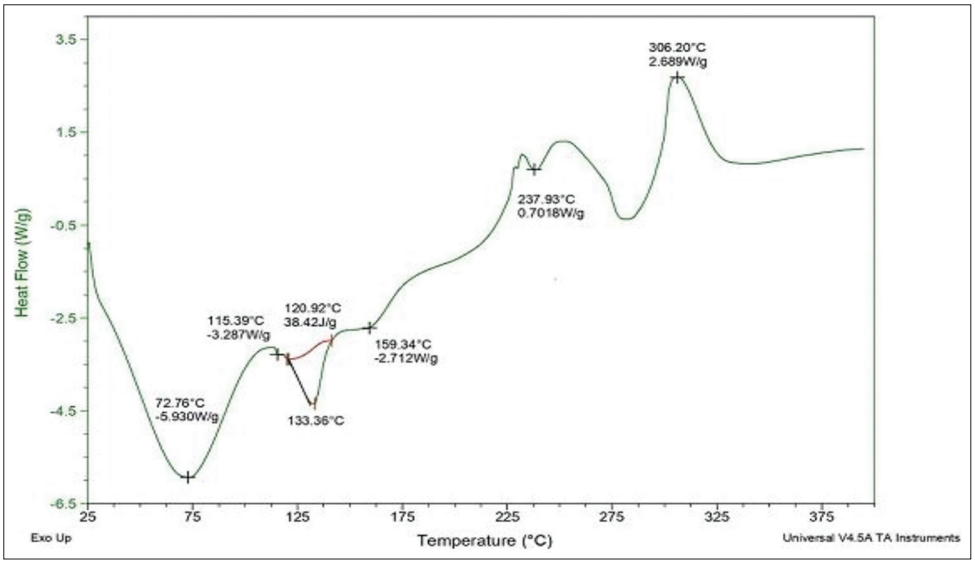

Figure 4: Differential scanning calorimetry of drug with excipients

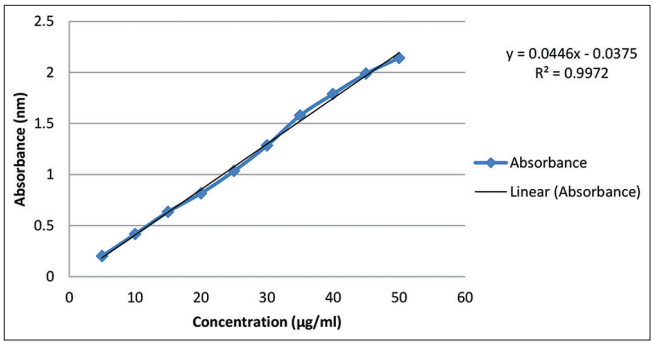

Figure 5: Standard calibration curve of perindopril erbumine

Optimization and validation

The best formulation of PE-ES-NPs was selected using the Design Expert software's numeric point prediction method, with the goals of minimal particle size and high encapsulation efficiency in mind. With a desire of 0.956, the optimal formulation for PE-ES-NPs included a volume of 4.8 mL of acetone, a drug loading of 20.2%, and a surfactant content of 0.94 weight percent. Particle size (128.68 nm) and entrapment efficiency (64.85%) of PE-ES-NPs were found to be consistent with those predicted by Design Expert

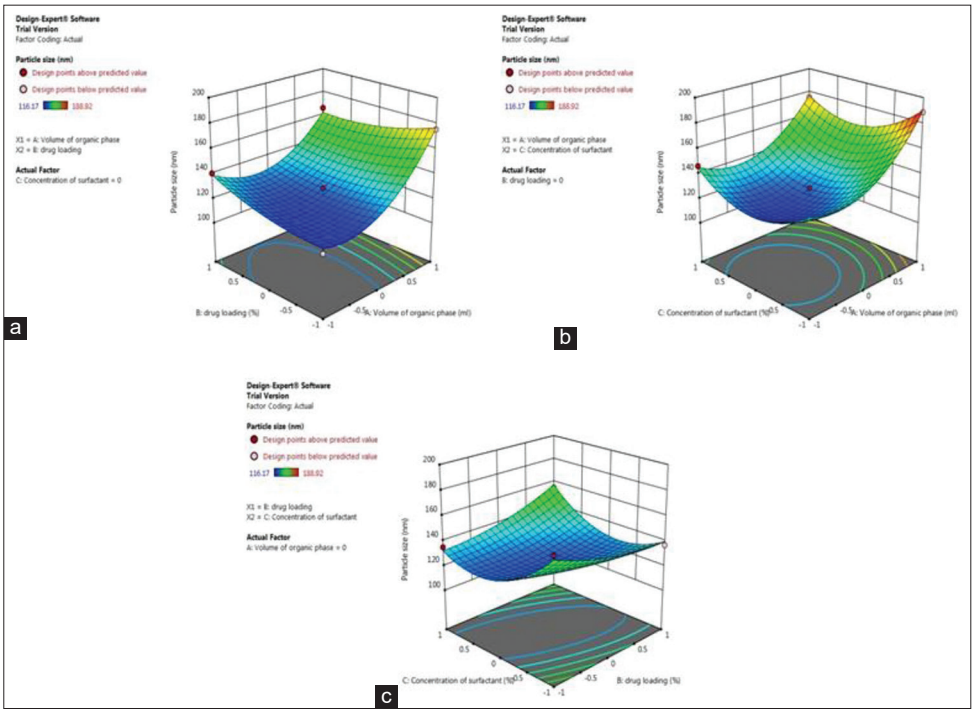

Figure 6: Effect of drug loading, surfactant concentration, and organic phase volume on particle size in polyethersulfone nanoparticles (a), nanoparticles (b), and nanoparticles (c) in three-dimensional response surface plots

Table 5: ANOVA for quadratic model for encapsulation efficiency (response Y_2)

Source	Sum of squares	df	Mean square	*F*		*P*
Model	1067.55	9	118.62	21.30	0.0003	Significant
A-volume of organic phase	60.34	1	60.34	10.84	0.0133	
B-drug loading	415.01	1	415.01	74.53	<0.0001	
C-concentration of surfactant	7.82	1	7.82	1.40	0.2746	
AB	3.92	1	3.92	0.7040	0.4292	
AC	0.0090	1	0.0090	0.0016	0.9690	
BC	1.66	1	1.66	0.2988	0.6016	
A^2	6.64	1	6.64	1.19	0.3108	
B^2	464.54	1	464.54	83.42	<0.0001	
C^2	74.85	1	74.85	13.44	0.0080	
Residual	38.98	7	5.57			
Lack of fit	4.65	3	1.55	0.1807	0.9043	Not significant
Pure error	34.33	4	8.58			
Cor total	1106.53	16				

ANOVA: Analysis of variance

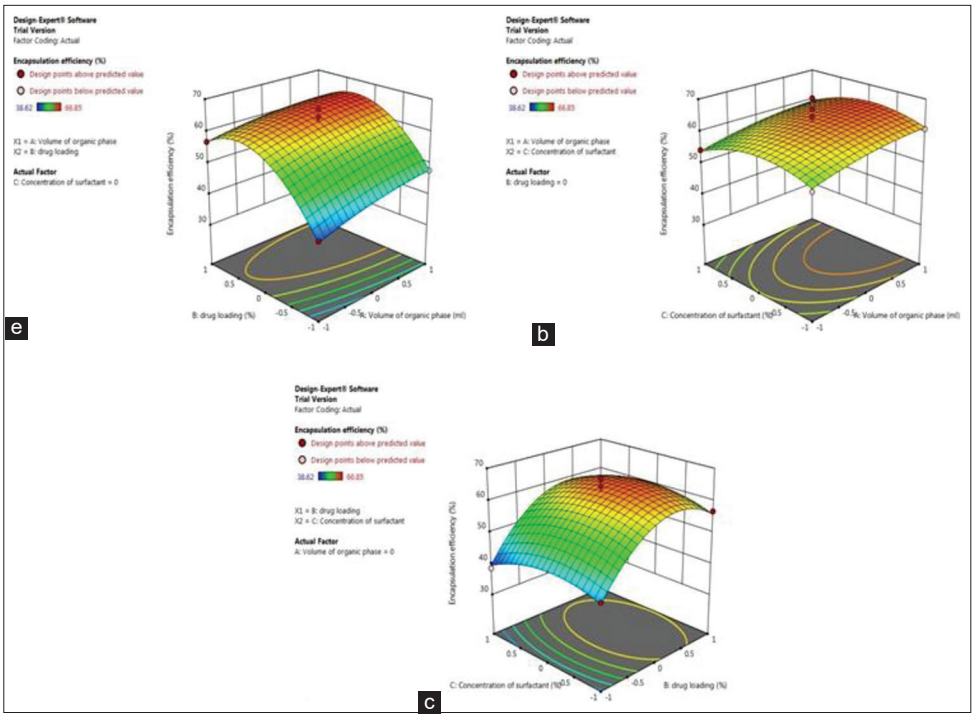

Figure 7: Three-dimensional response surface for PE-ES-NPs showing effect of (a) drug loading and volume of the organic phase, (b) concentration of surfactant and volume of the organic phase, and (c) concentration of surfactant and drug loading on encapsulation efficiency

software® (120.43 nm and 63.65%, respectively). Therefore, the PENP9 batch of formulation was selected as the best possible option.

Determination of particle size

One of the most crucial factors is the particle size defining features of NPs. NPs of perindopril erbumine in the best formulation were on average 128.68 nm in size. NPs with PDI values of 0.336 and intercepts of 0.963 were found in the particle size study. PE-ES-NPs particle size distribution as a percentage of intensity is shown in Figure 8.

Determination of zeta potential

PE-ES-NPs zeta potential may be used as a stability indicator and mentioned in Figure 9. The zeta potential of perindopril erbumine PENP 9 NPs was measured to be −28 mV 0.05 mV, and their polydispersity index was reported to be 0.220. The peak area of the observed zeta potential is 100% intense. Low polydispersity index and negative zeta potential demonstrate uniform particle distribution and physical stability of the delivery method.

In vitro drug release study

The *in vitro* drug release from optimized PE-ES-NPs was studied at a pH of 7.4 [Figure 10]. Drug release from NPs was somewhat modest for the first 2 h, but beyond that time,

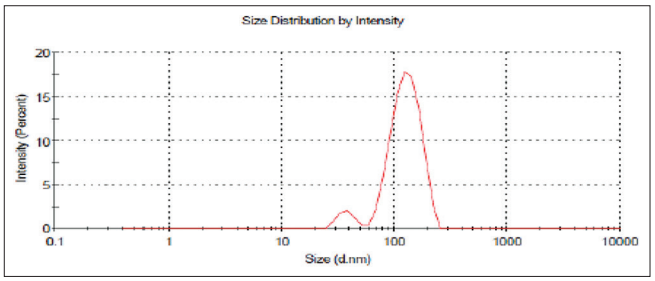

Figure 8: Percentage intensity of particle size distribution of perindopril erbumine nanoparticles

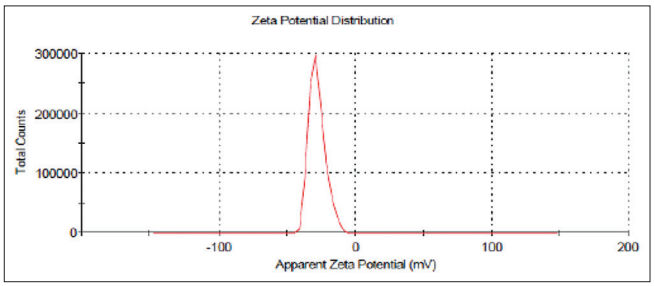

Figure 9: Zeta potential distribution of perindopril erbumine nanoparticles

it was steady and increased, suggesting that drug loss was significantly reduced. Figure 10 shows that the percentage of medication release varied between 15.35% and 89.28%.

The *in vitro* dialysis bag diffusion technique release data were used to test hypotheses about a range of mathematical models.

Table 6: Kinetic release models for the optimized perindopril erbumine nanoparticles

Formulation	Zero order (R^2)	First order (R^2)	Higuchi (R^2)	Korsmeyer-Peppas kinetics	
				R^2	*n*
Perindopril erbumine nanoparticles	0.7723	0.5168	1.000	0.9999	0.156

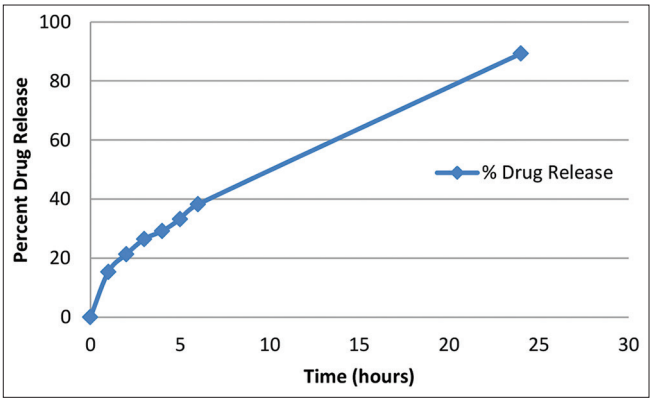

Figure 10: *In vitro* drug release profile of optimized formulation PENP 9

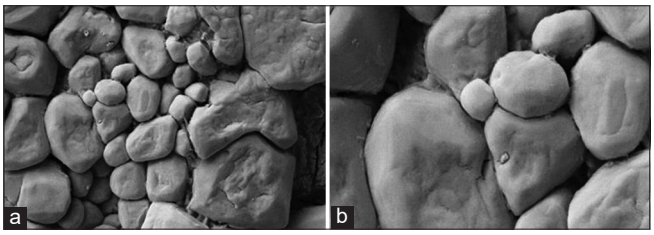

Figure 11: SEM of prepared nanoparticles (a) magnification at 10K and (b) Magnification at 25K

The Higuchi equation best described the rate of release of NPs of perindopril erbumine. Diffusion of the medication from both homogeneous and granular matrices is described by the Higuchi equation. The Korsmeyer-Peppas model predicts Fickian diffusion kinetics, and a diffusion exponent (n) of 0.156 supports this idea. Table 6 displays the R2 and n2 exponential values. According to the published kinetic data, the Higuchi formulation of PE-ES-NPs is the most accurate, followed by the Korsmeyer-Peppas, Zero Order, and First Order formulations.

Surface morphology

To get a deeper understanding of morphology, scanning electron microscopy is important. SEM research from Figure 11 revealed that PE-ES-NPs are round to oval in form, with a polymeric surface that has been assembled.

CONCLUSION

The study concluded that the nano-particulate technology for the potential to improve therapeutic efficacy and decrease dosage frequency for drug that need repeated doses such as perindopril erbumine.

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