Abstract

Investigations of in vitro/in vivo correlations (IVIVC) between in vitro dissolution and in vivo bioavailability are increasingly becoming an integral part of Sustained release (SR) product development to minimize unnecessary human testing and optimization of formulation which is certainly a time consuming and expensive process. In the present study an in vitro/in vivo correlation was established for slow, moderate and fast release SR formulations of Enalapril Maleate 20 mg tablets exhibiting different in vitro release rate characteristics using Enalapril Maleate Immediate Release formulation (ENVAS 10 mg) as a reference formulation.

Enalapril Maleate SR tablets of different release rates were prepared using wet granulation method. In vitro release rate data of all formulations under study were obtained using the States Pharmacopeia (USP) apparatus I. The drug release mechanism of all formulations were assessed using different kinetics models as Zero order Kinetics, First order kinetics, Hixon-Crowell model, Korsmeyer-Peppas models applied to interpret release order and mechanism of drug release from matrix systems.

The in vivo bioavailability and pharmacokinetics of these formulations were performed with a randomized, four-treatment, single dose, parallel pharmacokinetics study on fast-, moderate and slow-released Enalapril Maleate sustained release 20 mg tablet and Envas 10 mg tablet (2 tablets) of Cadila Pharmaceuticals Ltd., India as reference formulation in 24 healthy, adult, male, human subjects under fasting and fed condition allocated by randomization sheet. The plasma samples were analysed by Reverse Phase UPLC coupled with mass detector.

In Vitro release profiles of slow, fast and medium sustained released Enalapril maleate Tablets were analyzed by Weibull model. A unit impulse response (UIR) was assessed using the Immediate Release (IR) formulation as a reference. The deconvolution of the in vivo concentration time data was performed using the UIR to estimate an in vivo drug release profile.

IVIVC Level A and Level C were tried to attempt. Basic Level A IVIVC was tried to developed by drawing a plot between the percentage drug absorbed of a formulation and its
percentage drug dissolved followed by the regression analysis of each curve to evaluate the strength of correlation determining whether the curve is linear or non-linear.

Multiple Linear level C IVIVC models were developed using dissolution data at 0.25, 0.50, 1.0, 1.5, 2.0 and 4.0 h. Cmax and AUC were correlated by using level C model at above different time points.

The deconvolution-based level A models for all SR formulations were curvilinear. However, a unique IVIVC Level A model applicable to all SR formulations could not be developed using the deconvolution approach, hence time scaled approach was used to correlate. A time-scaling technique was used to consider the rate difference between in vitro dissolution and in vivo absorption in the process of IVIVC. The time scaling common to all formulation was not possible as that depend of the rate.

The linear regression analysis resulted in a significant correlation ($r^2>0.9$) for all three formulations. The results suggest Multiple Linear level C developed for Enalapril Maleate SR formulations.