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Evaluation of dosage forms. III: Studies on commercial acetaminophen tablet dosage forms *

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Summary

Dissolution-dialysis studies on commercial tablets of acetaminophen have been carried out in order to establish the applicability of this technique as a suitable in vitro method for the evaluation of acetaminophen dosage forms. While disintegration time or dissolution rate studies did not give a true indication of bioavailability, an excellent correlation was found between the dialysis rate constant (K) and the pharmacokinetic parameter AUC obtained from bioavailability studies on human volunteers.

Introduction

Having established the feasibility of the dissolution-dialysis technique as a method for monitoring the bioavailability of analgin tablet formulations (Razdan and Rastogi, 1990), we now report its applicability for the evaluation of acetaminophen tablet dosage forms.

Acetaminophen is a widely used OTC antipyretic-analgesic (Prescott and Wright, 1973). There are conflicting reports concerning the bioavailability of its various formulations. While McGilveray et al. (1971) found no significant differences among the various formulations on the basis of blood level or urinary excretion data, Gwilt et al. (1963) and Sotiropoulus et al. (1981) reported that the differences were indeed significant. Further, some workers have reported that in vitro and in vivo data could be correlated (Sotiropoulos et al., 1981), whereas others (Mattok et al., 1971) observed no evidence of a correlation between in vitro and in vivo results.

Materials and Methods

The five acetaminophen tablets, designated as test products A–E, each containing 0.5 g acetaminophen were procured from the open market.

The test products were assayed spectrophotometrically for acetaminophen content (Mattok et al., 1971). The absorbance was measured with a Carl Zeiss spectrophotometer at 243 nm. Ac-

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etaminophen content was computed from a standard curve prepared for this purpose using pure acetaminophen. The uniformity of content (USP, 1975a) was determined by individually assaying 10 randomly selected tablets. The method followed for the determination of acetaminophen content was the same as that of the assay.

The disintegration time of the test products was determined according to the USP method (1975b) on a Disintegration Test Machine USP/BP (Indian Equipment Corp., Bombay). The test was performed on six randomly selected tablets placed in the tubes moving up and down in a medium of distilled water maintained at 37 ± 5 °C. Three such runs were conducted on each of the test products.

Bioavailability

The bioavailability was evaluated on human volunteers using salivary excretion data (Glynn and Bastain, 1973), following a latin square design. Six healthy male volunteers with a mean age of 24 ± 1.10 years and a mean weight of 57.33 ± 7.58 kg were selected. None of the subjects had any enzyme-inducing agents at least 30 days prior to initiation of the study. During the study, none of the subjects received medication or alcohol.

The overnight fasted subjects were administered orally two tablets of each of five brands containing 0.5 g acetaminophen or 1 g pure acetaminophen powder at 06:30 h along with 150 ml water. The mouth was rinsed promptly with another 100 ml water which was swallowed.

No food or liquid was permitted during the first 2 h of the administration of test product or acetaminophen after which the subjects were allowed to take normal food and beverages. An interval of 1 week between the administration of test products or acetaminophen was chosen as a protective measure against potential carry-over effects.

Samples of saliva were collected predose and at 15, 30, 45, 60, 90, 120, 150, 180 and 240 min post-administration of the test products or acetaminophen powder and processed according to the method of Adithan and Thangam (1982). The acetaminophen content of samples was determined by measuring the absorbance at 615 nm of the colored chromagen obtained after the treatment of samples with *o*-cresol and ammonia (Miceli et al., 1979).

The pharmacokinetic parameters, namely, area under the saliva concentration curve (AUC), maximum saliva concentration (C_{max}), and time taken to reach peak saliva concentration (t_p) were calculated after correcting the AUC and C_{max} for drug content. AUC was computed using the trapezoidal rule.

Dissolution rate

Dissolution rate studies were performed according to the USP method (1975c) in 0.1 N hydrochloric acid and phosphate buffer of pH 7.4. For each test product three runs were carried out. The acetaminophen content of samples, withdrawn during the study in the two media, was determined by measuring the absorbance at 243 nm and computing the acetaminophen content from the standard curves constructed for this purpose in two media (Mattok et al., 1971).

The dissolution characteristics, namely, percentage dissolved over a period of 20 min (A_{20}) and the time taken for 50% of the drug to dissolve (T_{50}), were determined after correcting for drug content. The T_{50} values were calculated from the graphs obtained by plotting log concentration of undissolved drug vs time.

Dissolution-dialysis

Dissolution-dialysis studies were carried out in 0.1 N hydrochloric acid and phosphate buffer of pH 7.4, using the apparatus and method described by Razdan and Rastogi (1990).

The acetaminophen content of samples withdrawn from the two media at 15-min intervals up to a duration of 210 min of the experiments was obtained following the method used in the dissolution rate studies. From the data obtained during these studies in the two media, the dialysis rate constant was calculated using the following equation (Razdan and Rastogi, 1990).

$$K\ (\text{min}^{-1}) = -\left[\frac{(\text{slope})(2.3\ V_I V_O)}{V_I + V_O}\right]$$

TABLE 1

Characteristics of commercial acetaminophen tablets (test products A–E)

Test product	Standard	Acetaminophen content [a] (percent label claim)	Content uniformity	Disintegration time [a] (min,s)
A	I.P.	97.98 (1.49)	Complies	0,55 (0,09)
B	I.P.	99.74 (1.10)	Complies	1,46 (0,07)
C	I.P.	98.84 (1.41)	Complies	10,45 (4,45)
D	I.P.	101.53 (0.68)	Complies	1,20 (0,04)
E	I.P.	101.57 (1.89)	Complies	2,02 (0,05)
Anova				$p < 0.01$ H.S.

Values in parentheses indicate S.D. H.S., highly significant.
[a] Mean of three readings/runs.

where V_1 and V_O represent the volume of fluid in the dissolution and dialysis chambers, respectively, the corresponding values being 500 and 1100 ml.

The analysis of data, linear fitting demonstrated by least-square regressional analysis, slope (m) and dialysis rate constant (K) were determined on a computer (Model PDP 11/34).

Results and Discussion

The drug content, content uniformity and disintegration time (Table 1) of the five test products were within the Pharmacopoeial limits (Pharmacopoeia of India, 1955). Statistical analysis of the disintegration time showed significant differences and the different formulations could be rated as: A > D > B > E > C.

Statistical analysis of the dissolution characteristics, namely, A_{20} and T_{50} (Table 2) values in

TABLE 2

Dissolution characteristics [a] of commercial acetaminophen tablets (test products A–E) in 0.1 N hydrochloric acid (HCl) and phosphate buffer of pH 7.4

Test product	0.1 N HCl		Phosphate buffer	
	A_{20} [b]	T_{50} [c] (min)	A_{20} [b]	T_{50} [c] (min)
A	48.38 (3.36)	20.20 (1.27)	41.13 (1.96)	26.00 (0.22)
B	92.08 (1.48)	2.80 (0.08)	65.53 (0.36)	6.20 (0.50)
C	21.26 (2.33)	31.00 (2.00)	19.12 (1.37)	40.00 (3.60)
D	83.40 (1.11)	5.80 (0.70)	66.49 (3.79)	6.40 (0.80)
E	86.32 (0.42)	5.20 (0.40)	64.45 (1.61)	6.60 (0.99)
Anova	$p < 0.01$ H.S.	$p < 0.001$ H.S.	$p < 0.001$ H.S.	$p < 0.001$ H.S.

Values in parentheses indicate S.D. H.S., highly significant.
[a] Mean of three runs.
[b] Percent of drug dissolved in 20 min.
[c] Time taken to dissolve 50% drug.

TABLE 3

Pharmacokinetic characteristics of commercial acetaminophen tablets (test products A – E) and acetaminophen powder

Test product	AUC	C_{max}	t_p (min)
A	17.45	10.68	30
	(3.15)	(1.39)	
B	26.89	18.41	45
	(2.54)	(0.97)	
C	24.99	11.43	45
	(6.39)	(2.12)	
D	22.84	10.95	30
	(3.93)	(4.69)	
E	25.16	13.37	45
	(4.18)	(2.01)	
Acetaminophen	31.25	18.87	30
powder	(4.92)	(1.35)	
Anova	$p < 0.001$	$p < 0.001$	
	H.S.	H.S.	

Values in parentheses indicate S.D. H.S., highly significant.

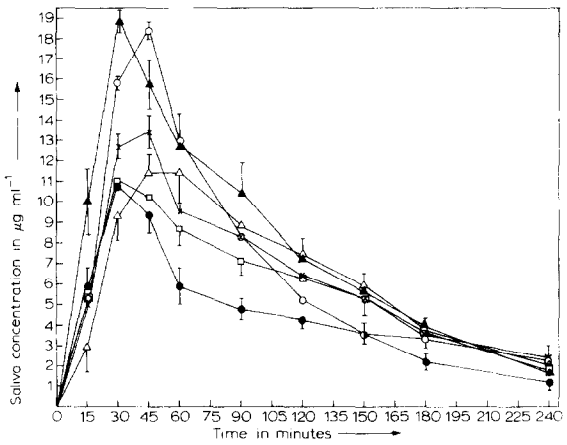

Fig. 1. Mean saliva concentration vs time curve of acetaminophen powder and commercial acetaminophen tablets. Test product A (●——●), B (○——○), C (△——△), D (□——□), E (x——x) and acetaminophen powder (▲——▲).

both 0.1 N hydrochloric acid and phosphate buffer of pH 7.4 also showed significant differences. However, the rating of the test products in the two media of both of the above dissolution parameters was not the same. In the case of the A_{20} values (Table 2), the rank orders of formulations in 0.1 N hydrochloric acid and phosphate buffer of pH 7.4 were B > E > D > A > C and D > B > E > A > C, respectively. When the T_{50} values (Table 2) were compared, rank orders of B > E > D > A > C in 0.1 N hydrochloric acid and B > D > E > A > C in phosphate buffer of pH 7.4 were observed.

The mean saliva concentration-time curves of the five test products and acetaminophen powder are depicted in Fig. 1. Statistical analysis of the AUC and C_{max} values (Table 3) showed highly significant differences. On the basis of the AUC data (Table 3), the five test products could be rated as B > E > C > D > A.

Analysis of the disintegration time (Table 1) and AUC data (Table 3) of the five formulations did not result in any significant correlation; $r =$

TABLE 4

Dialysis rate constants (K) [a] *of commercial acetaminophen tablets (test-products A–E) in 0.1 N hydrochloric acid (HCl) and phosphate buffer of pH 7.4*

Medium	Test products					Anova
	A	B	C	D	E	
0.1 N HCl	0.304	0.462	0.371	0.322	0.391	$p < 0.001$
	(0.001)	(0.012)	(0.003)	(0.013)	(0.008)	H.S.
Phosphate	0.226	0.367	0.302	0.261	0.310	$p < 0.001$
buffer	(0.018)	(0.003)	(0.003)	(0.016)	(0.010)	H.S.
Pairwise	$p < 0.01$	$p < 0.01$	$p > 0.05$	$0.05 > p > 0.01$	$p < 0.01$	
comparison	H.S.	H.S.	N.S.	P.S.	H.S.	

Values in parentheses indicate S.D. H.S., highly significant; P.S., possibly significant; N.S., not significant.

[a] Mean of three runs.

TABLE 5

Dialysis rate constants (K) [a] *of acetaminophen powder and commercial acetaminophen tablets (test products A–E) in 0.1 N hydrochloric acid (HCl) and phosphate buffer of pH 7.4*

Medium	Acetaminophen powder	Test products					Anova
		A	B	C	D	E	
0.1 N HCl	0.579 (0.008)	0.304 (0.001)	0.462 (0.012)	0.371 (0.015)	0.322 (0.003)	0.391 (0.013)	$p < 0.001$ H.S.
Phosphate buffer	0.408 (0.005)	0.226 (0.018)	0.367 (0.003)	0.302 (0.003)	0.261 (0.016)	0.310 (0.010)	$p < 0.001$ H.S.

Values in parentheses indicate S.D. H.S., highly significant.
[a] Mean of three runs.

0.336 ($p > 0.25$). Similarly, comparison of the dissolution parameters in the two media (Table 2) with the AUC data (Table 3) also yielded a poor correlation. The correlation coefficients (r) for the comparison of the A_{20} values in 0.1 N hydrochloric acid and phosphate buffer of pH 7.4 with the AUC data were of the order of 0.338 ($p > 0.25$) and 0.240 ($p > 0.25$), respectively. In the case of the T_{50} values, the correlation coefficient (r) in 0.1 N hydrochloric acid was -0.334 ($p > 0.25$) and -0.298 ($p > 0.25$) in phosphate buffer of pH 7.4.

Since no correlation with regard to ranking of the five test products could be demonstrated when the AUC data were compared with the disintegration time or the dissolution parameters, A_{20} and T_{50} values, the dialysis rate constants (K) were compared.

Statistical analysis of the K values in 0.1 N hydrochloric acid and phosphate buffer (Table 4) resulted in highly significant differences. The rating of the five formulations on the basis of their K values in both media was B > E > C > D > A, the order obtained when the AUC values were compared. Further, comparison of the K values of the five test products with that of pure acetaminophen in both media showed highly significant differences (Table 5), indicating that the cell used in the present study was sensitive enough to detect the influence of formulation factors.

The observation of higher K values in 0.1 N hydrochloric acid as compared to those in phosphate buffer of pH 7.4 indicates that the results are in conformity with the pH-partition theory (Bates and Gibaldi, 1970).

An analysis of in vitro data (K values) and the in vivo data (AUC) of the five test products demonstrated a significant correlation. The correlation coefficients (r) in 0.1 N hydrochloric acid and phosphate buffer of pH 7.4 were 0.8538 ($p < 0.025$) and 0.920 ($p < 0.01$), respectively.

The above results amply demonstrate the superiority of the dialysis rate constant (K) for the in vitro evaluation of acetaminophen tablet dosage forms. Furthermore, these results are also indicative of the suitability of the designed cell for such evaluation.

The advantages of the dissolution-dialysis technique over the conventional in vitro methods, i.e. disintegration time and dissolution rate, are thus demonstrated. Studies on other drugs with different physico-chemical characteristics are currently in progress in order to determine whether this method is universally applicable for in vitro evaluation.

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