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Development and Optimization of Self-Microemulsifying Drug Delivery System (SMEDDS) for Improved Carbamazepine Delivery

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ABSTRACT

The present study aims to develop and optimize the self-microemulsifying drug delivery system (SMEDDS) of carbamazepine to improve the solubility and hence the in vitro drug release. The SMEDDS was developed using Capryol 90 (oil), Tween-80 (surfactant), and Transcutol (cosurfactants). The results indicated that the maximum drug entrapment was found to be 99.96% while minimum encapsulation of 93.95%. The optimum formulation had a droplet size of 8.57 nm, zeta potential as -27.3mV and cumulative drug release was over 90%.
The results of in-vitro dissolution study were fitted into various kinetic models. The drug's release process was identified as first-order, followed by Korsmeyer-Peppas kinetics. The release data for the optimized batch of CBZ (CBZ-OPT) in 0.1N HCl & Simulated Gastric Fluid were compared with the marketed formulation. The results showed that the drug release from the optimized formulation was significantly higher as compared to the commercial formulation. Overall, this paper demonstrates the improved efficacy of carbamazepine- loaded SMEDDS with improved dissolution. Current studies suggest that SMEDDS plays an important role in improving the dissolution of the poorly soluble drug Carbamazepine.

Keywords: *Carbamazepine; Bioavailability, Ternary phase diagram, SMEDDS, Self-micro emulsifying drug delivery systems; Epilepsy*

INTRODUCTION:

This study aims to develop and optimize the self-micro emulsifying drug delivery system (SMEDDS) of carbamazepine to improve the solubility and thus the in vitro drug release of the drug carbamazepine is an anticonvulsant drug primarily used to treat epilepsy and related neuropathic pain. It is a BCS Class II drug. It is used as a complement to other medications in schizophrenia and as a second-line agent in bipolar disorders.

MATERIAL AND METHODS:

Materials:
A gift sample of pure carbamazepine was obtained from Sun Pharmaceutical Industries Limited, Gurugram. PEG 400 and Propylene glycol were kindly supplied by Siddhi Vinayak Industries, Ahmedabad. Transcutol was procured from Sigma Aldrich, Germany. Capryol 90 was procured from Gattefosse Pharmaceuticals, Mumbai. Tween 80 was procured from Dev International, Ahmedabad, India. Additionally, other materials and reagents used in this study were of analytical grade.

Methods:

Solubility analysis of Carbamazepine was investigated to choose the vehicle in which drug is most soluble. This vehicle would be considered most appropriate for formulating SMEDDS. Solubility of CBZ was evaluated in several oils, surfactants and co-surfactants. In order to assess the solubility, excess of Carbamazepine was added to selected surfactants, co-surfactants and oils. This mixture was stirred on a wrist action shaking machine (Macro Scientific Works, Delhi, India) for up to 48 h. Samples were centrifuged for 10 minutes. After appropriate dilution using methanol, the supernatant aliquot was analyzed for the drug Carbamazepine via UV-spectrophotometer (Shimadzu 1800, Kyoto, Japan) at 284 nm [1].

The result as a straight line in the chosen concentration range revealed that the drug obeyed Beer's Lambert law.

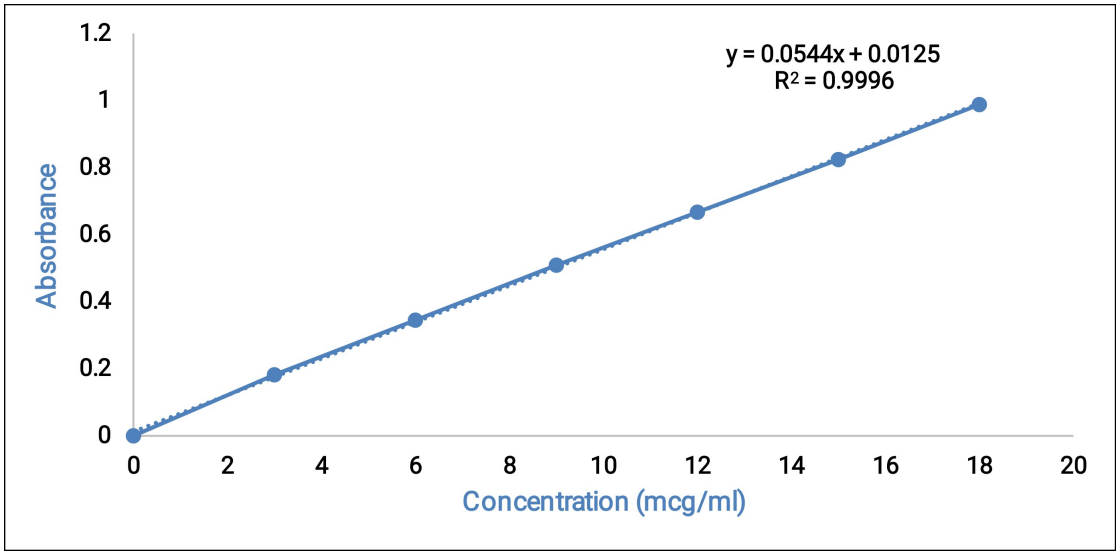

Figure 1: Standard Curve of (CBZ) Carbamazepine in Methanol

Pseudoternary Phase Diagrams

The borderlines of the microemulsion region were established using a pseudo-ternary diagram. Phase diagrams were created to establish the ideal concentration of oil, surfactant, and co-surfactant, as well as to study the largest existing region of micro emulsion. After conducting solubility and emulsification tests, a ternary phase diagram was created by combining capryol 90 as Oil, tween-80 as surfactant, and transcutol as a co-surfactant. Each part of the triangle showed the highest point.

Blank SMEDDS formulations were prepared for each component by altering concentrations of oil, surfactant, and co-surfactant. The efficiency of microemulsion formation was finalized by addition of 10 µL of this mixture slowly to 10 mL of (DW) distilled water. This was then lightly stirred using a magnetic stirrer. The droplet size of the microemulsion was measured using photon correlation spectrometry. This was done to ensure that the droplets were formed naturally, without any external influence. The S_{mix} ratio which has shown maximum microemulsion area was selected for further optimization study [2].

Preparation of Carbamazepine loaded SMEDDS using DOE - Design of Experiments

The blank formulations were created by mixing oil, surfactant, and cosurfactant. The mixtures were mixed vigorously to create a clear and uniform solution. The CBZ-loaded SMEDDS formulations were created by integrating 10.0 mg of CBZ into 100 µl of blank SMEDDS formulation.

Various statistical designs have been used for experimentations and investigations. D-optimal mixture design is the most widely used model for optimizing SMEDDS. To establish the optimized formulation, D-optimal mixture design was finalized. Capryol 90 (X1), Tween 80 (X2), and Transcutol (X3) were the independent variables. These are considered as the important factors for self-micro emulsification. The base design allowed 16 experiments to fit a cubic model, hence 16 formulations were prepared [2-3]. To formulate the same, following variables were selected:

- First Response Variable (Y1): Mean Droplet Size
- Second Response Variable (Y2): Percentage (%) of drug released in 15 mins

Component	Vehicle	Range (%)	
		Minimum	Maximum
Oil (X1)	Capryol 90	5	20
Surfactant (X2)	Tween 20	20	60
Cosurfactant (X3)	Transcutol	30	70

Table 1: Variables considered in the D-optimal Mixture Design

S. No.	Capryol 90 (Oil) (% v/v)	Tween 80 (Surfactant) (% v/v)	Transcutol (Co-surfactant) (%v/v)
F1	5	25	70
F2	5.58	48.43	45.97
F3	8.20	52.90	38.88
F4	20	20	60
F5	14.74	27.12	58.13
F6	13.33	34.88	51.78
F7	5	60	35
F8	10	60	30
F9	15.13	48.24	36.61
F10	20	35.13	44.86
F11	20	20	60
F12	7.01	41.67	51.30
F13	5	34.0417	60.9583
F14	20	41.45	38.55
F15	20	50	30
F16	10	20	70

Table 2: Formulation design of Carbamazepine (CBZ) SMEDDS

Rheological Study:

Brookfield viscometer (Brookfield DV-E viscometer) with Spindle No 40 and rpm 12 was used to determine the viscosity of SMEDDS formulation.

Drug content:

In a volumetric flask, were SMEDDS equivalent to 100mg taken. These SMEDDS were dissolved in 100ml of glacial acetic acid. The solution was then filtered. Approx. 1ml was pipetted out and was then transferred to

100ml volumetric flask. This was then diluted upto mark with glacial acetic acid. The solution was analyzed via spectrophotometer at 284nm. Using standard calibration curve, the amount or content of Carbamazepine was determined in the SMEDDS formulation.

***Zeta potential**:*

SMEDDS formulation (20 µL) containing CBZ was diluted in 1000 µL of double-distilled water. This microemulsion was transferred to the cuvette after gentle shaking, and the zeta potential was measured (Malvern, UK).

In-vitro release studies:

In-vitro release tests were performed as per USP XXIV. 0.1N HCl and simulated gastric fluid (SGF) pH 1.2 was used as dissolution medium. Following parameters were fixed in the apparatus:

- Volume: 500 mL
- Temperature: 25°C.
- Speed: 100 rpm.
- Time intervals for sampling: 10, 20, 30, 40, 50, 60, 80, 100 & 120 min
- The dissolution was conducted using dialysis bag.

Prior to initiation of release experiment, the dialysis bag was pretreated for 24 hours by soaking it in the dissolution media. Carbamazepine loaded microemulsion was kept in a dialysis bag containing 5 mL of the dissolution medium. 1 mL sample was removed at predefined intervals. Sink conditions were maintained by replacing the defined amount of dissolution medium into the apparatus. The amount of drug content is the samples was then analyzed using U.V visible spectrophotometric method at 284 nm [4].

Release Kinetic Study

The findings from the in-vitro dissolution study were incorporated into the kinetic models. The purpose of the study was to investigate the process of drug release from the self-micro emulsifying formulation. [6].

Transmission electron microscopy

The morphology and structure of the droplets from the optimized formulation was examined using a TEM i.e. transmission electron microscope using acceleration voltage as 80 kV (JEM 1010, Tokyo, Japan). The final formulation was then diluted with water (1:1,000). A droplet of this sample was placed on a copper mesh. This was dried and was examined at 25°C [5].

Stability Studies

The physical stability of the SMEDDS formulation is critical and is of utmost importance. The stability can be affected due to precipitation of the drug in an excipient matrix. Improper physical stability of the formulation can lead to phase separation of excipients that affects bioavailability, as well as therapeutic efficacy. To ensure that the formulation is physically stable, data was generated by exposing the formulation to following cycles:

- *Heating Cooling Cycle*: 6 cycles of heating and cooling were conducted. The formulation was exposed at each temperature i.e., temperature ranging from 4°C i.e., refrigerator temperature to 45°C, for no less than 48 hours. Following their stability, those formulations underwent centrifugation.

- *Centrifugation*: Formulations that successfully complete the above-mentioned heating-cooling cycle were spun for a period of 30 minutes at 3500 rpm. Formulations that did not show phase separation were selected for freeze-thaw testing.

- *Freeze-thaw Stress Cycle*: Formulations were subjected to 3 cycles of freezing and thawing between a temperature range 21°C - 25°C by storing at each temperature for at least 48 hours. Formulations that pass this test exhibit excellent stability without cracking, creaming, or phase separation [4].

RESULTS AND DISCUSSION

Pseudo ternary Phase Diagrams

To decide the suitability of ingredients in SMEDDS formulations, a pseudo-ternary phase model was developed in the drug-free condition. Capryol 90 was used as oil component, Tween 80 as surfactant, and Transcutol as a cosurfactant. The objective was to calculate the proportion of each component for the formulation. The dark grey area of the SMEDDS domain was created using oil volume ratios from 5% to 20% and surfactant/co-surfactant ratios from 10% to 80%.
This resulted in a homogenous dispersion which was transparent and clear. The dark gray area symbolized SMEDDS region where the presence was less clear or had a bluish white hue. This SMEDDS region was used to further investigations as it was found to have the highest self-emulsifying capacity. It was noticed that unstable emulsions were created when the concentration of oil exceeded 50% of the formulation. Additional experiments were conducted by incorporating 10.0 mg of CBZ into 100 µl of the chosen SMEDDS system. Certain formulations with a low ratio of surfactant to cosurfactant resulted in the formation of cbz precipitation.

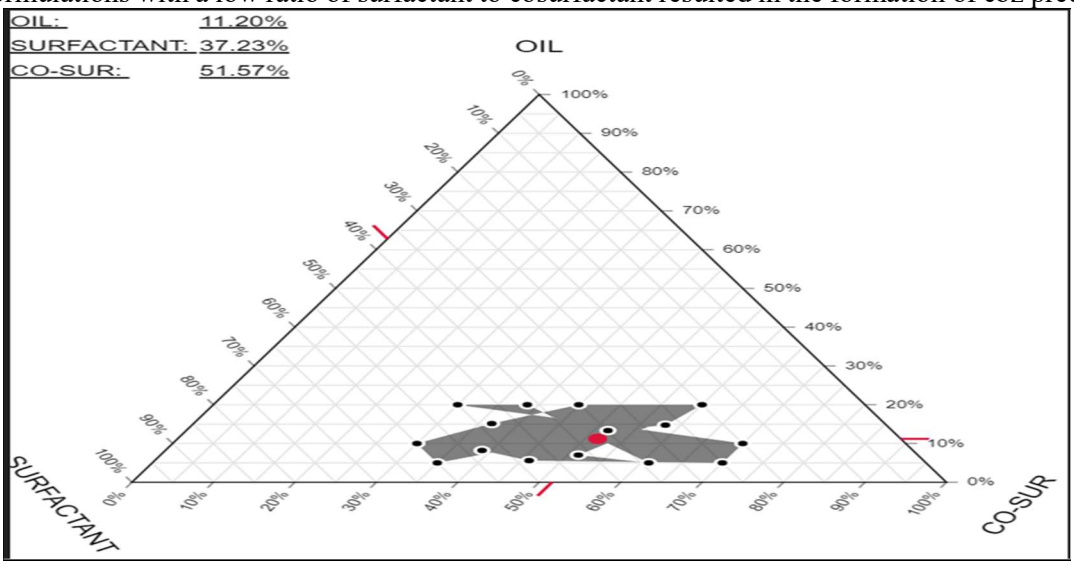

Figure 2: Pseudo ternary phase diagram

Rheological Study:

Brookfield's viscometer was used to determine the viscosity of SMEDDS formulation. The viscosity of formulation batches ranged between 330.5 - 978.7 cps.

Drug content:

The results indicated that the maximum drug entrapment was found to be 99.96% for batch F7 while minimum entrapment of 93.95% was found with F4.

Zeta potential:

The zeta potential analysis was performed for all batches using the Malvern zeta sizer. The results are depicted below:

S. No	Formulation Code	% Drug content	Zeta potential mean (mV)	Viscosity
1.	F1	94.52	-29.42	552.5
2.	F2	99.87	-32.31	606.2
3.	F3	94.28	-35.54	422.7
4.	F4	93.95	-30.82	978.7
5.	F5	95.31	-21.43	886.6
6.	F6	97.69	-33.59	594.5
7.	F7	99.96	-27.38	458.5
8.	F8	99.27	-30.17	493.2
9.	F9	96.12	-33.11	799.4
10.	F10	94.43	-41.36	962.2
11.	F11	95.67	-35.24	330.5
12.	F12	98.85	-32.61	512.3
13.	F13	96.91	-30.91	747.1
14.	F14	97.38	-27.12	664.8
15.	F15	94.91	-33.82	918.5
16.	F16	95.82	-34.73	825.8

Table 3: Results for the various parameters of microemulsion batches (F1-F16)

In-vitro release studies:

After analysing the findings from the in-vitro drug release studies, a graph was created to visually represent the percentage of drug released over time. The findings revealed that the drug release from the final formulation was significantly higher than that of the marketed formulation. The formulation exhibited a 96.1% release rate. The in-vitro release data for the optimized batch of Carbamazepine (CBZ-OPT) in 0.1N HCl & Simulated Gastric Fluid is presented in the table below

S. No.	Time (hrs)	0.1 N HCl	Simulated Gastric Fluid
1.	0	0.00±0.00	0.00±0.00
2.	5	42.765±0.028	43.674±0.032
3.	10	67.384±0.036	68.932±0.026
4.	15	90.115±0.021	91.287±0.037
5.	20	89.439±0.038	90.558±0.041
6.	30	87.578±0.035	89.672±0.037
7.	60	85.849±0.029	87.365±0.032
8.	80	85.627±0.035	86.693±0.023
9.	100	84.741±0.041	85.788±0.038
10.	120	83.126±0.035	84.983±0.044

Table 4: In-vitro release data for Carbamazepine (CBZ-OPT) in 0.1 N HCl & Simulated Gastric Fluid

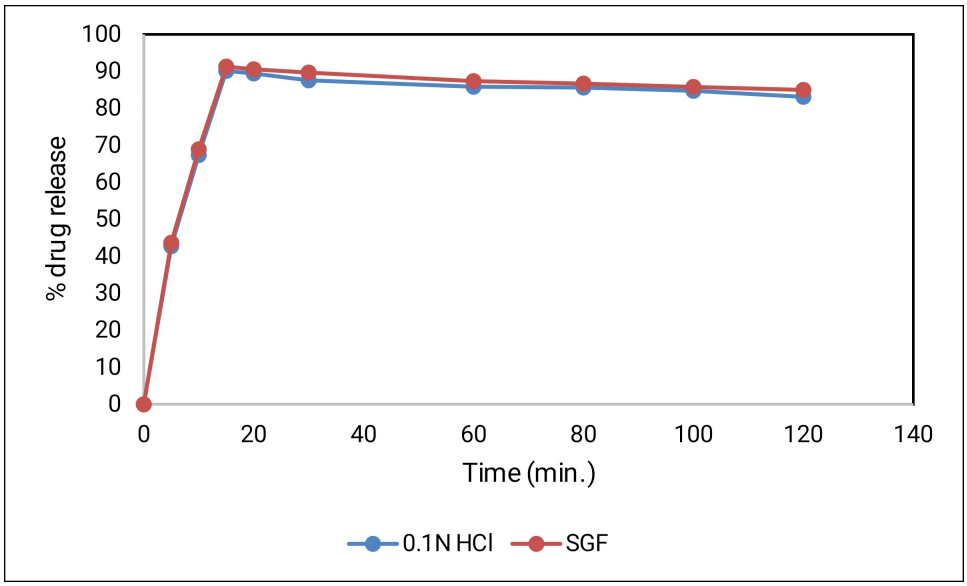

Figure 3: Graph for In-vitro release data Carbamazepine (CBZ-OPT) in 0.1N HCl & Simulated Gastric Fluid

It has been proposed that SMEDDS formulations lead to the creation of microemulsions. Microemulsions have smaller particles that enable a quicker release of the drug into the watery part of the body compared to the commercial product containing carbamazepine. Consequently, the formulation of carbamazepine in the SMEDDS formulation would result in enhanced absorption and improved bioavailability.

Transmission electron microscopy

To check the morphology of the droplets of the optimized CBZ SMEDDS formulation, TEM (Transmission electron microscope) was used. The TEM image is shown below:

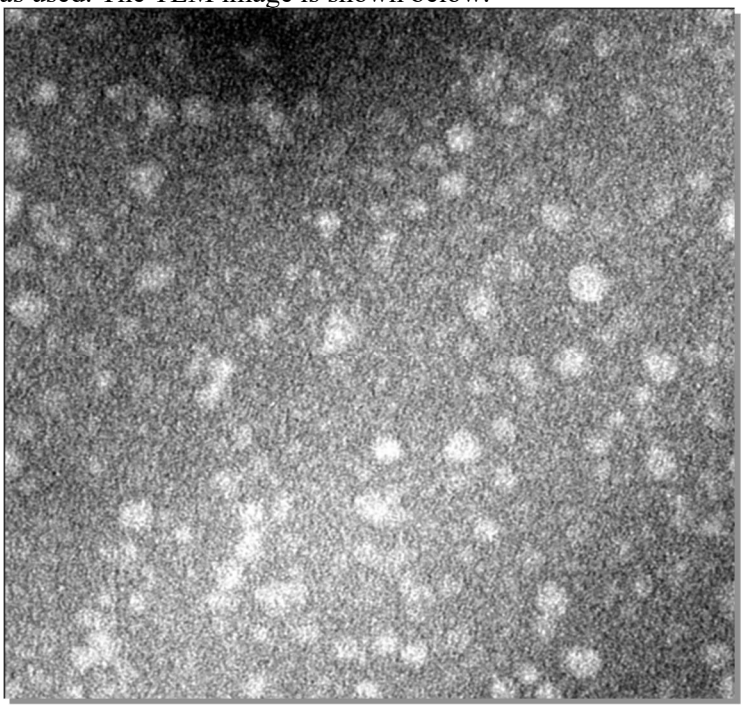

Figure 4: TEM images of the SMEDDS formulation

Release Kinetic Study

To establish the mechanism of drug release from the microemulsion in 0.1N HCl (pH 1.2), the release data of optimized batch was fitted into several kinetic models like Zero & First Order, Higuchi & Korsemeyer-peppas models.

Formulation Code	Zero Order		First Order		Higuchi		Korsemeyer-Peppas	
	0.1 N HCl (pH 1.2)							
CBZ-OPT	m	R^2	m	R^2	m	R^3	m	R^3
	0.3299	0.508	0.0058	0.989	0.1069	0.871	0.9158	0.895

Table 5: Estimated value of R2 after fitting dissolution data of optimized batch of Carbamazepine SMEDDS formulation (CBZ-OPT) into various release kinetic models in 0.1N HCl (pH 1.2)

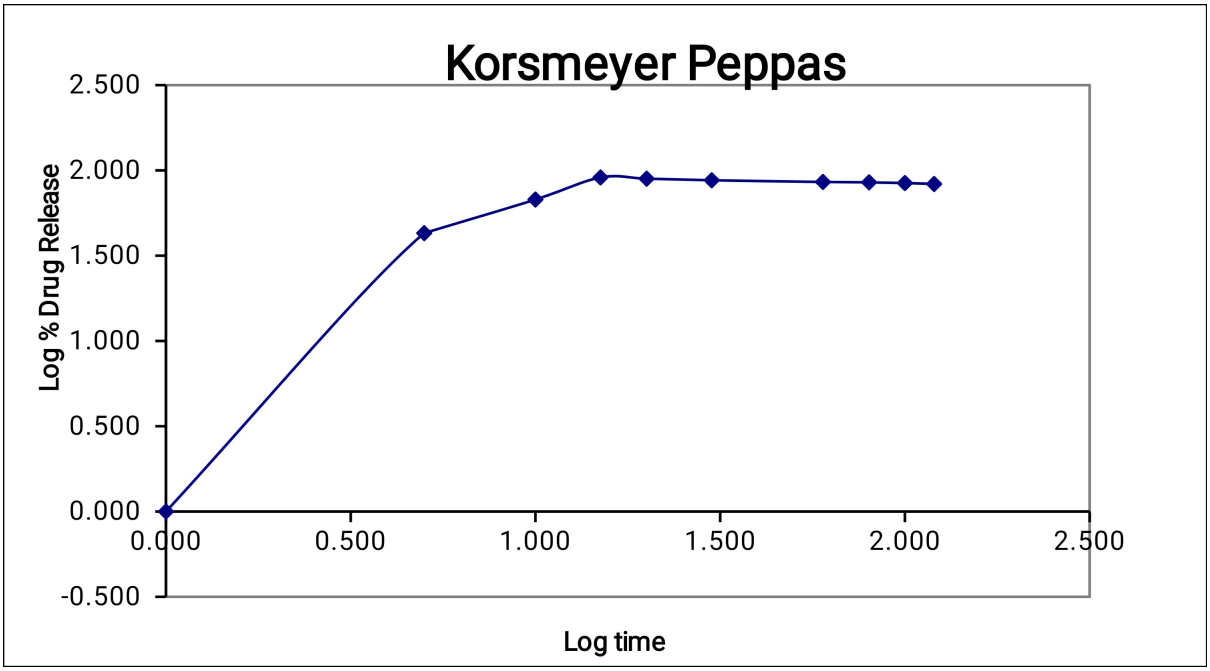

Figure 5: Korsmeyer peppas Release Kinetics of Carbamazepine SMEDDS Optimized Batch (CBZ-OPT, 0.1N HCl)

Findings from kinetic release study showed that the drug's release process was identified as first-order, followed by Korsmeyer-Peppas kinetics.

Thermodynamic Stability Studies

No substantial changes in the formulation during stability studies was observed. Hence, the formulation is considered to be stable. The results of the thermodynamic stability studies have been reported in the table below.

Formulation	Heating cooling cycles	Centrifugation	Freeze thaw stress cycle
CBZ-OPT	No Phase separation	No Phase separation	No Phase separation

Table 6: Results of thermodynamic stability studies

Conclusions

The purpose of the present thesis was to design and improve self-micro emulsifying drug delivery systems (SMEDDS) for poor water-soluble drugs oral delivery. Poor water solubility and less absorption are major limitations for various drugs despite their good therapeutic efficacy. The improvement in the performance of poorly water-soluble drugs can be achieved by using SMEDDS as a carrier for the delivery of drugs belonging to the classes II and IV. The current study was done to determine the role of self-emulsifying formulas in enhance the bioavailability of carbamazepine. SMEDDS represents an alternative of many oral formulations for lipophilic compounds.

In conclusion, the development and optimization of self-microemulsifying drug delivery system (SMEDDS) for improved delivery of Carbamazepine has shown promising results. The optimized formulation exhibited a high drug entrapment rate, small droplet size, and over 90% drug release. The in-vitro dissolution study demonstrated a significant enhancement in drug release compared to the marketed formulation. The use of SMEDDS has shown to improve the solubility and permeability of the poorly soluble drug Carbamazepine, suggesting its potential for enhancing drug efficacy. Further studies can explore the benefits of SMEDDS in improving the bioavailability of other poorly water-soluble drugs.

References:

1. Nagare Sonali.A ,DhobaleAvinash.V, NajanAnita.A. “Formulation and Evaluation of Carbamazepine nanoemulsion for brain targeted drug delivery via intranasal route. Indo American Journal of Pharmaceutical Research.2018:8(07).

2. Dong Woo Yeom, Ye Seul Song, Sung Rae Kim, Sang Gon Lee, Min Hyung Kang, Sangkil Lee, Young Wook Choi. Development and optimization of a self-microemulsifying drug delivery system for atorvastatin calcium by using d-optimal mixture design. International Journal of Nanomedicine 2015:10. 3865-3878.

3. Zhang N, Zhang W, Jin Y, Quan DQ. Studies on preparation of carbamazepine (CBZ) supersaturatable self-microemulsifying (S-SMEDDS) formulation and relative bioavailability in beagle dogs. Pharmaceutical development and technology. 2011 Aug 1;16(4):415-21.

4. Ramprasad Chintalapudi, T. E. G. K. Murthy, K. Rajya Lakshmi, G. Ganesh Manohar. Formulation, optimization, and evaluation of self-emulsifying drug delivery systems of nevirapine. International Journal of Pharmaceutical Investigation, 2015; 5 (4): 205-13.

5. Deleanu M, Toma L, Sanda GM, Barbălată T, Niculescu LȘ, Sima AV, Deleanu C, Săcărescu L, Suciu A, Alexandru G, et al. Formulation of Phytosomes with Extracts of Ginger Rhizomes and Rosehips with Improved Bioavailability, Antioxidant and Anti-Inflammatory Effects In Vivo. Pharmaceutics. 2023; 15(4):1066. https://doi.org/10.3390/pharmaceutics15041066

6. Nisha GS, Vaishali P, Geeta R, Prabhakar P, Harish NM, Marina K, Charyulu RN. Formulation and evaluation of self microemulsifying drug delivery system of carbamazepine. Int. J. Res. Pharm. Sci., 2(2), 2011, 162-169.

7. Manoj P. Borse and Sugandha V. Mulgund. UV spectrophotometric estimation of carbamazepine in bulk and tablet dosage form, Der Pharmacia Lettre, 2015, 7 (5):272-275.

8. Barakat, N. S., Elanazi, F. K., &Almurshedi, A. S. (2008). The influence of various amphiphilic excipients on the physicochemical properties of carbamazepine-loaded microparticles. Journal of Microencapsulation, 26(3), 251–262.

9. Ashok Kumar Janakiraman , Tahani Islam, Kai Bin Liew , Manogaran Elumalai and J. C. Hanish Singh, Improved oral bioavailability of poorly water-soluble vorinostat by self-microemulsifying drug delivery system, Beni-Suef Univ J Basic Appl Sci (2022) 11:99.