

**FORMULATION, DEVELOPMENT AND EVALUATION OF SELF NANOEMULSIFYING DRUG  
DELIVERY SYSTEM OF SELECTED DRUGS**

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## INDEX

<b>Sr. No.</b>	<b>Title</b>	<b>Page No.</b>
1	Title of the Thesis	1
2	Abstract	1
3	Brief description of the state of the art of the research topic	1
4	Definition of the problem	2
5	Objective and scope of the work	2
6	Original contribution by the thesis	3
7	Methodology of the Research	3
8	Results of Lercanidipine HCl SNEDDS	5
9	Results of Cinacalcet HCl SNEDDS	8
10	Achievement with respect to objectives	12
11	Conclusion	13
12	Copies of papers published and a list of all publications arising from the thesis	13
13	Patents	13
14	References	13

## 1. TITLE

### FORMULATION, DEVELOPMENT AND EVALUATION OF SELF NANOEMULSIFYING DRUG DELIVERY SYSTEM OF SELECTED DRUGS

## 2. ABSTRACT

BCS Class-II drugs have poor oral bioavailability due to its limited aqueous solubility. Lercanidipine HCl, an antihypertensive orally administered drug belongs to a group of medicines called Calcium Channel Blockers of the third generation as well as Cinacalcet HCl, a calcimimetic orally administered drug with poor aqueous solubility were selected as drug candidates for the research work. In this study, an attempt was made to develop a self nanoemulsifying drug delivery system (SNEDDS) to enhance oral bioavailability of selected drugs. Received complimentary samples of selected drugs were subjected for identification and compatibility study by FTIR. Based on solubility in different solvents and their combinations, oil, surfactant, and co-surfactant were identified for both drugs separately. SNEDDS were prepared using a pseudo-ternary phase diagram method. Various parameters like dispersion time, globule size and drug release etc. were screened for  $3^2$  full factorial design. The optimized formulations of selected drugs were evaluated by various parameters like globule size, polydispersity index, zeta potential, drug content and *in-vitro* drug release study. Optimized formulations were subjected to accelerated stability study according to ICH guidelines. *In vitro* drug release study was also carried out to compare optimized SNEDDS with the available marketed conventional tablet. The results of the present study revealed the prospective use of SNEDDS of poorly water-soluble drug like Lercanidipine HCl and Cinacalcet HCl.

## 3. BRIEF DESCRIPTION ON THE STATE OF THE ART OF THE RESEARCH TOPIC

Hypertension is a major contributor to the global disease burden, occurring as an insidious accompaniment to aging populations [1, 2]. Hypertension management aims to reduce the long-term risk of cardiovascular complications and involves lifestyle modifications and antihypertensive drug therapy. In recent years, increasing attention has been focused on SNEDDS, generally enclosed by soft or hard capsules to facilitate oral administration. The absolute bioavailability of Lercanidipine is about 10%, because of the high first-pass metabolism in the fed condition of the patient.[3] According to the 2004 US Renal Data

Report, >300,000 patients with end-stage renal disease (ESRD) require dialysis. Despite dramatic advances in medicine, the mortality rate for patients with ESRD remains >20% per year [4]. Secondary hyperparathyroidism is a serious complication of dialysis and can lead to renal osteodystrophy and other organ dysfunctions [5, 6]. Cinacalcet is indicated for the treatment of hypercalcemia in patients with parathyroid carcinoma or for secondary hyperparathyroidism in patients with chronic kidney disease who require dialysis [7]. In some embodiments; it was found that the nanoparticulate Cinacalcet compositions exhibit improved bioavailability as compared to known non-nanoparticulate Cinacalcet compositions [8]. In the present study, an attempt was made to enhance the solubility, stability and *in-vitro* drug release of various drugs of BCS class II drug by formulating it as SNEDDS. The formulation was characterized by various parameters for its ability to form nanoemulsion.

#### 4. DEFINITION OF THE PROBLEM

Lercanidipine HCl and Cinacalcet HCl are from BCS class II having log P 6.4 [9] and log P 6.5 [10] respectively making both drugs suitable candidates for the development of SNEDDS. Hence, the aim of the present investigation was to design and formulate SNEDDS of antihypertensive drug Lercanidipine HCl and calcimimetic drug Cinacalcet HCl as oral drug delivery systems to increase *in vitro* drug release; hence its bioavailability, perform the various evaluation studies and to compare with conventional marketed formulations.

#### 5. OBJECTIVES AND SCOPE OF WORK

- To perform the preformulation study of selected BCS Class II drugs.
- To perform scanning and calibration curve preparation of selected drugs.
- To prepare nanoemulsion using Pseudoternary phase diagram method using selected excipients.
- To optimize SNEDDS formulation by  $3^2$  full factorial design.
- To characterize developed SNEDDS by various physicochemical parameters as well as analytical techniques.
- To study *in-vitro* drug release profile of optimized formulation and compare with marketed preparation.
- To perform accelerated stability studies according to ICH guidelines.

## 6. ORIGINAL CONTRIBUTION BY THE THESIS

The entire work in this synopsis, as well as thesis, is the original work, with research papers as the backbone. The details of the associated papers are as follows:

### 6.1. LIST OF PUBLICATIONS

1. Vijay L. Ghor, Dasharath M. Patel, Abdel Omri.

**Formulation and Optimization of Self Nano Emulsifying Drug Delivery System Of Lercanidipine Hydrochloride Using Response Surface Methodology** in International Journal of Pharmaceutical Research And Bio-Science( ISSN- 2277-8713).

IJPRBS, 2017; Volume 6(4): 162-176 (Indexed In Hinari, DOAJ, DRJI, GIF, IIFS, SJIF, GOOGLE SCHOLAR, NEW JOUR, JGATE and more international Database)

2. Vijay L. Ghor, Dasharath M. Patel, Abdelwahab Omri

**Enhancement of Solubility and *in vitro* Drug Release Study for Lercanidipine Hydrochloride Loaded Liquid Self Nano Emulsifying Drug Delivery System using Factorial Design** in International Journal of Pharmaceutical Research(ISSN -0975-2366).

IJPR, 2018; Vol.10 (1):112-119 (indexed in Scopus and listed in [https://www.ugc.ac.in/ugc\\_notices.aspx?id=1604](https://www.ugc.ac.in/ugc_notices.aspx?id=1604) as per GTU guideline)

### 6.2. PAPERS PRESENTED

1. **Development and Characterization of Self Nanoemulsifying Drug Delivery Systems (SNEDDS) of Lercanidipine HCl** at Nootan Pharmacy College, Visnagar, Gujarat, India sponsored by SERB-DST and APTI supported National Conference on 9-10th March 2017

2. **Formulation and optimization of Self Nano Drug Delivery System of Lercanidipine HCl using 3<sup>2</sup> full factorial design** in Pharmavision 2017 at Ahmedabad, Gujarat, India on 9-10th September 2017. Earned 2nd prize.

## 7. METHODOLOGY OF RESEARCH, RESULTS / COMPARISONS

### Screening of components

The most important measurement for the screening of SNEDDS components is the solubility of poorly soluble drug in oils, surfactants, and co-surfactants. In this study excess amount of drug was added to 2 ml of each vehicle separately in the screw-capped glass vial. The mixtures were vortexed for 30 s to facilitate solubilization and shaking (2000 rpm) in a thermostatically controlled water bath at 37°C for 72 h. Then, the mixtures were centrifuged at 10,000×g for 15 min (Eppendorf, NY, USA) and the supernatants were filtered to remove the undissolved drug. 100µL of the supernatant was diluted with methanol and was quantified by using UV spectrophotometry[11].

### **Preparation of SNEDDS**

A series of SNEDDS formulations were prepared using various oils, Surfactants, and Co-surfactants. In all the formulations, the level of Lercanidipine HCl was 10 mg and for Cinacalcet HCl 30 mg was added in the oil phase and solubilized. Then the mixture of surfactant and co-surfactant (Smix) was added in the oil phase, mixed by gentle stirring, vortex mixing, and heating at  $37\pm0.5^{\circ}\text{C}$ . Series of liquid formulations were prepared using various surfactants and cosurfactant concentrations.

### **Drug and surfactant compatibility study**

Compatibility of drugs with oil, surfactant, and co-surfactant was carried out to check the physical and chemical compatibility. Compatibility studies of excipients used in L-SNEDDS were performed using a Perkin-Elmer FTIR machine (Spectrum GX, USA) by scanning from 4000 to 400  $\text{cm}^{-1}$ . The IR spectrum of the formulation mixture was compared with those of API, oil and surfactants and peaks matching were done to detect any drug - excipients incompatibility peaks [12].

All the formulations passed the physical as well as chemical compatibility tests. The formulations did not show any changes during the compatibility studies and were found to be stable. Further studies were carried out using these formulations.

### **Pseudoternary phase diagram**

The existence of nanoemulsions regions was determined by using pseudo-ternary phase diagrams. SNEDDS were diluted under agitation conditions using water titration method. The mixtures of oil and Smix at certain ratios were diluted with water in a drop wise manner. Phase diagrams were constructed in presence of drug to obtain the best concentrations of oil, surfactant, and co-surfactant. SNEDDS form fine oil-water emulsion upon addition to an aqueous media under gentle agitation. Distilled water was used as an aqueous phase for the construction of phase diagrams. The amount of water which, as well as transparency-to-turbidity transitions, was derived from the weight measurements. These values were then used to establish the boundaries of the nanoemulsion area corresponding to the chosen value of oils and Smix ratio [13].

### **3<sup>2</sup> Full factorial design [14-16]**

The effect of the independent variables studied was oil (Capmul MCM) and surfactant: co-surfactant (Polysorbate 20: Transcutol P) ratio denoted as X1 and X2 respectively. The

dispersion time, globule size and % release of the drug were taken as dependent variables and denoted as Y1, Y2, and Y3.

### **Characterization of SNEDDS**

The SNEDDS were characterized for

- Particle size and PDI [17]
- Zeta potential [17]
- *In-vitro* drug release study [18]
- Drug content
- Accelerated stability study as per ICH Guidelines [19]

## **8. RESULTS OF LERCANIDIPINE HCL SNEDDS**

### **Scanning and calibration curve**

Lercanidipine HCl Scanning and the calibration curve was prepared in methanol in the range of 2.5-25µg/ml by UV-Visible spectrophotometer showed  $\lambda_{\text{max}}$  at 236 nm and the regression equation was found to be  $y = 0.041x - 0.022$  with regression co-efficient 0.999

### **Screening of Components**

Based on the solubility of Lercanidipine HCl and combination of oil/surfactant and co-surfactant Capmul MCM ( $26.39 \pm 1.32$ ) Polysorbate 20 ( $24.49 \pm 1.68$ ) and Transcutol P ( $30.29 \pm 0.24$ ) were selected respectively for the development of the formulation.

### **Drug and surfactant compatibility study**

All the formulations passed the physical as well as chemical compatibility tests. The formulations did not show any changes during the compatibility studies and were found to be stable. Further studies were carried out using these formulations.

### **Pseudoternary phase diagram**

Self-Nanoemulsifying formulation generates fine oil-water emulsions with only gentle shakeup, upon their introduction into the aqueous phase. Pseudoternary phase diagram of Capmul MCM (oil), Polysorbate 20/ Transcutol P(S/Cos) revealed that 1:1 ratio as wider Nanoemulsion area.

### **Preliminary Trials**

Preliminary batches were formulated and their results of dispersion status and dispersion time were recorded.

### **Factorial design**

Oil and S: CoS ratio was selected as independent factors X1 and X2 respectively. Dispersion time (Y1), Globule size (Y2), Drug release (Y3) were selected as dependent factors for 3<sup>2</sup> factorial for optimization of the formulation. By using Design Expert software LS-5 was found to be the optimized batch. The formulation found robust upon dilution up to 3000x with distilled water

### **Cloud point**

The cloud point should be above 37°C. In this study, the cloud point of the optimized formulation was found 80 °C.

### **Accelerated Stability Tests: Centrifugation and Freeze-Thaw Cycle**

Optimised formulation of SNEDDS survived for freeze-thaw cycling as it was reconstituted without any phase separation and no drug precipitation after exposure to freeze-thaw cycling.

### **Dispersion time, Globule size, Zeta potential and PDI**

A perfect SNEDDS formulation should possess the ability to disperse completely and quickly when subjected to dilution under mild agitation. Dispersion time of optimized formulation was 36 seconds. The globule size of the emulsion is a key factor in self-emulsification performance as it determines the rate, extent of drug release and drug absorption. Also, it has been reported that the smaller globule size of the emulsion droplets may lead to more rapid absorption and improve the bioavailability. The optimal batch was LS-5 with mean globule size 50 nm in water. Emulsion droplet polarity is also a very important factor in characterizing emulsification efficiency. Since zeta potential signifies the degree of repulsion between neighboring, like charged particles in the dispersion, it can be related to the stability of colloidal dispersions. The optimal batch LS-5 has the least zeta potential i.e. -24.12 mV which is the highest zeta potential towards the negative side. The zeta potential governs the stability of Nanoemulsion, it is important to measure its value for the stability of samples. A negative force means a negative potential between the droplets. The PDI observed with LS-5 was 0.267.

### ***In- vitro* drug release study**

The drug release profile for formulations LS-1 to LS-9 revealed that the formulation LS-5 showed the highest release rate among all the liquid SNEDDS formulations i.e. 96.19 % in 60 min which is highest among all batches. Thus, the *in-vitro* study concludes that the release of Lercanidipine HCl was greatly enhanced by SNEDDS formulation. The batch LS-5 was thus taken for further studies and comparison.



SNEDDS, marketed tablet, and API released 96.19 %, 74.85 % and 46.51 % of Lercanidipine HCl respectively in 60 min. The dramatic increase in the rate of release of Lercanidipine HCl from SNEDDS compared to pure drug indicated quick dispersibility and ability to keep the drug in the solubilized state.

*In-vitro* drug release studies revealed the faster rate of drug release from SNEDDS. From the results of *in vitro* study, we may be concluded that the SNEDDS formulation has approved to be superior. Thus the development of SNEDDS is the promising approach for improving the oral bioavailability of poorly soluble drugs.

### **Stability study**

The stability study of the formulation is carried out according to ICH guidelines at long-term condition ( $25\pm 2^{\circ}\text{C}/60\pm 5\%\text{RH}$ ) and accelerated condition ( $40\pm 2^{\circ}\text{C}/75\pm 5\%\text{RH}$ ) for six months by storing the SNEDDS in the respective stability chamber. The samples were evaluated at 0, 3 and 6 months for physical appearance, average particle size, and zeta potential. The developed formulations were found to be stable. No change in the physical appearance of the formulation was observed during the stability studies. No significant change in the Z-average size and zeta potential were observed.

### **Optimization of Formulation Variables**

$3^2$  factorial design was employed for optimization of formulation variables and Design Expert Software was used for statistical analysis by ANOVA, generating model equations and constructing contour plots and 3D surface plots for each response. Amount of drug with respect to lipid and concentration of surfactant were investigated as independent variables at three levels and the critical quality attributes selected were dispersion time, particle size and percentage release of drug as responses. A total of 9 experiments were designed by the software with 2 centre points. Experiments were run in random order to increase the predictability of the model. ANOVA was also applied to determine the significance and the magnitude of the effects of the formulation variables and their interactions. ANOVA for Response 1 (Dispersion time), Response 2 (Particle size) and Response 3 (% drug release) indicated that Quadratic best fits for dispersion time, particle size, and % drug release. P-values were found less than 0.05 indicated model terms to be significant.

### **Experimental validation of design space**

Experimental validation of DoE trials for formulation variables was undertaken by formulation and characterization of nanoemulsion at the checkpoint batch suggested by the software. The observed values (Dispersion time 36 min, Particle size 50nm and drug release

96.19 % ) were comparable with the predicted values (Dispersion time 37.11 Particle size 64.67 nm, drug release 94.39 %) establishing the reliability of the optimization procedure.

### **Evaluation by response surface methodology**

#### **A. Dispersion time response**

The Model F-value of 47.74 implies the model is significant. There is only a 0.46% chance that a "Model F-Value" this large could occur due to noise. P value was found to be 0.0046, with a value less than 0.0500 indicating model terms are significant.

"Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. The ratio of 19.100 indicates an adequate signal. This model can be used to navigate the design space.

#### **B. Globule size response**

The Model F-value of 65.19 implies the model is significant. There is only a 0.29% chance that a "Model F-Value" this large could occur due to noise. P value was found to be 0.0029, with a value less than 0.0500 indicating model terms are significant.

"Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. The ratio of 20.733 indicates an adequate signal thus the proposed model can be used to navigate the design space.

#### **C. Percentage release of drug response**

The Model F-value of 9.20 implies the model is significant. There was only a 4.86 % chance that a "Model F-Value" this large could occur due to noise. P value was found to be 0.0486, with a value less than 0.0500 indicating model terms are significant.

Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. The ratio of 9.191 indicates an adequate signal. This model can be used to navigate the design space.

Since the values of  $r^2$  are relatively high for all the responses, i.e., 0.9876 for dispersion time, 0.9909 for globule size and 0.9388 for % release polynomial equations form an excellent fit to the experimental data and are highly statistically valid.

## **9. RESULTS OF CINACALCET HCL SNEDDS**

### **Scanning and calibration curve**

Cinacalcet Hydrochloride Scanning and the calibration curve was prepared in methanol in the range of 2.5-60 µg/ml by UV-Visible spectrophotometer showed  $\lambda_{max}$  at 281 nm and the regression equation was found to be  $y = 0.015x + 0.020$  with regression co-efficient 0.999

### **Screening of components**

Based on the solubility of Cinacalcet HCl and the combination of oil, surfactant and co-surfactant Capmul MCM ( $111.40 \pm 2.00$  mg/ml) Polysorbate 80 ( $19.80 \pm 0.73$  mg/ml) and PEG 400 ( $46.00 \pm 0.24037$  mg/ml) were selected respectively for the development of the formulation.

### **Drug and surfactant compatibility study**

All the formulations passed the physical as well as chemical compatibility tests. The formulations did not show any changes during the compatibility studies and were found to be stable. Further studies were carried out using these formulations.

### **Pseudoternary phase diagram**

Self-Nanoemulsifying formulation generates fine oil-water emulsions with only gentle shakeup, upon their introduction into the aqueous phase. Pseudoternary phase diagram of Capmul MCM (oil), Polysorbate 80/ PEG 400 (S/Cos) revealed a 2:1 ratio as wider Nanoemulsion area.

### **Preliminary Trials**

Preliminary batches were formulated and their results of dispersion status and dispersion time were recorded.

### **Factorial design**

Oil and S: CoS ratios were selected as independent factors X1 and X2 respectively. Dispersion time (Y1), Globule size (Y2) and drug release (Y3) was selected as dependent factors for  $3^2$  full factorial design for optimization of the formulation. By using Design Expert software CS-7 was found to be the optimized batch. The formulation found robust upon dilution up to 3000x with distilled water

### **Cloud point**

The cloud point should be above 37°C. In this study, the cloud point of optimized formulation was to be 76°C.

### **Accelerated Stability Tests: Centrifugation and Freeze-Thaw Cycle**

Optimised formulation of SNEDDS survived for freeze-thaw cycling as it was reconstituted without any phase separation and no drug precipitation after exposure to freeze-thaw cycling.

### **Dispersion time, Globule size, Zeta potential and PDI**

A perfect SNEDDS formulation should possess the ability to disperse completely and quickly when subjected to dilution under mild agitation. Dispersion time of optimized formulation was found 54 seconds. The globule size of the emulsion is a key factor in self-emulsification performance as it determines the rate, extent of drug release and drug absorption. Also, it has

been reported that the smaller globule size of the emulsion droplets may lead to more rapid absorption and improve the bioavailability. The optimal batch was CS-7 with mean globule size 13.4nm nm in water. Emulsion droplet polarity is also a very important factor in characterizing emulsification efficiency. Since zeta potential signifies the degree of repulsion between neighboring, like charged particles in the dispersion, it can be related to the stability of colloidal dispersions. The optimal batch CS-7 has the least zeta potential i.e. -25.42 mv which highest zeta potential towards the negative side. The zeta potential governs the stability of nanoemulsion, it is important to measure its value for the stability of samples. A negative force means a negative potential between the droplets. The PDI observed with CS-7 was 0.271.

### ***In- vitro* drug release study**

The drug release profile for formulations CS-1 to CS-9 revealed that the formulation CS-7 showed highest release rate among all the liquid SNEDDS formulations i.e. 97.18 % in 75min which is highest among all batches. Thus, the *in-vitro* study concludes that the release of Cinacalcet HCl was greatly enhanced by SNEDDS formulation. The batch CS-7 was thus taken for further studies and comparison.

SNEDDS, marketed tablet, and API released 97.18 %, 80.76 % and 36.01 % of Cinacalcet HCl respectively. The dramatic increase in the rate of release of Cinacalcet HCl from SNEDDS compared to pure drug and tablet indicates quick dispersibility and ability to keep the drug in the solubilized state.

*In vitro* drug release studies revealed a faster rate of drug release from SNEDDS. From the results of *in vitro* study, we may conclude that the SNEDDS formulation has approved to be superior. Thus the development of SNEDDS is the promising approach for improving the oral bioavailability of poorly soluble drugs.

### **Stability study**

The stability study of the formulation is carried out according to ICH guidelines at long-term condition ( $25\pm 2^{\circ}\text{C}/60\pm 5\%\text{RH}$ ) and accelerated condition ( $40\pm 2^{\circ}\text{C}/75\pm 5\%\text{RH}$ ) for six months by storing the SNEDDS in the respective stability chamber. The samples were evaluated at 0, 3 and 6 months for physical appearance, average particle size, and zeta potential. The developed formulations were found to be stable. No change in the physical appearance of the formulation was observed during the stability studies. No significant change in the Z-average size and zeta potential were observed.

### **Optimization of Formulation Variables**

$3^2$  full factorial design was employed for optimization of formulation variables and Design Expert Software was used for statistical analysis by ANOVA, generating model equations and constructing contour plots and 3D surface plots for each response. Amount of drug with respect to lipid and concentration of surfactant were investigated as independent variables at three levels and the critical quality attributes selected were dispersion time, particle size and percentage release of drug as responses. A total of 9 experiments were designed by the software with 2 centre points. Experiments were run in random order to increase the predictability of the model. ANOVA was also applied to determine the significance and the magnitude of the effects of the formulation variables and their interactions. ANOVA for Response 1 (dispersion time), Response 2 (Particle size) and Response 3 (% drug release) indicated that Quadratic best fits for dispersion time, particle size, and % drug release. P-values less than 0.05 indicated model terms to be significant.

### **Experimental validation of design space**

Experimental validation of DoE trials for formulation variables was undertaken by formulation and characterization of nanoemulsion at the checkpoint batch suggested by the software. The observed values (Dispersion time 54 min, Particle size 13.4 nm and drug release 97.18 %) were comparable with the predicted values (Dispersion time 52.92 Particle size 12.39 nm, drug release 97.00 %) establishing the reliability of the optimization procedure.

### **Evaluation by response surface methodology**

#### **A. Dispersion time response**

The Model F-value of 30.58 implies the model is significant. There is only a 0.89% chance that a "Model F-Value" this large could occur due to noise. P value was found to be 0.0089, with a value less than 0.0500 indicating model terms are significant.

The Predicted  $R^2$  of 0.7679 is in reasonable agreement with the Adjusted  $R^2$  of 0.9487; i.e. the difference is less than 0.2.

"Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. The ratio of 15.016 indicates an adequate signal. This model can be used to navigate the design space.

## **B. Globule size response**

The Model F-value of 19.62 implies the model is significant. There is only a 1.69% chance that an F-value this large could occur due to noise. P value was found to be 0.0169, with a value less than 0.0500 indicating model terms are significant.

The Predicted  $R^2$  of 0.7218 is in reasonable agreement with the Adjusted  $R^2$  of 0.9209; i.e. the difference is less than 0.2.

"Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. The ratio of 12.172 indicates an adequate signal thus the proposed model can be used to navigate the design space.

## **C. Percentage release of drug**

The Model F-value of 47.76 implies the model is significant. There was only a 0.46 % chance that a "Model F-Value" this large could occur due to noise. P value was found to be 0.0046, with a value less than 0.0500 indicating model terms are significant.

The Predicted  $R^2$  of 0.8919 is in reasonable agreement with the Adjusted  $R^2$  of 0.9669; i.e. the difference is less than 0.2.

Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. The ratio of 20.941 indicates an adequate signal. This model can be used to navigate the design space.

Since the values of  $r^2$  are relatively high for all the responses, i.e., 0.9808 for dispersion time and 0.9703 for globule size, and for % release 0.9876 polynomial equations form an excellent fit to the experimental data.

## **10. ACHIEVEMENTS WITH RESPECT TO OBJECTIVES**

- The solubility of both BCS class II drug enhanced.
- FTIR study indicates that all the excipients used are compatible.
- The Globule size (less than 100nm), zeta potential (toward the highest negative side) and PDI (less than 0.3) of optimal formulations fit in criteria of SNEDDS.
- The  $3^2$  full factorial design was applied for the SNEDDS formulations. The data shows that values are strongly dependent on the selected independent variables.
- The *in-vitro* study concludes that releases of drugs were greatly enhanced by SNEDDS formulation.
- The optimal formulations had the maximum release rate as compared to the marketed drugs and pure drugs.
- Stability studies revealed that formulations were stable.

## 11. CONCLUSION

It was observed that dispersion time increased with increase in drug-to-lipid ratio and decrease with the concentration of surfactant. Particle size was also observed to reduce with an increase in surfactant concentration. This may be because high concentrations of the surfactant would have reduced the surface tension and facilitated the particle partition. It was observed that S:CoS ratio had a positive effect on % release. The result obtained from the current study, it can be concluded that the proposed objective of the present research work of enhancing bioavailability of Lercanidipine HCl and Cinacalcet HCl of BCS Class II drugs achieved and it can be applied for other drugs of the BCS class II.

## 12. COPIES OF PAPERS PUBLISHED AND A LIST OF ALL PUBLICATIONS ARISING FROM THE THESIS

As per point 6.1 and 6.2

## 13. PATENTS (IF ANY) ----- NA-----

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