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Advances in Bioresearch

## ORIGINAL ARTICLE

# Preparation, Formulation and *In-Vitro* Evaluation of Ebastine SMEDDS Using Different Oils, Surfactants and Cosurfactants

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**ABSTRACT**
*The present study aimed to prepare, formulate, and evaluate self-micro emulsified (SMEDDS) of Ebastine using different oils, surfactants and co-surfactants for the enhancement of solubility of poorly water-soluble drug, Ebastine. Solubility study was conducted with different oils, surfactants and co-surfactants for the selection of oil, surfactant a co-surfactant for further studies. Solid SMEDDS were prepared using Microcrystalline Cellulose in 1:1 ratio using homogenizer in china dish. The Liquid SMEDDS and Solid SMEDDS were characterized to evaluate the best formulation. Particle size analyser, scanning electron microscopy (SEM), differential scanning calorimetry (DSC) and FTIR studies performed to evaluate the physicochemical properties of solid SMEDDS and also to evaluate the compatibility of drug with excipients used in the formulations. Based on the Solubility studies, castor oil and capryol were selected as oils, Tween 20 and cremaphore RH 40 selected as surfactants and PEG 400 selected as co-surfactant based on their higher solubilities. Ternary phase diagrams have plotted using the ratio of Smix was selected as 1:1, 2:1, 3:1. Results revealed that the castor oil formulation showed that Smix ratio of 2:1 has more emulsification area as compared to Smix ratio of 1:1 and 3:1 and Capryol 90 formulation Smix ration of 3:1 have more emulsification area as compared to 1:1 and 2:1. Studies on the dispersibility test, thermodynamic stability studies, cloud point measurement, refractive index, percentage transmittance and viscosity determination revealed that formulations EBC6, EBT6 were selected as optimized formulations. In-vitro drug release study revealed that EBC6 (86.27%), EBT (85.08%) in 2hours and selected as optimized formulations.*
***Keywords:*** *SMEDDS, solubility, Ternary phase diagram,*

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## INTRODUCTION

Most of the drug molecules have serious problems of poor aqueous solubility and lead to low bioavailability upon administration of such molecules (1). Low solubility of the drug may lead to limited dissolution rate of drug molecules and may leads to low bioavailability for administered drugs and molecules orally and may leads to limited absorption of the drug. Various techniques have been used to enhance the oral bioavailability of drugs which are poorly soluble in water (2-8).

Oral route is one of the major routes of delivery of drugs for chronic treatment of most of the diseases. Oral delivery of 50% of drug molecules have thwarted because of high lipophilicity of drug molecules. Approximately 40% of the new drug entities exhibit low aqueous solubility which became a challenge in developing optimum oral dosage forms and enhance the bioavailability of new products of pharmaceuticals. To overcome these problems, many strategies have been used to modify the solubility and maintain the drug in dissolved state throughout gastric transit time (9-11). The strategies may include the addition of surfactants, cyclodextrins, salt formation, micronization process, pH changes, nanonization, solid dispersions and use of permeation enhancers (12-18).

The drug availability for absorption can be enhanced by presenting the drug in colloidal dispersion form. The most used approaches contain digestion of pharmaceutical active ingredient in inert lipids containing oils, surfactants dispersions, liposomes, emulsions and self-emulsifying oil formulations (SMEDDS) (19,20).

SMEDDS is an emulsion-based formulation containing blend of oils, surfactants in suitable proportions which rapidly forms oil in water micro emulsion (O/W) with moderate gastric motility in the GIT when exposed to aqueous medium. To enhance solubility and emulsification, organic solvents and co-surfactants can also be added to the formulations. A transparent micro emulsion with smaller droplets and thermodynamically stable SMEDDS formulations are produced. Formation of rapid emulsions helps to keep the drug in dissolved state having smaller droplet size and larger surface area can accelerate the absorption rate of the formulation (21, 22).

Many techniques have been adopted to convert liquid conventional SMEDDS into solid SMEDDS such as adsorption on to solid carrier, spray drying, melt extrusion, spray cooling, super critical fluid-based methods etc. Out of all these methods, adsorption method is the simplest method among all and involves the addition of liquid SMEDDS to the carrier in a blender to get soli SMEDDS. The resulting powder may be filled into capsules or compressed into tablets after addition of suitable excipients. Liquid SMEDDS can be absorbed at high levels of nearly 70% W/W on to suitable carrier 23.

The present study aimed to prepare, formulate and evaluate self-micro emulsified (SMEDDS) of Ebastine using different oils, surfactants and cosurfactants for the enhancement of solubility of poorly water-soluble drug, Ebastine. Ebastine is a non-sedating H1 antihistamine used for the treatment of Utricaria having poor water solubility.

## MATERIAL AND METHODS

### Chemicals and Reagents

Ebastine drug sample was a gift sample form Vasudha Pharma chem., Hyderabad, Castor oil, Sesame oil, Oleic acid procured from Universal scientific Appliances, surfactants and cosurfactants, Microcrystalline cellulose were purchased from SD Fine chemicals All other chemicals and reagents were of Analytial grade.

### Determination of melting point

Melting point Ebastine was determined using an open capillary tube method with digital melting point apparatus.

Solubility of Ebastine

Ebastine Solubility was determined in various medias like methanol, ethanol, 6.8 phosphate buffer, Dichloromethane, Dimethylsulfoxide etc.

Drug - Excipients Compatibility studies

A proper designing and formulation of dosage form requires physical, chemical and biological characteristics considerations of drug as well as excipients which have used in the formulations of the products (Ebastine) [24-26].

Fourier Transform Infra-Red Studies (FTIR)

FTIR spectra could be obtained for formulations with the pure drug and excipients used with shimadzu FTIR spectrophotometer. The drug samples and drug with excipients samples were thoroughly blended using dry powder KBr crystals. Compressed the mixture of drug and excipients and obtained a pellet. The produced disc was placed in spectrophotometer and spectrum was recorded [27,28].

Differential scanning Calorimetry (DSC)

Differential scanning calorimetry is a thermo analytical technique in which difference in the amount of heat required to increase the temperature of a sample and reference are measured as a function of temperature. Accurately weighed Ebastine has analyzed using an automatic thermal analyzer system (DSC60 Shimadzu Corporation, Japan). All the samples were runned at the scanning rate of 10$^{o}$C/min from 50$^{o}$C to 300$^{o}$C [29].

Determination of λmax:

Standard stock solution containing Ebastine was prepared by dissolving 100 mg of Ebastine in 10 ml of Methanol in 100 ml volumetric flask to dissolve the drug. Then the volume was made up to 100 ml using phosphate buffer of pH 6.8 to obtain a concentration of 100µg/ml. the stock solution is further diluted using a phosphate buffer pH (6.8) to prepare 10 µg/ml concentration. The resultant solution was scanned in the range of 200-400 nm in UV spectrophotometer (UV -1700 shimadzu Corporation, Japan) to obtain absorption maximum (λmax) using phosphate buffer as blank.

Preparation of standard curves

From the above prepared stock solution, solutions containing 5 to 30 µg/ml concentrations were prepared using the phosphate buffer pH 6.8 solution. The absorbances of these solutions were measured at λmax by UV-spectrophotometer (UV-1700 Shimadzu corporation Japan). A standard curve is plotted using concentration and the absorbance obtained X-axis and Y-axis

Determination of solubility of Ebastine

Determined the Solubility of Ebastine in various oils (oleic acid, sesame oil, castor oil, Capryol 90), surfactants (tween 80, tween 60, tween 20, span 80, cremophor RH), co-surfactant (Propylene glycol, polyethylene glycol (PEG) 400) by dissolving excess amount of Ebastine in 2 ml of each of oils, surfactants and co-surfactants selected in stoppered vials. The mixtures were continuously stirred by vortex mixer for 10mins and kept in the water bath shaker at 37°C±0.5°C for 78hrs until equilibrium was attained. The samples equilibrated were centrifuged at 3000rpm for 15mins and filtered the supernatant through 0.45µm membrane filter and diluted using suitable solvent. Determined the drug content using ultraviolet-visible (UV-VIS) spectrophotometer.

Screening of surfactant

To determine the appropriate surfactant with good solubilization capacity, an emulsifying ability of different surfactants (tween 80, tween 60, tween 20, span 80, cremophor RH) with the screened oils were investigated. 300 mg of oil phase and 300 mg of surfactant were weighed and vortexed for two minutes followed by warming at 40- 45$^0$C for 30 seconds. So, an isotropic mixture has been obtained. Small quantity (50 mg) of isotropic mixture was taken and diluted by distilled water which was previously filtered through 0.45µm membrane filter in a volumetric flask Number of flask inversions were observed visually to produce a clear emulsion [30,31]. The resultant emulsions allowed to stand for 2 hours after that transmittance were observed at 263nm. The surfactant which has formed a clear emulsion with lesser number of inversions and more transmittance was selected.

Screening of co-surfactant

For ensuring co- surfactant with good solubilizing capacity, after screening of an oil emulsifying ability of different co- surfactants (Propylene glycol, polyethylene glycol 400) with the screened oil was investigated. 300 mg of oil phase and 300 mg of surfactant were weighed and vortexed for two minutes followed by warming at 40- 45 C for 30 seconds to form isotropic mixture. 50 mg of isotropic mixture was taken and diluted with double distilled water previously filtered through 0.45µm membrane filter in a volumetric flask. A number of flask inversions were observed visually to form a clear emulsion. The resulting emulsions allowed standing for 2 hours after that transmittance were observed at 263nm. The co- surfactant which forms a clear emulsion with lesser number of inversions and with more transmittance was selected.

Construction of pseudo ternary phase diagram

Ternary phase diagrams were constructed with oil, surfactant/co-surfactant and water using water titration method at room temperature. The procedure consisted of preparing solutions of different ratio of surfactant to co-surfactant by weight such as 1:1, 2:1, 3:1 etc., these solutions then vortexed for 5mins and placed at 50°C for one hour, so that an isotropic mixture was obtained [32]. Each of these solutions were used for preparing a mixture containing oil and Smix (mixture of surfactant and co-surfactant) in the following ratios by weight, 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1 and after preparation vortexed for 5 mins followed by placing in oven at 50° C for one hour. All the mixtures were then placed at room temperature for 24 hours.

FORMULATION OF LIQUID SMEDDS

From the ternary phase diagram, the ratio of surfactant to co-surfactant was optimized. Then by varying ratio of oil to Smix, different formulations were prepared. Formulations were prepared by preparing optimized ratio of Smix first, for this surfactant and co-surfactant were accurately weighed and then vortexed for 5-10min [33]. After that Smix was placed in oven at 50$^0$C for one hour. Oil with different ratio was added to Smix. Then these formulations were vortexed for 5-10mints and placed in oven at 50°C for one hour so that an isotropic mixture was formed. Drug was loaded to these isotropic mixtures at the end and vortexed by vortex shaker until clear solution was obtained.

CHARACTERIZATION OF LIQUID SMEDDS

**Visual assessment**

Ebastine liquid SMEDDS were diluted with purified water (100 ml) and gently stirred with magnetic stirrer by maintaining the temperature at 37$^0$ C.

Dispersibility test

The dispersibility test of SMEDDS was carried out using standard USP paddle type dissolution test apparatus, formulation was added to 500 ml of water at 37±0.5$^0$C and the paddle was rotated at 50 rpm.

Determination of self-emulsification time:

The emulsification time of SMEDDS was determined by adding one ml of formulation drop wise to 500 ml distilled water at 37±0.5° C with agitation using dissolution paddle rotating at 50 rpm.

**Heating cooling cycle**

The optimized SMEDDS formulations were diluted with 100 times distilled water. Six cycles between cooling temperature (4°C) and heating temperature (45°C) with exposure at each temperature for not less

than 48 hours were carried.

**Centrifugation**

Optimized SMEDDS formulations were diluted with 100 times distilled water and centrifuged at 3500rpm for 30 mins.

**Freeze thaw cycle**

In this study three freeze thaw cycle formulations were exposed between temperatures 21°C-25°C for each temperature cycle not more than 48 hours. For the better estimation six such cycles ran for each batch of formulation [34].

Cloud point measurement

Dilute the formulation 1 ml with 1000 ml of water in beaker and place it in a water bath with gradually increasing the temperature until the diluted formulation turned to cloudy or turbid.

Robustness to dilution

Robustness to dilution was studied by diluting SMEDDS to 50, 100, 1000 times with water, phosphate buffer pH 6.8, phosphate buffer pH 7.4. The diluted SMEDDS were stored for 12 hours and observed for any signs of phase separation or drug precipitation.

Refractive index and percent transmittance

The refractive index was measured using Abbes refractometer. The percentage transmittance of the system was measured at wavelength using UV-spectrophotometer keeping distilled water blank. Stability of micro emulsion formulation with respect to dilution was checked by diluting one ml of formulation with 100 ml of distilled water and measuring transmittance using U.V. Spectrophotometer. Transmittance of samples was measured at 237 nm and for each sample three replicate assays are performed.

Viscosity determination

The rheological properties of the micro emulsion are evaluated by Ostwald viscometer. Viscosity determinations confirm whether the system was w/o or o/w. If a system has low viscosity, then it is o/w type of the system and if high viscosities then it is w\o type of the system.

Absolute drug content in L-SMEDDS

Liquid SMEDDS containing Ebastine, equivalent to 4 mg was diluted in suitable quantity of methanol. The sample was mixed thoroughly to dissolve the drug in methanol by stirring. The solvent extract is filtered through 0.45 µm membrane filter. Drug content was determined by measuring the absorbance in UV spectrophotometer against the standard solution of drug.

Conversion of liquid SMEDDS into solid S-SMEDDS

Solid SMEDDS were prepared by mixing liquid SMEDDS containing Ebastine with microcrystalline cellulose (MCC) in 1:1 proportion. Liquid SMEDDS was added drop wise over MCC and homogenized using glass rod to ensure uniform distribution in a China dish.

Physiochemical characterization of SMEDDS

**Micromeritic properties**

Prepared solid- SMEDDS were evaluated for micromeritic properties such as angle of repose, bulk density and tapped density, compressibility index and Hausner's ratio [35].

a) Angle of Repose

Angle of Repose is defined as the maximum angle possible between the surface of the pile of powder and horizontal plane. Angle of repose has been used as indirect methods of quantifying powder flow ability, because of their relationship with inter particle cohesion.

$$\text{Angle of Repose } (ø) = \tan^{-1} (h / r)$$

Where, h = height of the heap,

r = radius of the heap

**b) Bulk Density**

Apparent bulk density is determined by pouring the weighed granules into a graduated cylinder via funnel and measuring the volume.

c) Tapped Density

A known quantity of sample was transferred to a graduated cylinder and placed on tapped density apparatus and operated for a fixed number of taps (100). It is the ratio of weight of sample to tapped volume.

$$\text{Tapped density} = \frac{\text{Weight of the powder (W)}}{\text{Tapped volume of powder Vf}}$$

d) Compressibility (or) Carr's index

Based on the apparent bulk density and the tapped density, the percentage compressibility of the bulk drug is studied by using

$$\text{Carr's index (\%)} = \frac{\text{Tapped density - bulk density}}{\text{Tapped density}} \times 100$$

**e) Hausner's ratio**

Hausner's ratio is defined as the ratio of tapped density to bulk density of the powders. The Hausner's ratio is a number that is correlated to the flow ability of a powder (or) granular material.

Drug content:

The S-SMEDDS containing Ebastine, equivalent to 4 mg was diluted in suitable quantity of methanol and sonicated for 10-15 mins. Then it was filtered through a 0.45µm membrane filter. Drug content was analyzed by measuring absorbance using UV spectrophotometer.

***In-vitro* drug release from S-SMEDDS**

The *in-vitro* drug release of prepared S-SMEDDS was assessed in triplicate using United States Pharmacopoeia (USP) Dissolution Type II apparatus (Paddle type) at 37±0.5°C. S-SMEDDS containing 4 mg equivalent of drug was placed in 900 ml of dissolution medium (phosphate buffer pH 6.8with methanol in 9:1 ratio). The revolution speed of the paddle was maintained at 100 rpm. At predetermined time intervals, 5 ml of dissolution medium was collected, filtered and the same volume of fresh dissolution medium was replenished to maintain the sink conditions. The samples were analyzed for the drug concentration using UV-VIS spectrophotometer at 237 nm.

## RESULTS AND DISCUSSIONS

Determination of solubility

The components in the formulation of SMEDDS were selected to have maximum solubility of Ebastine along with good miscibility with each other to produce an isotropic and stable system. The solubility of Ebastine in various vehicles was screened and the results were presented in table 1 and figure 1. Ebastine had significantly higher solubility in Castor oil (96.73±0.05%) and Capryol 90 (95.86±0.12%) than sesame oil, sunflower oil, oleic acid. Among surfactant and co-surfactants, Propylene glycol (90.73±0.19%), Propylene glycol 400 (89.86±0.15%), Cremophor RH 40 (88.56±0.08%) showed highest solubility.

**Table 1: Solubility of Ebastine in various Vehicles**

| S.NO | VEHICLE | SOLUBILITY (%) |
|---|---|---|
| 1 | Castor oil | 96.73±0.05 |
| 2 | Capryol 90 | 95.86±0.12 |
| 3 | Propylene glycol | 90.73±0.19 |
| 4 | Polyethylene glycol 400 | 89.86±0.15 |
| 5 | Cremophor RH 40 | 88.56±0.08 |
| 6 | Tween 80 | 87.71±0.32 |
| 7 | Twen 60 | 83.55±0.18 |
| 8 | Tween 20 | 81.49±0.72 |
| 9 | Oleic acid | 56.36±0.03 |
| 10 | Sunflower oil | 39.54±0.47 |
| 11 | Span 80 | 24.67±0.24 |
| 12 | Sesame oil | 20.86±0.61 |

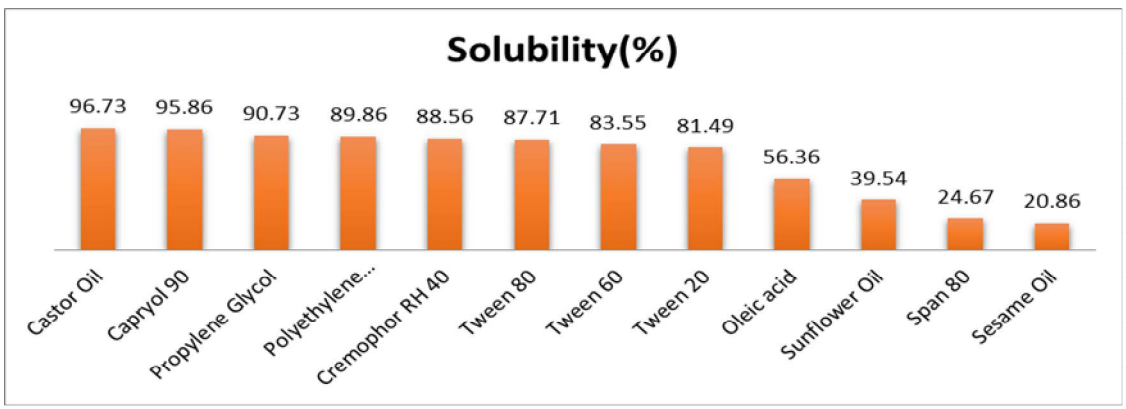


**Figure 1: Solubility of Ebastine in various Oils**

Screening of components

Surfactants and co-surfactants are selected based on the % Transmittance. Out of various surfactants and co-surfactant screened, Cremophor RH 40 revealed 96.52±0.5%, and with castor oil. And Tween 20 revealed 96.63±0.13%. Tween 20 and Cremophor RH 40 showed the highest values amongst all others and were selected for the development of the formulation. Similarly, in the case with co-surfactants PEG 400 resulted in higher % Transmittance value (97.30±0.18% and 97.19±0.27%) for both the oils castor oil and capryol 90 and the results were shown in table 2 and figure 2a, 2b.

**Table 2: % Transmittance values of Surfactant and Co-surfactant**

| S.NO | COMPONENTS | % TRANSMITTANCE VALUE | |
|---|---|---|---|
| | | WITH CASTOR OIL | WITH CAPRYOL 90 |
| 1 | Cremophor RH40 | 96.52±0.58 | 91.26±0.42 |
| 2 | Tween 80 | 47.78±0.20 | 43.42±0.19 |
| 3 | Tween 60 | 73.18±0.37 | 64.49±0.47 |
| 4 | Tween 20 | 94.45±0.39 | 96.63±0.33 |
| 5 | Span 80 | 47.86±0.57 | 43.92±0.28 |
| 6 | Propylene glycol | 87.36±0.40 | 89.64±0.29 |
| 7 | PEG 400 | 97.30±0.18 | 97.19±0.27 |

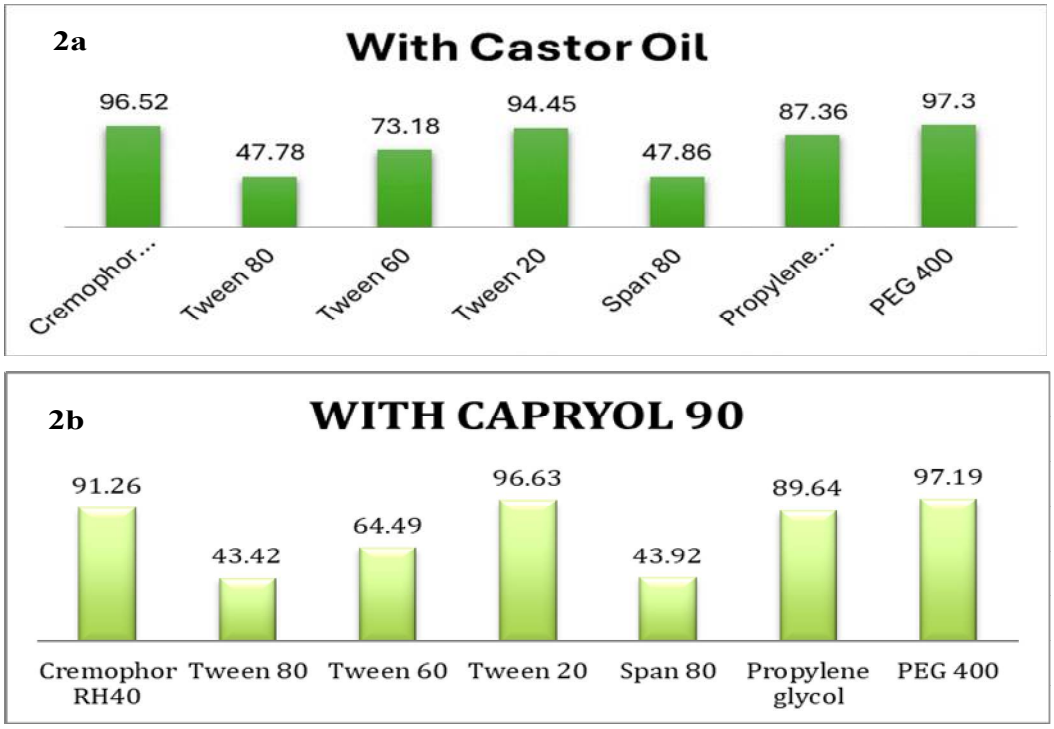


**Figure 2.** % Transmittance of Surfactant and Co-surfactant with Castor oil & Capryol 90

Construction of Pseudo ternary phase diagram

The micro emulsion region was determined by plotting data in pseudo ternary phase diagram. The selected oil, surfactants and co-surfactants were used to formulate micro emulsion. Nine different combinations of oil and Smix were selected to construct phase diagram for two types of formulation (castor oil and Capryol 90). The ratio of Smix was selected as 1:1, 2:1, 3:1. The diagrams are depicted in **figures 3a, 3b, 3c and 4a, 4b, 4c.** Figures show that castor oil formulation with Smix ratio of 2:1 had more emulsification area compared to Smix ratio of 1:1 and 3:1. And for the Capryol 90 formulation Smix ration of 3:1 had more emulsification area compared to 1:1 and 2:1.

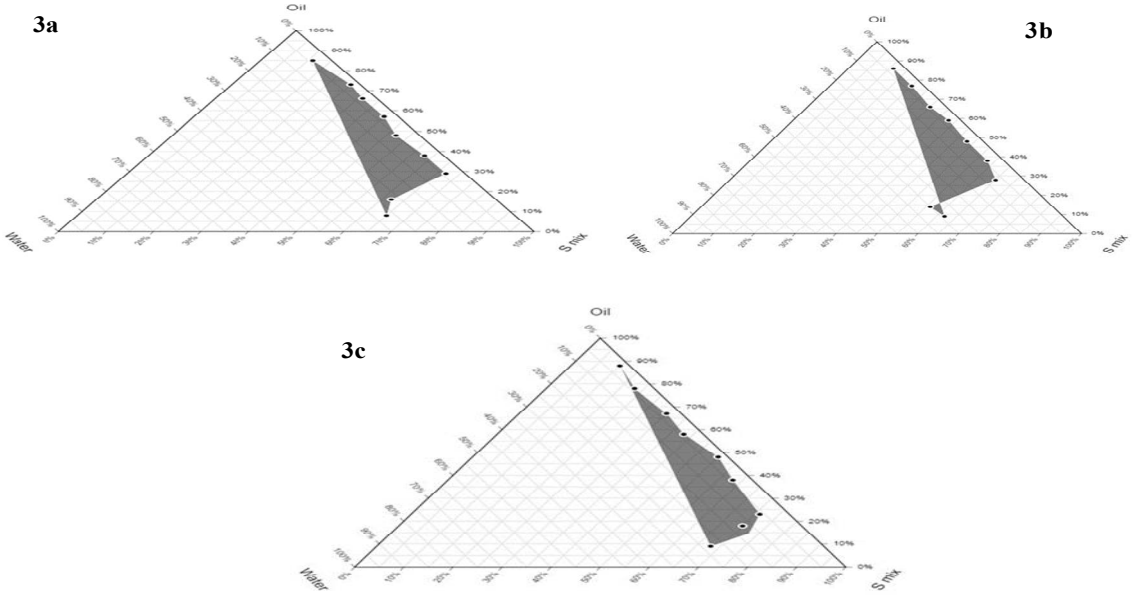


**Figure 3a, 3b, 3c: Ternary Phase Diagrams 1:1, 2:1, 3:1 ratio with Castor Oil**

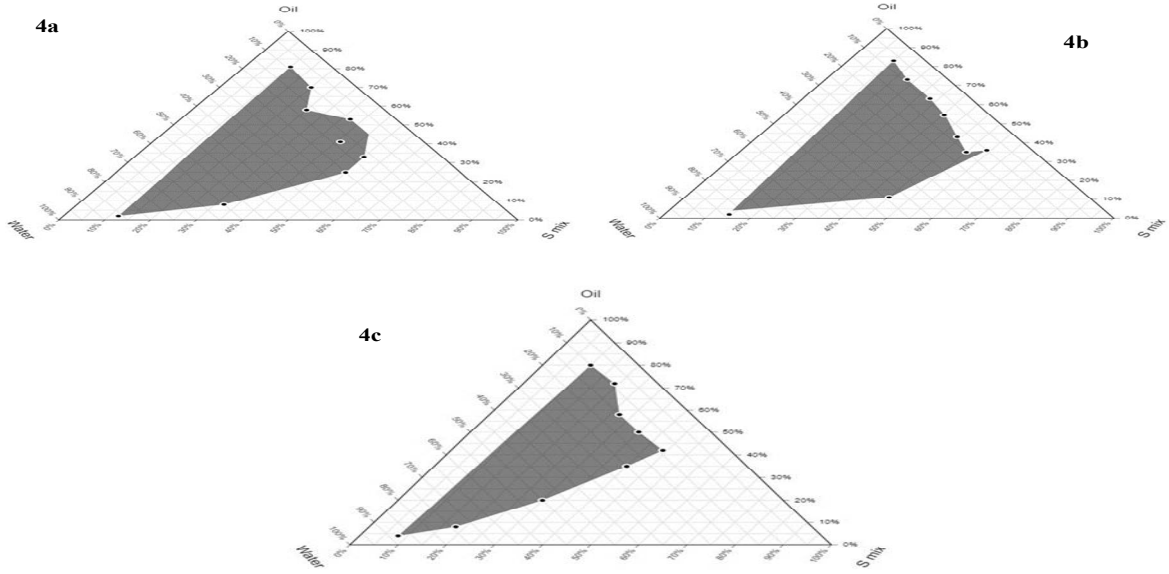


Figure 4. **Ternary Phase Diagrams 1:1, 2:1, 3:1 ratios with Capryol 90**

FORMULATION OF LIQUID SMEDDS

Based on the pseudoternary phase diagrams, the formulation with the best self-emulsifying properties, containing castor oil with Smix of cremophore RH 40 and Polyethylene glycol 400, and Capryol 90 with Smix of Tween 20 and Polyethylene glycol 400 were formulated with varying ratios of oil, surfactant, and co-surfactant**.**

CHARACTERIZATION OF LIQUID SMEDDS

**Dispersibility test and Visual assessment**

Ebastine liquid SMEDDS was diluted with purified water (100 ml) and gently stirred with magnetic stirrer and maintained at $37^0$ C. The results were represented in Table 4a & 4b.

**Table 4.** Dispersibility Test and Visual Assessment of SMEDDS Formulation

| CODE NO. | DISPERSIBILITY AND APPEARANCE | S E TIME | GRADE |
|---|---|---|---|
| **EBC1** | Transparent | Within 1 min | C |
| **EBC2** | Clear and Transparent | Within1 min | A |
| **EBC3** | Dull | Within 2 mins | B |
| **EBC4** | Transparent | Within 1 min | B |
| **EBC5** | Dull | Within1 min | A |
| **EBC6** | Transparent | Within 1 min | B |
| **EBC7** | Clear | Within 2 mins | C |
| **EBC8** | Clear | Within 1 min | C |
| **EBC9** | Clear | Within 1 min | B |
| **EBT1** | Clear and transparent | within 1 min | A |
| **EBT2** | Transparent | within 1 min | B |
| **EBT3** | Transparent | within 1 mint | B |
| **EBT4** | Clear and Transparent | within 2 mins | A |
| **EBT5** | Clear | within 1 min | A |
| **EBT6** | Transparent | within 2 mins | C |
| **EBT7** | Dull | within 3 mins | D |
| **EBT8** | Clear | within 1 min | A |
| **EBT9** | Dull and Turbid | within 2 mins | E |

Thermodynamic stability studies

SMEDDS are thermodynamically stable systems and are formed at a particular concentration of oil, surfactant, and water, with no phase separation, creaming or cracking. Those formulations, which survived thermodynamic stability tests, were taken for further studies. It was observed that formulations EBC3, EBC5, EBC7, EBC9, EBT2, EBT3, EBT7 and EBT9 did not pass the thermodynamic stress tests and thus were dropped for further study. The results were shown in Table 5a, 5b.

**Table 5.** Thermodynamic stability assessment of Oleic Acid & Capryol 90 SMEDDS

| Formulation | Heating cooling cycle | Centrifugation | Freeze thaw cycle |
|---|---|---|---|
| **EBC1** | √ | √ | √ |
| **EBC2** | √ | √ | √ |
| **EBC3** | × | × | × |
| **EBC4** | √ | √ | √ |
| **EBC5** | × | × | × |
| **EBC6** | √ | √ | √ |
| **EBC7** | × | × | × |
| **EBC8** | √ | √ | √ |
| **EBC9** | × | × | × |
| **EBT1** | √ | √ | √ |
| **EBT2** | × | × | × |
| **EBT3** | × | × | × |
| **EBT4** | √ | √ | √ |
| **EBT5** | √ | √ | √ |
| **EBT6** | √ | √ | √ |
| **EBT7** | × | × | × |
| **EBT8** | √ | √ | √ |
| **EBT9** | × | × | × |

√ - Passed × - Failed

Cloud point measurement:

It gives information about the stability of micro emulsion at body temperature. The results were represented in **table 6.** The cloud point of all the SMEDDS except EBC3, EBC5, EBC7, EBC9, EBT2, EBT3, EBT7 and EBT9 were found to be higher than 85$^{o}$C, indicating that micro emulsion was stable at physiological temperature without risk of phase separation.

**Table 6: Measurement of Cloud Point**

| S.NO | Formulation | Cloud Point ($^{o}$ C) | Formulation | Cloud Point ($^{o}$ C) |
|---|---|---|---|---|
| 1 | **EBC1** | 87 | **EBT1** | 85.6 |
| 2 | **EBC2** | 86.5 | **EBT2** | UNSTABLE |
| 3 | **EBC3** | UNSTABLE | **EBT3** | UNSTABLE |
| 4 | **EBC4** | 86 | **EBT4** | 86 |
| 5 | **EBC5** | UNSTABLE | **EBT5** | 86.5 |
| 6 | **EBC6** | 86.5 | **EBT6** | 86 |
| 7 | **EBC7** | UNSTABLE | **EBT7** | UNSTABLE |
| 8 | **EBC8** | UNSTABLE | **EBT8** | 87.5 |
| 9 | **EBC9** | 88 | **EBT9** | UNSTABLE |

Robustness to dilution

After diluting SMEDDS to 50, 100 and 1000 times with water, buffer pH 7.4 and pH 6.8 and storing for 12hrs, it was observed that there was no sign of phase separation or drug precipitation in formulations except EBC3, EBC5, EBC7, EBC9, EBT2, EBT3, EBT7 and EBT9 which turned hazy after standing for long hours. The results were shown in Table 7 a & 7 b.

**Table 7 a & 7b: Results of Robustness to Dilution**

| S.No | MEDIUM | PHASE SEPARATION | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | **EBC1** | **EBC2** | **EBC3** | **EBC4** | **EBC5** | **EBC6** | **EBC7** | **EBC8** | **EBC9** |
| 1 | Distilled water | No | No | No | No | No | No | No | No | No |
| 2 | Phosphate buffer pH 6.8 | No | No | Yes | No | Yes | No | Yes | Yes | No |
| 3 | Phosphate buffer pH7.4 | No | No | Yes | No | Yes | No | Yes | Yes | No |
| | | | | | | | | | | |
| 4 | Distilled water | No | No | No | No | No | No | No | No | No |
| 5 | Phosphate buffer pH 6.8 | No | Yes | Yes | No | Yes | No | Yes | No | Yes |
| 6 | Phosphate buffer pH 7.4 | No | Yes | Yes | No | No | No | Yes | No | Yes |

Refractive index and percent transmittance:

The results of Refractive index and percentage Transmittance were shown in Table 8. Formulations EBC6, EBC9, EBT1, EBT4, EBT6 and EBT8 had transmittance value greater than 90%, suggesting their clarity. And the refractive indices of formulations EBC2, EBC6, EBC9, EBT4, EBT5 and EBT6 had the values nearer to RI of water.

**Table 8: Refractive Index and % Transmittance Values**

| S.No | Formulation | RI Value | Transmittance | Formulation | RI Value | Transmittance |
|---|---|---|---|---|---|---|
| 1 | **EBC1** | 1.337±0.0006 | 85.67±0.18 | **EBT1** | 1.338±0.0010 | 91.48±0.24 |
| 2 | **EBC2** | 1.335±0.0005 | 87.29±0.27 | **EBT2** | UNSTABLE | UNSTABLE |
| 3 | **EBC3** | UNSTABLE | UNSTABLE | **EBT3** | UNSTABLE | UNSTABLE |
| 4 | **EBC4** | 1.339±0.0007 | 85.10±0.26 | **EBT4** | 1.334±0.0009 | 90.62±0.28 |
| 5 | **EBC5** | UNSTABLE | UNSTABLE | **EBT5** | 1.335±0.0007 | 89.58±0.31 |
| 6 | **EBC6** | 1.331±0.0007 | 97.62±0.37 | **EBT6** | 1.332±0.0005 | 96.19±0.11 |
| 7 | **EBC7** | UNSTABLE | UNSTABLE | **EBT7** | UNSTABLE | UNSTABLE |
| 8 | **EBC8** | UNSTABLE | UNSTABLE | **EBT8** | 1.338±0.0010 | 92.56±0.34 |
| 9 | **EBC9** | 1.333±0.0005 | 92.72±0.08 | **EBT9** | UNSTABLE | UNSTABLE |

**Viscosity determination:**

From the viscosity determination it was observed that as the concentration of co-surfactant increased

viscosity of the formulation also increased. So, formulation F1-F4 was highly viscous due to higher co-surfactant concentration. Out of 18 formulations, EBC6 and EBT6 (oil-35% and Smixture-65%) showed optimum viscosity due to optimum concentration of oil, surfactant and co-surfactant. The results were shown in table 9.

**Table 9: Viscosity Measurement of SMEDDS**

| S.No | Formulation | Viscosity (cps) | Formulation | Viscosity (cps) |
|---|---|---|---|---|
| 1 | **EBC1** | 0.2442±0.008 | **EBT1** | 0.8259±0.005 |
| 2 | **EBC2** | 0.2448±0.010 | **EBT4** | 0.8267±0.007 |
| 3 | **EBC4** | 0.24457±0.012 | **EBT5** | 0.8283±0.006 |
| 4 | **EBC6** | 0.2462±0.009 | **EBT6** | 0.8304±0.008 |
| 5 | **EBC9** | 0.2459±0.007 | **EBT8** | 0.8275±0.004 |

Absolute drug content in L-SMEDDS & S-SMEDDS:
The results were represented in Table 10, 11 and figure 5a and 5b. From the results, formulation EBC6 and EBT6 showed the highest drug content amongst all the other formulations.

**Table 10: Drug content determination in L-SMEDDS**

| S.No. | Formulation | Drug Content (%) | Formulation | Drug Content (%) |
|---|---|---|---|---|
| 1 | **EBC1** | 94.29±0.09 | **EBT1** | 95.38±0.22 |
| 2 | **EBC2** | 93.38±0.18 | **EBT2** | 94.46±0.34 |
| 3 | **EBC3** | 94.41±0.08 | **EBT3** | 93.85±0.19 |
| 4 | **EBC4** | 95.33±0.26 | **EBT4** | 94.56±0.26 |
| 5 | **EBC5** | 96.12±0.31 | **EBT5** | 95.65±0.31 |
| 6 | **EBC6** | 98.34±0.19 | **EBT6** | 98.30±0.39 |
| 7 | **EBC7** | 95.29±0.45 | **EBT7** | 95.48±0.40 |
| 8 | **EBC8** | 95.73±0.21 | **EBT8** | 96.48±0.25 |
| 9 | **EBC9** | 95.35±0.10 | **EBT9** | 95.62±0.37 |

**Table 11: Drug content determination in S-SMEDDS**

| S.No. | Formulation | Drug Content (%) | Formulation | Drug Content (%) |
|---|---|---|---|---|
| 1 | **EBC1** | 96.19±0.07 | **EBT1** | 95.32±0.22 |
| 2 | **EBC2** | 95.41±0.13 | **EBT2** | 94.47±0.37 |
| 3 | **EBC3** | 95.46±0.16 | **EBT3** | 95.53±0.48 |
| 4 | **EBC4** | 96.53±0.37 | **EBT4** | 96.51±0.24 |
| 5 | **EBC5** | 93.62±0.13 | **EBT5** | 94.39±0.18 |
| 6 | **EBC6** | 98.48±0.19 | **EBT6** | 98.08±0.34 |
| 7 | **EBC7** | 96.49±0.73 | **EBT7** | 96.59±0.09 |
| 8 | **EBC8** | 96.25±0.38 | **EBT8** | 96.20±0.56 |
| 9 | **EBC9** | 93.20±0.14 | **EBT9** | 96.65±0.33 |

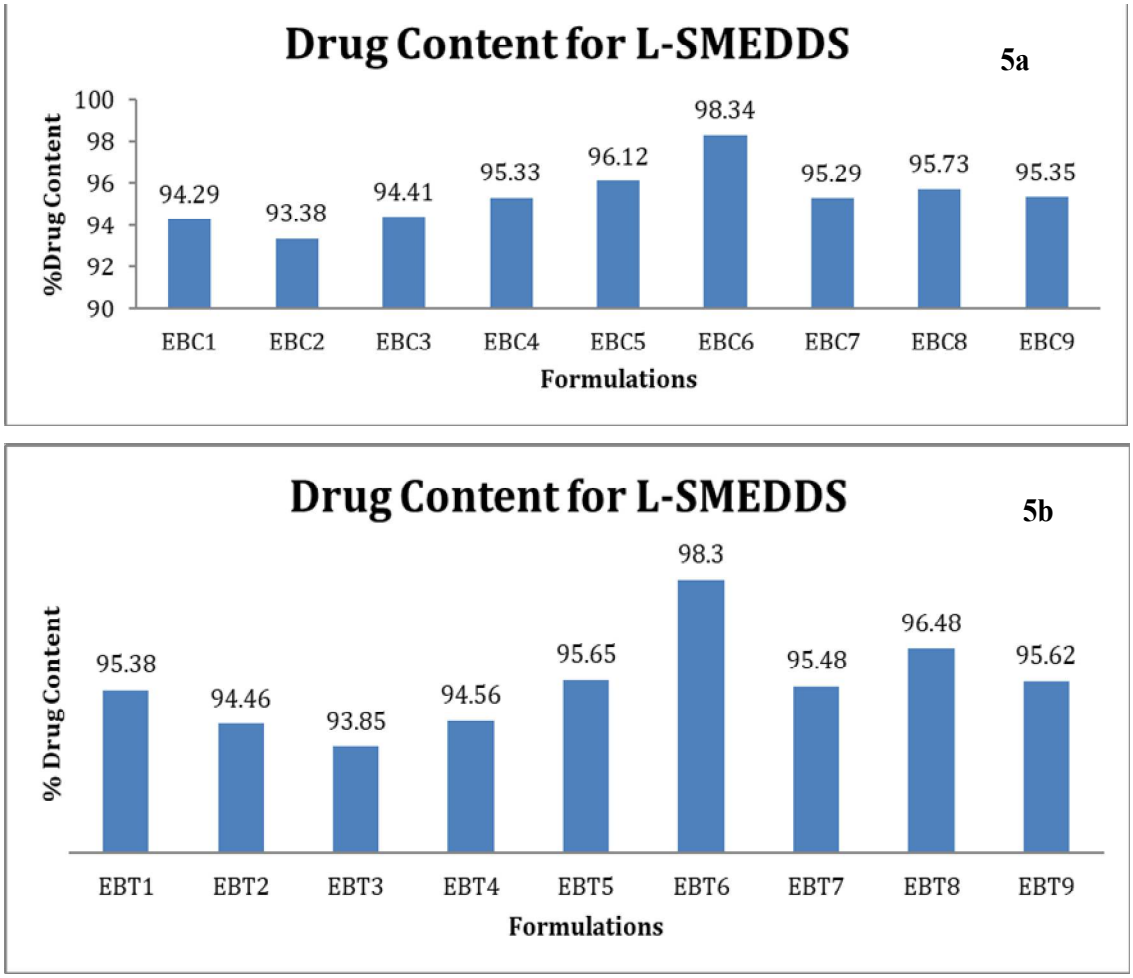


**Figure 5.** Drug content of a)- L-SMEDDS; b)- S-SMEDDS

Conversion of liquid SMEDDS into solid S-SMEDDS:
Solid SMEDDS were prepared by mixing liquid SMEDDS containing Ebastine with microcrystalline cellulose in 1:1 proportion. Liquid SMEDDS was added drop wise over MCC and homogenized using glass rod to ensure uniform distribution of formulation in a china dish.

**Characterization of S-SMEDDS**
**a) Micromeretic properties**
Angle of Repose
Angle of repose for the best formulation (EBC6 and EBT6) was 26°54' and 28°38' respectively. The results suggested that the powder blend of formulation showed good flow properties. The results of angle of repose of formulations were shown in **table 12 a & 12 b.**
Bulk density
The bulk densities for the best formulations (EBC6 & EBT6) were 0.3441±0.004g/ml and 0.3439±0.012g/ml. The results indicated that the powder blends of formulation had good flow properties. The results were summarized in **table12 a & 12 b.**
Tapped density
Tapped densities for the best formulations (EBC6 & EBT6) 0.4029±0.007g/ml and 0.4035±0.0013g/ml respectively. The results were summarized in **table 12 a & 12b.**
Carr's index
The Carr's index of the best formulations EBC6 & EBT6 were found to be 14.60±0.007% and 14.77±0.001%, indicating that the powder blend was excellent. The results were summarized in **table 12 a & 12 b.**
Hausner's ratio:
The Hausner ratio of the best formulations (EBC6 & EBT6) were found to be 1.17±0.005 and 1.17±0.006. The results were summarized in **table 12 a & 12 b.**

***In vitro* drug release from S-SMEDDS:**

The results of in-vitro drug release studies from Ebastine SMEDDS formulation were represented in Table 13a and 13b and figure 6a & 6b.

Formulation EBC6 and EBT6 showed the highest percentage drug release of 86.27±0.16% and 85.08±0.38% at the end of two hours respectively than the other formulations.

**Table 12. Micromeritic Characterization of SMEDDS**

| S. No | Parameter | EBC1 | EBC2 | EBC3 | EBC 4 | EBC5 | EBC6 | EBC7 | EBC8 | EBC9 |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Angle of Repose | 29°33' ±0°32' | 28°8± 0°34' | 28°76'± 0° 17' | 28°26' ±0°24' | 27°32' ±0° 31' | 25°19'± 0 °39' | 27°43'± 0° 16' | 28°26'± 0°39' | 28°44' ±0 °62' |
| 2 | Bulk density g/ml | 0.3433 ±0.007 | 0.345 8±0.0 08 | 0.3467± 0.008 | 0.338 5±0.0 05 | 0.3427 ±0.008 | 0.3441 ±0.004 | 0.3433± 0.004 | 0.3438 ±0.007 | 0.3436±0 .008 |
| 3 | Tapped density | 0.4041 ±0.001 | 0.409 6±0.0 09 | 0.4082± 0.006 | 0.403 9±0.0 03 | 0.4088 ±0.06 | 0.4029 ±0.007 | 0.4051± 0.007 | 0.4050 ±0.004 | 0.4057±0 .004 |
| 4 | Carr's index % | 15.04± 0.003 | 15.16 ±0.00 4 | 15.07±0 .005 | 16.19 ±0.00 4 | 16.17± 0.007 | 14.60± 0.004 | 15.25±0 .003 | 15.11± 0.005 | 15.30±0. 004 |
| 5 | Hausner's ratio | 1.18±0. 04 | 1.18± 0.06 | 1.18±0. 03 | 1.19± 0.05 | 1.19±0. 03 | 1.17±0. 05 | 1.18±0. 04 | 1.18±0. 07 | 1.18±0.0 3 |
| | **Parameter** | **EBT1** | **EBT2** | **EBT3** | **EBT4** | **EBT5** | **EBT6** | **EBT7** | **EBT8** | **EBT9** |
| 1 | Angle of Repose | 27°52± 1 °19' | 27°28 ±0 °26' | 27°72±0 °51' | 27°33 ±0 °61' | 27°14± 0 °09' | 26°11± 0 °36' | 27°42±0 °56' | 27°44 '±0°3 5' | 27°31±0 °11' |
| 2 | Bulk density g/ml | 0.3434 ±0.008 | 0.342 1±0.0 11 | 0.3430± 0.002 | 0.339 8±0.0 07 | 0.3419 ±0.010 | 0.3439 ±0.003 | 0.3401± 0.012 | 0.3408 ±0.008 | 0.3410±0 .011 |
| 3 | Tapped density | 0.4036 ±0.004 | 0.403 4±0.0 09 | 0.4041± 0.012 | 0.404 5±0.0 08 | 0.4025 ±0.009 | 0.4035 ±0.003 | 0.4042± 0.011 | 0.4040 ±0.006 | 0.4038±0 .012 |
| 4 | Carr's index % | 15.05± 0.002 | 15.19 ±0.00 9 | 15.12±0 .005 | 16.00 ±0.00 7 | 15.06± 0.003 | 14.77± 0.001 | 15.86±0 .010 | 15.64± 0.008 | 15.55±0. 004 |
| 5 | Hausner's ratio | 1.18±0. 04 | 1.18± 0.05 | 1.18±0. 03 | 1.19± 0.09 | 1.18±0. 04 | 1.17±0. 06 | 1.19±0. 07 | 1.19±0. 08 | 1.18±0.0 5 |

**Table 13. *In-vitro* Drug Release Studies of S-SMEDDS**

| Time | Cumulative % Drug Release | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **EBC 1** | **EBC 2** | **EBC 3** | **EBC 4** | **EBC 5** | **EBC 6** | **EBC 7** | **EBC 8** | **EBC 9** |
| **0** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **5** | 65.18±0.39 | 65.81±0. 30 | 66.56±0. 37 | 66.54±0.1 2 | 67.23±0.3 9 | 69.11±0.4 0 | 69.02±0. 27 | 68.51±0.1 8 | 68.43±0.47 |
| **10** | 72.63±0.44 | 68.59±0. 47 | 67.89±0. 17 | 68.75±0.4 3 | 69.68±0.2 9 | 71.34±0.5 3 | 70.24±0. 11 | 70.09±0.1 6 | 70.31±0.41 |
| **20** | 74.19±0.29 | 73.26±0. 13 | 71.69±0. 23 | 70.08 ±0.40 | 70.86 ±0.13 | 75.71±0.0 8 | 73.36±0. 19 | 71.17±0.2 2 | 73.18±0.19 |
| **30** | 76.14±0.16 | 74.14±0. 20 | 73.44 ±0.23 | 72.02±0.4 1 | 71.98±0.2 5 | 78.53±0.2 9 | 76.52±0. 38 | 72.63±0.2 1 | 74.16±0.28 |
| **45** | 76.39±0.18 | 75.86±0. 34 | 75.63±0. 39 | 73.39±0.3 9 | 72.87±0.2 8 | 79.96±0.3 2 | 77.14±0. 34 | 73.59±0.2 1 | 75.89±0.29 |
| **60** | 77.07±0.11 | 76.39 ±0.22 | 76.13±0. 41 | 74.54±0.3 8 | 74.13±0.3 4 | 81.54±0.3 8 | 77.90±0. 26 | 74.96±0.2 3 | 77.31±0.26 |
| **80** | 77.48±0.31 | 76.17±0. 19 | 77.01±0. 37 | 75.16±0.3 5 | 75.46±0.1 9 | 82.26±0.1 2 | 78.77±0. 31 | 76.03±0.2 0 | 79.76±0.38 |
| **100** | 77.96±0.42 | 77.46±0. 36 | 77.84±0. 29 | 76.73±0.2 6 | 76.77±0.3 4 | 84.33±0.1 0 | 79.58±0. 64 | 78.01±0.3 0 | 80.54±0.25 |
| **120** | 78.56±0.35 | 78.31±0. 42 | 78.63±0. 33 | 77.95±0.2 0 | 78.93±0.1 5 | 86.27±0.1 6 | 81.11±0. 28 | 79.79±0.5 8 | 82.19±0.23 |
| | **EBT 1** | **EBT 2** | **EBT 3** | **EBT 4** | **EBT 5** | **EBT 6** | **EBT 7** | **EBT 8** | **EBT 9** |
| **0** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **5** | 67.35±0.32 | 64.07 ±0.32 | 66.57±0 .09 | 66.88±0. 10 | 69.21±0.2 4 | 70.23±0.21 | 69.16±0. 14 | 69.02±0.3 4 | 69.07±0.17 |
| **10** | 69.38±0.22 | 65.88±0.2 3 | 68.34±0.3 2 | 68.38±0.26 | 70.79±0.3 5 | 72.30±0.30 | 71.22±0.2 2 | 71.10±0.06 | 71.00±0.20 |
| **20** | 71.16±0.19 | 68.52±0.4 | 70.59±0.4 | 69.93±0.17 | 72.83±0.2 | 74.91±0.16 | 73.61±0.3 | 72.97±0.18 | 72.71±0.24 |

| | | 3 | 4 | | 4 | | 5 | | |
|---|---|---|---|---|---|---|---|---|---|
| **30** | 72.54±0.13 | 69.74±0.13 | 71.40±0.41 | 71.21±0.12 | 74.25±0.65 | 76.73±0.27 | 74.79±0.29 | 74.52±0.59 | 74.32±0.32 |
| **45** | 73.91±0.20 | 70.98±0.31 | 73.58±0.26 | 72.46±0.20 | 76.09±0.35 | 78.19±0.13 | 76.23±0.20 | 76.34±0.50 | 75.70±0.21 |
| **60** | 74.59±0.30 | 72.13±0.23 | 75.11±0.21 | 73.16±0.47 | 77.14±0.31 | 80.48±0.29 | 77.78±0.34 | 77.41±0.51 | 76.96±0.45 |
| **80** | 75.87±0.27 | 73.01±0.21 | 76.90±0.20 | 74.05±0.46 | 78.33±0.13 | 82.37±0.37 | 78.97±0.35 | 78.69±0.18 | 78.29±0.22 |
| **100** | 77.02±0.20 | 74.30±0.27 | 78.46±0.35 | 75.62±0.34 | 79.86±0.22 | 84.12±0.16 | 80.59±0.21 | 80.17±0.17 | 80.05±0.31 |
| **120** | 78.11±0.25 | 75.21±0.32 | 80.34±0.16 | 77.09±0.24 | 81.47±0.18 | 85.08±0.38 | 81.99±0.21 | 82.12±0.15 | 81.58±0.25 |

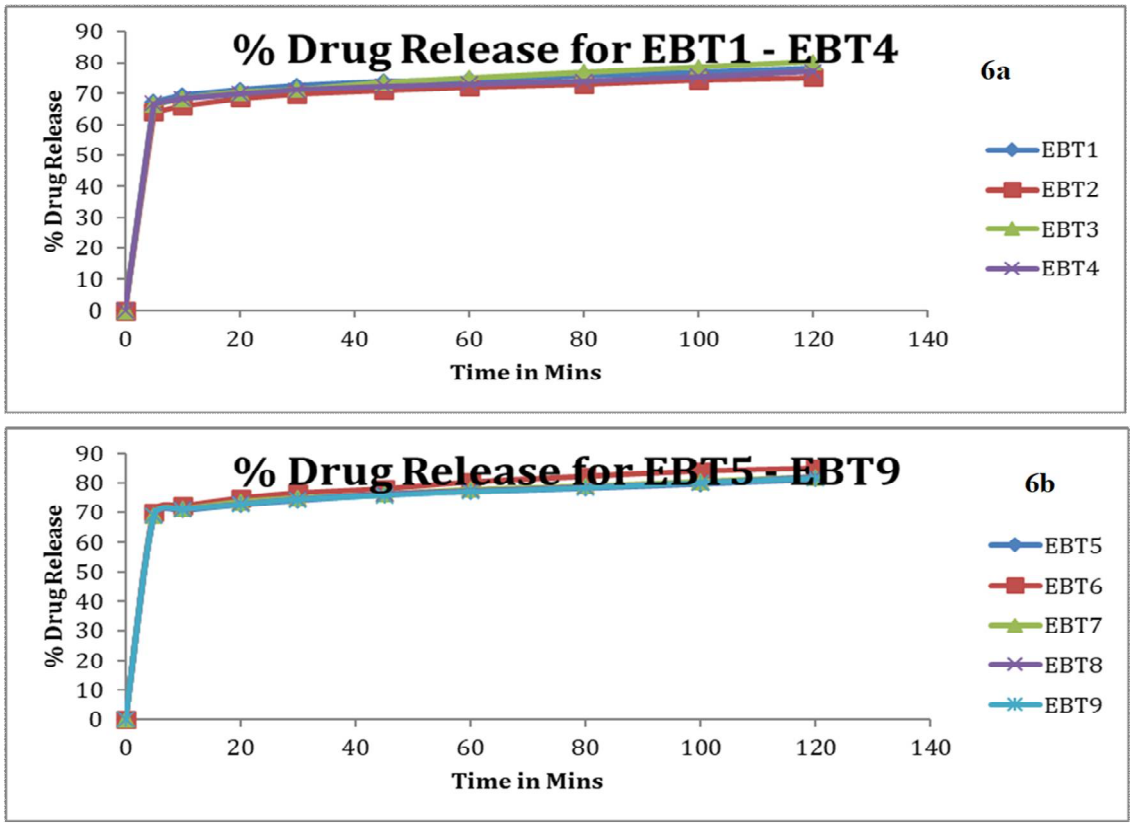


**Figure 6. *In-vitro* Drug Release Studies of S-SMEDDS**

## CONCLUSION

Different formulations were prepared using Ebastine, oils, surfactants and co-surfactants. Optimized formulations EBC6 and EBT6 were selected and showed increased solubility, dissolution rate and bioavailability. The dissolution profiles of all the formulations showed a drug release of greater than 75% of drug release in 120mins. Among all formulations EBC6 and EBT 6 have released drug 86.27% & 85.08%. Thus, our study confirmed that the SMEDDS formulations can be potentially used as an alternative to the traditional oral formulations for the poorly soluble drugs like Ebastine to improve its solubility and dissolution.

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