# Development and characterization of Mecitentan loaded self-micro emulsifying drug delivery system

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**KEYWORDS**

Bioavailability, self-micro emulsifying drug delivery systems, solubility, Mecitentan.

**ABSTRACT:**

**Introduction:**

Mecitentan is a selective endothelin receptor antagonist used in the treatment of pulmonary arterial hypertension (PAH). However, its poor solubility significantly limits its bioavailability. To overcome this challenge and enhance the drug's therapeutic efficacy, a novel self-micro emulsifying drug delivery system (SMEDDS) was explored. SMEDDS are isotropic mixtures of oil, surfactants, and cosurfactants that form fine oil-in-water emulsions upon contact with gastrointestinal fluid, which are absorbed into the lymphatic pathways, bypassing the first-pass hepatic effect.

**Objectives:**

The objective of this study was to develop and evaluate a SMEDDS formulation for Mecitentan that addresses its solubility issues and enhances its bioavailability.

**Methods:**

In the formulation, oleic acid, Labrafil M 2125 CS, PEG-400, and Labrasol ALF were selected as the mixed oil, surfactant, and cosurfactant, respectively. The formulation was assessed for droplet size, polydispersity index (PDI), zeta potential, and drug release rate. The resulting SMEDDS was characterized in terms of these parameters to determine its potential in improving the release and bioavailability of Mecitentan.

**Results:**

The droplet size of the SMEDDS formulation ranged from 37.8 to 176 nm, with a PDI value of 0.271, indicating a narrow size distribution. The zeta potential was measured at -1.6 mV, and the formulation exhibited an 81.50% drug release, suggesting significant enhancement in the release profile of Mecitentan.

**Conclusions:**

The self-micro emulsifying drug delivery system (SMEDDS) was found to be effective in improving the drug release and bioavailability of Mecitentan, addressing its solubility limitations and offering a promising strategy for enhancing its therapeutic efficacy in the treatment of pulmonary arterial hypertension.

## 1. Introduction

Mecitentan is a potent, selective endothelin receptor antagonist employed in the treatment of pulmonary arterial hypertension (PAH). Despite its therapeutic potential, Mecitentan is classified as a Biopharmaceutics Classification System (BCS) class II drug, characterized by low solubility and high permeability (Khadka et al., 2015). This poor aqueous solubility often leads to suboptimal bioavailability, presenting a significant challenge in the clinical efficacy of the drug. Addressing these limitations requires innovative drug delivery approaches to enhance its solubility and subsequent absorption in the gastrointestinal tract. A promising strategy to overcome the solubility and bioavailability issues of poorly soluble drugs like Mecitentan is the development of self-micro emulsifying drug delivery systems (SMEDDs) (Bhalani et al., 2022*)*. SMEDDs are isotropic mixtures comprising oils, surfactants, and cosurfactants that can spontaneously form fine oil-in-water emulsions when in contact with gastrointestinal fluids. This spontaneous emulsification process results in the production of micro-sized droplets, which significantly increase the surface area for drug dissolution, thus enhancing the drug's solubility and absorption (Kyatanwar et al., 2010). The primary advantage of SMEDDs lies in their ability to bypass the first-pass hepatic metabolism. When these emulsions are absorbed via the lymphatic pathway, the drug directly enters the systemic circulation, thereby avoiding extensive metabolism in the liver. This mechanism is particularly beneficial for drugs like Mecitentan, where first-pass metabolism significantly reduces the bioavailable dose. Consequently, SMEDDs can substantially improve the pharmacokinetic profile of the drug, leading to enhanced therapeutic efficacy (Meirinho et al., 2022). In the formulation of SMEDDs, the selection of appropriate components is crucial. Oleic acid was chosen as the oil phase due to its excellent solubilizing capacity for lipophilic drugs and its ability to promote lymphatic transport. Labrafil M 2125 CS, a well-known surfactant, was selected for its high solubilization capacity and compatibility with a wide range of drugs. Polyethylene glycol (PEG-400) and Labrasol ALF were employed as cosurfactants to further reduce the interfacial tension and stabilize the microemulsion, ensuring the formation of droplets in the nanometre range (Laddha et al., 2014). Characterization of the formulated SMEDDs involves evaluating key parameters such as droplet size, polydispersity index (PDI), zeta potential, and drug release profile. The droplet size is a critical determinant of the drug's dissolution rate and absorption; smaller droplets provide a larger surface area for drug release. In this study, the resulting droplet sizes ranged from 37.8 to 176 nm, with a PDI value of 0.271, indicating a narrow size distribution and uniformity of the emulsion (Ansari et al., 2023). The zeta potential, measured at -1.6 mV, reflects the stability of the emulsion, with values close to zero suggesting good physical stability. Moreover, the SMEDDs formulation demonstrated an impressive 81.50% drug release, indicating its potential to significantly enhance Mecitentan's bioavailability. This study aims to explore the development and characterization of a Mecitentan-loaded SMEDDs to address the solubility and bioavailability challenges of the drug. By leveraging the unique properties of SMEDDs, this research seeks to provide a viable and effective delivery system that enhances the therapeutic efficacy of Mecitentan in the treatment of pulmonary arterial hypertension. The findings from this study could offer valuable insights into the formulation strategies for other poorly soluble drugs, paving the way for improved drug delivery and patient outcomes (Kang et al., 2004).

## 2. Objectives

The main objective of this study is to improve solubility and bioavailability of Mecitentan by developing self-micro emulsifying drug delivery system.

## 3. Materials and Methods

Mecitentan was purchased from Sigma-Aldrich, India. Oleic acid and Labrafil M 2125 CS were obtained from Genuine Chemical Co., Mumbai, India. PEG-400 was sourced from Loba Chemi Pvt. Ltd., Mumbai, India. Labrasol ALF was acquired from SDFCL Chem. Ltd., Bangalore, India. All other reagents and chemicals used were of analytical grade.

### 3.1 Pre-formulation studies:

#### 3.1.1 Determination of melting point

The melting point of Mecitentan was determined using the capillary tube method. In this method, one end of a capillary tube is sealed, and a small amount of the drug sample is placed inside the tube. The temperature at which the drug melts is then recorded.

#### 3.1.2 FTIR

The drug was mixed with potassium bromide separately and triturated in glass mortar pestle. The triturated mixture was compressed and processed further for FTIR spectra by scanning in the range of 4000-400cm-1 using Infrared spectrophotometer (Shimadzu, IR affinity-1). Since hydrogen or covalent bonds are related to FTIR, the spectra offer comprehensive details about the chemical compounds' structural configurations. FTIR is used to identify the drug's functional identity and to find out how it interacts with excipients (Mirza et al., 2011)

#### 3.1.3 Differential Scanning Calorimetry

The differential scanning calorimetry of the drug was performed by differential scanning calorimeter (Waters TA instruments).

### 3.2 Quantification of Mecitentan:

#### 3.2.1 Preparation of standard stock solution

A 5% w/v sodium lauryl sulphate (SLS) solution was prepared. Then, 10 mg of Mecitentan was weighed and transferred into a beaker containing the 5% w/v SLS solution. The mixture was sonicated for 15 minutes, and the final volume was adjusted to achieve a concentration of 100 µg/mL, resulting in the standard stock solution. This solution was scanned in the UV range of 200–400 nm using the solvent as a blank (Alizadeh et al., 2018)

#### 3.2.2 Determination of calibration curve of Mecitentan

The calibration curve was established with concentrations of 3, 6, 9, 12, 15, and 18 µg/mL. Absorbance was measured at 260 nm against the 5% w/v SLS solution (Khoshneviszadeh et al., 2015)

### 3.3 Formulation of SMEDDs:

#### 3.3.1 Solubility studies

The solubility of the drug was tested in various solvents, including oils, surfactants, and cosurfactants, using the shake flask method followed by sonication. Specifically, 5 mL of each solvent was placed in separate vials, and an excess amount of the drug was added. The mixtures were stirred with a cyclomixer for 10 minutes and then sonicated for 12 hours. After sonication, the supernatant was filtered, and the solubility was measured using UV-Visible spectroscopy.

Additionally, the mixtures were observed for any phase separation to assess their stability (Gunnam et al., 2018)

### 3.3.2 Construction of ternary phase diagrams

Constructing ternary phase diagrams is a preliminary step before starting the formulation. It helps identify the optimal emulsification region for combinations of oil, surfactant, and cosurfactant (Ahmad et al., 2013). The water titration method involves titrating homogeneous mixtures of oil, surfactant, and cosurfactant with water at room temperature. Mixtures of oil, surfactant, and cosurfactant were prepared in ratios ranging from 9:1 to 1:9 and placed in screw-cap glass tubes. These mixtures were vortexed and then slowly titrated with aliquots of water (Chouhan et al., 2016)

### 3.3.3 Method of preparation of SMEDDs

Oleic acid was taken in 25 ml of the beaker and put on a magnetic stirrer and half of the drug was added and stirred till the drug was dissolved. Labrasol ALF as surfactant and PEG 400 as co-surfactant were properly mixed in another beaker. And remaining quantity of the drug was added and stirred till the mixture became clear. Then surfactant and co-surfactant were mixed with oil phase slowly on a magnetic stirrer at 500 rpm. The stirring was continued for 30 minutes to get a clear oily phase (Mukeri et al., 2023). The liquid SMEDDs were converted into solid SMEDDs using appropriate adsorbent.

### 3.4 Characterization of SMEDDs:

### 3.4.1 Thermodynamic stability test

The thermodynamic stability of the SMEDDs was evaluated through the following tests:

a. Heating-Cooling Cycle: The formulation was subjected to different temperatures, including refrigeration (4°C), room temperature, and a stability chamber set at 45°C. Each temperature cycle lasted 48 hours, after which the formulations were observed for any phase separation (Bajaj et al., 2012).
b. Centrifugation: The formulations were centrifuged at 3500 rpm for 30 minutes and subsequently examined for phase separation (Nasr et al., 2016).
c. Freeze-Thaw Cycle: The formulations were exposed to freezing conditions at -21°C and thawing conditions at +25°C. Each cycle lasted 48 hours, and the formulations were inspected for phase separation (Yang et al., 2020).

### 3.4.2 Phase separation study

The SMEDDS formulations were diluted with 50 mL of distilled water and stored at 25°C for 24 hours. The samples were then visually inspected for phase separation and drug precipitation (Wu et al., 2015).

### 3.4.3 Emulsification study

The emulsification efficiency was tested using a USP Type II dissolution apparatus. One millilitre of each formulation was added to 100 mL of distilled water maintained at 37°C, with the paddle rotating at 50 rpm to provide gentle agitation (Chintalapudi et al., 2015).

### 3.3.4 Determination of % transmittance

A 5 mL sample of the SMEDDS formulation was prepared, and the percentage transmittance was measured using a UV spectrophotometer at 638 nm, with distilled water serving as the blank (Jaiswal et al., 2014).

### 3.4.5 *In Vitro* dissolution test

The *in vitro* dissolution study was conducted using a USP Type II apparatus. Five millilitres of the SMEDDS formulation were introduced into the apparatus, with water used as the dissolution medium. The temperature was maintained at 37°C ± 0.5, and the paddle speed was set to 50 rpm. At predetermined intervals, 5 mL samples were withdrawn and replaced with an equal volume of fresh water. The absorbance of the samples was measured using a UV spectrophotometer at 260 nm (Raju et al., 2011).

### 3.4.6 Drug content

To determine the drug content, 5 mL of the SMEDDS formulation was prepared, and 1.06 mL of this solution was dissolved in ethanol. The drug content in the ethanol extract was then analysed using a UV spectrophotometer (Saggar et al., 2019).

### 3.4.7 Droplet size and zeta potential analysis

The droplet size and zeta potential of the SMEDDS formulation were measured using a zeta potential analyser. A polydispersity index (PDI) value greater than 0.7 indicates poor stability of the formulation (Kim et al., 2023).

### 3.4.8 Micromeritics properties of solid SMEDDS

Micromeritics evaluation including angle of repose, bulk density, tapped density, hausner's ratio and carr's index was performed for SMEDDs of Mecitentan.

### 3.4.9 XRD Characterization of pure drug Mecitentan and SMEDDS of Mecitentan

The X-ray diffraction (X-RD) of pure drug of Mecitentan and SMEDDS of Mecitentan were obtained using X-RD instrument XPERT-PRO in Central University of Gujarat (Central instrumentation facility). The scanning speed was 2°/min between 0 and 80.

### 3.4.10 Stability studies of Mecitentan SMEDDs

The stability study of Mecitentan SMEDDs were performed in stability chambers for period of 3 months as per ICH guidelines. At periodic time interval visual examination, % transmittance and% drug content were measured as an indicator of stable characteristic.

## 4. Result and discussion

### 4.1 Pre formulation studies

### 4.1.1 Melting point

A capillary tube approach was utilized in order to ascertain the melting point of the Mecitentan sample that was taken for testing. The results demonstrated a melting transition at a temperature of 136 ± 0.3°C, which is indicative of the compound's excellent purity and crystalline form.

### 4.1.2 FTIR

The drug was mixed with potassium bromide separately and triturated in glass mortar pestle. The triturated mixture was compressed and processed further for FTIR spectra by scanning in the range of 4000-400cm$^{-1}$ using Infrared spectrophotometer (Shimadzu, IR affinity-1). Since hydrogen or covalent bonds are related to FTIR, the spectra offer comprehensive details about the chemical compounds' structural configurations. FTIR is used to identify the drug's functional identity and to find out how it interacts with excipients.

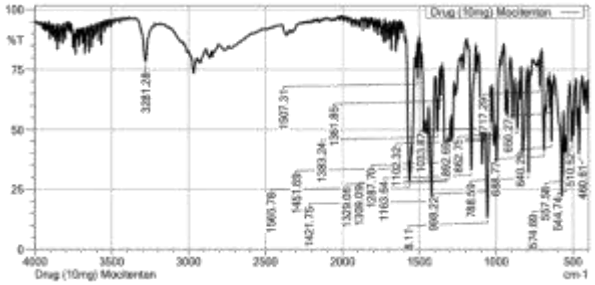



**Figure 1: FTIR Spectra of Mecitentan**

**Table 1: FTIR range of functional group in Mecitentan**

| Sr. No. | Functional Group | Range |
|---|---|---|
| 1. | -C-H Alkynyl (Stretch) | 3281.28 |
| 2. | -C=O Aldehyde (Stretch) | 1565.78 |
| 3. | -C=C Alkenyl (Stretch) | 1451.69 |

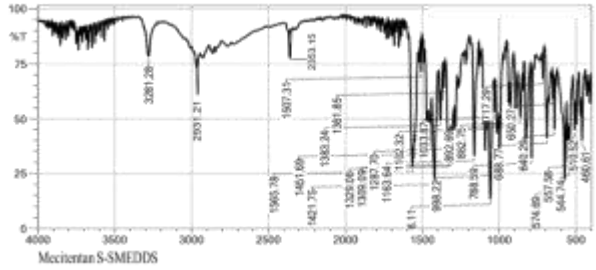
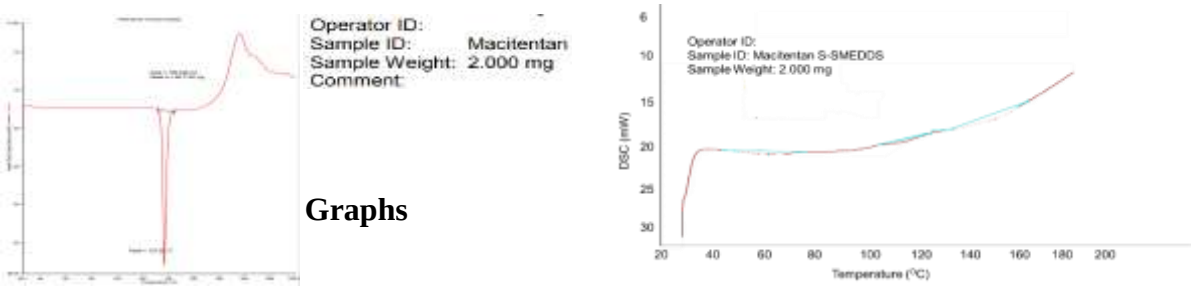



**Figure 2: FTIR Spectra of Mecitentan SMEDDS**

**Table 2: FTIR range of functional group in Mecitentan**

| Sr no. | Function group | Range |
|---|---|---|
| 1 | -C-H Alkynyl (Stretch) | 3281.28 |
| 2 | -O-H (Stretch) | 2931.21 |
| 3 | -N-O (Stretch) | 1565.78 |

### 4.1.3 Differential Scanning Calorimetry (DSC)




### 4.2 Quantification of Mecitentan:

### 4.2.1 Preparation of calibration curve

The UV spectrum of Mecitentan shows maximum wavelength at 262 nm. The absorbance was measured and presented in Table 1. The graph was plotted between and concentration and absorbance (figure 2).

**Table 3: Absorbance of Mecitentan in Methanol**

| Sr No. | Concentration (µg/mL) | Absorbance (mean±SD) |
|---|---|---|
| 1. | 0 | 0±0 |
| 2. | 4 | 0.103±0.098 |
| 3. | 8 | 0.201±0.201 |
| 4. | 12 | 0.311±0.309 |
| 5. | 16 | 0.388±0.380 |
| 6. | 20 | 0.456±0.452 |
| 7. | 24 | 0.565±0.562 |
| 8. | 28 | 0.679±0.675 |
| 9. | 32 | 0.724±0.721 |
| 10. | 40 | 0.934±0.931 |

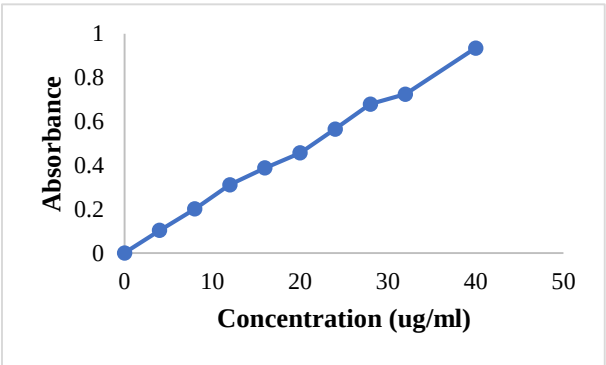



**Figure 4: Standard curve of Mecitentan in Methanol.**

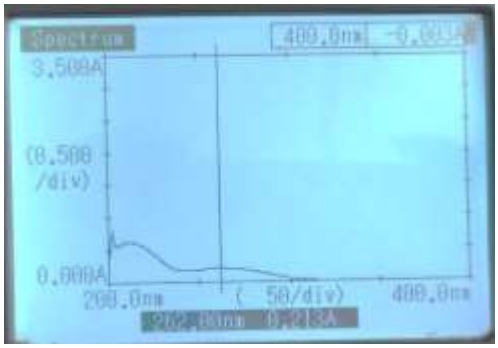



**Figure 5: UV Spectra of Mecitentan**

### 4.3 Formulation of SMEDDs

#### 4.3.1 Solubility studies

The solubility of Mecitentan was superior in Capmul PG8NF compared to other oils such as coconut oil, olive oil, soybean oil, Captex 355, Captex 200, LL WL 1349, and Labrafil M 2125 CS. Consequently, Capmul PG8NF was chosen as the oil for subsequent investigation. Mecitentan exhibited the greatest solubility in PEG 400 and Tween 80. Tween 80 was chosen as the surfactant for further investigation, taking into account cost and availability. The solubility of Macitentan in PEG 400 exceeded that of other co-surfactants. Consequently, it was chosen as a co-surfactant for subsequent investigation. Based on solubility, Capmul PG8NF, Tween 80, and PEG 400 were chosen as the oil, surfactant, and co-surfactant, respectively, for the formulation of a microemulsion containing Mecitentan.

**Table 4: Solubility of drug in oil,surfactant and co-surfcantant**

| **Surfactants** | **mg/ml** |
|---|---|
| Cremophor® RH 40 | 15.44±1.39 |
| Tween 80 | 22.45±2.73 |
| Tween 20 | 12.37±0.88 |
| Span 80 | 15.86±1.32 |
| Labrasol | 18.74±1.68 |
| **Co-surfactant** | **mg/ml** |
| PEG 400 | 11.76±0.93 |
| Transcutol P | 8.75±0.64 |
| **Oils** | **mg/ml** |
| Oleic Acid | 8.13±1.33 |
| Coconut oil | 1.44±0.03 |
| Olive oil | 6.44±0.39 |
| Soyabean oil | 0.86±0.05 |
| Captex 355 | 4.89±0.22 |
| Captex 200 | 5.24±0.37 |
| LL WL 1349 | 9.82±0.68 |
| Capmul PG8NF | 14.83±1.54 |

#### 4.3.2 Ternary phase diagrams

The existence of microemulsion regions was determined by using pseudo-ternary phase diagrams. Microemulsions were diluted under agitated conditions using the water titration method. The mixture of 2 oils with surfactant/co-surfactant mixture at certain weight ratios were diluted with water in a

drop-wise manner. Surfactant and co-surfactant (Smix) in each group were mixed in different weight ratios (1:1, 1:2, 2:1, 1:3). For each phase diagram, oil and specific *S*mix ratios were mixed well in different volume ratios ranging from 1:9 to 9:1. Pseudo-ternary phase diagrams were developed using aqueous titration method.

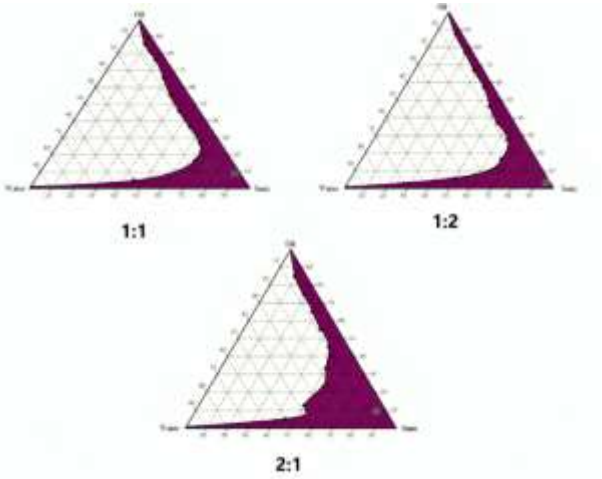



**Figure 6: Ternary Phase diagram for different ratio of Smix**

### 4.4 Characterization of SMEDDs

#### 4.4.1 Thermodynamic stability

The proposed formulation of SMEDDs was found to be stable in different conditions of temperature. This shows that SMEDDs can have desirable stability at different ambience.

#### 4.4.2 Phase separation study

No separation was found upon addition of water which confirms the possibility of formation of stable microemulsion in GIT upon ingestion of SMEDDs by oral route.

#### 4.4.3 Emulsification study

The emulsion was formed by addition of small quantity of SMEDDs into distilled water. There were no sign of turbidity or precipitation in media which confirms stable emulsion.

#### 4.4.4 % transmittance

The % transmittance was found 99.39% confirming existence of thermodynamically stable monophasic system.

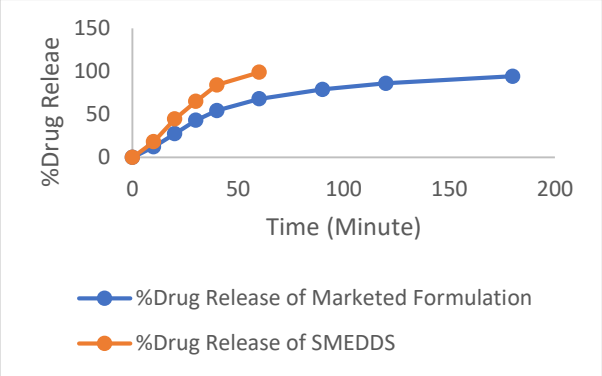
#### 4.4.5 *In vitro* dissolution study

The *in vitro* drug release of the pure drug and SMEDDS was done in phosphate buffer of pH 6.8 by using inverted test tube method by keeping the drug and formulation in dialysis membrane. The study was performed for 180 minutes. The results showed that SMEDDs showed faster release as compared to marketed formulation.

**Table 5: Absorbance of Pure drug and SMEDDs**

| Time (Minute) | % of Drug release in Phosphate Buffer pH 6.8 | |
|---|---|---|
| | Marketed | SMEDDS |

| | Formulation | |
|---|---|---|
| **0** | 0 | 0 |
| **10** | 12.36 | 18.25 |
| **20** | 27.46 | 44.72 |
| **30** | 43.12 | 65.15 |




| | | |
|---|---|---|
| **40** | 54.54 | 84.36 |
| **60** | 68.15 | 99.01 |
| **90** | 79.15 | |
| **120** | 86.17 | |
| **180** | 94.35 | |

**Figure 7: Comparison of *in vitro* % drug Release**

### 4.4.6 Drug content

The drug content of SMEDDs was found to be in the range of 98.70–99.9%. This shows the chemical stability of drug in proposed formulation.

### 4.4.7 Droplet size and zeta potential

The particle size of SMEDDS of Mecitentan was measured with the help of Malvern Zeta sizer after filtering the formulation through membrane filter of 0.22µm.

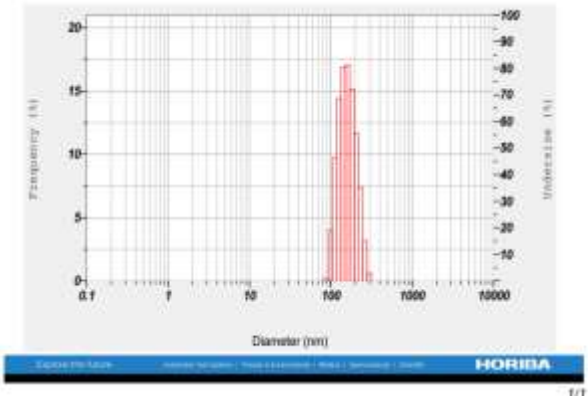



**Figure 8: Globule size of SMEDDs of Mecitentan**

### 4.4.8 Micromeritics Properties of solid SMEDDS

As per the result Angle of repose is poor, Carr's index is good and Hausner's ratio is giving good flow.

**Table 6: Micromeritics properties of SMEDDs of Mecitentan**

| Test | Result |
|---|---|
| Angle of Repose | 50.31° |
| Bulk Density (gm/ml) | 0.6 |
| Tapped Density (gm/ml) | 0.5 |
| Hausner's Ratio | 1.3 |
| Carr's Index | 15% |

### 4.4.9 XRD Characterization of pure drug Mecitentan and SMEDDS of Mecitentan

XRD of Mecitentan shows intense drug peak, which is due to the crystalline nature of drug. The characteristic XRD peaks of drug was disappeared in SMEDDs which proved conversion of crystalline drug into amorphous form.

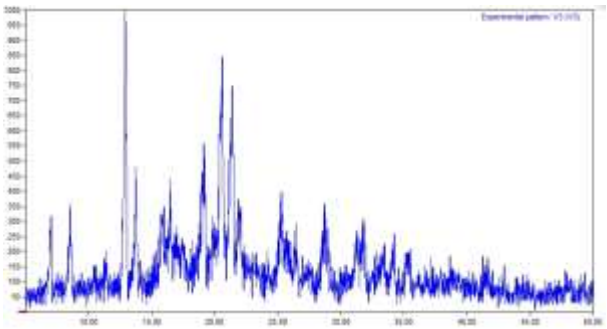


**Figure 9: XRD of Mecitentan**

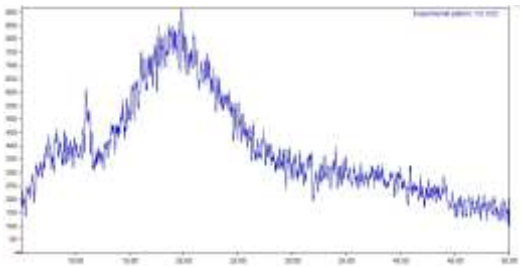


**Figure 10: XRD of Mecitentan SMEDDs**

### 4.4.10 Stability Studies of Mecitentan SMEDDs

The results of stability studies depicted that the solid-SMEDDS formulation remained clear even after 3 months at temperature 25°C ± 2°C and 40°C ± 0.1°C. There was no phase separation in both the systems at each time. Formulations were found to be consistent with respect to their drug content, *in vitro* drug release, phase separation and transparency during the stability study.

**Table 7: Visual examination, % Transmittance, %Drug Content after 1 month**

| Stability study after 1 month | |
|---|---|
| **Parameter** | **Storage condition: 40 ±2°C / RH: 75 ± 5%** |
| Visual examination | No colour change<br>No precipitation<br>No phase separation |
| % Transmittance | 99 ± 0.35% |
| % drug content | 98.34 ± 0.48 |

Table 8: Visual examination, % transmittance, % drug Content after 3 months

| **Stability study after 3 months** | |
|---|---|
| **Parameter** | **Storage condition: 25 ±2°C / RH: 60 ± 5%** |
| Visual examination | No colour change<br>No precipitation<br>No phase separation |
| % transmittance | 98 ± 0.34% |
| % drug content | 98.21 ± 0.59 |

## 5. Conclusion

Through comprehensive characterization and evaluation tests, it has been determined that the development and characterization of the Mecitentan-loaded self-micro emulsifying drug delivery system (SMEDDS) significantly enhances the drug release profile of Mecitentan. The SMEDDS formulation has demonstrated superior solubilization and absorption properties, which are crucial for the bioavailability of poorly water-soluble drugs like Mecitentan. The detailed analysis of various parameters, including droplet size, zeta potential, and dissolution studies, indicates that the SMEDDS provides a stable and efficient delivery mechanism. The improved drug release can be attributed to the formation of fine oil-in-water microemulsions in the gastrointestinal tract, facilitating faster and more complete absorption of Mecitentan. Therefore, the SMEDDS approach is validated as an effective strategy for enhancing the therapeutic efficacy of Mecitentan.

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