Development and characterization of Tolvaptan loaded self-micro emulsifying drug delivery system

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Abstract

Tolvaptan, a selective vasopressin receptor antagonist, is a drug with poor solubility used to treat hyponatremia. To address the solubility issue and enhance its bioavailability, a novel self-micro emulsifying drug delivery system (SMEDDS) was employed. SMEDDS are isotropic mixtures of oil, surfactants, and cosurfactants that, upon contact with gastrointestinal fluid, spontaneously form fine oil-in-water emulsions. These emulsions are then absorbed into lymphatic pathways, bypassing the first-pass hepatic effect. In this formulation, oleic acid, Labrafil M 2125 CS, PEG-400, and Labrasol ALF were selected as the mixed oil, surfactant, and cosurfactant, respectively. The resulting droplet sizes ranged from 37.8 to 176 µm with a polydispersity index (PDI) value of 0.271. The zeta potential was measured at -1.6 mV, and an 81.50% drug release was observed in the formulation. This study concludes that the self-micro emulsifying drug delivery system is effective in improving the drug release and bioavailability of Tolvaptan.

Keywords: Bioavailability, self-micro emulsifying drug delivery systems, solubility, Tolvaptan

Introduction

Tolvaptan, chemically known as N-[4-[(7-chloro-2,3,4,5-tetrahydro-5-hydroxy-1H-1-benzazepin-1-yl) carbonyl]-3-methylphenyl]-2-methyl benzamide, is a selective vasopressin V2-receptor antagonist used in the management of hyponatremia associated with heart failure and the treatment of autosomal dominant polycystic kidney disease (ADPKD)[1]. It works by inhibiting the action of vasopressin, leading to an increase in free water clearance and a

subsequent decrease in body water without affecting electrolyte balance. However, Tolvaptan's clinical utility is hindered by its poor aqueous solubility, which leads to variable oral bioavailability and challenges in achieving consistent therapeutic plasma levels. The oral route is the most convenient for drug delivery, particularly for highly lipophilic drugs within the gastrointestinal tract (GIT)[2]. However, a significant challenge in the GIT is the low bioavailability of drugs, primarily due to their poor aqueous solubility in the gastrointestinal fluid. To address this issue, self-micro emulsifying drug delivery systems (SMEDDS) have been developed to enhance the solubility and bioavailability of poorly soluble drugs. SMEDDS are isotropic mixtures of oils, surfactants, and cosurfactants that, upon contact with the GI fluid, spontaneously form fine oil-in-water emulsions with droplet sizes ranging from 100 to 300 nm. These fine emulsions are absorbed into the lymphatic pathways, effectively bypassing the first-pass hepatic metabolism, which can significantly reduce drug efficacy[3]. SMEDDS are particularly suitable for drugs classified under BCS Class II and IV, as these drugs are poorly soluble but exhibit high permeability. Unlike traditional emulsions, SMEDDS are both sensitive and metastable. Tolvaptan, a selective vasopressin V2 receptor antagonist, is a prime candidate for SMEDDS formulation due to its poor solubility and low bioavailability. Tolvaptan is used to treat hyponatremia (low blood sodium levels) associated with conditions such as congestive heart failure[4]. The drug works by binding to the vasopressin V2 receptor, counteracting the effects of vasopressin, which leads to a decrease in the synthesis and transport of aquaporin channels. This mechanism increases free water clearance, raises plasma sodium concentration, and reduces urine osmolality. The typical dosage range for Tolvaptan is between 15–60 mg/day. Given the low oral bioavailability of Tolvaptan, enhancing its solubility and bioavailability through a novel approach like SMEDDS is essential[5]. Therefore, a comprehensive attempt was made to develop and characterize a Tolvaptan SMEDDS formulation. This innovative delivery system aims to improve the therapeutic efficacy of Tolvaptan by overcoming the solubility and bioavailability challenges inherent to its current oral formulations[6]. Through this development, it is anticipated that the SMEDDS formulation of Tolvaptan will provide a more effective treatment option for patients suffering from hyponatremia and related conditions, thereby improving clinical outcomes and patient quality of life[7].

Materials and methods:

Tolvaptan was purchased from Sigma-Aldrich, India. Oleic acid and Labrafil M 2125 CS were obtained from Genuine Chemical Co., Mumbai, India. PEG-400 was sourced from Loba Chemi

Pvt. Ltd., Mumbai, India. Labrasol ALF was acquired from SDFCL Chem. Ltd., Bangalore, India. All other reagents and chemicals used were of analytical grade.

Methods

Pre-formulation studies

Determination of Melting Point

The melting point of Tolvaptan was determined using the capillary tube method. In this method, one end of a capillary tube is sealed, and a small amount of the drug sample is placed inside the tube. The temperature at which the drug melts is then recorded.

Solubility Studies

The solubility of the drug was tested in various solvents, including oils, surfactants, and cosurfactants, using the shake flask method followed by sonication. Specifically, 5 mL of each solvent was placed in separate vials, and an excess amount of the drug was added. The mixtures were stirred with a cyclomixer for 10 minutes and then sonicated for 12 hours. After sonication, the supernatant was filtered, and the solubility was measured using UV-Visible spectroscopy. Additionally, the mixtures were observed for any phase separation to assess their stability[8].

Determination of λmax of Tolvaptan

Preparation of Standard Stock Solution

A 5% w/v sodium lauryl sulfate (SLS) solution was prepared. Then, 10 mg of Tolvaptan was weighed and transferred into a beaker containing the 5% w/v SLS solution. The mixture was sonicated for 15 minutes, and the final volume was adjusted to achieve a concentration of 100 µg/mL, resulting in the standard stock solution. This solution was scanned in the UV range of 200–400 nm using the solvent as a blank[9].

Determination of Calibration Curve of Tolvaptan

The calibration curve was established with concentrations of 3, 6, 9, 12, 15, and 18 µg/mL. Absorbance was measured at 260 nm against the 5% w/v SLS solution[10].

Construction of Ternary Phase Diagrams

Constructing ternary phase diagrams is a preliminary step before starting the formulation. It helps identify the optimal emulsification region for combinations of oil, surfactant, and cosurfactant [11].

Water Titration Method

The water titration method involves titrating homogeneous mixtures of oil, surfactant, and cosurfactant with water at room temperature. Mixtures of oil, surfactant, and cosurfactant were prepared in ratios ranging from 9:1 to 1:9 and placed in screw-cap glass tubes. These mixtures were vortexed and then slowly titrated with aliquots of water[12].

FTIR

The drug was mixed with potassium bromide separately and triturated in glass mortar pestle. The triturated mixture was compressed and processed further for FTIR spectra by scanning in the range of 4000-400cm^{-1} using Infrared spectrophotometer (Shimadzu, IR affinity-1). Since hydrogen or covalent bonds are related to FTIR, the spectra offer comprehensive details about the chemical compounds' structural configurations. FTIR is used to identify the drug's functional identity and to find out how it interacts with excipients [13].

Method of preparation

Oleic acid was taken in 25 ml of the beaker and put on a magnetic stirrer and half of the drug was added and stirred till the drug was dissolved. Labrasol ALF as surfactant and PEG 400 as co-surfactant were properly mixed in another beaker. And remaining quantity of the drug was added and stirred till the mixture became clear. Then surfactant and co-surfactant were mixed with oil phase slowly on a magnetic stirrer at 500 RPM. The stirring was continued for 30 minutes to get a clear oily phase [14].

Evaluation Parameters

Thermodynamic Stability Test

The thermodynamic stability of the SMEDDS was evaluated through the following tests:

a. Heating-Cooling Cycle: The formulation was subjected to different temperatures, including refrigeration (4°C), room temperature, and a stability chamber set at 45°C. Each temperature cycle lasted 48 hours, after which the formulations were observed for any phase separation [15].

b. Centrifugation: The formulations were centrifuged at 3500 rpm for 30 minutes and subsequently examined for phase separation [16].

c. Freeze-Thaw Cycle: The formulations were exposed to freezing conditions at -21°C and thawing conditions at +25°C. Each cycle lasted 48 hours, and the formulations were inspected for phase separation [17].

Phase Separation Study

The SMEDDS formulations were diluted with 50 mL of distilled water and stored at 25°C for 24 hours. The samples were then visually inspected for phase separation and drug precipitation [18].

Emulsification Study

The emulsification efficiency was tested using a USP Type II dissolution apparatus. One millilitre of each formulation was added to 100 mL of distilled water maintained at 37°C, with the paddle rotating at 50 rpm to provide gentle agitation [19].

Determination of Percentage Transmittance

A 5 mL sample of the SMEDDS formulation was prepared, and the percentage transmittance was measured using a UV spectrophotometer at 638 nm, with distilled water serving as the blank [20].

***In Vitro* Dissolution Test**

The *In vitro* dissolution study was conducted using a USP Type II apparatus. Five millilitres of the SMEDDS formulation were introduced into the apparatus, with water used as the dissolution medium. The temperature was maintained at 37°C ± 0.5, and the paddle speed was set to 50 rpm. At predetermined intervals, 5 mL samples were withdrawn and replaced with an equal volume of fresh water. The absorbance of the samples was measured using a UV spectrophotometer at 260 nm [21].

Drug Content Test

To determine the drug content, 5 mL of the SMEDDS formulation was prepared, and 1.06 mL of this solution was dissolved in ethanol. The drug content in the ethanol extract was then analyzed using a UV spectrophotometer [22].

Cloud Point Determination

For cloud point determination, 0.5 mL of the SMEDD formulation was placed in a test tube and gradually heated in a water bath. The temperature at which cloudiness appeared was

recorded as the cloud point. The temperature and time at which precipitation occurred were noted [23].

Robustness to Dilution

One millilitre of each formulation was diluted 50, 100, and 250 times with different buffers, including water, phosphate buffer pH 6.8, and 0.1N HCl. These diluted samples were stored for 24 hours and then observed for any phase separation [24].

Viscosity Measurement

Ten millilitres of the SMEDDS formulation were measured for viscosity using a viscometer model equipped with spindle C. The measurement was taken at 25 ± 0.5°C with a spindle speed of 50 rpm [25].

Scanning Electron Microscope (SEM) Analysis

The external morphology of the optimized SMEDDS formulation was examined using a scanning electron microscope (SEM)[26].

Droplet Size and Zeta Potential Analysis

The droplet size and zeta potential of the SMEDDS formulation were measured using a zeta potential analyser. A polydispersity index (PDI) value greater than 0.7 indicates poor stability of the formulation [27].

Results

Pre-formulation study

1. Preparation of standard curve

1.1. Preparation of stock solution

50mg of drug was weighed & dissolved in 50ml ethanol. From the above solution, 100µg/ml solution was prepared by taking 1ml from above solution and diluting up to 10ml with ethanol. The solution was scanned in the UV region (200-400nm) using UV spectrophotometer (Shimadzu, UV-1800240)

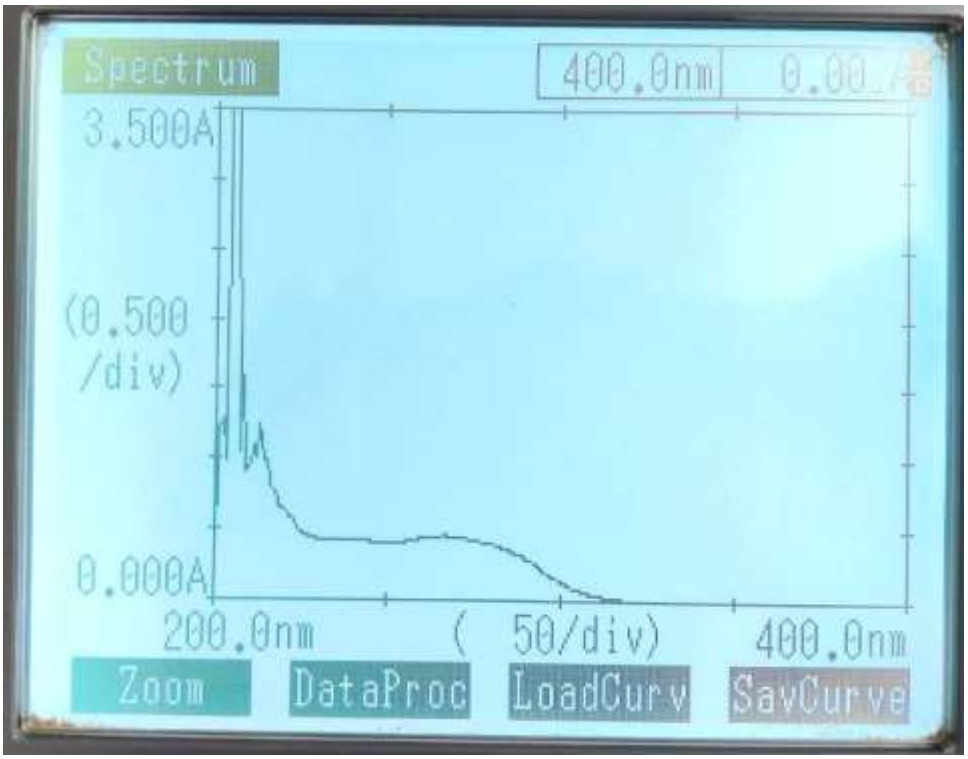


Figure 1: UV Spectra of Tolvaptan

1.2. Preparation of calibration curve

From 100µg/ml solution, standard dilutions of 0, 0.5, 1, 1.5, 2 and 2.5 µg/ml were formulated by transferring 0, 0.05, 0.1, 0.15, 0.2, and 0.25ml in 10ml volumetric flasks and volume was made up to mark. The absorbance was measured and graph was plotted between and concentration and absorbance.

Table 1: Absorbance of Tolvaptan in Methanol

S. No	Concentration (µg/ml)	Absorbance (mean, n=3)	Standard deviation
1.	0	0	0
2.	0.5	0.189	0.006557
3.	1.0	0.395	0.031241
4.	1.5	0.566	0.031225
5.	2.0	0.768	0.028618
6.	2.5	0.956	0.014572

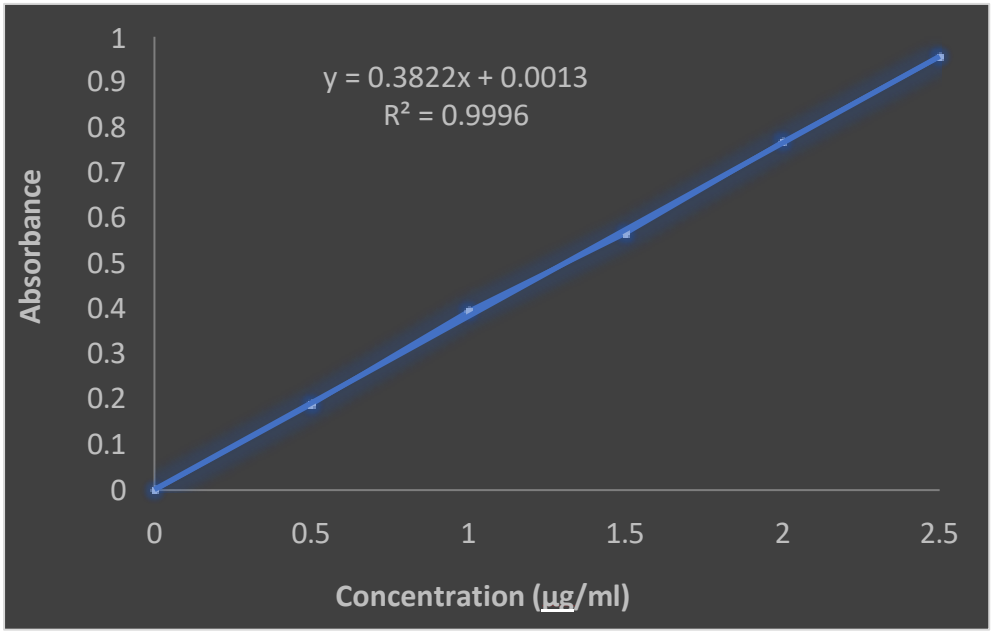


Figure 2: Standard curve of Tolvaptan in Methanol.

2. Differential Scanning Calorimetry (DSC)

The differential scanning calorimetry of the drug was done using differential scanning calorimeter (Waters TA instruments).

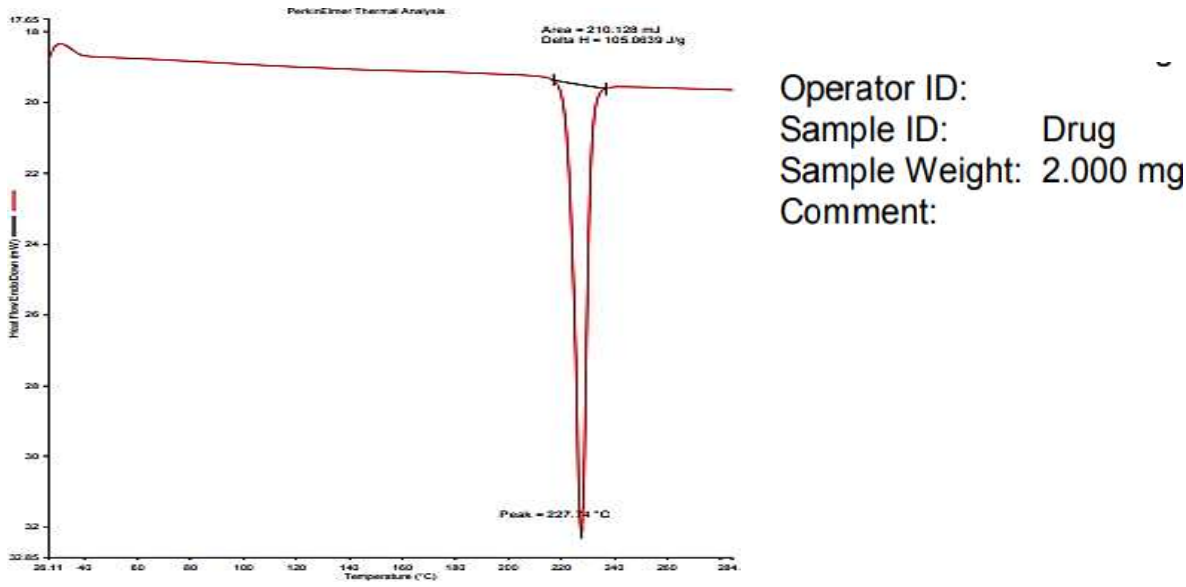


Figure 3: DSC graph of Tolvaptan

3. FTIR

The drug was mixed with potassium bromide separately and triturated in glass mortar pestle. The triturated mixture was compressed and processed further for FTIR spectra by scanning in the range of 4000-400cm^{-1} using Infrared spectrophotometer (Shimadzu, IR affinity-1).Since hydrogen or covalent bonds are related to FTIR, the spectra offer comprehensive details about the chemical compounds' structural configurations. FTIR is used to identify the drug's functional identity and to find out how it interacts with excipients.

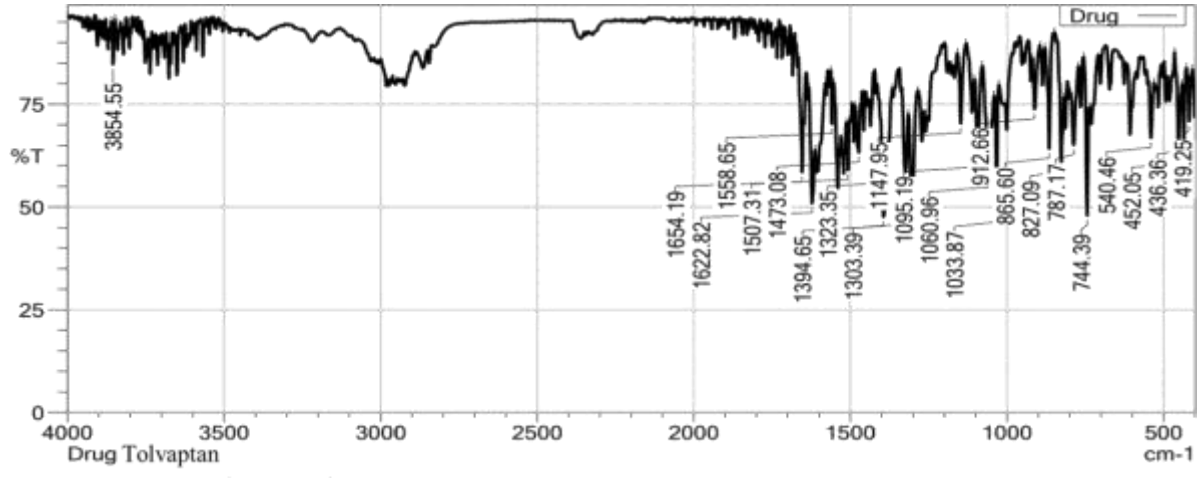


Figure 4: FTIR Spectra of Tolvaptan

Table 2: FTIR range of functional group in Tolvaptan

S. No.	Functional Group	Range
1	-O-H Phenol (Stretch)	3854.55
2	-C=O Aldehyde (Stretch)	1654.19
3	-C=C Alkenyl (Stretch)	1622.82

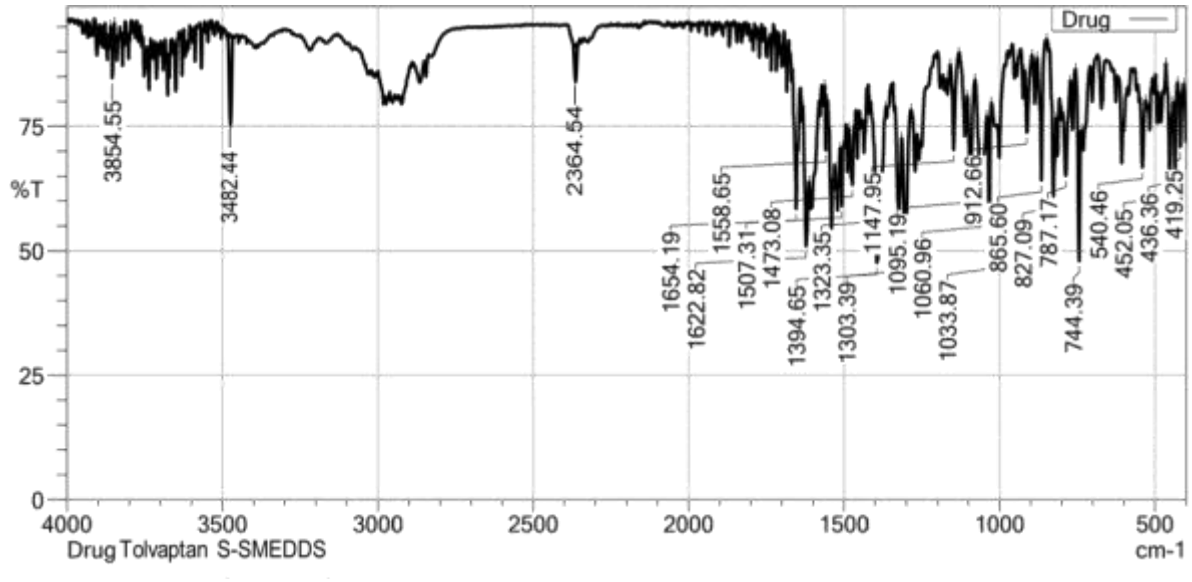


Figure 5: FTIR Spectra of Tolvaptan SMEDDS

Table 3: FTIR range of functional group in Tolvaptan SMEDDS

S. No.	Functional Group	Range
1	-O-H Phenol (Stretch)	3854.55
2	-C=O-H Aldehyde (Absorption)	1654.19
3	-C=CH Aromatic (Bending)	2364.54

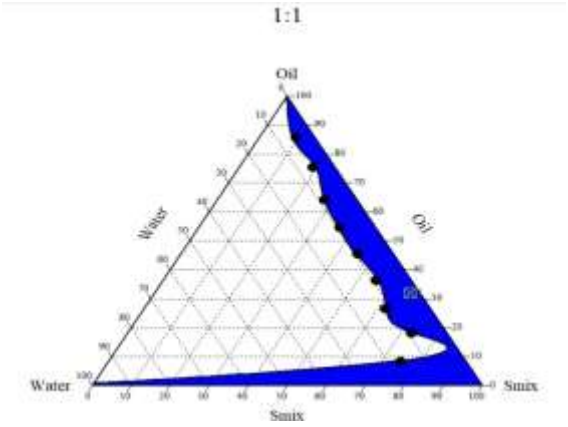
4. Construction of Ternary Phase Diagram

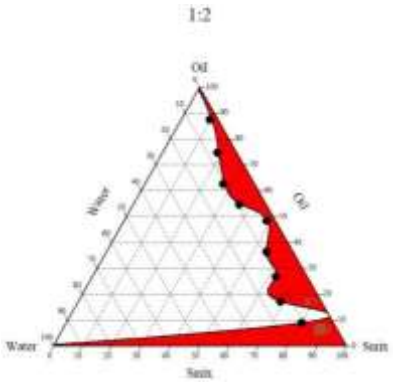
The existence of microemulsions regions were determined by using pseudo-ternary phase diagrams. Microemulsions were diluted under agitated conditions using water titration method. The mixture of 2 oils with surfactant/co-surfactant mixture at certain weight ratios were diluted with water in a drop-wise manner. Surfactant and co-surfactant (Smix) in each group were mixed in different weight ratios (1:1, 1:2, 2:1, 1:3). For each phase diagram, oil and specific *S*mix ratio were mixed well in different volume ratios ranging from 1:9 to 9:1. Pseudo-ternary phase diagrams were developed using aqueous titration method.

Table 4: Ternary phase reading for different Smix Ratio

(1:1) Smix Ratio	(1:2) Smix Ratio	(2:1) Smix Ratio	(1:3) Smix Ratio

	Oleic acid	Labrasol : PEG400			Oleic acid	Labrasol : PEG400			Oleic acid	Labrasol : PEG400			Oleic acid	Labrasol : PEG400	
s. no	oil	Smix	water	s. no	Oil	Smix	Water	s. no	Oil	Smix	Water	s. no	Oil	Smix	Water
1	0.1	0.9	0.2	1	0.1	0.9	0.12	1	0.1	0.9	0.117	1	0.1	0.9	0.1
2	0.2	0.8	0.1	2	0.2	0.8	0.16	2	0.2	0.8	0.093	2	0.2	0.8	0.07
3	0.3	0.7	0.13	3	0.3	0.7	0.12	3	0.3	0.7	0.083	3	0.3	0.7	0.13
4	0.4	0.6	0.1	4	0.4	0.6	0.1	4	0.4	0.6	0.09	4	0.4	0.6	0.11
5	0.5	0.5	0.1	5	0.5	0.5	0.03	5	0.5	0.5	0.027	5	0.5	0.5	0.08
6	0.6	0.4	0.1	6	0.6	0.4	0.1	6	0.6	0.4	0.018	6	0.6	0.4	0.07
7	0.7	0.3	0.09	7	0.7	0.3	0.12	7	0.7	0.3	0.044	7	0.7	0.3	0.06
8	0.8	0.2	0.06	8	0.8	0.2	0.07	8	0.8	0.2	0.033	8	0.8	0.2	0.07
9	0.9	0.1	0.05	9	0.9	0.1	0.03	9	0.9	0.1	0.032	9	0.9	0.1	0.06





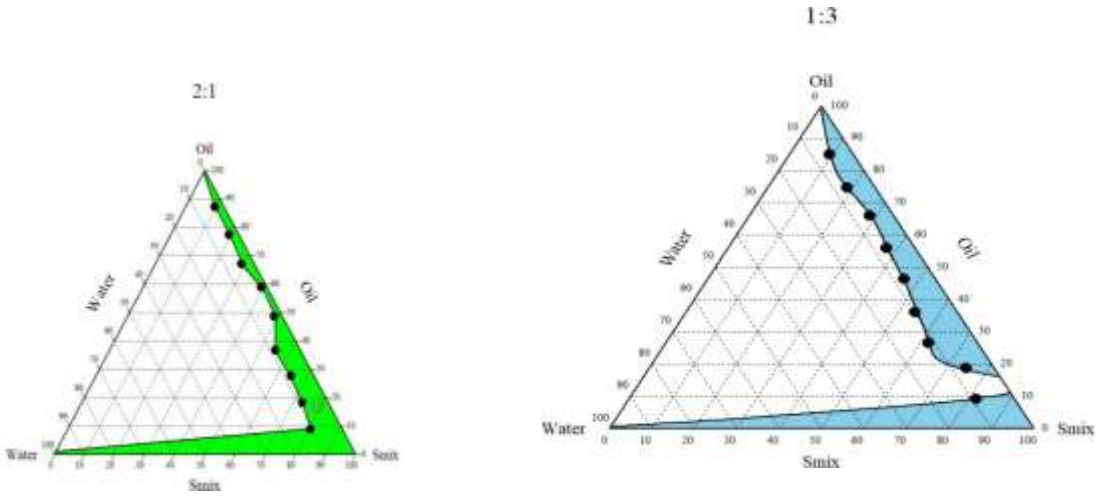


Figure 6: Ternary Phase diagram for different ratio of Smix

5. Organoleptic Properties

The organoleptic characteristics of the formulation was characterized by visual inspection.

Table 5: Organoleptic Properties of Tolvaptan

Appearance	**Solid Powder**
Odour	**None**
Colour	**Pale Yellow**
Taste	**Bitter**

6. Micromeritics Properties of solid SMEDDS

Micromeritics evaluation was performed of solid powder of SMEDDS of tolvaptan. As per the result Angle of repose is poor, Carr's index is good and Hausner's ratio is giving good flow.

Table 6: Micromeritics properties of SMEDDS of Tolvaptan

Test	**Result**
Angle of Repose	**52.22°**
Bulk Density (gm/ml)	**0.52**
Tapped Density (gm/ml)	**0.47**
Hausner's Ratio	**1.92**
Carr's Index	**11.51%**

7. Drug Content

Solid-SMEDDS were dissolved in sufficient quantity of methanol and was sonicated for 10-15 mins and filtered, and the absorbance of filtrate was read at 267 nm on UV- Visible Spectrophotometer (Shimadzu-1800, Japan). S-SMEDDS contains 99.06–99.9% drug.

8. Particle size measurement:

The particle size of the SMEDDS of Tolvaptan was measured with the help of Malvern Zeta sizer after filtering the formulation through membrane filter of 0.22µm.

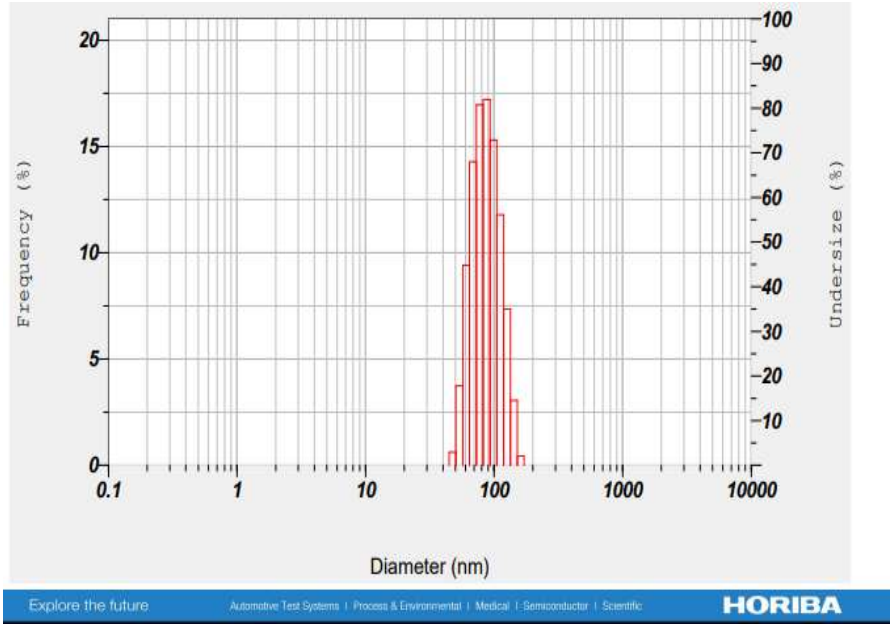


Figure 7: Globule size of SMEDDS of Tolvaptan

9. XRD Characterization of pure drug TOL and SMEDDS of TOL

The X-ray diffraction (X-RD) of pure drug of Tolvaptan and SMEDDS of tolvaptan were obtained using X-RD instrument XPERT-PRO in Central University of Gujarat (Central instrumentation facility). The scanning speed was 2°/min between 0 and 80.

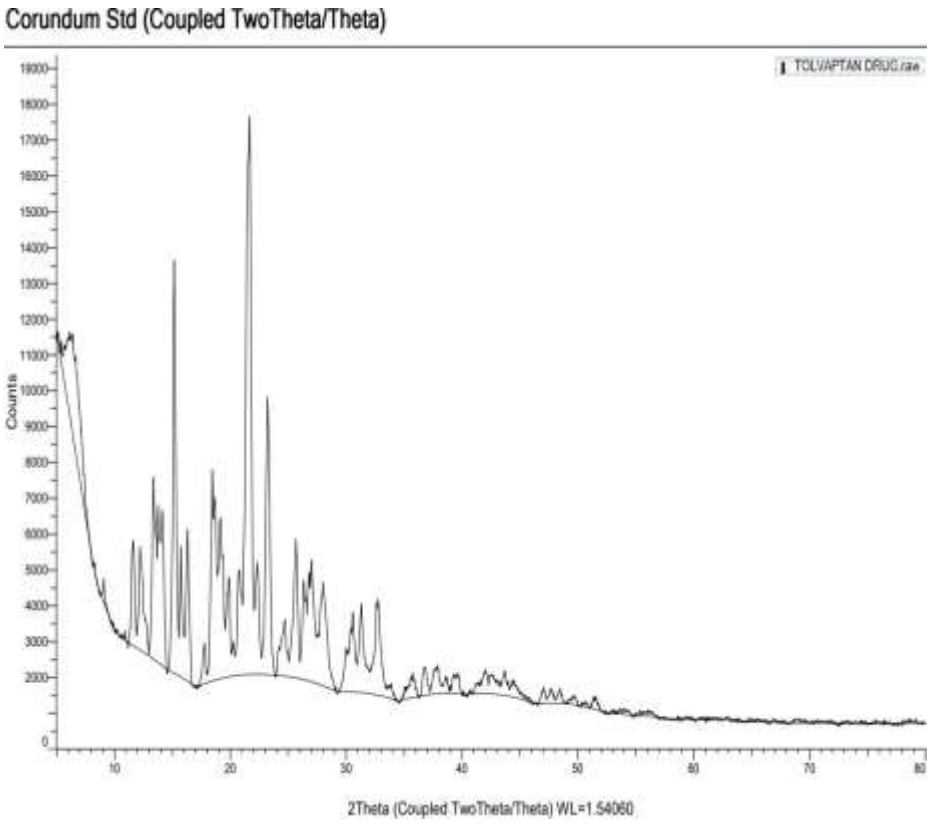


Figure 8: XRD of Tolvaptan

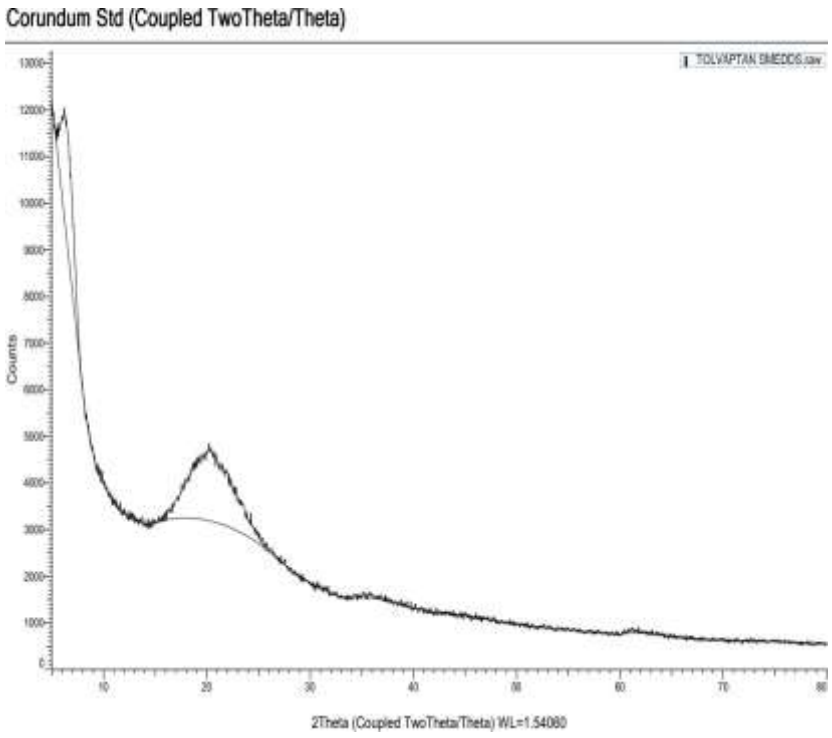


Figure 9: XRD of Tolvaptan SMEDDS

10. In-vitro Drug release Comparison between marketed formulation and SMEDDS

The In-vitro drug release of the marketed formulation was done in phosphate buffer of pH 6.8 by using dissolution apparatus type II and drug release of SMEDDS was done by using inverted test tube method by keeping the formulation in dialysis membrane. The study was performed for 180 minutes. The results showed that SMEDDS showed faster release as compared to marketed formulation.

Table 7: Absorbance of Pure drug and SMEDDS

Time (Minute)	% of Drug release in Phosphate Buffer pH 6.8	
	Marketed formulation	SMEDDS
0	0	0
10	13.24	20.61
20	26.35	48.69
30	41.67	62.55
40	52.56	81.22
60	66.45	98.71
90	78.89	
120	87.68	
180	93.98	

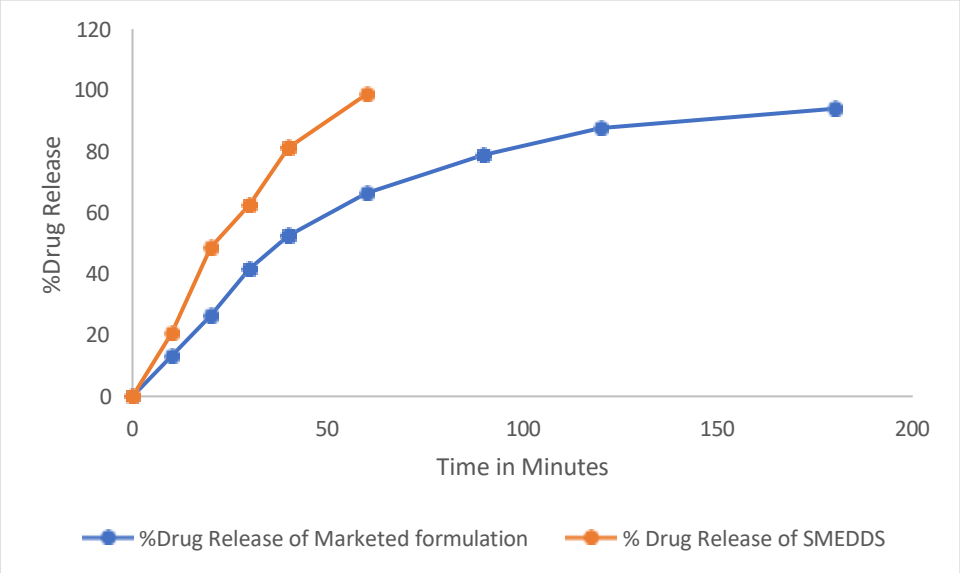


Figure 10: Comparison of In-vitro % drug Release of Marketed formulation and SMEDDS

11. Stability Studies of Tolvaptan

The stability studies are performed at Day 1, at month and at 3 months for noticing the changes in globule size, polydispersity index and zeta potential. The results of stability studies depicted that the solid-SMEDDS formulation remained clear even after a period of 3 months at temperature 25°C ± 2°C and 40°C ± 0.1°C. There was no phase separation in both the systems at each time. Formulations were found to be consistent with respect to their drug content, *in vitro* drug release, phase separation and transparency during the stability study.

Table 8: Stability Study of SMEDDS of Tolvaptan

		Globule size (nm)		PDI		Assay		ZP	
		Avrg	SD	Avrg	SD	Avrg	SD	Avrg	SD
Day 1	**Refrigeration**	189.6666667	1.527525	0.135333	0.004509	99.6	0.264575	-29	1
	25°C/60%RH	195	1	0.143667	0.009609	99.26667	0.152753	-26.3333	1.527525
	40°C/75%RH	179.6666667	1.527525	0.182	0.009165	98.96667	0.493288	-26.6667	1.527525
After 1 months	**Refrigeration**	235	1	0.214	0.006083	99.1	0.2	-22.3333	1.527525
	25°C/60%RH	233.6666667	0.57735	0.3	0.008718	98.53333	0.51316	-24.6667	0.57735
	40°C/75%RH	210.3333333	2.081666	0.309667	0.001528	93.46667	0.602771	-22.6667	0.57735
After 3 months	**Refrigeration**	243.3333333	2.081666	0.370667	0.018339	97.43333	1.059874	-18	1
	25°C/60%RH	245.3333333	1.154701	0.368333	0.002517	95.3	1.153256	-17.5	0.5
	40°C/75%RH	247.6666667	1.527525	0.385	0.017776	84.50333	0.921973	-15.6667	0.57735

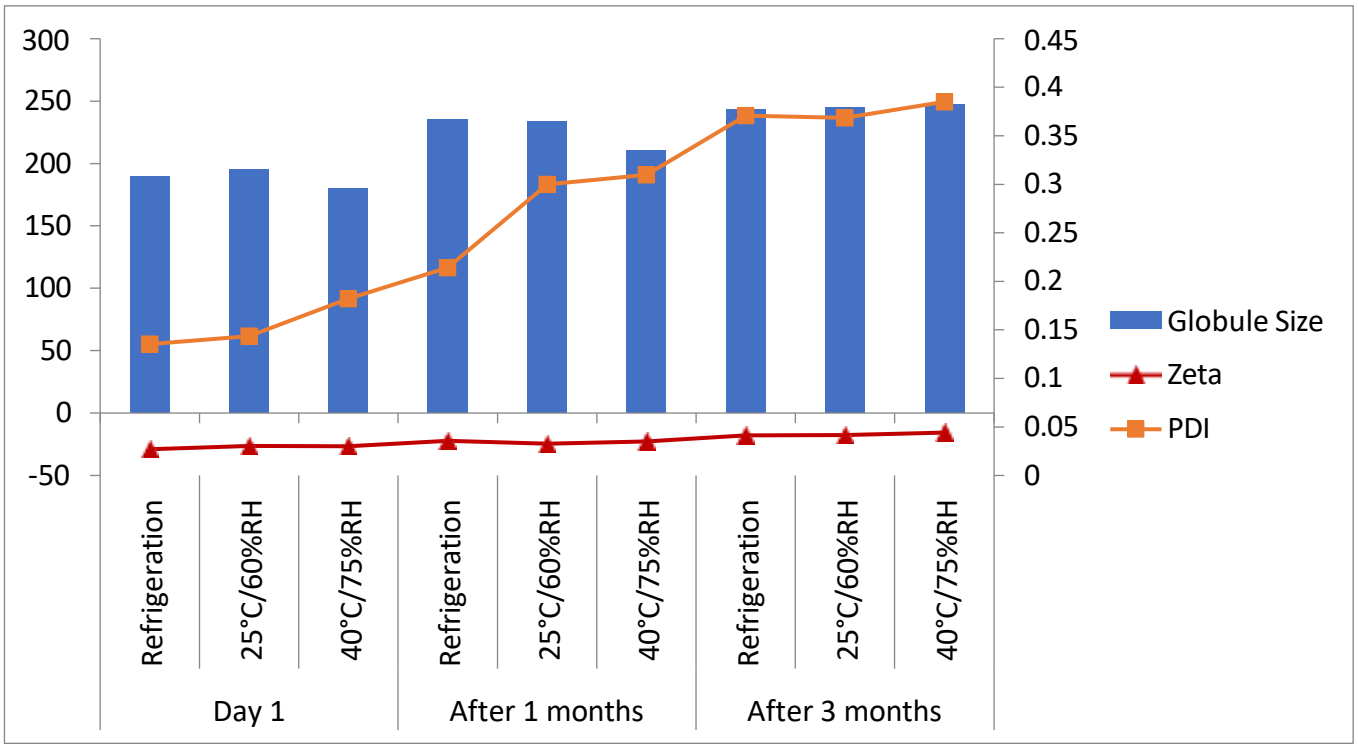


Figure 11: Stability study of Tolvaptan SMEDDS

Table 9: Visual examination, % Transmittance, %Drug Content after 1 month

Stability study after 1 month	
Parameter	Storage condition: 40 ±2°C / RH: 75 ± 5%
	TOL
Visual examination	No colour change
	No precipitation
	No phase separation
% Transmittance	97 ± 0.52 %
% of drug content	97.28 ± 0.65 %

Table 10: Visual examination, % Transmittance, %Drug Content after 3 months

Stability study after 3 months

Parameter	Storage condition: 25°C±2°C/60±5% RH
	TOL
Visual examination	No colour change No precipitation No phase separation
% Transmittance	97 ± 0.78 %
% of drug content	96.12 ± 0.43 %

CONCLUSION

Through comprehensive characterization and evaluation tests, it has been determined that the development and characterization of the Tolvaptan-loaded self-micro emulsifying drug delivery system (SMEDDS) significantly enhance the drug release profile of Tolvaptan. The SMEDDS formulation has demonstrated superior solubilization and absorption properties, which are crucial for the bioavailability of poorly water-soluble drugs like Tolvaptan. The detailed analysis of various parameters, including droplet size, zeta potential, and dissolution studies, indicates that the SMEDDS provides a stable and efficient delivery mechanism. The improved drug release can be attributed to the formation of fine oil-in-water microemulsions in the gastrointestinal tract, facilitating faster and more complete absorption of Tolvaptan. Therefore, the SMEDDS approach is validated as an effective strategy for enhancing the therapeutic efficacy of Tolvaptan.

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