BIOPHARMACEUTICS & DRUG DISPOSITION, VOL. 17, 259–272 (1996)

THEOPHYLLINE CONTROLLED-RELEASE FORMULATIONS: *IN VIVO–IN VITRO* CORRELATIONS

ZHILING YU*‡, JOSEPH B. SCHWARTZ† AND EDWIN T. SUGITA†

*Department of Clinical Pharmacology and Statistics, ALZA Corporation, 950 Page Mill Road, P. O. Box 10950, Palo Alto, CA 94304, U.S.A.
†Department of Pharmaceutics, Philadelphia College of Pharmacy and Science, Philadelphia, PA 19104, U.S.A.

ABSTRACT

Four experimental controlled-release oral solid dosage formulations were developed and the *in vitro* dissolution characteristics of theophylline from these formulations were studied in USP apparatus I. Pharmacokinetic evaluation of these formulations was carried out in eight beagle dogs under fasting conditions. Theophylline in a 5% dextrose injection USP, oral solution, and Slo-Phyllin® were used as controls to estimate the *in vivo* dissolution of these four formulations in the GI tract. The percentage cumulative amounts of drug absorbed and the percentage cumulative amounts of drug released into the GI tract from these four controlled-release formulations were obtained by numerical deconvolution methods. The *in vivo* and *in vitro* dissolution data demonstrated good correlation indicating that *in vitro* dissolution tests can be used to optimize the further design of controlled drug release oral solid dosage formulations for theophylline.

KEY WORDS: *in vitro–in vivo* correlations; theophylline; controlled-release formulations; *in vivo* dissolution; *in vitro* dissolution; beagle dog

INTRODUCTION

Earlier studies in the field of controlled drug delivery have focused on the design and *in vitro* testing of the delivery system. Few studies have attempted to reveal the drug release kinetics in the gastrointestinal (GI) tract. Such data are essential for the scientist to understand the *in vivo* behavior of drug delivery systems. Knowledge of the drug release kinetics in the GI tract can help in the design of *in vitro* dissolution tests that adequately correlate with *in vivo* data. Such correlations can be used to optimize the controlled drug release systems, saving time and cost. They can also be used to develop predictive models, increasing experimental efficiency. More importantly, once such correlations have been established, *in vitro* tests can be used to control batch to batch bioequivalence.

‡To whom correspondence should be addressed at ALZA Corporation, 950 Page Mill Road, P. O. Box 10950, Palo Alto, CA 94304, U.S.A.

CCC 0142–2782/96/030259–14

Received 3 March 1995
Accepted 16 August 1995

Although the GI tract introduces a large number of variables which may significantly influence both the rate and the extent of drug absorption,[1] oral drug administration remains the most important method of administering drugs for systemic effects. Among the various drug formulations, solid dosage forms represent the preferred class.[2]

To reduce the risks and to minimize the cost of human study, an animal model for testing is preferred. The dog has been shown to be a suitable animal model for *in vivo* drug release studies.[3–18]

The overall objective of this study was to correlate the *in vitro* drug release and the *in vivo* drug delivery characteristics of the same drug from several controlled-release oral solid dosage formulations exhibiting different *in vitro* release mechanisms, using the beagle dog as an animal model.

Theophylline is a bronchodilator used primarily in the treatment of chronic obstructive pulmonary disease. Its pK_a is 8·8 and its aqueous solubility is $8{\cdot}3\,g\,L^{-1}$. Its activity is related to its serum concentration and the bronchodilator effect is proportional to the logarithm of that concentration up to $20\,\mu g\,mL^{-1}$. Its effective serum therapeutic range is between 10 and $20\,\mu g\,mL^{-1}$. Theophylline is rapidly, consistently, and completely absorbed when administered as a liquid; peak plasma levels are attained within 2–3 h. The elimination half-life is 5–9 h in nonsmoking healthy subjects.[19,20]

The elimination half-life of theophylline in dogs is about 5·7 h and the apparent specific volume of distribution is $0{\cdot}73$–$0{\cdot}82\,L\,kg^{-1}$. The absorption of theophylline from plain uncoated beads is rapid and complete in dogs.[21,22] Toxicity occurs at higher plasma theophylline concentrations in dogs (37–$60\,\mu g\,mL^{-1}$) than in man ($>20\,\mu g\,mL^{-1}$).[23] Plasma protein binding of theophylline in dogs has been reported as 44%[22] and 9·9%.[24] Recently, several researchers have completed theophylline absorption and bioavailability studies in dogs.[25–28]

In this study, four experimental controlled-release oral solid dosage formulations exhibiting different *in vitro* release mechanisms were developed. The *in vitro* and the *in vivo* dissolution characteristics of these formulations were studied, and their *in vitro–in vivo* correlations were assessed.

EXPERIMENTAL SECTION

Materials and methods

Formulations. Four experimental controlled-release oral solid dosage formulations containing 200 mg theophylline per capsule or tablet were manufactured. Formulation 1 (FT-1) is a hard gelatin capsule (size 0) containing uncoated beads with 50% theophylline (theophylline anhydrous No. 325, Knoll) and 50% Avicel RC-581 MCC (Avicel RC-581 microcrystalline cellulose, NF, FMC Corporation). Formulation 2 (FT-2) is

a hard gelatin capsule (size 0) containing uncoated beads with 50% theophylline and 50% Avicel PH-101 MCC (Avicel PH-101 microcrystalline cellulose, NF, FMC Corporation). Both FT-1 and FT-2 were manufactured by a process previously described.[29,30] Formulation 3 (FT-3) is a hard gelatin capsule (size 0) containing coated beads prepared by coating FT-2 with Surelease (Colorcon Inc.) and HPMC (hydroxypropyl methylcellulose, E5 Premium Grade, Dow Chemical Company) with 18% weight increase of solid among them are 16% HPMC and 84% Surelease by a process previously described.[31] Formulation 4 (FT-4) is a swellable matrix tablet containing theophylline, Klucel (Klucel HXF anhydrous, hydroxypropyl cellulose, Hercules Inc.), lactose (lactose anhydrous, Sheffield), and magnesium stearate (Mallincrodt) at a ratio of 50:30:19:1 and was manufactured by a direct compression process previously described.[32]

Theophylline in 5% dextrose injection USP was a gift from Dr. Theodore J. Roseman of Baxter Healthcare Corporation. Slo-Phyllin® (syrup) was purchased from Rorer Pharmaceutical Corporation. Theophylline oral solution was prepared by dissolving theophylline anhydrous in purified water (100 mg/14 mL).

In vitro dissolution tests. Dissolution tests were carried out on each controlled-release formulation the day before the animal experiment. The dissolution testing was performed using a rotating basket apparatus, which is described in USPXX as the USP Dissolution Test Apparatus I. Testing was conducted at a basket rotational speed of 50 rpm. The dissolution medium was 900 mL of purified water USP, 0·1 N hydrochloric acid, or pH 7·2 phosphate buffer maintained at 37 °C. The sample size was adjusted to be equivalent to 200 mg of active ingredient. A sample was removed through a 40–60 μm sintered glass filter (gas dispersion tube) at different sampling times. The sample was replaced with an equal volume of purified water USP. The samples were diluted with purified water USP for UV analysis at 272 nm.

Analytical method. Plasma concentrations of theophylline were determined by a previously described HPLC method.[33]

Animal studies. Eight healthy male beagle dogs weighing between 10 and 13 kg were studied. The beagle dogs were housed in a room with air and humidity control. Each dog was fasted for 12–18 h prior to each study day. After dosing, food but not water was withheld until the end of each study. Each dog received the same formulation on the same day. There was a washout period of at least 2 weeks between two consecutive studies. Each beagle dog received the same dose: 20 mL (80 mg theophylline anhydrous) of theophylline in 5% dextrose injection USP for bolus intravenous injection; 37·5 mL (200 mg theophylline) of Slo-Phyllin®; 14·0 mL (100 mg theophylline) of oral solution; and one tablet or capsule (200 mg theophylline anhydrous) for each CR formulation. Venous

blood samples (2–3 mL) were taken via the cephalic vein. Clotting of blood samples was prevented by use of a Vacutainer tube which contained 45 USP units of sodium heparin. Plasma was immediately separated by centrifugation at 3000 rpm for 15 min and stored at −20 °C. Before assaying, the plasma was allowed to reach room temperature, vortexed for 10 s, and the residual clot removed.

Data analysis. The unit (1 mg) impulse response model parameters of individual beagle dogs after a bolus intravenous injection of theophylline were estimated by fitting the normalized unit dose (1 mg) plasma theophylline concentration time data to the following two-term exponential equation:

$$C_\delta(T) = c_1 e^{-\lambda_1 T} + c_2 e^{-\lambda_2 T} \tag{1}$$

where c_1, c_2 are coefficients and λ_1, λ_2 are exponents.

The percentage cumulative amount of drug absorbed at time T, $P_{abs}(T)$, from Slo-Phyllin® and oral solution were obtained by the nonlinear regression numerical deconvolution method[34] and the plasma theophylline concentration following a bolus intravenous injection was defined as the impulse response. In the nonlinear regression numerical deconvolution method, the drug absorption rate function $R_{abs}(T)$, and the percentage cumulative amount of drug absorbed at time T, $P_{abs}(T)$, were represented by the following equations:

$$R_{abs}(T) = u(T - T_{lag}) k_a P_{abs}^{\infty} e^{-k_a(T - T_{lag})} \tag{2}$$

$$P_{abs}(T) = u(T - T_{lag}) P_{abs}^{\infty} (1 - e^{-k_a(T - T_{lag})}) \tag{3}$$

where k_a is the first-order absorption rate constant, P_{abs}^{∞} is the calculated total percentage cumulative amount of drug absorbed, T_{lag} is the lag time and $u(t)$ is the unit step function:

$$u(t) = 0 \qquad \text{for } t < 0 \tag{4}$$

$$u(t) = 1 \qquad \text{for } t \geqslant 0 \tag{5}$$

The percentage cumulative amounts of drug absorbed at time T, $P_{abs}(T)$, from the four controlled-release formulations were obtained by the fixed-step-number equal-step-length numerical deconvolution method,[34] and the plasma theophylline concentration following a bolus intravenous injection was defined as the impulse response.

The percentage cumulative amounts of drug released into the GI tract from CR formulations 1 and 2 were obtained by the nonlinear regression numerical deconvolution method, and the following equation was used to define the unit impulse response $C_{\delta a}(T)$:

$$C_{\delta a}(T) = \frac{c_1 k_a}{k_a - \lambda_1}(e^{-\lambda_1 T} - e^{-k_a T}) + \frac{c_2 k_a}{k_a - \lambda_2}(e^{-\lambda_2 T} - e^{-k_a T}) \quad (6)$$

In the nonlinear regression numerical deconvolution method, the drug release rate function $R_{GI}(T)$, and the percentage cumulative amount of drug released into the GI tract at time T, $P_{GI}(T)$, were approximated by the RRSBW distribution function[35] and are represented by the following equations:

$$R_{GI}(T) = \frac{\beta P^{\infty}_{RRSBW}}{\tau_d^{\beta}} T^{\beta-1} e^{-\left(\frac{T}{\tau_d}\right)^{\beta}} \quad (7)$$

$$P_{GI}(T) = P^{\infty}_{RRSBW}(1 - e^{-\left(\frac{T}{\tau_d}\right)^{\beta}}) \quad (8)$$

where P^{∞}_{RRSBW} is the calculated total percentage cumulative amount of drug released, τ_d is the time parameter, and β is the shape parameter of the RRSBW distribution.[35]

The percentage cumulative amounts of drug released into the GI tract from CR formulations 3 and 4 were obtained by the fixed-step-number equal-step-length numerical deconvolution method, and the unit impulse response was defined by equation (6).

RESULTS AND DISCUSSION

In vitro dissolution studies

The *in vitro* dissolution profiles are shown in Figure 1. In 0·1N HCl or pH 7·2 phosphate buffer, the Avicel RC-581 MCC spheres remained intact. An inert matrix model best describes the spheres in 0·1N HCl and in pH 7·2 phosphate buffer. The spheres exhibited 100% release after 2 h of dissolution testing. We have found that, in water, the swollen gel-like mass filled the sample basket at the end of the dissolution test. A hydrogel model best describes the spheres in water. For formulation 2, spheres remained intact and unswollen during the dissolution process. The spheres exhibited complete release after 2 h of dissolution testing. An inert matrix model best describes the drug release mechanism. However, at this high drug loading level (50:50), the release may actually be complicated by the matrix break-up and irregular geometry of the spheres. Spheres remained intact and unswollen during the dissolution process for formulation 3. The drug release mechanism is assumed to be the diffusion of drug across the porous membrane. In formulation 4, Klucel HXF (hydroxypropyl cellulose, HPC) is a water insoluble cellulose ether with hydroxypropyl groups present on the molecule. In water and 0·1 N HCl, the polymer containing dispersed drug absorbs a significant amount of water to

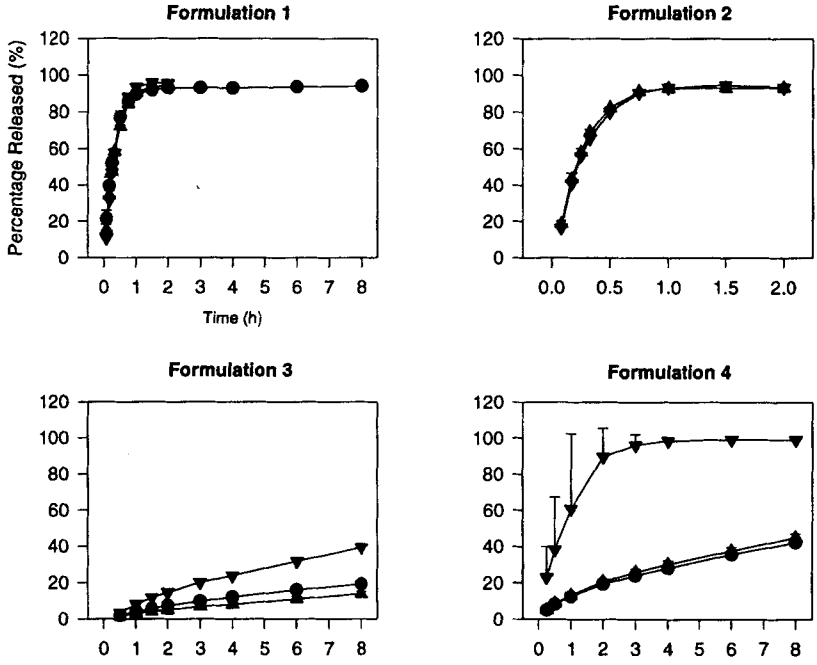

Figure 1. *In vitro* dissolution of theophylline from four different formulations: —●—, in purified water; —▲—, in 0·1 N HCl; —▼—, in pH 7·2 phosphate buffer

form an elastic gel, which tends to sustain drug release. Surprisingly, the tablet dissolves in pH 7·2 phosphate buffer. Presumably, this is due to the interaction between the polymer and water soluble diluent anhydrous lactose.

In vivo dissolution studies

The unit impulse response model parameters for each beagle dog after a bolus intravenous injection of theophylline are shown in Table 1. The first-order drug absorption model parameters for the dogs after an oral administration of theophylline aqueous solution and Slo-Phyllin® (syrup) are presented in Tables 2 and 3 respectively. Tables 2 and 3 show that the drug was absorbed completely from oral solution. The overestimated total percentage cumulative amount of drug absorbed from the Slo-Phyllin® suggests nonlinearity at higher dose levels. Since the pharmacokinetic study for Slo-Phyllin® was conducted within 2 h, the estimated parameters are considered accurate.

The plasma theophylline concentration–time profiles for each controlled-release formulation are shown in Figure 2. The results of calculated percentage

Table 1. Unit (1 mg) impulse response model parameters for individual beagle dogs after a bolus intravenous injection of theophylline. The unit impulse response was approximated by the equation $C_\delta(T) = c_1 e^{-\lambda_1 T} + c_2 e^{-\lambda_2 T}$, where c_1, c_2, λ_1, λ_2 are parameters

Parameter	Unit	Dogs							
		A	B	C	D	E	F	G	H
c_1	$\mu g\,mL^{-1}$	0·015 39	0·076 83	0·060 79	0·025 74	0·043 88	0·042 12	0·009 42	0·048 18
c_2	$\mu g\,mL^{-1}$	0·081 78	0·102 54	0·043 34	0·086 11	0·08571	0·083 03	0·082 39	0·113 35
μ_1	h^{-1}	1·3845	18·077	0·396 18	4·1816	3·3777	9·3711	0·131 09	11·238
λ_2	h^{-1}	0·072 19	0·191 08	0·053 50	0·166 14	0·113 96	0·135 73	0·113 84	0·169 19

Table 2. First-order drug absorption model parameters for individual beagle dogs after an oral administration of theophylline anhydrous solution, obtained from the nonlinear regression numerical deconvolution method, where k_a is the first-order rate constant, and $P\infty_{abs}$ is the calculated total percentage cumulative amount of theophylline absorbed. These parameters are based on the oral solution data provided by Mr. Galal El-Sayed

Parameter	Unit	Dogs							
		A	B	C	D	E	F	G	H
k_a	h^{-1}	3·9312	11·054	0·957 23	4·3024		5·4067	0·676 90	1·2006
P^{∞}_{abs}	%	83·862	117·64	119·59	107·61		104·28	88·736	109·70

Table 3. First-order drug absorption model parameters for individual beagle dogs after an oral administration of Slo-Phyllin®, obtained from the nonlinear regression numerical deconvolution method, where k_a is the first-order rate constant, P_{abs}^{∞} is the calculated total percent cumulative amount of theophylline absorbed, and T_{lag} is the lag time

		Dogs							
Parameter	Unit	A	B	C	D	E	F	G	H
k_a	h^{-1}	4·6629	4·2270	3·9986	2·4657	2·1555	1·0987	1·2097	1·4642
P_{abs}^{∞}	%	139·05	129·32	140·00	145·02	148·79	157·53	153·12	141·50
T_{lag}	h	0·068 55	0·063 66	0·060 99	0·083 17	0·118 36	0·123 87	0·137 17	0·071 88

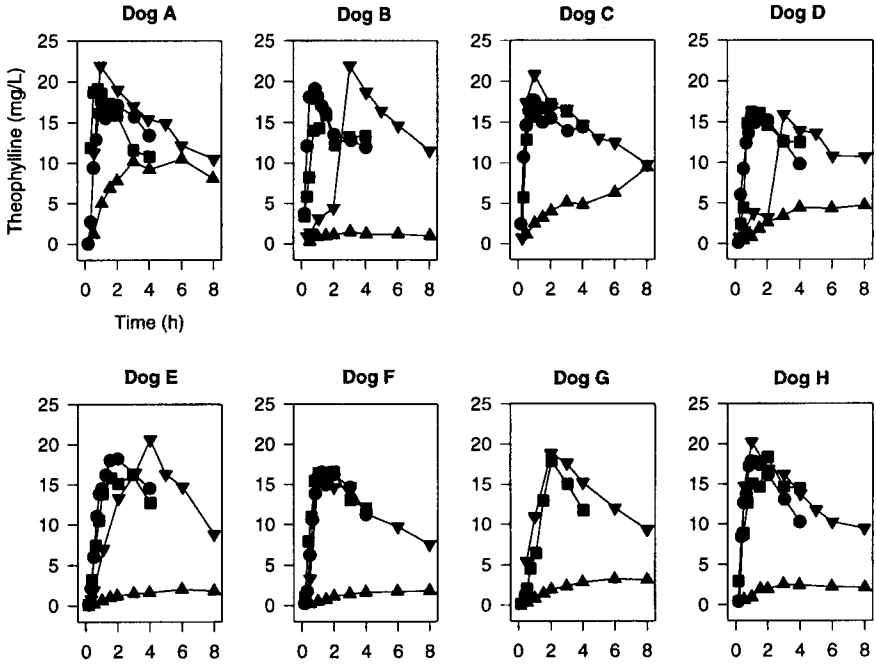

Figure 2. Plasma concentration–time curves of theophylline for four different formulations: —●—, formulation 1; —■—, formulation 2; —▲—, formulation 3; —▼—, formulation 4

cumulative amount of drug absorbed for each formulation are shown in Figure 3. The results of calculated percentage cumulative amount of drug released into the GI tract for each formulation are shown in Figure 4. For formulation 4, since dose dumping was observed, the estimated total percentage cumulative amount of drug absorbed from the Slo-Phyllin® was used to calibrate the calculation.

Due to the variability of the data, the percentage cumulative amount of drug released into the GI tract can not be generated for dog H of formulation 1, dogs A and H of formulation 2, and dogs G and H of formulation 4.

In vivo–in vitro correlations

The point to point ratios of percentage cumulative amount of theophylline released *in vivo* versus *in vitro* for each formulation are shown in Figure 5. The *in vivo–in vitro* drug release profiles for each formulation are shown in Figure 6. Figures 5 and 6 show that drug was released completely within 30 min from both formulations 1 and 2. Although *in vivo* drug release rates from both formulations 1 and 2 are shown to be slower than those *in vitro*, caution must be taken in interpreting the results, because the dissolution rate for both

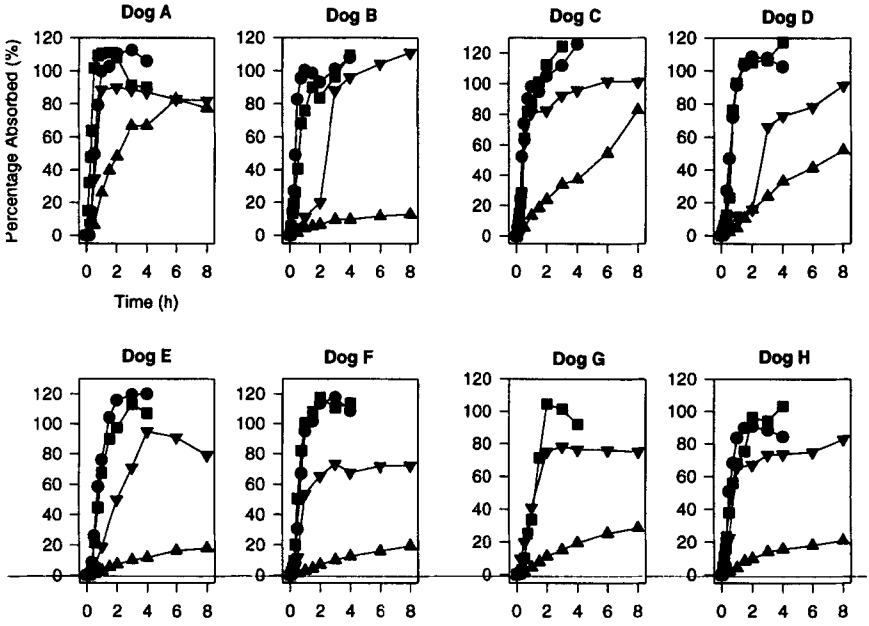

Figure 3. Percentage cumulative amount of theophylline absorbed against time for four different formulations: —●—, formulation 1; —■—, formulation 2; —▲—, formulation 3, —▼—, formulation 4

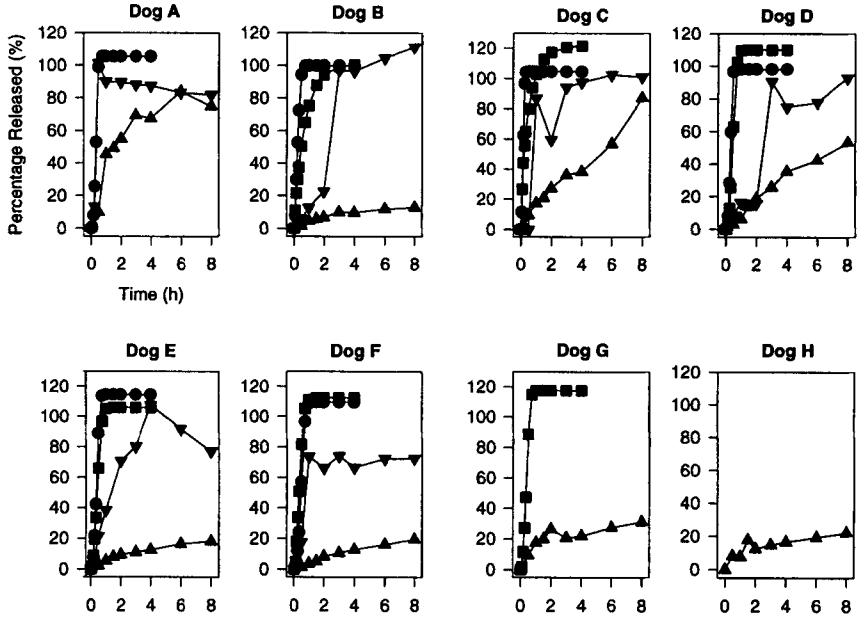

Figure 4. Percentage cumulative amount of theophylline released against time for four different formulations: —●—, formulation 1; —■—, formulation 2; —▲—, formulation 3; —▼—, formulation 4

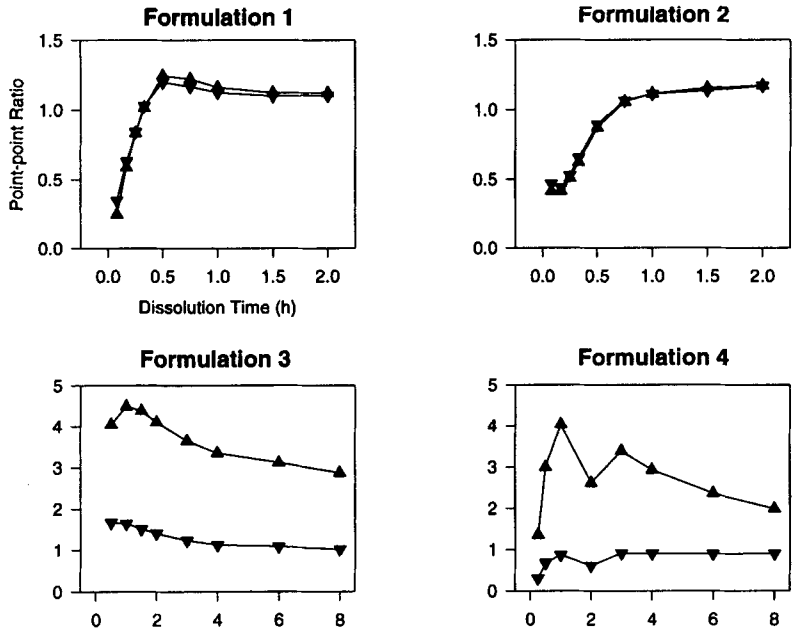

Figure 5. Point–point *in vivo–in vitro* correlations of four different formulations: —▲—, *in vivo* against in 0·1 N HCl; —▼—, *in vivo* against in pH 7·2 phosphate buffer

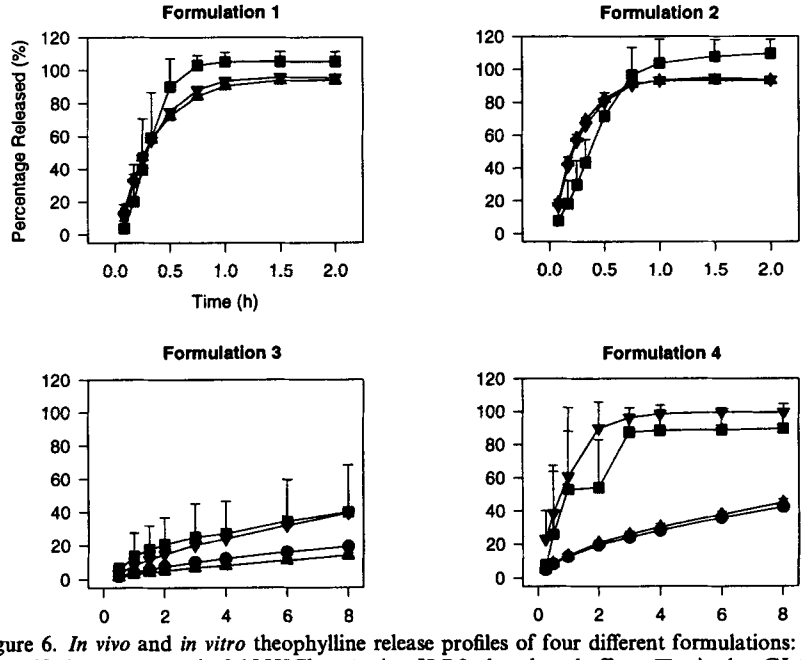

Figure 6. *In vivo* and *in vitro* theophylline release profiles of four different formulations: —●—, in purified water; —▲—, in 0·1 N HCl; —▼—, in pH 7·2 phosphate buffer; —■—, in dog GI tract

formulations is so fast that the *in vivo* dissolution rate is very sensitive to variations of drug absorption rate from oral solution. We believe that these results show good *in vivo* and *in vitro* correlations for both formulations 1 and 2.

In vivo–in vitro correlations for formulations 3 and 4 are more mechanistic. Figure 1 shows that the dissolution rate for formulation 3 is pH and/or ionic strength dependent; therefore, variations of *in vivo* dissolution rate would be expected among the beagle dogs. From Figure 4, the drug release profiles for formulation 3 indicate that the coated beads may have broken up, suggesting that the physical strength of the coated beads is at the critical level. Figures 5 and 6 indicate that for formulation 3, there is a better correlation between the *in vivo* dissolution rate and the *in vitro* dissolution rate pH 7·2 phosphate buffer. From Figure 4, it is obvious that formulation 4 dissolved in the GI tract between 0·5 and 3 h which is what was observed in the *in vivo* dissolution study in pH 7·2 phosphate buffer. Figures 5 and 6 further indicate a good correlation between the *in vivo* dissolution rate and the *in vitro* dissolution rate in pH 7·2 phosphate buffer, and also that the formulation 4 dissolves in the intestinal tract.

We conclude that the *in vivo* and *in vitro* dissolution data demonstrates a good correlation indicating that *in vitro* dissolution tests can be used to optimize the further design of controlled drug release oral solid dosage formulations for theophylline.

ACKNOWLEDGEMENTS

We are grateful to Dr. Stuart C. Porter of Colorcon Inc. for providing Surelease and Dr. Theodore J. Roseman of Baxter Healthcare Corporation for providing the theophylline in 5% dextrose injection USP.

We are also grateful for the assistance provided by Ms. Agnes Maderich, Ms. Nancy Davis, and Mr. Galal El-Sayed. Ms. Agnes Maderich provided the technical assistance in developing the HPLC plasma theophylline assay. Ms. Nancy Davis assisted us in taking blood samples. Mr. Galal El-Sayed generated the oral solution data.

REFERENCES

1. A. Rubinstein, V. Hon Kin Li, P. Gruber and J. R. Robinson, Gastrointestinal-physiological variables affecting the performance of oral sustained release dosage form. In *Oral Sustained Release Formulations: Design and Evaluation*, A. Yacobi and E. Halperin-Walega (Eds), Pergamon, New York, 1988, pp. 125–148.
2. E. Rudnic and J. B. Schwartz, Oral solid dosage forms. In *Remington's Pharmaceutical Sciences*, 18th ed, A. R. Gennaro (Ed.), Mack, Pennsylvania, 1990, p. 1633.

3. C. S. Cook, C. L. Hauwald, A. Y. Grahn, K. Kowalski, A. Karim, R. Koch, G. L. Schoenhard and J. A. Oppermann, Suitability of the dog as an animal model for evaluating theophylline absorption and food effects from different formulations. *Int. J. Pharm.*, **60**, 125–132 (1990).
4. Z. Hussein and M. Friedman, Release and absorption characteristics of novel theophylline sustained-release formulations: *in vitro-in vivo* correlation. *Pharm. Res.*, **7**, 1167–1171 (1990).
5. G. K. Shiu, A. LeMarchand, A. O. Sager, R. B. Velagapudi and J. P. Skelly, The beagle dog as an animal model for a bioavailability study of controlled-release theophylline under the influence of food. *Pharm. Res.*, **6**, 1039–1042 (1989).
6. Z. Hussein, M. Bialer, M. Friedman and I. Raz, Comparative pharmacokinetic evaluation of sustained-release theophylline formulations in dogs and humans. *Int. J. Pharm.*, **37**, 97–102 (1987).
7. M. Bialer, M. Friedman and J. Dubrovsky, Relation between absorption half-life values of four novel sustained release dosage forms of valproic acid in dogs and humans. *Biopharm. Drug Dispos.*, **7**, 495 (1986).
8. C. Y. Lui, G. L. Amidon, R. R. Berardi, D. Fleisher, C. Youngberg and J. B. Dressman, Comparison of gastrointestinal pH in dogs and humans: implications on the use of the beagle dog as a model for oral absorption in humans. *J. Pharm. Sci.*, **75**, 271–274 (1986).
9. H. Ogata, N. Aoyagi, N. Kaniwa, A. Ejima, T. Kitaura, T. Ohki and K. Kitamura, Evaluation of beagle dogs as an animal model for bioavailability testing of cinnarizine capsules. *Int. J. Pharm.*, **29**, 121–126 (1986).
10. M. Bialer, M. Friedman, J. Dubrovsky, I. Raz and O. Abramsky, Pharmacokinetic evaluation of novel sustained release dosage of valproic acid in humans, *Biopharm. Drug Dispos.*, **6**; 401–411 (1985).
11. H. Ogata, N. Aoyagi, N. Kaniwa, T. Shibazaki, A. Ejima, Y. Takagishi, T. Ogura, K. Tomita, S. Inoue and M. Zaizen, Bioavailability of metronidazole from sugar coated tablets in humans. II. Evaluation of beagle dogs as an animal model. *Int. J. Pharm.*, **23**, 289–298 (1985).
12. H. Ogata, N. Aoyagi, N. Kaniwa, T. Shibazaki, A. Ejima, N. Takasugi, E. Mafune, T. Hayashi and K. Suwa, Bioavailability of nalidixic acid from uncoated tablets in humans–Part II: Bioavailability in beagles and its correlation with bioavailability in humans and *in vivo* dissolution rates. *Int. J. Clin. Pharmacol. Ther. Toxicol.*, **22**, 240–245 (1984).
13. M. Bialer, M. Friedman and J. Dubrovsky, Comparative pharmacokinetic analysis of a novel sustained release dosage form of valproic acid in dogs. *Biopharm. Drug Dispos.*, **5**, 1–10 (1984).
14. M. Bialer, M. Friedman and J. Dubrovsky, Effect of sustained release on pharmacokinetics of valproic acid in the dog. *Int. J. Pharm.*, **20**, 53–63 (1984).
15. N. Aoyagi, H. Ogata, N. Kaniwa, M. Koibuchi, T. Shibazaki, A. Ejima, N. Tamaki, H. Kamimura, Y. Katougi and Y. Omi, Bioavailability of griseofulvin from tablets in beagle dogs and correlation with dissolution rate and bioavailability in humans. *J. Pharm. Sci.*, **71**, 1169–1172 (1982).
16. H. Ogata, N. Aoyagi, N. Kaniwa, M. Koibuchi, T. Shibazaki, A. Ejima, T. Shimamoto, T. Yashiki, Y. Ogawa, Y. Uda and Y. Nishida, Correlation of the bioavailability of diazepam from uncoated tablets in beagle dogs with its dissolution rate and bioavailability in humans. *Int. J. Clin. Pharmacol. Ther. Toxicol.*, **20**, 576–581 (1982).
17. W. Barr, The use of physical and animal models to assess bioavailability. *Pharmacology*, **8**, 55–101 (1972).
18. W. A. Cressman and D. Summer, The dog as a quantitative model for evaluation of nondisintegrating sustained-release tablets. *J. Pharm. Sci.*, **60**, 132–134 (1971).
19. C. W. Bierman and P. V. Williams, Therapeutic monitoring of theophylline rationale and current status. *Clin. Pharmacokinet.*, **17**(6), 377–384 (1989).
20. D. J. Rowe, I. D. Watson, J. Williams and D. J. Berry, The clinical use and measurement of theophylline. *Ann. Clin. Biochem.*, **25**, 4–26 (1988).
21. B. C. McKiernan, C. A. Neff-Davis, G. D. Kortiz, L. E. Davis and D. R. Pheris, Pharmacokinetic studies of theophylline in dogs. *J. Vet. Pharmacol. Therap.*, **4**, 103–110 (1981).
22. T. Kuze, H. Miyazaki and T. Taneike, Theophylline: pharmacokinetics, metabolism and urinary excretion in dogs. *Nippon Yakurigaku Zasshi — Folia Pharmacologica Japonica*, **91**(5), 325–334 (1998).
23. I. J. Munsiff, B. C. McKiernan, C. A. Neff-Davis and G. D. Kortiz, Determination of the acute toxicity of theophylline in conscious dogs. *J. Vet Pharmacol. Therap.*, **11**, 381–389 (1988).

24. I. J. Munsiff, G. D. Koritz, B. C. McKiernan and C. A. Neff-Davis, Plasma protein binding of theophylline in dogs. *J. Vet Pharmacol. Therap.*, **11**, 112–114 (1988).
25. D. L. Munday, A. R. Fassihi and C. De Villiers, Bioavailability studies of a theophylline oral controlled release capsule containing film coated mini-tablets in beagle dogs. *Int. J. Pharm.*, **69**, 123–127 (1991).
26. J. Liaw, A. Rubinstein and J. R. Robinson, Bioavailability study of theo-dur tablets in the fasted cannulated dog. *Int. J. Pharm.*, **59**, 105–114 (1990).
27. J. Limberg, D. Harrison, M. Hocking and H. Derendorf, Theophylline absorption and gastric emptying after partial gastrectomy in dogs. *J. Pharm. Sci.*, **79**, 968–969 (1989).
28. G. D. Koritz, B. C. McKiernan, C. A. Neff-Davis and I. J. Munsiff, Bioavailability of four slow-release theophylline formulations in the beagle dog. *J. Vet. Pharmacol. Therap.*, **9**, 293–302 (1986).
29. R. E. O'Connor, J. Holinej and J. B. Schwartz, Spheronization I: processing and evaluation of spheres prepared from commercially available excipients. *Am. J. of Pharm.*, **156**, 80–87 (1984).
30. R. E. O'Connor and J. B. Schwartz, Spheronization II. drug release from drug-diluent mixtures. *Drug Dev. Ind. Pharm.*, **11**, 837–1857 (1985).
31. G. H. Zhang, *Mechanisms of Drug Release from Spheres Coated with Aqueous Ethyl Cellulose Based Dispersions*. Ph.D. Thesis, Philadelphia College of Pharmacy and Science, Philadelphia, PA, 1989.
32. X. Y. Zhang, *Evaluation of Polymers for Controlled Release in Direct Compression Tablet Formulations*. M. S. Thesis, Philadelphia College of Pharmacy and Science, Philadelphia, PA, 1988.
33. Z. Yu, *Theophylline Controlled Release Formulations: In Vivo–In Vitro Correlation*. Ph.D. Thesis, Philadelphia College of Pharmacy and Science, Philadelphia, PA, 1992.
34. Z. Yu, J. B. Schwartz, E. T. Sugita and H. C. Foehl, Five modified numerical deconvolution methods for biopharmaceutics and pharmacokinetics studies. *Biopharm. Drug Disposit.*, submitted.
35. F. Langenbucher, Parametric representation of dissolution-rate curves by the RRSBW distribution. *Pharm. Ind.*, **38**, 472–477 (1976).