In Vitro Conditions for the Study of the In Vivo Performance of Sustained-Release Theophylline Matrix Tablets Administered in Fasted Conditions and with a High-Fat Diet

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ABSTRACT

Dissolution profiles of theophylline (TP) from three types of sustained-release (SR) matrix tablets (plastic [PL], lipid [LP], and hydrophilic [HP]) in different dissolution media, with and without enzymes, were established. Also investigated was the influence of a treatment of the tablets with peanut oil prior to the dissolution test. The in vivo behavior of the tablets under the fasted state and with the concomitant administration with a high-fat diet was previously evaluated; the diet produced changes in the absorption profiles for the three matrix tablets in comparison with fasted administration. Level A correlations were obtained between cumulative percentage dissolved (CPD) and cumulative percentage absorbed (CPA). For the fasted condition, better correlations were obtained with water as the dissolution medium for the HP and LP matrix; for PL matrix, the best correlation was obtained with a medium with gradual change of pH. The pretreatment with peanut oil showed better correlations for the fed state.

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INTRODUCTION

Matrix systems are widely used for sustained-release (SR) formulations because of the advantage of employing conventional technology for their production (1). The bioavailability (BA) of such systems could be affected by the presence of food, depending on the characteristics of the matrix former (2–4).

Absorption of theophylline (TP) from three SR tablets, using Eudragit RSPM™ as the plastic (PL) matrix, Carbopol 974P™ as the hydrophilic (HP) matrix, and Cutina HR™ as the lipophilic (LP) matrix, administered in fasted and fed states, was studied. The administration with high-fat meals showed a variable delay in the absorption process for the different formulations (5,6).

Efforts have been made to obtain in vitro–in vivo correlations that reflect the influence of food on the BA of SR preparations, using physiological and nonphysiological substances in the dissolution media, including biliary salts, pH changes with different buffers, pancreatic enzymes, and different fat substances such as fatty acids and peanut oil (7–9).

The aim of this work was to study the influence of different dissolution media, using some of the above-mentioned substances, on the release of TP from the matrix systems and to attempt to correlate changes in the dissolution profiles with changes observed in the absorption profiles when the tablets were administered in the fasted state and with a high-fat meal.

MATERIALS AND METHODS

Dosage Forms

Tablets were obtained by wet granulation according with the composition described in Table 1.

Dissolution Testing

All dissolution testing was performed using USP apparatus 2 (paddle) at 100 rpm at 37°C using 900 ml of dissolution medium. Dissolved TP was analyzed by ultraviolet (UV) spectrophotometry at 270 nm.

Dissolution Media

Dissolution media were water; gastric fluid simulated TS with and without enzyme (10); intestinal fluid simulated TS with and without enzyme (10); intestinal fluid simulated TS without enzyme and added with lipase (Sigma L-3126; Sigma, St. Louis, MO), 3 g/L, and taurocholic acid (TCA) (Sigma T-0750), 1.5 g/L; and medium with gradual change of pH (pH profile) that simulated gastrointestinal pH conditions (11).

Also, a pretreatment with peanut oil according to the following conditions was used: Tablets were shaken for 2 hr with 10 ml of peanut oil (Baker S901-07); they were then isolated, and release profiles were determined using water (LP and HP matrix) and the medium with gradual change of pH (PL matrix) as the dissolution media.

Pharmacokinetic Studies

Cumulative percentage absorbed (CPA) was obtained through the Wagner-Nelson method from previous works (5,6).

In Vivo–In Vitro Correlation

Level A linear correlation between mean CPA and mean cumulative percentage dissolved (CPD), at the same time, was evaluated using linear regression (r) and slopes (m). To correlate fasted administration with the

Table 1

Composition of the Sustained-Release Tablets

	LP Matrix	PL Matrix	HP Matrix
Theophylline	300 mg	300 mg	300 mg
Matrix former	Cutina HR, 41.4 mg	Eudragit RSPM, 60 mg	Carbopol 974P, 150 mg
Binder	PVP, 8.7 mg	Eudragit S100, 20 mg	Eudragit S100, 15.6 mg
Avicel PH 101		20 mg	
Spray-dried lactose		20 mg	20 mg
Magnesium stearate		4.5 mg	5 mg
Aerosil		0.5 mg	0.5 mg

in vitro dissolution condition, dissolution media without enzymes and biliary salts were used. Dissolution media with enzymes, biliary salts, or pretreated with peanut oil were used to correlate with the high-fat administration.

RESULTS AND DISCUSSION

Figure 1 shows the absorption profiles obtained when the three matrix tablets were administered after fasting and with a high-fat diet. The high-fat diet produced a delay in the absorption process from the LP and PL matrices. The HP matrix evidenced a delay during the first 3 hr, followed by a higher absorption rate during the next 9 hr (5,6).

The pH of the dissolution medium affected the liberation of TP from PL and HP tablets (Fig. 2). The PL matrix had faster TP liberation at around pH 7, and the HP tablets were faster at acidic pH; the latter is in agreement with the swelling conditions of Carbopol 974P (12). The LP matrix did not evidence such dependence. Inclusion of gastrointestinal enzymes and biliary salts had a relevant effect only on the LP matrix (Fig. 2), with liberation mechanisms that are mainly through erosion; a medium with TCA promotes better contact between the fat component of the matrix and the dissolution medium. However, in general terms, these physiological compounds were not able to reproduce changes observed in vivo with a high-fat diet for any of the three formulations (results not shown). Figure 2 shows the most relevant dissolution profiles used to correlate with the in vivo observations; Fig. 3 shows the best correlations obtained for fed and fasted conditions.

A good level A correlation is obtained when a combination of a high linear regression r and a slope m near 1 is achieved, indicating that the curves are essentially superimposable (10). For the fasting condition, absorption profiles were conveniently described in vitro using water as the dissolution medium for LP ($r = 0.9836$, $m = 0.9246$) and HP ($r = 0.9848$, $m = 0.7112$) matrices (Fig. 3). In the PL matrix, the best correlation was obtained using the medium with the gradual change of pH ($r = 0.9856$, $m = 0.8278$).

Good correlations were obtained for some TP SR formulations using a pretreatment of the formulations with peanut oil, performed before the dissolution test (9). Water, as a dissolution medium for LP and HP matrices, and the medium with a gradual change of pH for the PL matrix were selected because they showed the best correlations with the fasted condition. Figure 3 shows the correlations obtained. Comparing these results with the absorption profiles (Fig. 1), it can be noticed that the trend of the changes obtained by introducing peanut oil are the same. Probably, it was more obvious for the HP matrix, for which the in vitro profiles showed a delay during the first 2 hr and then a higher dissolution rate, in a shape very similar to the absorption profile (Fig. 1).

An excellent correlation was obtained for the LP ma-

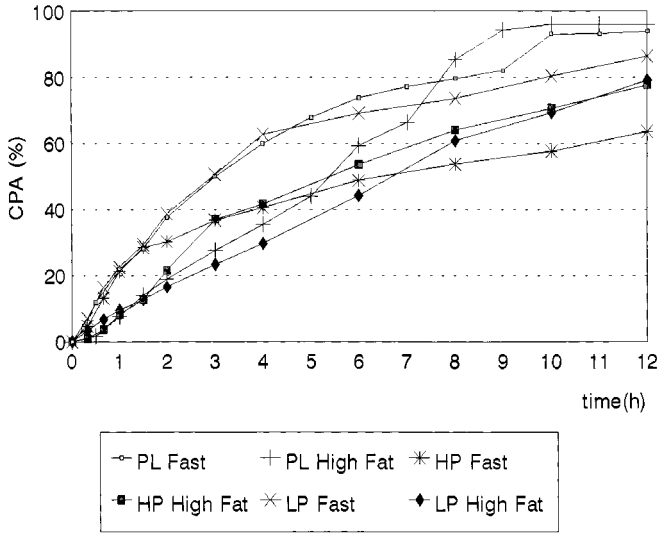

Figure 1. Absorption profiles obtained after the administration of the three formulations under fasting and fed conditions.

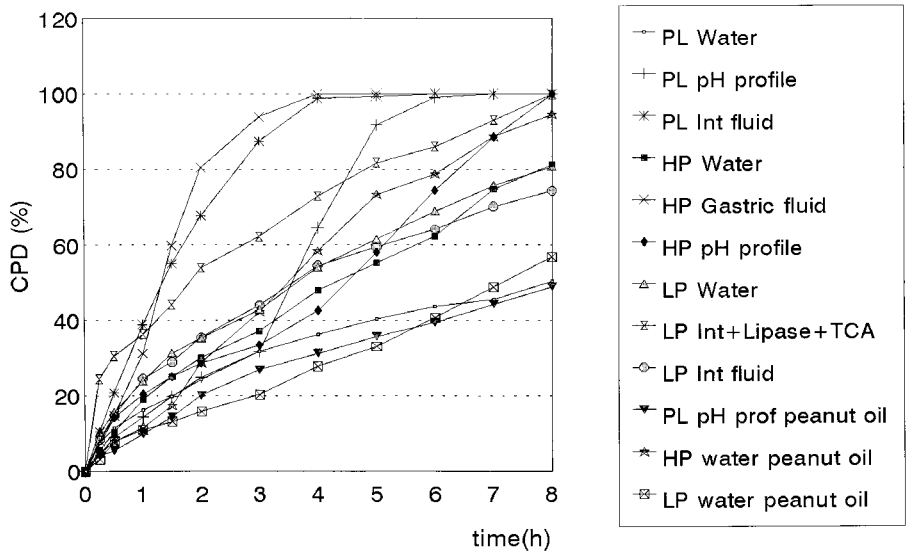

Figure 2. dissolution profiles obtained using different dissolution media with the different matrix tablets.

trix ($r = 0.9987$, $m = 1.0912$), indicating that absorption and dissolution profiles were practically superimposable. In the PL matrix, the pretreatment with peanut oil improved both r (0.9926) and m (1.2804), but we did not find the best experimental conditions in order to get a slope closer to 1. In the HP matrix, peanut oil improved linear regression ($r = 0.9913$), but not the slope ($m = 0.7114$); in spite of the m value, this condition reflects very closely the general trend for this formulation, with smaller rates during the first 2 or 3 hr, followed by higher dissolution rates.

CONCLUSION

Absorption profiles obtained after the administration of the three matrix tablets under fasted conditions were

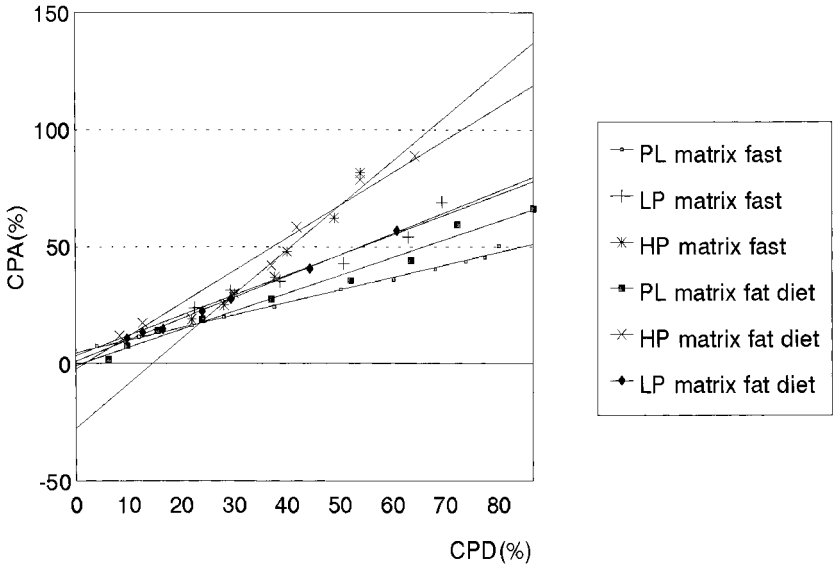

Figure 3. In vivo–in vitro correlations obtained for fasted and fed conditions.

reflected by in vitro tests using water as the dissolution medium for the LP and HP matrix and using a medium that resembles pH changes along the gastrointestinal tract for the PL matrix. Changes produced in the absorption profiles by a high-fat diet were correlated better with a pretreatment of the tablets with peanut oil, followed by a dissolution test using water for Cutina HR and Carbopol 974P matrices and a medium with a gradual change of pH for the Eudragit RSPM matrix.

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REFERENCES

1. N. Lordi, Sustained release dosage forms, in *The Theory and Practice of Industrial Pharmacy* (L. Lachman, H. Lieberman, and J. Kanig, Eds.), Lea and Febiger, Philadelphia, 1986, pp. 430–456.
2. R. Toothtaker and P. Welling, Annu. Rev. Pharmacol. Toxicol., 20, 173–199 (1980).
3. L. Williams, J. Davis, and D. Lowenthal, Med. Clin. North Am., 77(4), 815–829 (1993).
4. W. Charman, C. Porter, S. Mithani, and J. Dressman, J. Pharm. Sci., 86(3), 269–281 (1997).
5. M. N. Gai, A. M. Thielemann, and A. Arancibia, Int. J. Clin. Pharmacol. Ther. Toxicol., 31, 547–552 (1993).
6. M. N. Gai, A. Isla, M. T. Andonaegui, A. M. Thielemann, and C. Seitz, Int. J. Clin. Pharmacol. Ther., 35(12), 565–571 (1997).
7. L. Wearley, A. Karim, F. Pagone, J. Streicher, and A. Wickman, Drug Dev. Ind. Pharm., 14(1), 13–28 (1988).
8. M. P. Dandellot Keller, P. Buri, and E. Charollais, Pharm. Acta Helv., 67(3), 66–69 (1992).
9. P. K. Maturu, V. K. Prasad, W. N. Worsley, G. K. Shiu, and J. P. Skelly, J. Pharm. Sci., 75(12), 1205–1206 (1986).
10. U.S. Pharmacopeial Convention, *The United States Pharmacopeia 23/National Formulary 18*, Author, Rockville, MD, 1995.
11. S. Das and B. Gupta, Drug Dev. Ind. Pharm., 14(4), 537–544 (1988).
12. *Carbopol Resins Handbook.*