QbD-Enabled Development of Self-Nanoemulsifying Drug Delivery Systems of Olmesartan with Improved Bioavailability Potential

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INTRODUCTION

The current studies entail systematic development, optimization and evaluation (in vitro, in vivo and in vivo) of self-nanoemulsifying drug delivery systems (SNEDDS) of a BCS class II drug, olmesartan, exhibiting low oral bioavailability (26%) owing to high hepatic first-pass effect and poor aqueous solubility, employing rational QbD-based approach. The parentemic QTPP and CQAs were formulated. Ishikawa Fishbone diagrams were constructed for establishment of cause-effect relationship (C-E) followed by risk analysis using risk estimation matrix (REM). Initially, the analytical QTPP approach was employed for reverse phase HPLC method development on C18 column using acetonitrile-water (70:30, v/v) as mobile phase with photodiode array detector. The method was validated for linearity, sensitivity, accuracy, precision and stability. The method was successfully employed for the initial in vitro studies comprising of permeation and absorption parameters for the pure drug as evident from the in situ SPIP and in vivo pharmacodynamic studies in anesthetized Wistar rats. In vitro-pharmacodynamic studies in hypertensive rats also indicated marked reduction in mean arterial pressure by SNEDDS vis-

DEFINING QTPP, CQAs & CMAs

SNEDDS >> MKT >> Pure drug

EXPERIMENTAL

Ishikawa Fishbone Diagram

RESULTS & DISCUSSION

In Vivo Drug Release Studies

3D-Response Surfaces Plots for Various CQAs

In Vivo Cytotoxicity Studies in Caco-2 Cell Lines by MTT Assay

In Vivo Uptake of SNEDDS in Caco-2 Cells

Level C correlations between various absorption and dissolution parameters (a) Tfrac and Tzero, Cmax and MD

CONCLUSIONS

- Liquid SNEDDS >> MKT >> Pure drug
- Comparison of the observed response parameters vis-a-vis those predicted using RSM, confirmed excellent degree of pragmatic ability of the experimental design (O-O), with overall mean S.D of bias as 0.155 ± 3.548
- Highly statistically significance of Level A, B, C and D IVIVC corroborates that bioavailability enhancement is a direct function of the in vitro drug dissolution
- In vitro cytotoxicity and uptake studies of the SNEDDS corroborated lack of toxicity and efficient cellular uptake as evident from the confocal microscopic images
- Stability studies (accelerated) for 4 months exhibited nearly analogous drug release profiles
- The foregoing illustrate that the SNEDDS formulation follows linear drug independence

REFERENCES