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Original Article

Development of a Solid Self-emulsifying Drug Delivery System of *Boswellia serrata*

Vidhi Bhatia*, MS Arohi Paul

ABSTRACT

Background: Self-emulsifying drug delivery system (SEDDS) and solid-SEDDS of *Boswellia serrata* extract (BSE) was aimed at overcoming the problems of poor solubility and bioavailability. **Materials and Methods:** The formulation strategy included a selection of oil phase, surfactant and co-surfactant based on qualitative and quantitative saturated solubility studies. A ternary phase diagram was constructed to identify the self-emulsifying region using water uptake studies. Pseudoternary phase diagrams were plotted using 1:1, 2:1 and 3:1 ratios of surfactant and co-surfactant to identify the maximum micro-emulsification region. The prepared formulations of SEDDS were evaluated for their physical appearance, stability, drug content, and globule size determination. Solid-SEDDS were prepared by adsorption technique using mannitol (4.5% w/w) and were evaluated for physical appearance, stability, drug content, and globule size. *In-vitro* studies were performed to compare the release of solid drugs, SEDDS and S-SEDDS. **Results:** The formulation containing *Boswellia serrata* (200 mg), Capmul MCM C8 (15% w/w), Tween 20 (33.333% w/w), Transcutol HP (16.666% w/w) was concluded to be optimized. The release pattern was signified more than 80% release in 30 min in case of S-SEDDS and SEDDS, and 40% release after 120 min in case of solid drug. Solid-SEDDS may be considered a better solid oral dosage form as solidified formulations are more ideal than liquid ones in terms of their stability. **Conclusion:** Results suggest the potential use of SEDDS and solid-SEDDS to improve the dissolution and hence oral bioavailability of poorly water-soluble drugs like *Boswellia serrata* through oral route.

Keywords: Bioavailability, Phase diagram, Solid-self-emulsifying drug delivery system, *Boswellia serrata*.

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INTRODUCTION

Boswellia serrata extract (BSE) is known to be a potent anti-inflammatory agent used to treat disorders like inflammatory bowel disease, osteoarthritis, ulcerative colitis. They belong to the class of pentacyclic triterpenic acid. BSE is a blend of basic oil, gum and sap where fundamental oil is a blend of monoterpenes, diterpenes and sesquiterpenes additionally containing phenolic mixes and a diterpene alcohol (serratol).

BSE are seen to be non-redox, non-competitive inhibitors of 5-lipoxygenase (5-LO) and block its translocation. 5-LO is essentially communicated in hematopoietic cells and is a key catalyst in the biosynthesis of leukotrienes from arachidonic acid (AA). Leukotrienes are normally delivered eicosanoid lipid mediators, which might be answerable for the impacts observed with asthma, sensitivities, inflammation and irritation, and BSE are acknowledged inhibitors of leukotriene biosynthesis. It also involves inhibition of human leucocyte elastase enzyme found in neutrophils responsible for inflammatory and hypersensitivity conditions like glomerulonephritis, emphysema, chronic bronchitis and asthma. Also enhances inhibition of cathepsin G and acetylcholinesterase promoting anti-inflammatory activity.[1]

Besides its advantages, BSE has certain limitations, mainly with respect to its patient compliance. In spite of BCS class II drug and high log *p* value (6.5-8), it possesses low water solubility and poorly absorbed in the body through systemic circulation. However, it has limited bioavailability (1%) following oral administration due to significant extensive phase 1 metabolism in liver. Peak serum concentrations are achieved approximately 4.5 hr following oral administration and half-life is 6 hr. Commercially available formulations include tablets and topical preparations like creams and gels. Since half-life of BSE is 6 hr, it has to be commonly administrated after every 6 hr for osteoarthritis.[2] Its repeated high dosing is the major reason for its patient non-compliance. Thus, the rationale behind selecting BSE as drug of choice is to reduce its dosing frequency by increasing the bioavailability of the drug by improving the solubility of to demonstrate

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the necessary therapeutic activity. Moreover, it is always useful to develop formulation fororal route as it is most common route of administration.

Of many drug delivery systems that aid in increasing the solubility and bioavailability one is to develop Self-emulsifying drug delivery system (SEDDS). Self-emulsifying drug delivery systems (SEDDS) are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants, or alternatively, one or more hydrophilic solvents and co- solvents/surfactants that have a unique ability of forming fine oil-in-water (o/w) micro emulsions upon mild agitation followed by dilution in aqueous media, such as gastrointestinal (GI) fluids. SEDDS spread readily in the GI tract and the digestive motility of the stomach and the intestine helps in the agitation necessary for self-emulsification. Co-administration of lipid with the lipophilic drug is as advantageous because it contributes to the enhancement of bioavailability of the drug. Surfactant and co-surfactant molecules get favourably absorbed at the liquid interface during the process of emulsion formation, reducing the interfacial energy of the system. Rapid emulsion formation helps to keep the drug in a dissolved form; however, small droplet size offers a considerably larger interfacial surface area which further accelerates the absorption rate of drug with limited solubility. This feature makes SEDDS a meaningful choice for oral delivery of lipophilic, low bioavailable drugs having adequate lipid solubility. Moreover, the lipoidal part of SEDDS encourages the intestinal lymphatic uptake of drugs which further helps in avoiding the presystemic biotransformation of drug molecules.[3-5]

Choosing the right combination of lipid (oil), surfactant, and co-surfactant is one of the important points in designing SEDDS formulations. Selection of a good self-emulsifying formulation depends on the (1) the solubility of the drug in oil/surfactant/co- surfactant (2) emulsion forming area as determined by phase diagram, and (3) the globule size distribution of the developed SEDDS.[3]

There are various reasons or challenges in developing lipid based systems, like so far there are no definite *in-vitro* evaluation or characterization tests which can simulate or predict the *in-vivo* performance of drug administered in lipoidal formulations, second is liquid nature of these formulations which make them failure at commercial success because of issues in manufacture, handling, storage, supply and incompatibility problems with the shells of soft gelatin and same time retain risk of stability issues too. To overcome these limitations of liquid SEDDS many different approaches like spray drying, melt granulation, adsorption on solid carrier and other techniques have been explored and used to transform the lipid based formulation into solid oral dosage form. But among these, the adsorption technique is simple and economic and utilizes addition of liquid formulation onto the solid carriers by mixing in a blender. The resulting powder may then be filled directly into capsules or, alternatively, mixed with suitable excipients before compression into tablets. A significant benefit of the adsorption technique is good content uniformity. The SEDDS can be allowed to adsorb at high levels up to 70% w/w on to suitable carrier.[6]

The aim of the study is to formulate solid self-emulsifying drug delivery system (readily dispersible powder) using a herbal extract.

MATERIALS AND METHODS

Materials

Boswellia serrata extract (BSE) was obtained from Konark Pvt. Ltd., Mumbai, India. Capmul MCM C8 was purchased from Abitec, India. Tween 20 (Polyoxyethylene sorbitan monolaurate, HLB 16.7) was purchased from Seppic, India. Transcutol HP was purchased from Gattefosse, India. Mannitol was purchased from Roquette, India. Other chemicals used were of analytical grade.

Methods

Pre-Formulation Studies

Screening of Excipients: Excipients for formulating SEDDS and S-SEDDS were selected based on literature and availability.

Qualitative Studies

Physical Parameters: Evaluation of physical parameters like loss of drying, ash value, alcohol soluble extractive value and water-soluble extractive value was carried out.[7]

Phytochemical Sceening: The phytoconstituent was subjected to phytochemical screening separately using reagents and chemicals. Screening involved qualitative determination of alkaloid, glycoside, terpenoids, steroids, flavonoids, tannins and phenolic compounds. The phytoconstituent was subjected to qualitative examination as per the Pharmacopoeia of India (IP).[7]

Thin Layer Chromatography (TLC): TLC analysis was conducted on pre-coated silica gel $60F_{254}$ TLC plates. The plates were visualizing in day light, in short ultraviolet (UV) and long UV. The R*f* value is the "retardation factor" or "ratio-to-front" value expressed as a decimal fraction. The R*f* value was calculated using following formula:

R*f* = Distance travelled by solute/Distance travelled by solvent front

Procedure

Standard Solution:10 mg of standards dissolved in 10ml of methanol and filtered it to remove insoluble matter. The filtrates were used for spotting on silica gel plate.

Test Solution: 0.5g of extract dissolved in 100 ml of methanol and filtered it to remove insoluble matter. The filtrates were used for spotting on silica gel plate.

Mobile phase: Hexane: ethyl acetate (6:4)

Derivatizing agent:10% sulphuric acid in methanol[8]

Fourier Transform Infrared (FTIR) Spectroscopy of Phytoconstituent: The FTIR spectrum of the phytoconstituents were recorded at resolution of $4cm^{-1}$ over the range $4000\text{-}500cm^{-1}$ and the principal peaks from spectrum were studied and interpreted based on their frequencies. The FTIR was performed on Shimadzu IR Affinity.[9]

Solubility Studies: 25 mg phytoconstituent was taken in a test tube and to it 0.1 ml of oil was added in incremental amounts and vortexed till the phytoconstituent gets completely solubilized in the oil which is observed visually and results were noted.[10]

Miscibility Studies: This study is performed taking 1:1 ratio of respected oil and surfactant and oil and co-surfactant and shaken manually and observed visually to check the components were miscible or not.[10]

Quantitative Studies

Saturation Solubility Studies: Excess drug (100 mg) was taken in 1 ml of various oils, surfactants and co-surfactants and samples were kept in the shaker water bath at 37°C and 150 rpm for 24 hr. The samples were then centrifuged at 3000 rpm for 15 min. The samples were suitably diluted and analyzed using HPLC.

Based on the qualitative and quantitative studies, respective oil, surfactant and co-surfactant was selected for further water-uptake studies.[10]

Water Uptake Studies: It is performed using the selected oil and surfactant alone and in combination with co-surfactants in various ratios like 1:1, 2:1, 3:1 etc. Using this data, ternary phase diagram is plotted to get the suitable micro emulsification region. Oil and respective surfactant alone or in combination with co-surfactant was added in the ratio 0.1:0.9, 0.2:0.8, 0.3:0.7, 0.4:0.6, 0.5:0.5, 0.6:0.4, 0.7:0.3, 0.8:0.2,

0.9:0.1 in respective test tubes and 50 µL water was added in incremental amounts till the solution gets turbid or gel like consistency. This activity was repeated for all the given surfactants and co-surfactants to plot the pseudoternary phase diagram to determine the micro emulsification region (o/w region).[11]

Construction of Ternary Phase Diagram: Ternary phase diagram was constructed using the data obtained from water uptake studies in order to obtain the appropriate concentration ranges of oil and surfactant that can result in large existence area of stable micro emulsion.[11]

Construction of Pseudoternary Phase Diagram: Pseudoternary phase diagrams were plotted using co-surfactant to obtain maximum o/w region.[11]

Analytical Method Development

High Performance Liquid Chromatography (HPLC)

Phytoconstituent was analysed using Reverse phase HPLC analytical technique to obtain λ_{max} of the most suitable constituent of the phytoconstituent based on its pharmacological activity.

The initial trial was taken based on literature. Then the method was allowed for modification using different mobile phase compositions, columns and flow rate. Method providing a good peak shape and resolution and high number of theoretical plates is selected for further analytical development.

Standard Preparation: 200 mg of standard was sonicated for 30 min with 50 ml methanol and volume was made up with methanol till 100 ml.

Final concentration: 2000 ppm

Sample Preparation: 200 mg of drug powder (phytoconstituent) was sonicated for 30 min with 50 ml methanol and volume was made up with methanol till 100 ml.[2]

Forced Degradation Studies

Procedure: Forced degradation studies were performed in 0.05N HCL, 0.1N HCL, 0.2N HCL and 0.05N NaOH and 0.2N NaOH and in 3% and 30% H_2O_2 in order to determine the degradation pathways of the drug by HPLC method in acidic, alkaline and oxidation conditions.

Acidic Conditions

A suitable quantity (50 mg) of phytoconstituent was taken and to it, 50 ml of diluent (methanol) was added and sonicated for 30 min. After sonication, 5 ml HCL was added and kept aside for 1, 2, 3 hr respectively with intermittent shaking. Later, 5ml NaOH was added for neutralization and diluent was added and allowed to sonicate for 10 min, later, volume was made up with the diluent and solution was filled in the vials and injected into HPLC system at λ_{max} 260 nm. Samples and standard were prepared in duplicates.

Alkaline Conditions

A suitable quantity (50 mg) of phytoconstituent was taken in 100 volumetric flask and to it, 50 ml of diluent (methanol) was added and sonicated for 30 min. After sonication, 5 ml NaOH was added and kept aside for 1, 2, 3 hr respectively with intermittent shaking. Later, 5 ml HCL was added for neutralization and diluent is added and allowed to sonicate for 10 min, later, volume was made up with the diluent and solution was filled in the vials and injected into HPLC system at λ_{max} 260 nm. Samples and standard were prepared in duplicates.

Oxidative Conditions

A suitable quantity (50 mg) of phytoconstituent was taken in 100 volumetric flask and to it, 50 ml of diluent (methanol) was added and sonicated for 30 min. After sonication, 5 ml H_2O_2 (3% and 30%) was added and kept aside for 1, 2, 3 hr respectively with intermittent shaking. Later, diluent was added and allowed to sonicate for 10 min, and volume was made up with the diluent and solution was filled in the vials and injected into HPLC system at λ_{max} 260 nm. Samples and standard were prepared in duplicates.

Thermal Degradation Studies

50mg phytoconstituent was accurately weighed in a petri plate. The samples were placed in vacuum oven at 105°C for 1, 2 and 3 hr respectively. After reaching the time point, samples were withdrawn and transferred to 100 ml volumetric flask and 50 ml diluent was added and allowed to sonicate for 30 min. Later, volume was made up with diluent and samples were filled into the vials and analyzed using HPLC at λ_{max} 260 nm.

Photo Degradation Studies

50 mg phytoconstituent was accurately weighed in a petri plate. The samples were exposed to sunlight for 1, 2 and 3 hr respectively. After reaching the time point, samples were withdrawn and transferred to 100ml volumetric flask and 50 ml diluent was added and allowed to sonicate for 30 min. Later, volume was made up with diluent and samples were filled into the vials and analyzed using HPLC at λ_{max} 260 nm.[12]

Formulation of SEDDS:[13-16] The excipients selected for further developing a formulation was based on solubility and water uptake studies. An oral liquid SEDDS formulation was prepared. In the initial step, pseudoternary plots which provided maximum o/w micro-emulsification region was selected to carry out optimization of micro emulsification composition. Critical dose of the phytoconstituent is 200mg. Based on the visual observation, particle size and stability of the entire system, the optimized formula was taken ahead for adsorption.

Each formula contains 2 ml microemulsion loaded with 400 mg phytoconstituent equivalent to 2 doses. As per dose and given compositions selected for oil and S-mix, extract was accurately weighed in test tubes. Accurate amount of co-surfactant and oil was added and was allowed to be placed in the water bath and manual shaking of the mixture was carried out. Temperature for the water bath was set at 30°C and gradually increased to increase the rate of solubilization. At temperature 60°C, rate of solubilization was the highest. Later on, the mixture was sonicated for 5-10 min and again heated on the water bath to ensure complete solubilization and uniformity of the phytoconstituent. Surfactant was added in the fixed amount and Step 4 was again repeated. Water was then added in all the formulations to form microemulsion. Particle size analysis was then carried out by diluting the microemulsion (ME) to 250 ml water for formulations and was kept aside at room temperature for visual observation. After 24 hr, particle size analysis was repeated to check the physical stability of ME.

Evaluation of SEDDS[13-16]

Physical Evaluation: Color and physical appearance were tested by visual observation.

Particle Size Analysis for Optimization of ME Composition

Preparation of Sedds: Equivalent to 1 dose, ME formulations was diluted to 250 ml with water in a beaker and gently mixed manually. The resultant emulsion was then subjected to particle size analysis using Malvern particle size analyzer for optimization of ME composition.

Drug Content (ASSAY): Equivalent to 1 dose, SEDDS was transferred to a 100 mL volumetric flask and diluted with 50 ml of methanol. The mixture was sonicated for 30 min and then diluted to 100 ml with

methanol. The mixture was filtered through a 0.45 µm PVDF membrane filter to remove any particles. The first 5 µl of the filtrate was discarded and the subsequent was collected. Appropriate aliquots of filtrates were used for the HPLC analysis at λ_{max} of 260 nm. Samples were prepared in triplicates.

Formulation of S-SEDDS:[17-18] To overcome the limitations of SEDDS like failure at commercial success because of difficulties in manufacture, handling, storage, supply and incompatibility problems with the shells of soft gelatin and same time retaining risk of stability issues S-SEDDS is formulated. In order to transform the lipid-based formulation into an oral dosage form by adsorption technique which is simple and economic it involves addition of liquid formulation onto the solid carriers by mixing technique. Also, to increase the flow properties of the S-SEDDS, the material was granulated with a suitable granulating agent and dried using fluid bed dryer. Adsorption of SEDDS was carried out using two adsorbents, microcrystalline cellulose (water insoluble) and mannitol (water soluble). Adsorption: 10g SEDDS is accurately weighed in the mortar and pestle. Starting from 5g, subsequent amounts of adsorbent was added till the final product (powder) loses its stickiness to make sure the entire SEDDS was completely adsorbed. Wet granulation: To increase the flow properties, the material was granulated with water. Water was added until the material loses its brittleness and forms a cohesive mass. The material was passed through the sieve no. 10 and allowed to dry using fluid bed dryer. LOD was noted before and after drying. The dried material was allowed to pass through the sieve no. 20 to form uniform granules. The powder was evaluated based on particle size and flow properties. For particle size, equivalent to one dose was taken and diluted to 250 ml Milli-Q-water and the mixture was allowed to settle for 24 hr and supernatant was utilized to evaluate the globule size of the formulation.

Evaluation of S-SEDDS[17]

Particle Size Analysis: Equivalent to 1 dose, S-SEDDS was diluted to 250 ml with water in a beaker and gently mixed manually. The resultant emulsion was then subjected to particle size analysis using Malvern particle size analyzer.

Flow Properties: Flow properties of the powder was evaluated based on the following parameters: Carr's index**,** Hausner's ratio and Angle of Repose

Drug Content (ASSAY): Equivalent to 1 dose, S-SEDDS was transferred to a 100 mL volumetric flask and diluted with 50 mL of methanol. The mixture was sonicated for 30 min and then diluted to 100 mL with methanol. The mixture was filtered through a 0.45 µm PVDF membrane filter to remove any particles. The first 5 µL of the filtrate was discarded and the subsequent was collected. Appropriate aliquots of filtrates were used for the HPLC analysis at λ_{max} of 260 nm. Samples were prepared in triplicates.

In-vitro Release Studies[17]

Comparison of pure drug, self-emulsifying drug delivery system and solid-self-emulsifying drug delivery system

Dissolution study was first performed for the drug suspension, and then for SEDDS. The reason behind this was to compare a compiled dissolution profile of the drug, SEDDS and to claim the benefit of SEDDS and compare the release with S-SEDDS. It is performed to check the time required for the complete release of the active from the formulation.

Since SEDDS are liquid based formulations, direct administration of liquid into the dissolution media to carry out drug release studies is not possible. Therefore, capsules are prepared by filling with SEDDS (equivalent to one dose for each capsule) and sealed using gelatin band sealing and placed in the sinkers and then dropped into the media to avoid floating.

Dissolution was carried out using the USP-II apparatus using 900 ml of water as dissolution media and 50 RPM as paddle rotation speed. Water was selected as the dissolution media since the end formulation prepared is a readily dispersible powder in water. Hence, drug release holds importance when the powder is administered using a glass of water. Sample collected at each time points were filtered and subjected to quantitative analysis by HPLC method of analysis. Analysis was performed using n=3 samples for each batch size. For the last time point, RPM was increased to 200 as the recovery stage to solubilize the remaining active phamaceutical ingredient (API) in the media.

Dissolution protocol

- Apparatus: Paddle
- RPM: 50
- Media: Water
- Media volume: 900 ml
- Time points: 5, 15 30, 45, 60, 90 and 120 min
- Temperature: 37°C
- pH value: 7

Dissolution for S-SEDDS was carried out using the USP-II apparatus using 900 ml of water as dissolution media and 50 RPM as paddle rotation speed.

Since S-SEDDS were in the form of ready to disperse powder, for dissolution quantity equivalent to one dose was taken and allowed to disperse in 50 ml water and then added to the dissolution vessel.

Sample collected at each time points were filtered and subjected to quantitative analysis by HPLC method of analysis.

Stability Studies[17]

The stability studies of the formulations were performed based on the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines.

The final optimized SEDDS and S-SEDDS was subjected to stability studies for a duration of 1 month at various temperature and humidity conditions.

1. 25 ± 2°C /60% ± 5% RH
2. 40 ± 2°C /75% ± 5% RH

The samples were tested and evaluated initially and then at 15th day and 30th day.

RESULTS AND DISCUSSION

Pre-Formulation Studies

Screening of excipients: Excipients for formulating SEDDS and S-SEDDS were selected based on literature and availability (Table 1).

Qualitative Studies Physical Parameters

The physical parameters of drug were evaluated to assess drug purity and identity. Following are the results for the evaluated physical parameters (Table 2).

The extract procured was found to be complying with the specifications. Phytochemical Screening: The extracts were subjected to phytochemical screening separately using reagents and chemicals. Screening involved qualitative determination of alkaloid, glycoside, terpenoids, steroids, flavonoids, and tannins. The powdered extract obtained was subject to qualitative examination as per the Pharmacopoeia of India (IP). Phytochemical screening was performing to confirm the presence of

Table 1: Screening of excipients.

Oils	Surfactants	Co-surfactants	Adsorbents
Capmul MCM C8	Tween 20	Transcutol HP	Avicel PH 101
Capmul PG8	Tween 80	Acconon MC8	Mannitol (Pearlitol 200SD)
Capmul PG12	Labrasol	PEG 400	
Labrafac PG	Kolliphor EL	Propylene glycol	
Labrafac Lipophile WL-1349	Kolliphor TPGS		
Capmul GMO			

Table 2: Physicochemical Parameters of BSE.

Parameter	Extract	Limits
Description	Light brown coloured powder with characteristic odour and characteristic taste.	Creamish white to brown coloured free flowing powder with characteristic odour and characteristic taste
Loss on Drying	4.5%	NMT 6%
Ash value (%)	2.6%	NMT 5%
Alcohol Soluble extractive value (%)	99.45%	NLT 90%
Water Soluble extractive value (%)	28.82% w/w	NMT 30%
Acid Insoluble Ash (%)	0.4%	NMT 2%

Table 3: Phytochemical Screening of Extract.

Test	Observation	Inference
1.Killer Killiani test	Reddish brown colour at the junction of two liquid and bluish green on upper layer.	Presence of cardiac glycosides
2.Ferric chloride test	Appearance of blue- black color.	Presence of tannins
3.Libermann-Burchard's test	Color change from violet to blue or green.	Presence of steroids
4.Salkowski's test	A reddish-brown band in the chloroform layer.	Presence of steroids and triterpenes
5.Mayer's reagent test	Cream precipitate	Presence of alkaloids
6.Shinoda's test	The formation of pink, reddish pink or brown colour.	Presence of flavonoids
7.Foam test	Formation of stable persistent foam.	Presence of saponins

phytoconstituents in given extracts. The powdered extract showed the presence of alkaloids, glycosides, saponins, steroids, triterpenoids, flavonoids and tannins (Table 3).

Thin Layer Chromatography

The solvents used for mobile phase and R*f* value of extract are mentioned in following Table 4. It was observed from the above results that the R*f* values of both Extract and standard match, hence the presence of phytoconstituents was confirmed.

FTIR of Phytoconstituent: The FTIR of phytoconstituent results are mentioned in Figure 1 and Table 5.

Solubility Studies

Since BSE has limited solubility in water and low bioavailability in biological fluids, it is important to increase the solubility of BSE to formulate SEDDS. For this, determining the solubility of drug in various oils plays a vital role. Minimum amount of drug should get solubilized in least quantity of oil. Oils showing good solubility of drug was utilized for further formulation studies. Results of solubility study of extract in oils revealed that Capmul MCM C8, Capmul PG8 and Labrafac PG have highest solubilisation capacity for BSE (Table 6).

Table 4: TLC of BSE Extract.

Drug	Mobile Phase	R_f value	Derivatizing Agent
BSE	Hexane: ethyl acetate (6:4)	Sample-0.28 Standard- 0.29	10% sulphuric acid in methanol

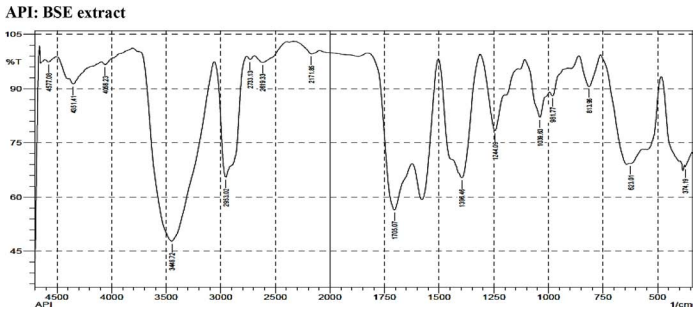


Figure 1: FTIR Spectrum of BSE extract.

Table 5: Interpretation of graph and drug structure by FTIR.

Wave Number (CM^{-1})	Functional Groups
$3448cm^{-1}$	OH stretching
$2953cm^{-1}$	C-H stretching
$1705cm^{-1}$	C=O stretching of arylic acid
$1396cm^{-1}$	C-H bend
$1244cm^{-1}$	C-CO-C stretching of aryl ketone
$1039cm^{-1}$ and $981cm^{-1}$	Ring structures of cyclohexane

Table 6: Observation Table for qualitative solubility studies.

Oil	Volume of oil added (ml)	Observation
Capmul MCM C8	0.5 ml	Entire drug gets solubilized
Capmul PG8	0.3ml	Entire drug gets solubilized
Capmul PG12	1 ml	Drug is dispersed
Labrafac PG	0.7 ml	On heating, drug gets solubilized
Labrafac Lipophile WL-1349	1 ml	On heating, drug remains dispersed
Capmul GMO	0.5 ml	Drug is dispersed

Miscibility Studies

Since formulation of SEDDS comprises of oil, surfactant and co-surfactant, oils used should be miscible with surfactants and co-surfactants. Various surfactants and co-surfactants which were selected from this method will be used for further formulation studies (Table 7 and 8).

Capmul PG8 and Capmul MCM C8 showed miscibility with Tween 20, Tween 80, Labrasol, Kolliphor EL and Kolliphor TPGS. Labrafac PG was immiscible with Tween 20, Labrasol and Kolliphor EL and found miscible with Tween 80 and Kolliphor TPGS.

Quantitative Studies

Saturation Solubility Studies

To develop SEDDS of BSE, it should possess good solubility in the oil, surfactants and co- surfactants of system. Saturation solubility studies of extract in various available oils, surfactants and co-surfactants were performed using developed analytical method for HPLC (Figure 2, 3, and 4).

Table 7: Observation Table for Qualitative Miscibility Studies of oils with surfactants.

Surfactants	Observations		
	Oils		
	Capmul PG 8	Capmul MCM C8	Labrafac PG
Tween 80	Miscible	Miscible	Miscible
Tween 20	Miscible	Miscible	Immiscible
Labrasol	Miscible	Miscible	Immiscible
Kolliphor EL	Miscible	Miscible	Immiscible
Kolliphor TPGS	Miscible	Miscible	Miscible

Table 8: Observation Table for Qualitative Miscibility Studies of oils with co- surfactants.

Co-Surfactants	Observations		
	Oils		
	Capmul PG 8	Capmul MCM C8	Labrafac PG
PEG-400	Miscible	Miscible	Immiscible
Acconon MC 8	Miscible	Miscible	Immiscible
Transcutol HP	Miscible	Miscible	Miscible

Capmul PG8, Capmul MCM C8 was found to be miscible in all co-surfactants whereas Labrasol was found to be immiscible with PEG 400 and Acconon MC 8.

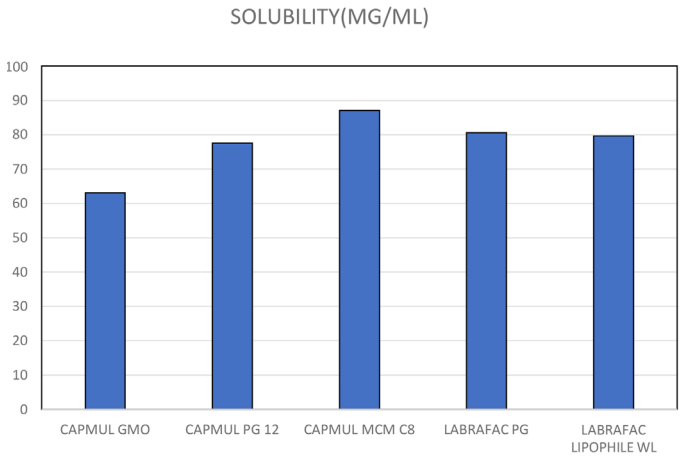


Figure 2: Saturation Solubility studies of oils.

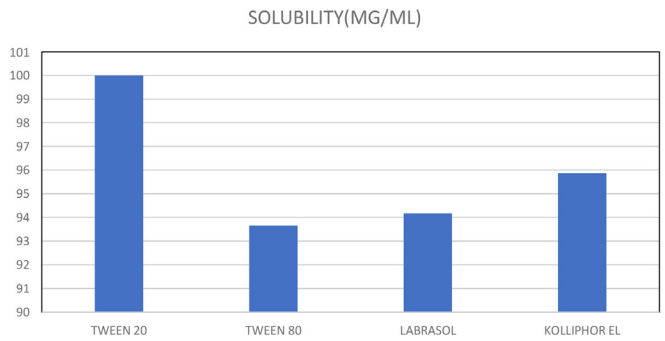


Figure 3: Saturation Solubility studies of surfactants.

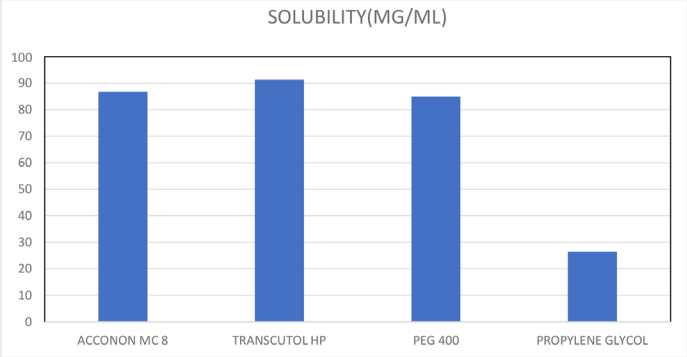


Figure 4: Saturation Solubility studies of co-surfactants.

Table 9: Water uptake studies in oil, surfactant and co-Surfactant.

Sl No.	Oil	Surfactant	Co-Surfactant	Ratio of surfactant mix
1.	Capmul MCM C8	Tween 20	Transcutol HP	1:1
2.	Capmul MCM C8	Tween 20	Transcutol HP	2:1
3.	Capmul MCM C8	Tween 20	Transcutol HP	3:1

Maximum solubility of BSE was observed in Capmul MCM C8, Tween 20 and Transcutol HP.

Therefore, based on solubility studies (qualitative and quantitative analysis) and miscibility studies, the components selected to carry out water uptake studies were

- Capmul MCM C8
- Tween 20
- Transcutol HP

Water Uptake Studies

This study was performed in absence of BSE. Water uptake studies was initially carried out using Capmul MCM C8 and Tween 20 to obtain the ternary phase diagram. Then, various ratios of combinations of Tween 20 and Transcutol HP was evaluated with Capmul MCM C8 to obtain the pseudoternary phase diagram. Based on the micro emulsification region and the desired o/w region, final pseudoternary diagram was selected to carry out optimization of the ME composition for SEDDS (Table 9).

Construction of Ternaryphase Diagram

The aim for constructing ternaryphase diagram was to explore the microemulsion region. The oil used was Capmul MCM C8 and surfactant used was Tween 20. The phase diagram was constructed in the absence of BSE (Figure 5).

Maximum micro emulsfication region was obtained.

Construction of Pseudoternary Phase Diagram

Pseudoternary phase diagrams are constructed using oils and different ratios of Tween 20 and Transcutol HP in order to derive the micro emulsion region and obtain wider o/w region. This study was also performed in the absence of the drug (Figure 6,7, and 8).

Based on o/w region and maximum micro emulsion region, pseudoternary phase diagrams, Capmul MCM C8 with Tween 20: Transcutol HP in 1:1 and 2:1 ratio was selected.

Further optimization of ME compositions was carried using both the pseudoternary phase diagrams.

Analytical Method Development

High Performance Liquid Chromatography: The trials conducted are mentioned in Table 10 along with the HPLC method given in the Table 11 and chromatogram in Figure 9.

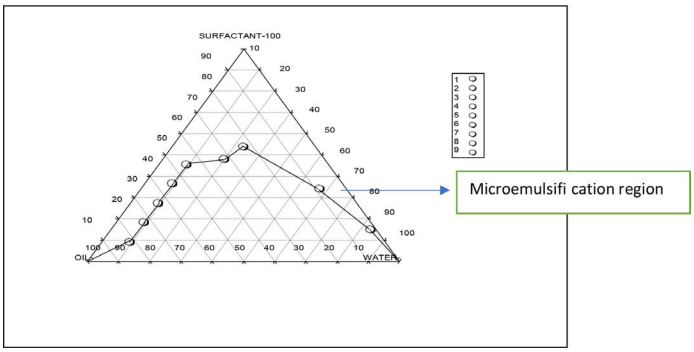


Figure 5: Ternary phase diagram.

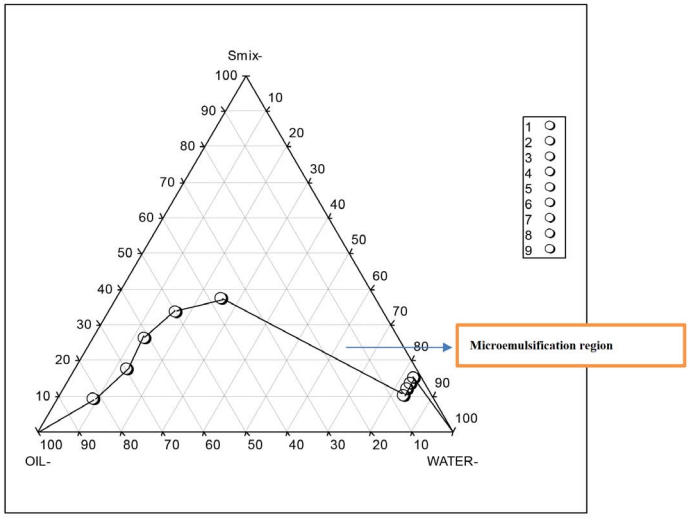


Figure 6: Pseudoternary phase diagram of surfactant and co-surfactant in 1:1 ratio.

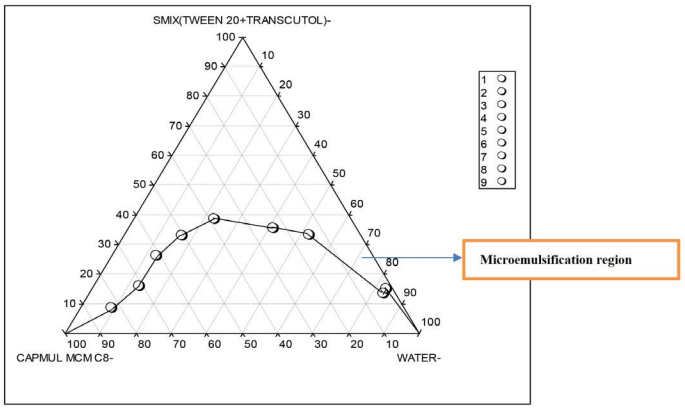


Figure 7: Pseudoternary phase diagram of surfactant and co-surfactant in 2:1 ratio.

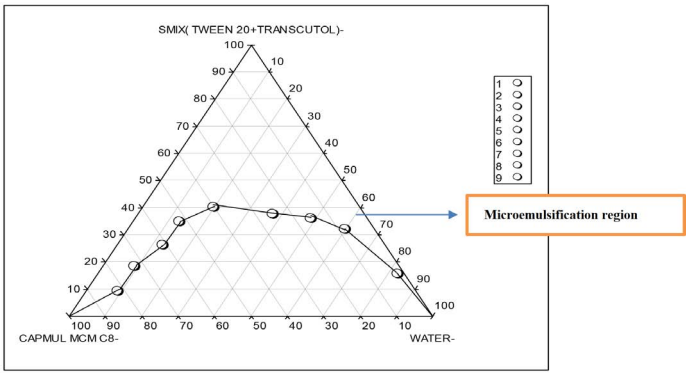


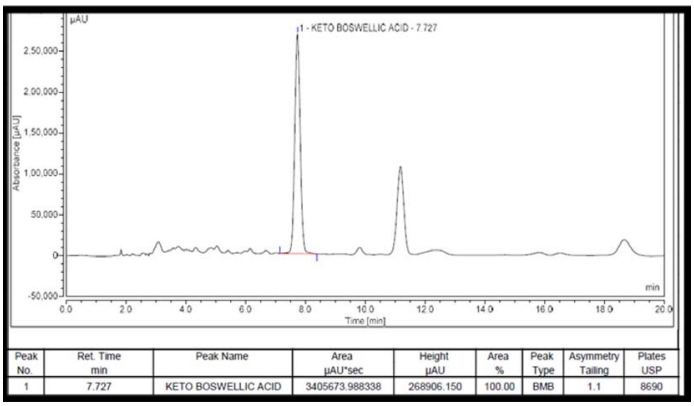
Figure 8: Pseudoternary phase diagram of surfactant and co-surfactant in 3:1 ratio.

Table 10: Trials conducted using HPLC.

Trials	Method	Results
1	➢ Mobile phase- Acetonitrile (ACN)/Water 90:10 adjusted to pH 4 with glacial acetic acid ➢ Column: Kromasil C8 ➢ Flow rate: 2ml/min	Poor peak shape and resolution
2	➢ Mobile phase- ACN/Water 90:10 adjusted to pH 4 with glacial acetic acid ➢ Column: Kromasil C18 ➢ Flow rate: 2ml/min	Poor peak shape and resolution
3	➢ Mobile phase- ACN/Water 90:10 adjusted to pH 6 with glacial acetic acid ➢ Column: Inertsil ODS 3 ➢ Flow rate: 2ml/min	Poor resolution
4	➢ Mobile phase- ACN/Water 90:10 adjusted to pH 2.5 with glacial acetic acid ➢ Column: Inertsil ODS 3 ➢ Flow rate: 2ml/min, 1.5ml/min	Better peak shape with high number of theoretical plates
5	➢ Mobile phase- ACN/Water 90:10 adjusted to pH 2.5 with glacial acetic acid ➢ Column: Inertsil ODS 3 ➢ Flow rate: 1ml/min	Good peak shape with resolution and theoretical plates

Table 11: HPLC Method for BSE Extract.

Standard Preparation	HPLC Parameters
200 mg of extract was sonicated for 30 min with 50ml methanol and volume was made up with methanol till 100 ml. Final concentration: 2000 ppm	➢ Mobile phase-ACN/Water 90:10 adjusted to pH 2.5 with glacial acetic acid ➢ Column- Inertsil ODS 3 ➢ Flow rate- 1ml/minutes ➢ Wavelength- 260nm ➢ Injection volume- 40 µl ➢ Run time- 20 min ➢ Column Oven Temperature- 30°C ➢ Auto sampler temperature- 10°C



Peak No.	Ret. Time min	Peak Name	Area µAU*sec	Height µAU	Area %	Peak Type	Asymmetry Tailing	Plates USP
1	7.727	KETO BOSWELLIC ACID	3405573.988338	268906.150	100.00	BMB	1.1	8690

Figure 9: HPLC chromatogram of BSE.
HPLC analytical method was developed for BSE.

Forced Degradation Studies

It was carried out in acidic and alkaline medium and also in presence of hydrogen peroxide to initiate oxidation reaction to analyze if any degradation was observed. Approximately, 10% degradation of extract was seen in 0.2N HCL, 3% degradation was seen in 0.05N and 0.2N NaOH. No degradation was observed in case of 30% and 3% H_2O_2. In case of thermal degradation about 6.5% degradation was observed over the period of 3 hr. In case of photo degradation about 4% degradation was observed over the period of 3 hor.

Formulation of SEDDS

Based on the selection of two pseudoternary plots, optimization of ME composition was carried out separately for both the plots. Initially, the pseudoternary plots were created using the software and accordingly 9 points were selected for each plot from the o/w region itself taking into account the ME region. 18 SEDDS formulations (9 each) were made and diluted with water to form microemulsion and on the basis of opaqueness observed visually only 4 formulations were selected, rest were turbid and rejected. The selected formulations were further carried for zeta sizer and polydispersity index (PDI) (Table 12 and 13; Figures 10 and 11).

The selected SEDDS formulations were then evaluated for particle size and physical stability.

Evaluation of SEDDS

Physical evaluation

Based on physical appearance of SEDDS of selected formulations from optimization of ME composition, all formulas showed a clear transparent system and no phase separation was observed. When equivalent to 1 dose formulas was diluted to 250 ml water, BSE-036 F5 showed a slight turbid system followed by BSE-035 F9, BSE-36 F8 and BSE-036 F7.

BSE-036 F7 showed a translucent system when 1 dose from this formula was diluted with 250 ml water.

Table 12: Optimization of ME composition from pseudoternary phase diagram with oil and surfactant mix in 1:1 ratio.

Sr. No	% Oil	% S-mix	Water
F1	10	30	60
F2	15	30	55
F3	10	25	65
F4	5	30	65
F5	5	35	60
F6	10	35	55
F7	15	40	45
F8	5	20	75
F9	15	50	35

Table 13: Optimization of ME composition from pseudoternary phase diagram with oil and surfactant mix in 2:1 ratio.

Sr. No	% Oil	% S-mix	Water
F1	10	30	60
F2	5	30	65
F3	5	35	60
F4	10	35	55
F5	15	40	45
F6	5	20	75
F7	15	50	35
F8	10	45	45
F9	15	45	40

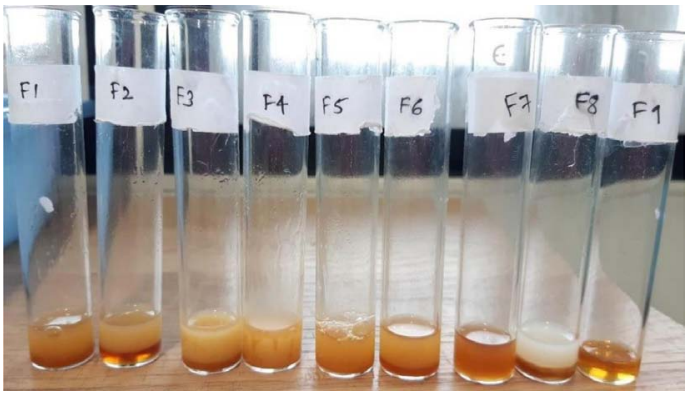


Figure 10: Optimization of ME composition from pseudoternary phase diagram with oil and surfactant mix in 1:1 ratio post evaluation (Batch no. BSE-35).

Particle Size Analysis for SEDDS

Particle Size analysis was carried out for the selected formulations. The targeted particle size was between 100-200 nm for efficient absorption of the extract. The observed particle size range was between 150-250nm. Out of 4 formulas selected, BSE-036 F7 provided the least particle size

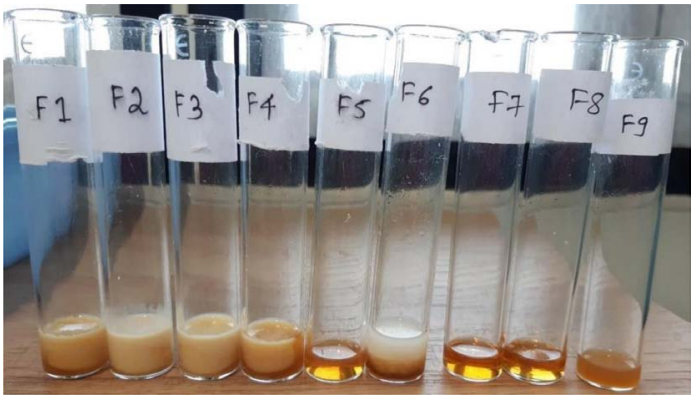


Figure 11: Optimization of ME composition from pseudoternary phase diagram with oil and surfactant mix in 2:1 ratio post evaluation (Batch no. BSE-36).

Table 14: Particle Size analysis of freshly diluted SEDDS.

Batch no	Particle size (nm)	PDI	% Intensity		
			Peak 1	Peak 2	Peak 3
BSE036 F5	247.7	0.258	100	-	-
BSE036 F7	159	0.248	100	-	-
BSE036 F8	167.2	0.280	94.1	4.6	1.3
BSE035 F9	181.2	0.230	98.6	1.4	-

due to higher concentration of oil and S-mix providing good micro emulsification. BSE-036 F5 showed the highest particle size due to less concentration of S-mix providing limited micro emulsification whereas BSE-036 F8 and BSE-036 F9 showed low particle size due to higher concentration of oil and S-mix.

The PDI obtained for all the formulations varied from 0.230 to 0.280. PDI below 0.3 indicates good uniformity in the globule size distribution after dilution with water. PDI of BSE-036 F9 (0.230) was found to be lowest than other formulations. Lower the PDI, better is the dispersibility of the formulation.

Samples diluted with water were kept side and particle size analysis was repeated for all selected formulas after 24 hr to indicate physical stability and observe any phase separation based on visual observation. All samples showed no phase separation. However, when particle size analysis was repeated variations were observed, such as in case of BSE-036 F8 unusual behavior and unexpected results was observed with respect to percent intensity of peak 2 as compared to the previous particle size analysis carried out for freshly diluted samples. It was observed to happen due to the presence of fibre in the cuvette providing high % intensity of peak 2 in freshly diluted sample particle size analysis.

Out of all samples, BSE-036 F7 was found to be stable since no significant difference was observed in particle size and PDI and contribution to percent intensity of peaks was low. Also, it provided the least particle size favoring increase in effective surface area for absorption and improved bioavailability and also it provided a translucent system as compared to the rest of the turbid systems (Table 14 and 15).

BSE-036 F7 (880mg) was selected as the final optimized SEDDS formula based on its globule size, PDI and physical stability on visual observation (Figure 12).

Table 15: Particle Size analysis of diluted SEDDS after 24 hr.

Batch no	Particle size (nm)	PDI	% Intensity		
			Peak 1	Peak 2	Peak 3
BSE036 F5	247.9	0.265	95	5	-
BSE036 F7	157.5	0.247	99.1	0.9	-
BSE036 F8	166.9	0.3	98.1	1.9	-
BSE035 F9	185.1	0.212	98.2	1.8	-

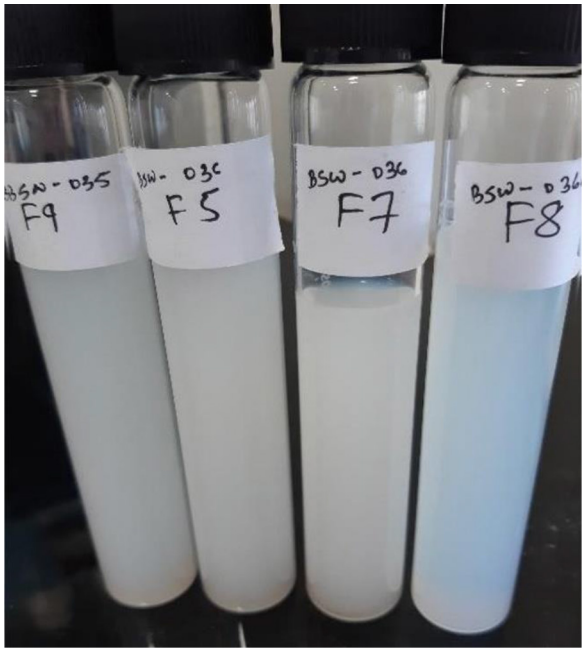


Figure 12: Diluted SEDDS to 250ml water.

Table 16: Assay Results for BSE-036 F7.

Sample	Assay (%)
SAMPLE 1_1	97%
SAMPLE 1_2	96.9%
SAMPLE 1_3	96.5%

Drug content was found in the range between 95-105% hence indicating uniform dispersion of drug in formulation.

Drug Content (ASSAY)

Drug content of the optimized formula of SEDDS, BSE-036 F7 was evaluated using HPLC (Table 16).

Formulation of S-SEDDS

The optimized SEDDS formula was converted into S-SEDDS using two adsorbents. The two adsorbents used were mannitol (water soluble polymer) and avicel PH 101 (water insoluble polymer). In order to increase the flow properties of S-SEDDS formulated using these adsorbents, wet granulation method was utilized.

Trials for formulation of S-SEDDS using Avicel PH 101 as an adsorbent:

S-SEDDS was formulated using Avicel PH 101 in 1:3 ratio (SEDDS: S-SEDDS; Figure 13)

Trials for formulation of S-SEDDS using Mannitol as an adsorbent:

Slight stickiness was observed in the material on visual observation inferring that increase in amount of Mannitol is required for adsorption (Figure 13 and 14).

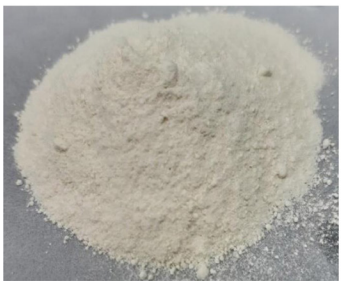
Evaluation of S- SEDDS

Particle Size Analysis

Particle size analysis was evaluated for the following trials:

Increased particle size was observed when S-SEDDS were prepared using Mannitol. The probable reasons were presence of residual content (ethanol) in the product which resulted in change in globule size of the formulation, mannitol influence in materials dissolved in the microemulsion which is responsible to produce the large particle size because of its crystalline nature. Also, no significant difference was observed in the particle size as compared to BSE-039 (Figure 19).

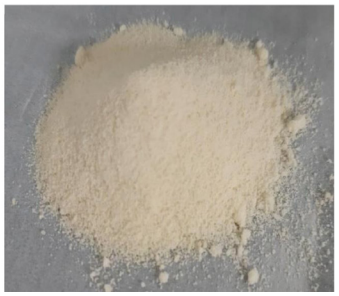
S-SEDDS was formulated using Avicel PH101 in 1:3 ratio (SEDDS: S-SEDDS; Figure 13)



- **Parameters:**
  - Water (Binding agent): 20gm
- **Fluid bed dryer:**
  - Air flow rate: 15ml/minutes
  - Temperature: 40°C
  - Time: 20 min

Figure 13: S-SEDDS using Avicel PH 101.

A. S-SEDDS was formulated using Mannitol in 1:3.5 ratio (SEDDS: S-SEDDS; Figure 14)

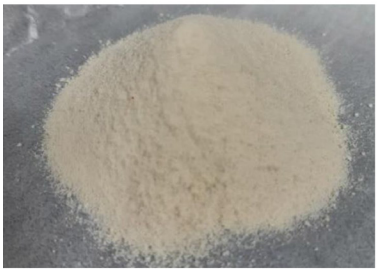


S SOLUBILIT
O
(Binding agent):

- **Fluid bed dryer:**
  - Air flow rate: 15ml/minutes
  - Temperature: 40°C
  - Time: 15 min
  - LOD before drying: 4.89%

Figure 14: S-SEDDS using Mannitol in 1:3.5 ratio.

B. S-SEDDS was formulated using Mannitol in 1:4.5 ratio (SEDDS: S-SEDDS; Figure 15)



- **Parameters:**
  - Ethanol (Binding agent): 10gm
- **Fluid bed dryer:**
  - Air flow rate: 15ml/minutes
  - Temperature: 50°C
  - Time: 10 min
  - LOD before drying: 3.22%

Figure 15: S-SEDDS using Mannitol in 1:4.5 ratio.
No stickiness was observed in the material (Figure 15).

1. BSE-038 [S-SEDDS using Avicel PH 101 (1:3); Figure 16]

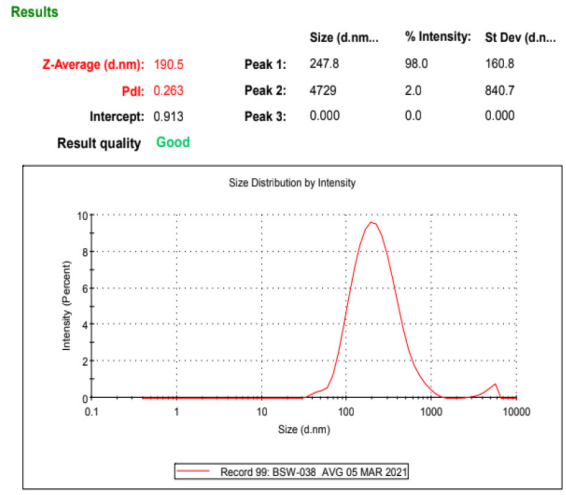


Figure 16: Particle size analysis of S-SEDDS using Avicel PH 101.
No significant difference in particle size was observed for S-SEDDS as compared to optimized SEDDS providing the desired results.

2. BSE-039 [S-SEDDS using mannitol (1:3.5); Figure 17]

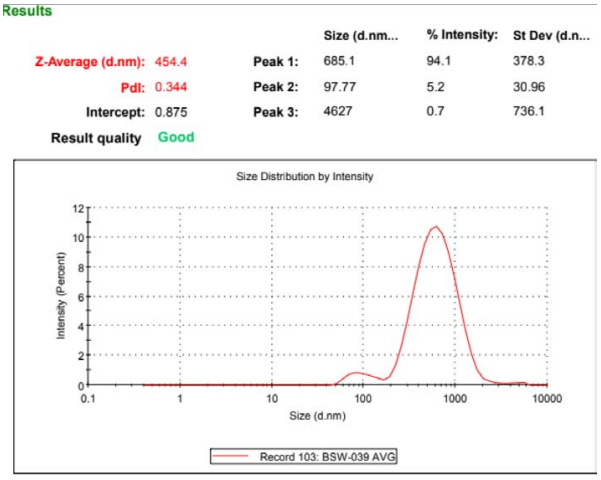


Figure 17: Particle size analysis of S-SEDDS using Mannitol in 1:3.5 ratio.

3. BSE-040 [S-SEDDS using Mannitol (1:4.5); Figure 18]

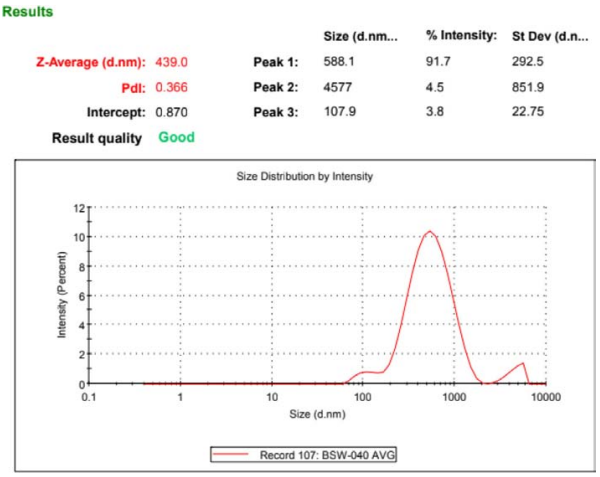


Figure 18: Particle size analysis of S-SEDDS using Mannitol in 1:4.5 ratio.

Figure 19: Diluted S-SEDDS to 250 ml water.

Table 17: Flow properties of S-SEDDS.

Flow properties	BSE-038	BSE-039	BSE-040
Carr's index	25.3158	25.1349	13.8889
Hausner's ratio	1.271	1.26	1.160
Angle of repose	32°	34°	34°

Flow Properties

Flow properties of the powder was evaluated based on the following parameters (Table 17).

- Based on flow properties, BSE-038 gave a passable flow and due greater number of fines it provided angle of repose of 32°
- Based on flow properties, BSE-039 gave a passable flow
- Based on flow properties, BSE-040 gave a good flow
- Therefore, BSE-038 and BSE-040 was selected to carry out further assay and *in-vitro* release studies.

Drug Content (ASSAY):

Drug content of the selected batch of S-SEDDS was evaluated for drug content using HPLC (Table 18).

Drug content was found in the range between 95-105% complying with the specifications hence indicating uniform dispersion of drug in S-SEDDS formulation.

***In-vitro* Release Studies:** Dissolution studies were performed for the drug suspension, SEDDS and S-SEDDS (S-SEDDS MCC and S-SEDDS Mannitol). Since the drug suspension had the least solubility, the release was not observed for more 40% in 120 min. Whereas in case of SEDDS, due to increased solubility the formulation served to provide enhanced release of more than 80% in 30 min. This behaviour of drug release was due to their globule size. Globule size is inversely proportional to the surface area that means lesser the globule size more is the surface area and surface area is directly proportional to the dissolution. Thus, least globule size with higher surface area formulation had the highest dissolution. For S-SEDDS, the results were also in the same pattern as of SEDDS. The overall dissolution rate was observed to be low in solid-SEDDS in contrast to SEDDS because of increased globule size of solid-SEDDS, and globule size is inversely proportional to the dissolution rate

Table 18: Assay results for S-SEDDS.

Sample	Assay (%) [BSE-040]	Assay (%) [BSE-038]
SAMPLE 1_1	98.1%	97.9%
SAMPLE 1_2	98.5%	98.2%
SAMPLE 1_3	99.1%	98.5%

Table 19: Percent Cumulative release of SEDDS and S-SEDDS.

Time (minutes)	%CR SEDDS	%CR S-SEDDS Mannitol [BSE-040]	%CR S-SEDDS MCC [BSE-038]	%CR Pure Drug
5	29.55	29.55	25.8	10.8
15	67.56833	67.58917	55.94333	14.61
30	80.69292	79.21375	63.75333	18.44083
45	84.13833	84.15083	67.855	22.2925
60	90.97542	87.23792	75.7275	26.165
90	92.22292	92.585958	83.64167	33.80833
120	97.22458	94.96833	85.2225	40.36833

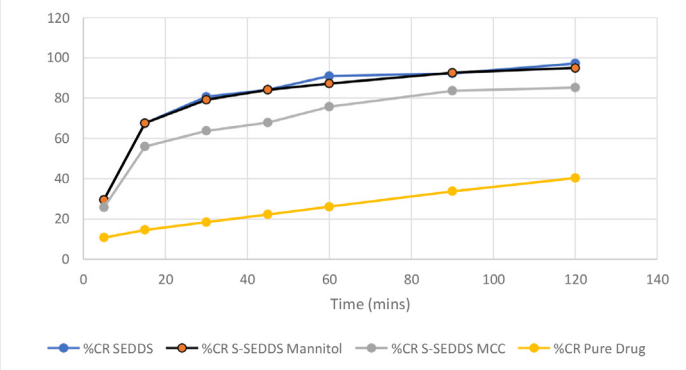


Figure 20: *In-vitro* release studies.

therefore dissolution got reduced. Also, the release pattern signified more than 80% release in 30 min in case of S-SEDDS Mannitol and more than 60% release in 30 min in case of S-SEDDS MCC (Table 19, Figure 20).

SEDDS and S-SEDDS showed enhanced drug release profile indicating increased solubility of the drug. Since S-SEDDS Mannitol showed greater drug release as compared to S-SEDDS MCC, hence this batch was finalized serving the objective of the end formulation.

Stability Studies: There was no significant change in any of evaluated parameter for the specified period of time for SEDDS (BSE-036 F7) and S-SEDDS (BSE-040). The drug content was also found to be within the specified limits with no significant change observed. Hence, it can be concluded that the formulations were stable at the specific conditions of temperature and humidity (Table 20).

CONCLUSION

Self-emulsifying drug delivery system is a vital tool in overcoming the formulation difficulties and improving the oral bioavailability of hydrophobic/lipophilic drugs. In this study, SEDDS and solid- SEDDS formulations of poorly water-soluble drug, *Boswellia serrata* were successfully prepared by the sonication method and adsorbent technique respectively for oral administration. Further, they were assessed for *in vitro* performances. Among various formulations, BSE-036-F7 in SEDDS

Table 20: Stability studies.

Conditions	Time	Parameters	SEDDS	S-SEDDS
25±2C/60%±5%RH	0 day	Appearance	Transparent, No phase separation	Translucent
		Particle size	200.3nm	450.4nm
		Drug content	98%	98.2%
	15 days	Appearance	Transparent, No phase separation	Translucent
		Particle size	210.6nm	462.7nm
		Drug content	97.9%	98%
40±2C/75%±5%RH	0 day	Appearance	Transparent, No phase separation	Translucent
		Particle size	200.1nm	450.5nm
		Drug content	97.7%	97.5%
	15 days	Appearance	Transparent, No phase separation	Translucent
		Particle size	215.2nm	460.3nm
		Drug content	97.5%	97.4%
	30 days	Appearance	Transparent, No phase separation	Translucent
		Particle size	230.7nm	470.8nm
		Drug content	97.1%	97%

and BSE- 040 in solid-SEDDS showed promising results in the terms of physical appearance, globule size analysis, *in vitro* drug release and stability. It could be summarized that SEDDS formed from capmul MCM C8 oil, tween 20 and transcutol HP as oil, surfactant and co-surfactant is a promising approach to improve the solubility, dissolution rate and hence bioavailability of BSE. The optimized formulations showed significantly improved drug release as compared to pure drug. Solid-SEDDS were preferred over SEDDS in terms of stable dosage form. It can be concluded that BSE solid- SEDDS offer more predictable and more extensive drug release/absorption than the corresponding conventional formulations. The results from the study showed the utility of solid-SEDDS to enhance solubility and bioavailability of sparingly soluble compounds like *Boswellia serrata*, which can be helpful to reduce dose of the drug. The present exploratory work successfully illustrates the potential utility of solid-SEDDS for the delivery of poor water-soluble compounds.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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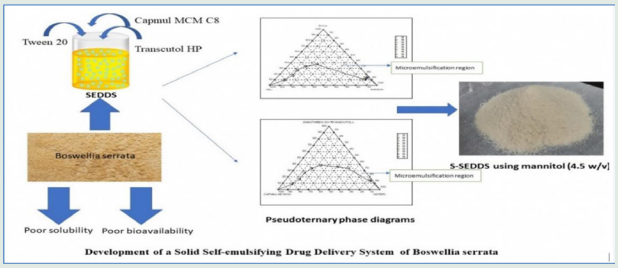
GRAPHICAL ABSTRACT



SUMMARY

In this study, SEDDS and solid- SEDDS formulations of poorly water-soluble drug, *Boswellia serrata* were formulated using oil Capmul MCM C8, surfactant Tween 20, co-surfactant transcutol HP and adsorbent as mannitol by sonication method and adsorbent technique respectively for oral administration.

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