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IN VITRO TO *IN VIVO* PROFILING: AN EASY IDEA FOR BIOWAIVER STUDY

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Abstract: The aim of this article was to assess and apply the *in vitro* to *in vivo* profiling (IVIVP), a new biowaiver approach, in designing a product with specific release pattern. The IVIVP was established by plotting the observed and predicted plasma drug concentrations. For IVIVP, convolution approach was employed to estimate plasma drug concentrations from *in vitro* dissolution profiles. The IVIVP for T1S exhibited a good correlation coefficient (R^2 = 0.963) followed by the T2 (R^2 = 0.682), T3 (R^2 = 0.665), T1 (R^2 = 0.616), and Mepressor® (R^2 = 0.345). Establishing an IVIVP, based on the convolution approach, can be more useful and practicable in the biowaiver studies, rather than present not useful practice of IVIVC estimated *via* deconvolution approach. This paper also elaborates that there is good correlation between the *in vitro* and *in vivo* profiles of the developed metoprolol tartrate formulations, particularly for T1S.

Key words: metoprolol tartrate, eudragit® FS, convolution, IVIVP

Biowaiver study is, actually, the comparative dissolution analysis approximating the *in vivo* absorption of a drug product. *In vitro-in vivo* correlation (IVIVC, estimated *via* deconvolution approach), a predictive mathematical model, is an vital tool that is used in developing and evaluating the drug products. The IVIVC represents an association between the *in vitro* dissolution profiles and *in vivo* performance of drug. The *in vivo* performance is computed from plasma drug concentration-time data. Then, a plot is drawn between these *in vitro* and *in vivo* profiles to get a straight line (1, 2).

Based on FDA guidelines, level A IVIVC is expected for modified release formulations of BCS class I drugs (like metoprolol tartrate) where dissolution is the rate limiting step. The main advantage of IVIVC is the prediction capability of *in vivo* performance of an alternative formulation of predefined nature from specific dissolution characteristics and IVIVC function (1, 3).

No literature is existing which has employed IVIVC (straight line equation) to approximate the relevant *in vivo* profiles, since it is mathematical impossibility. Thus, it should be observed that establishing an IVIVC cannot be employed for the development and evaluation of drug products aside from its complex procedure (1-3).

The requirement for the development and assessment of drug product should be the approximation of plasma drug profiles, thus one should possibly make use of the suggested terminology of *in vitro* to *in vivo* profiling (IVIVP), rather than IVIVC.

This paper represents a fraction, IVIVP, of our project that was planned for the development and characterization (*in vitro* as well as *in vivo*) of tabletted microparticles of eudragit® FS loaded with metoprolol tartrate followed by the development of IVIVP.

MATERIALS AND METHODS

Materials

Metoprolol tartrate (Novartis Pharmaceuticals, Karachi, Pakistan), eudragit® FS (Rohm Pharma, Germany) as well as analytical grade liquid paraffin, methanol, and petroleum ether (Merck, Germany)

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were used in this study. Mepressor® 200 mg SR tablets (Batch No. 457X, Novartis Pharma, Pakistan) was employed as reference product.

Tabletted microparticles of eudragit® FS loaded with metoprolol tartrate

The compendially acceptable tablet formulations [T1, T2 and T3 which represent the drug to polymer ratio (w/w) of 1 : 1, 1 : 1.5 and 1 : 2] were fabricated compressing the eudragit® FS microparticles loaded with metoprolol tartrate. There was 200 mg metoprolol in each tablet (4). Sequential pH change dissolution approach and pharmacokinetic studies involving high-performance liquid chromatography, as detailed previously (4, 5), were used for testing various drug products.

Computation of absorption data and IVIVC development

The IVIVP was established by plotting the observed and predicted plasma drug concentrations along x- and y-axis, respectively, and then, the regression analysis of each curve was done to assess the strength of correlation in order to determine whether the curve is linear or non-linear. The closer is the value of determination coefficient to 1, the stronger is the correlation and linear is the curve (6). The convolution of *in vitro* dissolution data is accomplished to predict the plasma drug concentration from dissolution data using equation:

$$C(t) = \int_0^t C_\delta(t-u)X'_{vitro}(u)du$$

where, C_δ = unit impulse response which is determined from the intravenous bolus dose results or standard oral solution profiles, u = variable of integration, and X'_{vitro} = drug input rate *in vitro* from oral drug products.

For this prediction, pharmacokinetic information (like bioavailability factor, volume of distribution, elimination rate constant and half life) of drug taken from the literature is used in the conversion of *in vitro* drug release (%) data into discrete values of

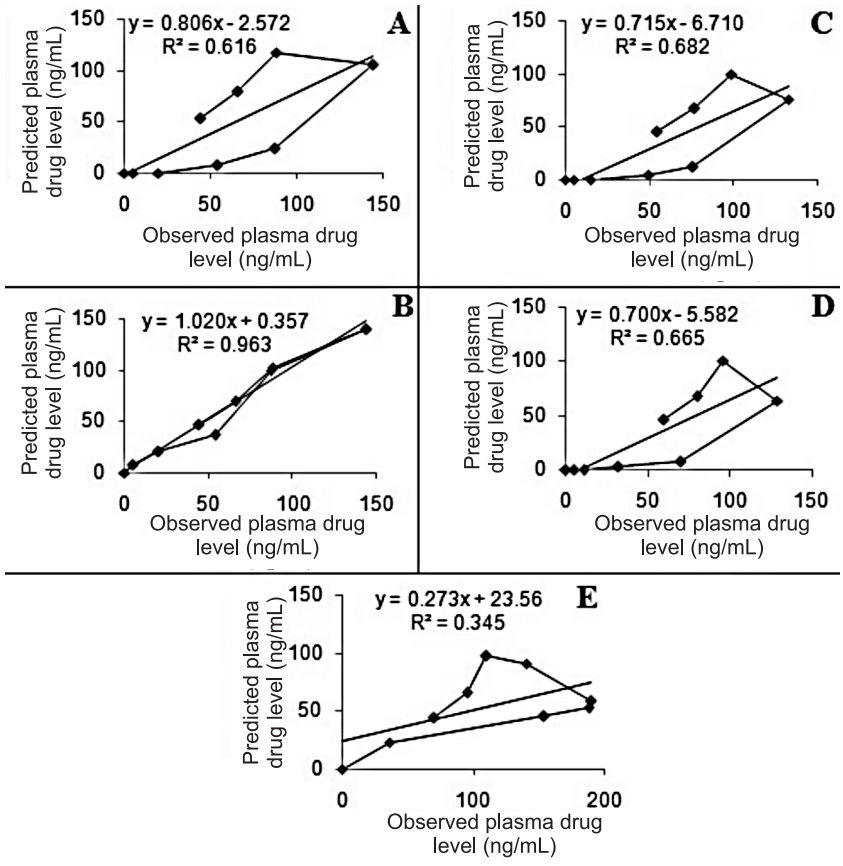

Figure 1. Level A IVIVP for formulations T1 (**A**), T1S (**B**), T2 (**C**), T3 (**D**) and Mepressor® (**E**)

drug released during each sampling interval followed by the calculation of bioavailable amounts of drug in each interval. The calculated data are used in determining the decrease of plasma drug concentrations during each interval followed by the addition of all drug concentrations at each time point, and then, the calculation of the predicted plasma drug level at each time point (6).

Statistical analysis

The statistical analysis of results was carried out by one way analysis of variance using software, SPSS version 13.0 (IBM, USA). The level of significance was set at 0.05.

RESULTS AND DISCUSSION

This article describes the assessment and application of IVIVP in designing a product with specific release pattern. Since the approximation of plasma drug concentration data is needed from dissolution profiles for the fabrication of drug products, such data can be acquired by amalgamating the *in vitro* dissolution profiles with the pharmacokinetic parameters of the drug. This amalgamating and independent step is termed as the convolution approach (6). In this context, present article involves the description and application of this easy and realistic approach in approximating the plasma drug concentration-time profiles on the basis of convolution methodology.

The IVIVP for T1S exhibited a good correlation coefficient ($R^2 = 0.963$) followed by the T2 ($R^2 = 0.682$), T3 ($R^2 = 0.665$), T1 ($R^2 = 0.616$), and Mepressor® ($R^2 = 0.345$) (Fig. 1). Significantly high ($p < 0.05$) values for correlation coefficient for T1S suggests that the nature of used dissolution medium closely resembles the human physiology conditions. Similar results were observed when IVIVC for T1S was developed using deconvolution approach where the highest value of R^2 i.e., 0.973 was found for T1S (6, 7). The employed dissolution medium was 0.1 M HCl, pH 6.8 phosphate buffer, and 0.1% sodium dodecyl sulfate as an attempt to simulate the biochemistry of gastrointestinal tract environment. In addition, the results also support the hypothesis for employing eudragit® FS in formulation development for metoprolol which is efficiently absorbed in the intestine compared to that in the stomach. The use of surfactant perhaps enhances the dissolution rate resulting in a decrease in dissimilarity between the dissolution conditions of *in vitro* and *in vivo* environment (8).

In brief, convolution approach is successfully applied for the development of an IVIVP a targetted release formulation as a model system. This approach exhibits the benefit of treating the data typically available from a formulation development program to be used for developing an IVIVP.

CONCLUSION

Establishing an IVIVP, based on the convolution approach, can be more useful and practicable in the biowaiver studies, rather than present not useful practice of IVIVC estimated *via* deconvolution approach. This paper also elaborates that there is good correlation between the *in vitro* and *in vivo* profiles of the developed metoprolol tartrate formulations, particularly for T1S.

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