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Original Article

COMPUTATIONAL TOOLS ASSISTED FORMULATION OPTIMIZATION OF NEBIVOLOL HYDROCHLORIDE LOADED PLGA NANOPARTICLES BY 3^2 FACTORIAL DESIGNS

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ABSTRACT

Objective: The aim of the present study was to formulate and optimize the PLGA polymeric nanoparticle of Nebivolol Hydrochloride for sustained release of drug

Methods: The drug-excipients interaction was explored by molecular docking studies with *in silico* tools. The drug-loaded polymeric nanoparticles were prepared by emulsion solvent evaporation method using 3^2 factorial design and characterized for particle size, zeta potential, and entrapment efficiency. Shape and surface morphology was analysed by SEM and TEM. *In vitro* drug release study was performed by using a diffusion membrane.

Results: The docking analysis inferred that the drug has interacted well with PLGA and PF-68, which could prevent the drug crystal formation. The optimized polymeric nanoparticles had a particle size of 291 nm and entrapment efficiency of 83.4% and were found to be within 95% of CI of the predicted value, which is acceptable. SEM and TEM studies showed that the formed polymeric nanoparticles were smooth, spherical in shape and uniform in size. *In vitro* drug release study of optimized formulation showed sustained release for prolonged time period

Conclusion: Based on the computational studies and *in vitro* release studies, the developed Nebivolol hydrochloride loaded in PLGA nanoparticles could be a promising formulation in oral drug delivery for the treatment of hypertension.

Keywords: Nebivolol hydrochloride, *In silico*, Factorial design, Polymeric nanoparticle

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INTRODUCTION

Computational modelling is a potential aid in comparison to experimental limitations. It can handle the parameter independently and distinguish the actions responsible for the experimental outcome. Beyond the works conducted in the laboratory, computational studies found it effective and convenient to simulate interactions under different situations [1]. In pharmaceutical drug development stages, formulation design has an inevitable role. It includes the selection of excipients, solubility prediction, encapsulation efficiency, release patterns, drug absorption, and stability and so on. The introduction of computational approaches like quantitative structure-activity relationships (QSARs), molecular modelling, molecular mechanics, computational fluid dynamics, and physiologically based pharmacokinetics (PBPK) model [2], Design of Experiment (DoE) [3] etc., reduces complex experimental efforts and thereby expedite the drug innovations and its regulatory process.

Nanoparticles are defined as particulate dispersions or solid particles with a size in the range of 10-1000 nm. The entrapment and encapsulation of the drug will occur in the nanoparticles matrix. Based on the material and method used, nanoparticles can be as Polymeric nanoparticle (nanospheres or nanocapsules), solid lipid nanoparticle, nanocrystal etc., [4, 5]. Nanoparticles are colloidal structures composed of synthetic or semi-synthetic polymers such as PLGA, Eudragit, cellulose derivatives, poly"-caprolactones etc., [6, 7]. Polymeric NPs is a newer platform being investigated for oral delivery applications, which are usually formed through a self-assembly process. The choice of polymer and self-assembly conditions give considerable changes in design by enabling modulation of physicochemical variables (size, surface charge, hydrophobicity) and drug release properties (controlled or triggered). The nanoparticles that are formed from biodegradable or biocompatible polymers are accepted by US Food and Drug Administration (FDA) for drug delivery applications [8]. The controlled release of both hydrophilic and hydrophobic drugs over a long period of time can be obtained by incorporating the drug into a polymeric nanosystem and during this time, the unwanted side effects in the body can be minimized [9]. Thus protect the biologics from harsh pH and severe enzymatic degradation. Even though a different number of polymers have been considered for preparing biodegradable nanoparticles, Poly-DL-lactic–co-glycolic acid (PLGA), a synthetic non-toxic biodegradable copolymer, has been greatly used for controlled drug delivery system [10].

Hypertension is a common asymptomatic condition in which the arterial is elevated and is a major risk factor of cardiovascular complications. Beta-blockers a class of antihypertensive plays vital role in the management of hypertension and cardiac failure results in the reduction of cardiac deaths [11]. Nebivolol is a highly cardioselective third-generation beta-blocker efficient and preferable than other beta-blockers. In conjunction with, it acts as a vasodilator, anti-atherosclerotic agent and anti friabilator agent. But the oral intake of Nebivolol confront problems such as gastrointestinal disturbances, high first-pass metabolism and thus leads to poor bioavailability [12, 13]. In order to avoid first-pass metabolism and increase bio availability the goal has been set to the development and characterization of PLGA nanoparticulate loaded with Nebivolol Hydrochloride.

MATERIALS AND METHODS

Materials

Polylactide-co-glycolide 50/50 (PLGA 50/50, molecular weight of 45,000 g/mol) and Pluronic F 68 (F68) were procured from Yaro chem. Products, Mumbai and Loba chemie, Mumbai, respectively. Sample of Nebivolol Hydrochloride was received from Cipla Ltd., banglore. All other chemicals and solvents used in the study were of analytical grade and others were of pharmaceutical grade.

Methods

Drug interactions by *in silico* studies

All the computational formulation design studies were performed in the Material Science (MS) Suite (version 2.6) of Schrödinger (Schrödinger, LLC, New York). Structure of all the components of formulation such as nebivolol hydrochloride (NEB), methanol, acetone and water, were taken from the internet and converted to

the 3D structure using 2D sketcher, which was used for the computational formulation design. Polymers such as PLGA and Poloxamer-188(PF68) structure were prepared using the Polymer Builder module. LigPrep module was used for the optimization of structures using OPLS3 force field. *In silico* interaction study of nebivolol with PLGA and Poloxamer-188 was done by Maestro 11.7 (Schrodinger) software. The binding affinity was assessed in terms of binding free energies (kcal/mol). The energy minimization protocol was executed to prepare NEB PLGA (50:50) and PF68 models.

Formulation and optimization of polymeric nanoparticle loaded with Nebivolol hydrochloride

Experimental design

Based on a literature survey and studies that have been published, the factors that influence polymeric nanoparticles were identified and employed in DoE. The polymeric nanoparticle formulated with PLGA as a polymer and stabilizer Pluronic F-68 [14]. These two factors were considered for the design of the experiment [15]. A 3^2 factorial design was adopted, in order to optimize their concentrations [16]. The particle size and % entrapment efficiency were the dependent parameters as shown in table 1.

The obtained responses were subjected to multiple correlation analysis using Design Expert® software (version 11.0.3.0 64-bit, Stat-Ease, Inc. Minneapolis, MN, and U. S. A. The equation generated from the experimental design is as follows:

$$Y_i = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1 X_2 + \beta_4 X_1^2 + \beta_5 X_2^2 1$$

Where Y_i is the measured response of the dependent variables,β_0-β_5 are the regression coefficients for the observed experimental values of Y_i, X_1X_2 and X_1^2,X_2^2 represents the interaction term and quadratic term of the independent variables, respectively. The negative sign indicates antagonist effect while positive signs of the coefficient values in the equations obtained after data analysis represent agonist effect of the independent variables. The extent of the impact of the corresponding independent variable can be represented by magnitude of beta coefficient. Statistically significant F ratio ($p<0.05$) and adjusted coefficients of determination (adjusted R^2) between 0.8 and 1.0 were set as criteria for getting an adequate model. Different factor combinations were obtained and experimentally run to measure the responses.

Table 1: Factors and their level

Independent factor	Level		
	Low (-)	Medium (0)	High (1)
Polymer (mg) (X1)	20	50	80
Amount of stabilizer (%w/v) (X2)	0.5	1	1.5
Dependable factor	Goal		
Particle Size in nm (Y1)	Minimum		
% Entrapment efficiency (Y2)	Maximum		

Preparation of polymeric nanoparticle

Polymeric nanoparticle loaded with Nebivolol Hydrochloride was prepared by emulsion solvent evaporation method [17]. The nebivolol loaded PLGA nanoparticles were prepared with the different ratios of drug and PLGA polymer (1:2, 1:5 and 1:8) and stabilizer concentration (05, 1 and 1.5 %). Dissolve 10 mg drug in1 ml methanol. The polymeric solution of PLGA 50:50 was prepared by dissolving PLGA in the organic solvent, acetone at room temperature. Both drug and polymeric solution mixed together. The resultant solutions were added either drop-wise or completely to the aqueous solution containing stabilizer. The mixture was then kept under magnetic stirring for 2-3 h at constant rpm and further sonicated for required time using a probe sonicator. The formed oil-in-water (O/W) emulsion was kept overnight to evaporate the organic solvents under gentle stirring. The nanosuspensions were prepared and centrifuged at 10,000 rpm, 4 °C for 20 min. The polymeric nanoparticles were collected and the un-entrapped drugs were removed by washing at least two times with double distilled water. The nanosuspension recovered was pre freezed and freeze dried to get powdered nanoparticles and kept for further use.

Characterization of polymeric nanoparticle loaded with nebivolol hydrochloride

Particle size, PDI and zeta potential

PDI indicates the size distribution (polydispersity or monodispersity) of polymeric nanoparticles. Particle size and PDI was determined by Zeta sizer by dynamic light scattering (Nano ZS, Malvern Instruments, UK). The Zeta potential of a particle is the overall charge that the particles obtain in a particular medium. Zeta potential values help to assess the stability of the formulation [18, 19].

Percentage entrapment efficiency

Take the required ml of the polymeric nanoparticle suspension in Tarsus centrifuge tube of 15 ml capacity and it is centrifuged by cold centrifugation at 10000 rpm for 30 min at 4 °C. After centrifugation, the supernatant and the sediment are separated. The concentration of Nebivolol Hydrochloride present in the supernatant was analysed by UV spectroscopic method at 281 nm. The percentage entrapment efficiency was calculated using the following formula [19].

$$\% \text{ Entrapment efficiency} = \frac{\text{Total amount of drug} - \text{Amount of free drug}}{\text{Total amount of Drug}} \times 100$$

Scanning electron microscopy

The shape of particle can be determined by Scanning Electron microscopy (SEM). The morphological study of optimized polymeric nanoparticle was carried out using SEM (Zeis Sigma). In this method a drop of polymeric nanoparticle system was mounted on a clear glass stub, air-dried and coated with Polaren E 5100 Sputter coater and visualized under Scanning Electron Microscope.

Transmission Electron Microscopy (TEM)

The morphology of formulation was observed under TEM (TECNAI 200Kv TEM, Fei, Electron optics Oregon USA) by using negative staining method. A drop of NPs, diluted with water (1/50 times), was spread on a 200 mesh copper grid coated with carbon film and kept for about 3 min. A drop of phosphotungstic acid (2% w/w) was dripped on the grid for 30 sec and excess droplet was removed using a filter paper. Finally, the grid was air-dried for about 2h and then used for microscopic analysis.

Drug excipients compatibility study by using Fourier transforms infrared spectroscopy (FTIR)

The FTIR analysis was performed to know the chemical interaction between the drug and polymer inside the prepared nanoparticles. Fourier Transform Infrared spectroscopy was performed using a Shimadzu FTIR Spectrophotometer and from 4000 to 400 cm-1 region, 8300 the spectrum was recorded and verified with the reference standard

***In vitro* drug release studies**

The *in vitro* drug release studies were carried out using a two-sided open tube with a cellophane membrane previously soaked in the phosphate buffer of pH 6.8 on one end. The 2 ml of polymeric nanoparticle suspension containing Nebivolol Hydrochloride is placed on the cellophane membrane. The receptor compartment consists of 50 ml of phosphate buffer pH 6.8 and the medium was

mixed with a magnetic stirrer at a constant speed and the temperature was adjusted to 37±0.5 °C. At predetermined time intervals, 5 ml sample was withdrawn from the reservoir compartment and absorbance was measured at 281 nm.

Drug release kinetics and mechanism of drug release

The data obtained from drug release profile studies were subjected to kinetic analysis for first-order (log cumulative percentage of drug v's time), and zero-order kinetics (cumulative amount of drug released vs time). Mechanism of drug release was determined by fitting to korsmeyer-peppas model (cumulative log percentage of drug released v's log time) and Higuchi's matrix model (cumulative percentage of drug released v's square root of time).

RESULTS AND DISCUSSION

Drug interactions by *in silico* studies

The docking-free energy of was shown in table 2. The docking-free energy of NEB-PLGA, NEB-PF68, PLGA-PF-68 was −3.4,-3.2 and −3.9 kcal/mol, respectively. The negative values showed that the interaction of drug with excipients in order to prevent drug crystal formation, which helped to enhance the drug dispensability in the polymers. Molecular Interaction conformations is shown in fig. 1. The interactions of PLGA and PF-68 might lead to higher drug loading efficiency.

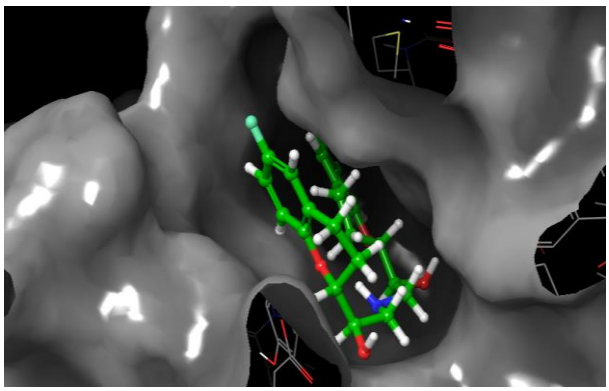


Fig. 1: D Molecular interaction conformations of NEB-PLGA

Table 2: Molecular docking studies of components of nanoparticles

S. No.	Drug-excipients	Docking-free energy (kcal/mol)
1.	NEB-PLGA	-3.4
2.	NEB-PF-68	-3.2
3.	PLGA-Poloxomer	-3.9

Formulation and characterization of polymeric nanoparticles

NEB-loaded polymeric nanoparticles were successfully formulated by employing 3^2 full factorial design and constituents' effect (polymer, surfactants) on its attributes was analyzed. The independent variables, i.e. polymer and stabilizer concentration at three levels, were evaluated for their concomitants on particle size and % entrapment efficiency. The results obtained are given in table 3. All the responses studied were affected by the selected parameters and it can be understood from the results of regression analysis and ANOVA of particle size is given in table 4.

Table 3: Results of responses of polymeric nanoparticle as per 3^2 full factorials

Form. code	A polymer (mg)	B surfactant (%)	Y_1 particle size (nm) ±SD	Y_2 %EE ±SD	PDI	Zeta Potential
F1	20	0.5	386.65±3.21	70.64±1.91	0.156	-8.50
F2	50	0.5	423.0±4.19	82.0±1.45	0.480	-7.55
F3	80	0.5	494.63±5.02	87.67±2.19	0.309	-10.8
F4	20	1	380.5±2.91	79.7±1.86	0.231	-14.7
F5	50	1	471.3±3.83	89.98±1.65	0.310	-12.0
F6	80	1	512.5±3.92	93.25±1.17	0.221	-9.32
F7	20	1.5	233.83±4.11	75.01±2.16	0.145	-16.1
F8	50	1.5	313.5±3.02	82.03±2.31	0.321	-11.4
F9	80	1.5	327.8±5.13	89.14±1.81	0.160	-13.9

n=3, mean±SD

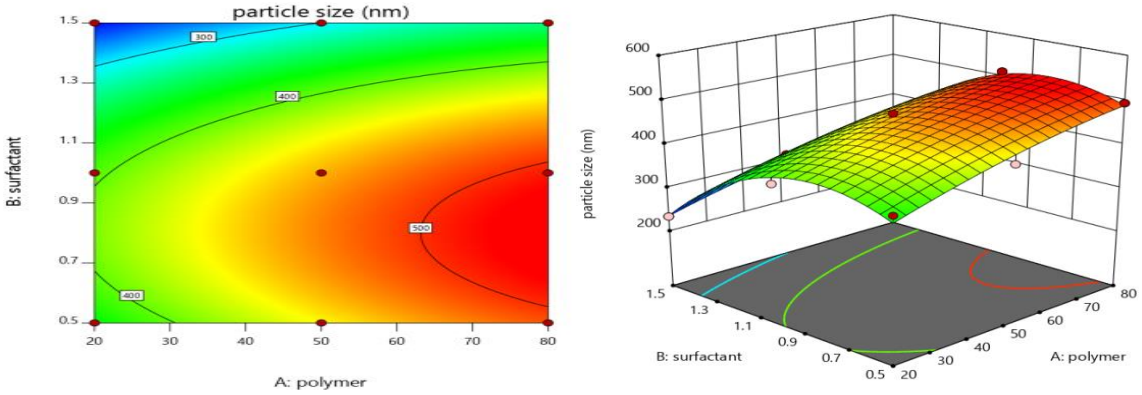
Table 4: Summary of regression analysis and ANOVA

S. No.	Factor	Particle size (Adjusted R^2= 0.7757)		%Entrapment efficiency (Adjusted R^2=0.9361)	
		Estimated beta coefficient	'P-value	Estimated beta coefficient	'P' value
1.	Intercept	+463.62	0.0088*	+89.05	0.0055
2.	A-Polymer	+55.66	0.0072	+7.45	0.0010
3.	B-Surfactant	-71.53	0.0035	+0.9767	0.1925
4.	AB	-3.50	0.7584	-0.7225	0.3862
5.	A^2	-13.28	0.4330	-2.10	0.1287
6.	B^2	-91.53	0.0084	-6.56	0.0074

Particle size

The dimension of particle has a significant role in the delivery of drug across cell membrane as per literature reported. The polymer and stabilizer effects on the particle size were obtained from the 3^2 full factorials experimental design (table 3 and fig. 2) showed that an increased amount of polymer (20 to 80 mg), significantly increased the particle size. The reason could be that during emulsification, the viscosity of organic phase increases due to the large amount of polymer and led to the formation of nanosized droplets with a large

surface area at the interface [20]. Similar results were observed by Sahin A *et al.,* where increasing PLGA polymer concentration increased average particle size. It is demonstrated that solvent diffusion into the external phase become more slowly with increasing viscosity of the organic phase, and provokes larger polymer aggregation [21]. On the other hand; stabilizer concentration increases, the particle size reduces and thereby aggregation decreases. The formation of large size particle could be due to the reduced interfacial stability resulting from the insufficient amount of surfactant and finally led to the aggregation of nanoparticles [22]. The average vesicle size of the polymeric nanoparticle prepared was found to range between 233 to 512 nm.



(a) **(b)**

Fig. 2: (a) 2D Counter plot and b) 3D Response surface curve depicting the effect of polymer and surfactant on the particle size of polymeric nanoparticle

The effect of formulation variables on particle size can simultaneously studied by the application of regression analysis. Quadratic model implied significant with model f-value of 30.72. The Predicted R^2 of.0.7757 is in reasonable agreement with the Adjusted R^2 of 0.9489; i.e. the difference is less than 0.2. The results are given in table 4. The quadratic equation computed from the analysis results given as follows:

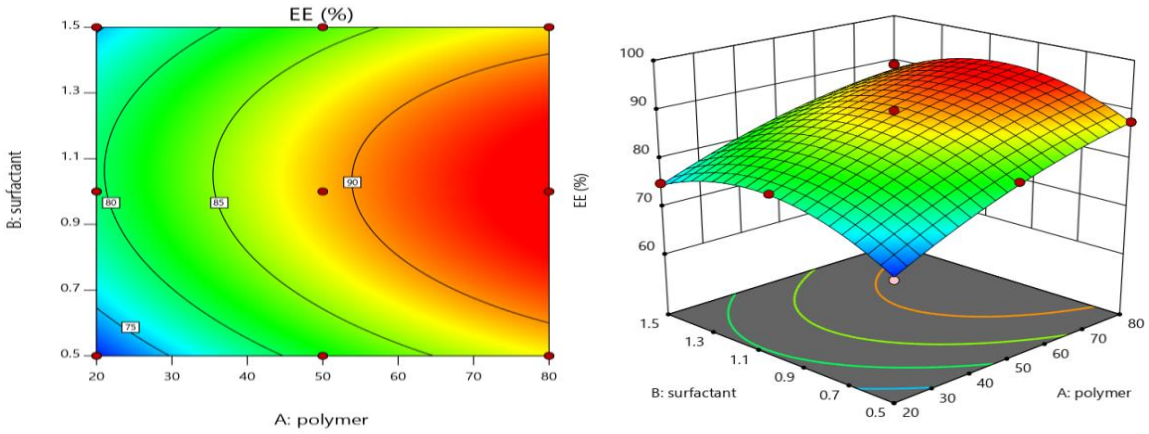
$$\text{Particle Size}=+463.92+55.66\,(A)*-71.53(B)*-3.50(AB)*-13.28\,(A^2)*-91.53\,(B^2)*$$

Where A, B are the polymer and stabilizer concentration respectively, the coefficient in this equation represents the 'standardized beta coefficient' and the variable significance was indicated by asterisk sign (*). The developed regression model was found to be significant ($p<0.05$) statistically with a high adjusted R^2value of 0.9917. The model has a curvature at higher levels of formulation variables indicates the significance of quadratic term B^2 on particle size. Simultaneously, the response surface also represented the effect of interaction as well as linear term on the particle size.

Drug entrapment efficiency

The effect of polymer and Stabilizer concentration on the entrapment efficiency of formulations obtained from the 3^2full factorial design shown in table 3 and fig. 3 that with the increase in polymer concentration, the entrapment efficiency of polymeric nanoparticles formulations significantly increasing. This is due to increased polymer concentration increase the viscosity of organic phase which will resist the diffusion of drug into aqueous phase leading to the incorporation of more drugs inside nanoparticle [23]. The present result also corroborated with the prior study reported by Sharma N *et al.,* [24].

The entrapment efficiency is found to increases till 1 % of stabilizer further increasing the concentration of stabilizer leads to decrease in the entrapment efficiency. Poloxamer stabilize the PLGA nanoparticle at the interface by diffusing out the water molecules. The increasing concentration of poloxamer favors the aqueous solubility of drug which in turn leads to increased partition of drug in water thereby decreasing entrapment efficiency.



(a) **(b)**

Fig. 3: a) Counter plot and b) Response surface curve depicting the effect of polymer and surfactant on the entrapment efficiency of polymeric nanoparticles

Regression analysis was simultaneously applied to understand the effect of formulation parameters on the entrapment efficiency. Quadratic model implied significant with model f-value of 42.67. The Predicted R^2 of 0.8524 is in reasonable agreement with the Adjusted R^2 of 0.9631; i.e., the difference is less than 0.2. The results are shown in table 4. The generated quadratic equation from the results of the analysis is given below:

$$\text{Entrapment efficiency} = +89.05 + 7.45\,(A) + 0.9767\,(B) - 0.7225\,(AB) - 2.10\,(A^2) - 6.56\,(B^2)$$

Where A, B are the polymer and surfactant concentration; the coefficient value in this equation represents the standardized beta coefficient and the asterisk sign indicates the significance of the parameters. The regression model obtained an adjusted R^2value of 0.9631 and was found to be statistically significant ($p<0.05$).

PDI and zeta potential

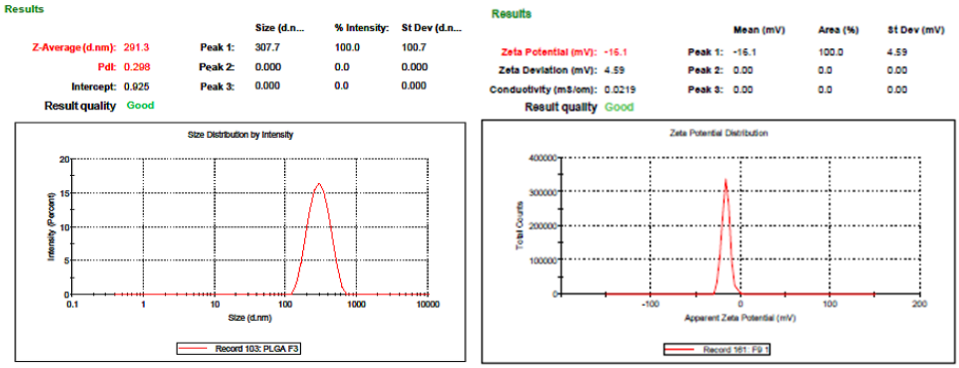
The numerical value of PDI ranges from 0.0 (for a perfectly uniform sample with respect to the particle size) to 1.0 (for a highly polydisperse sample with multiple particle size populations). In drug delivery applications using lipid-based carriers, a PDI of 0.3 and below is considered to be acceptable and indicates a homogenous population of vesicles [25]. The PDI value nanoparticles shown in table 3 and it is 0.3 for most of the formulation indicates that particles are more homogeneous distributed in the formulation.

The zeta potential analysis for the prepared polymeric nanoparticle formulations was also done using Malvern zeta sizer. The higher Zeta potential values of a formulation indicate increased stability of the polymeric nanoparticles. The zeta potential for the prepared polymeric nanoparticle was found within the range-7.55 to-15.1. The negative value shows that the carboxylic groups in the end of PLGA polymer will allow the passing of molecules across lipid barrier and prolong the circulation time.

The nanoparticles were optimized based on the response with particle size in the range 200-300 nm and maximum entrapment efficiency. The software generated the solution with desirability more than 0.8. The optimized batch was formulated by using 33.56 mg of PLGA and 1.449% of pluronic F-68 respectively and analyzed for particle size and percentage entrapment efficiency. The observed value of these responses was found to be within 95% of CI of the predicted value which is acceptable as shown in table 5.

Table 5: Point prediction of optimized batch with 95% confidence interval

Response	Predicted mean	Observed	Std dev	95% CI low for mean	95% CI high for mean
particle size	292.668	291.4	20.7984	249.085	336.252
EE	80.2683	83.45	1.42823	77.2754	83.2612



(a) **(b)**

Fig. 4: a. Particle size and b. Zeta potential of optimized formulation

Scanning electron microscopy and transmission electron microscopy

The shape and surface morphology of the prepared drug loaded polymeric nanoparticle were determined by scanning electron microscopy (SEM). The particles were found to be uniform, smooth, and having a spherical shape and amorphous (fig. 5). The TEM photographs given in fig. 6 showed the polymeric nanoparticle formulation is nearly spherical in shape with a particle size of 10 nm. TEM images would give a better understanding of the real geometric size of the particle.

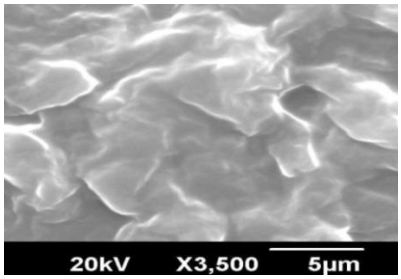


Fig. 5: SEM of optimized PN

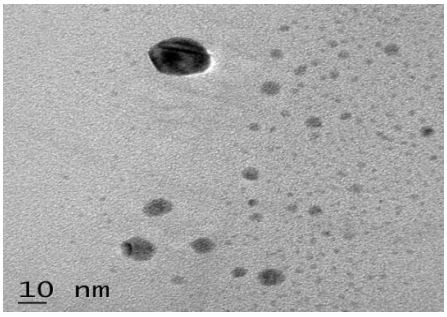


Fig. 6: TEM of optimized PN

Drug excipient compatibility study by FTIR

FTIR spectra obtained with pure drug were concordant with the standard spectra give in literature. The IR spectra of pure drug nebivolol hydrochloride showed principal peaks at 3186 cm-1 is due to O-H stretching, 1212.06 cm-1 is due to C-F, 1490.7 cm-1 is due to C-N stretching FTIR spectra of pure Nebivolol and Nebivolol loaded PLGA nanoparticles were shown in fig. 12a and b. The major IR peaks (wave number, cm-1) of pure drug and optimized formulation

are given below; Pure NBH: 3186.9, 2983.53, 1490.7, 1212.06, 1074.64, 1027.9, 814.38, 778.06, 726.7; Optimized PLGA nanoparticles: 3222.9, 2935.18, 1461.94, 1215.53 1084.01, 1022.10, 930.72, 707.65. There is no significant change in spectra in the Nebivolol loaded PLGA nanoparticles indicates that there was no incompatibility between them [26].

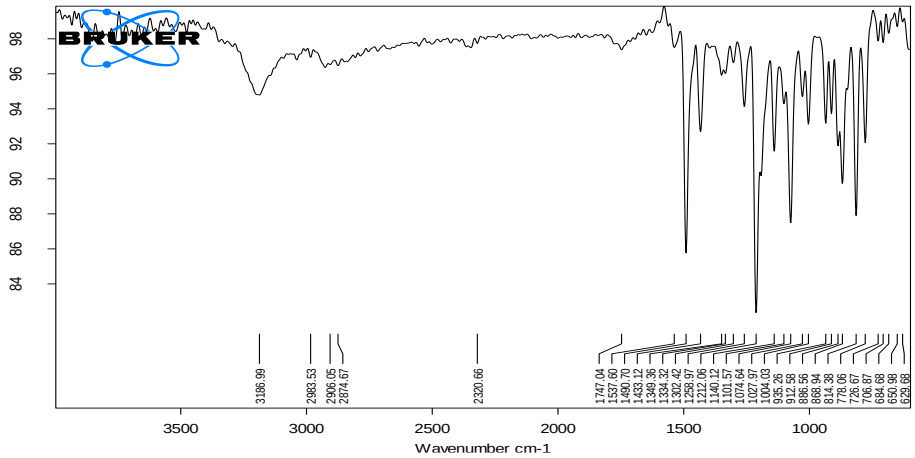


Fig. 7: FTIR spectrum of nebivolol hydrochloride

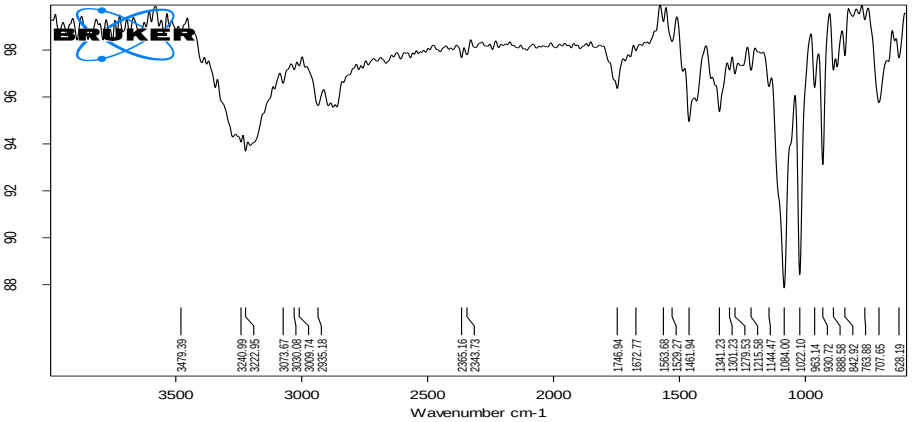


Fig. 8: FTIR spectrum of optimized formulation of polymeric nanoparticle

In vitro drug release of polymeric nanoparticles

In vitro drug release profile of the polymeric nanoparticle was given in fig. 9. From this, it was concluded that nebivolol nanoparticle showed slower drug release in comparison with pure drug formulation. The release design of drug revealed a biphasic pattern where they initially showed bust release, followed by sustained release. The initial burst of the release of Nebivolol was due to the immediate dissolution and release of drug adsorbed on the surface of the nanoparticle, followed by slow and sustained release of drug present on the core of the polymer matrix. Similar results were found by Lu B *et al.,* (27) and Kamajar N *et al.,* [28]. The maximum amount of drug that has been released from the optimized formulation after 24 h was found to be 61% when compared to the pure drug that had a release of 89%. This implies that nebivolol coated uniformly with PLGA and resulted in prolonged release of drug.

Drug release kinetics

The *in vitro* release kinetics of the optimized formulation of polymeric nanoparticle and the pure drug solution were studied using various kinetic models (table 6). The interpretation of data was done by analyzing the regression coefficient. The prepared optimized formulation of polymeric nanoparticle followed first order release kinetics with a regression coefficient (R^2) of 0.933 when compared to the zero-order kinetic model which has a regression coefficient (R^2) of 0.849. The drug release mechanism of polymeric nanoparticle was studied by comparing the Higuchi model and Korsemeyer-peppas exponential model. The drug release plot of Higuchi model showed good linearity with a regression coefficient (R^2) of 0.968 for optimized formulation. This indicated that the release from nanoparticle was diffusion controlled. The nebivolol release from nanoparticle follows first order kinetics and was regulated by two mechanisms i.e., diffusion coupled with erosion mechanism [29].

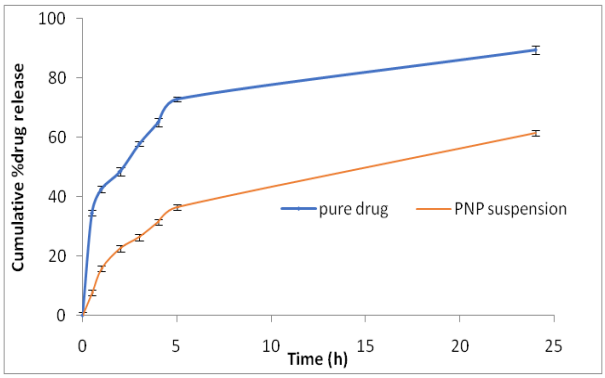


Fig. 9: Comparative *in vitro* drug release study of pure drug with optimized polymeric nanoparticle suspension. The values are expressed as mean±SD of three consecutive experiments

Table 6: Comparison of *in vitro* drug release kinetics of pure drug with optimized polymeric nanoparticle suspension

Formulation code	Kinetic models								
	Zero order		First order		Higuchi		Korsmeyer-peppas		
	R^2	K	R^2	K	R^2	k	R^2	K	N
Pure drug	0.70	1.92	.904	-0.03	0.86	12.8	0.65	1.64	0.17
PLGA Polymeric nanoparticle suspension	0.84	1.93	0.93	-0.01	0.968	12.4	0.895	1.16	0.45

CONCLUSION

The drug-excipients interaction was explored by molecular docking studies. The Polymeric nanoparticles containing Nebivolol HCl was prepared by single emulsion solvent evaporation using PLGA as polymer and poloxamer-188 as surfactant. 3^2factorial designs were adopted for optimization using "Design Expert" software. Different microscopic images showed that the formed polymeric nanoparticles were smooth, spherical in shape and uniform in size with a size less than 300 nm. *In vitro* drug release study of the optimized PLGA nanoparticle showed sustained release for prolonged time period. It follows first order release kinetics and mechanism of drug release followed Higuchi model. Based on *in vitro* release studies, the developed Nebivolol hydrochloride loaded in PLGA nanoparticles could be promising formulation in oral drug delivery for the treatment of hypertension.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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