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Research paper

Mechanistic understanding of time-dependent oral absorption based on gastric motor activity in humans

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Abstract

The relationship of gastric motor activity and gastric emptying of 0.7 mm caffeine pellets with their absorption was investigated in the fed state in healthy human subjects by simultaneous monitoring of antral motility and plasma concentrations. A kinetic model for gastric emptying-dependent absorption yielded multiple phases of gastric emptying and rate constants (k_g) with large inter-individual differences and large variability in onset of gastric emptying (50–175 min). The model suggests that 50% of the dose is emptied in 1–2 h and over 90% emptied by 3.5 h following dosing, in all subjects. The maximum values of k_g (k_g(max)) were much greater than those reported for emptying of liquids in the fasted state and were comparable to k_g values in the late Phase II/III of the migrating motor complex (MMC). The model described the observed irregular absorption rate–time and plasma concentration–time profiles adequately but not in detail. The model was more successful at simulating double-peak phenomena in absorption rate profiles and onset of caffeine absorption. The results suggest that gastric emptying regulates drug absorption of small particles in the fed state. Further, estimates of k_a derived using the time-dependent absorption model were closer to the intrinsic absorption rate constant for caffeine.

Keywords: Time-dependent absorption; Gastric motor activity; Gastric emptying; Fed state; Absorption rate constant; Absorption rate; Plasma concentration–time profile; Caffeine

1. Introduction

Drug absorption kinetics after oral administration can be determined using membrane permeability, drug dissolution and gastrointestinal (GI) motility, although intestinal metabolism and secretion must be considered as factors influencing the drug absorption for some drugs [1–3]. Gastric emptying can be the rate-limiting step in absorption of high permeability-high solubility drugs classified as Class I in the Biopharmaceutics Classification System [2], because the absorption from the stomach is generally very small due to the very small effective surface area of stomach and the 1–1.5-mm thick mucus layer covering the mucosal surface [1]. Acetaminophen orally administered as a liquid solution is known to be regulated by gastric emptying under fasted conditions [4]. Lipka et al. reported that

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fasted-state gastric motility determined the rate and the extent of celiprolol absorption in dogs [5]. The retardation of GI transit, especially that of gastric emptying, is reported to cause the delay of T_{max} for several drugs after oral administration in the fasted state in rats [6]. The increased variability in plasma concentration–time curves of cimetidine has been shown to be related to variability in gastric emptying [7]. The appearance of double peaks in plasma concentration–time curves is a typical example of variability of plasma profiles and has been observed with several drugs [4,5,8–14]. Several hypotheses based on region-dependent variation in absorption [13], enterohepatic recirculation [15,16], variable gastric emptying and intestinal transit rates [4,5,17], and intestinal bacterial reconversion of biliary metabolite [18] have been proposed to account for these observations.

The possible role of gastrointestinal motility as a major determinant of the phenomena of secondary maxima occurring in the fasted state has been previously addressed [16,19]. Gastrointestinal motility in the fasted state is characterized by cyclical fluctuations in contractile activity of the stomach and intestine and is composed of four phases [20]. The initial basal phase, Phase I, is characterized by a complete lack of contractions followed by a 'preburst' activity, also termed Phase II, wherein the contractions increase in number and activity. Phase III is characterized by large-amplitude contractions that occur at the maximum frequency observable and is followed by an intermediate stage, Phase IV, before the cycle repeats itself. Phase IV is sometimes absent and is a transition period between the intense activity in Phase III and the basal quiescent Phase I. This cyclical pattern of contractile activity is termed the migrating motility complex (MMC). The regulation of MMC has been reported to be under both humoral and neural control. Thus, gastric motor activity in MMC regulates gastric emptying in the fasted state [21,22]. Gastric emptying in the fed and fasted state is governed by antral motility in conjunction with pyloric resistance and duodenal feedback mechanisms [21,23]. In the fed state, the MMC is largely abolished; however, low amplitude contractions facilitate gastric emptying of small solid particles through the pylorus.

It has been suggested that beyond a certain size (2–7 mm) [24,25], gastric emptying occurs predominantly during Phase II and III of the fasted-state MMC. In a previous study we demonstrated that gastric emptying of 0.7 mm caffeine pellets occurred in the fed state whereas 3.6 mm acetaminophen pellets emptied following onset of Phase II contractions in the fasted state, corroborating size-dependent gastric emptying [26]. Although gastric motor activity has often been monitored [23] and its qualitative relationship with drug absorption described in several reports [19,23,26,27], quantitative models correlating drug absorption kinetics to gastric motor activity data have yet to be published. In the present report we utilized the gastric motility and plasma concentration–time data that were simultaneously determined in the previous study [26], and developed a kinetic model to describe absorption rate–time and plasma concentration–time profiles in terms of the measured gastric motor activity in each subject.

2. Materials and methods

2.1. Materials

Spherical enteric-coated caffeine pellets, 0.7 mm in diameter, were manufactured under cGMP guidelines in collaboration with Pharmacia Upjohn Co. (now Pfizer) (Kalamazoo, MI) and have been described in detail earlier [26]. The diameter of the pellets was measured using a direct digital micrometer (Mitutoyo; Tokyo, Japan) [26]. Hydroxypropylmethylcellulose (HPMC) was obtained from The Dow Chemical Co. (Midland, MI). All other chemicals were purchased from Sigma Chemical Company (St. Louis, MO) and were of analytical grade or better. HPLC grade solvents were used in all the assays.

2.2. Caffeine pellet dose and viscous caloric meal

The caffeine dose consisted entirely of single pellets, as all fused pellets were manually removed prior to weighing. The *in vitro* characterization of the pellet and drug release in various media have been described earlier [26]. Thus, it was determined that no drug marker was released at pH 2.0 for 2 h and that 80–100% of caffeine was released within 20 min at pH 6.0 [26]. The viscous caloric meal consisted of HPMC, glucose, and water. The target viscosity of 4000 cP was achieved with K15MP HPMC using the hot/cold dispersion method [28]. Each 200-ml viscous meal contained 100 kcal of glucose by incorporation of a glucose tolerance beverage (General Medical Corp., Richmond, VA). The viscosity level of each meal was assessed at 37 °C with a Rheo-Tech Visco-Elastic Rheometer (Rheo-Tech International Ltd.) and was considered acceptable if it was within ±200 cP of the target viscosity. The 4000-cP viscosity meal was chosen since the most significant relationship between the onset of absorption and gastric motility was observed with a 4000-cP viscous caloric meal compared to either the 6000- or 8000-cP viscosity meal [26]. It was also noted that neither gastric motility patterns nor plasma pharmacokinetic parameters such as AUC, C_{max}, and T_{max} were affected in the range of viscosities examined [26].

2.3. Human study protocol

Twelve healthy subjects (10 males and 2 females) gave informed written consent to participate in the study. This investigation complied with tenets of the Declaration of Helsinki promulgated in 1964 and was approved by the University of Michigan Institutional Review Board. The subjects were 22–39 years of age and were within 20% of their ideal body weight. Subjects were deemed healthy based on medical history, physical examination, complete blood count and serum chemistries. Persons with a history

of renal, hepatic, gastrointestinal, cardiovascular or psychiatric disease were excluded from the study, as were subjects with a history of clinical illness within 2 weeks of the start of their participation in the study. In addition, all subjects were medication-free, including over-the-counter agents, for at least 3 days prior to the study. Subjects refrained from ingesting xanthine-containing foods and beverages (including caffeine) for 48 h before each study. Following an overnight fast, subjects were intubated with a gastric manometric catheter (PVC ICM[3]9 Arndorfer; Greendale, WI). After a 10-min quiescent period in the fasted state, the subjects were administered 150 ml of the viscous caloric meal over a 5-min time period. Fifteen minutes later, an additional 50 ml of the viscous caloric meal and the entire pellet dose, containing 100 mg of caffeine, was administered simultaneously. Monitoring of the gastric motor activity continued for 4 h post-dose as the subject remained seated upright. Since circadian variations have been shown to affect gastric emptying as well as drug pharmacokinetics and pharmacodynamics [29–33], it is relevant to note that the pharmacokinetic and gastric motility data presented in this study were obtained following morning dosing and as such would be valid only for morning dosage conditions.

2.4. Gastric motor activity

Gastric motor activity was determined using a manometric catheter placed in the antrum. A 5-cm weighted tip was located at the distal end with side holes placed radially 1.5 cm apart starting 1 cm from the tip. Gastric motor activity was monitored by pressure measurements with a capillary infusion pump system with pressure transducers connected to a meter, a transducer amplifier and a Model 4600 Data acquisition signal analysis system (Gould Inc., Valley View, OH). The measurements were recorded with the DASA VIEW II computer software (Gould Inc.) at a data-sampling rate of 10 per second. The most active channel was analyzed using software designed in our laboratory that allowed analysis of motility data using a variety of filtering variables. After the noise was filtered and peak detection was completed, gastric motor index (MI) corresponding to the area under the peak of gastric motor activity was obtained.

2.5. Collection of blood samples and drug analysis

Blood samples (3 ml) were obtained through a forearm venous catheter for multiple blood draws and placed in heparinized Vacutainer® vials (Becton Dickinson, Rutherford, NJ). The sampling time-points were: pre-dose, every 15 min for 4 h, then every hour for 4 h and then at 12 and 24 h. The blood samples were immediately centrifuged at 3000 rpm for 5–10 min at 4 °C. Plasma was removed, stored at −20 °C until analyzed for caffeine content. The caffeine concentrations in plasma samples were assayed by high-performance liquid chromatography using a modification of the methods reported by Alkaysi et al. [34] and by O'Connell and Zurzola [35]. The HPLC system consisted of a Waters 717 Plus autosampler, a Waters M-6000A pump system and a UV absorbance detector (Applied Biosystems, Ramsey, NJ). The reversed-phase column used was a Hypersil BDS C18 column (5 μm, 250 × 4.6 mm, Alltech Associates, Deerfield, IL) equipped with a guard column. The mobile phase used was acetonitrile:methanol:acetic acid:distilled water (2.5:10:0.075:87, v/v). The flow rate used was 1.0 ml/min and the UV detection wavelength was set at 268 nm. Assay of plasma samples was carried out as follows. In a typical assay, plasma samples were thawed at room temperature and an internal standard, 2-acetoamidophenol (Sigma Chemical Co., St. Louis, MO) was added to the plasma sample. Following addition of methanol and zinc sulfate solution, the mixture was vortexed for 1 min and centrifuged at 12,500 rpm and 4 °C for 15 min. The supernatant was filtered through a 0.45-μm syringe filter (Acrodisc 3 CRPTFE, Gelman Sciences, Ann Arbor, MI) and 30 μl of the filtrate was directly injected onto the HPLC for analyses. Standard curves using solutions of caffeine in distilled water were constructed and were found to be linear ($r^2 > 0.99$) with a coefficient of variance of <0.05. The limit of quantitation (LOQ) was 0.05 μg/ml [26].

2.6. Modeling

2.6.1. Assumptions and fundamental conditions for modeling

The first assumption is that gastric emptying obeys first-order kinetics and that gastric emptying rate constants are proportional to gastric motor activity. It is assumed that absorption of caffeine from the enteric-coated pellets does not occur in the stomach and that caffeine is absorbed only from the intestine. It is also assumed that the dissolution process can be ignored since it has been shown that the enteric-coated pellets release caffeine rapidly *in vitro* in pH 6.0 medium [26]. Furthermore, the absorption rate constant of caffeine is assumed to be invariant, although we have reported that it could vary in a time-dependent manner [36]. Both the fraction of dose absorbed and the bioavailability of caffeine are also assumed to be 100% based on previous reports [37,38]. Since the pharmacokinetics of caffeine after bolus injection can be described by a one-compartment model [37,39,40], a three-compartment model with stomach and intestine compartments (Fig. 1) was employed in this analysis. Excretion from the intestine as feces can be ignored because caffeine is absorbed completely [37,38].

2.6.2. Determination of motility phases and their slopes

To utilize the data of gastric motor activity (Fig. 2a), the cumulative peak area of gastric motor activity was plotted against time, resulting in the motor index curve (MI curve) (Fig. 2b). In order to determine the phases from which the slope can be calculated the procedure described below was followed.

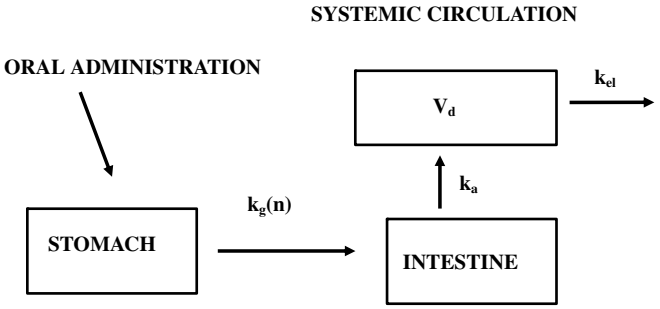

Fig. 1. Schematic of gastric motor activity-based pharmacokinetic model. k_{el}, k_a, $k_g(n)$, and V_d are elimination constant, absorption rate constant, gastric emptying rate constant (n designates phase number) and volume of distribution, respectively.

(a) The slope at each time-point of the MI curve was determined using a 3-point interval starting with the time-point.
(b) The differences in slopes at each time-point compared to that immediately following was calculated and plotted as a function of time (DS curve, not shown). The slope differences at every time-point was used to construct the DS curve. The various phases determined using the MI and DS curves were designated using lower-case Arabic numerals in order to distinguish them from the phases associated with MMC that are generally designated using upper-case Roman numerals.

2.6.3. Determination of gastric emptying rate constants and cumulative output from stomach

Gastric emptying rate constant, $k_g(n)$ at phase n is described by Eq. (1).

$$k_g(n) = k_g(\max) \cdot \frac{\text{Slope}_n}{\text{Slope}_{\max}} \quad (1)$$

The slopes of the various phases were determined from the MI curve. $\text{Slope}_{\max}$ thus represents the largest slope in the MI curve and $k_g(\max)$ is the largest value of k_g in a given subject.

In the case of unabsorbable drugs, the percent of dose remaining in the stomach ($MG_n(t)$) and the cumulative percent of dose outputted from the stomach ($MO_n(t)$) are interrelated as described by Eqs. (2) and (3), respectively.

$$\begin{aligned}
MG_1(t) &= D \cdot \exp(-k_g(1) \cdot t)/D \cdot 100 \quad (0 \leqslant t < T_1)\\
MG_2(t) &= MG_1(T_1) \cdot \exp(-k_g(2) \cdot (t - T_1))/D \cdot 100 \quad (T_1 \leqslant t < T_2)\\
&\vdots\\
MG_n(t) &= MG_{n-1}(T_{n-1}) \cdot \exp(-k_g(n) \cdot (t - T_{n-1}))/D \cdot 100 \quad (T_{n-1} \leqslant t \leqslant T_n) \quad (2)
\end{aligned}$$

$$\begin{aligned}
MO_1(t) &= 100 - MG_1(t) \quad (0 \leqslant t < T_1)\\
MO_2(t) &= 100 - MG_1(T_1) \quad (T_1 \leqslant t < T_2)\\
&\vdots\\
MO_n(t) &= 100 - MG_{n-1}(T_{n-1}) \quad (T_{n-1} \leqslant t \leqslant T_n) \quad (3)
\end{aligned}$$

where D is the dose of caffeine.

The cumulative percent of dose outputted from the stomach as a function of time, termed the CO curve, can therefore be calculated using Eqs. (1)–(3). A range of $k_g(\max)$ values satisfying Eq. (1) would yield a variety of sets of $k_g(n)$ values for each subject. Using the different sets of $k_g(n)$ values a range of CO curves were generated using Eqs. (2) and (3). The most reasonable estimate of the CO curves so generated was determined by comparison with the cumulative fraction of dose-absorbed curve obtained by deconvolution of the plasma concentration–time curve in each subject. The cumulative fraction of dose-absorbed curve, termed the CFA curve, was calculated using a modified Wagner–Nelson method with Kinetica 2000® software. The CO curve that was considered to be the most reasonable estimate was chosen based on the following criteria:

(1) The output value (CO curve) should be equal to or higher than the fraction-dose absorbed (CFA curve) at each time-point, and
(2) Following completion of absorption of drug outputted in a given period or phase or when no absorption occurs for an extended period, the CO and CFA curves should be superimposable upon each other.

Fig. 2c depicts example CO and CFA curves.

2.6.4. Determination of absorption rate coefficient

The percentage of drug in the intestine ($MI_n(t)$) and absorption rate of drug ($Ra_n(t)$) are described by Eqs. (4) and (5), respectively.

$$\begin{aligned}
MI_1(t) &= \frac{D \cdot k_g(1)}{k_g(1) - k_a} \cdot (\exp(-k_a \cdot t) - \exp(-k_g(1) \cdot t)) \quad (0 \leqslant t < T_1)\\
MI_2(t) &= MI_1(T_1) \cdot \exp(-k_a \cdot (t - T_1)) + \frac{MG_1(T_1) \cdot k_g(2)}{k_g(2) - k_a} \cdot (\exp(-k_a \cdot (t - T_1)) - \exp(-k_g(2) \cdot (t - T_1))) \quad (T_1 \leqslant t < T_2)\\
&\vdots\\
MI_n(t) &= MI_{n-1}(T_{n-1}) \cdot \exp(-k_a \cdot (t - T_{n-1})) + \frac{MG_{n-1}(T_{n-1}) \cdot k_g(n)}{k_g(n) - k_a} \cdot (\exp(-k_a \cdot (t - T_{n-1})) - \exp(-k_g(n) \cdot (t - T_{n-1}))) \quad (T_{n-1} \leqslant t \leqslant T_n) \quad (4)\\
Ra_1(t) &= k_a \cdot MI_1(t) \quad (0 \leqslant t < T1)\\
Ra_2(t) &= k_a \cdot MI_2(t) \quad (T_1 \leqslant t < T_2)\\
&\vdots\\
Ra_n(t) &= k_a \cdot MI_n(t) \quad (T_{n-1} \leqslant t \leqslant T_n) \quad (5)
\end{aligned}$$

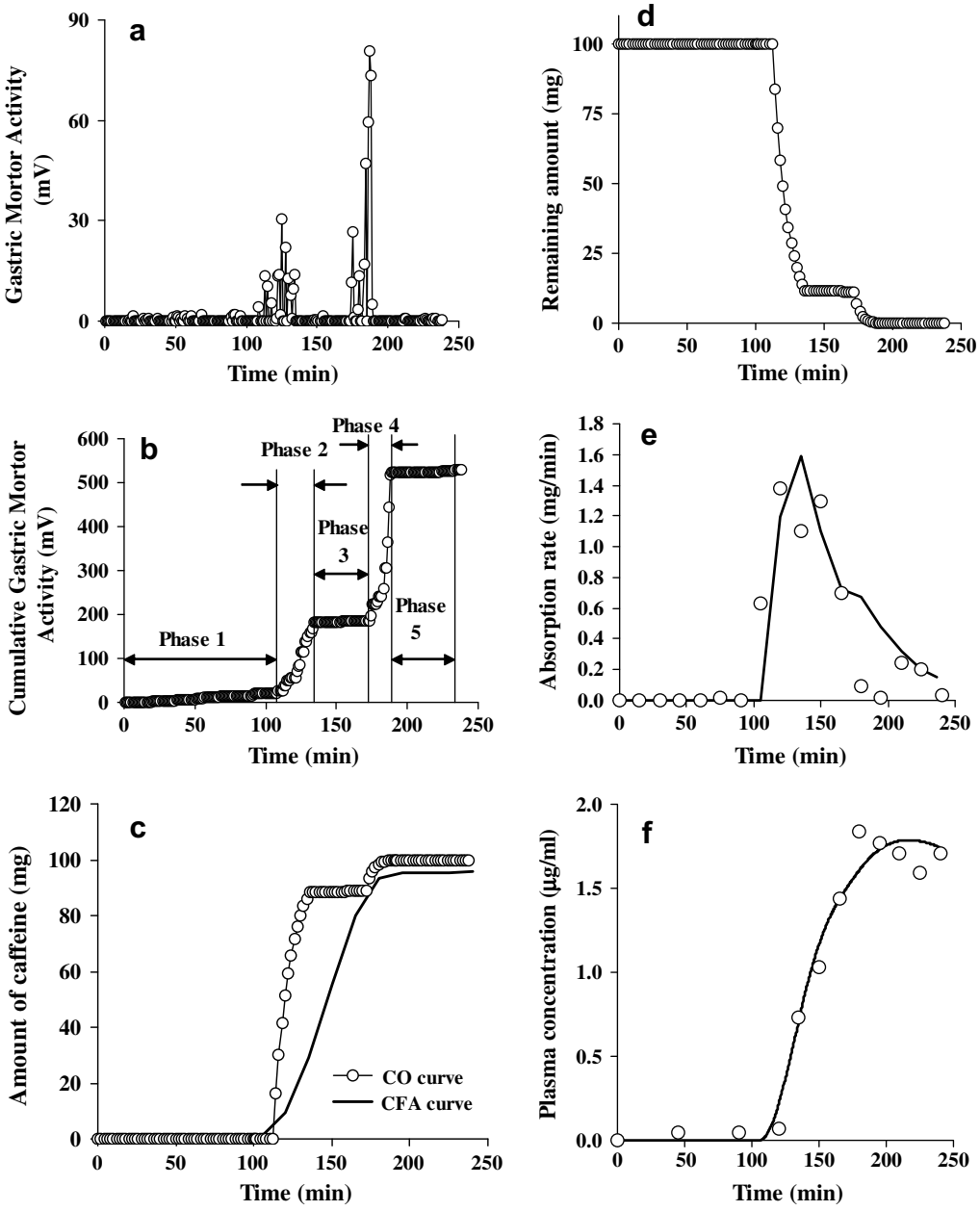

Fig. 2. Simulation of plasma concentration–time profile using gastric motor activity-based kinetic model for Subject 6. (a) Gastric motor activity–time profile, (b) MI curve, (c) CO and CFA curves, (d) Gastric emptying–time profile, (e) Absorption rate–time curves (RA curves): (○) open circles represent "observed values" obtained by deconvolution using modified Wagner–Nelson method; (—) solid line represents profile calculated using the model described in Section 2. (f) Plasma concentration–time curves: (○) open circles represent experimentally observed values; (—) solid line represents profile simulated using the model described in Section 2.

where k_a is the absorption rate constant. The absorption rate–time curves (RA curves) were simulated using Eqs. (4) and (5) and k_a values that provided the best fit to the RA curve obtained by modified Wagner–Nelson method as judged using AIC values or area under the absorption rate–time profile, and/or the maximum value of the absorption rate.

2.6.5. Simulation of plasma concentration–time curve

Laplace transform of plasma concentration can be expressed as follows:

$$\widetilde{C}p^{\mathrm{po}}(s) = \frac{D_{\mathrm{po}}}{D_{\mathrm{iv}}} fa(s) \cdot \widetilde{C}p^{\mathrm{iv}}(s) \tag{6}$$

where $\widetilde{C}p^{\mathrm{po}}(s)$ and $\widetilde{C}p^{\mathrm{iv}}(s)$ are Laplace transforms of plasma concentrations after oral and intravenous administrations, respectively, and $\tilde{f}a(s)$ is a Laplace transform of fraction of dose absorbed and D_{po} and D_{iv} are doses for oral and intravenous administrations. Using the RA curves, distribution volumes (V_d) and elimination rate constants (k_{el}), the plasma concentration–time profiles were simulated by convolution method (multi-function convolu-

tion simulator program [41]) according to Eq. (6). The pharmacokinetic parameters k_{el} and AUC were calculated using a modified Wagner–Nelson method with Kinetica 2000® software. V_d was calculated from k_{el} and AUC assuming fraction-dose absorbed was equal to unity from the relation, $V_d = \text{Dose}/\text{AUC}/k_{el}$.

3. Results

The interrelationship between gastric emptying and absorption parameters developed in this study is schematically represented in Fig. 1. A typical example of the modeling of gastric emptying and absorption parameters using experimental gastric motor activity and plasma–concentration curves for Subject 6 is shown in Fig. 2. The raw manometric data (Fig. 2a) and the cumulative motor activity curve (Fig. 2b) clearly indicate the presence of two 'active' phases (Phases 2 and 4) and three 'quiescent' or near 'quiescent' phases (Phases 1, 3, and 5). The terms 'quiescent' and 'active' are strictly used here to define the presence or absence of gastric motility activity in the fed state. Fig. 2c shows the cumulative fraction-dose absorbed (CFA curve) for Subject 6 obtained by deconvolution of the plasma concentration–time curve. The CFA curve indicates that absorption of caffeine during the quiescent phases, Phase 1 (0–105 min) and Phase 5 (195–240 min) is quite negligible. The majority of the absorption of caffeine occurs over the period encompassing the two active phases, Phases 2 and 4 (105–195 min). A variety of cumulative output curves, CO curves, were generated using Eqs. (1)–(3) and the CO curve that best fulfilled the comparison criteria with the CFA curve outlined earlier is also shown in Fig. 2c. The values of gastric emptying constants for Subject 6 that yielded the CO curve shown in Fig. 2c are listed in Table 1. An examination of the CO curve in Fig. 2c indicates that the fraction-dose absorbed is higher than the output values at a few time-points around 100 min. However, the discrepancy in the curves may be acceptable since the period between 0 and 105 min was treated as a single phase based on the near-constant gastric motor activity evidenced in Fig. 2b and the corresponding DS curve (not shown). Furthermore, some discrepancies are expected because absorption data were only available every 15 min due to the plasma-sampling interval in human studies. The largest k_g value, $k_g(\max)$, for Subject 6 was 0.25 min^{-1} corresponding to Phase 4.

Fig. 2d shows a plot of the amounts of caffeine remaining in the stomach as a function of time for Subject 6. It is seen from Fig. 2d that gastric emptying commences in Subject 6 approximately 110 min following dosing and that ~90% of dose was emptied from the stomach in Phase 2 with the remainder outputted over the next 50 min. The calculated absorption rate–time curve (RA curve) obtained with Eqs. (4) and (5) that best fit the absorption rate–time curve derived from plasma concentration–time curves using modified Wagner–Nelson method are both shown in Fig. 2e. The calculated curve shown in Fig. 2e was judged to be the best fit to the experimentally derived data based on AIC values. It is seen from Fig. 2e that the calculated RA curve describes the onset of caffeine absorption accurately and the overall shape of the RA curve in a reasonable manner, although the model equations do not define the complicated profile in detail. The values of k_{el} and V_d obtained from the plasma concentration–time curves as well as the k_a value used in Eqs. (4) and (5) that best fit the data for Subject 6 are shown in Table 2. Fig. 2f shows a comparison of the plasma concentration–time curves simulated using Eq. (6) with the experimental data for Subject 6.

Table 1
Gastric emptying rate constants of caffeine after oral administration in humans

$k_g(n)$[a] (min^{-1})	Subject											
	1	2	3	4	5	6	7	8	9	10	11	12
$k_g(1)$	0.0020	0	0	0.0021	0	0	0	0	0	0.0008	0	0
$k_g(2)$	0.0744	0.0617	0.2069	0.0326	0.1031	0.0897	0.0706	0.0171	0.0457	0.0952	0.0543	0.0519
$k_g(3)$	0.0018	0.0057	0.0007	0.0085	0.0321	0.0010	0.0003	0.0614	0.0020	0.0005	0.0094	0.0012
$k_g(4)$	0.1100	0.0410	0.2200	0.0620	0.2400	0.2500	0.1270	0.0064	0.0473	0.0201	0.0924	0.5250
$k_g(5)$	0.0013	0.0046	0.0012	0.0024	0.0019	0.0012	0.0014	0.0236	0.0130	0.1600	0.0422	0.0010
$k_g(6)$	–	0.0548	–	0.0442	0.0828	–	0.0879	0.0038	0.0930	0.0017	0.2800	0.2941
$k_g(7)$	–	0.0041	–	0.0054	0.0074	–	0.0036	0.0209	0	–	0.0123	–
$k_g(8)$	–	0.0900	–	0.0081	–	–	0.0161	0.0137	0.1999	–	0.0785	–
$k_g(9)$	–	0.0032	–	0.0005	–	–	0.0062	0.0750	0.0120	–	0.0131	–
$k_g(10)$	–		–	–	–	–	0.0346	0.0002	0.2300	–	–	–
$k_g(11)$	–	–	–	–	–	–	0.0006	0.0144	0.0041	–	–	–
$k_g(12)$	–	–	–	–	–	–	0.0212	0.0007	0.0838	–	–	–
$k_g(13)$	–	–	–	–	–	–	0	0.0088	0.0249	–	–	–
$k_g(14)$	–	–	–	–	–	–	0.0405	0.0123	–	–	–	–
$k_g(15)$	–	–	–	–	–	–	0	0.0251	–	–	–	–
$k_g(16)$	–	–	–	–	–	–	0.0180	0.0029	–	–	–	–
$k_g(17)$	–	–	–	–	–	–	0.0024	–	–	–	–	–
Number of phases	5	9	5	9	7	5	17	16	13	6	9	6

[a] $k_g(n)$ is the gastric emptying rate constant and the number in the parenthesis indicates the phase in the gastric emptying-time profile.

Table 2
Pharmacokinetic parameters describing the absorption kinetics of caffeine after oral administration to humans

Subject No.	k_{el}[a] (min^{-1})	V_d[a] (ml)	k_a[a] (min^{-1})	AIC	Criteria[b]
1	0.00105	60343	0.0650	16.50	AIC
2	0.00180	46220	0.0680	34.91	PHA
3	0.00147	42676	0.0673	27.55	AIC
4	0.00410	39150	0.0395	−0.21	AIC
5	0.00168	39444	0.0315	27.28	AIC
6	0.00371	40107	0.0290	5.87	AIC
7	0.00276	49621	0.0890	16.18	AIC
8	0.00391	24660	0.0452	10.73	AIC
9	0.00275	48455	0.0402	−9.55	AIC
10	0.00277	51816	0.0657	18.50	PHA
11	0.00207	76818	0.0526	19.93	AIC
12	0.00462	41599	0.0610	20.57	AIC
Mean	0.00272	46742	0.0545	15.69	–
SD	0.00115	12836	0.0179	12.45	–

[a] k_{el}, V_d, and k_a represent the elimination rate constant, volume of distribution and absorption rate constant of caffeine, respectively.
[b] Criteria used to choose the best fit: AIC, Akaike's information criteria; PHA, peak height of absorption rate.

The gastric emptying rate constants derived for all the other subjects in the manner described for Subject 6 are also listed in Table 1. Table 1 indicates that the largest number of phases was obtained in Subject 7 (17 phases) and the largest k_g(max) value of 0.525 min^{-1} was associated with Subject 12 in Phase 4. The values of k_{el}, V_d, and k_a for all other subjects obtained in the manner described for Subject 6 are also shown in Table 2. Figs. 3–5 show gastric emptying profiles, RA curves and plasma concentration–time curves, respectively, for all subjects examined. The correlation between onset of gastric emptying and onset of absorption is depicted in Fig. 6. The time to Phase 2 (Fig. 3) indicates onset of gastric motility activity and gastric emptying. Two interrelated absorption parameters were used to determine their correlation with gastric motility. Thus, the initial time-point at which plasma concentration exhibits a dramatic increase (maximum slope) and the time-point at which 'observed' absorption rate shows a significant enhancement (Fig. 5) were chosen to evaluate the dependence of onset of absorption on gastric emptying. Excellent linear correlations between onset of Phase 2 with initial maximum in plasma concentration slope ($r^2 = 0.91$, $p < 0.001$) and with initial absorption rate enhancement time ($r^2 = 0.96$, $p < 0.001$) were observed. Fig. 7 shows a plot of plasma concentrations obtained using the model against observed plasma concentrations in all subjects. An excellent linear correlation of calculated values with observed plasma concentrations was observed ($r^2 = 0.91$; $p < 0.001$).

4. Discussion

Gastric emptying is one of the most important factors in determining the absorption kinetics of orally administered drugs. Although it has been shown qualitatively that the appearance of drug in plasma could be correlated with gastric motor activity [19,23,26,27], there has been no evidence to show whether gastric motor activity is directly related with the kinetics of oral drug absorption. In the present study, we developed a model that can mechanistically describe the absorption rate–time and plasma concentration–time profiles after oral administration by utilizing the actual data of gastric motor activity.

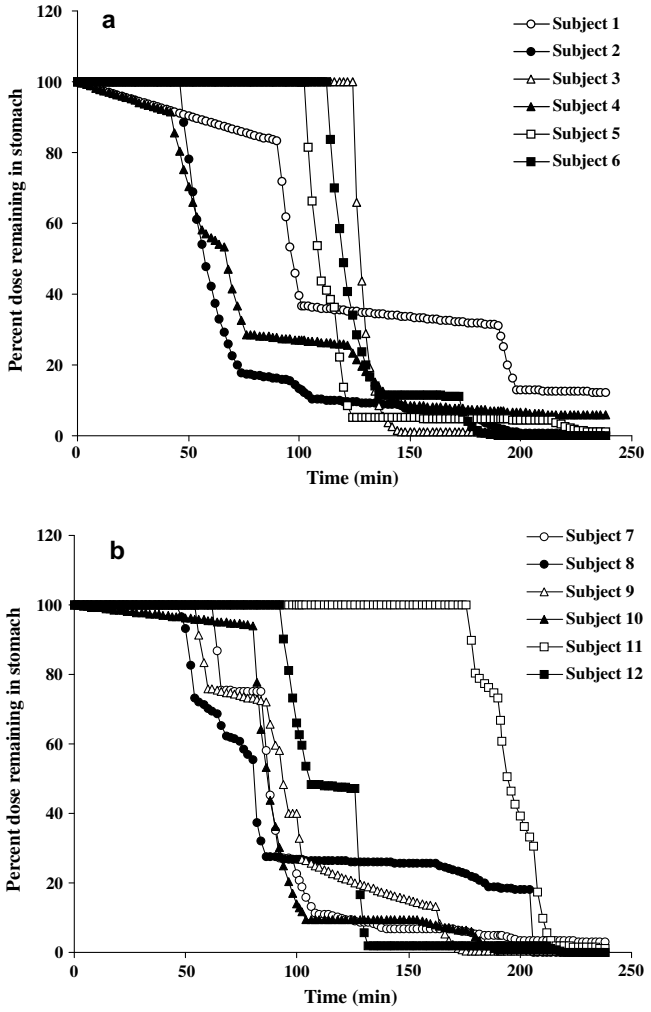

Fig. 3. Gastric emptying-time profiles: percentage of caffeine remaining in stomach calculated using gastric motor activity-based model. (a) Subjects 1–6, (b) Subjects 7–12.

Intubation methods to determine gastric motility have been sometimes viewed as a perturbant of the very motility patterns they measure [42,43]. However, literature reports suggest that such perturbation is minimal based on the similarity of motility patterns obtained using scintigraphy, paracetamol tracer methods and intubation techniques [44]. The methodology used in the analysis of gastric motor activity allowed the objective identification and determination of the duration of phases with near-constant gastric motor activity and those that exhibited contractile activity. Gastric-emptying profiles in the fed state calculated using

the model described in this study reveal large inter-individual differences with complicated profiles (Fig. 3). The findings are in contrast to data reported for acetaminophen administration in the fasted state [4]. The differences may be related to the regulation of fed-state gastric motor activity by intestinal feedback mechanisms, hypertonicity, low pH, amino acid, fatty acid, and monoglyceride in duodenum, that result in complicated gastric-emptying patterns. These factors may be less important in the fasted state since gastric emptying is largely controlled by MMC [21]. In the present study, with the exception of Subject 11, gastric emptying of 0.7 mm caffeine pellets occurred following an initial 'quiescent' phase of 1–2 h (ranging from 44 min in Subject 4 to 124 min in Subject 3; ~175 min in Subject 11) after oral administration in the fed state. About 50% of the oral dose was emptied in this initial 'active' phase. In general, more than 90% of the dose was emptied from the stomach within 3.5 h following dosing and one or two 'quiescent' phases wherein no emptying was evident were always noted in all subjects.

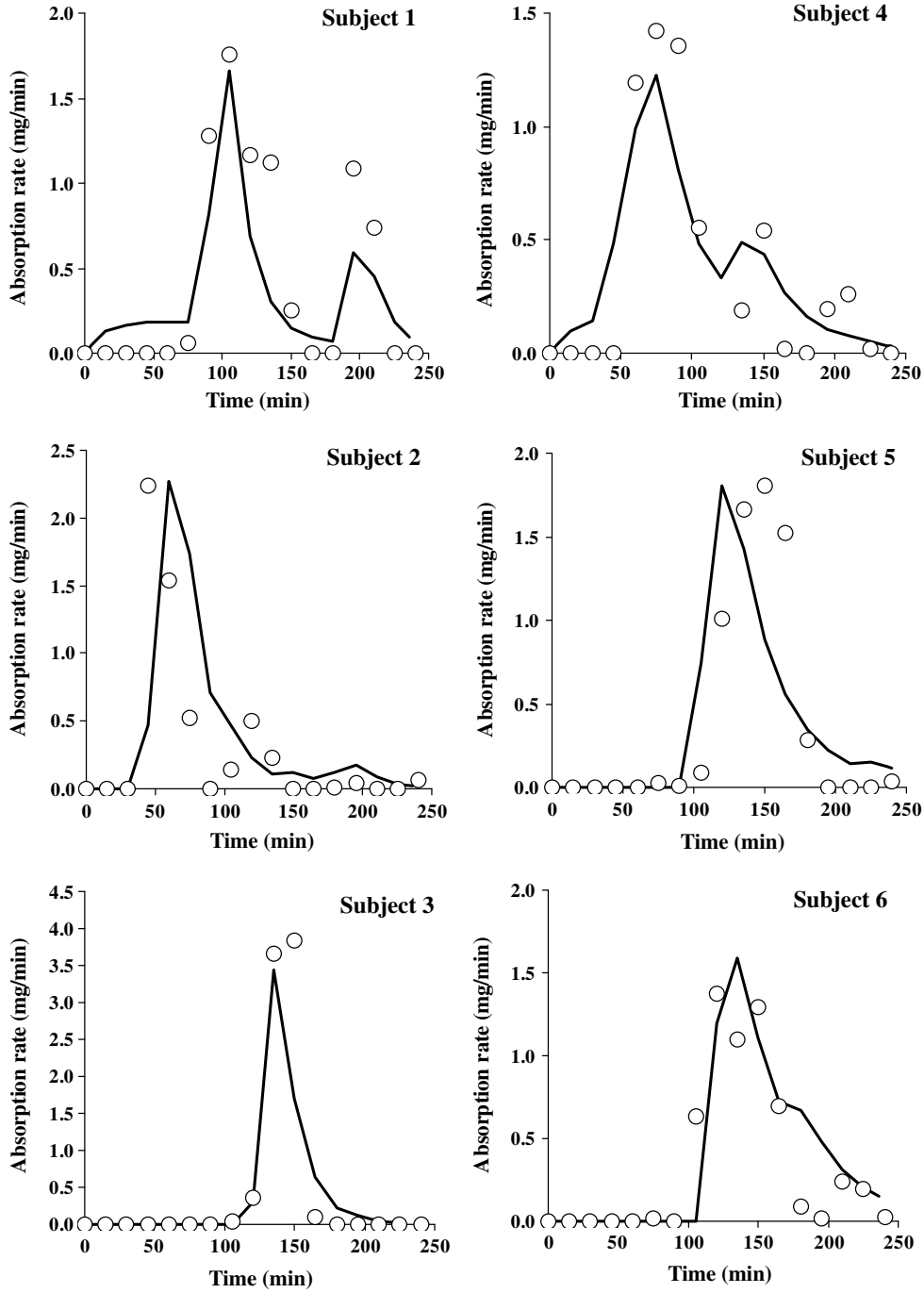

Fig. 4. Caffeine absorption rate–time curves (RA curves). (○) Open circles represent "observed values" obtained by deconvolution using modified Wagner–Nelson method; (—) Solid lines represent the absorption rate–time profiles determined using the gastric motor activity-based kinetic model described in the Section 2.

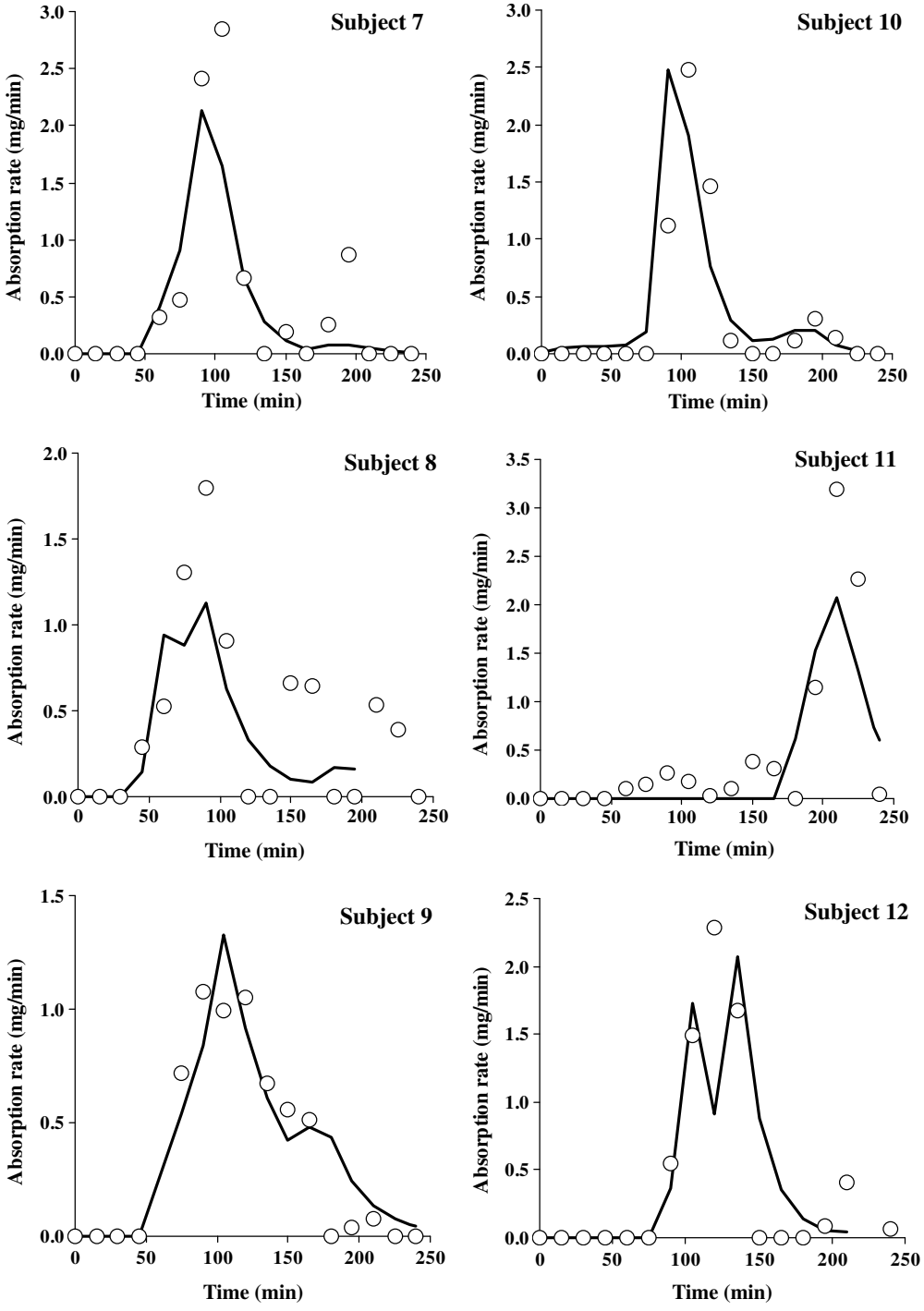

Fig. 4 (*continued*)

A novel concept proposed recently involves the existence of a "Magenstrasse" or a 'stomach highway' that is generated when fundic contractions act in concert with antral contractile waves [45]. Contrary to conventional antral motility-driven gastric emptying, drug particles that are released in the "Magenstrasse" would be rapidly emptied (within 10 min) into the duodenum followed by a gradual emptying from 'non-Magenstrasse" areas of the stomach. Although such a scenario would give rise to irregular or multiple plasma-peak phenomena, the absence of significant levels of caffeine at early time-points (Fig. 5), appears to be more consistent with conventional gastric motility profiles.

The gastric emptying rate constants obtained with the various subjects in the fed state (Table 1) suggest that k_g(max) values are larger than k_g values reported previously for liquids in fasted state [4,46,47]. The comparable magnitudes of k_g(max) values to k_g values in the late Phase II/III observed by Oberle et al. [27] ($0.171 \pm 0.066\ \text{min}^{-1}$, $0.236 \pm 0.069\ \text{min}^{-1}$) suggest that gastric motility in the

fed state may be similar to the intense contractions that occur at Phase III in the fasted state.

The values of k_{el} and V_d determined in various subjects following oral administration of caffeine pellets are comparable to those reported previously [40,48]. The values of k_a obtained in the present study ranging from 0.029 to 0.089 min^{-1} were comparable to those reported previously [40,49]. However, the k_a values in this study determined using amounts of caffeine in the intestine, the site of absorption, are not influenced by gastric emptying and could be closer to the intrinsic k_a value. On the other hand, k_a values determined using conventional models have been reported to be influenced by gastric emptying and increased from $0.018 \pm 0.007\ min^{-1}$ in gastric stasis to $0.122 \pm 0.110\ min^{-1}$ in control [49]. The influence of gastric emptying on k_a arises mainly because conventional compartment models do not take into account the actual amounts of drug in the intestine that vary in a time-depen-

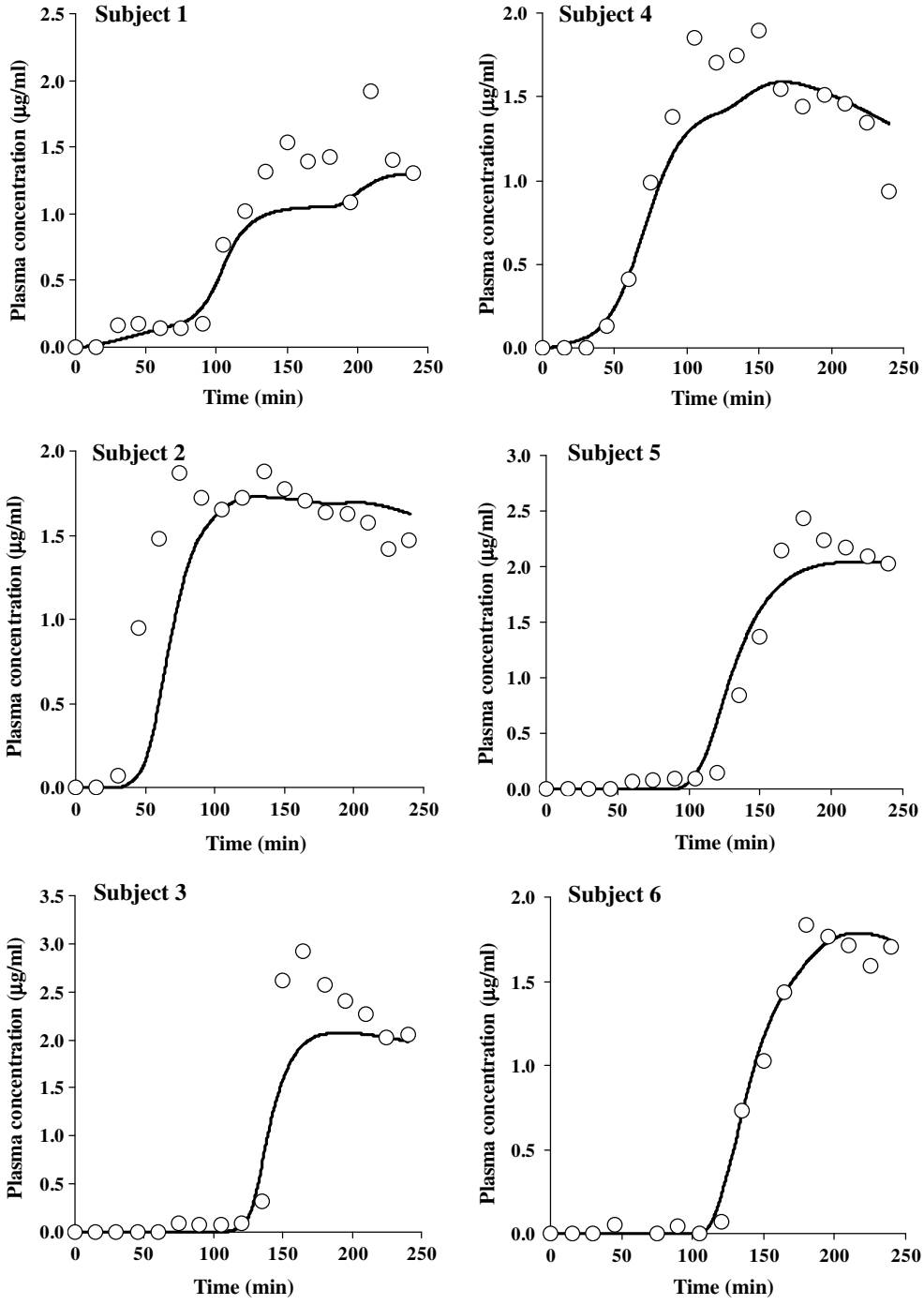

Fig. 5. Caffeine plasma concentration–time curves. (○) Open circles indicate experimental plasma concentrations; (—) Solid lines represent plasma concentration curves simulated using the gastric activity-based kinetic model described in Section 2.

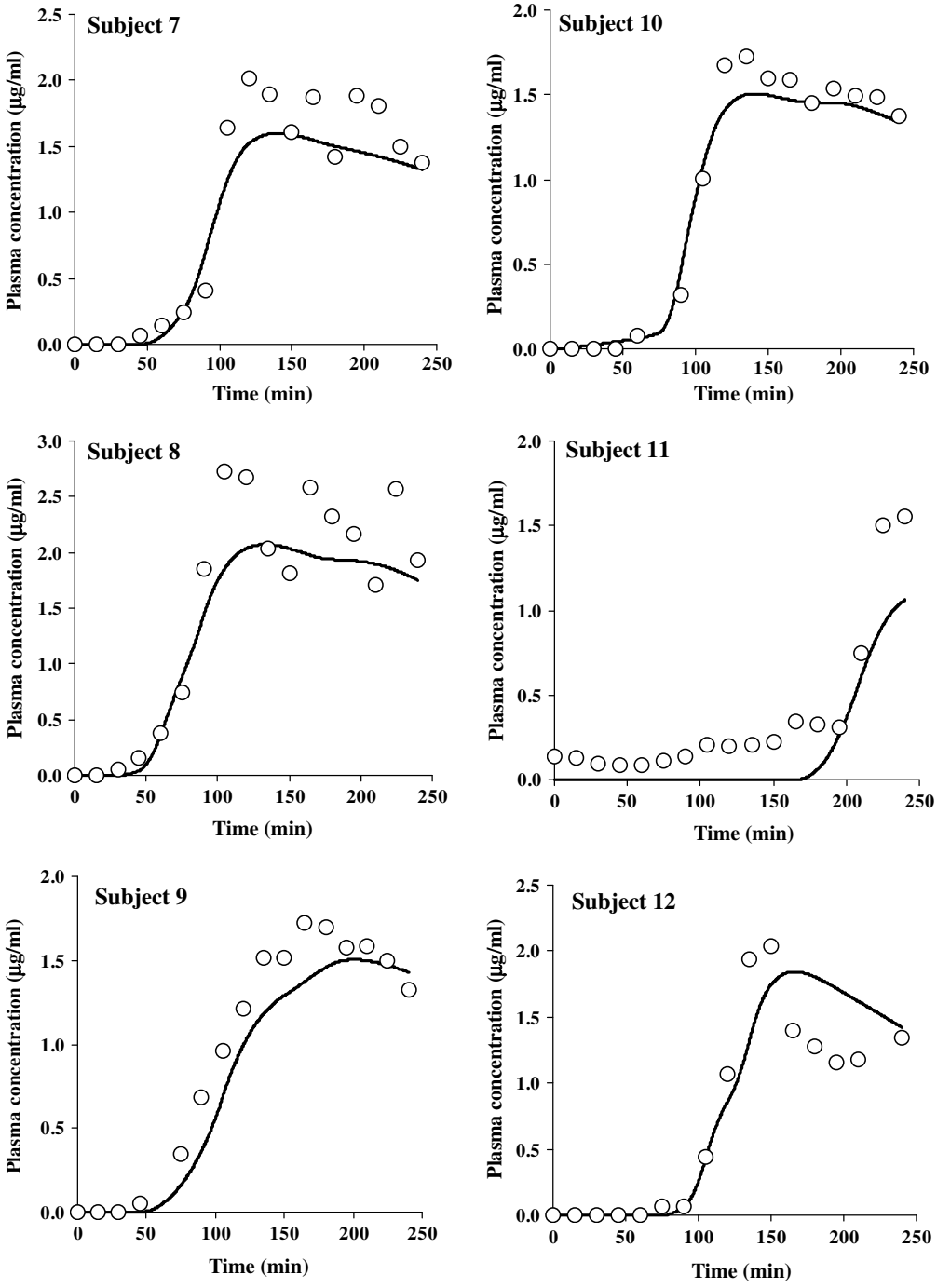

Fig. 5 (*continued*)

dent manner with gastric emptying. Although gastric emptying can regulate the absorption process of BCS Class I drugs such as caffeine, it is not expected to affect the intrinsic absorption rate constant.

The absorption rate curves derived in this study appear to describe observed rate profiles reasonably well (Fig. 4). Although the model does not characterize the complicated profiles entirely, the excellent description of double-peak phenomena in a few subjects (Subjects 1, 2, 4, and 10) suggests that gastric motor activity and gastric emptying are indeed responsible for double peaks in absorption rates. Further, the excellent correlation of onset of Phase 2 with onset of absorption rate and plasma concentration enhancement (Fig. 6, $r^2 > 0.91$, $p < 0.001$) clearly suggests that onset of caffeine absorption is regulated by gastric emptying. The choice of the interdependent factors allowed an objective determination of onset of absorption and obviated issues related to determination of plasma-level significance at early time-points. It is also evident that the simulation of plasma concentration–time curves using the

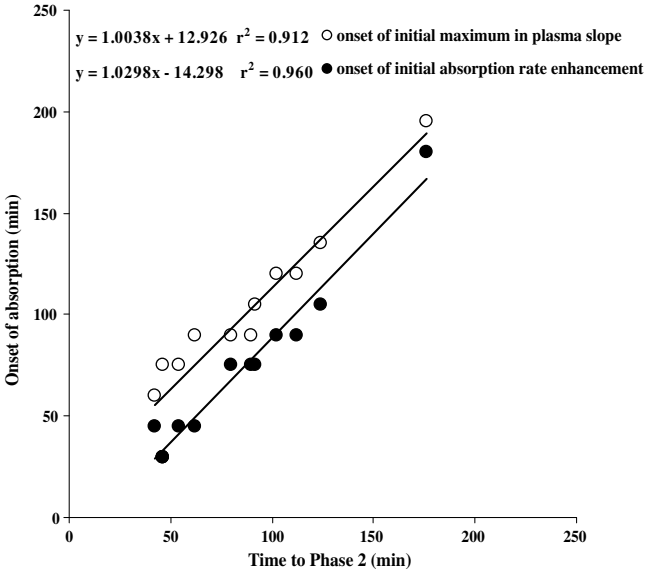

Fig. 6. Correlation of gastric emptying with onset of absorption: (○) Initial time-point at which plasma concentration exhibits a dramatic increase (maximum slope) versus time to Phase 2; (●) Initial time-point at which 'observed' absorption rate shows a significant enhancement versus time to Phase 2.

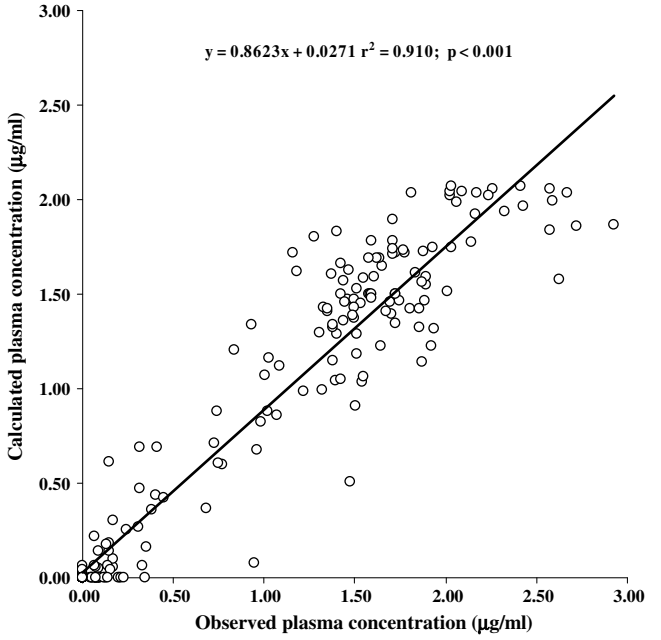

Fig. 7. Correlation between observed and calculated caffeine plasma concentrations.

kinetic model adequately described observed plasma profiles (Fig. 5). The statistically significant linear correlation of caffeine plasma concentrations calculated from the model with observed plasma concentrations in all subjects (Fig. 7) indicates that the gastric motor activity-based pharmacokinetic model would have some validity.

In conclusion, the model developed in the present study utilized gastric motor activity data to provide a mechanistic understanding of the relationship between gastric motor activity and/or gastric emptying with absorption kinetics of caffeine following oral administration in the fed state. The results indicate that gastric emptying of caffeine administered as pellets was regulated by gastric motor activity. The absorption kinetics of caffeine was closely related to gastric-emptying profiles suggesting that gastric emptying is an important determinant of double-peak phenomena in absorption rate–time profiles and of irregular plasma concentration–time profiles following oral administration. Furthermore, the determination of absorption rate constants using the model developed in this study is more precise than those determined with conventional compartment models and closer to the intrinsic absorption rate constant since they are not influenced by gastric emptying.

Acknowledgments

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