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FORMULATION AND EVALUATION OF SATRANIDAZOLE BY SELF EMULSIFYING DRUG DELIVERY SYSTEM

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Keywords:

Satranidazole, Surfactants, Pseudo ternary phase diagrams, SEDDS

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ABSTRACT: Background: Satranidazole is a class II drug per bio-pharmaceutical classification systems with poor aqueous solubility and antiprotozoal and anti-bacterial properties. **Aim:** Therefore, the purpose of the present study was to enhance the solubility of Satranidazole using a self-emulsified drug delivery system (SEDDS). **Methods:** SEDDS was prepared using Satranidazole (10 mg) and dissolved in the oil phase, *i.e.*, rice bran oil and GMO (1:9). The co-surfactant, propionic acid, was added to the oil phase, and then Tween 80 was added with continuous stirring. The mixture was allowed to homogenize at 40 °C for 24 h and was stored in a stoppered glass vial until further evaluation. The total amount of the mixture was kept constant at 0.37 ml to be filled in size 2 capsules for dissolution study. **Physico-Chemical Evaluation:** Four SEDDS formulations were prepared (F-1 to F-4) and evaluated for let size analysis, stability studies, zeta potential, drug content and *in-vitro* drug release. **Results:** Based on self-emulsification time & dispersibility, droplet size analysis, drug content and in vitro drug release, S-1formulation was selected as an optimized formulation that showed a maximum drug release of 98.15 ± 1.84 % in 45 min. **Conclusion:** Hence SEDDS formulations can be a potential alternative to available traditional oral drug delivery systems of Satranidazole to improve its solubility.

INTRODUCTION: The poor oral bioavailability arising from poor aqueous solubility should make drug research and development more difficult. Various approaches have been developed with a focus on enhancing the solubility, dissolution rate, and oral bioavailability of poorly water-soluble drugs [1]. Self-emulsifying drug delivery systems (SEDDS) are isotropic mixtures of oils, surfactants, co-surfactants and co-solvents forming oil-in-water nano-emulsions upon gentle dispersion in an aqueous environment, e.g., gastrointestinal fluids. These oral lipid-based drug delivery systems were originally established to improve the bioavailability of small, poorly water-soluble molecules.

Recently, the delivery of hydrophilic macromolecules in SEDDS has gained increasing attention to take advantage of its beneficial properties, such as easy up-scaling, nano-size of formed droplets, and protection of the loaded substance from chemical and enzymatic degradation [2]. Despite these encouraging results, SEDDS as liquid formulations still faces shortcomings, especially when it comes to long-term storage stability. Peptide and protein

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drugs tend to precipitate, dena-ture or even degrade during storage. Unfortunately, there is a significant lack of studies accounting for peptide or protein storage stability in liquid lipid matrices [3]. To improve the ease of administration, which is of great importance for chronic diseases such as T2D, oral delivery systems for exenatide are in development [4, 7] and SEDDSs are among the most promising approaches [5, 8, 9]. Satranidazole (STZ) is a new drug in the class of nitro-imidazole derivative compounds. It is chemically known as 1-methylsulfonyl-3-(1-methyl-5-nitro-2-imidazolyl)-2-imidazolidinone and therapeutically is a potential anti-bacterial and antiprotozoal which used management of amoebiasis [10]. The properties of longer half-life and higher blood levels demonstrated in the Pharmacokinetic studies of Satranidazole as in humans resulted in necessitating less frequent dosing of SZ compared to metronidazole. These properties combined with its greater potency are believed to contribute to its therapeutic efficacy [11].

MATERIALS & METHODS: Satranidazole was obtained as a gift sample from Alkemlabs, Mumbai. Ricebranoil, Palmoil, Flaxseed oil, Glycerylmonooleate, Isopropyl myristate, Glycerylmono - stearate, Labrafaclipophile, Tween 60, Tween 80, Tween 20, Lauroglycol 90, Propionic acid, Propyleneglycol, Capryol 90, Transcuto lP, Maisine 35-1 used were of analytical grade.

METHODS: Determination of melting point**.** The melting point of Satranidazole was determined using the open capillary method. The drug powder sample was packed into capillary, and the melting point of Satranidazole was determined by using the digital melting point apparatus shown in **Table 1**[12].

Determination of UV Absorption Maxima: The UV spectrometry method for estimation of Satranidazole was used referring to the reported method (Acharjya *et al.* 1431-36). Solution of Satranidazole (100 µg/ml) was prepared in 0.1 NHCl with the help of methanol and was scanned for absorption between. 200 to 400 nm using double beam 1700UV-Visible spectrophotometer (Shimadzu Corporation, Kyoto, Japan). Satranidazole exhibited UV absorption maxima at 318 nm [12].

UV-Spectral Analysis of Satranidazole: 25 mg of Satranidazole was dissolved in 1 ml of methanol, and the solution was diluted up to 250mlwith0.1NHClnavolumetricflask to obtain a stock solution of 100µg/ml [12].

Calibration curve of Satranidazole: In a series of 10 ml volumetric flask, the stock solution was serially diluted to getaliquots in the range of 5-25 µg/ml. The absorbance of the resulting solution was measured using a UV spectrophotometer against blank prepared without Satranidazolein similar manner. The calibration curve is shown in **Fig. 2**. The results of regression analysis of calibration curve are depicted in **Table 2** [12].

U. V. Method Validation: The developed method was validated to ICH guidelines.

Linearity and Range: Stock solution of Satranidazole (2-10 ml of 0.01 mM solution) were transferred into10ml standard flasks and made volume using distilled water. The absorbance of the solutions of different concentrations was measured at 318 nm against distilled water as blank.

Detection Limit (DL): DL was calculated from the formula DL=3.3I/S**,** Where I intercept and Sis slope of the calibration curve.

Quantification Limit (QL): QL is formulated from formula QL=10I/S

Precision: To evaluate repeatability of the method, pure drug solution (within the working limits) was analyzed and is repeated six times. The intermediate precision of the method was demonstrated by intra-day variation studies. In intra-day studies, three repeated standard and sample solution measurements were made in a day and the percentage RSD was calculated. The relative standard deviation (%) was less than 2.0 and high precision for the proposed method.

Accuracy and Recovery Studies: To ensure accuracy, known amounts of pure drug were added to the solvent and these samples were reanalyzed by the proposed method and also % recovery was determined.

Accuracy and Recovery Studies: To ensure the accuracy, known amounts of pure drug were added to the solvent and these samples were reanalyzed by the proposed method, and also % recovery was determined.

Thermal Analysis of Satranidazole: Procured sample of Satranidazole was subjected to DSC analysis; the thermogram was recorded using Shimadzu DSC -60 thermal analyzer. The observation is shown in **Table 9,** and the thermogram was shown in **Fig. 4.**

FT-IR Spectroscopy of Satranidazole: The IR spectral characteristics of Satranidazole were compiled in **Table 5,** and the spectrum was recorded in **Fig. 4.**

FT-RAMAN Spectroscopy of Satranidazole: Raman spectroscopy of Satranidazole is a pectro scopic technique used to observe vibrational, rotational, and another low-frequencymodesina systems.

Raman spectroscopy is commonly used in chemistry to provide a structural fingerprint by which molecules can be identified. Raman spectroscopy is one of the vibrational spectroscopic techniques used to provide information on molecular vibrations and crystal structures.

This technique uses a laser light source to irradiate a sample and generates an infinitesimal amount of Raman scattered light detected as a Raman spectrum singa CCD camera. The characteristic fingerprinting pattern in a Raman spectrum makes it possible to identify substances including polymorphs and evaluate local crystallinity, orientation and stress.

X-Ray Diffraction of Satranidazole: X-ray powder diffraction (XRPD) was performed to identify the crystalline form of ETR used in this experiment and shown in **Fig. 5.**

Saturation Solubility Study of Satranidazole by Shake Flask Method: Saturation solubility of Satranidazole was determined in all the liquid excipients as well as in dissolution medium, *i.e.,* 0.1 NHCl by shake flask method (Baka, Comer and Takács-Novák 335-41).

An excess amount of drug was added to 2 ml of each liquid excipient and 0.1 NaCl. The mixture was heated at 40 °C on a water bath for 10 min. The samples were stirred for 24 h on the rotary shaker and centrifuged at 2000 rpm for15 min. The 10 h was allowed for a heterogeneous system to reach equilibrium. Super natant was filtered through What man filter paper (0.45 µm) and analyzed for Satranidazole a t318 nm using UV spectrophotometer (Shimadzu, Japan). Whenever required, filtrates were suitably diluted with methanol.

Construction of Pseudo-ternary phase Diagrams: Phase diagrams were drawn to identify the blends of oil-surfactant-co-surfactant that gives nano-emulsion employing water titration method. The mixture of rice bran oil and GMO (1:9) asanoil phase was mixed with three different combinations of surfactants and co-surfactants in the ratio of 0:10, 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1 and 10:0. The results and discussion section depict the combinations of surfactant sandco-surfactants employed. The water was added dropwise to the oil surfactant co surfactant blends.

Using Pro Sim software, the points at which the mixture transits from clear-turbid-clear were noted and plotted on the ternary/pseudo-ternary phase diagrams. The aim was to identify the blend of excipients that give the maximum isotropic region in the diagram and maximum fully dilutable lines. (Parmar *et al.* 327-38; Amsalem *et al.* [15, 22].

Formulation of SMEDDS: From the results of the pseudo-ternary phase diagrams, the only composition giving fully dilatable lines were taken for the formulation development. Satranidazole (10 mg) was dissolved in the oil phase *i.e.,* rice bran oil and GMO (1:9).

The co-surfactant, propionic acid, was added to the oil phase and then Tween 80 was added with continuous stirring. The mixture was allowed to homogenize at 40 °C for 24 h and was stored in a stoppered glass vial until further evaluation. The total amount of the mixture was kept constant at 0.37 ml to be filled in size 2 capsules for dissolution study.

RESULTS AND DISCUSSION:

Determination of Melting Point: The melting point of Satranidazole was 184 °C which is the same as reported in the literature (182-187 °C).

UV Spectral Characteristics of Satranidazole: The Solution of Satranidazole (100 µg/ml) was prepared in 0.1 NHCl with the help of methanol

and was scanned for absorption between 200 to 400 nm using a double beam 1700 UV-Visible spectrophotometer (Shimadzu Corporation, Kyoto, Japan). Satranidazole exhibited UV absorption maxima at 316 nm.

Thermal Analysis of Drug: The DSC thermogram of the Satranidazole shows a sharp endothermic peak at 195.280 ºC) and found similar with reported value. The DSC thermogram is mentioned in **Table 1** and **Fig. 1.**

TABLE 1: DSC PARA METERS OF SATRANIDAZOLE

Parameters	Value
Weight of Satranidazole (mg)	8.2000 mg
Integra lm J norm alized-Jg^-1	-693.21
Rate of Heating (°C/min)	-115.54
DSC Peak (°C)	195.28
On set of DSC Peak (°C)	190.97
End set of DSC Peak (°C)	199.53
Extrapol. Peak °C	195.55

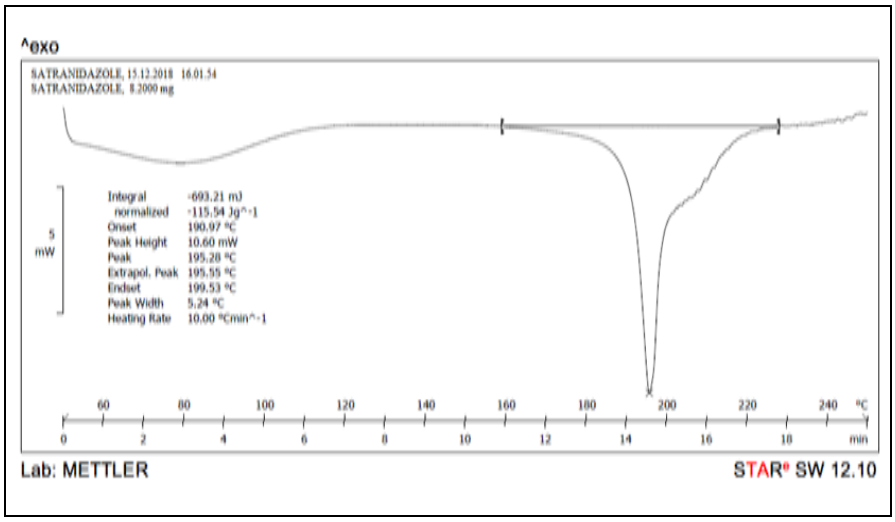

FIG. 1: DSCOFSATRANIDAZOLE

FT-IR Spectroscopy of Satranidazole:

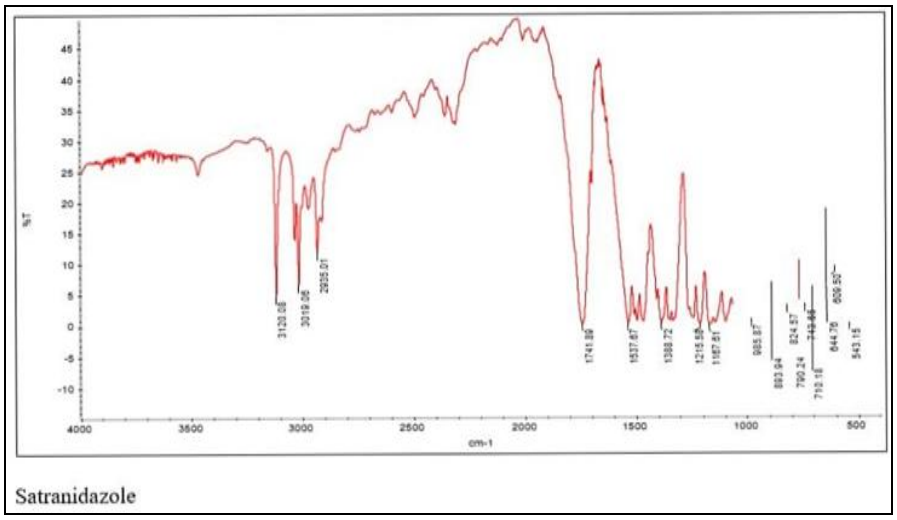

FIG. 2: FT-IR SPECTRUM OF SATRANIDAZOLE

FT-RAMAN Spectroscopy of Satranidazole:

Solubility Study: Triacetin, the only short-chain triglyceride showing solubility of 109 mg/ml of Satranidazole, was taken as an oil phase. The non-ionic surfactant sandco-solvents were used, as reported earlier.

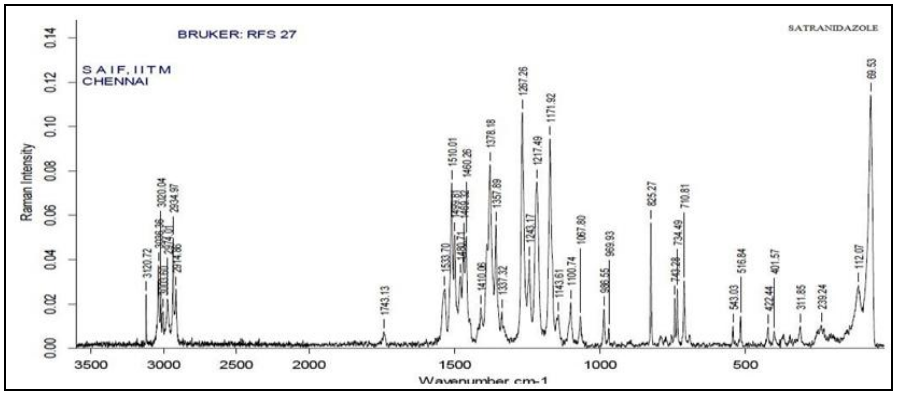

FIG. 3: FT-RAMAN SPECTROSCOPY OF SATRANIDAZOLE

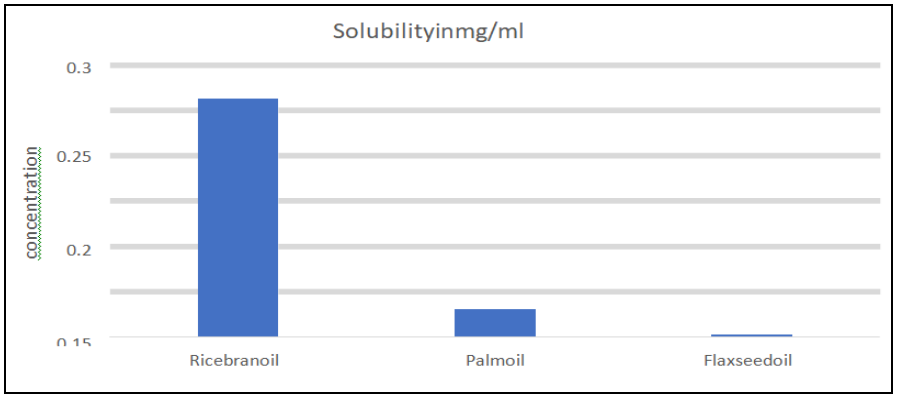

FIG. 4: SOLUBILITY IN VARIOUS OILS

Solubility of Satranidazole in Various Surfactants:

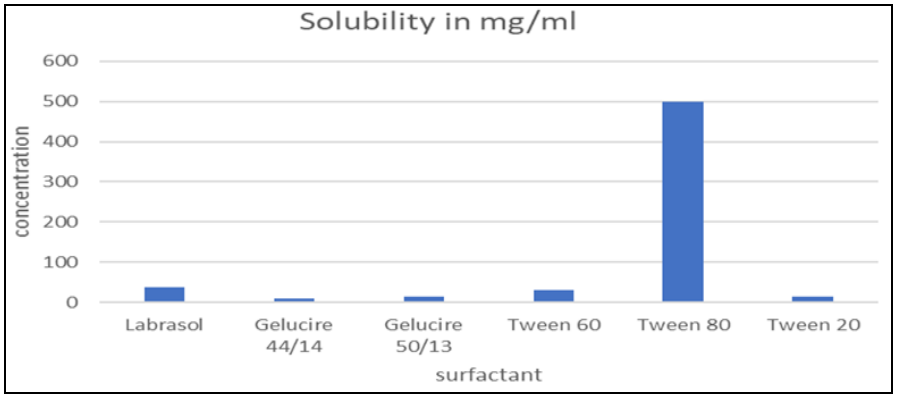

FIG. 5: SOLUBILITY OF SATRANIDAZOLE INVARIOUS SURFACTANTS

Solubility of Satranidazole in various Cosurftants

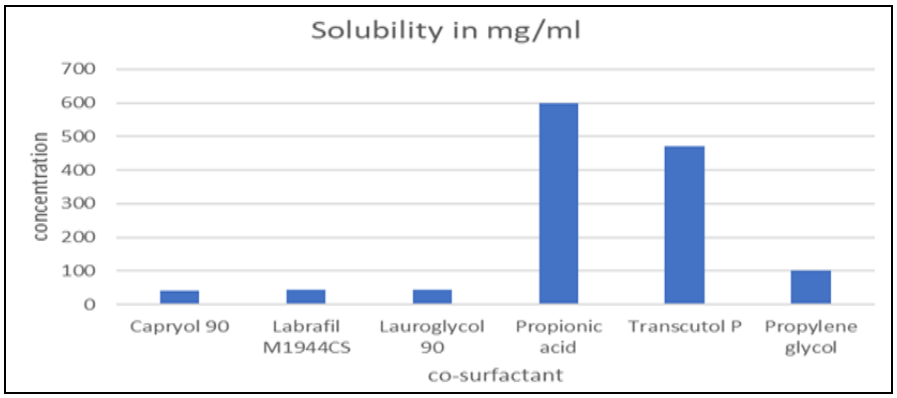

FIG. 6: SOLUBILITY OF CO-SURFACTANT

Pseudo-ternary Phase Diagrams: While titrating the triacetin and different surfactant and co-surfactant mixture with water, it was observed that Triacet in was not compatible with co-surfactants &/orco-solvents likePEG 400, propylene glycol, and Transcu to lP.

Being fully dispersible in water, the Triacet in as when mixed with other co-solvents resulted into unstable microemulsion which showedrapid creaming and coalescence. When mixed with only surfactants such as tween 20 and tween 80, satisfactory microemulsions were formed. Both tween 80 and tween 20 gave more than 65% isotropic region with 4 and 5 fully dilutable lines, respectively.

Again here, tween 80 provided better microemulsion, which was stable even after 24 h., while with tween 20, little creaming was observed after storage. Therefore, Triacetinwitht ween 80 was selected for preparing SMEDDS.

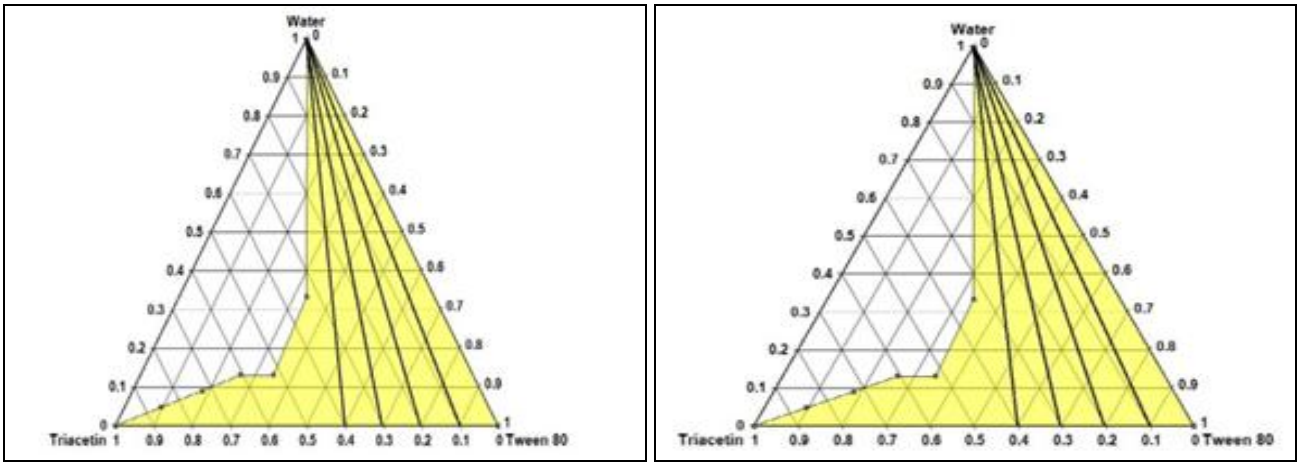

FIG. 7: PHASE DIAGRAMS OF TRIACET IN WITH TWEEN 80(A) AND TWEEN 20(B)

TABLE 2: EVALUATION OF SMEDDS BATCHES

Batch	Self-Nano emulsification Time	Cloud pointIn°C	Globule sizein nm(PDI)	Zeta Potential (mV)	%Transmittanceand-phaseclarity
S1	12Sec	65	200 (0.47)	-	98.32%Transparent
S2	21Sec	64	238.3 (0.45)	-	98.12% Transparent
S3	15 sec	69	260 (0.31)	-	98.01% Transparent
S4	14Sec	67	317.8(0.37)	-3.33	97.63% Transparent

Characterization of Pre-concentrates: The pre-concentrates spontaneously resulted in transparent micro emulsion in less than 25 sec. as indicated by self-micro emulsification time and % transmittance. The globule size increased with the increase in amount of oil. The cloud points were as high as 65 °C, which indicates that they formed microemulsion will have good stability. There were no signs of phase separation for 24 h.

FIG. 8: SMEDDS S1OPTIMIZED BATCH FORMULATION

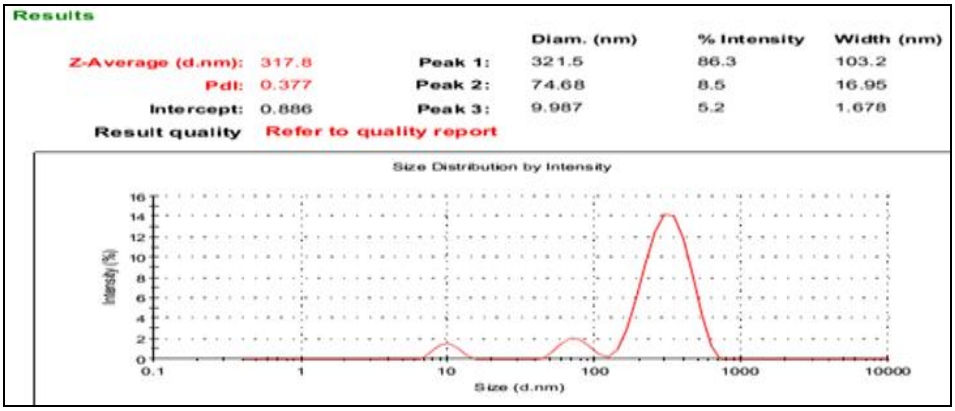

FIG. 9: GLOBULESIZED IS TRIBUTION OF BATCHS 4

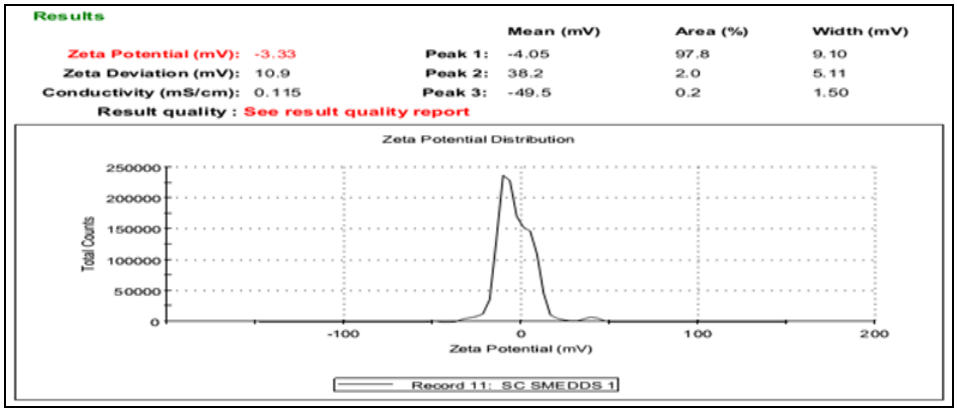

FIG. 10: ZETAPOTENTIAL GRAPH FOR BATCHC

***In-vitro* Release of Satranidazole from-SMEDDS:** The results of the *in-vitro* drug release study showed that batches S1 and S2 exhibited93% drug release in the first 5 min and more than 95% drug release within 60 min. While batches S3 and S4 showed slower release initially, however, they were comparable to batches S1 and S2 at later time points. There as on for delay in dissolution in case of batches S3 and S4 may be attributed to a higher amount of triacetin and lower amount of tween 80, which resulted in big globules compared to LC-SMEDDS.

TABLE 3: %DRUG RELEASE OF SATRANIDAZOLE FROM SC-SMEDDS

Time in min	% Cumulative drug release from batches			
	S1	S2	S3	S4
5	93.94± 1.24	93.05± 5.47	83.13±1.84	69.63±2.47
10	94.22± 1.54	94.08± 2.37	88.41±4.17	74.52±2.41
15	95.6± 1.57	93.55± 2.94	95.35±2.45	75.98±2.83
30	97.85± 1.95	94.08± 3.48	97.25±1.29	85.24±3.24
45	98.15± 1.84	94.99± 1.29	97.32±2.51	91.09±1.28
60	99.48± 2.37	95.2± 1.58	98.79±3.58	96.95±1.53

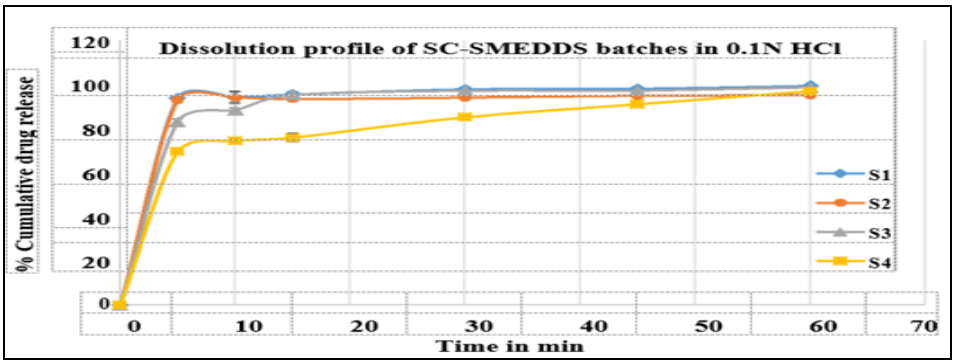

FIG. 11: % DRUG RELEASED IN 0. 1 NHCL FROM SC-SMEDDS BATCHES

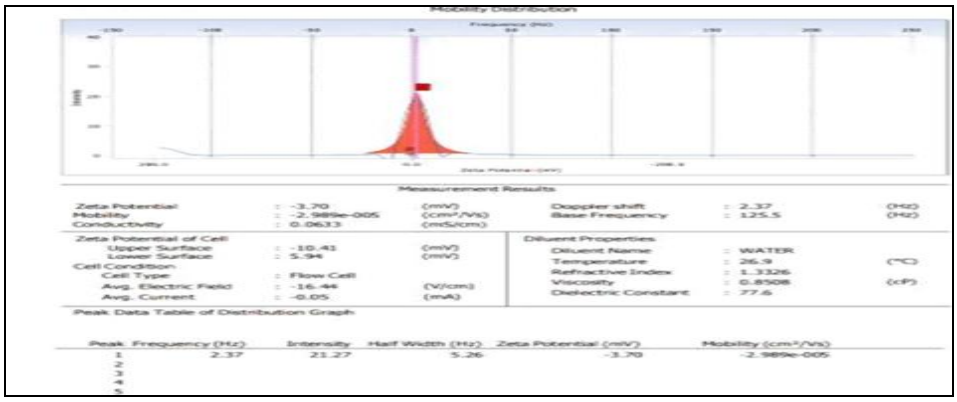

FIG. 12: ZETA POTENTIAL RESULTS

Stability Studies:

Effect of Dilution: On visual assessment, no precipitation or phase separation was found, which indicates that all the formulations were stable on dilution.

Thermo Dynamic Stability Studies: On visual assessment, no precipitation or phase separation was found, indicating that all the formulations were stable on thermodynamic studies.

Short Term Stability Study: During short term stability studies, optimized formulation S1 was withdrawn at the interval of one month and evaluated for drug content, droplet size and self-emulsification. From the results, it was observed that there was no significant change in droplet size drug content.

CONCLUSION: Self-emulsifying drug delivery systems containing satranidazole were formulated using various ratios of oil, surfactant, and co-surfactant mixture in an attempt to increase its release rate and bioavailability. SEDDS of satranidazole showed an improved dissolution rate and absorption. Satranidazole SEDDS showed more significant anti-bacterial and parasitic activity). The present study demonstrated the successful preparation of self-emulsifying drug delivery systems of satranidazole.

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CONFLICTS OF INTEREST: The authors declare no conflict of interest exists.

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