Iranian Journal of Pharmaceutical Research (2003) 33-38
Received: June 2002
Accepted: February 2003

*Original Article*

# An Investigation into the Optimization of Release Profile of Lithium Carbonate from Matrix-type Tablets Containing Carbopols, Pemulen and Eudragits

Reza Aboofazeli*, Seyed Alireza Mortazavi

*Department of Pharmaceutics, School of Pharmacy, Shaheed Beheshti University of Medical Sciences and Health Services, Tehran, Iran.*

**Abstract**

The influence of various polymers on the release rate of lithium carbonate from matrix-type tablets was investigated in an attempt to formulate a sustained release solid dosage form. For this purpose, tablets containing 450 mg of lithium carbonate along with various amounts of Carbopol 934P, 971P, 974P, Pemulen and Eudragit RLPO as retarding agents and inactive ingredients (e.g. PVP, Avicel or starch) were prepared using wet granulation technique. Tablets prepared were initially placed in a phosphate buffer solution for 7 h and those formulations from which a minimum of 80% lithium carbonate released, were selected for coating process. The amount of drug released was determined by using atomic absorption spectroscopy. The dissolution rate of enteric coated matrix-type tablets were then evaluated in both acidic and basic mediums (1 h and 11 h, respectively). The results showed that Pemulen and Carbopol 971P are not suitable polymers for preparing tablets with desirable release profile, at all concentrations examined. However, it was observed that Carbopol 934P, 974P and Eudragit RLPO are capable of producing tablets with desirable release pattern, at concentrations of 2, 1.5 and 3%, respectively. Tablets containing Eudragit RLPO were found to have the greatest drug release profile, while Carbopol 974P showed the slowest release rate.

**Keywords:** Lithium carbonate; Carbopols; Eudragits; Matrix-type tablets; Drug release profile; Sustained release; Formulation.

## Introduction

Lithium, as one of its salts, is the main drug used for the control of bipolar disorders (manic depression). It is also used in recurrent or unipolar depression as an alternative to tricyclics. Lithium has a narrow therapeutic/toxic ratio. Recommended therapeutic serum concentrations range from 0.4 to 1.2 or even 1.4 mmol/l, with higher concentrations required for acute mania. However, it is necessary to emphasize that serum concentrations should be adjusted for each patient, since individual patients vary in their sensitivity to lithium as well as their elimination ratio (1).

Many of the side effects of lithium are dose related. Initial adverse effects of lithium therapy include nausea, diarrhea, vertigo, polyuria with polydipsia and muscle weakness. Those effects occurring at therapeutic serum concentrations include anorexia, constipation or diarrhea, epigastric discomfort, headache and vertigo (1).

Lithium is readily and completely absorbed from the gastrointestinal tract when taken as one of its salts and peak serum concentrations are obtained between 0.5 to 3 hours after ingestion from conventional solid dosage forms, depending upon formulation of the preparation (2, 3). Following the administration of lithium salts, there is a wide inter-subject

* Corresponding author:
E-mail: raboofazeli@itmrc.com

variation between both the serum concentrations obtained following a given dose, and between those required for therapeutic effect. On the other hand, there is only a narrow margin between therapeutic and toxic plasma concentration of lithium. Therefore, individual titration of lithium dosage is essential to ensure constant appropriate concentrations for the patient involved (1).

Incorporation of lithium salts within matrices containing a suitable polymer can provide a sustained release formulation, capable of controlling the release rate of the drug over an extended period of time and producing a desirable blood serum level with little or no fluctuation, which in turn lead to a decrease in the occurrence of drug toxicity. In this investigation, attempts were made to formulate a sustained release dosage form of lithium carbonate with an optimum release pattern, using various Carbopols, Pemulen and Eudragit RPLO as retarding polymers. In the first step, various formulations were prepared and characterized from the physico-chemical point of view. In the second step, the appropriate formulations were selected for coating stage and finally the dissolution behavior and release kinetics of coated tablets were evaluated.

## Experimental

### Materials

Lithium carbonate powder, monobasic potassium phosphate, dibasic sodium phosphate, hydrochloric acid, ethyl alcohol and acetone were all purchased from Merck Chemical Company (Germany). Various Carbopols, including Carbopol 934P (C934P), Carbopol 971P (C971P), Carbopol 974P (C974P) and Pemulen were obtained from B.F. Goodrich Company (UK). Eudragit RLPO and Avicel pH 101 were gifted by Akbarieh Company (Iran). Magnesium stearate, polyvinyl pyrrolidone (PVP) and corn starch were obtained as gifts by Tolidarou Pharmaceutical Company (Iran). Diethyl phthalate (DEP) and cellulose acetate phthalate (CAP) were gifted by Hakim Pharmaceutical Company (Iran).

### Methods

*Construction of calibration curves*

Calibration curve of lithium carbonate in a pH 6.8 phosphate buffer was constructed by preparing standard solutions containing 0.5, 1.0, 1.5, 2.0, 2.5 and 3.0 mg/l lithium carbonate. The absorbance of these solutions was determined at 671 nm, using atomic absorption spectroscopy. The calibration curve was found to be linear over the concentration range of 0.5 – 3.0 mg/l, and hence was used to determine the amount of lithium carbonate released from tablet matrices.

Calibration curve of the drug in an acidic medium (0.1 N HCl) was also constructed by preparing standard solutions containing 0.5, 1.0 and 1.5 mg/l of drug, followed by the determination of absorbance, using atomic absorption spectroscopy. A linear relationship was obtained over the concentration range studied.

*Preparation of matrix-type tablets*

Matrix-type tablets containing 450 mg of lithium carbonate along with various amounts of Carbopols, Eudragit RLPO and inactive ingredients (such as PVP, Avicel and microfine cellulose) were prepared by the wet granulation technique. In the first step, active and inactive ingredients (except magnesium stearate) were weighed and screened through a 60-mesh sieve. Required materials were then combined and the mixtures wetted by ethyl alcohol and then granulated using a laboratory granulator

**Table 1.** Composition (%) of lithium carbonate matrix-type sustained release tablet formulations, prepared by wet granulation technique.

| Formulation Series | A | | | | B | | | C | | | | D | | | E | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | C934P | Avicel | PVP | C974P | Avicel | PVP | Starch | C971P | Avicel | PVP | Pemulen | Avicel | PVP | Eudragit RLPO | Avicel | PVP |
| **1** | 5 | 5 | 5 | 5 | 5 | 5 | - | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| **2** | 4 | 10 | 5 | 4 | 10 | 5 | - | 4 | 10 | 5 | 4 | 10 | 5 | 4 | 10 | 5 |
| **3** | 3 | 15 | 5 | 3 | 15 | 5 | - | 3 | 15 | 5 | 3 | 15 | 5 | 3 | 15 | 5 |
| **4** | 3 | 15 | 3 | 3 | 15 | 3 | - | 3 | 15 | 3 | 3 | 15 | 3 | 3 | 15 | 3 |
| **5** | 2 | 15 | 3 | 2 | 15 | 3 | - | 2 | 15 | 3 | 2 | 15 | 3 | 3 | 19 | 2.5 |
| **6** | 2 | 19.5 | 3 | 2 | 19.5 | 3 | - | 2 | 19.5 | 3 | 2 | 19.5 | 3 | - | - | - |
| **7** | 2 | 19.5 | 3 | 2 | 14.5 | 3 | 5 | 1.5 | 1.5 | 3 | 1.5 | 20 | 3 | - | - | - |
| **8** | 2 | 19.5 | ** | 1.5 | 20 | 3 | - | - | - | - | - | - | - | - | - | - |

* In formulation A7, water was used as granulating solvent.

** Gelatin was used instead of PVP.

equipped with a 1.25 mm sieve. Granules obtained were then screened through a 14-mesh sieve and dried at room temperature for 24 h. Finally, dried granules were passed through a 14-mesh and then a 60-mesh sieve and following the addition of a given amount of magnesium stearate, they were compressed into tablets.

*Assay*

Assay of prepared tablets was performed according to the monograph of lithium carbonate extended release tablets in United Stated Pharmacopeia XXIII (4).

*Coating of matrix-type tablets*

In order to prepare the coating solution, solvent (acetone–ethyl alcohol mixture) and polymer (CAP) were mixed in a beaker and stirred until a clear solution was obtained. Plasticizer (DEP) was then added to the solution, while stirring. Tablets were placed in a laboratory coating pan, positioned at a specific angle. The coating solution was sprayed on the tablets, while the heated air was directed into the pan and onto the tablet bed surface.

*Dissolution test*

The amount of lithium carbonate released from various tablet formulations was determined using a USP apparatus I (rotating basket) dissolution tester, set at 100 rpm and a temperature of 37 ±0.5°C (4). Dissolution test was performed in both acidic and basic media. In this study, tablets were placed initially in 900 mL of a pH 1.5 hydrochloric acid solution for about 1 h and 5 ml samples were taken after 0.5 and 1 h, while the volume of the dissolution medium was kept constant by replacing it with equal volumes of fresh solution. After 1 h, the dissolution medium was completely removed and replaced with 900 ml of pH 6.8 phosphate buffer solution and samples (5 ml) were removed in predetermined

**Table 2.** Results of quality control tests carried out on lithium carbonate matrix-type sustained release tablets containing Carbopols, Eudragit RLPO or Pemulen, prepared by wet granulation technique .

| Formulation | Hardness (Kp) (n=10) | Friability (%) (n=10) | Weight variation (%) (n=10) | Max. drug released after 7 h (%) |
|---|---|---|---|---|
| A1 | 9.2 ± 0.3 | 0.11 | 2.53 ± 0.20 | 58.20 ± 1.29 |
| A2 | 8.9 ± 0.5 | 0.20 | 2.61 ± 0.17 | 64.06 ± 1.71 |
| A3 | 9.1 ± 0.4 | 0.22 | 3.01 ± 0.11 | 67.81 ± 1.13 |
| A4 | 8.7 ± 0.2 | 0.25 | 3.51 ± 0.31 | 71.93 ± 2.01 |
| A5 | 8.5 ± 0.2 | 0.25 | 2.67 ± 0.19 | 76.15 ± 1.89 |
| A6 | 7.1 ± 0.3 | 0.38 | 2.54 ± 0.09 | 87.26 ± 1.01 |
| A7 | 7.5 ± 0.2 | 0.29 | 3.76 ± 0.11 | 88.11 ± 1.92 |
| A8 | 7.3 ± 0.2 | 0.32 | 2.16 ± 0.06 | 91.45 ± 0.60 |
| B1 | 10.5 ± 0.4 | 0.09 | 2.58 ± 0.10 | 61.17 ± 1.20 |
| B2 | 10.0 ± 0.3 | 0.15 | 2.64 ± 0.09 | 65.44 ± 1.73 |
| B3 | 9.6 ± 0.4 | 0.20 | 2.63 ± 0.15 | 67.05 ± 1.97 |
| B4 | 8.5 ± 0.5 | 0.27 | 3.30 ± 0.32 | 70.21 ± 3.19 |
| B5 | 8.5 ± 0.5 | 0.27 | 2.81 ± 0.09 | 71.53 ± 2.21 |
| B6 | 7.5 ± 0.4 | 0.19 | 2.44 ± 0.07 | 73.78 ± 1.00 |
| B7 | 6.0 ± 0.1 | 0.35 | 3.04 ± 0.22 | 60.91 ± 3.01 |
| B8 | 6.5 ± 0.2 | 0.23 | 2.38 ± 0.07 | 81.01 ± 0.96 |
| C1 | 10.7 ± 0.6 | 0.17 | 2.31 ± 0.04 | 41.22 ± 0.81 |
| C2 | 10.4 ± 0.5 | 0.16 | 2.20 ± 0.04 | 42.57 ± 1.01 |
| C3 | 9.4 ± 0.4 | 0.24 | 2.34 ± 0.10 | 47.19 ± 0.50 |
| C4 | 7.8 ± 0.4 | 0.33 | 2.66 ± 0.09 | 51.10 ± 1.66 |
| C5 | 5.5 ± 0.3 | 0.36 | 2.58 ± 0.20 | 55.81 ± 2.31 |
| C6 | 5.7 ± 0.2 | 0.36 | 2.49 ± 0.05 | 62.00 ± 1.19 |
| C7 | 6.0 ± 0.3 | 0.40 | 2.23 ± 0.15 | 68.11 ± 1.70 |
| D1 | 10.7 ± 0.5 | 0.05 | 2.09 ± 0.04 | 37.11 ± 0.63 |
| D2 | 10.5 ± 0.5 | 0.09 | 2.16 ± 0.04 | 38.97 ± 1.07 |
| D3 | 9.0 ± 0.4 | 0.19 | 2.29 ± 0.10 | 41.81 ± 0.76 |
| D4 | 8.1 ± 0.3 | 0.31 | 2.68 ± 0.09 | 45.07 ± 1.29 |
| D5 | 6.3 ± 0.5 | 0.38 | 2.60 ± 0.04 | 53.49 ± 2.00 |
| D6 | 4.4 ± 0.3 | 0.40 | 2.34 ± 0.07 | 55.90 ± 2.99 |
| D7 | 4.3 ± 0.3 | 0.39 | 2.15 ± 0.09 | 65.12 ± 1.98 |
| E1 | 11.2 ± 0.5 | 0.28 | 2.04 ± 0.05 | 43.15 ± 0.95 |
| E2 | 10.5 ± 0.5 | 0.30 | 2.10 ± 0.04 | 50.61 ± 2.92 |
| E3 | 9.2 ± 0.4 | 0.29 | 2.50 ± 0.09 | 57.11 ± 1.89 |
| E4 | 8.3 ± 0.4 | 0.31 | 2.01 ± 0.03 | 63.52 ± 3.20 |
| E5 | 7.4 ± 0.2 | 0.35 | 2.06 ± 0.05 | 95.01 ± 2.19 |

intervals over 11 h. The amount of drug released in both acidic and basic media was calculated, using the corresponding calibration curves.

## Results and Discussion

In the past few decades, sustained release drug delivery systems have attracted a great deal of attention in pharmaceutical researches, mainly due to their therapeutic advantages. Because of the importance of lithium carbonate in the treatment of manic depression, the preparation of a sustained release dosage form could not only increase the efficacy of treatment and patient compliance, but also can produce desirable blood concentrations and decrease the incidence of adverse effects.

In this study, various Carbopols, Eudragit RLPO and Pemulen were used as retarding polymers in an attempt to formulate a sustained release matrix-type dosage form of lithium carbonate. Based on the results of preformulation studies, it was observed that tablets with desirable physical characteristics could be prepared by using the wet granulation technique, due to the improvement of flowability and compressibility of lithium carbonate granules. Table 1 shows the composition of various formulations containing lithium carbonate and different polymers and inactive ingredients, prepared in this study. Table 2 indicates the results of physico-chemical quality control tests (including friability, hardness, weight variation, assay and dissolution time) performed on the formulations mentioned in Table 1.

In order to evaluate the amount of drug released at different time intervals, attempts were made to establish an appropriate limit, based on the existing pharmacokinetic information and some adverse effects of lithium carbonate and also the physiology of the gastrointestinal tract. Diarrhea is one of the common adverse effects of lithium carbonate (5). Studies have shown that an ideal sustained release preparation should release its drug content mainly in the small intestine. Conventional tablets and capsules enter the small intestine after 3-6 h, in the presence of food (6). On the other hand, following the administration of sustained release formulations, peak concentrations are delayed and may occur between 3 to 6 h after administration (7-10). Considering the fact that absorption of lithium is rapid and complete throughout the small intestine, one could conclude that a high percentage of drug should be released from tablets after 7 h in dissolution test. Therefore, not only the peak plasma concentrations and optimum bioavailability could be achieved, but also the occurrence of

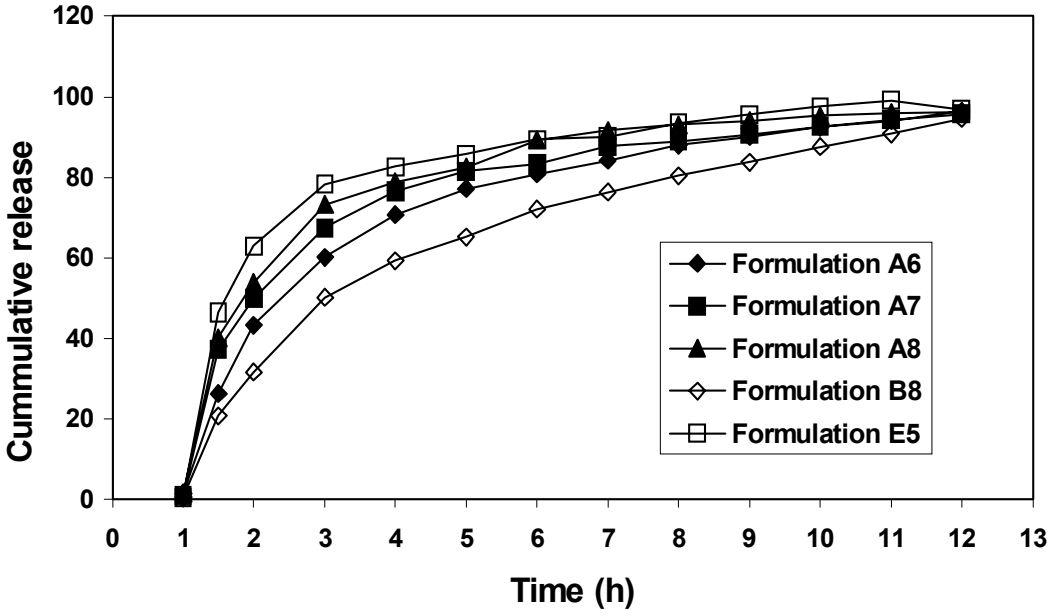


**Figure 1.** Release pattern of lithium carbonate from various coated, sustained-release matrix-type tablets in acidic and basic media (n=3).

**Table 3.** Dissolution time limits established for matrix-type sustained release lithium carbonate tablets.

| Time (h) | Drug released (%) |
|---|---|
| 1 | Less than 50 |
| 3 | 40 – 70 |
| 5 | 70 – 85 |
| 7 | 80 – 95 |
| 11 | 90 – 100 |

diarrhea would be prevented. Table 3 shows the release percent range of lithium carbonate for a sustained release preparation, considered in this study.

When investigating the influence of C934P on the release rate of lithium carbonate from tablet matrices, polymer concentrations ranging from 1.5 – 5% were employed. Tablets containing greater than 2% C934P were found to release their drug content relatively slow and produced an undesirable drug release profile, while a polymer concentration less than 3% was found to be suitable for producing a desirable release in the screening dissolution test, falling inside the determined limits.

When considering the effect of C974P on the release rate of lithium carbonate, polymer concentrations higher than 1.5% were observed to produce undesirable release profiles. Results have also shown that Eudragit RLPO contents between 3-5% caused relatively slow and unacceptable drug release profiles. However, by reducing the amount of polymer present within the formulation from 5 to 3%, along with an increase in Avicel content and a decrease in PVP concentration, the drug release pattern improved, in terms of the determined limits.

When Pemulen and C971P were used as the retarding agents, in all polymer concentrations examined, an undesirable and unacceptable drug release rate was observed. Overall, among the polymers investigated, C934P, C974P and Eudragit RLPO were found to be suitable for preparing matrix-type lithium carbonate tablets. As can be seen in Table 2, all preparations possessed desirable characteristics. However, since more than 80% of the drug released from formulations A6, A7, A8, B8 and E5 after 7 h, when placed in phosphate buffer medium, these formulations were selected for the enteric-coating process.

**Table 4.** Correlation coefficients of drug release curves for enteric coated tablets, based on three kinetic models.

| Formulation | Dissolution Time (h) | Correlation coefficients | | |
|---|---|---|---|---|
| | | Zero order | First order | Higuchi model |
| A6 | 0.5 – 11 | 0.9036 | 0.8245 | 0.9641 |
| A7 | 0.5 – 11 | 0.8850 | 0.8299 | 0.9519 |
| A8 | 0.5 – 11 | 0.8642 | 0.8134 | 0.9383 |
| B8 | 0.5 – 11 | 0.9481 | 0.8688 | 0.9890 |
| E5 | 0.5 – 11 | 0.8820 | 0.8315 | 0.9983 |

In the final stage of this study, the amount of lithium carbonate released from enteric coated tablets was calculated over 12 h in both acidic and basic media (1 h and 11 h, respectively). Figure 1 depicts the release profiles obtained from the enteric coated tablets. The kinetic of drug release from the coated formulations was also assessed. The kinetic models evaluated were zero order, first order and Higuchi model. It should be noted that due to the presence of an acid-resistant film, the amount of the drug released after 1 h in acidic medium was negligible. Therefore, for all selected formulations. The release kinetic of drug in buffer solution was evaluated and analyzed statistically. The results obtained by assessing the drug release patterns showed that over a period of 11 h (in buffer medium), all enteric coated formulations most likely follow a Higuchi model of release. Table 4 indicates the correlation coefficients of drug release curves, calculated over 11 h, based on the above-mentioned kinetic models.

In general, Carbopols when placed in an aqueous medium, form a hydrogel due to water absorption. As the thickness of this hydrogel layer increases (depending upon the amount of water absorbed), the release rate decreases (11). The formation of a hydrogel layer seems to be potentially higher for Pemulen and C971P compared to C934P and C974P, and therefore, even a reduction in the amount of polymer, did not improve the drug release profile in Pemulen and C971P-containing formulations. The addition of starch to formulation resulted in a further decrease in release rate, despite its disintegrating property. This effect could be explained by considering the fact that swelling of starch would possibly further increase the thickness of the hydrogel layer produced by Carbopols and hence, influence drug release from the matrices. It seems that Eudragit RLPO can not form a hydrogel layer around matrices, and therefore, its content was kept constant at 3% in order to prevent disintegration of tablets in the dissolution medium. A decrease in the content of PVP as well as an increase in the amount of Avicel, caused a high penetration of dissolution medium into the matrices and hence improved release profile.

In conclusion, C934P, C974P and Eudragit RLPO were found to be suitable polymers for preparing sustained release tablet matrices containing lithium carbonate.

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