ARTICLE

Solubility enhancement of Nebivolol via Self emulsifying drug delivery system using Box–Behnken Design: Optimization and Evaluation

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ABSTRACT

The present study aimed to develop, optimize, and evaluate a Nebivolol-loaded self-emulsifying drug delivery system (N-SEDDS) to improve the drug's solubility, dissolution rate, and oral bioavailability by employing a Quality by Design (QbD) approach to manage high blood pressure. N-SEDDS formulations were prepared in thirteen batches NS1-NS13, using Capryol 90 (oil phase), Tween 80 (surfactant), and PEG 400 (co-surfactant). No interaction with excipient was observed with drug by FTIR compatibility study. Formulations were optimized using Box–Behnken Design and evaluated for droplet size, polydispersity index (PDI), zeta potential, pH, Refractive index (RI), %Transmittance, Cloud point, Emulsification time, Thermodynamic stability, Drug content, Cumulative % in vitro drug release. Among all formulations, NS2 was identified as the optimized batch, exhibiting a droplet size of 109.8±0.13 nm, PDI of 0.113, zeta potential of −29.4 mV, drug content of 93.12±0.43%, and cumulative % in vitro drug release of 95.66±0.35% after 120min. The optimized formulation also demonstrated excellent physical stability, rapid emulsification, and thermodynamic stability. In conclusion N-SEDDS could be a better approach for solubility and bioavailability enhancement in oral, topical, parental route in the management of hypertension.

Keywords: Nebivolol, Nebivolol hydrochloride, Self-emulsifying drug delivery system, Quality by Design, Box–Behnken Design, SEDDS

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INTRODUCTION

Hypertension is one of the most prevalent cardiovascular disorders worldwide and remains a major cause of morbidity and mortality. Effective management of hypertension requires antihypertensive agents that provide consistent therapeutic efficacy and good patient compliance. Nebivolol is a third-generation, highly selective β_1-adrenergic receptor blocker with a unique nitric oxide-mediated vasodilatory action, which distinguishes it from conventional β-blockers. Owing to its dual mechanism of action, nebivolol effectively reduces blood pressure, improves endothelial function, and exhibits fewer adverse metabolic effects, making it a preferred therapeutic option for the treatment of hypertension and chronic heart failure [1–3]. Despite its clinical advantages, the oral delivery of nebivolol is limited by its poor aqueous solubility and extensive first-pass hepatic metabolism, resulting in variable absorption and relatively low oral bioavailability [4,5]. Poor dissolution of lipophilic drugs within the gastrointestinal tract often leads to inadequate plasma drug concentrations and inconsistent therapeutic outcomes. Therefore, improving the solubility and dissolution characteristics of nebivolol has become an important objective in pharmaceutical formulation research.[6]

Among various formulation strategies developed to enhance the oral delivery of poorly water-soluble drugs, lipid-based drug delivery systems have attracted considerable attention. Self-emulsifying drug delivery systems (SEDDS) are isotropic mixtures of oils, surfactants, and co-surfactants that spontaneously form fine oil-in-water emulsions upon gentle agitation in gastrointestinal fluids[7–9]. The formation of micro- or nano-sized droplets markedly increases the interfacial surface area available for drug dissolution, thereby improving drug solubilization, intestinal absorption, and oral bioavailability [10,11]. In addition, lipid-based formulations may facilitate lymphatic transport and reduce hepatic first-pass metabolism, further enhancing systemic drug exposure[12]. The performance of a SEDDS depends on the appropriate selection and optimization of formulation components. Solubility screening, compatibility studies, pseudo-ternary phase diagram construction, thermodynamic stability testing, droplet size analysis, polydispersity index, self-emulsification time, drug content, and in vitro dissolution studies are essential parameters during formulation development.[13–16] Furthermore, the implementation of Quality by Design (QbD) and statistical optimization techniques such as Box–Behnken Design enables systematic evaluation of formulation variables and ensures the development of a robust and reproducible product [17,18]. Considering the physicochemical characteristics of Nebivolol, incorporation into a SEDDS offers a promising approach for improving its dissolution behavior, oral absorption, and therapeutic efficacy. Therefore, the present study aimed to formulate, optimize, and evaluate a N-SEDDS using suitable lipid excipients to enhance its physicochemical properties for the management of hypertension [19, 20].

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MATERIALS AND METHODS

MATERIALS

Nebivolol was procured from Yarrow chem products, Mumbai, India. Capryol 90, Span 80, Tween 80, PEG 400, phosphate-buffered saline (PBS, pH 7.4), dialysis membrane (MWCO 1000 Da), and deionized water were procured from Cosmo Chem Pvt. Ltd. India. Methanol, All chemicals, solvents, and excipients were procured from Research Lab Fine Chem Lab.

METHODS

Identification of surfactant and co-surfactant (Smix) Ratio

Different Smixratio were evaluated to identify the optimum ratio for formation of a stable nanoemulsion system (NS). Capryol 90 was selected as the oil phase, Tween 80 as surfactant, and PEG 400 as co-surfactant. Smix ratios of Tween 80 and PEG 400 were prepared in different proportions such as 1:1, 1:2, 2:1, 3:1, and 4:1 (Table 1). Each Smix ratio was mixed with the oil phase in different proportions and titrated with distilled water using the water titration method. The formulations were visually observed for clarity, transparency, phase separation, and turbidity. The NE region obtained from each Smix ratio was plotted on pseudo-ternary phase diagrams.

Table 1: Optimization of Smix Ratio

Ratio (Tween 80 : PEG 400)	Oil (capryol 90) (mL)	Surfactant (Tween 80) (mL)	Co-surfactant (PEG 400) (mL)	Total Water Added (mL)
1 : 1	0.5	0.50	0.50	0.6
1 : 2	0.5	0.33	0.67	0.4
2 : 1	0.5	0.67	0.33	0.5
3 : 1	0.5	0.75	0.25	0.3
4 : 1	0.5	0.80	0.20	0.2

Identification of NE region (capryol 90)

Solubility study, oil, surfactant and co-surfactant were selected to construct a pseudo ternary phase diagram. Capryol 90 were selected as oil phase; Tween 80 and PEG 400 were selected as surfactant and co-surfactant respectively. From pseudo-ternary Phase diagram, a stable micro-emulsion zone was identified. For the identification of a NE zone, S mixratio was kept at 1:1. The S mix Concentration was increased from 1 to 9 by keeping oil phase as constant. Oil and surfactant mixture were mixed at a ratio of 1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8 and 1:9, Respectively. To each of the mixture distilled water was added drop wise until the first sign of turbidity occurred; the solution was allowed to equillibrate. (Table 2).

Table 2: Oil–Smix Ratio Optimization for SEDDS

Ratio (Oil : Smix)	Oil (Capryol 90) (mL)	Surfactant (Tween 80) (mL)	Co-surfactant (PEG 400) (mL)	Total Water Added (mL)
1 : 1	0.5	0.25	0.25	0.3
1 : 2	0.5	0.5	0.5	0.4
1 : 3	0.5	0.75	0.75	0.4
1 : 4	0.5	1	1	0.5
1 : 5	0.5	1.25	1.25	0.5
1 : 6	0.5	1.5	1.5	0.6
1 : 7	0.5	1.75	1.75	0.7
1 : 8	0.5	2	2	0.8
1 : 9	0.5	2.25	2.25	0.8

Method of preparation of NE

The accurately measured oil, surfactant, and co-surfactant were transferred into a clean, dry glass vial. Nebivolol (5 mg) was added to the mixture. The vial was tightly capped and placed on a vortex mixer, vortexed at moderate speed for 5–10 minutes until a clear and homogeneous solution [21].

Experimental design

The response surface methodology (RSM) was employed to perform QbD approach for constructing and investigating the polynomial models, using fewer experimental runs. Box-behnken design comprising of 3-factors and 3- levels was employed to examine the quadratic response surfaces by assessing the effect of predefined independent variables on different response dependent variables Particle size (nm), Drug content (%) and Cumulative % *in vitro* drug release (%) was coded as Y1, Y2 and Y3. Three independent variables namely Oil conc (A) (%), Surfactant conc (B) (%) and Co-surfactant (PEG 400) (mL) (C) were chosen. Each of the variables was varied at two different levels, known as high, and low levels. All the finalized independent variables and the response variables are described in Table 3. The NE formulations were shown in Table 4 as per DOE.

Table 3: List of Independent and Dependent variables in Box-behnken design

Independent variables	Low value (-1)	High value(+)
Oil conc (A) (%)	8	14
Surfactant (B) (%)	40	48
Co-surfactant (C) (%)	40	48
Dependent variables	Constraints	
Particle size (nm)	Minimize	
Drug Content (%)	Maximize	
Cumulative in vitro drug release (%)	Maximize	

Table 4: DOE suggested Experimental batches*

Formulation code	Nebivolol (mg)	Oil conc (%)	Surfactant (%)	Co- surfactant (%)
NS1	5	11	48	40
NS2	5	14	44	40
NS3	5	14	40	44
NS4	5	8	48	44
NS5	5	11	48	48
NS6	5	8	44	40
NS7	5	14	44	48
NS8	5	11	40	40
NS9	5	11	44	44
NS10	5	8	40	44
NS11	5	14	48	44
NS12	5	8	44	48
NS13	5	11	40	48

* The Methyl paraben (0.1%) & freshly prepared distilled water q.s.was added in each formulation.

Evaluation of N-SEDDS

Determination of Droplet Size

The average droplet size, PDI, and zeta potential were examined through dynamic light scattering technique (HORIBA SZ-100V2). Initially, all samples NS1-NS13 were diluted separately with distilled water (1:10) to revoke the multi-scattering effect, reduce the expected formulation viscosity. The particle size data was reported as the Z-average mean diameter. All measurements were reported in triplicate at ambient temperature (25◦±2◦C) and an angle of 90◦ to the incident beam [22,23].

pH measurement

These were measured for all samples at 25°C using a digital calibrated pH meter (contech CPH-102 & CPH-103). Three measurements were taken for one sample and recorded.

Determination of RI, Transmittance (%) & Transparency

The RI of the designed sample was determined via a calibrated Abbe's refractometer. A small amount of the sample was introduced on the instrument's glass slide, and the corresponding scale reading was recorded. Each formulation (100µL) was added to a vial containing 10mL of double distilled water and cyclomixed for 1 minute. Each sample was observed for % Transmittance. [24,25].

Cloud point measurement

Each formulation was diluted with water in the ratio of 1:100 and placed in a water bath with a gradual increase in temperature. At the cloud point, drop in sample was measured [26].

Determination of Emulsification Time

Accurately take a fixed quantity of the prepared formulation (1 mL) and added 100 mL distilled water maintained at room temperature in a beaker. Stirred using a magnetic stirrer at a constant speed (50–100 rpm). Started a stopwatch immediately after adding the formulation into the aqueous phase. Observed the system carefully for the formation of a clear or uniformly dispersed emulsion. Recorded the time required for complete emulsification (i.e., when no oil droplets or phase separation was visible). Repeated the experiment in triplicate and reported the average emulsification time.

Freeze thaw cycles and centrifugation

Each cycle involved freezing the formulations at -4°C for 24 h, monitored through thawing at 40°C for 24 h. After each freeze-thaw cycle, visual inspections for phase separations and drug precipitation were performed. Subsequent the completion of three cycles, the formulation underwent centrifugation at 3000 rpm for five min. Subsequently, visual assessments were conducted to identify some phase or drug separation indications. Only formulations exhibiting no drug or phase separation indications were chosen for further investigations.

Percantage drug content

Drug content was determined to assess the uniformity and efficiency of drug incorporation in the formulation. An aliquot of 1 mL of the formulation (equivalent to a known amount of drug) was dissolved in 9 mL phosphate buffer 7.4 to achieve complete dissolution and filtered. The clear filtrate was analyzed using a UV–Visible spectrophotometer at 285 nm. Drug content (%) was calculated using following equation [27,28]:

Drug Content (%) = Measured drug concentration/ Theoretical drug concentration *100

Cumulative % *In-vitro* drug Release Studies

In-vitro release tests of the formulations and drug solution were performed using pretreated dialysis membrane in phosphate buffer 7.4 (37±2ºC) at 100 rpm. 2 mL of samples was withdrawn at regular time intervals of 5, 10, 15, 20, 30, 45, 60, 120 min and the same amount of fresh phosphate buffer was replaced every time to maintain sink condition. The samples were analyzed in triplicate at 285 nm by UV. Cumulative amount of drug released was calculated by using calibration curve [29]. The drug release kinetics were studied as Zero-order, First-order and Higuchi model.

RESULTS AND DISCUSSION

SEDDS components screening and selection

Identification of Smix Ratio

The Smix ratio optimization study successfully identified the optimum surfactant and co-surfactant ratio required for the formation of a stable capryol 90 NE system. Different Smix ratios of Tween 80 and PEG 400 were evaluated using pseudo-ternary phase diagrams and aqueous titration method. Among all the tested ratios, Tween 80: PEG 400 at 1:1 ratio produced the largest NE region with excellent transparency, rapid emulsification, and good physical stability and selected as the optimized ratio for further development and characterization of NE formulation. Lower surfactant concentrations resulted in turbid formulations, whereas higher surfactant concentrations increased viscosity and reduced stability (Fig. 1).

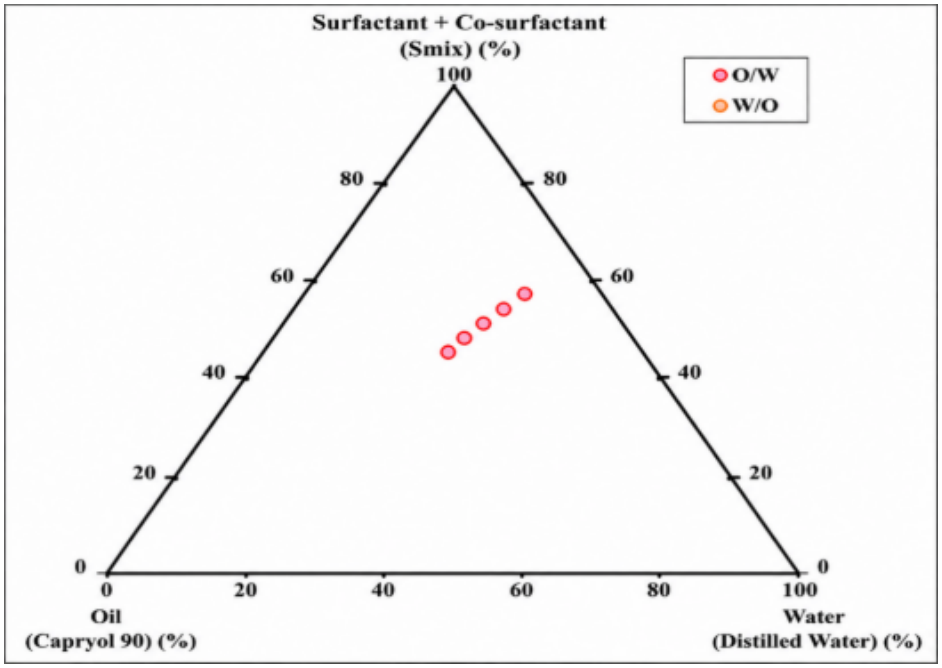

Figure 1: Optimization of Smix Ratio

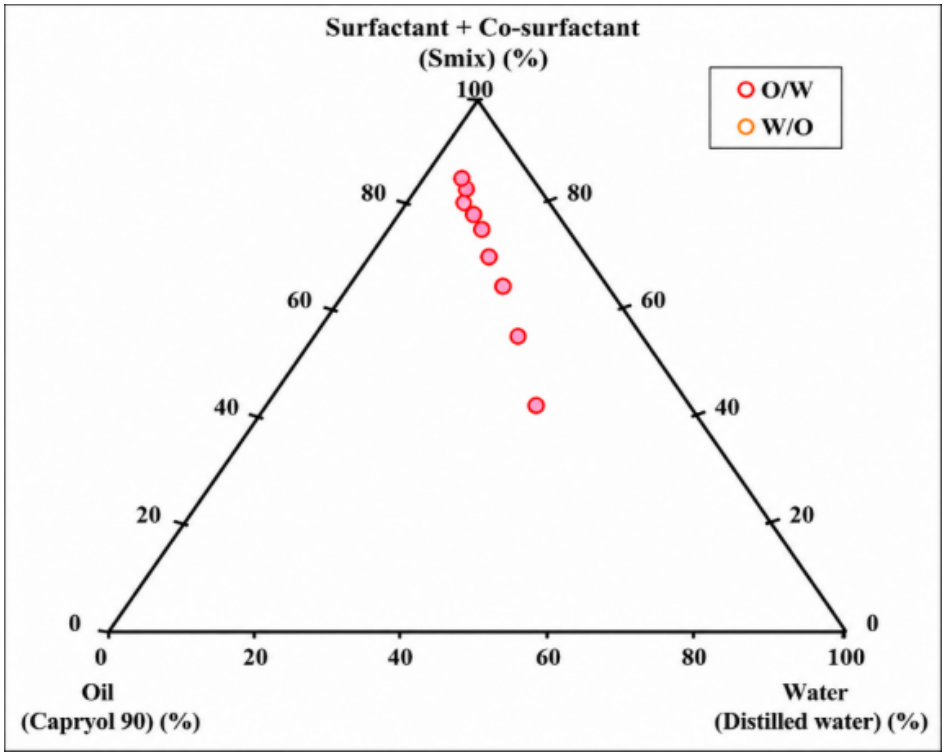

Figure 2: Oil–Smix Ratio Optimization for SEDDS

Identification of NE region (capryol 90)

The pseudo-ternary phase diagram of capryol 90 demonstrated successful formation of stable O/W NE regions using Tween 80 and PEG 400 as Smix. Increasing Smix concentration enhanced emulsification efficiency, transparency, and water incorporation capacity. Among all formulations, the 1:8 oil-to-Smix ratio showed a broader and more stable NE region and was selected as the optimized formulation for further studies. The pseudo-ternary phase diagram confirmed successful nanoemulsion formation of capryol 90 using Tween 80 and PEG 400. Higher Smix concentrations improved nanoemulsion stability and dispersion characteristics. The 1:8 oil-to-Smix ratio exhibited better transparency, stable O/W nanoemulsion region, and improved water incorporation, making it the optimized formulation for further nanoemulsion development (Fig. 2).

Result and discussion of N-SEDDS

The droplet size of the N-SEDDS formulations ranged from 109.8±0.13 to 163.2±0.93nm, with PDI values of 0.113–0.144 and zeta potential values of −16.7 to −29.4 mV, indicating good homogeneity and physical stability. The pH of all SEDDS formulations ranged from 6.28 ±0.15 to 6.67±0.13, indicating suitability for oral administration. The RI values (1.335–1.349) confirmed the formation of isotropic systems, while high transmittance values (83.8–94.6%) indicated good clarity and efficient self-emulsification as shown in Table 5.

Table 5: Evaluation parameters of NS1-NS13

Formulation Code	Particle size (nm)	PDI	Zeta potential (mV)	pH	RI	% Transmittance	Transparency
NS1	123.4±0.14	0.132	-21.6	6.67±0.13	1.338	86.1	Transparent
NS2	109.8±0.13	0.113	-29.4	6.52±0.21	1.335	94.6	Highly transparent
NS3	115.1±0.36	0.134	-21.3	6.46±0.96	1.340	88.2	Transparent
NS4	138.9±0.04	0.133	-23.8	6.45±0.11	1.342	90.4	Highly transparent
NS5	141.1±0.91	0.139	-22.3	6.42±0.03	1.344	87.4	Transparent
NS6	162.7±0.11	0.138	-19.2	6.39±0.84	1.346	89.6	Transparent
NS7	125.4±0.08	0.141	-19.7	6.36±0.44	1.347	85.8	Slightly turbid
NS8	150.2±0.64	0.144	-25.0	6.36±0.19	1.343	91.1	Highly transparent
NS9	128.3±0.22	0.123	-24.6	6.33±0.17	1.345	88.3	Transparent
NS10	163.2±0.93	0.126	-24.9	6.31±0.66	1.348	84.6	Slightly turbid
NS11	129.4±0.71	0.138	-22.1	6.30±0.51	1.349	83.8	Slightly turbid
NS12	126.3±0.33	0.124	-16.7	6.28±0.15	1.341	90.8	Highly transparent
NS13	129.7±0.05	0.138	-22.5	6.40±0.16	1.346	86.5	Transparent

The cloud point temperature of the SEDDS formulations ranged from 64.6°C to 72.4°C, indicating good thermal stability above physiological temperature. Emulsification time varied between 24 and 50 s, demonstrating rapid self-emulsification of all formulations.The drug content of the SEDDS formulations ranged from 82.60±0.65% to 93.12±0.43%, indicating

satisfactory drug loading and uniformity among the formulations. The *in vitro* dissolution study demonstrated a gradual increase in drug release from all SEDDS formulations over 120 min (Fig. 3). The cumulative drug release at the end of the study ranged from 84.19±0.24 to 95.66±0.35%. The results were shown in Table 6. The chemical kinetics plots were shown in Fig 4 for different model.

Table 6: Cloud Point Temperature, Emulsification Time and Cumulative % In vitro drug release of NS1-NS13

Formulation Code	Cloud Point Temperature (°C)	Emulsification Time (s)	Drug Content (%)	Cumulative % In vitro drug release after 120 min.
NS1	67.8	38	86.18 ± 0.54	90.32±0.02
NS2	72.4	24	93.12 ± 0.43	95.66±0.35
NS3	69.6	32	90.43 ± 0.47	90.77±0.91
NS4	68.2	36	87.56 ± 0.58	86.09±0.54
NS5	66.5	41	84.40 ± 0.62	86.83±0.71
NS6	65.9	44	89.20 ± 0.45	87.69±0.09
NS7	64.8	48	90.76 ± 0.41	89.17±0.07
NS8	70.1	29	86.69 ± 0.51	90.03±0.75
NS9	69.2	34	91.25 ± 0.34	88.43±0.65
NS10	65.4	46	83.20 ± 0.67	85.8±0.97
NS11	64.6	50	82.60 ± 0.65	91.06±0.08
NS12	67.1	31	92.80 ± 0.39	84.19±0.24
NS13	66.2	43	86.52 ± 0.56	86.54±0.04

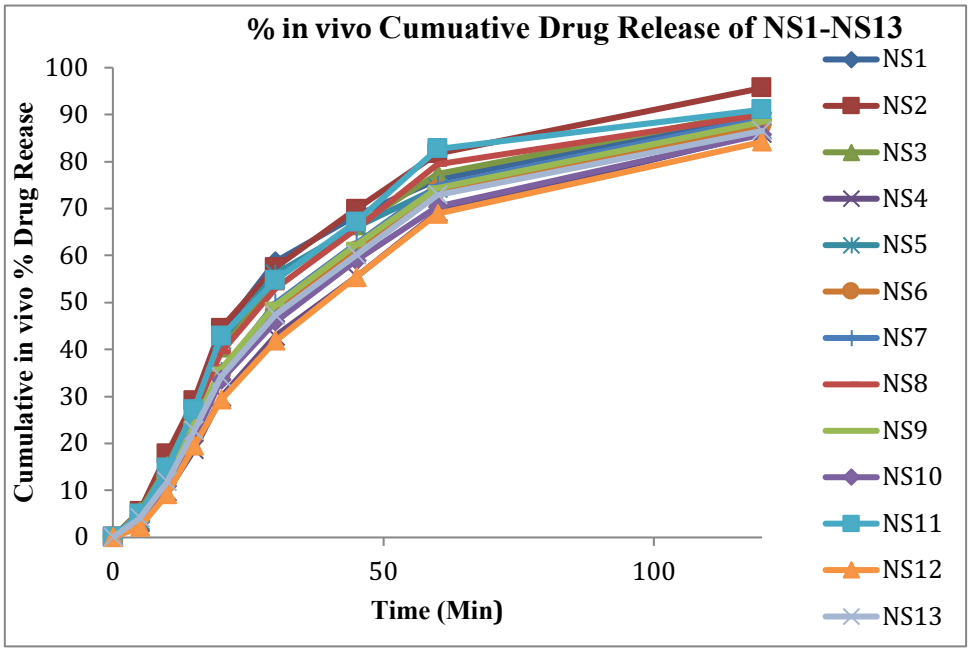

Figure 3: In vitro Dissolution study NS1 to NS13

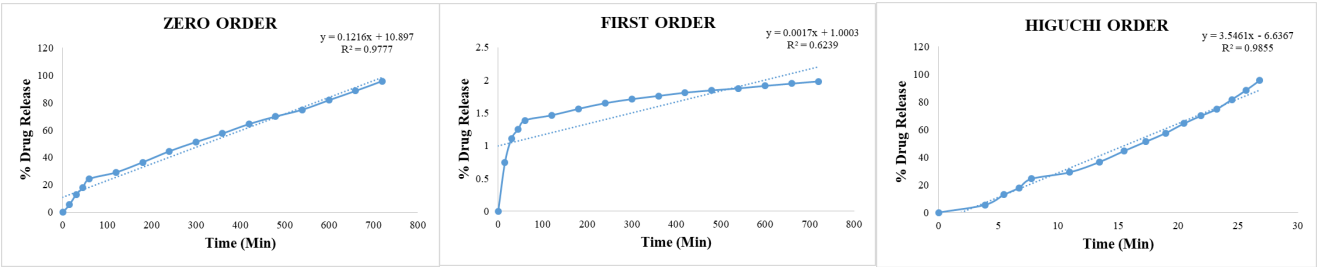

Figure 4: Kinetic release in vitro models

Among all formulations, NS2 exhibited the smallest droplet size (109.8±0.13nm), the lowest PDI (0.113), and the highest magnitude of zeta potential (−29.4 mV), suitable pH, RI, exhibited the highest transmittance (94.6%) and was highly transparent, suggesting superior formulation quality and stability. NS2 exhibited the highest cloud point (72.4°C) and the shortest

emulsification time (24 s), indicating superior thermal stability and excellent emulsification efficiency, highest drug content (93.12±0.43%), and uniform distribution within the optimized formulations. It exhibited the highest cumulative drug release (95.66±0.35%) after 120 min. indicating superior dissolution performance. Thus, based on all results, NS2 was selected as the optimized formulation for further stability study. It was observed that NS2 remained stable throughout three freeze–thaw cycles and centrifugation studies, with no evidence of phase separation, drug precipitation, or drug separation**.** These findings demonstrate excellent physical stability and confirm that the developed formulations possess sufficient robustness to withstand thermal stress and mechanical forces during storage and handling.

CONCLUSION

The present study successfully developed and optimized a N-SEDDS using QbD approach. The optimized formulation was obtained using Capryol 90, Tween 80, and PEG 400 in an optimized composition identified through pseudo-ternary phase diagram studies and Box–Behnken experimental design. The optimized batch (NS2), demonstrating excellent physicochemical characteristics and enhanced dissolution performance. The formulation also showed suitable pH, high transmittance, rapid emulsification, high cloud point temperature, and excellent stability during freeze–thaw and centrifugation studies, while FTIR analysis confirmed the absence of significant drug–excipient interactions. Overall, the developed SEDDS represents a promising oral lipid-based drug delivery system capable of improving the solubility, dissolution, and potential oral bioavailability of Nebivolol, thereby offering an effective strategy for the management of hypertension.

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