DESIGN AND EVALUATION OF A CONTROLLED-RELEASE THEOPHYLLINE TABLET
PRELIMINARY COMMUNICATION

M.N. GAI - R. PEZOA - J. CORBEAUX - A. ARANCIBIA

DEPARTAMENTO DE CIENCIAS Y TECNOLOGÍA FARMACÉUTICA
FACULTAD DE CIENCIAS QUÍMICAS Y FARMACÉUTICAS
UNIVERSIDAD DE CHILE-CASILLA 233 - SANTIAGO (CHILE)

SUMMARY — *A 300 mg controlled-release theophylline formulation was developed as a tablet prepared by wet granulation using the acrylic resins Eudragit S 100® and Eudragit RSPM®. The tablet was compared with a marketed controlled-release capsule using* in vivo *and* in vitro *tests. The* in vitro *dissolution of theophylline from the tablets followed an apparent zero order kinetics. The* in vivo *comparison was performed in a cross over fashion in four healthy volunteers who received one tablet or capsule every 12 hours during seven days. The results showed no statistically significant differences in AUC, t_{max} and in plasma theophylline concentrations at the different times. Nevertheless, concentrations were lower after the administration of the tablets than when the volunteers received the capsules. On the other hand, the apparent elimination half lives obtained after the tablets were longer than with the capsules. An excessive retardation in the release of theophylline from the tablet could be responsible for this fact.*

RIASSUNTO — *Viene preparata una compressa a cessione controllata contenente 300 mg di teofillina mediante granulazione per via umida, utilizzando resine acriliche Eudragit S 100® e Eudragit RSPM®. La compressa viene confrontata con una capsula a cessione controllata del mercato, utilizzando prove* in vivo *e* in vitro. *Lo studio* in vivo *viene condotto su 4 volontari sani, che ricevono una compressa o capsula ogni 12 ore per 7 giorni. I risultati non mostrano differenze statisticamente significative nei valori di AUC, t_{max} e nelle concentrazioni plasmatiche di teofillina ai differenti tempi. Tuttavia, le concentrazioni plasmatiche sono state inferiori dopo la somministrazione delle compresse in confronto con quelle ottenute dopo somministrazione delle capsule. D'altra parte, la vita media apparente di eliminazione ottenuta con le compresse, è stata superiore a quella ottenuta con le capsule; ciò potrebbe essere attribuito ad un eccessivo ritardo nella liberazione della teofillina dalla compressa.*

Introduction

Theophylline has been employed for various therapeutic purposes for many years. Its short half life in many patients, the wide subject-to-subject variation in the pharmacokinetic parameters and its narrow therapeutic range are its major limitations (1, 2, 3).

Controlled-release formulations have been developed in order to avoid the fluctuation of plasma concentrations in the steady state with a 12 hour dosage, which represents a great advantage in the mode of administration of theophylline (3, 4, 5, 6).

Acrylic acid-derived resins were used in the formulation developed in this work, namely, Eudragit RSPM® and Eudragit S 100®. The combination of both types of resins allows modifications in the release characteristics of the drug from the dosage form according to the intended requirements (7, 8).

This preliminary report shows the suitability of the matrix employed in controlling theophylline release. However, further studies are required.

Materials and methods

Tablet Manufacturing

Tablets were obtained by wet granulation, and an Eudragit S 100® solution in ethanol was used as a binding agent. The formulation contained theophylline (300 mg), Lactose (20 mg), Avicel® (20 mg), Aerosil® (0.5 mg) Eudragit S 100® (25.5 mg) - Eudragit RSPM® (80 mg) and Magnesium Stearate (2.2 mg).

The following tests were performed:

- Hardness: the hardness of 20 tablets was determined in a TBS/S Erweka Durometer.
- Friability: 20 tablets were tested in a Roche Friabilometer at 25 rpm for 4 minutes.
- Mean weight, weight variation, and assay of theophylline were performed according to the USP XXI techniques (9).
- Dissolution rates: a USP Apparatus 2 Dissolution equipment (9) was used to perform the dissolution kinetic tests at 37°C and 100 rpm. Tablets were placed in 900 ml of USP simulated gastric fluid, without enzyme, for 1 hour and later transferred to 900 ml of USP simulated intestinal fluid, without enzyme, during 7 more hours. Samples taken at 0.5-1-2-3-4-5-6-7 and 8 hours were assayed by UV spectrophotometry.

Study design

An *in vivo* cross-over study comparing the tablet with a marketed slow-release capsule was performed on 4 healthy, non-smoking, male volunteers. The subjects were put on a nonmethylxanthine diet at least 5 days prior to the experiment, and underwent a 6 day treatment with either product to be evaluated, each time prior to the pharmacokinetic experiments. A 300 mg dose was given every 12 hours, the last one administered in the morning of day 7th. Each subject received both the capsule and the tablet, in separate occasions two weeks apart.

Plasma concentrations were determined at 0-3-4-6-8-12 and 24 hours.

Theophylline assay was carried out by High Performance Liquid Chromatography under the following conditions:

Mobile solvent: 7% acetonitrile in 0.01 M sodium acetate/acetic acid buffer pH 4.0; Flow rate: 2.0 ml/minute; Detector: UV (254nm); Internal standard: 8-chlorotheophylline, 40 mg/ml. Theophylline extraction: 1 ml of plasma was placed in a stoppered centrifuge tube with further addition of 0.2 ml of 25% HCl and 5 ml of chloroform/isopropanol 95: 5. After mixing for 20 minutes in a rotator ("Roto-torque" Heavy duty rotator Cole Parmer Instrument) in a 45° angle at 20 rpm, the mixture was centrifuged for 5 minutes at 1500 g.

1 PS Whatman filter paper was used to remove the aqueous phase and 2 ml of the filtrate were evaporated to dryness in a waterbath at 50°C with a nitrogen stream. The residue was dissolved in 1 ml of water and 80 ul were injected into the chromatograph. The calibration curve was performed in a similar way. Methylxanthine free human plasma was employed, and known theophylline amounts were added. This method is based on the one proposed by Adams *et al.* (14).

Pharmacokinetic analysis

Area under the plasma concentration versus time curve (AUC); initial, maximum and final steady state concentrations in one interval (Co, Cmax and Cf respectively); elimination first order rate constant K and elimination half life $t^1/_2$: were calculated according to classic pharmacokinetic techniques using the SAS computer program (10, 11, 12).

Statistical analysis

The paired student's t-test was used to assess the statistical differences observed in the pharmacokinetic parameters; p used was 0.05 for all the comparisons.

Results and discussion

Tablets met the USP XXI weight variation and assay requirements as shown in Table I. A hardness ranging from 6 to 7 $\overrightarrow{kg}$ was established to obtain tablets of good physical characteristics and suitable handling conditions. Friability also met the technological manufacturing standards.

TABLE I

Characteristics of the 300 mg theophylline tablets.

Hardness $\overrightarrow{kg}$	Friability (%)	Uniformity of dosage units	Assay %	Mean weight (mg)
6.65 ± 0.52	0.3%	Met the USP XXI requirements	101.3%	432.3 ± 3.7

Fig. 1 shows the mean dissolution profile of six tablets. The dissolution process followed an apparent zero order kinetics as can be seen in this

figure, which shows that a graphic of the dissolved percentage of theophylline versus time is a straight line obeying the equation:

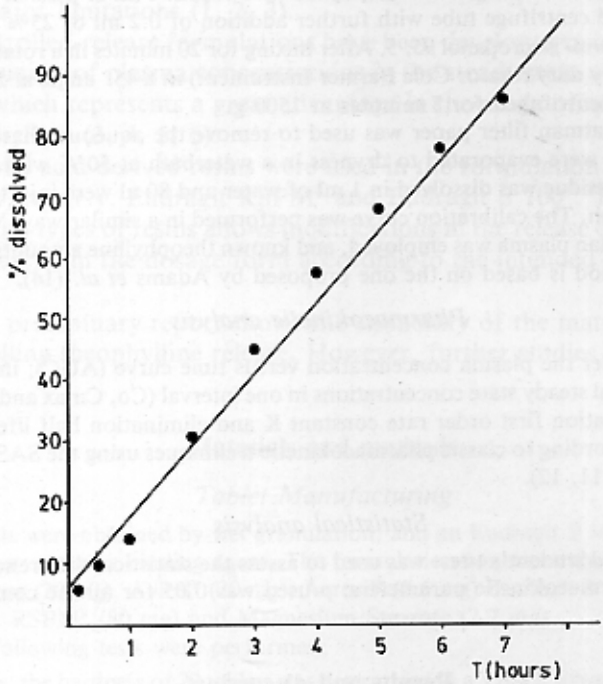

Fig. 1

Dissolution profile of theophylline tablets. The variation coefficient for each point of the figure was less than 3.2%.

$$\text{Amount dissolved (mg)} = 35.139 \cdot t \text{ (hours)} + 18.637$$

The mean value of the apparent zero order dissolution rate constant was $k_o = 35.139$ mg hour^{-1}. These results are similar to those reported by McGinity *et al.* who also employed an acrylic resin (7). During preliminary experiments we studied the dissolution of tablets of greater hardness (up to 9 Kg) finding that they exhibited practically equal dissolution kinetics. This is an important fact since it allows a greater manufacturing flexibility of the tablets.

The *in vivo* data (Table II) exhibited a great subject-to-subject variation in both formulations. This fact has been widely described for theophylline kinetic behaviour in man (3).

TABLE II

Theophylline plasma concentrations after the adiminstration of a 300 mg dose given in a capsule (C) or as the experimental tablet (T).

Subjects	TIME (hours)													
	0		3		4		6		8		12		24	
	T	C	T	C	T	C	T	C	T	C	T	C	T	C
1	6.0	10.5	6.3	13.0	7.1	13.4	7.7	13.2	6.3	11.6	5.1	9.5	3.2	3.6
2	7.7	11.7	9.1	12.7	9.1	14.4	8.8	16.4	7.9	12.5	6.7	11.2	3.7	5.2
3	7.7	9.6	7.1	12.4	8.7	12.4	9.6	13.1	8.1	11.0	6.7	9.2	4.8	4.7
4	4.0	9.2	5.0	8.9	5.5	9.3	5.2	9.1	4.2	8.0	3.9	4.5	0.9	1.5
$\overline{C}$	6.35	10.25	6.88	11.75	7.6	12.38	7.83	12.95	6.63	10.78	5.6	8.6	3.15	3.75
S.D.	1.76	1.11	1.71	1.92	1.65	2.21	1.92	2.99	1.81	1.95	1.36	2.87	1.64	1.64
V.C.%	27.72	10.83	23.92	16.34	21.71	17.85	24.52	23.09	27.30	18.09	24.29	33.37	52.06	43.73

When comparing C_o and C_f in both products (Table III), it can be observed that the latter is lower. This situation may be due to the circadian variation described for theophylline, which reports that the absorption process is significantly lower at night (13).

TABLE III

Steady - state concentrations in one interval after the administration of a 300 mg dose of theophylline given as a capsule (C) or as the experimental tablet (T).

	Co (ug/ml)		C_{max} (ug/ml)		C_f (ug/ml)	
	T	C	T	C	T	C
1	6.0	10.5	7.7	13.9	5.1	9.5
2	7.7	11.7	9.1	16.4	6.7	11.2
3	7.7	9.6	9.6	13.1	6.7	9.2
4	4.0	9.2	5.5	9.3	3.9	4.5
$\overline{M}$	6.35	10.25	7.98	13.18	5.60	8.60
S.D.	1.76	1.11	1.84	2.94	1.36	2.87
V.C.%	27.7	10.8	23.1	22.3	24.3	33.4

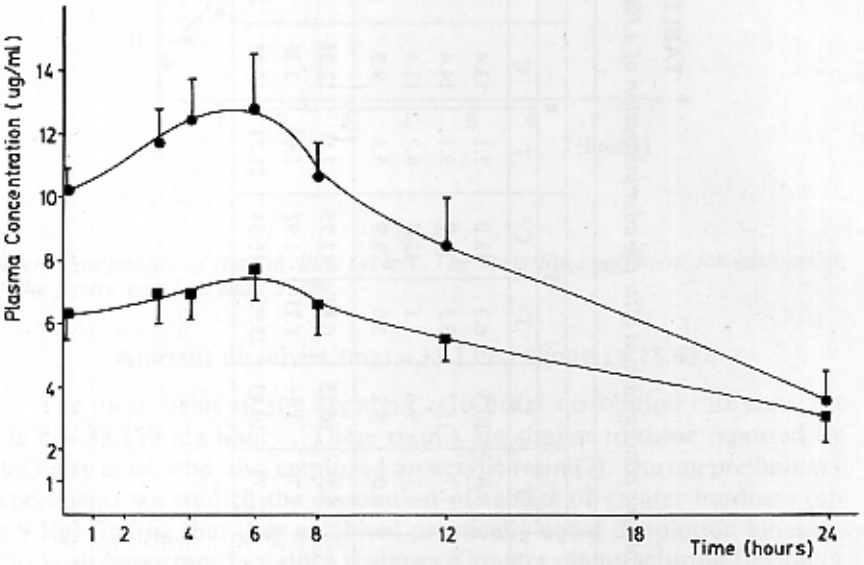

Fig. 2

Mean STEADY STATE theophylline plasma concentrations following the administration of the drug as a capsule (●) or as the experimental tablet (■) to 4 healthy volunteers. Bars correspond to standard error of the mean.

Fig. 2 shows the mean plasma concentrations of theophylline at the steady state after the administration of both dosage forms to four volunteers. No statistically significant differences were found when AUC, C_{max} and C_o at the steady state were compared (Tables III and IV). This is probably due to the high individual variation and the small number of subjects participating in the study.

Upon individual analysis of the results, the tablet showed lower concentrations and smaller areas under the plasma concentration/time curve (AUC) than the capsule (Tables II and IV); for these reasons, some differences between the two pharmaceutical formulations can be pointed out.

TABLE IV

Partial and total areas under the plasma concentration versus time curves (AUC) in μ/hour/ml in the steady state.

	0-24 hours		0-12 hours		12-24 hours	
	T	C	T	C	T	C
1	126.6	221.4	76.8	142.8	49.8	78.6
2	160.5	255.7	98.1	157.3	62.4	98.4
3	164.7	218.8	95.7	135.4	69.0	83.4
4	83.9	132.8	55.1	96.8	28.8	36.0
$\overline{M}$	133.9	207.18	81.42	133.07	52.5	74.1
S.D.	37.46	52.36	19.97	25.84	17.69	26.76
V.C.%	28.0	25.3	24.5	19.4	33.7	36.1

When comparing C_o and C_f between the two products the percent decrease in concentration during the interval, was lower for the tablet than for the capsule, whereas the concentrations obtained at 24 hours showed almost no difference in both formulations.

Thus, tablets showed a lower fluctuation in plasma concentrations than the capsules. This may be due to a longer absorption time from the tablet. The calculated tablet apparent elimination half life was longer (15.0 ± 6.3 hours) than that of the capsule (11.2 ± 4.0 hours). Absorption of theophylline from the tablets was probably delayed further than from the capsules, although there were not statistically significant differences.

The AUCs of the capsules turned out to be greater in all the volunteers at all intervals. The relative bioavailability of the tablets compared with the capsules was 0.65. However the mean relative bioavailability measured during the first 12 hours period was 0.60, which is lower than the total value. On the other hand, the bioavailability during the final 12 h period was 0.77. This would indicate a slower release of theophylline from the tablet, apparently for a longer time than from the capsule. This could be the reason

for the longer apparent elimination half lives observed upon tablet administration.

Our results indicate that the use of acrylic resins may be considered as a suitable mean to prepare a matrix for delaying theophylline release *in vivo*. However, on the basis of these results it can be concluded that changes in the formulation are necessary in order to optimize bioavailability. In this sense the present report should be taken as preliminary. We continue working on this point.

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