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# QBD-based systematic development of BosentanSNEDDS: Formulation, characterization and pharmacokinetic assessment

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ABSTRACT

The aim of this study was to develop self-nanoemulsifying drug delivery system (SNEDDS) of bosentan using quality by design (QBD) approach with better bioavailability. The major component of the formulation *vis-à-vis* lipid (Capmul MCM), surfactant (LABRASOL) and co-surfactant (PEG 600) were selected on the basis of saturation solubility. Mixture of LABRASOL and PEG 600 in the ratio of 1:1 showed better nano emulsifying region as depicted by pseudo ternary phase diagram. The optimum mixture of Capmul MCM, LABRASOL and PEG 600 were selected by using response surface method (RSM) with central composite design (CCD). Pharmacokinetic study was conducted to determine various critical parameters. The optimized formulation showed 98.5% drug release in 15 min, globule size of 62.5 nm, emulsification time of 12 s and PDI of 0.146. TEM study revealed the drug entrapment within the oil globules of nano size range. Pharmacokinetic study of optimized formulation indicated faster dissolution and absorption which was evidenced from significantly higher $C_{max}$, larger AUC and lower $T_{max}$ than pure drug bosentan. Thus the present study confirms potential of SNEDDS in enhancing the oral bioavailability of bosentan.

## 1. Introduction

Self-emulsifying drug delivery systems (SEDDS) are isotropic mixture of oils and surfactants and co-solvent or co-surfactant which undergoes self-emulsification in gastrointestinal tract (GIT) [1]. The peristaltic movement of stomach and intestine render the agitation required for self-emulsification [2,3]. These formulations when exposed to GIT fluid form oil in water nanoemulsion [4]. The process of self-emulsification was spontaneous as the free energy required is either low positive or negative [5]. The presence of endogenous materials such as bile salts, phospholipids and cholesterol in the intestinal lumen instigate an alteration in lipid composition and results in the formation micelles, vesicles, and liquid crystalline phases leading to improvement in solubilisation capacity and subsequent absorption of drug [6,7]. The solubilisation and absorption of drug depend on the lipid composition [8]. The nanoemulsions can be defined as thermodynamically stable, transparent (or translucent) dispersions having the globule size in the range of 10–100 nm [9]. The major advantage of nanoemulsion include very low interfacial tension and large oil in water (o/w) interfacial area. Nanoemulsion has exhibited enormous possibilities in nanoformulation of various inorganic substances [10].

Drugs with high lipophillicity (log P > 2), low melting point, low bioavailability and poor solubility in water are suitable for SEDDS [11,12]. The mechanism of action of bosentan is dual endothelin receptor antagonist which acts by blocking the action of endothelin molecules. It has particular action on narrowing of the blood vessels and lead to high blood pressure. Hence Bosentan is used for the treatment of pulmonary artery hypertension (PAH) [13]. The absolute bioavailability of bosentan is approximately 50% and food does not affect absorption. Terminal elimination half-life is about 5 h in healthy adult subjects. The marketed product of bosentan are available in the dose of 62.5 mg and 125 mg. Bosentan has high lipophillicity (log P = 4.94), low melting point (1040C) and is categorized under BCS II drug. Based on the above criteria bosentan qualifies for selection as drug for SNEDDS [14].

A step wise approach to formulation development of SEDDS has to be followed when more than two excipients are used. The ternary phase diagram was used for optimizing the ratio of surfactant and co-surfactant in order to achieve large area of micro or nano emulsifying region [15,16]. HLB coupled with response surface methodology (RSM) approach was adopted for optimization of SEDDS [17]. The pharmaceutical Quality by Design (QbD) can be defined as a systematic development of dosage form that start with predefined objectives considering product and process control based on quality risk management [18].

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**Table 1**
Quality target product profile (QTPP) for SNEDDS of bosentan.

| QTPP elements | Target | Justification |
|---|---|---|
| Dosage form | SNEDDS | lipid-based self-nano emulsifying system helps in bioavailability enhancement of bosentan |
| Dosage type | Rapid release | Faster onset of action leading to better therapeutic benefits |
| Dosage strength | 62.5 mg | Unit dose of bosentan |
| Route of administration | Oral | Recommended route for delivery of bosentan to reduce the hypertension like conditions |
| Pharmacokinetics | Higher Cmax, lower Tmax and higher AUC | Higher drug levels in systemic circulation promote better therapeutic action |
| Stability | 6 months of Accelerated stability testing | To study maintenance of therapeutic efficacy of the drug during storage period |

**Table 2**
Critical quality attributes (CQAs) for SNEDDS of BOSENTAN and their justifications.

| Quality attributes of the drug product | Target | Is this a CQA? | Justification |
|---|---|---|---|
| Physical attributes | Acceptable to patients | No | Colour, odour and appearance were not considered as critical science not effect efficacy of dosage form |
| Assay and content uniformity | 100% | No | SNEDDS being the homogenous dispersions containing drug solubilised in the blend of lipidic excipients, these variables were regarded as less critical. |
| Drug release (Q15) | 100% | Yes | Drug release rate is important for fast absorption of the drug in blood; hence was regarded as highly critical. |
| Emulsification time | Low | Yes | Lower values of emulsification time helps in ease of formation of nanoemulsion; hence was taken up as highly critical. |
| Globule size | < 100 nm | Yes | Smaller globule size allows easy penetration through GI epithelial lining and paracellular pathways; hence was regarded as highly critical. |
| PDI | Low | Yes | Highly important for achieving the therapeutically effectiveness hence considered as highly critical |

**Table 3**
Design matrix for factor screening as per Teguchi design with seven factors at two levels along with actual and coded values.

| RUN | A | B | C | D | E | F | G |
|---|---|---|---|---|---|---|---|
| 1 | 2 | 1 | 2 | 1 | 2 | 1 | 2 |
| 2 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 3 | 1 | 2 | 2 | 2 | 2 | 1 | 1 |
| 4 | 2 | 2 | 1 | 1 | 2 | 2 | 1 |
| 5 | 2 | 1 | 2 | 2 | 1 | 2 | 1 |
| 6 | 1 | 1 | 1 | 2 | 2 | 2 | 2 |
| 7 | 1 | 2 | 2 | 1 | 1 | 2 | 2 |
| 8 | 2 | 2 | 1 | 2 | 1 | 1 | 2 |
| FACTOR | CODE | | LOW LEVEL (1) | | | HIGH LEVEL(2) | |
| CAPMUL MCM | A | | 300 mg | | | 400 mg | |
| LABRASOL | B | | 150 mg | | | 200 mg | |
| PEG 600 | C | | 150 mg | | | 200 mg | |
| STIRRING TIME | D | | 60 min | | | 120 min | |
| STIRRING SPEED | E | | 25 rpm | | | 50 rpm | |
| STIRRING TYPE | F | | magnetic | | | mechanical | |
| TEMPERATURE | G | | 298 K | | | 313 K | |

QbD methodology involves defining the quality target product profile (QTPP) and critical quality attributes (CQAs) based on the dosage form requirement. Then different critical material attributes (CMAs) and critical process parameters (CPPs) are identified, screened which corresponds to different CQAs. After which the product is optimized using design of experiments (DoE) through response surface methodology (RSM) using proper model [19]. Design of experiments (DOE) is a statistical tool to determine the relationship between influential factors and CQAs which then lead to manage process inputs in order to optimize the output [20]. Hence the objective of the present research work is to prepare self-emulsifying DDS for the selected drug bosentan by systematic approach using QbD based central composite design.

## 2. Materials

Bosentan was provided as ex-gratis by MSN Pvt Ltd, Hyderabad, India. Labrafac PG (propylene glycol dicaprylocaprate), Labrafac WL1349 (medium chain triglycerides), Labrafil M2125CS (linoleoylmacrogolglycerides), Peceol (glycerylmonoleate), Labrasol (caprylocaproylmacrogolglycerides), Plurololique (Polyglyceryl-6dioleate) and Plurol CC497 (polyglyceryl-3-dioleate) were kindly supplied as gift samples from M/s Gattefosse Pvt Ltd. India. Cremophor EL (polyoxyethylene castor oil) and Triacetin (1,2,3-triacetoxypropane) was kindly provided ex-gratis by M/s BASF GmbH (Minden, Germany). Capmul MCM (Propylene glycol monocaprylate), Captex 355 (Glycerol Tricaprylate/Caprate) and Captex 200 (propylene glycol dicaprylate/dicaprate) were kindly provided as gift samples from M/s Abitec Pvt Ltd, USA. All other chemicals and solventwere of analytical grade or highest quality and were used as such as obtained.

## 3. Methods

### 3.1. Defining QTPP and CQAs

The QTPP elements such as dosage form, dosage type, dosage strength, route of administration, pharmacokinetic parameter stability were set-up considering the need of enhancing the oral bioavailability, pharmacological activity and stability. The quality characteristics of the drug product of bosentan along with justification have been discussed in Table 1. Various quality attributes (QAs) such as physical attributes, drug content, emulsification time, globule size, drug release and PDI were identified. These attributes were assessed on the basis of biopharmaceutical performance and were assigned as critical quality attributes. The justifications for selection of CQAs affecting the SNEDDS formulations were depicted in Table 2. The drug released in 15 min (Q15), globule size in nm, Polydispersity index (PDI) and emulsification time (ET) in sec were identified as the potential CQAs [21].

### 3.2. Screening of excipients on the basis of solubility study

Solubility study was conducted for the selection of excipient such as oil, surfactant and co-surfactant. Excess amount of drug was added separately in different oil, surfactant and co-surfactant in glass vial and kept on a mechanical shaker for 48 h at room temperature. Further it was left standing at room temperature for 24hand then mixed in cyclomixer for 10 minfollowed by centrifuged at 2800 rpm for 5 min. The