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Influence of amount of hard fat in suppositories on the in vitro release rate and bioavailability of paracetamol II. A comparison between three compositions and a rectal solution

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Abstract

The flow-through cell has been used to investigate whether it is possible to discover any relationship between the in vitro dissolution rate of paracetamol from suppositories and the plasma concentrations reached after administration to eight healthy volunteers. A rectal solution was used as a reference. Three suppository compositions were varied with regard to amount of drug substance in relation to total suppository weight and size. The in vivo study was designed to explore the use of statistical moment analysis and convolution/deconvolution in the association of in vivo data and in vitro dissolution results. An increase in both rate and extent of bioavailability was observed when decreasing the fraction and increasing the size, but it was not explained to what degree each of these factors contributed. The flow-through method using a 22.6 mm cell, primarily developed for oral dosage forms, was found to produce dissolution profiles which associated well with the plasma concentration profiles obtained both when a statistical moment analysis and the convolution method was applied. The most optimal flow rate studied was 28 ml/min which reflected the in vivo situation better than a lower or a higher flow rate.

Key words: Dissolution testing; Flow-through method; Flow rate; Paracetamol; Fraction of drug substance; Suppository; Rectal solution; Bioavailability; Numerical convolution

1. Introduction

Limited work has been reported discussing the possibility of correlating in vitro dissolution data from rectal dosage forms with in vivo plasma concentration profiles. Several methods have been proposed for testing such correlations for oral controlled/modified-release dosage forms. Skelly et al. (1990) and the Pharmacopeial Forum (1991) discuss in vitro-in vivo correlation in terms of level A, B and C correlations mentioning methods such as those of Wagner-Nelson (1963, 1964), and of Loo and Riegelman (1968), numerical deconvolution/convolution (Langenbucher, 1982;

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Langenbucher and Möller, 1983), statistical moment analysis (Gibaldi, 1984) and single-point correlation (Skelly and Shiu, 1993). Siewert (1991, 1993) summarizes the recommendations and the experiences using the correlation methods referred to above for controlled/modified release products. In biopharmaceutical studies on rectal dosage forms, a qualitative ranking is mainly used based on plasma concentrations vs time profiles in vivo and in vitro dissolution profiles (Roller, 1977; Tukker et al., 1981; Abd Elbary et al., 1983). Single-point correlations are also reported (Ritschel and Banarer, 1973; Terhaag et al., 1985), but only one example of the use of convolution/deconvolution and statistical moment analysis for rectal formulations is found in the literature (Möller, 1984). The purpose of the present study was to investigate whether it is possible to detect any quantitative relationship between in vitro dissolution rate and plasma concentration profiles of paracetamol after administration of lipophilic suppositories with different release profiles.

2. Materials and methods

2.1. Chemicals

Paracetamol, Ph.Eur. and Hard fat, Witepsol H12, Ph.Eur., were used.

A defined particle size of paracetamol was used. The aqueous solubility is 14.3 mg/ml at room temperature and 21.4 mg/ml at 37°C. The partition coefficient (log D) octanol water is 0.5 with the aqueous phase at a pH of 7.4. The pK_a is 9.5 (Albert and Serjeant, 1984).

2.2. Rectal dosage systems

The different paracetamol suppository compositions tested are shown in Table 1. Compositions B and C are the same as the B and C suppositories tested by Gjellan et al. (1994) except that the compositions studied in this paper do not contain 60 mg of codeine phosphate. The suppositories were produced manually on a small scale by homogenising paracetamol, 1000 mg per suppository, into the melted suppository base. The melt was poured into plastic containers (composition C and D) or stainless-steel moulds (composition B). The weights of 20 separate suppositories were checked and found to be within ±5% of the theoretical weight. The content of paracetamol was checked and found to be 1000 mg ± 5%. Panodil™ enemas, 500 mg/enema, were used as reference.

Table 1
Complete composition of the suppositories administered in the clinical study

Suppository	Hard fat (g)	Paracetamol (mg)	Fraction drug subst. [a] (%)	Total weight supp. (g)
B	1.43	1000	41.2	2.43
C	2.20	1000	31.3	3.20
D	3.40	1000	22.7	4.40

[a] Fraction drug substance = (amount paracetamol (g))/(total weight suppository (g)).

2.3. In vitro dissolution tests

The in vitro dissolution rate of paracetamol was examined using the flow-through cell (Disotest/Dissotest CY, Sotax AG, Basel, Switzerland). The size of suppository D made it impossible to use Apparatus I and II and the dissolution cell specially designed for suppositories (12 mm), and only the large cell (22.6 mm) was used for this composition. However, both the suppository cell and the large cell were used to characterise compositions B and C. Water, deaerated by heat, at a temperature of 37 ± 0.5°C was used as a dissolution medium. A flow rate of 8 ml/min was tested in the 12 mm cell which theoretically is calculated to 28 ml/min in the 22.6 mm cell. In addition to 28 ml/min, 14 ml/min and 50 ml/min were tested in the 22.6 mm cell. Both cell-types have a filter head with a large mesh metal filter and one and three prefilters (Millipore, AP 25, France) were used. The tests were performed with six suppositories of each type. The amount of dissolved paracetamol, given as a percentage of the labelled amount dissolved, was detected spectrophotometrically at 243 nm.

2.4. Design of bioavailability study

The volunteers were informed orally and in writing about the aim of the study which was carried out according to the Declaration of Helsinki. All gave their written consent to participate. The study was approved by the Ethics Committee at Södersjukhuset, Stockholm, Sweden.

The trial was designed as a randomised open cross-over study and was performed at approx. 1-week intervals. Eight healthy female (4) and male (4) volunteers aged between 23 and 43 years participated. The subjects fasted 8 h before and 3 h after the administration of the suppositories. They had a microenema (Klyx™, 120 ml, Ferring) about 1 h before administration of the dosage forms in order to standardize the experimental conditions (Oosterhuis and Jonkman, 1993). Any defecation within the next 6 h was recorded. The content of two enema containers was administered to obtain a dose of 1000 mg of paracetamol. To facilitate the retention of the enema in the rectum, the volunteers lay in a horizontal position and remained in this position for 3 h after drug administration. The suppositories were administered in the same way. No other medicines (with the exception of oral contraceptives) or alcohol were allowed 48 h prior to or during each trial period. Blood specimens were collected in heparinised Venoject™ tubes before and 15, 30, 45, 60, 80, 100 min and 2, 2.5, 3, 4, 6, 8, 10, and 12 h after each drug administration. The samples were centrifuged within 30 min and the plasma separated and stored at −20°C until assayed.

The content of paracetamol in the plasma samples was analysed according to the method described by Nielsen et al. (1992).

2.5. Calculation of pharmacokinetic data

The observed maximum plasma concentration (C_{max}) of paracetamol and the corresponding time to reach C_{max} (T_{max}) were estimated for each subject. The overall elimination rate constant (β) of paracetamol was determined for each subject by linear regression analysis of the terminal linear part of the log plasma concentration vs time curve. The biological half-life ($t_{1/2}$) was obtained from the ratio $\ln 2/\beta$. The area under the plasma concentration vs time curve, AUC, was calculated using the trapezoidal rule between zero and the last detectable plasma concentration. The logarithmic trapezoidal rule was applied during the declining part of the curve in order to increase the accuracy. The remaining area was obtained from the ratio between the last detectable plasma concentration and the calculated elimination rate constant. The total area under the curve ($AUC_{0-\infty}$) was obtained by summation of the areas. The relative bioavailabilities of B–D were determined by finding the quotient of AUC total for the suppositories and the enema.

The mean residence time (MRT) was calculated by use of $MRT = AUMC/AUC$ where AUMC is the area under the first moment curve (Gibaldi, 1984). The mean dissolution time in vivo ($MDT_{in\ vivo}$) for the suppositories was determined by subtracting the MRT of the solution from the MRT of the suppositories (Gibaldi, 1984). $MDT_{in\ vitro}$ was estimated from the ratio between the area above the curve obtained when the cumulative percentage dissolved was plotted vs time up to infinity and the percentage finally dissolved (Brockmeier and Hattingberg, 1982). If 100% of the drug was not finally dissolved, the tail of the curve was estimated after fitting the data to an exponential model described by:

$$f(t) = 1 - e^{-k(t - t_{lag})} \text{ when } t > t_{lag}$$

$$f(t) = e^{-kt} \text{ when } t_{lag} = 0$$

$$f(t) = 0 \text{ when } t < t_{lag}$$

where k is the exponent and $\ln(-kt_{lag})$ denotes the intercept. A possible lag time is expressed by t_{lag}.

The plot of $MDT_{in\ vivo}$ vs $MDT_{in\ vitro}$ includes the co-ordinate (0,0) since the MDT of a solution in vitro and in vivo is zero. This assumes that the paracetamol in the solution does not precipitate after administration in vivo.

Numerical convolution was used to simulate the plasma concentration vs time profiles [$R(t)$] (Langenbucher, 1982) for each person assuming that the superposition principle was applicable.

The in vitro dissolution data for each suppository [$I(t)$] were convoluted with the mean plasma concentration data after administration of the enema [$W(t)$]. A time module of 15 min was used with linear interpolation in all estimations. Since the mean extent of bioavailability from the suppositories was not equal to that of the enema, the simulated plasma concentrations were adjusted for the difference by multiplying by the relative bioavailability found for each suppository composition according to Nicklasson et al. (1987).

2.6. Statistical methods

Descriptive statistics were applied to describe the in vitro dissolution profiles of the different suppository compositions tested. Student's t-test was used to make a paired comparison of the MDTs in Table 2 calculated for composition B–D using the two different cells of 12 and 22.6 mm. Statistical significance was declared for an outcome of p values less than or equal to 0.05. Parametric analysis of variance for a four-period cross-over model was applied to the logarithms of the data for AUC_{tot}, C_{max}, MRT, $T_{1/2}$ and T_{max} separately using patient (random) effects, period effects, treatment effects and carry-over effects. Since no carry-over effects were close to significant ($p > 0.169$ for $t_{1/2}$ was the smallest p value) these effects were eliminated from the analysis of variance models. Even though no period effects were significant (ranging from $p = 0.112$ to $p = 0.913$), they were retained in the model. Since the design was balanced, all estimates (except for the error terms) are identical to arithmetic means of the logarithms, i.e., geometric means of the original data. The logarithms were used to obtain normally distributed data in the estimation of the quotients of C_{max} and AUC in relation to the enema. In addition, two-sided 95% confidence intervals were calculated for these quotients. In addition an analysis of variance was performed using the original data, without using logarithmic transformation, in order to estimate means in the original scale. The models did not use any carry-over effects since they were non-significant (the smallest value was $p = 0.124$).

Table 2
Mean dissolution time in vitro ($MDT_{in\ vitro}$) of compositions B–D obtained in the flow-through cell using the suppository cell (12 mm) and the cell with a diameter of 22.6 mm at flow rates of 8 ml/min and 28 ml/min, respectively

Parameter	$MDT_{in\ vitro}$ (8 ml/min) (h)		$MDT_{in\ vitro}$ (28 ml/min) (h)		
	B	C	B	C	D
Mean ($n = 6$)	1.7 [a]	1.3	1.2 [b]	1.2 [b]	0.6
Minimum	1.1	1.0	1.1	1.0	0.5
Maximum	2.5	1.6	1.4	1.3	0.8
S.D.	0.48	0.23	0.12	0.18	0.12

[a] Significantly separated ($p < 0.05$) from the $MDT_{in\ vitro}$ obtained from B at 28 ml/min.
[b] Significantly separated ($p < 0.05$) from the $MDT_{in\ vitro}$ obtained from D at 28 ml/min.

3. Results

3.1. In vitro dissolution results

In Table 2 the MDTs of B and C in the 12 mm cell and of B–D in the 22.6 mm cell are listed. Fig. 1 presents the dissolution profiles of B–D in the 22.6 mm cell. Compositions B and C are not separated from each other in the 12 mm cell at a flow rate of 8 ml/min when comparing the MDTs or in the 22.6 mm cell at the corresponding flow rate (28 ml/min). However, the MDTs of B obtained at the two different flow rates in the two cells are significantly separated. Composition D releases paracetamol significantly faster than B and C.

3.2. Pharmacokinetics and extent of bioavailability

Reported adverse events concerning the dosage form were defecation urge and loose stool. Five subjects experienced these effects after the enema, three after D and C and four subjects after B. Two subjects had a bowel movement within the time period of 6 h. One ocurred at 5.5 h after the administration of D and the other approx. 4 h after the enema. The individual AUC for these two subjects after D and the enema was 253 and 380 μmol l^{-1} h compared to the group means which were 318 ($\pm$74) and 291 ($\pm$95) μmol l^{-1}

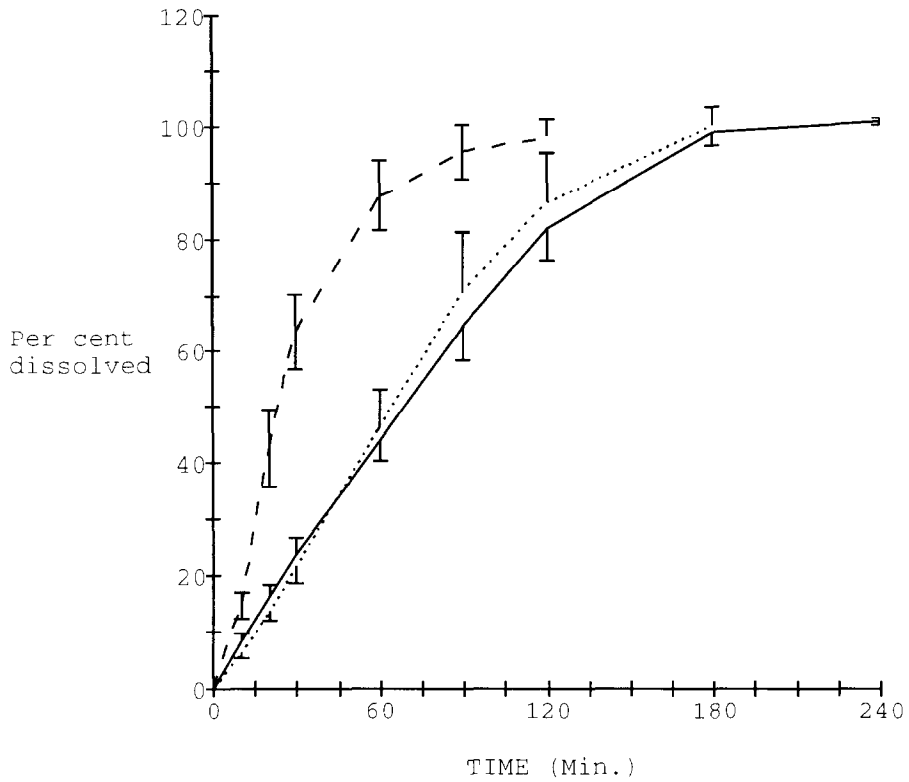

Fig. 1. In vitro dissolution rate of paracetamol from composition B (2.4 g) (continuous line), C (3.2 g) (dotted line) and D (4.4 g) (dashed line) at a flow rate of 28 ml/min in the 22.6 mm cell. Error bars denote standard deviations.

h, respectively. This means that the individual AUC values were within the standard deviation interval of the means.

The plasma concentration vs time profiles are shown in Fig. 2. The mean pharmacokinetic data of paracetamol calculated after the administration of the rectal solution, B–D are listed in Table 3. Table 4 shows the 95% confidence intervals after the pairwise comparison of the pharmacokinetic parameters after suppository adminis-

Table 3
Mean pharmacokinetics ($n = 8$) of paracetamol (standard deviations within parentheses)

Treatment	C_{max} (μmol/l)	T_{max} (h)	MRT (h)	$MDT_{in\ vivo}$ (h)	$T_{1/2}$ (h)	AUC_{tot} (μmol l^{-1} h)	Rest area (%)	F_{rel}
Enema	51	3.4	5.6		2.6	318	7.2	
	(13)	(1.4)	(0.6)		(0.3)	(74)	(2.1)	
B (2.4 g)	30 [a]	5.0 [a]	7.1 [a]	1.5	2.6	230	11.7	0.7
	(13)	(1.1)	(0.8)	(0.8)	(0.4)	(110)	(4.2)	(0.2)
C (3.2 g)	32	4.1	6.4	0.8	2.6	233	9.4	0.7
	(12)	(0.8)	(0.9)	(1.0)	(0.5)	(115)	(4.2)	(0.3)
D (4.4 g)	43	3.6	6.1	0.5	2.6	291	8.4	0.9
	(13)	(1.4)	(0.6)	(0.7)	(0.5)	(95)	(2.3)	(0.1)

[a] Significantly different from D ($p < 0.05$).

Table 4
Resulting confidence levels (95%) after pairwise comparison of pharmacokinetic parameters of paracetamol after suppository administration

Treatment comparison	C_{max}	T_{max}	MRT	$T_{1/2}$	AUC_{tot}
B vs C	0.65–1.35	0.88–1.65	0.99–1.24	0.88–1.19	0.74–1.37
B vs D	0.47–0.97	1.07–2.01	1.05–1.30	0.87–1.18	0.55–1.02
C vs D	0.50–1.04	0.89–1.66	0.94–1.17	0.85–1.16	0.55–1.02

Table 5
Resulting confidence levels (95%) after comparison of pharmacokinetic parameters of paracetamol from suppositories and enemaexp

Treatment comparison	C_{max} ratio	T_{max} ratio	MRT ratio	$T_{1/2}$ ratio	AUC_{tot} ratio, F_{rel}
B vs enema	0.39–0.81	1.14–2.14	1.14–1.42	0.85–1.16	0.49–0.92
C vs enema	0.42–0.86	0.95–1.77	1.03–1.28	0.84–1.13	0.49–0.91
D vs enema	0.58–1.19	0.77–1.46	0.98–1.22	0.84–1.14	0.66–1.22

tration. These parameters were also compared with the enema, and the 95% confidence intervals are listed in Table 5.

A mean C_{max} of 51, 30, 32 and 43 μmol/l was reached 3.4, 5.0, 4.1 and 3.6 h after the administration of the enema, B, C and D, respectively. The C_{max}, T_{max} and MRT of B were significantly separated from D. The half-lives were 2.6 h for all the compositions tested. The total AUCs of the suppositories were not significantly different from each other at the 95% significance level. The comparisons included the mean estimated rest areas ($AUC_{12-\infty}$)which were between 7 and 12% expressed as percentages of the total area under the curve. The relative extent of bioavailability of the suppositories compared to the enema was 0.7, 0.7 and 0.9 for B, C and D, respectively. The 95% c.i. of the relative biavailability and the C_{max} ratio in Table 5 show that none of the suppositories was bioequivalent to the enema.

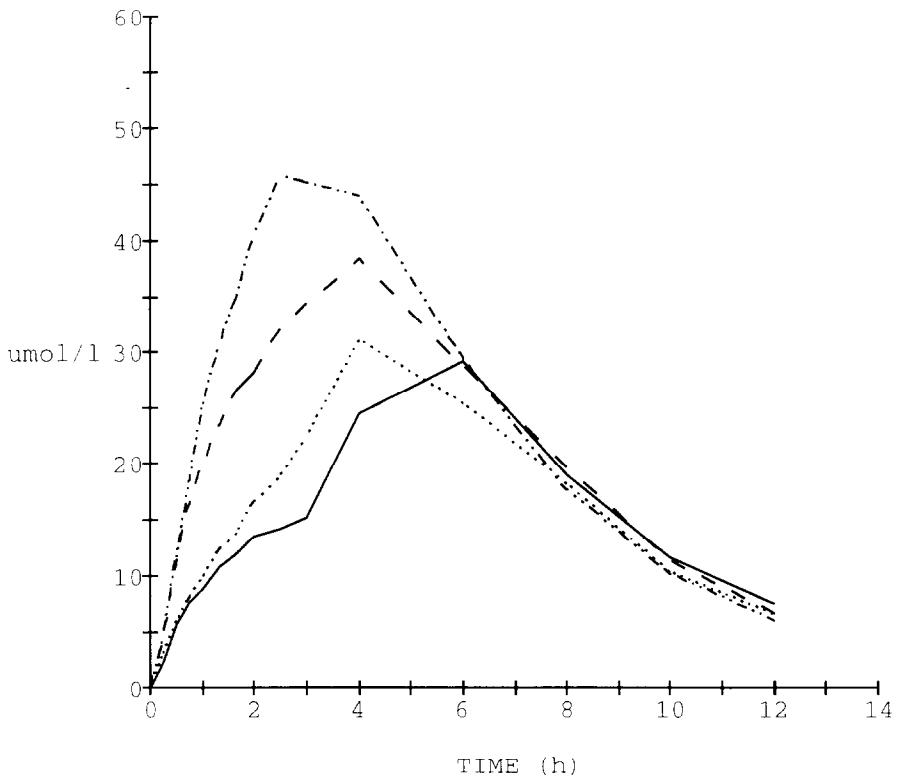

Fig. 2. Linear plot of average plasma concentration of paracetamol (μmol/l) after administration of enema (dotted-dashed line), suppository composition B (continuous line), C (dotted line) and D (dashed line).

3.3. Association between in vitro data and in vivo plasma concentration data

Fig. 3 shows the MDTs in vivo for the suppositories plotted vs MDT in vitro obtained in the 22.6 mm cell at 28 ml/min which gives the best fit. The fitted straight line through the three coordinates is described by the equation $y = 1.03x - 0.03$ ($r^2 = 0.86$, MSE = 0.09). The slope value of 1.03 shows that there is a 1:1 correlation at level B according to Skelly et al. (1990) between the MDTs obtained in vivo and in vitro. Using the in vitro data obtained at 14 ml/min and 50 ml in the 22.6 mm cell in a similar plot resulted in the equation $y = 0.52x + 0.11$ ($r^2 = 0.60$, MSE = 0.25) and $y = 1.65x + 0.09$ ($r^2 = 0.58$, MSE = 0.26), respectively. The deconvolution method could not be used to calculate the in vivo dissolution profiles because of inconsistency in the data. Fig. 4a–d instead illustrates the convoluted plasma concentrations vs time profiles for B, C and D. Besides the experimentally observed plasma profiles, Fig. 4a shows the adjusted simulated curve of composition B and Fig. 4b depicts the unadjusted simulated curve. It can be seen that level of the simulated profile deviates more in the elimination phase for C and D than for B independent of which in vitro method is being applied. Besides, all curves deviate from the experimentally found concentrations during the first 1–2 h and more rapid absorption is achieved than is simulated by convolution. The best association is obtained for composition B where the adjusted curve illustrates a close relation to the entire profile, suggesting a correlation at the A level for paracetamol suppositories.

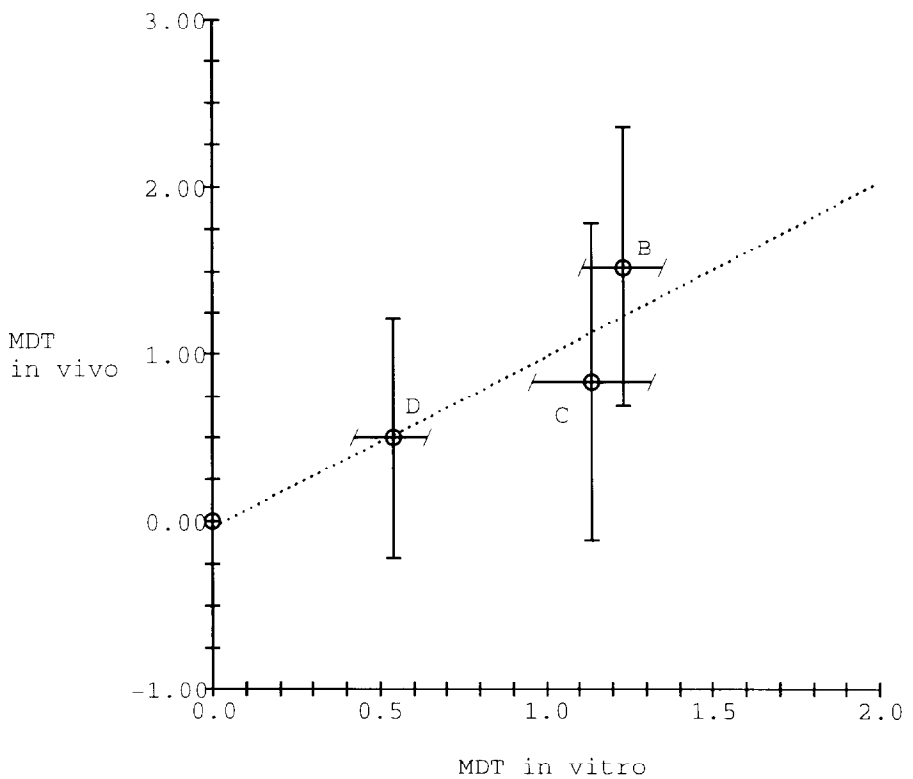

Fig. 3. MDT in vivo vs MDT in vitro for compositions B–D. In vitro dissolution results obtained from the flow-through cell, 22.6 mm, at a flow rate of 28 ml/min. Error bars denote standard deviations.

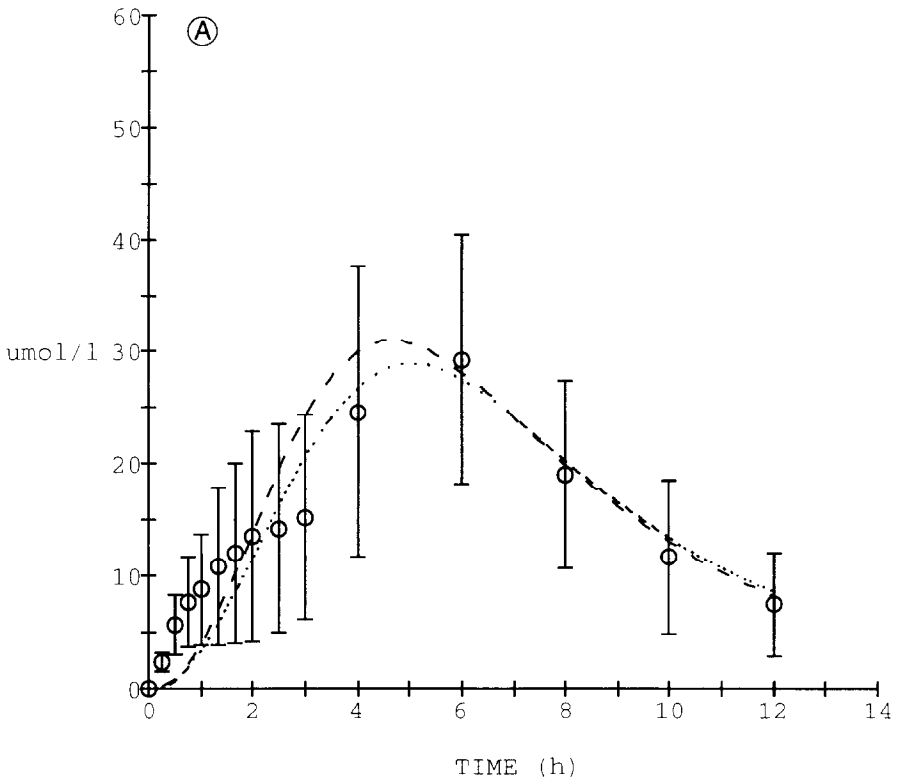

Fig. 4. (a,b) Linear plot of average plasma concentration of paracetamol after administration of composition B (2.4 g) (○). Simulated plasma concentrations of paracetamol for each suppository composition using the [$I(t)$] obtained at 28 ml/min (dashed line) and 14 ml/min (dotted line) in the flow cell of 22.6 mm. (a) Adjusted and (b) not adjusted. Error bars denote standard deviations. (c,d) Linear plot of average plasma concentration of paracetamol after administration of composition (c) C (3.2 g) (□) and (d) D (4.4 g) (△). Adjusted simulated plasma concentrations of paracetamol for each suppository composition using the [$I(t)$] obtained at 28 ml/min (dashed line) and 14 ml/min (dotted line) in the flow cell of 22.6 mm. Error bars denote standard deviations.

4. Discussion

4.1. Influence of agitation and type of cell on the dissolution rate

The comparison of the MDTs in vitro of the smallest suppository B, obtained at theoretically corresponding flow rates in the 12 mm and 22.6 mm cells, shows that times are significantly separated. This effect is not seen for composition C. Consequently, paracetamol is released faster from B in the larger cell. The reason might be that the hydrodynamic conditions are different in the two cell types due to their different designs. Thus, the suppository cell contains two continuous chambers while the larger cell contains just one chamber directly connected to the filter head. The discrepancy might be more pronounced when comparing different compositions. This, however, requires further studies to be evaluated. It should also be emphasised that more dissolution medium passes in the larger cell to obtain corresponding flows and thereby corresponding agitations. This is expected to influence the dissolution process since more medium is available for dissolution per unit time and this is in favour of the small-volume suppository B.

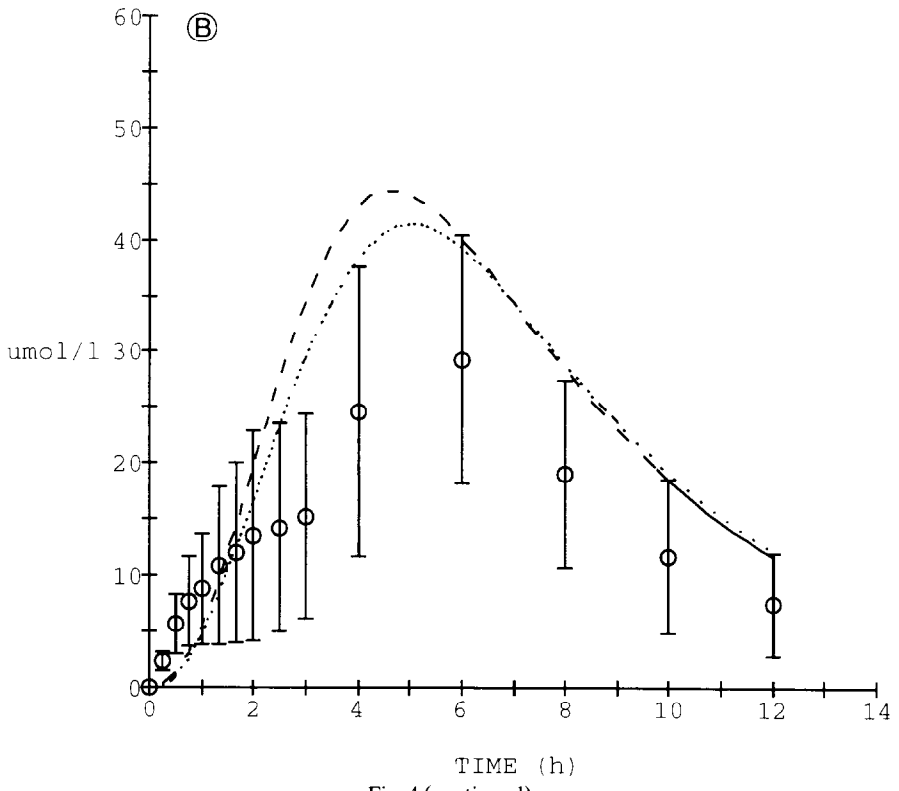

Fig. 4 (continued).

4.2. Influence of fraction and size on bioavailability

The pharmacokinetic results and the plotted mean plasma concentration vs time curves show that compositions B and C behave similarly. However, the C_{max}, T_{max} and MRT of B are significantly different from those of D which is not the case for C. It is interesting to note that the difference in vivo is small between composition B and C although the difference in fraction of paracetamol is 10%. The difference in fraction between C and D is the same. Another differing parameter is the weight and both C and D are heavier than B, 33 and 83%, respectively. The size of the suppository is thus of great importance for the rate of absorption and extent of bioavailability when administering a 1000 mg paracetamol dose. The contribution of each of the two formulation factors to the effect is unknown. It is, however, evident that the increased bioavailability seen by Gjellan et al. (1994) when the fraction is decreased is not as obvious in this study. The reason is probably the differences in study design including the number of volunteers, use of enema and the body position of the subjects after drug administration.

4.3. Association between in vitro data and in vivo plasma concentration data

From the plasma concentration vs time profiles in Fig. 2 and the in vitro dissolution profiles in Fig. 1, it is evident that a flow rate of 28 ml/min in the 22.6 mm cell ranks the compositions correctly in the in vivo situation. The plot of $MDT_{in\ vitro}$ and $MDT_{in\ vivo}$ shown in Fig. 3 demonstrates that a 1:1 relationship is reached. This is further supported by Fig. 4a–d where the simulated plasma concentration vs time curves are close to the experimental data. The best

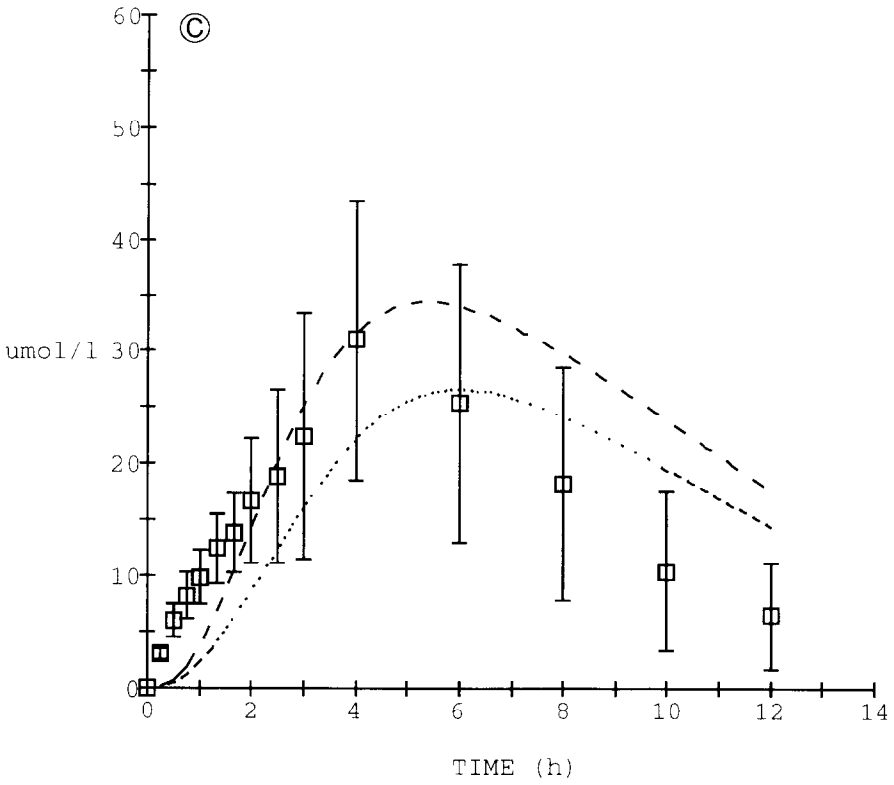

Fig. 4 (continued).

association is obtained after insertion of the smallest suppository with the highest fraction of paracetamol. A striking phenomenon is the poor fitting in the initial absorption phase. The real absorption rate is thus consistently faster from the compositions in vivo than the convoluted values based on in vitro dissolution data [$I(t)$] and the plasma data after administration of the enema [$W(t)$]. It remains unknown why this effect appears.

5. Conclusion

The flow-through method has been used to evaluate the effects of fraction of paracetamol and size of a suppository on the in vitro dissolution rate. The cell with a diameter of 22.6 mm, normally used for oral dosage forms, created testing conditions which produced dissolution profiles that associated well with the bioavailability after administration to healthy volunteers. Association methods such as statistical moment analysis and numerical convolution were found to be applicable to rectal dosage forms.

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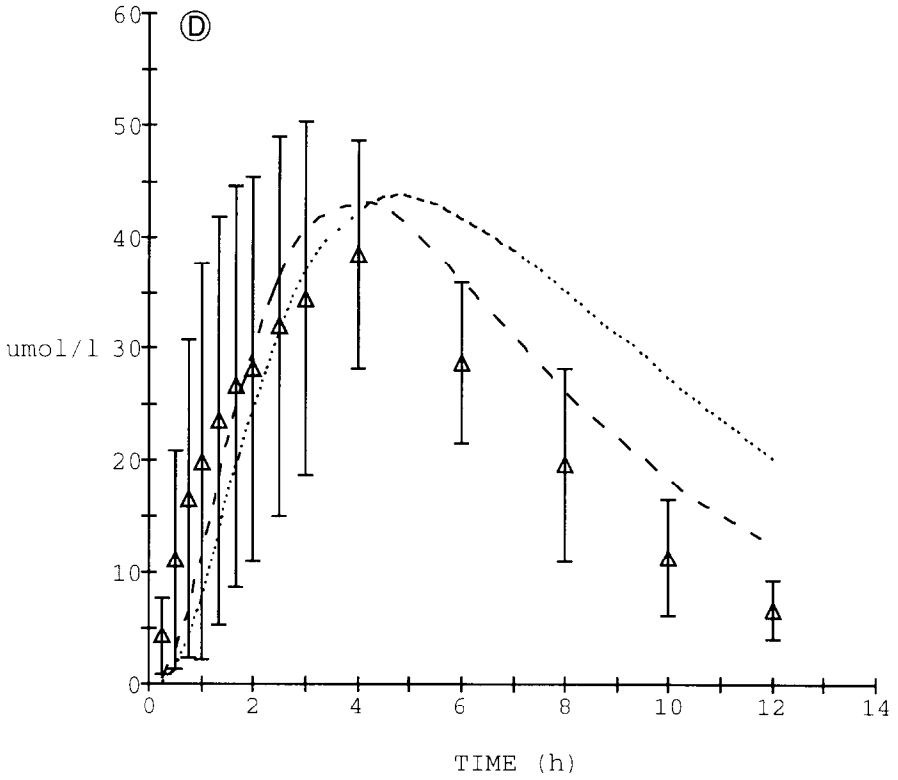

Fig. 4 (continued).

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