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# FORMULATION AND IN-VITRO EVALUATION OF MUCOADHESIVE SOLID SELF-MICROEMULSIFYING SYSTEM TRANSNASAL DELIVERY SYSTEM

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## ABSTRACT

The current study set out to create an S-SMEDDS of OXZ to improve the drug's solubility and stability in the final product. Sodium starch glycolate was employed as the adsorbent in the adsorption to solid carrier technique since it was needed in amounts ranging from 0.5 to 0.95 grammes to transform 1 millilitre of L-SMEDDS into a free-flowing powder. The 9OSF1-S, 9OSF2-S, 9OSF3-S, 9OSF4-S, and 9OSF5-S Out of all the prepared S-SMEDDS powders, 5RSF1-S, 5RSF2-S, 5RSF3-S, 5RSF4-S, and 5RSF5-S demonstrated superior flow properties. Using the proper ratio of sodium starch glycolate to LSMEDDS, ten S-SMEDDS formulations were created. In vitro dissolution studies revealed that 9OSF4-S and 5RSF3-S, two of the eight S-SMEDDS formulations, had the best flow characteristics and the highest drug release when compared to pure drug. Because 9OSF4-S and 5RSF3-S had the best and highest results from the in vitro dissolving investigation, they were chosen for more research. In the case of 5RSF3-S, the particle size and zeta potential were 164.24 nm and - 13.9 mv, respectively, but in the case of 9OSF4-S, they were 78.13 nm and - 21.5 mv. For both S-SMEDDS formulations, 9OSF4-S and 5RSF3-S, an accelerated stability study (40 ± 2 °C/75 ± 5% RH) and a real-time stability study (25 ± 2 °C/60 ± 5% RH) were conducted. All of the findings show that the current study's stated objective of increasing permeability—aside from bioavailability—of the weakly soluble medication oxcarbazepine through improved drug solubility was effectively achieved.

**KEYWORDS:** Self-Microemulsifying System, Nasal Delivery System, Oxcarbazepine,

## INTRODUCTION

The literature has documented a number of techniques to improve medication penetration through biological membranes1. As an alternative to oral and parenteral routes, nasal administration allows the medicine to enter the bloodstream.[1] Compared to other drug delivery methods, nasal drug delivery offers a number of advantages. Vascularised epithelium lines the nasal canal, providing a greater surface area that is beneficial for drug absorption. Compared to the digestive system, it has a low level of enzymatic activity.[2] It avoids first-pass metabolism in the liver. Therefore, the gastrointestinal membrane is little irritated.[3] Due to its non-invasive nature, ease of use, improved patient compliance, and affordability, nasal drug delivery may be chosen over alternative drug delivery methods.[4-5] By breaking down the blood-brain barriers, nasal drug delivery also has the benefit of delivering medications to the brain.[6] Oxcarbazepine (OXC) is a mood stabiliser and anticonvulsant medication that is mostly used to treat epilepsy but is also used to treat mood and anxiety problems. It is a carbamazepine derivative.[7] 10, 11-dihydro10-oxo-5H-dibenz (b,f)azepine-5-carboxamide is its chemical name. It has a partition value of 1.31 and dissolves poorly in water (308 mg/L). It falls under the iminostilbene class of antiepileptic drugs, which also act on neuropathy by blocking sodium and calcium channels, on bipolar disorder by reducing aberrant brain electrical activity, and on convulsions by post-tetanic potentiation of synaptic transmission.[8–10]

SMEDDS are homogeneous, transparent blends of medications, oils, surfactants, and occasionally cosolvents and cosurfactants. After oral administration, this mixture forms a stable oil-in-water microemulsion in the gastrointestinal system when mildly agitated with an aqueous media.[11] Interfacial tension is significantly decreased by the use of two or more surfactants and cosurfactants, and the oral bioavailability and dissolving profile of hydrophobic medicines are improved when the drug is present in a solubilised state and the droplet size of SMEDDS is small.[12, 13] SMEDDS can be given as a powder that is then turned into tablets or put into hard gelatin capsules, or as a liquid using a soft gelatin capsule.[14] Considering the advantages and huge potential of SMEDDS, we developed and optimized oxcarbazepine-incorporated SMEDDS to enhance the

solubility and bioavailability of oxcarbazepine in this study.

## MATERIALS AND METHODS

**Materials:** Oxcarbazepine was obtained from Mylan Laboratories, located in Ahmedabad, India, Span 20, 80, Tween 20, 80 and propylene glycol from Chemical Point (Germany), oleic acid from Central Drug House(P) LTD (India), methanol from Sigma-Aldrich (Bljika), and hydrochloric acid from ReAgent Chemicals (UK).

### Preparation of S-SMEDDS

**Adsorption to solid carriers:** The ideal L-SMEDDS formulation was converted into free-flowing powders using the adsorption onto solid carrier approach. Materials with a large surface area and good disintegration capabilities comprised the adsorbent I solid carriers. Up to 70% (w/w) of the material can be absorbed by the chosen carrier. During the conversion process, the liquid formulation was added to carriers while being continuously mixed in a blender.[15, 16]

**Preparation of S-SMEDDS formulation:** An attempt was made to create S-SMEDDS formulations utilising optimised L-SMEDDS formulations following expedited stability testing. The adsorption to solid carrier approach was used to prepare them. Solid-SMEDDS were created using sodium starch glycolate as a solid carrier in the following ratios: (adsorbent: L-SMEDDS) 0.55:1, 0.65:1, 0.75:1, 0.85:1, and 0.95: 1. The set amount of L-SMEDDS was added to the mortar and well mixed with the adsorbent. A 250 µm mesh was used to filter the granular bulk in order to achieve homogeneous particle size. Until they could be examined further, the produced powder samples were stored in a desiccator.[17, 18] Table 1 provided the composition of S-SMEDDS including oxcarbazepine using sodium starch glycolate.

**Table 1: Represents ratio of S-SMEDDS and solid carrier for the preparation of S-SMEDDS.**

| Code | LSMEDDS (ml) | Sodium Starch Glycolate (gm) | Code | LSMEDDS (ml) | Sodium Starch Glycolate (gm) |
|---|---|---|---|---|---|
| 9OSF | 1 | 0.55 | 5RSF | 1 | 0.50 |
| | 1 | 0.65 | | 1 | 0.60 |
| | 1 | 0.75 | | 1 | 0.70 |
| | 1 | 0.85 | | 1 | 0.80 |
| | 1 | 0.95 | | 1 | 0.90 |

### Measurement of flow properties of S-SMEDDS [19-21]

**Angle of repose:** The angle of repose was then computed using equation 1:

Tan ø = *h*/r ……. Eq. (1)

Where h: height, r: the radius of the pile of powder.

**Carr's index:** The percentage compressibility of granules were determined using poured bulk density and tapped bulk density which is given as carr's compressibility index. Equation 2 was given;

Carr's index (%) = Tapped bulk density -poured bulk density/Tapped bulk density…. ……Eq. (2)

**Hausner's ratio:** Hausner's ratio was calculated by the ratio of tapped density and bulk density given in equation 3.

Hausner's ratio = $V_0$ / $V_i$……Eq. (3)

Where $V_0$ = Bulk density , $V_i$ = Tapped density

**Table 2: Limits for flow properties of powder.**

| Sl. No | Type of flow | Angle of repose | Carr's index | Hausner's ratio |
|---|---|---|---|---|
| 1 | Excellent | 25 to 30 | 10 | 1 to 1.11 |
| 2 | Good | 31 to 35 | 11 to 15 | 1.12 to 1.18 |
| 3 | Fair | 36-40(aid not needed) | 16 to 20 | 1.19 to 1.25 |
| 4 | Passable | 41-45(may hang up) | 21 to 25 | 1.26 to 1.34 |
| 5 | Poor | 46-55(must agitate) | 26 to 31 | 1.35 to 1.45 |
| 6 | Very poor | 56 to 65 | 32 to 37 | 1.46 to 1.54 |
| 7 | Very very poor | >66 | >38 | >1.60 |

**Drug content analysis:** Methanol was used to dilute each S-SMEDDS formulation (which is equivalent to 30 mg of oxcarbazepine) and then gently blended. A tabletop centrifuge (Remi Motors, Mumbai, India) was then used to centrifuge the diluted samples for 30 minutes at 10,000 rpm. After passing through a 0.45 µm Millipore filter, the supernatant portion was measured at lambdamax 305 nm using a UV-VIS spectrophotometer.[22]

**Droplet size and zeta potential analysis:** "Using a particle size analyser (Malvern Zetasizer Nano ZS 90), the mean particle size of the prepared S-SMEDDS formulations was examined After being serially diluted 100 times with distilled water, each S-SMEDDS

formulation was shaken for one minute and filtered through a 0.45 µm millipore filter". A particle size analyser was used to evaluate each formulation after it had been serially diluted in a 1:100 (v/v) ratio.[23, 24]

**In vitro dissolution study:** Using USP dissolving apparatus II, Oxcarbazepine was released in vitro from two optimised S-SMEDDS, L-SMEDDS, and pure drug (Oxcarbazepine). Separately, 300 mg of the pre-concentrate and 300 mg of pure oxcarbazepine were put in 900 ml of 0.1N HCl pH 1.2 at 37 ± 0. 5 °C while being rotated at 50 rpm A 0.45 µm filter was used to filter the 1 ml samples that were taken at regular intervals (15, 30, 45, and 60) A UV-visible spectrophotometer was used to evaluate it after it had been suitably diluted with dissolving medium.[25] An equivalent volume of the dissolution media was substituted in order to maintain the volume constant during the test Each sample's release investigations were carried out in triplicate. Every measurement was carried out three times.

**Fourier Transform Infrared spectrophotometer (FTIR) study:** FTIR evaluates the drug's compatibility with the formulation's excipients. In an FTIR spectrophotometer, the FTIR spectra of S-SMEDDS, physical mixture, sodium starch glycol, and plain medication were scanned within the 4000-400 $cm^{-1}$ range.[26]

**Stability assessment:** Optimal S-SMEDDS stability was assessed for six months at 40 ± 2 °C / 75 ± 5% RH and 25 ± 0.5 °C I 60 ± 5% RH. At one, three, and six-month intervals, the samples' "in vitro drug release, particle size were examined and contrasted with L-SMEDDS.[27, 28]

## RESULTS AND DISCUSSION

**Preparation of S-SMEDDS containing oxcarbazepine:** To improve stability and get around the drawbacks of L-SMEDDS, S-SMEDDS containing oxcarbazepine were created in this study. For the production of free flowing S-SMEDDS, sodium starch glycolate was selected as an inert solid adsorbent due to its high adsorption capacity and specific surface area (BET) of 175–225 $m^2/g$. Table 3 lists the quantity of sodium starch glycolate needed to make S-SMEDDS with oxcarbazepine using OSF9 and RSF5 L-SMEDDS.

**Table 3: The ratio of L-SMEDDS to Sodium starch glycolate for the preparation of SSMEDDS containing oxcarbazepine (using OSF9 and RSF5 L-SMEDDS)**

| Formulation code | L-SMEDDS used | The amount of Sodium starch glycolate used for the adsorption of L-SMEDDS (g) |
|---|---|---|
| 9OSF1-S | OSF9 | 0.55 |
| 9OSF2-S | | 0.65 |
| 9OSF3-S | | 0.75 |
| 9OSF4-S | | 0.85 |
| 9OSF5-S | | 0.95 |
| 5RSF1-S | RSF5 | 0.50 |
| 5RSF2-S | | 0.60 |
| 5RSF3-S | | 0.70 |
| 5RSF4-S | | 0.80 |
| 5RSF5-S | | 0.90 |

To create S-SMEDDS containing oxcarbazepine, two L-SMEDDS containing oxcarbazepine made with 10% oleic acid (OSF9) and 50% rice bran oil (RSF5) were adsorbed onto the surface of sodium starch glycolate in varying proportions. Separately, 1 ml of OSF9 L-SMEDDS and RSF5 LSMEDDS were adsorbed onto the sodium starch glycolate surface. For future research, the produced S-SMEDDS containing oxcarbazepine were appropriately stored in a desiccator.

**Evaluation and characterization of S-SMEDDS containing oxcarbazepine**

**Micromeretic properties of S-SMEDDS:** Table 4 shows the results of measurements of several flow characteristics parameters, including Hausner's ratio, Carr's index, and angle of repose of S-SMEDDS containing oxcarbazepine (made using OSF9 and RSF5 LSMEDDS).

**Table 4: The results of micromeretic properties of S-SMEDDS.**

| Formulation code | Angle of repose (°) (mean ± SD) | Carr's index (%) (mean ± SD) | Hausner's Ratio (mean ± SD) | Flow property |
|---|---|---|---|---|
| 9OSF1-S | 41.35 ± 0.25 | 14.41 ± 0.16 | 1.53 ± 0.31 | Very poor |
| 9OSF2-S | 36.12 ± 0.15 | 28.36 ± 0.16 | 1.42 ± 0.23 | Poor |
| 9OSF3-S | 25.22 ± 0.21 | 15.66 ± 0.18 | 1.21 ± 0.16 | Good |
| 9OSF4-S | 19.02 ± 0.59 | 11.32 ± 0.15 | 1.12 ± 0.14 | Excellent |
| 9OSF5-S | 43.65 ± 0.25 | 33.22 ± 0.14 | 1.56 ± 0.31 | Very poor |
| 5RSF1-S | 41.81 ± 0.16 | 27.41 ± 0.23 | 1.34 ± 0.18 | Poor |

| | | | | |
|---|---|---|---|---|
| 5RSF2-S | 26.61 ± 0.17 | 15.80 ± 0.15 | 1.21 ± 0.24 | Good |
| 5RSF3-S | 20.32 ± 0.19 | 13.91 ± 0.25 | 1.14 ± 0.11 | Excellent |
| 5RSF4-S | 25.22 ± 0.21 | 15.66 ± 0.18 | 1.21 ± 0.16 | Good |
| 5RSF5-S | 43.65 ± 0.25 | 33.22 ± 0.14 | 1.56 ± 0.31 | Very poor |

#Data expressed as mean ± SD (n = 3)

**Drug content analysis:** Table 5 displays the drug content (%) of the manufactured S-SMEDDS containing oxcarbazepine (90SF4-S and 5RSF3-S S-SMEDDS). 90SF4-S and 5RSF3-S S-SMEDDS were discovered to have drug contents of 97.11 ± 0.45% and 95.76 ± 0.34%, respectively. In contrast to 5RSF3-S S-SMEDDS, 90SF4-S S-SMEDDS had the highest drug content, which may be because the drug (in this case, oxcarbazepine) was more soluble.

**Particle size and zeta potential determination:** Table 5 displays the zeta potential and particle size data of the prepared S-SMEDDS containing oxcarbazepine (90SF4-S and 5RSF3-S S-SMEDDS). The nanometre range of particle size was indicated by the average particle sizes of 90SF4-S S-SMEDDS and 5RSF3-S S-SMEDDS, which were 78.13 nm and 164.24 nm, respectively. According to the particle size analysis, the average particle size of 5RSF3-S SSMEDDS was much larger than that of 90SF4-S SSMEDDS. For 90SF4-S S-SMEDDS, the zeta potential value was determined to be - 21.5 mv, but for 5RSF3-S S-SMEDDS, it was - 13.9 mv. Therefore, the zeta potential of S- SMEDDS containing oxcarbazepine (90SF4-S and 5RSF3-S S-SMEDDS) was found to confer.

**Table 5: Results of drug content (%), particle size (nm) and zeta potential of two S-SMEDDS containing oxcarbazepine (9OSF4-S and 5RSF3-S S-SMEDDS).**

| Formulation code | Drug content (%) (mean±SD) | Average particle size (nm) | Zeta potential (mV) |
|---|---|---|---|
| 9OSF4-S | 97.11 ± 0.45% | 78.13 | - 21.5 |
| 5RSF3-S | 95.76 ± 0.34% | 164.24 | - 13.9 |

#Data expressed as mean ± SD (n = 3)

**In vitro dissolution:** Figure 1 lists the cumulative percentage drug release for oxcarbazepine (pure drug), S-SMEDDS (90SF4-S and 5RSF3-S), and L-SMEDDS (OSF9 and RSF5).

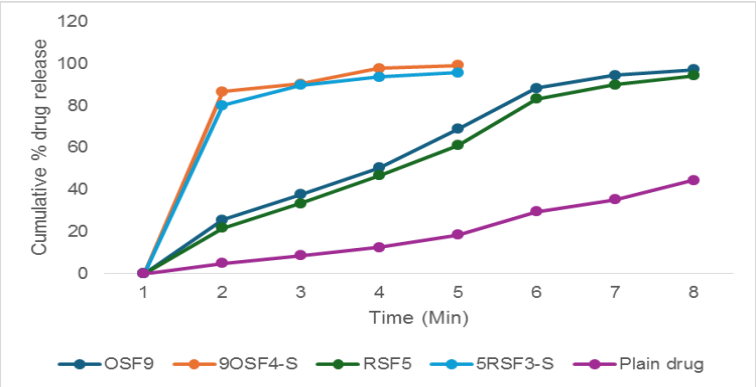


**Fig. 1: Comparison of in vitro drug release profile of OSF9, 9OSF4-S, RSF5 and 5RSF3-S with pure oxcarbazepine (mean ± SD (n = 3)).**

**Analysis of in vitro drug release kinetics and mechanism:** The kinetics of S-SMEDDS containing oxcarbazepine in 0.lN HCl pH 1.2 using a variety of mathematical model techniques, including zero-order, first-order, Higuchi, Hixson-Crowell, and Korsmeyer-Peppas. To evaluate these models' precision and capacity for prediction, their $R^2$ values were computed.

**Table 6: Results of curve fitting of in vitro drug release data of S-SMEDDS containing oxcarbazepine (9OSF4-S and 5RSF3-S) in 0.1N HCl pH 1.2**

| Code | $R^2$ values | | | | | Release exponent (n) |
|---|---|---|---|---|---|---|
| | Zero order model | First order model | Higuchi model | Hixson-Crowell model | Korsemeyer- Peppas model | |
| 9OSF4-S | 0.6664 | 0.9122 | 0.8968 | 0.9248 | 0.9904 | 0.148 |
| 5RSF3-S | 0.6288 | 0.9246 | 0.8740 | 0.8184 | 0.9748 | 0.122 |

#Data expressed as mean ± SD (n = 3)

The greatest $R^2$ value (i.e., $R^2$ = 0.9904 for 90SF4-S S-SMEDDS and $R^2$ = 0.9748 for 5RSF3-S S-SMEDDS) across the drug releasing period led to the Korsemeyer-Peppas model being offered as the best fit model based on the aforementioned respective R2 values of the various models. This could be explained by oxcarbazepine diffusion, suggesting that oxcarbazepine release is controlled by diffusion.

**FTIR analysis:** Figure 2 displays the FTIR spectra of three different substances: pure oxcarbazepine, sodium starch glycolate, a physical mixing of the medication (oxcarbazepine) and sodium starch glycolate, and S-SMEDDS that contain oxcarbazepine, 9OSF4-S, and 5RSF3-S S-SMEDDS.

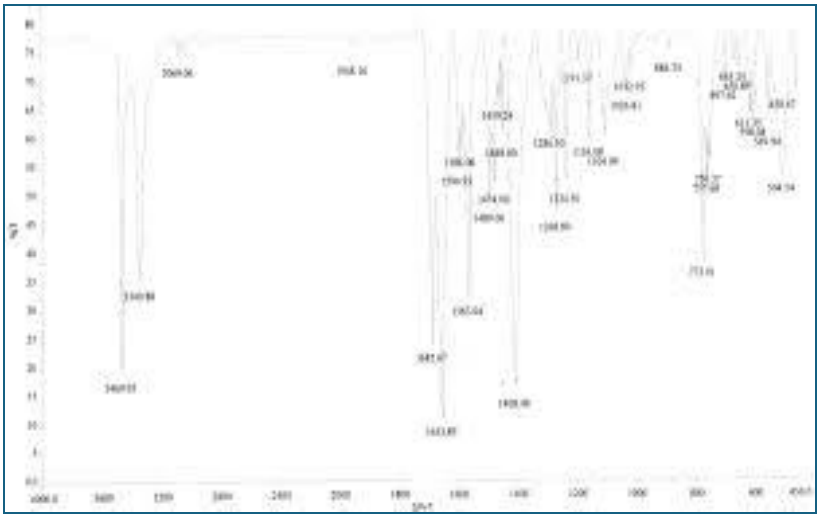

**Fig. 2: FTIR spectra of 9OSF4-S S-SMEDDS and 5RSF3-S S-SMEDDS.**

**Table 7: FTIR spectra of two S-SMEDDS containing oxcarbazepine (9OSF4-S and 5RSF3-S S-SMEDDS) and oxcarbazepine (pure drug)**

| Assignment | 9OSF4-S | 5RSF3-S |
|---|---|---|
| C-H Stretching (Aromatic) | 3436.17 cm-1 | 3437.34 cm-1 |
| $CH_3$(C-H stretching) | 2869.58 cm-1 | 2857.22 cm-1 |
| C=O stretching | 1734.13 cm-1 | 1733.58 cm-1 |
| C=N Stretching | 1645.65 cm-1 | 1645.98 cm-1 |
| C-H Bending | 1456.73 cm-1 | 1457.02 cm-1 |
| C=S Stretching | 1349.70 cm-1 | 1349.58 cm-1 |

**Stability assessment of L-SMEDDS containing oxcarbazepine and S-SMEDDS containing oxcarbazepine:** The results of S-SMEDDS (90SF4-S and 5RSF3-S) at both real and accelerated stability conditions were shown in tables 8 to 11. These results included appearance, colour, drug content, and in vitro drug release.

**Table 8: Characterization tests results initially and after real stability studies of 9OSF4-S.**

| Parameter | Initial Data | Real time stability condition | | |
|---|---|---|---|---|
| | | 1M | 3M | 6M |
| Appearance | Dry powder | no change | no change | no change |
| Colour | White | White | White | White |
| Assay (%) | 98.50 ± 0.01 | 98.15 ± 0.13 | 97.62 ± 0.19 | 96.54±0.09 |
| % drug release | 99.98 ± 0.01 | 99.75 ± 0.04 | 99.62 ± 0.04 | 99.31 ± 0.15 |

#Data expressed as mean ± SD (n = 3)

**Table 9: Characterization tests results initially and after Accelerated time stability studies of 9OSF4-S.**

| Parameter | Initial Data | Real time stability condition | | |
|---|---|---|---|---|
| | | 1M | 3M | 6M |
| Appearance | Dry powder | no change | no change | no change |
| Colour | White | White | White | White |
| Assay (%) | 98.50 ± 0.01 | 95.29 ± 0.33 | 89.17 ± 0.15 | 84.46 ± 0.6 |
| % drug release | 99.98 ± 0.01 | 98.31 ± 0.27 | 98.12 ± 0.13 | 97.34 ± 0.3 |

#Data expressed as mean ± SD (n = 3)

**Table 10: Characterization tests results initially and after real stability studies of 5RSF3-S.**

| Parameter | Initial Data | Real time stability condition | | |
|---|---|---|---|---|
| | | 1M | 3M | 6M |
| Appearance | Dry powder | no change | no change | no change |
| Colour | White | White | White | White |
| Assay (%) | 92.42 ± 0.60 | 92.05 ± 0.08 | 91.28 ± 0.25 | 90.21 ± 0.25 |
| % drug release | 97.42 ± 0.62 | 96.30 ± 0.26 | 95.13 ± 0.12 | 94.40 ± 0.36 |

#Data expressed as mean ± SD (n = 3)

**Table 11: Characterization tests results initially and after accelerated time stability studies of 5RSF3-S.**

| Parameter | Initial Data | Real time stability condition | | |
|---|---|---|---|---|
| | | 1M | 3M | 6M |
| Appearance | Dry powder | no change | no change | no change |
| Colour | White | White | White | White |
| Assay (%) | 92.42±0.60 | 90.22±0.1 | 88.28±0.25 | 86.14±0.14 |
| % drug release | 97.42±0.62 | 95.58±0.78 | 94.08±0.76 | 92.12±0.71 |

#Data expressed as mean ± SD (n = 3)

## CONCLUSION

For the majority of medications, which have poor gastrointestinal absorption, improving solubility and bioavailability has been a significant challenge. Plasma concentration is more variable and less well-controlled when oral bioavailability is low. The SMEDDS system has gained widespread acceptance because of its excellent performance in improving permeability and solubility; it also reduces the extensive first pass effect by lowering gut wall metabolism. A new invention called S-SMEDDS was created to address the problems and limitations of liquid or semisolid medication delivery systems. Because of its great stability, simplicity of handling, portability, compact size, and high repeatability, it is more widely used and more successful than liquid self-emulsifying formulation. Thus, it can be concluded that by S-SMEDDS (9OSF4-S and 5RSF3-S), the stability was improved as well as they (9OSF4-S and 5RSF3-S) can facilitate the effective delivery of poorly soluble drugs with better therapeutic advantage.

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