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on drug absorption:  
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George A. DIGENIS and Erik P. SANDEFER

Division of Medicinal Chemistry and Pharmaceutics,  
College of Pharmacy University of Kentucky, Lexington, KY 40536-0082  
(606)257-1970; FAX (606)257-7585

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## Introduction

Over the last twenty years, we have observed instances where food and/or specific dosage formulations have profoundly affected gastrointestinal transit and oral drug absorption. In some instances we have shown that variations in gastrointestinal transit have proportionally altered oral bioavailability of compounds known to exhibit large inter- and intra-subject variability. Thus, the ability to evaluate the *in vivo* gastrointestinal behavior of pharmaceutical dosage forms and correlate this character to resulting drug levels ultimately provides a valuable basis for the rational design of drug delivery systems as well as a means to explain apparent drug absorption anomalies. To study this relationship, the techniques of external gamma scintigraphy have provided a noninvasive method to quantitate gastrointestinal transit and also to assess the *in vivo* condition of the drug delivery system.

The effects of food on drug absorption have been well documented in the literature (1,2), however, few studies have attempted to *systematically* identify the causal agents to explain altered oral bioavailability. Indeed, many factors may influence oral drug absorption. A partial listing of these factors include the intimate interaction of the following; a) gastrointestinal physiology and residence of the drug at its site of absorption, b) chemical nature of food nutrients (e.g. caloric value, amount of fats, carbohydrates, protein and fiber) and the timing of the meal relative to dose administration, c) chemical and physical properties of the drug and d) formulation factors which affect the *in vivo* rate and gastrointestinal site of drug release from its delivery system.

The following communication will describe some of our findings in the format of case studies. Our intent is to demonstrate the need to methodically study the factors which effect oral drug absorption by combining the techniques of external gamma scintigraphy with conventional pharmacokinetics. By making these *in vivo* / *in vivo* correlations, this knowledge will contribute towards the design of drug delivery systems which perform consistently and predictably and will ultimately advance drug therapies.

### 1. Case study 1: the effect of variable gastric emptying on the oral bioavailability of an acid-labile compound

This first case study demonstrates the influence of gastric residence on the oral bioavailability of an acid sensitive compound. It also shows that intrasubject changes in drug absorption can be explained by the day-to-day variations in gastric emptying.

Solutions of the acid-labile monomer of polyvinylpyrrolidone, N-vinyl pyrrolidinone (NVP), were orally administered to fasted beagles at doses of 5, 10 and 20 mg/kg. Plasma levels of NVP were extremely erratic as indicated by the Cmax of the 5 mg/kg dose being greater in some instances than the Cmax of the 20 mg/kg dose. Because of the acid sensitivity of NVP, it was shown that slow gastric emptying manifested in poor NVP absorption, and when gastric emptying was rapid, NVP absorption was maximized (3). This is demonstrated graphically in Figure 1 for beagle 3487 given a

20 mg/kg dose on three separate occasions. The top graph in Figure 1 shows that when gastric emptying was slow, NVP levels were low, and when gastric emptying was rapid as shown in the bottom graph of Figure 1, NVP levels were greatest.

The results from this study demonstrated the need to monitor gastrointestinal transit when measuring the bioavailability of an acid labile compound.

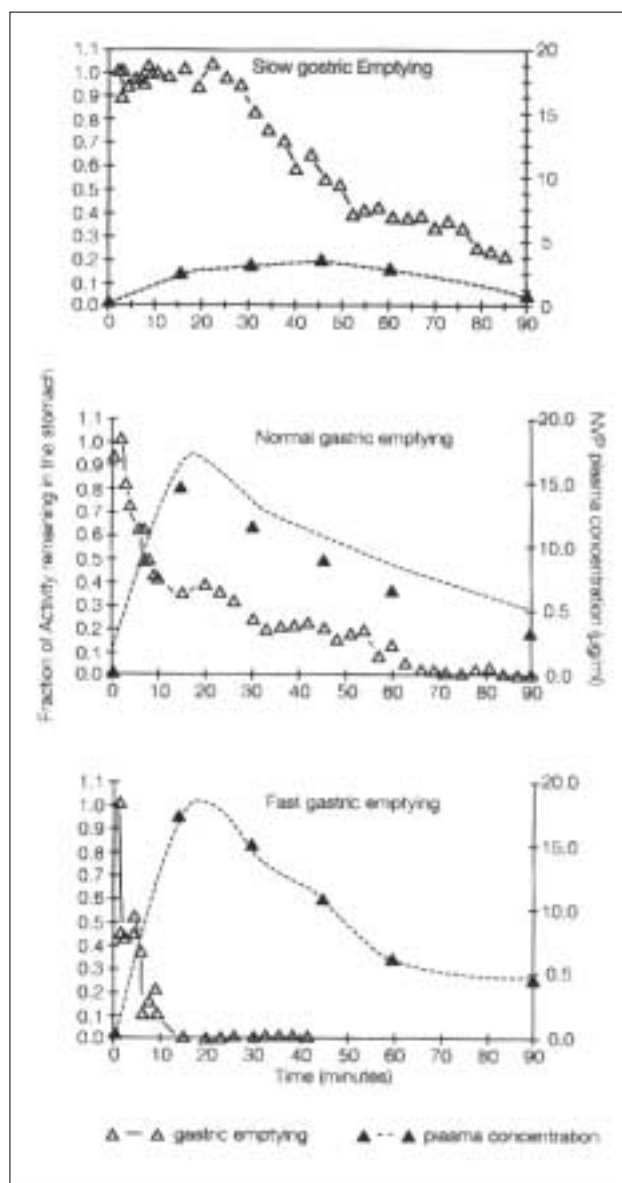


Figure 1. Intrasubject correlations (Beagle #3487). Three modes of gastric emptying and the corresponding NVP plasma levels (20 mg/kg).

## 2. Case study 2: an enteric coated multiparticulate of erythromycin and diminished absorption with food intake after dose administration

Though we have frequently used this study as an example in several symposia and publications, it still provides a powerful illustration regarding the effect of food on gastrointestinal transit and absorption of erythromycin from an enteric coated multiparticulate.

Briefly, this study investigated a marketed erythromycin product (Eryc<sup>®</sup> 250 mg, Parke-Davis) administered under fasted and non-fasted conditions. An extremely important distinction in dosing regimen between this study and others which have previously evaluated gastrointestinal transit (4) was that the fed condition was achieved 30 min **after** drug dose, thus, the dosage was actually swallowed while the subjects were still under a fasted condition. The majority of studies which have examined the effect of food on gastrointestinal transit have given the dosage form on a full stomach with food typically ingested 30 min **before** drug dose. Additionally, the standard breakfast meal used in this study was high in carbohydrate and relatively low in fat (765 cal, 133 g carbohydrate, 21 g protein and 18 g fat).

The manufacture of similar enteric beads and *in vitro* testing after neutron activation has previously been reported (5). The *in vivo* study has also been described in the literature in the form of an abstract (6), a research article (7), and in a review article which described the uses of neutron activation and gamma scintigraphy (8). This particular dosage form was radiolabeled with samarium-153 ( $\gamma = 103$  keV,  $t_{1/2} = 46.7$  hr) and only five radiolabeled beads were in each unit dose; the remainder was unadulterated ERYC<sup>®</sup>, thus, by radiolabeling only a few of the beads we were able to determine the gastrointestinal site of bead disintegration and drug release.

The results of this study showed striking differences in the plasma concentration curves of erythromycin between the fasted and fed condition. All subjects showed earlier  $T_{max}$  and lower  $C_{max}$  when the enteric formulation was administered under this fed dosing regimen where food intake was 30 min post drug dose. To summarize these differences, the area under the concentration curves are expressed as a bar graph shown in Figure 2. Without exception, all subjects showed a decrease in AUC in the fed condition, and the mean for the fed condition was approximately 50% of the fasted study.

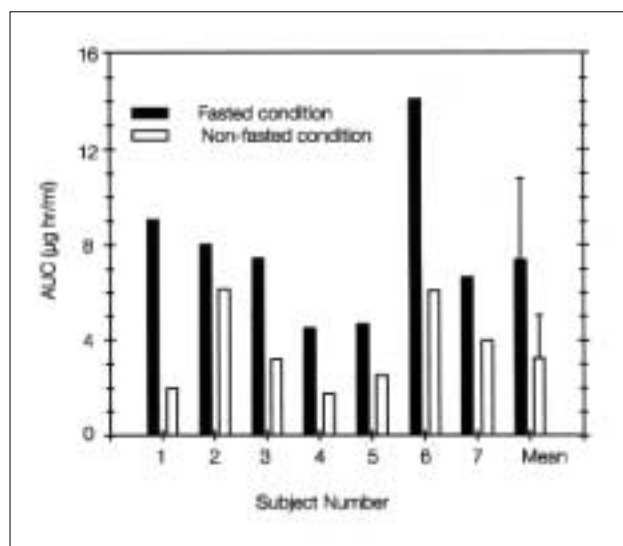


Figure 2. AUC's following oral administration of 250 mg E-mycin from enteric coated multiparticulate (Eryc, Parke-Davis).

We were initially inclined to explain reduced bioavailability in the fed condition due to an initial transient rise in gastric pH which occurs with food intake. This in turn may compromise the integrity of the enteric coating. We conjectured that as the stomach became more acidic again, a percentage of the erythromycin was hydrolyzed, thus, the bioavailability in the fed condition should inherently be less than the fasted condition. However, the results from analyzing the scintigraphic images showed a far different outcome. It was evident that some subjects emptied the enteric multiparticulates even before the meal was ingested at 30 min post dose (e.g. subjects 2, 3, 5, 6, Figure 3A), thus, the enteric coating was not exposed to the transient pH rise for these subjects, yet these individuals still showed reduced AUC's, in the fed condition. Most dramatic from the scintigraphic analysis was the rapid transit of intact beads through the proximal small intestine in the fed condition as compared to the fasted condition. Because of this rapid transit, enteric coating dissolution and drug release occurred more distal in the small intestine for the fed study as compared to the site of release for the fasted condition. The gastric emptying (GE) and small intestine transit time (SITT) results are depicted graphically for individual subjects in Figure 3. The figure to the left shows that gastric emptying was not effected by a meal at 30 min post dose, however, small intestine transit was always faster in the fed study.

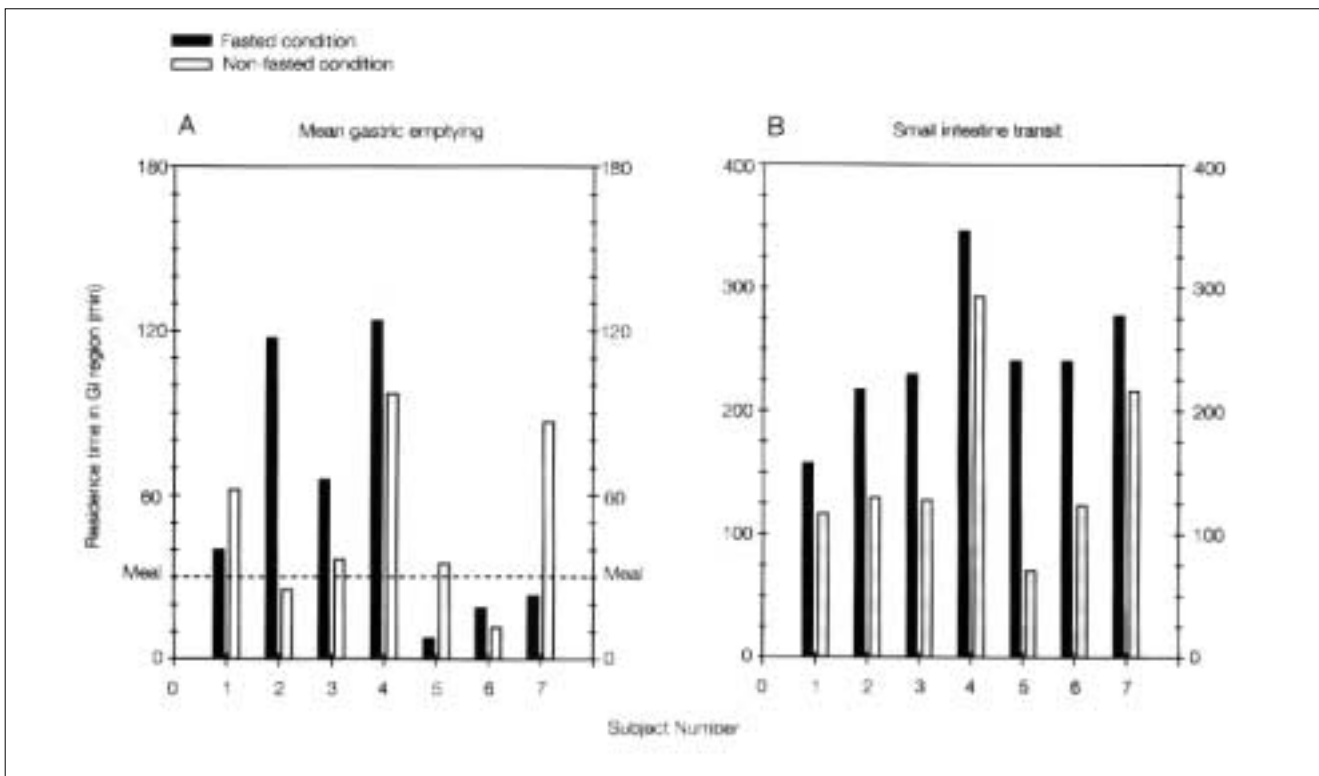


Figure 3. Individual gastric emptying (A) and small intestine transit (B) of  $^{153}\text{Sm}$ -labeled ERYC<sup>®</sup> beads administered under fasted and fed condition.

The physiologic cause for this change in small intestine transit warrants further investigation since these results and conclusions are contradictory to that which is published in the pharmaceutical literature, i.e., food does not change the small intestinal transit time of pharmaceutical dosage forms (4) at least when food is ingested 30 min *before* drug dose. It is our opinion that food may not affect the absolute transit time from pylorus to cecum, but the manner in which it transits the small intestine can be very different.

The most straight forward explanation based on these data is that the intake of food at 30 min post dose resulted in a feedforward mechanism inducing increased small intestine motility. Because of this increased motility, contents already present in the small intestine were pushed rapidly towards the colon where absorption of erythromycin is less efficient. Increased motility is certainly a well documented phenomenon with regard to the gastrocolonic response following food intake where there is frequently an urge to defecate following a meal. How-

ever, the regulatory mechanisms which control gut function are numerous and other explanations are possible (9). It is also conceivable that the induced intestinal transit and apparent rapid gastric emptying was due to an anticipatory response to feeding (10).

It is reasonable that other delayed or sustained release formulations may be susceptible to altered oral absorption when administered under this particular dosing regimen for drugs not absorbed throughout the gastrointestinal tract or if the drug, like erythromycin, is poorly absorbed by the oral route (50% or less oral bioavailability). Regardless of the physiologic reasons for this phenomenon, there are instances where therapeutic drug levels are not achieved when particular delivery systems are used as the following example will describe.

As a point of completeness, the individual erythromycin concentration curves are included in Figure 4.

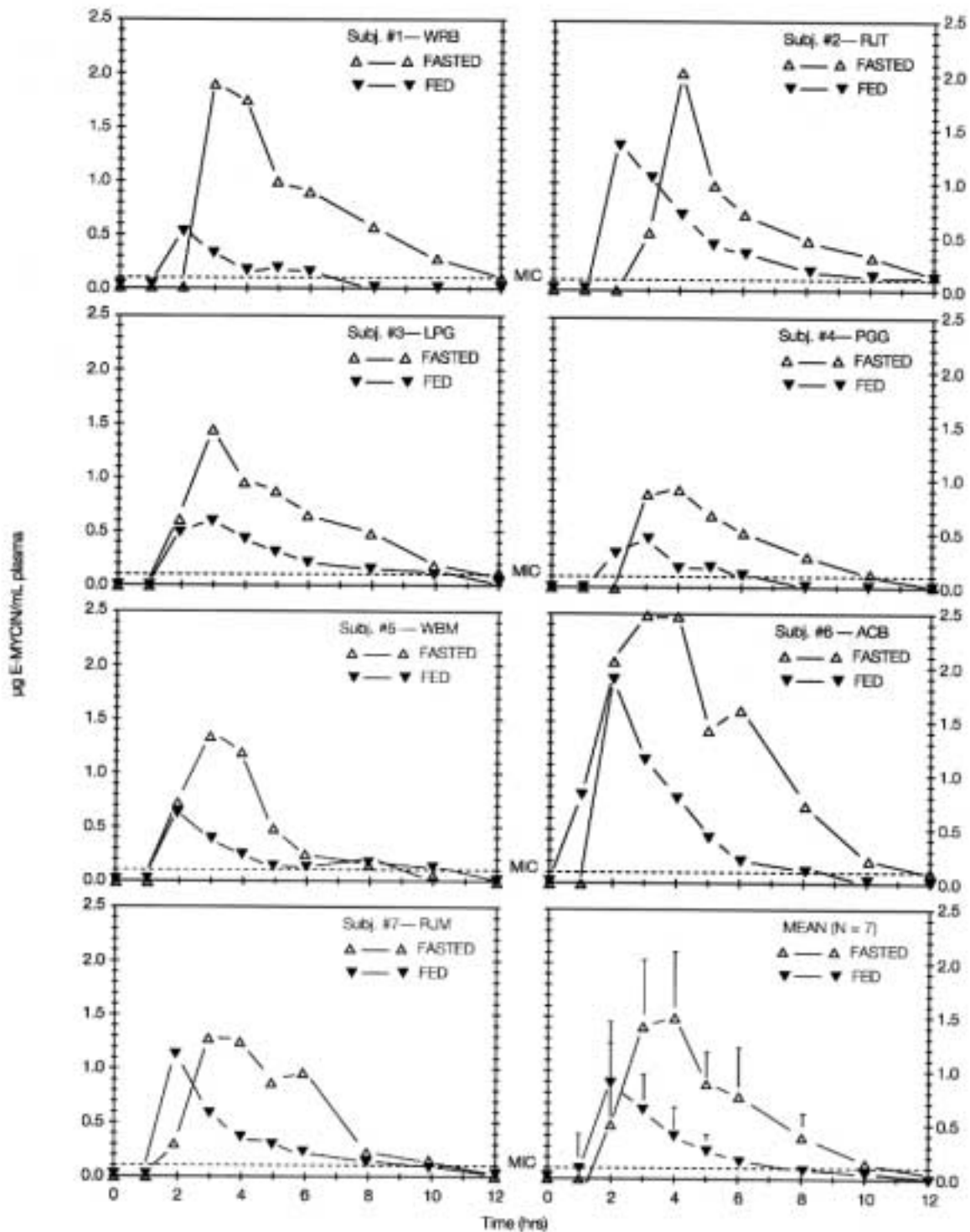


Figure 4. Individual and mean E-mycin concentration/time curves following 250 mg dose from an enteric-coated multiparticulate (ERYC™): fasted vs fed.

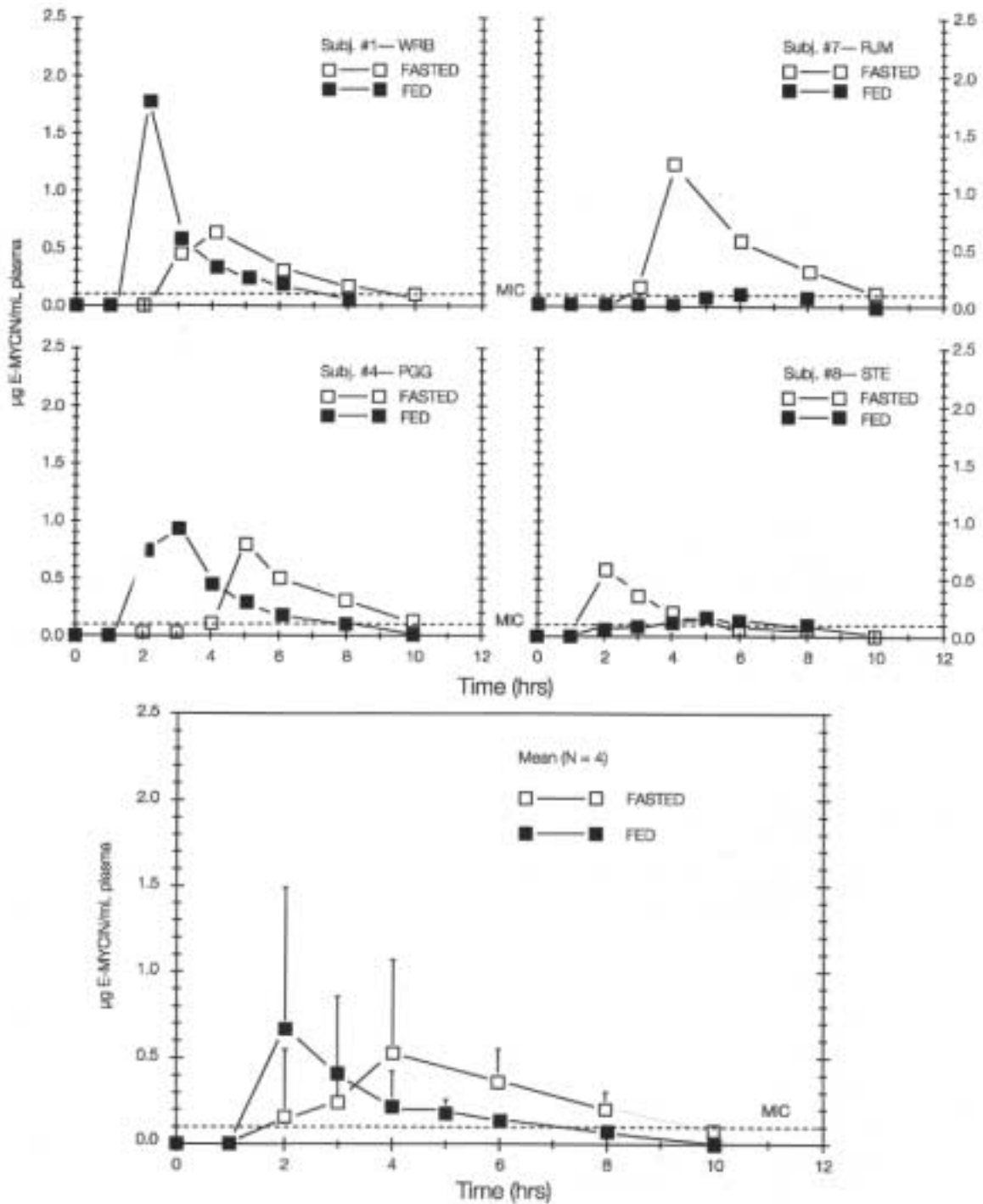
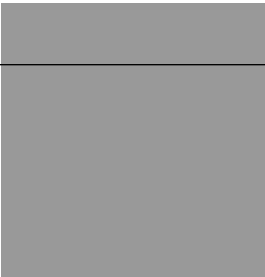


Figure 5. E-mycin enteric coated tablet (250 mg free base: fasted vs fed) individual and mean E-mycin concentration/time curves.

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### 3. Case study 3: an enteric coated erythromycin tablet and the effect of food intake after dose administration

The preceding study encouraged us to examine if enteric coated *tablets* are susceptible to similar food effects when a standard breakfast meal is ingested 30 min after drug administration. To test this, a mated erythromycin (250 mg) tablet was chosen, and administered to four subjects in a two-way complete cross-over study under the fasted and fed condition. The exact dosing regimen was used with an identical standard breakfast meal consumed at 30 min post dose. Three of the four subjects were also in the preceding ERYC® study.

The results of this study are shown in Figure 5. The mean data shows the typical "left shift" of the curve for this particular fed condition as indicated by an earlier  $T_{max}$ . This observation was consistent with the results from the multiparticulate study described in case study 2. Though the mean data indicated that the dosage form was efficacious and adequate blood levels were achieved (MIC = 0.10 µg/mL), the individual plasma concentration profiles indicated a far different result. The enteric tablet was not able to provide therapeutic blood levels when administered under the fed condition to subjects 007-RJM and 008-STE.

The reason for this failure was obvious upon analysis of the scintigraphic images. Subject 007-RJM showed gastric emptying of the tablet at 16 min post dose, and when this subject ate at 30 min post dose, scintigraphic imaging revealed that the *intact* enteric tablet rapidly moved through the small bowel and reached the cecum at 40 min post dose. The tablet was later observed to transit to the transverse colon by 2 hr post dose and tablet disintegration was noted at 5 hr. This rapid transit was confirmed by defecation of the radioactivity at 5.5 hr post dose. Subject 008-STE showed similar results with gastric emptying of the tablet actually occurring while the subject was still eating the breakfast meal at 44 min post dose. This was followed by rapid transit of the intact tablet to the ascending colon at 160 min where the enteric coated tablet was observed to have disintegrated. However, it should also be noted that subject 001-WRB showed improved erythromycin plasma levels under the fed condition. This was apparently due to very rapid enteric polymer dissolution and tablet disintegration in the early small intestine as indicated by the scintigraphic images.

Nonetheless, as with the example given in Case Study 2, peristalsis of the small intestine is apically reinduced when food is consumed at 30 min post dose. This increased motility in turn effects the transit time of the dosage form through the optimal absorptive regions which results in lower erythromycin plasma levels. The observation of dosage form failure occurring in two of the four subjects suggests that the single unit enteric tablet may perform less consistently than its multiparticulate counterpart.

We have not yet mentioned that radiolabeled placebo pellets in a capsule (3 mm, density 2.0 g/mL) were coadministered with the erythromycin tablet so that a direct comparison between the gastrointestinal transit of a single unit dose versus a multiparticulate dosage form could be made. Consistent with results in Case Study 2, the placebo pellets reached the cecum earlier in the fed study as compared to the fasted study, however, it was apparent that some of the pellets were still in the distal small intestine of subjects 007-RJM and 008-STE whilst the tablet had already entered the colon. The premature arrival of the erythromycin tablet before the placebo pellets may or may not be formulation dependent; more studies are needed to reach a definitive conclusion regarding this. However, the present observation tends to support the idea that consistent and predictable drug delivery is more easily achieved with a multiparticulate enteric formulation when the intended site of drug release is the small intestine.

### 4. Case study 4: the effect of pre-dose food consumption on the onset of acetaminophen absorption from an enteric coated tablet

This fourth case study represents a more common dosing schedule where food was consumed 30 min *before* dose administration. The original objective of this investigation was to determine the site of drug delivery of an enteric coated tablet designed to release in the proximal small intestine. Each tablet contained two drug markers and was radiolabeled with neutron activated samarium-153 oxide, Acetaminophen (325 mg) was used as marker of drugs absorbed throughout the small intestine (and probably the colon, too), and riboflavin (30 mg) was used to indicate the efficacy of drug release in the proximal small intestine. A complete cross-over study was conducted in six subjects under fed and



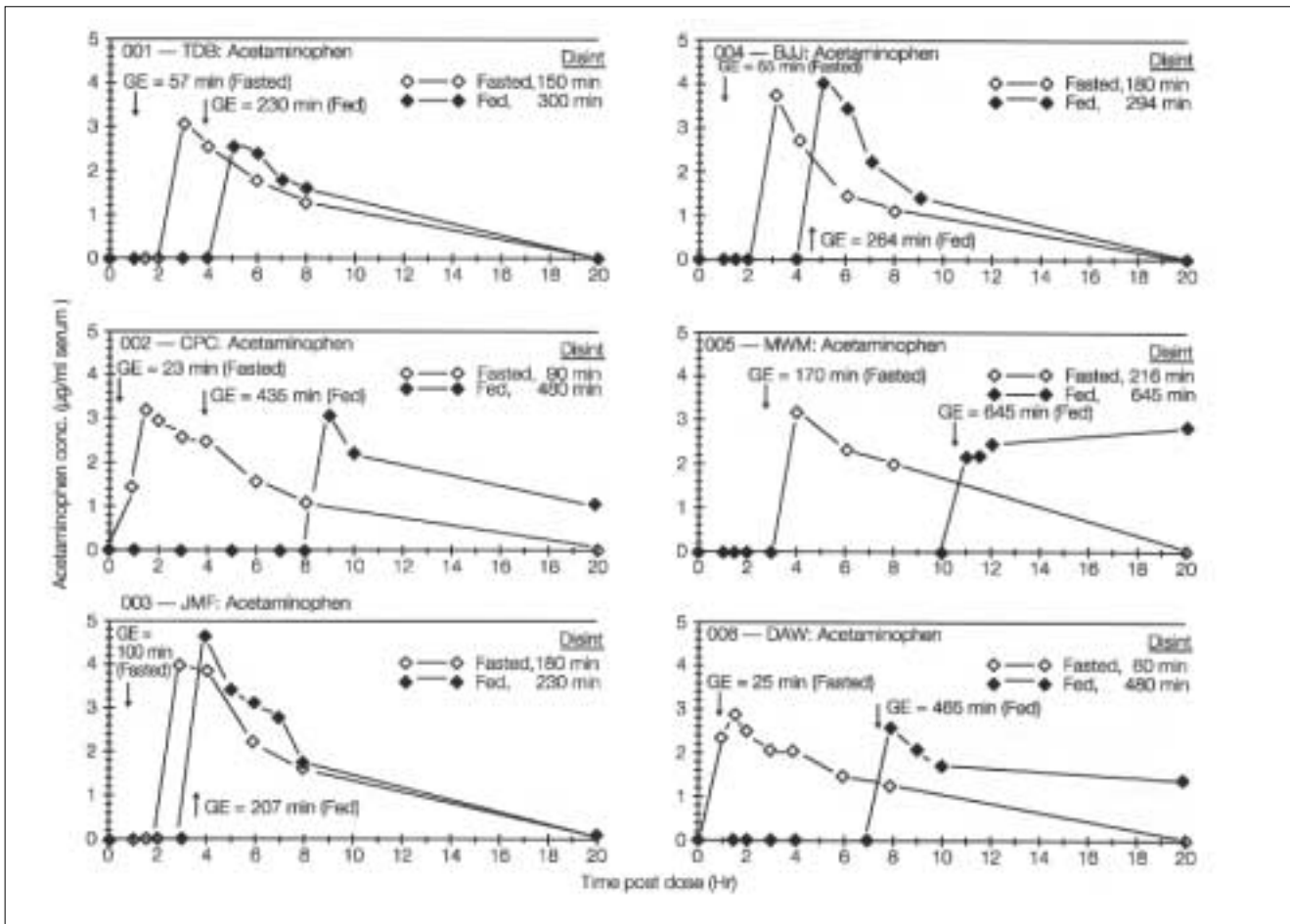


Figure 6. Individual APAP levels from an enteric coated tablet (325 mg APAP) in fasted and fed (30 min before dose) volunteers. GE = Gastric Emptying; Disint = Tablet Disintegration.

fasted conditions and two additional subjects were administered an uncoated tablet to serve as controls (11). The standard meal was consumed 30 min before drug dose and was high in fat (1030 calories, 118 g carbohydrate, 38 g protein, 134 g fat); no other food was ingested until it was confirmed that the tablet was out of the stomach.

The purpose of providing this case study is to demonstrate the well known incidence of prolonged gastric residence of large single unit doses in the prodose fed stomach, and also to make comparisons between the results seen in case studies 2 and 3 where food was consumed 30 min after drug dose. For the purpose of this communication, only acetaminophen serum levels will be described for the enteric coated tablet. These are shown in Figure 6.

During the actual data acquisition of this study, it was obvious that gastric residence was extremely long in some subjects. The original study protocol designated blood sampling times at 0, 1, 1.5, 2, 3, 4, 6, 8 and 20 hr which were certainly adequate for the fasted condition. However, it became quite apparent with subjects dosed in the fed condition that the sampling times were not modified during the acquisition period, then some subjects probably would show zero absorption through 8 hr with a jump in APAP concentration at the 20 hr sample. Fortunately, we realized this early during the acquisition period and modified the sampling times depending upon when gastric emptying of the enteric tablet was observed. As figure 6 indicates, gastric emptying of the tablet in the fed condition was extremely variable with a range of 207 to 645 min

(mean  $\pm$   $\sigma$  = 374  $\pm$  171 min). intuitively, the onset of APAP absorption showed a concomitant delay in the fed condition dependent upon the gastric emptying time. As stated previously, the gastric retention of similar dosage forms is well known, and in fact, we have since observed gastric retention as long as 24 hr when a standard breakfast is consumed at 30 min before dose followed by a standard lunch at 5 hr and dinner at 10 hr. Such extreme gastric residence of single unit enteric tablets can have profound implications on drug concentrations whether the therapy is chronic or acute.

The gastric emptying times of enteric tablets in this Case Study with a high fat meal (1030 cal, 134 g fat) ingested at 30 min before dose was drastically different than that observed in Case Study 3 when a low fat meal (765 cal, 18 g fat) was consumed 30 min after dose. The gastric emptying time of the enteric erythromycin tablets in the fed condition for Case Study 3 ranged from 16 to 68 min (mean  $\pm$   $\sigma$  = 41  $\pm$  21 min). There is considerable information which is needed to fully elucidate these differences of meal timing and drug absorption, however, it should be apparent that depending on the type of drug therapy required and the absorption characteristics of a drug, the dosing regimen of enteric coated products can have a significant effect in the successful treatment of a disease.

## 5. Case study 5: the effect of an effervescent excipient (sodium acid pyrophosphate) on intestinal transit and ranitidine absorption

The next three case studies do not describe direct food effects on drug absorption, but instead, will recount intra- and inter-subject differences in gastrointestinal transit which resulted in proportional changes in drug absorption. These examples will still have implications of possible food effects due to the character of absorption changes which will be described.

Case Study 5 was indeed an interesting one since it showed the anomalous result of an effervescent ranitidine solution being less bioavailable than a Zantac® tablet (150 mg ranitidine, Glaxo, Inc.). Of several effervescent formulations tested, all were bioequivalent to the immediate release Zantac® with the exception of one which contained sodium acid pyrophosphate (SAPP, 1.132 g) as the acid excipient (12); this formulation was approximately 50%

bioequivalent to the control tablet. Since the formulation also contained several other excipients which were unique to it, a separate study was necessary to isolate the causal agent which was ultimately determined to be SAPP (12).

It was hypothesized that faster gastrointestinal transit was the cause for this reduced ranitidine absorption. A study was completed to test the influence of SAPP (1.132 g) on gastrointestinal transit by gamma scintigraphy, thus, twelve fasted subjects each received 200 mL of water with or without SAPP and were imaged continuously until all radioactivity (<sup>111</sup>InCl<sub>3</sub>) had entered the cecum or colon.

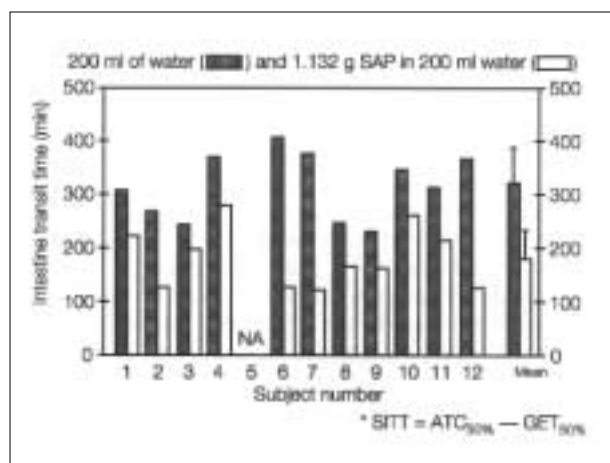


Figure 7. Small intestine transit time (SITT\*) in fasted subjects administered.

The results to this study are shown in Figure 7. As indicated by Figure 7, it is readily apparent that all subjects showed faster small intestine transit when administered the SAPP solution. The mean SITT values were reported as 325  $\pm$  66 min and 185  $\pm$  52 min for the control and SAPP solutions, respectively ( $p$  = 0.0002). The effect of SAPP on intestinal transit is consistent with the pharmacologic action of sodium phosphate salts, thus, SAPP may be considered in this case a saline cathartic where water is osmotically maintained in the gut lumen to indirectly stimulate peristalsis.

This study contradicts the conventional wisdom that bioequivalence to standard solid oral formulations will be either met or exceeded by oral solution formulations. This result may also have implications towards food effects on drug absorption in instances where a drug therapy has been ingested with substantial amounts of liquids that are high in phosphates or a similar pharmacologic agent.

## 6. Case study 6: the influence of gastric emptying time and the gastrointestinal site of absorption on the bioavailability of a poorly soluble drug

It is frequently the case with the gamma scintigraphy experiment that much more is learned about the drug and potential delivery systems than what is hoped for while setting the initial objectives. This following example supports such a concept.

The drug under consideration was a potent hypolipidemic agent in phase 1 studies. It had poor solubility ( $< 1 \mu\text{g/mL}$ ), and for this reason oral bioavailability was low, however, the absolute extent of oral absorption was unknown since a sensitive serum assay was unavailable. We were contacted to conduct an « input / output » study where nonabsorbable radioactive samarium-153 oxide was co-administered with the drug, and feces samples were collected for a one week period. Thus, the percent dose orally absorbed would be equal to the percent of samarium-153 oxide recovered in the feces minus the percent of drug dose in the feces. Blood and urine were also collected with the guarantee that a sensitive drug assay was forthcoming for these matrices.

A hygienic and convenient method was implemented to collect feces samples on an outpatient basis. The amount of radioactive  $^{153}\text{Sm}$  ( $t_{1/2} = 46.7 \text{ hr}$ ,  $\gamma = 103 \text{ keV}$ ) was determined in whole homogenized feces samples using a conventional gamma camera as a quantitative detector. These samples were eventually freeze dried and the drug content in the powdered feces was determined by extraction and HPLC / MS. The results from two of the six subjects are shown in Figure 8. As Figure 8 indicates, the transit of non-absorbable samarium oxide correlated very well with the non-absorbed drug dose, even to the point of inflection between the first and third samples of subject DUR-006 (lower graph in Figure 8). This confirmation that the radioactive marker and the non-absorbed dose moved through the gastrointestinal tract at similar rates was important to demonstrate since one of the criticisms which the technique of gamma scintigraphy often suffers is that the transit of the actual drug is not evaluated. To our knowledge, this was the first time that this has been unequivocally demonstrated.

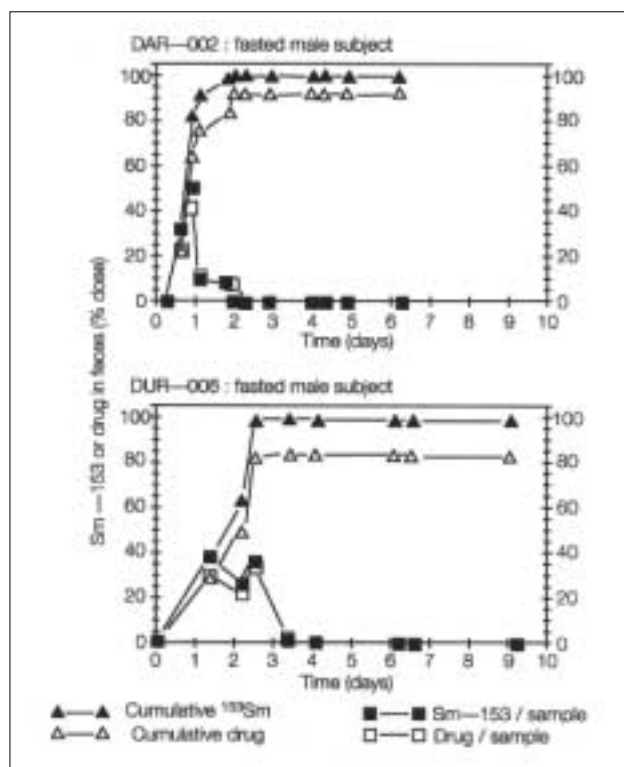


Figure 8.  $\text{Sm-153}$  oxide and hypolipidemic drug determination in feces: confirmation of similar rates of gastrointestinal transit.

To our good fortune, a sensitive plasma assay was validated by study's end which allowed us to examine for *in vivo / in vivo* correlations between gastrointestinal transit and systemic drug absorption. Shown are the individual plasma concentration curves in Figure 9. The plasma profiles demon-

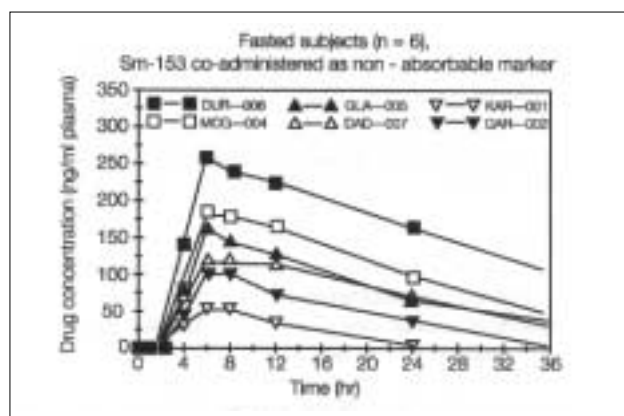


Figure 9. Intersubject variation on the absorption of a hypolipidemic drug (800 mg).

trated a remarkable consistency with the absorptive phase starting in *all subjects* at 4 hr and a  $T_{max}$  achieved at 6 hr. However, the extent of absorption appeared to be highly variable with an inter-subject AUC ranging from 554 to 7519  $\text{ng} \cdot \text{hr mL}^{-1}$  ( $3363 \pm 2470 \text{ ng} \cdot \text{hr mL}^{-1}$ ,  $\text{rsd}\% = 73\%$ ). This was nearly a 14-fold variation in drug plasma AUC.

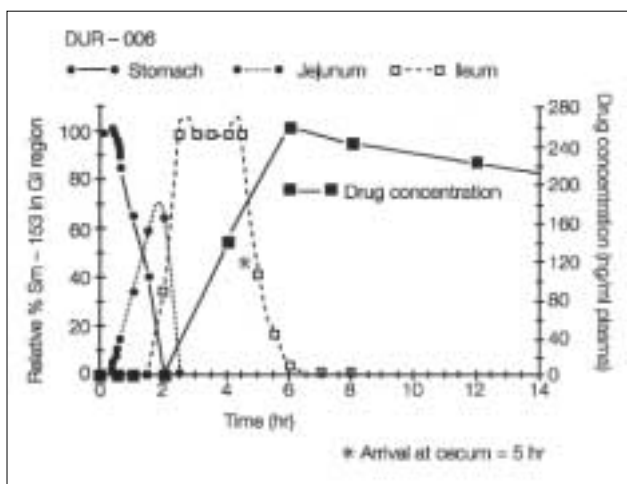


Figure 10. GI transit of  $^{153}\text{Sm}$  oxide and correlation with drug plasma levels. Evidence of delayed drug absorption in the distal small intestine.

The typical strategy we use to explain such absorption anomalies is to examine if correlations exist between gastrointestinal transit and drug absorption. This is most easily accomplished by overlaying the drug plasma profile over the gastrointestinal transit profile. An example of such a plot is shown in Figure 10, and may require a brief explanation. The left y-axis in Figure 10 indicates the relative percent of  $^{153}\text{Sm}$  in the stomach, jejunum or ileum, while the right y-axis is drug concentration. Since it was shown in Figure 8 that both the drug and radioactive marker transit through the GI tract at the same rate, it is possible to elucidate the region of drug absorption by correlating the position of the radioactive marker at the start of the drug absorption phase. Figure 10 indicates that for subject DUR-006, the absorption phase coincided with the arrival of the radioactive marker at the terminal jejunum, and maximum drug concentration was achieved as the radioactive marker moved across the ileal-cecal junction into the ascending colon. This in fact was consistent with the other five subjects, thus, the delay in absorption was apparently dependent upon the arrival of the drug at its region of

absorption in the ileum. There are of course other possibilities to explain this delay such as sequestration of the drug in the liver followed by gall bladder emptying with meal intake. This is a distinct possibility since a standard breakfast meal was provided at 2 hr post dose, however, to definitively evaluate this would require additional studies with variable dosing and meal timing.

Regarding the large inter-subject variability and the extent of absorption shown in the plasma concentration profiles of Figure 9, possible explanations are again sought by evaluating *individual* GI transit / drug concentration overlay plots like that shown above in Figure 10. It was apparent after completing this analysis for all six subjects that  $C_{max}$  was the greatest when subjects exhibited slow gastric emptying, i.e., subject DUR-006 shown in Figure 10 had the *slowest* gastric emptying and also had the greatest  $C_{max}$  while subject DAR-002 had the smallest  $C_{max}$  (Figure 9) and the fastest gastric emptying.

Once a qualitative trend like this is observed, a quantitative analysis can be completed by generating plots of gastrointestinal residence values versus pharmacokinetic values. Accordingly, a plot of the area under the gastric emptying curve (x-axis) versus the area under the plasma concentration curve (y-axis) was generated and is shown in Figure 11. This relationship predicted that drug absorption will be improved under the fed condition since gastric emptying is slower in the presence of food. Another phase I study was completed to and evaluate the effect of food given 30 min before dose. Food increased average AUC values 15-fold (verbal communication) and the inter-subject variability was

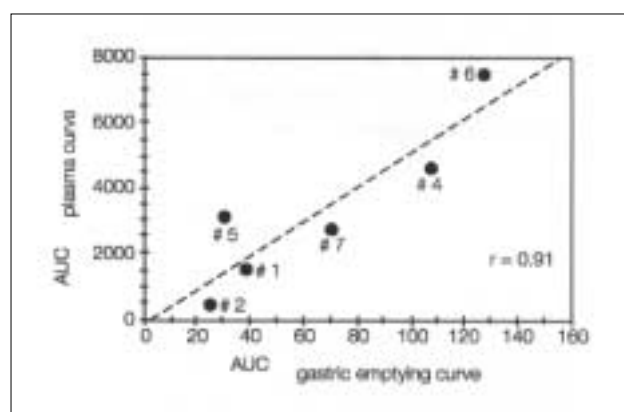


Figure 11. Influence of gastric emptying upon drug absorption. Slow gastric emptying improved absorption of hypolipidemic drug inter subject comparisons ( $n = 6$ , fasted study).

much less as compared to the fasted condition, thus, the prediction made from the data in Figure 11 proved correct. Furthermore, the follow-up fed study also showed a delay in the onset of drug absorption and a late  $T_{max}$  (verbal communication) which supported the hypothesis of regional absorption of this drug in the terminal ileum.

In summary, the added benefits of conducting a gastrointestinal transit study concomitant with initial phase 1 clinical studies are that it ultimately aids in the formulation development of the delivery system, and it also helps to interpret errant results which frequently are discarded as outliers or trivial observations. It is in fact these « outliers » which frequently contribute the greatest when we staid to sort through the data and make the *in vivo* / *in vivo* correlations. From the results discussed with this case study, it is apparent that the oral absorption of this drug will be the greatest if dosed after a meal. Formulation factors which may also improve its absorption would of course be a gastric retentive system, and it may also benefit from enhancer systems which target the terminal ileum and bile salt transport system, e.g., triglycerides, fatty acids as well as bile salts may prove to be useful absorption enhancers for this insoluble drug.

## 7. Case study 7: intestinal transit changes observed from an enteric formulation containing absorption enhancers and an acid-labile, low-permeability cephalosporin

We recently examined the use of enhancers to improve the bioavailability of the acid-labile, highly polar cephalosporin, ceftriaxone sodium (Rocephin®, Hoffmann-La Roche). Enteric coated formulations of ceftriaxone, without absorption enhancers, were previously shown to be ineffective in achieving any oral bioavailability of the drug. The formulation tested was a hard gelatin capsule (No. 1) containing a semisolid emulsion of medium chain fatty acids, triglycerides esters of polyethylene glycol, ceftriaxone sodium, and coated with the enteric polymer polyvinyl acetate phthalate (PVAP). Intact enteric coated capsules were radiolabeled via neutron activation techniques using 3 mg of samarium oxide per capsule and a 5 sec irradiation resulting in the production of 9  $\mu$ Ci of Sm-153 per capsule (8).

Six fasted normal males were administered 250 mg (one capsule) and 500 mg (2 capsules)

doses of ceftriaxone on separate occasions. Scintigraphic imaging revealed that arrival of radioactivity into the colon was faster with the 500 mg dose as compared to the 250 mg dose of ceftriaxone. Quantitative analysis of the data showed a SITT of  $250 \pm 200$  min for the 250 mg dose, and  $108 \pm 71$  min for the 500 mg dose of ceftriaxone. All subjects with the exception of #005 showed a dramatic decrease in small intestine transit with the 500 mg dose. These data are shown in Figure 12. Note that since each capsule was enteric coated, SITT in this study was defined as the time of arrival of radioactivity into the colon minus the time of capsule rupture.

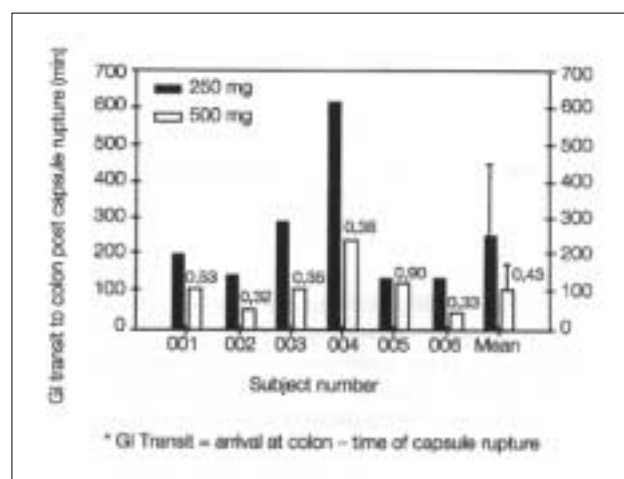


Figure 12. Gastrointestinal transit\* to colon after rupture of enteric capsule. Formulation: cephalosporin in semi-solid base of sodium caprylate, laureth-12 and miglyo 812, PVAP coated capsule.

On the basis of the results from the erythromycin study (Case Studies 2 and 3) and the sodium acid pyrophosphate / ranitidine work (Case Study 5), it was expected that the AUC of the 500 mg dose (shorter small bowel residence) would not be twice the value of the AUC of the 250 mg dose (longer small bowel residence) due to decreased residence time in the small intestine where it was expected that the drug was optimally absorbed.

Surprisingly the extent of ceftriaxone sodium from the 500 mg dose was considerably higher than that of the 250 mg dose as shown in the mean plasma concentration curve in figure 13.

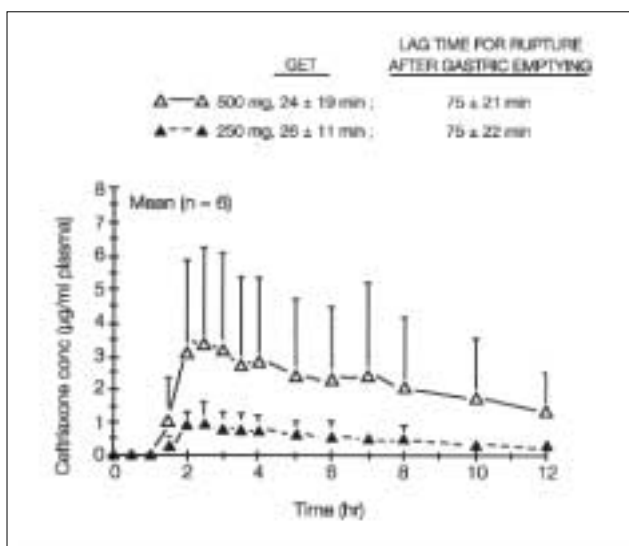


Figure 13. Mean ceftriaxone plasma concentration following oral administration to fasting subjects ( $n = 6$ ).

The AUCs resulting from the administration of a 500 mg dose of the cephalosporin in five of six subjects was greater than twice the value obtained with the 250 mg dose and the overall mean was 4.8 times greater from the 500 mg dose compared to the 250 mg dose. Again, the only subject which did not fit this observation was subject #005 where the AUC's from the two doses were equal. These results are indicated as a bar graph in Figure 14.

Intra-subject comparisons were made to determine if there was a quantitative relationship between the changes in intestinal transit and cephalosporin absorption. Figure 15 shows graphically this relationship between intra-subject changes in SITT ( $\text{GI Transit}_{500 \text{ mg dose}} / \text{GI Transit}_{250 \text{ mg dose}}$ ) and the intra-subject area under the drug concentration curve ( $\text{AUC}_{500 \text{ mg dose}} / \text{AUC}_{250 \text{ mg dose}}$ ). As indicated in Figure 15, these results show that individual subjects who had the greatest intra-subject decrease in small intestine transit (i.e. shorter residence time in the small intestine as indicated by a ratio less than 1.0) paradoxically showed the greatest intra-subject increase in drug AUC. This result is exactly the opposite of our initial prediction.

The compelling questions are why did intra-subject small bowel residence decrease and why did this paradoxically manifest with increased intra-subject drug absorption. At this time we can only surmise that these observations were caused by the

presence of the absorption enhancers and their related absorption mechanisms. One possibility is due to the presence of the fatty acid and glycerides being released in the distal small intestine from the enteric coated capsule.

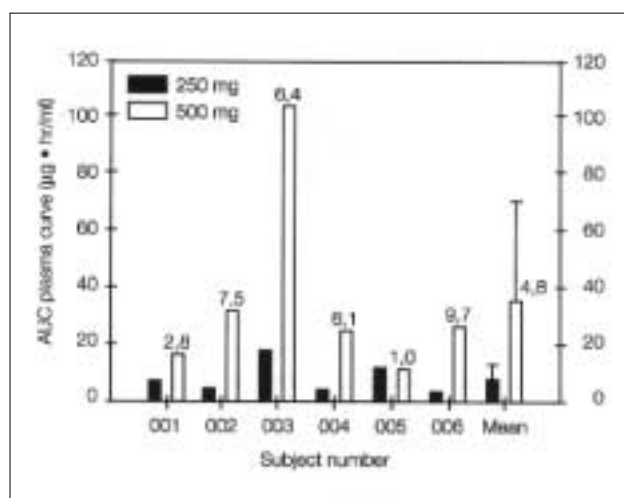


Figure 14. AUC's for two dose levels (250 mg vs 500 mg) of an acid-labile and poorly absorbed cephalosporin. Formulation: semi-solid base, PVAP coated enteric capsule.

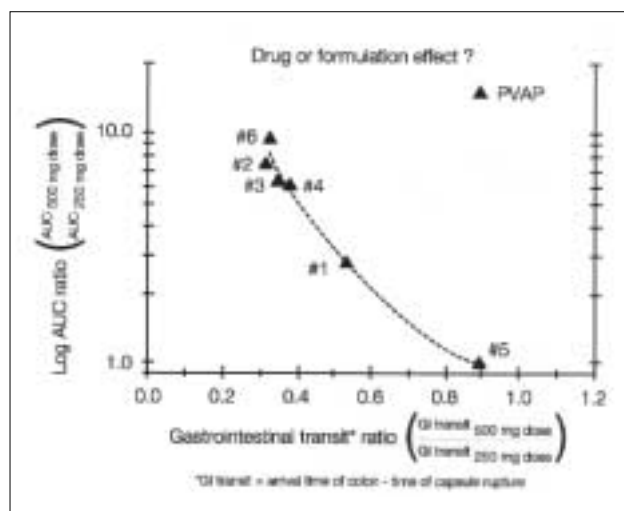



Figure 15. Effect of intestinal transit on absorption of an acid-labile and poorly absorbed cephalosporin. Formulation: semi-solid in enteric coated capsule.

It is known that fatty acids in the upper G1 tract inhibit gastric emptying by feedback mechanisms (9). Likewise, free fatty acids and partially digested

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fat in the ileum will also decrease jejunal motility and slow jejunal transit; this phenomenon is referred to as the "ileal brake" (13). However, it has been demonstrated that short chain fatty acids (SCFA's) in the canine ileum stimulate localized motility and propulse ileal contents into the colon (14). Colon contents are rich with SCFA's from bacteria metabolism of polysaccharides, and this provides a built-in mechanism to maintain homeostasis should contents in the colon backflush into the ileum. It is possible that a similar mechanism is responsible for faster SITT when large doses of the absorption enhancers are released in the ileum region, i.e. the presence of high local concentrations of the medium chain fatty acid, caprylic acid, may stimulate ileum transit and the radioactive label was therefore observed to quickly enter the colon upon capsule rupture.

This may be a viable explanation for the observed changes in intestinal transit, but increased absorption of this polar cephalosporin with decreased small bowel residence is more difficult to explain. It is known that short chain fatty acids are absorbed rapidly in the colon followed by a net flux of sodium, potassium and water (15). It is possible that a similar absorption mechanism in the colon is followed by this highly charged and water soluble cephalosporin. Though the results from this study are preliminary and the conclusions drawn at this time are circumstantial, it nonetheless warrants further investigation of similar *in vivo* studies which evaluate the effect of absorption enhancers on gastrointestinal transit and drug absorption.

## Summary

The preceding examples have demonstrated the important influence which small intestine transit, gastric emptying, site of drug absorption and site of drug release may have on systemic drug levels. Admittedly, the residence time of a drug or its delivery system at a region of absorption is only one part of the complex processes which occur during absorption, however, it is nonetheless an integral parameter to evaluate. These are but a few examples which we can provide from our own experiences where food or "food-like" excipients have effected drug absorption. There are certainly many more instances which are of interest to the drug formulator. It is hoped that the examples given in this communication will emphasize the existing need to systematically study variables which effect gastrointestinal transit and the influence these variables have on drug absorption.

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