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Generated surface area measurement of disintegrating tablets

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The surface areas generated by the disintegration and dissolution of six commercial brands of phenylbutazone tablets B.P. 100 mg have been measured using a Model TA Coulter Counter. The graphs of surface area generated against time were all of the same shape and always reached a maximum value. The initial surface area increase was due to tablet disintegration and deaggregation and followed first order kinetics. A good correlation between the slope of this initial increase and disintegration time was found. The maximum surface area generated correlated at the probability level of better than 99·9% with the dissolution rate measured as t_{60}. The subsequent decrease in surface area, after this maximum, was considered to be due to phenylbutazone dissolution and was also first order rate controlled.

Little attention appears to have been focussed on characterizing the breakdown pattern during tablet disintegration and dissolution. The B.P. merely requires a tablet or capsule to disrupt into particles which pass a 10 mesh screen. Kelly (1945) recognized the importance of continued disintegration beyond this end point. Berry & Ridout (1950) and later Roland (1967) defined various breakdown processes which they attributed to the choice of disintegrant. Nogami, Hasegawa & Nakai (1959a, b) estimated the size distribution of particles from disintegrating tablets by measuring heats of solution using a modified method of Suito & Hirai (1951). This procedure allowed them to quantify the observations of Berry & Ridout (1950). Sanders (1969) and Sandell (1970) attempted to measure the extent of deaggregation by a tedious wet-sieving method. This technique was refined by Shotton & Leonard (1972) who wet-sieved coarse tablet fragments and analysed the fine particles using a Coulter Counter and was used by Gillan & Hunter (1974) to examine generic phenylbutazone tablets. These methods, however, were crude and not capable of monitoring the changes in particles size during disintegration and subsequent dissolution. Wells & Rubinstein (1976) using a Model T_A Coulter Counter, showed that the disintegration, deaggregation and dissolution properties of digoxin tablets 250 μg, an uncoated low dosage tablet, could be characterized by generated surface area measurement. The present paper reports results obtained using six commercial brands of phenylbutazone tablets 100 mg representing a high dosage, sugar-coated tablet.

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MATERIALS AND METHODS

Materials

Six commercial brands of sugar-coated phenylbutazone tablets B.P. 100 mg were used. Product D was enteric coated.

The surface area apparatus

The apparatus is shown in Fig. 1. A 1·25 litre beaker contains 1 litre of buffered, simulated intestinal fluid at pH 6·5 (Stricker, 1970) which had been previously filtered through a 0·22 μm membrane and is maintained at 37° ± 0·1° by a surrounding thermostatic bath. The beaker contents are stirred by a 4 cm magnetic stirrer at 150 rev min^{-1}. A 10 mesh stainless steel basket of external dimensions identical to that used in the U.S.P. dissolution test, containing

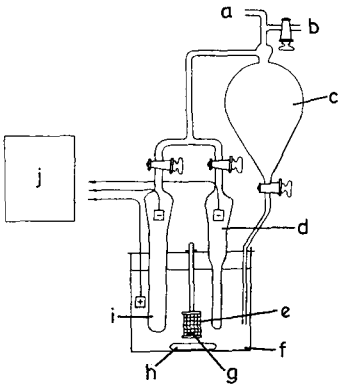

FIG. 1. The surface area apparatus. a—To vacuum, b—vent, c—1 litre separating flask, d—140 μm orifice tube, e—10 mesh basket (stationary), f—simulated intestinal fluid at pH 6·5, g—tablet, h—magnetic stirrer, i—2000 μm orifice tube, j—Model TA Coulte Counter.

the tablet under investigation, is maintained in a stationary and central position, 2 cm above the base of the beaker. Two Coulter Counter orifice tubes, 140 and 2000 μm are placed one on each side of this basket and connected in parallel to a 1 litre separating funnel maintained under vacuum. Both tubes are linked by a switch to a Model T_A Coulter Counter and automatic pen recorder. By using 2000 and 140 μm orifice tubes, particles in the range 2·0–1000 μm can be measured quickly and automatically (2·0–65 μm for the 140 μm orifice tube and 65–1000 μm for the 2000 μm orifice tube). To prevent blockage, the lower end of the 140 μm tube is covered by a 125 μm wire basket.

To effect a measurement, samples of fluid were drawn, at suitable time intervals, through one of the orifice tubes and into the separating funnel. Since this Coulter Counter can handle and process the data instantaneously, it was possible to evaluate the change in surface area of the suspension as disintegration and dissolution proceeded. After a measurement the suspension was immediately returned to the beaker from the separating funnel by releasing the vacuum. A 2000 μm tube analysis was conducted first, followed by a 140 μm tube analysis. The time of sampling was adjusted according to the degree of statistical precision required and was normally in the range 10–60 s. The Model T_A recorded the total number of particles and displayed the distribution as a weight percentage histogram in 16 channels. This histogram could be plotted automatically but it was found more convenient to extract the results from the instrument's digital facility.

The surface area generated S_T was computed using the following equation*:

$$S_T = \frac{V_2 N \pi d_{16}{}^3 10^{-8}}{V_1(X_{16} + 2X_{15} + 4X_{14} \ldots)} \sum_{n=1}^{n=16} \frac{X_n}{d_n} \text{ cm}^2 \quad (1)$$

V_1 is the volume of suspension passing through the Coulter Counter orifice tube in ml. V_2 is the total volume of suspension in ml. N is the total number of particles counted in sample V_1. d_n is the mean particle diameter in μm in channel n and X_n is the percentage of the total volume of all the particles counted, occupied by particles in channel n. V_1 was found by prior calibration. V_2 was constant at 1000cm^3. d_1 to d_{16} were evaluated by prior calibration of the instrument for a particular tube size. The only variables were X_n and N and these values were extracted from the instruments' digital display, enabling S_T to be calculated. A computer program was written to facilitate this calculation. Equation (1) is derived on the assumption that the particles are solid spheres. Each channel on the Model T_A Coulter Counter is related to the next in particle size, by $\sqrt[3]{2}$. Since d_n^3 is proportional to particle volume, reducing the channel number doubles particle volume for each successive channel.

* A derivation of this equation can be obtained on request from the Editorial Department, Journal of Pharmacy and Pharmacology, 1 Lambeth High Street, London, SE1 7JN, U.K.

Solution rate

Solution rates in the surface area apparatus were determined by withdrawing 10 ml samples of dissolution fluid at suitable time intervals, filtering through a 0·22 μm membrane filter, and assaying by ultraviolet spectrophotometry at 265 μm. A dissolution curve was plotted and the time at which 60 mg of phenylbutazone achieved solution was interpolated (t_{60}).

Disintegration time

Disintegration times were determined in the B.P. apparatus without the use of the guided disc. Disintegration times were also measured in the surface area apparatus. The end point was taken to be the time for all tablet fragments to pass through the 10 mesh basket. This time was termed the basket disintegration time.

RESULTS AND DISCUSSION

When the surface area generated was plotted against the logarithm of the time, similar curves were obtained for all the brands, as exemplified by that for brand C in Fig. 2. After an initial time lag, there was a sharp linear increase in surface area to a maximum, followed by a decrease to a constant value, thought to be the surface area of the insoluble excipients. Both the 2000 and 140 μm analyses followed this pattern. The increase in generated surface area was considered to be due to tablet disintegration and deaggregation, the straight line regression indicating that this proceeded by first order kinetics. The subsequent decrease in surface area was considered to be due to phenylbutazone dissolution, similarly following first order kinetics. By mathematically summing the 140 and 2000 μm orifice tube deaggregation regressions, and separately the dissolution regressions, the total surface area in the range 2–1000 μm could be plotted and this plot is also shown in Fig. 2, with the corresponding regression analyses in Table 1. The deaggregation and dissolution regres-

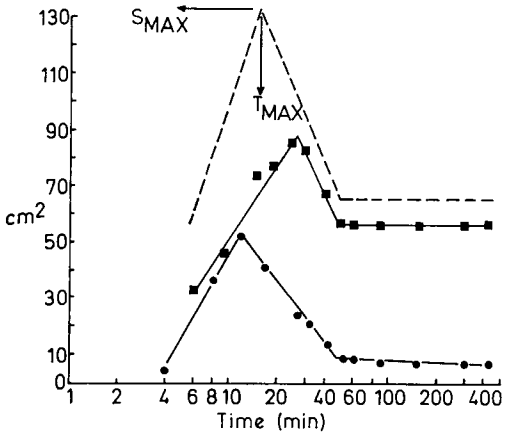

FIG. 2. Generated surface area (cm²) during the deaggregation and dissolution of brand C. ■ From the 140 μm tube. ● From the 2000 μm tube. – – – Calculated total generated surface area from both tubes.

sions were solved simultaneously to yield S_{max}, the maximum generated surface area attained, and the time T_{max} at which this occurred. Both these values are also shown in Table 1. The dissolution rates and disintegration times of the brands are shown in Table 2. A very good correlation ($P < 0.001$, r = 0.9952) was found to exist between t_{60} and S_{max}, the equation being:

$$\log S_{max} = 2.292 - 0.004t_{60} \quad (2)$$

Comparison of the B.P. disintegration time and the slope of the first linear regression produced a good correlation, $P < 0.05$, r = 0.899, the equation being:

$$m_1 = 238 - 1.79D \quad (3)$$

where m_1 = slope of first linear regression; D = B.P. disintegration time in min.

Additionally, supporting the working hypothesis, a good correlation was found between the log of the

Table 2. *Phenylbutazone tablets B.P.: dissolution and disintegration data.*

Brand	Disintegration time using B.P. apparatus min	Disintegration time 10 mesh basket min	t_{60} min
A	25·75	34	27
B	11·50	9	27
C	52·50	27	37·5
D*	—	65	57
E	42·25	420	92
F	120	420	210

* Enteric coated tablets.

Table 1. *Regression analysis of surface area/log time for 6 commercial brands of phenylbutazone tablets B.P.*

Brand	Orifice tube μm	Deaggregation phase: Slope cm²/log min	Intercept cm²	r	Confidence	Dissolution phase: Slope cm²/log min	Intercept cm²	r	Confidence	Tmax	Surface area max. Smax
A	140	74·3	−6·6	0·9818	$P = <0.001$	−101·06	258·7	0·9466	$P = <0.1$	32·6	105·8
	2000	69·0	−35·3	0·997	$P = <0.01$	−80·08	146·2	0·9561	$P = <0.01$	16·5	48·7
	140 + 2000	143·3	−41·9			−181·14	404·96			23·84	155·47
B	140	100·1	−27·3	0·9855	$P = <0.01$	−83·98	222·8	0·8915	Not sig.	22·8	108·7
	2000	154·3	−121·3	1·000	$P = <0.001$	−42·3	80·7	0·9586	$P = <0.01$	10·65	37·2
	140 + 2000	254·4	−148·6			−126·28	303·5			15·4	153·5
C	140	74·9	−20·7	0·9821	$P = <0.001$	−100·25	228·2	0·9818	$P = <0.02$	26·37	85·74
	2000	102·0	−56·3	0·9989	$P = <0.05$	−70·2	127·6	0·9954	$P = <0.001$	11·69	52·6
	140 + 2000	176·9	−77·0			−170·45	335·8			17·62	143·41
D*	140	149·9	−170·97	0·9765	$P = <0.01$	−51·1	174·2	0·9891	$P = <0.01$	52·2	86·4
	2000	15·7	−10·2	0·7764	$P = <0.1$	−37·2	78·7	0·966	$P = <0.05$	47·9	16·2
	140 + 2000	165·6	−181·17			−88·3	252·9			51·2	101·9
E	140	53·3	−21·2	0·9542	$P = <0.02$	−81·2	164·6	0·9858	$P = <0.02$	24·1	52·4
	2000	85·7	−77·1	0·8723	$P = <0.05$	−82·1	144·0	0·9730	$P = <0.05$	20·78	35·8
	140 + 2000	139·0	−98·3			−163·3	308·6			22·2	88·8
F	140	10·6	−7·34	0·9387	Not sig.	−25·6	49·0	0·9178	$P = <0.05$	14·0	19·51
	2000	12·2	−8·6	0·9866	$P = <0.02$	−16·0	31·4	0·9199	$P = <0.05$	26·2	8·70
	140 + 2000	22·8	−1·26			−41·6	80·4			18·5	27·65

r = regression coefficient • Enteric coated tablets

slope of the second linear regression (i.e. the declining phase) m_2 and t_{60} ($P < 0.05$, $r = 0.8414$) indicating that this phase was dissolution rate controlled.

$$\log m_2 = 2.281 - 0.0029 t_{60} \quad (4)$$

Comparison of the disintegration times using the B.P. method and the basket disintegration times, shows that although the values differ they are still in rank order with the exception of brand C (Table 2). The numerical differences between the two methods are probably due to the differing modes of agitation and to the interpretation of the end point, since although subcoating may remain above the 10 mesh screen, core material must pass through. In some formulations, notably brand C and brand F, a proportion of core fragments continued to adhere to the subcoating making the measurement of a precise disintegration time in the B.P. apparatus highly subjective. No correlation was found to exist between disintegration time and dissolution rate. With similar dissolution rates, brand A exhibited more than twice the disintegration time of brand B. However, in brand F, the inability to disintegrate completely produced a long t_{60} and a correspondingly low maximum generated surface area. It does seem, therefore, that disintegration time measurements of coated tablets, because of the subjectivity of measurement and lack of correlation with dissolution rate will only indicate gross dissolution differences between tablets and that in any case the end-point of 60 min is much too lenient. Indeed, long disintegration times have also been questioned recently by Sandell & Mellström (1975) for other coated tablets. Phenylbutazone is known to cause necrosis of the gastric lining and any large drug aggregates remaining on the coating material and in contact with the stomach wall will cause a localized high concentration likely to produce ulceration.

Wells & Rubinstein (1976) found a good correlation between T_{max} and the B.P. solution rate of digoxin tablets B.P. No such correlation was found for phenylbutazone tablets. For digoxin tablets the T_{max} values varied from 2·07 to 24·20 min, whereas with phenylbutazone, the values only varied from 15·40 to 23·84 min (excluding the enteric coated product). For a low dosage tablet, where the drug to excipient ratio is extremely low, the maximum surface area generated (S_{max}) will be almost totally dependent upon the excipients and therefore no meaningful correlations with S_{max} were found for digoxin tablets, the drug to excipient ratio being about 0·0025. However, for phenylbutazone tablets, where the ratio is about 0·83, the drug will largely determine the maximum surface area attained and this explains the good correlation between S_{max} and dissolution rate for phenylbutazone tablets, where T_{max} varied little between the brands. For enteric coated tablets exemplified by brand D, a long initial lag time before onset of the generated surface area increase was found (12·4 min). This was due to the enteric coat and compared with values of 1·1–5·1 min found for the other brands.

The general conclusions from this work are that this new surface area generated test apparatus sensitively monitors the rate and extent of tablet breakdown and drug dissolution. It may thus provide a useful quality control and diagnostic tool for indicating the *in vitro* performance of formulated tablets.

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