DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 14(15-17), 2143-2150 (1988)

FURTHER CONSIDERATIONS IN CORRELATING IN VITRO - IN VIVO DATA EMPLOYING MEAN-TIME CONCEPT BASED ON STATISTICAL MOMENTS

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ABSTRACT

Dissolution of a dosage form in vivo is often the rate-limiting factor determining the bioavailability and subsequently the therapeutic response. If a good correlation exists between an in vitro dissolution parameter and some bioavailabilty parameter, then monitoring of dissolution profile should permit the prediction of bioavailability.

The concept of Mean Residence Time based on statistical moments provides one method for correlating in vitro - in vivo data. The exemplification of this approach involving urinary excretion data is relatively straight forward. For plasma drug concentration-time data, however, this may not be the case realistically. This paper sets forth the mechanics of correlating in vitro data with bioavailability data employing both urinary excretion data as well as plasma data.

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INTRODUCTION

One of the earliest applications of statistical moments to biological systems was provided in a report concerned with the kinetics of body cholesterol in man (1). Since then, statistical moments have become increasingly popular and have been widely employed in different areas of bioavailability determinations, in vivo - in vitro correlations in particular (2-4).

The theory of statistical moments is based on the preliminary assumption that the movement of the individual drug molecules through the body compartment is governed by probability. Furthermore, the time course of drug concentrations in plasma can usually be regarded as a statistical distribution curve (2). Thus, the residence time of the drug in the body can be conceived as a frequency distribution with the mean and variance about the mean (5).

Mean Residence Time (MRT) as defined by Dost (6) is the statistical mean of the times the individual molecules in the system at $t = 0$ are retained within that system before elimination (biological system) or, liberation (dosage form dissolution in vivo). According to von Hattingberg and co-workers (7), cumulative dissolution and in vivo disposition curves may be viewed as frequency distribution curves of the individual times the drug molecules for a specific dose each reside within the respective system - that is, within the in vitro dissolution medium and the test subject. Using Pearson's concept of statistical moments to characterize frequency distributions, one can evaluate in vitro/in vivo experimental data (7). Hence, if a good correlation exists between the MRT for in vitro dissolution and MRT for a suitable in vivo disposition parameter, then the relatively simple procedure of monitoring the dissolution profile should allow the prediction of in vivo availability. It is the intention of this paper to set forth the mechanics of

correlating in vitro dissolution data with in vivo data originating from urinary excretion profiles as well as plasma profiles. It is anticipated that the inherent simplicity and wide applicability of this approach will be recognized through this publication.

METHODOLOGY

The mean of all individual occupancy (or residency) times (MRT) is given by the equation:

$$MRT = \frac{\int t \, dM(t)}{\int dM(t)} \qquad (1)$$

where

t = elapsed time

m = the mass of drug (number of molecules) within the system

Partial integration and rearrangement of Eqn. (1) yields:

$$MRT = \frac{{}_0\int^{\tau} [M(\tau)dt - M(t)]dt}{{}_0\int^{\tau} dM(t)} \qquad (2)$$

Since $M(\tau)$ and $M(t)$ are continuous within the interval, Eqn. (2) can be further simplified as follows:

$$MRT = \frac{{}_0\int^{\tau} M(\tau)dt - {}_0\int^{\tau} M(t)dt}{{}_0\int^{\tau} dM(t)}$$

or

$$MRT = \frac{M(\tau) - {}_0\int^{\tau} M(t)dt}{{}_0\int^{\tau} dM(t)} \qquad (3)$$

$M(\tau)$ from Eqn. (3) is the value of the integrand at the end of the integration interval; $dM(t)$ is the total mass of the drug under consideration (dose).

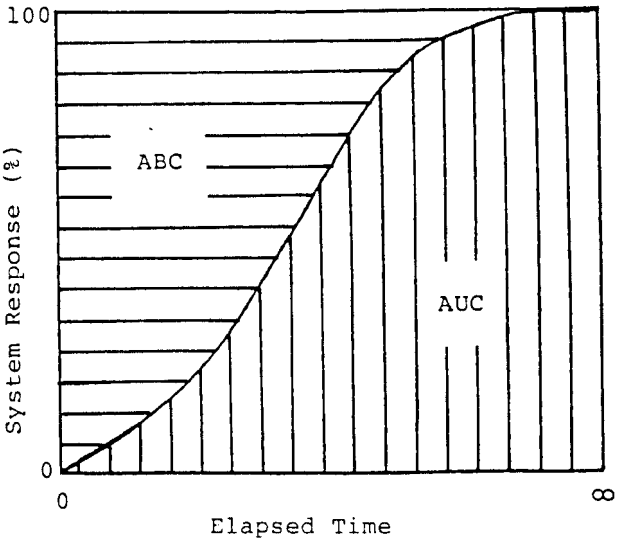

Fig. 1: Schematic Representation of System Response as a Function of Elapsed Time

The physical meaning of the above relationships may be more evident from an examination of Fig. 1, in which system response (whether in vitro dissolution or in vivo response) is portrayed as a function of time elapsed in the in vitro or in vivo system (MRT sys). The numerator in Eqn. (3) reflects the amount of drug that has not yet dissolved, or, consequently, the pharmacokinetic response yet to be observed. As a result, the numerator is nothing more than the area-between-the-curve-and-the-plateau (ABC) corresponding to 100% response (refer Fig. 1). Thus

$$MRT = \frac{ABC}{\text{Total mass of drug}} \qquad (4)$$

If M(t) is defined as the mass of the drug within an in vivo system, i.e., the amount of the drug remaining in the system, or the amount of drug yet to be eliminated, then ABC is identical to the area under the curve (AUC) since $M(\tau)\big|_{t=\infty}=0$. Thus

$$MRT = \frac{ABC}{AUC} \qquad (5)$$

If $M(\tau)$ is defined as the mass of drug that has yet to undergo dissolution, Fig. 1, is typical as well of *in vitro* dissolution curves. Thus, the mean residence time for dissolution (MRT *in vitro*) must be similar to the mean residence time *in vivo* (MRT *in vivo*).

The exemplification of MRT principle involving cumulative urinary excretion data for which the representation of "system response" as a function of time is relatively straight forward. For plasma drug concentration-time data, however, this may not be the case realistically.

When interpreting plasma drug concentration-time data, it must be noted that system response in accordance with the mean residence time concept, corresponds to the AUC as a function of time. The distinction between AUC of system response as a function of time and the AUC of an *in vivo* drug concentration-time plot may be difficult to envisage unless one examines a graph such as that in Fig. 2. Upon examination of the AUC as a function of time segment of Fig. 2, it is evident that;

$$MRT_{\underline{in\ vivo}} = \frac{ABC'}{AUC'}$$

or simply,

$$MRT_{\underline{in\ vivo}} = \frac{ABC'}{Y} \qquad (6)$$

Demonstration of a good correlation (high coefficient of correlation accompanied by a p value < 0.05) is indicative of high predictability. The utility and inherent simplicity of this model independent approach to *in vitro* /*in vivo* data correlation can be illustrated by transforming data, reported to possess poor correlation between *in vitro* and *in vivo* parameters.

APPLICATIONS

P.J. McNamara, *et al.*, (8) evaluated the *in vitro* dissolution and *in vivo* availability relationship for six furosemide tablet formulations to

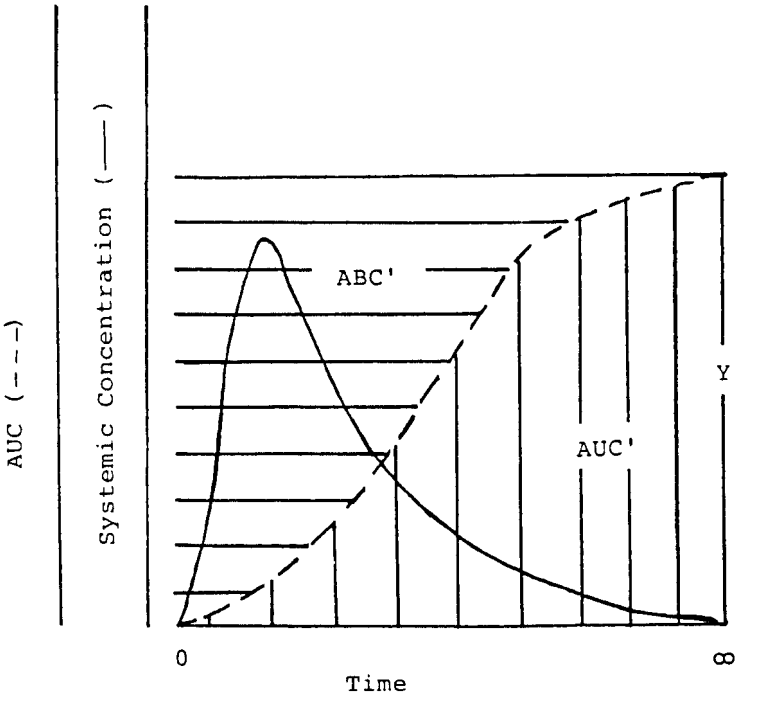

Fig. 2 : Schematic Representation of Transformation of Blood-Concentartion-Time Data for Determination of MRT

evaluate bioequivalency. The dissolution studies were conducted in acetate buffer at pH 4.6 and pH 5.6 employing a USP Apparatus II at 50 rpm. Bioavailability was determined by characterizing plasma-concentration-time profiles as well as cumulative-urinary-excretion-time profiles. The investigators reported poor correlation when in vitro dissolution parameters such as T_{30} at pH 4.6 or T_{30} at pH 5.6 and urinary excretion data as well as compared with plasma-levels data (r ranging between -0.67 and 0.62 accompanied by a p value > 0.1).

Three of the six formulations yielded data which were acceptable from the standpoint of essentially complete dissolution data as well as the attainment of a plateau for urinary excretion data and essentially

TABLE I

Correlation of $MRT_{in\ vitro}$ and $MRT_{in\ vivo}$

Computed for Data Reported by McNamara, et al., (8).

Factor	Furosemide Tablet Formulations A	C	D	Correlation Coefficient*
$MRT_{in\ vivo}$ (urinary excretion data)	0.74	1.18	1.12	0.99
$MRT_{in\ vitro}$ (dissolution data)	1.26	1.34	1.33	0.98
$MRT_{in\ vivo}$ (plasma data)	10.72	11.46	11.20	

* $p < 0.05$

complete characterization of plasma profile. Examining these data using the mean-time concept, one can transform the data for the determination of mean residence time both in vitro and in vivo (urinary excretion and plasma data). Correlating $MRT_{in\ vitro}$ and $MRT_{in\ vivo}$ for urinary excretion data yielded an improved correlation ($r = 0.99$, $p < 0.05$) as shown in Table I. Also, significantly improved correlation was obtained when $MRT_{in\ vitro}$ and $MRT_{in\ vivo}$ for plasma data (employing the method for the computation of mean-time as described earlier) were compared ($r = 0.98$, $p < 0.05$) as shown in Table I.

CONCLUSIONS

Dissolution of a dosage form in vivo is often the rate-limiting factor determining the physiologic availability of the drug. It is

apparent that if a good correlation exists between an in vitro dissolution parameter and some parameter of bioavailability, then monitoring of dissolution profile should permit the prediction of bioavailability.

The simplicity and utility of this approach (mean-time) and its employment in correlating in vitro /in vivo data is obvious. The ease of data transformation, as demonstrated, can assist in facilitating data correlation thus improving the prospects for reproducibility in in vivo performance of a formulation from batch-to-batch.

REFERENCES

1. W. Perl and P. Samuel, Cir. Res., 25, 191 (1969).
2. K. Yamaoka, T. Nakagawa and T. Uno, J. Pharmacokinet. Biopharm., 6, 547 (1978).
3. D. J. Cutler, J. Pharm. Pharmacol., 30, 476 (1978).
4. U. V. Banakar and L. H. Block, Pharm. Tech., 7, 107 (1983).
5. S. Riegelman and P. Collier, J. Pharmacokinet. Biopharm., 8, 509 (1980).
6. F. H. Dost, Klin. Wschr., 36, 655 (1958).
7. H. M. von Hattingberg, D. Brockmeier and D. Voegele, "A Method for In Vivo - In Vitro Correlation Using the Additivity of Mean Times in Biopharmaceutical Models", in Methods in Clinical Pharmacology, N. Reidbrock, B. Woodcock and G. Neuhaus, eds., Wiesbaden, Viewig (1980) pp 85-93.
8. P.J. McNamara, T.S. Foster, G.A. Digenis, R.B. Patel, W.A. Craig, P.G. Welling, R.S. Rapaka, V.K. Prasad and V.P. Shah, Pharm. Res., 4, 150 (1987).