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DEVELOPMENT AND CHARACTERIZATION OF AMLODIPINE LOADED SELF-NANO EMULSIFYING DRUG DELIVERY SYSTEM NEEDS FOR EFFECTIVE HYPERTENSION TREATMENT

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ABSTRACT

Through the development of Self-Nanoemulsifying Drug Delivery Systems (SNEDDS), the current project aims to improve the oral bioavailability and therapeutic efficacy of amlodipine, a weakly water soluble hypertension medication. Tween 20 was used as the surfactant and peppermint oil as the lipid phase to create amlodipine-loaded SNEDDS. Using particle size and entrapment efficiency as response parameters, the Box-Behnken Design was utilized to optimize important formulation factors, such as oil content, surfactant ratio, and homogenization time. The optimized formulation (Batch A2) showed physical stability with a particle size of 90.6 nm, entrapment effectiveness of 98.05%, and zeta potential of –24.5 mV. High transparency, an 83°C cloud point, and advantageous drug release characteristics were found in characterization investigations. Similar to the common medication captopril, moderate antihypertensive efficacy was shown by in vitro ACE inhibition studies. The formulation's resilience over a month in a refrigerator was further confirmed by stability tests. The results of this study show that SNEDDS greatly increase the solubility, stability, and antihypertensive effectiveness of amlodipine, providing a viable method for the oral administration of lipophilic medications.

KEYWORD: Amlodipine, Antihypertension, SNEDDS.

INTRODUCTION

The Renin-Angiotensin-Aldosterone System (RAAS), which controls blood pressure and fluid balance, is one of the main mechanisms underlying hypertension (HTN), a chronic condition marked by persistently elevated blood pressure and one of the leading risk factors for cardiovascular diseases (CVD). It is a significant global public health concern because it frequently coexists with other risk factors like obesity, diabetes mellitus, metabolic syndrome, and hyperlipidemia, increasing the risk of heart disease and stroke. Over activation of RAAS leads to vasoconstriction, sodium and water retention, and increased blood volume, thereby elevating blood pressure. Management of hypertension involves various classes of antihypertensive drugs, including ACE inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), calcium channel blockers, vasodilators, and centrally acting sympatholytic agents, which help in controlling blood pressure and reducing cardiovascular risk.[1,2]

SNEDDS is an effective drug delivery system for enhancing the oral absorption of poorly water-soluble drugs, especially in BCS Class II and IV.[7,9,10]

Amlodipine is a long-acting calcium channel blocker used to treat hypertension. It inhibits L-type calcium channels in vascular smooth muscle. This reduces calcium influx, causing vasodilation and decreased peripheral resistance. As a result, it effectively lowers blood pressure.[2,18]

MATERIAL AND METHODS

MATERIAL: The materials used for the experimental work include amlodipine, which was obtained from LGM Pharma. Tween-20, peppermint oil, sodium chloride, potassium dihydrogen orthophosphate, disodium hydrogen phosphate, and concentrated hydrochloric acid were all procured from Loba Chemie Pvt. Ltd. Distilled water was sourced from Bisleri International Pvt. Ltd., while methanol was obtained from Zenith Bio Chemical Industries Pvt. Ltd. All other chemicals used in the study were in the analytical grade.[11,12]

METHOD

The nano emulsion was prepared using the high-speed homogenization method followed by sonication. The oil phase (peppermint oil) and surfactant (Tween 20) were accurately mixed, and the drug (amlodipine) was dissolved in this mixture. The resulting system was subjected to high-speed homogenization to reduce droplet size, followed by sonication to obtain a fine and stable nano emulsion with nanoscale droplets.[12,18,20]

Pseudo-Ternary Phase Diagram: Pseudo-ternary phase diagrams were constructed to identify the nanoemulsion region and optimize formulation composition. The system consisted of oil (lipid phase), surfactant/co-surfactant mixture (Smix), and water. The surfactant and co-surfactant were combined in different weight ratios (1:1, 1:2, and 2:1), while oil and Smix were mixed in varying proportions ranging from 1:9 to 9:1.

Each mixture was prepared by accurately weighing the components and heating above the melting point of the lipid phase to obtain a homogeneous system. Distilled water was then gradually added under continuous mixing to determine phase behavior. The nano emulsion region was identified as the transparent and thermodynamically stable area in the phase diagram. The extent of this region indicates the efficiency of the selected surfactant system in emulsification and drug solubilization. The diagram of provides a basis for selecting optimal component ratios for the development of a stable nanoemulsion formulation.[7,12,13]

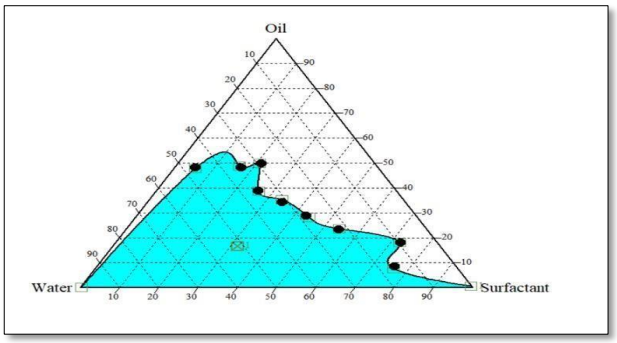


Fig 1: Pseudo ternary phase diagram with oil and surfactant ratios.

Analytical Methods

Determination of λmax of Amlodipine

The maximum absorbance wavelength (λmax) of amlodipine was determined using a Shimadzu UV-1800 double-beam UV– Visible spectrophotometer with 1 cm matched quartz cuvettes.

In Methanol

A stock solution (1000 µg/mL) was prepared by dissolving accurately weighed amlodipine in methanol and diluting to volume. It was further diluted to obtain a working solution of 2 µg/mL. The solution was scanned over 200–400 nm using methanol as blank, and λmax was recorded.

In PBS (pH 7.4)

A stock solution (1000 µg/mL) was prepared in methanol and diluted to 100 µg/mL. Further dilution with phosphate buffer saline (pH 7.4) yielded a 10 µg/mL solution. The sample was scanned between 200–400 nm using PBS as blank to determine λmax.

In PBS (pH 6.8)

Similarly, a stock solution (1000 µg/mL) was prepared and diluted to 100 µg/mL. An aliquot was further diluted with PBS (pH 6.8) to obtain a 6 µg/mL solution. The solution was scanned in the range of 200–400 nm against PBS blank, and λmax was noted.

Calibration Curve of Amlodipine in Methanol

A standard stock solution (1000 µg/mL) of amlodipine was prepared in methanol and diluted to obtain a secondary stock solution of 100 µg/mL. Appropriate aliquots (0.1–1.0 mL) were further diluted to 10 mL with methanol to obtain concentrations in the range of 1–10 µg/mL.

The absorbance of each solution was measured at 234 nm using methanol as blank. A calibration curve was plotted between absorbance and concentration, and the regression equation along with correlation coefficient (R^2) was determined.[12,18]

Formulation of amlodipine loaded SNEDDS by using Box-Behnken Experiment Design: Nanoemulsion formulation was optimized using the Box-Behnken design (BBD). Encapsulation efficiency and particle size were selected as response variables, while probe sonication cycles, oil concentration, and surfactant concentration were considered as independent variables. The design evaluates factor interactions efficiently with a limited number of experimental runs. Independent variables were studied at three levels: low (-1), medium (0), and high (+1), based on preliminary studies.[6]

Table 1: Independent and dependent variables along with their levels in box Behnken design.

Independent Variables	Levels		
	Low (-1)	Medium (0)	High (+1)
Probe cycle (min)	45 min	60 min	75 min
% oil	2%	4%	6%
% surfactant	10%	12%	14%
Dependent variables	**Criteria**		
Particle size (nm)	Minimize		
% Entrapment Efficiency	Maximize		

Composition of Nanoemulsion Formulations

Nanoemulsion formulations were developed using a Box-Behnken design consisting of 13 experimental runs (A1-A13). Probe sonication time (45-75 min), oil concentration (2-6%), and surfactant concentration (10-14%) were selected as independent variables. The formulations were prepared by systematically varying these parameters at three levels to study their effect on formulation characteristics, ensuring efficient evaluation of variable interactions.[11]

Fabrication of amlodipine loaded SNEDDS by High-speed homogenization technique: A total of 13 formulations were developed using a Box-Behnken Design (BBD) and prepared through a modified high-speed homogenizer followed by sonication. Initially, a lipid phase peppermint oil was blended with a surfactant phase made up of Tween 20. These two mixtures (referred to as Oil and Surfactant, respectively) were combined in a single beaker. To this combined mixture, 50 mg of amlodipine was added and make up volume up to 50 ml by using deionized water. And then followed by using high speed homogenizer at 1300 rpm with respective time. Take 0.1 ml solution by using micropipette and make up the volume up to 10 ml with deionized water. Sonicate the solution for a while and filter with Whatman filter paper.[20]

Optimization of amlodipine loaded SNEDDS

Entrapment Efficiency (%EE)

Entrapment efficiency of the amlodipine-loaded nanoemulsion was determined by quantifying the total drug content (Y1) and the unencapsulated drug (Y2). The formulation was diluted with methanol and sonicated to ensure complete drug extraction, followed by analysis using UV–visible spectrophotometry. For estimation of unentrapped drug, the nanoemulsion was centrifuged at 8000 rpm for 60 min, and the supernatant was collected, diluted, and analyzed. The percentage entrapment efficiency was calculated using the equation.[5,11,19]

$$\%EE = [(Y1 - Y2) / Y1] \times 100.$$

Particle Size Analysis

Particle size and distribution of the nanoemulsion were determined by dynamic light scattering (DLS). The sample was suitably diluted with distilled water and analyzed using a particle size analyzer to obtain mean droplet size.[7,11,19]

Characterization of Amlodipine Loaded SNEDDS

Zeta Potential Analysis: The surface charge of the optimized amlodipine-loaded nanoemulsion was determined using a zeta potential analyzer. The sample was placed in a carbon electrode cell and analyzed at 25 °C to evaluate colloidal stability.[11,19]

Cloud Point Determination: The optimized SNEDDS formulation was heated gradually in a water bath after being diluted 100 times with deionized water. The cloud point was defined as the temperature at which turbidity first manifested. To ensure reproducibility, the measurement was repeated using cycles of heating and cooling.[7,22]

Percent Transmittance: A UV-visible spectrophotometer was used to measure the percent transmittance over the wavelength range of 200–400 nm, using deionized water as the blank. The nanoemulsion was diluted 100 times with deionized water.[5,21]

Antihypertensive Activity (ACE Inhibition Assay): Captopril was used as a standard and hippuryl-histidyl-leucine as a substrate to assess ACE inhibitory activity. The reaction mixture was terminated with hydrochloric

acid after being incubated with the ACE enzyme at 37 °C. Ethyl acetate was used to extract the released hippuric acid, and absorbance was measured at 450 nm. The conventional equation was used to determine the % inhibition.[1,8,17,23]

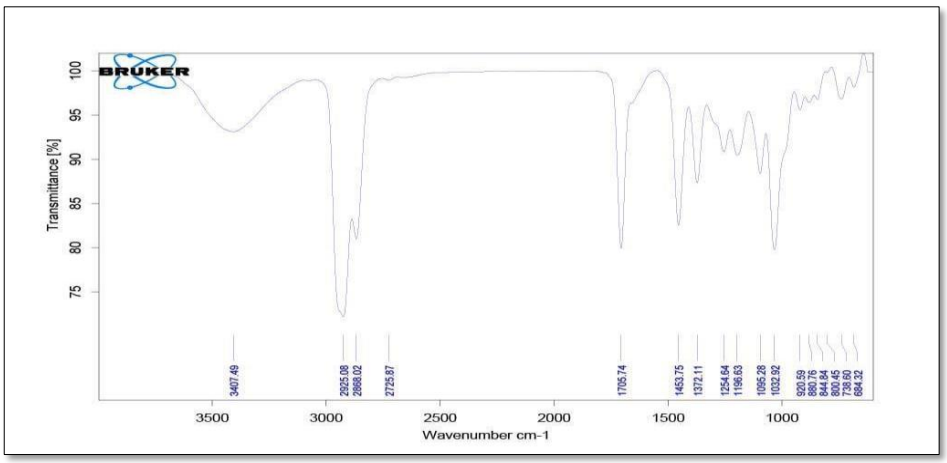
ACE Inhibition (%) = [(Abs450 control − Abs450 sample) / Abs450 control] × 100

Study of Stability: For two months, the improved nanoemulsion was kept in a refrigerator between 2 and 8 °C. To evaluate formulation stability, variables such drug content, particle size, and zeta potential were examined at predefined intervals. [7, 19]

RESULTS AND DISCUSSION

Identification Tests: Amlodipine's physicochemical and spectral features were assessed in order to identify it. Upon visual assessment, the medication was found to have a solid with a somewhat yellow look. Using Thiele's tube method, the melting point was found to be 138 °C, which is in line with reported values. Its distinctive absorption was confirmed by UV spectrophotometric measurement, which revealed a maximal absorbance at 238 nm. Furthermore, FTIR analysis revealed that the obtained infrared spectrum was comparable with the reference spectrum, indicating the authenticity and purity of the drug sample.

FTIR study

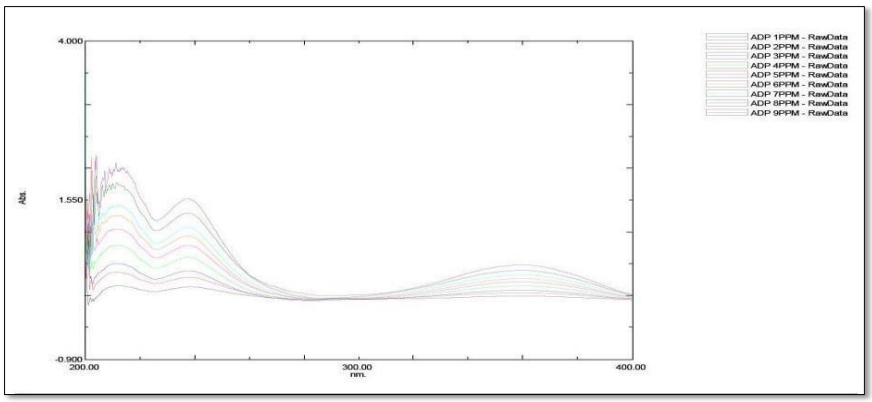


FTIR spectrum of pure amlodipine drug.

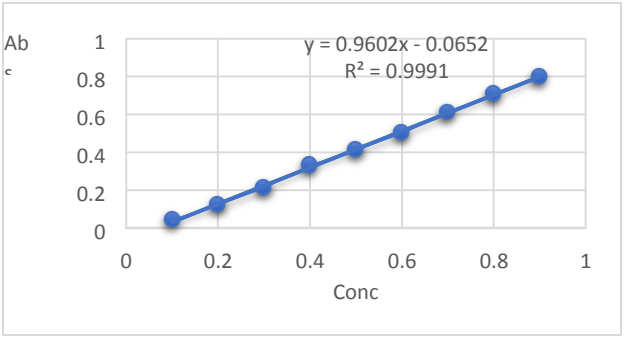
Solubility: The solubility study indicated that amlodipine exhibited higher solubility in peppermint oil (0.2 mg) compared to orange oil (0.1 mg) among lipids, and among surfactants, Tween 20 showed greater solubility (0.2 mg) than Tween 80 and PEG (0.1 mg each), suggesting peppermint oil and Tween 20 as suitable components for formulation.

Analytical methods

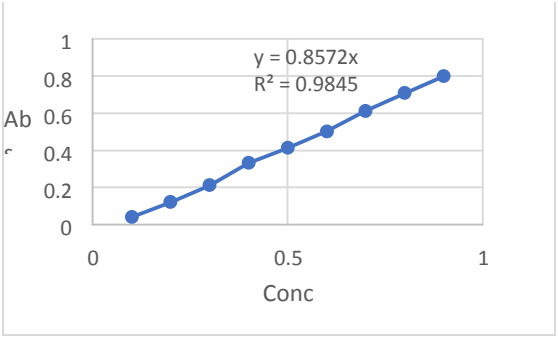
(a) Calibration of amlodipine:



Overlay spectrum of amlodipine



Determination of calibration curve of amlodipine in PBS (pH 7.4)



Determination of calibration curve of amlodipine in PBS (pH 6.8)

Calibration curve values of Amlodipine in methanol solution by UV- spectrophotometer visible

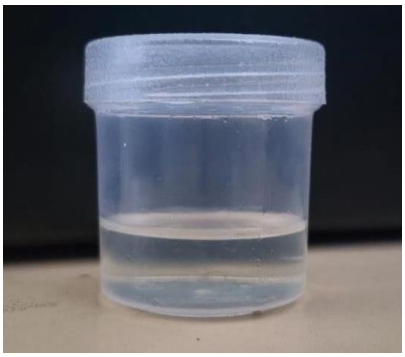
Concentration	Absorbance
0.1	0.408
0.2	0.886
0.3	1.328
0.4	1.904
0.5	2.35
0.6	2.84
0.7	3.277
0.8	3.764
0.9	4.201

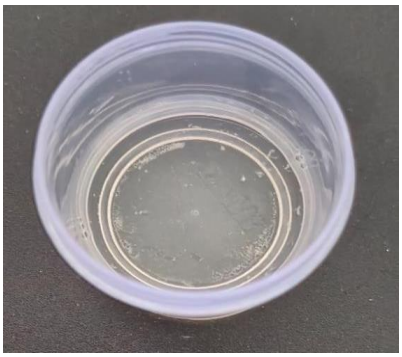
Concentration	Absorbance
0.1	0.04
0.2	0.121
0.3	0.211
0.4	0.331
0.5	0.413
0.6	0.502
0.7	0.611
0.8	0.707
0.9	0.798

Optimization of amlodipine: Box Behnken design was employed for optimization of the formulation. 3 factors and 2 responses were studied. Probe cycles, % oil, and % Surfactant were the independent variables A, B, and C, accordingly. The dependent variables K1 and K2 were % EE, and particle size (nm) accordingly. The effects of fixed factors like temperature, sonication duration, and weighing on reactions. should hold. The impact of independent factors on answers varied along with alterations in their concentration. Additionally, dependent variables and responses are impacted by the interactions between independent factors.

Experimental design

Formulation code	Independent variables			Dependent Variables	
	Probe Cycle	Oil	% surfactant	% EE	Particle Size (nm)
A1	75 min	4	10	97.85	110.7
A2	60 min	2	14	98.05	90.6
A3	60 min	4	12	98.02	130.4
A4	75 min	6	12	97.93	340
A5	75 min	2	12	98.17	116.9
A6	45 min	4	10	98.23	131.5
A7	60 min	6	10	97.67	125.7
A8	45 min	6	12	98.12	364.8
A9	45 min	4	14	98.67	217.2
A10	60 min	2	10	98.36	542.2
A11	75 min	4	14	97.98	100.1
A12	60 min	6	14	98.13	201.9
A13	45 min	2	12	98.33	111.2



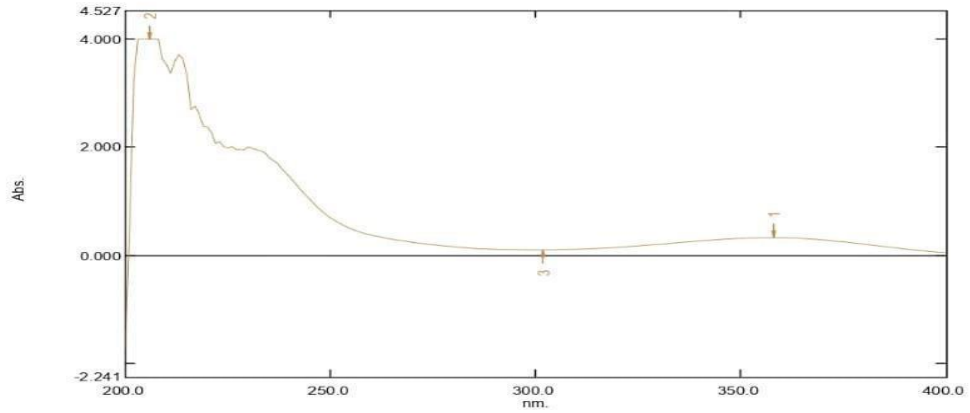


Optimized batch A2

Impact of Formulation of Variables

Drug content %EE

The effect of probe cycle (A), % OF oil (B), and % of Surfactant (C) on the % EE/drug content of amlodipine loaded SNEDDS was demonstrated using a contour plot and a 3D surface response plot. The independent factors exhibited both positive and negative effect on the drug content. According to the quadratic equation, the probe cycle (A) and % oil (B) has a negative influence on the entrapment efficacy of amlodipine loaded SNEDDS but % Surfactant (C) appear to have a positive influence. Batch A7 showed significantly lower amlodipine content while A2 showed highest amlodipine content.



Entrapment efficacy of optimized batch.

ANOVA Quadratic Model for Entrapment Efficacy

Factor coding is **Coded**. Sum of squares is **Type III - Partial**

The **Model F-value** of 5.54 implies the model is significant. There is only a 3.69% chance that an F-value this large could occur due to noise. **P-values** less than 0.0500 indicate model terms are significant. In this case A, AB are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model. The **Lack of Fit F-value** of 10.92 implies there is an 8.50% chance that a Lack of Fit F-value this large could occur due to noise. Lack of fit is bad -- we want the model to fit. This relatively low probability (<10%) is troubling.

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	3.85	9	0.4278	5.54	0.0369	significant
A-Peppermint Oil	1.95	1	1.95	25.27	0.0040	
B-Tween 20	0.4608	1	0.4608	5.97	0.0584	
C-Time	0.0741	1	0.0741	0.9603	0.3721	
AB	0.5112	1	0.5112	6.62	0.0498	
AC	0.1521	1	0.1521	1.97	0.2193	
BC	0.1190	1	0.1190	1.54	0.2694	
A^2	0.3606	1	0.3606	4.67	0.0830	
B^2	0.1264	1	0.1264	1.64	0.2568	
C^2	0.0510	1	0.0510	0.6605	0.4533	
Residual	0.3859	5	0.0772			
Lack of Fit	0.3637	3	0.1212	10.92	0.0850	significant
Pure Error	0.0222	2	0.0111			
Cor Total	4.24	14				

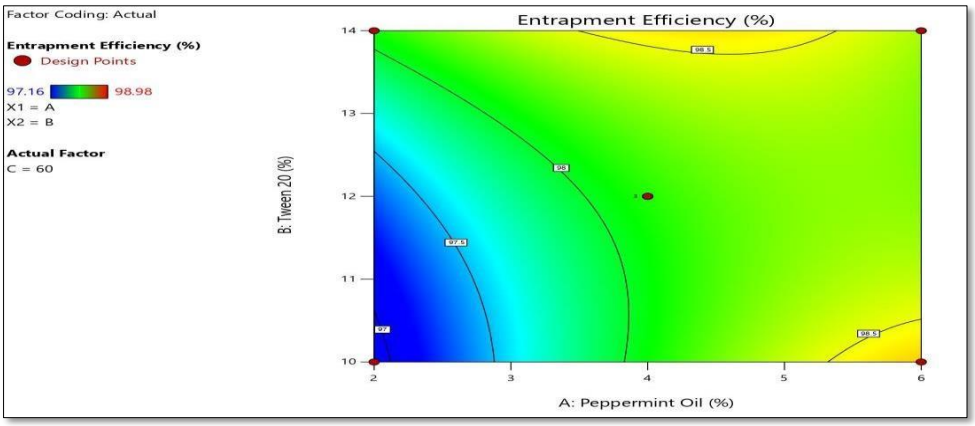
Fit Statistics

Std. Dev.	0.2778	**R^2**	0.9089
Mean	98.12	**Adjusted R^2**	0.7449
C.V. %	0.2831	**Predicted R^2**	-0.3854
		Adeq Precision	8.9496

A negative **Predicted R^a** implies that the overall mean may be a better predictor of your response than the current model. In some cases, a higher order model may also predict better.

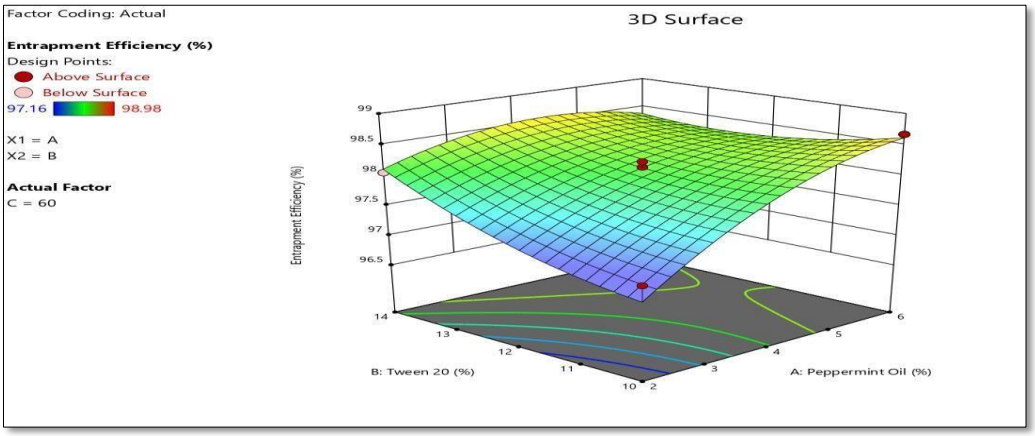
Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 8.950 indicates an adequate signal. This model can be used to navigate the design space.

Final Formula for Coded Factors: With individual impacts of factors A (+0.4937), B (+0.2400), and C (+0.0962), the model displays a baseline value of 98.13, suggesting that all three variables have a favorable impact on entrapment efficiency. The interaction terms show that whereas AC (+0.1950) and BC (+0.1725) have positive contributions, AB has a negative influence (-0.3575). A^2 (-0.3125) and B^2 (-0.1850) have a mixed effect on the reaction, while C^2 (+0.1175) significantly increases it. All things considered, the formula aids in estimating entrapment efficiency and evaluating the proportional influence of formulation variables using coded levels.



Counter

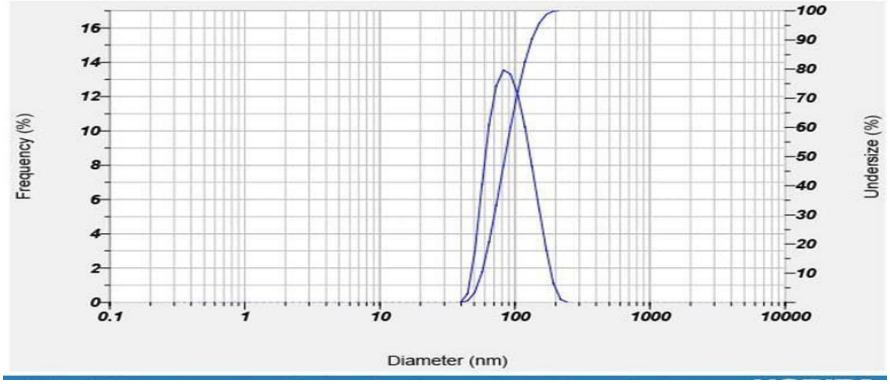
Plot of Entrapment Efficacy



3D surface for Entrapment efficacy

Particle size: Using contour and 3D surface plots, the effects of probe cycle (A), oil concentration (B), and surfactant concentration (C) on the drug content and particle size of amlodipine-loaded SNEDDS were assessed. The findings show that these factors affect the reaction in both positive and negative ways. Probe cycle and oil concentration had a negative effect on entrapment efficiency, but surfactant concentration had a favorable

effect, according to the quadratic model. Among the formulations, batch A2 exhibited the smallest particle size, while batch A10 showed the largest, indicating the significant role of formulation variables in controlling particle size.



Particle size of optimized batch (A2)

Particle size

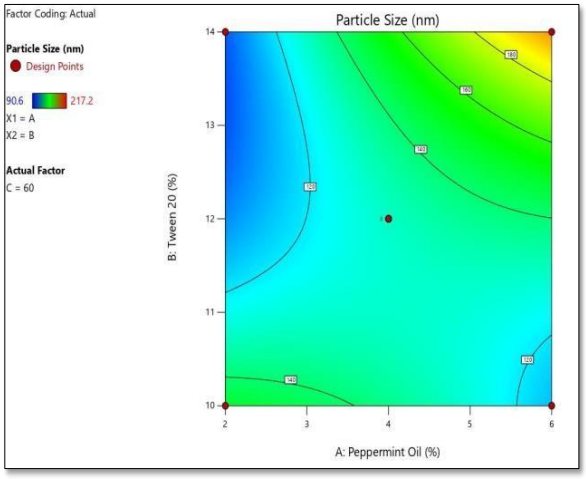
Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	15347.70	9	1705.30	6.55	0.0261	significant
A-Peppermint Oil	1993.96	1	1993.96	7.66	0.0395	
B-Tween 20	741.13	1	741.13	2.85	0.1523	
C-Time	3077.20	1	3077.20	11.82	0.0185	
AB	4303.36	1	4303.36	16.53	0.0097	
AC	652.80	1	652.80	2.51	0.1741	
BC	3340.84	1	3340.84	12.83	0.0158	
A^2	105.52	1	105.52	0.4054	0.5523	
B^2	1058.20	1	1058.20	4.07	0.0998	
C^2	5.73	1	5.73	0.0220	0.8878	
Residual	1301.46	5	260.29			
Lack of Fit	1299.46	3	433.15	431.71	0.0023	significant
Pure Error	2.01	2	1.00			
Cor Total	16649.16	14				

The model was developed using coded factors and evaluated by Type III (partial) sum of squares. The obtained model F-value of 6.55 indicates that the model is statistically significant, with only a 2.61% probability that such a value could arise due to random noise. Analysis of p-values (<0.05) identified factors A, C, and interaction terms AB and BC as significant contributors, whereas other terms were found to be insignificant ($p > 0.10$), suggesting that model reduction may enhance predictive performance. However, the lack of fit was also significant (F-value = 431.71, p = 0.23%), indicating poor agreement between the model and experimental data, and suggesting the need for further model refinement or inclusion of additional terms.

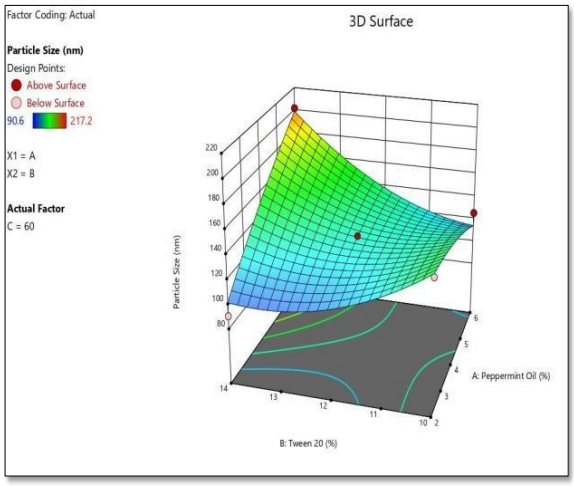
Fit Statistics

Std. Dev.	16.13	**R^2**	0.9218
Mean	134.88	**Adjusted R^2**	0.7811
C.V. %	11.96	**Predicted R^2**	-0.2491
		Adeq Precision	7.8219

With a baseline value of 129.37, the final regression equation in terms of coded factors shows that the main effects (A, B, C), their interactions (AB, AC, BC), and quadratic terms (A^2 B2, C2) all have an impact on particle size. A and B have a positive impact on particle size, while C and interaction terms like BC have a negative impact. Comparing coefficient magnitudes to determine factor importance is made possible by the coded model, which represents high and low values as +1 and -1, respectively. However, the model's poor predictive reliability is indicated by the negative predicted R2, suggesting that the mean response might be a stronger predictor than the model itself. Nevertheless, an adequate signal-to-noise ratio is confirmed by an Adequate Precision value of 7.822 (>4), suggesting that the model can still be utilized to efficiently explore the design space.



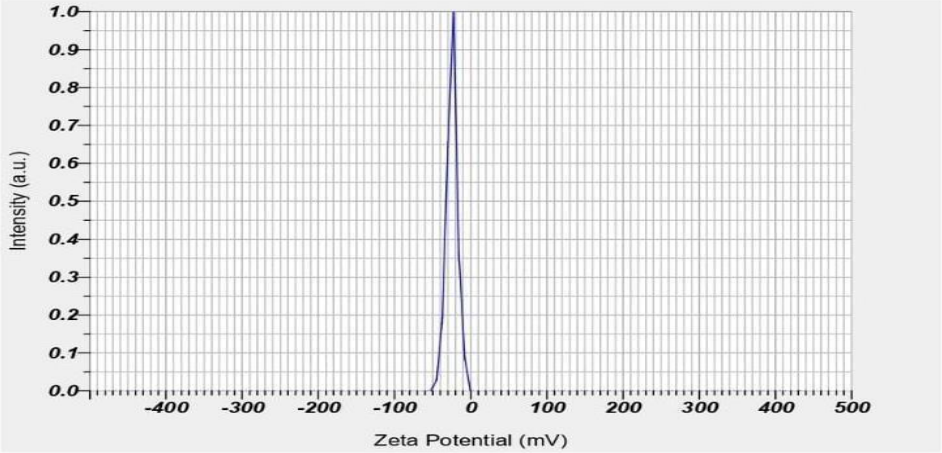
Counter plot of Particle



3D surface for particle size

Description of the SNEDDS formulation loaded with amlodipine

Analysis of Zeta Potential: At 25˚C, the optimized batch (A2) had a zeta potential of -24.5 mV. It was discovered that the zeta potential value was negative, indicating that Amlodipine loaded SNEDDS are highly robust.

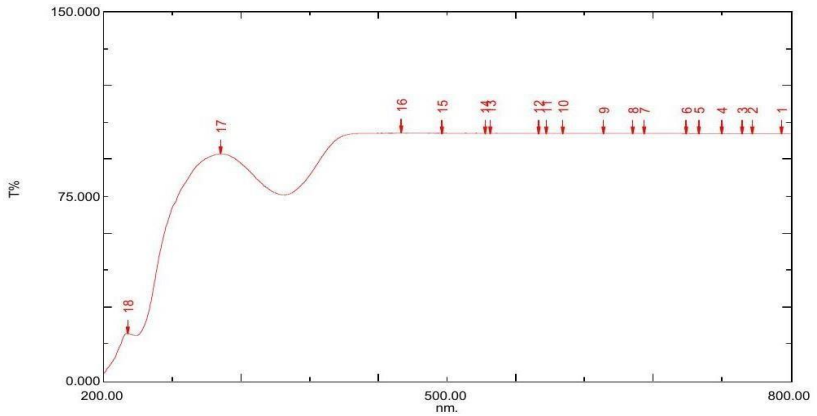


Zeta potential of optimized Amlodipine Loaded SNEDDS

Cloudy Point

The cloud point is a key indicator of SNEDDS stability. For effective in vivo performance, it should be above 70°C. In the optimized formulation, the cloud point was recorded at 83°C ± 1°C, suggesting that the SNEDDS is thermally stable under physiological conditions.

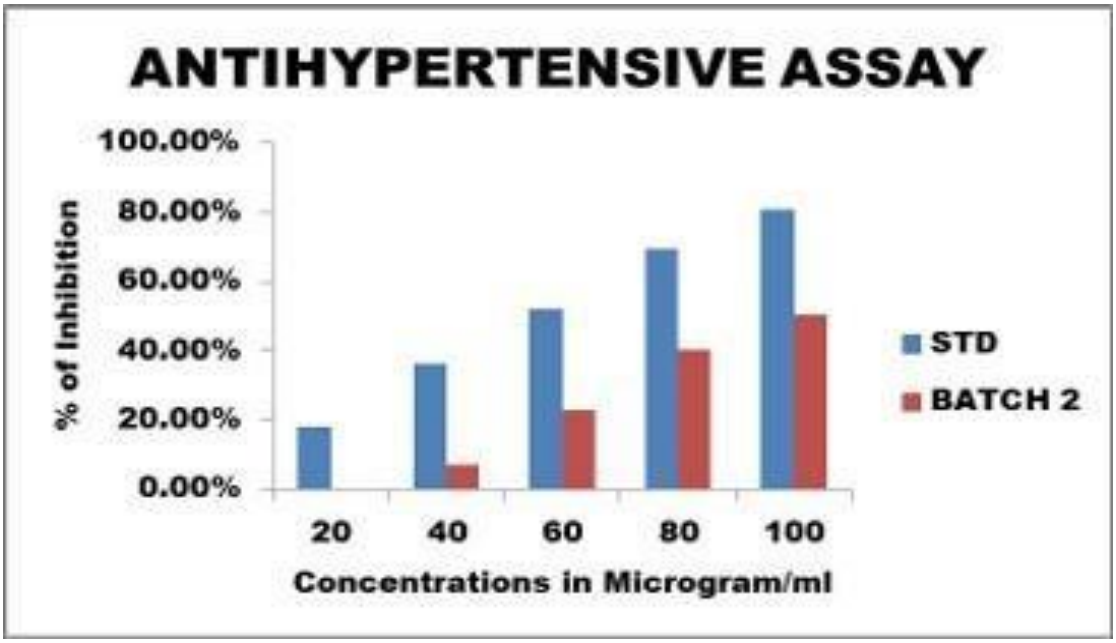
Transmittance: The resulting SNEDDS appeared clear and transparent, with a measured transmittance of 100. 586 at 600 nm and 75.586 at 356 nm. This high level of clarity indicates that the particles within the SNEDDS were very small and evenly distributed, resulting in a uniform solution.



Stability: The improved formulation was kept at 2 – 4 °C for one month. After a month, an improved formulation's % entrapment efficiency, zeta potential, and particle size were assessed. Particle size was slightly increased, entrapment efficiency declined and zeta potential was decreased.

Antihypertensive activity

Sr no	Sample code	Concentration (µg/ml)	Absorbanceat450nm				% Inhibition	IC50 (µg/ml)
			Test1	Test2	Test3	Mean		
1	Control		1.72	1.73	1.70	1.71	-	
2	Standard (Captopril)	20	1.42	1.40	1.38	1.40	18.12%	
		40	1.07	1.10	1.11	1.09	36.25%	57.96
		60	0.81	0.83	0.83	0.82	52.04%	
		80	0.52	0.55	0.50	0.52	69.59%	
		100	0.35	0.32	0.33	0.33	80.70%	
3	Batch 2	20	1.71	1.71	1.70	1.71		
		40	1.59	1.58	1.59	1.59	7.01%	
		60	1.33	1.30	1.33	1.32	22.80%	99.71
		80	1.02	1.02	1.02	1.02	40.35%	
		100	0.85	0.84	0.85	0.85	50.29%	



CONCLUSION

At the different concentrations the sample code Batch 2 shows the good ACE Inhibition activity as compared to standard Captopril. On the basis of inhibition, we can conclude that, test sample has moderately good antihypertensive activity.

CONCLUSION

The present study successfully developed and optimized an amlodipine-loaded Self-Nanoemulsifying Drug Delivery System (SNEDDS) to address the challenges of poor aqueous solubility and limited oral bioavailability associated with the drug. Utilizing the Box-Behnken Design, various formulation parameters were evaluated, and the optimized batch (A2) was prepared using high-speed homogenization and sonication techniques. The optimized formulation exhibited a desirable nano-size droplet diameter of 90.6 nm, with a high entrapment efficiency of 98.05%, indicating excellent drug encapsulation. The zeta potential was found to be –24.5 mV, suggesting good physical stability of the nanoemulsion due to sufficient electrostatic repulsion between droplets. The purity and homogeneity of the nano emulsion were verified by transmittance values of 100.586% at 600 nm and 75.586% at 356 nm, and the cloud point of 83°C showed thermal stability, guaranteeing that the formulation stays stable under physiological settings. Additionally, the new formulation's medicinal relevance was shown by the mild antihypertensive activity shown by the in vitro ACE inhibition assay. Overall, the study found that the SNEDDS methodology greatly improved amlodipine's solubility, stability, and bioavailability, indicating that it is a viable and effective method for oral administration of poorly water-soluble antihypertensive drugs.

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