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RESEARCH PAPER

A New Rapidly Absorbed Paracetamol Tablet Containing Sodium Bicarbonate. II. Dissolution Studies and In Vitro/In Vivo Correlation

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ABSTRACT

The objective of this study was to compare the in vitro dissolution profile of a new rapidly absorbed paracetamol tablet containing sodium bicarbonate (PS) with that of a conventional paracetamol tablet (P), and to relate these by deconvolution and mapping to in vivo release. The dissolution methods used include the standard procedure described in the USP monograph for paracetamol tablets, employing buffer at pH 5.8 or 0.05 M HCl at stirrer speeds between 10 and 50 rpm. The mapping process was developed and implemented in Microsoft Excel® worksheets that iteratively calculated the optimal values of scale and shape factors which linked in vivo time to in vitro time. The in vitro–in vivo correlation (IVIVC) was carried out simultaneously for both formulations to produce common mapping factors. The USP method, using buffer at pH 5.8, demonstrated no difference between the two products. However, using an acidic medium the rate of dissolution of P but not of PS decreased with decreasing

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stirrer speed. A significant correlation ($r = 0.773$; $p < .00001$) was established between in vivo release and in vitro dissolution using the profiles obtained with 0.05 M HCl and a stirrer speed of 30 rpm. The scale factor for optimal simultaneous IVIVC in the fasting state was 2.54 and the shape factor was 0.16; corresponding values for mapping in the fed state were 3.37 and 0.13 (implying a larger in vitro–in vivo time difference but reduced shape difference in the fed state). The current IVIVC explains, in part, the observed in vivo variability of the two products. The approach to mapping may also be extended to different batches of these products, to predict the impact of any changes of in vitro dissolution on in vivo release and plasma drug concentration–time profiles.

Key Words: *Deconvolution; Dissolution test; In vitro–in vivo correlation; Paracetamol*

INTRODUCTION

Over the past two decades, dissolution test methodology has been introduced in many pharmacopeais and it is widely acknowledged that in vivo–in vitro comparison of percentage drug release can provide valuable information. A further step, establishing in vivo–in vitro correlation (IVIVC), is even more useful as it has the power to attribute observed changes in in vivo profile to in vitro differences and to predict in vivo dissolution from a given change of in vitro drug release. Such methods have been used successfully to relate in vivo release and even therapeutic outcome of different products to their in vitro dissolution characteristics (1–3). Also, they have been used to discriminate inter-batch differences within a product with the aim of setting specifications for in vitro release as a guide to potential in vivo acceptability of the formulation (4).

A number of IVIVC approaches have been reported for a variety of paracetamol (acetaminophen) formulations (5–7). However, the composition of any new formulation may have a pronounced effect on optimal in vitro conditions with respect to dissolution media and stirring speed. Thus, adequacy of dissolution tests to discriminate between products with regard to in vivo release should be tested for each new product. Previous IVIVCs may not apply to new products, particularly if they are formulated in a significantly different way.

Accordingly, we report the results of an IVIVC study on a newly developed rapidly absorbed paracetamol/sodium bicarbonate tablet in comparison with conventional tablets.

Bioequivalence data used to determine in vivo release were obtained from a previous study (8) by a compartmental deconvolution approach. Dissolution was investigated using different paddle speeds with varying dissolution media. We used a mapping technique to establish the in vitro test conditions that give the best IVIVC for the two test formulations. The details of such comprehensive mapping techniques have been described by others (9,10). However, their use has not become common practice and, to our knowledge, they have not been applied to establish IVIVC for paracetamol formulations.

MATERIALS AND METHODS

Dissolution Tests

Dissolution tests were carried out according to the USP monograph for acetaminophen tablets using the paddle apparatus with 900 mL of phosphate buffer at pH 5.8 (11). Additional tests were carried out using the paddle apparatus with 900 mL of 0.05 M HCl at paddle speeds in the range of 10–50 rpm.

Paracetamol concentrations were determined at 5, 10, 15, 20, 25, and 30 min for dissolution tests using phosphate buffer (pH 5.8) and at 5, 10, 15, 30, and 60 min for dissolution tests using 0.05 M HCl. Paracetamol was assayed using a HP UV 4852A diode array spectrophotometer with Conat dissolution software. The assay method was validated and found satisfactory with respect to accuracy, precision, linearity, specificity, and solution stability.

Model-independent similarity of dissolution profiles, f_2, was determined using Eq. (1) according to Moore and Flanner (12), as recommended in the FDA's Guidance for Industry (13) and in CPMP's

Note for Guidance on the Investigation of Bioavailability and Bioequivalence (14):

$$f_2 = 50 \times \log\left(100 \Big/ \sqrt{\left(1 + \frac{\sum_{1}^{n}(F_P - F_{PS})^2}{n}\right)}\right) \quad (1)$$

A value of f_2 equal to 50 (average difference of 10% on all sampling points) was taken as the cut-off value for "similarity." Only one sampling time point after 85% dissolution was used (15).

Deconvolution of Pharmacokinetic Profiles

User-defined compartment models were set up using the TopFit 2.0 software (Gustav Fischer, Stuttgart, Germany) according to the scheme shown in Fig. 1. Serum paracetamol concentration–time profiles following administration of conventional and sodium bicarbonate tablets (8) were fitted simultaneously by these models such that disposition parameters were common for both products in all four arms of the study in each individual. Goodness-of-fit was evaluated by inspection of residual errors and the Akaike Information Criterion (AIC) was used to discriminate between rival models. Individual release profiles for all products were reconstructed by the program using individual kinetic parameters of in vivo absorption based on the best overall pharmacokinetic model for each individual. A correction factor based on the individual area under curve (AUC) values of paracetamol following administration of paracetamol tablets in the fed state was used to account for the differences in total bioavailability. Thus, the constructed release was represented as percentage of dose released relative to total absorbed dose from paracetamol tablets in the fed state. In the majority of individuals the AUC of paracetamol was highest after administration of paracetamol tablets in the fed state (8).

IVIVC Using Time Mapping

The in vivo release of drug from each product was obtained using the mean release at each time point from the corresponding profiles for each individual. The time scale of these profiles was changed by a function, Ψ, such that:

$$F_{\text{in vivo}}(t_{\text{in vivo}}) = F_{\text{in vitro}}[\Psi(t_{\text{in vitro}})] \quad (2)$$

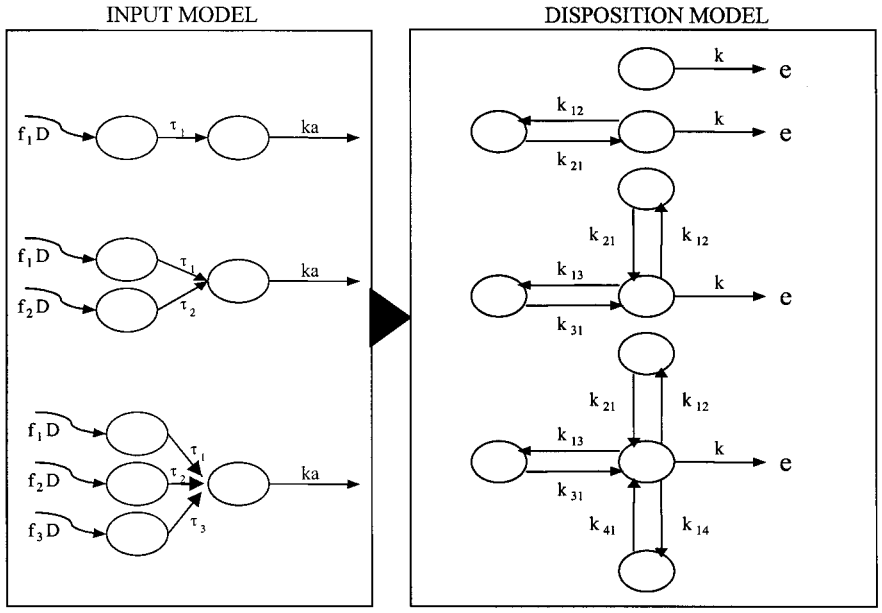

Figure 1. Pharmacokinetic models used for simultaneous fitting of serum paracetamol data following administration of the conventional and new paracetamol/sodium bicarbonate formulations in the fed and fasted states. To obtain best fits, any combination of input and disposition models was tested.

where $F_{\text{in vitro}}$ and $F_{\text{in vivo}}$ are the fractions of drug released during the in vitro dissolution test and the fraction absorbed in vivo, respectively. The link function, Ψ, comprised a time scale factor (*scale*) and a time shape factor (*shape*):

$$\Psi(t_{\text{in vitro}}) = \exp\left\{scale \times [(t_{\text{in vitro}})]^{shape}\right\} \quad (3)$$

Optimal values of *scale* and *shape* were calculated iteratively using Solver within Excel such that weighted sums of squares for the differences between $F_{\text{in vitro}}$ and $F_{\text{in vivo}}$ were minimized upon simultaneous fit of the conventional and new paracetamol/sodium bicarbonate data. Only one data point after full dissolution (95%) was used for fitting data with each model, and the sum of squares was normalized by the squared inverse of the observations ($1/y^2$) and the number of data points from each formulation to assure equal effect of the two formulations on calculated values of the mapping factors. The convergence criterion was the default setting in Excel, and initial values were obtained by manual insertion of the parameter values and inspection of graphical superposition.

RESULTS

Dissolution Tests

The dissolution tests using phosphate buffer (pH 5.8) indicated that >95% of paracetamol had dissolved within 10 min from both test products (data not shown). Dissolution profiles using 0.05 M HCl at different stirrer speeds for the conventional and sodium bicarbonate formulations are shown in Fig. 2. Paddle speed had a major effect on the dissolution profile of the conventional formulation. However, the latter effect was much less pronounced for the sodium bicarbonate formulation. The similarity between dissolution profiles in different conditions for each product, as measured by f_2, is reported in Table 1. Assuming 50 as the minimal cut-off point for similarity, dissolution profiles at different paddle speeds were dissimilar for the conventional formulation. However, the dissolution profiles of the sodium bicarbonate formulation were similar at all stirring speeds except 50 rpm.

The dissolution profiles of the conventional and sodium bicarbonate formulations were different at all stirring speeds. The similarity factor for dissolution of the two formulations increased as stirring speed increased, such that at 50 rpm the two dissolution curves had borderline similarities ($f_2 = 48$).

Deconvolution of Pharmacokinetic Profiles

Model fits to data from a representative subject are shown in Fig. 3. Pharmacokinetic data from some individuals were best fitted with models consisting of two absorption compartments and one or two disposition compartments. However, the best model for the majority of subjects required two

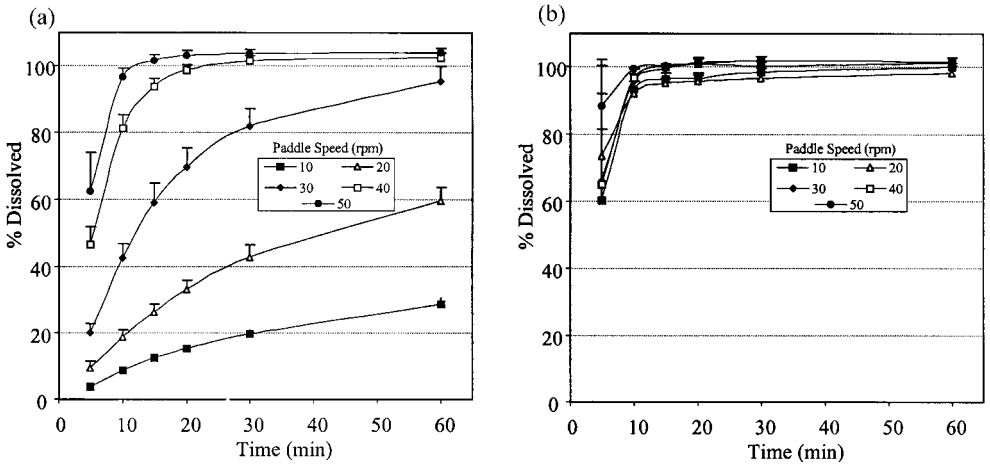

Figure 2. In vitro dissolution curves for paracetamol from (a) conventional paracetamol and (b) new paracetamol/sodium bicarbonate formulations in 0.05 M HCl solution at different stirring speeds.

Table 1

Values of Similarity Factor, f_2, for Different Dissolution Curves[a]

	10 rpm	20 rpm	30 rpm	40 rpm	50 rpm
10 rpm	**6**	52	68	69	35
20 rpm	36	**11**	61	58	47
30 rpm	15	25	**22**	95	40
40 rpm	7	12	28	**49**	39
50 rpm	5	8	16	43	**48**

[a]Values above the diagonal refer to the new paracetamol/sodium bicarbonate tablets at corresponding paddle speeds. Values below the diagonal refer to conventional tablets at corresponding paddle speeds. Numbers in bold refer to the similarity of the conventional and new paracetamol/sodium bicarbonate formulations at each corresponding paddle speed.

absorption compartments with three disposition compartments. Thus, while the absorption model appeared to be the same for all individuals, the disposition model was different. The fraction of dose residing in each of the two absorption compartments was dissimilar in different individuals, and it also varied in the fasted and fed states. A summary of pharmacokinetic parameters is given in Tables 2 and 3. Confidence intervals (95% CI) for observed individual release profiles of the conventional and sodium bicarbonate formulations in the fasted and fed states, together with the mean (and 95% CI for mean) release profiles are shown in Fig. 4.

Median population releases calculated from individual release profiles were similar to the mean values over the entire study period apart from the region before a lag time was present. This caused

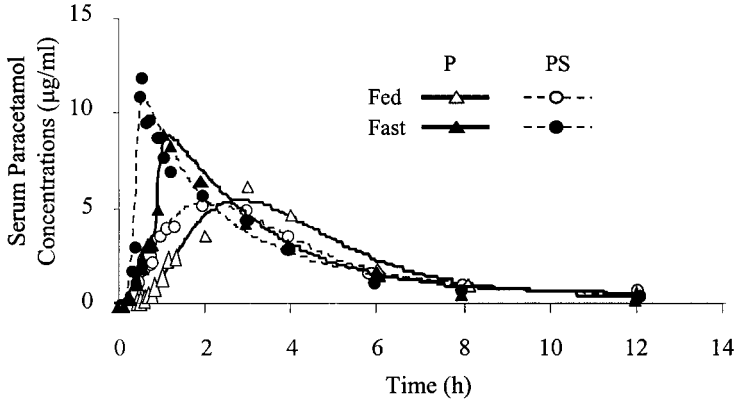

Figure 3. Simultaneous data fit (lines) to observed serum paracetamol concentrations (markers) following four different treatments in a representative subject.

Table 2

Values of Pharmacokinetic Parameters Obtained by Deconvolution (Model Fit) Used to Simulate In Vivo Drug Absorption Profiles (Convolution) [n = 27; Median (Lower and Upper 5% Centiles)][a]

	f_1	t_{lag1} (hr)	τ_1 (hr^{-1})	f_2	t_{lag2} (hr)	τ_2 (hr^{-1})	Rel_{AUC}	k_a (hr^{-1})
PS (fed)	0.47 (0.09,0.88)	0.1 (0.0,0.2)	1.29 (0.08,3.42)	0.53 (0.13,0.91)	0.26 (0.1,0.6)	7.86 (0.59,15)	91 (69,113)	5.80 (0.44,19.8)
PS (fasted)	0.37 (0.03,0.84)	0.11 (0.0,0.2)	3.88 (0.05,15)	0.63 (0.16,0.97)	0.26 (0.2,0.4)	12.00 (0.79,23.89)	88.74 (63,107)	10.03 (0.58,15)
P (fed)	0.25 (0.02,0.77)	0.06 (0.0,0.2)	5.34 (0.19,15)	0.75 (0.23,0.99)	0.52 (0.2,0.9)	4.37 (0.56,15)	100	2.04 (0.48,6.15)
P (fasted)	0.46 (0.06,0.90)	0.09 (0.0,0.2)	3.19 (0.22,13.92)	0.54 (0.10,0.94)	0.32 (0.1,0.7)	9.93 (0.20,20)	90 (71,113)	5.78 (0.47,15)

[a]P = paracetamol; PS = paracetamol/sodium bicarbonate; Rel_{AUC} = relative AUC (P fed state as the reference).

Table 3

Average (Lower and Upper 5% Centile) Values of Disposition Parameters Obtained by Simultaneous Model Fitting of All Data [Conventional Paracetamol (P: Fast, Fed); Paracetamol/Sodium Bicarbonate (PS: Fast, Fed)] in Each Individual[a]

No. of Disposition Compartments	λ_1 (hr^{-1})	λ_2 (hr^{-1})	λ_3 (hr^{-1})	k_{21}(hr^{-1})	k_{31}(hr^{-1})
1 ($n=3$)	17.63 (5.00,28.95)	—	—	—	—
2 ($n=4$)	26.52 (9.68,38.5)	0.41 (0.23,0.79)		3.54 (1.48,7.35)	—
3 ($n=20$)	29.07 (9.67,50)	1.83 (0.31,7.80)	0.09 (0.01,0.20)	6.62 (1.17,28.96)	0.19 (0.02,0.59)

[a]The micro-constants shown in Fig. 1 can be calculated from the hybrid macro-constants λ_1, λ_2, λ_3, and relevant inter-compartmental constants given in the above table, as follows:

1-compartmental $k = \lambda_1$

2-compartmental $k = (\lambda_1 \times \lambda_2)/k_{21}$; $k_{12} = (\lambda_1 + \lambda_2) - (k + k_{21})$

3-compartmental $k = (\lambda_1 \times \lambda_2 \times \lambda_3)/(k_{21} \times k_{31})$; $k_{12} = [(k_{21} - \lambda_1) \times (k_{21} - \lambda_2) \times (k_{21} - \lambda_3)]/[k_{21} \times (k_{21} - k_{31})]$;
$k_{13} = (\lambda_1 + \lambda_2 + \lambda_3) - (k + k_{21} + k_{12} + k_{31})$.

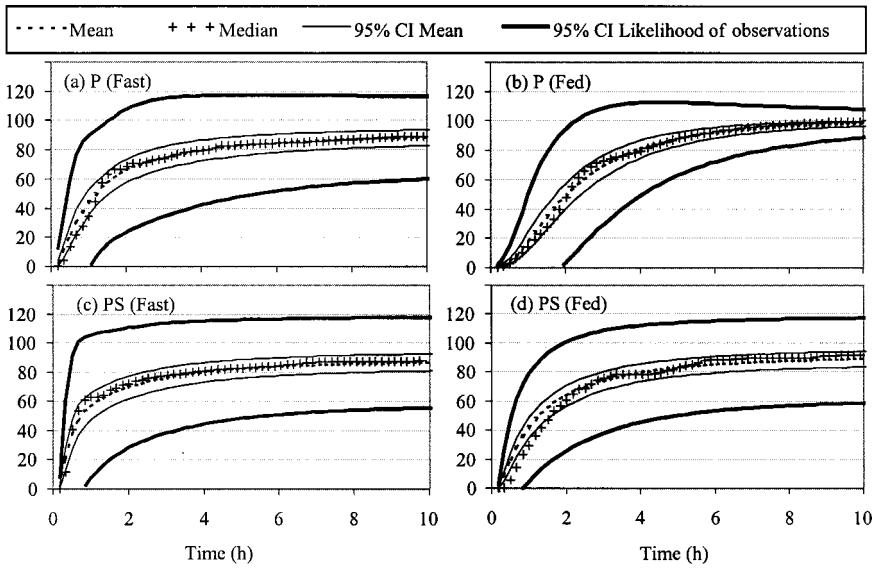

Figure 4. The in vivo release profiles of the conventional (a,b) and new paracetamol/sodium bicarbonate formulations (c,d) in the fasted (a,c) and fed (b,d) states.

deviations from the normal distribution of release within the study population at these time points. The relative in vivo release profiles for the conventional and sodium bicarbonate formulations are shown in Fig. 5 as ratios and percentages of dose released, respectively. These graphs indicate that the largest discrepancy between the relative release of the two products occurs 20–30 min after administration. However, the manifestation of this, as the maximum difference in the extra dose released, is seen approximately 1 and 2 hr after administration during fasting and fed states, respectively.

IVIVC Using Time Mapping

Separate mapping for each product generated better fits than simultaneous evaluation (data not shown). However, ideal mapping is considered to be formulation-independent, and this could be achieved only by simultaneous fitting of data. This

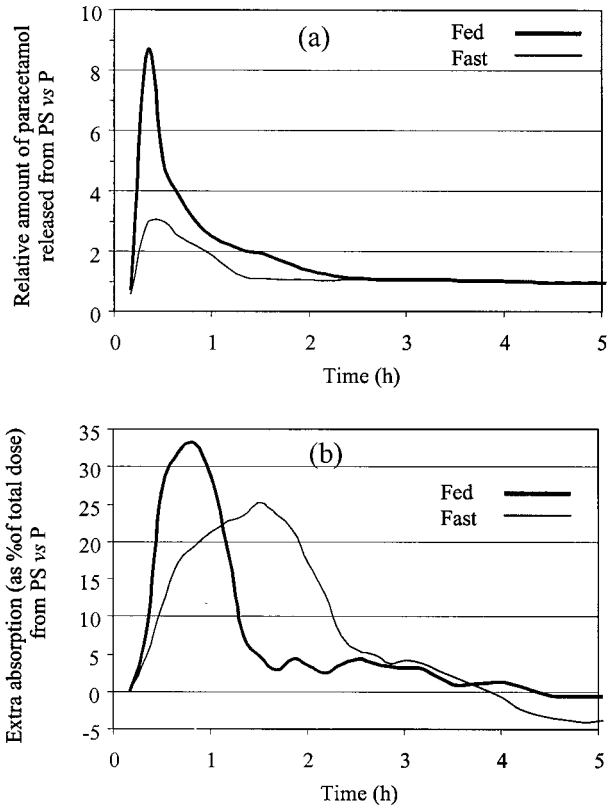

Figure 5. The relative in vivo release from the new paracetamol/sodium bicarbonate formulation to that of the conventional formulation in the fed and fasted states. (a) The ratio of cumulative drug released from corresponding formulations. (b) The absolute difference in cumulative drug release at each time point.

Table 4

Results of IVIVC at Different Paddle Speeds (Numbers in Italic Represent the Best Model Fits)

	0 rpm	20 rpm	30 rpm	40 rpm	50 rpm
			Fasting State		
Scale factor	2.63	2.66	2.54	0.94	0.97
Shape factor	0.06	0.09	0.16	0.84	0.87
AIC[a]	−6.2	−8.9	*−21.2*	*−31.0*	−12.6
			Fed State		
Scale factor	3.19	3.35	3.37	3.25	1.9885
Shape factor	0.07	0.09	0.13	0.21	0.55
AIC[a]	−15.4	−16.6	*−26.0*	*−20.7*	−17.3

[a]AIC = Akaike Information Criterion [$AIC = N_{observations} \times \ln(WRSS) + 2N_{parameter}$], where WRSS = weighted residual sum of squares.

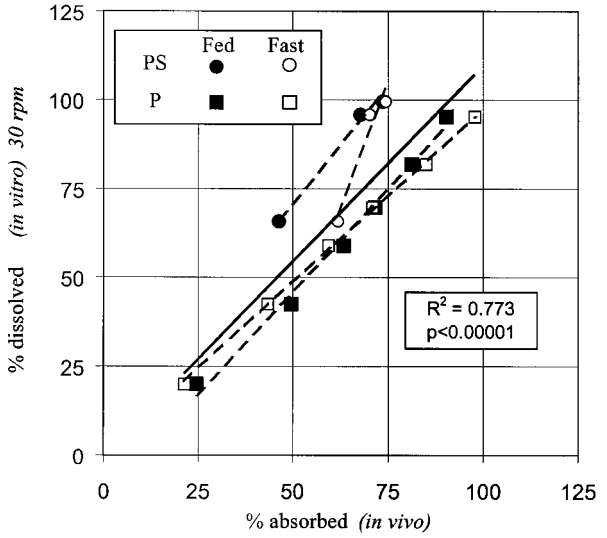

Figure 6. Correlation between in vitro and in vivo paracetamol release after applying time mapping to the in vivo profile.

produced a variable weighted residual sum of squares (WRSS) at various stirring speeds for corresponding mapping factors, which was also corrected for the number of observations using AIC (Table 4). The best mappings were obtained for dissolution data at 30 and 40 rpm when both fed and fasted conditions were reviewed together. However, since the former stirring speed was more discriminative, 30 rpm was used for the final IVIVC. The corresponding in vivo–in vitro release comparisons at this paddle speed after applying the mapping process are shown in Fig. 6. The correlation between the two sets of values (from both formulations together) was statistically significant ($p < .00001$). The correlation coefficient was 0.773 and the slope of the regression line was not statistically different from unity.

DISCUSSION

The results obtained with the dissolution tests employing the USP method for paracetamol tablets, i.e., the paddle apparatus using phosphate buffer pH 5.8 at 37°C and a stirrer speed of 50 rpm, demonstrated that under these conditions both formulations dissolved rapidly within 10 min. Therefore, the USP method clearly cannot

distinguish potentially significant differences between the in vivo release of the two formulations. The European Pharmacopoeia does not have an individual monograph for paracetamol tablets. However, the guidelines state that the pH of the dissolution media is usually set within the range of 1 to 7.6. If tablets are tested using either the paddle or basket apparatus then a stirrer speed from 50 to 100 rpm is normally chosen (16). The dissolution tests conducted using 0.05 M HCl (i.e., pH 1.3) demonstrated no differences in the dissolution rates between the conventional and sodium bicarbonate formulations using a standard stirrer speed of 50 rpm.

The FIP guidelines for dissolution testing of solid products (17) state that "in vitro dissolution data should at least allow some interpretation with regard to in vivo biopharmaceutical performance." Using slower stirrer speeds, the dissolution of paracetamol from conventional tablets was slower than that from the new paracetamol/sodium bicarbonate tablets, which was consistent with in vivo observations of shorter t_{max} and higher C_{max} for the sodium bicarbonate formulation relative to the conventional formulation (8). However, slower stirring did not change the dissolution rate of the sodium bicarbonate formulation significantly, with $>90\%$ paracetamol dissolving after 10 min under all conditions tested.

Deconvolution of pharmacokinetic profiles indicated a clear difference in the in vivo release of paracetamol from the conventional and sodium bicarbonate formulations. The maximum discrepancy between the two formulations in the fasting state occurred after 50 min, when the sodium bicarbonate formulation had released 75% of the dose vs. 44% release from the conventional formulation (an additional release of 31%). Corresponding values of the maximum discrepancy during the fed state were 90 min and 39% extra dose release (66% from the sodium bicarbonate formulation and 27% from the conventional formulation).

The mechanism whereby sodium bicarbonate enhances the rate of paracetamol absorption following oral administration has not been fully elucidated. On ingestion of sodium bicarbonate in vivo carbonation will occur as a result of the reaction of bicarbonate with gastric acid, resulting in production of gaseous carbon dioxide. In vivo carbonation has been reported to increase the pressure gradient across the gastroduodenal junction in dogs and to alter the permeability of gastrointestinal epithelium and the gastric mucous, so enhancing drug absorption rates (18,19). However, as we have reported previously (20), the addition of calcium carbonate (another carbon dioxide source) to paracetamol tablets had no effect on the rate of drug absorption. It therefore seems unlikely that improved permeability through the gastrointestinal epithelium or gastric epithelium as a result of in vivo carbonation plays a significant role in enhancing paracetamol absorption. Moreover, in one recent healthy volunteer study (21) the volumes of gas obtained following oral ingestion of sodium bicarbonate were considerably less than the theoretical volume which may be expected. In a previous study involving fasted volunteers we postulated that this could be due to a variety of factors, including a faster in vivo dissolution rate and an increase in gastric emptying rate (20). Two previous studies have demonstrated that sodium bicarbonate exerts a maximal gastric emptying effect at concentrations that are approximately isotonic (22,23). The concentration of sodium bicarbonate following ingestion of two paracetamol/sodium bicarbonate tablets with 100 mL of water in fasted volunteers will be approximately isotonic. However, this is unlikely to be the case in the fed state where there will be a considerable dilution effect. Furthermore, following food additional solutes will be present, some of which may have a retarding effect on gastric emptying (24). Therefore, while an enhanced gastric emptying mechanism appears plausible in the fasted state, it would appear to be less likely to account for the faster absorption observed in the fed state when other mechanisms such as an enhanced dissolution rate may play a more dominant role.

Although dissolution rate testing according to standards set by pharmacopoeias may serve as a good quality control tool for many solid oral dosage forms, establishment of an IVIVC, in particular level A correlation (25), should provide more physiologically meaningful data. In a recent review by Dressman et al. (26) it was concluded that to achieve such a level of correlation the conditions for in vitro dissolution should be optimized for each drug. However, as shown for theophylline (27), these might well be very different for various formulations of the same drug. In order to assess the possible relationship of enhanced absorption rate from the sodium bicarbonate formulation and rate of in vitro dissolution, we attempted to map each of the

in vivo release profiles obtained from the deconvolution studies onto the dissolution profiles at different stirrer speeds. The mapping process was more successful in superimposing in vivo and in vitro release profiles for some stirring conditions than others. The best mapping was based on a stirring rate of 30 rpm. One recent study (28) assessed the hydrodynamic flow around dosage for two different sustained-release tablets of paracetamol in the human gastrointestinal (GI) tract by comparing the characteristics of in vivo release and in vitro release using a range of paddle stirrer speeds (10, 50, and 100 rpm). They showed that hydrodynamic flow around the dosage forms could be extremely low. Our data are consistent with these findings in showing that the current paddle speed of 50 rpm set by the US Pharmacopeia may be extreme.

The shape factor defined by our IVIVC analysis indicates the non-linear nature of the relationship between in vitro and in vivo dissolution (10). Thus, linear time scaling (29) may not be adequate to achieve the best IVIVC. The fact that level A correlation was not internally consistent in a recent report on glibenclamide IVIVC (30) may indicate that, in contrast to the author's assumption, the relationship was not linear. One reason that the application of non-linear IVIVC has not become common practice could be its complexity. However, our study shows that the application of non-linear models does not require specialized software and can be done easily with readily accessible programs such as Excel.

It should be borne in mind that the ultimate aim of in vitro dissolution tests is not just to discriminate between formulations. It is possible that dissolution tests that are too discriminatory may establish in vitro differences that do not necessarily reflect measurable in vitro release variation. Such examples are shown for nifedipine formulations (31) and emphasize the paramount importance of IVIVC as the best way of choosing optimal in vitro conditions and avoiding over-interpretation of in vitro differences. Thus, despite a more pronounced separation of the dissolution curves for conventional and sodium bicarbonate formulations at 10 or 20 rpm, the latter speeds were not the optimal rates to correlate with in vivo data.

In regard to translation of proportional changes in dissolution and their consequences to clinically important features of plasma drug concentration profiles, our group, using a one-compartmental model, has also indicated that large dissolution differences may result in negligible changes of clinically important surrogate markers of absorption rate (32). Similar results have been demonstrated for more complex pharmacokinetic models by Elkoshi (33). The latter damping effect of pharmacokinetics, together with statistical considerations (34), should be considered when setting acceptance intervals for in vitro release profiles.

CONCLUSIONS

The application of the USP dissolution test for paracetamol to the immediate release formulations of conventional paracetamol and sodium bicarbonate did not accurately reflect the conditions encountered in the stomach with respect to pH and hydrodynamics. We have shown that under acidic conditions the rate of dissolution for conventional paracetamol tablets is dependent on stirrer speed, whereas this does not appear to be the case for the new paracetamol/sodium bicarbonate formulation. Thus, under these more discriminating conditions, paracetamol is released faster from the new formulation than from conventional tablets.

We successfully used a mapping technique to establish a simultaneous IVIVC relationship for the conventional and new paracetamol/sodium bicarbonate formulations that may indicate a major role for dissolution as a determinant of wide differences of the two products in regard to in vivo release. By extending current mapping to characterize interbatch variability, it would be possible to predict the impact of any given change on therapeutically important parameters, such as C_{max} and t_{max}, and to establish acceptance limits for in vitro dissolution. On reviewing the literature on IVIVC, and considering the flexibility and utility of empirical non-linear in vitro–in vivo link functions, it appears that the latter has been under-utilized.

ACKNOWLEDGMENT

Note: The paracetamol/sodium bicarbonate formulation in this study is marketed by GSK Consumer Healthcare as Panodil Zapp (Denmark, Sweden) and Panadol Actifast (UK).

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