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RESEARCH PAPER

Evaluation of Dosage Forms. IV. Studies on Commercial Phenylbutazone Tablet Dosage Forms

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ABSTRACT

In order to determine the feasibility of dissolution–dialysis as a suitable technique for in vitro evaluation, studies on commercial phenylbutazone tablets were carried out. Although disintegration time and dissolution parameters did not give a true indication of bioavailability, an excellent correlation was obtained between the dialysis rate constant (K) and various pharmacokinetic parameters obtained from bioavailability studies on human volunteers.

INTRODUCTION

In continuation of our studies (1–3) on determining the feasibility of dissolution–dialysis as an in vitro technique for monitoring bioavailability, we now report our results of studies on phenylbutazone tablet dosage forms. Phenylbutazone, a pyrazolone derivative, is a commonly used drug in rheumatoid arthiritis and related disorders. Because of its very low solubility in water and poor wettability, bioavailability problems are associated with its formulations (4,5). Searl and Pernarowski (6) reported differences in physiological availability of different brands of phenylbutazone tablets marketed in Canada, but no such differences have been reported in tablets marketed in India (7). Lovering and Mainville (8) tried to correlate the dissolution behavior of 23 tablet formulations of phenylbutazone with bioavailability. Using four different methods, significant correlation was obtained between mean time for 60% of the drug to dissolve and bioavailability.

MATERIALS

For the present study, five commercial phenylbutazone tablets, namely Zolandin (S. G. Pharmaceuticals, Vadodara, India), and phenylbutazone tablets (Tuton Pharmaceuticals, Ahmedabad, India, Unicure Pharmaceuticals, Ghaziabad, India, Uni-Sule Pharmaceuticals, Sonepat, India, and Paam Pharmaceuticals, New Delhi,

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India), each containing 100 mg of phenylbutazone and designated as test products A–E, respectively, were procured from open market. All of the tablets were coated. Phenylbutazone powder Pharmacopoeia of India (IP) (Ranie Chemical, Maharashtra, India) was dried in vacuum at 80°C for 4 hr before use. All other items used were either guaranteed or analytical reagent grade.

METHODS

The test products A–E were assayed spectrophotometrically at 264 nm (9). The phenylbutazone content was computed from the standard curve prepared for this purpose. In each case three determinations were carried out. For uniformity of content, 10 randomly selected tablets were assayed individually using the procedure described.

The disintegration time of test products was determined according to IP (10) for coated tablets using a disintegration test machine United States Pharmacopiea/ British Pharmacopoiea (USP/BP) (Indian Equipment Corp., Bombay). Three such runs were conducted on each test product.

Bioavailability Studies

The bioavailability studies were carried on human volunteers following Latin square design. Five adult, healthy, male volunteers, in the age group of 22–26 years and each weighing 55–75 kg, participated in the study. Selected volunteers had no gastrointestinal disease or allergy. Use of other drugs and alcoholic beverages was not allowed 48 hr prior to and also during the course of study. In order to minimize the gastric discomfort, the volunteers were allowed a light standard breakfast 2 hr prior to initiation of study. Each subject received a single but different brand of phenylbutazone tablet (100 mg) along with 100 ml of water, each time during the study. A gap of 3 weeks between the administration of test products was allowed as a protective measure.

Whole blood samples (5 ml) were collected predose and at 2, 4, 6, 8, 24, and 48 hr following the administration of test product. For the determination of phenylbutazone content in the blood samples, a modification of the method reported by Burn et al. (11) was followed. Plasma (2 ml) was acidified by addition of 0.5 ml of 3 N hydrochloric acid and the mixture was allowed to stand for 10 min. Next, the acidified plasma was shaken for 30 min with 20 ml of *n*-heptane containing 3% isoamyl alcohol and centrifuged. The organic layer (15 ml) was removed and shaken for 30 min with 5 ml of 2.5 N sodium hydroxide solution and centrifuged. The aqueous layer was next transferred to another test tube and its absorption determined at 264 nm on a UV spectrophotometer (Carl Zeiss, Germany). The blanks used were the corresponding blood samples withdrawn prior to administration of test product and were processed exactly in the same manner. For the purpose of computing phenylbutazone content of the blood samples, a standard curve, in the concentration range of 5–50 μg/ml, was prepared in the same manner.

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

Dissolution Rate Studies

The dissolution rate studies were carried out according to IP (12) in phosphate buffer of pH 7.4 on dissolution rate test apparatus (Indian Equipment Corp.). Before the start of the experiment, the coated tablet was kept in water at room temperature for 2 min to remove the colored matter. The uncoated tablet was next placed in the basket and the basket immersed in dissolution medium (900 ml) kept at 37 ± 2°C. The basket was rotated at 100 rpm. Samples (7 ml) were withdrawn at 5, 10, 15, 20, 30, 45, 60, 80, 100, and 120 min. The samples so withdrawn were immediately replaced with fresh dissolution media. The phenylbutazone content was determined by measuring absorbance at 264 nm and was computed from the standard curve of pure phenylbutazone prepared in the dissolution medium. The dissolution characteristics, percent dissolved in 30 min (A_{30}), time taken for 50% of the drug to dissolve (T_{50}), and the dissolution rate constant (k), were obtained after correcting for the drug content. The T_{50} and k were calculated using log concentration of undissolved drug versus time profile.

Dissolution–Dialysis Studies

Dissolution–dialysis studies were conducted in phosphate buffer of pH 7.4, using the apparatus and method described by Razdan and Rastogi (2).

The phenylbutazone content of the samples (5 ml), withdrawn at 15-min intervals up to a period of 120 min, was determined spectrophotometrically in the same man-

ner as in dissolution studies. From the data obtained, the dialysis rate constant (K) was calculated using Eq. (1), where V_I and V_O represent the volume of fluid in dissolution chamber (500 ml) and dialysis chamber (1100 ml), respectively.

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

The analysis of data, straight line fit demonstrated by least-squares regression analysis, slope (m), and the dialysis rate constant (K) calculations were carried out with the help of a computer.

RESULTS AND DISCUSSION

All five test products conformed to the compendial standards (13,14) (Table 1). Comparision of disintegration time (Table 1), showed highly significant differences ($p < 0.01$) among the five test products. The mean plasma concentration–time curves of the five test products are depicted in Fig. 1. Statistical analysis of AUC and C_{max} values (Table 2) showed highly significant differences ($p < 0.001$). On the basis of AUC and C_{max} data (Table 2), the test products could be rated as A > B > E > C > D. An analysis of AUC and C_{max} data showed highly significant correlation. The value of correlation coefficient (r) obtained was 0.989 ($p < 0.001$).

Stella (15) reported that comparison of dissolution of phenylbutazone is more meaningful at pH greater than the pK_a of phenylbutazone, hence the dissolution rate studies were carried out in phosphate buffer of pH 7.4.

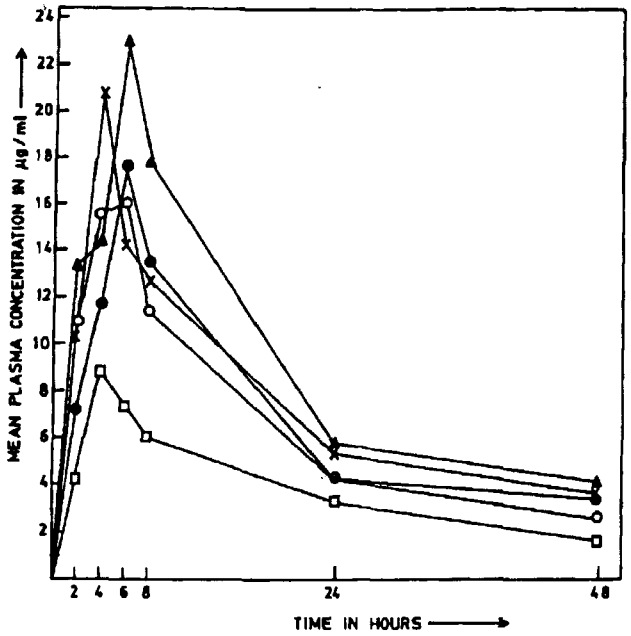

Figure 1. Mean plasma concentration vs. time curve of commercial phenylbutazone tablets. Test products A (▲), B (X), C (○), D (□), and E (●).

Table 1

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

Test Product	Standard	Phenylbutazone Content (mg) Label Claim	Phenylbutazone Content (mg) Actual[a] (SD)	Uniformity of Content	Disintegration Time[a] (min · sec) (SD)
A	IP	100	96.24 (3.57)	Complies	9.11 (0.16)
B	IP	100	99.32 (3.51)	Complies	55.50 (0.41)
C	BP	100	99.01 (3.16)	Complies	20.25 (0.74)
D	BP	100	101.57 (2.89)	Complies	6.50 (0.41)
E	IP	100	99.89 (4.03)	Complies	44.00 (0.51)
ANOVA			$p > 0.05$, NS		$p < 0.01$, HS

[a]Mean of three separate runs; ANOVA: analysis of variance; NS: not significant; HS: highly significant.

Table 2

Pharmacokinetic Characteristics of Phenylbutazone Tablets (Test Products A–E)

Test Product	AUC (μg-hr/ml) (SD)	C_{max} (μg/ml) (SD)	t_p (hr)
A	426.50 (18.07)	22.95 (0.57)	6
B	353.20 (7.17)	20.65 (0.47)	4
C	304.89 (18.95)	15.95 (2.31)	6
D	180.89 (15.59)	8.81 (0.60)	4
E	319.59 (20.23)	17.59 (1.95)	6
ANOVA	$p < 0.001$, HS	$p < 0.001$, HS	

ANOVA: analysis of variance; AUC: area under plasma concentration curve; C_{max}: maximum plasma concentration; t_p: time required to reach maximum plasma concentration; HS: highly significant.

The dissolution profile of the five test products A–E is given in Fig. 2. Statistical analysis of the dissolution parameters (percent dissolved in 120 min [A_{120}], time taken to dissolve 50% [T_{50}], and the dissolution rate constant [k] [Table 3]) showed highly significant differences ($p < 0.001$) among the test products.

Comparision of disintegration time (Table 1) and AUC (Table 2) did not show any correlation: $r = 0.256$ ($p > 0.25$). Similarly, AUC exhibited no correlation with any of the dissolution parameters (Table 3): $r = 0.122$ ($p > 0.25$) for A_{120}, $r = 0.249$ ($p > 0.25$) for T_{50}, and $r = 0.197$ ($p > 0.25$) for k values.

In the absence of any correlation between the AUC data and disintegration time and dissolution parameters, the K values were compared.

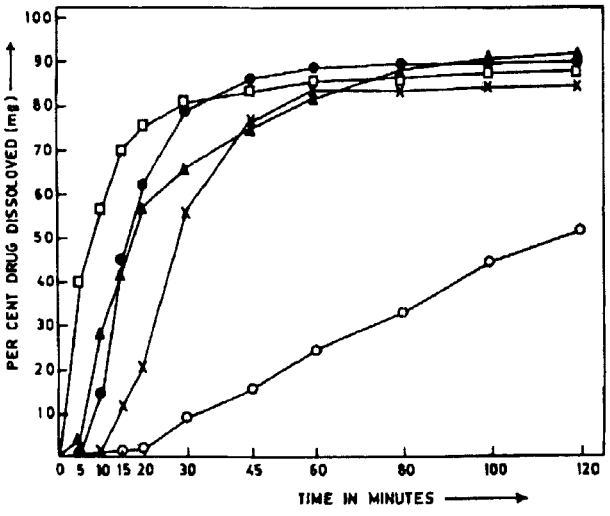

Figure 2. The dissolution profile of commercial phenylbutazone tablets. Test products A (▲), B (X), C (○), D (□), and E (●).

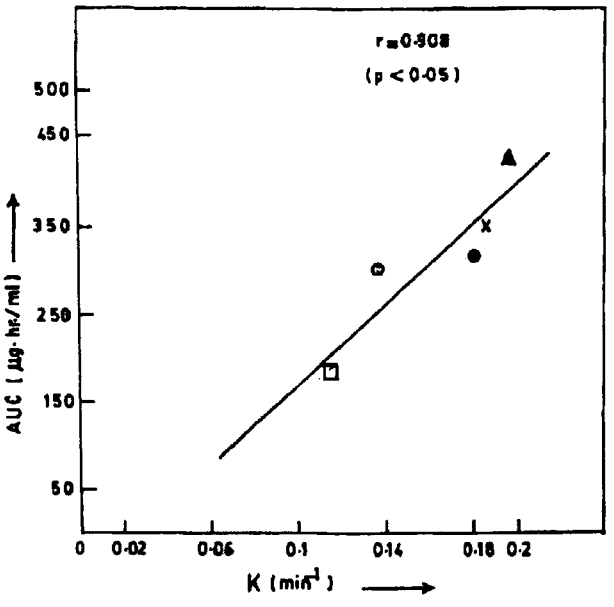

Figure 3. Correlation between the dialysis rate constant (K) and area under plasma concentration curve (AUC) of commercial phenylbutazone tablets. Test products A (▲), B (X), C (○), D (□), and E (●).

Table 3

Dissolution Characteristics[a] of Commercial Phenylbutazone Tablets (Test Products A–E) in Phosphate Buffer of pH 7.4

Test Products	Dissolution Characteristics		
	A_{120} (SD)	T_{50} (SD)	k (min^{-1}) (SD)
A	91.06 (0.47)	32.67 (0.31)	0.021 (0.00)
B	83.94 (0.07)	37.17 (0.03)	0.019 (0.00)
C	51.04 (0.32)	111.65 (0.62)	0.006 (0.00)
D	87.34 (0.22)	48.78 (0.75)	0.014 (0.00)
E	89.55 (0.11)	33.52 (0.03)	0.021 (0.00)
ANOVA	$p < 0.001$, HS	$p < 0.001$, HS	$p < 0.001$, HS

[a]Mean of three separate runs; ANOVA: analysis of variance; A_{120}: percent dissolved in 120 min; T_{50}: time taken to dissolve 50%; k: dissolution rate constant; HS: highly significant.

Statistical analysis of K values (Table 4) showed highly significant differences ($p < 0.001$). The ranking of the test products according to K values was A > B > E > C > D; the same rank order was obtained for AUC and C_{max} data. Correlation of K values (Table 3) with that of AUC and C_{max} data (Table 2) was significant. The r values obtained when K values were compared with AUC values were 0.908 ($p < 0.05$) (Fig. 3), and when dialysis rate constants were compared with C_{max} data, the r value was 0.939 ($p < 0.05$) (Fig. 4).

In addition, comparision of K value of the five test products with K value of pure phenylbutazone (Table 4) showed highly significant differences ($p < 0.001$), indicating the cell used in the present study was sensitive

Table 4

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

Test Products	Dialysis Rate Constant (K) (SD)
A	0.199 (0.01)
B	0.187 (0.023)
C	0.138 (0.002)
D	0.117 (0.003)
E	0.182 (0.022)
Phenylbutazone powder	0.382 (0.002)
ANOVA[b]	$p < 0.001$, HS

[a]Mean of three separate runs; ANOVA: analysis of variance; HS: highly significant.

[b]For products A–E and phenylbutazone powder.

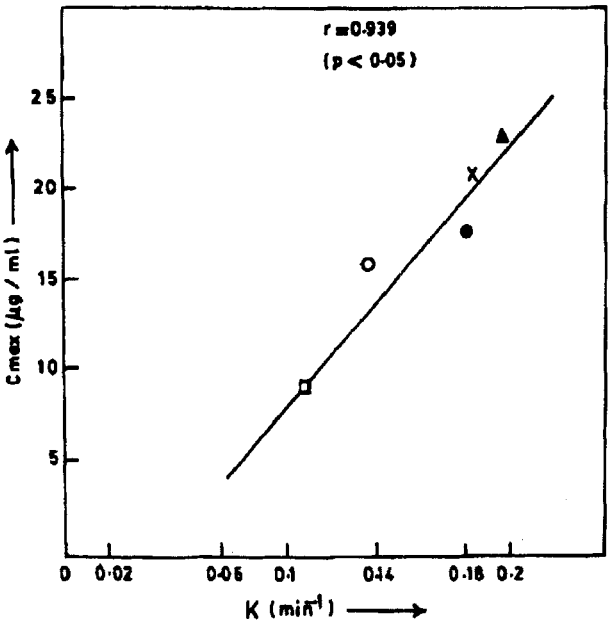

Figure 4. Correlation between the dialysis rate constant (K) and maximum plasma concentration (C_{max}). Test products A (▲), B (X), C (○), D (□), and E (●).

enough to detect the influence of formulation factors.

The above results amply demonstrate the superiority of dialysis rate constants over dissolution parameters for the in vitro evaluation of phenylbutazone tablet formulation. Studies on other drugs with different physicochemical characteristics are in progress to determine the universality of this technique for in vitro evaluation.

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