Effect of Aging on Physical Properties of Phenylbutazone Tablets

D. BARRETT * and J. T. FELL ‡ x

Abstract □ A study was made of the influence of age on the physical properties of phenylbutazone tablets BP, with special reference to *in vitro* dissolution rates. Past batches of tablets showed a progressive decrease in dissolution rate with age. This effect could be simulated in short periods by using elevated temperatures. The effect appears to be connected with the subcoat layer of the sugar coating of the tablet which adheres more strongly to the tablet core and slows down its disintegration.

Keyphrases □ Phenylbutazone tablets—effect of aging on physical properties ■ Aging—effect on physical properties of phenylbutazone tablets □ Stability—effect of aging on physical properties of phenylbutazone tablets ■ Dissolution rate—effect of aging, phenylbutazone tablets

The effects of storage time and temperature on such tablet properties as hardness and disintegration time have been examined (1–5). The results were highly dependent on the formulation under study.

Alam and Parrott (6) recognized the importance of dissolution rate and the possible effect that changes in this property with time may have on bioavailability. In a study using hydrochlorothiazide tablets, they showed a close correspondence between changes in dissolution rate occurring at elevated temperatures and those occurring after prolonged storage at room temperature. Retardation of dissolution rate was also reported (7) for sodium salicylate tablets, and a possible effect with acetaminophen tablets was mentioned (8).

The present study was undertaken to examine the effect of age on the physical properties of phenylbutazone tablets BP. These tablets are sugar coated, and both the cores and the sugar-coated tablets have been examined. Several studies examined the *in vitro* dissolution behavior and *in vivo* availability of various brands of phenylbutazone tablets (9–13). Wide variations between brands were noted, but the influence of the age of the product does not appear to have been taken into account.

EXPERIMENTAL

Tablets—All tablets examined were 100-mg phenylbutazone tablets prepared to BP standards. A series of both cores and coated tablets with varying manufacturing dates were obtained which had been prepared according to the same formulation and standards. Relevant information is given in Table I.

The most recently manufactured batch was subjected to controlled temperature studies. Tablets were stored in tightly sealed, well-filled bottles and were exposed to temperatures of 20 (representing an even room temperature), 37, and 50°. Tablets stored at elevated temperatures were allowed to attain room temperature before testing and were stored at 20° until all tests were completed. Testing was carried out at suitable time intervals dependent on storage temperature.

Dissolution Studies—Tablet dissolution was studied by the beaker method of Levy and Hayes (14). The dissolution fluid, contained in a 2-liter beaker (13-cm diameter, 19 cm high) was 1 liter of simulated intestinal fluid USP without pancreatin, maintained at 37 ± 0.5°. The fluid was stirred with a Perspex paddle consisting of three blades (2 cm long, 1.3 cm high) set at an angle of 30° to the vertical on a 1.5-cm diameter shaft. This paddle was immersed centrally in the dissolution fluid to a depth of 2.7 cm below the surface of the fluid and 4.8 cm from the bottom of the beaker. The paddle was driven at a constant speed of 75 rpm.

The colored outermost layers of the sugar coat were removed by washing prior to dissolution to prevent any possible interference with the assay. The tablet was placed centrally in the fluid, and 2-ml samples were withdrawn at suitable time intervals and filtered[1]. After suitable dilution, the samples were assayed spectrophotometrically for phenylbutazone at 264 nm. Each tablet was allowed to dissolve in its entirety. The excipients present in the tablet, other than the color, did not interfere with the assay.

Disintegration Time—This was measured using the disintegration apparatus of BP 1973, using 250 ml of simulated intestinal fluid without pancreatin at 37°. The disintegration times of the tablets were determined individually.

Tablet Strength—The strength of the tablet cores was measured by diametral compression using a standard testing instrument[2]. Tensile failure was not observed in all cases, and the results are expressed as the mean breaking load of five individual determinations.

RESULTS AND DISCUSSION

The results from the dissolution studies were interpreted by apparent first-order kinetics as derived by Wagner (15). Plots of log (percent undissolved) against time gave straight lines, the slopes of which were taken as a measure of the dissolution rate. The data were plotted down to 10% undissolved; lines were fitted to these plots by the method of least-squares linear regression using a desk computer[3], programmed accordingly. Correlation coefficients indicated that a significant linear correlation existed ($p = 0.05$) in all cases.

Experiments with tablets in which interference by the color was not a problem indicated that the preliminary washing did not affect the slopes of the dissolution plots. Parameters such as a $t_{50\%}$ value, which would include a lag time with the sugar-coated tablets, were not used because these would be affected slightly by the washing procedure.

The slopes of these plots for tablets manufactured at different times are given in Table I. There was a continuing decrease in the mean regression line slope with age for both the cores and the sugar-coated tablets. The most marked change, however, occurred with the sugar-coated tablets. These results, of course, must be treated with caution because initial dissolution rates are unknown and the differences may merely be due to interbatch variation. However, the progressive decrease in dissolution rate strongly suggests an aging effect.

The vastly greater change in dissolution rate for the sugar-coated tablets than for the cores indicates that if an aging effect is present, it is in some way connected with a change in the sugar coat. Visual observation of the tablets in the dissolution apparatus showed different "break-up" patterns for tablets of different ages. All of the cores and the more recently manufactured sugar-coated tablets disintegrated readily.

With Batch 02/70, there was a tendency for fragments of the core to adhere to the subcoat. With Batches 05/69 and 04/69, the

[1] Millipore filters (0.45 μm), Millipore U.K. Ltd., London NW10 7SP, United Kingdom.

[2] Floor model, Instron Ltd., High Wycombe, United Kingdom.

[3] Model 9810 A, Hewlett-Packard, Loveland, CO 80537

Table I—*Results from Past Batches of Tablets*

Batch Number[a]	Tablet Cores: Mean (*SD*) of Regression Line Slopes	Tablet Cores: Mean (*SD*) of Disintegration Time, min	Strength, kg	Sugar-Coated Tablets: Mean (*SD*) of Regression Line Slopes	Sugar-Coated Tablets: Mean (*SD*) of Disintegration Time, min
07/72	−0.0319 (0.00427)	5.8 (1.76)	3.13	−0.0250 (0.00217)	9.7 (1.93)
03/71	−0.0220 (0.00214)	11.6 (1.89)	1.97	−0.0221 (0.00207)	19.4 (1.78)
02/70	−0.0206 (0.00099)	1.5 (0.40)	1.24	−0.0194 (0.00195)	9.5 (0.80)
05/69	−0.0193 (0.00171)	1.2 (0.19)	1.76	−0.0059 (0.00326)	~15[b]
04/69	−0.0183 (0.00187)	4.7 (1.69)	2.05	−0.0022 (0.00091)	~40[b]

[a] Dates of manufacture. Cores: 07/72, Dec. 1972; 03/71, Mar. 1971; 02/70, Mar. 1970; 05/69, May 1969; and 04/69, Apr. 1969. Sugar coated: 07/72 Jan. 1973; 03/71, Apr. 1971; 02/70, Apr. 1970; 05/69, May 1969; and 04/69, May 1969. [b] Disintegration times could not be determined more precisely due to the tendency of fragments of the tablet core to adhere to fragments of the subcoat, making it difficult to detect the end-point of the test.

Table II—Results from Tablets Stored at Controlled Temperatures

Storage Conditions	Tablet Cores: Mean (*SD*) of Regression Line Slope	Tablet Cores: Mean (*SD*) of Disintegration Time, min	Strength, kg	Sugar-Coated Tablets: Mean (*SD*) of Regression Line Slope	Sugar-Coated Tablets: Mean (*SD*) of Disintegration Time, min
Initially	−0.0235 (0.00292)	13.8 (5.13)	2.06	−0.0274 (0.00346)	7.6 (1.86)
20°, 6 weeks	−0.0254 (0.00211)	14.4 (4.39)	2.33	−0.0272 (0.00179)	8.1 (4.10)
20°, 14 weeks	−0.0248 (0.00271)	14.1 (4.61)	2.41	−0.0283 (0.00369)	7.9 (1.67)
37°, 3 weeks	−0.0259 (0.00265)	7.7 (2.03)	2.61	−0.0260 (0.00153)	6.9 (1.66)
37°, 6 weeks	−0.0234 (0.00144)	9.9 (2.12)	2.96	−0.0272 (0.00215)	6.9 (2.09)
37°, 14 weeks	−0.0241 (0.00261)	10.6 (2.27)	2.75	−0.0240 (0.00258)	8.7 (2.17)
50°, 2 weeks	−0.0223 (0.00123)	12.7 (5.82)	3.13	−0.0252 (0.00276)	7.5 (2.51)
50°, 4 weeks	−0.0237 (0.00133)	15.1 (4.67)	3.06	−0.0288 (0.00228)	16.4 (7.84)
50°, 6 weeks	−0.0223 (0.00333)	13.5 (6.46)	3.00	−0.0231 (0.00665)	20.8 (8.67)
50°, 9 weeks	−0.0240 (0.00241)	14.1 (4.76)	3.01	−0.0151 (0.00373)	~25[a]
50°, 14 weeks	−0.0231 (0.00203)	13.9 (5.01)	2.98	−0.0115 (0.00510)	~40[a]

[a] See Table I.

tablet split into two halves, and these persisted throughout the test. The subcoat appeared to adhere to the core and prevent it from breaking up completely, thus impeding dissolution. Differences in the extent of this adherence would account for the greater spread of results noted with these tablets.

In the case of Batch 04/69, the core showed continued resistance to break up even after the tablet coat had broken away. This could have been due to the presence of a film of adhesive material from the coating process on its surface.

The strength and disintegration times of these tablets are given in Table I. A progressive change in disintegration time with age of manufacture was not apparent with the tablet cores. Of the sugar-coated tablets, Batch 03/71 had a high disintegration time, not in keeping with its dissolution rate, but Batches 05/69 and 04/69 both had disintegration times that may be correlated with their extended dissolution times. The values of the breaking loads of the tablets did not show any trend with age.

The results from the controlled temperature studies are given in Table II. In the 14-week storage period, the dissolution rate from the tablet cores remained essentially unchanged. Sugar-coated tablets stored at 20 and 37° were similar, but those stored at 50° showed an aging effect. Results after 14 weeks of storage at 50° show an increasing reduction in dissolution rate with a wider spread in the values. These results agree qualitatively with those from the tablets manufactured during the past 5 years.

The break-up pattern of the tablets stored at 50° was similar to that observed with the older tablets. Again it appeared that the innermost subcoat was in some way impeding tablet break up and dissolution. Tablet subcoats are often a gelatin–acacia mixture, the materials that both Alam and Parrott (6) and Kristofferson and Keto (7) found were most susceptible to aging effects when used as granulating agents.

No appreciable change in disintegration times for cores stored at 20 or 50° was noted, although there appeared to be a decrease in those stored at 37°. For the sugar-coated tablets, storage at 20 or 37° did not affect the disintegration time, except for 14 weeks at 37°, but an increase was observed at 50° which may be related to the decrease in dissolution rate. The strength of the tablet cores rose with storage at all temperatures to a constant value. This increase does not appear to be related to dissolution rate or disintegration time, as was also observed previously (6).

The results presented indicate an aging effect with phenylbutazone tablets that appears to be connected with the subcoating of the sugar coat. This raises the possibility of the effect being present in other sugar-coated tablets. The use of elevated temperatures enables qualitative simulation of the aging in short time periods.

REFERENCES

(1) G. E. Ewe, *J. Amer. Pharm. Ass., Sci. Ed.*, **23**, 1205(1934).

(2) H. Burlinson and C. Pickering, *J. Pharm. Pharmacol.*, **2**, 630(1950).

(3) J. B. Ward and A. Trachtenberg, *Drug. Cosmet. Ind.*, **91**, 35(1962).

(4) L. A. Bergman and F. J. Bandelin, *J. Pharm. Sci.*, **54**, 445(1965).

(5) R. N. Duvall, K. T. Koshy, and R. E. Dashiell, *ibid.*, **54**, 1196(1965).

(6) A. S. Alam and E. L. Parrott, *ibid.*, **60**, 263(1971).

(7) E. Kristofferson and K. Keto, *Farm. Aikak.*, **82**, 45(1973).

(8) G. L. Mattok, I. J. McGilveray, and C. A. Mainville, *J. Pharm. Sci.*, **60**, 561(1971).

(9) R. O. Searl and M. Pernarowski, *Can. Med. Ass. J.*, **96**, 1513(1967).

(10) W. H. Thomas and W. B. McCarthy, *N. Z. Med. J.*, **72**, 250(1970).

(11) H. Turakka, M. M. Airaksinen, V. E. Krogerus, and V. Vallinkoski, *Acta Pharmacol. Toxicol., 4th Suppl.*, **29**, 60(1971).

(12) G. R. Van Petten, H. Feng, R. J. Withey, and H. F. Lettau, *J. Clin. Pharmacol.*, **11**, 177(1971).

(13) R. J. Withey, H. Feng, D. Cook, G. R. Van Petten, and H. F. Lettau, *ibid.*, **11**, 187(1971).

(14) G. Levy and B. A. Hayes, *N. Engl. J. Med.*, **262**, 1053(1960).

(15) J. G. Wagner, "Biopharmaceutics and Relevant Pharmacokinetics," 1st ed., Drug Intelligence Publications, Hamilton, Ill., 1971, pp. 118–120.

ACKNOWLEDGMENTS AND ADDRESSES

Received June 10, 1974, from the *Pharmacy Department, Burnley General Hospital, Burnley BB10 2PQ, United Kingdom, and the ‡Department of Pharmacy, The University, Manchester M13 9PL, United Kingdom.

Accepted for publication August 9, 1974.

The authors thank Thos. Kerfoot & Co., Ltd., Vale of Bardsley, United Kingdom, for the supplies of tablets, and the Manchester Regional Hospital Board for the provision of a studentship to D. Barrett.

x To whom inquiries should be directed.

NOTES

5-Chloro-2-pyrimidinyl Analog of Dantrolene

THOMAS J. SCHWAN x and K. O. ELLIS

Abstract □ 1-{[5-(5-Chloro-2-pyrimidinyl)furfurylidene]amino}-hydantoin, a structural analog of the skeletal muscle contraction antagonist dantrolene, was synthesized and found to have no skeletal muscle relaxant activity.

Keyphrases □ Dantrolene—synthesis and screening for muscle relaxant activity of 5-chloro-2-pyrimidinyl analog □ 1-{[5-(5-Chloro-2-pyrimidinyl)furfurylidene]amino}hydantoin—structural analog of dantrolene, synthesized and screened for muscle relaxant activity □ Muscle relaxant activity—5-chloro-2-pyrimidinyl analog of dantrolene

The unique skeletal muscle relaxant activity of dantrolene, 1-{[5-(*p*-nitrophenyl)furfurylidene]amino}hydantoin (I), has been demonstrated (1, 2). It has been pharmacologically categorized as a skeletal muscle contraction antagonist (3).

The 5-chloro-2-pyrimidinyl group was shown to replace effectively the *p*-nitrophenyl moiety in a series of nonsteroidal hypocholesterimic agents (II) (4). Thus, the 5-chloro-2-pyrimidinyl analog of the prototype was desired for evaluation for skeletal muscle relaxant activity.

DISCUSSION

Although the requisite 5-(substituted phenyl)-2-furaldehydes were prepared previously by coupling of the appropriate diazonium salt with furfural (5), reaction of diazotized 5-chloro-2-aminopyrimidine with furfural failed to give the desired aldehyde (III). Accordingly, an alternate route to III was devised.

Condensation of furamidine hydrochloride with mucochloric acid, using the general procedure of Budesinsky (6), gave 5-chloro-2-(2-furyl)-4-pyrimidinecarboxylic acid (IV), which was smoothly decarboxylated to 5-chloro-2-(2-furyl)pyrimidine (V) (Scheme I).

Formylation of V gave the aldehyde III, the structure of which is supported by NMR data. Although the NMR spectrum does not completely rule out a 2,3-orientation of substituents in the aldehyde, previous studies in these laboratories showed that 2-phenylfuran is formylated at the 5-position of the furan ring (7). Thus, a 2,5-disubstituted structure was assigned to III.

Treatment of III with 1-aminohydantoin hydrochloride gave VI, the 5-chloro-2-pyrimidinyl analog of I.

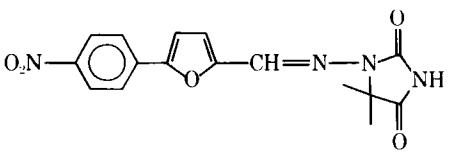
In gross observational testing in mice similar to that described by Irwin (8), VI caused no measurable skeletal muscle relaxation in oral doses up to 1600 mg/kg po. Furthermore, there was no indication of CNS activity or acute toxicity.

Direct skeletal muscle contraction antagonism was tested in the curarized pithed rat gastrocnemius muscle preparation (9). Compound VI did not affect the twitch response of the gastrocnemius muscle over a dose range of 1.0–25 mg/kg iv, indicating that it had no skeletal muscle contraction antagonism activity.

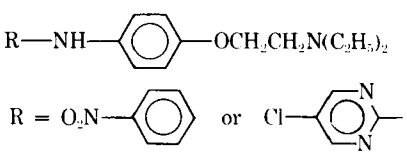
EXPERIMENTAL[1]

5-Chloro-2-(2-furyl)-4-pyrimidinecarboxylic Acid (IV)—Two solutions were prepared: Solution A contained 852 g (15.78 moles) of sodium methoxide in 6360 ml of methanol, and Solution B contained 903 g (5.34 moles) of mucochloric acid in 2285 ml of methanol.

To a solution of 1150 g (7.83 moles) of furamidine hydrochloride in 2610 ml of methanol stirred at 55° was added rapidly 3800 ml of Solution A. The reaction was endothermic. The mixture was reheated to 55°, and 1625 ml of Solution B was added while the mix-



I



II

[1] Melting points were determined on a Mel-Temp apparatus and those below 230° are corrected. IR spectra were determined as mineral oil mulls using a Perkin-Elmer 137B spectrophotometer. The NMR spectrum was obtained on a Varian A-60A instrument and was compared with tetramethylsilane as an internal standard.