QbD-based Systematic Development of Self-Nanoemulsifying Systems for Improved Oral Bioavailability of Olmesartan

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ABSTRACT SUMMARY
The current studies entail development of novel self-nanoemulsifying drug delivery systems (SNEDDS) of olmesartan, employing rational QbD-based approach for enhancing its oral bioavailability. The above aim may be achieved by improving its aqueous solubility and intestinal permeability. In vitro drug release, ex vivo permeation, in situ perfusion studies and in vivo pharmacokinetic studies in rats showed marked improvement in biopharmaceutical performance of the developed formulations. Cytotoxicity studies using MTT assay and histopatological studies in intestinal cells revealed lack of cytotoxicity and thereby safety and efficacy of the developed formulations.

INTRODUCTION
Olmesartan is a potent AT II receptor antagonist that has been clinically approved used for the treatment and management of hypertension. It exhibits relatively low oral bioavailability, i.e., 28% owing to extensive hepatic first-pass metabolism and P-gp efflux.

Self-nanoemulsifying drug delivery systems (SNEDDS) are the recent technological innovations, extensively explored for their stellar potential to enhance drug dissolution and permeability, bypassing hepatic first-pass effect, reduction of P-gp efflux and intra/inter-subject variability in gastrointestinal absorption.

This calls for the systematic development of lipid-based self-nanoemulsifying formulations employing rational QbD approach, thus furnishing improved understanding of the product and processes with minimal experimentation to yield the best solutions.

EXPERIMENTAL METHODS
Adopting a QbD approach, the quality target product profile (QTPP) and critical quality attributes (CQAs) for development of SNEDDS were initially defined. Ishikawa fish-bone diagram was plotted for establishing cause-effect relationship, followed by risk analysis using risk estimation matrix and Taguchi screening design were employed for identification of high risk factors.

Preformulation studies were carried out employing equilibrium solubility and pseudoternary phase titration studies in various lipids, surfactants, and/or co-surfactants. Based on these studies, the CMAs critically affecting the performance of SNEDDS were identified. Systematic optimization of SNEDDS was carried out by Design of Experiment (DoE) employing D-optimal mixture design, evaluating their CQAs like globule size, emulsification efficiency, drug release in 15 min and percent permeated in 45 min.

Data analysis was carried out by apt mathematical modeling followed by response surface analysis, while “trading-off” CQAs to embark upon the optimized formulation. Cationic SNEDDS were prepared by adding charge inducer in apt concentration to the optimized SNEDDS. In situ perfusion studies of the optimized formulations were performed in rats to compute the permeability and absorptivity parameters. Pharmacokinetic studies were conducted to evaluate the in vivo performance of olmesartan SNEDDS and C-SNEDDS vis-à-vis the marketed formulation in unisex Wistar rats. Cytotoxicity studies on the optimized formulation were carried out by histopatological examination in rat intestine.
under light microscopy and MTT assay on Caco-2 cell line model.

RESULTS AND DISCUSSION

Based on the preformulation studies (i.e., equilibrium solubility studies and pseudoternary phase diagram plots), followed by risk assessment and factor screening studies, oleic acid (i.e., lipid), Tween 80 (i.e., surfactant) and Transcutol HP (i.e., cosolvent) were selected as the CMAs for SNEDDS, and oleyl amine was used as charge inducer for the C-SNEDDS.

The optimized formulation was earmarked in the design space region, as depicted in Figure 1, exhibiting globule size <100 nm, excellent emulsification (<1 minute), drug release (>90% release within 15 min) and enhanced intestinal permeability (>85% permeation in 45 min).

![Figure 1: Design space depicting the optimized SNEDDS of olmesartan](image)

In vivo pharmacokinetic studies revealed remarkably superior oral bioavailability enhancement by optimized C-SNEDDS (i.e., 2.9-fold), SNEDDS (i.e., 2.2-fold) vis-à-vis the marketed brand (WinBp-20™) (Figure 2).

Evaluation of the cytotoxicity by MTT assay indicated insignificant difference in percent cell viability between C-SNEDDS and SNEDDS. The histopathological studies also corroborated the absence of cellular cytotoxicity of the test formulations on rat intestinal cells (i.e., Caco-2 cell lines).

CONCLUSIONS

The studies, in a nutshell, successfully vouch the utility of QbD approach in development of the optimized C-SNEDDS and SNEDDS for enhancing the oral bioavailability potential of poorly water soluble drugs like olmesartan undergoing extensive hepatic first-pass effect and P-gp efflux, while retaining their biological safety at the same time.

![Figure 2: Rat plasma level time profile of optimized SNEDDS, C-SNEDD vis-à-vis the marketed brand (WinBp-20™)](image)

REFERENCES