A DIFFERENTIAL EQUATIONS APPROACH TO *IN VITRO – IN VIVO* CORRELATION MODELLING

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In vitro drug dissolution-time profiles can be used to predict *in vivo* drug plasma concentration-time profiles if an appropriate model can be found to describe the relationship between *in vitro* and *in vivo* dissolution. Such a relationship is referred to as an *In Vitro – In Vivo* Correlation (IVIVC). Establishing an IVIVC model has become an integral part of the drug development process. The main applications of these models are to reduce the number of human studies required in drug development, to act as a surrogate for human bioequivalence studies and in setting dissolution specifications. As a result, considerable effort goes into their development and "the ability to predict, accurately and precicely, expected bioavailability characteristics for an extended release (ER) drug product from dissolution profile characteristics is a long sought after goal" [1].

Many methods of developing IVIVC models have been developed. Previous research has highlighted a number of statistical concerns with a group of methods based on deconvolution[2] and has shown that a convolution-based method based on that of O'Hara et al[3] produces superior results[4]. Implementation of this convolution-based method involves the production of a user-written subroutine for the NONMEM[5] software package, a task that can be time consuming and complex. As a result, this methodology, despite its advantages over the deconvolution-based approach, is not in widespread use.

Another approach, based on systems of differential equations, has been proposed[6] It has been shown[7] that the convolution based and differential equation based models can be mathematically equivalent. Software which implements a differential equation based approach has been developed. This method utilises existing NONMEM libraries and is an accurate method of modelling which is far more straightforward for users to implement. This research shows that, when the system being modelled is linear, the use of differential equations will produce results that are practically identical to those obtained from the convolution method.

The use of a differential equation based model could also allow for the possibility of accurately modelling non-linear systems and further investigation is being carried out into the case where the drug is eliminated by a nonlinear, saturable process. The convolution and deconvolution methods assume that the system being modelled is linear but, in practice, this is not always the case. Our work to date has shown that the convolution-based method is superior, but when presented with nonlinear data even this approach will fail. It is expected that, in the nonlinear case, the use of a differential equation based method would lead to more accurate predictions of plasma concentration.

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