International Journal of Pharmaceutics, 85 (1992) 113–120

IJP 02790

Study on the release of indomethacin from suppositories: in vitro-in vivo correlation

G. Lootvoet [a], E. Beyssac [a], G.K. Shiu [b], J.-M. Aiache [a] and W.A. Ritschel [c]

[a] *Biopharmaceutics Department, Faculty of Pharmacy, 28 Place Henri Dunant, 63001 Clermont-Ferrand Cedex (France),* [b] *Food and Drug Administration, 200 C. Street, S.W., Washington, DC 20204 (USA) and* [c] *University of Cincinnati, Medical Center, 3223 Eden Avenue, Cincinnati, OH 45267-004 (USA)*

(Received 1 November 1991)
(Accepted 2 February 1992)

Key words: Suppository; Indomethacin; In vitro release; Flow-through cell; Dialysis rotating cell; In vitro-in vivo correlation

Summary

The in vitro dissolution kinetics of three different suppository formulations of indomethacin was studied using two different apparatuses, namely, a flow-through cell (Dissotest ®) and a dialysis rotating cell (Pharmatest ®). A comparison between both apparatuses was carried out and two types of dissolutions became apparent depending on whether the excipient used in the formulation was either hydrophilic or lipophilic. The distinction between dissolution profiles was more evident using the flow-through cell. From the in vivo curves parameters furnished by the manufacturers, in vitro/in vivo correlations were performed. A linear relationship was established between the in vitro results obtained and the in vivo percentages absorbed that were calculated according to the Wagner-Nelson method. Simulated blood concentration-time curves were generated from the in vitro released data and the pharmacokinetic parameters obtained. A good superimposition of the experimental plasma concentrations and the simulated curves was obtained with the flow-through cell and the hydrophilic suppository dosage form whereas the simulation with the lipophilic suppository gave imperfect results irrespective of the apparatus used.

Introduction

The aim of this work was to compare two different apparatuses designed for drug release studies from suppositories: a flow-through cell and a dialysis rotating cell. The study was carried out with three different suppository formulations of indomethacin.

Correspondence to: J.-M. Aiache, Biopharmaceutics Department, Faculty of Pharmacy, 28 Place Henri Dunant, 63001 Clermont-Ferrand Cedex, France.

A correlation was attempted between in vitro results and in vivo data by two methods, namely (Wagner and Nelson, 1963) percentage absorbed in vivo vs percentage dissolved in vitro, and (Islasse, 1985) simulated blood level-time curve from in vitro release vs actual blood level-time curve.

Materials and Methods

In vitro dissolution testing

The testing instruments proposed for drug release studies from suppositories can be divided in

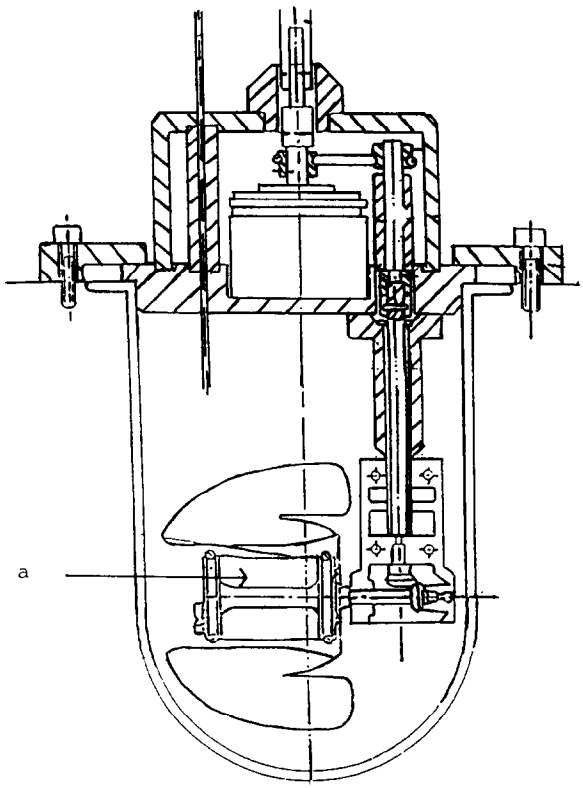

Fig. 1. Pharmatest ® apparatus, a membrane type (MC) dissolution instrument.

two groups, depending on the presence or absence of a dialysis membrane.

The principle of all apparatuses with a membrane is to separate the suppository from the dissolution medium. Advantages are to avoid surface variations between the suppository and the receptor phase, and to make sampling and dosing easier. The Pharmatest ® (MC) (Fig. 1) was chosen as a membrane type of equipment for this study: it consists of a horizontally rotating cylinder (a) provided with dialysis tubing, or a hydrophilic membrane filter in which the suppository is introduced.

The volume inside the cell of 5 ml is filled with the same buffer as the receptor medium (900 ml of phosphate buffer, pH 7.2).

The cell rotates at 50 rpm. A hydrophilic dialysis membrane was selected, and the temperature was maintained at 37 °C during the test.

Systems without any membrane are also available for dissolution testing: they involve a high control of lipid/aqueous, aqueous interface, where the lipid phase would be the melt of a hydrophobic suppository base, and the aqueous phase is the dissolution medium.

Among these devices Dissotest ® (Fig. 2), a flow-through cell (FC), was selected which consists of a pump and a six-suppository cell module. A special cell design exists for suppositories: two adjacent vertical chambers join at the top by means of a convex cavity (a'). The suppository is placed into the first chamber and then, after melting, moves into the second chamber. A continuous flow of solvent is running through the melt mass. The lipophilic base, being lighter than the hydrophilic solvent, will stay on top.

This lower two-chamber part fits into a top composed of a metal grill which holds a filter (Millipore SM 0.5 μm) (b'). Each cell is connected at the bottom to a pump (c') and at the top to the dissolution medium, which is continuously stirred. The buffer recycles from the cell to the flask. Two flow rates of phosphate buffer, pH 7.2, were studied for each formulation: 15 and 20 ml/min.

The experiments were carried out with three formulations of indomethacin: formulation A (supplied by Merck Sharp and Dohme): indomethacin 100 mg, PEG; formualtion B (supplied by Ricker): Indomethacin 100 mg, semi-synthetic glycerides, colloidal silicon dioxide; formulation C (supplied by Ratiopharm): indomethacin 100 mg, semi-synthetic glycerides, colloidal silicon dioxide.

Samples were withdrawn periodically for 6 h and measured by UV absorbance at 318 nm. A standard curve was first established with pure indomethacin in buffer.

In vivo data

For the three products, the manufacturers furnished an in vivo curve and some parameters such as AUC and V_d. Each in vivo concentration-time curve represents the mean after rectal administration to 10 healthy volunteers. The in vivo concentration-time course of the three products can pharmacokinetically best be described by a

one-compartment open model. Analysis of the curves was performed with the SIPHAR program, using the Wagner-Nelson analysis method (1963), which allows one to estimate the absorption rate constant (k_a) and elimination rate constant (k_e).

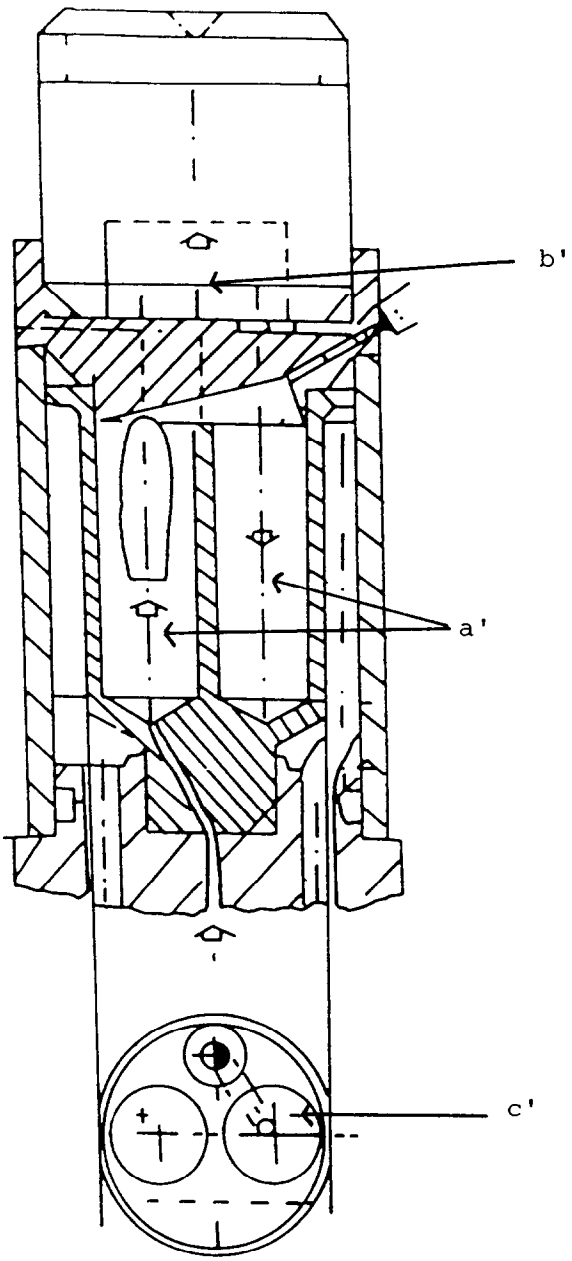

Fig. 2. Dissotest ® apparatus, a flow-through cell type (FC) dissolution instrument.

Results

Comparison between two apparatuses

Two types of dissolution profiles became apparent for both the flow-through cell FC (DISSOTEST®) (Fig. 3) and the membrane cell MC (PHARMATEST®) (Fig. 4), namely, one for the hydrophilic suppository, and another for the lipophilic suppositories.

The difference always exists, and in each case, dissolution is faster from the hydrophilic (A) than from the lipophilic suppositories (B and C). The distinction is more evident in the flow-through cell where the release kinetics follows one of the following patterns:

Either it is very fast and maximal within the first hour (for hydrophilic suppositories), or slow and never exceeds 50% dissolved (for lipophilic suppositories).

In fact, the mechanism of drug released by the flow-through cell has been described by Islasse (1985). A hydrophilic suppository base dissolves in the buffer, and the drug is quickly removed by the flow of the solvent. A lipophilic base first melts over about 30 min, and then floats at the top part of the second chamber. Drug exchange at the lipid/water interface becomes the rate-limiting step of release.

The release kinetics is quite similar for both fatty suppositories irrespective of the apparatus used. However, the amount of drug dissolved at the end of the experiment (6 h) is greater in the membrane cell.

In the membrane method, the drug must be dialyzed through a hydrophilic membrane, and the drug measurements are made in the medium outside the membrane; it appears that indomethacin diffuses almost linearly from a lipophilic base.

In vitro-in vivo correlation

The in vivo percent absorbed of the ultimate amount of drug absorbed as a function of time was derived using the Wagner-Nelson model and

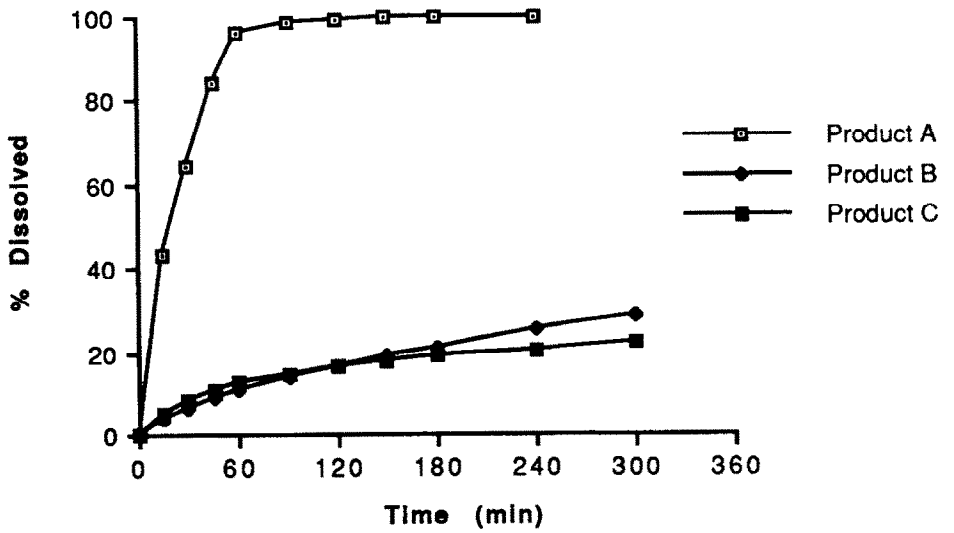

Fig. 3. Dissolution profiles of indomethacin suppositories; 1000 ml phosphate buffer, pH 7.2; flow-through cell, 20 ml/min.

compared with the in vitro percent dissolved. The in vivo percent percent absorbed relative was calculated as follows:

% absorbed relative

$$= \left[\frac{C(t)k_e + \mathrm{AUC}(0 \rightarrow t)}{\mathrm{AUC}(0 \rightarrow \infty)} \times 100 \right]$$

where k_e is the elimination constant, $\mathrm{AUC}(0 \rightarrow t)$ denotes the area under the curve from 0 to t, and $\mathrm{AUC}(0 \rightarrow \infty)$ is the area under the curve from 0 to infinity.

A linear relationship was established for each dosage from under all experimental conditions (Fig. 5).

The flow-through cell with a flow rate of 20 ml/min generally gives the best results: the regression coefficients are higher than 0.9 which indicates good linearity. Thus, a relationship existing between both parameters could be useful to predict in vivo concentration curves from in vitro dissolution curves.

Blood concentration-time curve simulation

Knowing the pharmacokinetic parameters of a subject with regard to a dosage form, blood concentrations are generated by way of a computer program (Aiache et al., 1984) from in vitro percent dissolved data. This simulation program integrates differential equations describing the exchange between different compartments.

The goal was to reproduce the in vivo concentration-time curves, and to validate the dissolution methods.

In vivo data curves show two pharmacokinetic phases for each product: absorption and elimina-

TABLE 1

Actual and simulated indomethacin concentration-time data for preparation A

Time (h)	Simulated concentration from FC (μg/ml)	Simulated concentration from, MC (μg/ml)	Actual blood concentration in vivo (μg/ml)
0	0	0	0
0.5	1.37	0.25	1.36
1	2.90	0.71	3.06
1.5	3.24	1.21	3.19
2	2.85	1.68	2.70
3	1.90	2.31	1.78
4	1.20	2.26	1.02
5	0.76	1.70	0.52
6	0.48	1.10	0.29
7	0.30	0.70	0.22
8	0.19	0.44	0.15
10	0.08	0.17	0.09

For simulation in vitro release data from both flow-through cell (FC) and membrane cell (MC) were used.

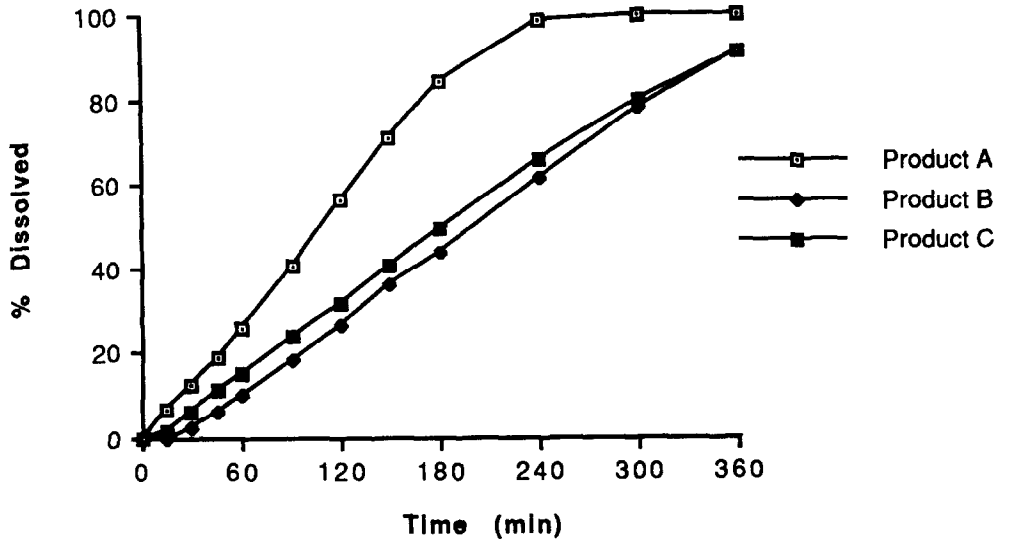

Fig. 4. Dissolution profiles of indomethacin suppositories; 900 ml phosphate buffer, pH 7.2; membrane cell, 50 rpm.

tion. Simulated values were obtained using parameters supplied for in vivo data (k_e, k_a, AUC and V_d) and in vitro percent dissolved, either by the flow-through cell (20 ml/min) or the membrane cell.

Product A The results are presented in Table 1. In order to verify their validity, the simulated curves were drawn on the same graph as the actual concentration-time curves. In the first case (FC), superimposition is shown, in contrast to the second case (MC), where the simulated curve does not at all match with the actual blood level-time curve.

Product B The results of simulation are listed in Table 2. Superimposition of the curves failed in both cases; the simulated curves generated

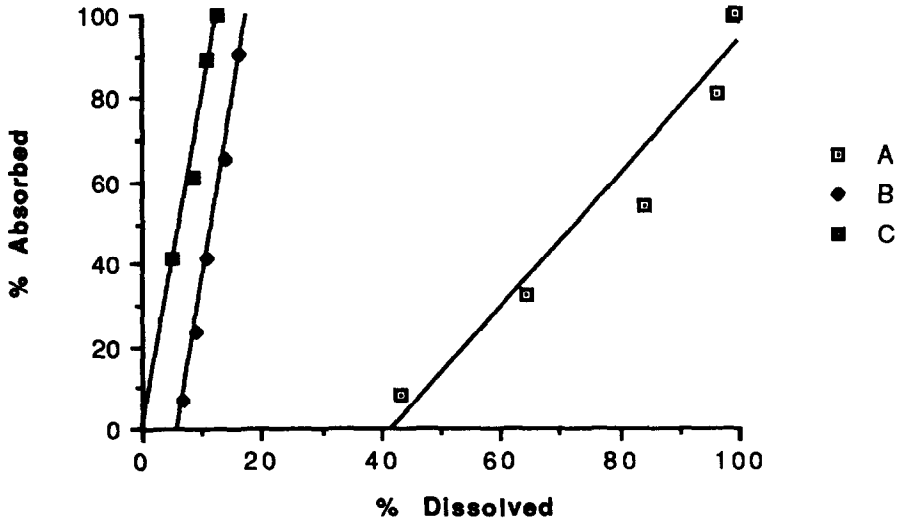

Fig. 5. In vitro/in vivo correlations for indomethacin from different suppository preparations (FC method).

from either FC data or MC data are completely different from the actual in vivo concentration-time curve.

Product C The results of simulated concentrations compared with actual concentrations are summarized in Table 3. As for drug B, superimposition was attempted but failed in both cases.

Discussion

For both in vitro drug release apparatuses studied, two kinds of dissolution profile can be observed: one type for hydrophilic suppositories (product A), and another for lipophilic suppositories (products B and C).

The MC generated a greater release rate with lipophilic suppositories than the FC. The FC resulted in a faster release rate with the hydrophilic suppository than the MC.

However, the diffference between the two lipophilic formulations is quite constant, except with the use of FC at a flow rate of 15 ml/min, where the difference disappears.

Simulated blood concentration-time curves were generated from the in vitro release data for both types of release apparatus (FC and MC). The simulated concentration-time curves resulted in superimposition with the actual in vivo blood level curves only in case of the hydrophilic suppository product and only by the flow-through cell method.

If one compares the AUCs obtained from the simulated blood level-time curves with those of the actual values (see Table 4), it seems that the in vitro methods are able to simulate the extent of bioavailability within about $\pm 10\%$. For the hydrophilic suppository, the FC method resulted in the best prediction, being 9.25% above the actual in vivo AUC whereas the MC method resulted in 12.73%. For the lipophilic suppositories only the MC method gave acceptable results, namely -3.52 and -10.53%, respectively, for preparations B and C. The FC methods resulted in deviation of the predicted AUC between -57 and -75%. Further studies with other drugs need to be performed in order to determine whether this method may serve as a useful test in the future.

Regarding C_{max} and T_{max} predicted from in vitro data, only the FC method for the hydrophilic suppository preparation resulted in a perfect match with the in vivo data, whereas the MC method for the hydrophilic preparation, and both methods for the lipophilic products did not give comparable results to the in vivo data, which

TABLE 2

Actual and simulated indomethacin concentration-time data for preparation B

Time (h)	Simulated concentration from FC (μg/ml)	Simulated concentration from MC (μg/ml)	Actual blood concentration in vivo (μg/ml)
0	0	0	0
0.5	0.04	0.01	0.165
1	0.12	0.08	0.923
1.5	0.18	0.20	1.316
2	0.22	0.33	1.665
3	0.27	0.58	1.405
4	0.28	0.76	0.921
6	0.28	0.95	0.434
8	0.27	0.73	0.197
12	0.26	0.18	0.053

For simulation in vitro release data from both, flow-through cell (FC) and membrane cell (MC) were used.

TABLE 3

Actual and simulated indomethacin concentration-time data for preparation C

Time (h)	Simulated concentration from FC (μg/ml)	Simulated concentration from MC (μg/ml)	Actual blood concentration in vivo (μg/ml)
0	0	0	0
0.5	0.07	0.04	1.17
1	0.18	0.19	2.33
1.5	0.23	0.34	1.50
2	0.25	0.47	1.25
3	0.25	0.69	1.00
4	0.22	0.85	0.86
6	0.17	0.93	0.43
8	0.14	0.71	0.29
12	0.12	0.21	0.19

For simulation in vitro release data from both flow-through cell (FC) and membrane cell (MC) were used.

TABLE 4

Areas under simulated and actual concentration-time curves and percent deviation, and predicted and actual T_{max} and C_{max}, along with percent deviation

Preparation		Actual blood level	Simulated FC	% deviation	Simulated MC	% deviation
AUC (μg h ml^{-1})	A	9.9750	10.8975	+9.25	11.2450	+12.73
	B	6.8022	2.9150	−57.15	6.5625	−3.52
	C	7.8375	2.0075	−74.39	7.0125	−10.53
T_{max} (h)	A	1.5	1.5	0	3	100
	B	2.0	4.0	100	6	300
	C	1.0	2.0	100	6	600
C_{max} (μg ml^{-1})	A	3.19	3.24	1.59	2.31	−27.59
	B	1.67	0.28	−83.23	0.95	−43.11
	C	2.33	0.25	−89.27	0.93	−60.09

is self-explanatory considering the different course of the curves.

The hydrophilic base (PEG) resulted in total drug release in vitro within about 1 h by the FC method, and within about 5 h by the MC method. Converting the in vitro release data into simulated blood concentration-time curves resulted in nearly perfect superimposition with the actual blood level-time curve in the case of the FC method, but not by the MC method. Since T_{max} is a function of input and output

$$T_{max} = \frac{I_n\left(\frac{k_a}{k_{el}}\right)}{k_a - k_{el}}$$

and since k_a is dependent on drug release (k_r), i.e., apparent k_a cannot be faster than k_r, the MC method shows drug release that is too slow to correspond to the in vivo data.

Also, the two lipophilic drug products (B, C) have a lower bioavailability than that of the hydrophilic drug product (A). Additionally, one lipophilic product (B) has a markedly delayed rate of bioavailability. The lower extent of bioavailability from the lipophilic drug product may be due to higher affinity of the drug for the suppository base than for the rectal fluid, i.e., it is explained by the drug's partition characteristics. Indeed, indomethacin's apparent partition coefficient between methylene chloride/phosphate buffer pH 7.1 is 16.3 (O'Brien et al. 1984).

Conclusion

In vitro dissolution of indomethacin from three different commercially available suppository preparations, one hydrophilic base and two lipophilic bases, was studied using two different suppository dissolution instruments, one based on a flow-through cell (FC) (Dissotest®), the other on a membrane cell (MC) (Pharmatest ®). The in vitro release data were then transformed into simulated plasma concentration-time profiles, which then were compared to actual mean blood level curves obtained in man with the same formulations.

In vitro drug release from the hydrophilic base (PEG) occurred within 1 h using the FC, and within 5 h using the MC. Converting the in vitro release data from the FC method into a simulated blood level curve, an excellent correlation was obtained with the actual blood level curve, but not with the MC method.

Regardless of the in vitro dissolution instrument used, no in vitro-in vivo correlation by means of simulated blood level curves could be obtained for the lipophilic suppository dosage forms. Total percent dissolved was too low in the flow-through

cell to be correlated. Although dissolution was greater in the MC, the results were not better for in vivo simulations, than FC results.

When the AUCs of the simulated concentration-time profiles were compared to the actual values, the 'predicted extent of bioavailability from in vitro data' was within about $\pm$ 10% for the hydrophilic base using the FC method, and for the lipophilic bases using the MC method. 'The rate of predicted bioavailability' measured from simulated T_{max} and C_{max} matched with in vivo data only for the hydrophilic base and the FC method.

References

Aiache, J.M., Turlier, M. and Tanguy, A. Pharmacokinetics data processed by microcomputer for the formulation of optimal drug dosage form. *Eur. J. Drug Metab. Pharmacokinet.*, 9 (1984) 89–109.

Islasse, M., Etude de la cinétique de libération des principes actifs à partir des suppositoires. Mémoire de DESS, Faculté de Pharmacie de Clermont-Ferrand, 1985.

O'Brien, M., McCauley, J. and Cohen, E., Indomethacin. In Plorey, K. (Ed.), *Analytical Profiles of Drug Substances*, Vol. 13, American Pharmaceutical Assoc., Washington, DC, 1984, p. 227.

Wagner, J.G. and Nelson, E., Percent absorbed time plots derived from blood levels and for urinary excretion data. *J. Pharm. Sci.*, 52 (1963) 610–613.