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RESEARCH PAPER

Evaluation of the In Vitro and In Vivo Performance of Two Sustained-Release Lithium Carbonate Matrix Tablets. Effect of Different Diets on the Bioavailability

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ABSTRACT

Two sustained-release (SR) lithium carbonate (Li) matrix tablets, which use a hydrophilic (HP) matrix of hydroxypropylmethylcellulose (Methocel 4K MP) and a lipid (L) matrix of hydrogenated castor oil (Cutina HR) as sustaining agents, have been studied. In vitro performance through dissolution tests in different media was established. The L and HP formulations were affected by the composition of the dissolution media, and liberation was complete in 8 hr using a variable-pH medium that simulates the gastrointestinal (GI) pH. Liberation was better described by the diffussional model of the square root of time for the L matrix and by zero-order kinetics for the HP matrix. Absolute bioavailability (BA) and food-induced changes on BA of both formulations were studied. The in vivo study design was a 4 × 4 Latin square involving 12 subjects who received two tablets of a 300-mg dose of SR formulations while fasting or with a standarized normal, high-fat, or high-fat/high-protein meal. The results for both formulations showed no differences in the disposition parameters and mean residence time when the tablets were administered with any type of diet. Changes in rate of absorption were found when both types of tablets were administered with any class of diet. The analysis of the ratio C_{max}*/AUC (area under the curve) evidenced that changes in* C_{max} *were attributable to a higher rate*

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of absorption for the HP matrix and to a higher amount absorbed for the L matrix. In the last, high-fat and high-fat/high-protein diets produced higher AUCs than under fasting condition. The SR Li tablets formulated with hydrogenated castor oil were affected more by high-fat food, probably because of the increase of pancreatic and biliary secretions promoted by the meal, which would affect the matrix itself. The HP matrix was also affected, but to a lesser extent. The magnitude of the change in C_{max} *observed with this matrix probably is not important from a clinical point of view. Absolute BA was very low for the lipid matrix; in addition, since it is more seriously affected by food, probably it is not a good choice for a drug such as lithium. The in vivo behavior of the HP matrix makes it advisable to invest in efforts to achieve increased BA. Comparing in vitro and in vivo results, the focus should be achieving sustained, but complete, in vitro liberation in not more than 3 hr, with simulation of the transit time through the stomach and small bowel since lithium ion is only absorbed to this point.*

INTRODUCTION

Lithium salts are used in the treatment of mania and for the prevention of recurrent attacks of manic-depressive illness. Lithium ion is readily absorbed from the gastrointestinal (GI) 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 15 to 30 hr. The drug is not metabolized, and it has a narrow therapeutic index. Long-term therapy has to be adjusted to get serum concentrations between 0.6 and 1.2 mEq/L (4.2 to 8.3 mg/L) because higher concentrations may cause severe side effects (1–4).

Conventional lithium carbonate (Li) dosage forms make the drug immediately available for absorption, producing rapid and relatively high blood levels. The goal of sustained-release (SR) Li preparations is to diminish the incidence of side effects, controlling drug liberation during the first hours after the administration, thus preventing high blood levels because the drug itself has a long half-life.

Matrix systems are widely employed for SR tablets because of the advantage of using conventional technology for production. Three classes of excipients, each with its own advantages, are used to obtain the matrix: plastic, hydrophilic (HP), and lipid (L) substances (5).

Drugs are absorbed after oral administration as a consequence of a complex array of interactions among the drug, its formulation, and the GI tract. Food may affect drug bioavailability (BA), inducing some physiological changes, like changes in gastric pH, gastric emptying rate, intestinal motility, and secretions (6–8). These modifications are dependent on the type of meal and could be of great relevance when drugs are administered in SR formulations. Many excipients used to achieve SR behavior depend on the environmental conditions of the GI tract for provision of a more or less sustained delivery of the drug.

Changes in drug absorption could be clinically significant, depending on the type of drug and the extent of the change. For drugs with a narrow therapeutic index such as Li, well-defined therapeutic serum levels, which require titration to a patient's condition, the changes could be very important.

In addition, food could alter the in vivo performance of SR products, which have designs that allow the liberation of the drug over several hours; in spite of administration far from mealtimes, they will necessarily be in contact with food while the system is still liberating drug.

Dumping is another risk factor of SR products. Dose dumping has been demonstrated for some SR theophylline products; theophylline is also a drug with a narrow therapeutic index. The mechanism to explain dumping remains unclear as yet, but the presence of a fatty food was responsible for the phenomenon, probably due to the interference between some components of the diet and the SR system (9).

The purpose of this paper is (*a*) to characterize the behavior of the formulations in different dissolution media, (*b*) to evaluate absolute BA of the formulations, and (*c*) to evaluate possible changes in the BA, including dumping, of two SR Li tablets when they were concomitantly administered with different types of food: normal, high-fat, and high-fat/high-protein diets, using the fasting condition followed by a normal diet as the control situation. One of the tablets used hydroxypropylmethylcellulose, Methocel K 4MP™ as the HP matrix, and the other

used hydrogenated castor oil, Cutina HR™ as the L matrix.

The selection of the different diets was based on the following considerations: normal diet because this is the type of meal most frequently used to take the tablet; high-fat diet because of the possibility of dose dumping (9), and high-fat/high-protein diet because it is a common meal combination in our local population. Previous work from our group demonstrated that the BA of an SR theophylline tablet, formulated in a plastic matrix, was affected more by this last diet (10).

SUBJECTS, MATERIALS, AND METHODS

In Vitro Dissolution Testing

Tests were performed using the USP dissolution apparatus no. 2 (paddle) at 37°C and a stirring rate of 100 rpm. For the tests, 900 ml of the following dissolution media were used: water, simulated gastric fluid TS without enzyme (11), simulated intestinal fluid TS without enzyme (11), and a medium with a gradual change of pH (pH profile) (12). Samples were obtained at appropriate times in order to define the dissolution profiles properly. Six replications of tests were made for each medium.

Formulations

Formulations used in this study were developed in our laboratory, and their composition were as follows:

	HP Matrix	L Matrix
Lithium carbonate	300 mg	300 mg
PVP K 30	—	9.45 mg
Cutina HR	—	15 mg
Methocel K4 MP	120 mg	—
Eudragit S100	15.5	—
Avicel PH 101	—	15 mg
Magnesium stearate	2.2 mg	—
Stearic acid	—	3 mg
Aerosil	0.22 mg	—
PEG 4000	—	22.5 mg

In the HP matrix formulation, Li and Methocel K4 MP were granulated with an ethanolic solution of Eudragit S100 (12.5%). In the L matrix formulation, Li was granulated with an ethanolic solution of PVP (10%). For both formulations, the granulate was obtained by passing it through an 18 mesh screen and drying at 40°C for 2 hr. The dried granulate was mixed with the other components of the formulation, and the tablets were compressed on a single-punch press to flat tablets of 11 mm diameter with a hardness of 6 kg.

Bioavailability Testing

Study Design

Two studies, one for each formulation, were conducted with healthy young male volunteers. They were informed about the course, risks, and aims of the study, and they gave their written consent. Subjects were instructed to abstain from strenous physical exercise. Clinical laboratory tests and physical examinations of all the subjects were performed to check health status. The study protocol was approved by the ethics committee of the faculty.

The experiment used a crossover design, with a 4×4 Latin square sequence and a 3-week washout period. There was a random assignment of 12 subjects to treatment sequences in blocks of 3 subjects.

The volunteers fasted overnight. On the day of the study, they swallowed two tablets with the selected breakfast or with 150 ml of tap water (control). For the control, the fast was maintained for 3 hr; at this time, the control subjects received a normal breakfast.

Lunch was served after 6 hr and an evening meal after 10 hr from the beginning of the experiment according to the class of diet selected for each group.

Collection of Blood and Urine Samples

Venous blood samples(about 10 ml) were collected for 72 hr through an indwelling catheter in a forearm vein. Serum was separated by centrifugation, and it was stored at −20°C until assayed. Urine was collected at appropriate intervals during the 72 hr. Urine volume was measured for each sample, and an aliquot was frozen until analysis.

Serum, Urine, and Dissolution Lithium Assay

Calibration curves were prepared with human serum, urine, or dissolution media, added to known lithium concentrations, and treated in the same way as the samples. Quantitation of lithium was made by atomic absorption spectrophotometry, diluting the samples in order to work according the following instrumental conditions: working range, 0–4 ppm; wavelength, 670.8 nm; and an oxidizing air/acetylene flame.

Meals

Three types of diet were employed in the study: normal, high fat, and high fat/high protein. The control situation was the fasting condition followed by a normal diet.

All the diets were adjusted to make them isocaloric with a normal sodium intake. All the components of each meal were weighed, and their quantities were modified according to the kind of diet. Total caloric intake on the day of the experiment was 2200 kcal for all the subjects and all the diets.

1. Normal diet: breakfast and evening meal of milk, sugar, bread, butter, and marmalade; lunch of meat, rice, tomato salad, bread, apple, and juice. Caloric intake of normal diet was from 10.6% protein, 25.8% fat, and 63.6% carbohydrates.
2. High-fat diet: breakfast and evening meal of milk, sugar, bread, and butter; lunch of meat, tomato salad, french fried potatoes, bread, apple, and juice. Caloric intake of high-fat diet was from 10.6% protein, 42.1% fat, and 47.3% carbohydrates.
3. High-fat/high protein diet: breakfast and evening meal of milk, sugar, bread, butter, and fresh cheese made with low-fat milk; lunch of meat, french fried potatoes, tomato salad, bread, apple, and juice. Caloric intake of high-fat/high-protein diet was from 14.9% protein, 42.9% fat, and 42.2% carbohydrates.

Kinetic Analysis

In vitro dissolution data were fitted to order zero and order one kinetics; a diffusional model of the square root of time was also used. From the in vivo data, the area under the curve (AUC) of the plasma concentration versus time, maximum concentration C_{max}, time at which C_{max} is reached t_{max}, half-life β, renal clearance, and Vd β were calculated by the classical pharmacokinetic methods. The statistical moment theory was used to calculate the mean residence time (MRT). The total amount of drug excreted in the urine Xu^{∞} was obtained using the following equation (13):

$$[Xu]_t = Xu^{\infty} - \frac{1}{1 - e^{-\beta\Delta t}} [(Xu)_{t+1} - (Xu)_t]$$

As lithium is almost completely excreted in the urine and considering that the subjets were instructed to abstain from strenous physical exercise, the fraction absorbed F was calculated from the total amount excreted in the urine divided by the amount administered.

Statistical Analysis

A multiway analyis of variance (ANOVA) and least significance difference (LSD) test were employed to assess the differences among the elimination half-lives, MRT, and the relation C_{max}/AUC ($p < .05$). A nonparametric test was used for the statistical analysis of t_{max} ($p < .05$). Bioequivalency of the formulation given under fed and fasted conditions was established when the 90% confidence interval for the AUC and C_{max} fell within the interval 0.80 to 1.25.

RESULTS AND DISCUSSION

Figures 1 and 2 show the mean dissolution profiles obtained for the HP and L tablets, respectively, with the different media. Both formulations were affected by the composition of the media. Liberation after 8 hr was around 80% in water, 40% in intestinal fluid, and almost 100% in the medium with the gradual change of pH. The behavior in gastric fluid evidenced a great difference between the two types of tablets.

Dissolution data fit a zero-order kinetics better for the HP matrix and fit the diffusional model of the square root of time for the L matrix (14). Dissolution constants are listed in Table 1.

The difference between the two tables in their behavior in gastric medium could be explained by the difference in the binder solution since both excipients used to form the L and HP matrices should not be affected by the pH of the dissolution medium. The HP tablet used Eudragit S100™, an acrylic resin, as the binder solution; the L tablet used PVP (polyvinylpyrrolidone) solution. Eudragit S100 is insoluble at acidic pH and becomes soluble at pH 7.

As the granulating process was conventional, the solution would not form a continuous layer of the acrylic resin over the drug, allowing part of Li to be dissolved by the gastric fluid. In the L tablet, PVP does not act as a barrier, and the medium had the possibility of being inmediately in contact with the drug, liberating an increased amount because lithium is a carbonate and easily soluble in acidic media.

We selected a medium with variable pH in order to simulate the physiological pH time profile (12). Both formulations showed an SR behavior, but as in the gastric fluid, the L tablet released a greater amount of drug than the HP tablet during the first 3 hr, when the pH was below 3.

Figures 3 and 4 show the mean profiles of serum concentration versus time in 12 subjects after the administra-

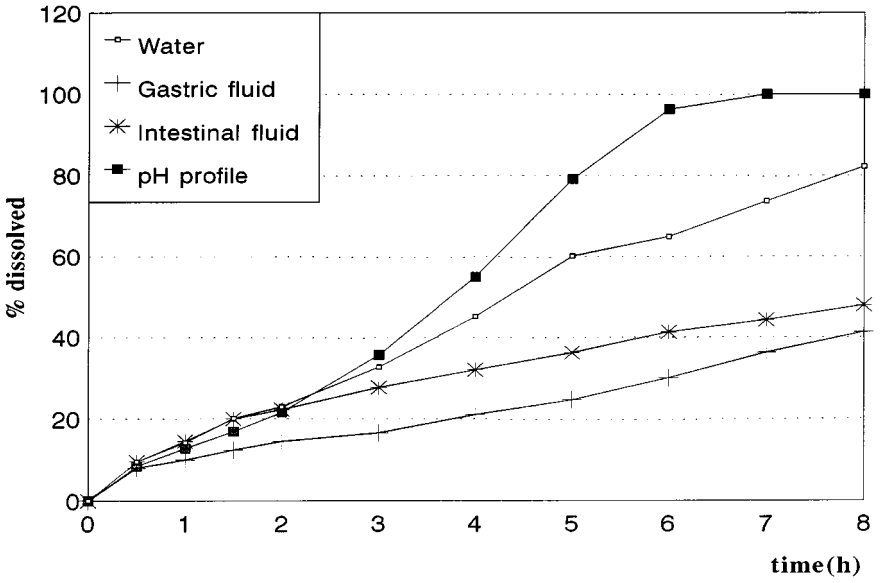

Figure 1. Dissolution profiles obtained for the hydrophilic matrix in different dissolution media.

tion of the SR Li tablet in HP and L matrices, respectively, with the different diets. The pharmacokinetic behavior fit a two-compartment model better according to previous work of our group and others (2,3,15,16). The presence of any kind of food produced a higher C_{max} than the fasting state for both formulations. No evidence of dose dumping was observed in any particular subject for both matrix formulations.

Tables 2 and 3 summarize the pharmacokinetic parameters obtained after the administration of both Li tablets with the different diets. They showed high interindividual variation, characteristic for this drug. The results of the

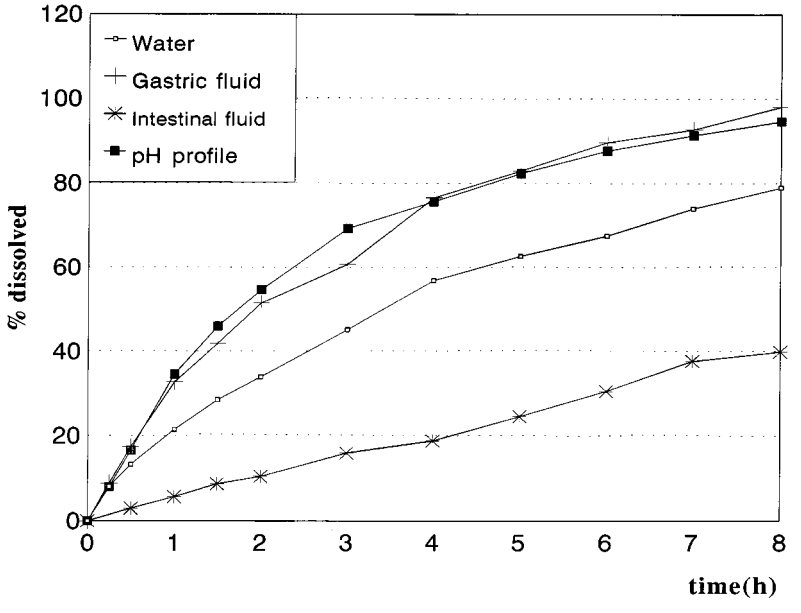

Figure 2. Dissolution profiles obtained for the lipid matrix in different dissolution media.

Table 1

Dissolution Constants for HP and L Tablets in Different Dissolution Media (Mean ± SD)

Dissolution Medium	kd (mg/hr) HF Tablet	kd (mg/hr$^{1/2}$) L Tablet
Water	30 ± 6.1	12.6 ± 1.2
Gastric fluid	13.2 ± 2.0	16.5 ± 1.5
Intestinal fluid	13.2 ± 0.7	6.3 ± 0.6
pH profile	56.7 ± 5.2	17.7 ± 1.8

statistical analysis of pharmacokinetic parameters are shown in Table 4. The half-life β was quite long and did not show statistical differences among the different diets. Calculated values for renal clearance and Vd β demonstrated that lithium did not change its elimination or its distribution when the SR tablets were administered with the different meals (Tables 2 and 4).

Table 3 contains the pharmacokinetic parameters more related to BA. The administration of the HP and L tablets with any class of meal produced C_{max} significantly higher than the fasting situation (Table 4).

With the L matrix tablet, we found that t_{max} was higher in fed conditions than in the fasting one, indicating that any type of food produced a delay in the rate of absorption (Tables 3 and 4). For high-fat and high-fat/high-protein diets, we observed higher AUCs and C_{max}, and some differences were observed between the high-fat and high-fat/high-protein diets, especially in *F*, indicating that a higher proportion of proteins also could be important when combined with a high fat content for the meal. The AUC was smaller for the HP matrix with the normal diet (Tables 3 and 4). Considering that the AUC is the parameter normally used to evaluate the amount absorbed, we would expect the same trend in Xu^{∞}. Although we hardly controlled such experimental conditions as sodium intake and physical activity, a controversial result was obtained with the urinary data. As lithium is 95% eliminated in urine, recollection of all the drug eliminated this way can be considered the fraction of the dose absorbed *F*. Comparing the AUCs for the fasted and normal diets, they became bioequivalent for the L matrix and nonbioequivalent for the HP matrix. The opposite conclusion is obtained from the analysis of urinary data (Figs. 5 and 6 and Tables 3 and 4). In accordance with previous reports, special care has to be taken with high-fat diets since they were responsible for some dose-dumping problems (9,17). High fat concentrations in the GI tract may affect the integrity of SR formulations, causing them to dose dump to toxic levels. The influence of food has been documented for a number of SR theophylline products, and it has become especially important for Theo-24, which

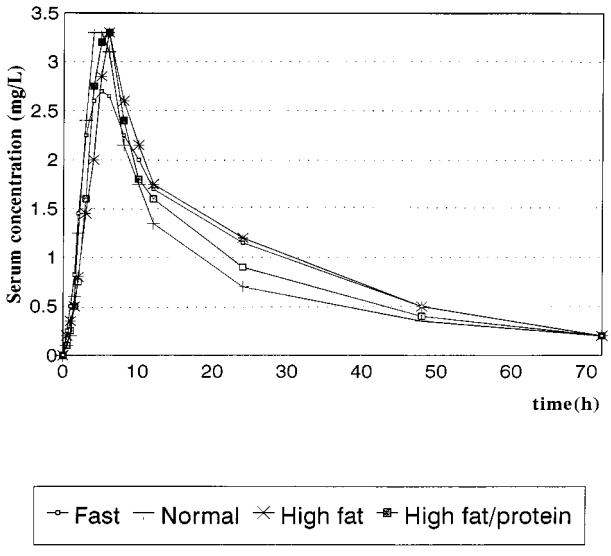

Figure 3. Mean serum concentration of lithium obtained after the administration of the hydrophilic matrix sustained-release tablet in fasting and fed conditions after a single dose of 600 mg lithium carbonate.

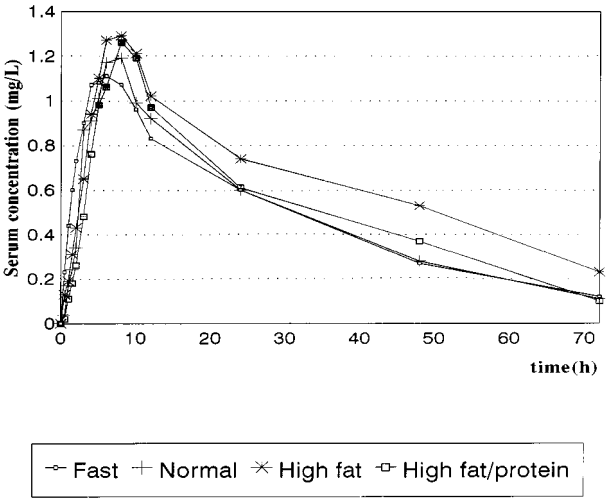

Figure 4. Mean plasma concentration of lithium obtained after the administration of the lipid matrix sustained-release tablet in fasting and fed conditions after a single dose of 600 mg lithium carbonate.

Table 2

Disposition Parameters for HP and L Tablets Administered with the Different Diets (Mean ± SD)

Formulation	Parameter	Fast	Normal	High Fat	High Fat/ High Protein
HP matrix	*t* 1/2 (hr)	19.22 ± 4.12	18.60 ± 1.46	19.31 ± 3.89	19.33 ± 2.02
	Vd β (L/kg)	0.670 ± 0.205	0.657 ± 0.139	0.667 ± 0.178	0.674 ± 0.158
	Clearance (L/hkg)	0.058 ± 0.010	0.056 ± 0.008	0.046 ± 0.006	0.050 ± 0.006
L matrix	*t* 1/2 (hr)	20.90 ± 4.87	19.06 ± 5.44	21.44 ± 4.47	18.61 ± 4.52
	Vd β (L/kg)	0.728 ± 0.216	0.675 ± 0.260	0.742 ± 0.199	0.650 ± 0.213
	Clearance (L/hkg)	0.051 ± 0.021	0.049 ± 0.015	0.048 ± 0.008	0.050 ± 0.031

dose dumped when it was administered with a high-fat meal. Regarding this aspect and analyzing the performance of the two tablets administered with both high-fat diets used in this study, the AUC and Xu^{∞} were coincident (Table 3). In summary, Xu^{∞} remains a good parameter for evaluation of changes in absolute BA for Li.

The MRT was practically unaltered for both formulations in the presence of food; values are in agreement with those of SR formulations and for drugs with a long half-life like Li; as a measure of the amount of time required for the intact drug molecule to move through the body, it can be concluded that this time is the same for fasting and nonfasting conditions.

For many SR products, it could be difficult to establish t_{max}; consequently, it is hard to assess if changes in C_{max} are due to changes in the amount or rate of absorption since in pharmacokinetics C_{max} is considered a hybrid parameter that changes with quantity and speed of absorption. Some authors use the ratio C_{max}/AUC as an attempt to make C_{max} independent of the extent absorbed and as a clearer, more unambigous measure of the absorption rate than C_{max} (18,19). To distinguish if the higher C_{max} values were more attributable to changes in the amount absorbed or in the rate of absorption, we considered it appropriate to evaluate the ratio C_{max}/AUC; the statistical analysis showed differences among the fasted state and any fed state, indicating that changes in C_{max} are more probably due to changes in the rate of absorption in the HP matrix tablet (Tables 2 and 4). The statistical analysis of the ratio did not show differences when comparing the

Table 3

Bioavailability Parameters for HP and L Tablets Administered with the Different Diets (Mean ± SD)

Formulation	Parameter	Fast	Normal	High Fat	High Fat/ High Protein
HP matrix	AUC (mgh/L)	72.29 ± 17.35	59.48 ± 8.90	73.95 ± 13.72	65.46 ± 9.20
	C_{max} (mg/L)	3.05 ± 0.44	3.69 ± 0.99	3.56 ± 0.45	3.68 ± 0.68
	t_{max} (hr)	5.1 ± 1.4	4.8 ± 0.5	5.4 ± 1.2	5.2 ± 1.3
	Xu^{∞} (mg)	58.3 ± 9.0	55.7 ± 5.2	52.9 ± 8.7	53.1 ± 6.4
	C_{max}/AUC (1/hr)	0.0456 ± 0.0139	0.0639 ± 0.0241	0.0503 ± 0.0137	0.0572 ± 0.0134
	F (%)	51.8 ± 7.7	48.9 ± 6.2	51.6 ± 8.0	49.7 ± 6.0
	MRT (hr)	26.56 ± 4.41	24.94 ± 2.24	27.74 ± 4.23	26.57 ± 3.55
L matrix	AUC (mgh/L)	38.74 ± 19.47	38.10 ± 17.89	45.32 ± 8.71	40.55 ± 16.10
	C_{max} (mg/L)	1.30 ± 0.50	1.32 ± 0.53	1.41 ± 0.23	1.37 ± 0.47
	t_{max} (hr)	5.4 ± 1.7	6.8 ± 2.3	7.0 ± 1.6	7.7 ± 1.6
	Xu^{∞} (mg)	23.76 ± 11.47	31.16 ± 8.14	30.77 ± 9.30	40.35 ± 11.47
	C_{max}/AUC (1/hr)	0.0359 ± 0.0086	0.0356 ± 0.008	0.0324 ± 0.0072	0.0365 ± 0.0104
	F (%)	21.0 ± 9.5	27.6 ± 6.8	27.3 ± 8.2	35.7 ± 9.5
	MRT (hr)	30.5 ± 7.3	29.3 ± 7.8	33.1 ± 6.0	28.7 ± 5.9

Table 4

Statistical Relations Among the Pharmacokinetic Parameters for Both Tablet Types

Formulation	Parameter	Fast Versus Normal Diet	Fast Versus High-Fat Diet	Fat Versus High-Fat/ High-Protein Diet
HP matrix	*t* 1/2	NS	NS	NS
	Vd β	NS	NS	NS
	Cl	NS	NS	NS
	AUC	NBE	BE	BE
	C_{max}	NBE	NBE	NBE
	t_{max}	NS	NS	NS
	Xu^{∞}	BE	BE	BE
	C_{max}/AUC	S	S	S
	F	BE	BE	BE
	MRT	NS	NS	NS
L matrix	*t* 1/2	NS	NS	NS
	Vd β	NS	NS	NS
	CL	NS	NS	NS
	AUC	BE	NBE	NBE
	C_{max}	NBE	NBE	NBE
	t_{max}	S	S	S
	Xu^{∞}	NBE	NBE	NBE
	C_{max}/AUC	NS	NS	NS
	F	NBE	NBE	NBE
	MRT	NS	NS	NS

S = significant; NS = nonsignificant; BE = bioequivalent; NBE = nonbioequivalent.

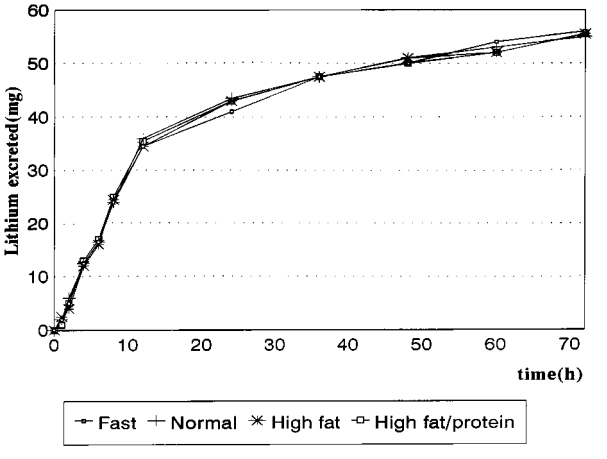

Figure 5. Mean cumulative urinary excretion of lithium obtained after the administration of the hydrophilic matrix sustained-release tablet in fasting and fed conditions.

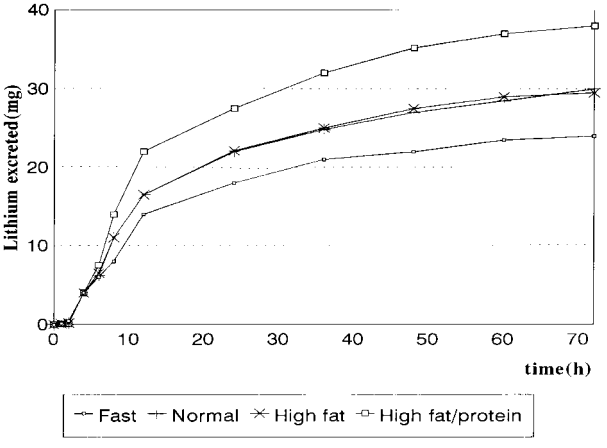

Figure 6. Mean cumulative urinary excretion of lithium obtained after the administration of the lipid matrix sustained-release tablet in fasting and fed conditions.

different diets with the fast administration, indicating that changes in C_{max} are more probably due to a high amount absorbed in the L matrix tablet (Tables 3 and 4).

Matrix systems that use water-insoluble materials that are potentially erodible may be sensitive to physiological changes produced by the presence of food. In a lipid matrix, release characteristics of the drug are more sensitive to digestive fluid composition than other types of matrices that use insoluble polymers. In vitro dissolution experiments using 3% lipase in a pH7 buffer demonstrated that diprophylline formulated in a Cutina HR matrix had a faster rate of liberation compared to the buffer without lipase (20).

Solid food in general and products of lipid digestion produce a delay in gastric emptying (6,8). For many drugs, this delay would be reflected in a delay of the absorption process considering that the stomach is not a good site for absorption. Delay in gastric emptying produced by any of the type of meal used in this study would be responsible for the delay in t_{max} observed for the L matrix (Tables 3 and 4). As t_{max} is dependent on the rates of absorption and elimination and there is no change in the half-life and clearance, this suggests that food ingestion at the same time as drug administration slowed drug absorption without affecting the disposition kinetics of lithium.

Both meals with a high fat content produced higher AUCs and C_{max} than the fasted situation for the L matrix. Total release of drugs from a wax-lipid matrix is not possible since a certain fraction of the drug is coated with an impermeable wax film. Release would be more effectively controlled if surfactants and lipases are present (5). As high-fat foods stimulate bile flow and secretions, the surface-active effect of bile salts combined with the erosion promoted by the lipase action would be the responsible factor for the increase in the amount absorbed (8).

The inclusion of a higher proportion of proteins in the meal produced changes more related to the high-fat proportion than with the high-protein content since the behavior was closer that of the high-fat diet. Some differences were observed in AUC between the high-fat and high-fat/high-protein diets for the L and HP matrices. The most important physiological changes induced by a high-protein diet are the increase in the splanchnic blood flow and the delay in gastric emptying, with the latter also seen with the high-fat diet; according to the general trend observed for AUC, the increase in blood flow did not seem to play a major role for these formulations.

The L matrix needs a relatively small amount of excipient in order to obtain adequate control of the liberation of the drug. For drugs such as lithium that have a high subject-to-subject variation and that require doses over 200 mg or more, the use of the L matrix to obtain a SR tablet offers a possibility for developing different strengths of the dosage form. As the amount of excipient needed to form the lipid matrix is a low proportion within the formulation, it is possible to obtain tablets of adequate size with different doses that are not difficult to swallow. Also, hydrophilic substances are reported in the literature as good alternatives for obtaining adequate control of drug liberation. The SR tablets formulated in the HP matrix in general are considered as safe systems because, even though the structure makes the immediate release of a small amount of drug unavoidable, this amount located in the surface of the tablet is a very small quantity, and there is no risk of dumping a large part of the dose. The appropriate liberation of the drug from such a system depends on the capacity of the excipient to form a viscous layer quickly when it meets water, thus controlling the liberation of the drug. The matrix system can pass along the GI tract without breaking up, releasing the active principle progressively (21). The formulation studied in this work used a matrix formed by hydroxypropylmethylcellulose, a semisynthetic cellulose derivative that has the advantage of the ionic and pH environment having no effect on their gelling capacity (22).

Regarding the absolute BA obtained in the fasted situation, a small proportion of Cutina HR produced an excessive delay of drug liberation and a very low BA. Since lithium is absorbed only until reaches the ileum (4), some physiological changes produced by the presence of food were not enough to liberate all the tablet dose before the tablet left the small bowel. Considering that the L formulation has a low proportion of Cutina HR and its in vivo behavior is affected by the presence of food, it probably is not advisable to invest effort in improving this formulation. On the contrary, the HP matrix tablet did not show complete BA, but the modifications of its in vivo performance produced by the presence of food are minor from a clinical point of view. Considering this fact, it would be appropriate to improve the formulation by making some changes in the proportion of matrix former and including more excipients for enhancing the porosity of the matrix.

The comparative analysis of dissolution kinetics and in vivo concentration profiles and urinary cumulative amount of drug suggests that, for SR Li preparations, 8-hr sustained dissolution kinetics is not indicative of good in vivo performance. According to the absorption characteristics of the lithium ion, the focus should be on achieving complete in vitro liberation in not more than 3 hr by trying to simulate the transit time through the stomach and small bowel.

CONCLUSIONS

The L matrix showed poor BA and was affected in the amount of drug absorbed, especially by diets with a high fat proportion. Considering these results, it probably is not a good alternative for Li SR formulation. The coadministration of an HP matrix with any class of food produced changes in the rate of absorption, but this change is not enough to be considered a problem from a clinical point of view. It became evident that efforts should be made to improve the absolute BA of this formulation. As an in vitro control method for Li SR formulations, it would be appropriate to develop dissolution tests that consider sustained, but total, dose liberation in 3 hr.

ACKNOWLEDGMENT

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