Effect of altered gastric emptying and gastrointestinal motility on metformin absorption

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Aims The purpose of this *in vivo* human study was to assess the effect of altered gastric emptying and gastrointestinal motility on the absorption of metformin in healthy subjects.

Methods An open-label, three treatment, three period crossover study was conducted in 11 healthy volunteers. Each subject received 550 mg metformin hydrochloride in solution alone; 5 min after a 10 mg i.v. dose of metoclopramide; and 30 min after a 30 mg oral dose of propantheline. Metformin solution was radiolabeled by the addition of ^{99m}Tc-DTPA. The gastrointestinal transit of the solution was monitored by gamma scintigraphy and the pharmacokinetic data were correlated with the scintigraphic findings.

Results Scintigraphic data indicated that pretreatment with metoclopramide decreased gastric emptying time and increased gastrointestinal motility while pretreatment with propantheline had the opposite effect. The systemic disposition of metformin was not altered by pretreatment with metoclopramide and propantheline, as judged by unchanged renal clearance and elimination half-life of metformin. Extent of metformin absorption was essentially unchanged after pretreatment with metoclopramide. However, AUC(0,∞) and % UR (percent dose excreted unchanged in urine) generally increased with increase in gastric emptying time and small intestinal transit times. GI overlay plots showed that the absorption phase of metformin plasma profile always coincided with gastric emptying and the beginning of decline of metformin plasma concentrations was usually associated with the colon arrival. Only in cases where the intestinal transit was drastically prolonged by propantheline pretreatment, was a decline in plasma levels observed prior to colon arrival.

Conclusions Metformin is primarily absorbed from the small intestine. The extent of metformin absorption is improved when the gastrointestinal motility is slowed. These findings have significant implications in the design of a metformin modified release dosage form.

Keywords: absorption, gamma scintigraphy, gastrointestinal motility, metformin

Introduction

Metformin hydrochloride has been successfully used for many years in the treatment of type 2 diabetes. Absolute bioavailability of a 500 mg metformin dose is approximately 50% and the bioavailability decreases as the dose

increases [1]. The bioavailability of metformin decreases in presence of food with a 20% lower AUC and 35% lower C_{max} [2]. The absorption is also delayed, with t_{max} prolonged by nearly 40 min. After i.v. administration, metformin undergoes near complete excretion in urine and probably does not undergo metabolism in humans. After oral administration, about 50% of the drug is excreted in urine and the remainder in faeces. Metformin therapy is associated with gastrointestinal side-effects that include gastric discomfort, nausea and diarrhoea. Novel

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formulation strategies for metformin are being pursued which may lead to an improvement in bioavailability, a reduction in dosing frequency, and/or a decrease in gastrointestinal (GI) side-effects. This study was conducted to understand the basic biopharmaceutic properties of metformin by assessing the effects of altered gastric emptying and GI motility on metformin absorption.

Metoclopramide is a prokinetic agent that stimulates gastric emptying and GI transit. Its mode of action appears to involve antagonism of the inhibitory neurotransmitter dopamine, and increase in acetylcholine release [3]. Propantheline inhibits GI motility and diminishes gastric acid secretion [4]. It is used as an adjunctive therapy in the treatment of peptic ulcer. The rate and extent of absorption of many drugs are affected by changes in GI motility. Pretreatment with metoclopramide, which increases gastrointestinal motility and propantheline, which decreases the motility, have been used as models to assess the effect of altered gastric emptying and GI motility on drug absorption [5–7].

Gamma scintigraphy has been used extensively as a noninvasive technique for *in vivo* evaluation of oral dosage forms. It has been used to assess the GI performance of enteric-coated dosage forms [8], localization of drug-release sites [9], variation in gastrointestinal transit of pharmaceutical dosage forms [10] and also to understand the mechanism of food effect as it relates to gastrointestinal transit [11]. Such studies not only provide an insight into the fate of the oral dosage form but also allow the systemic exposure of drug in relation to the transit of the dosage form in the GI tract to be evaluated and drug release/absorption to be examined [12].

Prior information on the absorption properties of metformin suggests that metformin is slowly and incompletely absorbed from the GI tract and the absorption appears to be saturable [2]. Physiological factors, such as gastric emptying and small intestinal transit, can affect the absorption and pharmacokinetic profile of metformin. Changes in the gastric emptying and intestinal transit of a metformin dosage form may alter the absorption processes and therefore, bioavailability. As a consequence, studying metformin absorption under altered motility conditions should help understand absorption properties of metformin. Changes in GI motility in this study were accomplished by pretreatment with metoclopramide and propantheline whilst transit of the drug solution was monitored by gamma scintigraphy.

Methods

Study design

This study was conducted as an open-label, randomized, single dose, three treatment, crossover design. The

treatments administered were: 550 mg metformin solution alone (met alone); 550 mg metformin solution 5 min after a 10 mg i.v. dose of metoclopramide (met_[met]) and 550 mg metformin solution 30 min after a 30 mg oral dose of propantheline (met_[prop]). The dosing solution in all treatments contained 4 MBq ^{99m}Tc-DTPA in addition to metformin. Serial plasma and urine samples were collected up to 32 h post dose. Scintigraphic images were taken with a gamma camera throughout the 32 h period to follow the GI transit and its relationship to drug absorption.

Subjects

A total of 12 healthy male/female (nine males and three females) volunteers who met all eligibility requirements and successfully passed the exclusion criteria were admitted to the study after signing an informed consent. One subject was withdrawn because of a diagnosis of sinusitis between periods 1 and 2 which was judged to be unrelated to drugs used in this study. Eleven subjects completed the study (mean age of 29 years with a range of 21–40 years). The mean body weight of the subjects was 77.4 kg (range of 61–99 kg) and the mean height was 176 cm (range of 156–195 cm). The clinical protocol for the study was approved by the Quorn Research Review Committee, Leicestershire, UK.

Protocol

The subjects entered the test facility in the morning prior to drug administration and were confined to the test facility until the 12 h post dose blood sample and 8–12 h urine sample were collected. The subjects returned to the test facility for the collection of 24, 28 and 32 h blood samples, remaining urine samples and additional scintigraphic imaging. The subjects fasted overnight and were only allowed to drink water until the following morning on dosing days. Subjects continued to fast until 4 h after dosing. A standard lunch and dinner were provided at 4 and 10 h post dose, respectively. Subjects ate the same meals during each of the three study periods. There was at least a 7 day washout between consecutive treatments.

Metformin HCl was dissolved in 60 ml of water and radiolabeled via the addition of ^{99m}Tc-DTPA (4 MBq in approximately 0.2 ml). Subjects ingested the dosing solution and an additional 60 ml water which was used to rinse the vial. To accelerate GI transit, a 10 mg dose of metoclopramide was administered intravenously over 2 min, 5 min prior to the metformin dose. In order to delay upper intestinal transit, a 30 mg dose of propantheline was administered orally 30 min prior to the metformin dose with 120 ml water. For the control treatment (met alone) and metformin with metoclopra-

mide ($\text{met}_{[\text{met}]}$), subjects drank 120 ml of water 30 min prior to the metformin dose in order to keep the fluid intake constant for all treatments.

For scintigraphic imaging, anterior and posterior anatomical markers containing 0.1 MBq $^{99\text{m}}\text{Tc}$ were taped to the skin where the mid clavicular line meets the right costal region so that they lay in approximately the same transverse plane as the pylorus. After the radiolabeled metformin solution was administered, anterior and posterior scintigraphic images were recorded at frequent intervals for up to 12 h post dose with a gamma camera (General Electric Maxicamera) with a 40 cm field of view and fitted with a low energy parallel hole collimator. Images were recorded at approximately 10 min intervals up to 8 h post dose and then at approximately 30 min intervals until 12 h post dose. The following morning, further images were acquired between 24 and 32 h post dose. The subjects remained moderately active during the study period and all images were acquired with the subjects standing in front of the gamma camera.

Serial blood samples (7 ml) were collected using Becton-Dickinson 7 ml Vacutainers or equivalent, which contained K_3EDTA as the anticoagulant. The collection times were predose, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 24, 28 and 32 h after drug administration. Immediately after collection, each blood sample was gently inverted a few times for complete mixing with the anticoagulant and then placed in chipped ice. Within 1 h of collection, the blood was centrifuged to separate the plasma. The separated plasma was transferred to a screw capped polypropylene tube. Serial urine samples for determination of metformin were collected at predose and over 0–4 h, 4–8 h, 8–12 h, 12–24 h and 24–32 h post dose. Subjects were asked to void at the end of each collection interval and a 10 ml aliquot of the urine sample was saved for analysis. Plasma and urine samples were stored frozen at -20°C until analysis.

Sample assays

Plasma and urine samples were analysed for metformin by validated h.p.l.c. procedures. Plasma samples (0.5 ml) were loaded onto conditioned BondElut C8 columns (Varian Associates, Palo Alto, CA) after addition of phenformin as internal standard. The columns were washed with ether and allowed to air dry under vacuum. Metformin and the internal standard were then eluted with 0.5 ml 70% acetonitrile in 10 mM potassium phosphate, pH 3.5. The eluate was centrifuged and the supernatant was injected onto the h.p.l.c. column. Urine samples (100 μl) were extracted with 1.5 ml acetonitrile after addition of the internal standard. The samples were vortexed, centrifuged and the supernatant was evaporated to dryness. The dried extracts were reconstituted with 0.5 ml of 10 mM

potassium phosphate buffer, pH 7.0 and a 100 μl aliquot was injected onto the h.p.l.c. column. Separation was achieved at room temperature on a Spherisorb 5 SCX column (5 μm , 25 cm $\times$ 4.6 mm) using a mobile phase of 40% methanol in 100 mM potassium phosphate, pH 7.0 at a flow rate of 1.0 ml min^{-1} . The h.p.l.c. instrumentation consisted of a guard column (Spherisorb 5 SCX, 5 μm , 30 $\times$ 4.6 mm) and Shimadzu SPD6A/10 A detector at 236 nm. Data were acquired using Turbochrom laboratory automation system from Perkin Elmer. Peak heights were used in the calibration curves and in the calculation of unknown concentrations. The retention times of internal standard and metformin were approximately 7 min and 8.5 min, respectively. The standard curves were linear with correlation coefficients of ≥ 0.989 and 0.996 for plasma and urine, respectively. The standard curve range was 50–2500 ng ml^{-1} for plasma and 0.5–25 $\mu\text{g ml}^{-1}$ for urine. The lower limit of quantification (LLQ) was set at the lowest standard concentration. During analyses of study samples, the mean observed concentrations of the quality control (QC) samples were within 6.6% for plasma and 4.6% for urine. The overall between- and within-day variability of the QC samples was less than 11.4% RSD (relative standard deviation) for plasma and 13.5% for urine assay, respectively. The overall data confirm the accuracy and precision of the analytical runs and study sample stability.

Pharmacokinetic analysis

Each plasma concentration-time profile was analysed by noncompartmental methods [13]. C_{max} and t_{max} were determined as the highest observed concentration and the time to reach the maximum concentrations, respectively. The terminal log-linear phase of the plasma concentration-time curve was defined by the data points yielding the minimum mean square error in the regression analysis. The apparent elimination half-life ($t_{1/2}$) was calculated from the slope of the terminal log-linear phase. $\text{AUC}(0, t)$ (where t is the last time point at which quantifiable plasma concentration is observed) was calculated using a combination of the trapezoidal and log-trapezoidal rules. The linear trapezoidal rule was used in the portion prior to the log-linear phase and the log trapezoidal rule was used in the log-linear phase. $\text{AUC}(0, \infty)$ was calculated as the sum of $\text{AUC}(0, t)$ and the extrapolated area determined by dividing the observed concentration at the time of last $>\text{LLQ}$ concentration by the slope of the terminal log-linear phase. The percent of dose excreted unchanged in urine (%UR) was calculated as the cumulative amount of drug in urine over 32 h divided by the dose. Renal clearance (CL_{R}) was calculated as the ratio of the cumulative amount of metformin in urine to plasma $\text{AUC}(0, \infty)$.

Scintigraphic analysis

Regions of interest (ROIs) were drawn around the position of stomach, which was identified by reference to both the external marker and the preceding images. To assess the background counts, a second ROI was drawn on each image away from the main area of activity. At later time points, a third ROI was drawn to identify arrival of the activity in the colon. The data were corrected for background radioactivity and radioactive decay. The error in parameter estimates due to variations in depth of the segments scanned was minimized by calculation of the geometric mean of the corresponding anterior and posterior views.

The data were analysed to obtain the time to empty 50% and 90% radioactivity from the stomach ($GE_{50\%}$ and $GE_{90\%}$, respectively), time to empty 50% radioactivity from the small intestine ($SITT_{50\%}$) and time to arrive 50% radioactivity at the colon ($ATC_{50\%}$). Initial gastric emptying was very rapid for all three treatments. However, as more solution emptied from the stomach it became apparent that, while pretreatment with metoclopramide maintained a rapid gastric emptying profile, propantheline pretreatment resulted in prolonged gastric retention in many subjects.

Statistical analysis

To assess the effect of altered gastric emptying time and GI motility on the bioavailability and pharmacokinetics of metformin, an analysis of variance was performed for each pharmacokinetic parameter with sequence, subject within sequence, period, direct treatment effect and first order carryover effect of treatment as factors. Comparisons were made between met_[met] and met alone and between met_[prop] and met alone. Analysis of the variable t_{max} was

Figure 1 Mean plasma metformin concentration *vs* time profiles after metformin alone ($\blacklozenge$), metformin after metoclopramide ($\triangle$) and metformin after propantheline ($\circ$).

based on ranks. For the other variables, direct effect of treatment means were calculated by the method described by Little *et al.* [14], were presented as 'adjusted means' and treatment comparisons were based on differences between them. Confidence intervals were calculated for the adjusted means, the differences between adjusted means and the corresponding ratios of adjusted effect means. Values of C_{max} and $AUC(0,\infty)$ were *a priori* log transformed and the resulting estimates of means and mean differences were exponentiated to express the results as geometric means and ratios of geometric means on the original scales of measurement. For the other variables, confidence intervals for the ratios were obtained by Fieller's method as described by Locke [15].

All tests of statistical hypotheses were carried out at the 5% level of significance and all treatment comparisons were two-sided. Interval estimates for treatment differences and ratios were two-sided and were calculated using 95% confidence coefficients. No adjustments were made for multiple comparisons.

For the transit variables $GE_{90\%}$ and $SITT_{50\%}$, the Pearson's correlation coefficient was calculated *vs* both $AUC(0,\infty)$ and %UR for each subject. The individual correlation coefficients were summarized by means, s.d.s and 95% confidence intervals.

Figure 2 Correlation plot of $AUC(0,\infty)$ and %UR *vs* $GE_{90\%}$ (time to empty 90% of radioactivity from the stomach) in individual subjects.

Figure 3 Correlation plot of AUC(0,∞) and %UR with SITT_{50%} (time to empty 50% of radioactivity from the small intestine) in individual subjects.

Results

Safety and tolerance assessment

There were no serious adverse events reported. In all 32 adverse events were reported with six on met alone treatment, 10 on met_[met] treatment and 16 on met_[prop] treatment. The most commonly observed adverse events were dry mouth, dizziness, abdominal pain, nausea/vomiting and headache. The adverse event of dry mouth was associated with the administration of propantheline. Thus, contrary to the numerous side-effects expected with the prokinetic metoclopramide and anticholinergic propantheline, these pretreatments were very well tolerated in this study.

Pharmacokinetics of metformin and relationship to GI transit

Mean (s.d.) plasma pharmacokinetic parameters are summarized in Table 1. Mean plasma concentration-time profiles (Figure 1) indicated that plasma metformin concentrations peaked slightly earlier in the met_[met] treatment while those in the met_[prop] treatment peaked slightly later than the met alone treatment. However, the difference in $t_{\max}$ was not statistically significant. There

were no statistically significant differences in $C_{\max}$, $t_{1/2}$ and renal clearance of metformin between treatments. AUC(0,∞) and %UR were unaffected by pretreatment with metoclopramide. However, pretreatment with propantheline caused a 19% increase in AUC(0,∞) and 26% increase in %UR relative to met alone treatment (95% CI (0.979, 1.451) and (1.022, 1.570), respectively) (Table 1). The increase in %UR was statistically significant.

Mean (s.d.) GI transit parameters are summarized in Table 2. The initial gastric emptying was rapid for met alone and met_[met] treatments, the GE_{50%} value averaged 6 min with a range of 0–14 min for met alone treatment and 0–16 min for met_[met] treatment. However, pretreatment with propantheline slowed gastric emptying and extended the mean GE_{50%} to 41 min (range of 3–255 min). The time for 90% of radioactivity emptying from the stomach displayed clear differences between treatments. The mean GE_{90%} values were 26 min, 41 min and 187 min, respectively, for the met_[met], met alone and met_[prop] treatments. Pretreatment with metoclopramide also increased the rate of small intestinal transit. Conversely, propantheline pretreatment extended the small intestinal transit time. The mean SITT_{50%} values were 145 min, 216 min and 355 min, respectively, for the met_[met], met alone and met_[prop] treatments.

The extent of metformin absorption represented by AUC(0,∞) and %UR was correlated with gastric emptying as well as small intestinal transit times. AUC(0,∞) generally increased with GE_{90%} (mean correlation = 0.75, 95% C.I. = (0.58, 0.93)) and SITT_{50%} (mean correlation = 0.66, 95% C.I. = (0.36, 0.97)). Also, %UR generally increased with GE_{90%} (mean correlation = 0.72, 95% C.I. = (0.42, 1.00)) and SITT_{50%} (mean correlation = 0.63, 95% C.I. = (0.22, 1.00)). These correlations are shown graphically in Figures 2 and 3.

Discussion

As documented in the literature, pretreatment with metoclopramide produced an accelerated gastric emptying and reduced small intestinal transit of the metformin solution. Pretreatment with propantheline slowed both gastric emptying and small intestinal transit. The systemic kinetics of metformin were not changed by pretreatment with either metoclopramide or propantheline as judged by unaltered plasma elimination half-life and renal clearance. Therefore, changes in bioavailability and pharmacokinetics of metformin could be regarded as a consequence of altered absorption. Metoclopramide pretreatment showed a slightly reduced $t_{\max}$ for metformin while propantheline pretreatment slightly increased $t_{\max}$, consistent with the alterations in the GI motility. Propantheline pretreatment caused an increase in the metformin absorption pre-

Table 1 Mean (s.d.) Plasma and urine pharmacokinetic parameters of metformin when administered alone (met alone) and after pretreatment with metoclopramide (met_[met]) and propantheline (met_[prop]).

Parameter	Met alone	Treatment		Comparison ^b	Statistics ^c Ratio of means	95% Confidence interval
		Met _[met]	Met _[prop]			
C _{max} (ng ml ⁻¹)	1639 (484)	1642 (522)	1634 (498)	TC2 vs TC1 TC3 vs TC1	0.972 0.972	(0.797, 1.184) (0.802, 1.177)
t _{max} ^a (h)	3.0 (2.0, 5.0)	2.5 (0.75, 3.5)	3.5 (1.0, 6.0)			
AUC(0,∞) (ng ml ⁻¹ h)	9938 (2727)	9674 (3376)	12259 (3583)	TC2 vs TC1 TC3 vs TC1	0.917 1.192	(0.749, 1.123) (0.979, 1.451)
t _{1/2} (h)	2.56 (0.52)	2.93 (1.10)	3.14 (0.84)	TC2 vs TC1 TC3 vs TC1	1.168 1.185	(0.958, 1.432) (0.979, 1.444)
CL _R (ml min ⁻¹)	387 (112)	394 (180)	403 (114)	TC2 vs TC1 TC3 vs TC1	1.040 1.047	(0.892, 1.213) (0.903, 1.216)
%UR	49.9 (9.13)	47.9 (16.1)	64.2 (8.48)	TC2 vs TC1 TC3 vs TC1	0.949 1.260	(0.737, 1.218) (1.022, 1.570)

a: median (range) b: TC1: met alone; TC2: met_[met]; TC3: met_[prop] c: Point estimates and 95% confidence intervals are based on adjusted means derived from ANOVA.

sumably as a combined effect of slower delivery of drug into the upper small bowel and prolonged residence time in the small intestine.

Overlay plots of plasma metformin concentrations and GI transit profiles of radioactivity were generated to assist in the evaluation of metformin pharmacokinetics in relation to GI transit. Figure 4 illustrates such a plot for subject 5 in the study. In general, the absorptive portion of the plasma metformin profile was reflective of gastric emptying of the solution. Rapid gastric emptying was usually associated with a rapid rise in plasma concentrations, while slow gastric emptying corresponded to a slow increase in metformin plasma concentrations. This suggests that metformin is not appreciably absorbed from the stomach. On the other hand, as the solution arrived at the colon, the metformin plasma concentrations began to decline suggesting there is no significant drug absorption from the large bowel. This is consistent with the earlier work by Tucker *et al.* [1] who showed by deconvolution analysis that the available oral dose was absorbed over about 6 h post dose.

Table 2 Mean (s.d.) GI transit parameters after metformin alone and after pretreatment with metoclopramide and propantheline (*n* = 11).

Parameter	Met alone	Met _[met]	Met _[prop]
GE _{50%}	6 (5)	6 (5)	41 (75)
GE _{90%}	41 (33)	26 (20)	187 (138)
SITT _{50%}	216 (50)	145 (49)	355 (103)
ATC _{50%}	222 (50)	151 (52)	396 (116)

GE_{50%} and GE_{90%} time (min) to empty 50% and 90%, respectively, of radioactivity from the stomach, SITT_{50%} time (min) to empty 50% of radioactivity from the small intestine, ATC_{50%} time (min) for 50% of radioactivity to arrive at the colon.

Since metformin is not appreciably absorbed from the stomach, the proportion of the administered radiolabeled marker emptying from the stomach accurately represents the proportion of the administered metformin dose emptying from the stomach. This results in good correlation of the gastric emptying curve with the metformin plasma concentrations in the absorption phase (Figure 4). The association between colon arrival of the solution and plasma metformin concentrations was more complex. When gastric emptying and GI transit were rapid, as was usually the case in the met alone and met_[met] treatments, the start of decline in plasma drug concentrations was usually associated with the arrival of the solution at the colon, indicating the absorption had either stopped or markedly decreased. However, when upper GI motility was slowed, as was usually the case in the metformin with propantheline treatment, often the decline in metformin concentrations did not coincide with the entry of the solution into the colon. In fact, the metformin concentrations began to decline prior to colon arrival by up to 5 h in a number of subjects. An example of this pattern is shown in Figure 5 (bottom panel).

During transit through the small bowel following met alone or metformin_[met] treatments, the rate of drug absorption was rapid enough to maintain a rise in plasma concentrations until colon arrival. When GI motility was reduced substantially with propantheline pretreatment, colon arrival was delayed for up to 8 h and metformin plasma concentrations began to decline prior to this time. It was noted from the urine data that the amount of metformin not absorbed was significant (30–40%). Clearly, this portion of the dose remaining in the GI tract should have been sufficient to maintain the rate of absorption until the solution reached the colon. One possible explanation is that a significant amount of unabsorbed

Figure 4 GI overlay plots of subject 5 for all treatments a: metformin alone; b: metformin with metoclopramide; c: metformin with propantheline. (+) stomach, (Δ) colon, ($\circ$) plasma.

metformin was in the distal intestinal region where the permeability of metformin is relatively poor.

If the drug has an 'absorption window' in the upper GI tract as well as saturable component associated with absorption process, then delayed gastric emptying, giving rise to a slower rate of metformin input from the stomach, should facilitate drug absorption. Similarly, slower small intestinal transit should prolong the residence time of metformin in the 'absorption window' and also enhance absorption. Correlation of GI motility ($GE_{90\%}$ and $SITT_{50\%}$) with the extent of metformin absorption was examined to test these hypotheses. Since slower gastric emptying was usually associated with slower small intestinal transit, either or both of these two mechanisms may contribute to the increase in the extent of absorption. The study results showed that the relationship between

Figure 5 GI overlay plots of subject 10 for all treatments a: metformin alone; b: metformin with metoclopramide; c: metformin with propantheline. (+) stomach, (Δ) colon, ($\circ$) plasma.

both $GE_{90\%}$ and $SITT_{50\%}$ with extent of metformin absorption ($AUC(0, \infty)$ and $\%UR$) was strong (correlation coefficient of approximately 0.7), suggesting that reduced GI motility does facilitate improved metformin absorption.

Metformin is currently administered as either twice or three times a day regimen for the treatment of type 2 diabetes. A modified release dosage form may allow a reduced dosing frequency leading to greater convenience and better patient compliance. The results from this study clearly indicate that a conventional strategy such as prolonging the release of metformin from the dosage form throughout the GI tract will not work for metformin since it is primarily absorbed from the small intestine. Finally for drugs with a suspected window of absorption in

the upper small bowel, e.g. carrier mediated, saturable kinetics, the alteration of intestinal transit can be a useful approach to probe the absorption process.

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