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▲ To whom inquiries should be directed.

TECHNICAL ARTICLES

Dissolution Profiles for Capsules and Tablets Using a Magnetic Basket Dissolution Apparatus

R. E. SHEPHERD, J. C. PRICE▲, and L. A. LUZZI

Abstract □ Dissolution studies were carried out on commercially available dosage forms of lithium carbonate, 300 mg. A magnetic basket dissolution apparatus was developed by the authors because of the unavailability of a single system to evaluate both capsules and tablets. The magnetic basket allowed reproducible positioning of either a capsule or a tablet in a hydrodynamic system such that the dissolution of the two different dosage forms could be studied using the same parameters. Log-probability analyses of the data showed significant differences in the dissolution of the two dosage forms. The results were highly reproducible.

Keyphrases □ Dissolution profiles, capsules and tablets—magnetic basket dissolution apparatus and method □ Lithium carbonate tablets and capsules—comparison of *in vitro* dissolution rates, magnetic basket apparatus □ Magnetic basket dissolution apparatus—dissolution rates of both tablets and capsules □ Tablets and capsules—magnetic basket dissolution apparatus and method

During recent years it has become evident to pharmaceutical scientists and the Food and Drug Administration that dosage forms of the same active ingredients manufactured using different inert materials and different techniques may not bring about the same desired blood levels of active ingredient in the same time frame. Recently, for example, this was found to be the case for chloramphenicol capsules (1) when generic and trademark products were compared.

A number of variables affect the deaggregation of a tablet or capsule and the dissolution of a drug from these dosage forms (2–6). The rate of absorption of the drug is often directly proportional to the dissolution rate of the drug from the dosage form (2). Also, different dissolution rates from different dosage forms, *i.e.*, capsules and tablets, of the same strength are a probability even when emanating from the same manufacturer (7).

A method is needed for evaluating the dissolution rates for all drug products, whether in tablet or capsule form, using the same parameters. Literature dealing with the dissolution apparatus (6, 8, 9) shows that methods are not available which are applicable to both tablets and capsules and that particular methodologies are not capable of yielding reproducible dissolution profiles. For the USP XVIII the U. S. Pharmacopeial Committee adopted a dissolution procedure and apparatus for tablets and capsules in which a single-point determination is made for an active ingredient. Evaluation of the USP apparatus (USP XVIII, NF XIII, Method I) has shown that a "sieving" action by the screen takes place and that the screen may become clogged by granules or, in the case of capsules, by gelatinous particles (6, 9). An additional problem may be the inability to maintain homogeneity of the dissolution medium.

The NF XIII Dissolution Test Method II employs the USP–NF disintegration testing apparatus, except that 40-mesh screens are used. This device has been described as having a high agitation intensity and, therefore, has the disadvantage that small differences in formulation characteristics may not be revealed (9). In addition, the 40-mesh screen specified could lead to clogging, as in the USP–NF Method I.

Table I—Analysis and Comparison of Three Commercial Lots of Lithium Carbonate, 300 mg.

Analytical Test	Product A Capsule	Product B Capsule	Product D Tablet
Uniformity of capsule fill:			
Mean capsule fill, mg.	394.93	306.81	—
Range of capsule fill, mg.	385.52–406.44	294.33–320.85	—
Standard deviation	7.14	6.93	—
Uniformity of tablet weight:			
Mean tablet weight	—	—	497.64
Range of tablet weight	—	—	485.50–502.48
Standard deviation	—	—	7.87
Content uniformity assay:			
Mean content	299.78	307.14	297.45
Range content	266.32–311.98	293.40–330.54	290.37–314.72
Standard deviation	12.57	11.14	6.71
Average percent of label claim	99.93	102.38	99.15

It has been suggested (8) that the Levy beaker method (10) is the most simple and adaptable method for dissolution rate determinations. This method, used with low agitation, allows a mounding of particles on the bottom of the beaker, which in turn seems to result in acceptable correlation between *in vivo* and *in vitro* results.

It is obvious at this time that an accurate and precise dissolution apparatus for both tablets and capsules is essential, especially when therapeutic and toxic levels of a drug are very close (*e.g.*, lithium carbonate). Presently, lithium carbonate is being marketed in 300-mg. capsule and tablet dosage forms. The therapeutic plasma levels (0.5–1.5 meq./l.) and toxic levels (1.5–2.5 meq./l.) are very close. Because of the critical proximity of therapeutic and toxic blood levels in the use of lithium and the apparent lack of simple, rapid, reproducible *in vitro* dissolution methodology to obtain profiles from both tablets and capsules, the present study was made using a modification of the Levy beaker method.

The modification allows exact placement of tablets and capsules, which ensures reproducible hydrodynamics of the system and eliminates the "floating" capsule. It was hypothesized that the data collected from such a procedure would allow examination of the dosage form which would lead to certain unique control procedures, as well as to a better method of correlation of *in vitro* and *in vivo* results for both tablets and capsules.

The purpose of this report is to show that the magnetic basket approach does yield reproducible dissolution results for both tablets and capsules.

EXPERIMENTAL

A modified beaker method was used to follow the deaggregation and dissolution of lithium carbonate tablets and capsules. The beaker method was modified with the addition of a magnetic basket holder. In addition, to maintain a constant pH in the system, a pH stat apparatus with an automatic readout assembly[1] was used.

Dissolution Apparatus—A modified Levy beaker apparatus was constructed and evaluated for this work (Fig. 1). It consists of an 800-ml. beaker with an apparatus that allows precise and reproducible placement of the dosage form to be tested. Exact placement of the basket was ensured by attaching a magnetic bar to the outer bottom of the beaker and affixing a second magnet to the cylindrical wire basket. The second magnet, with attached basket, oriented itself with exact reproducibility each time it was placed into the beaker.

The stainless steel wire basket was 50 mm. long and had an inner diameter of 11 mm. for capsules and 15 mm. for tablets. The larger inner diameter basket did not give reproducible results for these capsules, since they could assume more than one position within the larger basket. An epoxy resin and hardener[2], which is nonreactive in both acidic and alkaline solutions, was used in construction of the magnetic basket. It was constructed of 8-mesh screen (U. S. Standard) and held in place by a stiff nichrome wire (approximately 0.73 mm. in diameter) 15 mm. above the internal magnet when measured from the bottom of the cage. The wire selected was sturdy enough to prevent accidental bending during routine handling and dissolution testing. The baskets used in this study were equipped with a septum to allow precise placement of two tablets or capsules for simultaneous dissolution. The septum was added to eliminate the possibility that the two dosage forms could come together and thus alter the dissolution pattern. Each cylindrical basket was equipped with 8-mesh hinged doors opening at the ends of the cylinder. The dosage form to be tested was placed in the dry

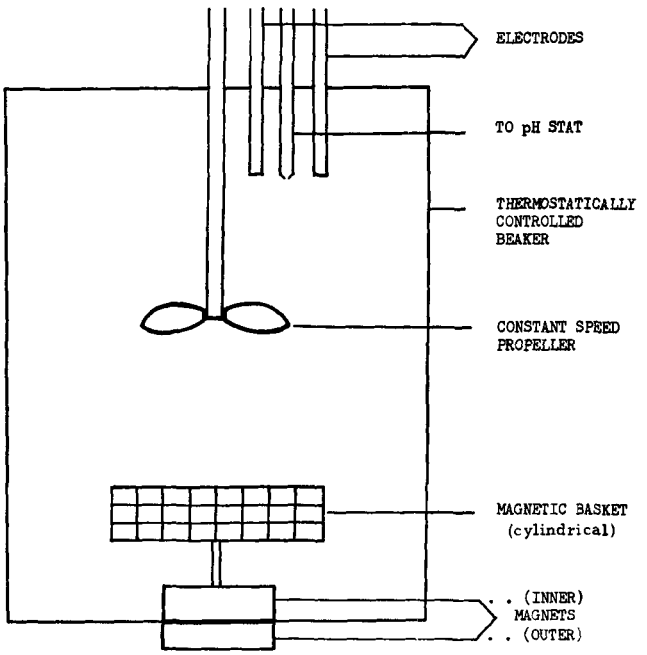

Figure 1—*Diagram of magnetic basket apparatus (not drawn to scale).*

[1] Radiometer-Copenhagen, 72 EM Drupvej, Copenhagen NV, Denmark.

[2] E-Pox-E, Woodhill Chemical Sales Corp., Cleveland, OH 44128

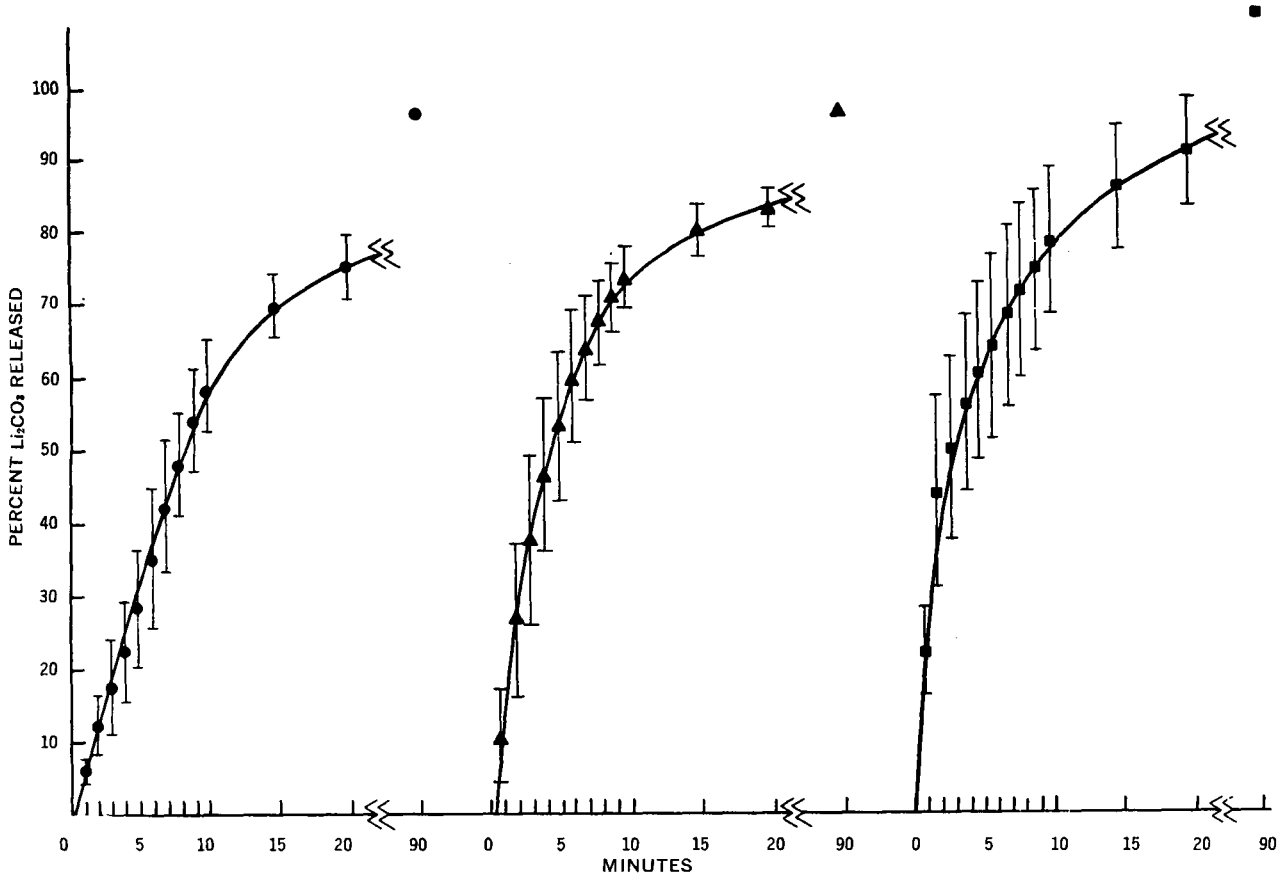

Figure 2—*Dissolution profiles for the capsule formulations at pH 3. Legend: ●, Product A; ▲, Product B; and ■, Product C. Bars indicate standard deviation from the mean.*

basket, and the basket and magnetic assembly was placed in the dissolution medium. The magnet on the basket oriented itself to the permanently attached magnet on the outside of the beaker bottom, thus assuring reproducible placement for each test.

The rate of stirring was electronically controlled at 60 r.p.m. by a constant-speed, torque-controlled unit[3] coupled to a servo motor generator[4]. A three-bladed propeller, having a stirring diameter of 51 mm., with blades set at a 60° angle to each other and 45° from vertical orientation, provided agitation. The blades had a diameter of 18 mm. and were attached to a shaft 7 mm. in diameter. Dissolution temperature was controlled by a constant-temperature, circulating water bath[5] attached to a double-walled circulating bell jar apparatus.

An 800-ml. beaker containing 600 ml. of dissolution medium was immersed in the constant-temperature jar at 37 ± 0.5° and allowed to equilibrate. During each run the propeller was centered in the beaker and immersed to a depth of 41 mm. Electrodes were immersed to a depth of 27 mm. and were 7 mm. from the beaker wall. Upon equilibration, the contents of the 800-ml. beaker were adjusted to pH 3, the magnetic basket containing the dosage form to be examined was immersed, and titration was carried out automatically at pH 3 using 1 *N* HCl as the titrant. The choice of pH 3 for the dissolution media was predicated on the reported (11) state of the unfasting stomach, which is usual for administration of this drug.

Chemicals and Materials—The capsules and tablets tested were manufactured by three different firms and were purchased locally[6]. For purposes of this study, the capsules were labeled as A and B and the tablet was labeled D. Experimental capsules were filled by the investigators and contained approximately 300 mg. of lithium carbonate and were labeled as C. Sufficient samples of tablets and capsules were obtained at one time so that all tests were carried out on only one lot number from each firm. A lithium carbonate[7] standard, which was used for atomic absorption spectroscopy, was prepared by passing the material through a No. 30 mesh screen (U. S. Standard), drying it at 110° for 24 hr., allowing it to cool in a desiccator, and assaying titrimetrically.

Analytical Methods—An atomic absorption spectrophotometer[8], equipped with a lithium hollow cathode lamp, was used to assay dosage units from each lot and dissolution medium samples for the tablet determinations. Capsule dissolution rates were followed *via* the pH stat readout, while tablet dissolution was followed by atomic absorption analysis (12). In addition, selected confirmatory determinations were carried out for each capsule run using the atomic absorption instrumentation. Suitable standards and blanks were prepared for use in these assays (13). Filtered samples were taken using a volumetric pipet fitted with a cotton plug.

RESULTS AND DISCUSSION

USP XVIII capsule and tablet weight variation determinations were carried out for the commercial products, and the products met the requirements specified. These results, along with the analytical results from the content uniformity assays, are shown in Table I.

To evaluate the dissolution of lithium carbonate dosage forms from the available commercial sources, it was first necessary to design an apparatus for both capsule and tablet dosage forms. Preliminary work using available methods, those in which the capsule is allowed to float in the dissolution medium or in which a wire spiral is used to hold the capsule, did not yield reproducible

[3] Model 4425, Cole Parmer Instrument and Equipment Co., Chicago, Ill.
[4] Model E600-013, Electro-Craft Corp., Hopkins, Minn.
[5] Haake-Berlin, Polyscience Corp., Evanston, IL 60202
[6] Manufactured by the following companies: Smith Kline & French Laboratories, Philadelphia, Pa.; Rowell Laboratories, Baudette, Minn.; and J. B. Roerig Division, Pfizer, Inc., New York, N. Y.
[7] Lithium Carbonate Purified, Lot 58-59, Lithium Corporation of America, Bessemer City, N. C.
[8] Model 290B, Perkin-Elmer Co., Norwalk, Conn.

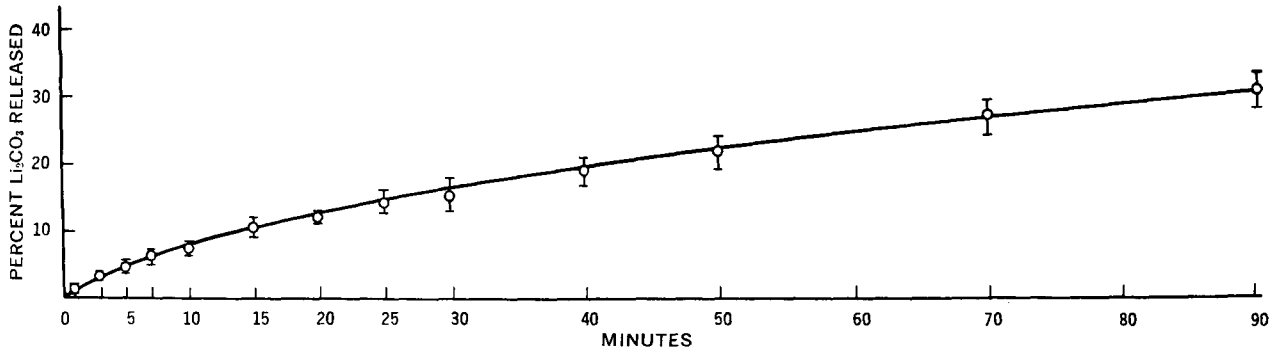

Figure 3—*Dissolution profile at pH 3 for Product D (tablet).*

results. These preliminary findings for the "floating" methods were confirmed by the work of Hersey (8) and Lin *et al.* (9). Lin *et al.* (9) and Wagner (6) reported that the USP XVIII–NF XIII dissolution apparatus causes dispersion of powder from the capsule by a sieving action through the screen and causes some clogging of the screen by undissolved gelatinous masses. The USP XVIII–NF XIII dissolution apparatus may be satisfactory for making a single-point dissolution determination at a time after complete dissolution of the gelatin. However, it does not appear to be the method of choice for dissolution rate profiles, especially at times prior to gelatin dissolution. Of the methods examined, only the magnetic basket (modified beaker) method was capable of consistent sample placement and, thus, of maintaining a reproducible hydrodynamic system. The choice of the appropriate screen size prevented clogging while still allowing the powder to accumulate in a mound at the bottom of the beaker. Sieving action was also held to a minimum by choice of the proper screen size but primarily by maintaining the basket in a stationary position. Because these variables were controlled by the magnetic basket assembly, it was possible to obtain reproducible results.

Figures 2 and 3 were constructed from data using the magnetic basket method and show the mean value for six dissolution determinations of Products A through C. The plots in Fig. 2 were constructed from pH stat data, which were confirmed by atomic absorption assay. The mean value and standard deviation shown for the individual points were calculated by use of the standard form. The points were corrected for the buffering effect of the hard gelatin capsules on the dissolution medium, *i.e.*, the quantity of titrant consumed by emptied gelatin capsules. Time zero for the dissolution rate profiles in Fig. 2 was taken as the point at which the first increment of standard acid was automatically added by the pH stat equipment. Visual observations confirmed that this time coincided with the time of capsule rupture. The average time required for capsule rupture was 3.16 ± 0.37 min.

Figure 2 also shows that by use of this system, products could be differentiated by their dissolution rates. As shown by Levy and Hayes (10), dissolution from a mound of granulation is controlled by the effective surface area of the mound and other components of the granulation. From this it would be expected that the rank order dissolution rates should relate directly to formulation factors, *e.g.*, the quantity of diluent in each product, provided that a mound was formed. This can be seen in Fig. 2 and Table I. Product A contained the greatest amount of diluent and exhibited the slowest release rate; Product B contained a lesser quantity of diluent and exhibited a somewhat faster release rate. Product C, which contained no diluent, yielded the most rapid release. Semilogarithmic plots failed to yield straight lines, thus indicating that first-order dissolution did not occur.

Figure 3 shows the dissolution rate profile for Product D (tablet). The data used were obtained from atomic absorption assays while constant pH was maintained during release of lithium from the tablet. Atomic absorption analysis was necessary since the tablet ingredients obviously contained alkaline material, in addition to lithium carbonate, which precluded the use of the pH stat data. A minimum of three assay readings was made for each point for a minimum of five runs. The mean of these readings was used for determining the quantity of lithium carbonate released. As can be seen, this product released approximately 30% of the active ingredient over 90 min. Compared to capsule dissolution, this is very low and is probably due to several formulation factors. A comparison of the dissolution of the active ingredient from these tablets using the USP XVIII–NF XIII dissolution apparatus and the magnetic basket indicates that the results obtained are similar. In addition, when the tablets were placed in the USP–NF apparatus at 300 r.p.m. for 4 hr. and longer, the tablets remained essentially intact.

The log probability relationship is most frequently used to describe the size distribution of particulate matter. Using particle size and cumulative percent released as the variables, straight and/or curved lines can result. A straight line indicates that a sample with a normal distribution of particles has been examined, *i.e.*, all particles belong to the same population. A curved line indicates that the sample examined contains particles from more than one population. A similar treatment of the data from the lithium carbonate dosage forms in this experimentation helps to explain the dissolution data and, in addition, the resultant explanations are supported by visual observations.

Figure 4 is a log probability approach to the dissolution data collected using the magnetic basket dissolution technique. A rank

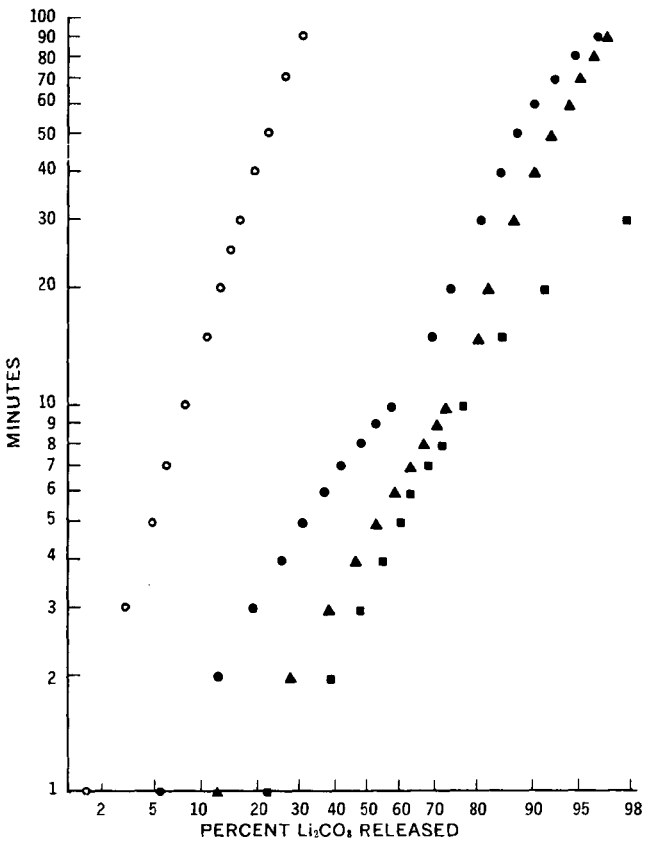

Figure 4—*Log probability plot for dissolution data collected at pH 3. Key:* ○, *Product D (tablet);* ●, *Product A (capsule);* ▲, *Product B (capsule); and* ■, *Product C (capsule).*

order for dissolution was found. It can also be seen from Fig. 4 that dissolution over 90 min. for Product D is represented by a straight line and accounts for 30% of the active ingredient. This line may be interpreted to indicate that dissolution data are obtained from an unchanging group of parameters. In this case, the primary factor controlling dissolution was probably surface area, as substantiated by the observation that very little or none of the tablet parts left the basket in an undissolved state over the 90-min. period. The minimal disintegration that did occur may have exposed additional drug surface and, when combined with diminishing drug surface area due to dissolution, resulted in no net change of exposed drug surface.

The three types of capsules examined were all observed to have completed release of encapsulated material at the end of 10–15 min. This observation manifests itself in Fig. 4. Data collected after this time do not result in straight lines, probably because of the diminishing surface from which dissolution could take place. Levy and Hayes (10) pointed out that dissolution is controlled by the effective surface area of the mound of material remaining after disintegration is completed. Since no additional material is falling to the mound, it is apparent that the effective surface area of the mound decreases with time; therefore, the rate of dissolution changes.

The initial portion of the curve for Product B is a straight line for about 15 min. This may be explained by recalling that this product had very little diluent included (Table I). Dissolution of the particles while falling to the growing mound and some dissolution from the mound account for the major portion of the dissolution that takes place during the first 15 min. The break of the line at 15 min. is then due to a change in parameters in the sense that one parameter (*i.e.*, the falling particles) contributing to dissolution is eliminated.

Examination of the points for Products A and C indicates that the initial parts of these curves are not straight lines. A possible explanation for the data from Product C may be that of rapidly changing surface area brought about by the use of a wide range of particle sizes. The capsules were prepared in these laboratories, and no attempt to size the particles was made (obviously particle-size studies should be continued). The nonlinearity of the points for Product A may be due to an irregular shielding effect of the diluents (Table I). Although perfect sink conditions were not maintained, the solubility of lithium carbonate so far exceeds the limit of total content for these experiments that the effect of solute in solution was minimal.

CONCLUSIONS

This investigation was undertaken with the hypothesis that there was no significant difference in the dissolution rates for capsule and tablet dosage forms of lithium carbonate presently on the market. It was found that the antithesis was true. It was evident during preliminary studies that there is a vast and obvious difference in dissolution of this active ingredient from the tablets and capsules used. The main thrust of this investigation then was to find a method of comparing dissolution from tablets and from capsules that would meet the criteria set down by Wagner (6). Preliminary results agreed with those of previous investigators (6, 8, 9) in that no published method yielded reproducible results for both capsules and tablets.

The magnetic basket which was developed during this investigation allows evaluation of dissolution from both capsule and tablets with reproducible results. The system was used to differentiate dissolution rates between products, both in capsule and tablet forms. Dissolution profiles up to 70% of active ingredients can be followed with this system. It lends itself to an automated analysis system as well as to manual sampling, and the system seems to meet the criteria summarized by Wagner (6) for a dissolution apparatus. Investigations using the magnetic basket apparatus showed that the dissolution rates of the lithium carbonate products in capsule form are threefold over those of the tablet.

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▲ To whom inquiries should be directed.