Bioavailability and Dissolution Parameters of Seven Lithium Carbonate Products

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Abstract □ Seven commercial products and a standard powder of lithium carbonate were administered to healthy human volunteers in a crossover study. An analysis of variance of saliva levels and urinary excretion as well as an analysis of variance of peak concentration and the area under the curve from 0 to 24 hr for the saliva levels showed no significant difference between the powder and products, but a significant difference between subjects. A significant difference was found between the time of peak saliva levels, which was attributed to faster powder absorption. A dissolution study using the USP basket method at 50 and 100 rpm and the Levy beaker at 50 rpm also showed no significant difference between products after the lag time for the capsule dosage forms. With a regression analysis, a significant correlation was found between the saliva levels of the products at 2 hr and dissolution in the USP basket at 50 rpm at 4 min.

Keyphrases □ Lithium carbonate—bioavailability and dissolution, various commercial products, powder, humans □ Bioavailability—lithium carbonate, various commercial products, powder, humans □ Dissolution rate—lithium carbonate, various commercial products, powder, humans □ Antidepressants—lithium carbonate, bioavailability and dissolution, various commercial products, powder, humans

Lithium salts have been used extensively in the management of the manic episodes in manic–depressive illness (1–3). Lithium carbonate is the salt form of choice and is used in most oral products available in this country.

The therapeutic plasma range (0.5–1.5 mEq/liter) and the toxic plasma levels (>1.6 mEq/liter) are very close (4). This critical proximity in combination with large variability in patient drug response requires careful plasma level monitoring during lithium therapy.

Lithium carbonate pharmacokinetics have been defined, and the bioavailabilities of several different products have been investigated (5–10). Shepherd *et al.* (11) investigated the dissolution of three lithium carbonate capsule dosage forms and one tablet product and found a large difference in *in vitro* drug release. The USP later required a dissolution standard for lithium carbonate products of 60% dissolved in 30 min at 100 rpm using the basket method (12).

The purpose of this study was to investigate the bioavailabilities of the seven oral lithium carbonate products currently available in this country and to compare *in vitro* drug release as a function of dissolution methods and their defined parameters.

EXPERIMENTAL

Dosage Forms—Seven commercial dosage forms containing 300 mg of lithium carbonate/tablet or capsule were used[1]. Lithium carbonate powder was used as received from the manufacturer.

***In Vivo* Studies**—Seven healthy male subjects, 22–48 years old and within 90–110% of their ideal weight (13), volunteered for this study. Informed written consent was obtained from each subject. Each volunteer was given a general physical examination including a chest X-ray, an ECG, and normal blood and urine profiles prior to initiation of the study. All were within normal limits. Volunteers were asked to refrain from taking any medications or alcohol prior to and during the study.

Following an overnight fast, each subject was instructed to void and to drink 250 ml of water. An hour later, the zero-time urine and saliva samples were taken and 600 mg of drug was administered. The powder was administered as a suspension in water. Cumulative urine samples were subsequently taken at 1, 2, 3, 4, 6, 8, 12, and 24 hr. Fifteen to 20 ml of urine and the saliva samples were refrigerated immediately. Each subject was instructed to drink 250 ml of water after each urine collection for the first 2 hr. Subjects were allowed to eat after the 2-hr sample.

Urine samples were diluted and analyzed, with appropriate blanks, at 670.8 nm using an atomic absorption spectrophotometer[2]. Results are expressed in terms of percent drug excreted. Saliva samples were taken simultaneously with urine samples. All subjects produced saliva freely in amounts from 1 to 6 ml. Saliva samples were diluted with water, homogenized by shaking for 30 min, and analyzed.

The seven products and the powder were administered to the seven volunteers according to an 8 (formulations) × 7 (subjects) crossover design.

***In Vitro* Studies**—Two dissolution apparatuses were used, the USP basket (12) and the modified Levy beaker method (14–16). A stirring rate

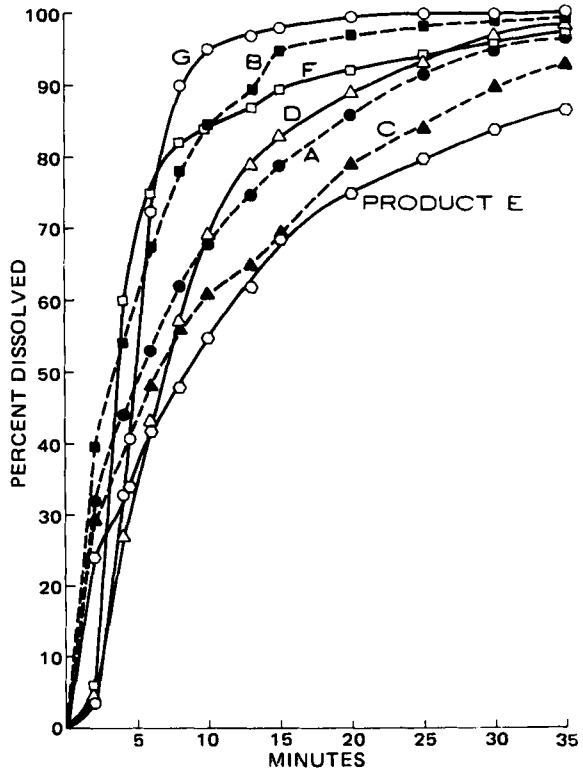

Figure 1—*Average percent dissolved for seven lithium carbonate products in the USP basket at 50 rpm.*

[1] Product A (lot 760475, tablet), Philips Roxane Laboratories, Columbus, OH 43216; Product B (lot 106J07, capsule), Smith Kline and French Laboratories, Philadelphia, PA 19101; Product C (tablet), Pfizer Inc., New York, NY 10017; Product D (lot 760074, capsule), Philips Roxane Laboratories; Product E (lot 62202, tablet), Roerig Division of Pfizer, New York, NY 10017; Product F (lot 59666, capsule), Rowell Laboratories, Baudette, MN 56623; Product G (lot 61631, tablet), Rowell Laboratories; and Product H (lot 76-18, powder), Philips Roxane Laboratories.

[2] Model 360, Perkin-Elmer, Norwalk, Conn.

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Table I—Cumulative Urinary Excretion [a] of the Seven Lithium Carbonate Dosage Forms and the Powder [b]

Hours	Dosage Form A	B	C	D	E	F	G	Powder
1	3.12	2.59	3.08	2.58	2.88	2.24	3.38	4.90
	(2.69)[c]	(1.31)	(2.05)	(1.55)	(2.57)	(1.48)	(2.22)	(2.47)
2	7.77	7.31	8.03	8.58	7.71	6.91	9.17	11.94
	(3.97)	(2.94)	(3.35)	(4.39)	(4.69)	(2.53)	(3.94)	(4.64)
3	10.14	13.08	12.88	12.85	13.41	12.49	15.24	18.53
	(4.48)	(3.65)	(4.27)	(5.31)	(6.34)	(3.92)	(4.66)	(6.69)
4	14.32	18.78	17.38	17.30	18.60	17.59	19.62	21.98
	(6.58)	(4.90)	(5.13)	(5.76)	(7.48)	(4.88)	(5.39)	(7.28)
6	25.27	24.98	24.20	23.06	27.51	26.72	28.02	28.38
	(18.42)	(6.55)	(6.32)	(7.96)	(7.77)	(7.94)	(6.39)	(8.58)
8	31.23	30.02	30.26	30.20	33.76	32.84	32.66	34.49
	(10.52)	(6.55)	(7.92)	(7.28)	(9.24)	(9.93)	(7.59)	(9.90)
12	39.07	39.93	38.32	38.02	41.40	41.64	42.18	41.26
	(11.73)	(7.15)	(8.42)	(6.12)	(10.77)	(11.39)	(8.94)	(9.43)
24	56.19	50.12	53.77	53.87	58.67	60.67	59.96	58.00
	(17.23)	(8.46)	(13.01)	(5.58)	(12.91)	(15.01)	(10.89)	(10.89)

[a] Percent of dose excreted. [b] Average of seven subjects. [c] Standard deviation.

Table II—Saliva Lithium Concentration [a] as a Function of Time

Hours	Dosage Form A	B	C	D	E	F	G	Powder
1	0.262	0.319	0.329	0.306	0.265	0.499	0.317	0.972
	(0.152)[b]	(0.081)	(0.257)	(0.170)	(0.115)	(0.588)	(6.180)	(1.262)
2	0.438	0.424	0.499	0.493	0.483	0.749	0.494	0.867
	(1.83)	(0.111)	(0.347)	(0.211)	(0.200)	(0.820)	(0.288)	(0.865)
3	0.456	0.510	0.682	0.579	0.511	0.916	0.624	0.647
	(0.174)	(0.233)	(0.620)	(0.269)	(0.285)	(0.950)	(0.434)	(0.681)
4	0.398	0.391	0.408	0.361	0.374	0.620	0.349	0.468
	(0.170)	(0.176)	(0.281)	(0.200)	(0.232)	(0.550)	(0.143)	(0.521)
6	0.298	0.287	0.294	0.267	0.277	0.479	0.291	0.341
	(0.139)	(0.120)	(0.161)	(0.137)	(0.178)	(0.465)	(0.135)	(0.322)
8	0.213	0.219	0.222	0.224	0.206	0.374	0.220	0.279
	(0.111)	(0.087)	(0.126)	(0.09)	(0.139)	(0.375)	(0.109)	(0.303)
12	0.155	0.157	0.142	0.161	0.137	0.251	0.160	0.100
	(0.070)	(0.076)	(0.061)	(0.051)	(0.092)	(0.272)	(0.072)	(0.153)
24	0.099	0.100	0.075	0.093	0.053	0.158	0.085	0.107
	(0.434)	(0.050)	(0.041)	(0.034)	(0.028)	(0.196)	(0.046)	(0.086)

[a] Average in micrograms per milliliter for seven subjects. [b] Standard deviation.

Table III—C_{pk} [a] and t_{pk} [a] of Lithium in Saliva

Subject	A		B		C		D		E		F		G		Powder	
	t_{pk}	C_{pk}	t_{pk}	C_{pk}	t_{pk}	C_{pk}	t_{pk}	C_{pk}	t_{pk}	C_{pk}	t_{pk}	C_{pk}	t_{pk}	C_{pk}	t_{pk}	C_{pk}
1	2.5	0.30	2.5	0.32	3	0.70	3	0.43	2	0.59	3	0.92	2.2	0.74	1	0.49
2	4	0.56	2	0.47	3	0.53	3	0.53	2	0.70	2	0.49	2	0.34	1	0.56
3	3	0.67	3	0.72	3	0.30	3	1.72	3	0.70	3	0.84	3	0.70	2	1.23
4	3	0.26	3.2	0.34	3	0.40	3	0.38	3	0.34	3	0.22	3	0.45	2	0.32
5	2	0.68	3	0.90	3	2.08	2.5	0.98	3	1.02	3	3.0	3	1.56	1	3.78
6	2.5	0.37	2.2	0.38	3.2	0.30	2	0.50	2	0.20	3	0.40	3	0.26	2	0.38
7	2.5	0.68	2.2	0.64	2.5	0.64	3	0.43	3	0.58	3	0.56	3	0.37	2	0.55

[a] Peak concentration in milliequivalents per liter and time in hours.

of 50 rpm was used for the modified Levy beaker, and rates of 50 and 100 rpm were used for the USP basket method. Temperature was controlled at 37.0 ± 0.5°. Six hundred milliliters of potassium biphthalate buffer (pH 3.0) was used as the dissolution medium.

At appropriate times, a 1-ml sample was withdrawn and an equal volume of medium was added to maintain a constant volume. Samples were filtered, diluted, and analyzed at 670.8 nm using the atomic absorption spectrophotometer.

RESULTS AND DISCUSSION

***In Vivo* Studies**—Table I shows the cumulative percent of dose excreted in the urine for the seven lithium carbonate products and powder as a function of time. There was little apparent difference in urinary excretion among all eight doses during the 24 hr of sampling. Comparison of these results with work previously reported (8) shows an excellent agreement in cumulative excretion of lithium at 4, 8, and 24 hr.

An analysis of variance using a repeated measures design was employed at each sampling time. This analysis showed no significant difference in drug excretion between brands ($p = 0.05$) during any sampling time up to 24 hr. However, a significant difference was found among subjects at all time intervals. These results aptly illustrate the wide variability mentioned previously and the need to monitor individual patients during drug administration.

Since it has been reported that the saliva/plasma lithium concentration ratio is constant and reproducible for a given individual (17), the saliva lithium concentration also was determined for the dosage forms and the powder for all seven subjects (Table II). Very little difference was apparent, although the average drug concentration produced by the powder seemed to be higher at 1.0 and 2.0 hr. However, the repeated-measures analysis of variance at each sample time showed no significant difference between the products or the powder ($p = 0.05$). Again, the difference among subjects was significant at all sample times.

The constant plasma/saliva lithium ratio makes feasible a comparison of the saliva peak drug level (C_{pk}), the peak level time (t_{pk}), and the area under the saliva level curve (AUC) as a means of measuring the bio-

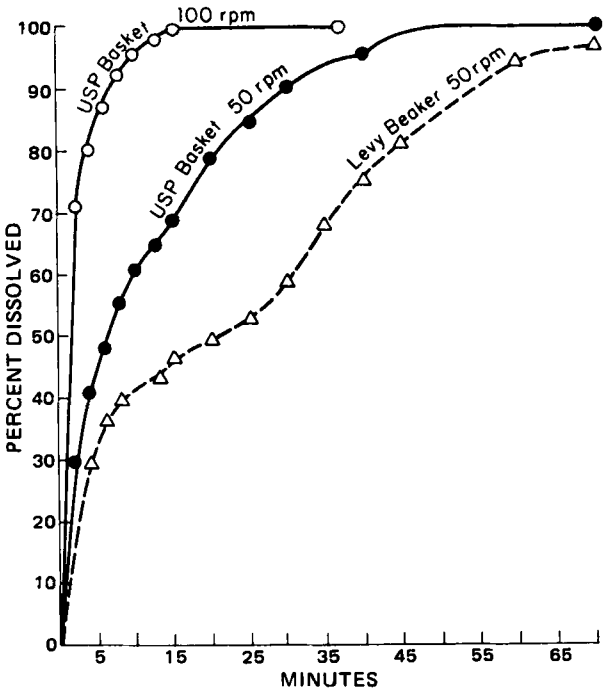

Figure 2—*Dissolution profiles for Product C using the three different dissolution methods/agitation speeds.*

availability of the seven products and powder. Table III shows the C_{pk} and t_{pk} values for each administered dose in each subject. The peak level time is presented as an estimate based on saliva data interpolation.

A two-way analysis of variance for peak concentration to include seven subjects and eight dose administrations produced an F value (7, 42) of 1.16 for the between-brands comparison and an F value (6, 42) of 9.08 among these subjects. These results indicated that no significant differences ($p = 0.05$) existed among the peak saliva concentrations for the seven different lithium carbonate brands and the powder. Significant differences existed among the subjects.

A further analysis of variance of the time required to reach the peak saliva lithium concentration was performed. An F value (7, 42) of 6.80 was calculated for the between-brands comparison. This result indicated a significant difference ($p = 0.05$). A Newman–Keuls (18) analysis was performed to determine which of the t_{pk} means of the administered brands or powder was significantly different. The powder, with an average t_{pk} of 1.57 hr, was different from all of the commercial products. No significant difference was found among any of the remaining seven lithium carbonate products. Interestingly, the calculated F value (6, 42) of 1.84 indicated no significant difference ($p = 0.05$) among subjects for t_{pk}.

The area under the saliva level curve for 0–24 hr was calculated using the trapezoidal rule with average AUC values of 4.406 (Brand E), 4.823 (Brand A), 4.962 (Brand C), 4.972 (Brand D), 4.981 (Brand G), 4.992 (Brand B), 6.789 (powder), and 8.020 (Brand F). A two-way analysis of variance for the AUC *versus* subjects produced an F value (7, 42) of 1.02 for the between-brands comparison, which was not significant ($p = 0.05$). The calculated F value (7, 42) of 6.13 for the between-subjects comparison was significant.

***In Vitro* Dissolution Studies**—The seven lithium carbonate brands were dissolved using three systems: a modified Levy beaker method at 50 rpm and the USP basket method at 50 and 100 rpm.

Figure 1 illustrates the average percent dissolved for all seven products in the USP basket at 50 rpm. This method and agitation speed illustrate the behavior seen in both the USP basket at 100 rpm and the Levy beaker.

These results were compared using an analysis of variance. The percent of drug dissolved was transformed using a log arc sine transformation to ensure homogeneity of variance and additivity of effects (19). Since previous work had determined that an analysis of variance across time produces significant interaction effects (20), a 7 (brands) × 3 (methods/rpm) with five replications repeated-measures analysis of variance at each sample time was performed. This analysis showed a significant difference between brands ($p = 0.05$) in drug dissolution from the dosage forms at 2 and 4 min. Comparison of the average percent dissolved showed that these differences were due to capsule dosage forms Brands B, D, and F, which displayed the expected lag time. However, the analysis of variance showed a significant difference in the dissolution between methods at all sample times. Figure 2 illustrates an example comparison, using Product C, of the average percent dissolved for each method and agitation speed. The order of decreasing rate of dissolution was USP 100 rpm, USP 50 rpm, and Levy 50 rpm for all brands at all sampling times.

All products adhered to the USP regulation that 60% of drug dissolve in 30 min at 100 rpm in the USP basket. In fact, the time to achieve 60% dissolution ranged from <2 min for Brands C and E to <8 min for Brand F.

A correlation of the *in vivo* saliva concentrations of the different lithium carbonate brands with the *in vitro* drug release from the dosage forms at all possible combinations of sample times was attempted using a regression analysis. A significant correlation at the 0.95 level was found for the Levy 50-rpm and USP 50-rpm methods at the 2-min sample time *versus* the *in vivo* time of 1 hr. However, comparison of the presented results showed that this correlation occurred during the only *in vitro* sample time that showed a significant difference between brands and at the *in vivo* sampling time that had no difference between brands. Apparently, the regression analysis produced a mathematical correlation of little practical significance.

A second significant correlation was found at the 0.99 level for the USP basket at 50 rpm at 4 min with the *in vivo* sample time of 2 hr. In this comparison, the significance level was higher. The analysis of variance of both the *in vivo* and *in vitro* data for the USP basket at 50 rpm showed no significant difference between brands, and the dosage forms were in that phase of absorption and dissolution where drug release was significant. This finding seems important since the assumption inherent in *in vivo–in vitro* correlation requires a comparison based on drug release from dosage form, manifested as dissolution or as absorption. To determine the practicality of this means of correlation as a control method, further work employing dosage forms designed to produce diverse drug concentration levels is necessary.

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