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The effect of media and other variables on the BP solution rate test for slow lithium carbonate tablets

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The British Pharmacopoeial test for assessing the solution rate of slow lithium carbonate tablets has been evaluated using 'controlled release' tablets containing 400 mg of lithium carbonate. No significant differences in lithium release were found when the volume of media used in the test was reduced from 250 ml to 200 ml, the final stage of the test in pH 6·8 phosphate buffer reduced from 5 to 3 h, the number of tablets in each thimble reduced from three to one, or the prescribed phosphate buffers replaced with phthalate and Tris, respectively. A four-fold increased concentration of phosphate in the phosphate buffers used resulted in a significant retardation in lithium solution rate. This was not attributable to an ionic strength effect but possibly to the formation of trilithium phosphate at the interface. Dissolution studies using the USP Basket Method showed a significantly slower release rate of one tablet into 900 ml of phosphate buffer compared with Tris buffer. This difference was markedly increased when three tablets were investigated in 200 ml of similar media. These differences were considered to be due to the formation of the much less soluble trilithium phosphate in the phosphate buffers.

The British Pharmacopoeia (BP) (1980a) describes a novel method for assessing the solution rate of slow lithium carbonate tablets. The method involves a modification of the BP (1973) disintegration apparatus and a unique technique to obtain data that are assessed against set criteria. The test involves an evaluation of 3 × 400 mg lithium carbonate tablets placed in an extraction thimble in a tube of the disintegration apparatus. Release is sequentially evaluated into a 0·6% v/v solution of hydrochloric acid (≤30% release in 2 hours) followed by two phosphate buffers, one of pH 6·0 (≥30% and ≤50% release in one further hour) and the other of pH 6·8 (≥70% and ≤95% in 5 further hours) with the continued operation of the apparatus. A criterion that prescribes less than total release of lithium carbonate after 8 h, may warrant further consideration for a drug known to induce diarrhoea when it enters the large bowel (Borg et al 1974). This is the only pharmacopoeial standard test known to the authors that describes a solution rate test for a slow release tablet formulation. The BP (1980b) included a statement that the present test has only been retained until a more satisfactory one is developed.

Recently, we reported that the intrinsic dissolution rates of lithium carbonate discs were markedly reduced in phosphate buffer due to the formation of trilithium phosphate on the surface of the discs (Wall et al 1985). As the BP (1980a) test results in high concentrations of lithium ion in the dissolution medium, any formation of trilithium phosphate during dissolution could influence the test results. The effect of phosphate buffers on the dissolution of slow lithium carbonate tablets has been evaluated to determine if such an effect occurs.

The basket method, which is commonly used in dissolution rate testing, has also been modified to provide data in media volumes similar to those used in the BP test.

MATERIALS AND METHODS

Lithium carbonate tablets were Priadel (Delandale Laboratories) batches 5404 and 820615X3. These tablets were labelled 'controlled release tablets each containing 400 mg Lithium Carbonate BP' but complied with the drug content and diameter specifications for Slow Lithium Carbonate Tablets BP. All other materials used were of AR grade. Water was de-ionized water distilled from an all-glass still.

BP solution rate test

Solution rate tests were carried out in a disintegration apparatus (Manesty, Liverpool), conforming with that described in the BP (1973). Durable extraction thimbles 80 mm long and 22 mm internal diameter (Whatman) were inserted in the tubes of the apparatus. Three tablets were placed inside each thimble for the standard tests. Tests were carried out

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at least in quadruplicate. Unless stated otherwise, the media used were those prescribed by the BP (1980a). All samples were replenished to their original volumes before analysis.

USP basket method

The apparatus conformed with the United States Pharmacopeia (1980a) requirements (Hanson Research Corp., USA). In all cases the basket method was employed. The first set of experiments involved six tablets tested individually in 900 ml of media at 37·0° ± 0·1 °C and 60 rev min^{-1}. The media were Simulated Intestinal Fluid USP (1980b) without addition of pancreatin (SIF), or Tris buffer of similar pH, buffer capacity and ionic strength (adjusted with sodium chloride). Samples of 5 ml were removed with replacement at pre-determined intervals with total release evaluated at >24 h. A second set of experiments involved testing three tablets at 100 rev min^{-1} within each basket and release evaluated into 200 ml of phosphate buffer pH 6·8 as prescribed in the BP (1980a) for the solution rate test for slow lithium carbonate tablets at 37 ± 0·1 °C. At least four replicates were studied and the media were placed in beakers of 55 mm internal diameter and 140 mm deep and the baskets centred within each beaker. In these studies 2 ml samples were collected with replacement at appropriate time intervals and total release was evaluated at >24 h.

Lithium analysis

Analysis of lithium was by flame emission spectrophotometry as previously described (Wall et al 1982). Statistical differences were evaluated using Student's *t*-test for unpaired comparisons, significant differences being assigned at the $P \leq 0{\cdot}05$ level.

RESULTS AND DISCUSSION

BP solution rate test

Data obtained from studies carried out using the BP solution rate test, or modifications of this test, are summarized in Table 1. The BP requirements for compliance with the test are applied to the results for a single set of three tablets evaluated. Data generated under condition 2 were used to evaluate the statistical significance of subsequent modifications to the test. The test contains no requirement for replicates and hence no guidance is provided for mean data. This is at variance with data from dissolution tests on conventional tablets using the basket method. Owing to this situation, data in Table 1 provide results from one set of three tablets that best represents the replicates tested, under the stated conditions.

It is evident that there is considerable variation in the data, especially that from the pH 6·8 phosphate buffer (column 4). Presumably a less consistent release of the remaining 30–40% of drug is a factor contributing to the variability. Table 1 also indicates

Table 1. The effect of modifications to the BP test on the dissolution of slow lithium carbonate tablets.

	% of Lithium carbonate released (mean ± s.d.)		
Conditions employed	HCl (0·6%)	Phosphate (pH 6·0)	Phosphate (pH 6·8)
1. Mesh of tube just cleared media surface	44·8 (42·1 ± 2·3) F[a]	62·7 (57·6 ± 2·3) F	79·2 (77·9 ± 10·2) P
2. 200 ml of media[b] used	43·6(44·3 ± 2·7) F	59·4 (58·4 ± 3·1) F	89·6 (84·9 ± 9·6) P
3. Replace phosphate buffers with phthalate and Tris at the same pH and ionic strength	45·5 (47·5 ± 2·9) F	66·9 (68·2 ± 2·9) F (Phthalate)	89·0 (84·0 ± 10·0) P (Tris)
4. Time in pH 6·8 buffer reduced from 5 to 3 h	48·9 (45·1 ± 2·9) F	66·5 (58·5 ± 2·8) F	82·6 (81·8 ± 10·1) P
5. Evaluating one tablet instead of three	46·0 (48·2 ± 2·4) F	69·0 (67·1 ± 2·8) F	81·4 (78·6 ± 3·4) P
6. Phosphate buffer concns increased to 0·20 mol dm^{-3}	35·1 (37·0 ± 2·9) F	43·1 (45·9 ± 4·0) P[c]	52·4 (53·7 ± 6·9) F[d]
7. Batch 820615X3	48·8 (48·4 ± 1·7) F	59·5 (61·2 ± 1·5) P	77·5 (79·2 ± 2·0) P
8. Batch 820615X3 in phosphate buffers of ionic strength 0·2 ml dm^{-3} (NaCl)[e]	47·2 (47·8 ± 3·9) F	61·8 (63·4 ± 1·8) P	85·3 (83·4 ± 1·6) P

[a] BP test criteria for each stage; F = fail; P = pass.
[b] All subsequent evaluations were in 200 ml of media.
[c] Significantly different ($P < 0{\cdot}01$) with data in Set 2.
[d] Significantly different ($P < 0{\cdot}02$) with data in Set 2.
[e] Identical phosphate buffer concentration as in Set 7 but ionic strength adjusted with NaCl.

compliance of the representative set of data with BP requirements.

The BP does not state an exact volume of fluid to be used in the test. Data generated from condition 1 (Table 1) in which the mesh at the bottom of the tube when raised to the uppermost position just cleared the surface of the media, required that 250 ml of fluid be present in the beakers. These data were not significantly different from those generated under condition 2 where the volume of media used was 200 ml. No significant differences were found when the final stage of the test (in pH 6·8 phosphate buffer) was reduced from 5 h to 3 h, (condition 4), the number of tablets in each thimble reduced from three to one (condition 5), or the prescribed phosphate buffers were replaced with phthalate and Tris of similar pH and ionic strength, respectively (condition 3). A significant difference was found when the concentration of phosphate in the phosphate buffers was increased from the specified 0·05 mol dm^{-3} to 0·20 mol dm^{-3} (condition 6), but otherwise identical conditions were used. The ionic strengths of these media were not the same, but experiments where sodium chloride was added to the 0·05 mol dm^{-3} phosphate buffer specified in the BP test to give phosphate buffer of ionic strength equivalent to 0·2 mol dm^{-3}, gave results that were not significantly different from the data from the 0·05 mol dm^{-3} buffers.

Two of the three media prescribed for the BP test are phosphate buffers. Under the conditions involved in intrinsic dissolution testing, trilithium phosphate was found to be precipitated on to the surface of the discs (Wall et al 1985). The BP requires that three 400 mg lithium carbonate tablets be analysed in each thimble. Since the volume of fluid is low (200–250 ml) and non-sink conditions apply (based on lithium carbonate) it was of interest to determine if these conditions gave rise to the type of interaction encountered in the intrinsic dissolution experiments. It could be concluded that if an interaction occurred its effect would not be statistically significant. The inherent variability in the last stage of the test may mask such an interaction. Such an interaction could also contribute to the variability of the data derived from the pH 6·8 phosphate buffer variation (column 4). The data derived from Tris buffer (Table 1, column 3) do not support this. A four-fold increase in phosphate concentration in the buffer did induce a statistically significant retarded release of lithium ion.

Any interaction that might have occurred may be limited, compared with the intrinsic dissolution interaction, for a number of reasons. Under the test conditions, 40–50% of the lithium carbonate content was removed in the first stage into hydrochloric acid. This is well in excess of the ≤30% prescribed by the BP (1980a). The conditions of the test also may not be conducive to a saturated layer of solution being formed in contact with the tablet surface. The movement of the tablets in and out of the fluid may be a factor, although some fluid always remained in the thimbles in contact with the tablets. However, increasing the concentration of phosphate in the buffers must overcome the factor(s) involved since the amount of lithium carbonate released is significantly retarded. The lack of conformity of batch 5404 with the BP criteria caused us to evaluate a second batch (820615X3) but this also gave similar results although the variability of release into pH 6·8 buffer was lower from this batch.

Some methodological difficulties were encountered in performing the BP test. Change-over from one solution to the next was complicated and required that sufficient time be allowed for complete drainage from the thimble and tube. Splashing also tended to occur, particularly in the first few minutes of the first stage. This was reduced by using 200 ml of fluid and hence the liquid of each tube was well below the mesh raised to its full height. Prior wetting of the thimbles with some media also reduced splashing and the tendency of the thimbles to work their way up the holding tube and out of the dissolution media. It was also found that the temperature of the medium inside the thimbles was 2–3 °C lower than that in the cylinder of fluid.

Dissolution studies using the basket method

Although the rotating basket method has not been applied as a pharmacopoeial standard for testing the dissolution rate of 'controlled release' tablets it is frequently used for conventional tablets. Dissolution data obtained by this method can be subjected to greater analysis than the BP test for slow lithium carbonate tablets.

Fig. 1a shows the comparative release patterns from one Priadel tablet (Batch 5404) into simulated intestinal fluid (SIF) (a phosphate solution) and also into Tris buffer. Near the end of the release it can be seen that statistically significant differences occurred between the percentage released into SIF and into Tris buffers. These differences are clearly demonstrated in the first-order release plot (Fig. 1b). The profile in SIF departs from first-order release and increasingly slows after 90 min.

Dissolution studies were also carried out on three

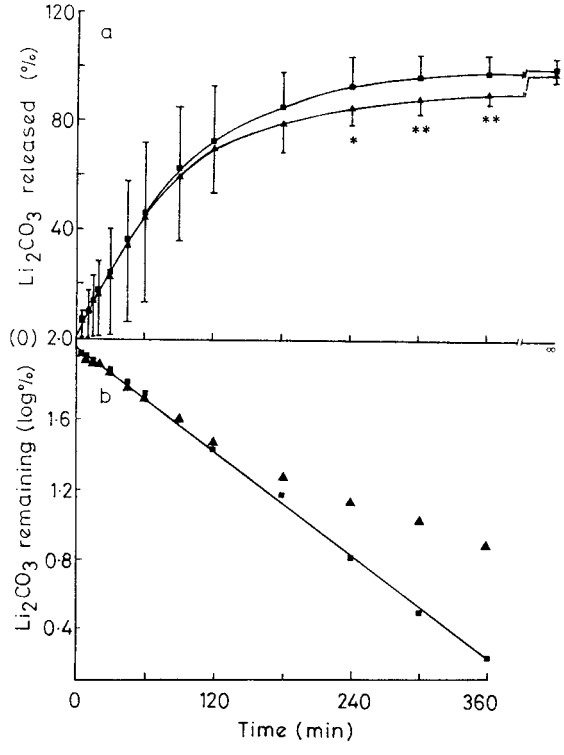

FIG. 1. (a) Mean (±2 s.d.) dissolution rates for one tablet evaluated in 900 ml of Tris ■——■ and SIF ▲——▲. * $P < 0.01$, ** $P < 0.001$. (b) First-order release plot of the mean data from (a). The line illustrates the least squares fit of data in Tris buffer.

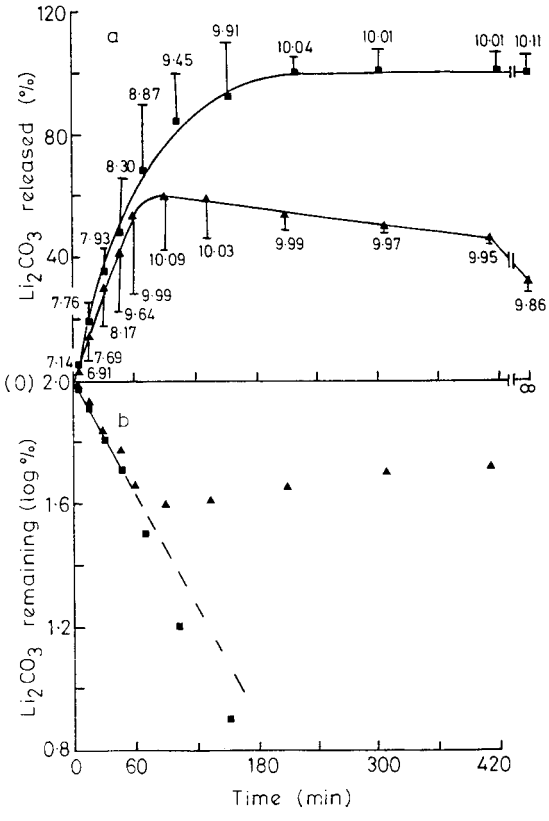

FIG. 2. (a) Mean (±2 s.d.) dissolution rates for sets of three tablets evaluated in 200 ml of Tris buffer ■——■ and a phosphate buffer of pH 6·8 ▲——▲. The pH values of the bulk solution are shown adjacent to each point. (b) First-order release plot of the mean data obtained from (a). The broken line is extrapolated from the least squares fit, applied to the initial four points of data obtained in Tris buffer.

tablets using the rotating basket apparatus. These experiments used a similar volume of fluid to that used in the BP tests. A pH 6·8 phosphate buffer, as prescribed by the BP for the solution rate test, was used. It is evident (Fig. 2) that a maximum of 60% of the lithium carbonate was released and this occurred at approximately 90 min. Subsequent samples showed a loss of lithium carbonate from the solution, this effect being emphasized in the infinity time sample. The gradual loss of lithium ion from solution is likely to be due to the formation of trilithium phosphate, as was found in the intrinsic dissolution studies (Wall et al 1985). Trilithium phosphate has a solubility of 0·434 g $litre^{-1}$ at 37 °C (Wall 1978) compared with lithium carbonate which has a solubility of 11·9 g $litre^{-1}$ at 37 °C (interpolated from data of Linke 1965).

Since trilithium phosphate is approximately 27-fold less soluble, only 86·8 mg of it needs to be formed (≈7% of the lithium carbonate in solution at total release) before precipitation will occur. The common ion effect of Li^+ in solution would be expected to depress further the solubility of trilithium phosphate in the experimental conditions used, giving rise to precipitation of trilithium phosphate at lower concentrations. Further support for the possible formation of trilithium phosphate is provided from the pH measurements of the bulk solution (Fig. 2a). It is clear the buffer has insufficient capacity for this system and the bulk pH has risen to a maximum value of 10·09 after 90 min of dissolution. The slight lowering of pH at longer time intervals may be due to the precipitation reaction.

An investigation under similar conditions using Tris buffer of similar pH and ionic strength showed complete release of lithium carbonate after 220 min (Fig. 2a). However, the pH rise was slightly retarded compared with phosphate, to a value 10·04 at 100% release and this value (approx.) was maintained.

It must be emphasized that the conditions used in these experiments are not the same as those prescribed for the solution rate test of the BP (1980a). Initially, with the BP test, there is a requirement to remove ≤30% of the 1200 mg of lithium carbonate into hydrochloric acid. A further stepwise extraction of ≥30% to ≤50% is required into a phosphate buffer of pH 6·0 before final testing in a pH 6·8 phosphate buffer where the total amount released is required to be ≥70% and ≤95%. However, when one 400 mg tablet of lithium carbonate was tested in 900 ml of phosphate buffer (Fig. 1a,b) there is clear evidence of an interaction. Data in Fig. 2a,b provide confirmation by indicating a markedly enhanced effect. With the phosphate buffer (SIF) used to derive Fig. 1a, the pH of the bulk solution only increased by 0·5 of a pH unit through the course of the run. Hence the interaction must occur in the saturated layer at the surface of the tablet where the pH is much higher, providing there is sufficient concentration of PO_4^{3-} to induce precipitation.

The rate constants for the dissolution of lithium carbonate into Tris buffers, obtained from Figs 1b and 2b are 1·15 and 1·37 × 10^{-2} min^{-1}, respectively. The latter value was obtained from the first four points since later points show faster release. This may have been due to the tablet formulation since greater than 50% of drug had been released from the tablet at this stage. Considering the rate constants have been obtained under different experimental conditions, they are in acceptable agreement.

It is concluded that experiments made with the basket method for dissolution have clearly demonstrated an interaction of lithium carbonate released from tablets with phosphate buffers. Although no significant interaction could be demonstrated in the phosphate buffers prescribed in the BP solution rate test, under the conditions of that test a propensity for the interaction to occur exists.

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