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Dissolution of 4 controlled-release theophylline formulations in milk

P. Macheras [1], M. Koupparis [2] and E. Apostolelli [1]

Departments of [1] Pharmacy and [2] Chemistry, University of Athens, Athens (Greece)

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Summary

The dissolution of 4 controlled-release theophylline formulations was studied in a low-fat (0.75%) milk and in a buffer of pH 6.5. A flow-injection dialysis–UV spectrophotometric method was developed to determine the drug in the milk samples. Calibration curves were linear up to 250 μg/ml for theophylline and aminophylline and up to 450 μg/ml for choline theophyllinate, with detection limits of 18.5, 5.4, and 14.7 μg/ml, respectively, in a 5.0 ml minimum sample volume. Lower dissolution profiles in milk than in buffer were observed for 3 of the formulations examined. One theophylline formulation exhibited relatively similar dissolution profiles in both media. The use of milk as a food-simulating medium in dissolution studies is suggested for the in vitro evaluation of the release rate of drugs from controlled-release formulations. The proposed technique can be applied in such studies.

Introduction

Controlled-release formulations function as effective carriers for prolonging drug release for sustained biological action. These drug products are designed so that the rate of systemic drug absorption is limited by the rate of drug release via the drug delivery system. The objective of each design is to control the release rate from the delivery system so that relatively stable serum concentrations can be maintained.

Theophylline is a bronchodilator for the treatment of bronchial asthma exhibiting maximum potential benefit with minimal risk of toxicity when the serum concentration is maintained within the 10–20 mg/liter therapeutic range (Jacobs et al. 1976; Hendeles et al. 1977; Kordash et al. 1977). Based on this therapeutic necessity, over the last few years a number of controlled-release theophylline formulations have been developed to offer the advantage of reduced fluctuation of serum theophylline concentrations and decreased frequency of administration (Spangler et al. 1978; Lonnenholm et al. 1980; Meyer et al. 1980; Mellstrand and Svedmyr 1980; Leeds et al. 1982a). However, a number of studies have shown that the rate and extent of theophylline absorption varies significantly among the controlled-release formulations (Weinberger et al. 1978; Spangler et al. 1978, 1980; Jonkman et al. 1981a; Lesko et al. 1981; Williams et al. 1982, 1983). In addition, it has been found that the influence of food on the absorption of theophylline is dependent upon the formulation (Jonkman et al. 1981b; Pedersen 1981; Leeds et al. 1982b; Osman et al. 1983; Thompson et al. 1983; Lagas and Jonkman 1983; Pedersen and Moller-Petersen 1984; Sips et al. 1984). It is

Correspondence: P. Macheras or M. Koupparis, Department of Pharmacy, Athens University, 104, Solonos Street, Athens 10680, Greece.

conceivable, therefore, that these findings call for in vitro methods to predict the extent and/or the rate of absorption in patients for all such products under fasting and non-fasting conditions.

Two groups of investigators, Jonkman et al. (1981b) and Wearley et al. (1985) have described in vitro dissolution methods to explore interactions between food and controlled-release theophylline formulations under conditions which simulate the normal gastrointestinal environment. The first group, based on the principle that the effect of food on theophylline absorption is a result of influence of food on gastric pH, suggested the exposure of controlled-release theophylline formulations to an acid, then to a buffered solution of pH 1 and 6.8 respectively. This group reported that only formulations with pH independent dissolution kinetics correlated well with the in vivo data. The second group studied the disolution of controlled-release theophylline formulations in buffers ranging in pH from 1.2 to 8.0 containing a bile acid, a fatty acid and a combination of these media. The conclusion of their study is that the combined action of fatty acids and bile salts appears to play an important role in altering the release rate of theophylline controlled-release products dosed with a high-fat meal.

The present report describes further studies on this topic. The dissolution of 4 commercially available controlled-release theophylline formulations is studied in milk. The use of milk as a food-simulating medium and the importance of examining the dissolution of controlled release formulations under conditions which are more akin to the in vivo situation, have been pointed out recently (Macheras et al., 1986). Investigations into the effect of milk on the dissolution of conventional oral solid dosage forms showed that both the rate and the extent of dissolution could be profoundly affected by milk (Macheras et al., 1986). The fundamental feature of the controlled-release theophylline formulations is that the dissolution of drug is not dependent upon environmental factors such as pH, type of dissolution medium etc. Therefore, a study was undertaken to establish the dissolution profiles of these formulations in milk. For comparative purposes their dissolution was also studied in buffer.

Experimental

Reagents

Concentrated stock standard solutions in phosphate buffer, 250 μg/ml for theophylline and aminophylline, and 500 μg/ml for choline theophyllinate, were prepared from pure drugs obtained from local manufacturers [1]. Working standard solutions in phosphate buffer, in the range of 20–250 μg/ml for theophylline and aminophylline and 50–450 μg/ml for choline theophyllinate, were prepared daily from the stock solutions, kept in the refrigerator, by appropriate dilutions with phosphate buffer. Similar stock and working standard solutions were prepared in milk daily.

Phosphate buffer 0.010 M of pH 6.5 was prepared using KH_2PO_4 and concentrated 18 M NaOH solution. Low-fat milk [2] (cow milk, 0.75% in fat) was used as dissolution medium.

Controlled-release formulations theophylline (Theo-dur [3], 200 mg), aminophylline (Phyllotemp [4], 225 mg) and choline theophyllinate (oxtriphylline) (Xantair [5], 424 mg; Choledyl [6], 400 mg) were used in this study.

Instrumentation and procedures

The rotating basket method was used for the dissolution studies, using a 250-mesh screen basket, rotating at 100 rpm. Volumes of 900 ml of milk or buffer, thermostated at $37 \pm 0.5°C$ were used as the dissolution medium. Aliquots of 5.0 ml, for the dissolution experiments in milk, and 2.0 ml for the comparison experiments in buffer, were withdrawn at appropriate time intervals using plastic syringes with ±0.05 ml accuracy. Samples were filtered using paper filter in in-line plastic holders [7] fitted

[1] Anhydrous theophylline: Lavipharm, Greece. Aminophylline: Remek, Greece. Choline theophyllinate: Elpen, Greece.
[2] Landgenossenschaft Ennstal, Austria.
[3] Theo-dur tablets, Key Pharmaceuticals, Inc., Miami, FL (U.S.A.), formulated by Lavipharm, Greece; Lot Nr. 60202.
[4] Phyllotemp retard tablets, Mundipharma SA, Switzerland; Lot Nr. WD007.
[5] Xantair retard membrane-coated tablets, Zyma, Cheshire, England, formulated by Ciba-Geigy, Greece, Lot Nr. L001 L 84.
[6] Choledyl film-coated tablets, Warner Lambert Co., U.S.A., formulated by Elpen, Greece, Lot Nr. 85478.
[7] Millipore, U.S.A.

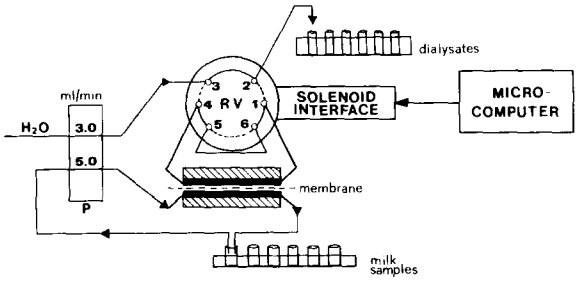

Fig. 1. Schematic diagram of the automated flow-injection dynamic dialyzer for drug measurements in milk. P, peristaltic pump; RV, 3-way (6-position) rotary valve with pneumatic actuator (Rheodyne, U.S.A.).

on the syringe tips. The withdrawn volume was substituted immediately with fresh dissolution medium kept at the same temperature.

Milk samples and standards (5.0 ml) were dialyzed using an automated flow-injection dynamic dialyzer (Macheras et al., 1986) shown in Fig. 1. A semipermeable membrane [8] with 20-μm pores, hydrated for a short time before use, was set in the dialyzer unit to establish two identical compartments of 1.0 ml volume each and 670 mm^2 dialysis surface. This system, interfaced to a microcomputer, permits the carrier solution (H_2O) to stop in the "receiving chamber" for a preselectable very precise "dialysis time" while the milk sample is being circulated continuously through the "donor chamber" at a rate of 5.0 ml/min (the dead volume of the tubings and the donor chamber is 2.5 ml). Then, the dialyzed drug is transferred by the carrier solution and the whole is collected in tubes for measurement. In succession the carrier solution washes out the "receiving chamber", for a preselectable very precise "wash time". A "dialysis time" of 60 s and "wash time" of 30 s were found appropriate for these experiments.

A double-beam spectrophotometer [9] was used for the manual absorbance measurements, using the phosphate buffer as blank in the reference beam. The milk dialysates, of 1.5 ml volume, were measured after the addition of 2.0 ml of phosphate buffer. Samples (and standards) of the phosphate buffer dissolution medium were measured after a 1:10 dilution with buffer. Absorbance measurements were performed at the λ_{max} of the drugs in phosphate buffer pH 6.5, i.e. 271 nm for theophylline and aminophylline, and 277 nm for choline theophyllinate.

[8] Cuprophan membranes, Technicon Chem. Co.

[9] Perkin Elmer, lambda 7, UV/VIS spectrophotometer.

Results and Discussion

In order to develop and optimize a method for the determination of the drugs in milk samples, based on dynamic dialysis–UV spectrophotometry, the dialysis characteristics of the drugs at pH 6.5, similar to that of milk, must be examined.

The dialysis rate constants K_d of the 3 drugs were determined, according to Eqn. 1:

$$\ln(D_o - D_i/D_o) = -K_d t \quad (1)$$

using a special computer program to increase stepwise the dialysis time t (Macheras et al., 1986). D_o is the drug concentration in the solution under dialysis of large enough volume so that the drug concentration remains constant through the successive dialysis runs, and D_i is the drug concentration in the "receiving compartment", calculated from the drug concentration in each successive dialysate after the correction for the dilution by the carrier solution. Standard solutions of the drugs in phosphate buffer of D_o equal to 100 μg/ml and volume of 100 ml were dialyzed, the "dialysis time" being increased from 0.5–5 min with a step of 0.5 min. Table 1 shows the dialysis rate constants for the 3 drugs at pH 6.5 and 25°C along with the statistical treatment of the data.

TABLE 1

Dialysis rate constants of the drugs at pH 6.5 at 25°C

Drug	K_d (±S.D.) (min^{-1})	r
Theophylline	0.0776 ± 0.0025	0.996
Aminophylline	0.0832 ± 0.0032	0.994
Choline theophyllinate	0.0760 ± 0.0026	0.995

S.D., standard deviation of 10 runs; r, correlation coefficient of Eqn. 1.

TABLE 2

Calibration curves for the determination of drugs in milk with the dynamic dialysis-UV spectrophotometric method

Drug (range, μg/ml)	Equation of linear regression	r
Theophylline (20–250)	milk: $A = 0.1912\ (\pm 0.0134) + 0.00217\ (\pm 0.00009) \cdot C$	0.997
	buffer: $A = 0.0003\ (\pm 0.0053) + 0.00246\ (\pm 0.00004) \cdot C$	0.9996
Aminophylline (20–250)	milk: $A = 0.2115\ (\pm 0.0034) + 0.00187\ (\pm 0.00002) \cdot C$	0.9997
	buffer: $A = 0.0059\ (\pm 0.0038) + 0.00200\ (\pm 0.00002) \cdot C$	0.9997
Choline theophyllinate (50–450)	milk: $A = 0.1976\ (\pm 0.0065) + 0.00133\ (\pm 0.00002) \cdot C$	0.9994
	buffer: $A = 0.0065\ (\pm 0.0096) + 0.00134\ (\pm 0.00004) \cdot C$	0.999

Samples of 5.0 ml volume were dialyzed once for 60 s. Dialysates of 1.50 ml volume were diluted with 2.0 ml of phosphate buffer and measured. Values are means (± S.D.).

The good linearity ($r = 0.994 - 0.996$) and the low relative standard deviations obtained (± 3.2 – 3.8%) show the validity of the technique for the rapid evaluation of experimental dialysis rate constants.

By choosing 60 s dialysis time the percent of dialysis ($\%D_i$), as it was calculated by the equation:

$$\%D_i = 100\ (1 - e^{-K_d t}), \qquad (2)$$

was found to be 7.47% for theophylline, 7.98% for aminophylline and 7.32% for choline theophyllinate. Consequently, sink conditions prevailed during dialysis runs.

Typical calibration curves for the determination of the drugs in milk samples, using the proposed dynamic dialysis-UV spectrophotometric method, are shown in Table 2, along with calibration curves from standard solutions in phosphate buffer for comparison. Good linearity was obtained in all cases ($r = 0.997 - 0.9997$). A blank of about 0.2 absorbance units was found for the milk, due to dialysable species in milk absorbing at the wavelength of measurement. This blank remained very reproducible for the same lot of milk. A slight decrease in the slopes of the calibration curves in milk, in comparison with those in buffer, show a partition of theophylline (11.8% decrease) and aminophylline (6.5% decrease) in the milk phases. No decrease was observed for choline theophyllinate.

From the statistical treatment of the calibration curves in milk, the detection limits for the determination of the drugs can be evaluated (concentration giving analytical measurement, greater than the blank, 3 × the standard deviation of the blank). Detection limits equal to 18.5 μg/ml for

TABLE 3

Dissolution of theophylline controlled-release tablet (Theo-dur 200 mg) in milk and phosphate buffer, pH 6.5, at 37°C.

Time (h)	% Dissolved (± S.D., n = 4)		% Difference (milk–buffer)	t-test	
	Milk	Buffer		Experimental	Theoretical (95%)
1.0	11.2 (± 2.0)	19.2 (± 1.4)	−41.7	6.554 *	
2.0	27.8 (± 2.8)	24.5 (± 0.7)	13.5	2.286 n.s.	
3.0	35.4 (± 4.0)	29.2 (± 1.0)	21.2	3.007 *	
4.0	42.8 (± 4.0)	36.8 (± 2.8)	16.3	2.458 *	2.447
5.0	48.6 (± 3.4)	48.2 (± 4.7)	0.8	0.138 n.s.	
6.0	58.6 (± 4.0)	56.7 (± 4.9)	3.4	0.600 n.s.	
7.0	68.6 (± 4.1)	63.6 (± 4.6)	7.8	1.623 n.s.	

* = significant at 0.05 level; n.s. = not significant at 0.05 level.

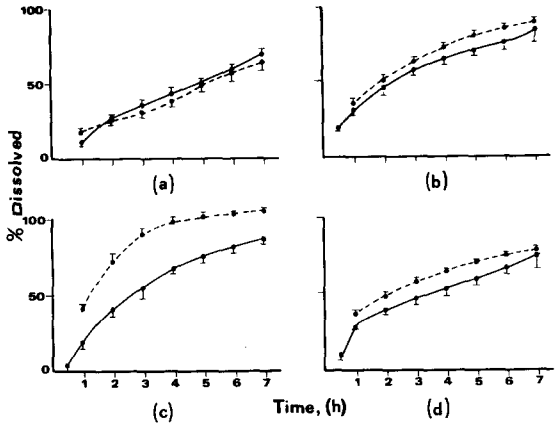

Fig. 2. Dissolution curves of: (a) Theo-dur (theophylline), (b) Phyllotemp (aminophylline), (c) Xantair (choline theophyllinate) and (d) Choledyl (choline theophyllinate) tablets, in milk (———) and phosphate buffer, pH 6.5 (- - - - -), at 37°C. Each point is mean ± S.D. of 4 experiments.

theophylline, 5.4 μg/ml for aminophylline and 14.7 μg/ml for choline theophyllinate, were found. The minimum volume of the milk sample is 5.0 ml (twice the dead volume of the dialyser) to provide sample circulation without air bubbles.

The precision of the developed method for the determination of the drugs in milk samples (dialysis, dilution of dialysates with buffer and absorbance reading), was tested by performing 5 successive measurements of two standard milk solutions containing 50 and 450 μg/ml of choline theophyllinate. S.D.s (in absorbance units) of ±0.0046 (mean 0.3244, RSD % 1.4) and ±0.0128 (mean 0.1502, RSD % 1.3) were respectively obtained.

Dissolution profiles in both media for the formulations studied are shown in Fig. 2. The precision of the dissolution experiments was excellent for such type of work, the standard deviation (expressed in % of dissolved drug) varying from ±0.1% to ±6.1% for the studies in milk and from ±0.4% to ±4.9% for the studies in buffer ($n = 4$). The mean percentages of dissolution for each time point in milk were tested for any significant difference with that in buffer, using a t-test at 95% confidence level (Tables 3–6). Two of the formulations studied, Phyllotemp and Xantair, showed lower dissolution profiles in milk than in buffer as demonstrated by the statistically significant differences found in the percentages of theophylline dissolved for all time points examined (Tables 4 and 5). A lower dissolution profile in milk than in buffer was also observed for Choledyl, but statistical equivalence was noted in the percentage of theophylline dissolved for the last time point of the experimental period (Table 6). Contrary to these, Theo-dur tablets showed a slightly higher dissolution profile in milk than in buffer though not statistically significant for all time points at the level considered (Table 3). It is interesting to note, however, that the dissolution of theophylline from the Theo-dur tablets was remarkably lower at the first hour probably due to the limited wetting of the tablets in milk. Overall, though, Theo-dur showed a similar pattern of dissolution in both media.

TABLE 4

Dissolution of aminophylline controlled-release tablet (Phyllotemp 225 mg) in milk and phosphate buffer, pH 6.5, at 37°C

Time (h)	% Dissolved (± S.D., $n = 4$)		% Difference (milk–buffer)	t-Test	
	Milk	Buffer		Experimental	Theoretical (95%)
1.0	30.1 (±1.6)	36.0 (±1.4)	−16.4	5.550 *	
2.0	43.7 (±1.3)	51.7 (±1.9)	−15.5	6.950 *	
3.0	56.8 (±1.6)	63.7 (±1.9)	−10.8	5.556 *	
4.0	64.3 (±2.2)	72.8 (±1.5)	−11.7	6.384 *	2.447
5.0	69.8 (±1.6)	80.0 (±2.0)	−12.8	7.964 *	
6.0	73.6 (±3.2)	85.1 (±1.5)	−13.5	6.508 *	
7.0	81.8 (±4.1)	88.4 (±1.4)	−7.5	3.047 *	

* Significant at 0.05 level.

TABLE 5

Dissolution of choline theophyllinate controlled-release tablet (Xantair 424 mg) in milk and phosphate buffer, pH 6.5, at 37°C

Time (h)	% Dissolved (±S.D., $n = 4$)		% Difference (milk–buffer)	t-Test	
	Milk	Buffer		Experimental	Theoretical (95%)
1.0	17.5 (±2.6)	41.4 (±3.7)	−57.7	10.570 *	
2.0	42.2 (±5.4)	74.4 (±4.4)	−43.3	9.245 *	
3.0	54.5 (±5.2)	91.5 (±3.4)	−40.4	11.911 *	
4.0	67.6 (±3.4)	98.4 (±1.8)	−31.3	16.012 *	2.447
5.0	75.0 (±2.3)	102.5 (±1.1)	−26.8	21.573 *	
6.0	80.8 (±2.8)	103.6 (±0.5)	−22.0	16.032 *	
7.0	86.5 (±1.6)	104.9 (±0.7)	−17.5	21.072 *	

* Significant at 0.05 level.

TABLE 6

Dissolution of choline theophyllinate controlled-release tablet (Choledyl 400 mg) in milk and phosphate buffer, pH 6.5, at 37°C

Time (h)	% Dissolved (±S.D., $n = 4$)		% Difference (milk–buffer)	t-Test	
	Milk	Buffer		Experimental	Theoretical (95%)
1.0	29.1 (±0.1)	38.0 (±0.3)	−23.4	56.288 *	
2.0	38.7 (±3.4)	49.2 (±0.8)	−21.3	6.012 *	
3.0	45.6 (±2.3)	57.6 (±0.9)	−20.8	9.717 *	
4.0	52.0 (±3.2)	64.4 (±0.5)	−19.2	7.657 *	2.447
5.0	58.4 (±2.1)	70.0 (±0.4)	−16.6	10.852 *	
6.0	65.4 (±1.3)	74.7 (±0.7)	−12.4	12.598 *	
7.0	73.3 (±6.1)	78.7 (±0.4)	−6.9	1.767 n.s.	

* = significant at 0.05 level; n.s. = not significant at 0.05 level.

The diversity of the results obtained could be attributed to the different mechanisms involved in the release of drugs from the formulations. Whatever the reasons, the fact that the rate of dissolution of theophylline in milk is dependent upon the formulation can be related with the remark made by Welling (1984), based on in vivo studies, that the extent of the interaction between food and controlled-release theophylline formulations appears to be formulation-dependent. In addition to this, the retarding effect of milk on the dissolution of theophylline can be linked with the delayed appearance of drug in plasma in non-fasted individuals observed in the studies of Heimann et al., 1982; Leeds et al., 1982b; and Osman et al., 1983.

Effects such as those summarized above are likely also to be important for drugs which, like theophylline, are marketed in controlled-release formulations. The proposed dissolution testing in a food-simulating medium, milk, may indeed have more general applications in rationalizing the effect of food on bioavailability of drugs formulated in controlled-release dosage forms.

References

Heimann, G., Murgescu, J., and Bergt, U., Influence of food intake on bioavailability of theophylline in premature infants. *Eur. J. Clin. Pharmacol.*, 22 (1982) 171–173.

Hendeles, L., Bighley, L., Richardson, R.H., Hepler, C.D. and Carmichael, J., Frequent toxicity from IV aminophylline infusions in critically ill patients. *Drug Intell. Clin. Pharm.*, 11 (1977) 12–18.

Jacobs, M.H., Senior, R.M. and Kessler, G. Clinical experience with theophylline: relationships between dosage, serum concentration and toxicity. *J. Am. Med. Assoc.*, 235 (1976) 1983–1986.

Jonkman, J.H.G., Berg, W.C., de Vries, K., de Zeeuw, R.A.,

Shoenmaker, R. and Grimberg, N. Disposition and clinical pharmacokinetics of theophylline after administration of a new sustained release tablet. *Eur. J. Clin. Pharmacol.*, 21 (1981a) 39–44.

Jonkman, J.H.G., Shoenmaker, R., Grimberg, N., and de Zeeuw, R.A., A new in vitro dissolution test for controlled release theophylline tablets. *Int. J. Pharm.*, 8 (1981b) 153–156.

Kordash, T.R., VanDellen, R.G., and McCall, J.T., Theophylline concentrations in asthmatic patients after administration of aminophylline. *J. Am. Med. Assoc.*, 238 (1977) 139–141.

Lagas, M. and Jonkman, J.H.G., Greatly enhanced bioavailability of theophylline on postprandial administration of a sustained release tablet, *Eur. J. Clin. Pharmacol.*, 24 (1983) 761–767.

Leeds, N.H., Gal, P., Purohit, A.A. and Walter, J.B., Relative bioavailability and release pattern of whole and halved sustained-release theophylline tablets, *Clin. Pharm.*, 1 (1982a) 163–164.

Leeds, N.H., Gal, P., Purohit, A.A. and Walter, J.B., Effect of food on the bioavailability and pattern of release of a sustained-release theophylline tablet. *J. Clin. Pharmacol.*, 22 (1982b) 196–200.

Lesko, L.J., Canada, A.T., Eastwood, G.L. and Clemente, D.R., The relative bioavailability of a controlled-release theophylline formulation after multiple doses. *Immunol. Allerg. Pract.*, 3 (1981) 15–22.

Lonnenholm, G., Foucard, T. and Lindstrom, B., Treatment of chronic asthma in children with a sustained-release preparation of theophylline in addition to beta-stimulating agents. *Eur. J. Respir. Dis.*, Suppl. 109, 61 (1980) 95–98.

Macheras, P., Koupparis, M., and Tsaprounis, C. Drug dissolution studies in milk using the automated flow-injection serial dynamic dialysis technique *Int. J. Pharm.*, 33 (1986) 125–136.

Mellstrand, T. and Svedmyr, N., Absorption of theophylline from conventional and sustained-release tablets. *Eur. J. Respir. Dis.*, Suppl. 109, 61 (1980) 54–66.

Meyer, M.C., Straugh, A.B. and Lieberman, P., A multiple-dose study of sustained-release theophylline and aminophylline. *Chest*, 78 (1980) 300–303.

Osman, M.A., Patel, R.B., Irwin, D.S. and Welling, P.G., Absorption of theophylline from enteric coated and sustained release formulations in fasted and non-fasted subjects. *Biopharm. Drug Dispos.*, 4 (1983) 63–72.

Pedersen, S., Delay in the absorption rate of theophylline from a sustained release theophylline preparation caused by food. *Br. J. Clin. Pharmacol.*, 12 (1981) 904–905.

Pedersen, S. and Moller-Petersen, J., Erratic absorption of a slow release theophylline sprinkle product. *Pediatrics*, 74 (1984) 534–538.

Sips, A.P., Edelbroek, P.M., Kulstad, S., De Wolff, F.A. and Dijkman, J.H., Food does not effect bioavailability of theophylline from Theolin retard. *Eur. J. Clin. Pharmacol.*, 26 (1984) 405–407.

Spangler, D.L., Kalof, D.D., Bloom, F.L. and Witting, H.J., Theophylline bioavailability following oral administration of six sustained-release preparations. *Ann. Allerg.*, 40 (1978) 6–11.

Spangler, D.L., Vanderpool, G.E., Carrol, M.S. and Tinkelman, D.G., Bioavailability and multiple dose characteristics of a new sustained release theophylline tablet. *Ann. Allerg.*, 45 (1980) 355–359.

Thompson, P.J., Kemp, M.W., McAlister, W.A.C. and Turner-Warwick, M., Slow release theophylline in patients with airway obstruction with particular reference to the effects of food upon serum levels. *Br. J. Dis. Chest*, 77 (1983) 293–298.

Wearley, L., Karim, A., Pagone, F., Streicher, J. and Wickman, A., Possible in vitro model for explaining the effect of food on the absorption of theophylline from oral release products. *Proc. Int. Symp. Control. Rel. Bioact. Mater.*, 12 (1985) 39–40.

Weinberger, M., Hendeles, L. and Bighley, L., The relation of product formulation to absorption of oral theophylline. *N. Engl. J. Med.*, 299 (1978) 852–857.

Welling, P.G., Interactions affecting drug absorption *Clin. Pharmacokinet.*, 9 (1984) 404–434.

Williams, R.L., Upton, R.A. and Bostrom, A., Relative bioavailability of two sustained-release theophylline formulations versus an immediate-release preparation., *J. Asthma*, 20 (1983) 27–30.

Williams, R.L., Upton, R.A., Seidehamel, R.J. and Riegelman, S., Multiple-dose bioavailability of a sustained-release theophylline product: Quibron-T/SR Dividose Tablets. *Cur. Ther. Res.*, 31 (1982) 45–55.