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The influence of test conditions on the disintegration time of gelatin capsules

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The British Pharmacopoeia test for capsule disintegration is basically the same test as that used to measure tablet disintegration and as such it has some shortcomings, particularly in the determination of the end point. The results were significantly affected by the capsule size, the nature of the test solution, the temperature, and whether single capsules were tested instead of groups of five. The effect of temperature on capsule solubility was demonstrated. A modified test was applied to both hard and soft capsule products selected from the British Pharmacopoeia. Recommendations are made for new specifications for an official pharmacopoeial test.

The British Pharmacopoeia 1968 uses for the "Disintegration test for capsules" the same test and apparatus as that used for tablets except that a repeat test using a guided disc is not permitted. One of the main problems with the capsule disintegration test is the determination of a finite end point. The official apparatus was designed for tablets (Hoyle, 1946; Prance, Stephenson & Taylor, 1946) and when applied to capsules, with their different physical properties, it has given rise to a number of problems. Capsules disintegrate by first opening at the weakest point, the radius or seal, releasing the contents and leaving a partly dissolved empty shell (Czetsch-Lindenwald, 1962). The end point as defined by the British Pharmacopoeia is "the capsules are disintegrated when no particle of solid remains above the gauze which would not readily pass through it". The exact determination of this point is difficult because as the capsule disintegrates it releases its contents and leaves an adhesive gelatin mass. A more exact end point would be when all the capsule and its contents have passed through the mesh, and on this basis experiments have been made to examine the effect of altering some of the test variables on the disintegration time of hard gelatin capsules.

METHODS

Effect of temperature on capsule solubility

The solubility of capsules was measured at different temperatures using the method of Boymond, Sfiris & Amaker (1966). This consists of placing a ball-bearing inside the capsule, suspending the capsule body in the test solution and measuring the time for it to fall from the capsule.

Five capsules were placed in holders in a strip of stainless steel, the diameter of each hole being such that the body and not the cap could pass through. The holder was suspended over a crystallizing dish 12 cm in diameter so that the bodies were immersed in 500 ml of test solvent, which was stirred at 70 rev/min with a small blade (4·5 cm diameter) polythene stirrer, the position of which in relation to the sample holder was kept constant. The beaker was placed in a water bath and the

temperature of the test liquid maintained within $\pm 0{\cdot}2°$ of the nominal figure. The test was performed over a range of temperatures from 33° to 41° at 2° intervals. Opaque white capsules (Elanco) were used, size 0 and size 4, containing ball bearings of weight 1·046 g $\pm$ 1 mg and 0·258 g $\pm$ 1 mg and diameter 6·35 mm and 4·76 mm respectively. Two test solvents were compared, water and 0·6% hydrochloric acid solution. The end point was taken when the ball bearing hit the base of the beaker. Three determinations on groups of five capsules were made for each set of conditions.

Effect of alteration of test conditions on filled capsules

A Manesty Tablet Disintegration Apparatus Mark II was used. This complies with the specifications of the British Pharmacopoeia 1968. The tests were made at $37° \pm 0{\cdot}2°$ which was achieved by placing the centre tube and rack assembly of the apparatus in a Techne Tempette water bath. The end point was taken as the time at which no further particles of capsule shell or contents remained above the mesh. Opaque white capsules were used throughout to aid in the observation of this end point which was made directly from above the tubes.

Five factors were varied and each tested at two levels: the test solution (W) and its container (B), the capsule size (S) and contents (C) and the treatment of the surface of the apparatus (T). The British Pharmacopoeia specifies water (W_1) as the test solvent. This was compared with 0·6% hydrochloric acid solution (W_2) which is used in the monograph for Erythromycin Estolate capsules and for enteric coated products. The quantity of water is defined as "having a depth of not less than 15 cm" but it does not indicate the volume or size of the container. Two sizes of beakers were compared; one 4·5 cm diameter (Manesty Apparatus) (B_1) containing 250 ml at 15 cm depth; and one 9·0 cm diameter (1 litre tall-form) (B_2) containing 950 ml at 15 cm depth. Two sizes of hard gelatin capsules were compared, a large capsule size 0 (S_1) and a small capsule size 4 (S_2). Two common pharmaceutical diluents were compared, lactose B.P. (C_1), which is soluble, and starch B.P. (C_2), which is insoluble. These were filled into capsules by hand to ensure well-packed capsules having fill weights within $\pm 5\%$. As gelatin becomes adhesive when it melts, an attempt to prevent the capsule adhering to the sides of the tube and the mesh was made by treating the apparatus with an aerosol silicone release agent (T_1); comparative tests were made with an untreated apparatus (T_2).

Two series of experiments were performed in a 2^3 factorial experiment in a full factorial design (Davies, 1960). Series I experiments compared medium, capsule size and capsule contents, Series II experiments compared container size, capsule size and untreated and siliconed apparatus.

In Series I experiments the apparatus was treated with an aerosol silicone release agent. In Series II experiments the test solution was 0·6% hydrochloric acid solution and the capsules were filled with equal parts of starch and lactose. Each series consisted of two sets of experiments, one using a sample of five capsules as specified in the British Pharmacopoeia and the other using single capsule samples. Six replicates were made for each set of conditions.

Effect of modified test on B.P. capsule products

Experiments were made with hard and soft capsule products, randomly selected from those included in the 1968 B.P. and the addendum 1969 to the B.P., to assess the effect of using 0·6% hydrochloric acid instead of water and of using single capsules

instead of samples of five. For the single capsule test, six determinations were made for each product. The temperature was maintained at 37° ± 0·2°. The test solution container was a beaker 4·5 cm in diameter. The end point was taken as the time at which no further particles of capsule remained above the mesh. For single capsules the disintegration time of each capsule was recorded and that for the slowest sample was the one used.

RESULTS AND DISCUSSION

The end point in the disintegration test as defined in the British Pharmacopoeia involves a decision being taken on what would readily pass through the mesh in the test apparatus. The course of capsule disintegration shows that the last particle to remain is usually a piece of adhesive shell which sticks to the mesh and the end point is taken at the time when all the capsule and its contents has dissolved or disintegrated. The behaviour of the last fragments of capsule shell appear to be the rate controlling step in most of the experiments, except for capsules filled with non-wetting insoluble materials where the contents remain and are the final particles to pass through the mesh.

The analysis of variance showed that two factors have a significant effect on disintegration time; the nature of the test solution and the capsule size. There is a significant difference between the results obtained with single capsules and samples of five; five capsules always took longer to disintegrate (see Table 1).

Table 1. *Effect of altering test variables on the disintegration time (s) of capsules.* Mean figures of six replicates.

Sample size	Contents	*Disintegration time (s) for capsules of sizes:* 0(s_1)	4(s_2)	0(s_1)	4(s_2)	
		Series I experiments, variables:				
		Water (W_1)		Acid (W_2)		
5	Lactose (C_1)	544	538	493	387	mean
5	Starch (C_2)	619	447	498	372	488
1	Lactose (C_1)	495	377	353	330	mean
1	Starch (C_2)	463	368	282	273	368
		Series II experiments, variables:				
	Treatment	(B_1) (4·5 cm)		(B_2) (9·0 cm)		
5	Untreated (T_1)	689	496	636	517	mean
5	Siliconed (T_2)	533	506	558	462	550
1	Untreated (T_1)	488	362	555	392	mean
1	Siliconed (T_2)	452	383	558	377	433

The instruction to take five capsules in the official test presumably has the intention of evaluating intra-batch variation in disintegration, the end point being the breakdown of the slowest capsule to disintegrate. In practice this appears not to occur because after the contents have emptied from the shells these collapse and if they come into contact with each other they form an adhesive mass, the thickness of which may be several times that of a normal capsule. The larger the size of the capsules the greater the probability of agglomeration. This we believe to be the reason why the size factor had a greater effect in our experiments with samples of five capsules than in individual trials. In all our experiments, the size of capsule

was a significant factor because it affected the numbers of wires in the mesh that became coated with gelatin as the shell collapsed, the greater the number of wires coated the longer the shell took to dissolve. A measure of intra-batch variation can best be obtained, therefore, by measuring individual capsules in replicate. For tablet testing, the U.S.P. XVIII has adopted the use of six replicates.

In the single capsule experiments there was a significant interaction between beaker and capsule size effects (see Table 3). The size of the beaker affects only the results on the larger size capsules; capsules take longer to disintegrate in the larger beaker. A separate parts analysis showed that beaker size and capsule size were both significant as main effects except at the size 4 (S_2) levels. This we believe to be due to the fact that as the beaker diameter decreases, the amount of turbulence caused by the reciprocal motion of the tube increases, which is significant only with the larger size capsules and reflects the retarded dissolution of the final pieces of shell.

Treatment of the apparatus with a silicone release agent did not produce a significant effect on the results (see Table 3). The adhesion of the final particles of capsule shell to the mesh was not prevented, but it was apparent during the tests that the capsule contents did not coat the surface of the test tube or mesh.

The effect of changing the test medium from water to an acid solution significantly shortened the disintegration time as shown in Tables 1 and 2. An acid solution more closely approximates to the *in vivo* situation. The Czechoslovakian (3rd edition, 1970) the German (B.R.D. VIII, 1968) and the Japanese (1961) Pharmacopoeias have all adopted an acid solution for this test.

The change in rate of solution of empty capsules over the range 35°–39° of the B.P. test was shown to be about 30% (see Fig. 1). There was no significant difference between acid and water but there was a difference between capsule sizes. These variations were probably caused by the mechanical conditions of the test and the way in which the ball bearing left the capsule. Some fell straight through the bottom of the capsule whereas others were held suspended by strands of gelatin after the shell

Table 2. *Effect of altering test variables on the disintegration time of capsules. Magnitude of effects.* All results subtracted from means (x) of each experiment in Table 1.

Sample size	Contents	*Disintegration time (s) for capsules of sizes:* 0(s_1)	4(s_2)	0(s_1)	4(s_2)
		Series I experiments, variables:			
		Water (W_1)		Acid (W_2)	
5	Lactose (C_1)	+56	+50	+5	−101
5	Starch (C_2)	+131	−41	+10	−116
1	Lactose (C_1)	+127	+9	−15	−38
1	Starch (C_2)	+95	0	−86	−95
	$\bar{x}$ for sample of 5 capsules = 488 s	for sample of 1 capsule = 368 s			
		Series II experiments, variables:			
	Treatment	(B_1) (4·5 cm)		(B_2) (9·0 cm)	
5	Untreated (T_1)	+149	−54	+86	−33
5	Siliconed (T_2)	−17	−46	+8	−88
1	Untreated (T_1)	+55	−71	+122	−41
1	Siliconed (T_2)	+19	−50	+125	−56
	$\bar{x}$ for sample of 5 capsules = 550 s	for sample of 1 capsule = 433 s			

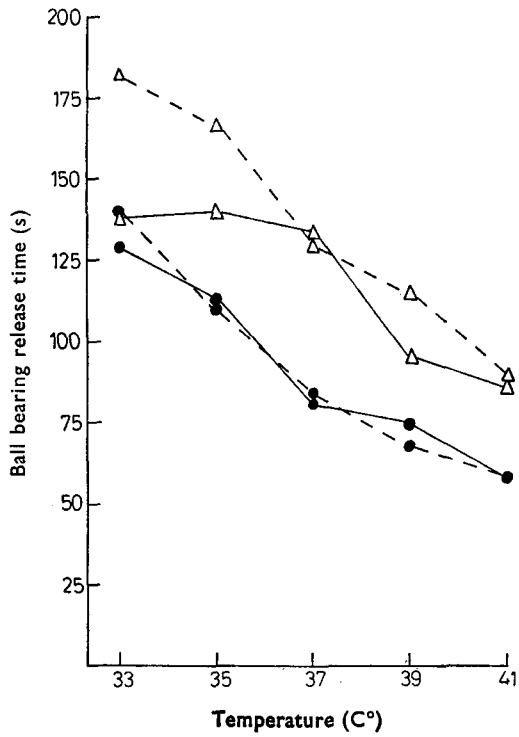

FIG. 1. The variation of capsule solubility with temperature. Each point represents the mean of fifteen determinations using opaque white capsules. △ = size 0 capsules; ● = size 4 capsules; —— = in 0·6% hydrochloric acid solution; — — = in water.

Table 3. *Statistical analysis of changes in the test variables on the disintegration time of hard gelatin capsules.* The figures in this table represent the variance ratios (F).

Effect	Source	Sample 5	Sample 1	Source	Sample 5	Sample 1
Main factors ..	Medium (W)	16·97**	64·72**	Beaker (B)	0·12	(14·40) +
	Size (S)	17·83**	34·15**	Size (S)	7·99**	(111·82)+
	Contents (C)	0·08	1·66	Treatment (T)	3·28	(0·10)+
Interaction between pairs	W × S	0·31	2·28	B × S	0·00	8·56**
	W × C	0·01	0·02	B × T	0·06	0·08
	S × C	3·81	0·38	S × T	1·47	0·01
Interaction of all factors	W × S × C	2·42	0·03	B × S × T	0·82	2·58

+ Approximate figures, invalidated by interaction B × S.

** Highly significant.

At $P = 0{\cdot}05$, F = 4·08 and at $P = 0{\cdot}01$, F = 7·31 (Fisher & Yates, 1963).

had collapsed. The other experiments with filled capsules indicated that the last piece of capsule to remain above the mesh was a piece of shell. Therefore any change in gelatin solubility caused by faulty temperature control could materially alter the results. A reduction in the temperature range would be expected to give more reproducible results.

The results obtained in the modified test on B.P. capsule products were analysed statistically using a non parametric significance test, the Wilcoxon matched-pairs signed-ranks T test (Beyer, 1968). For samples of 5 capsules ($n = 29$) $T = 299$ at $P = 0{\cdot}05$ $T = 141$ and at $P = 0{\cdot}01$ $T = 111$; and for single capsules ($n = 28$) $T = 165$ at $P = 0{\cdot}05$ $T = 130$ and at $P = 0{\cdot}01$ $T = 102$. These showed that the results taken in acid solution were significantly different from those in water. The approximate mean times for the experiment were: samples of 5 capsules in acid = 550 s and in water = 800 s; and samples of single capsules in acid = 480 s and in water 570 s. The disintegration times were shorter in acid solution than in water and shorter when single capsules were tested rather than samples of five. Not all products are soluble in acid solutions and, because of this, cloxacillin and phenoxymethylpenicillin capsules produced a fine adhesive powder that coated the mesh.

The experiments showed that if a finite end point is taken "the time for all the capsule to pass through the mesh" certain test conditions need to be redefined. To obtain a measure of intra-batch variation and to obtain a more distinct end point, the test sample should be a single capsule and six replicates should be performed simultaneously. If this is done the diameter of the test beaker needs to be defined to control the volume of the test solution and to overcome some of the effects of capsule size on the results. The use of 0·6% hydrochloric acid solution, although it shortens disintegration in most cases, cannot be applied universally and consideration needs to be given to the nature of the capsule contents. To improve the reproducibility of results the temperature range over which the test is performed needs to be narrowed.

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