**Supplementary Tables**

**Table S1: Quality target product profile (QTPP) postulated for SNEDDS of Bedaquiline**

|  |  |  |
| --- | --- | --- |
| **QTPP elements** | **Target** | **Justification** |
| **Dosage form** | SNEDDS | Selection of lipid-based solid self-nano emulsifying system helps in the oral bioavailability enhancement of poorly bioavailable drug, Bedaquiline. |
| **Dosage type** | Sustain release | Faster onset of action leading to enhanced therapeutic benefits. |
| **Dosage strength** | 5 mg | Unit dose of Bedaquiline incorporated in a single formulation of SNEDDS |
| **Route of administration** | Oral | Recommended route for delivery of Bedaquiline |
| **Stability** | 6 months of Accelerated and long-term stability studies | To maintain therapeutic potential of the drug during storage period |
| **Container closure system** | Airtight glass bottles | To protect against the degradation of the drug and lipids in the presence of atmospheric air. |
| **Alternative methods of administration** | Salt, polymorphs, solid dispersions, nano crystals, co-crystals, inclusion complexes | These systems can only improve the dissolution rate (but not the extent) of which may eventually lead only to enhancement in rate of oral adsorption. |
| **Contraindications** | None | None |

**Abbreviations:** QTPP, quality target product profile; SNEDDS, self-nano emulsifying drug delivery system

**Table S2: Critical quality attributes (CQAs) for SNEDDS of Bedaquiline and their justifications.**

|  |  |  |  |
| --- | --- | --- | --- |
| **CQAs** | **Target** | **Is this a CQA** | **Justification** |
| Physical attributes  colour | Acceptable to patient | No | Color, odor and appearance were not considered as critical, as these are not directly linked to patient efficacy and safety. |
| Odour and appearance | Acceptable to patient | No |
| Assay and content uniformity | 100% | No | SNEDDS being the homogenous dispersions containing drug solubilized in the blend of lipidic excipients, these variables were regarded as less critical. |
| Drug release | 100% | Yes | Drug release rate is important for fast absorption of the drug in blood; hence was regarded as highly critical. |
| Liquefaction time | Low | yes\* | Lower value of liquefaction time is important for faster drug release from the dosage form. Thus, it was considered as critical. |
| Emulsification time | Low | yes\* | Lower values of emulsification time help in ease of formation of nanoemulsion; hence was taken up as highly critical. |
| Globule size | <100nm | yes\* | Smaller droplet size allows easy penetration through GI epithelial lining and paracellular pathways; hence was regarded as highly critical. |
| Mean dissolution time | Low | yes\* | It is an indicator of faster and complete drug release solubilization of drug in the dissolution medium, thus taken up as highly critical. |
| PDI | Low | yes\* | Highly important for achieving the therapeutically effectiveness he hence considered as highly critical. |

\*CQAs considered as critical

**Abbreviations:** CQAs, critical quality attributes; SNEDDS, self-nano emulsifying drug delivery system, PDI, polydispersity index

**Table S3: Protocol of stability study**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Name of Product: BDQ-F-SNEDDS** | | | **Purpose of Study : New Formulation** | |
| **Batch Size : 100 ml** | | | **Batch No. : BDSND22** | |
| **Sr. No.** | **Storage Condition** | **Storage**  **Period** | **Testing Frequency (Monthly)** | **Tests** |
| 1. | 40 ± 2 ºC & 75 ± 5 % | 6 Months | 0  3  6 | Following test to be performed at all stations of both Accelerated and Long Term Studies.  Physical Appearance  Phase Separation  Caking  Size (nm)  PDI %  Entrapment Efficiency |
| 2. | 25 ± 2 ºC & 60 ± 5 % | Upto Shelf Life | 0  3  6  9  12  18  24 |

**Abbreviations:** BDQ-F-SNEDDS, Bedaquiline-fumarate-self-nano emulsifying drug delivery system, PDI, polydispersity index

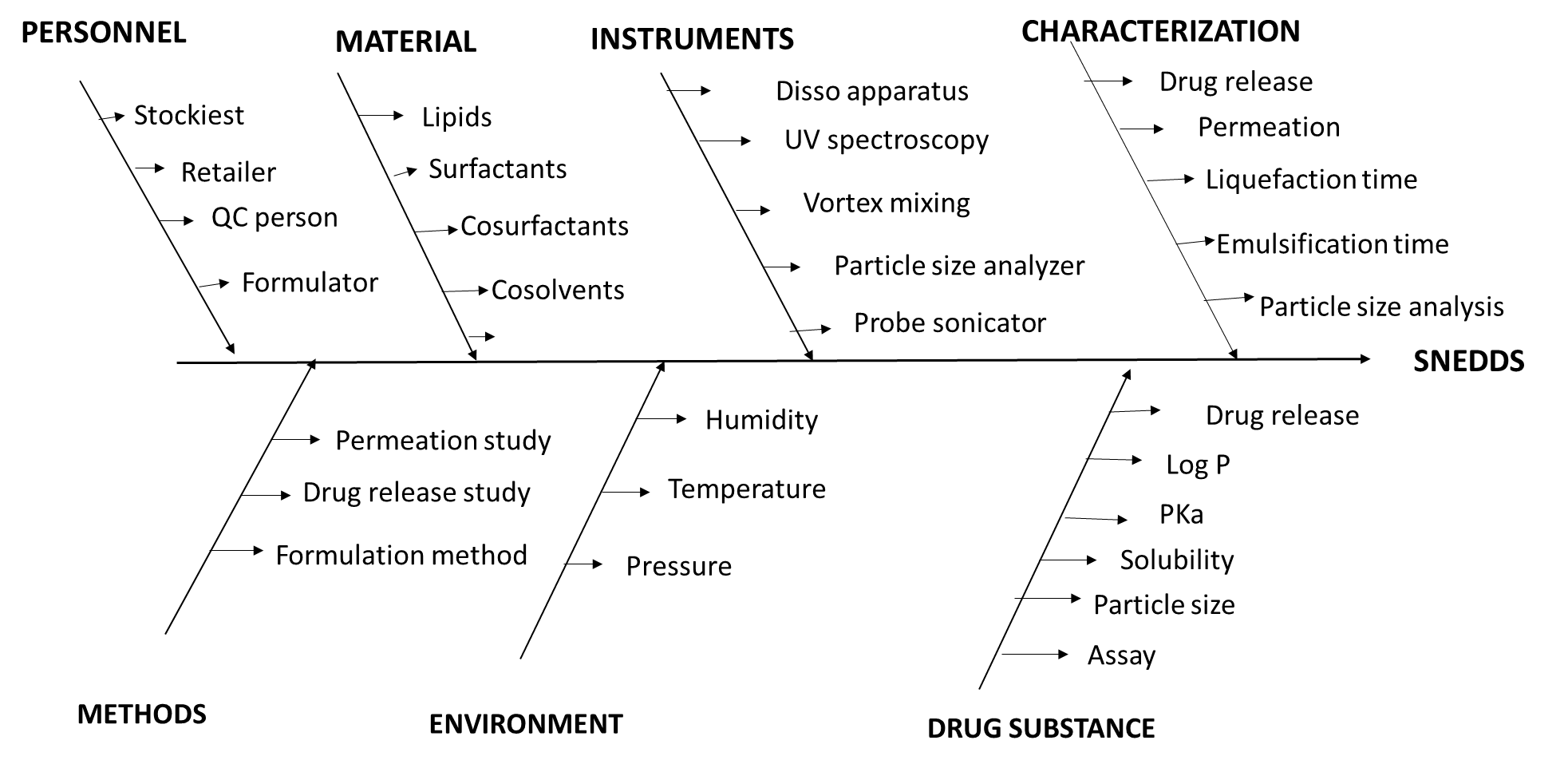
**Table S4: Responses to selected factors**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Run** | **Factor 1**  **A: Oil**  **(%)** | **Factor 2**  **B: Smix**  **(%)** | **Factor 3**  **C: Sonication time (sec)** | **Response 1**  **droplet size**  **(nm)** | **Response 2 PDI** | **Response 3**  **Transmittance**  **(%)** |
| 1 | 30 | 50 | 30 | 125.9 | 0.21 | 93.6 |
| 2 | 10 | 50 | 60 | 94.3 | 0.168 | 98.5 |
| 3 | 20 | 60 | 60 | 95.2 | 0.237 | 97.8 |
| 4 | 20 | 50 | 45 | 89.8 | 0.21 | 96.9 |
| 5 | 20 | 60 | 30 | 83.1 | 0.19 | 97.2 |
| 6 | 10 | 50 | 30 | 86.7 | 0.176 | 97.8 |
| 7 | 10 | 60 | 45 | 78.4 | 0.16 | 98.9 |
| 8 | 30 | 60 | 45 | 119.1 | 0.236 | 94.4 |
| 9 | 10 | 40 | 45 | 90.25 | 0.11 | 97.3 |
| 10 | 20 | 40 | 30 | 97.5 | 0.153 | 95.6 |
| 11 | 30 | 40 | 45 | 130.5 | 0.325 | 93.1 |
| 12 | 30 | 50 | 60 | 135.7 | 0.449 | 93.9 |
| 13 | 20 | 40 | 60 | 105.6 | 0.331 | 96.4 |
| 14 | 20 | 50 | 45 | 88.5 | 0.2 | 96.8 |

**Abbreviations:** PDI, polydispersity index

**Supplementary Figures**

**Figure S1: Ishikawa fishbone diagram illustrating a cause-and-effect relationship among the formulation and process variables for the formulation of SNEDDS.**



**Figure S2: Pseudoternary phase diagram showing different ratios of Smix 1:0, 1:1, 1:2, 2:1, 3:1, 4:1, 5:1**

Shape, polygon

Description automatically generated

**Figure S3: Linear correlation plot between observed and predicted values of droplet size, PDI and Transmittance and their corresponding residual plots.**

