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DISSOLUTION RATES OF COMMERCIAL PHENYLBUTAZONE TABLETS: INTER-AND INTRA-BRAND EFFECTS

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ABSTRACT

A study has been carried out to investigate the dissolution rate profiles of twelve batches of sugar-coated phenylbutazone tablets belonging to four commercial brands. Using the rotating basket method, significant inter-brand and inter-batch variations in dissolution rates were found. Only two batches of one brand passed the B.P. dissolution limit whilst other batches had percentages dissolution between 0.3 and 58 after 45 min. Batches with poor dissolution characteristics exhibited significant tablet-to-tablet variations in dissolution rates; a finding which was not observed in the relatively fast-dissolving batches. When the paddle method was substituted for the B.P. basket method, the dissolution rates were relatively faster but similar dissolution failure was found. However, the tablet-to-tablet dissolution variability was decreased in some of the batches. The observed differences in dis-

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solution rates of the batches examined were unrelated to their disintegration times. Inspite of the poor dissolution characteristics of most of the batches studied, no apparent chemical degradation was found. It is recommended that when evaluating the dissolution rates of brands of phenylbutazone tablets, a number of batches from each brand should be tested.

INTRODUCTION

Phenylbutazone is included in the list of drugs which show differences in bioavailability (1). Bioavailability problems associated with phenylbutazone tablets, as evidenced by the presence of intact tablets in the stool, have been reported as early as 1953 (2). The first study definitively identifying bioavailability differences with phenylbutazone tablets was reported by Searl and Pernarowski (3). Of 23 Canadian brands examined, 22% failed to comply with the in-vitro dissolution requirements and significant differences in the absorption rates were reported. That in-vitro dissolution rates of phenylbutazone tablets can reflect differences in bioavailability, have been confirmed by McGilveray et al. (4). Both the U.S.P. (5) and B.P. (6) specify dissolution tests in the monographs of phenylbutazone tablets.

The failure of batches of phenylbutazone tablets to comply with the dissolution requirements and to exhibit the expected therapeutic performance have been reported by a number of authors. Recently, Wojdak and Pasich (7)

studied the release characteristics of the drug from sugar-coated tablets. In an artificial gastric juice, the percent drug release was about 32% after 2 hr, whilst maximum release occurred after 4.5 hr in an artificial intestinal juice. Manek et al. (8) examined the bioavailability of five sugar-coated brands of phenylbutazone marketed in India. They found significant differences between the bioavailability of the products; two brands gave about 50% the bioavailability of phenylbutazone powder.

The poor dissolution characteristics reported for some batches of phenylbutazone tablets cannot be attributed solely to the formulation of the cores. Since phenylbutazone tablets should be either film-or sugar-coated, the possible effects of the coat on the dissolution rates cannot be ruled out. Barrett and Fell (9) and Matsui et al. (10) found a progressive decrease in the dissolution rates of sugar-coated phenylbutazone tablets when stored at 50° and 60°. It was suggested that the reduction in dissolution rates was due to the adherence of the subcoat layer to the core and hence slowed down its disintegration (9).

Dissolution rate differences can exist not only between brands but also between batches of the same brand (inter-batch) and between tablets of the same batch(inter-tablet effects). Sugar-coated tablets are particularly susceptible to dissolution variability due to inter-batch and inter-tablet effects as the result of possible non-uniformity of the coat. No studies appeared to have been

made of the inter-tablet dissolution variability of phenylbutazone tablets and the effect of batch dissolution characteristic on this property.

The objectives of the present work have been to study the dissolution rate profiles of some commercial batches of sugar-coated phenylbutazone tablets and to examine the inter-tablet dissolution variability within the batch. An attempt has been made to correlate the dissolution properties of the batches examined with their ages, disintegration times and content uniformity.

MATERIALS

Samples of twelve commercial batches of sugar-coated phenylbutazone tablets (200 mg) were purchased. The batches belong to four brands; one was imported (Brand I) and three are locally-manufactured (Brands II, III and IV). Table 1 shows the dates of manufacture and expiry dates for some of the batches examined.

METHODS

Each batch was examined by the following tests:

Content Uniformity

This was carried out using the U.S.P. procedure.

Disintegration Time

Single tablets were examined using the B.P. apparatus. A total of six tablets were tested for each batch.

Dissolution Rate

The apparatus and procedure adopted were according to the B.P. (using the rotating basket at 100 r.p.m., in

TABLE 1

Dates of Manufacture and Expiry Dates for Batches of Sugar-Coated Phenylbutazone Tablets (200 mg).

Batch	Date of manufacture*	Expiry date**
Ia	Not available	Feb. 1986
Ib	Nov. 1981	Not stated
Ic	Not available	Not stated
Id	Not available	Not stated
IIa	April 1976	Not stated
IIb	June 1976	Not stated
IIc	July 1978	Not stated
IIIa	Not available	Not stated
IIIb	Not available	Not stated
IVa	Feb. 1982	Not stated
IVb	June 1981	Not stated
IVc	Feb. 1982	Not stated

* Obtained from the manufacturer

** Stated on the pack.

a medium of pH 7.5). Instead of the single point measurement at 45 min, as specified in the B.P., the dissolution rates of the batches were determined over a period of 1 hr. Aliquots (5 ml each) were sampled after 10, 20, 30, 45 and 60 min and the contents of phenylbutazone in the filtered solutions were determined at 264 nm after suitable dilution. In addition to the B.P. basket method, the U.S.P. dissolution apparatus 2 (the paddle method) was used to evaluate the dissolution rates in the same medium and at the same speed (100 r.p.m.).

Single tablet dissolution was carried out and a total of twelve runs were made for each batch. A six-station dissolution tester, was used with a sampling system(Dissoette, Model QC 72R 24-6M, Hanson Research Corporation, CA, USA).

UV Spectrophotometric Examination

This was carried out as a measure of the chemical stability of phenylbutazone in the batches. As decomposition proceeds, the absorbance at 264 nm decreases and the λ max. gradually shifts toward 234 nm. The absorbance ratio (A264/A234) can thus be taken as a measure of drug stability (10). Tablet grinds were treated with methanol and after filtration and adjustment to volume, the solution was suitably diluted with 0.01N NaOH. The absorbance ratio A264/A234 was determined for some of the batches. The value obtained for phenylbutazone powder B.P, similarly treated, was taken as a standard.

RESULTS

Figures 1 and 2 show the dissolution rate profiles of the batches of phenylbutazone tablets examined. For Brands I and II significant differences in the dissolution rates were found between the batches. This inter-batch dissolution variability was less significant in the batches of brands III and IV.

Table 2 shows the disintegration times, content uniformity, absorbance ratio (A264/A234) and percent dissolution after 45 min (the sampling time specified in the B.P dissolution test). Of the twelve batches studied, only two batches of

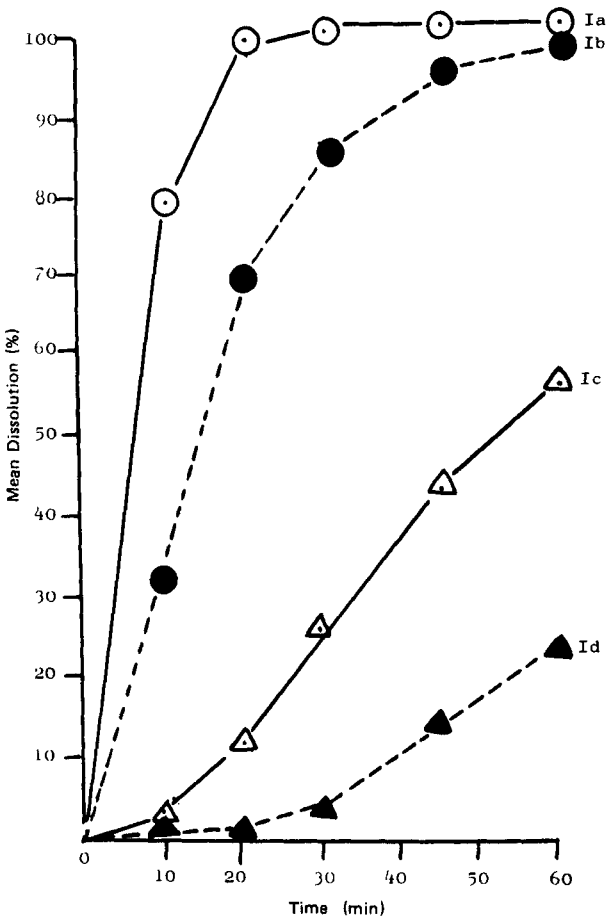

FIGURE 1

Dissolution rates of four batches of phenylbutazone tablets, Brand I using the B.P. method (Mean of 12 runs).

Brand I (Ia and Ib) complied with the B.P dissolution limit (not less than 75% dissolution after 45 min). Other batches (Ic and Id) of the same Brand failed the B.P. test. With the exception of batches IIb and IIc all the batches disintegrated within 1 hr.

Content uniformity testing of the batches revealed that all

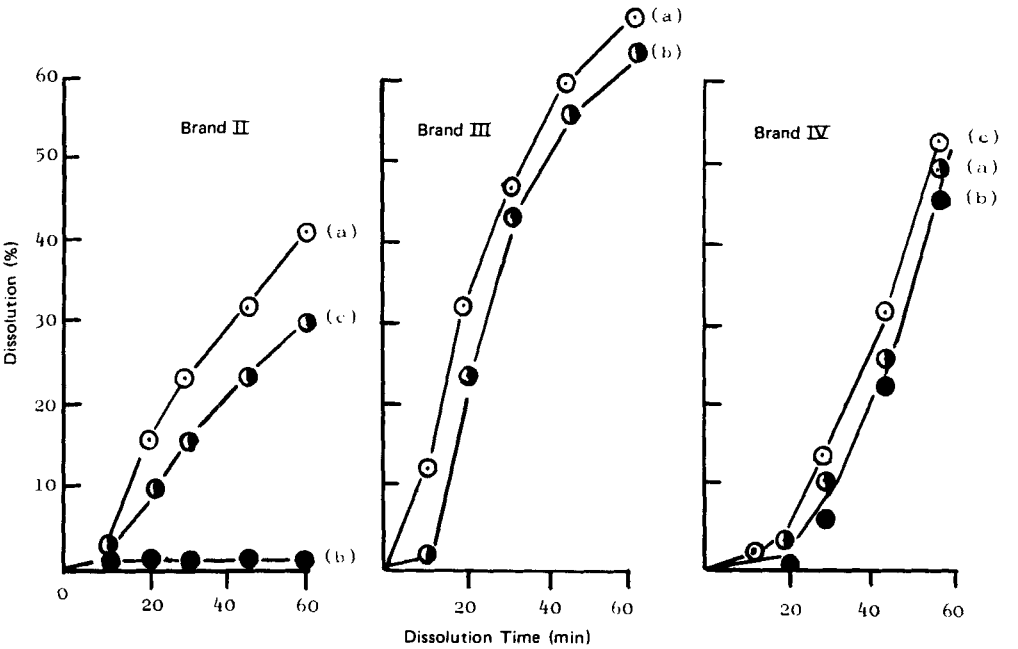

FIGURE 2

Dissolution rates of batches of phenylbutazone tablets, Brands II, III and IV using the B.P. rotating basket method (mean of 12 runs).

the batches (except batch IIIb) passed the test. UV-absorbance ratio (A264/A234) indicated no apparent chemical degradation since an insignificant difference was found between the absorbance values of the batches examined and that of phenylbutazone powder, B.P. (Table 2).

According to Wagner (11), dissolution results can be plotted as log % drug undissolved versus time. This procedure tends to linearize results which would otherwise give curves and the resulting straight lines obey the dissolution

TABLE 2

Disintegration Times, Content Uniformity, Absorbance Ratio (A264/A234) and Percent Dissolution After 45 min of Some Batches of Phenylbutazone Tablets

Batch	Disintegration Time (min)	Content Uniformity (Range %)	Absorbance Ratio*	Percent Dissolution (± SD)** (n= 12)
Ia	< 60	94.8-106.8	1.89	103.2 (2.8)
Ib	< 60	96.5-105.1	-	96.7 (3.4)
Ic	< 60	93.8-107.2	-	44.1 (8.4)
Id	< 60	96.7-105.3	1.89	14.7 (10.8)
IIa	< 60	99.6-108.1	1.89	30.5 (26.1)
IIb	> 60	96.7-111.0	1.89	0·3 (0.9)
IIc	> 60	86.2-111.0	1.88	21.9 (15.7)
IIIa	< 60	85.2- 99.6	1.84	56.8 (11.8)
IIIb	< 60	25.8-107.2+	1.85	58.0 (26.1)
IVa	< 60	91.9-106.3	1.86	24.2 (12.7)
IVb	< 60	99.6-106.3	1.85	22.8 (9.3)
IVc	< 60	97.6-107.2	-	25.7 (9.1)

* Absorbance ratio (A264/A234) for phenylbutazone powder, B.P. was 1.88.

** The B.P. dissolution limit: not less than 75% after 45 min.

\+ This batch failed the U.S.P. content uniformity test.

TABLE 3

Mean Values of the Slopes and First-Order Dissolution Rate Constants (K_S) Derived From the Wagner's Plot. (n= 12)

Batch	Age (months)	Slope (±SD)	K_S, min^{-1} (±SD)
Ia	N.A*	0.069 (0.009)	0.159 (0.022)
Ib	13	0.028 (0.006)	0.064 (0.014)
Ic	N.A	0.010 (0.008)	0.023 (0.018)
Id	N.A	0.004 (0.003)	0.009 (0.007)
IIa	80	0.005 (0.003)	0.011 (0.007)
IIb	78	N.D**	N.D**
IIc	53	0.003 (0.002)	0.007 (0.005)
IIIa	N.A	0.007 (0.002)	0.016 (0.004)
IIIb	N.A	0.010 (0.008)	0.023 (0.018)
IVa	10	0.008 (0.005)	0.018 (0.011)
IVb	18	0.008 (0.005)	0.018 (0.011)
IVc	10	0.009 (0.004)	0.021 (0.009)

* Not available.

** Not determined; percent dissolution after 1 hr was 0.3 (±0.9).

equation: $\log (W^{\infty} - W) = \log M - K_S/2.303 \cdot t$ where, $(W^{\infty} - W)$ is the amount of drug undissolved after time 't', 'K_S' is the first order dissolution rate constant and 'M' is a constant which depends on the surface area available for dissolution and the solubility of the drug. when the dissolution data were plotted according to Wagner (11), straight lines were obtained, some of the batches showed lag periods (20-30 min) as in batches Ic, Id, IIa, IIc and IVb. Table 3

TABLE 4

Inter-Tablet Dissolution Variability of Some Batches of Phenylbutazone Tablets as Measured by the Basket and Paddle Methods at 100 R.P.M. (Buffer of pH 7.5). (n= 12)

Batch	% Dissolution After 45 min*				Coefficient of Variation x 100	
	Basket		Paddle			
	Low	High	Low	High	Basket	Paddle
Ia	95.6	106.8	-	-	2.7	N.D**
Ib	90.5	101.7	-	-	3.6	N.D
Ic	27.2	58.6	-	-	18.9	N.D
Id	2.8	36.2	-	-	73.8	N.D
IIa	0.0	70.0	0.0	65.3	85.6	103.1
IIb	0.0	3.0	0.0	3.1	N.D	N.D
IIc	0.3	46.5	0.0	50.0	71.8	100.0
IIIa	31.4	69.8	65.5	81.5	20.8	7.5
IIIb	28.8	94.8	31.9	87.9	45.3	38.0
IVa	12.8	58.9	61.2	94.8	52.5	13.8
IVb	14.3	41.0	62.0	84.4	41.0	10.4
IVc	16.2	44.5	-	-	35.3	N.D

* The dissolution time specified in the B.P. test.

** Not determined.

shows mean values of the slopes (calculated by the least squares method) and K_s. About 23 fold increase was observed between the K_s values of batches Ia and IIc.

The inter-batch dissolution variability is shown in Fig. 3 and Table 4 for the four Brands. Batches with fast dissolution characteristics (Ia and Ib) showed relatively less dissolution variability (low coefficients of variation) and higher values were found for the poorly-dissolving batches.

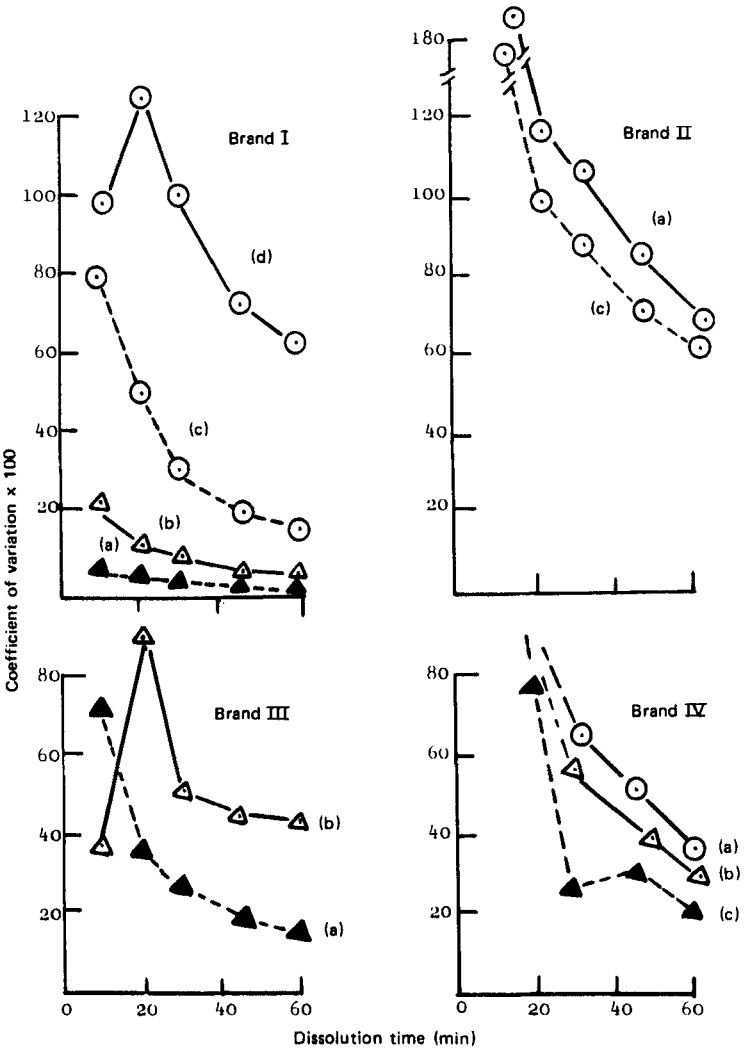

FIGURE 3

Plots showing the coefficients of variation versus dissolution times for batches of Brands I, II, III and IV (n= 12).

In general, as dissolution proceeded the coefficients of variation between tablets were decreased.

At the sampling time specified in the B.P. dissolution test (45 min), significant tablet-to-tablet dissolution variability was found in some batches. Figure 4 is a representative plot for batches IIa and IIIb. For batch IIIb, five tablets (numbers 3, 9, 10, 11 and 12) out of twelve passed the B.P. dissolution limit. Dissolution rate testing using the paddle method at the speed of agitation (100 r.p.m.) gave relatively faster dissolution rates and lower coefficients of variation (Table 4). A representative dissolution rate plot is shown in Figure 5. Batches which failed the B.P. dissolution limit, also failed to pass the limit when the paddle method was used.

DISCUSSION

Drug release from sugar-coated tablets occurs only when the coat disintegrates and break-up of the core takes place. The latter process may be affected by the sealing step (12-14) and the formulation of the core. Failure of the sugar coat to disintegrate will significantly delay the process of drug dissolution due to the limited area exposed. This was reported for a number of sugar-coated tablets including those containing water-soluble drugs (15,16).

In the present study, some of the tablets examined remained intact at the end of the dissolution time due to adherence of the subcoat to the core. In other tablets, the coat partially disintegrated exposing the content to

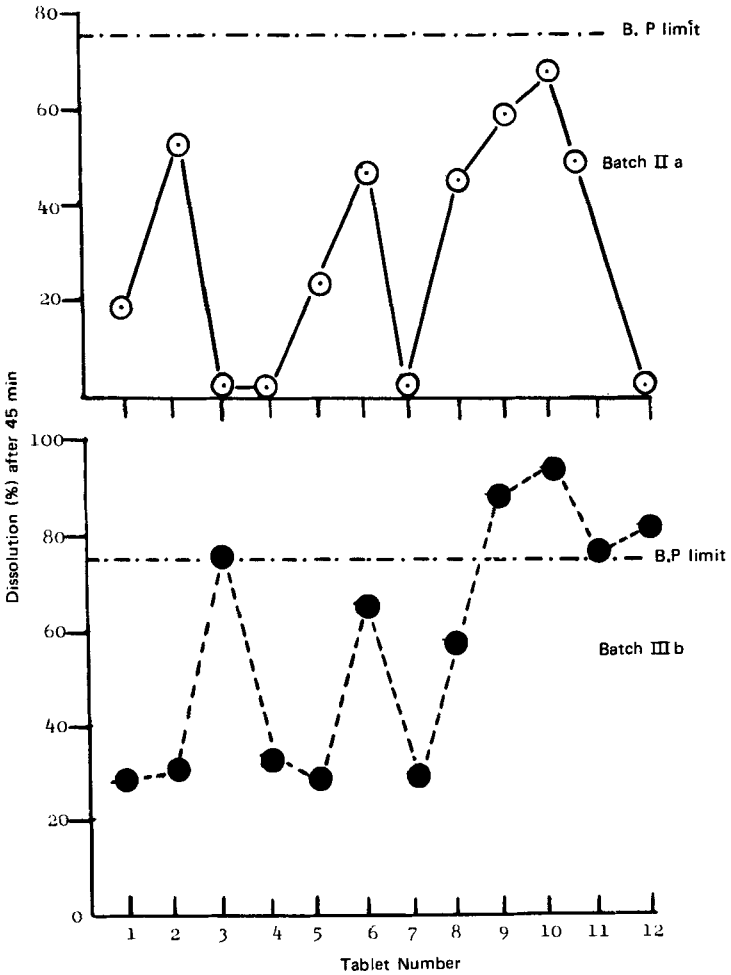

FIGURE 4

Tablet-to-tablet dissolution variability at 45 min (B.P. sampling time) for phenylbutazone tablets batches IIa and IIIb (B.P. basket method).

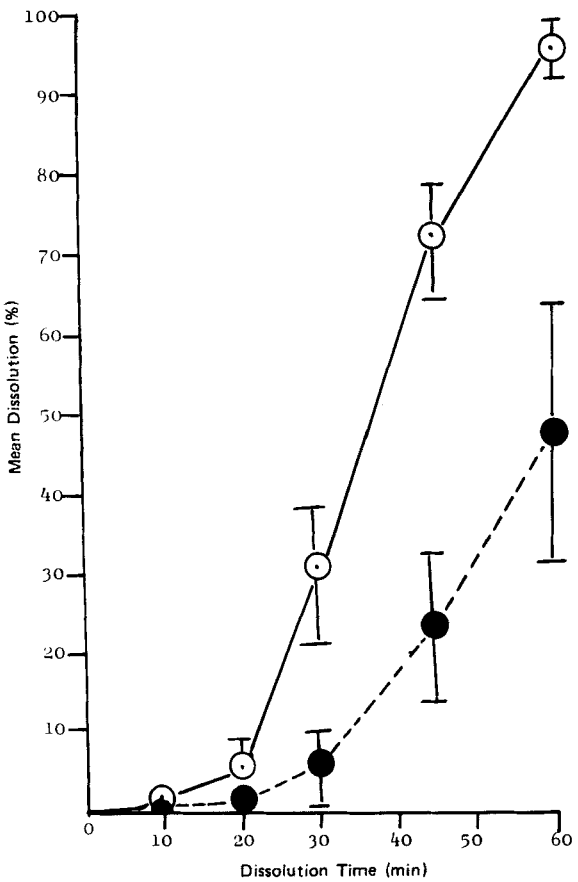

FIGURE 5

Dissolution rates of phenylbutazone tablets using the paddle (⊙—⊙) and (●--●) basket methods at 100 r.p.m. Vertical lines are standard deviations. Batch IVb (Mean of 12 runs).

the dissolution medium. Two batches failed to disintegrate within 1 hr (batches IIb and IIc). However, other batches which disintegrated within 1 hr failed to comply with the B.P. dissolution limit; hence suggesting no correlation between disintegration and dissolution data for the batches of phenylbutazone tablets studied.

The replicate runs (n= 12) enabled the statistical evaluation of the inter-batch dissolution variability (within the same brand) and the inter-tablet effect (within the same batch). For Brands I and II the inter-batch effect was more pronounced. Batches Ia and Ib with relatively fast dissolution characteristics had minimum tablet-to-tablet dissolution differences as was reflected in the low coefficients of variation.

Possible factors contributing to the observed tablet-to-tablet dissolution variability include differences in the subcoat thickness and/or the level of interactions amongst components of the coat. An interaction was reported between gelatin and calcium carbonate, commonly added in the subcoat, which led to the insolubility of the sugar coat upon storage (17). Also, excessive drying of gelatin films may result in the formation of an insoluble gelatin (18).

Inspite of the poor dissolution rates of the drug from most of the batches examined, all (except one) passed the content uniformity test. Also, no apparent chemical degradation was found in the batches exhibiting poor dissolution

properties. It follows, therefore, that the problem at hand is one form of physical instability arising from insolubility of the sugar coat.

Since ageing can accelerate such form of instability (9,10) an attempt was made to correlate the dissolution behaviour of the batches with their ages. No definite correlation could be made since the 'ages' of some batches were not available. However, it seems that formulation of the sugar coat plays a decisive role since batch Ib (13 months) had a relatively much faster dissolution rate profile than batches IVa and IVc (10 months).

Improvement and standardization of the sugar coating process would not only enhance drug dissolution but also minimize the inter-brand and inter-tablet variations in dissolution rates.

Amongst the twelve batches of phenylbutazone tablets studied, only one batch (Ia) had an expiry date. Since physical instability can occur upon storage of sugar-coated tablets, expiry dates should be specified.

The present work reports significant interbatch dissolution variation of some phenylbutazone brands. It is suggested, therefore, that in evaluating the dissolution rates of brands of phenylbutazone tablets, a number of batches from each brand should be examined.

CONCLUSIONS

This work has provided further evidence towards a growing awareness of the problem of physical instability of

sugar-coated tablets. The following conclusions may be drawn from this study:

1. Sugar-coated phenylbutazone tablets suffered drastic changes in disintegration and dissolution characteristics due to the poor break-up of the subcoat.
2. Significant inter-batch and inter-tablet dissolution variations were found and the use of only five tablets in the B.P. dissolution test may not reveal this variation in dissolution rate.
3. In view of the physical instability of sugar-coated tablets, as reported in literature and in the present work, expiry dates should be specified for such dosage forms.

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