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Influence of amount of hard fat in suppositories on the in vitro release rate and bioavailability of paracetamol and codeine. I. A comparison of three suppository compositions in vivo

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Summary

The flow-through cell at a flow rate of 16 and 8 ml/min has been used to investigate how the amount of paracetamol and codeine phosphate, in relation to the total weight of a lipophilic suppository, influences the in vitro dissolution rate. Two in vivo studies explored how the rate and extent of bioavailability in humans varied as a function of fraction of drug substances. Despite an approx. 20-fold difference in aqueous solubility between paracetamol and codeine phosphate, the lipophilicity controlled the in vitro release and bioavailability. Decreasing the amount of paracetamol and codeine phosphate in relation to total suppository weight and increasing the size of the suppository resulted in a faster absorption rate and an increased extent of bioavailability. This was more pronounced for paracetamol. The flow-through cell was found to produce dissolution profiles which were in agreement with the plasma concentration profiles obtained, indicating that the lower flow rate reflected the in vivo situation more correctly than the higher flow rate. The intra-individual variation when administering one composition on two different occasions was found to be relatively small for five of the subjects who participated in both studies.

Introduction

In order to achieve fast drug absorption from melting suppositories it is important that the drug is rapidly released and dissolved in the rectal fluid. The rate of dissolution is influenced by several formulation factors such as the particle size of the dispersed drug (Schoonen et al., 1979; Moolenaar et al., 1979a), the amount of drug substance in relation to suppository volume (Moolenaar et al., 1979a) and the viscosity of the vehicle at body temperature (Schoonen et al., 1980). The contact area between the suppository and the rectal fluid governed by the volume might also influence the dissolution rate (Moolenaar et al., 1979a,b).

Since the spread of suppository mass is limited to 5–7 cm up into the rectal cavity (Jay et al.,

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1985; Sugito et al., 1988), it is of interest to design a composition that utilises the available absorption area as effectively as possible. An in vitro dissolution technique might be a helpful tool for this purpose provided that it discriminates between dissolution profiles from different compositions and is consistent with the plasma concentration profiles in man.

Several dissolution techniques have been described (Bornschein et al., 1985), and the flow-through method (Gjellan and Graffner, 1989; Langenbucher et al., 1989) has been one of the techniques suggested for characterising the dissolution rates from different suppository compositions.

The aim of the present study was to investigate how the proportion of paracetamol and codeine phosphate with respect to the total suppository weight, focusing in particular on paracetamol, influences the in vitro dissolution rate and the extent of bioavailability in man.

Experimental

Chemicals

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

The particle size of paracetamol and codeine phosphate was determined by a sieve method, more than 90% of the particles being less than 71 μm and 97% less than 320 μm, respectively. The solubility is 14.3 mg/ml for paracetamol and 250–400 mg/ml for codeine phosphate at room temperature (Martindale, 1989). The partition coefficient (log D) between octanol and water (pH 7.4) is 0.5 and 0.23. pK_a for paracetamol is 9.5 and for codeine base 8.2 (Albert and Serjeant, 1984; Newton and Kluza, 1978; Hansch et al., 1987).

Rectal dosage systems

The different paracetamol suppository compositions tested are shown in Table 1 and 2. Suppository A (Citodon™) was taken from ordinary manufacture (Astra Läkemedel AB, Sweden). The other compositions were produced manually on a small scale by homogenising paracetamol into the melted base. The melt was poured into moulds of stainless steel or plastic containers (composition C).

The weights of 20 separate suppositories were checked and found to be within ±5% of the theoretical weight.

TABLE 1

Complete composition of the suppositories with different fractions of paracetamol

Paracetamol (mg)	Hard fat (g)	Fraction of paracetamol [a] (%)	Total suppository weight (g)
500	1.78	21.9	2.28
600	1.71	26.0	2.31
700	1.65	29.8	2.35
750	1.62	31.6	2.37
800	1.58	33.6	2.38
850	1.55	35.4	2.40
900	1.50	37.5	2.40
1000	1.43	41.2	2.43

[a] Fraction of paracetamol (%) = $\frac{\text{amount of paracetamol (g)}}{\text{total suppository weight (g)}}$.

In vitro dissolution tests

The in vitro dissolution rate of paracetamol was examined by means of the flow-through cell with a diameter of 12 mm (Disotest/Dissotest CY, Sotaxag, Basel, Switzerland). Water, deaerated by heat, at a temperature of 37 ± 0.5°C with

TABLE 2

Complete composition of the suppositories administered in the clinical studies 1 and 2 containing paracetamol and codeine phosphate

Suppository	Paracetamol (mg)	Codeine phosphate (mg)	Fraction drug substance [a] (%)	Hard fat (g)	Total weight suppository (g)
A [b]	500	30	23.2	1.75	2.28
B	1000	60	43.6	1.30	2.43
C	1000	60	33.1	2.14	3.20

[a] Fraction drug substance = $\frac{\text{amount paracetamol + codeine phosphate (g)}}{\text{total weight suppository (g)}}$

[b] A is equivalent to the Citodon™ suppository, Astra Läkemedel AB, Sweden.

flow rates of 16 and 8 ml/min, was used as dissolution medium. The function of the cell has been described by Gjellan and Graffner (1989).

The tests were performed with three to six suppositories of each type. The amount of dissolved paracetamol and codeine phosphate, given as a percentage of the declared amount, was detected spectrophotometrically at 243 nm for suppositories containing only paracetamol and by HPLC with UV detection at 214 nm for suppositories containing both substances.

Design of the bioavailability studies

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

Study 1 Eight female and eight male volunteers aged between 21 and 41 years participated. Each subject received two suppositories of A (2×2.28 g)and one of B (1×2.43 g). Thus, the weight of an A dose was about twice that of B.

Study 2 Eight female and ten male volunteers aged between 22 and 43 years were included. Two suppositories of A (2×2.28) and one of C (1×3.2 g) were administered. The weight of an A dose was 1.4 times that of C.

Both trials were designed as a randomised open cross-over study and the treatments were performed about 1 week apart.

The subjects fasted 8 h before and 3 h after the administration of the suppository. They were encouraged to have a bowel moment before each drug administration and any defecation within the next 6 h was recorded.

Blood specimens were collected in heparinised Venoject® tubes before and 20, 40, 60, 80, and 100 min and 2, 2.5, 3, 4, 6, 8, 10, and 12 h after each drug administration. The samples were centrifuged within 1 h and the plasma was separated and stored at −20°C until assayed.

Five of the volunteers participated in both studies which were performed about 2 years apart. Since composition A was administered on both occasions, plasma concentration profiles were compared.

Assay

Bioanalytical method Paracetamol was analysed according to the HPLC method described by Nielsen et al. (1992) and codeine was analysed according to the HPLC technique described by Quiding et al. (1986).

Calculation of pharmacokinetic data

The observed maximum plasma concentration (C_{max}) of paracetamol and codeine and the corresponding time taken to reach it (T_{max}) were estimated for each subject. The overall elimination rate constant (β) of the two substances was determined for each subject by linear regression analysis of the terminal linear part of the log plasma concentration versus 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. 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 and C compared to A were determined using the quotient of total AUC (AUC_{tot}) for the two formulations.

Statistical methods

Descriptive statistics were applied to describe the in vitro dissolution profiles.

The nonparametric Wilcoxon 2-sample test was used to compare the amount of paracetamol dissolved at different sampling times for compositions with different fractions of paracetamol.

The Wilcoxon rank sum test was applied when carry-over, period and treatment effects were tested.

Wilcoxon's signed rank test was used in the pairwise comparisons of t_{max} and $t_{1/2}$ at a confidence level (c.i.) of 95%. Bioequivalence between

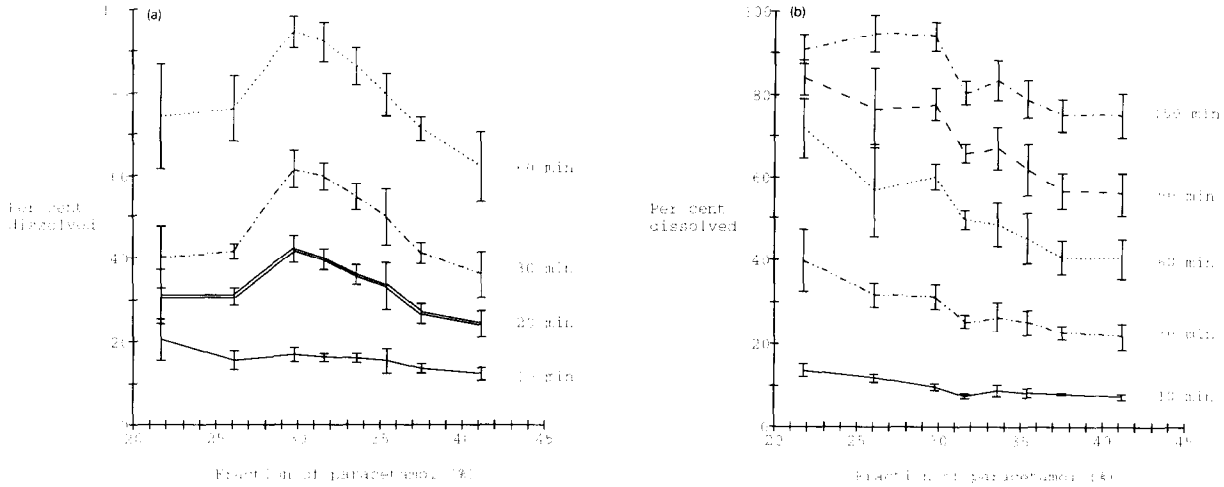

Fig. 1. Per cent paracetamol dissolved from suppositories with different fractions of the drug substance (Table 1) at a flowrate of (a) 16 ml/min and (b) 8 ml/min. Standard deviation given as error bars. Samples taken at (———) 10 min, (═══) 20 min, (– · · –) 30 min), (· · · · · ·) 60 min, (— — —) 90 min and (– · – · –) 150 min.

A and B and A and C was tested by use of the 90% c.i. following a logarithmic transformation according to FDA's current bioequivalence evaluation criterion. The 90% c.i. should lie within the interval from 0.8 to 1.25 when the lower and upper confidence limits have been exponentialized. The C_{max} ratio was investigated in the same way as the relative bioavailability.

Results

Influence of agitation on in vitro dissolution rate

Fig. 1 (a and b) shows the percentage of paracetamol dissolved from suppositories with different fractions of the compound. Figs 2 and 3 show the dissolution profiles of paracetamol from A (23%) and B (44%), and A and C (33 %) at flow rates of 16 and 8 ml/min.

Since the dissolution profiles of paracetamol and codeine phosphate were almost superimposable for each composition A–C, only the profiles for paracetamol are reported here.

The compositions of 22, 34 and 41% of paracetamol, which are focused on below, are close to the clinically tested suppositories with fractions of 23% (A), 33% (C) and 44% (B).

Flow rate of 16 ml / min The composition with the highest fraction of paracetamol generally produced the lowest release rate.

At a flow rate of 16 ml/min a maximum was found with regard to a fast in vitro release rate. Such a composition was based on a fraction of about 30–32% of paracetamol (w/w).

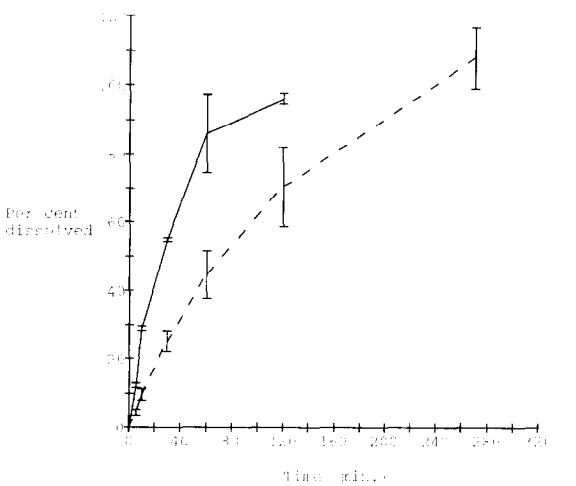

Fig. 2. In vitro dissolution rate of paracetamol from composition A (———) and B (— — —) (in vivo study 1), at a flow rate of 16 ml/min.

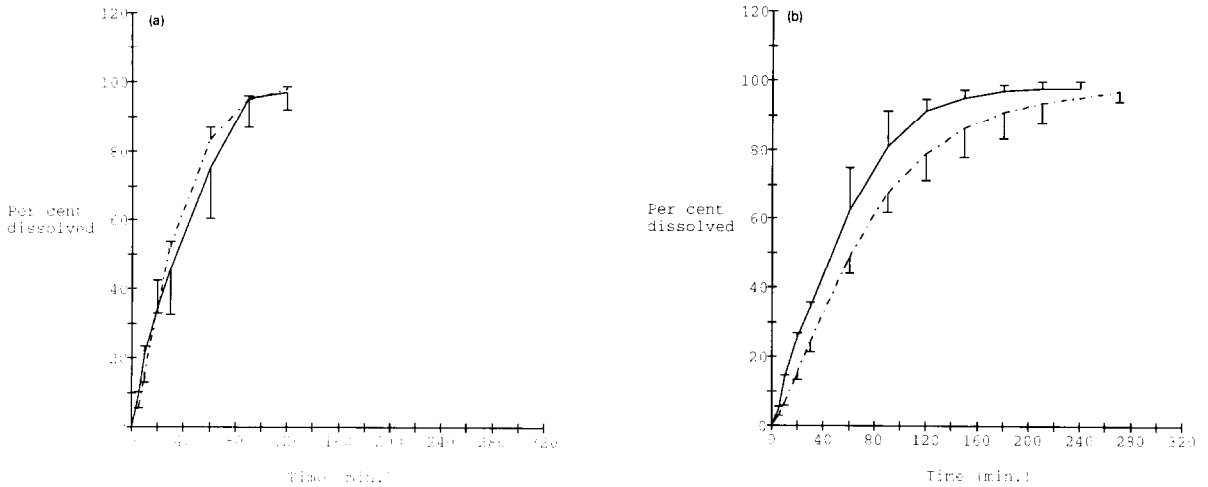

Fig. 3. In vitro dissolution rate of paracetamol from composition A (———) and C (– · – · –) (in vivo study 2), at a flow rate of (a) 16 ml/min and (b) 8 ml/min.

A significant separation from the 41% composition was found at all times at a c.i. level of 99% for the 34% composition. That of 22% was only significantly separated at 10 and 20 min (c.i. levels of 96 and 99%). The 22 and 34% compositions were significantly different from each other at 10, 20 and 30 min (c.i. levels of 93–99%).

Fig. 2 illustrates the delayed in vitro dissolution profile for paracetamol from the clinical compositions in study 1, B compared to A. A decrease in the fraction of drug substance from 44 to 33% by increasing the mass to a weight of 3.2 g resulted in almost superimposable dissolution profiles for C and A as illustrated in Fig. 3a.

Flow rate of 8 ml/min A flow rate of 8 ml/min resulted in a slower dissolution rate and different profiles compared to when 16 ml/min was used. Besides, no maximum was seen. An increasing fraction of paracetamol was followed by a corresponding decrease in the dissolution rate. The lowest fraction of paracetamol (22%) in relation to weight resulted in a faster dissolution

TABLE 3

Pharmacokinetic data of paracetamol (μmol/l) and codeine (nmol/l) following rectal administration of 1 g and 60 mg, respectively, as two suppositories of A and one of B in study 1 (n = 16) and as two of A and one of C in study 2 (n = 18) (standard deviations within parentheses)

Study 1	C_{max}		T_{max} (h)		$t_{1/2}$ (h)		AUC_{tot} (μmol h l^{-1})	
	A	B	A	B	A	B	A	B
Paracetamol	41.0 (±15.6)	22.3 (±9.8)	1.8 (±0.5)	3.5 (±1.8)	4.4 (±2.0)	6.6 (±2.3)	303.7 (±84.3)	282.5 (±123.4)
Codeine	438.2 (±189.0)	345.6 (±176.0)	1.3 (±0.3)	2.2 (±0.8)	2.4 (±0.7)	3.1 (±0.9)	1819.4 (±678.9)	1944.5 (±861.9)
Study 2	C_{max}		T_{max} (h)		$t_{1/2}$ (h)		AUC_{tot} (μmol h l^{-1})	
	A	C	A	C	A	C	A	C
Paracetamol	44.7 (±12.7)	36.8 (±12.9)	1.9 (±0.6)	2.4 (±0.8)	3.6 (±0.9)	4.8 (±2.2)	301.3 (±100.5)	301.1 (±100.8)
Codeine	357.6 (±154.0)	330.6 (±139.2)	1.3 (±0.5)	1.4 (±0.3)	2.2 (±0.7)	2.6 (±0.6)	1364.6 (±699.5)	1326.8 (±636.5)

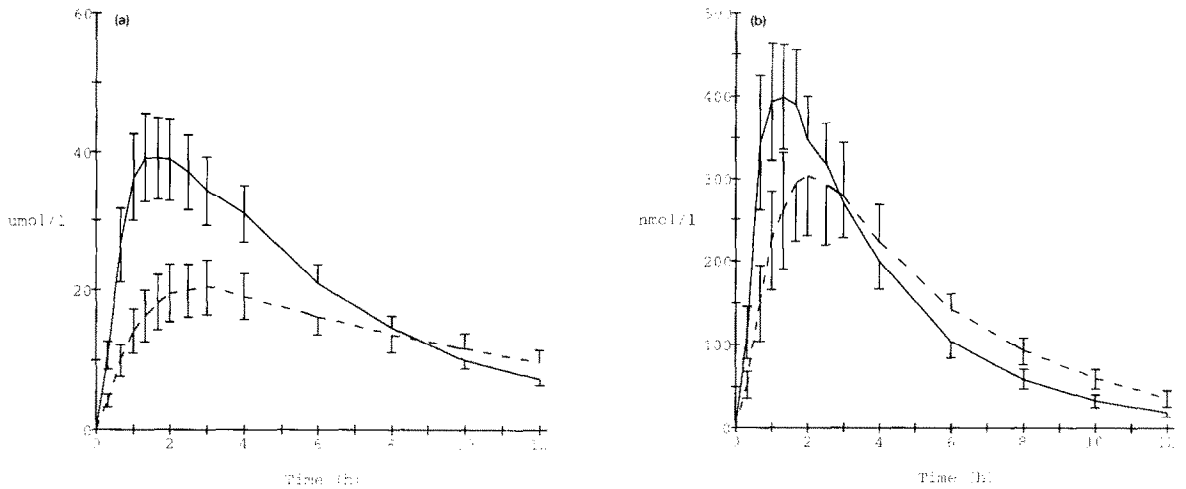

Fig. 4. Average plasma concentration of (a) paracetamol (μmol/l) and (b) codeine (nmol/l) after administration of two suppositories of composition A (———) and one suppository of composition B (— — —) in in vivo study 1. Error bars denote 90% confidence intervals.

rate at all sampling times. Three compositions were compared statistically (22, 34 and 41%) and were all found to be significantly separated from each other according to dissolution rate at all sample times at a c.i. level of 93–99%. In contrast to what was shown by using a flow rate of 16 ml/min, the lower flow of 8 ml/min indicated that a faster release was obtained from A compared to C (Fig. 3b).

Pharmacokinetics and extent of bioavailability

The mean pharmacokinetic data of paracetamol and codeine calculated after the administration of A (22%), B (44%) and C (33%) are shown in Table 3. The mean plasma concentration vs time profiles are shown in Figs 4 and 5.

Study 1 The bioavailability of B differed significantly from that of A according to both rate and extent for paracetamol and rate for codeine.

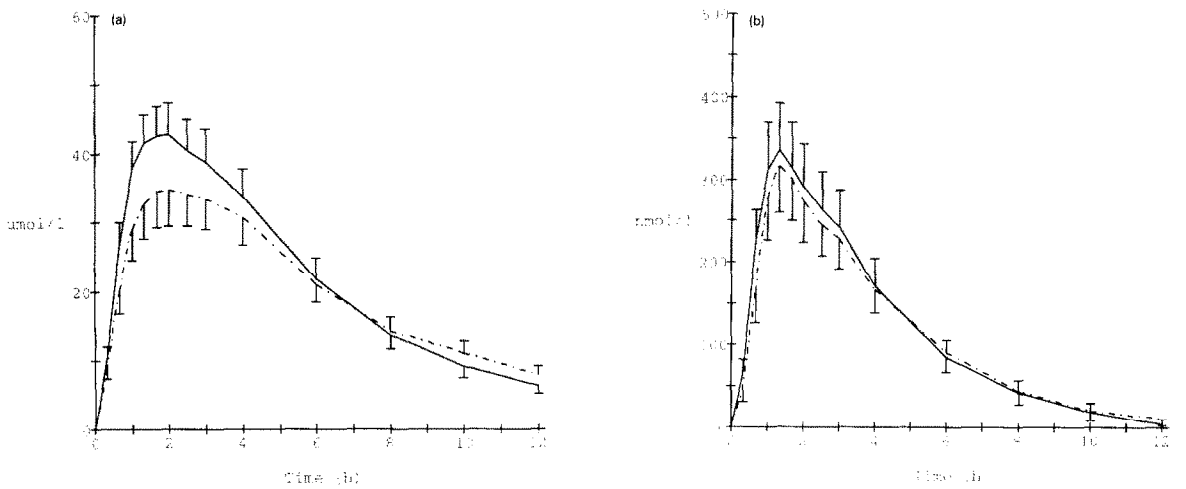

Fig. 5. Average plasma concentration of (a) paracetamol (μmol/l) and (b) codeine (nmol/l) after administration of two suppositories of composition A (———) and one suppository of composition C (–·–·–) in in vivo study 2. Error bars denote 90% confidence intervals.

A mean C_{max} of 41 and 22 μmol/l of paracetamol was reached 1.8 and 3.5 h after the administration of A and B, respectively. The corresponding figures for codeine were 438 and 346 nmol/l after 1.3 and 2.2 h. The half-lives of paracetamol and codeine were 4.4 and 2.4 h after A and 6.6 and 3.1 h after B. The statistical analysis between A and B showed significant differences in C_{max}, T_{max} and $T_{1/2}$ for both substances. The increase in half-lives is probably explained by a slower absorption rate which indicates that the elimination rates are apparent. The rest areas in per cent for paracetamol were 16 and 33% after administration of A and B, respectively. The corresponding values for codeine were 5 and 10%.

The relative extent of bioavailability of B compared to A was 0.9 with respect to paracetamol and 1.1 with respect to codeine. The C_{max} ratio for B in relation to C was 0.54 for paracetamol and 0.79 for codeine.

Study 2 No significant differences were seen between A and C comparing the relative bioavailability of paracetamol and codeine.

By increasing the amount of hard fat it is possible to achieve a relative bioavailability which is equivalent to that after administration of A.

A mean C_{max} of 45 and 37 μmol/l of paracetamol was reached 1.9 and 2.4 h after the administration of A and C, respectively. The corresponding values for codeine were 358 and 331 nmol/l after 1.3 and 1.4 h. The half-life for paracetamol was 4.8 h and for codeine 2.6 h after administration of C and 3.6 and 2.2 h, respectively, after A.

The relative bioavailability of C compared to A based on the total area under the curve was 1.0 with respect to both paracetamol and codeine.

The estimated rest area ($AUC_{12-\infty}$) of paracetamol, calculated as a percentage of the total area, showed a mean of 11 and 19%. The remaining area did not exceed 10% for any of the subjects or formulations concerning codeine.

No significant differences were estimated in T_{max} for codeine and no difference in $T_{1/2}$ for either paracetamol or codeine in the comparison between A and C. Despite a 1 week intermission between the two treatments, a carry-over effect was observed which meant that the difference in T_{max} for paracetamol could not be calculated.

The 90% c.i. of the C_{max} ratio was within the equivalence limits for codeine ($F_{rel} = 0.92$) but not for paracetamol ($F_{rel} = 0.82$).

Volunteers participating in both studies

Table 4 lists the pharmacokinetic results after administration of two suppositories of A to five subjects on two different occasions. Both drug substances were absorbed at a relatively similar rate and to a comparable extent despite the 2 year interval between the studies.

TABLE 4

Pharmacokinetic data of paracetamol (μmol / l) and codeine (nmol / l) following rectal administration of two suppositories of A to five volunteers participating both in study 1 and study 2 about 2 years apart (standard deviations within parentheses)

Subject	Study	C_{max}		T_{max} (h)		$t_{1/2}$ (h)		AUC_{tot} (μmol h l^{-1})	
		PARA	COD	PARA	COD	PARA	COD	PARA	COD
1	1	26.0	213.8	2.0	1.3	3.5	2.5	221.9	1059.8
	2	44.2	230.0	1.7	1.0	2.6	3.4	273.0	872.8
2	1	34.2	332.7	1.7	1.7	3.0	2.5	196.7	1731.6
	2	33.1	323.0	2.5	1.0	3.8	2.3	239.1	1304.1
3	1	74.0	951.2	2.0	0.7	3.9	2.6	520.2	3754.6
	2	70.3	821.0	2.0	1.0	6.1	2.0	530.0	2935.4
4	1	47.9	571.8	1.3	1.3	4.2	2.7	313.5	2607.5
	2	49.5	476.0	3.0	1.3	3.9	3.5	382.5	2600.4
5	1	70.2	480.6	1.3	1.0	3.7	1.4	409.9	1492.3
	2	54.8	334.0	1.3	1.3	4.8	1.9	444.7	1077.0

PARA, paracetamol; COD, codeine.

Comparison of the values of C_{max} and AUC_{tot} between studies 1 and 2 indicates that the two substances behaved differently.

Subjects 1 and 5 had the most widely separated C_{max} for paracetamol but the total area under the curves for these subjects were less separated. For codeine a similar difference was seen for subject 5 for both C_{max} and AUC_{tot} but not for subject 1. For codeine the results of C_{max} and AUC_{tot} were generally on a higher level in study 1 than study 2. This tendency was not observed for paracetamol.

Discussion

Influence of agitation on dissolution rate

The suppository compositions tested in vivo had different in vitro dissolution rates for both paracetamol and codeine depending on whether the flow rate of the dissolution medium was 8 or 16 ml/min. A change of the flow rate is indicative of a change in agitation and amount of medium available. This is probably important when using a slightly soluble substance, like paracetamol. The reason why a release optimum was obtained at a comparatively high flow rate is, however, unknown.

The in vitro dissolution results also show that the release profiles of paracetamol and codeine were superimposable and independent of the suppository compositions. The standard deviations were also similar which means that the release of the substances occurred simultaneously. The solubility of codeine phosphate in water is approx. 17–28 times greater than that of paracetamol. However, the partition coefficients (log D) are close for the two substances. The dissolution data therefore indicate that the flow rates tested do not reflect the different aqueous solubilities of the substances, but rather the similarity in the release from the fatty base. The diffusion process through the melt to the interface between fat and media thus seems to be the rate-controlling step for both.

From the in vitro dissolution tests it is apparent that the amount of paracetamol and codeine phosphate in relation to the total weight influences the release rate. When increasing the fraction of drug, the ability to spread is diminished. This is seen visually in the flow-through cell at both flow rates. A consequence of this is reduced contact area between mass and dissolution medium.

Association between in vitro data and in vivo plasma concentration data

Both the pharmacokinetic results from absorption study 1 and the in vitro dissolution profiles from A and B illustrate the difference in release rate and bioavailability due to the increased fraction of drug in B.

The increased amount of suppository base in C gives the same relative extent of bioavailability as A shown in study 2. The in vitro dissolution profiles of the two compositions show the same similarity.

It is shown that a flow rate of 8 ml/min illustrates the in vivo situation better than 16 ml/min due to a less extensive agitation and less dissolution medium available. However, 16 ml/min shows an obvious difference between compositions A and B.

The fraction of drug substance in relation to total suppository weight therefore influences the rate of absorption and the plasma concentration levels. This effect may be due to an improved rectal spreading of the melting suppository mass when the fraction of drug substance is low.

It has been shown earlier that the weight of a suppository, and thus the drug fraction, influences the absorption rate and maximum plasma concentration levels for paracetamol (Moolenaar et al., 1979a). Our study confirms these results, since the increased size of the suppository from B to C seems to have a positive effect on the bioavailability of paracetamol. The increased size of C may thus contribute to a greater contact area between suppository mass and rectal fluid which indicates that a greater bioavailability is achieved despite a comparatively large fraction of drug substance compared to A. It should thus be borne in mind that it has not been explained whether the drug fraction or the size of the suppository contributes most to the increased ab-

sorption rate and the extent of bioavailability of C.

Volunteers participating in both in vivo studies

The intra-subject variation in plasma concentration vs time levels were studied for five volunteers who received two suppositories of A in both studies 1 and 2. Two exceptions were observed where two volunteers had different absorption rate and maximum plasma levels of paracetamol and codeine on the two separate occasions.

The reason why paracetamol and codeine seem to differ in absorption on comparing the two studies might be the physical-chemical properties of the drugs. The lower solubility of paracetamol compared to codeine phosphate makes paracetamol more sensitive to the amount of rectal fluid which is limited. This suggests that the spreading of the suppository mass is more critical for paracetamol than for codeine phosphate. A similar influence may a difference in bowel content on the two occasions.

Conclusion

The effects of the fraction of drug substance have been evaluated by the flow-through cell at two different flow rates. The in vitro dissolution profiles are ranked in the same way as the plasma concentration vs time curves in humans. It can be concluded that the flow-through cell can create testing conditions which generate results that are consistent with the in vivo situation.

The amount of paracetamol in relation to total suppository weight has been found to be of importance for the absorption rate and the extent of bioavailability when administered rectally. This effect was not so obvious for codeine phosphate.

The administration of two suppositories of the same formulation 2 years apart showed that similar plasma concentration profiles were obtained for both substances.

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