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LEVEL A *IN VITRO/IN VIVO* CORRELATIONS: A QUALITY CONTROL TOOL OR BIOEQUIVALENCE PREDICTOR FOR EXTENDED-RELEASE SOLID ORAL DOSAGE FORMS?

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ABSTRACT

Attempts to establish and utilize *in vitro/in vivo* correlations for the assessment of extended-release (ER) solid oral dosage forms was re-emphasized at a recent International Congress. In 1988 the United States Pharmacopeial's (USP) Subcommittee on Biopharmaceutics proposed 3 levels of such correlations, A, B and C in decreasing order of importance. The highest order, level A, is assumed when successful prediction of the complete drug serum/plasma concentrations *versus* time profile using dissolution data is achieved. This report describes the successful establishment of Level A correlations for 2 different ER oral dosage forms of theophylline using the "Biorelevant" technique first proposed by Leeson *et al* in 1985. Dissolution studies were undertaken on the 2 different formulations, namely, Theodur ® 300 mg tablets, and Retafyllin 300 mg tablets. The dissolution studies were performed using the USP Apparatus 2 (paddle) in buffered media over the pH range 3.0 to 7.5. These data were subsequently used to simulate *in vivo* profiles, which, under specific dissolution conditions were extremely well correlated with the *in vivo* data following administration of the respective dosage forms to healthy human volunteers.

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INTRODUCTION

The use of *in vitro* dissolution studies in the preformulation development of new dosage forms, and in particular for the design of ER solid oral dosage forms is being extensively pursued.

The need to establish and utilize *in vitro/in vivo* correlations for the assessment of ER solid oral dosage forms was the topic of much discussion and interest at a recent International Congress (1). Whereas the USP Subcommittee on Biopharmaceutics (2) proposed 3 levels of such correlations, A, B and C in decreasing order of utility, Level A correlations are deemed to provide the most useful information.

The utility of *in vitro* dissolution data as a basis for the design and development of a product to predict *in vivo* performance requires the establishment of a specific *in vitro - in vivo* correlation. In this respect, relating the *in vitro* dissolution behaviour of an ER dosage form to the whole plasma concentration time curve by incorporating the drug's pharmacokinetic parameters has previously been shown to provide valuable data relating to the prediction of the absorption and disposition of the specific drug from its formulation following administration (3). Several authors have also previously proposed this type of correlation (4-6).

Robinson and Eriksen (4) described a mathematical and analog computer process which enabled the analysis of the kinetic relationships which govern the rate of release of drugs from modified-release dosage forms. Mathematical equations were derived which permitted the calculation of doses, release constants and the subsequent generation of a plasma concentration versus time curve which most closely approximated the "ideal" curve. Vaughan and Leach (5) demonstrated an *in vitro - in vivo* correlation for digoxin tablets by employing a transformation method which used a product's *in vitro* dissolution data to predict the plasma drug concentrations. Aarons and Rowland (6) however, cautioned that the method proposed by Vaughan and Leach (5) was formulation dependent and that caution should be exercised when dealing with rapidly dissolving formulations.

Wiegand and Taylor (7) were, however, the first authors to report such an *in vitro-in vivo* correlation for an extended-release product. However, it was not until 1985 that this approach to the development and assessment of ER dosage forms was used (3). It would appear that the latter authors were the first to demonstrate this technique as a predictive tool, or as a general retrospective method to demonstrate that a dosage form behaved according to what was anticipated. This approach has recently been demonstrated for dosage forms of chlorpheniramine by Williams *et al.*, (8).

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The premise of biorelevant dissolution involves the use of *in vitro* dissolution data to predict an *in vivo* response for a particular drug released from a specific dosage form. The proposed method employs the formulation's dissolution data and the drug's pharmacokinetic parameters. From this, plasma drug concentrations *versus* time curves for various formulations are predicted.

Following bioavailability studies conducted on theophylline ER dosage forms (Theodur® and Retafyllin) by the Biopharmaceutics Research Institute at Rhodes University (9, 10), using 6 healthy human volunteers, it was found that the mean *in vivo* profiles obtained following single dose administration were similar.The two products were found to be bioequivalent in a subsequent multiple dose study involving 10 volunteers BRI 21/90 (11). However, initial dissolution studies conducted on these formulations suggested that the release of theophylline from the two dosage forms was different, with Retafyllin exhibiting a faster rate of release. These findings thus suggested that the *in vivo* profiles of the two products were expected to be different. The purpose of this study was to ascertain whether biorelevant dissolution conditions could be established for the accurate prediction of *in vivo* performance of the two different formulations.

MATERIALS

Theodur®, 300 mg tablets (Adcock Ingram, South Africa) and Retafyllin 300 mg tablets (Orion Pharmaeutica, Finland) were obtained commercially. Theophylline raw material was supplied by South African Druggists. Orthophosphoric acid was purchased from Holpro Analytics, South Africa and sodium hydroxide pellets were purchased from Merck, South Africa.

METHODS

Single dose bioavailability studies

Sixteen serum samples were collected over a 36 hour period following single dose administration in the fasting state of 300mg theophylline in the form of either Retafyllin (9) or Theodur® (10). Serum theophylline concentrations were determined by means of an Abbott TDX system (Abbott Laboratories, USA) from which individual serum concentration *versus* time plots were prepared. The mean serum concentration time plots were calculated (Biopak, Microcomputer programme, Clin Trials Inc., Lexington, USA) with C_{max} and T_{max} values being estimated directly from the mean data for purposes of comparison to simulated data sets only. No statistical comparison of individual data sets was attempted due to differences in trial subjects, numbers, etc.

Multiple dose bioavailability studies

Sixteen serum samples were collected over a single 12 hour dosing interval following the 7th dose of either Retafyllin 300mg or Theodur® 300mg in a

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randomized cross-over study employing 10 volunteers (11). The pharmacokinetic parameters AUC_{0-7} , C_{max} and %PTF (12) were calculated (Biopak, Microcomputer programme, Clin Trials Inc., Lexington, USA). Ninety-five percent classical confidence intervals and 90% intervals for the natural logarithm of each parameter were calculated in terms of a bioequivalence range of 0.8 - 1.2 for the untransformed data and 0.8 - 1.25 for the log transformed data.

Dissolution media

All dissolution studies were carried out in a phosphate buffer medium of 0.05M (900 ml) and adjusted to the required pH using sodium hydroxide. Dissolution media were prepared at pH values of 3.0, 4.0, 5.0, 6.0, 6.8 and 7.5.

Dissolution studies

The dissolution studies were undertaken using the USP rotating paddle apparatus (Pharmatest PTW-S Dissolution Apparatus, Pharmatest, Germany). The temperature of the dissolution medium was maintained at $37\pm0.5°C$ and the paddle agitation rate was 50 rpm. Dissolution rate determinations on 6 replicates of each dosage form were carried out and samples of 3.0 ml were removed from the various dissolution media at hourly intervals between zero hours and 12 hours. A 24 hour sample was also taken. An equal volume of fresh dissolution medium was immediately replaced in the dissolution vessel in order to maintain sink conditions. The absorbance of all undiluted samples was measured at 254nm using a Beckman DU 68 spectrophotometer (Beckman Instruments, USA) and the concentration of theophylline calculated by reference to linear calibration lines constructed from reference standards prepared in dissolution media of the relevant pH under study.

Simulations

Simulation of the *in vivo* profiles was carried out with the aid of a personal computer. Theophylline pharmacokinetic parameters reported by Hendeles *et al.*, (13) were employed in the computer simulations as follows: $k = 0.087\ h^{-1}$, $k_a = 1.20h^{-1}$ and $Vd = 0.50$ l/kg, assuming a one compartment open model. The serum concentrations of theophylline implied that drug was released from the dosage form according to first order kinetics involving three consecutive sequences, *viz:* an immediate release fraction and a fast and slow first order releasing fraction determined by using the equations originally proposed by Leeson *et al.* (3) and are given in the Appendix.

RESULTS AND DISCUSSION

Dissolution rate studies

Visual inspection of the dissolution process revealed that the Theodur® tablets showed swelling of the tablet matrix after about one hour into the test. The swelling was more pronounced in media of about pH 5.0. After 2 to 6 hours the tablets showed varying degrees of disintegration depending on the pH of the

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medium, with this occurring earlier at higher pH's. At twenty-four hours, the tablet matrix had broken up completely and only beads were still visible in the dissolution medium. Visual inspection of the Retafyllin tablets during the dissolution process indicated that fine material was suspended in the bulk of the medium after one hour. After about two hours, the tablet showed signs of swelling and disintegration was complete after about seven hours. These trends were evident throughout the pH range. The results of the dissolution rate studies are depicted in Figure 1 a-f and indicate that the release of theophylline from the Retafyllin and Theodur® products was similar under acidic conditions (pH 3.0 and 4.0) but quite different at pH values greater than pH 5.0. Since the two products produced similar mean serum concentration *versus* time profiles following single dose administration (Figure 2) and were shown to be bioequivalent following multiple dose administration (Table 1), simulation studies were performed to establish the biorelevant dissolution conditions for each of the two products in order to establish the most predictive dissolution conditions for each product for subsequent product development and/or batch-to-batch quality control procedures.

Simulation of in-vivo profiles

The application of this method involves the determination of the order of release of the drug from the particular dosage form. To ascertain this, the dissolution rate profiles were stripped and using linear regression and the method of residuals, the dissolution rate order and the relevant dissolution rates were obtained. These are summarised in Tables 2 and 3 for Theodur® and Retafyllin® respectively. Assessment of the dissolution rate profiles revealed that Theodur® exhibited a first order release component combined with an instant releasing portion in dissolution media of pH 3.0 to 6.0. Beyond this there was evidence of a zero order component combined with a first order component (Table 2). Inspection of the Retafyllin dissolution profiles indicated that the release of theophylline occurred by first order processes irrespective of the pH of the dissolution medium (Table 3).

The results of the simulation of the predicted *in vivo* profiles for Theodur® and Retafyllin® are illustrated in Figures 3a-f (Theodur®) and 4a-f (Retafyllin). [In each case the predicted profiles (simulation) are superimposed onto the mean *in vivo* profiles obtained from the single dose studies].

The simulations obtained for Theodur® from dissolution data at the lower pH's, i.e. pH 3.0, 4.0 and 5.0 (Figures 3a-c), did not provide accurate predictions. In each of these cases the predicted profiles showed noticeably lower values for C_{max} compared to the values obtained from the mean profiles. The profiles of particular interest, are those obtained at pH 6.0 (Figure 3d). It is clear that the simulated profile is almost entirely superimposable onto the actual mean profile. The C_{max} values are 4.96 and 4.77 mg/ℓ for the mean serum profile and simulated profile respectively, with the T_{max} value for both being 8 hours.

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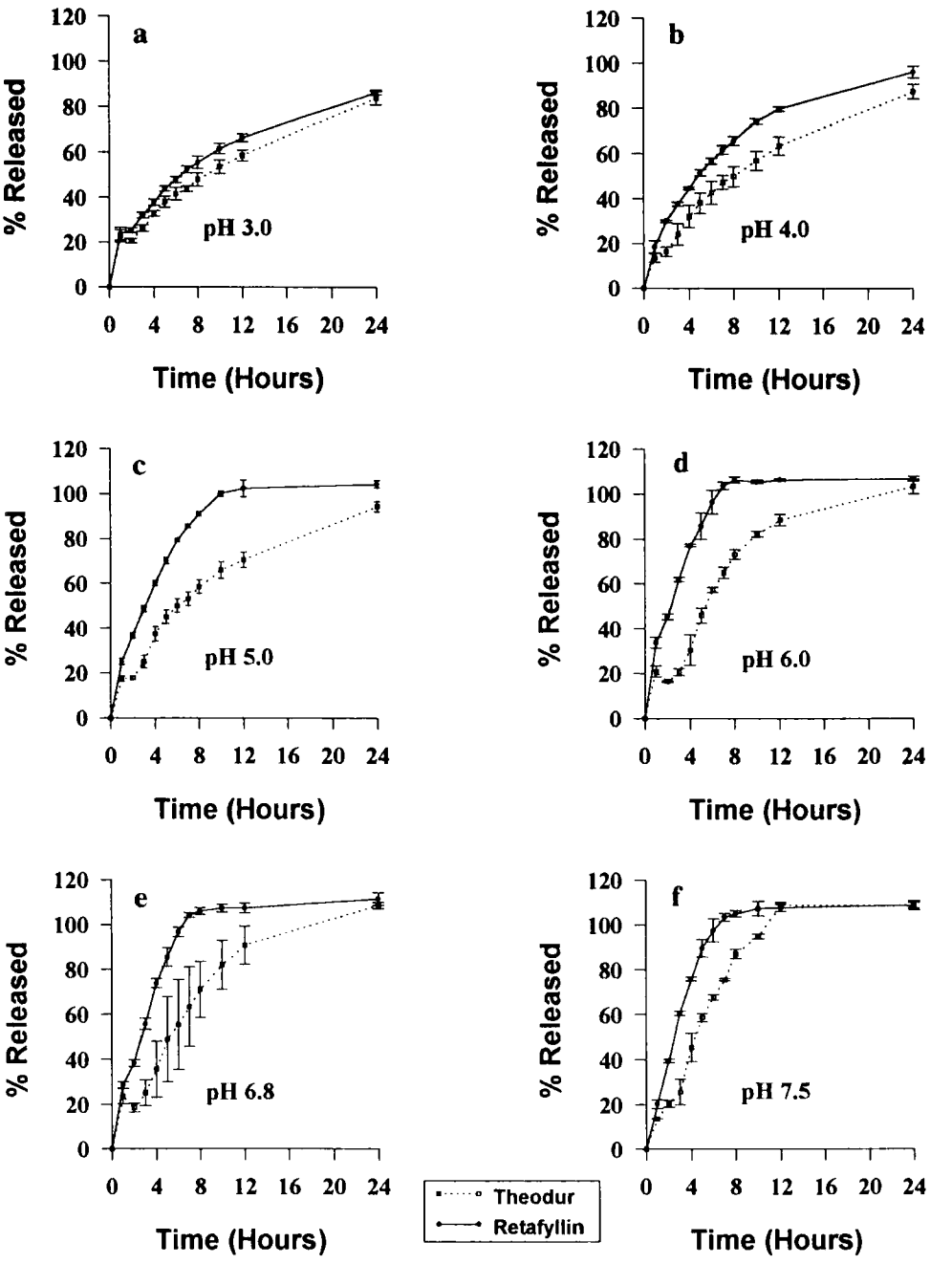

FIGURE 1

Cumulative percentage of theophylline released from Theodur ® and Retafyllin *versus* time.

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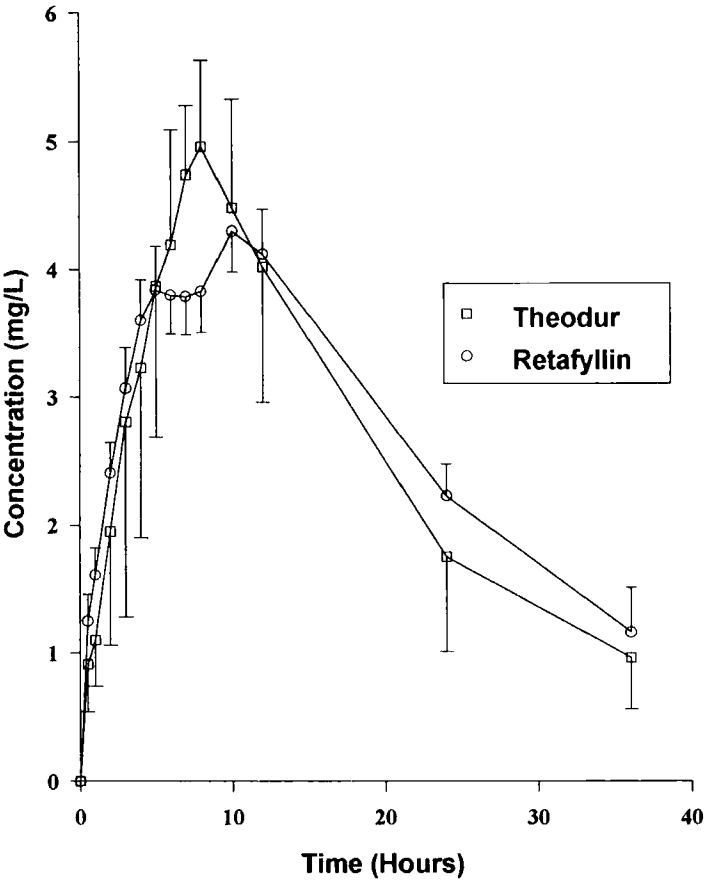

FIGURE 2

Mean serum concentration *versus* time profiles of theophylline.

The simulations for Retafyllin are depicted in Figures 4a-f. The pH at which the best simulation was obtained was found to be pH 4.0 (Figure 4b) as opposed to pH 6.0 for Theodur®. The T_{max} value of 10 hours compares favourably with the T_{max} value obtained *in vivo* from the mean serum profile. The predicted C_{max} was determined as 4.05 mg/ℓ which is in close agreement with the mean *in vivo* value of 4.30 mg/ℓ. The simulated profile at pH 6.0 (Figure 4d) exhibited a shorter T_{max} and a correspondingly higher C_{max}, which were not in agreement with the mean *in vivo* data.

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TABLE 1

Summary of the Statistical Analysis [a] of Multiple-dose Pharmacokinetic Characteristics of Theodur® and Retafyllin.

Pharmacokinetic Characteristic	Ratio of means	Confidence limits	Confidence intervals
$AUC_{0-\tau}$ [b]	0.97	95%	87-107
$lnAUC_{0-\tau}$ [c]	0.97	90%	89-106
C_{max} [d]	0.95	95%	87-103
lnC_{max} [e]	0.95	90%	88-102
%PTF [f]	0.96	95%	80-111
ln%PTF [g]	0.96	90%	86-107

[a] From Ref. 11

[b] Area under the serum concentration *versus* time profile for a dosing interval at steady-state

[c] Natural log of $AUC_{0-\tau}$

[d] Maximum serum concentration

[e] Natural log of C_{max}

[f] Percentage peak-trough fluctuation calculated from 100 $(C_{max} - C_{min})/C_{av}$ where C_{min} = trough serum concentration and C_{av} = average serum concentration at steady state

[g] Natural log of %PTF

CONCLUSIONS:

The simulation of the expected serum concentration time *versus* profiles employing pharmacokinetic data and dissolution parameters has enabled reasonable predictions of the *in vivo* situation. The data clearly show the limitations of a single dissolution test procedure for the comparison of ER products. Whereas a comparative dissolution test performed at pH 3.0 suggests

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TABLE 2

Summary of Dissolution Rate Order and Rate Constants for Theodur®

pH	Dissolution rate order	Dissolution rate constant
3.0	20% instant release fraction with a single first order fraction equivalent to 80% of the dose	$K_s = 0.07h^{-1}$
4.0	15% instant fraction with a single first order fraction	$K_s = 0.09h^{-1}$
5.0	18% instant release fraction with a single first order fraction	$K_s = 0.12h^{-1}$
6.0	15% instant release fraction with a single first order fraction	$K_s = 0.22h^{-1}$
6.8	20% instant release with zero order release for 8 hours followed by a first order fraction	$K_0 = 31.58mg/h$ $K_d = 0.38h^{-1}$
7.5	10% instant release fraction with zero order release for 8 hours followed by first order fraction	$K_0 = 29.46mg/h$ $K_d = 0.39h^{-1}$

that the two products would be expected to produce similar *in vivo* behaviour, as was indeed the case (Table 1; Fig 2), comparative dissolution rate tests carried out at pH's greater than 3 imply the opposite.

The optimal predictive conditions however, for release of theophylline from Retafyllin was established at pH 4. The results of dissolution tests at higher pH's for this formulation would be misleading. Considering the release of theophylline from the Theodur® formulation, whilst a dissolution test at pH 6 appears to precisely predict *in vivo* performance, tests carried out at pH's 6.8 and 7.5 give similar predictive results with the *in vitro* data from pH 6.0 being optimally predictive. It is evident that optimum biorelevant dissolution conditions for each formulation must be established as early as possible during development in order to increase the predictive power of subsequent dissolution testing. It appears from the data presented that each formulation has its own characteristic biorelevant

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TABLE 3

Summary of Dissolution Rate Order and Rate Constants for Retafyllin.

pH	Dissolution rate order	Dissolution rate constant
3.0	20% instant release fraction with a single first order fraction	$K_s = 0.08\ h^{-1}$
4.0	A single first order fraction	$K_s = 0.14\ h^{-1}$
5.0	Two first order fractions, a slow fraction of 70% and a fast fraction of 30 %	$K_f = 0.39\ h^{-1}$ $K_s = 0.25\ h^{-1}$
6.0	A single first order fraction	$K_s = 0.45\ h^{-1}$
6.8	Two first order fractions, a fast fraction of 45% and a slow fraction of 55%	$K_f = 1.07\ h^{-1}$ $K_s = 0.25\ h^{-1}$
7.5	Two first order fractions, a fast fraction of 25% and a slow fraction of 75%	$K_f = 1.15\ h^{-1}$ $K_s = 0.46\ h^{-1}$

dissolution test requirement in order to establish a correlation between the *in vivo* and the *in vitro* situation and conforms to the correlation Level A requirement proposed by the USP Subcommittee on Biopharmaceutics (2) for ER solid oral dosage forms.

In vitro testing by the process of "Biorelevant" dissolution testing represents a viable method with which to assess ER solid oral dosage forms. This implies that under the specific dissolution rate conditions established for each product, it should be possible to assess the effects of storage, minor formulation modifications, manufacturing site changes and other relatively small alterations on the *in vivo* performance of each of the investigated ER products.

Bearing in mind that dissolution rate testing is considered to be an extremely valuable quality control tool for solid oral dosage forms, the establishment of *in vitro/in vivo* correlations for such products, in particular, a Level A correlation, should provide more physiological meaningful data for such products. Whereas compendial monographs incorporating dissolution rate conditions for specific products provide a means to obtain relatively rudimentary data to monitor

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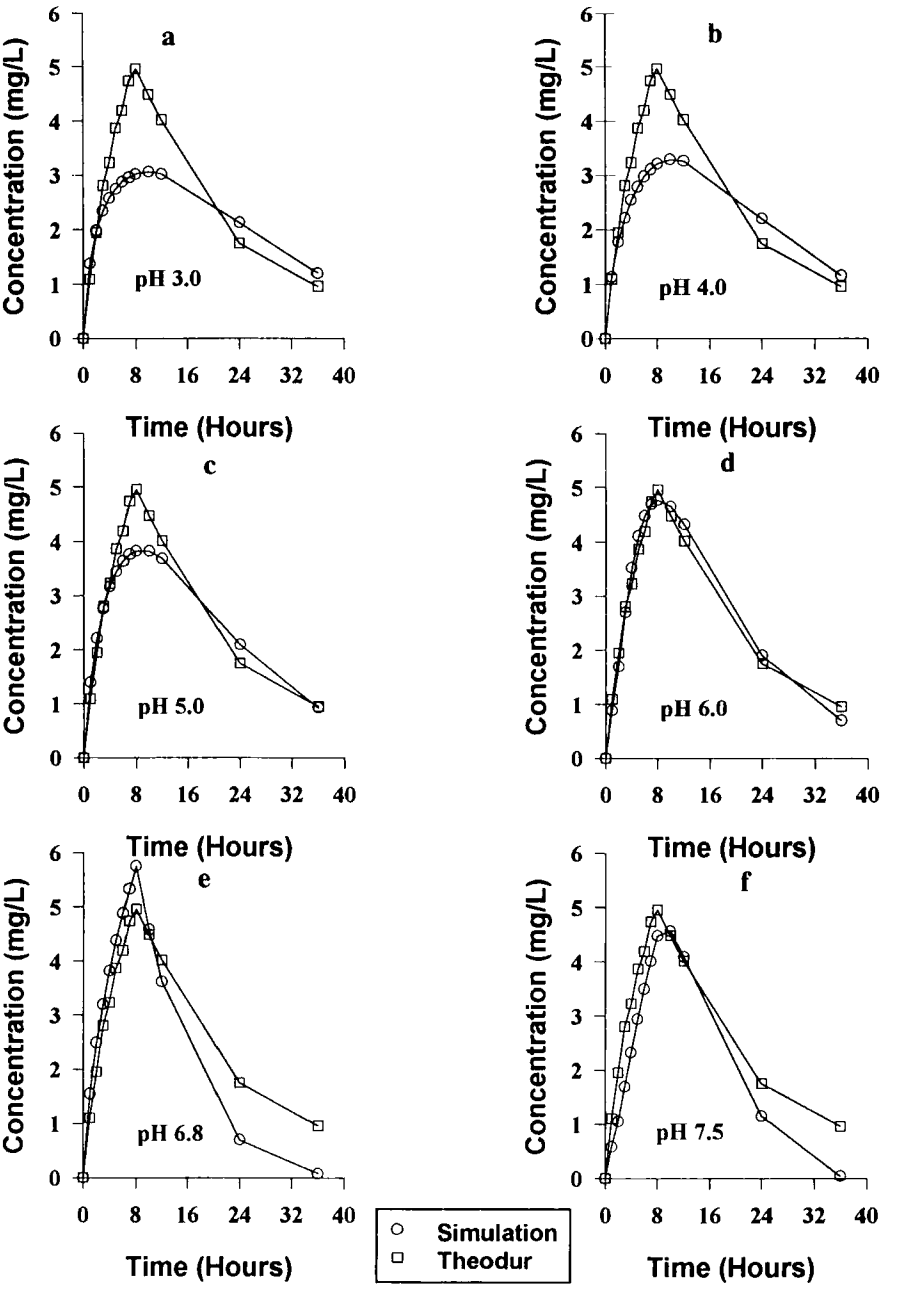

FIGURE 3

Simulated concentration *versus* time profiles of Theodur® superimposed on *in vivo* data

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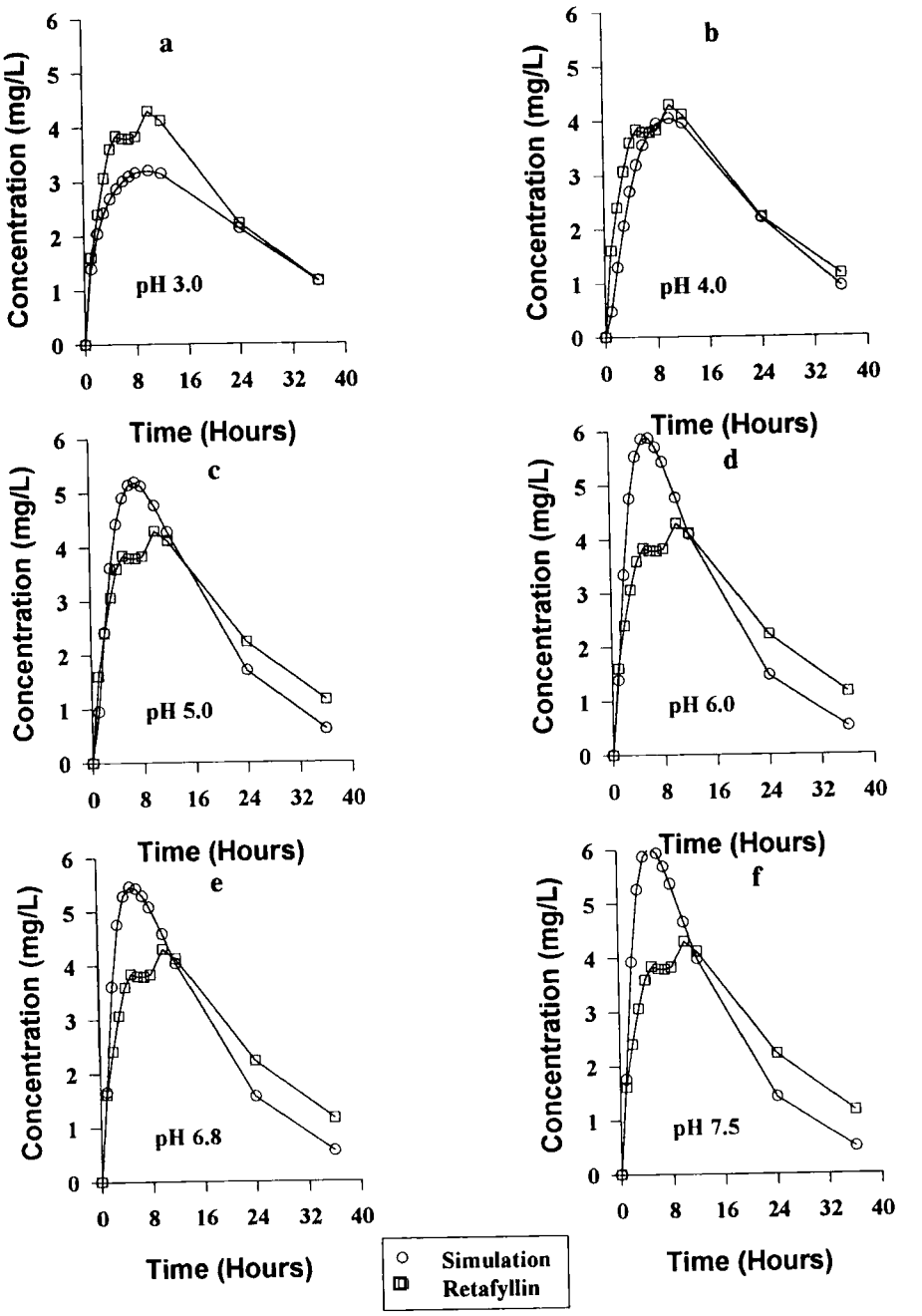

FIGURE 4

Simulated concentration *versus* time profiles of Retafyllin superimposed on *in vivo* data

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batch-to-batch variability of such products, the conditions specified in such monographs are often far from ideal.

This is particularly so for ER solid oral dosage forms as recently demonstrated with indomethacin ER products (14) whereby two different ER formulations containing the same drug complied with the USP (15) dissolution specifications yet resulted in bio-inequivalence following comparative bioavailabilty testing in human volunteers. Reliance on *in vitro* data from a single uncorrelated dissolution test was thus shown to be misleading, both from the quality control point of view and also *in vivo* performance.

The question however remains whether correlated *in vitro* data simply provides enhanced information for quality control of ER products or whether such data can be of use to predict product performance *in vivo*.

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APPENDIX

Equation 1

$$C_{im} = \frac{k_a F_{im} D}{(K_a - K_{el})\, V_d} \left[\exp(-K_{el}\, t) - \exp(-K_a\, t) \right]$$

Equation 2

$$C_f = \frac{k_a K_f F_f D}{V_d} [A + B + C]$$

where:

$$A = \frac{\exp(-K_f\, t)}{(K_a - K_f)\,(K_{el} - K_f)}$$

$$B = \frac{\exp(-K_a\, t)}{(K_f - K_a)\,(K_{el} - K_s)}$$

$$C = \frac{\exp(-K_{el}\, t)}{(K_f - K_{el})\,(K_a - K_{el})}$$

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Equation 3

$$C_s = \frac{K_a K_s F_s D}{V_d} [D+E+F]$$

where:

$$D = \frac{\exp(-K_s t)}{(K_a - K_s)(K_{el} - K_s)}$$

$$E = \frac{\exp(-K_a t)}{(K_s - K_a)(K_{el} - K_a)}$$

$$F = \frac{\exp(-K_{el} t)}{(K_s - K_{el})(K_a - K_{el})}$$

The total drug concentration is obtained by the following summation:
Equation 4

$$C_p = C_{im} + C_f + C_s$$

The equation used to predict concentrations assuming that the dosage form exhibits a zero order release and a first order release fraction are as follows:
Equation 5 (During t_o)

$$C_z = \frac{K_0}{V_d K_e} [1 - \exp(-K_e t)] -$$

$$\frac{K_0}{V_d (K_e - K_a)} [\exp(-K_a t) - \exp(-K_e t)]$$

Equation 6 (After t_o)

$$C = \frac{K_a K_d (D - t_0 K_0)}{(K_a - K_d)(K_e - K_d) V_d} \exp(-K_d t)$$

$$+ \frac{K_a}{V_d (K_e - K_a)} \left\{ \frac{K_0}{K_a} [1 - \exp(-K_a t_0)] - \frac{K_d (D - t_0 K_0)}{K_a - K_d} \exp(-K_a t) \right\}$$

$$+ \frac{K_a}{V_d (K_e - K_a)} \left\{ \frac{K_d (D - t_0 K_0)}{K_e - K_d} - \frac{K_0}{K_a} [1 - \exp(-K_a t_0)] \right\} \exp(-K_e t)$$

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$$+ \frac{K_0}{V_d}\left\{\frac{1}{K_e}\left[1-\exp\left(-K_e t_0\right)\right]\right.$$

$$\left. - \frac{1}{K_e - K_a}\left[\exp\left(-K_a t_0\right) - \exp\left(-K_e t_0\right)\right]\right\}\exp\left(-K_e t\right)$$

The total drug concentration is obtained by a summation of equations 5 and 6.
Definitions of terms:

C_z	concentration due to the zero order release fraction
C	drug concentration due to first order processes
C_p	total drug concentration
C_{im}	concentration due to immediate release fraction
C_f	concentration due to fast release fraction
C_s	concentration due to slow release fraction
K_a	absorption rate constant
K_e	elimination rate constant
t	time
V_d	apparent volume of distribution
D	dose
F_{im}	immediate release fraction of dose
F_f	fast release fraction
F_s	slow release fraction
K_f	rate constant of fast fraction
K_s	rate constant of slow fraction
K_o	zero order release rate constant
K_d	first order release rate constant
t_o	time of zero order release

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