ORIGINAL ARTICLE

Design and Development of Self-Emulsifying Drug Delivery Systems of Tolvaptan

D. Madhuri[1], B. Pavan Kumar[2], D. Ravi Sankar Reddy[2], S. K. Babi Parveen[2], Ch. Srujani[3]

[1]Department of Pharmacy, Central University of Rajasthan, Ajmer, Rajasthan, India, [2]University College of Pharmaceutical Sciences, Acharya Nagarjuna University, Guntur, Andhra Pradesh, India, [3]Department of Pharmaceutical Sciences, Babasaheb Bhimarao Ambedkar University, Lucknow, Uttar Pradesh, India

Abstract

Tolvaptan, a selective vasopressin receptor antagonist, is a poorly soluble drug. It is used to treat hyponatremia. To solve the solubility problem and enhance bioavailability, a novel approach of self-emulsifying drug delivery systems was used. These are isotropic mixtures of oil, surfactants, and cosurfactants, when they contact with the GI fluid spontaneously produce fine oil-in-water emulsion and are subsequently absorbed into lymphatic pathways, bypassing the first-pass hepatic effect. Cinnamon oil and orange oil were used as oils, Tween 80, Tween 60, and Tween 20 were used as surfactants and propylene glycol, poly ethylene glycol 400, and ethanol are used as cosurfactants for the formulation and there by evaluated. The droplet sizes are in ranges of 37.8–176 μm and PDI value is 0.271. The zeta potential value is −1.6 mV and the amount of drug release is that 81.50% was observed in F_5 formulation. It conclude that the self-micro emulsifying drug delivery system is suitable for Tolvaptan drug to improve the drug release and there by bioavailabilty.

Key words: Bioavailability, self-emulsifying drug delivery systems, solubility, Tolvaptan

INTRODUCTION

Oral route is the most convenient route for drug delivery due to the high lipophilicity in GIT.[1,2] The major problem in GIT is low bioavailability, due to the drugs having poor aqueous solubility in the GI fluid. Hence, the solubility of poorly soluble drugs and bioavailability is increased by formulating self-emulsifying drug delivery system (SEDDS).[2] SEDDS are isotropic mixtures of oil, surfactants, and cosurfactants, when they contact with the GI fluid spontaneously produce fine oil-in-water emulsion.[2,3] It produces emulsion with a droplet size ranges from 100 to 300 nm.[4] They are subsequently absorbed into lymphatic pathways, bypassing the first-pass hepatic effect.[5,6] BCS Class II and IV drugs are more suitable for SEDDS formulation.[7,8] These are sensitive and metastable compared to emulsion.[9] Tolvaptan is a selective vasopressin V2 receptor antagonist.[10,11] It used to treat hyponatremia (low blood sodium levels) associated with various conditions like congestive heart failure. It is poorly soluble and bioavailability is low. The recommended dosage ranges of Tolvaptan drug is 15–60 mg/day. Tolvaptan binds to the vasopressin V2 receptor and counteracts the actions of vasopressin thereby decreases the synthesis and transport of aquaporin channels leads to increases the free water clearance, plasma sodium concentration, and decreases the urine osmolality.[12] The oral bioavailability of Tolvaptan was very low, thereby to enhance its solubility and bioavailability a novel approach like SEDDS is needed. Hence, an attempt was made to develop and characterize the Tolvaptan SEDDS.

MATERIALS AND METHODS

Materials

The Tolvaptan drug was gifted by MSN laboratories, Hyderabad, India. Cinnamon oil and Orange oil were

Address for correspondence:
Dr. D. Madhuri, Department of Pharmacy, School of Chemical Sciences and Pharmacy, Central University of Rajasthan, Ajmer, Rajasthan, India.
E-mail: madhuridesavathu@gmail.com

Received: 18-04-2023
Revised: 18-06-2023
Accepted: 26-06-2023

purchased from Genuine Chemical Co. Mumbai, India. Tween 80 was purchased from Loba Chemi Pvt. Mumbai, India. Ltd. Tween 60 was purchased from SDFCL chem. Ltd. Bangalore, India. Propylene glycol was purchased from Fisher scientific India Pvt. Ltd. Mumbai, India. Poly Ethylene Glycol-400 (PEG 400) was purchased from Loba Chemie Pvt. Ltd. Mumbai, India. All other reagents and chemicals are of analytical grade.

Methods

Pre-formulation studies

Determination of melting point

The melting point of the Tolvaptan drug was determined using capillary tube method. In this method take a capillary tube and seal one end and small amount of drug sample was placed in a capillary tube. The temperature at which drug melts was noted.

Solubility studies

Drug sample was added in different solvents such as oils, surfactants, and cosurfactants and its solubility was determined by Shake flask method followed by Sonication. 5 mL of each solvent was taken separately in a vial and excess drug was added. The mixture was stirred using cyclomixer for 10 min and sonicated for 12 h. Supernatant was filtered and its solubility was observed using UV-Visible spectroscopy. The mixture was observed for any phase separation for its stability.[13]

Determination of λ_{max} of Tolvaptan drug

Preparation of standard stock solution

About 5% w/v sodium lauryl sulfate solution was prepared. Weigh 10 mg of Tolvaptan drug and transferred into a beaker containing of 5% w/v SLS solution and sonicated for 15 min and make up the final volume we get 100 µg/mL concentration. It is standard stock solution. The solution was scanned in UV ranges 200–400 nm using solvent as a blank.[14]

Determination of calibration curve of Tolvaptan drug

The calibration curve determined with beer limits of 3, 6, 9, 12, 15, and 18 µg/mL. The absorbance was observed at 260 nm against 5% w/v SLS solution.[15]

Construction of ternary phase diagrams

This is often the primary step before starting the formulation. It is useful to spot best emulsification region of oil, surfactant, and cosurfactant combinations.[16]

Water titration method

This method is carried out by titration of homogenous mixtures of oil, surfactant, and cosurfactant with water at room temperature. Mixtures of oil, surfactant, and cosurfactant were prepared varied from 9:1 to 1:9 and weighed within the same screw-cap glass tubes and were vortexed. Each mixture was then slowly titrated with aliquots of water.[17-19]

Method of preparation[20]

15 mg of drug was placed in clean glass vial and dissolved in oil by vortex mixer and add various ratios of surfactant mixture [Table 1]. These components were mixed by gently stirring and vortex mixing for 30 min.

Evaluation parameters

Thermodynamic stability test

In this test, the SEDDS were subjected to following tests.

a. Heating-cooling cycle: In this method, the formulations were exposure to different temperatures of refrigerator (4°C), room temperature, stability chamber at 45°C were carried. At each temperature, the formulations were stored for 48 h and observe the phase separation.[21]
b. Centrifugation: The developed formulations were subjected to centrifugation at 3500 rpm for 30 min and observe for phase separation.[22,23]
c. Freeze-Thaw cycle: In this test, the formulations were subjected to temperature of −21°C (freeze condition) and +25°C (thaw condition) and store for 48 h and observe for phase separation.[24]

Phase separation study test

SEDDS formulation subjected to dilution of 50ml with distilled water and stored at 25°C for 24 h and observed visually for phase separation and precipitation of drug.[25]

Emulsification study test

The emulsification study was performed in an USP Type II dissolution test apparatus. 1ml of each formulation taken and added to 100 mL distilled water maintained at 37°C with paddle rotating at 50 rpm for gentle agitation.[26]

Determination of percentage transmittance

5 mL of SEDDS formulation was prepared and the percentage of transmittance was measured using UV spectrophotometer keeping distilled water as blank at 638 nm.[27]

In vitro dissolution test

For the *in vitro* dissolution study, USP apparatus Type II was used. In this 5 mL of SEDDS formulation introduced and water is used as dissolution medium and maintain temperature at 37°C ± 0.5 and rpm is 50. Dissolution samples (5 mL) were withdrawn at predetermined time intervals and replaced with an equivalent amount of fresh water. The absorbance of the samples was checked by UV spectrophotometer at 260 nm.[28]

Drug content test

5 mL of SEDDS formulation was prepared from that 1.06 mL was dissolved in ethanol solvent. Drug content within the solvent extract is analyzed by UV spectrophotometer.[29]

Table 1: Preparation of various formulations with different compositions

S. No	Formulation	Oil (%)	Surfactant (%)	Cosurfactant (%)
S_{mix} (8:1)		Cinnamon oil	Tween 80	Propylene Glycol
1	F1	12.5	77.7	9.8
2	F2	11.1	78.93	9.97
3	F3	10	81	9
S_{mix} (7:1)		Cinnamon oil	Tween 80	PEG 400
4	F4	11.1	78.93	9.97
5	F5	10	81	9
S_{mix} (8:1)		Cinnamon oil	Tween 80	PEG 400
6	F6	12.5	77.7	9.8
7	F7	11.1	78.93	9.97
8	F8	10	81	9

Cloud point determination

0.5 mL of SMEDD formulation was taken in a test tube and placed in water bath and gradually increase the temperature. The appearance of cloudiness in sample was noted as cloud point. Note down the temperature and time at which the precipitates forms in test tube.[30]

Robustness to dilution

1ml of every formulation was subjected to 50, 100, and 250 fold dilution to each different buffers of water, phosphate buffer pH 6.8, and 0.1N HCL and kept them for 24 h. After that, the formulations are observed for any phase separation.[31]

Viscosity measurement

SEDDS formulation of 10 mL was taken and its viscosity was measured using viscometer using spindle C at 25 ± 0.5°C with 50 rpm.[31]

Determination of scanning electron microscope (SEM)

The developed formulation subjected to SEM study to reveal the external morphology of the optimized formulation.[32]

Droplet size and zeta potential analysis

The developed formulation subjected to measure the zeta potential and droplet size by zeta potential analyzer.[33,34] The PDI value more than 0.7 indicates poor stability of formulation.

RESULTS AND DISCUSSION

Pre-formulation studies

Organoleptic properties

The drug was characterized by following organoleptic properties

- Nature: Amorphous powder
- Color: white color
- Odor: Odorless.

Determination of melting point

The melting point of Tolvaptan drug was found in range between 204 and 216°C. The melting point was determined by capillary method by visual observation. The melting point of Tolvaptan is within the range of reference melting point (215°C). Hence, the drug shows that it does not have any impurities and it was stable.

Solubility studies

The solubility of Tolvaptan drug was studied in different medium. The results for solubility study of Tolvaptan drug are given in following Tables 2 and 3 and the Cinnamon oil has shown the best solubility [Figure 1].

Determination of λ_{max} of Tolvaptan drug

The spectrum showed the maximum wavelength λ_{max} at 260 nm.

Determination of calibration curve of Tolvaptan drug

The calibration curve determined with concentrations of 3, 6, 9, 12, 15, and 18 µg/mL [Figure 2]. The absorbance was observed at 260 nm against 5% w/v SLS solution.

Determination of thermodynamic stability test

Heating-cooling cycle: No phase separation from F_1 to F_8 formulations at 45°C and at 4°C for 48 hrs. Centrifugation: No phase separation was observed in formulations F_1 to F_8 at 25°C for 30 min. It concludes on the basis of thermodynamic stability studies, it says that the developed formulations were thermodynamically stable and has good stability and did not show any phase separation.

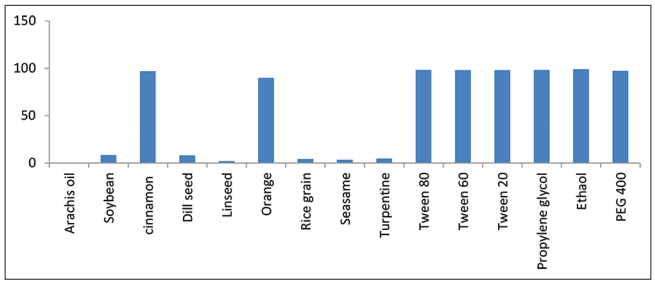

Figure 1: Solubility of Tolvaptan in oils/surfactants/ cosurfactants

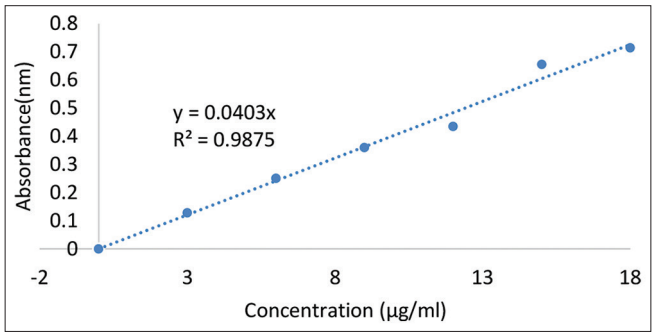

Figure 2: Calibration curve of tolvaptan

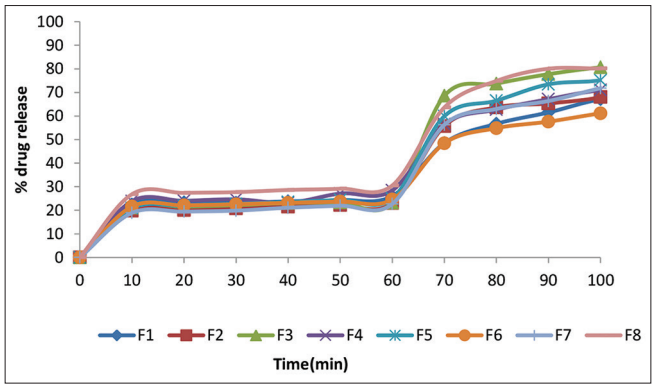

Figure 3: Percentage drug release studies

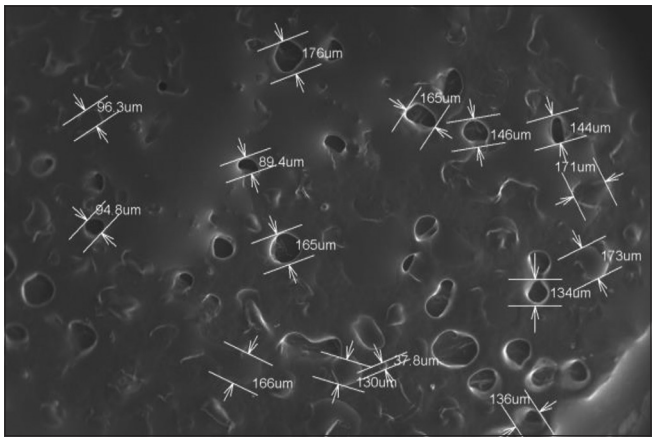

Figure 4: Determination of scanning electron microscopy for optimized formulation

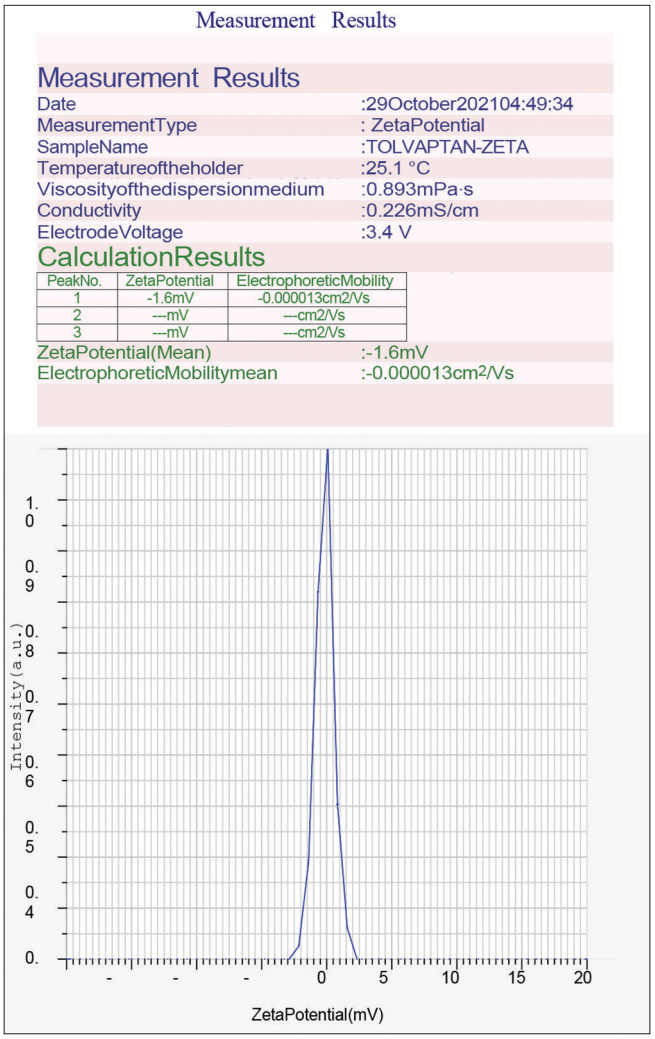

Figure 5: Zeta Potential of Optimised formulation

Table 2: Determination of solubility of drug in various oils

S. No	Oils	Solubility (mg/mL)
1	Arachis oil	18.56±0.2
2	Pure soybean oil	20.19±0.3
3	Cinnamon oil	97.30±0.5
4	Dill seed oil	18.08±0.2
5	Linseed oil	21.56±0.4
6	Orange oil	90.73±0.6
7	Pure rice brain oil	24.78±0.3
8	Sesame oil	23.46±0.5
9	Turpentine oil	24.87±0.4

Determination of phase separation study test

No phase separation was observed in formulations F_1 to F_8. This indicates that the developed formulations are stable and clear.

Table 3: Determination of solubility of drug in various surfactants and cosurfactants

S. No	Surfactants	Solubility (mg/mL)
1	Tween 80	98.34±0.1
2	Tween 60	98.14±0.3
3	Tween 20	98.06±0.2
Co-surfactants		
1	Propylene glycol	98.21±0.3
2	Ethanol	99.02±0.1
3	PEG 400	97.36±0.2

Determination of emulsification study test

No phase separation was observed in formulation F_1–F_8 at 37°C in USP II apparatus at 100 rpm. The emulsification time of developed formulations was observed in range between 3 s and 4 s. The minimum emulsification time was observed in F_2, F_4, F_5, F_7, and F_8 is 3 s. The maximum emulsification time was observed in F_1, F_3, and F_6 4 s. It can conclude that the developed formulation forms the emulsion with the GI fluid within 1 min.

Determination of percentage transmittance

The percentage transmittance of developed formulation was found in range between 99.77 and 92.46. The minimum percentage transmittance was observed in formulation F_1 is 92.46%. The maximum percentage transmittance was observed in formulation F_5 and F_8 is 99.77%. Hence, it concludes that the percentage transmittance gives the clarity of the formulations.

Determination of *in vitro* dissolution test

The amount of drug release was found in ranges between 64.97% and 81.5%. The minimum drug release was observed in F_6 formulation is 64.97%. The maximum drug release was observed in F_5 formulation is 81.5%. It concludes that the developed formulation shows better bioavailability compared to pure drug [Figure 3].

Determination of drug content

The drug content in formulation $F_1$to F_8 was found in range between 71.25 and 102.5%. The minimum drug content was observed in F_1 formulation is 71.25%. The maximum drug content was observed in F_5 formulation is 102.5%. Hence, it concludes the developed formulation contains required drug.

Determination of cloud point

The cloud point of formulations was observed in range between 204°C and 218°C. The minimum cloud point was observed in F_1 formulation at 204°C. The maximum cloud point was observed in F_7 formulation at 218°C. Hence, it can be concluded that the developed formulations are stable and produce stable emulsion.

Determination of robustness to dilution

No phase separation was observed in formulation F_1–F_8 of 50, 100, and 250 mL dilutions of distilled water, 0.1N HCL and pH 6.8 phosphate buffer. Hence, it concludes that the developed formulations are stable at three different mediums.

Determination of viscosity

The viscosity of formulations F_1–F_8 was observed in range between 861.8cps and 913.4 cps. Apart from the viscosity, the emulsification time also observed, and it concludes that the self-emulsification time of F_1–F_8 formulations was less than 1 min with the decrease of viscosity.

Determination of SEM for optimized formulation

The droplet size in formulation was found in range from 37.8 to 176 µm means the droplets are in spherical and micro size [Figure 4] and then the formulation said to be self-micro emulsifying drug delivery system. Thus, it concludes that the smaller droplet size increases the surface area it leads to increase in bioavailability of drug.

Determination of droplet size and zeta potential

The developed formulation F_5 has polydispersity index value that is 0.271 which indicate homogenous droplet population and narrow globule size distribution and it indicates stability of emulsion. The zeta potential value is −1.6 mV [Figure 5]; it indicates that the emulsion has good stability.

SUMMARY

Tolvaptan is a selective vasopressin V2 receptor antagonist. It used to treat hyponatremia (low blood sodium levels). It is a BCS Class II drug. Tolvaptan exhibits high solubility in cinnamon oil, orange oil, and surfactants of Tween 80, Tween 60, Tween 20, and co-surfactants of propylene glycol, PEG 400, and ethanol. Formulation was prepared using the oil and surfactant ratios which are determined from the ternary phase diagram. The F_5 formulation shows better drug release is 81.5%. The zeta potential value is −1.6mV and PDI value is 0.271 which indicates the stability of emulsion.

CONCLUSION

By observing the characterization and evaluation tests conclude that the self-micro emulsifying drug delivery system is suitable for Tolvaptan drug to improve the drug release.

ACKNOWLEDGMENT

We express our profound thanks to MSN laboratories to give a gift sample of API.

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Source of Support: Nil. **Conflicts of Interest:** None declared.