ELSEVIER

International Journal of Pharmaceutics 104 (1994) 253–270

international journal of pharmaceutics

Development and application of a pharmacokinetic simulation program for oral controlled release dosage forms – DIPS

H.P. Jones [a,*], R. Clements [b], D.J. Hearn [b], M.J. Gamlen [a]

[a] *Pharmaceutical Development Laboratories,*
[b] *RD & M Computing, Wellcome Foundation Ltd, Dartford, Kent DA1 5AH, UK*

(Received 20 August 1993; accepted 18 October 1993)

Abstract

A pharmacokinetic simulation computer program has been developed to assist in the development of prolonged release dosage forms – Dissolution Input Plasma Simulator (DIPS). DIPS accepts conventional cumulative in vitro release data obtained with a standard dissolution test, without any form of curve fitting, using a simple 'time slicing' procedure. To allow for, and understand, the complex relationship that may exist between release and actual absorption of the drug molecule into the systemic circulation, a series of sequential first order absorption rate constants are set up. The 'sequential absorption profile' (SAP), when optimised and combined with the in vitro dissolution curve, produces a simulated curve giving a good fit to the in vivo profile for that particular product/dissolution test. Entering in different release data (either theoretical or experimental) produces a predicted plasma profile. DIPS generates both single and multiple dose simulations for drugs fitting the one- and two-compartment open models. The program was originally developed for studies on the antihistamine acrivastine. The predictive capabilities of DIPS were assessed using bioavailability data obtained from studies on bupropion, metoprolol, felodipine and paracetamol. With four of these drugs a high degree of correlation was obtained between actual and predicted plasma levels, following the estimation of the SAP for the slowest releasing batch in each study. The lower degree of predictability for felodipine was attributed to the dissolution test, which may have underestimated the in vivo release rate of this extremely insoluble molecule.

Key words: Acrivastine; Controlled release; Gastrointestinal absorption; Pharmacokinetic simulation; Dissolution rate

1. Introduction

The use of in vitro dissolution techniques and their correlation with in vivo bioavailability is of pivotal importance to the development of oral controlled release dosage forms. It would be extremely useful to be able to predict blood level profiles following single and multiple dosing, from product dissolution data. If actual dissolution curves can be approximated to zero- or first-order kinetics, it is comparatively straightforward to generate blood level simulations. Equations to generate these profiles for drugs fitting the one-

* Corresponding author.

Elsevier Science B.V.
SSDI 0378-5173(93)E0322-H

or two-compartment pharmacokinetic open model are well established (Wagner, 1975).

In practice dissolution rates are not always zero or first order and therefore it may not be possible to fit experimentally determined data to simple equations. Functions such as the Weibull distribution may be useful in certain circumstances (Langenbucher, 1972). A further problem is that the actual absorption process (i.e., passage across the gut wall) is not always rapid in relation to the dissolution process. The relationship between drug release in vivo and drug absorption can change significantly during passage of a dosage form along the GI tract, with absorption becoming progressively rate limiting. Therefore as the dissolution rate of a series of related formulations is reduced, not only will C_{max} and t_{max} change but a reduction in bioavailability may occur as measured by plasma area under the curve (AUC) data.

These considerations were evident as a result of human studies with acrivastine formulations. Acrivastine (Cohen et al., 1985) is a rapid acting, non-sedating antihistamine molecule related to triprolidine. It is well absorbed in man from conventional rapid release dosage forms, being excreted primarily as the unchanged drug. However, it has a short plasma half-life (2 h), necessitating three times daily dosing and this led to the development of a prolonged release dosage form that would allow a reduction in dosing frequency. Unpublished studies following colonic administration of acrivastine, and also of experimental controlled release dosage forms, indicated that absorption was slow, incomplete and site dependent. Therefore, it was considered useful to develop a suitable simulation program to optimise the release profile in terms of producing a product with an acceptable pharmacological profile and maximum bioavailability.

The main requirements were that it would: (i) accept cumulative percentage release versus time dissolution data, either measured or theoretical; (ii) allow for sequential changes in absorption rate with time, during passage along the gastrointestinal tract; and (iii) be suitable for drugs fitting the one- and two-compartment open models. Additional requirements were that it would run on any IBM PC, PS/2 or clone and possess user-friendly data entry and file storage facilities.

The purpose of this paper is to describe the theory, operation and retrospective evaluation, using suitable published studies, of the program called the Dissolution Input Plasma Simulator (DIPS).

2. Theoretical basis

2.1. Overview

DIPS produces concentration against time data simulating the controlled release of a drug into the GI tract and its subsequent absorption, distribution and elimination. The results produced by DIPS are based on the two-compartment pharmacokinetic model (2 COM) shown in Fig. 1.

DIPS is able to produce results for the one-compartment open model (1 COM) by using the same model as above, but setting the distribution rate constants K_{12} and K_{21} to zero in all calculations.

DIPS addresses drug absorption at a rate varying with the position in the tract. Concentration values cannot therefore be predicted by use of a single equation. The calculation method used by DIPS involves the repeated application of pharmacokinetic equations producing a number of similar curves starting at regular intervals over

D = amount of drug available for absorption

K_a = first order absorption rate constant

K_{12}, K_{21} = first order distribution rate constants

K_{el} = first order elimination rate

C_p = Drug concentration in the plasma compartment

C_t = Drug concentration in the tissue compartment

D_p = Drug amount in plasma compartment

D_t = Drug amount in tissue compartment

V_p = Volume of plasma compartment

V_t = Volume of tissue compartment

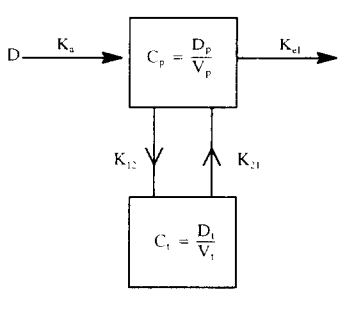

Fig. 1. Schematic representation of the two-compartment open model.

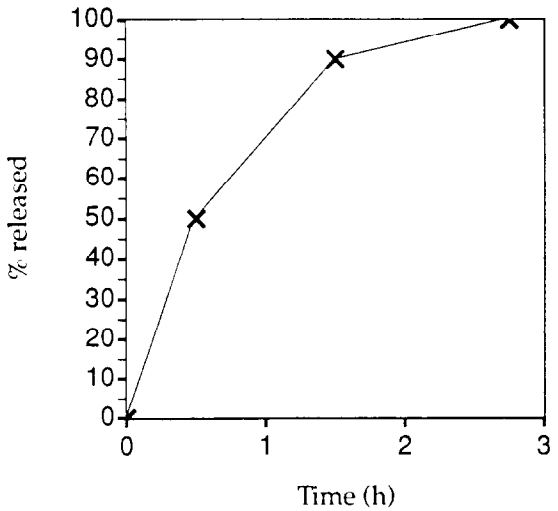

Fig. 2. Hypothetical dissolution curve.

the absorption period, which are summed to simulate a continuous process.

2.2. Treatment of dissolution data

In controlled release dosage forms, the dissolution curve of the product determines the amount of drug released. DIPS makes use of 'time slicing' – a method which divides the absorption process into intervals and assumes that during each interval a finite amount of dissolved drug is released for absorption. It makes the assumption, as used by Chiou (1980), that all the drug absorbed during a time interval is absorbed at the midpoint of the interval. To calculate the amount of dissolved drug available for absorption at the midpoint of an interval, the dissolution curve is used (see Fig. 2) and linearity is assumed between known points on this curve.

Using Fig. 2 as an example, in each interval of 0.1 h until 0.5 h, 10% of the total dose administered is released for absorption.

Where the dissolution curve approaches linearity, frequent data points are not required and would have little effect on improving accuracy. However, in areas of the curve where the gradient may be changing very rapidly, more dissolution points are required to obtain an accurate representation of the curve.

The only constraint placed on the size of the time slice by the dissolution data is that it should divide exactly into each dissolution time point to avoid the time interval spanning a change in dissolution rate and therefore introducing unnecessary complications into the calculation of drug plasma concentration.

2.3. Treatment of absorption data

Determination of concentration values starts from time zero and continues up to the last required output time. The period between output points is divided into time intervals according to the time slice value. At the midpoint of each time interval the calculated amount of available drug, from the dissolution data, is subjected to the absorption process to provide a concentration in the compartments of the model.

The changing concentration value in a compartment is represented by a curve starting from the midpoint of the time interval and continuing through the output points until the final output point. If there are n time slices up to the output point, each providing a small amount of dissolved drug, $d_1 \rightarrow d_n$, which is then able be absorbed for a length of time $t_1 \rightarrow t_n$, producing concentration amounts $C_1 \rightarrow C_n$ in a compartment, then the total concentration, C, in that compartment at the output point will be:

$$C = \sum_{i=1}^{n} C_i \qquad (1)$$

This process is presented diagrammatically in Fig. 3

The size of the time slice determines the number of curves generated by the simulation. The more curves generated, the greater the accuracy in the predicted concentration values and the closer the model comes to simulating a continuous dissolution process over the period of absorption. However a point is reached beyond which decreasing the size of the time slice increases computing time without any additional improvement in accuracy of the generated curve.

2.4. Absorption rate changes

If the absorption rate remains constant throughout the simulation, then the concentration values at each output point can be calculated by extending each of the individual curves, $C_1 \rightarrow C_n$, throughout the simulation and summing the values at those points.

However, such an assumption may be incorrect as the absorption rate of the dissolved molecule may differ in different regions of the GI tract. As a result, the continuation of the original curves would give incorrect plasma concentrations after the absorption rate has changed. To solve this problem the time at which the absorption rate changes, becomes a 'stop point' at which the generation of the current curves ceases. The concentration value is then calculated in the same way as for a required output point. From this point until the next stop point new curves are generated, using a new absorption rate.

The concentration values $c_1 \rightarrow c_n$ are calculated by applying the relevant equation, using the drug amount $d_1 \rightarrow d_n$ being absorbed for each length of time $t_1 \rightarrow t_n$. To calculate a total concentration value at the first stop point, the values $c_1 \rightarrow c_n$ are summed to give C.

To calculate the drug concentration at the second stop point, the process needs to be repeated, but two factors must be taken into account:

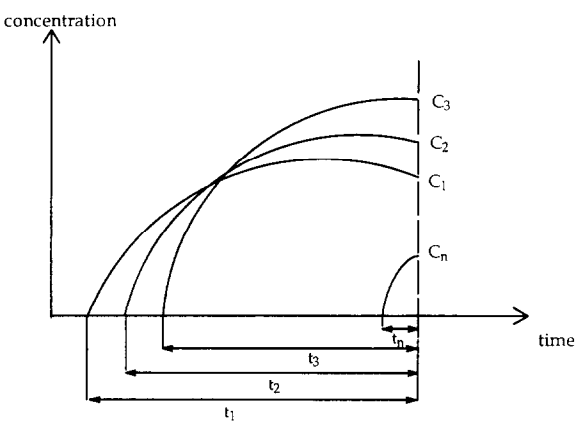

Fig. 3. Diagrammatic representation of Eq. 1.

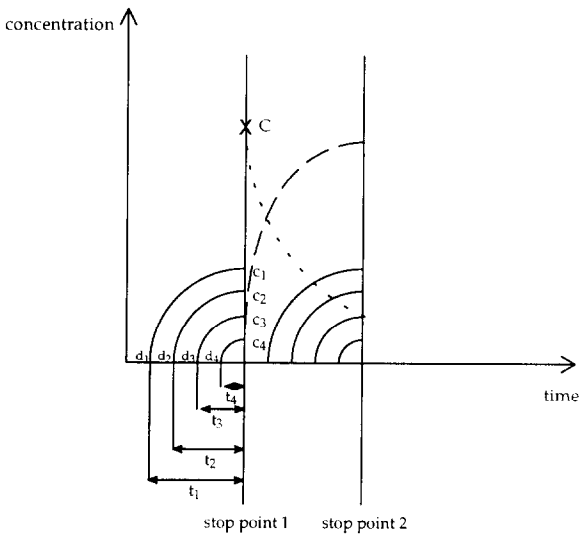

Fig. 4. Schematic representation of concentration in each compartment.

(i) Not all the drug which became available up until the first stop point will have been absorbed into a compartment during that period. Therefore, an amount of drug, D_{na}, is immediately available, to be absorbed for the duration of the second period until the next stop point. This curve is shown in Fig. 4 as the dashed line.

(ii) Calculating the concentration from absorption of drug released in the second period does not take into account drug present at the end of the previous period. Some of this drug will still be in the compartment, dependent upon distribution and elimination and is shown as the dotted curve in Fig. 4.

Calculation of the concentration at subsequent stop points is handled in the same way.

This concept was subsequently extended to make all output points throughout the simulation into stop points. This provided the major advantage of reducing the number of curves contributing to the overall concentration and therefore reducing the time spent on computation, especially as contributions from early curves become insignificant as time progresses.

2.5. Calculation of concentrations

The use of the time slicing method simulates a small amount of drug, D, becoming available for absorption into the plasma compartment at the midpoint of each time interval. Each subsequently generated curve is used to calculate a concentration value for both the plasma and tissue compartments, produced by D being absorbed up until the required stop point.

The values for C_p and C_t (see Fig. 1) after a time interval, t, the time between the start of a curve and the required stop point, are given by the following equations (Wagner, 1975):

$$C_p = \frac{Dk_a}{V_p}\left[\frac{(K_{21}-\alpha)}{(K_a-\alpha)(\beta-\alpha)}e^{-\alpha t} + \frac{(K_{21}-\beta)}{(K_a-\beta)(\alpha-\beta)}e^{-\beta t} + \frac{(K_{21}-K_a)}{(\alpha-K_a)(\beta-K_a)}e^{-K_a t}\right] \quad (2)$$

$$C_t = \frac{DK_{12}K_a}{V_t}\left[\frac{e^{-\alpha t}}{(K_a-\alpha)(\beta-\alpha)} + \frac{e^{-\beta t}}{(K_a-\beta)(\alpha-\beta)} + \frac{e^{-K_a t}}{(\alpha-K_a)(\beta-K_a)}\right] \quad (3)$$

where

$$\alpha+\beta = K_{12}+K_{21}+K_{el} \quad (4)$$

$$\alpha\beta = K_{21}K_{el} \quad (5)$$

The use of the above equations enables the individual concentrations in each compartment to be calculated for each of the generated curves, up to each stop point. Fig. 4 shows a simplified version of these curves, which can be applied to either compartment, using, e.g., four time slices between required stop points.

As (K_a) is a first-order process, after time t the amount of drug D, which has not yet been absorbed is given by:

$$D_{na} = De^{-k_a t} \quad (6)$$

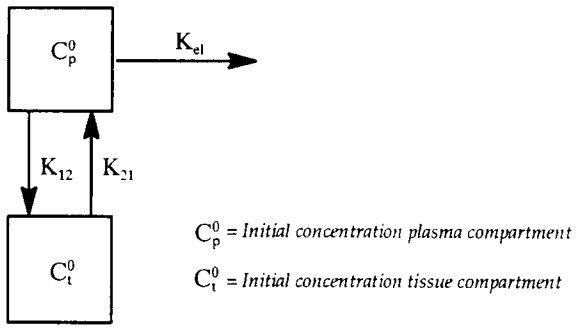

Fig. 5. Schematic diagram of distribution and elimination omitting the effect of absorption.

This allows the unabsorbed drug available at the start of a time period, (i), to be calculated, and hence the associated curve to be generated for that period.

To calculate (ii), we use the model described (Fig. 5) which acts independently from the ongoing absorption process, allowing initial values for the concentration in each compartment to undergo elimination, and distribution between compartments.

Based on the above model, the rate of change of drug concentration in the compartments is given by Eq. 7 and 8:

$$\frac{dC_p}{dt} = K_{21}\frac{D_t}{V_t} - K_{12}\frac{D_p}{V_p} - K_{el}\frac{D_p}{V_p} \quad (7)$$

$$\frac{dC_t}{dt} = K_{12}\frac{D_p}{V_p} - K_{21}\frac{D_t}{V_t} \quad (8)$$

Solving gives

$$C_p = \left[\frac{D_p^0(K_{21}-\alpha)+D_t^0K_{21}}{V_p(\beta-\alpha)}\right]e^{-\alpha t} + \left[\frac{D_p^0(\beta-K_{21})-D_t^0K_{21}}{V_p(\beta-\alpha)}\right]e^{-\beta t} \quad (9)$$

Similarly

$$C_t = \left[\frac{D_t^0(\beta-K_{21})+D_p^0K_{12}}{V_t(\beta-\alpha)}\right]e^{-\alpha t} + \left[\frac{D_t^0(K_{21}-\alpha)-D_p^0K_{12}}{V_t(\beta-\alpha)}\right]e^{-\beta t} \quad (10)$$

Eq. 9 and 10 therefore represent the concentration values remaining for C_p and C_t after time t has elapsed assuming no further absorption takes place, and can be incorporated into the overall calculation of results.

2.6. Study designs

2.6.1. Acrivastine bioavailability study (unpublished Wellcome study; Whiteman et al., 1986)

The purpose of this study was to compare an experimental controlled release capsule formulation administered in both the fasted and fed state with an immediate release capsule given in the fasted state. Both products contained 12 mg acrivastine. The dissolution rate was determined on six individual products using the USP (XXI) rotating paddle apparatus at 50 rpm with 900 ml 0.1 M hydrochloric acid. Solutions were assayed spectrophotometrically.

The study was carried out on six volunteers in a three-way randomised crossover schedule with a washout period of 6 days. The two fasted limbs followed an overnight fast and products were given with 100 ml of water. For the other limb, the controlled release capsules were given with a light breakfast. Blood samples were taken up to 25 h and assayed for acrivastine by radioimmunoassay.

The mean blood level data for the immediate release capsules was fitted to the one-compartment open model (1 COM) using conventional graphical techniques. The calculated elimination rate constant (K_{el}) and volume of distribution (V_p) were employed for subsequent DIPS simulations.

2.6.2. Bupropion bioavailability study (unpublished Wellcome study; Yuen et al., 1985)

The study compared the plasma profiles following oral administration of: (i) 2×100 mg bupropion hydrochloride immediate release tablets; (ii) 2×130 mg bupropion maleate capsules ($\equiv 200$ mg hydrochloride); (iii) 200 mg bupropion hydrochloride controlled release (fast) capsules; and (iv) 200 mg bupropion controlled release (slow) capsules.

Dissolution data were obtained on the two controlled release formulations using the BP (1983) rotating basket apparatus at 100 rpm with 900 ml deionised water as the dissolution medium. Five individual determinations were performed and solutions were assayed spectrophotometrically.

12 healthy volunteers took each of the preparations on a randomised basis at intervals of not less than 2 weeks. Treatments were given following an overnight fast with 200 ml water. Blood samples were taken over a 25 h period and assayed for bupropion by HPLC.

The mean blood level data for the immediate release tablets were fitted to the 1 COM (as for acrivastine). The calculated K_{el} and V_p values were employed for subsequent DIPS simulations. The data for the bupropion maleate capsule were not further assessed, since it was present as a second immediate release product and was shown to be bioequivalent to the bupropion hydrochloride immediate release tablets.

2.6.3. Metoprolol bioavailability study (Sandberg et al., 1991)

This study evaluated three experimental controlled release tablet formulations, in vitro and in vivo, together with an aqueous solution given orally and intravenously. The tablet formulations contained metoprolol succinate CR pellets with an ethyl cellulose coating membrane which was then mixed with microcrystalline cellulose and compressed to give a rapidly disintegrating tablet. The dissolution rate was measured on the controlled release dosage forms using the USP (XXII) rotating paddle apparatus. Various stirrer speeds (50, 100, 150 rpm) and pH values (1.2, 4.0, 6.8) were employed. Individual determinations on six products were performed. Since release rate was independent of stirring rate and pH, the 100 rpm/pH 6.8 data were used as supplied by the authors.

10 healthy male volunteers each took all of the preparations (95 mg metoprolol succinate) in a randomised five-way crossover study with a minimum 5 day washout period. Treatments were given following an overnight fast with water; 200 ml with the controlled release dosage forms and

100 ml with the 100 ml solution. An intravenous solution was given as an infusion. Blood samples were taken at intervals up to 30 h. Plasma metoprolol levels were determined by gas chromatography.

We fitted the mean oral solution blood level

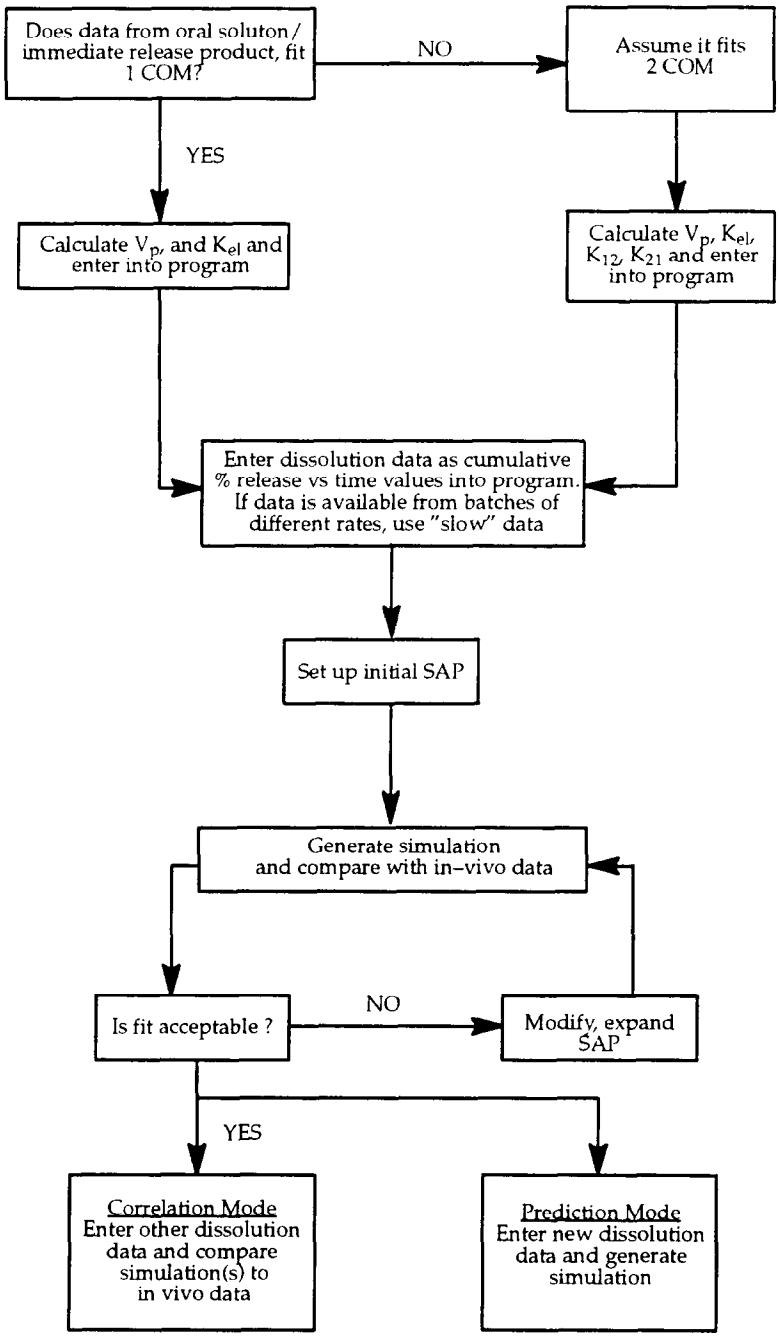

Fig. 6. Flow diagram showing operation of DIPS.

data to the two-compartment open model (2 COM) using conventional graphical techniques. The micro rate constants (K_{12}, K_{21}, K_{el}) and V_p were calculated using standard equations and employed in the subsequent DIPS simulations.

2.6.4. Felodipine bioavailability study (Wingstrand et al., 1990)

The aim of the study was to measure the bioavailability of three experimental formulations vs an oral solution, and to assess the relationship between in vitro and in vivo data. The tablets containing 10 mg felodipine were all erodible matrix products containing primarily hydroxypropylmethylcellulose. 10 ml of a water-ethanol solution of drug (1 mg/ml) was employed as a control.

The authors determined the dissolution rate of the controlled release tablets using the USP (XXII) rotating paddle apparatus at 50 rpm, modified with a fixed stationary basket containing the product suspended above the paddle. A wetting agent (1% sodium dodecyl sulphate) was added to the 500 ml phosphate buffer solution. Six determinations were carried out on each product and the concentration of dissolved drug was determined spectrophotometrically.

16 healthy volunteers each took the four formulations at weekly intervals in an open randomised crossover study. Subjects took 200 ml of water with the preparations following an overnight fast. Blood samples were collected at intervals up to 24 h and plasma felodipine levels were determined by gas chromatography.

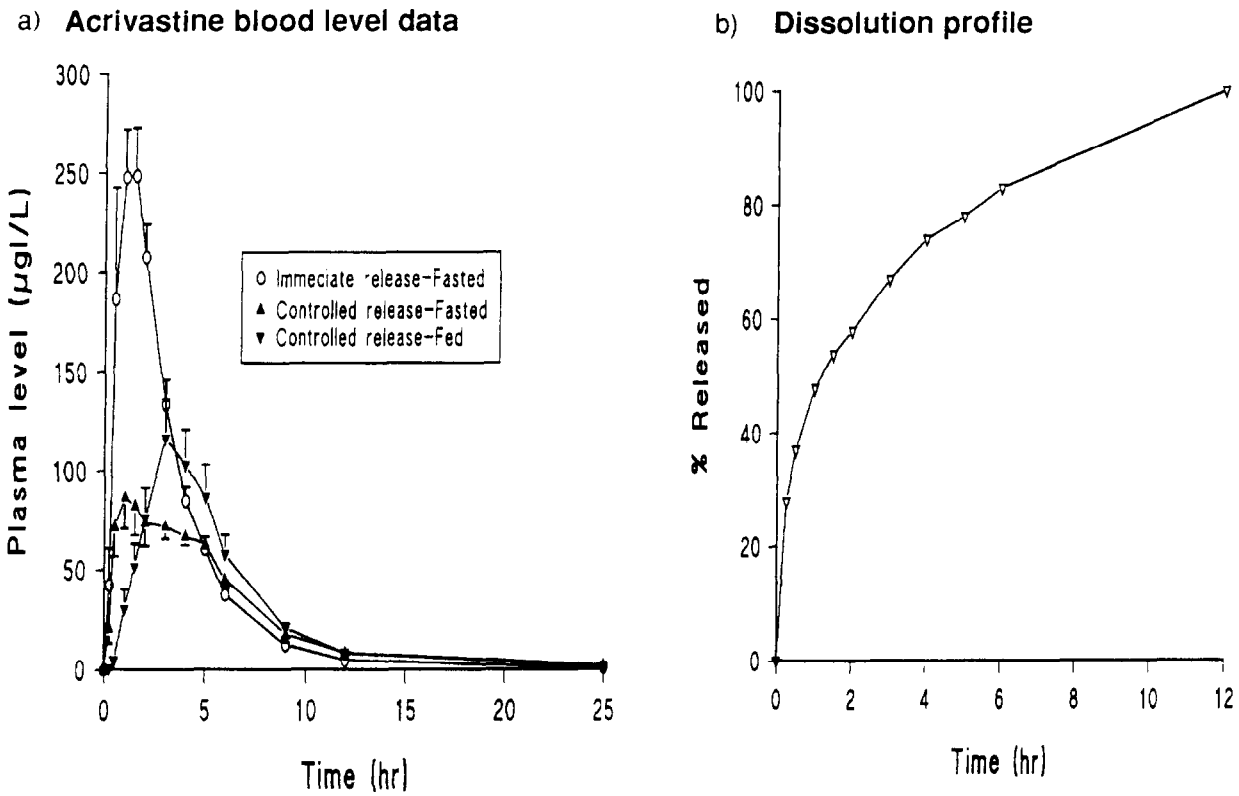

Fig. 7. Mean (a) blood level profiles ($n = 6$, $\pm$SE) and (b) CR dissolution curve ($n = 6$) for acrivastine formulation. Comparison of (c) blood level profiles with DIPS simulation and (d) upper and lower dissolution specification predictions (12 mg) with immediate release (8 mg) simulation.

We fitted the mean felodipine solution blood level data to the 2 COM (as for metoprolol). The micro rate constants were calculated in an identical manner to that employed for metoprolol and these were employed for subsequent DIPS simulations.

2.6.5. Paracetamol bioavailability study (Van Bommel et al., 1991a,b)

This paper compared the in vitro dissolution and in vivo plasma profiles of two novel controlled release dosage forms containing paracetamol as the model drug. The two CR formulations were prepared by coating sugar cores with a mixture of ethyl cellulose, drug and xylitol. The pellets were packed into hard gelatin capsules. An oral solution was used as a control.

Dissolution data were generated with the USP (XXII) rotating paddle method, and also with a flow-through apparatus. A variety of dissolution media were employed. Since the results obtained showed no significant differences, the authors used the mean value and these have been used for the DIPS simulations.

11 healthy volunteers took part in an open and randomized, three-way study with a minimum washout period of 1 week. Each formulation (approx. 450 mg paracetamol) was given with 200 ml water following an overnight fast or as a solution containing 450 mg drug in 200 ml water. Blood samples were taken at intervals up to 33 h. Plasma paracetamol levels were determined by HPLC.

We fitted the mean data from the oral solution limb to the 1 COM (as for acrivastine) and the calculated K_{el} and V_p values were employed for the DIPS simulations.

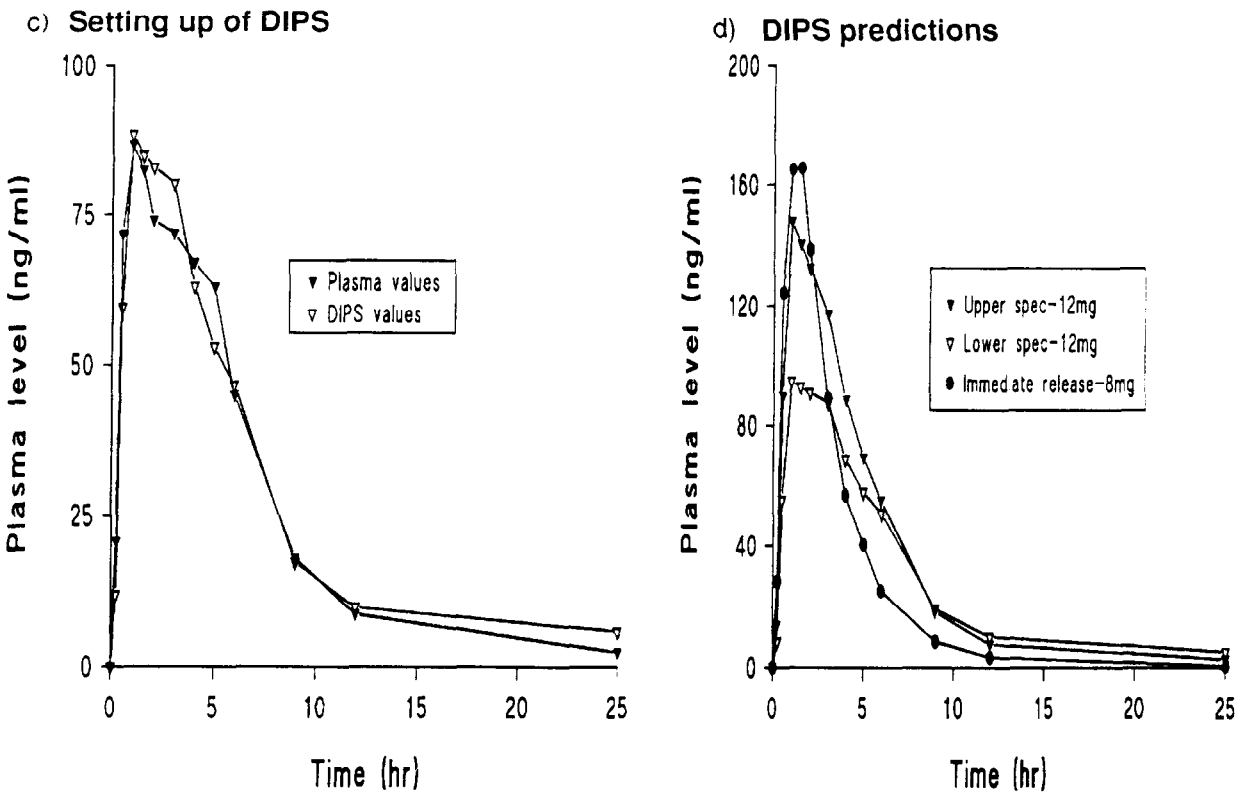

Fig. 7 (continued).

3. Results and discussion

3.1. Acrivastine study

The mean blood level profiles for the immediate release (IR) capsules given in the fasted state and the controlled release capsule administered both in fasted and fed states are shown in Fig. 7a, with the associated dissolution curve in Fig. 7b. Having entered the dissolution data and the estimated pharmacokinetic parameters, the sequential absorption profile (SAP) was optimised to given an acceptable fit to the fasted CR mean blood level profile (Fig. 7c). It should be noted that the fed CR data were not further employed in the context of this publication, since simulations were only required for administration of the product in the fasted state. Acrivastine exhibits site-dependent absorption and it was found necessary to employ five sequential first-order rates over a 24 h period (see Table 1). If the dissolution test is predictive of release in vivo, then the SAP is indicating the rate of absorption of dissolved drug as the dosage form moves along the GI tract; e.g., from 0.75 to 3 h, $K_a = 0.4\ h^{-1}$ and from 3 to 6 h = 0.15 h^{-1}. The significant reduction in absorption after about 3 h is in agreement with unpublished studies on colonic absorption of the drug.

The proposed in-house dissolution specification values were entered and the resultant single dose simulations are shown in Fig. 7d, together

Table 1
Summary of DIPS data

Drug	Sequential absorption profile (SAP) [a]			Correlation parameters	
	Time (h)	Rate (h^{-1})	% absorbed [b]	r^2 [c]	Slope [d]
Acrivastine	0 – 0.25	1	70	not applicable	
	0.25– 0.75	2.5			
	0.75– 3	0.4			
	3 – 6	0.15			
	6 –24	0.02			
Bupropion	0 – 2	5	85	0.984	0.984
	2 – 4	1		(fast)	
	4 –12	0.2			
Metoprolol	0 – 0.25	0	48	0.948	0.959
	0.25– 2	2		(fast)	
	2 – 6	0.5		0.894	1.038
	6 –30	0.1		(medium)	
Felodipine	0 – 3	10	56	0.352	0.839
	3 – 6	1		(fast)	
	6 –10	0.175		0.511	0.769
	10 –14	0.15		(medium)	
	14 –24.5	0.04			
Paracetamol	0 – 1	5	89	0.982	1.080
	1 – 3	0.75		(fast)	
	3 – 5	0.3			
	5 –12	0.15			
	12 –24	0.1			

[a] Determined by iterative fitting of DIPS curve to mean plasma curve of slow product or only tested product.
[b] Percentage absorbed at 24 h predicted by DIPS for slow product or only tested product.
[c] Correlation coefficient ^{2} for linear least-squares relationship between DIPS curve (fast and/or medium product) and mean plasma curve at each corresponding time point.
[d] Slope of line for linear least-squares relationship between DIPS curve (dependent variable) and mean plasma curve (independent variable).

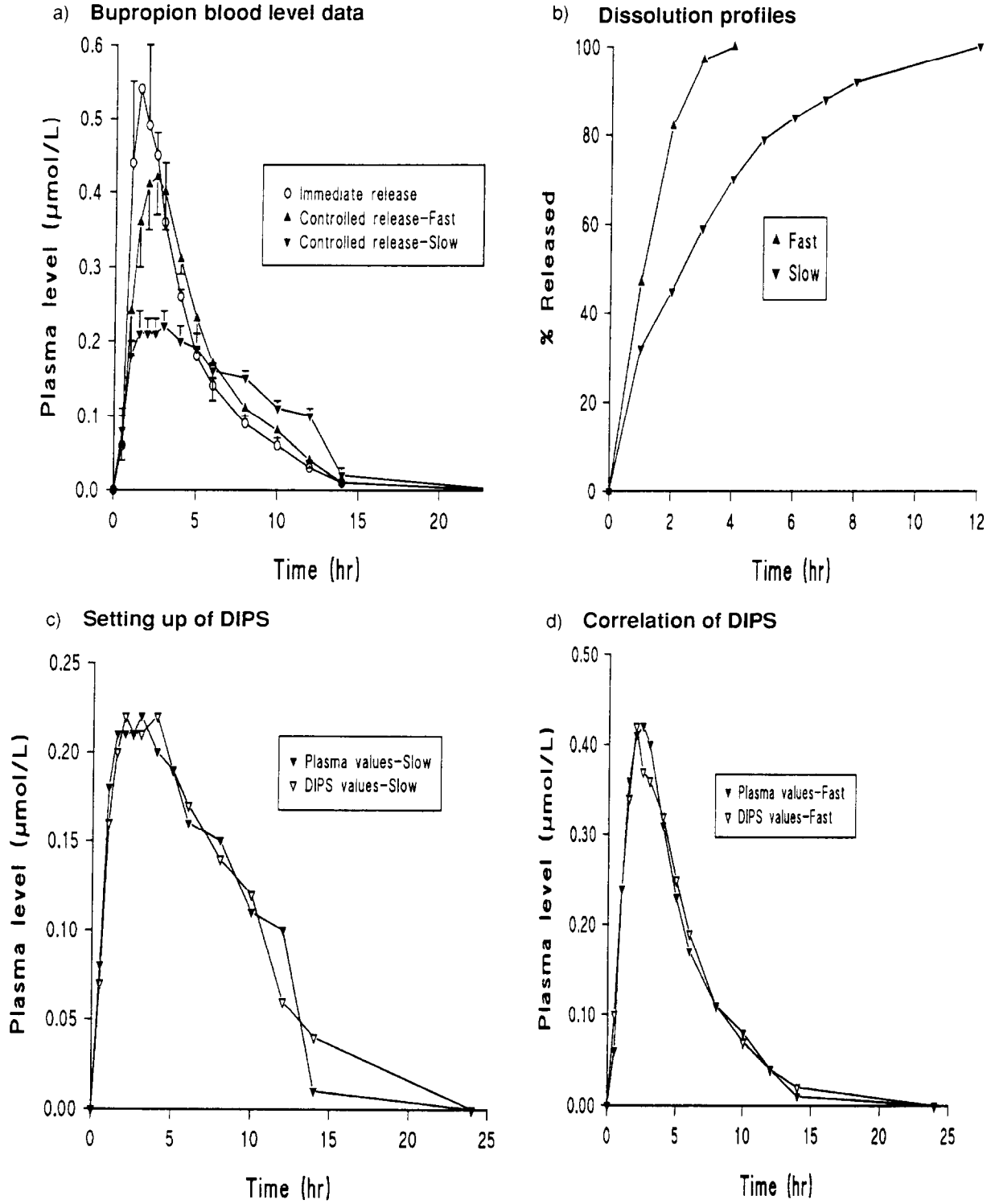

Fig. 8. Mean (a) blood level profiles ($n = 12$, $\pm$SE) and (b) dissolution curves ($n = 5$) for bupropion formulations. Comparison of blood level profiles of (c) slow and (d) fast releasing products with DIPS simulations.

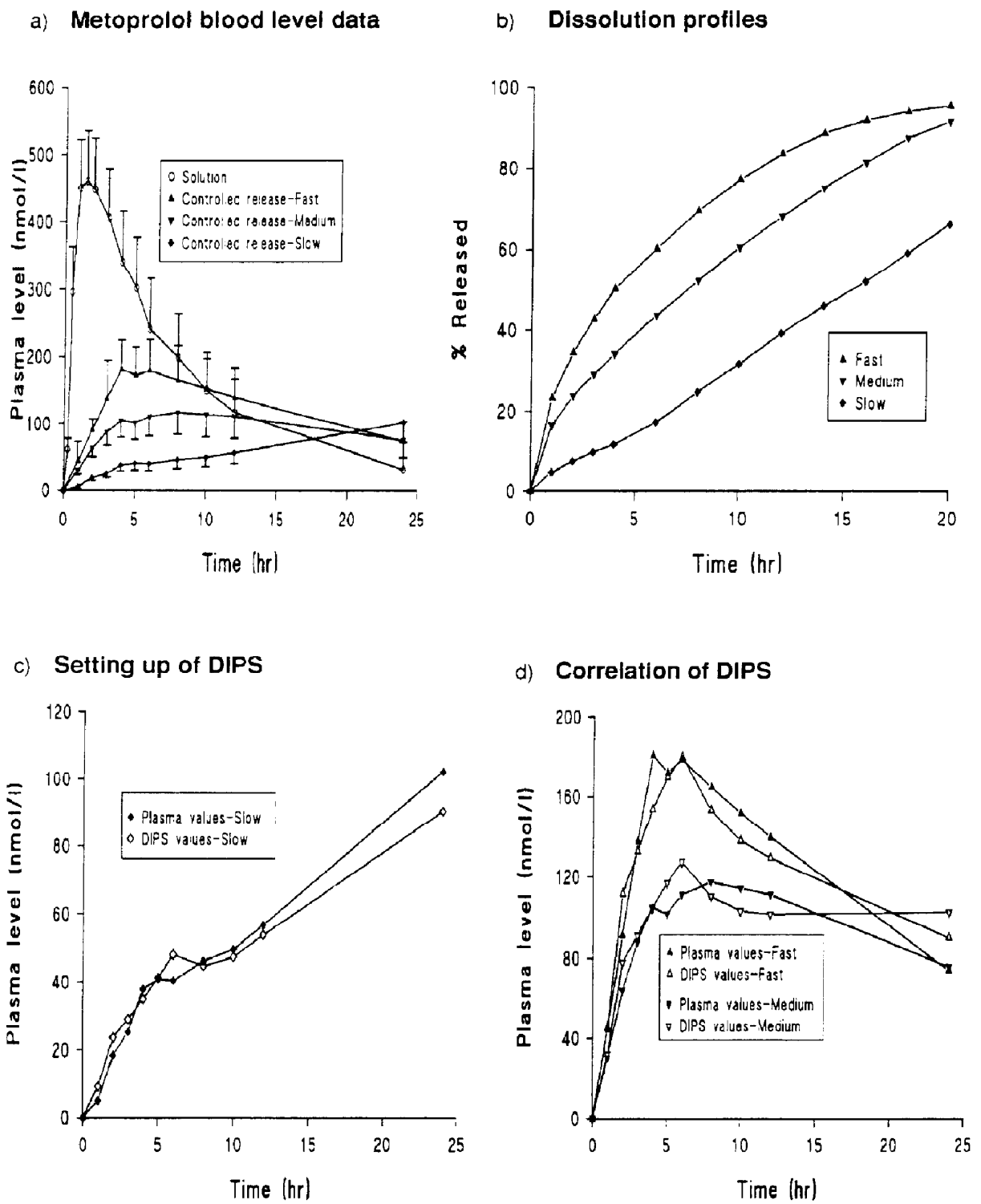

Fig. 9. Mean (a) blood level profiles ($n = 10$, $\pm$SE) and (b) dissolution curves ($n = 6$) for metoprolol formulations. Comparison of blood level profiles of (c) slow and (d) fast/medium releasing products with DIPS simulations.

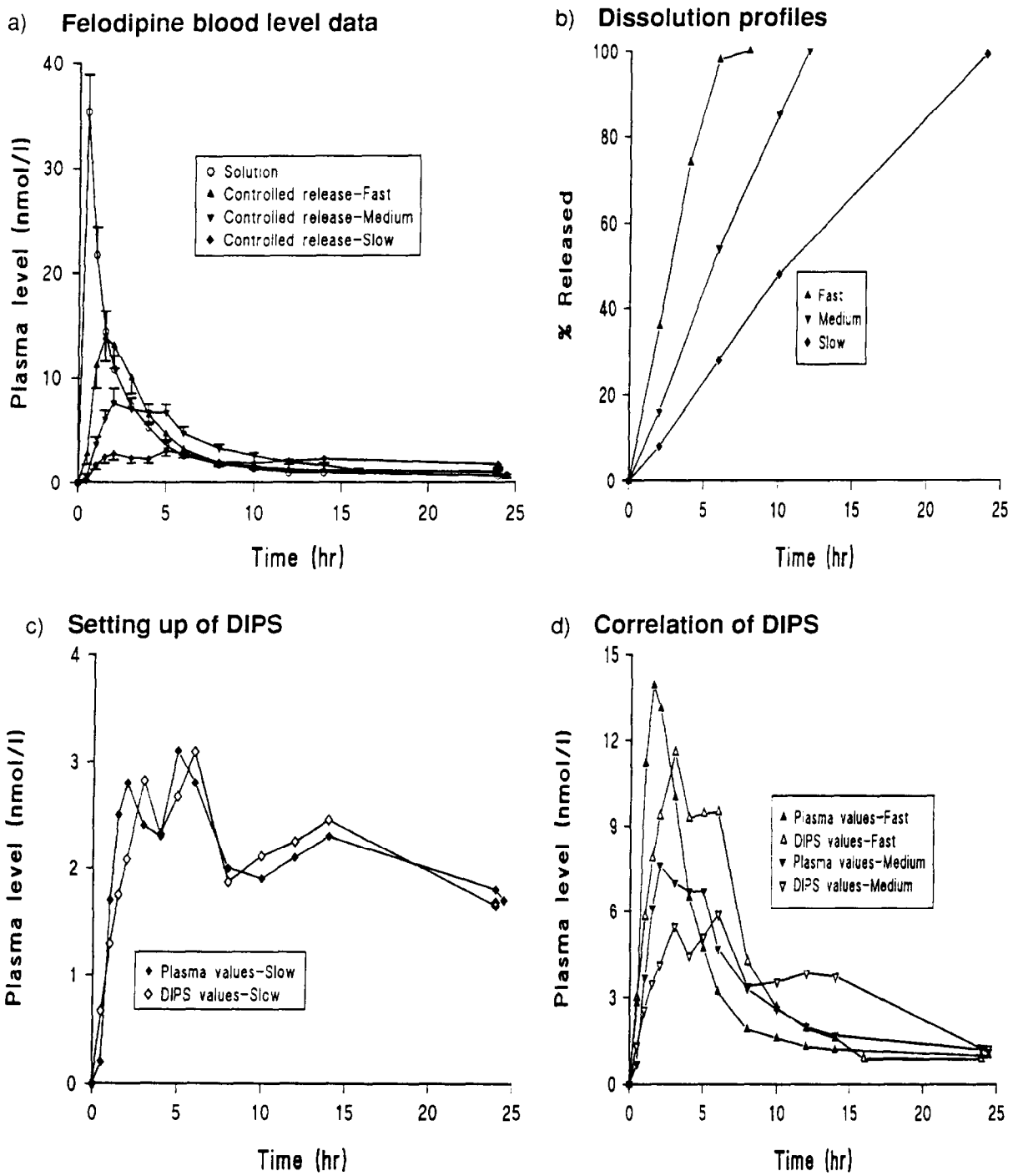

Fig. 10. Mean (a) blood level profiles ($n = 16$, $\pm$SE) and (b) dissolution curves ($n = 6$) for felodipine formulations. Comparison of blood level profiles of (c) slow and (d) fast/medium releasing products with DIPS simulations.

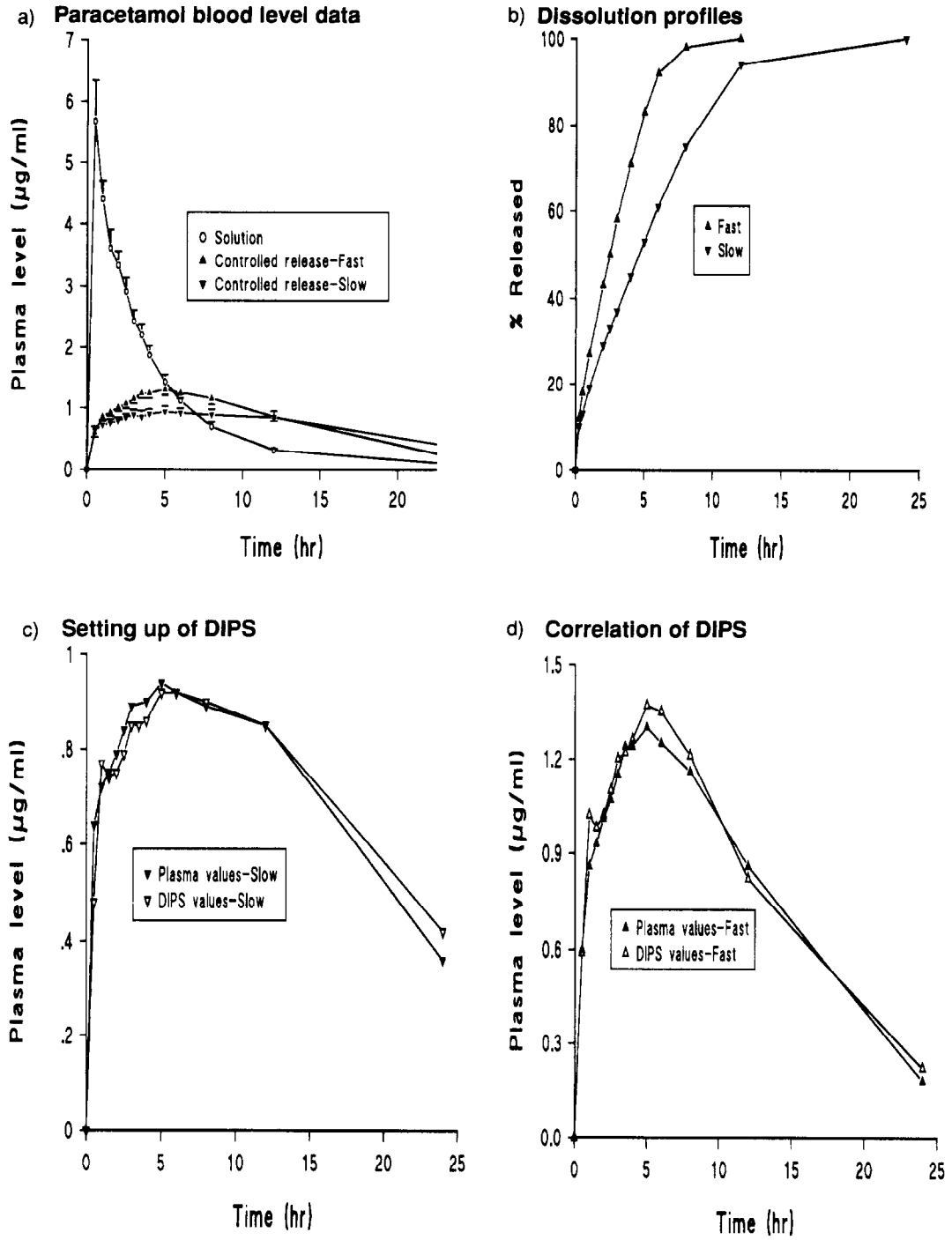

Fig. 11. Mean (a) blood level profiles (n = 11, ±SE) and (b) dissolution curves (n = > 6) for paracetamol formulations. Comparison of blood level profiles of (c) slow and (d) fast releasing products with DIPS simulations.

with an 8 mg IR profile calculated assuming linear pharmacokinetics from the 12 mg IR in vivo profile. The peak level (C_{max}) for the upper specification curve is seen to be less than for the IR profile which satisfied one of the criteria for the development of the dosage form. Also, the upper and lower simulations indicate higher plasma levels between 3 and 12 h compared to the IR profile. Fig. 7d also shows that the AUC of the slower profile is less than that of the upper profile, indicating that DIPS is predicting that bioavailability will decrease if the release rate is progressively reduced.

3.2. Other retrospective studies

In the previous example, DIPS was employed in the prediction mode where simulations were employed to show the likely effect on blood level profiles where only limited in vivo data would be available as a result of testing a single formulation rather than a range of in vitro profiles. The confidence that can be placed on predictions obtained with a program such as DIPS depends on demonstrating a high degree of correlation from analysis of suitable human bioavailability studies. The examples relating to bupropion, metoprolol, felodipine and paracetamol were chosen to evaluate the program, and illustrate various aspects of its use and possible limitations.

The procedure employed was the same as that employed for acrivastine except that the SAP was generated using the values for the slowest releasing formulation. This made the best use of the in vivo data in understanding the relationship between dissolution and absorption in the GI tract as it examined drug absorption over the longest time period. The dissolution data from the other, faster releasing formulation(s) were entered, and the resultant predictions compared to the actual mean blood level profile(s). The blood level profiles and the 'setting up' and 'correlated' curves are shown in Fig. 8–11. A summary of SAPs, % absorbed (calculated by DIPS and employing the dissolution and SAP values) and correlation parameters, is shown in Table 1.

Buproprion {(±)-2-*tert*-butylamine-3′-chloropropiophenone} is well absorbed orally and has a terminal plasma elimination half-life of 14 h (Findlay et al., 1981). The extent of correlation for the fast releasing profile between the DIPS and the mean in vivo profile can be seen to be excellent. The linear least-squares analysis, comparing actual and simulated plasma values at equivalent time points (without weighting any of the data values but forcing through the intercept), gave values for the square of the correlation coefficient (r^2) and slope both equal to 0.984 for the fast releasing product.

For metoprolol a similar result was obtained, DIPS again showing a good correlation with the mean blood level data for the fast ($r^2 = 0.948$, slope 0.959) and medium ($r^2 = 0.894$, slope = 1.038) releasing products. The paper of Sandberg et al. (1991) showed reduced bioavailability for the CR formulations which was inversely related to dissolution rate. The authors concluded that this was due to increased first pass metabolism with time, but that incomplete absorption was probably a factor for the slowest releasing product. The dissolution data showed that for this particular profile only about 66% had been released in vitro after 20 h. Therefore, it may be under these circumstances that elimination from the GI tract had occurred before all the drug had been released, leading to reduced bioavailability.

The felodipine data for the medium releasing product were extrapolated to 100% release assuming a zero-order profile, since the published data showed only 85% release at 12 h. The resulting profile (Fig. 10d) showed that DIPS underestimated the rate of entry of drug into the systemic circulation for the fast and medium product particularly, as demonstrated by reference to the C_{max} values. This was the case, even with the SAP set to give an initial absorption rate of 10 h^{-1} over 3 h (i.e., not rate limiting). Consequently, the correlation between the predicted plasma profiles for the fast and medium products compared to the actual mean blood level data was poor.

Reference to the paper from which the data were obtained (Wingstrand et al., 1990) suggests that the dissolution test may be underestimating the rate of release in vivo. Felodipine is unusual in that it is one of the few examples of a very

poorly water soluble molecule (0.5 mg/l) presented in CR form. The dissolution data were generated in a buffer solution of unknown pH, containing 1% sodium dodecyl sulphate as a wetting agent to obtain sink conditions which might have been expected to increase the release rate. However, comparison in the paper between in vitro and in vivo release (obtained by numerical deconvolution) for the fast and medium releasing products did suggest that the dissolution test was underestimating release in vivo. Therefore, the poor correlation obtained in this example using DIPS is not unexpected.

The last example used for the validation of DIPS is taken from the papers of Van Bommel et al. (1991a,b) for two related experimental CR tablets containing paracetamol. Again the SAP was optimised to give an acceptable fit to the actual blood level profile of the slower of the two formulations. The predicted r^2 and slope values for the fast batch were 0.985 and 1.083, respectively. Fig. 11d shows the excellent correlation between actual and predicted plasma levels with only a 5% difference in C_{max} and identical t_{max} values. The dissolution rate was shown to be highly independent of the test conditions employed, particularly in relation to changes in pH and stirring conditions. Therefore, the release in vitro is likely to be very similar to that in vivo. Our conclusion (based on the SAP obtained with DIPS) is that a progressive decrease in absorption rate of paracetamol occurs through the small intestine, with an initially high rate (5 h^{-1}) for a period of about 1 h, and then a progressive decline in absorption rate as the dosage form moves along the GI tract.

4. General discussion

Linear least-squares regression analysis has been employed to estimate the quality of fit between simulated and mean in vivo blood level values at equivalent time points, together with the use of non-compartmental parameters such as C_{max}, t_{max} and AUC. This approach has also been employed by Brockmeier (1986) and Smolen et al. (1979). Experience obtained with the examples described in this paper suggest that a minimum value of $r^2 = 0.9$ and slope $= 1 \pm 0.1$ are acceptable.

Various authors have used alternative criteria in estimating the accuracy of fit, including Leeson et al. (1985) who assessed how closely a simulated profile approached the mean blood level profile, ± 1 SD. However, reference to certain of the examples in our paper suggests that such a criterion is arbitrary and potentially misleading, since factors other then release/absorption in vivo (e.g., first pass metabolism) may be the major factors in determining inter- and intra-subject variability. For this reason we employed the regression line comparison of the simulated and actual profiles.

An important consideration in relation to the accuracy of DIPS predictions is the design of the dissolution test. The relationship between drug release in vivo and drug absorption, as stated in section 1, can be complex and it is necessary that the dissolution test accurately models release in the GI tract, otherwise confidence in DIPS predictions will be reduced. Ideally, the release rate should be independent of pH, agitation conditions and ionic strength of the medium. For two of the examples employed in this publication (metoprolol and paracetamol), the dissolution data available show that the in vitro release profiles were unaffected by changes in pH and agitation conditions. Under these conditions it is considered that the dissolution test should be predictive of release in vivo.

Only one of the studies described in this paper (i.e., acrivastine) included administration in the fed state. DIPS cannot make predictions about the likely effect of food on the plasma profile of a CR dosage form unless an initial in vitro/in vivo relationship has been established. Its subsequent use would also be dependent on understanding whether any change in plasma profile is due to food modifying release in vivo or to other factors such as delayed stomach emptying. This would be an area worthy of further study with this technique.

Of the examples taken from the literature, only felodipine presented difficulties in terms of setting up the SAP. As discussed earlier it is

considered that the felodipine dissolution test was underestimating the release in vivo and therefore the calculated SAP was not accurate in terms of predicting absorption in vivo. The use of a parameter such as the SAP is considered essential for situations where the drug molecule (e.g., acrivastine) is incompetely absorbed, particularly from the lower GI tract. Deconvolution techniques cannot be employed for incompletely drugs (Nicklasson et al., 1987), unless suitable data exist following direct administration of drug solutions into different regions of the tract.

Three of the drugs used as examples in this paper undergo significant first pass metabolism (bupropion, metoprolol and felodipine). However, the correlation obtained between simulated and in vivo profiles for the fast and fast/medium releasing products for bupropion and metoprolol, respectively, show that extensive and variable metabolism does not preclude the use of DIPS as a predictive technique. However, there may be drugs whose metabolism is increased (as a result of administration in CR form), when the rate at which they enter the systemic circulation is reduced. This does not invalidate the concept of the SAP but does mean the value obtained may include a component related to metabolism. When reduced bioavailability of a CR product is observed it is not always apparent whether this is solely due to release/absorption factors or increased metabolism. To assess this, it would be necessary to measure metabolite as well as intact drug levels. Therefore, the % absorbed values calculated by the program and shown in Table 1 should be interpreted carefully.

The mathematical accuracy of DIPS has been rigorously assessed in relation to the treatment of the dissolution data. By using theoretical dissolution data with zero- and first-order kinetics we have checked the accuracy of the time slicing process. The size of the time slice is a factor in determining the accuracy of the simulated data and is routinely set at 0.01 h. For a first-order dissolution curve, we have shown that the errors in terms of the simulated plasma concentrations are less than $\pm 2\%$. As the release rate approaches linearity (i.e., zero-order), the error approaches zero. The concept of the sequential absorption profile (SAP which appears similar to that containcd in a paper of Iga (1986) has also been shown to be mathematically correct both from first principles and using theoretical values.

5. Conclusion

The DIPS program has proved to be a user friendly system employing readily available hardware. It has been employed in the development of a controlled release capsule formulation of acrivastine, a molecule exhibiting site-dependant gastrointestinal absorption. Simulations were generated for the proposed in vitro dissolution specification. The ability to use dissolution data without any kinetic modelling and to set up sequential absorption profiles (SAP) is considered to be of value in the development of a wide variety of drug molecules and dosage forms as controlled release entities. A high degree of correlation was obtained between predicted and actual blood level profiles of bupropion, metoprolol and paracetamol CR dosage forms based on retrospective assessment.

6. References

Brockmeier, D., In vitro/in vivo correlation of dissolution using moments of dissolution and transit times. *Acta Pharm. Technol.*, 32 (1986) 164–174.

Chiou, W.L., New compartment and model independent method for rapid calculation of drug absorption rates. *J. Pharm. Sci.*, 69 (1980) 57–62.

Cohen, A.F., Hamilton, M.J., Liao, S.H.T., Findlay, J.W.A. and Peck, A.W., Pharmacodynamic and pharmacokinetics of BW825C: A new antihistamine. *Eur. J. Clin. Pharmacol.*, 28 (1985) 197–204.

Findlay, J.W.A., Van Wyck Fleet, J., Smith, P.G., Butz, R.F., Hinton, M.L., Blum, M.R. and Schroeder, D.H. Pharmacokinetics of bupropion, a novel antidepressant agent, following oral administration to healthy subjects. *Eur. J. Clin. Pharmacol.*, 21 (1981) 127–135.

Iga, K., Ogawa, Y., Yashiki, T. and Shimamoto, T., Estimation of drug absorption rates using a deconvolution method with nonequal sampling times. *J. Pharmacokinet. Biopharm.*, 14 (1986) 213–225.

Langebucher, F., Linearization of dissolution rate curves by the Weibull distribution. *J. Pharm. Pharmacol.*, 24 (1972) 979–981.

Leeson, L.J., Adair, D., Clevenger, J. and Chiang, N. The In vitro development of extended release solid oral dosage forms. *J. Pharmocokinet.*, 13 (1985) 493–514.

Nicklasson, M., Graffner, C. and Nilsson, M., Assessment of in vivo drug dissolution by means of numerical deconvolution considering gastrointestinal availability. *Int. J. Pharm.*, 40 (1987) 165–171.

Sandberg, A., Abrahamsson, B., and Sjogren, J., Influence of dissolution rate on the extent and rate of bioavailability of metoprolol. *Int. J. Pharm.*, 68 (1991) 167–177.

Smolen, V.F., Ball, L. and Scheffler, M., Predicting the time course of in vivo bioavailability from in vitro dissolution tests: control systems engineering approaches. *Pharm. Tech.*, 3 (1979) 89–102.

Van Bommel, E.M.G., Raghoebar, M. and Tukker, J.J., Kinetics of acetaminophen after single and multiple dose oral administration as a gradient matrix system to healthy male subjects. *Biopharm. Drug Dispos.*, 12 (1991a) 355–366.

Van Bommel, E.M.G., Raghoebar, M. and Tukker, J.J., Comparison of in vitro and in vivo release characteristics of acetaminophen from gradient matrix systems. *Biopharm. Drug Dispos.*, 12 (1991b) 367–371.

Wagner, J., *Fundamentals of Clinical Pharmacokinetics*, Drug Intelligence Publications, IL, 1975.

Wingstrand, K., Abrahamsson, B., and Edgar, B., Bioavailability from felodipine extended-release tablets with different dissolution properties, *Int. J. Pharm.*, 60 (1990) 151–156.