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RESEARCH PAPER

Critical Dissolution Tests of Oral Systems Based on Statistically Designed Experiments. III. In Vitro/In Vivo Correlation for Multiple-Unit Capsules of Paracetamol Based on PLS Modeling

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ABSTRACT

The main aims of the present study were to establish an in vitro/in vivo correlation for multiple-unit capsules of paracetamol by means of statistical prediction models and to investigate the effect of a number of in vitro variables on the discussion rate of paracetamol from the formulation. A fractional factorial screening design was used to investigate the effects of the variables agitation, pH, osmolality, viscosity, and the presence of bile salt on the dissolution rate of paracetamol. The effects were evaluated in two separate partial least-squares models, in which the responses were expressed as the cumulative percentage of paracetamol dissolved at specified time-points (model I) and as the shape (β) and scale (η) parameters according to the Weibull function (model II).

It was concluded that agitation and viscosity had significant effects on the dissolution rate of paracetamol. Statistical models based on the responses from models I and II were then used to predict the in vitro conditions most closely correlated with the in vitro dissolution of paracetamol after administration of the formulation to 10 healthy volunteers. The predicted optimal in vitro conditions were similar for the two models and not too far from what is expected from the gastrointestinal tract. The experimental verification of the in vitro conditions showed that both

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models were equally good, and contributed to high degrees of correlation with the in vivo dissolution behavior of the formulation during 9 hr. The relationships obtained when plotting the percentage dissolved in vitro versus in vivo were $y = 1.1x$ *(*$r^2 = 0.98$*) and* $y = 1.1x$ *(*$r^2 = 0.94$*) for models I and II, respectively. Based on these results, it is difficult to state a preference for one of the models. Finally, the use of statistical prediction models to develop critical in vitro tests is a successful approach in the establishment of associations between dissolution behavior in vitro and in vivo for oral extended-release systems.*

INTRODUCTION

The nonsalicylate analgesic and antipyretic drug paracetamol (acetaminophen) has been successfully used for many years. It has, however, been suggested that a better therapeutic effect might be achieved in some cases by prolonging the efficacy of each dose of paracetamol by administering it as an extended-release (ER) formulation (1–4). Such a system would enable a reduced dosing frequency and maintain a stable therapeutic effect for an extended period.

The rate and extent of absorption of paracetamol are controlled by the dissolution and intestinal permeation of the pure drug, both of which are known to be rapid and complete following oral administration of conventional rapidly dissolving formulations (5–7). The application of an ER technique, however, will intentionally influence the dissolution behavior and be a critical factor for the absorption and the therapeutic effect. The clinical rationale of an ER formulation of paracetamol has thus to be investigated only when there is a system available which takes full account of the specific physical, chemical, and pharmacokinetic properties of paracetamol (Table 1).

In a previous study in healthy volunteers we have shown that the rate and extent of absorption are controlled by the release rate from experimental multiple-unit formulations of pure paracetamol cores with membrane-controlled dissolution (8). The peak plasma concentration time and the area under the plasma concentration versus time curve were prolonged and reduced, respectively, when the in vitro dissolution rate from the formulations was decreased. The same ranking was obtained for three different formulations when the dissolution rate in vitro or in vivo was considered. Consequently, the use of an ER-coating technique on pure paracetamol cores seems to be a promising approach.

To ensure batch-to-batch bioequivalence of a paracetamol ER product, it is necessary to use a control method, before it is released onto the market, which has been shown to produce in vitro data that are quantitatively associated with the dissolution rate in vivo. Before such a correlation can be found, both the dissolution technique and the composition of the dissolution liquid have to be characterized. We have shown that statistically designed experiments are highly capable of making such characterizations (9–11). A partial least-squares (PLS) model is preferable to multiple linear regression for the evaluation of the dissolution data since the latter always depends on the values obtained at preceding time-points (11). The cumulative amount released versus time curve has been used in our previous investigations. Since it is known that the shape of the release profile might play a role, it seems of interest also to apply the Weibull function (12,13) to release data and to investigate the shape and scale parameters in a statistical model.

The primary aim of the present study was to arrive at a correlation for the dissolution rate in vitro and in vivo from an ER-coated multiple-unit formulation of paracetamol. Underlying aims were to find the critical

Table 1

Biopharmaceutical Properties of Paracetamol (5,6,8,31)

Drug	Solubility (mg/ml) (Water, 37°C)	pK_a	Partition Coefficient (Octanol/Water, pH 7.4)	Relative Bioavailability (p.o./i.v., %)
Paracetamol	21.4	9.5	0.5	60–90

in vitro dissolution variables by means of a statistical model and to compare the dissolution in the model by using cumulative curves as such or as described by the parameters' shape and scale.

MATERIALS AND METHODS

Dosage Forms

Paracetamol cores (100%) were coated in a fluidized-bed apparatus using an aqueous suspension of ethylcellulose 10 cps (Aquacoat®, Dow Chemicals Inc., Philadelphia, PA). A dose corresponding to 500 mg was dispensed in hard gelatin, ER capsules. Effervescent tablets containing 500 mg paracetamol came from the Swedish market (Alvedon®, Astra, Södertälje, Sweden).

In Vitro Dissolution Test

The in vitro dissolution tests were performed using the apparatus II method (paddle) (14). The substances used in the dissolution media were hydrochloric acid 5 M, sodium chloride, acetic acid 100%, glucose, ethanol 99.5%, povidone 90 (Kollidon®, BASF AG, Germany), and sodium taurocholate (Sigma Chemical Co., Sweden). All chemicals were of analytical grade. The media were prepared by mixing all the components with a magnetic stirrer for at least 2 hr. Milli-Q water used was deaerated with helium for 20 min. The osmolality was adjusted by adding glucose and the measurements were performed as described elsewhere (10,11). A rotational viscosimeter (Stress Tech, Rheologica Instruments AB, Lund, Sweden) was used to determine the viscosity after the addition of povidone 90 (50.4–66 g/l, depending on the desired viscosity). The shear rate and shear stress were 180–190 sec^{-1} and 3.47–6.18 N/m^2, respectively. The pH, osmolality, viscosity, and temperature of the media were checked before each experiment. The temperature of all the samples was held constant at 37°C and the measurements were done in duplicate.

The different media were used in a randomized order, according to Table 2. The hard gelatin capsules were emptied and only the ER cores of paracetamol were used. Six parallel vessels containing 900 ml of dissolution medium were used in each test. Samples were taken at 20, 30, 45, 60, 90, 120, 180, 240, 360, 420, and 540 min. The amount of paracetamol dissolved was analyzed by high-performance liquid chromatography (HPLC) with UV detection at 245 nm.

Table 2

Experimental Worksheet; Variables Investigated and Their Levels

Exp. No.	Run Order	pH	Viscosity (mPa · sec)	Bile Salt (mM)	Osmolality (mmol/kg)	Agitation (rpm)
1	20	1.2	0	0	250	75
2	2	7.4	0	0	250	25
3	18	1.2	30	0	250	25
4	4	7.4	30	0	250	75
5	1	1.2	0	0.04	250	25
6	5	7.4	0	0.04	250	75
7	11	1.2	30	0.04	250	75
8	3	7.4	30	0.04	250	25
9	8	1.2	0	0	450	25
10	13	7.4	0	0	450	75
11	17	1.2	30	0	450	75
12	16	7.4	30	0	450	25
13	15	1.2	0	0.04	450	75
14	7	7.4	0	0.04	450	25
15	9	1.2	30	0.04	450	25
16	10	7.4	30	0.04	450	75
17[a]	12	4.3	15	0.02	350	50
18[a]	6	4.3	15	0.02	350	50
19[a]	14	4.3	15	0.02	350	50
20[a]	19	4.3	15	0.02	350	50

[a]Replicates.

Statistical Experimental Design

The fractional factorial screening design chosen was a 2^{5-1} design, comprising 16 runs. In order to examine repeatability, four replicates were added at the center (see Table 2). The resolution was V+, i.e., showing unconfounded main effects and two-factor interactions (15). The effects of the variables were varied from a low to a high level and two separate models were tested. The responses in model I were expressed as the cumulative percentage of paracetamol dissolved at specified time-points from 30 to 540 min. The responses in model II were expressed as the shape (β) and scale (η) parameters according to the Weibull function (16):

$$\%R(t) = (1 - \exp(-t/\eta)^{\beta})\ 100 + \gamma \quad (1)$$

where $\%R(t)$ is the estimated percentage of drug dissolved at time t. The shape parameter (β) describes the form of the in vitro curve, while the scale parameter (η) represents the time when 63.2% of the drug is dissolved (13). γ is added to the equation to compensate for the deviation from 100% drug dissolved. β and η were calculated for the dissolution profiles by the least-squares method, using the Solver function in Microsoft Excel 5.0c.

The effects of the significant variables according to model II were obtained by predicting β and η in Modde. The prediction was made with all of the variables at their mid-levels except for the variable in question, which was varied at a low and a high level. In order to transform the effects to percentage of dissolved paracetamol, β and η were transformed to in vitro dissolution profiles.

The effects were then calculated as the difference between the maximum and minimum value obtained.

The in vitro evaluation of the tests was performed in Modde 3.0 (Umetri AB, Umeå, Sweden) by using a PLS model (17). The experimental settings in Table 2 were used as X and the responses were used as Y. The accuracy of the statistical model used is described by the R^2 and Q^2 parameters. R^2 is the fraction of the data explained by the model, whereas Q^2 is the predictive ability of the model. R^2 and Q^2 values close to 1 indicate good models. The statistical significance of the variables and interaction terms was $\alpha = 0.05$. The effects of the variables investigated were expressed as percentage of paracetamol dissolved.

Design of the In Vivo Study

The in vivo study was performed at St. Göran's Hospital in Stockholm, Sweden, and was approved by the local Ethics Committee. Each volunteer was fully informed both in writing and verbally about the aim of the study, which was carried out according to the Declaration of Helsinki. The investigation was conducted as a randomized, single-dose, crossover study in 10 healthy volunteers aged 18–45 years (five females and five males).

The subjects received two effervescent tablets or two ER capsules on two different occasions with at least 1 week between the trial periods. The subjects were fasted overnight and drug administration took place at 8 a.m. The two effervescent tablets were dissolved in 75 ml of tap water and the glass was rinsed with an additional 25 ml. The capsules were administered with approximately 100 ml of tap water. A standardized breakfast was allowed 4 hr after drug administration. Venous blood samples were collected in heparinized Venoject® tubes 1/3[a], 2/3[a], 1, 2, 4, 6, 8, 10, 12, 24[b], 28[b], and 32[b] hr after dosing ([a]: only after effervescent tablets, [b]: only after ER capsules). The samples were centrifuged and stored at approximately −20°C until assayed. The sample analysis has been described elsewhere (2).

The mean cumulative in vivo dissolution of paracetamol from the ER formulation was calculated by numerical deconvolution of the individual plasma versus time profiles (18). The effervescent tablet dissolved in water was used as the reference. The calculations were performed by a program developed in RS/1 Command language (BBN Software Products Corp., Boston, MA). β and η were calculated for the in vivo dissolution profile according to the Weibull function (16).

In Vitro/In Vivo Correlation

The statistical model used for predicting the in vitro conditions which produce a close association with the dissolution in vivo has been successfully applied previously (10,11). The in vitro conditions were adjusted to the in vivo data using the least-squares method and the Solver function in Microsoft Excel 5.0c. The general equation was

$$\%\text{Dissolved} = \text{Constant} + \sum_i (\beta_i x_i) + \sum_i \sum_j (\beta_{ij} x_i x_j) + \varepsilon \quad (2)$$

where β_i corresponds to the unscaled and regular coefficients for the ith factor calculated in Modde, β_{ij} is the unscaled and regular coefficients for the interaction between the ith and the jth factors, x_i represents the ith variable and the constant represents the mean value of all the experiments. The experimental error is shown by ε.

The difference sum of squares, which is the difference between the in vivo curve and the predicted or verified in vitro curve, was used as a measure to compare the two statistical models. The association between the in vitro and in vivo profiles was compared by linear regression, obtained after plotting the percentage of paracetamol dissolved in vitro versus the percentage of paracetamol dissolved in vivo, at the same times.

RESULTS AND DISCUSSION

Evaluation of In Vitro Drug Dissolution

The 20 in vitro dissolution profiles of the paracetamol ER cores are presented in Fig. 1(a). At 8–9 hr, an unexplained deviating curve shape is seen for some of the experiments. The variation among the replicates is shown in Fig. 1(b). The maximum standard deviation was 2.6% at 6 hr.

All of the responses were normally distributed and did not need to be transformed for any of the models. The interaction terms that had to be included in both models were pH*viscosity, pH*bile salt, pH*osmolality, viscosity*bile salt, viscosity*osmolality, and viscosity*agitation. No significant model error was seen ($p \geq 0.05$).

Model I

The R^2 and Q^2 values were found to be within the ranges 0.80–0.97 and 0.34–0.66, respectively. Figure 2 shows a linear relationship in which the observed and the predicted percentage of paracetamol dissolved at 240 min are almost equal. The time chosen is representative of all of the responses in model I.

Model II

The R^2 and Q^2 values obtained for model II were 0.91–0.95 and 0.61–0.67, respectively. The relationship between the predicted and observed responses was found to be the same as for model I. The parameters found to describe the shape of the dissolution curves in vitro are presented in Table 3. The β values obtained for experiments 1–20 were 0.7–1.1, which reflects small differences between the shape of the dissolution profiles. Generally, the shape of an exponential dissolution curve is characterized by a β value close to 1. When $\beta > 1$, the curve is S-shaped with an upward curvature, whereas $\beta \to \infty$ indicates a curve degenerating to a step function (13). The η values obtained were 7.3–17 hr, which means that there are large variations between the different dissolution profiles, when considering the time when 63.2% of the drug is dissolved.

Effects of Variables Investigated

The variables observed to have statistically significant effects on the amount of paracetamol dissolved ($p = 0.05$) were agitation and viscosity, as shown in Figs. 3(a) and (b). Both these effects are consistent with the Noyes–Whitney theory of dissolution (19). The results were similar irrespective of which model was used.

Model I

An increased agitation from 25 to 75 rpm increased the dissolution and the maximum effect occurred at 540 min, i.e., 9 ± 2.3%. An increase from 100 to 150 rpm was previously found to have an insignificant effect on the dissolution rate, which means that agitation rates as

Table 3

The Obtained Shape and Scale Parameters for Experiments 1–20, for the In Vivo Profile and the Predicted and Verified In Vitro Profiles from Statistical Models I and II

Experiment	Shape Parameter, β	Scale Parameter, η
1	0.8	542
2	0.9	513
3	0.9	992
4	1.1	598
5	0.8	512
6	0.8	440
7	1.0	700
8	0.9	1024
9	0.7	653
10	0.9	584
11	1.0	676
12	1.0	814
13	0.9	449
14	0.8	736
15	0.9	871
16	1.0	699
17	1.0	699
18	0.9	676
19	0.9	632
20	0.9	598
In vivo	0.6	1416
Model I pred.[a]	0.5	621
Model I exp.[b]	0.9	1199
Model II pred	0.7	1236
Model II exp.	0.7	1030

[a]pred. = Predicted values.
[b]exp. = Experimentally found values.

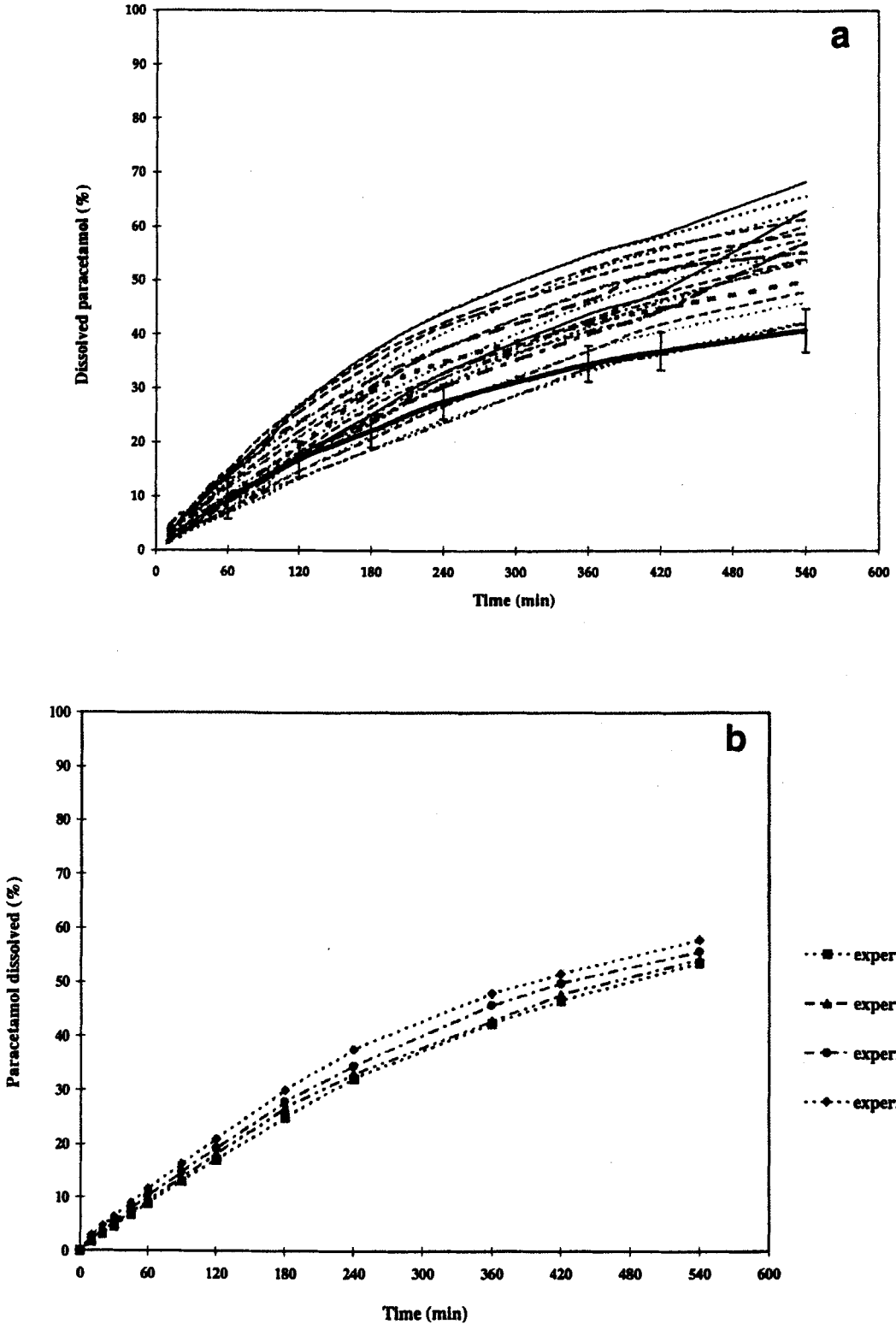

Figure 1. (a) The obtained dissolution profiles in vitro and in vivo (thick line). Error bars are denoted as standard deviations for the in vivo dissolution profile. (b) The obtained dissolution profiles from the replicates (experiments 17–20).

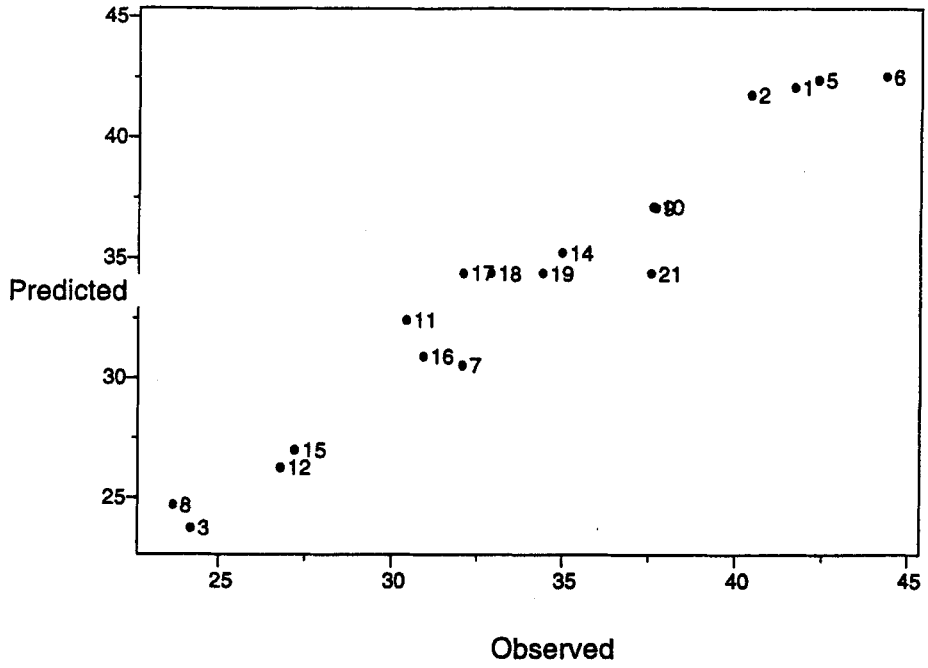

Figure 2. A plot of the observed versus the predicted percentage of paracetamol dissolved at 240 min. The numbers are the experiments.

low as 25–75 rpm are more critical for the dissolution rate of paracetamol from the present type of ER formulation (8). The viscosity, which was chosen to simulate possible food effects, decreased the dissolution rate. An increase from 1 to 30 mPa · sec decreased it by at most 12 ± 4.5% at 240 min. Generally, the presence of food in the gastrointestinal tract results in increased viscosity of the stomach contents, which may have a negative effect on the dissolution rate of drugs. However, it is known that paracetamol should not be administered with food, mainly because its absorption is dependent on the rate of gastric emptying, which on the other hand is dependent on the type of food administered (20). For example, it has been shown that absorption is delayed to varying extents, depending on whether a meal with a high content of carbohydrates, fiber, or fat is given (21–23). However, the total amount of paracetamol absorbed has been shown to be unaffected by food intake when administered in conventional rapidly dissolving formulations (20).

Model II

Generally, the results from model II are similar to those from model I. A positive effect of at most 8 ± 3.4% at 540 min was seen as a result of increased agitation and the dissolution rate of paracetamol decreased by 12 ± 3.6% at 360 min when the viscosity increased. Both agitation and viscosity were observed to have significant effects on both the β and η parameters. The effects of increased viscosity and agitation on β was, however, small: 0.2 ± 0.04 and 0.1 ± 0.04, respectively. In addition, the time needed to reach 63.2% dissolved drug was reached by 244 ± 55 min as a result of increased viscosity from 0 to 30 mPa · sec. The corresponding effect of the agitation was a decrease of 179 ± 55 min.

In Vivo Drug Dissolution

The mean dissolution profile of paracetamol after administration of the ER formulation to healthy volunteers is shown in Fig. 1(a). Close to 10, 30, and 35% of the dose is dissolved within 1.5, 6, and 9 hr, respectively, indicating a slow and incomplete dissolution of paracetamol in vivo. The range within the relative extent of bioavailability (capsule/effervescent tablet) between the 10 volunteers was 0.55–0.98 (mean 0.78 ± 0.14), which also indicated variable and incomplete absorption of paracetamol.

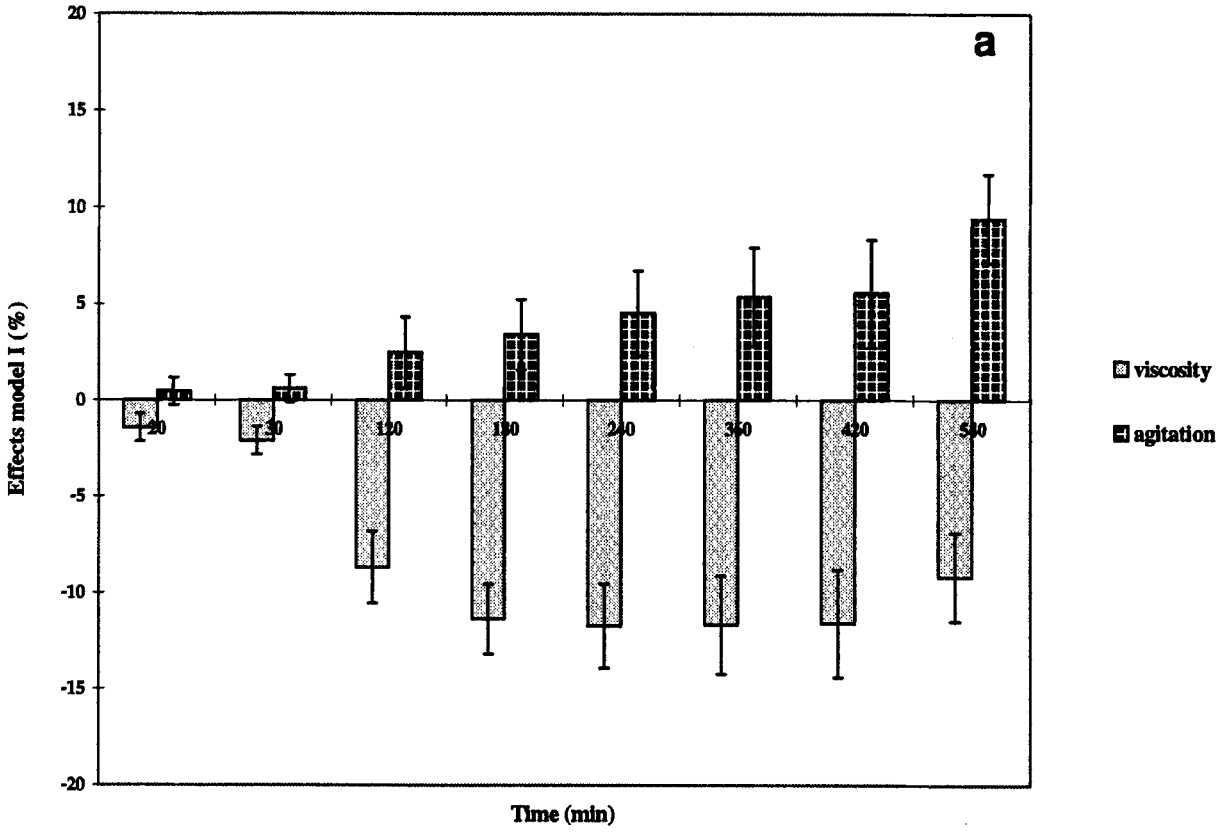

Figure 3. (a) Model I, the effects of the most significant variables, viscosity and agitation, on the dissolution rate of paracetamol. The error bars indicate 95% confidence intervals. (b) Model II, the effects of the most significant variables, viscosity and agitation, on the dissolution rate of paracetamol. The error bars indicate 95% confidence intervals.

The β and η values obtained for the in vivo profile were 0.6 and 23.6 hr, respectively (Table 3). Both the shape of the in vivo curve and the time when 63.2% of the drug has been dissolved were best reflected by the predicted and experimentally verified in vitro profile according to the optimal in vitro conditions from model II. The β and η values were 0.7 and 17.2–20.6 hr, respectively, indicating a close conformity with the values of the in vivo profile.

In Vitro/In Vivo Correlation

Optimal In Vitro Conditions

The predicted optimal in vitro conditions are presented in Table 4. The conditions are similar for the two models and close to what is expected from the gastrointestinal environment. A pH of 7.4 seems relevant, since the main absorption site of paracetamol is known to be the distal jejunum (24). The low agitation intensity predicted by our models is supported by studies in which the agitation intensity in the human gastrointestinal tract has been estimated by comparing the characteristics of in vitro and in vivo release of paracetamol ER formulations (25). The in vivo value for the osmolality is about 290 mmol/kg, although it rises after food intake and depends on the composition of the food. For example, it has been found that the osmolality in the gastric fluids rises to 440 mmol/kg after administration of, for example, a milk/doughnut meal (26,27). The predicted concentration of the bile salt was also within the known physiological limits, i.e., 0.75–1 mM (28). Although the predicted level was outside the experimental domain, it did not affect the results obtained in the evaluation of the models. The predicted levels of viscosity were, however, higher than the values in the fasted state, which are estimated to be 1–3 mPa · sec in the stomach and 5–8 mPa · sec in the small intestine (26).

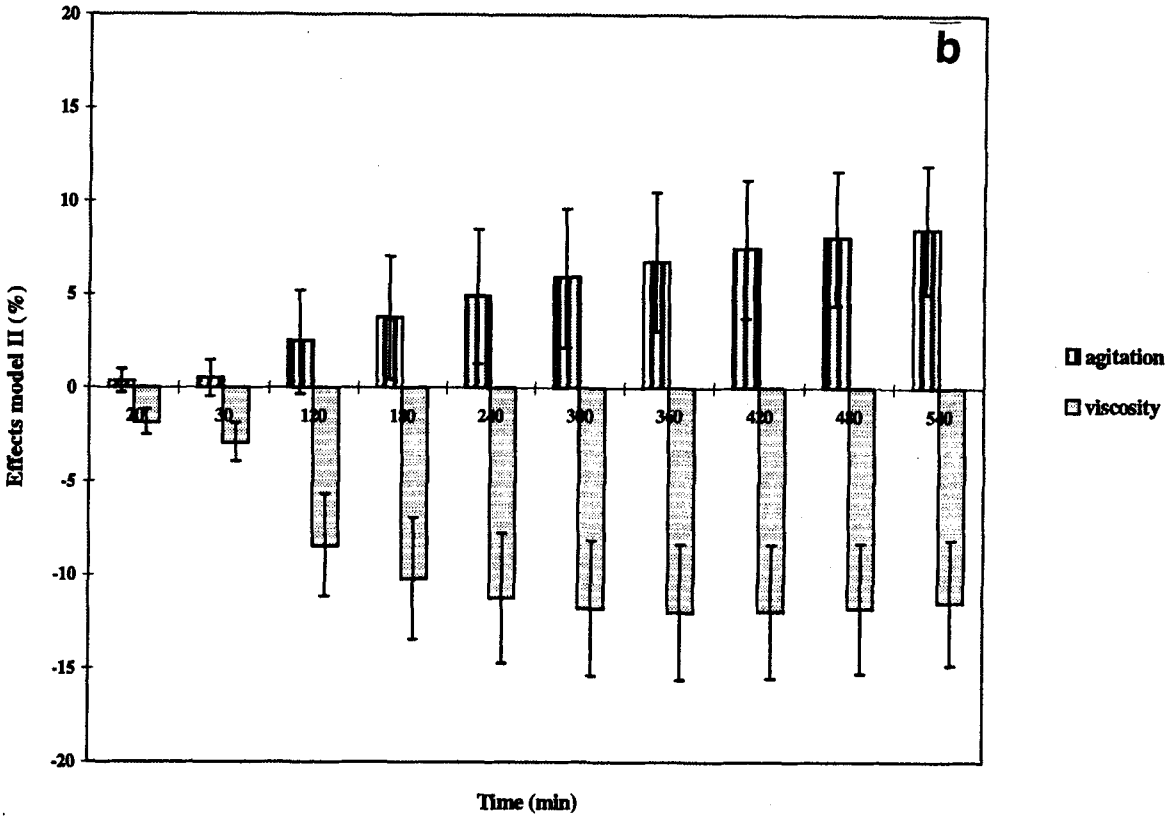

Figure 3. Continued

Evaluation of the Models

Models I and II were experimentally verified by testing the ER formulation in the predicted in vitro conditions. The experimentally measured values of viscosity, osmolality, and pH were used in the models instead of the predicted values. The difference sum of squares, which is the difference between the in vivo curve and the predicted or verified in vitro curve, was 58.1 for model I and 30.5 for model II (the mean standard deviation per datapoint was 2.9 and 2.1, respectively) (see Table 4). Accordingly, a small difference in favor of model II is seen. Figures 4(a) and (b) present a very

Table 4

The Predicted Optimal In Vitro Conditions for Models I and II

In Vitro Conditions	Model I	Model II
pH	7.4	7.4
Agitation (rpm)	25	25
Osmolality (mmol/kg)	280	450
Viscosity (mPa · sec)	23	30
Bile salt (mM)	0.08	0.10
Difference sum of squares[a]	10.2	10.5
(Mean standard deviation per datapoint, %)	(1.2)	(1.2)
Difference sum of squares[b]	58.1	30.5
(Mean standard deviation per datapoint, %)	(2.9)	(2.1)

[a]Theoretical difference sum of squares (in vivo-predicted).
[b]Experimentally found difference sum of squares (in vivo-verified).

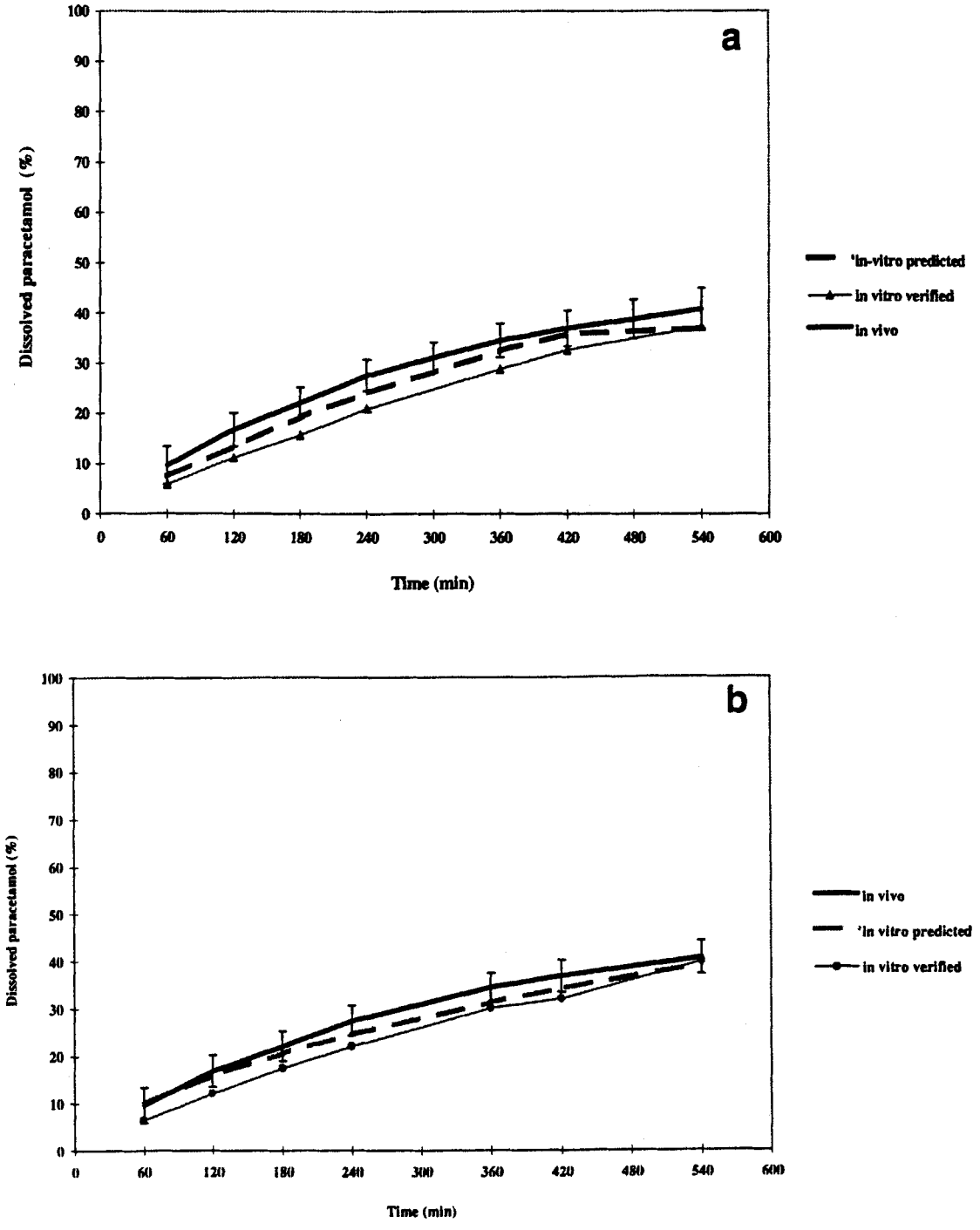

Figure 4. (a) Model I, the association between the predicted in vitro dissolution profile of 500-mg paracetamol cores, the verifying in vitro dissolution profile, and the in vivo dissolution curve. The prediction was based on the cumulative percentage of paracetamol dissolved (model I). The experimentally measured values of viscosity, osmolality, and pH were used in the models instead of the predicted values. (b) Model II, the association between the predicted in vitro dissolution profile of 500-mg paracetamol cores, the verifying in vitro dissolution profile, and the in vivo dissolution curve. The prediction was based on the shape of the in vitro curves (model II). The experimentally measured values of viscosity, osmolality, and pH were used in the models instead of the predicted values.

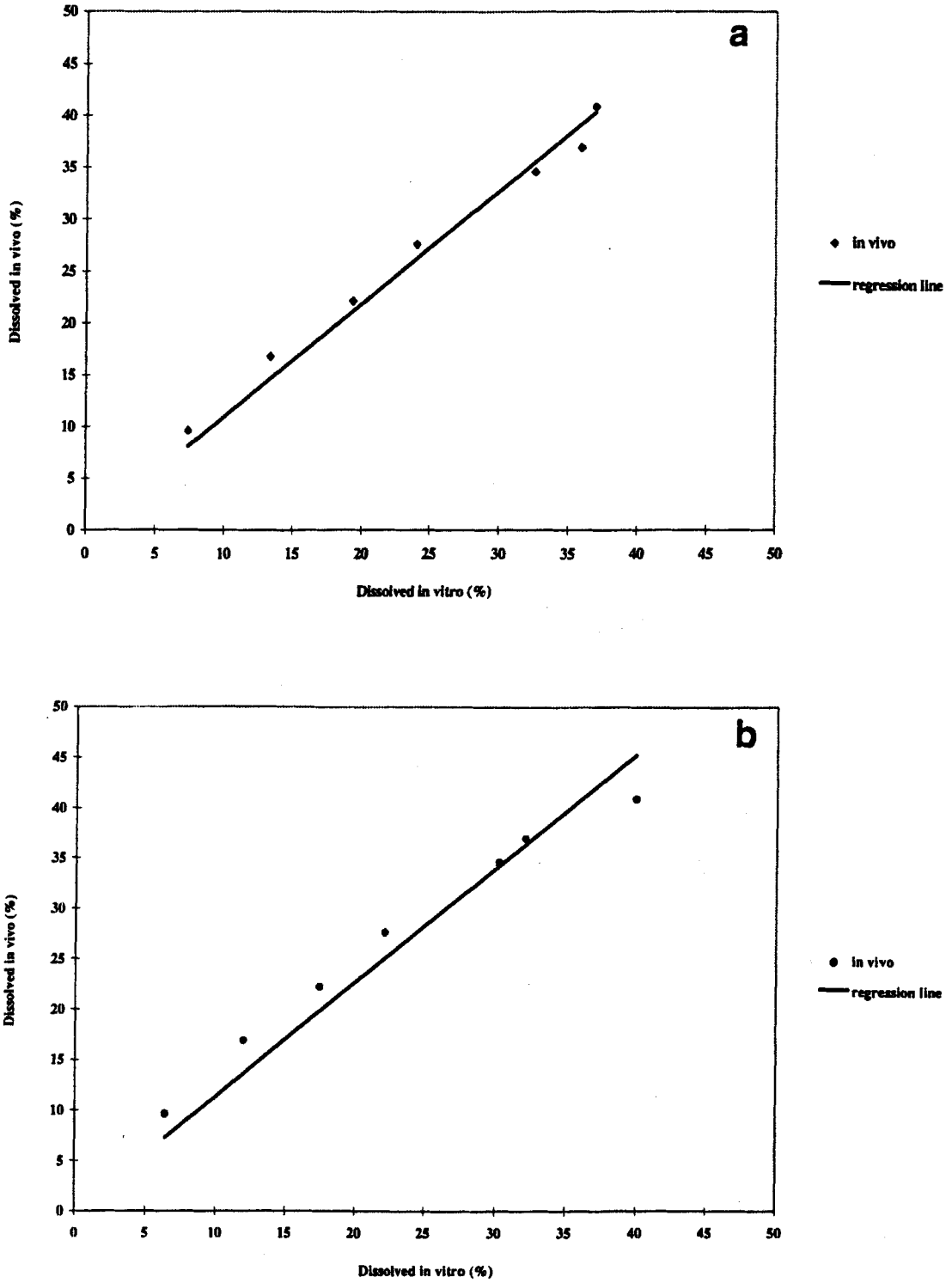

Figure 5. (a) A linear correlation between the dissolution of 500-mg paracetamol cores according to model I in vitro, and the mean dissolution in vivo calculated by numerical deconvolution ($N = 10$). (b) A linear correlation between the dissolution of 500-mg paracetamol cores according to model II in vitro, and the mean dissolution in vivo calculated by numerical deconvolution ($N = 10$).

close association between the predicted and the verifying in vitro dissolution profile of paracetamol cores, and the in vivo dissolution curve during 9 hr.

Plots of the percentage dissolved in vitro for models I and II versus the percentage dissolved in vivo [see Figs. 5(a) and (b)] also gave good correlations. The regression lines calculated without an intercept were found to be $y = 1.1x$ for model I ($r^2 = 0.98$) and $y = 1.1x$ ($r^2 = 0.94$) for model II. The slope of both lines differed significantly from 1 (confidence interval 0.95). In both cases, the dissolution rate in vitro was thus found to be insignificantly higher than that in vivo. The results described show that the two models produce similar results in this case, and it is impossible to state a preference for one of them. However, the use of a curve shape might offer an advantage in other situations, i.e., for other drugs or types of ER systems.

Biopharmaceutical Drug Classification

In accordance with recent discussions, the ratio of the permeation constant of paracetamol ER cores to the dissolution constant was calculated (29,30). The ratio was found to be close to 1, indicating that the rate-controlling step of paracetamol from the formulation is limited by both dissolution and permeation rate. Polli et al. have suggested that if the fraction of a dose absorbed is large and if the dissolution and permeation are about equal, it is possible to find moderate correlations ($0.95 > R^2 > 0.85$) between the dissolution rate of a drug in vitro and in vivo. Our results are in agreement with this suggestion.

CONCLUSIONS

An experimental ER system of the analgesic compound paracetamol was developed and used in this study. Our results indicate that it is possible to find an in vitro test that is predictive of the in vivo behavior of this ER formulation. PLS prediction models were used as suitable tools. The in vitro dissolution from the formulation was described both by the shape of the in vitro curve and by the cumulative percentage dissolved at specified time-points. High in vitro/in vivo correlations were achieved during 9 hr with both models and the two models were found to be equally good. It was concluded that agitation and viscosity had significant effects on the dissolution rate of paracetamol from the ER cores and had to be considered. The in vitro conditions that most closely correlated with the in vivo dissolution of paracetamol after administration of the formulation to 10 healthy volunteers were predicted. Finally, the use of statistical prediction models to develop critical in vitro tests is a successful approach in the establishment of associations between dissolution behavior in vitro and in vivo for oral ER systems.

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REFERENCES

1. H. Quiding, C. Ström, S. Engevall, O. Forsberg, and O. Larsson, Abstract of papers for American Society, Clin. Pharmacol. Ther., 45, 175 (1989).
2. J. C. Nielsen, P. Bjerring, L. Arendt-Nielsen, and K. J. Pettersson, Analgesic efficacy of immediate and sustained release paracetamol and plasma concentration of paracetamol. Double blind, placebo-controlled evaluation using painful laser stimulation, Eur. J. Clin. Pharmacol., 42, 261–264 (1992).
3. M. Hossain and J. W. Ayres, Pharmacokinetics and pharmacodynamics in the design of controlled release beads with acetaminophen as model drug, J. Pharm. Sci., 81, 5, 444–448 (1992).
4. M. Ahmed and R. P. Enever, Formulation and evaluation of sustained release paracetamol tablets, J. Clin. Hosp. Pharm., 6, 27–38 (1981).
5. M. Eandi, I. Viano, and S. Ricci Gamalero, Absolute bioavailability of paracetamol after oral and rectal administration in healthy volunteers, Drug. Res., 34(II), 8, 903–907 (1984).
6. B. Ameer, M. Divoll, D. R. Abernethy, D. J. Greenblatt, and L. Shargel, Absolute and relative bioavailability of oral acetaminophen preparations, J. Pharm. Sci., 77, 8, 995–958 (1983).
7. M. D. Rawlins, D. B. Henderson, and A. R. Hajib, Pharmacokinetics of paracetamol (acetaminophen) after intravenous and oral administration, Eur. J. Clin. Pharmacol., 11, 283–286 (1977).
8. C. Graffner, H. Arwidsson, and H. Quiding, in *Proceedings of the 16th International Symposium on Controlled Release of Bioactive Materials*, (R. Pearlman and J. Allen Miller, eds.), CRS Inc., Chicago, 1989.

9. C. Graffner, M. Särkelä, K. Gjellan, and G. Nork, Use of statistical experimental design in the further development of a discriminating in vitro release test for ethyl cellulose ER-coated spheres of remoxipride, Eur. J. Pharm. Sci., 4, 73–83 (1996)
10. R. Abuzarur-Aloul, K. Gjellan, M. Sjölund, M. Löfqvist, and C. Graffner, Critical dissolution tests of oral systems based on statistically designed experiments. I. Screening of critical fluids and in vitro/in vivo modelling of extended release coated spheres, Drug. Dev. Ind. Pharm., 23(8), 749–760 (1997).
11. R. Abuzarur-Aloul, K. Gjellan, M. Sjölund, and C. Graffner, Critical dissolution tests of oral systems based on statistically designed experiments. II. In vitro optimization of screened variables on ER-coated spheres for the establishment of an in vitro/in vivo correlation., Drug Dev. Ind. Pharm., 24(3), 1–10 (1998).
12. F. Langenbucher, Linearization of dissolution rate curves by the Weibull distribution, J. Pharm. Pharmacol., 24, 979–981 (1972).
13. F. Langenbucher, Parametric representation of dissolution-rate curves by the RRSBW distribution, J. Pharm. Ind., 38(5), 472 (1976).
14. United States Pharmacopeia, 23rd ed., The United States Pharmacopeial Convention, Inc., Rockville, MD, 1995.
15. G. E. P. Box, W. G. Hunter, and J. S. Hunter, *Statistics for Experimenters*, Wiley, New York, 1978.
16. W. J. Weibull, Appl. Mech., 18, 293 (1951).
17. A. Höskuldsson, PLS-regression methods, J. Chemom., 2, 211–228 (1988).
18. F. Langenbucher, Numerical convolution/deconvolution as a tool for correlating in vitro with in vivo drug availability, Pharm. Ind., 44, 1166–1172 (1982).
19. M. E. Aulton, *Pharmaceutics: The Science of Dosage Form Design*, Churchill Livingstone, Edinburgh, UK, 1992, p. 155
20. J. A. H. Forrest, J. A. Clements, and L. F. Prescott, Clinical pharmacokinetics of paracetamol, Clin. Pharmacokin., 7, 93–107 (1982).
21. J. M. Jaffe, J. L. Cloazzi, and H. Barry, Effects of dietary components of GI-absorption of acetaminophen tablets in man, J. Pharm. Sci., 60, 1646–1650 (1971).
22. J. C. Wessels, H. A. Koeleman, B. Boneschans, and H. S. Steyn, The influence of different types of breakfast on the absorption of paracetamol among members of an ethnic group, Int. J. Clin. Pharmacol. Ther. Toxicol., 30, 6, 208–213 (1992).
23. I. J. MacGilveray and G. L. Mattok, Some factors affecting the absorption of paracetamol, J. Pharm. Pharmacol., 24, 615–619 (1972).
24. T. Ueno, A. Tanaka, Y. Hamanaka, and T. Suzuki, Serum drug concentrations after oral administration of paracetamol to patients with surgical resection of the gastrointestinal tract, Br. J. Clin. Pharmacol., 39, 330–332 (1995).
25. N. Katori, N. Aoyagi, and T. Terao, Estimation of agitation intensity in the GI tract in humans and dogs based on in vitro/in vivo correlation, Pharm. Res., 12, 2 (1995).
26. H. A. Lieberman and L. Lachman, *Pharmaceutical Dosage Forms. Tablets*, Volume 2, Marcel Dekker, 1981, p. 271.
27. T. T. Karali, Comparison of the gastrointestinal anatomy, physiology and biochemistry of humans and commonly used laboratory animals, Biopharm. Drug Dispos., 16, 351–380 (1995).
28. P. R. Holt, Fats and bile salts. I. Physiologic considerations, J. Am. Diet. Assoc. 60(6), 491–495 (1972).
29. J. E. Polli, J. R. Crison, and G. L. Amidon, Novel approach to the analysis of in vitro-in vivo relationships, J. Pharm. Sci. 85(7), 753–760 (1996).
30. G. L. Amidon, H. Lennernäs, V. P. Shah, and J. R. Crison, A theoretical basis for a biopharmaceutical drug classification. The correlation of in vitro drug product dissolution and in vivo bioavailability, Pharm. Res. 12(3), 413–419 (1995).
31. Anne-Sophie Ohlberger, Pharmaceutical R&D, Astra Läkemedel AB, SE-151-85 Södertälje, Sweden, personal communication.