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Development of Bosentan Hydrochloride - Loaded Solid Self-Micro Emulsifying Drug Delivery System (SMEDDS) For the Treatment of Pulmonary Hypertension

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ABSTRACT

The main purpose of this research study was to investigate the potential of self- micro-emulsifying drug delivery system (SMEDDS) in improving the bioavailability of Bosentan (BOS) and its therapeutic effect. In this study the S-SMEDDS of BOS powder was prepared by spray drying technology. It contains S-SMEDDS of BOS (59.57%), anhydrous lactose (11.4%), pregelatinized starch (3%), microcrystalline cellulose (22%), Magnesium stearate (2%) and Talc (2%) were selected and final weight of tablet was 965 mg. The S-SMEDDS consists of well separated particle with smooth surface observed from SEM. Both the DSC and XRD analysis suggest that BOS in S-SMEDDS may be in molecular dispersion state. In-vitro dissolution test shows that S-SMEDDS of BOS tablet had faster release rate. Formulation (F3) released 99.80% BOS within 30 min. The similarity factor found between F3 and marketed formulation was 18.19 therefore it confirmed F3 formulation better release pattern than the marketed formulation and pure drug. Release profile treated with different kinetic equations it indicated S-SMEDDS tablet best fit to Zero order model, non Fickian confirms the release of drug by diffusion mechanism. In-vivo Adsorption study in rat showed that S-SMEDDS tablet (F3) increased significant bioavailability of BOS compared to the pure drug. The "%"relative bioavailability of F3 formulation was found to be 159 % compared to pure drug and marketed formulation of BOS. Thus the S-SMEDDS provide a useful oral solid dosage form for poorly water soluble and higher molecular weight drug BOS.

Methods: PubMed and Embase databases have been searched, and related studies are compiled and summarized.

Conclusion: The study successfully developed a solid self-microemulsifying drug delivery system (S-SMEDDS) for BOS using spray-drying technology, with an optimal composition of Campul MCM (30%), Tween 20 (50%), and propylene glycol (20%) in the liquid SMEDDS (L-SMEDDS). The S-SMEDDS powder exhibited well-separated, smooth-surfaced particles while retaining self-emulsifying properties. DSC and XRD analyses indicated that BOS was molecularly dispersed within the system. When formulated into tablets (F3), the S-SMEDDS demonstrated significantly faster drug release (99.80% within 30 minutes) compared to the marketed formulation and pure drug, as evidenced by a low similarity factor ($f_2 = 18.19$). Drug release followed zero-order kinetics with non-Fickian diffusion, suggesting a combined diffusion-based mechanism. These findings highlight the potential of S-SMEDDS tablets to enhance the dissolution and bioavailability of BOS.

Keywords: *Bioavailability; Self-nanoemulsifying drug delivery systems; Bosentan; oral solid dosage form; solubility*

1. INTRODUCTION

Oral drug delivery continues to be the preferred route of administration. However majority of newly discovered and existing drugs administered by oral route, frequently encounter bioavailability problems due to several reasons like poor dissolution, unpredictable Adsorption, low permeability, high molecular weight of drug, intra and inter subject variability and lack of dose proportionality. Lipinski's 'rule of five' predicts that poor Absorption or poor permeation is more likely when there are more than five hydrogen bond donors, there are more than ten hydrogen bond acceptors, the molecular weight > 500 and calculated log P more than 5.

Bosentan (BOS) represent high molecular weight drug (569.64) and having 11 hydrogen bond acceptor which exhibits inconsistent bioavailability. BOS belonging to BCS class-II drugs known as Endothelin Receptor Antagonists (ERA's) has slightly higher affinity for ETA (endothelin-1 type-A and–B) receptor than ETB. It has been used for the treatment of pulmonary hypertension3. The bioavailability of BOS is up to 50%. The low bioavailability of BOS is mainly attributed to its poor aqueous solubility, high molecular weight, eleven hydrogen bond acceptors and presystemic metabolism so it is necessary to find a proper approach that will increase solubility, dissolution rate and bioavailability of BOS.

In recent years, much attention has been paid to Self-Micro-Emulsifying drug delivery system, which has shown lot of reasonable success in improving oral bioavailability of poor aqueous soluble and low permeation drugs. SMEDDS are usually composed of isotropic mixture of oil, surfactant or co-surfactant and is capable of forming fine oil-in-water microemulsion upon gentle agitation provided by the GIT motion. Above study, had an attempt to develop a novel S-SMEDDS formulation containing BOS employing diverse solidification techniques spray drying. The S-SMEDDS are relatively more robust formulation with high stability, improved patient compliance and simple manufacturing. Therefore attempts were made to prepare the S-SMEDDS of BOS using porous carriers like Aerosil 200, Aerosil 300, Maltodextrin, etc. by spray drying technique to enhance its aqueous solubility and oral bioavailability by possible avoidance of hepatic first pass effect, improve membrane permeability by inhibition of P-gp efflux and enhance Adsorption through lymphatic pathway. Recently, an increased interest in novel analytical methods for pharmaceutical product analysis is observed. A variety of methods for drug quantification in pharmaceutical formulations, here attempt to drug quantification by ultrasonic interferometer technology/ ultrasonic resonator technology, called as rapid and non-destructive analytical methods9. This is an emerging and promising technique based on ultrasound wave. In general the marketing success of any pharmaceutical product depends on stability, bioavailability, cost and patient compliances of the pharmaceutical product and S-SMEDDS complied all the respective parameters which will help to gain market capital.

2. MATERIAL AND METHOD

Materials:

Excipient Screening

Excipients for the self-microemulsifying drug delivery system were selected based on BOS solubility, emulsification efficiency, pseudo-ternary phase diagrams, and microemulsion transmittance.

Solubility Studies

The solubility of BOS was assessed in different oils, surfactants, co-surfactants, and aqueous buffers. Excess BOS was added to 2 mL of each excipient in sealed vials, vortex-mixed, and sonicated until clear. The mixtures were equilibrated for 48 hours, centrifuged at 10,000 rpm for 15 min, and filtered (0.45 µm). The filtrate was diluted with methanol, and BOS concentration was measured via UV spectrophotometry at λmax 273.6 nm.

Pseudo-Ternary Phase Diagram Construction

Capmul MCM (lipid), Cremophor EL, and Tween 20 (surfactants) were combined with ethanol, Caproyl 90, and propylene glycol (cosurfactants) to prepare pseudoternary phase diagrams. Surfactant (S) and cosurfactant (CoS) were mixed in 1:1 and 3:1 ratios. Oil and S**:** CoS blends were combined in varying ratios (1:9 to 9:1) to identify microemulsion-forming regions. Each mixture was vortexed (15 min) in 10 ml test tube and titrated with water (shaking) until turbidity appeared, marking the endpoint.

Selection of Co-surfactant

The co-surfactant was chosen based on its emulsifying ability with the selected oil and surfactants, using a ternary phase diagram. A surfactant-co-surfactant mixture (2:1 ratio) was combined with Capmul MCM (oil) in a 1:1 ratio and homogenized. An isotropic mixture (100 mg) was diluted to 100 mL with water to form a microemulsion. Formation ease was assessed by vortex mixing cycles (VFI), and turbidity was evaluated visually. After 2 hours, % transmittance was measured at 638 nm (UV spectrophotometer, water as blank). The 2:1 surfactant-co-surfactant ratio helped determine the co-surfactant's effectiveness in enhancing self-emulsification.

3. METHODS

Formulation of (L-SMEDDS) For BOS

The L-SMEDDS were prepared by admixture of 10 % w/w BOS with oil and S: Co-s mixtures were facilitated to the Solublisation using cyclomixer for 5min, (Remi cylcomixer CM 101, Mumbai, India) then placed for sonication using probe sonicator (PCI Mumbai, India) till the mixture clear and it was allowed to equilibrate for 48hrs in water bath.

Different L-SMEDDS formulations were prepared by selecting the varied concentration of oil (25% to 65%w/w), surfactant (35% to 75%w/w) and co-surfactant (0 to 25% w/w) from pseudo ternary phase diagram. The proportion of oil, surfactant and co-surfactant was always kept 100% in all formulations.

Formulation of L-SMEDDS

The total Thirty Six formulations (LF1 to LF36) were prepared by varying oil, S: Co-S concentration as showed in Table 5.1. The "%" of oil, S/Co-S used herein was decided on the basis of requirement for spontaneous formation of Self-microemulsifying system[28].

Solid Self-Microemulsifying Drug Delivery System (S-SMEDDS)

Conventional SMEDDS are typically liquid, leading to drawbacks like poor stability, low portability, limited drug loading, and alternative dosage form options. To overcome these issues, S-SMEDDS have been developed by converting liquid self-micro emulsifying systems into solid powders, enabling versatile solid dosage forms.

Screening of Adsorbent Carrier for S-SMEDDS Preparation

S-SMEDDS was prepared using the spray drying technique. Different adsorbent carriers, including Aerosil 200, Aerosil 300, and maltodextrin, were evaluated individually and in combination.

The optimized L-SMEDDS (1g) was slowly added to a suspension of 300 mg adsorbent carrier in 100 mL ethanol under constant stirring (250 rpm, 15 min). The resulting suspension was spray-dried (Labultima LU-222 Advanced, Mumbai, India) under controlled conditions:

- **Inlet temperature:** 60°C
- **Outlet temperature:** 40°C
- **Aspiration rate:** 40 N/m²
- **Feed rate:** 1.5 mL/min

This process converted the liquid formulation into a **free-flowing powder** for solid dosage forms.

Development of S-SMEDDS Tablet of BOS

S-SMEDDS tablets were compressed by using free flowing of S-SMEDDS powder prepared by spray drying technique containing BOS mix with variable concentration of directly compressible excipients. Compositions of the S-SMEDDS tablet formulations

Experimental design:

Table: Development of S-SMEDDS Tablets containing BOS

Formulations Code / Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
S-SMEDDS of BOS	660	660	660	660	660	660	660	660
Lactose anhydrous	126.5	117	107.5	98	88.5	79	70.5	136
Pre-gelatinized starch	9.5	19	28.5	38	47.5	57	66.5	00

Microcrystalline Cellulose	150	150	150	150	150	150	150	150
Magnesium stearate	19	19	19	19	19	19	19	19

➢ **Development of S-Smedds Tablet of Bos**

S-SMEDDS tablets were compressed by using free flowing of S-SMEDDS powder prepared by spray drying technique containing BOS mix with variable concentration of directly compressible excipients. All formulation contain (22%w/w) MCC and lactose anhydrous as a directly compressible excipients formulation F1 to F7 contains (1-7%w/w) pregelatinised starch as a superdisintegrents and F8 was a control formulation without superdisintegrants final weight of each tablet was kept 965mg by varying the weight of lactose anhydrous. All formulations were studied pre-compression parameter before they compression into tablet 1 like, bulk density, tap density, angle of repose and compressibility index· It directly compressed using 12mm flat face punches of ten station rotary tablet machine (Cadmach, Germany) and after compression it evaluated for post-compression parameter like, hardness, thickness, weight variation, drug content, friability, *In-vitro* Disintegration test and *In-vitro* Dissolution studies.

4. RESULTS AND DISCUSSION

➢ **Screening of Excipients: Solubility studies**

Screening of excipients for the Development of Self Micro emulsifying Drug Delivery System was made on the basis of solubility of BOS in different vehicles, Emulsifying efficiency of excipients, and pseudo ternary phase diagram and percent transmittance of resultant micro emulsion.

Table: Solubility of BOS in vehicles

Sr.no	Vehicle	Solubility of BOS (mg/g)	Sr. no	Vehicle	Solubility of BOS (mg/g)
1	Labrafil M 1944	09.67 ± 0.15	14	Tween 80	39.17 ± 0.48
2	Labrafil lipophile WL 1349	15.80 ± 0.34	15	Cremophor El	71.48 ± 0.74
3	Capryol 90	45.64 ± 0.43	16	Cremophor RH 40	43.90 ± 0.29
4	Capmul MCM C8	79.83 ± 0.12	17	Labrasol	30.26 ± 0.49
5	Labrafac PG	10.64 ± 0.43	18	Poloxamer 188	26.66 ± 0.18
6	Captex 200	16.66 ± 0.23	19	Propylene Glycol	92.10 ±0.43
7	Captex 355	17.25 ± 0.45	20	Ethanol	68.00 ± 0.21
8	Oleic acid	09.67 ± 0.21	21	PEG 400	32.00 ±0.24
9	Capmul PG 12	12.90 ± 0.32	22	Lauroglycol FCC	21.00 ±0.34
10	Captex 500	08.42 ± 0.05	23	Water	0.01 ±0.44
11	Groundnut oil	05.78 ± 0.62	24	SGF pH 1.2	0.001 ±0.22
12	Peceol	07.30 ± 0.56	25	Phosphate Buffer pH 5	0.002 ±0.29

13	Tween 20	121.41 ± 0.89	26	Phosphate Buffer pH 7.4	0.43 ±0.09

***(n=3)**

Selection of surfactant: Emulsification efficiency of various nonionic surfactants with oil

Sr. no.	Surfactants	Number of volumetric flask inversions (VFI)	"%"Transmittance
1	Tween 20	2	92.52±0.20
2	Tween 80	4	53.88±0.05
3	Cremophor EL	2	94.69±0.50
4	Cremophor RH 40	3	95.85±0.85
5	Labrasol	5	53.80±0.92
6	Poloxamer 188	4	69.53±0.75

- **Screening of co-surfactant**

Table: Emulsifying ability of selected Composition system for screening of co-surfactants

Sr. no	Composition of System Oil :Surfactant/Cos (2:1) 1:1	No. of VFI	Transmittance (%)
1	Capmul MCM : (Cremophore EL+Propylene Glycol)	1	97.00±0.73
2	Capmul MCM : (Cremophore EL+Capryol 90)	1	95.20±0.48
3	Capmul MCM : (Cremophore EL+Ethanol)	1	96.20±0.68
4	Capmul MCM : (Cremophore EL+ PEG 400)	1	95.50±0.98
5	Capmul MCM : (Cremophore EL+Lauroglycol FCC)	2	83.10±0.46
6	Capmul MCM : (Tween 20 + Propylene Glycol)	1	97.80±0.82
7	Capmul MCM : (Tween 20 + Capryol 90)	2	69.80±0.54
8	Capmul MCM : (Tween 20 + Ethanol)	1	82.00±0.65
9	Capmul MCM : (Tween 20 + PEG 400)	2	78.00±0.89
10	Capmul MCM : (Tween 20 + Lauroglycol FCC)	2	88.20±0.92
11	Capmul MCM : [(Cremophore EL: Tween 20) + Propylene Glycol]	1	96.10±0.95
12	Capmul MCM : [(Cremophore EL: Tween 20) + Capryol 90]	2	72.20±0.53
13	Capmul MCM : [(Cremophore EL: Tween 20) + Ethanol]	1	90.20±0.24
14	Capmul MCM : [(Cremophore EL: Tween 20) + PEG 400]	2	80.80±0.46
15	Capmul MCM : [(Cremophore EL: Tween 20) + Lauroglycol FCC]	2	85.00±0.97

*(n=3), VFI: Volumetric Flask Inversion**.**

- **Construction of pseudoternary Phase Diagram**

Capmul MCM as lipid, Cremophore EL and Tween20 as surfactants and ethanol, caproyl 90, and propylene glycol as cosurfactants were selected for construction of pseudoternary phase diagram. From Figure 1 (a) and 1 (b) it is evident that Tween 20 – Capmul MCM – Propylene glycol system has larger microemulsification region as compared to other systems. In view of current investigation, due to larger microemulsion region and greater capacity for incorporation of oily phase, which is most desirable for BOS, Tween 20 – Capmul MCM – Propylene glycol system was selected for further studies.

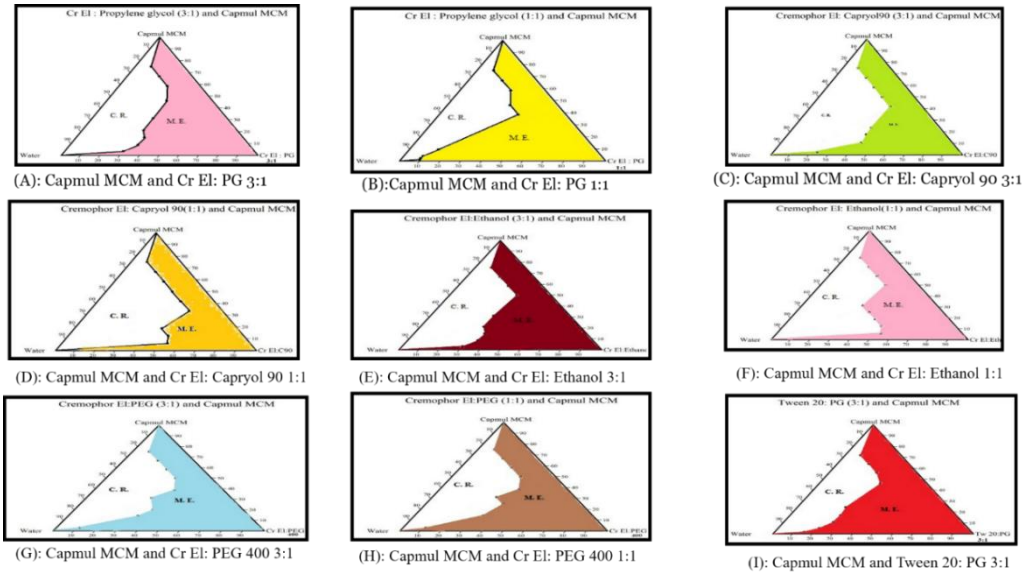

Figure. (a) Construction of pseudoternary Phase Diagram

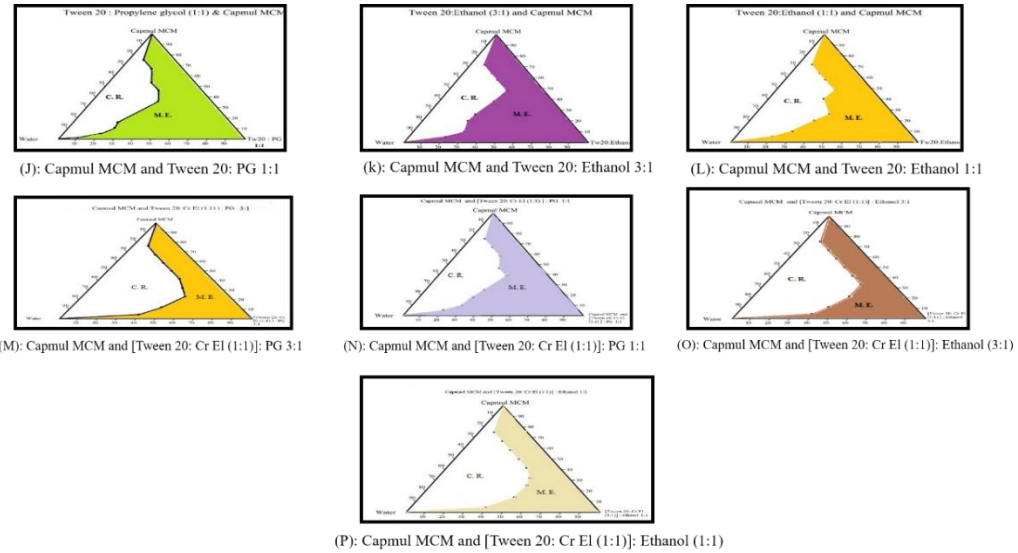

Figure (b): C.R. - Coarse Emulsion Region, M.E. - Microemulsion Region (shaded region)

Transmittance study and Ternary phase diagram study was carried out for the selection of cosurfactant, it was found that Capmul MCM and (Smix) Tween 20: PG to be the best system as it is showing highest "%"transmittance as well as highest microemulsion region in Ternary phase diagram depicted in Figure (a) and (b) without any signs of gelling at any concentration. Even combination of Capmul MCM and Cremophor El:PG showed high emulsification area but it showed gelling upon dilution with aqueous media at concentration above 50%, (i. e formation of more liquid crystal) which may influence on the fluidity and rate emulsification of the formulation.

When cosurfactant is added to the system, it lowers the interfacial tension, fluidizes the hydrocarbon region of the interfacial film, and increases the film curvature and decreases the bending stress of the interface. Small increase in a microemulsion region was observed with increases in cosurfactant concentration from 0 to 20%.

- **Evaluation of L-SMEDDS**

Drug content

The "%"drug content of each formulation is shown in Table 5. The formulations containing less than 91% drug content were rejected from further studies (LF 26 to LF 36). The low drug content may be due to low surfactant concentration in formulations which unable to solubilized the drug.

Table: Percent of BOS content in L-SMEDDS

FC	Drug Content (%)	FC	Drug Content (%)	FC	Drug Content (%)	FC	Drug Content (%)
LF1	99.11±0.23	LF10	99.98±0.22	LF19	94.29±0.45	LF28	89.40±0.60
LF2	100.0±0.35	LF11	97.00±0.43	LF20	94.38±0.23	LF29	88.53±0.32
LF3	99.67±0.45	LF12	97.43±0.45	LF21	94.04±0.67	LF30	88.00±0.75
LF4	99.98±0.76	LF13	97.75±0.65	LF22	94.77±0.87	LF31	88.12±0.28
LF5	97.89±0.87	LF14	96.46±0.67	LF23	93.44±0.75	LF32	87.00±0.15
LF6	98.11±0.98	LF15	96.64±0.87	LF24	91.35±0.72	LF33	87.04±0.20
LF7	98.87±0.41	LF16	95.23±0.89	LF25	91.00±0.43	LF34	86.29±0.50
LF8	98.69±0.13	LF17	95.59±0.92	LF26	90.76±0.29	LF35	86.45±0.43
LF9	99.45±0.14	LF18	95.34±0.24	LF27	90.94±0.30	LF36	81.56±0.50

FC- Formulation Code, *(n=3),

Though the drug determination is done by using UV spectrophotometer, an attempt to analyze the six concentration series BOS by ultrasonic interferometer technology was only suitable for analyzing liquid samples. Ultrasound velocity and attenuation determined as a comparative value. The velocity and attenuation value of placebo formulation subtracted with the value of drug containing formulation. There was a linear relationship found for series of (1-10%) BOS concentration.

The tendency of ΔA to be more sensitive to a drug concentration compared to ΔV. The value of ΔA was higher, increase with drug concentration. Its coefficient of correlation was found to be R2 = 0.9860, Y= 0.068x + 0.151 and ΔV decrease with increase in drug concentration. Its coefficient of correlation was found to be R2 = 0.9960, Y = -45.62x - 63.68 depicted in figure 2 and 3 respectively. Thus any change in velocity is/was attributed to difference in apparent density or compressibility of mixture. It indicates that density of formulation increase with drug load. Increase in density lead to decrease in value of ΔV. The drug quantification of all L-SMEDDS formulations was found to be +1.5 in acceptable range with reference to UV-spectrophotometer.

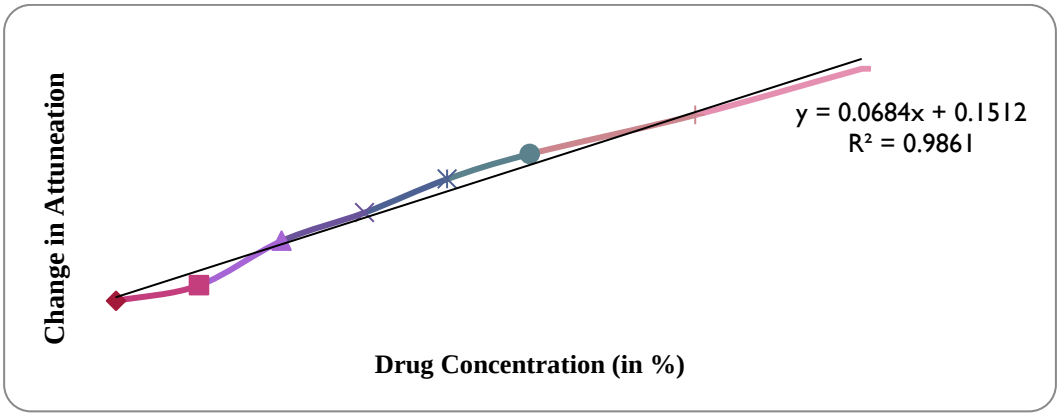

Figure: Drug concentration vs change in Attuneation

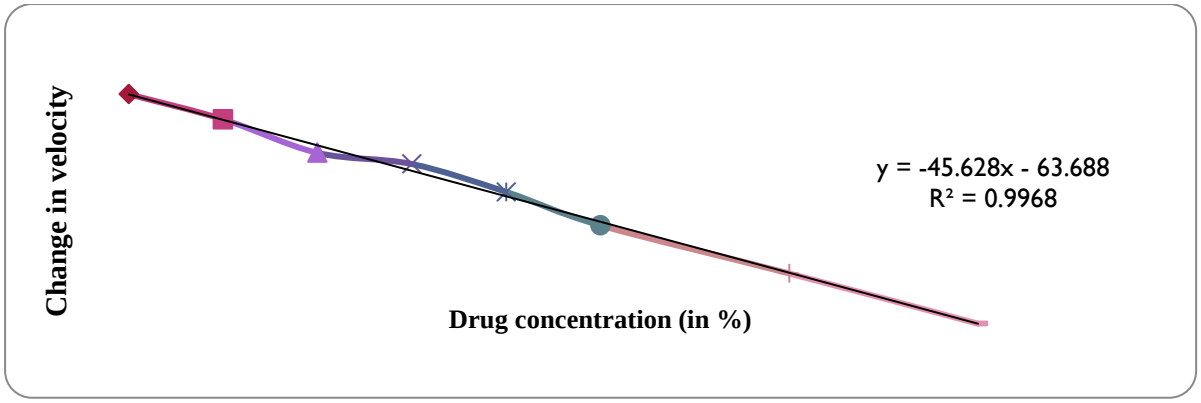

Figure Fig: Drug concentration vs change in velocity

- **Viscosity determination**

Table: Viscosity of L-SMEDDS of BOS

FC	Observation Viscosity (mPas)	FC	Observation Viscosity (mPas)
LF1	380	LF14	317
LF2	355	LF15	312
LF3	340	LF16	332
LF4	335	LF17	338
LF5	331	LF18	342
LF6	360	LF19	316
LF7	346	LF20	308
LF8	337	LF21	337
LF9	328	LF22	302
LF10	310	LF23	297
LF11	322	LF24	294
LF12	314	LF25	290
LF13	310		

FC- Formulation Code, mPas- mili pascal

The viscosity of all the formulations was found to be 290-380m pas. The concentration Smix affects the viscosity of formulation as a concentration of Smix increase the viscosity of formulation also increase, whereas the concentration of oil increases the viscosity of formulation decrease. The viscosity increased with increasing the concentration of cosurfactant. Ostensibly due to increase in film flexibility caused by hydrophilic nature of the cosurfactant. It effects on fluidity of L-SMEDDS formulation showed in table.

- **Robustness to dilution and measurement of cloud point**

All the diluted L-SMEDDS formulations were found to be stable and did not show any sign of phase separation and drug precipitation on storage. The Emulsifying ability evaluated by "%"transmittance of resultant microemulsion and their correlation with number of VFI as showed in Table. Rate of microemulsion formation was noted by counting the number of VFI to form a fine microemulsion with high "%"transmittance. High emulsification efficiency is therefore judged by a small number of flask inversions (lower than ten) in addition to high-percentage transmittance (higher than 90%). One flask inversion requires only one second.

One VFI indicate the SMEDDS get emulsified in one second and can produced microemulsion spontaneously in-vivo. The

number of VFI was least for formulation LF7 and LF10 as compared to other formulation but the "%"transmittance (i.e. clear emulsion) of LF10 was high as compared to LF7. This might be due to the LF10 containing the optimum S: Co-S (2.5:1) ratio with oil. The formulation LF1 to LF5 contains low concentration of oil and highest concentration Smix as compared to other. That's why they show more "%"transmittance for resultant microemulsion but the rate of microemulsion formation was slow (i.e. it required more energy/ agitation to formed microemulsion) as compared to LF7 and LF10. This might be due to the highest concentration of Smix lead to the formation of more liquid crystals therefore high amount of liquid crystal effect on the fluidity of the system therefore it required more energy to form a microemulsion.

As the cosurfactant concentration increases the ease of emulsification also increases (LF13, LF15, LF8, LF10, LF22, LF23, LF22 and LF24) by getting decrease in the number of inversions. As the concentration of oil increases the transmittance as well as the ease of emulsification decreases (LF16 - LF25). The transmittance of LF25 formulation was found less (72.4%) it may be due to least surfactant concentration (35%) this might be due to difference in CMC conc. of surfactant. Transmittance study gives only rough idea about the characteristics of resultant microemulsion. Thus transmittance of resulting microemulsion is governed by surfactant, cosurfactant and oil concentration.

On basis of Drug content, amount of oily phase, transmittance and ease of emulsification study ten batches (LF2, LF7, LF9, LF10, LF13, LF15, LF16, LF19 and LF22) were selected for further studies. Effect of drug loading was also observed in Table and it was found that transmittance of resultant microemulsion without drug was high as compared to with drug, which confirms that as the drug is added in formulation there is decrease in "%"transmittance and it may increase the droplet size of resultant emulsion or microemulsion. The efficiency of emulsification was found to be promising, when the Smix concentration was more than 60% of formulation system. However emulsification was not efficient with concentration of Smix less than 50%, because inadequate concentration of Smix causes poor emulsification. It was observed that increasing the concentration of the surfactant increased the spontaneity of self-emulsification process but decreased the extent of emulsification.

Measurement of Cloud point is a crucial parameter of the integrity of the microemulsion at elevated temperature particularly in case of non-ionic surfactant. At cloud-point phase separation may take place due to the dehydration of its ingredients, which can affect the formulation adversely. The cloud point of the all L-SMEDDS formulation was found to be in the range of 59–63◦C. The cloud point of the all formulation was observed to be sufficiently higher than the body temperature and the normal storage conditions. Hence, the formulation requires no specific temperature related conditions for application or storage of formulation.

Table: Transmittance of resultant microemulsions without drug

FC	No. of VFI	Transmittance*(%)	FC	No. of VFI	Transmittance* (%)
LF1	3	95.0	LF14	9	94.7
LF2	3	95.4	LF15	4	95.4
LF3	3	93.2	LF16	10	89.5
LF4	3	93.2	LF17	9	90.5
LF5	3	93.1	LF18	8	94.0
LF6	5	96.5	LF19	11	84.1
LF7	1	97.8	LF20	8	84.2
LF8	4	95.9	LF21	9	90.5
LF9	5	94.2	LF22	9	82.0
LF10	1	98.4	LF23	8	89.3
LF11	7	93.2	LF24	8	88.2
LF12	7	94.3	LF25	9	72.4
LF13	7	92.3			

FC= Formulation code; %T= percent transmittance; VFI= volumetric flask inversion

➢ **Determination of Droplet size distribution and zeta potential**

Droplet size of resultant microemulsion was found to be lowest for LF10 formulation 144.8nm. The results of "%"transmittance were supported by Droplet size evaluation. It observed when "%"transmittance value increased, the droplet size decreased. The effect of drug loading was observed and it was found that droplet size of all formulations was increased upon increasing drug loading. The average droplet size, zeta potential and polydispersity index of resultant microemulsion of L-SMEDDS (LF10) was found to be 144.8nm, -26mv and 0.32 respectively. The small polydispersity index suggested that the size distribution of the product is fairly monomodal, monodispersed size distribution and excellent dispersibility of globules of microemulsion. From the selected formulation batches showed in Table 5.12, the droplet size of resulting microemulsion was lowest for formulation LF10 (without and with drug loading). From the droplet size determination, five formulations having droplet size below 200 nm were chosen for further study (LF2, LF7, LF9, LF10, and LF15).

Table 8: Droplet size for L-SMEDDS formulations

Sr.no	FC	Without Drug		With Drug			
		%T	Dropletsize* (nm)	%T	Dropletsize (nm)*	Zeta Potential (mv) *	Polydispersity Index
1	LF2	95.4	059.6	89.1	148.0	-27.0	0.30
2	LF7	97.8	059.3	92.2	149.5	-26.5	0.31
3	LF9	94.2	106.6	86.8	195.7	-26.0	0.20
4	LF10	98.4	058.1	92.0	144.8	-26.0	0.32
5	LF13	92.3	119.6	86.8	231.9	-26.0	0.25
6	LF15	95.4	091.2	89.9	199.4	-25.0	0.28
7	LF16	89.5	134.8	83.3	239.5	-27.0	0.20
8	LF19	84.1	169.8	78.3	271.4	-24.5	0.30
9	LF22	82.0	176.7	75.1	289.9	-26.0	0.35
10	LF25	72.4	226.3	64.1	341.6	-22.0	0.30

FC- Formulation Code, *(n=3), %T= percent transmittance

Table 9: Transmittance of resultant microemulsions with drug

FC	Phase Separation After 2hr	No. of VFI	"%" T After 2hr	FC	Phase Separation After 2hr	No. of VFI	"%" T After 2hr
LF1	No	4	89.0	LF14	No	10	88.2
LF2	No	4	89.1	LF15	No	6	89.9
LF3	No	4	86.8	LF16	No	11	83.3
LF4	No	4	87.5	LF17	No	10	84.6
LF5	No	4	86.1	LF18	No	9	88.8
LF6	No	6	89.9	LF19	No	12	78.3
LF7	No	2	92.2	LF20	No	9	78.7

LF8	No	5	89.5	LF21	No	10	83.4
LF9	No	5	86.8	LF22	No	10	75.1
LF10	No	1	92.0	LF23	No	10	82.5
LF11	No	9	85.9	LF24	No	9	81.4
LF12	No	8	88.5	LF25	No	12	64.1
LF13	No	8	86.8				

FC= Formulation code; %T= percent transmittance; VFI= volumetric flask inversion

The droplet size and zeta potential measurement revealed that increased in concentration of oil proportionately increased the emulsion droplet size. However, increase in surfactant concentration decreased the droplet size, plausibly owing to increase in net zeta potential45. The surfactant forms a thin film at the interface and decreases the droplet size and helps in stabilization of the emulsion. The cosurfactant, on the other hand, have limited role on zeta potential rather on emulsification property.

- ***In-vitro* Diffusion Study**

Table: In vitro diffusion study of L-SMEDDS of BOS

Time (h)	Cumulative % Drug Diffused						
	LF2	LF7	LF9	LF10	LF15	MF	Pure drug
0	0	0	0	0	0	0	0
1	03.38 ±0.56	04.25 ±0.34	04.23 ±0.39	06.46 ±0.23	05.28 ±0.56	01.05 ±0.97	1.10 ±0.58
2	21.49 ±0.38	24.20 ±0.41	25.22 ±0.86	35.60 ±0.43	32.11 ±0.45	06.38 ±0.86	06.00 ±0.70
3	39.88 ±0.29	56.25 ±0.38	47.82 ±0.28	58.46 ±0.82	49.22 ±0.74	13.53 ±0.69	14.5 ±0.80
4	58.76 ±0.39	69.25 ±0.84	72.05 ±0.26	62.11 ±0.59	55.84 ±0.68	20.41 ±0.73	19.10 ±0.50
5	74.48 ±0.18	78.41 ±0.29	81.11 ±0.42	77.97 ±0.37	76.41 ±0.49	25.59 ±0.49	24.30 ±0.40
6	81.48 ±0.14	85.63 ±0.49	88.45 ±0.94	89.06 ±0.28	84.81 ±0.35	29.72 ±0.52	29.20 ±1.8
7	89.46 ±0.42	91.63 ±0.49	93.29 ±0.59	96.56 ±0.28	91.19 ±0.83	33.35 ±0.43	32.80 ±1.2
8	91.21 ±0.77	94.63 ±0.49	96.29 ±0.50	98.06 ±0.28	96.19 ±0.83	39.28 ±0.28	37.90 ±1.1

(n = 3)*LF- Liquid Formulation, MF- Marketed Formulation.

In Vitro diffusion study of L-SMEDDS formulations compared with marketed formulation and pure drug. All L-SMEDDS showed drug diffusion more than 91% at the end of 8hr. The formulation LF10, marketed formulation and pure drug showed 98.60, 39.28% and 37.90% drug diffuse respectively, shown in table 10. The formulation LF10 achieved highest drug diffusion due to smallest droplet size. As the droplet size decreases the rate of diffusion increases, when MF and pure drug diffusion compared with LF10 formulation showed significant difference (P>0.05). The droplet size, polarity of droplet, HLB value of surfactant, carbon chain length of oil, level of surfactant and cosurfactant influenced the diffusion of drug. Based on these studies, an optimized formulation developed.

- **Transmission Electron Microscope**

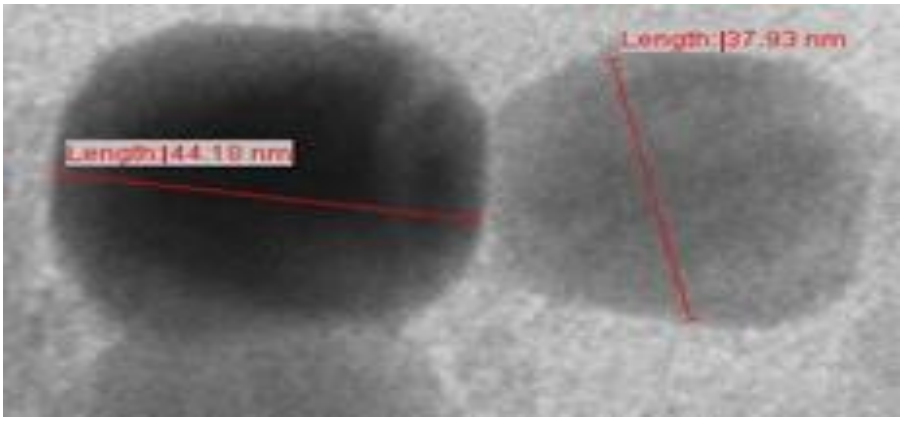

Figure:Transmission Electron Microscopy of L-SMEDDS of BOS

Shape and size of the resultant microemulsion produced by the dilution of LF10 formulation was further examined by using TEM. The nano oil droplets appeared spherical in shape. The droplets were also found to be of uniform size distribution depicted in figure

- **Development and Optimization of S-SMEEDS of BOS**

The S-SMEDDS was prepared by spray drying technology with different carriers to find out the maximum adsorbing capacity and free flow ability of S-SMEDDS.

- **Characterization of S-SMEDDS powder of BOS**
- **Adsorption capacity**

Prepared S-SMEDDS was evaluated by angle of repose and Adsorbing capacity. Maltodextrin and aerosil 300 did not show desired flowing properties and form a semisolid product.

Table: Different composition and evaluation of S-SMEDDS powder

Sr. no	Adsorbent (Ratio)	Angle of repose (θ)	Observation of Spray dried Product	Drug Content (mg/ 100mg S-SMEDDS)	Droplet Size (nm)	Polydispersity Index	No. of VFI
1	Aerosil 200: Maltodextrin (1:1)	--	Powder with slightly viscous nature	4.935	161.2	0.42	03
2	Aerosil 300: Maltodextrin (1:1)	--	Semisolid nature product	3.87	161.3	0.43	02
3	Aerosil 300	--	Powder with slight Semisolid nature	8.61	160.1	0.41	02
4	Aerosil 200	32°68’	Powder with good flow property	10.21	157	0.32	02

The aerosil 200 was found to be the best adsorbing carrier for preparation of S-SMEDDS of BOS. It showed superior oil Adsorption tendency, good flow and drug content. Further, it was observed that oil Adsorption capacity of aerosil200 three times more of its weight and got decreased with higher grades of silicon dioxide, i.e., aerosil 300. This may probably be due to increase in average particle size, which decreased the total pore volume and porosity49, 50. In porous carriers, the drug is adsorbed to certain extent as a thin layer of oil surrounding the particles.

Aerosil 200 shown highest drug loading capacity, the drug content was found to be 10.21mg /100mg for S-SMEDDS prepared by using Aerosil 200. This led us to select Aerosil 200 as carrier for further study. The highest drug content was

due to higher adsorbing capacity of Aerosil 200 as compared to other adsorbents.

Maltodextrin was also attempted as adsorbent along with Aerosil 200 in 1:1 proportion but there was no desired flowing property obtained and Drug content was also low as compared to Aerosil 200 alone. Aerosil 300 formed a viscous to semisolid product hence rejected from further study showed in Table 11. Oil adsorption capacity got decreased with higher grades of silicon dioxide. This may probably be due to increase in average particle size, which decreased the total pore volume and porosity. The reconstitution performance of S-SMEDDS found to be good for all S-SMEDDS powder excluding Maltodextrin: Aerosil200 (1:1) combination. Emulsifying performance of S-SMEDDS were marginally slower compared to L-SMEDDS, though the difference was statistically insignificant ($P<0.05$). This could be because of additional steps involved during emulsification such as desorption of liquid SMEDDS from voids of porous carries. The S-SMEDDS when exposed to aqueous media, lead to desorption of the liquid SMEDDS from the colloidal silicon dioxide due to stronger interaction between silica and aqueous media than those between silica and L-SMEDDS.

Measurement of droplet size and zeta potential of resultant microemulsions of S-SMEDDS

The average droplet size, polydispersity index and zeta potential of reconstituted microemulsion of S-SMEDDS was found to be 157nm, 0.32 and -26mv respectively Table 5.15. The droplet size of the microemulsion from the S- SMEDDS was slightly increased, but with lack of statistically significant difference, compared to the liquid SMEDDS ($P < 0.05$). From these results, adsorbing the liquid SMEDDS on Aerosil 200 by spray-drying did not seem to have a remarkable effect on droplet size. The S-SMEDDS preserved the self-micro emulsification performance of the liquid SMEDDS.

Table: Droplet size of resultant microemulsion of S-SMEDDS

Sr. No.	S-SMEDDS	Droplet size*	Polydispersity Index*	Zeta potential*
1	S-SMEDDS prepared using Aerosil200	157±0.30	0.32±0.20	-26mv

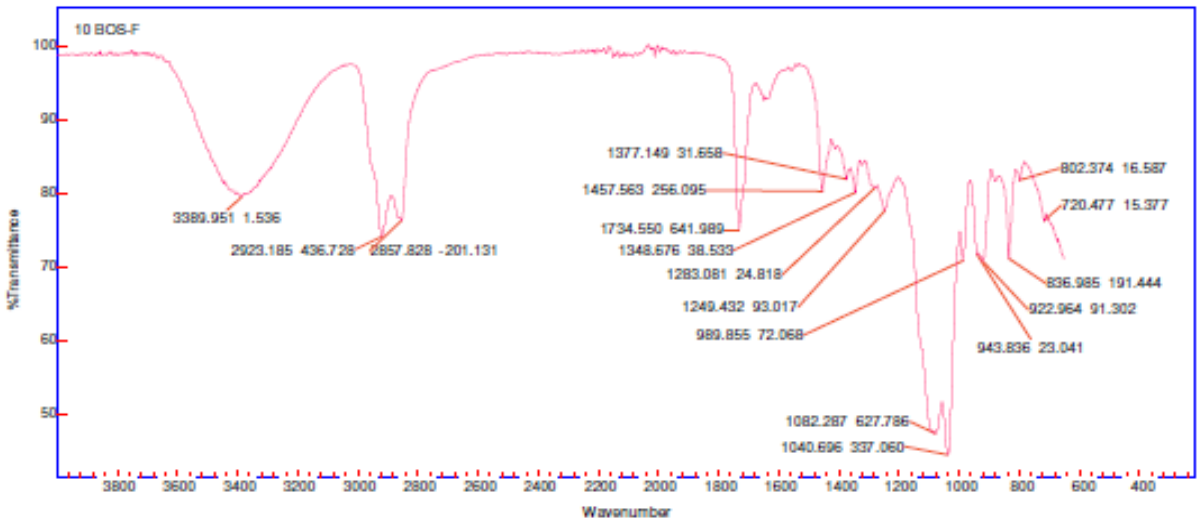

Figure FT-IR spectrum of S-SMEDDS of BOS

- **FT-IR spectra of S-SMEDDS**

An FTIR study was conducted to evaluate potential drug-excipient interactions in the formulation. The analysis focused on key functional groups, including S=O (asymmetric and symmetric stretching vibrations), N-H (asymmetric stretching and bending vibrations), and C=N (amine stretching vibrations).

The comparative assessment showed that all characteristic peaks of the drug remained consistent in the final formulation. However, some peaks exhibited reduced intensity or slight broadening, likely due to overlapping excipient signals or the drug's entrapment within the excipient matrix. These observations suggest no chemical interaction between the drug and excipients, confirming compatibility in the final formulation as evidenced by FTIR spectra.

- **DSC Study**

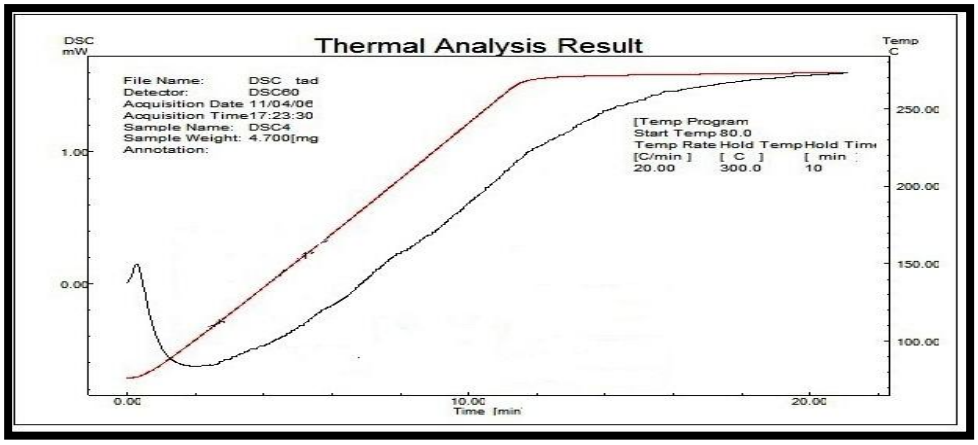

Figure (a): DSC of Aerosil 200

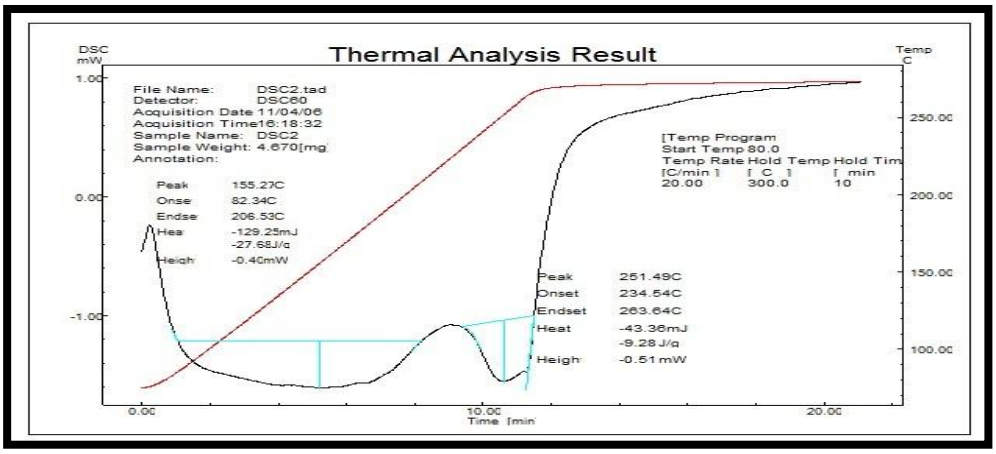

Figure (b): DSC of S-SMEDDS of BOS

The DSC thermograms of pure BOS, Aerosil 200, and S-SMEDDS of BOS are presented in Figures (a), and 5(b). Pure BOS exhibited a sharp endothermic peak at 114.2°C (range: 101–124°C), as shown in Figure 6(a). In contrast, no distinct peak was observed in the S-SMEDDS formulation DSC, indicating a change in the melting behavior of BOS. This suggests that the drug underwent solubilization and a loss of crystallinity within the SMEDDS, increasing molecular free energy, reducing the melting point, and ultimately enhancing solubility and dissolution rate. Additionally, DSC analysis of the drug-excipient mixtures in S-SMEDDS revealed no signs of incompatibility.

X-ray powder diffraction:

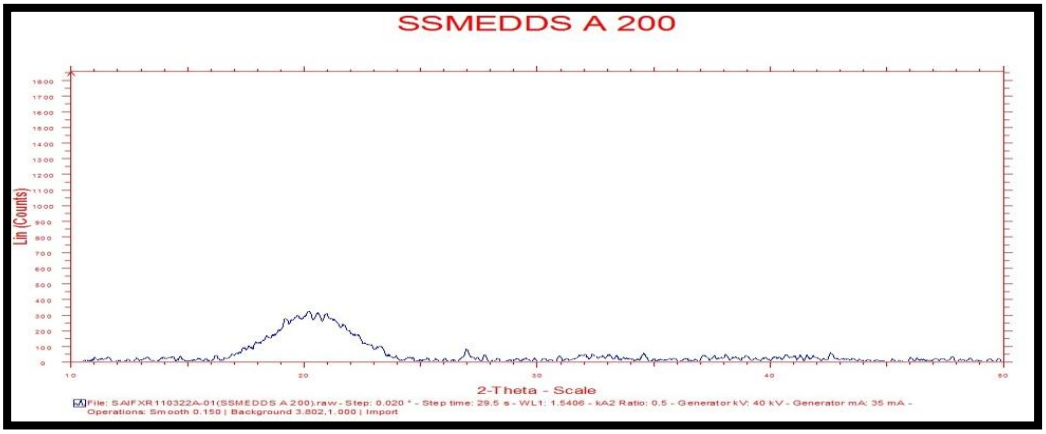

Figure XRD of S-SMEDDS of BOS

The X-ray powder diffractogram of pure BOS confirmed its crystalline nature. However, in the solid SMEDDS formulation of BOS, the absence of distinct peaks suggested that the drug existed in an amorphous state, solubilized within the lipidic excipients, or exhibited reduced crystallinity.

- **Morphological analysis of S-SMEDDS by SEM**

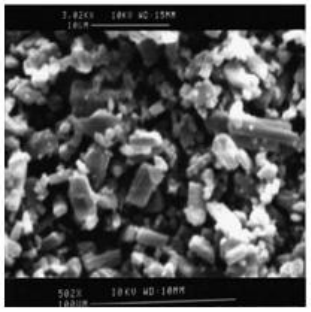

Figure (a): SEM of BOS

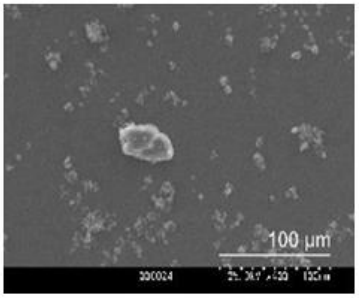

Figure (b): SEM of Aerosil 200

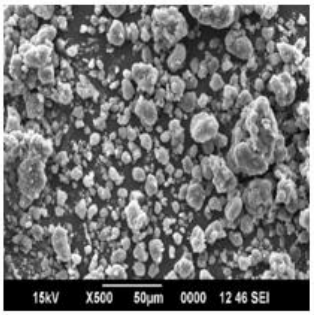

Figure (c): SEM of S-SMEDDS at 500X

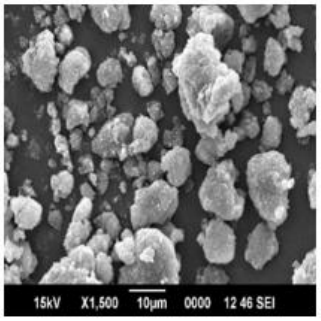

Figure (d): SEM of S-SMEDDS at 1500X

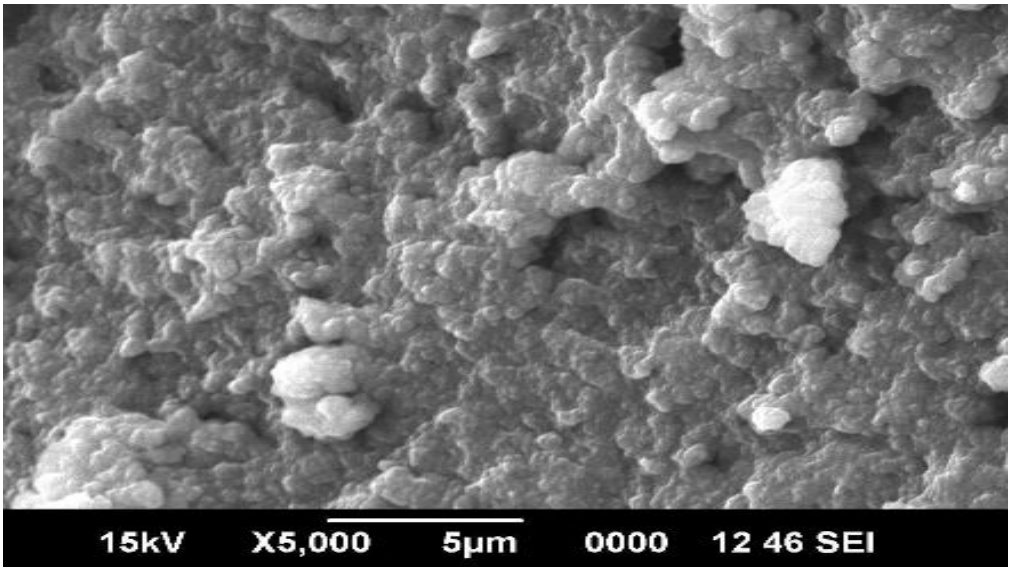

Figure 8 (e): SEM of S-SMEDDS at 5000X

From SEM study the surface of S-SMEDDS powder clearly shows the adsorption of liquid pre-concentrate on Aerosil 200 Figure (a-e). The Figure (a) indicates the crystalline nature of drug. The crystalline state of BOS has converted to amorphous form or it may be molecularly dispersed. The spray drying has achieved some spherical shape to S-SMEDDS powder.

- **Development of S-SMEDDS Tablet of BOS**

S-SMEDDS tablets were compressed by using free flowing of S-SMEDDS powder prepared by spray drying technique

containing BOS mix with variable concentration of directly compressible excipients. Compositions of the S-SMEDDS tablet formulations

- **Evaluation of S-SMEDDS Tablet of BOS**

Angle of Repose (Ɵ): The values were found to be in the range from 28º.30' to 32º.68'. This indicates good and passable flow property of the powder blend**.**

Compressibility Index: Compressibility index value ranges between 19.30% - 22.68% indicating that the powder blends have the required flow property

Table: Results of Pre-compression parameters

Formulation code	Pre-compression parameters			
	Angle of repose (θ)	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Carrs index
F1	30°08’	0.536	0.666	19.48
F2	32°68’	0.536	0.670	19.89
F3	29°56’	0.520	0.666	21.21
F4	29°19’	0.513	0.666	22.38
F5	28°92’	0.516	0.653	20.20
F6	29°76’	0.543	0.676	19.69
F7	31°22’	0.543	0.673	19.30
F8	28°30’	0.550	0.676	20.48

- **Post-compression Parameters:**

Hardness test: The hardness of tablets across batches ranged from 2.0 to 3.8 kg/cm². Batches F1, F2, F3, and F8 exhibited hardness above 3.6 kg/cm². However, batches F4–F7 faced punching issues, including picking, sticking, and lamination, preventing further post-compression studies**.**

Friability Test: The values of friability test were tabulated in Table. The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

Table: Results of Post-compression parameters

FC	Post-compression parameters					
	Thickness (n=3) (mm)	Hardness (kg/cm^2)	Friability (%)	Weight Variation %(n=10)	*In vitro* Disintegration Time (min.sec)*	Drug Content (%) ± S.D.
F1	6.00	3.8 ± 0.29	0.35	±2.1%	3.25	98.85 ± 0.36
F2	6.10	3.8 ± 0.50	0.67	±4.5%	2.40	99.13 ± 0.58
F3	6.21	3.6 ± 0.50	0.89	±2.6%	2.25	100.05± 0.49
F4	Nil	Nil	Nil	Nil	Nil	Nil

F5	Nil	Nil	Nil	Nil	Nil	Nil
F6	Nil	Nil	Nil	Nil	Nil	Nil
F7	Nil	Nil	Nil	Nil	Nil	Nil
F8	5.93	3.8 ± 0.77	0.30	±3.8%	3.26	98.43 ± 0.45

***(n=3)**

- **Drug Content**

The drug content uniformity was performed for all formulations and results are tabulated. Three trials from each batch were analyzed spectrophotometrically. The average value and standard deviations of all the formulations were calculated. The drugs content of the tablets were found to be between 96 to 99%. The results were within the range and that indicated uniformity of mixing. The cumulative percentage drug released by each tablet in the in-vitro release studies was based on the average drug content present in the tablet.

- **In vitro Disintegration test**

The results are shown in Table 14, which was determined as per Indian Pharmacopoeia specifications for all the developed formulations. All the formulations showed disintegration time less than 4 min. Formulations F3 and F2 showed rapid disintegration compared to other formulations this effect was due to the presence of superdisintegrant pregelatinized starch in formulation.

- **In-vitro dissolution study of S-SMEDDS tablet of BOS**

In the self-micro emulsifying systems, the free energy required to form a microemulsion, thereby allowing spontaneous formation of an interface between the oil droplets and water. It is suggested that the oil/surfactant/cosurfactant and water phases effectively swell, decrease the oil droplet size and eventually increase the release rate. In vitro drug release studies were performed for solid SMEDDS in SGF pH 1.2 and pH 6.8 Phosphate Buffer profiled in Table 14 (a, b) and Figure 9 (a, b). There was extremely significant found in release pattern in both dissolution media for all S-SMEDDS tablet formulations. Out of all S-SMEDDS tablet formulations F3 was showed highest drug release (within 25min 98.80%). This may be due to fast disintegration of F3 (2min 25sec) than other tablets. The fast disintegration of tablet was due to high concentration of superdisintegrant Pregelatinized starch in F3 as compared to F1, F2 and F8. F8 was control formulation without superdisintegrant. F8 showed slightly slow drug release as compared to other formulations. This may be due to higher disintegration time. From the dissolution data and other parameters study F3 Tablet was considered optimized formulation. The dissolution data of marketed tablet of BOS (Traceller 62.5mg) and pure drug were showed significant difference (P>0.05) in SGF pH1.2 and pH6.8 phosphate buffers in comparisons with S-SMEDDS tablets.

Table (a): In vitro Dissolution profile of S-SMEDDS Tablets in SGF pH 1.2

Time (min)	Cumulative % Drug Release*					
	F1	F2	F3	F8	M	Pure drug
0	0	0	0	0	0	0
5	13.45±0.65	16.8±0.10	21.39±0.64	9.25±0.55	0.83±0.60	0.25±0.98
10	39.6±0.80	41.3±0.30	45.5±0.93	28.6±0.65	1.46±0.30	0.8±0.70
15	57.5±0.90	64.1±0.15	68.3±0.45	56.5±0.45	4.86±0.25	1.9±0.80
20	78±0.35	81.2±0.51	88.1±0.68	75.8±1.20	11.57±0.45	5±0.90
25	90±0.80	91.8±0.88	98.8±0.79	89.1±0.58	16.99±0.66	9.5±1.30
30	95.1±0.85	97.1±0.65		94.2±0.90	21.73±0.72	14.3±1.25
35	98.2±0.95	98.6±0.75		97.8±0.95	25.84±0.51	18.8±1.50
40					29.28±0.55	21±1.40

45					32.59±0.65	23±1.05
50					35.78±0.80	25.5±1.10
55					37.29±0.90	28±1.20
60					40.07±0.95	29.07±1.35

(n=6)*

Table (b): *In vitro* Dissolution profile of S-SMEDDS Tablet in pH 6.8 phosphate buffer

Time (min)	Cumulative % Drug Release*					
	F1	F2	F3	F8	M	Pure drug
0	0	0	0	0	0	0
5	13.45±0.35	16.8±0.78	21.39±0.50	9.25±0.54	0.98±0.92	0.38±0.50
10	39.6±0.56	41.35±0.65	45.5±0.90	28.6±0.90	4.79±0.98	1.2±0.45
15	57.5±0.60	64.1±0.55	68.3±0.99	56.5±0.98	17.41±0.68	2.4±0.85
20	78±0.98	81.2±0.40	88.1±0.30	75.8±0.92	27.98±0.78	9.8±1.40
25	90±0.90	91.8±0.70	99.8±0.68	89.1±0.65	35.37±0.68	13.5±1.35
30	95.1±0.92	97.1±0.60		94.2±0.73	42.09±0.63	20±1.45
35	98.2±0.56	98.6±0.80		97.8±0.85	48.76±0.45	26±1.50
40					54.19±0.75	31.4±1.20
45					60.64±0.80	36±1.30
50					64.59±0.40	39.8±1.25
55					67.38±0.30	45.6±1.10
60					70±0.60	48.6±1.05

(n = 6)*

During dissolution, the S-SMEDDS undergo faster hydration to produce o/w microemulsions. The high specific surface area of these particles contributes towards improved dissolution compared to marketed tablet. The S-SMEDDS when exposed to dissolution medium, leads to desorption of the liquid SMEDDS from the silicon dioxide surface due to stronger interaction between silicon dioxide and dissolution medium than those between silicon dioxide and liquid SMEDDS. Drug release from S-SMEDDS was initially slower due to increase in diffusion path length for adsorbed liquid formulation in the matrix of porous carriers. Also, the capillary forces and wicking properties exhibited by the liquid-filled porous carriers, upon contact with dissolution fluid, In comparative drug release study the S-SMEDDS showed superior drug release compared to marketed preparation.

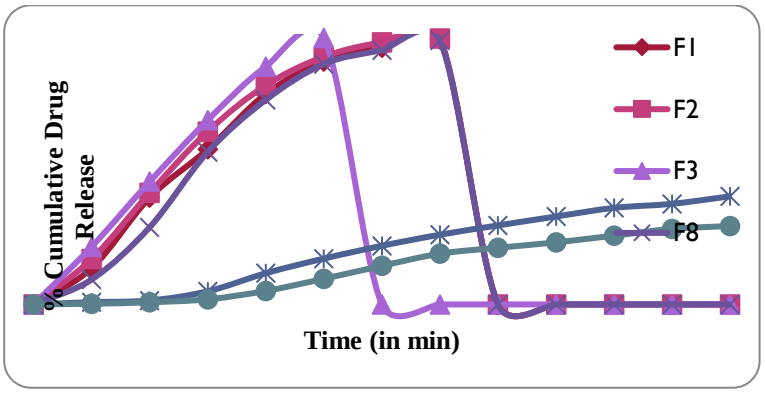

Figure (a): In vitro Dissolution profile in SGF pH 1.2

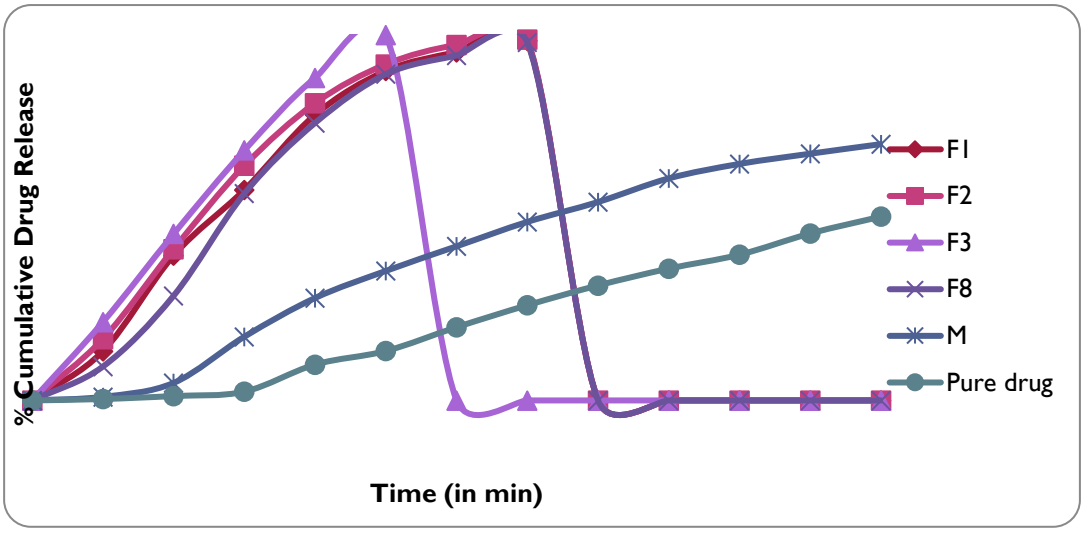

Figure 9 (b): In vitro Dissolution profile in pH 6.8 phosphate buffer

- Scanning Electron Microscopy of S-SMEDDS tablet

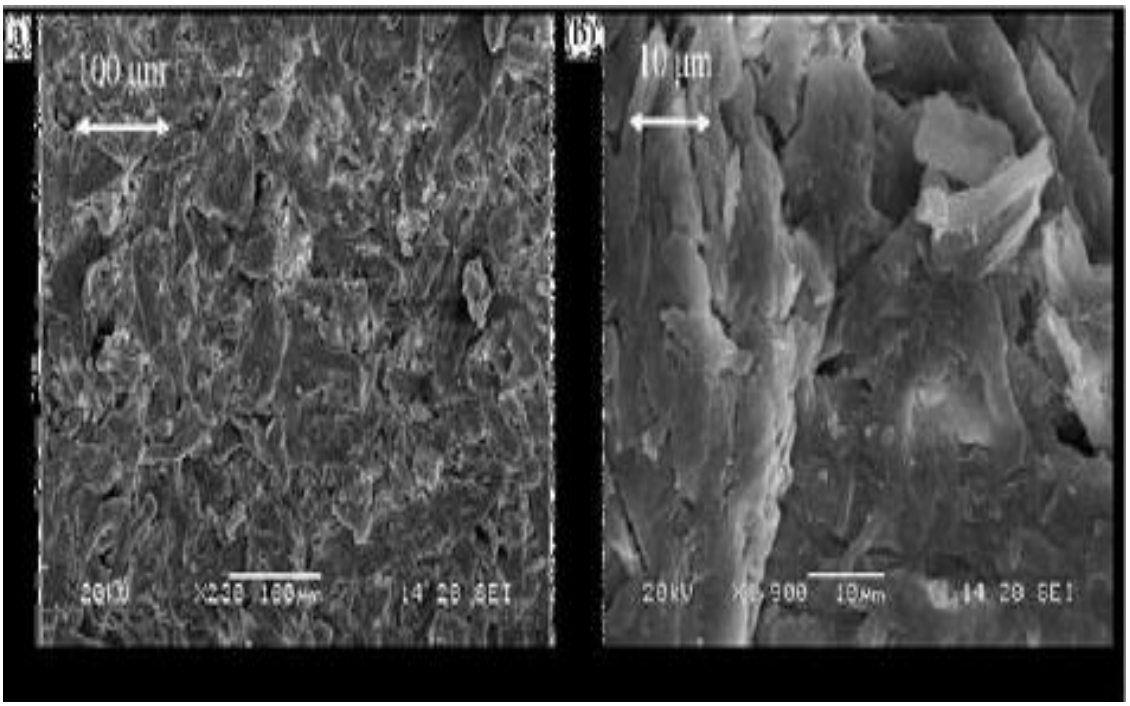

Figure 10 (a): SEM of Top surface of S-SMEDDS tablet (a) under 230X magnification (b) under 1900X magnification.

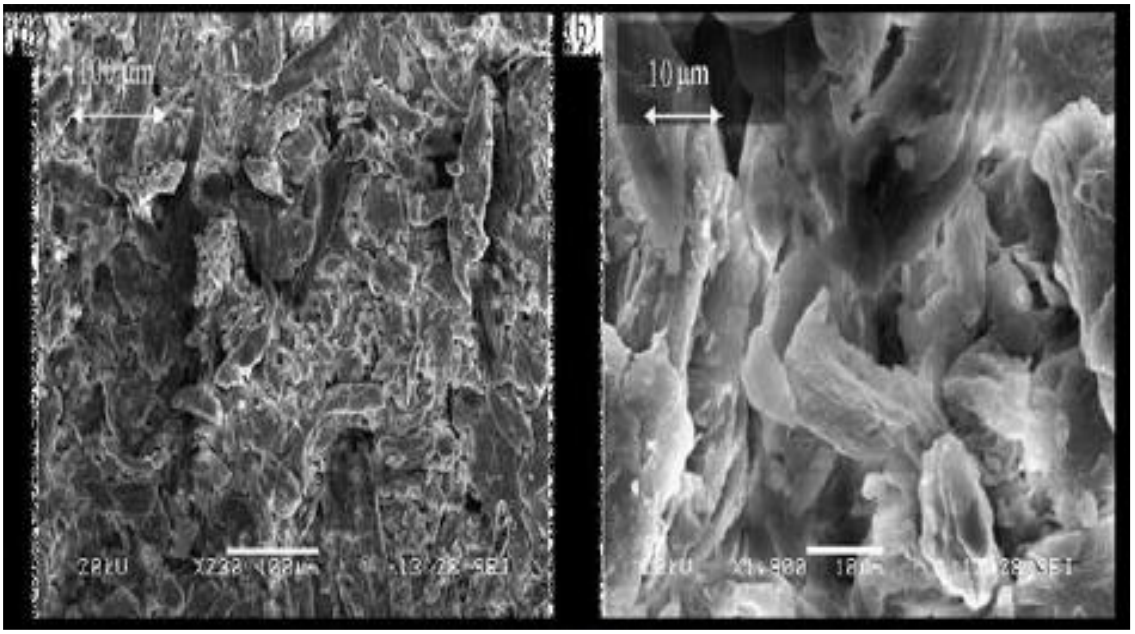

Figure 10 (b): SEM of bottom surface of S-SMEDDS tablet (a) under 230X magnification (b) under 1900X magnification.

- Assessment similarity factor f2 between marketed tablet and F3 formulation

From the dissolution study Table 15 in SGF1.2 pH and pH 6.8 phosphate buffer. It was cleared that there is dissimilarity or significant difference in release profile of F3 and marketed formulation in SGF1.2 pH as well as pH 6.8 phosphate buffers. The f2 value was obtained below 50. This indicates statistically significant difference in release profile. When in-vitro dissolution study of marketed tablet of BOS (62.5mg) was compared with S-SMEDDS F3 of BOS (62.5mg) in pH 6.8 phosphate buffer, marketed tablet showed 70.16 + 0.514% cumulative drug release in 60 min, while S-SMEDDS formulation F3 shows drug release 98.88 + 0.265% within 25min. Dissolution rate of F3 and marketed tablet in pH 6.8 phosphate buffer was higher as compared to dissolution rate in SGF1.2 pH because of high solubility of BOS toward alkaline pH.

Table: Similarity factor between marketed tablet and formulation (F3)

Sr. no	Dissolution medium	*f*2 similarity factor
1	SGF1.2 pH	18.1902
2	pH 6.8 phosphate buffer	19.8651

- **Kinetic treatment to dissolution data**

Table: Kinetic treatment to dissolution data of optimized formulation (F3) and marketed tablet

Equation	SGF pH1.2				pH 6.8 phosphate buffer			
	F3		M		F3		M	
	r^2	n	r^2	n	r^2	n	r^2	n
Zero order	0.9880	-	0.9780	-	0.9870	-	0.9750	-
First order	0.9300	-	0.9830	-	0.9310	-	0.9900	-
Hixson crowell	0.9820	-	0.9820	-	0.9800	-	0.9850	-

Korsmeyer-Peppas model	0.9600	0.87	0.8410	0.87	0.9620	0.89	0.8300	0.86
Higuchi model	0.9360	-	0.8840	-	0.9350	-	0.8800	-

F3- S-SMEDDS Tablet, M- Marketed Tablet

The release kinetics of the optimized batch F3 and the marketed formulation were evaluated using different kinetic models. Based on the coefficient of determination (r^2), the F3 batch followed zero-order kinetics most closely, followed by the Hixson-Crowell model, in both SGF (pH 1.2) and phosphate buffer (pH 6.8).

The Korsmeyer-Peppas model was applied to further analyze the drug release mechanism. The release exponent (n) for F3 in both media indicated non-Fickian (anomalous) transport, suggesting that drug release occurs through a combination of diffusion through the hydrated matrix and polymer relaxation. This confirms that the drug release from the S-SMEDDS tablet (F3) is primarily governed by a diffusion mechanism.

In contrast, the marketed formulation best fit the first-order kinetic model. The Korsmeyer-Peppas exponent (n) for this formulation also suggested non-Fickian behavior, but the release pattern differed from that of F3.

- **Stability Study of Optimized Formulation Of S-SMEDDS Of BOS (F3)**

Stability studies ratified that the optimized S-SMEDDS tablet (F3) was robust under the accelerated temperature and humidity conditions. High duration of the predicted shelf-life (i.e., 3.6 years) at room temperature, calculated using Arrhenius plot also corroborates the stability of the S-SMEDDS

Table: Results of stability study at 40+20C and 75 + 5% RH

Time (Days)	Parameters					
	Physical appearance	% Drug content	Disintegration Time	Droplet Size (nm)	Zeta potential	In-Vitro Dissolution test (within 25 min)
00	Circular shape with 6.21mm thickness, off white colure	100.00 ±0.15	2 min 26 sec	157	-26mv	98.88%
30	No Change	97.5± 0.36	2 min 27 sec	157.2	-26mv	96.70%
60	No Change	94.0± 0.42	2 min 27 sec	158	-26mv	92.5%
90	No Change	91.6± 0.76	2 min 32 sec	157.8	-26mv	90.34%
120	No Change	89.0± 0.57	2 min 31 sec	159	-26mv	87.96%
150	No Change	87.10 ±0.45	2 min 30 sec	159	-25mv	85.78%
180	No Change	86.0 ± 0.53	2 min 31 sec	160	-25mv	85.22%

(T= days)

Table: Percent drug remaining in F3 (S-SMEDDS tablet) stored at elevated temperature

Time (Day)	**% Drug content***			**% Log drug remaining**		
	at30±0.5°C	**at40±0.5°C**	**at50±0.5°C**	**at30±0.5°C**	**at40±0.5°C**	**at50±0.5°C**
00	100.0	100.0	100.0	2.0	2.0	2.0

30	99.50	97.50	71.20	1.9978	1.9890	1.8524
60	99.10	94.00	44.50	1.9960	1.9731	1.6483
90	98.40	91.60	30.20	1.9929	1.9618	1.4800
120	97.70	89.00	22.10	1.9898	1.9493	1.3443
150	96.30	87.10	15.10	1.9836	1.9400	1.1760
180	95.00	86.00	8.00	1.9777	1.9344	0.9030

(n =3)*

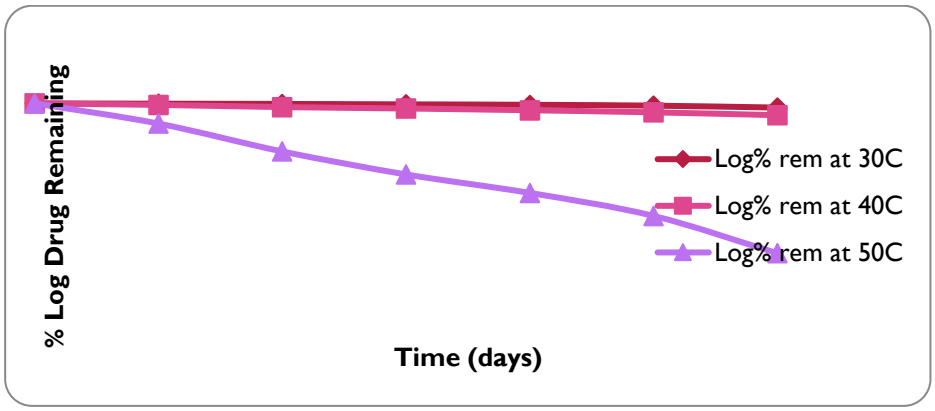

Figure 11: Log percent concentration of drug remaining versus time plot for F3

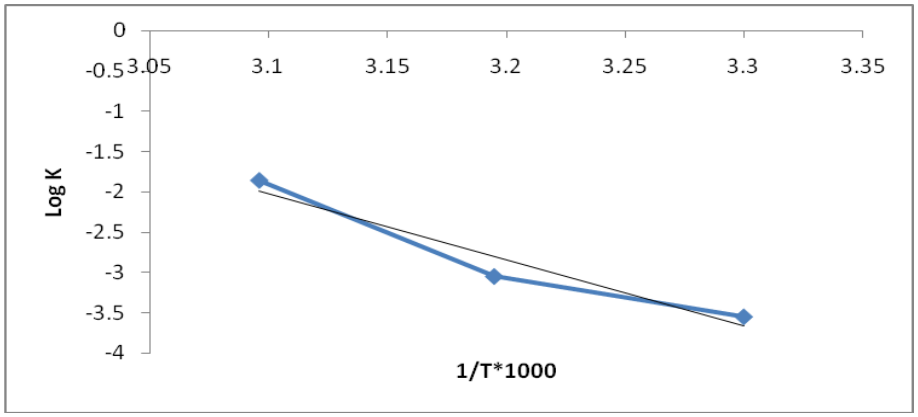

Figure 12: Arrhenius plot for solid self-micro emulsifying drug delivery system F3

Table: Degradation rate constant for BOS in F3

Temp. (in ^{0}C)	**Temp. (in ^{0}K)**	**1/T*1000**	**Slope**	**K**	**LOG K**
30 ^{0}C	303	3.300	-0.000121	0.000279	-3.55492
40 ^{0}C	313	3.194	-0.000379	0.000873	-3.05898
50^{0}C	323	3.095	-0.005890	0.013565	-1.86759
25 ^{0}C	298	3.355			

➢ **In-Vivo Study**

Table: Pharmacokinetic parameters and relative bioavailability of Pure Drug BOS, S-SMEDDS Tablet and Marketed Formulation

Sr. No	Parameter	Pure Drug	Marketed formulation	S-SMEDDS Tablet (F3)
1	t_{max} (hr)	04.00	3.89	3.44
2	C_{max} (mcg/ml)	14.85	17.24	26.28
3	$t^{1/2}$ (hr)	06.02	6.36	6.68
4	Ke (hr^{-1})	0.115	0.11	0.1036
5	AUC^{t}_{0} (mcg.hr/ml)	238	255.7	380.27
6	MRT^{t}_{0} (hr)	11.4	11.61	12.55
7	Ka (hr^{-1})	0.415	0.497	0.625
8	% F_{rel}	----	107	159

S-SMEDDS Tablet (containing 62.5mg of BOS per Tablet), Marketed Formulation (Tab. Tracleer containg 62.5 mg of BOS per Tablet), (mean ±SD, n=6). All the parameters were determined with statistical significance set at P>0.05.

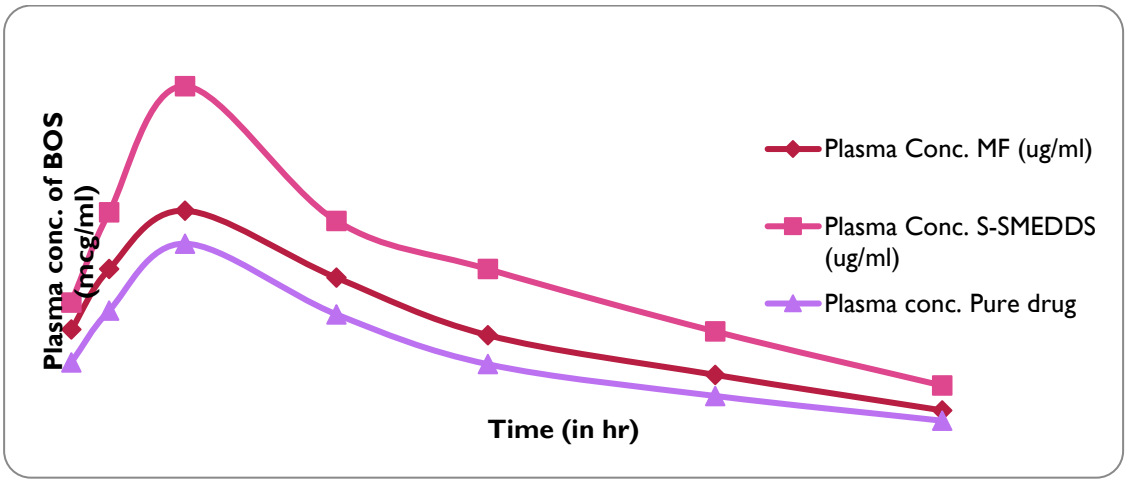

Figure 12: Plasma Concentration Time profile of pure drug, marketed formulation (Tab. Tracleer) and optimized S-SMEDDS tablet (F3) of BOS

The average plasma concentration profile as a function of time obtained during the in-vivo pharmacokinetic investigation carried out in Male Sprague-Dawley rats for pure drug BOS, marketed formulation (Tracleer Tablet containing 62.5mg BOS) and optimized (F3) S-SMEDDS Tablet containing 62.5mg BOS. The Cmax of S-SMEDDS was about 1.76 fold and marketed formulation 1.16 fold higher than pure drug BOS. The values of AUC 0-t of S-SMEDDS were 1.59 fold and marketed formulation showed 1.07 fold higher compared pure drug BOS. Tmax decreased to 3.44hr for S-SMEDDS and marketed formulation 3.89hr compared to pure drug. Other parameters like MRT 0-t, Ka and t1/2 are also found to be higher than pure drug and marketed formulation indicating enhanced bioavailability depicted in (Figure 12 and Table 20). The results of all pharmacokinetic parameters were found to be highly significant difference (P>0.05) for F3 S-SMEDDS tablet compared to pure drug and the marketed formulation. It confirmed that oral Adsorption of BOS was significantly improved by F3 S-SMEDDS.

5. CONCLUSION

The study successfully developed a solid self-microemulsifying drug delivery system (S-SMEDDS) for BOS, comprising Capmul MCM (30%), Tween 20 (50%), and propylene glycol (20%) in the liquid SMEDDS (L-SMEDDS), with drug

quantification performed using ultrasonic interferometry.

The optimized S-SMEDDS tablet formulation consists of 59.57% S-SMEDDS of BOS, 11.4% anhydrous lactose, 3% pregelatinized starch, 22% microcrystalline cellulose, 2% magnesium stearate, and 2% talc.

The final tablet weight was 965 mg. The S-SMEDDS powder, prepared via spray drying, exhibited well-separated, smooth-surfaced particles under SEM while retaining the self-emulsifying properties of L-SMEDDS. DSC and XRD analyses indicated that BOS likely existed in a molecularly dispersed state within the formulation.

In vitro dissolution demonstrated rapid drug release, with formulation F3 achieving 99.80% release within 30 minutes. A similarity factor (f2) of 18.19 confirmed F3's superior release profile over both the marketed formulation and pure drug. Kinetic analysis revealed zero-order release with non-Fickian diffusion as the predominant mechanism.

Stability studies under accelerated conditions showed no significant changes over six months, with a predicted shelf life of 3.6 years at room temperature.

In vivo studies in rats revealed that the S-SMEDDS tablet (F3) significantly enhanced BOS bioavailability, exhibiting 159% relative bioavailability compared to the pure drug and marketed formulation. These findings highlight S-SMEDDS as a promising strategy for improving the oral delivery of poorly soluble, high-molecular-weight drugs like BOS.

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