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Report

Formulation and *in Vitro-in Vivo* Evaluation of Sustained-Release Lithium Carbonate Tablets

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The release of lithium carbonate incorporated into polymethylmethacrylate, polyvinyl chloride, hydrogenated vegetable oil, and carbomer matrix tablets was studied *in vitro*. The formulation containing 10% carbomer showed a sustained-release profile comparable to that of a standard, commercially available, sustained-release preparation containing 400 mg lithium carbonate embedded in a composite material. *In vivo* the newly formulated and standard sustained-release lithium carbonate tablets were compared to an oral solution and conventional lithium carbonate tablets in 12 healthy subjects. These crossover studies showed that the sustained-release tablets produced a flatter serum concentration curve than the oral solution and conventional tablet, without loss of total bioavailability.

KEY WORDS: lithium; sustained release; pharmacokinetics; bioavailability; *in vitro*.

INTRODUCTION

Lithium carbonate is widely used in the treatment of mania and in preventing the recurrence of both manic and depressive symptoms. The therapeutic index of the drug is narrow, and side effects are common in patients whose serum lithium levels are maintained within the therapeutic range. Conventional lithium carbonate tablets make the drug immediately available for rapid absorption and relatively high peak blood levels. Adverse side effects are commonly associated with high lithium serum concentrations. In order to reduce the absorption peaks and the gastrointestinal side effects of lithium, and to avoid wide blood-level variations, sustained-release lithium preparations were developed (1–6). In addition, since patient compliance can be a problem during maintenance therapy, sustained-release tablets have the advantage of less frequent dosing than the three- to four-times-daily dosing required for the conventional immediate-release forms.

Knowledge of the biopharmaceutic parameters of a dosage form is essential to predict the performance of the dosage form when administered therapeutically. Lithium carbonate is sparingly soluble in water, and its absorption is dissolution rate limited. The USPXXI has required a dissolution standard for conventional lithium carbonate solid dosage forms. Bioavailability studies of lithium preparations have been carried out on both the conventional and the sustained-release products, and deficiencies were observed for both dosage forms (2,4,7).

One of the objectives of the present study was to examine, the *in vitro* release characteristics of lithium carbonate from different matrix tablets in order to assess the suitability of such formulations for the production of sustained-release dosage forms. The other objective was to evaluate the pharmacokinetic analysis of sustained-release dosage forms of lithium carbonate. An oral solution, a conventional immediate-release tablet, a sustained-release preparation which contains the drug embedded in a hydrophilic matrix, and a commercially available sustained-release tablet of lithium carbonate were administrated to healthy subjects. A comparative analysis was conducted between the pharmacokinetic parameters, and the sustained-release profiles of the various formulations were analyzed.

MATERIALS AND METHODS

Materials

The following materials were used: lithium carbonate (E. Merck, Darmstadt, F.R.G.), polyvinyl chloride (Pevikon PE 737P, Kemanord, Sweden), carbomer (Carbopol 934P, Goodrich, Zaventem, Belgium), hydrogenated vegetable oil (Lubritab, E. Mendell Co., Inc., Carmel, N.Y. 10512), polymethylmethacrylate (Eudragit, RSPM Röhm Pharma, Darmstadt, F.R.G.), lactose (Fast Flo, Foremost Food Company, San Francisco, Calif. 94104), carboxymethylcellulose sodium (Acdisol, FMC Corp./Food-Pharmaceutical Products Division, Philadelphia, Pa. 19103), microcrystalline cellulose (Avicel, pH 101, FMC Corp./Food-Pharmaceutical Products Division, Philadelphia Pa. 19103), magnesium stearate (E. Merck, GmbH Leverkusen, F.R.G.), 400-mg lithium carbonate controlled-release tablets (Priadel, Delandale Laboratories Limited, Canterbury, Kent CTI 3JF, England).

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Methods

Preparation of Tablets

Polymethylmethacrylate, polyvinyl chloride, carbomer, and hydrogenated vegetable oil were used as matrix materials in this investigation. The powders were mixed and directly compressed, with 1% of magnesium stearate incorporated as a lubricant prior to compression. Tablets were compressed on a single-punch tablet machine Korsch EK/O, at a tablet weight of 600 mg, using a flat, nonbeveled punch of 12-mm diameter, and tablet hardness was kept constant within the range of 7.5–8 kg on a Heberlein hardness tester. Sustained-release matrix tablets were formulated to contain 400 mg or 66% lithium carbonate, and 10, 7.5, or 5% matrix material of total tablet weight. Lactose was added as a filler to maintain constant tablet weight. Conventional lithium carbonate tablets were formulated to contain 300 mg lithium carbonate, 55 mg carboxymethylcellulose sodium, 200 mg microcrystalline cellulose, and 1% magnesium stearate.

In Vitro *Release of Lithium Carbonate from Tablets*

The dissolution of the manufactured and commercially available tablets was carried out with the paddle method according to USPXXI using a Prolabo (Paris) dissolution tester. The dissolution medium was 900 ml of distilled water at 37°C and the rotation velocity was 100 rpm. At appropriate time intervals, 3 ml of sample was withdrawn and an equal volume of medium was added to maintain a constant volume. Samples were filtered, diluted, and analyzed using a Perkin Elmer (Norwalk, Conn.) 2380 atomic absorption spectrophotometer at 670.8 nm.

In Vivo *Studies*

Two separate studies were performed, with 12 subjects participating in the single-dose study. The subjects were informed about the nature and purpose of the studies. Prior to the studies, the subjects were physically examined and asked for their medical history. All subjects were healthy and free of other drugs for at least 1 week prior to the studies and during the study.

Twelve subjects, four female and eight male, between 23 and 47 years of age [29.5 ± 11.3 (SD) years] and with body weights between 56 and 74 kg (64.6 ± 6.0 kg) volunteered for studies I and II. They were divided into two groups of six subjects. For study I, the first six subjects were divided into two groups. Initially one group received 800 mg of lithium carbonate dissolved in 250 ml of water and the other received two 400-mg sustained-release tablets of lithium carbonate with 250 ml of water. The sustained-release formulation used above contained 10% carbomer as hydrophilic matrix and was selected after *in vitro* dissolution rate experiments. One week later each subject received the alternate form.

For study II, three subjects swallowed three 300-mg conventional tablets with 250 ml of water, and three received two 400-mg sustained-release tablets of lithium carbonate (Priadel, 400 mg lithium carbonate). One week later, the drug administrations were reversed.

Before entering the study all subjects fasted for a minimum of 10 hr, and no food or liquid other than water was permitted for 4 hr following ingestion of the dose.

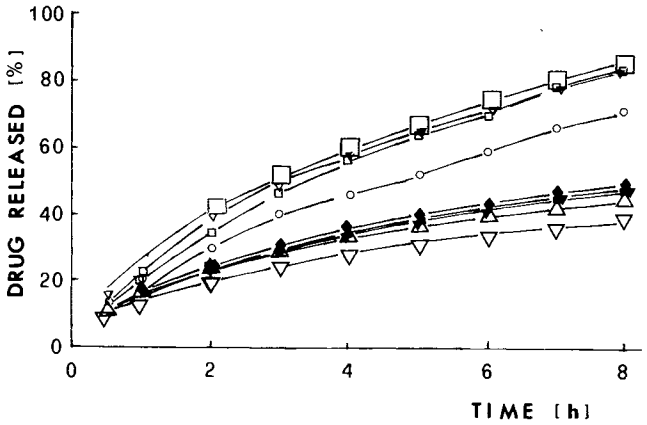

Fig. 1. Lithium carbonate release profiles from sustained-release matrix tablets. (▽) 10%, (△) 7.5%, and (□) 5% polyvinyl chloride; (○) 10%, (□) 7.5%, and (▽) 5% polymethylmethacrylate; (♦) 10%, (■) 7.5%, and (▼) 5% hydrogenated vegetable oil, respectively.

Before the drug administration a 5-ml blood sample was collected from each subject. Following drug administration, 5 ml of venous blood samples was obtained from either the left or the right antecubital fossa at 1, 2, 4, 6, 8, and 24 hr. The blood samples, which were allowed to clot, were centrifuged and the serum specimens were saved. Serum lithium levels were determined by atomic absorption spectrophotometry using a Perkin Elmer 2380 instrument.

Pharmacokinetic Analysis

The serum concentration of lithium after the administration of a conventional tablet, sustained-release tablets, and an oral solution could be described by a two-compartment open model with first-order absorption according to Eq. (1).

$$C = A_1^* e^{-\alpha t} + A_2^* e^{-\beta t} - A_3^* e^{-k_a t} \qquad (1)$$

where C is the serum concentration at time t, k_a is the absorption rate constant, and α and β are the rapid and slow disposition rate constants, respectively. A_1^*, A_2^*, and A_3^* are

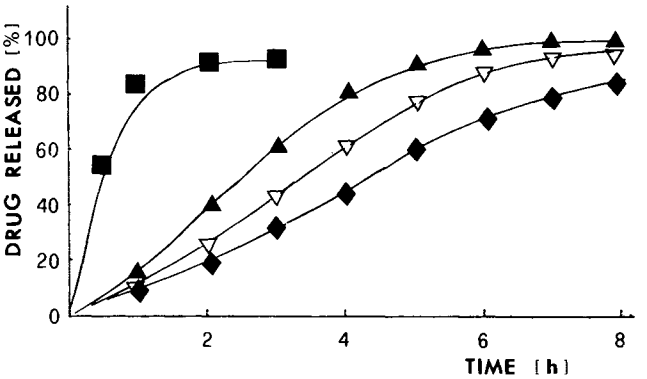

Fig. 2. Lithium carbonate release profiles from sustained-release matrix tablets. (♦) 10%, (▽) 7.5%, and (▲) 5% carbomer; (■) commercially available lithium carbonate tablet.

Table I. Release Rate Constants ($mg/hr^{1/2}$) of Sustained-Release Tablets

Formulation	Release rate constant ($mg/hr^{1/2}$), mean ± SD (CV); $n = 6$	Intercept (mg)
Polymethylmethacrylate		
5%	31.6 ± 0.6 (1.8%)	−5.8
7.5%	31.8 ± 2.9 (8.9%)	−7.6
10%	26.8 ± 1.8 (6.7%)	−6.6
Polyvinyl chloride		
5%	31.2 ± 3.4 (11%)	−3.0
7.5%	16.0 ± 1.3 (8.2%)	−0.3
10%	13.8 ± 0.5 (3.9%)	−0.2
Hydrogenated vegetable oil		
5%	18.7 ± 0.9 (4.8%)	−3.4
7.5%	17.5 ± 0.4 (2.6%)	−3.0
10%	16.9 ± 0.4 (2.5%)	−2.9
Carbomer		
5%	44.6 ± 0.9 (2.1%)	−16.5
7.5%	39.8 ± 1.2 (3.1%)	−17.3
10%	37.1 ± 1.4 (4.3%)	−15.4
Commercially available sustained-release tablet	57.4 ± 0.7 (1.3%)	7.0

coefficients which show the dimension of concentrations with $A_3^* = A_1^* + A_2^*$. The maximum observed concentration, C_{max}, and the time to reach this concentration, t_{max}, were recorded for each dose and each subject. The AUC values were calculated using the trapezoidal rule.

Statistical Analysis

Analysis of variance (ANOVA) was used in the statistical analysis of the pharmacokinetic parameters. The linear model included formulation and subject as factors.

RESULTS AND DISCUSSION

In Vitro

The results of the release experiments are summarized in Figs. 1 and 2, representing the percentage released as a function of time. Figures 1 and 2 show the release patterns of lithium carbonate from matrix tablets containing the same amount of the drug but different percentages of the different polymers. As expected, the drug was released more slowly from tablets with an increased polymer content.

When 5, 7.5, and 10% of polyvinyl chloride were incorporated into the formulation, the amount of lithium carbonate released decreased from 85 to 44 to 38%, respectively. Similar results were also obtained on polymethylmethacrylate and hydrogenated vegetable oil matrix tablets (Fig. 1). Carbomer showed even better results than the other matrix materials used. The concentrations of 5, 7.5, and 10% decreased the amount released in 8 hr from 99 to 95 to 84%, respectively (Fig. 2). It can be seen from Fig. 1 that polymethylmethacrylate, polyvinyl chloride, and hydrogenated vegetable oil matrix tablets have an initial rapid release of lithium carbonate. These differences may be attributed to porosity, dissolution or permeability of these materials.

The main objective was to have a release in the range of 25–40% by 2 hr, 40–60% by 4 hr, and 70–90% by 8 hr for the 12-hr sustained-release preparations (8,9). The 10% carbomer matrix tablets showed suitable release kinetics for a 12-hr sustained-release preparation.

It should be noted that the time necessary for the release of 90% of lithium carbonate in the commercially available sustained-release lithium carbonate tablets (Priadel) was 2 hr (Fig. 2). However, drug release from conventional tablets confirms with the requirements of USPXXI.

In order to investigate the mechanism of release, the percentage release versus time profile was evaluated for goodness-of-fit method. The details of the use of this statistical technique are given by Bamba *et al.* (10). For all the formulations prepared and the commercially available tablet Higuchi's (11) square-root equation ($100 - W = k_d \sqrt{t}$) shows a significantly better fit than first-order ($\ln W = -k_f t + i$) and cube-root ($\sqrt[3]{100} - \sqrt[3]{W} = k_c t$) equations, as determined by the F test.

The release rate constants were determined from the slopes of the linear square root plots (Table I). Decreasing content of polymethylmethacrylate, polyvinyl chloride, and hydrogenated vegetable oil increased the release rate, which may be due to changes in the porosity and tortuosity of the matrix after dissolution of the higher lactose content.

Since carbomer is an hydrophilic matrix, it is expected that the release rate be governed by gelation rate ($\ln W = -k_f t + i$). However, the best fit was obtained with the square-root equation, and the release rate constant determined from the slopes of the linear fitting for carbomer matrix tablets is given in Table I. Similar results were also

Table II. Mean Lithium Serum Concentrations ($mEq\ L^{-1}$) Following the Administrations of 800 mg Lithium Carbonate in Oral Solution and Two 400-mg Formulated, Two 400-mg Commercially Available Sustained-Release, and Three 300-mg Conventional Tablets of Lithium Carbonate ($n = 6$) (±Standard Deviation)

Time	Oral solution	Formulated sustained-release tablet	Commercially available sustained-release tablet (Priadel)	Conventional tablet
1	1.144 ± 0.033	0.243 ± 0.059	0.292 ± 0.073	0.502 ± 0.080
2	0.856 ± 0.095	0.414 ± 0.023	0.447 ± 0.080	0.659 ± 0.072
4	0.577 ± 0.060	0.579 ± 0.011	0.565 ± 0.023	0.526 ± 0.048
6	0.474 ± 0.044	0.511 ± 0.041	0.476 ± 0.034	0.453 ± 0.042
8	0.372 ± 0.040	0.430 ± 0.045	0.408 ± 0.046	0.398 ± 0.040
24	0.212 ± 0.039	0.238 ± 0.023	0.227 ± 0.047	0.210 ± 0.028

Table III. Pharmacokinetic Parameters Calculated (Mean ± SD) from Serum Lithium Profiles ($n = 6$)

Parameter	Oral solution[a]	Formulated sustained-release tablet[a]	Conventional tablet[b]	Priadel[a]
β (hr^{-1})	0.041 ± 0.009	0.037 ± 0.003	0.041 ± 0.006	0.038 ± 0.005
$t_{1/2}$ β (hr)	17.8 ± 4.4	18.8 ± 1.6	17.4 ± 2.5	18.3 ± 2.5
$AUC_{0\to24}$ (mEq · L^{-1} hr^{-1})	9.6 ± 0.9	8.8 ± 0.6	8.7 ± 0.7	8.5 ± 0.7
C_{max} (mEq/L)	1.144 ± 0.033	0.583 ± 0.011	0.659 ± 0.072	0.574 ± 0.017
t_{max} (hr)	1.0 ± 0.0	4.3 ± 0.8	2.0 ± 0.0	3.7 ± 0.8

[a] Lithium carbonate, 800 mg.
[b] Lithium carbonate, 900 mg.

obtained by Lapidus and Lordi (12), who applied the equations derived by Higuchi (11) and Desai (13,14) for drug release from insoluble matrix to compressed hydrophilic matrix. Water penetration is visualized as hydrating the polymer and dissolving lithium carbonate, which then diffuses out through the swollen matrix. The increase in the release rate of lithium carbonate by the addition of the water soluble diluent, lactose, to the carbomer matrix could result from a higher solubility of lactose and its subsequent effect on the tortuosity factor. As lactose dissolves, it diffuses outward and decreases the tortuosity of the diffusion path of lithium carbonate. A decrease in the amount of the matrix material causes a decrease in the embedding capacity of the matrix tablets.

In Vivo

Study I. Serum lithium concentrations and standard deviations achieved following oral administration of the solution and the formulated sustained-release tablets are presented in Table II. The solution yielded maximum concentrations, C_{max}, within 1 hr or less in all subjects ($P < 0.05$). The formulated sustained-release tablets resulted in C_{max} values lower than those produced by the solution ($P < 0.05$), and the t_{max} for the sustained release tablet was significantly longer ($P < 0.05$). The calculated mean values for the various pharmacokinetic parameters of the two compartment models are listed in Table III. The AUC values for the oral solution and formulated sustained-release tablets were 9.6 ± 0.9 and 8.8 ± 0.6 mEq · L^{-1} · hr^{-1} ($n = 6$), respectively. According to the results of the ANOVA, the AUC values for solution and sustained-release tablets did not significantly differ from one another.

On the other hand, there were no significant differences among subjects. The mean value of the slow disposition rate constant obtained after the administration of the formulated sustained-release formulation was 0.037 ± 0.003 hr^{-1}, which corresponds to a half-life of 18.8 ± 1.6 hr ($n = 6$) and is very close to the one obtained with the oral solution. The results are in agreement with several reports given in the literature (2,3,4,6).

Study II. Serum lithium concentrations after conventional and sustained-release tablets (Priadel) are shown in Table II. The parameters derived from the concentration–time data are summarized in Table III.

The sustained-release tablet exhibited significantly lower C_{max} values than conventional formulation as indicated by the ANOVA ($P < 0.05$). The mean t_{max} values were delayed from 2.0 to 3.7 ± 0.8 hr ($n = 6$) for sustained-release tablets. These values were significantly different ($P < 0.05$), and no difference was obtained between subjects ($P > 0.05$). The AUC values for conventional- and sustained-release tablets did not differ from one another ($P > 0.05$).

The mean disposition rate constants β were also determined and found to be 0.041 ± 0.006 hr^{-1} for conventional release and 0.038 ± 0.005 hr^{-1} for sustained release (Priadel) of lithium carbonate tablets ($n = 6$). These results are in full agreement with the previous single-dose data of Caldwell *et al.* (3) and Nielsen-Kudsk *et al.* (2,15).

The results of the present investigation using conventional- and sustained-release lithium carbonate tablets with varying dissolution characteristics demonstrate the dissolution or release rate dependency of lithium absorption from the gastrointestinal tract of man. However, a direct correlation between the dissolution profile and the relative bioavailability of the formulation was not observed.

The fluctuation in serum lithium level during the absorptive phase was lower when administering the conventional tablets than after the commercial sustained-release formulation. However, the sustained-release tablets employed in this study, containing lithium carbonate in an hydrophilic matrix (10% carbomer), may afford more uniform absorption characteristics and reduce the incidence of side effects as a result of high serum concentrations of lithium.

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