International Journal of Pharmaceutics, 103 (1994) 115–118

IJP 03340

In vivo evaluation of fluidized-bed coated pellets

M. Turkoglu [1], W.A. Ritschel and A. Sakr

University of Cincinnati, College of Pharmacy, Cincinnati, OH 45267 (USA)

(Received 22 March 1993)
(Modified version received 3 June 1993)
(Accepted 4 June 1993)

Key words: Beagle dog; Coated pellet; Theophylline; Fluidized bed; Pharmacokinetics; In vitro-in vivo correlation

Summary

An in vivo comparison of serum theophylline levels resulting from uncoated and coated pellets was made using the beagle dog as an animal model. The coated pellets were prepared from an aqueous ethyl cellulose dispersion (Aquacoat) in the rotary fluidized bed. A relative bioavailability of 52% was calculated for the coated pellets. The pharmacokinetic parameters of theophylline obtained from beagle dog were also determined. A significant correlation coefficient of 0.9584 was calculated between in vitro percent theophylline release and percent drug absorbed in vivo. Finally, it was concluded that the beagle dog model can be reliably used for the in vivo evaluation of controlled release dosage forms.

Introduction

Aqueous ethyl cellulose dispersions and their use in fluidized-bed coated controlled-release dosage forms have been the subject of many reports in recent literature (Lippold et al.., 1989; Yang and Ghebre-Sellassie, 1990; Wan and Lai, 1991; Zhang et al., 1991). However, there is a lack of information on the in vivo performance of fluidized-bed coated pellets, especially with the aqueous pseudo-latexes.

In our previous study, it was reported that the rotary fluidized bed (RFB) could be used to produce spherical granules and to coat them in the same equipment (Turkoglu and Sakr, 1992). The drug release rate and pattern of a controlled-release coated dosage form can be evaluated by the USP in vitro dissolution test. However, the most important data can only be obtained through in vivo experiments. The beagle dog model was chosen and used in this study. The purpose of the study was to evaluate RFB coated theophylline pellets in the beagle dog model in vivo.

Materials and Methods

Four beagle dogs (Hazelton Farms Inc., Kalamazoo, MI) weighing 9.5 ± 0.5 kg and 1.5 years old were used. The study was carried out in a randomized cross-over fashion. Theophylline pellets were prepared and coated in a rotary fluidized bed under optimized conditions, content

Correspondence to ([1] present address): M. Turkoglu, Marmara University, Faculty of Pharmacy, Haydarpasa, Istanbul 80010, Turkey.

SSDI 0378-5173(93)E0189-W

uniformity, and in vitro dissolution tests were carried out according to a previously described procedure (Turkoglu and Sakr, 1992).

Methods

Uncoated and coated pellets were placed in 00 size capsules; the average amount of theophylline (SD) for uncoated dosage forms was 117.2 (4.85) mg and for coated forms, 126.5 (8.73) mg. Capsules were administered perorally to the dogs which were fasted overnight with water available ad libitum. Administration of dosage forms was carried out at the same time of day between 8:00 and 8:30 a.m. Blood samples of 3 ml each were collected by venipuncture at 0, 0.25, 0.50, 0.75, 1.5, 2.0, 3.0, 5.0, 6.0, 8.0 and 12 h, then at 24 h for the uncoated and coated dosage forms. Blood samples were allowed to clot and serum was separated by centrifugation. Serum samples were immediately frozen and kept at −20°C until analysis.

Theophylline assay

Theophylline assay in serum was carried out according to the TDX procedures (TDX, Fluorescence Polarization Immunoassay, Abbott Laboratories Diagnostics Division, Irving, TX)). This technique combines the sensitivity of fluorescence methods with the specificity of immunoassay. TDX is a fully automated system, requiring a sample size of 50 μl of serum. A calibration run included the following serum samples which were spiked with theophylline at 0.0, 2.5, 5.0, 10.0, 20.0 and 40.0 μg/ml. The control samples had the following concentration of theophylline: 1.25, 7.0, 12.0 and 26.0 μg/ml. Both calibrators and controls were run in duplicate. The correlation coefficient of measured vs predicted values was 0.999. The relative standard deviations within runs were found to be 1.54% for 7.0 μg/ml, 0.54% for 12.0 μg/ml and 1.41% for 26.0 μg/ml.

Relative standard deviations among runs were calculated to be 2.86% for 7.0 μg/ml, 3.34% for 12.0 μg/ml and 2.04% for 26.0 μg/ml. The lowest measurable level with 95% confidence was 0.82 μg/ml for theophylline with this system.

Data analysis

Theophylline serum concentrations vs time data were analyzed by AUC-RPP software (Ritschel, 1986) for pharmacokinetic parameters. The statistical analysis for theophylline concentrations at corresponding time points and the curve fittings were performed using SAS statistical software (SAS Version 5.0, Statistics Software on VAX Main Frame, SAS Institute, Inc., Cary, NC).

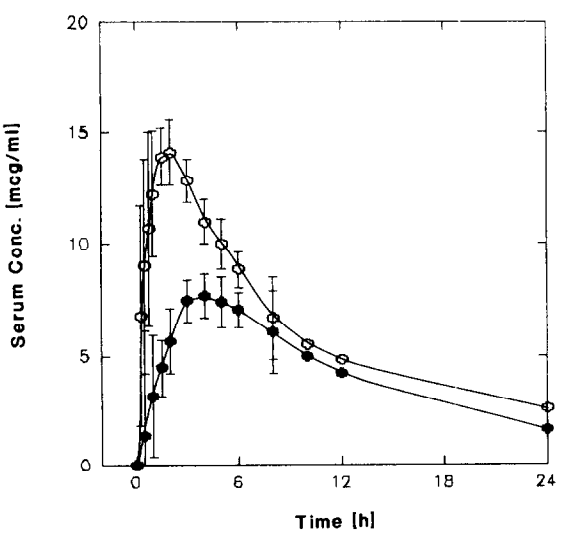

Fig. 1. Serum theophylline concentrations vs time in beagle dog model ($n = 4$) (SD). (●) Coated pellets, (○) uncoated pellets.

Results and Discussion

The results of theophylline serum concentration vs time for uncoated and RFB coated pellets are presented in Fig. 1. Comparing the serum concentrations at each time point for uncoated and coated dosage forms, by the ANOVA procedure, statistically significant differences ($\alpha = 0.05$) were found at all time points starting from 1 h to 8 h sampling time, coated pellets resulting in lower values. After 8 h sampling time no significant differences were observed between serum theophylline concentrations of uncoated and coated dosage forms. There was a statistically significant difference for t_{max}, C_{max} values between coated and uncoated pellets ($p = 0.0014$)

and $p = 0.0002$, respectively). Uncoated pellets resulted in a mean t_{max} value of 1.7 h with a 14.92 μg/ml serum theophylline concentration, whereas the coated pellets gave a mean t_{max} value of 3.5 h with a theophylline concentration of 6.75 μg/ml. The shift in the t_{max} value of the coated dosage form may be explained by the change of the drug release mechanism from simple dissolution/diffusion to membrane-controlled delivery. The rest of the pharmacokinetic parameters between coated and uncoated dosage forms were not found to be significantly different ($\alpha = 0.05$) (Table 1). A more precise assessment of the pharmacokinetic parameters would require a larger sample size, however, this was not one of the objectives of the study. The pharmacokinetic parameters were obtained using the compartment model independent analysis software AUC-RPP. The results are presented in Table 1.

An attempt to determine an in vitro-in vivo correlation was made between the percent of drug absorbed of ultimate amount of drug absorbed (Wagner-Nelson method) and the percent theophylline released in vitro. Fig. 2 shows the plot for the correlation. A correlation coefficient of 0.9584 was calculated between percent absorbed in vivo and that released in vitro. The

TABLE 1

Pharmacokinetic parameters [a] of theophylline from uncoated and coated pellets in beagle dogs mean (SD, n = 4)

Parameter	Uncoated	Coated
Dose (mg)	117.25 (4.85)	126.50 (8.73)
k_e (1/h)	0.1351 (0.02)	0.1082 (0.06)
k_a (1/h)	2.0680 (1.38)	0.6528 (0.20)
$t_{1/2}$ (h)	5.23 (0.87)	8.28 (5.04)
$t_{1/2a}$ (h)	0.465 (0.254)	1.180 (0.517)
V_d/F (l/kg)	0.72 (0.06)	1.47 (0.29)
CL_t/F (ml min^{-1} kg^{-1})	1.61 (0.279)	2.49 (0.98)
AUC (μg ml^{-1} h) (0 to infinity)	137.36 (23.71)	110.47 (64)
AUMC (μg ml^{-1} h^2) (0 to infinity)	1152.4 (448)	1833.0 (1948)
t_{max} (h)	1.70 (0.70)	3.50 (0.50) [b]
C_{max} (μg/ml)	14.92 (1.48)	6.75 (1.80) [b]
MRT (h)	8.18 (1.69)	13.80 (6.64)

[a] AUC-RPP.

[b] Statistically significant comparison at $\alpha = 0.05$ level.

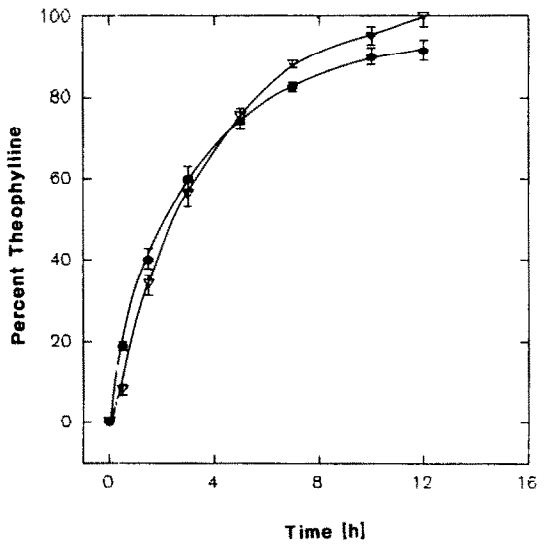

Fig. 2. In vitro-in vivo correlation between percent drug absorbed of ultimate amount of drug absorbed and percent released in vitro. (▽) Percent drug absorbed from in vivo data ($n = 4$, $r = 0.9584$); (●) percent drug released in vitro (900 ml distilled water, paddle method, 100 rpm).

Wagner-Nelson method was applied under the assumptions of the one-compartment open model and the absorption process not being the rate-limiting step.

A relative bioavailability calculation was carried out using the uncoated pellets as reference. Based on the comparison of the areas under the serum theophylline concentration-time curves from time 0 to infinity for both treatments, a relative bioavailability of 52% was calculated for RFB coated pellets. The likely explanation for the low bioavailability was that the coated granules did not have sufficient time in the GI tract of the animals to release all of their contents. During the experiments it was observed that all the animals excreted the pellets in the feces after 8–10 h of administration. The colon arrival time in the dog model was reported to be approx. 4 h (Anderson and Good, 1970; Robinson, 1990), and the shorter intestinal transit times in dog could result in a lower fraction absorbed for controlled-release dosage forms (Dressman, 1986). If one assumes that colonic absorption is much slower due to physiological differences between the colon and the small intestines and predominantly high

viscosity medium in the colon, controlled-release dosage forms will have 4–5 h to release their contents in the dog model which is shorter than the human case. For theophylline which is uniformly absorbed from the GI tract, therefore, there is no reason for it not to be bioavailable other than not being present in the site of absorption. After the in vitro dissolution test and the recovered pellets from the dog study, it was found that the pellets were intact and spherical. This study provides an in vivo comparison between RFB coated and uncoated pellets. Ethylcellulose coated pellets resulted in a lower rate and extent of drug release than the uncoated ones. The beagle dog was shown to be a good animal model to test controlled-release dosage forms in vivo. Further support was provided for this claim by a recent study (Aoyagi et al., 1992) in which the beagle dog was shown to be a better animal model than pigs or rabbits for bioavailability studies.

Acknowledgment

The authors are grateful to Mr Dirk Sorgenfrey for help during the in vivo experiments

References

Anderson, A.C. and Good, L.S., *The Beagle as an Experimental Dog*, Iowa State University Press, IA, 1970, pp. 226–231.

Aoyagi, N., Ogata, H., Kaniwa, N., Uchiyama, M., Yasuda, Y. and Tanioka, Y., Gastric emptying of tablets and granules in humans, dogs, pigs, and stomach-emptying-controlled rabbits. *J. Pharm Sci.*, 81 (1992) 1170–1173.

Dressman, J., Comparison of canine and human gastrointestinal physiology. *Pharm. Res.*, 3 (1986) 123–131.

Lippold, B.H., Sutter, B.K. and Lippold, B.C., Parameters controlling drug release from pellets coated with aqueous ethyl cellulose dispersion. *Int. J. Pharm.*, 34 (1984) 15–25.

Ritschel, W.A., AUC-RPP Basic computer program for compartment model independent analysis. *Methods Find. Exp. Clin. Pharmacol.*, 8 (1986) 633–640.

Robinson, J.R., Rubinstein, A. and Liaw, J., Bioavailability study of Theo-dur tablets in the fasted cannulated dog. *Int. J. Pharm.*, 59 (1990) 105–114.

Turkoglu, M. and Sakr, A., Mathematical modelling and optimization of a rotary fluidized bed coating process. *Int J. Pharm.*, 88 (1992) 75–87.

Wan, L. and Lai, W.F., Factors affecting drug release from drug coated granules prepared by fluidized bed coating. *Int. J. Pharm.*, 72 (1991) 163–174.

Yang, S.T. and Sellassie, I.G., The effect of product bed temperature on the microstructure of Aquacoat-based controlled-release coatings. *Int. J. Pharm.*, 60 (1990) 109–124.

Zhang, G., Schwartz, J.B., Schnaare, R.L., Wigent, R.J. and Sugita, E.T., Bead coating: II. Effect of spheronization technique on drug release from coated spheres. *Drug Dev. Ind. Pharm.*, 17 (1991) 817–830.