GSC Biological and Pharmaceutical Sciences

eISSN: 2581-3250 CODEN (USA): GBPSC2

Cross Ref DOI: 10.30574/gscbps

Journal homepage: https://gsconlinepress.com/journals/gscbps/

(RESEARCH ARTICLE)

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Formulation and evaluation of bilastine loaded solid Self-Nano Emulsifying Drug Delivery System (s-SNEDDS) for oral administration: *In-vitro* characterization

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GSC Biological and Pharmaceutical Sciences, 2023, 25(03), 167–178

Publication history: Received on 08 November 2023; revised on 23 December 2023; accepted on 25 December 2023

Article DOI: https://doi.org/10.30574/gscbps.2023.25.3.0529

Abstract

The aim of this study was to prepare an oral administrable SNEDDS for poorly water soluble drugs Bilastine. To choose the SNEDDS excipients, a ternary phase diagram and solubility assessment were conducted. A components of oil (capmul PG-NF) surfactant (Tween 40) and co-surfactant (Capryol 90) were used as the excipients. The optimized formulation was characterized for *In-vitro* analysis. The prepared S-SNEDDs exhibited good flow characteristics and Particle size (148.5dnm), zeta potential (−28.6), PDI (0.242), drug loading efficiency, % CDR of the optimized S-SNEDDs [TP3PG1 (2:8)] was found to be 103.61 ±0.678, 98.65% respectively. The formulation was stable over a 3-month storage period at 25 ◦C and 4 ◦C in terms of particle size, physical appearance, and drug loading. Overall, a range of lipid based SNEDDS liquid, solid formulations were successfully developed and seem to be a promising alternative to improving the solubility of poorly water-soluble drugs and evaluating *In-vitro* characterizations.

Keywords: Self-nanoemulsifying drug delivery system (SNEDDS); Capmul PG-NF; Tween 40; Capryol 90; Bilastine; solubility enhancement; *In-vitro* drug release.

1. Introduction

Bilastine is an antagonist that prevents histamine from acting on H1 receptors. It exhibits no or very little effect at receptors for other mediators, but has a strong affinity for histamine H1 receptors (3 and 5 times greater than cetirizine and fexofenadine, respectively). After oral administration, Bilastine is quickly absorbed and has a bioavailability of about 60% (which is decreased by 25–30% if food or grape juice is consumed) [1]. The maximum clinical effect lasts from 30 minutes to 8 hours (Tmax = 1.3 hours), with the antihistaminic action starting within 30 minutes. Between 84–90% is bound to plasma proteins. Bilastine exhibits low inter-individual variability and linear pharmacokinetics in the dose range (5 to 220 mg). In humans, Bilastine is not significantly metabolized and does not significantly interact with the CYP enzyme system, either as an inducer or an inhibitor. In both urine (28%) and faeces (67%), approximately 95% of the dose is eliminated unaltered. (16 hours) is how long Bilastine takes to start working [2]. Adults with seasonal and perennial rhino-conjunctivitis, urticarial infections, and allergic rhinitis should be treated with Bilastine to relieve their symptoms. The effectiveness of Bilastine has been found to be better than a placebo ($P<0.001$) and comparable to that of levocetirizine. Self-emulsifying drug delivery systems are isotropic mixtures of oils (natural or synthetic), surfactants (solid or liquid), hydrophilic solvents and co-solvents/surfactants. In order to solubilize the hydrophobic drug until absorption occurs, SNEDDS is becoming more and more popular for enhancing the rate of dissolution and oral absorption of lipophilic drugs [3]. SNEDDS typically contains less than 20% oil and is made with surfactants with an HLB > 12 concentration. For the formulation of SNEDDS, a variety of techniques including spray drying, melt granulation, and adsorption on inert solids like high pressure homogenizer, microcrystalline cellulose, and aerosol are used to achieve solidification [6].

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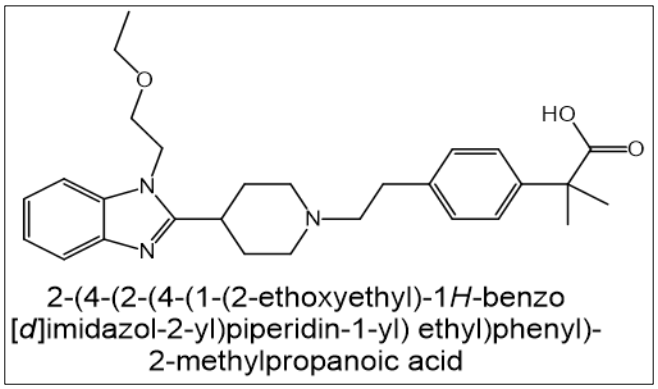

Figure 1 Structure of Bilastine

The purpose of this study to improve the solubility and *In-vitro* drug release of Bilastine by designing and developing an optimized SNEDDs formulation using different oil, surfactant and co-surfactant. Following a dispersibility test, the chosen formulations were assessed based on their percentage transmittance, drug content, zeta potential, particle size, and physical, chemical, and thermodynamic stabilities. Furthermore, formulations were evaluate to check various parameter of solid SNEDDS [3, 4].

2. Method and materials

2.1. Determination of Bilastine by using UV-spectroscopy method

2.1.1. Instrumentations

A UV Spectrophotometer (UV-1800 Shimadzu) operating in the 200–400 nm wavelength range was used for the spectrophotometric analysis. A UV-1800 Shimadzu spectrophotometer was used for the calibration study [5].

2.1.2. Materials

Bilastine was purchased from Hetero drug Pvt. Ltd, Hyderabad. Olive oil, Capmul PG-NF, Crodamol PC-LQ, Crodamol P30, Labrasol, Tween 40, Labrasol ALF, Labraf IF, Span 80, Transcutol p, Transcutol HP, Lauroglycol 90, Plurol oleique, Capryol from Gattefosse Mumbai. The analytical reagent grade acetonitrile, methanol and Hydrochloric acid were obtained from Rankem Chemicals. Neusilin US2 were gifted from Hetero drug Pvt. Ltd, Hyderabad. Millipore water was used during the whole study [3, 6].

2.2. Standard Stock Solution Preparation

Weighed 100 mg of Bilastine standard was transferred to a 100 ml volumetric flask and mixed with diluents to create a solution that contained 1000µg/ml of Bilastine. A 100 ml volumetric flask was filled with 10 ml of the stock solution, which was then extracted. Diluents are added to the volume to achieve the desired working standard solution of 100 µg/ml concentration [5].

2.3. Wavelength of standard drug (λ_{max})

In order to determine the wavelength range for the 10µg/ml method, distilled methanol was used as a blank and Bilastine was scanned in spectrum mode from 200 to 400 nm. The chosen wavelength range revolved around the 205 and 266 nm wavelength maxima (figure-02) [4].

2.4. Standard Curve of Bilastine by UV spectrophotometer (Shimadzu-1800)

Working stock solutions of Bilastine aliquots 0.5, 1, 1.5,2, and 2.5 ml were transferred into various volumetric flasks with a 10 ml capacity. Diluents were used to adjust the volume to the required concentration of 5, 10, 15, 20, and 25 µg/ml. At 205nm, the solutions' absorbance was measured. Plotting absorbance against drug concentration allowed for the construction of the calibration curve, and regression equations were generated [7].

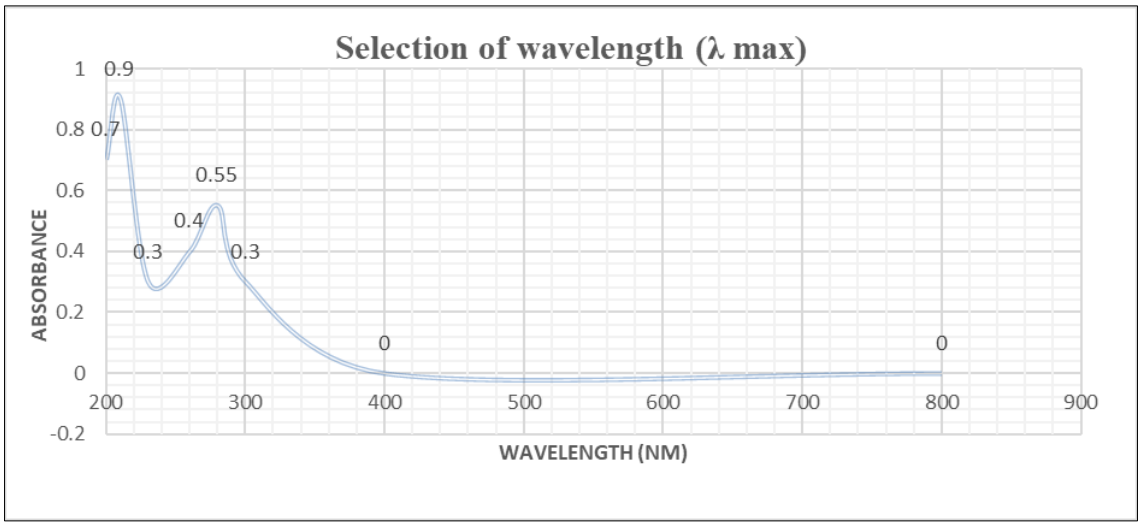

Figure 2 Wavelength of standard drug (λ_{max})

2.4.1. Solubility studies of bilastine

The Solubility study of poorly water soluble drug in oils, surfactants and co surfactants required for the screening of components for SNEDDS formulation. Since the goal of this study is to prepare an oral formulation, the drug's solubility in oils is more crucial because it affects SNEDDS's capacity to keep the drug in a solubilized state [1, 8]. To check solubility of Bilastine using different components of oils (olive oil, Capmul PG-NF, Crodamol PC-LQ, and Crodamol P30,Capmul MCM EP and surfactants and co-surfactants, such as Lauroglycol 90, Plurol oleique, Labrasol, Tween 40, Labrasol ALF, Labraf IF, Span 80, Transcutol p, Transcutol HP, Lauroglycol 90, etc. The drug was taken in a stopper glass vial of 5 mL capacity and mixed for 10 min with each component by using a vortex mixer. The vials were kept in an isothermal shaker (GFL1092, Burgwedel, Germany) at 50 ± 1.0 ◦C for 72 h until homogeneity is achieved [9,10]. The homogenate centrifugation was carried out at 1500 rpm for 10 minutes or 5000 rpm for 5 mints. Following collection, the supernatants were diluted in a mixed solvent and filtered through a 0.45 µm syringe and drug concentration was determined through A UV Spectrophotometer (UV-1800 Shimadzu) method [11].

2.4.2. Pseudo-ternary phase diagrams

The identification of nano-emulsions regions were determined by using pseudo-ternary phase diagrams. SNEDDS were diluted under agitation conditions using water titration method. The appropriate amount of oil, surfactant, and co-surfactant composition used to create Nano emulsion regions. Pseudo-ternary phase diagrams revealed that, despite the drug's higher solubility in the systems, the systems with Capmul PG-NF oil as the oily phase, Tween 40 as the surfactant, and Capryol 90 as the co-surfactant demonstrated stable nanoemulsifying properties. TP3PG1 demonstrated blue tinge emulsion (BTE) for Oil: Smix 1:9, 2:8, and clear transparent emulsion for 3.7, 4:6, 5:5, 6:4, and 9.1 for Smix 3:1 ratio formulation. And no liquid crystal stage appears during the titration process [9, 12]. Furthermore, it was discovered that the ability to form Nano emulsion decreased in six systems with increasing co-surfactant proportion when the systems contained Capmul PG-NF oil as the oily phase, tween 40 as a surfactant and Capryol 90 as co-surfactant. This observation also makes it confirm that surfactant plays a part in the proper range formation of the Nano emulsion. Figures -05 illustrate the Nano emulsion region that is seen in the formulations. Tables-03 provide the percentage composition of the water, Smix, and oil that were consumed during the titration [13].

2.5. Preparation of solid SNEDDs (S-SNEDDs) of Bilastine by adsorption technique

Based on three different SNEDDS of Bilastine characterization studies. To formulate as solid S-SNEDDs, a formulation with good stability, stable self-Nano emulsification properties, and a formulation with less particle size, less PDI, and a good dissolution profile was chosen. **Neusilin** and liquid SNEDDS with Bilastine were combined in a 3:1 ratio to prepared S-S-SNEDDs For a uniform distribution of the formulation, the contents were mixed using a glass rod after each addition. The resulting moist mass was stored until needed again after being filtered through sieve number 120 and dried at room temperature [7, 11].

2.6. Evaluations of S-SNEDDS

2.6.1. Flow properties of S-SNEDDs [3, 14]

Angle of repose

The funnel method was used to calculate the angle of repose of S-SNEDDs .The height of the funnel was adjusted so that its tip barely touched the top of the powder pile. Equation was used to calculate the sample's accurate weight at rest.

Tan θ=h/r

Where h and r is height and radius of powder cone.

2.6.2. Bulk density and tapped density

A quantity of 2gm of S-SNEDDS was added to 10ml of powder cone after its diameter was measured and angle was calculated. Measuring cylinder. Initial volume was noted and cylinder was allowed to fall under its own weight into a hard surface from a height of 2.5 cm at 2 second intervals. Tapping was continued until no further change in volume was noted. Bulk density and Tapped density were calculated using the following equations [15].

Bulk density (BD) = Weight of powder blend

$$\text{Bulk density (BD)} = \frac{\text{Weight of powder blend}}{\text{Volume of the packing}}$$

Tapped density (TD)

$$\text{Tapped density (TD)} = \frac{\text{Weight of powder blend}}{\text{Tapped Volume}}$$

Weight of powder blend Tapped Volume of the packing

2.6.3. Compressibility index

The compressibility index of the powder blend was determined by Carr's compressibility index method by using the equation.

Carr's compressibility index (%) = TD-BD X 100 TD

$$\text{Carr's compressibility index (\%)} = \frac{\text{TD} - \text{BD}}{\text{TD}} \times 100$$

2.6.4. Hauser's Ratio

A quantity that indicates how well a powdered (or granular) substance flows is called Hauser's Ratio. The equation can be used to calculate Hauser's ratio.

$$\text{Hausner's Ratio} = \frac{\text{TD}}{\text{BD}}$$

2.7. Drug content study

The S-SNEDDs Bilastine equivalent to 10 mg was precisely weighed and dissolved in an adequate amount of methanol. To extract the drug from the methanol, the solution was sonicated for 10 minutes and then filtered. Using a UV-Visible Spectrophotometer, the filtrate's absorbance was measured at 205 nm [16].

2.8. Study of dilution Effect on S-SNEDDS

Weighed 100 mg of S-SNEDDs accurately were added to a 100 ml double-distilled stirrer in a beaker at 37°C, and the mixture was gently stirred with a magnetic stirrer running at 100 rpm. It was noted that lubrication happened quickly. An emulsion's "good" tendency is determined by how quickly it lubricates in less than a minute and has a clear or transparent appearance [3, 4].

2.9. Determination of Droplet size

In a test tube, 100 mg of the S-SNEDDs formulation was diluted with 100 ml of distilled water, cyclomixed, and filtered. Using a Zeta seizer ZS90, the dynamic light scattering (DLS) technique was used to determine the droplet size and poly dispersibility index of the emulsion at a temperature of 25 °C [7].

2.10. Compatibility study by FT-IR

FT-IR Spectrophotometer was used to obtain the FT-IR spectrum of the formulation, Neusilin, and standard drug. Using an accumulation of 24 scans and a 4 cm resolution, the spectrums were captured within the 400–4000 cm^3 range. To check for interactions, the spectrum of the prepared formulation was compared to the spectrum of the drug in its pure form [17].

2.11. *In-vitro* Dissolution Study

Using a USP-Type II dissolution test apparatus (DS1800 Lab India) (Figure 4.5) in a 500 ml pH 1.2 buffer at 3740.5 °C and 100 rpm rotating speed, the *In-vitro* dissolution study of S-SNEDDs , which were filled into suitable size capsules, was conducted. Samples were taken out at intervals of 5, 10, 15, 30, 45, 60, 75, and 90 minutes, and they were filtered through a 0.45µ filter. To keep the volume constant, the dissolving medium was replaced in an identical volume following each sampling. A UV Spectrophotometer set at 205 nm was used to analyze the samples. Using the calibration curve, the drug's concentration was determined. Based on absorbance and concentration, the amount of drug released was computed [8, 19].

3. Results and discussion

3.1. Calibration Curve by UV-Spectrophotometer

The Standard plot which has been drawn using data obtained by UV-Spectrophotometrically presented in Table-01. Calibration curve is shown in Figure-03. The regression coefficient (R^2) value was found to be 0.994 [3].

Table 1 Absorbance value

S.NO.	Concentration (µg/ml)	Absorbance
1	2	0.201±0.11
2	4	0.334±0.13
3	6	0.516±0.21
4	8	0.667±0.16
5	10	0.778±0.23

All Value are expressed as Mean ±SD (n=3)

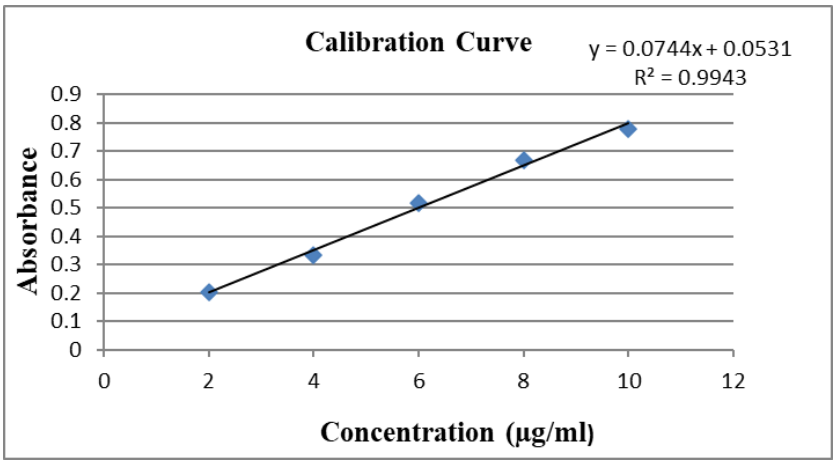

Figure 3 Calibration curve

3.2. Solubility study

Solubility studies were done to select the best oily phase, surfactant, and surfactant. For achieving optimum drug loading, the selection of a suitable oil that best solubilizes the drug is very crucial. Another importance of the solubility study is to decrease the total volume of the formula to be administered. In this study, oil (capmul PG-NF), surfactant tween 40 and co surfactant Capryol 90 use as were the used as excipient based on solubility results. The solubility of Bilastine in different oils, surfactants, and co-surfactants is presented in Table-02. In this study, the highest solubility of Bilastine was in oil (capmul PG-NF) 0.137±0.04 µg/ml, whereas the solubility was in surfactant (tween 40) 0.246±0.07 µg/ml and co-surfactants (Capryol 40) was 0.302±0.01 µg/ml. hence The high solubility of Bilastine was expected, since a lipophilic drug such as Bilastine (log P=5.02) is likely to exhibit greater solubility in capmul PG-NF, tween 40 and Capryol 90 chosen for optimize formulation [6, 8].

Table 2 Solubility study of Bilastine

Components	**Concentration (mg/ml)**
Oils	
Olive oil	0.171±0.03
Capmul MCM	0.228±0.05
Capmul PG-NF	0.137±0.06
Crodamol PC-LQ	0.249±0.04
Crodamol P30	0.101±0.02
Surfactants	
Labrasol	0.203±0.05
Tween 40	0.246±0.07
Labrasol ALF	0.196±0.03
Labraf IF	0.306±0.09
Span 80	0.356±0.02
Co-surfactants	
Transcutol P	0.156±0.03
Transcutol HP	0.151±0.07
Lauroglycol 90	0.223±0.02
Plurol Oleique	0.236±0.04
Capryol	0.302±0.01

All Value are expressed as Mean ±SD (n=3)

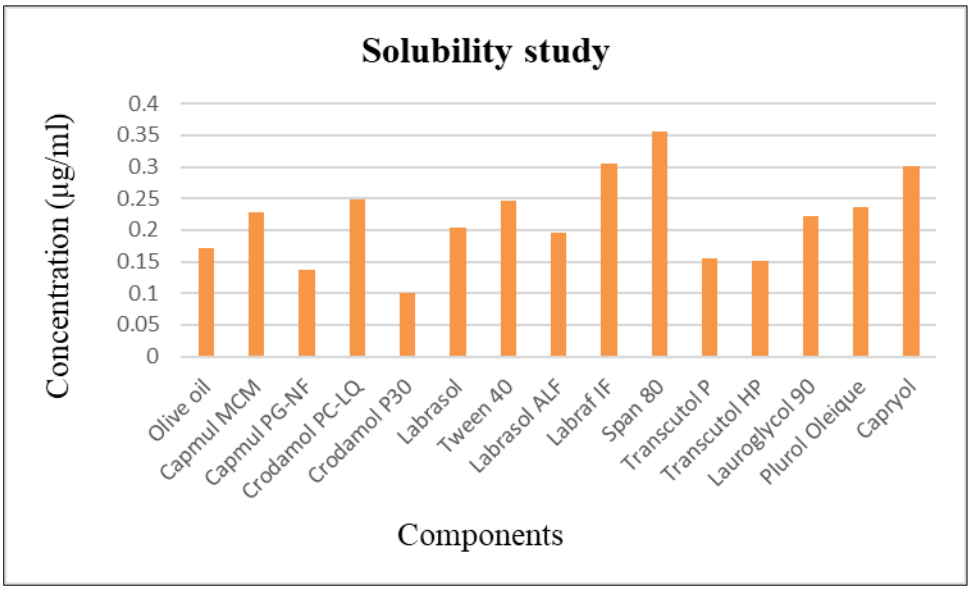

Figure 4 Solubility study of Bilastine (mean value ± SD of three distinct experiments displayed in the results)

3.3. Pseudo-ternary phase diagrams

To determine nano emulsion regions and the appropriate amount of oil, surfactant, and co-surfactant composition for SNEDDs formulation, pseudo-ternary phase diagrams was built. From a pseudo ternary phase diagram. The drug has been shown to be more soluble in systems, it was found that the systems comprising of Capmul PG-NF oil as the oily phase, tween 40 as a surfactant, and Capryol as a co-surfactant demonstrated stable Nano emulsifying properties. The TP3PG1 formulation for Smix 3:1 ratio revealed blue tinge emulsion (BTE) for oil. Smix 1:9, 2:8, and 3.7, 4:6, 5:5, 6:4, 9.1 with clear transparent emulsion [14]. The TP3PG1 clear transparent Emulsion (CTE) for Smix 3:1 ratio formulations is present in all Oil: Smix ratios, and no liquid crystal stage appears during the titration. Additionally, it was observed that by increasing the co-surfactant proportion, systems with Capmul PG-NF oil as the oily phase, Capmul PG-NF, tween 40 as a surfactant, and Capryol 90 as surfactant. Six systems exhibited a declining ability to form Nano emulsions. This observation also makes it evident that surfactant plays a part in the proper range formation of the Nano emulsion. Figure 07 illustrates the Nano emulsion region seen in the formulations. Table-03 provide the percentage composition of the water, Smix, and oil that were consumed during the titration and nano region shown in figure 05 [12, 13].

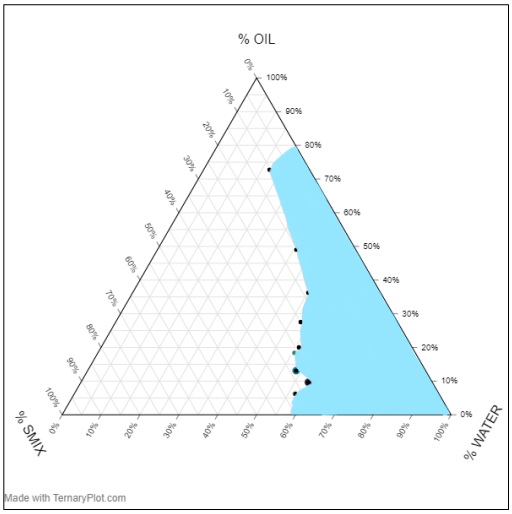

Figure 5 Pseudo- Ternary Phase Diagrams (TP3PG1)

Table 3 Percentage composition of oil (Capmul PG-NF), surfactant (tween 40) and co-surfactant (Capryol) upon titration with water

S.N	Formulation Name	Smix (mg)	Oil (mg)	Water (mg)	Total (mg)	% Smix	% water	% oil	Remarks
1	TP3PG1(1:9)	450	50	813	1313	34.27	61.91	3.80	BTE
2	TP3PG1(2:8)	400	100	759	1259	31.77	48.68	7.94	BTE
3	TP3PG1(3:7)	350	150	768	1268	27.60	60.56	11.82	BTE
4	TP3PG1(4:6)	300	200	679	1179	25.44	450	50	Milk white
5	TP3PG1(5:5)	250	250	635	1135	22.02	55.94	22.02	Milk white
6	TP3PG1(6:4)	200	300	518	1018	19.64	50.88	29.46	Milk white
7	TP3PG1(7:3)	150	350	490	990	15.15	49.49	35.35	Milk white
8	TP3PG1(8:2)	100	400	309	809	12.36	38.19	49.44	Milk white
9	TP3PG1(9:1)	50	450	102	602	8.305	16.94	74.75	Milk white

3.4. Preparation of Solid SNEDDS (S-SNEDDS) Formulations

The formulation of S-SNEDDs based on evaluation tests was selected for TP3PG1 (2:8) for preparation of solid SNEDDs of Bilastine. It was prepared by using an amount of capmul PG-NF oil (200 mg), tween 40 + Capryol (Smix-1800 mg), and drug (100mg) in an ideal compositions. Neusilin was used 1 gm as the carrier for S-SNEDDs, which are prepared using the optimal formulation through an adsorption technique [4, 5].

3.5. Evaluation of S-SNEDDS Bilastine

3.5.1. Flow properties of S-SNEDDs [2, 9]

The determination of the flow characteristics, including the Hausner's Ratio, bulk density, taped density, compressibility index, and angle of repose, it was found that the prepared S-SNEDDs exhibited good flow characteristics. Results are given in table-04.

Table 4 Flow properties of S-SNEDDs

Flow properties	TP3PG1 (2:8)
Angle of Repose	28.31 ±1.21
Bulk density	0.331 ±0.015
Tapped density	0.401±0.015
Compressibility	9.92±0.05
Hausner's Ratio	1.142 ±0.0067

Mean value are expressed as ±SD (n=3)

3.6. Drug content study

The amount of drug present in S-SNEDDs was determined. In which Drug content of the S-SNEDDs was found to be 103.61 ±0.678.

3.6.1. Droplet size and zeta potential

The determination of droplet size, poly Dispersibility index and zeta potential of reconstituted S-SNEDDs were found to be 148.5dnm, 0.242 and -28.6 that's uniform distribution of particle size at Nano region [20].

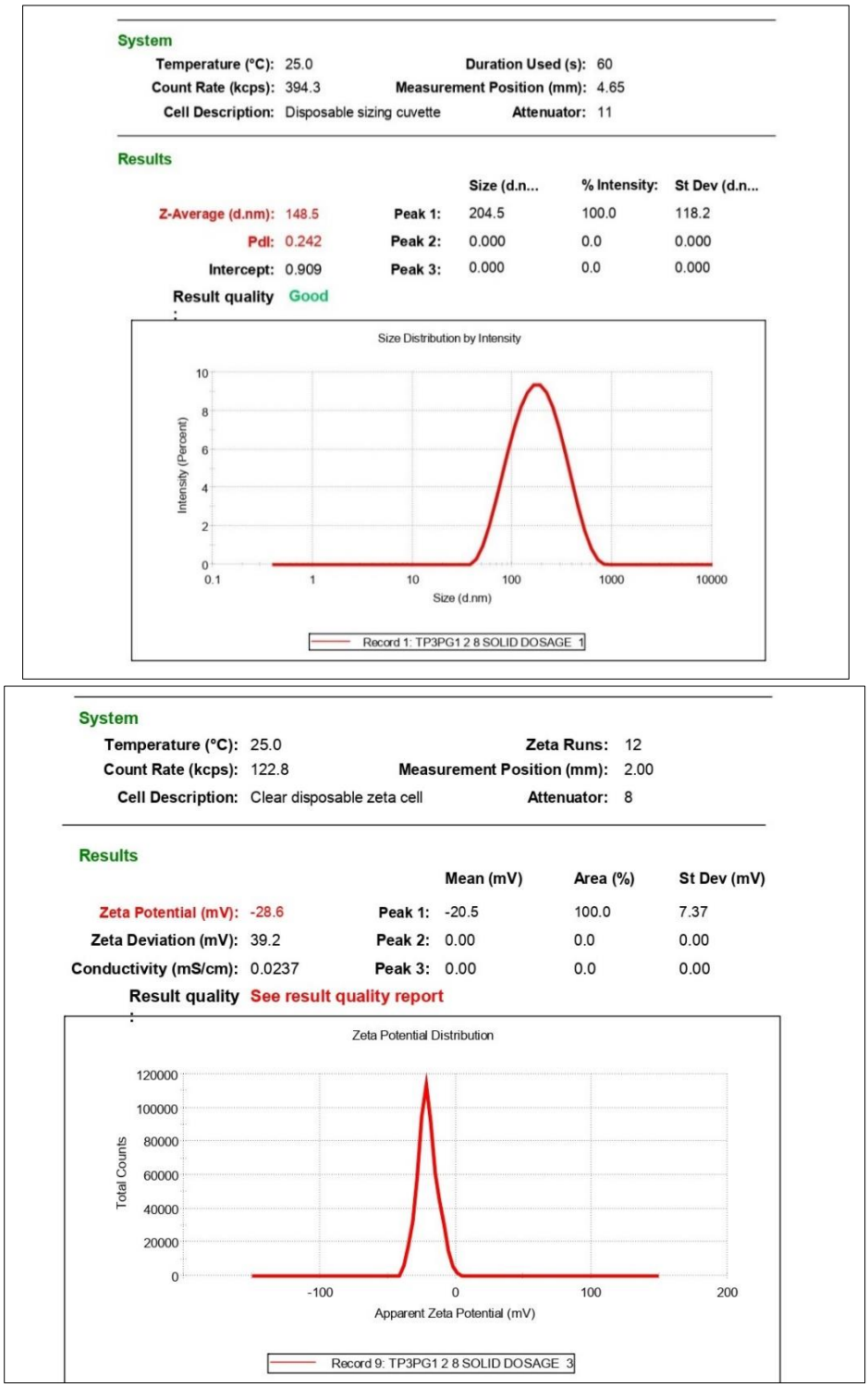

Figure 6 Droplet size and Zeta potential for solid Formulation (TP3PG1 (2:8)

3.7. Compatibility Study by FT-IR

In order to compare for any interactions, the drug-excipients mixture and solid formulation of Bilastine spectra were obtained and compared with pure drug spectrum. The FT-IR spectra of the optimized formulation and the pure drug were nearly identical (±10). It suggests that the combination of Neusilin and Bilastine did not interact during formulation. FT-IR functional groups stretching of pure drug, Neusilin and S-SNEDDs are shown in table-05 [17, 21].

Table 5 FT-IR functional groups stretching Studies

Formulation name	O-H stretch	C=N Stretch	C=O stretch	Alkyl C-H stretch
Pure drug	3340.66	1421.06	1716.32	2953.15
Neusilin	3439.61	1439.09	1725.60	2963.67 & 2895.12
TP3PG1 (2:8)	3339.61	1459.09	1722.70	2973.77 & 2889.22

3.8. *In-vitro* drug Dissolution study

In-vitro Dissolution study of (S-SNEDDs) Bilastine capsule, [TP3PG1 (1:9), TP3PG1 (2:8), and TP3PG1 (3:7)] was carried out using single paddle dissolution test apparatus. Drug release study of S-SNEDDs was conducted for 90 minutes in 0.1 N HCl. The drug release was found to be 90.4±0.052, 90.65±0.042, and 91.008 % percentage. It conclude that the formulation TP3PG1 (3:7) was found to have a higher percentage of drug release from S-SNEDDs. This demonstrated that the prepared S-SNEDDs enhanced the drug Bilastine solubility, which in turn raised the drug's percentage release of poorly water soluble drug. Results are given in Table-06 and Figure-07 [3, 7].

Table 6 Dissolution Studies (apparatus: basket type)

Time (minute)	% CDR (TP3PO1(1:9))	% CDR (TP3PO1(2:8)	% CDR TP3PO1(3:7)
5	25.2±0.02	24.75±0.16	35.46±0.19
10	53.6±0.12	49.10±0.14	56.04±0.13
15	62.26±0.05	57.56±0.03	57.52±0.05
30	79.62±0.11	70.84±0.02	73.5±0.07
45	75.46±0.13	65.10±0.16	72.73±0.09
60	87.85±0.21	81.03±0.17	78.43±0.13
90	90.4±0.16	90.65±0.15	91.368±0.17

All Value are expressed as Mean ±SD (n=3)

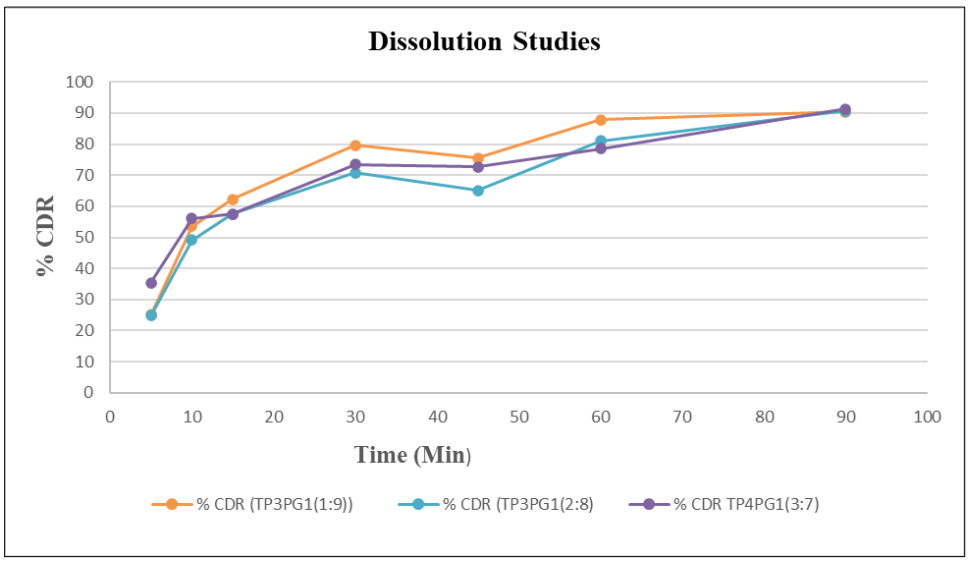

Figure 7 *In-vitro* release of S-SNEDDS from TP3PG1 (1:9), (TP3PG1 (2:8), TP3PG1 (3:7) in 0.1N HCl (mean±SD, n=3)

3.9. Accelerated stability studies

An accelerated stability study was performed at 25 ±0.5˚C / 60 ± 5 % RH and 40±0.5˚C / 75 ± 5 % RH for 1-3 months to evaluate parameters like effect of dilution, droplet size, PDI and the *In-vitro* drug release. S-SNEDDs was stable in the Effect of Dilution test. Droplet size was found to be 148.5 with PDI 0.239 indicating no effect on Droplet size after 1 and 3 month stability study. Percentage released of Bilastine was found to be 93.23±0.042, at the end of 1 and 3 month indicating no change in % drug release after 1 and 3 month stability study. According to the results, the formulation clearly show that it was stable over 1-3 month so accelerated stability study [5, 13].

4. Conclusion

The aim of this study was to prepare an oral administrable SNEDDS for poorly water soluble drugs Bilastine. To choose the SNEDDS excipients, a ternary phase diagram and solubility assessment were conducted. Different components of oil (capmul PG-NF) surfactant (Tween 40) and co-surfactant (Capryol 90) were used as the excipients. In this study, three different Bilastine loaded SNEDDS [TP3PG1 (1:9), TP3PG1 (2:8), TP3PG1 (3:7)] were prepared. Among these TP3PG1 (2:8) was for the selected as a stable for optimized formulation. The optimized formulation was characterized for several in vitro analysis. The prepared S-SNEDDs exhibited good flow characteristics and Particle size (148.5dnm), zeta potential (−28.6), PDI (0.242), drug loading efficiency, % CDR of the optimized S-SNEDDs [TP3PG1 (2:8)] was found to be 103.61 ±0.678, 98.65% respectively. The formulation was stable over a 3-month storage period at 25 ◦C and 4 ◦C in terms of particle size, physical appearance, and drug loading. Hence the recent approach demonstrated that Bilastine substantial increase solubility, dissolution rate after oral administration and it' also improved oral absorption of optimized formulation.

Compliance with ethical standards

Acknowledgments

All the authors would like to thank the Centre for pharmaceutical Science, University College of Engineering, and Science & Technology JNTU Hyderabad for providing lab facilities for this research work.

Disclosure of conflict of interest

All the authors declare no conflict of interest. Authors read and agreed with the final manuscript.

Funding

There was no any source of funding.

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