Available online at www.sciencedirect.com
ScienceDirect
International Journal of Pharmaceutics 352 (2008) 36–43
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Evaluation of *in vivo* dissolution behavior and GI transit of griseofulvin, a BCS class II drug

Yoshitsugu Fujioka, Yukiko Metsugi, Ken-ichi Ogawara, Kazutaka Higaki, Toshikiro Kimura *

Department of Pharmaceutics, Faculty of Pharmaceutical Sciences, Okayama University, 1-1-1 Tsushima-naka, Okayama 700-8530, Japan

Received 26 June 2007; received in revised form 29 August 2007; accepted 10 October 2007
Available online 16 October 2007

Abstract

Mean plasma concentration–time profile of griseofulvin, a BCS class II drug, orally administered as powders into rats, was predicted based on GITA model. However, it was very difficult to predict the individual plasma profile because of large inter-individual difference. As the absorption of griseofulvin would be rate-limited by the dissolution process, we tried to analyze the *in vivo* dissolution kinetics of griseofulvin by focusing on gastric emptying and intestinal transit as physiological factors influencing the *in vivo* dissolution kinetics. After oral administration of griseofulvin, theophylline and sulfasalazine into rats, gastric emptying and intestinal transit were simultaneously estimated by analyzing the absorption kinetics of theophylline and observing the appearance of sulfapyridine in plasma, respectively. Gastric emptying kinetics was not significantly correlated with absorption or dissolution behavior of griseofulvin. On the other hand, the cecum-arriving time reflecting the intestinal transit was significantly correlated with both AUC and total dissolved amount of griseofulvin. T_{max} of griseofulvin also increased with the increase of cecum-arriving time. These results clearly indicate that the longer residence time could lead to the higher dissolution and absorption of griseofulvin and that the variance of intestinal transit could be responsible for the inter-individual difference of the *in vivo* absorption behavior.

Keywords: Gastric emptying; Cecum-arriving time; Intestinal transit; *In vivo* dissolution; Griseofulvin; Biopharmaceutics classification system class II

1. Introduction

Recently, the candidate compounds for new medicines that were selected by combinatorial chemistry and/or high-throughput screening often show very poor suitability as a medicine in terms of ADME properties. Especially, insolubility or poor solubility in water is one of the most serious problems in the subsequent processes of drug development. As drugs need to be dissolved in the gastrointestinal (GI) tract for the absorption, poor solubility leads to the low bioavailability and very often the large variability in the absorption kinetics after oral administration (Rowland et al., 1968; Hägermark et al., 1976; Dressman and Reppas, 2000; Emara et al., 2002).

Absorption behavior after oral administration is influenced by physicochemical properties of the drug substance (solubility, lipophilicity and molecular size), physiological factors (composition, volume and hydrodynamics of the GI fluids, and GI transit) and dosage form (solution, powder and tablet). Among these many factors, the solubility in water and permeability of intestinal membrane have been focused, and the biopharmaceutics classification system (BCS), classifying drugs into four classes according to their solubility and permeability, has been proposed (Amidon et al., 1993, 1995). On the other hand, the absorption behavior after oral administration is highly variable time-dependently because of site dependency of permeability, time-dependent GI transit and variable dissolution environment due to the change in components and pH of GI-luminal fluid (Higaki et al., 2001; Kimura and Higaki, 2002). Particularly, focusing on the segment-dependent absorbability of drugs and GI transit, we have reported the successful analysis and prediction of oral absorption behaviors of drugs, dosed as solution, with various characteristics based on GI-transit-absorption (GITA) model (Kimura and Higaki, 2002; Yokoe et al., 2003).

* Corresponding author. Tel.: +81 86 251 7948; fax: +81 86 251 7926.
E-mail address: kimura@pharm.okayama-u.ac.jp (T. Kimura).

0378-5173/$ – see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2007.10.008

We have also succeeded in predicting the *in vivo* absorption kinetics of theophylline, classified into class I of BCS (high solubility and high permeability), orally administered as powders into rats (Kadono et al., 2002). Furthermore, we have shown that the mean plasma concentration–time profile of griseofulvin, BCS class II (low solubility and high permeability), was also predictable to some extent by utilizing a more suitable medium for *in vitro* dissolution study, MREVID (Fujioka et al., 2007). However, it was very difficult to predict the individual plasma profile of griseofulvin by utilizing pharmacokinetic parameters describing a typical profile of GI transit (Kadono et al., 2002) or *in vitro* dissolution (Fujioka et al., 2007) because of large inter-individual difference. As the absorption of griseofulvin is rate-limited by the dissolution process, the *in vivo* dissolution behavior could be responsible for the large variance of absorption behavior.

In the present study, we tried to analyze the *in vivo* dissolution kinetics of griseofulvin after oral administration as powders, and to investigate the relationship among the *in vivo* dissolution, gastric emptying and intestinal transit by assessing the absorption kinetics of theophylline, a marker for gastric emptying (Kadono et al., 2002), and the plasma appearance of sulfapyridine, a marker for cecum-arriving of drugs after oral dosing (Yamaguchi et al., 1994).

2. Materials and methods

2.1. Materials

Theophylline was purchased from Tokyo Chemical Industry Co. (Tokyo, Japan). Griseofulvin, sulfapyridine, aminophylline and 7-(2-hydroxyethyl)theophylline, an internal standard for theophylline and sulfapyridine, were purchased from Sigma Chemical Co. (St. Louis, MO, USA). Sulfasalazine and *p*-phenyl phenol, an internal standard for griseofulvin, were purchased from Nacalai Tesque Inc. (Kyoto, Japan). Particle sizes of theophylline, griseofulvin and sulfasalazine were 67.53 ± 2.70, 3.87 ± 0.19 and 12.56 ± 0.32 μm, respectively, which were determined by laser particle sizer (LDSA-1500A, Tohnichi Computer Applications Co. Ltd., Tokyo). Gelatin mini-capsules (length 8.4 mm; o.d. 2.6 mm) were obtained from Shionogi Quolicaps Co. (Osaka, Japan). All other chemicals and reagents were analytical grade commercial products.

2.2. Animals

Male Wistar rats (Japan SLC, Hamamatsu, Japan), maintained at 25 °C and 55% humidity, were allowed free access to standard laboratory chow (Clea Japan, Tokyo) and water. They were fasted for 24 h prior to and during the experiment, but were allowed free access to water. Rats weighing 230–290 g were randomly assigned to each experimental group. Our investigations were performed after approval by our local ethical committee at Okayama University and in accordance with "Principal of Laboratory Animal Care (NIH publication # 85-23)".

2.3. In vivo oral and intravenous administration studies

One day before drug administration, the jugular vein of a rat was cannulated with vinyl tubing (i.d., 0.5 mm × 0.8 mm; Dural Plastics & Engineering, Australia) under ether anesthesia. In the case of oral administration, griseofulvin, theophylline and sulfasalazine powders were intragastrically administered in a gelatin mini-capsule at a dose of 20 mg/kg for each drug, and then immediately 6.4 mL/kg of water was ingested. For intravenous administration, griseofulvin and aminophylline (theophylline ethylenediamine) were dissolved into the mixture of polyethylene glycol 400:water (1:1), and the resultant solution was administered into the tail vein at 2 mg/2 mL/kg for griseofulvin and 23.3 mg/2 mL/kg for aminophylline equivalent to 20 mg/2 mL/kg of theophylline. The dosed rats were allowed free moving and free access to water. Blood samples were periodically taken from the cannulated jugular vein. Plasma obtained by centrifugation was deproteinized by methanol and the resulting supernatant was introduced into HPLC for the analysis of griseofulvin, theophylline and sulfapyridine, which is generated from sulfasalazine by the cleavage of azo-bond due to microflora around the cecum and is absorbed there (Yamaguchi et al., 1994).

2.4. Analytical method

Griseofulvin, theophylline and sulfapyridine were determined by HPLC, which consists of a model LC-6A HPLC pump (Shimadzu, Kyoto), a model SIL-6A system controller (Shimadzu), and a model SPD-6A UV detector (Shimadzu) set at 293 nm for griseofulvin, or set at 272 nm for theophylline and sulfapyridine. A Inertsil® ODS-3 (300 mm × 4.6 mm i.d., GL-Sciences Inc., Tokyo) was used at room temperature. The mobile phase for griseofulvin was 0.1 M acetic acid:acetonitrile (55:45, v/v) delivered at 1.0 mL/min, and that for theophylline and sulfapyridine was 5 mM acetate buffer (pH 4.8):acetonitrile (90:10, v/v) delivered at 1.0 mL/min. The concentration range of standard curves was 0.04–2, 1–50 or 0.2–10 μg/mL for griseofulvin, theophylline or sulfapyridine, respectively. The squared correlation coefficient for standard curves was over 0.993. The coefficient of variation (CV) ranged from 0.63 to 10.52%.

2.5. Pharmacokinetic analysis

Area under the plasma concentration–time curve (AUC) and mean residence time (MRT) for plasma concentration were calculated by following the trapezoidal rule. The highest concentration observed was employed as C_{max} and the time for C_{max} was defined as T_{max}. The absorption rate profile was calculated by following Loo–Riegelman method (Loo and Riegelman, 1968) because the pharmacokinetics after intravenous administration was described by two-compartment model for both griseofulvin and theophylline.

Pharmacokinetic model shown in Fig. 1(A) was assumed to analyze the *in vivo* dissolution behavior of griseofulvin after oral administration as powders. Gastric emptying rate–time

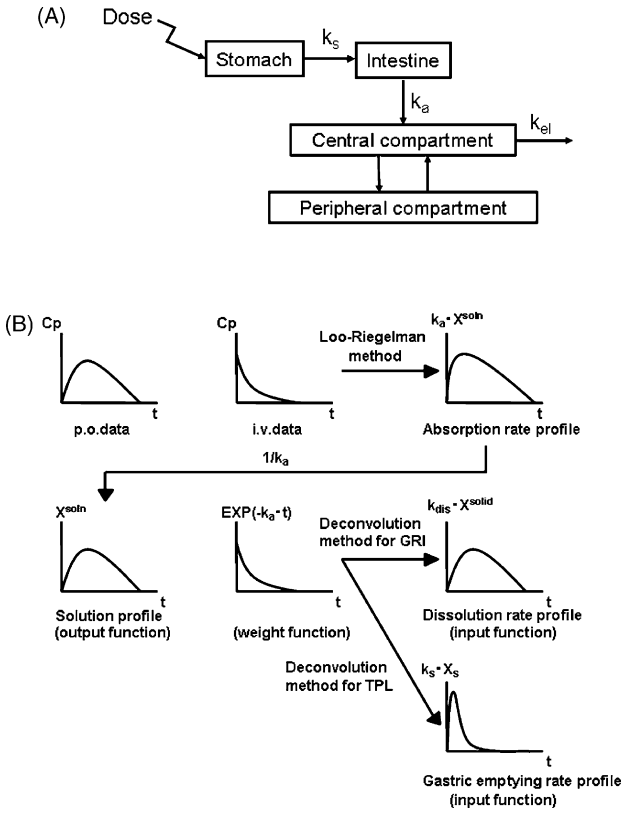

Fig. 1. Pharmacokinetic model (A) and outline (B) for analysis of absorption, dissolution and gastric emptying for griseofulvin after oral administration as powders into rats. k_s, gastric emptying rate constant; k_a, absorption rate constant; k_{el}, elimination rate constant; k_{dis}, dissolution rate constant; X^{soln}, dissolved drug amount remaining in the small intestine; X^{solid}, drug amount remaining as powders in the small intestine; X_s, drug amount remaining in the stomach.

profile and dissolution rate–time profile were calculated by following the procedure shown in Fig. 1(B). Briefly, the amount of drugs existing as solution–time profile, an output function, and the first-order absorption process, a weight function, were utilized to perform the deconvolution to obtain the dissolution rate–time profile for griseofulvin or the gastric emptying rate–time profile for theophylline, because it can be assumed that the absorption of griseofulvin or theophylline is rate-limited by dissolution (Fujioka et al., 2007) or gastric emptying (Kadono et al., 2002), respectively. Mean absorption time (MAT) and mean dissolution time (MDT) for griseofulvin were calculated based on the statistical moment theory utilizing the cumulative absorption–time profile and the cumulative dissolution–time profile, respectively (Tanigawara et al., 1982a,b).

Gastric emptying rate constant, k_s, was calculated by assuming the first-order kinetics for gastric emptying of theophylline and pharmacokinetic parameters after intravenous administration of griseofulvin or theophylline were calculated with MULTI program (Yamaoka et al., 1981).

Relationship between dissolution or absorption of griseofulvin and gastric emptying or cecum-arriving time was estimated by linear regression analysis.

3. Results and discussion

To estimate the *in vivo* dissolution behavior, which would be a main reason for the large variance in the absorption kinetics of griseofulvin, we paid attention to the gastric emptying behavior (Lipka et al., 1995; Takamatsu et al., 2002) and the intestinal transit kinetics (Jamali and Axelson, 1977; Dobson et al., 2002), mainly influenced by individual physiological condition.

In order to evaluate the gastric emptying, intestinal transit kinetics and absorption kinetics of griseofulvin in the same subject, we administered griseofulvin powder together with theophylline and sulfasalazine powders in a gelatin mini-capsule at a dose of 20 mg/kg for each drug into fasted rats. In the present study, theophylline was employed as a marker for gastric emptying, because theophylline is categorized to BCS class I as acetaminophen, which is used as a maker of gastric emptying behavior (Mizuta et al., 1990; Sunesen et al., 2005), and we reported that theophylline is dissolved in the stomach around 80% of dose and is absorbed immediately after entering into the small intestine (Kadono et al., 2002). Therefore, assuming that drugs are not absorbed from the stomach, but quickly and exclusively absorbed from the small intestine (Heading et al., 1973; Willems et al., 2001), we analyzed the gastric emptying kinetics based on the absorption kinetics of theophylline.

On the other hand, sulfasalazine was utilized as a marker for the intestinal transit. After orally administered, sulfasalazine is hydrolyzed by azoreductase derived from the microflora existing around the cecum to generate sulfapyridine and 5-aminosalicylic acid (Kellow et al., 1986). As the absorbability of sulfapyridine is very good (Khan et al., 1980; Yamaguchi et al., 1994; Tozaki et al., 1999), the time of the first appearance of sulfapyridine in the blood can be assumed to be the arrival time of drugs to the cecum (cecum-arriving time), which was determined by extrapolating the initial ascending part of the sulfapyridine plasma concentration curve to the axis of time periods (Peh and Yuen, 1996). As sulfasalazine is poorly soluble and poorly absorbable (Khan et al., 1980; Yamaguchi et al., 1994; Tozaki et al., 1999), it is expected that the gastric emptying and intestinal transit of sulfasalazine would be very similar to those of griseofulvin.

Fig. 2 shows the plasma concentration–time profiles of each rat after oral dosing of three drugs. Table 1 lists the pharmacokinetic parameters of griseofulvin, clearly indicating a very large variance in the absorption kinetics of griseofulvin after oral administration as powders. The large inter-individual difference in the absorption kinetics of griseofulvin was reported by other researchers (Rowland et al., 1968; Bates and Carrigan, 1975; Hägermark et al., 1976; Aoyagi et al., 1982) and also observed in our previous study where griseofulvin alone was orally administered (Fujioka et al., 2007). Although an inter-individual difference was observed in the absorption of theophylline to some extent, similar to the results in the previous study where theophylline alone was orally administered (Kadono et al., 2002), it was smaller than that of griseofulvin. T_{max} of theophylline (1.10 ± 0.56 h) was within 2 h for all of the subjects, compared with the values ranged from 2 to 8 h for griseofulvin. C_{max} of theophylline (31.9 ± 9.0 μg/mL) also has much smaller value of coefficient of variance (CV = 28%) than that of

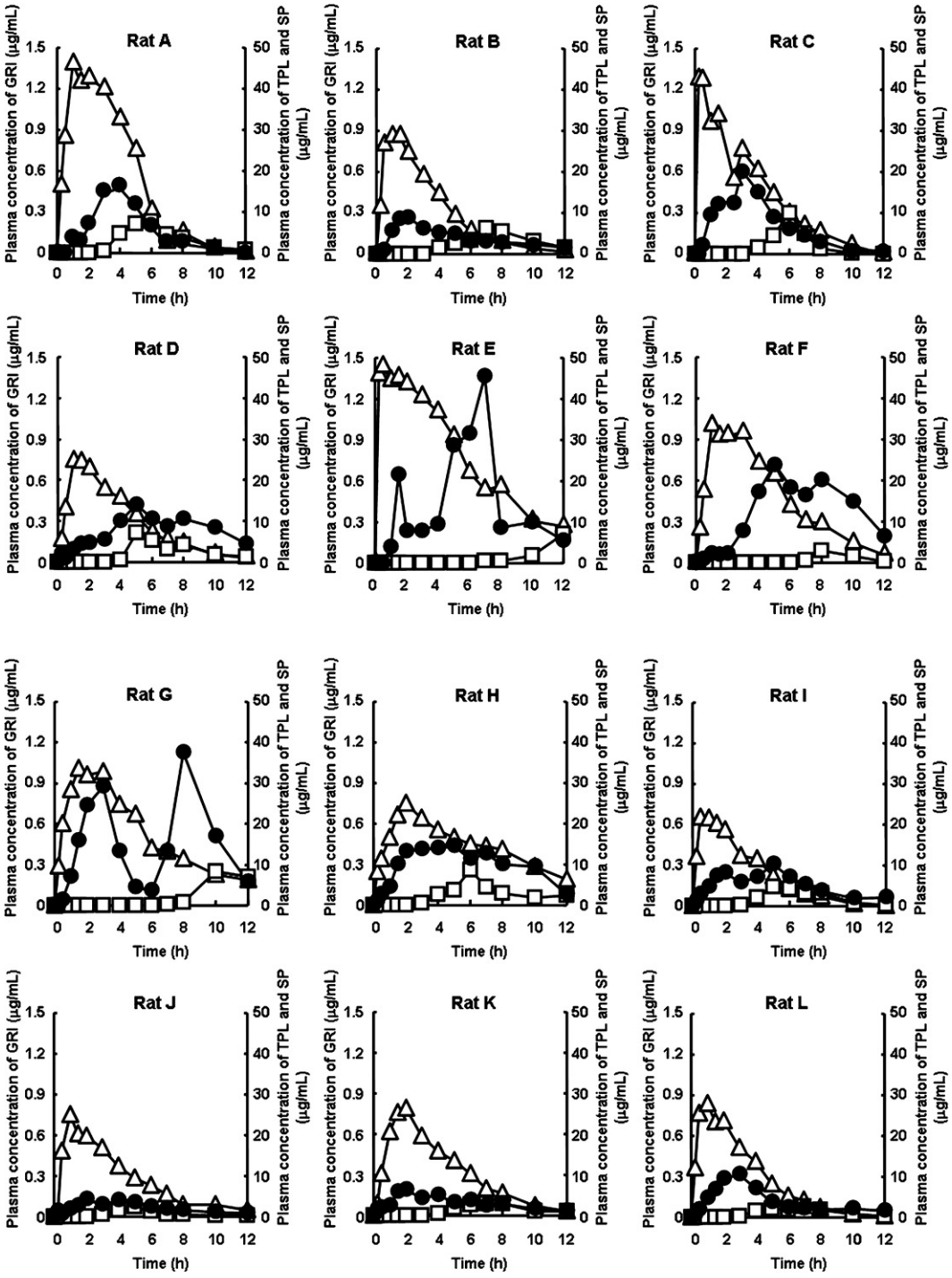

Fig. 2. Plasma concentration–time profiles of griseofulvin (GRI), theophylline (TPL) and sulfapyridine (SP) after oral administration of GRI, TPL and sulfasalazine as powders into rats. GRI, TPL and sulfasalazine were intragastrically administered at 20 mg/kg in a gelatin mini-capsule (length 8.4 mm; o.d. 2.6 mm), respectively. Keys: ●, GRI; △, TPL; □, SP.

griseofulvin (CV = 71%). The plasma concentration–time profile of sulfapyridine indicated that the intestinal transit kinetics was also individually varied very much (Fig. 2) and the cecum-arriving time shown in Table 2 confirmed the large difference in the intestinal transit, although it is suggested that the intestinal transit kinetics is not affected by the food (Davis et al., 1986a; Abrahamsson et al., 1993; Castiglione et al., 1998), the size (Tuleu et al., 1999) and the density (Davis et al., 1986b; Devereux et al., 1990; Tuleu et al., 1999).

Next, we conducted intravenous administration study in order to calculate the absorption rate–time profile for both griseofulvin and theophylline based on the results of *in vivo* oral absorption study. To assess the pharmacokinetics after intravenous dosing, both drugs were simultaneously administered

Table 1
Pharmacokinetics parameters of griseofulvin after oral administration as powders into rats

Rat	T_{max} (h)	C_{max} (μg/mL)	AUC (μg h/mL)	MRT (h)	F
A	4	0.47	1.95	4.68	0.34
B	2	0.27	1.21	3.96	0.21
C	3	0.60	2.44	3.95	0.42
D	5	0.42	3.30	7.69	0.57
E	7	1.37	6.02	7.10	1.04
F	5	0.72	5.19	7.59	0.89
G	8	1.12	6.04	6.66	1.04
H	5	0.44	3.78	6.03	0.65
I	5	0.31	1.86	5.37	0.32
J	2	0.13	0.75	5.45	0.13
K	2	0.19	1.11	6.38	0.19
L	3	0.31	1.52	5.38	0.26
Mean	4.25	0.53	2.93	5.85	0.51
S.D.	1.96	0.38	1.92	1.28	0.33

T_{max} and C_{max} were observed values. AUC and MRT were calculated from 0 to 24 h by trapezoidal rule. F means bioavailability. AUC of griseofulvin after intravenous administration was 0.58 ± 0.25 μg h/mL (Dose = 2 mg/kg).

because they might interact and change in pharmacokinetics when they are co-existing in plasma. Pharmacokinetics of griseofulvin and theophylline after intravenous administration of both drugs was not so different from that after dosing of each drug separately (Kadono et al., 2002; Fujioka et al., 2007), although we had experienced that the distribution volume of theophylline was significantly increased by the co-administration of another drug (intraperitoneal administration of propantheline) (Haruta et al., 1998). The equation describing the plasma concentration–time profile was obtained as follows: griseofulvin, C_p (μg/mL) $= 0.58e^{-16.45t} + 0.57e^{-1.14t}$ (dose, 2 mg/kg); theophylline, C_p (μg/mL) $= 32.96e^{-31.28t} + 35.06e^{-0.15t}$ (dose, 20 mg/kg). As the appearance of sulfapyridine in plasma was around 3 h or later after dosing (Fig. 2) and the absorbability of sulfasalazine was very low (Khan et al., 1980; Yamaguchi et al., 1994; Tozaki et al., 1999), we focused on the co-existence of griseofulvin and theophylline in plasma in terms of pharmacokinetic interaction.

Then, the absorption rate–time profiles were calculated for both griseofulvin and theophylline by Loo–Riegelman method (Loo and Riegelman, 1968). Based on the absorption rate–time profile of griseofulvin, total absorbed amount (% of dose) and mean absorption time (MAT) were calculated (Table 2), also indicating that the absorption behavior of griseofulvin was highly variable. Following the procedure shown in Fig. 1(B), the time course of dissolved drug amount remaining in the small intestine (solution profile) was calculated by utilizing the absorption rate constant (k_a). As shown in Fig. 1(A), we assumed that the small intestine was a single compartment in this analyzis, therefore, the mean values of k_a, 11.27 ± 1.89 and $10.96 \pm 2.89\ h^{-1}$ were used for griseofulvin and theophylline, respectively. They were calculated based on the results obtained by the *in situ* loop study for the different segments for griseofulvin (Fujioka et al., 2007) and for theophylline (Kadono et al., 2002).

In the next step, the deconvolution was performed by regarding the obtained "solution profile" as an output function and the first-order absorption process as a weight function. As a result, the dissolution rate–time profile for griseofulvin and the gastric emptying rate–time profile for theophylline were obtained as an input function (Fig. 3), because it can be assumed that the absorption of griseofulvin or theophylline is rate-limited by the dissolution (Fujioka et al., 2007) or gastric emptying (Kadono et al., 2002), respectively. The gastric emptying profiles clearly show that almost all of the drugs were put out from the stomach around 2 h after dosing for each subject (Fig. 3), although the gastric emptying rate constants (k_s) calculated based on the profile had some variation (Table 2). Gastric emptying kinetics obtained based on the absorption kinetics of theophylline might not neces-

Table 2
Pharmacokinetic parameters describing absorption, dissolution and gastric emptying behavior of griseofulvin after oral administration as powders into rats

Rat	Amount absorbed (% of dose)	Amount dissolved (% of dose)	MAT (h)	MDT (h)	k_s (h^{-1})	Cecum-arriving time (h)
A	35.88	32.77	3.81	3.50	1.54	3
B	22.43	20.77	3.09	2.84	3.58	3
C	44.99	43.72	3.08	2.81	1.86	4
D	61.01	57.04	6.81	6.27	2.85	5
E	109.03	109.11	6.23	5.58	1.96	9
F	95.60	89.64	6.71	6.17	1.37	7
G	109.74	99.47	5.79	5.40	1.08	8
H	69.49	64.27	5.16	4.66	0.67	4
I	34.50	32.58	4.50	4.15	4.29	3
J	13.89	12.96	4.58	4.18	1.37	3
K	20.47	19.00	5.50	5.04	1.50	4
L	27.85	25.33	4.51	4.04	3.61	3
Mean	53.74	50.56	4.98	4.55	2.14	4.67
S.D.	34.85	33.30	1.28	1.18	1.15	2.15

Amount absorbed and amount dissolved were obtained by the integration of absorption rate–time profile and of dissolution rate–time profile, respectively. MAT and MDT were calculated from 0 to 24 h by trapezoidal rule. Gastric emptying rate constant, k_s, was calculated by assuming the first-order kinetics. Cecum-arriving time was determined based on the first appearance time of sulfapyridine in plasma.

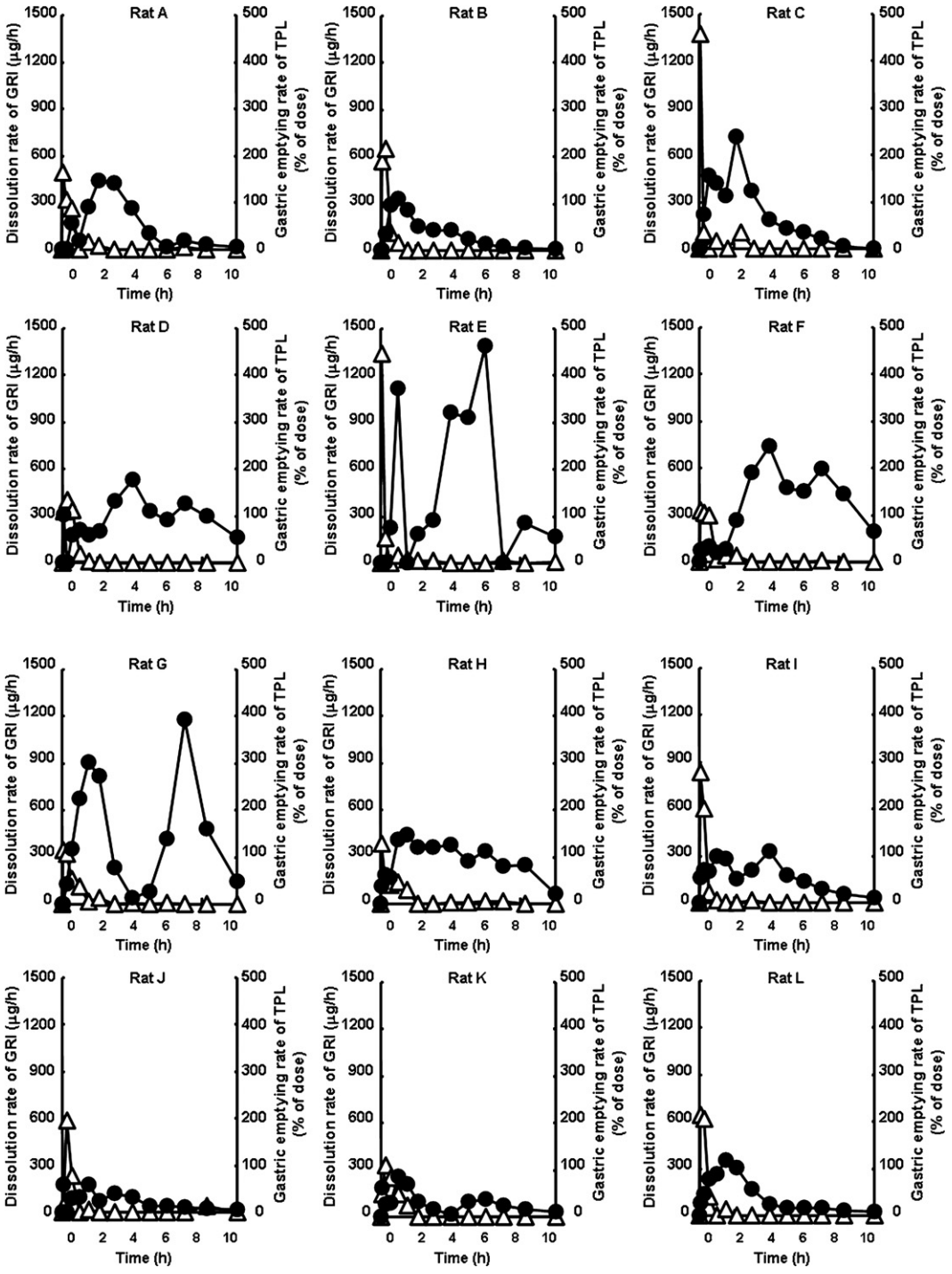

Fig. 3. Dissolution rate of griseofulvin (GRI) and gastric emptying rate of theophylline (TPL) after oral administration as powders into rats. Dissolution rate and gastric emptying rate were calculated by following the procedure shown in Fig. 1(B) and described in Section 2. Keys: ●, GRI; △, TPL.

sarily reflect the exact profile of gastric emptying of griseofulvin, because around 80% of theophylline would be dissolved in the stomach (Kadono et al., 2002) but griseofulvin would be emptied as powders. Usually, gastric emptying of powders would be delayed as compared with that of solution, but we reported that it is comparable each other and around 80% of glass beads, a model particle, could be put out from the stomach at 2 h after oral dosing (Kadono et al., 2002). Therefore, we considered that the gastric emptying behavior of theophylline generally reflects that of griseofulvin. The mean value of k_s ($2.14\,h^{-1}$) obtained in the present study is similar to the value reported previously ($1.99\,h^{-1}$) (Kadono et al., 2002; Fujioka et al., 2007), indicating the validity of the present approach to estimate the gastric emptying kinetics.

On the other hand, the dissolution rate profiles indicate the very large variability from the aspects of both time and extent

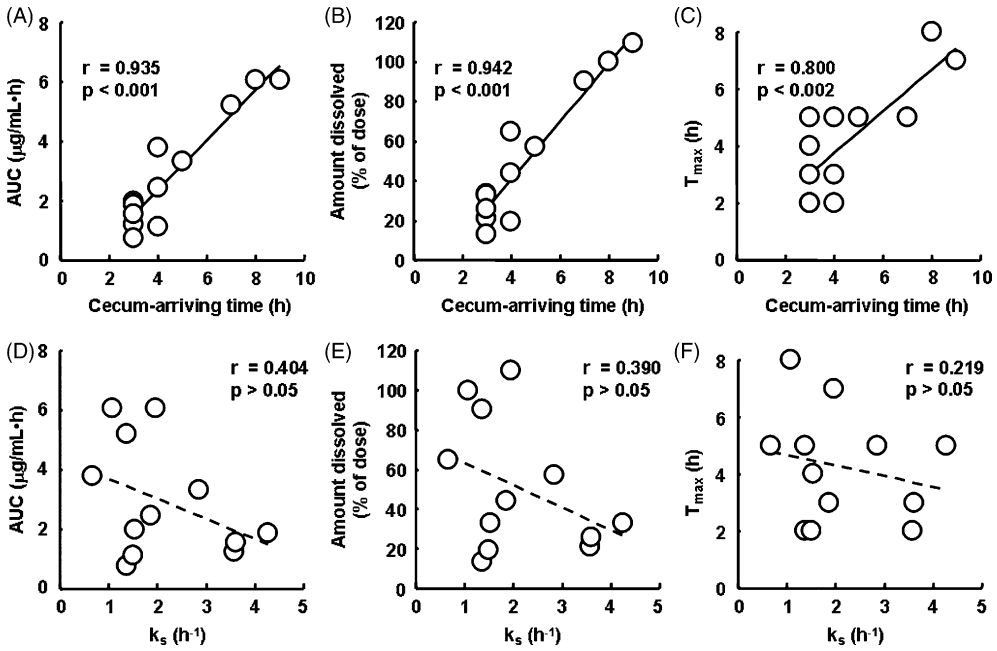

Fig. 4. Factors regulating *in vivo* dissolution and absorption behavior of griseofulvin after oral administration as powders into rats. Relationship between "AUC, amount dissolved or T_{max}" and "cecum-arriving time or gastric emptying rate constant, k_s" was examined by linear regression analysis. (A) AUC and cecum-arriving time; (B) amount dissolved and cecum-arriving time; (C) T_{max} and cecum-arriving time; (D) AUC and k_s; (E) amount dissolved and k_s; (F) T_{max} and k_s.

(Fig. 3). Most subjects show the irregular shape in dissolution rate–time profile, and the highest value of dissolution rate and the time to reach the highest dissolution rate ranged from 179.85 to 1389.87 μg/h and from 1 to 7 h, respectively. Total dissolved amount (% of dose) and the mean dissolution time (MDT) also indicate the high variability of *in vivo* dissolution behavior of griseofulvin (Table 2). Although total absorbed amount should be smaller than total dissolved amount theoretically, the absorbed amount was calculated to be a little bit larger than the dissolved amount here, which might be caused by small calculation error. However, the total amount absorbed was very close to the total amount dissolved and the values of MAT were also very similar to those of MDT, confirming that the dissolution process was the rate-limiting process for the absorption of griseofulvin.

Fig. 3 suggests that gastric emptying behavior has nothing to do with the *in vivo* dissolution behavior of griseofulvin, and the statistical analysis clearly indicated that there was no relationship between the absorption (AUC, T_{max}) or dissolution (amount dissolved) of griseofulvin and gastric emptying (k_s) (Fig. 4(D)–(F)). On the other hand, the cecum-arriving time reflecting the intestinal transit was significantly correlated with both AUC and total dissolved amount of griseofulvin. T_{max} of griseofulvin also increased with the increase of the cecum-arriving time. These results clearly indicate that the longer residence time could lead to the higher dissolution and absorption of griseofulvin and that the variance of intestinal transit could be responsible for the inter-individual difference of the *in vivo* absorption behavior. We evidenced that the longer residence time of drugs in the small intestine could result in the higher bioavailability for poorly absorbable drugs in the previous studies where the absorption of ampicillin was improved by the treatment with propantheline (Haruta et al., 1998) or loperamide (Kimura and Higaki, 2002) that attenuates the intestinal transit. In the present case for griseofulvin, the cecum-arriving time was significantly correlated with MDT as well ($p < 0.02$), and the longer residence time in the small intestine would increase the opportunity for griseofulvin to be dissolved before excreted into feces. However, dissolution rate–time profiles obtained in the present study were highly variable and complicated in shape, which cannot be explained simply by the variability in the residence time and remains to be clarified.

In conclusion, the large variance of *in vivo* absorption behavior of griseofulvin could be attributed to the *in vivo* dissolution behavior that is significantly influenced by the intestinal transit.

Acknowledgement

This work was supported in part by a Grant-in-Aid for Scientific Research (C) from the Ministry of Education, Sciences, and Culture of Japan.

References

Abrahamsson, B., Alpsten, M., Hugosson, M., Jonsson, U.L.F.E., Sundgren, A., Tolli, J., 1993. Absorption, gastrointestinal transit, and tablet erosion of felodipine extended-release (ER) tablets. Pharm. Res. 10, 709–714.

Amidon, G.L., Doo-Man, O., Curl, R.L., 1993. Estimating the fraction dose absorbed from suspensions of poorly soluble compounds in humans: a mathematical model. Pharm. Res. 10, 264–270.

Amidon, G.L., Lennernas, H., Shah, V.P., Crison, J.R., 1995. A theoretical basis for a biopharmaceutic drug classification: the correlation of *in vitro* drug product dissolution and *in vivo* bioavailability. Pharm. Res. 12, 413–420.

Aoyagi, N., Ogata, H., Kaniwa, N., Koibuchi, M., Shibazaki, T., Ejima, A., Tamaki, N., Kamimura, H., Katougi, Y., Omi, Y., 1982. Bioavailability of griseofulvin from tablets in beagle dogs and correlation rate and bioavailability in humans. J. Pharm. Sci. 71, 1169–1172.

Bates, T.R., Carrigan, P.J., 1975. Apparent absorption kinetics of micronized griseofulvin after its oral administration on single and multiple-dose regiments to rats as a corn oil-in-water emulsion and aqueous suspension. J. Pharm. Sci. 64, 1475–1481.

Castiglione, K.F., Read, N.W., French, S.J., 1998. Food intake responses to upper gastrointestinal lipid infusions in humans. Physiol. Behav. 64, 141–145.

Davis, S.S., Hardy, J.G., Fara, J.W., 1986a. Transit of pharmaceutical dosage forms thought the small intestine. Gut 27, 886–892.

Davis, S.S., Stockwell, A.F., Taylor, M.J., Hardy, J.G., Whalley, D.R., Wilson, C.G., Bechgaard, H., Christensen, F.N., 1986b. The effect of density on the gastric emptying of single- and multiple-unit dosage forms. Pharm. Res. 3, 208–213.

Devereux, J.E., Newton, J.M., Short, M.B., 1990. The influence of density on the gastrointestinal transit of pellets. J. Pharm. Pharmacol. 42, 500–501.

Dobson, C.L., Davis, S.S., Chauhan, S., Sparrow, R.A., Wilding, I.R., 2002. The effect of ileal break activators on the oral bioavailability of atenolol in man. Int. J. Pharm. 248, 61–70.

Dressman, J.B., Reppas, C., 2000. *In vitro–in vivo* correlations for lipophilic, poorly water-soluble drugs. Eur. J. Pharm. Sci. 11 suppl., S73–S80.

Emara, L.H., Badr, R.M., Elbary, A.A., 2002. Improving the dissolution and bioavailability of nifedipine using solid dispersions and solubilizers. Drug Dev. Ind. Pharm. 28, 795–807.

Fujioka, Y., Kadono, K., Fujie, Y., Metsugi, Y., Ogawara, K., Higaki, K., Kimura, T., 2007. Prediction of oral absorption of griseofulvin, a BCS class II drug, based on GITA model: utilization of a more suitable medium for *in vitro* dissolution study. J. Control. Release 119, 222–228.

Hägermark, Ö., Berlin, A., Wallin, I., Boréus, O.L., 1976. Plasma concentrations of griseofulvin in healthy volunteers and out-patients treated for onychomycosis. Acta Dermatovener. 56, 289–296.

Haruta, S., Iwasaki, N., Ogawara, K., Higaki, K., Kimura, T., 1998. Absorption behavior of orally administration drugs in rats treated with propantheline. J. Pharm. Sci. 87, 1081–1085.

Heading, R.C., Nimmo, J., Prescott, L.F., Tothill, P., 1973. The dependence of paracetamol absorption on the rate of gastric emptying. Br. J. Pharmacol. 47, 415–421.

Higaki, K., Yamashita, S., Amidon, G.L., 2001. Time-dependent oral absorption models. J. Pharmacokin. Pharmacodyn. 28, 109–128.

Jamali, F., Axelson, J.E., 1977. Influence of metoclopramide and propantheline on GI absorption of griseofulvin in rats. J. Pharm. Sci. 66, 1540–1543.

Kadono, K., Yokoe, J., Ogawara, K., Higaki, K., Kimura, T., 2002. Analysis and prediction of absorption behavior for theophylline orally administered as powders based on gastrointestinal-transit-absorption (GITA) model. Drug Metab. Pharmacokinet. 17, 307–315.

Kellow, J.E., Borody, T.J., Phillips, S.F., Haddad, A.D., Brown, M.L., 1986. Sulfapyridine appearance in plasma after salicylazosulfapyridine. Another simple measure of intestinal transit. Gastroenterology 91, 396–400.

Khan, A.K.A., Truelove, S.C., Aronson, J.K., 1980. The disposition and metabolism of sulphasalazine (salicylazosulfapyridine) in man. Br. J. Clin. Pharmacol. 13, 523–528.

Kimura, T., Higaki, K., 2002. Gastrointestinal transit and drug absorption. Biol. Pharm. Bull. 25, 149–164.

Lipka, E., Lee, I.-D., Langguth, P., Spahn-Langguth, H., Mutschler, E., Amidon, G.L., 1995. Celiprolol double-peak occurrence and gastric motility: nonlinear mixed effects modeling of bioavailability date obtained in dogs. J. Pharmacokinet. Biopharm. 23, 267–286.

Loo, J.C.K., Riegelman, S., 1968. New method for calculating the intrinsic absorption rate of drugs. J. Pharm. Sci. 57, 918–928.

Mizuta, H., Kawazoe, Y., Ogawa, K., 1990. Gastrointestinal absorption of chlorothiazide: evaluation of a method using salicylazosulfapyridine and acetaminophen as the marker compounds for determination of the gastrointestinal transit time in the dog. Chem. Pharm. Bull. 38, 2810–2813.

Peh, K.K., Yuen, K.H., 1996. Indirect gastrointestinal transit monitoring and absorption of theophylline. Int. J. Pharm. 139, 95–103.

Rowland, M., Riegelman, S., Epstein, W.L., 1968. Absorption kinetics of griseofulvin in man. J. Pharm. Sci. 57, 984–989.

Sunesen, V.H., Vedelsdal, R., Kristensen, H.G., Christrup, L., Müllertz, A., 2005. Effect of liquid volume and food intake on the absolute bioavailability of danazol, a poorly soluble drug. Eur. J. Pharm. Sci. 24, 297–303.

Takamatsu, N., Welage, L.S., Hayashi, Y., Yamamoto, R., Barnett, J.L., Shah, V.P., Lesko, L.J., Ramachandran, C., Amidon, G.L., 2002. Variability in cimetidine absorption and plasma double peaks following oral administration in the fasted state in humans: correlation with antral gastric motility. Eur. J. Pharm. Biopharm. 53, 37–47.

Tanigawara, Y., Yamaoka, K., Nakagawa, T., Uno, T., 1982a. Correlation between in vivo mean dissolution time and in vitro mean dissolution time of ampicillin products. J. Pharmacobiodyn. 5, 370–372.

Tanigawara, Y., Yamaoka, K., Nakagawa, T., Uno, T., 1982b. New method for the evaluation of in vitro dissolution time and disintegration time. Chem. Pharm. Bull. 30, 1088–1090.

Tozaki, H., Fujita, T., Odoriba, T., Terabe, A., Okabe, S., Muranishi, S., Yamamoto, A., 1999. Validation of a pharmacokinetics model of colon-specific drug delivery and the therapeutic effects of chitosan capsules containing 5-aminosalicylic acid on 2,4,6-trinitrobenzenesulphonic acid-induced colitis in rats. J. Pharm. Pharmacol. 51, 1107–1112.

Tuleu, C., Andrieux, C., Boy, P., Chaumell, J.C., 1999. Gastrointestinal transit of pellets in rats: effect of size and density. Int. J. Pharm. 180, 123–131.

Willems, M., Quartero, A.O., Numans, M.E., 2001. How useful is paracetamol absorption as a maker of gastric emptying? A systematic literature study. Dig. Dis. Sci. 46, 2256–2262.

Yamaguchi, T., Sasaki, K., Kurosaki, Y., Nakayama, T., Kimura, T., 1994. Biopharmaceutical evaluation of salicylazosulfanilic acid as a novel colon-targeted prodrug of 5-aminosaalicylic acid. J. Drug Target. 2, 123–131.

Yamaoka, K., Tanigawara, Y., Tanaka, H., Uno, Y., 1981. A pharmacokinetic analysis program (MULTI) for microcomputer. J. Pharmacobiodyn. 4, 879–885.

Yokoe, J., Iwasaki, N., Haruta, S., Kadono, K., Ogawara, K., Higaki, K., Kimura, T., 2003. Analysis and prediction of absorption behavior of colon-targeted prodrug in rats by GI-transit-absorption model. J. Control. Release 86, 305–313.