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Research paper

Saturable small intestinal drug absorption in humans: modeling and interpretation of cefatrizine data

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Abstract

This report describes an extended compartmental absorption and transit (CAT) model to estimate saturable small intestinal absorption. This model simultaneously considers passive absorption, saturable absorption, degradation, and transit kinetics in the human small intestine. Using cefatrizine as a model drug, we demonstrated that the extended CAT model, along with intravenous pharmacokinetic parameters, was able to explain the observed oral plasma concentration-time profiles. The model predicted comparable passive and saturable absorption characteristics for cefatrizine, particularly at high dose. The predicted fraction of dose absorbed was 74% at 250 mg, 61% at 500 mg, and 48% at 1000 mg, in agreement with the reported experimental data. The simulation study showed that no single physiological factor (gastric emptying, small intestinal transit, and absorption mechanism) could account for the large variability of cefatrizine absorption observed in the literature. © 1998 Elsevier Science B.V.

Keywords: Saturable absorption; Passive absorption; Cefatrizine; Compartmental absorption and transit model; Fraction of dose absorbed; Pharmacokinetic modeling

1. Introduction

Amino-β-lactam antibiotics, such as cefatrizine, are absorbed by a carrier-mediated system [1–4], which is saturable and might be responsible for dose-dependent absorption [5,6]. Commonly used linear absorption models evidently do not suffice in these cases. Recently, non-linear models with saturable time-constrained absorption were proposed to improve the fit of plasma concentration-time profiles [7,8]. A mechanistic and quantitative model, however, still needs to be developed to estimate dose dependent absorption and degradation in vivo.

A compartmental transit model was developed to characterize the transit process of oral dosage forms through the human small intestinal tract [9]. It was shown that the compartmental transit model was able to depict the transit process of non-absorbable drugs through the human small intestinal tract. The transit model was extended to incorporate linear intestinal absorption and a compartmental absorption and transit (CAT) model was then developed [10]. For highly soluble and passively transported drugs dosed in immediate release dosage forms, the fraction of dose absorbed, F_a, could be estimated by $F_a = 1 - (1 + 0.54\ P_{eff})^{-7}$, where P_{eff} is the effective intestinal membrane permeability in cm/h.

In this report, an extended CAT model was developed to estimate saturable intestinal absorption. This model simultaneously takes account of passive absorption, saturable absorption, degradation, and transit kinetics. To our knowledge, no other absorption models have considered all these processes despite the ample evidence of necessity [1–4]. The drug chosen for model validation is cefatrizine due to its saturable absorption characteristics [1–4,11–13]. It was shown that the extended CAT model, along with intravenous pharmacokinetic parameters, could estimate not only

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plasma concentration-time profiles, but also the fraction of dose absorbed.

2. Theoretical development

As illustrated in Fig. 1, the gastrointestinal tract is divided into three segments: stomach, small intestine, and colon. The proposed model simultaneously considers passive and saturable absorption, degradation, and transit in the human small intestine. Typically, gastric emptying follows a first-order process [14]. The transit flow in the human small intestine can be described by seven compartments, where a drug transfers from one compartment to the next one in a first-order fashion [9]. The colon is considered only as a reservoir and the colonic transit flow was not considered in this model. Assumptions for the extended CAT model are:

1. Absorption from the stomach and colon is minor compared with that from the small intestine and the drug is absorbed by both passive and saturable absorption mechanisms.
2. The drug is simultaneously degraded in the small intestine.
3. The dissolution from dosage forms is considered to be instantaneous.

Therefore, for highly soluble drugs dosed in immediate release dosage forms, the simultaneous absorption and transit in the gastrointestinal tract can be depicted as follows:
stomach

$$\frac{dY_s}{dt} = -K_s Y_s \tag{1}$$

small intestine

$$\frac{dY_n}{dt} = K_t Y_{n-1} - K_t Y_n - K_{an} Y_n - K_{dn} Y_n, \quad n = 1,\ 2,\ \ldots,\ 7 \tag{2}$$

where Y_s and Y_n (n = 1, 2, …, 7) are the percent of dose, t is the time, K_s, K_t, K_{an}, and K_{dn} (n = 1, 2, …, 7) are the gastric emptying, transit, absorption, and degradation rate constants. K_s is viable, and K_t has been determined to be 2.11 h^{-1} [9]. The rate constants of drug absorption K_{an} (n = 1, 2, …, 7) consist of saturable absorption that is compartment dependent and passive absorption that is compartment independent. K_{an} (n = 1, 2, …, 7) may be estimated by

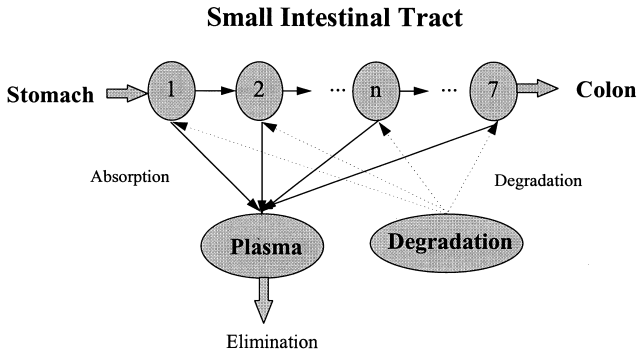

Fig. 1. A schematic diagram of a compartment absorption and transit (CAT) model. This model simultaneously considers passive absorption, saturable absorption, degradation, and transit in the human small intestine.

$$K_{an} = \frac{V_{\max,n}}{K_{mn} + C_{mn}} + K_{a1}, \quad n = 1,\ 2,\ \ldots,\ 7 \tag{3}$$

where $V_{\max,n}$, K_{mn}, and C_{mn} (n = 1, 2, …, 7) are the maximum rate of absorption, Michaelis constant of saturable absorption, and the concentration of the drug. K_{a1} is the passive absorption rate constant. The degradation rate constant K_{dn} (n = 1, 2, …, 7) may be also compartment dependent and can be estimated by

$$K_{dn} = K_{d1} + K_{d2} C_{mn}, \quad n = 1,\ 2,\ \ldots,\ 7 \tag{4}$$

where K_{d1} and K_{d2} are the first-order and second-order rate constants of degradation. Clearly, we could incorporate the other forms of degradation kinetics in Eq. (4).

The rate of absorption and degradation in the small intestine can be estimated based on the corresponding rate constant and percent of dose:

$$\frac{dY_a}{dt} = \sum_{n=1}^{7} K_{an} Y_n \tag{5}$$

$$\frac{dY_d}{dt} = \sum_{n=1}^{7} K_{dn} Y_n \tag{6}$$

where Y_a and Y_d are the percent of dose absorbed and degraded in the small intestine. The rate of drug exiting the small intestine or entering the colon can be estimated by

$$\frac{dY_c}{dt} = K_t Y_7 \tag{7}$$

From overall mass balance, we have

$$Y_s + \sum_{n=1}^{7} Y_n + Y_a + Y_d + Y_c = 100\% \tag{8}$$

At $t \to \infty$, Y_s and Y_n (n = 1, 2, …, 7) go to zero, so

$$Y_a + Y_d + Y_c = 100\% \tag{9}$$

The fraction of dose absorbed, F_a, can then be estimated by

$$F_a = Y_{a,\ t\to\infty} / 100 = \int_0^{\infty} \sum_{n=1}^{n=7} K_{an} Y_n \, dt / 100 \tag{10}$$

The fraction of dose degraded, F_d, and in the colon F_c could be estimated by $Y_d/100$ and $Y_c/100$ at $t \to \infty$. To predict oral plasma concentration-time profiles, the rate of drug absorption needs to relate to intravenous kinetics. For example, in the case of the one compartment model with the first-order elimination, the rate of plasma concentration change is estimated by

$$\frac{dC}{dt} = \frac{D}{100V} \frac{dY_a}{dt} - k_e C \tag{11}$$

where C is the plasma concentration in the central compartment, V is the volume of plasma (volume of distribution), D is the dose, and k_e is the elimination rate constant.

3. Materials and methods

3.1. Computer simulation

The model Eqs. (1)–(11) are a typical initial problem of an ordinary differential equation system. Due to its complexity, this system was numerically solved by ADAPT pharmacokinetic and pharmacodynamic modeling package [15]. A subroutine was written to accommodate the extended CAT model.

3.2. Model parameters

The intestinal absorption mechanism of cefatrizine has been studied by using in vitro and in vivo techniques [2]. It was found that the intrinsic membrane absorption in rats consists of saturable and passive transport processes [3,4]. Reigner et al. [7,16] studied the human saturable kinetics of cefatrizine absorption and it was hypothesized that saturable absorption occurred in the duodenum and jejunum. In addition, Barr et al. [6] recently found that no absorption of amoxicillin occurred in the human colon. The literature values of saturable and passive absorption kinetics of cefatrizine are summarized in Table 1.

It has been shown [9] that the transit flow of drugs in the small intestine can be described by seven compartments. We may visualize that the first half of the first compartment represents the duodenum, the second half of the first compartment, along with the second and third compartments, represents the jejunum, and the rest of the compartments, the ileum. Table 1 lists model parameters used in the simulations of plasma concentration-time profiles of cefatrizine.

Table 1

Model parameters used in the simulation of plasma concentration-time profiles of cefatrizine at oral doses of 250, 500 and 1000 mg

Parameter		Value	Reference
K_s (h)		4.0	[14]
K_t (h)		2.11	[9]
K_{a1} (h)		0.086	[1]
Duodenum	V_{max} (mM/h)	1.0	[7]
	Volume (ml)	50	[17]
Jejunum	V_{max} (mM/h)	1.0	[7]
	Volume (ml)	275	[17]
Ileum	V_{max} (mM/h)[a]	0.0	[7]
	Volume (ml)	275	[17]
K_m (mM)		0.6	[3,7]
K_{d1} (h)		0.0824	[1]
K_{d2} (mM/h)		0.00935	[1]

[a]It was assumed that there is no saturable absorption in the ileum except the first compartment to take account of the diminishing transporters (saturable absorption) from the jejunum to the ileum.

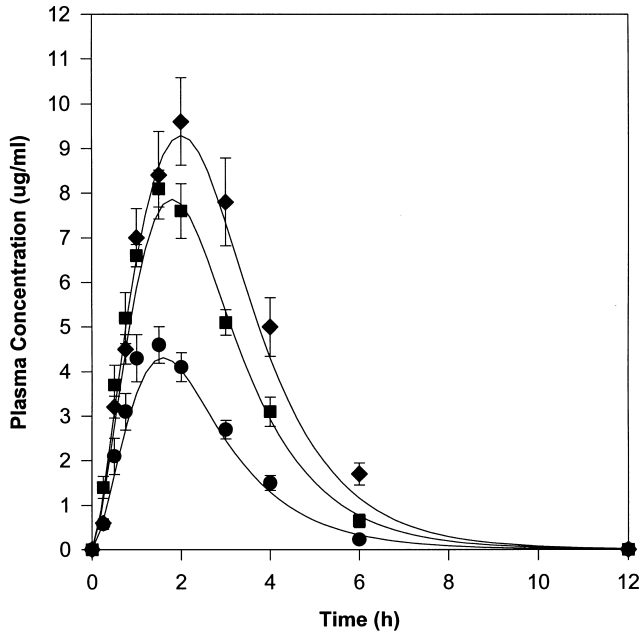

Fig. 2. Estimation of the plasma concentration profiles of cefatrizine at the oral doses of 250 (●), 500 (■), and 1000 mg (♦), where (———) represents the theoretical prediction from the CAT-based pharmacokinetic model and symbols represent the experimental points from [12].

It was assumed that there was no saturable absorption in the ileum except the first compartment that takes account of the diminishing transporters from the jejunum to the ileum. The gastric emptying is assumed to be in first-order fashion with the residence time of 0.25 h [14]. The volume of each compartment is the mean of the literature data [17]. The elimination rate constant and the volume of distribution are from intravenous kinetics [12]. Table 1 also shows the degradation parameters of cefatrizine determined by Nakashima et al. [1].

4. Results and discussion

4.1. Explanation of cefatrizine pharmacokinetics

Coupling with its intravenous pharmacokinetic parameters, the extended CAT model was used to predict the observed plasma concentration-time profiles of cefatrizine. The predicted results are shown in Fig. 2, where the plasma concentration-time profiles at three (250, 500 and 1000 mg) doses were shown to illustrate the ability of the extended CAT model to predict the dose-dependent absorption. Fig. 2 also shows the human experimental data from Pfeffer et al. [12]. The predicted peak plasma concentrations and peak times were 4.3, 7.9, and 9.3 μg/ml at 1.6, 1.8, and 2.0 h, in line with the experimental mean peak plasma concentrations of 4.9 ± 1.2, 8.6 ± 1.0, and 10.2 ± 2.1 μg/ml at the peak times 1.4 ± 0.4, 1.6 ± 0.2, and 2.0 ± 0.6 h. The reported absolute bioavailability was 75 and 50% at the 250- and 1000-mg oral doses [12], and compared favorably

Table 2

Summary of the fractions of dose absorbed, degraded in the small intestine, and in colon at oral doses of 250, 500 and 1000 mg for cefatrizine

Parameter	250 mg (%)	500 mg (%)	1000 mg (%)
Predicted fraction of dose absorbed	74	61	48
By passive transport	10	12	14
By saturable transport	64	49	34
Reported bioavailability [12]			
By AUC	77 ± 7	75 ± 10	47 ± 10
By urinary excretion	72 ± 12	77 ± 29	55 ± 19
Predicted fraction of dose in colon	16	25	33
Predicted fraction of dose degraded	10	14	19
Reported excretion in feces [13]		28 ± 04	32 ± 6

to the theoretical fraction of dose absorbed, as shown in Table 2. The calculated fraction of dose absorbed at a 500-mg dose is 61%, lower than the experimental bioavailability of 75% [12].

Table 2 summarizes the predicted fractions of dose absorbed, degraded in the small intestine, and in colon. With the increase of dose from 250 to 1000 mg, the fraction of dose absorbed decreases from 74 to 48%, while the fraction of dose in colon increases from 16 to 33%, and the fraction of dose degraded in the small intestine increases from 10 to 19%. Although the overall fraction of dose absorbed decreases with increasing dose, the fraction of dose absorbed by passive transport mechanism increases slightly. The decrease in the overall fraction of dose absorbed is mainly due to the saturable absorption mechanism. Sixty-four percent of dose at a 250-mg dose was absorbed by saturable absorption, compared to only 34% at a 1000-mg dose. Meanwhile, at a 1000-mg dose, 14% of dose was absorbed by passive diffusion, comparable to 34% by saturable absorption, suggesting that passive diffusion may not be excluded in the simulation of cefatrizine absorption. These findings were also supported by the experimental evidence [3,4].

The predicted fraction of dose degraded in the small intestine and the fraction of dose in the colon are given in Table 2. Because of the long mean residence time (35 h) in the colon [18], the majority of the drug in the colon may be degraded and the significant amount of cefatrizine was then not found in feces [11]. The reported excretion in feces was 28 and 32% at doses of 500 and 1000 mg, respectively [11], in fair agreement with the theoretical results. Certainly, the drug degraded in the small intestine could also be found in feces.

4.2. Effect of model parameter

The literature data of the model parameters, such as gastric emptying, transit time, and absorption mechanisms vary significantly and the mean values were then used for prediction above. It is of interest to know how the variations of these parameters influence the prediction results. Gastric emptying varies 50% in the literature [13] and small intestinal transit varies 40% [9]. V_{max} varies remarkably in the literature [1,3] and 50% variation was assumed. The deviation of K_m was from literature [3] and 50% variation of K_{a1} was assumed. Table 3 shows the mean and standard deviation of parameters evaluated. Because of the large variations of the parameters, only one standard deviation changes were simulated. The corresponding percentage changes in the fraction of dose absorbed are calculated by

$$\frac{F_a(\text{mean} \pm \text{SD}) - F_a(\text{mean})}{F_a(\text{mean})} \times 100$$

where SD is the standard deviation of the mean. The simulated results are shown in Table 3. Table 3 shows that no single factor results in over 25% variation in the fraction of dose absorbed.

The mean urinary recovery is around 60% upon 500-mg oral dosing of cefatrizine. However, it ranges from 37 to 82% in the literature [11,19–21] and the corresponding variation is about 40%. The variable recoveries could be attributed to differences in bioavailability. Our simulation study showed that no single physiological factor, including gastric emptying, small intestinal transit, and absorption mechanisms, could account for such a large difference. However, as we can see from Table 3, the overall effect of these physiological factors could account for up to 40% variability in bioavailability.

4.3. Model comparison

Reigner et al. [7] have examined the absorption kinetics of cefatrizine and proposed an empirical pharmacokinetic model, MM, that incorporated the Michaelis–Menten type of saturable absorption. This MM model was a statistically significant improvement over models incorporating either first- or zero-order absorption; however, the MM model fails to explain the reduced extent of absorption at high doses. Therefore, Couet et al. [16] introduced the absorption window concept in the MM model and proposed a MM-Δt model. The authors evaluated several Δt and found that the

Table 3

The effect of gastric emptying, small intestinal transit, and absorption mechanism on the fraction of dose absorbed of cefatrizine at an oral dose of 500 mg

Parameter	Mean ± SD [Ref.]	F_a (–SD) %	F_a (+SD) %
K_s (h)	4.0 ± 2.0 [14]	+6.5	–2.2
K_t (h)	2.11 ± 0.84 [9]	+20.1	–15.1
K_{a1} (h)	0.086 ± 0.043 [1,3]	–7.2	+6.2
V_{max} (mM/h) in duodenum	1.0 ± 0.5 [1,3]	–4.8	+4.3
V_{max} (mM/h) in jejunum	1.0 ± 0.5 [1,3]	–21.3	+15.6
K_m (mM)	0.6 ± 0.2 [3]	+6.0	–4.9

MM model with Δt of 1.5 h explained the bioavailability of cefatrizine best. An extended version of this MM-Δt model has been applied to ascorbic acid kinetics [22] and amoxicillin absorption [8]; however, since these models have not considered the effect of the degradation, a direct comparison between MM and CAT models appears not feasible.

A mechanical and quantitative absorption model is presented here. This model simultaneously considers passive absorption, saturable absorption, degradation, and transit in the human small intestine. It has been shown that the extended CAT-based pharmacokinetic model was able to interpret the cefatrizine dose-dependent oral pharmacokinetics. Consequently, an oral pharmacokinetic model can simultaneously account for passive absorption, saturable absorption, and degradation kinetics. We showed comparable passive and saturable drug absorption of cefatrizine, particularly at high dose. In addition, we also showed the large differences in the fraction of dose degraded among doses, which have not been considered before.

Absorption and degradation kinetics are the only model parameters that need to be determined to estimate the fraction of dose absorbed and to simulate intestinal absorption kinetics using the extended CAT model. Degradation kinetics may be determined in vitro and absorption parameters can also be determined using the human intestinal perfusion technique [23]; therefore, it may be feasible to predict the intestinal absorption kinetics based on in vitro degradation and in vivo perfusion data. Nevertheless, considering the complexity of the oral drug absorption, such prediction is only an approximation. In addition, the extended CAT-based pharmacokinetic model may be directly used to fit experimental pharmacokinetic data. It has been an advantage of the extended CAT model that we may simultaneously estimate the fraction of dose absorbed while curve fitting pharmacokinetic data. The risk involved is that, we assume no metabolism occurs.

References

[1] E. Nakashima, A. Tsuji, S. Kagatani, T. Yamana, Intestinal absorption mechanism of amino-β-lactam antibiotics. III. Kinetics of carrier-mediated transport across the rat small intestine in situ, J. Pharm. Dyn. 7 (1984) 452–464.

[2] A. Tsuji, Intestinal absorption of β-lactam antibiotics, in: M.D. Taylor, G.L. Amidon (Eds.), Peptide-Based Drug Design, ACS Professional Reference Book, American Chemical Society, Washington, DC, 1995, pp. 101–134.

[3] P.J. Sinko, G.L. Amidon, Characterization of the oral absorption of β-lactam antibiotics. I. Cephalosporins: determination of intrinsic membrane absorption parameters in the rat intestine in situ, Pharm. Res. 5 (1988) 645–650.

[4] P.J. Sinko, G.L. Amidon, Characterization of the oral absorption of β-lactam antibiotics. II. Competitive absorption and peptide carrier specificity, J. Pharm. Sci. 78 (1989) 723–727.

[5] J. Sjovall, A. Alvan, D. Westerlund, Dose-dependent absorption of amoxycillin and bacampicillin, Clin. Pharmacol. Ther. 38 (1985) 241–250.

[6] W.H. Barr, E.M. Zola, E.L. Candler, S.-M. Hwang, A.V. Tendolkar, R. Shamburek, B. Parker, M.D. Hilty, Differential absorption of amoxicillin from the human small and large intestine, Clin. Pharmacol. Ther. 56 (1994) 279–285.

[7] B.G. Reigner, W. Couet, J.-P. Guedes, J.B. Fourtilla, T.N. Tozer, Saturable rate of cefatrizine absorption after oral administration to humans, J. Pharmacokinet. Biopharm. 18 (1990) 17–34.

[8] V.K. Piotrovskij, G. Paintaud, G. Alvan, T. Trnovec, Modeling of the saturable time-constrained amoxicillin absorption in humans, Pharm. Res. 9 (1994) 1346–1351.

[9] L.X. Yu, J.R. Crison, G.L. Amidon, Compartmental transit and dispersion model analysis of small intestinal transit flow in humans, Int. J. Pharm. 140 (1996) 111–118.

[10] L.X. Yu, E. Lipka, J.R. Crison, G.L. Amidon, Transport approaches to the biopharmaceutical design of oral drug delivery systems: Prediction of intestinal absorption, Adv. Drug. Deliv. Rev. 19 (1996) 359–376.

[11] J.P. Santella, B. Tanrisever, Cefatrizine, a clinical overview, Drugs Exp. Clin. Res. 11 (1985) 441–446.

[12] M. Pfeffer, R.C. Gaver, J. Ximenez, Human intravenous pharmacokinetics and absolute oral bioavailability of cefatrizine, Antimicrob. Agents Chemother. 24 (1983) 915–920.

[13] R.C. Gaver, G. Deeb, Disposition of ^{14}C-cefatrizine in man, Drug Metab. Dispos. 8 (1980) 157–162.

[14] R.L. Oberle, T.-S. Chen, C. Lloyd, J.L. Barnett, C. Owyang, J. Meyer, G.L. Amidon, The influence of the interdigestive migrating myoelectric complex on the gastric emptying of liquids, Gastroenterology 99 (1990) 1275–1282.

[15] D.Z. D'Argenio, A. Schumitzky, Adapt II: Mathematical Software for Pharmacokinetic/Pharmacodynamic Systems Analysis, University of Southern California, Los Angeles, CA, 1992.

[16] W.R. Couet, B.G. Reigner, J.-P. Guedes, T.N. Tozer, Theoretical model for both saturable rate and extent of absorption: simulations of cefatrizine data, J. Pharmacokinet Biopharm. 19 (1991) 271–285.

[17] R.L. Oberle, G.L. Amidon, The influence of variable gastric emptying and intestinal transit rates on the plasma level curve of cimetidine; An explanation for the double peak phenomenon, J. Pharmacokinet. Biopharm. 15 (1987) 529–544.

[18] A.M. Metcalf, S.F. Phillips, A.R. Zinsmeister, R.L. MacCarty, R.W. Beart, B.G. Wolff, Simplified assessment of segmental colonic transit, Gastroenterology 92 (1987) 40–47.

[19] P. Actor, D.H. Pitkin, G. Lucyszyn, J.A. Weisbach, J.L. Bran, Cefatrizine (SK&F 60771), a new oral cephalosporin: serum levels and urinary recovery in humans after oral or intramuscular administration – comparative study with cephalexin and cefazolin, Antimicrob. Agents Chemother. 9 (1976) 800–803.

[20] M. Matsuzaki, H. Matsumoto, K. Ochiai, Y. Hirata, M. Hino, Absorption and excretion of cefatrizine, Jpn. J. Antibiotics 29 (1976) 83–89.

[21] V. Mastrandrea, S. Ripa, F. La-Rosa, A. Ghezzi, Pharmacokinetics of cefatrizine after oral administration in human volunteers, Int. J. Clin. Pharmacol. Res. 5 (1985) 319–323.

[22] V.K. Piotrovskij, Z. Kallay, M. Gajdos, M. Gerykova, T. Trnovec, The use of a nonlinear absorption model in the study of ascorbic acid bioavailability in man, Biopharm. Drug Dis. 14 (1993) 429–442.

[23] H. Lennernas, O. Ahrenstedt, R. Hallgren, L. Knutson, M. Ryde, L.K. Paalzow, Regional jejunal perfusion, a new in vivo approach to study oral drug absorption in man, Pharm. Res. 9 (1992) 1243–1251.