

Original Article

In Vitro – in Vivo Evaluation of Sustained - Release Lithium Carbonate Matrix Tablets: Influence of Hydrophilic Matrix Materials

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ABSTRACT

Background: Conventional Lithium carbonate (LC) tablets produce rapid and relatively high peak blood levels resulting in adverse effects. These drawbacks can be overcome by designing a suitable sustained or controlled-release LC preparation.

Methods: Sustained-release matrix tablets were therefore developed using different types and ratios of polymers including carbomer (CP), Na carboxymethylcellulose (Na CMC) and hydroxypropylmethylcellulose (HPMC), to assess the release profiles and in vivo performance of the formulations. The tablets were prepared by either direct compression (DC) or wet granulation (WG). In the DC method, 69% (450 mg) LC, 5, 10 or 15% CP or Na CMC (of total tablet weight), lactose and /or Avicel (to maintain constant tablet weight) were mixed and directly compressed. In the WG method, 450 mg LC and 10, 20, or 30% HPMC were granulated with Eudragit S100 solution, dried, and then compressed to formulate the tablets. In vitro and in vivo, newly formulated sustained-release LC tablets were compared with sustained-release commercial tablets (Eskalith® and Priadel®). In vivo studies were conducted in nine healthy subjects in a cross-over design, with a 3x3 Latin square sequence, and pharmacokinetic parameters were estimated using classical methods.

Results: The matrix tablets containing 15% CP exhibited suitable release kinetics and uniform absorption characteristics comparable to that of Eskalith®. In vivo, this formulation produced a smooth and extended absorption phase very much similar to that of Eskalith® with the identical elimination half-life and extent of absorption.

Conclusion: The matrix tablets containing 15% CP reduces the incidence of side effects often associated with high serum concentration of Lithium and blood level variations. Direct correlation between the dissolution profiles and the relative bioavailability of the formulations could be observed.

Keywords: Lithium carbonate, Matrix tablets, Sustained-release, In vitro-in vivo evaluation

Lithium carbonate (LC) is widely used for the prophylaxis and treatment of manic depression and mania and in the maintenance treatment of recurrent depression. Lithium ion is readily absorbed from the gastrointestinal tract; it is not bound to plasma proteins; its volume of distribution corresponds to 70% of body weight and elimination takes place through the kidneys, with a half-life of 20 to 24 hours. The therapeutic index of the drug is narrow (4.2 to 8.3 mg/L) and adverse effects are common even at therapeutic serum Lithium concentrations. Long-term therapy has to be adjusted to get serum

concentrations between 0.6 and 1.25 mEq/L (4.2 to 8.5 mg/L). Conventional LC tablets make the drug immediately available for absorption producing rapid and relatively high peak blood levels resulting in adverse effects associated with high Lithium serum concentrations¹⁻⁵. These drawbacks can be overcome by designing a suitable sustained-release LC preparation. The development of sustained-release or controlled-release formulations of this drug is therefore of therapeutic relevance and has drawn the attention of the pharmaceutical industries. The manufacturing procedures of presently

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available sustained release LC are generally patented. Probably the simplest and least expensive way to control the release of an active agent is to disperse it in an inert polymeric matrix. In polymeric systems, the active agent is physically blended with the polymer powder and then fused together by compression molding, which is a common process in the pharmaceutical industry⁶. Different types of polymers including carbopol (CP), sodium carboxymethylcellulose (Na CMC) and hydroxypropylmethylcellulose (HPMC) have been used to control the release of drug from the dosage forms⁷⁻¹⁴.

Objectives of the present study were:

- to prepare sustained release LC matrix tablets using hydrophilic matrix materials including CP, CMC and HPMC.
- to examine the in vitro release characteristics of LC from formulated tablets by varying types and compositions of matrix blend and
- to compare the in vivo serum concentration profiles of the adopted sustained-release tablet of LC with a commercially available sustained-release tablet of LC (Eskalith[®]) in healthy subjects.

Materials and Methods

The following materials were used: LC (E. Merck, Darmstadt, F. R. G), lactose (Fast Flo, Foremost Food Company, San Francisco, Calif. 94104), CP (Carbopol 934P, Goodrich, Zaventem, Belgium), Na CMC (Netherland GO 220), HPMC (K100M, Dow Chemical Company, USA), Microcrystalline cellulose (Avicel[®] pH 101), Eudragit[®] (Rom Pharma, USA), magnesium stearate, and commercially available LC sustained-release tablets (Priadel[®] and Eskalith[®]).

Preparation of Tablets

The hydrophilic matrix tablets were prepared by either direct compression or wet granulation technique. In the direct compression, sustained-release matrix tablets were formulated to contain 450 mg or 69% of LC, and 15, 10 or 5% of CP or Na CMC of total tablet weight. Microcrystalline cellulose and lactose were incorporated as filler excipients to maintain the tablet weight constant. Powder were mixed and lubricated with 1% (W/W) magnesium stearate and then directly compressed on a single punch tablet machine (KS 43373-202

Kilian Co, GMBH, Koln-Niehl) at a tablet weight of 650 mg, with a flat, non-beveled punch of 12-mm diameter. Tablet hardness was kept constant within the range of 7-8 kg as measured by an Erweka-TB 24 hardness tester.

In the wet granulation technique, 450 mg LC (69%) and HPMC (30, 20, or 10%) were granulated with an ethanolic solution of Eudragit[®] S100 (15.5 mg). Granulates were passed through an 18 mesh screen and dried at 40°C for 2 hours. The dried granulate was mixed with other formulation components, 3.3 mg magnesium stearate and 0.33 mg Aerosil[®], and then compressed into flat tablets of 11 mm diameter with a hardness of 6 kg.

Conventional LC tablets were formulated to contain 300 mg LC, 55 mg Na CMC, 200 mg microcrystalline cellulose and 1% magnesium stearate.

Lithium Assay

Calibration curves were prepared with human serum or dissolution media spiked with known concentrations of LC. Standard samples were treated in the same way as the unknown samples. Quantitation of Lithium was accomplished by atomic absorption spectrophotometer (Perkin-Elmer, USA-Norwalk, CT) at the wavelength of 670.8 nm.

In Vitro Dissolution Testing

The dissolution of the tablets was performed with the paddle method according to USP 25 using a dissolution tester (Pharma Test, PTZWS3, Germany). The dissolution medium was 900 ml of distilled water maintained at 37°C with a stirring rate of 100 rpm. At appropriate time intervals, 3 ml of samples were obtained and an equal volume of medium was added to maintain the volume constant. Samples were filtered, diluted, and analyzed for LC concentration in order to characterize the dissolution profiles.

Kinetic Analysis of Dissolution Data

The drug release data were fitted to the following simple exponential model $M_t/M_\infty = Kt^n$, where M_t corresponds to the amount of drug released in time; t , M_∞ is the total amount of drug released after an infinite time, K is a constant related to the

properties of the drug delivery system, and n is the release exponent related with drug release mechanism. When $n < 0.5$, the drug is released from the polymeric matrix with a quasi-Fickian diffusion mechanism. For $0.5 < n < 1$, an anomalous (non-Fickian) drug diffusion occurs. When $n > 1$, a non-Fickian Case II or zero order release kinetics could be observed^{15,16}. Mean dissolution time (MDT) was considered as a basis for comparison between the dissolution rates and was estimated by the following equation:

$$MDT = \frac{\int_0^{\infty} t.W_d(t).dt}{\int_0^{\infty} W_d(t).dt} = \frac{ABC}{W_0} \quad (1)$$

Where, ABC is the area between curves and W_0 is the actual quantity of drug, which is available for dissolution. ABC can be estimated algebraically or arithmetically. In either case, estimation of MDT requires knowledge of the time at which the dissolution process is complete¹⁷. In this study, ABC was calculated using arithmetic approach.

In Vivo Studies

The Ethics Committee on human studies of Isfahan University of Medical Sciences approved the study. Nine healthy adult male subjects aged 21-27 years and weighing 65-85 kg participated in the single-dose study. The volunteers were informed of the nature and purpose of the experiments and their written consent was recorded. Prior to study, clinical laboratory tests and physical examinations of all the subjects, including hematology, blood biochemistry, and urinalysis were performed to check their health status. On the basis of medical history, no subjects had a history or evidence of any acute or chronic diseases or drug allergy. All subjects were healthy and free of other drugs for at least one month prior to and during the experiments. In a randomized crossover fashion, based on a 3X3 Latin square sequence, each volunteer was given 450 mg LC on three occasions with a one-week washout period, once as a conventional tablet and twice as sustained-release tablets, either prepared by direct compression technique in our laboratory or reference standard tablets (Eskalith®). The drug was administered with 250 ml of water after overnight fasting.

The blood samples were collected for 48 hours through an indwelling catheter in a forearm vein at 0, 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 36, and 48 hours. The blood samples were allowed to clot and then centrifuged to get serum specimens.

Pharmacokinetic Analysis

A one compartment open model could describe the Lithium serum concentration after the administration of sustained-release formulations with first-order absorption according to equation (2). Following administration of immediate release formulation, the data was fitted to a two-compartment model according to Equation (3).

$$C = A(e^{-k_a t} - e^{-k_E t}) \quad (2)$$

$$C = A_1 e^{-\alpha t} + A_2 e^{-\beta t} + A_3 e^{-K_a t} \quad (3)$$

Where C is the serum Lithium concentration at time t, K_a is the absorption rate constant, K_E is the elimination rate constant, and α and β are the rapid and slow disposition rate constants, respectively. A , A_1 , A_2 and A_3 are coefficients which show the dimension of concentrations¹⁸. The maximum observed concentration, C_{max} , and the time to reach this concentration, t_{max} , were recorded for each dose and each subject. Pharmacokinetic parameters were calculated using PCNONLIN 4.1 (SCI Software, Lexington, Kentucky) as well as classical methods. All estimates maintained a minimum correlation coefficient of 0.97

Statistical Analysis

One-way analysis of variance (ANOVA) was used to assess the differences between pharmacokinetic parameters and to evaluate the differences between dissolution rate constants and mean dissolution times. Student t-test was used to compare two means where appropriate. P values of less than 0.05 were considered significant.

Results and Discussion

In Vitro

Release behaviors of LC from conventional, commercially available (Priadel® and Eskalith®) and formulated sustained-release tablets in distilled water are depicted in figure 1. Each data point represents the mean of six determinations. The drug release

kinetics including MDT and release exponents are also presented in table 1. The release profiles of LC from conventional and presently available sustained-release tablets, Priadel[®] and Eskalith[®], are shown in figure 1A. As illustrated, 90% of drug was released from conventional tablets within 30 minutes, which is in accordance with USP 25 requirements. However, this time for sustained-release tablets, Priadel[®] and Eskalith[®], was, 2 and 6 to 7 hours respectively. As shown in table 1, the MDT for Eskalith[®] and Priadel[®] is 1.9 ± 0.06 and 0.8 ± 0.03 , respectively. Eskalith[®], therefore, showed more sustained profiles leading to an anomalous mechanism.

As expected, the drug released much more slowly from tablets containing Na CMC than conventional or Priadel[®] tablets (figures 1A and 1B). No considerable differences in release rates were observed when 5% and 10 % of Na CMC was incorporated in tablets, however, drug release decreased significantly as 15% Na CMC was used in formulation (MDT, 2.9 ± 0.12 , 3.1 ± 0.09 , 3.8 ± 0.16 , respectively). As indicated in figure 1B, all tablets containing Na CMC showed a relatively rapid initial release of drug during the first hour (25-32%), but the release was followed by a sustained manner which reached 80%-85 % of the total content within 8 hours. Na CMC matrices, however, because of their polymer swelling and dissolution properties, did not show initial burst release as observed with HPMC matrices containing 10% of the polymer. The release exponent in this series was significantly greater than 0.5, which indicated anomalous drug release. Much greater MDT of all tablets containing Na CMC compared to Eskalith[®] indicated much slower release of the drug from this series of formulations. These formulations therefore were not selected for further in vivo studies.

The release patterns of LC from matrix tablets containing CP are illustrated in figure 1C. These profiles demonstrate that CP 15% has excellent retardant properties when used at 15% level, but less retardant effect at 10% and 5% level. As shown in figure 1C, when 15% CP was incorporated into formulation, an initial slow release of drug was achieved (10%-12 % during the 1st hour). However, the initial slow release pattern in the release profiles of tablets prepared using 5% and 10% CP was not

achieved. Increasing the amount of CP in the formulations from 5% to 15% resulted in a reduction in the drug release rate (MDT were 0.82 ± 0.02 , 1.3 ± 0.04 , and 2.50 ± 0.09 , respectively), leading to a shift from anomalous type of release towards a swelling-controlled, case II mechanism (table 1). This may be due to a reduction in regions of low micro viscosity and the closing of micro pores in the swollen state. Other investigators have observed similar types of results^{7, 19}. Decreasing content of Na CMC or CP increased the release rate, which also might be due to a decrease in the retardant content and/or to a change in the porosity and tortuosity of the matrix after dissolution of the higher content of water-soluble diluents, lactose and/or Avicel[®]. As lactose dissolves, it diffuses outward and decreases the tortuosity of the diffusion path of LC²⁰. It seems that the 15% CP matrix tablets (MDT, 2.5) exhibited comparable release kinetics with Eskalith[®]. This matrix tablet was therefore adopted for in vivo studies.

Figure 1D shows the mean dissolution profiles of tablets manufactured using HPMC as matrix material by wet granulation technique. Although all HPMC matrix tablets demonstrated relatively sustained release behavior, liberation after 4 hours was around 80%. Similar to Na CMC matrix tablets and Eskalith[®], they also exhibited an initial relatively rapid release of LC being more pronounced with the tablets containing 10% of HPMC as compared to those bearing 20% or 30% HPMC (MDT, 1.7 ± 0.07 , 2.2 ± 0.08 , and 2.3 ± 0.11 , respectively). The release was identified as anomalous most likely owing to the relative contributions of drug diffusion, polymer relaxation, and matrix erosion to drug release. HPMC matrices showed an initial burst of drug release rate, due to the time required for the formation of an efficient gel layer¹⁶. As the granulating process was conventional, the solution would not form a continuous layer of the acrylic resin over the drug. Therefore, such a structure makes the immediate release of some drugs unavoidable. Even small quantity may result in faster initial drug dissolution.

In Vivo

Serum Lithium concentrations and standard deviations achieved following oral administration of the conventional commercially available tablet,

Eskalith[®], and formulated sustained-release tablet, CP15%, are shown graphically in figure 2. The estimated mean values of pharmacokinetic parameters are also listed in table 2. Formulated sustained-release tablets were compared to a standard commercially available sustained-release tablet in order to determine their relative availability and sustained release characteristics. The formulated CP15% matrix sustained-release tablets resulted in C_{max} values similar to those produced by the commercially available sustained-release tablets (Eskalith[®]). However, higher C_{max} was yielded by conventional immediate release formulation.

As one would expect from inspection of the mean curves, the sustained release tablets had a significantly delayed t_{max} , showing 6.33 ± 0.82 for the Eskalith[®], 5.33 ± 0.82 for the CP and 2.54 ± 0.51 for the conventional tablets. The t_{max} of the Eskalith[®] and CP15% that showed a smooth and extended absorption phase was significantly longer than that obtained for conventional. This may reduce the incidence of side effects that is usually accompanied with Lithium therapy. The differences between AUC values for all tested formulations were not significant. This indicates that the extent of absorption was not different among all formulations. The mean value of the slow disposition rate constants obtained after the administration of the various formulations did not differ. This reflected in the elimination half-lives, which is quite long and did not show statistical differences among various formulations tested.

The mean absorption half-lives were found to be 1.56 ± 0.47 hours for standard sustained-release tablets, (Eskalith[®]), 1.22 ± 0.29 for CP15%, and

0.77 ± 0.35 hours for conventional preparation. The pharmacokinetic parameters estimated from serum Lithium concentrations profiles indicated that CP15% matrix tablets were sustained and exhibited a smooth and extended absorption phase as observed with commercially available sustained-release Eskalith[®]. The initial slow release of the drug observed in vitro in this formulation, will most likely result in a smooth and extended absorption phase of the drug from formulation in vivo.

Conclusion

In vitro release studies demonstrated that the release of LC from all formulated sustained matrix tablets were generally sustained. The drug release from matrices containing Na CMC, CP or HPMC was anomalous while matrices containing 15% of CP or 30% of HPMC essentially followed case II release. Therefore, Na CMC, CP, and HPMC can be used to modify release rates of LC in hydrophilic matrix tablets.

The data generated in the present investigation using sustained-release and conventional LC tablets indicated that the absorption of LC from gastrointestinal tract might depend mostly on the release rate. A direct correlation between the dissolution profiles of standard Eskalith[®] and CP with the relative bioavailability of the formulations could be observed. The sustained release effects of CP may prevent high peak blood levels and wide blood level variations in man to promote patient compliance during maintenance therapy.

Table 1. Mathematical modeling and drug release kinetics of Lithium carbonate commercially available and formulated sustained-release tablets. Data are mean \pm SD

Formulations		Exponent (n)*	R	MDT	Mechanism
<u>Carboxymethylcellulose</u>	5%	0.720 ± 0.015	0.977 ± 0.011	2.9 ± 0.12	Anomalous
	10%	0.587 ± 0.017	0.973 ± 0.012	3.1 ± 0.09	Anomalous
	15%	0.654 ± 0.026	0.988 ± 0.014	3.8 ± 0.16	Anomalous
<u>Carbomer</u>	5%	0.590 ± 0.023	0.899 ± 0.013	0.82 ± 0.02	Anomalous
	10%	0.692 ± 0.032	0.953 ± 0.017	1.3 ± 0.04	Anomalous
	15%	0.982 ± 0.047	0.968 ± 0.018	2.5 ± 0.09	Anomalous/Case II
<u>Hydroxypropylmethylcellulose</u>	10%	0.392 ± 0.041	0.987 ± 0.016	1.7 ± 0.07	Fickian
	20%	0.793 ± 0.018	0.968 ± 0.008	2.2 ± 0.08	Anomalous
	30%	0.884 ± 0.012	0.953 ± 0.009	2.3 ± 0.11	Anomalous/Case II
<u>Priadel</u>		0.577 ± 0.093	0.820 ± 0.025	0.8 ± 0.03	Anomalous
<u>Skalith</u>		0.836 ± 0.037	0.970 ± 0.018	1.9 ± 0.06	Anomalous/Case II

* Release exponent indicating the type of drug release mechanism

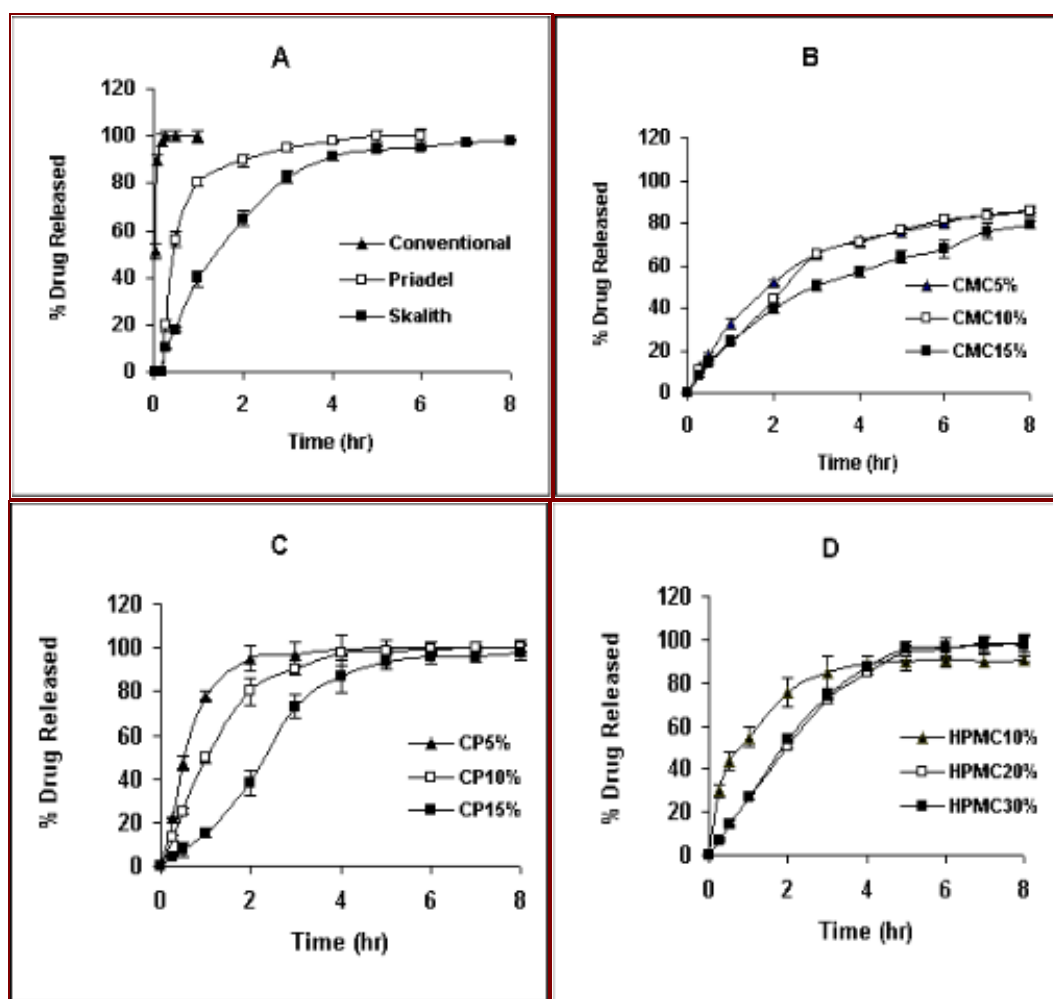


Figure 1. Release profiles of Lithium carbonate from commercially available tablets and formulated sustained-release matrix tablets (n=6).

Panel A: Commercially available Priadel[®], Eskalith[®] and immediate release formulation (IMR),

Panel B: Matrix tablets using Na carboxymethylcellulose (Na CMC)

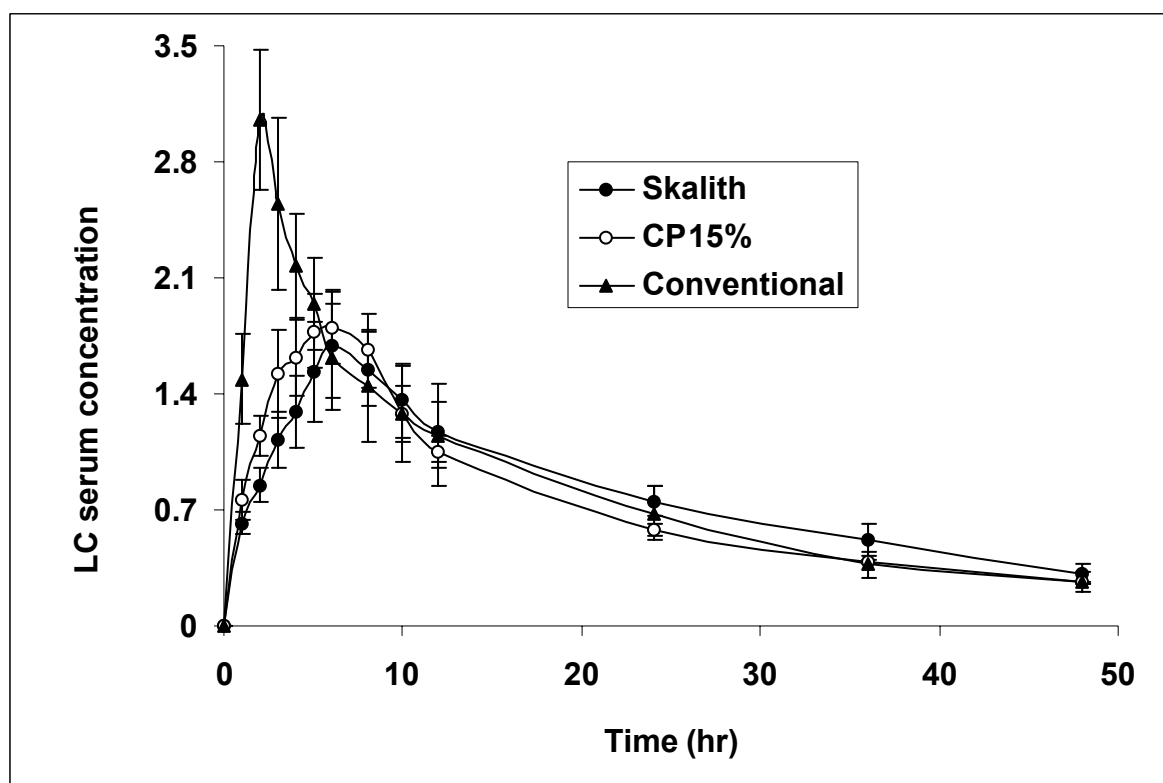
Panel C: Matrix tablets using carbopol (CP)

Panel D: Matrix tablets using of hydroxypropylmethylcellulose (HPMC)

Table 2. Pharmacokinetic parameters (Mean \pm SD) of various formulations calculated from serum Lithium profiles. (n = 9 volunteers)

PARAMETERS	Formulations			Statistical Analysis	
	Eskalith®	Conventional	Carbomer	Eskalith® vs Conventional	Eskalith® vs Carbomer
C_{max} (mg/L)	1.72 \pm 0.24	3.06 \pm 0.44	1.9 \pm 0.21	0.0012*	0.21
t_{max} (hr)	6.33 \pm 0.82	2.08 \pm 0.38	5.33 \pm 0.82	0.00007*	0.06
AUC _{0-∞} (mg.hr/L)	47.8 \pm 4.98	47.6 \pm 8.50	42.4 \pm 1.34	0.8831	0.07
$t_{1/2\beta}$ (hr)	19.3 \pm 3.61	17.7 \pm 1.94	20.2 \pm 1.44	0.1797	0.99
$t_{1/2a}$ (hr)	1.56 \pm 0.47	0.82 \pm 0.28	1.25 \pm 0.29	0.027*	0.03

* Significantly different

**Figure 2.** Mean serum concentration of Lithium (mg/L) following oral administration of 450 mg Lithium carbonate in commercially available (Eskalith®), and formulated sustained-release matrix tablet CP15% and conventional preparation. (n = 9 volunteers)

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