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COMMUNICATION

Evaluation of Dosage Forms. VI. Studies of Commercial Oxyphenbutazone Tablet Dosage Forms

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ABSTRACT

Dissolution-dialysis studies of commercial tablets of oxyphenbutazone were carried out to establish the applicability of this technique for the in vitro evaluation of oxyphenbutazone dosage form. While disintegration time and dissolution rate studies did not give a true indication of bioavailability, an excellent correlation was obtained between the dialysis rate constant K *and the pharmacokinetic parameters AUC and* C_{max}.

INTRODUCTION

In our search for an in vitro method that would reflect the bioavailability, and thus the therapeutic efficacy, of a dosage form, we have reported excellent results obtained in case of analgin (1), acetaminophen (2), phenylbutazone (3), and naproxen (4) using the dissolution dialysis method. We now report our results of studies of oxyphenbutazone tablet dosage forms.

Oxyphenbutazone, a metabolite of phenylbutazone, is a nonsteroidal anti-inflammatory and analgesic agent. It is official in IP (5), BP (6), and USP (7). It is weakly acidic and practically insoluble in water (8). It is rapidly absorbed from the gastrointestinal tract and slowly metabolized and excreted, mainly in urine (9). The rate and extent of absorption can be increased considerably by buffering oxyphenbutazone tablets (10). The estimates of bioavailability parameters were found to be higher with a buffered formulation. This was explained as being due to faster dissolution of drug (10).

Oxyphenbutazone has a long half-life in humans (72 hr) compared to dogs (0.5 hr), rats (8 hr), rabbits (4–5 hr), and other species (9). In humans, the peak plasma level is reached within 4–6 hr after oral administration

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of the drug. Because of the limited aqueous solubility of oxyphenbutazone, variation in its dissolution and its bioavailability are quite possible.

MATERIALS AND METHODS

Five commercial oxyphenbutazone tablets were procured from the open market: Suganril (S. G. Pharmaceuticals, Vadodara, India) and oxyphenbutazone tablets IP from four manufacturers (Omega Laboratories, Ghaziabad, India; Oboy Laboratories, Bombay, India; Medinest Pharma Pvt. Ltd., Hasur, India; Paam Pharmaceuticals Ltd., Bulandshahar, India). These were designated test products A to E, respectively. Each of the tablets was sugar coated, and each contained 100 mg of oxyphenbutazone.

For the assay of test products A–E, a quantity of powder from the tablets equivalent to 0.05 g of oxyphenbutazone was weighed accurately and extracted with 3 × 20 ml quantities of acetone; this was followed by filtration. The residue was washed further with another 2 × 10 ml of acetone. The combined filtrates were evaporated, and the residue was dissolved in 10 ml of 0.1 M sodium hydroxide. The solution so obtained was brought to 50 ml with 0.1 M sodium hydroxide. Next, 1 ml of this solution was diluted further to 100 ml with 0.1 M sodium hydroxide. The absorbance of this solution was measured at 254 nm in a Systronics UV-Vis spectrophotometer (model 108) using 0.1 M sodium hydroxide as a blank. The content of oxyphenbutazone was computed by taking 750 as the value of *E* (1%, 1 cm) (11). Three such determinations were carried out for each test product.

Content uniformity for each of the test products was determined by assaying 10 randomly selected tablets individually. The same procedure was followed as in the assay.

The disintegration time of tablets was determined according to the disintegration time test for coated tablets (12, p. 736). The test was carried out in a disintegration test machine IP/BP/USP supplied by Campbell Electronics (Bombay, India) using distilled water as the medium. Before the start of the test, the film coating was removed by putting the tablet in water for 2 min.

Bioavailability Studies

The bioavailability studies were carried out on human volunteers. Since oxyphenbutazone has a long half-life (9), which requires a long washout period, a balanced incomplete block design (BIBD) was used for the crossover study (13). Participants were 10 healthy male volunteers aged 22–24 and weighing 50–75 kg. Use of other

Table 1

Characteristics of Commercial Oxyphenbutazone Tablets (Test Products A–E)

Test Product	Standard	Oxyphenbutazone Content (mg)		Content Uniformity	Disintegration Time (min)[b]
		Label Claim	Actual[a]		
A	IP	100.00	97.49 (0.35)	Complies	13.70 (2.18)
B	IP	100.00	95.38 (0.07)	Complies	4.70 (1.03)
C	IP	100.00	98.82 (0.05)	Complies	24.30 (2.40)
D	IP	100.00	94.99 (0.94)	Complies	51.00 (6.13)
E	IP	100.00	95.75 (0.41)	Complies	32.70 (5.24)
ANOVA					$p < .001$[c]

Values in parentheses indicate standard deviation.
ANOVA = analysis of variance.
[a]Mean of 3 readings.
[b]Mean of 6 readings.
[c]Highly significant.

drugs or alcoholic beverages was not allowed for 1 week prior to and also during the study. A washout period of 25 days was given between the two trials.

Five brands of test products containing 100 mg of oxyphenbutazone were administered to subjects with a glass of water. To minimize the chances of gastric irritation due to the drug, volunteers were instructed to have a light breakfast 2 hr prior to administration of the test products. Blood samples (1 ml), withdrawn at 0, 1, 2, 3, 4, 6, 8, 10, 12, 24, and 48 hr after the administration of drug, were collected in a centrifuge tube containing 0.1 ml of 5% w/v sodium citrate solution. The samples were centrifuged, and the separated plasma was used for further analysis (14). The plasma (0.2 ml) was mixed with water (1 ml) and 3 M hydrochloric acid (0.2 ml). The acidic solution was next extracted with 1,2-dichloroethylene (4 ml) for 30 min. The organic layer (3 ml) after centrifugation was shaken with 2 ml of 2.5 M sodium hydroxide and centrifuged. The absorbance of the aqueous phase was measured at 254 nm in the Systronics UV-Vis spectrophotometer. The blanks used were the corresponding blood samples withdrawn at 0 hr. The oxyphenbutazone content of the samples was calculated from a standard curve obtained by plotting the absorption of oxyphenbutazone solution at 254 nm in 2.5 M sodium hydroxide solution over a range of 0.5–5 μg/ml.

The pharmacokinetic parameters, namely, area under plasma concentration curve AUC, maximum plasma concentration C_{max}, time to reach peak plasma concentration t_p, and absorption rate constant K_a were calculated after correcting for the drug content. The AUC was calculated by the trapezoidal rule (15, pp. 469–472), and K_a was calculated by the residual method (15, pp. 478–480).

Dissolution Rate Studies

The dissolution rate studies (12, pp. A82–A84) were carried out in phosphate buffer of pH 7.4 in Veego tablet dissolution test apparatus (IP/USP), allowing six determination at a time.

Before the start of the experiment, the film coating of the tablet was removed by immersing the tablet in water for 2 min. The dissolution vessel was immersed in a bath maintained at 37°C ± 2°C and filled with 1 L of phosphate buffer. After the medium attained a temperature of 37°C, the uncoated tablet was placed in a basket, and the basket was immersed in the medium and rotated at 100 rpm. Samples (2 ml) were withdrawn at 0, 5, 10, 15, 20, 30, 45, 60, 80, 100, and 120 min after the start of the experiment. The volume so withdrawn was replaced with fresh buffer maintained at 37°C.

The samples withdrawn from the dissolution medium were filtered through a G-3 sintered glass filter. The filtrate (1 ml) was diluted to 10 ml with 0.1 M sodium hydroxide, and the absorbance of the resulting solution was

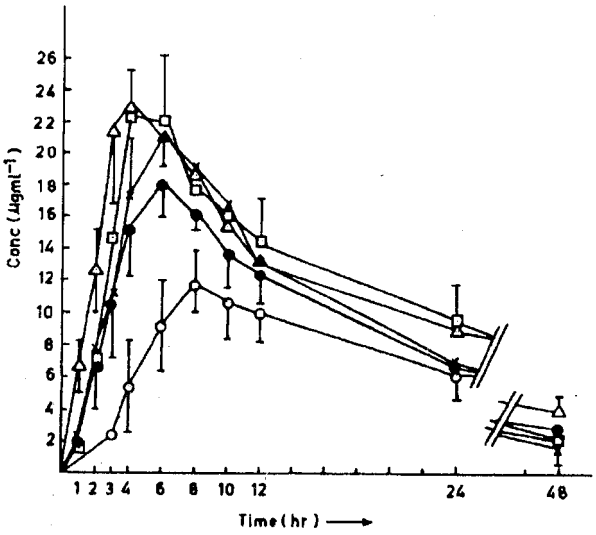

Figure 1. Plasma concentration-time profile of commercial tablets of oxyphenbutazone: test product A (x), B (△), C (□), D (○), and E (●).

Table 2

Pharmacokinetic Parameters[a] of Commercial Oxyphenbutazone Tablets (Test Products A–E)

Test Product	AUC (μg-hr-ml^{-1})	C_{max} (μg-ml^{-1})	t_p (hr)	K_a (μg-hr^{-1})
A	397.401	21.42	5.50	0.663
	(30.30)	(1.60)	(1.00)	(0.16)
B	482.606	24.54	3.75	0.867
	(35.17)	(2.42)	(0.50)	(0.13)
C	463.858	24.05	4.50	0.833
	(51.23)	(2.34)	(1.00)	(0.08)
D	285.932	12.00	7.50	0.441
	(31.30)	(1.62)	(1.00)	(0.05)
E	381.688	18.24	6.00	0.595
	(52.22)	(1.66)	(1.63)	(0.17)
ANOVA	$p < .001$[b]	$p < .001$[b]		$p < .01$[b]

Values in parentheses indicate standard deviation.
ANOVA = analysis of variance; AUC = area under plasma concentration curve; C_{max} = maximum plasma concentration; T_p = time required to reach maximum plasma concentration.
[a]Mean of four readings.
[b]Highly significant.

measured at 254 nm in the Systronics UV-Vis spectrophotometer.

The oxyphenbutazone content of the samples withdrawn was computed from a standard curve obtained by plotting the absorbance of oxyphenbutazone solutions prepared in a mixture of phosphate buffer and 0.1 M sodium hydroxide solution (1:9) over a range of 1–10 μg/ml. From the dissolution profile, a plot of log% undissolved against time was constructed. From the regression line of these points, percentage dissolved in 60 min A_{60}, time taken for 50% dissolution T_{50}, and dissolution rate constant k were calculated.

Dissolution-Dialysis Studies

Dissolution-dialysis studies were carried out in phosphate buffer of pH 7.4 using the apparatus and method described by Razdan and Rastogi (1). Before the start of the experiment, the film coat of the tablet was removed by immersing the tablet in water for 2 min. The samples (5 ml), withdrawn at 15-min intervals over a period of 210 min, were analyzed spectrophotometrically. The samples so withdrawn were replaced with fresh medium.

The absorbance of the samples was measured at 254 nm in the Systronics UV-Vis spectrophotometer using phosphate buffer as a blank. The oxyphenbutazone content of the samples was computed from the standard curve obtained by plotting absorbance of oxyphenbutazone solution in phosphate buffer of pH 7.4 over a range of 1–10 μg/ml.

The dialysis rate constant was calculated using the following equation:

$$K\ (\text{min}^{-1}) = [(m) + V_O)$$

where m is the slope, and V_I and V_O represent the volume of fluid in the dissolution chamber (500 ml) and dialysis chamber (1100 ml), respectively.

RESULTS AND DISCUSSION

All the test products conformed to the compendial standards (Table 1) (5). Statistical analysis of the disintegration time showed highly significant differences among the five test products. Based on the disintegration time, the five test products could be rated as B > A > C > E > D.

The plasma concentration-time profiles of the test products is given in Fig. 1. The various pharmacokinetic parameters (AUC, C_{max}, t_p, and K_a) are given in Table 2. The AUC, C_{max}, and K_a all showed highly significant differences. The rating of various test products in all the cases was B > C > A > E > D.

Oxyphenbutazone is a weak organic acid with a pK_a value of 4.7; its overall absorption rate is caused largely

Table 3

Dissolution Characteristics[a] of Commercial Oxyphenbutazone Tablets (Test Products A–E)

Test Product	A_{60} (%)	T_{50} (min)	k (min^{-1})
A	86.81	23.30	0.03
	(1.11)	(1.90)	(2.45×10^{-3})
B	95.92	15.44	0.05
	(1.11)	(0.49)	(1.43×10^{-3})
C	52.44	28.63	0.014
	(2.59)	(2.07)	(8.99×10^{-4})
D	1.99	1504.90	0.0005
	(0.12)	(69.71)	(4.71×10^{-5})
E	91.71	17.50	0.041
	(1.91)	(2.83)	(7.34×10^{-8})
ANOVA	$p < .001$[b]	$p < .001$[b]	$p < .001$[b]

Values in parentheses indicate standard deviation.
A_{60} = percentage dissolved in 60 min; ANOVA = analysis of variance; T_{50} = time taken to dissolve 50%; k = dissolution rate constant.
[a]Mean of 3 runs.
[b]Highly significant.

Table 4

Dialysis Rate Constants K[a] of Commercial Oxyphenbutazone Tablets (Test Products A–E) and Pure Oxyphenbutazone in Phosphate Buffer (pH 7.4)

Test Product	K	
A	0.1385	
	(0.003)	
B	0.1534	
	(0.001)	
C	0.1476	ANOVA
	(0.008)	$p < .002$[b]
D	0.0276	
	(0.004)	
E	0.1307	
	(0.011)	
Oxyphenbutazone powder	0.1958	
	(0.003)	
ANOVA	$p < .001$[b]	

Values in parentheses indicate standard deviation.
ANOVA = analysis of variance.
[a]Mean of three runs.
[b]Highly significant.

Table 5

Correlation Coefficient of In Vitro and In Vivo Parameters of Commercial Oxyphenbutazone Tablets (Test Products A–E)

In Vivo Parameters	In Vitro Parameters				
	Disintegration Time	Dissolution Parameters			
		A_{60} (%)	T_{50} (min)	k (min^{-1})	K
AUC	0.864 ($p > .05$)[a]	0.680 ($p > .1$)[a]	0.836 ($p > .05$)[a]	0.589 ($p > .1$)[a]	0.913 ($p < .05$)[b]
C_{max}	0.904 ($p > .05$)[a]	0.708 ($p > .1$)[a]	0.873 ($p > .05$)[a]	0.574 ($p > .1$)[a]	0.941 ($p < .05$)[b]
K_a	0.845 ($p > .05$)[a]	0.586 ($p > .1$)[a]	0.760 ($p > .05$)[a]	0.493 ($p > .1$)[a]	0.856 ($p < .05$)[a]

A_{60} = percentage dissolved in 60 min; AUC = area under plasma concentration curve; C_{max} = maximum plasma concentration; K = dialysis rate constant; k = dissolution rate constant; K_a = absorption rate constant; T_{50} = time taken to dissolve 50%.

[a]Not significant.

[b]Significant.

by its intestinal absorption (16). Hence, dissolution rate studies were carried out in phosphate buffer of pH 7.4.

Statistical analysis of dissolution characteristics (A_{60}, T_{50}) and the dissolution rate constant k (Table 3) in phosphate buffer also showed highly significant differences. The rating of the test products in all the cases was B > E > A > C > D, an order that was quite different from the rating obtained in bioavailability studies.

Statistical analysis of the dialysis rate constant K in phosphate buffer (Table 4) of pH 7.4 showed highly significant differences. The ranking of the test products was the same as for the pharmacokinetic parameters (Table 2) (i.e., B > C > A > E > D). When the K values of the test products were compared with the K value of oxyphenbutazone powder (Table 4), significant differences were observed, indicating that the dissolution-dialysis cell used showed the effect of formulation factors.

Comparison of in vivo parameters with in vitro parameters (Table 5) indicated no significant correlation between the disintegration time and AUC and K_a. Significant correlation, however, was obtained for disintegration time and C_{max} (Table 5).

Since the ranking of test products for disintegration time and pharmacokinetic parameters was different and the fact that, for comparison, AUC is a better parameter than C_{max}, it could be concluded that disintegration time did not reflect the true bioavailability.

Comparison of dissolution parameters with in vivo parameters did not show any significant correlation (Table 5). When dialysis rate constants were compared with AUC and C_{max} values, a significant correlation was observed (Table 5). Moreover, the ranking of test products was also the same as for the pharmacokinetic parameters.

The above results amply demonstrate the usefulness of the dialysis rate constant K for the in vitro evaluation of oxyphenbutazone tablet formulation over the conventional disintegration and dissolution rate parameters. Studies of other drugs of different physicochemical characteristics are in progress to demonstrate the universality of this method.

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