Evaluation of a Three Compartment *In Vitro* Gastrointestinal Simulator Dissolution Apparatus to Predict *In Vivo* Dissolution

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**ABSTRACT:** *In vitro* dissolution tests are performed for new formulations to evaluate *in vivo* performance, which is affected by the change of gastrointestinal (GI) physiology, in the GI tract. Thus, those environmental changes should be introduced to an *in vitro* dissolution test. Many studies have successfully shown the improvement of *in vitro–in vivo* correlations (IVIVC) by introducing those physiological changes into dissolution tests. The gastrointestinal simulator (GIS), a multicompartment *in vitro* dissolution apparatus, was developed to evaluate *in vivo* drug dissolution. A gastric-emptying rate along with transit rate are key factors to evaluate *in vivo* drug dissolution and, hence, drug absorption. Dissolution tests with the GIS were performed with Biopharmaceutical Classification System class I drugs at five different gastric-emptying rates in the fasted state. Computational models were used to determine *in vivo* gastric-emptying time for propranolol and metoprolol based on the GIS dissolution results. Those were compared with published clinical data to determine the gastric half-emptying time. In conclusion, the GIS is a practical tool to assess dissolution properties and can improve IVIVC. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association

**Keywords:** dissolution; ASD; GIS; gastric emptying; GastroPlus; *in vitro–in vivo* correlations (IVIVC); Gastrointestinal transit; In vitro models; Transit time; Dissolution rate

**INTRODUCTION**

Oral dosage forms disintegrate and dissolve in the gastrointestinal (GI) tract and are absorbed into the intestinal membrane. The drug concentration at the membrane determines the local absorption rate. The disintegration and dissolution rates of oral dosage forms depend on the physicochemical properties of the compound such as pKa, crystalline energy, solubility, surface area, formulation, as well as the physiological properties in the GI tract. The Biopharmaceutical Classification System (BCS) class I and III drugs are highly soluble in the GI tract and their dissolution rates not likely to be a rate-limiting step in drug absorption.1 However, BCS class II drugs are categorized as low solubility and high permeability and the dissolution rate of BCS class II drugs will likely determine the drug absorption rate. Therefore, for the formulation development, it would be valuable for BCS Class II drugs to be able to predict *in vivo* performance.

USP dissolution tests apparatus 1 (rotating basket) and 2 (paddle) are routinely used for screening and optimizing formulations and to assure product consistency and quality. Often, however, the test conditions do not reflect the *in vivo* environment of the GI tract. The physiological environment such as buffer species, buffer capacity, pH, bile salt, liquid volume, and gastric-emptying rate (motility) are expected to influence *in vivo* dissolution that affects the drug absorption.2–5 The incorporation of physiologically relevant environmental factors into an *in vitro* dissolution apparatus would likely lead to more accurate *in vitro* dissolution predictions. Numerous *in vitro* dissolution procedures have been proposed, such as using biorelevant media, a two-phase dissolution apparatus, a transfer model, and also the artificial stomach–duodenum (ASD) apparatus. Biorelevant media (FaSSGF, FaSSIF, FeSSIF, and bicarbonate buffers) have been introduced to improve IVIVC as these media more closely reflect the *in vivo* lumenal fluid.6–8 As it consists of both the drug dissolution component (aqueous phase) and the absorption component (organic phase), the two-phase dissolution apparatus can provide valuable insight to predict *in vivo* performance.9 The transfer model and the ASD can represent the environmental changes through the GI tract, such as liquid volume and pH, which can influence the amount of dissolved drug.

Kostewicz et al.10 utilized the transfer model for poorly soluble weak base drugs to predict *in vivo* precipitation rate with changing transit rate from the stomach to the duodenum. The precipitation rates in *in vitro* tests were evaluated in the fasted and the fed states. On the basis of these results, the transfer model better represented *in vivo* performance for the drugs studied. Carino and coworkers11,12 developed the ASD apparatus that is the two-compartment dissolution system consisting of chambers representing the stomach and duodenum. ASD dissolution tests of carbamazepine were performed to understand *in vivo* dissolution of different crystal forms of carbamazepine in the fasted and the fed states. The ASD accurately predicted drug absorption in dogs for the different crystal forms. The ASD system has successfully demonstrated *in vivo* phenomena and, therefore, supports the usefulness of the two-compartment dissolution system to improve IVIVC.

Because the residence time in the human jejunum and ileum is much longer than the transit time of the human duodenum (~30 min), most drugs will be absorbed along the small intestine. Thus, drug concentration in the jejunal chamber, rather than simply in the duodenal chamber alone, was considered important for *in vitro* dissolution to predict drug absorption.10,14
Weak basic drugs, for example, will be more readily dissolved in the acidic condition and then may precipitate or remain as a supersaturated solution upon entering the duodenum because of the higher luminal pH.\textsuperscript{15,16} Supersaturation will likely enhance the bioavailability of lipophilic weak basic drugs.\textsuperscript{17,18} The supersaturation and precipitation rate will be affected by the transit rate, because of the changes of drug concentration, buffer capacity, and pH that occur in association with the transit rate. Hence, the determination of transit rate from the gastric chamber to the duodenal chamber is an important factor in the multicompartment dissolution apparatus for the evaluation of \textit{in vivo} dissolution.

In this study, we developed an apparatus called gastrointestinal simulator (GIS), based on the ASD system of Carino and coworkers,\textsuperscript{11,12} which consists of the gastric, duodenal, and jejunal chamber, and we determined the gastric-emptying time and transit time required to simulate \textit{in vivo} performance of propranolol and metoprolol. The dissolution tests of propranolol and metoprolol were performed with the GIS at five different transfer rates representing the gastric-emptying rate. The predicted pharmacokinetics parameters were obtained by GastroPlus\textsuperscript{TM} based on dissolution results. Those results were compared with the clinical data to determine the appropriate transfer rate needed to best simulate the gastric half-emptying time in the GIS. This system may be able to perform better IVIVC by monitoring the dissolution rate, the dissolved drug concentration, and the potential measurement of drug precipitation and supersaturation in these chambers.

**MATERIALS AND METHODS**

**Materials**

Metoprolol tablets (100 mg) and propranolol tablets (40 mg) were obtained from Ingenus Pharmaceuticals (Orlando, Florida) and PLIVA (Sarajevo, Bosnia and Herzegovina), respectively. Metoprolol tartrate, propranolol hydrochloride, hydrochloric acid, sodium phosphate dibasic, and sodium chloride were obtained from Sigma–Aldrich Chemical Company (St. Louis, Missouri). Orthophosphoric acid 85\%, trifluoroacetic acid, methanol, and acetonitrile were obtained from Fisher Scientific Inc. (Pittsburgh, Pennsylvania). All chemicals were of analytical grade or of HPLC grade.

**Gastrointestinal Simulator**

The diagram of the GIS is shown in Figure 1a and consists of three dissolution chambers representing the stomach, the duodenum, and the jejunum. Four precision pumps are utilized to simulate gastric fluid secretion, duodenal fluid secretion, transfer of gastric chamber contents to the duodenal chamber, and also to transfer duodenal contents to the jejunal chamber. All pump speeds can be adjusted. The gastric and duodenal fluids were maintained at 37°C in the water bath, and pH probes were placed in the gastric and duodenal chambers to monitor pH at 60 s intervals. The paddles in the gastric and duodenal chambers were appropriately controlled to simulate relevant gastric and duodenal motility. The jejunal chamber was stirred at a

![Figure 1](https://example.com/figure1.png)

**Figure 1.** The diagram of GIS (a). The GIS dissolution model (b).
constant speed. Samples were taken from each chamber at a specific time, and supernatant was diluted with H2O–methanol (1/1, v/v) after centrifugation (2000g, 20 s). Dissolved drug concentration was determined by HPLC analysis.

GIS Condition, Process, and Theory

The GIS system was designed to represent the physiological conditions of the human GI tract in the fasted state. The test conditions were as follows. The gastric chamber was filled with 50 mL of 0.01 N HCl to represent the gastric fluid and 250 mL of water to represent the dose volume. The duodenal chamber was filled with 50 mL of 0.05 M sodium phosphate buffer (pH 6.5) to represent duodenal fluid, and the jejunal chamber was left empty. During dissolution testing, simulated gastric fluid (0.01 N HCl) and simulated duodenal fluid (0.1 M sodium phosphate buffer, pH 6.5) were pumped into each chamber at 1 mL/min. The tablet was placed into the gastric chamber to start the dissolution test. The gastric contents, both dissolved and undissolved material, were moved to the duodenal chamber at the first-order rate that could be set to any value as the gastric half-emptying time. Additionally, the duodenal contents were moved to the jejunal chamber with the same rate as the gastric half-emptying rate and the duodenal fluid secretion rate. The fluid volume in the duodenal chamber thus was maintained at 50 mL during dissolution testing.

Figure 1b shows the various dynamic processes in the GIS chambers. The test tablet is introduced into the gastric chamber where disintegration can occur. Immediate-release dosage forms are expected to disintegrate and potentially dissolve to some extent in the gastric chamber. However, dissolved drug may be precipitated in the gastric chamber depending on the physicochemical properties of the drug. The dissolved drugs, solid drug particles, and excipients present in the gastric chamber are transferred to the duodenal chamber. The mathematical models representing these processes are shown in Eqs. (1) and (2) as follows:

\[
\frac{dM_{sd,s}}{dt} = -k_{sd,s-d}M_{sd,s} - k_{rd,s-d}M_{rd,s} + k_{ps,s}M_{ps,s} \tag{1}
\]

\[
\frac{dM_{rd,d}}{dt} = k_{sd,d-s}M_{sd,d} - k_{rd,d-j}M_{rd,d} + k_{ps,d}M_{ps,d} \tag{2}
\]

where \(M_{sd,s}\) and \(M_{rd,d}\) are the amounts of solid drug (sd) and dissolved drug in solution (sl) in the gastric chamber, \(k_{sd,s-d}\) and \(k_{ps,s}\) are the dissolution rate constant and the precipitation rate constant in the gastric chamber, respectively. The transfer rate constants for solid drug and solution drug from the duodenal chamber to the gastric chamber are \(k_{rd,s-d}\) and \(k_{rd,s-d}\). The expressions for dissolution and precipitation rates are approximate mathematical expressions, included here for more symbolic purposes. They assume constant, first-order processes that are not affected by factors such as drug saturation solubility or variable pH in the bulk fluid and at the surface of the drug particles. These approximations are likely suitable for this particular study, because of the high solubility of propranolol and metoprolol. The development of mechanistic models for dissolution and precipitation rates in the GIS system was not within the scope of the current study.

In the duodenal chamber, weak acid drugs might be dissolved, whereas dissolved weak basic drugs might be precipitated. In the jejunal chamber, dissolution and precipitation proceed depending on the physicochemical properties of drugs. The amount of solid drug and dissolved drug in the duodenum and jejunum chamber is shown in Eqs. (3)–(6) as follows:

(Duodenal chamber)

\[
\frac{dM_{sd,d}}{dt} = k_{sd,d-s}M_{sd,d} - k_{rd,d-j}M_{rd,d} + k_{ps,d}M_{ps,d} \tag{3}
\]

(Jejunal chamber)

\[
\frac{dM_{sd,j}}{dt} = k_{rd,d-j}M_{rd,j} + k_{ps,j}M_{ps,d} \tag{4}
\]

\[
\frac{dM_{rd,j}}{dt} = k_{rd,d-j}M_{rd,j} + k_{ps,j}M_{ps,j} \tag{5}
\]

where \(M_{sd,d}\), \(M_{rd,d}\), \(M_{sd,j}\), and \(M_{rd,j}\) are the amounts of solid drug and dissolved drug in the duodenum and jejunal chambers, respectively. \(k_{sd,d}\), \(k_{ps,d}\), \(k_{ps,j}\), and \(k_{ps,j}\) are the dissolution rate constants and the precipitation rate constants in the duodenal and jejunal chambers, respectively. The transfer rate constants for solid drug and dissolved drug from the duodenal chamber to the jejunal chamber are \(k_{rd,d-j}\) and \(k_{rd,d-j}\).

In this study, the GIS was used with five different gastric half-emptying times (\(t_{1/2} = 5, 10, 15, 20,\) and 30 min). Oral drug absorption and pharmacokinetics parameters were predicted by GastroPlusTM (version 6.0; Simulation-Plus, Inc., Lancaster, California). The pharmacokinetics parameters (Cmax, Tmax, and AUC) between clinical data and in silico results were then compared to determine the gastric half-emptying time in the GIS that best simulated in vivo results.

GastroPlusTM Simulation

The physicochemical and biopharmaceutical properties of propranolol and metoprolol used in the GastroPlusTM prediction are presented in Table 1.19–26 The dissolution profiles with the GIS were created by adding together the dissolved drug in both the duodenal and jejunal chambers. The absorption was predicted by GastroPlusTM with those dissolution profiles for propranolol and metoprolol. No drug absorption from the stomach was assumed in this set of predictions, and the dosage form drug release was simulated as a controlled-release tablet in the GastroPlusTM based on the dissolution profiles of propranolol and metoprolol obtained with the GIS (Figs. 2e and 4e). Virtual trials were performed (\(n = 100\)) on each gastric half-emptying time to obtain plasma concentration curves and pharmacokinetics parameters.

RESULTS

Propranolol

Figures 2a and 2b present the mean dissolved drug concentration–time profiles in each chamber with the fastest
and slowest gastric half-emptying times, 5 or 30 min, in this set of experiments. Two 40 mg propranolol tablets (maximum dose, 80 mg) were placed into the gastric chamber to start the GIS dissolution study. Maximum dissolved drug concentration ($c_{\text{max}}$) in each chamber was influenced by the gastric half-emptying time and transit time; $c_{\text{max}}$ ratios between 5 and 30 min gastric half-emptying time ($c_{\text{max}}$ 5 min/$c_{\text{max}}$ 30 min) were increased by 15.5% (the gastric chamber), 30.2% (the duodenal chamber), and 13.4% (the jejunal chamber).

Figures 2c and 2d present the mean dissolved drug (%)–time profiles in each chamber with the fastest and slowest gastric half-emptying times, 5 or 30 min, in this set of experiments. Comparing the results of the GIS dissolution tests between 5 and 30 min gastric half-emptying time, the time of maximum dissolved drug ($t_{\text{max}}$) was delayed from 2.5 to 5 min in the gastric chamber, and from 12.5 to 25 min in the duodenal chamber. After achieving $t_{\text{max}}$ in respective chambers, the amounts of dissolved drug were steadily decreased as the contents were transferred to the next chamber. In contrast, the amounts of the dissolved drug in the jejunal chamber were steadily increased because of transfer from the duodenal chamber.

With five different gastric half-emptying times, the sum of the dissolved drug in the duodenal and jejunal chambers was calculated as shown in Figure 2e. The gastric half-emptying time influenced the drug amount in the duodenal and jejunal chambers. However, the gastric half-emptying time did not influence the dissolution rate of propranolol tablets, which were completely dissolved within 7.5 min (Fig. 2f).

Figure 3 shows that the predicted oral absorption of propranolol by GastroPlus™ using the dissolution profiles from the GIS along with human clinical data. Shifts in the plasma
Table 2. Mean Pharmacokinetics Parameters for Propranolol and Metoprolol Simulated by GastroPlus™

<table>
<thead>
<tr>
<th>Gastric Half-Emptying Time ($t_{1/2}$, min)</th>
<th>Propranolol</th>
<th></th>
<th>Metoprolol</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$C_{max}$ (ng/mL)</td>
<td>$T_{max}$ (h)</td>
<td>AUC$_\infty$ (ng h/mL)</td>
<td>$C_{max}$ (ng/mL)</td>
</tr>
<tr>
<td>5</td>
<td>110.8</td>
<td>2.0</td>
<td>858.6</td>
<td>89.6</td>
</tr>
<tr>
<td>10</td>
<td>98.6</td>
<td>2.5</td>
<td>827.3</td>
<td>79.5</td>
</tr>
<tr>
<td>15</td>
<td>91.4</td>
<td>3.0</td>
<td>824.4</td>
<td>69.1</td>
</tr>
<tr>
<td>20</td>
<td>81.0</td>
<td>3.5</td>
<td>803.0</td>
<td>60.7</td>
</tr>
<tr>
<td>30</td>
<td>70.9</td>
<td>4.1</td>
<td>779.1</td>
<td>50.0</td>
</tr>
<tr>
<td>Clinical data</td>
<td>109.5$^a$</td>
<td>2.1$^a$</td>
<td>821.6$^a$</td>
<td>88.4$^b$</td>
</tr>
</tbody>
</table>

$^a$Ref. 27.  
$^b$Ref. 28.

Virtual trials ($n = 100$).

centre{concentration–time curves were observed because of slow gastric half-emptying time. The plasma concentration–time profile with 5 min gastric half-emptying time displayed a plasma concentration curve very similar to clinical data. These results indicate that the gastric half-emptying time in the GIS should be between 5 and 10 min (Table 2).

Metoprolol

Figures 4a and 4b present the mean dissolved drug concentration-time profiles in each chamber with the fastest and slowest gastric half-emptying times, 5 or 30 min, in this set of experiments. One 100 mg metoprolol tablet (maximum dose, 100 mg) was placed into the gastric chamber to start the GIS dissolution study. The $C_{max}$ in each chamber was influenced by the gastric half-emptying time and transit time; $C_{max}$ ratios between 5 and 30 min gastric half-emptying time ($C_{max} \text{ 5 min}/C_{max} \text{ 30 min}$) were increased by 148% and 92.3% in the gastric and duodenal chambers, but were decreased by 6.3% in the jejunal chamber.

Figures 4c and 4d present the mean dissolved drug (%)–time profiles in each chamber with the fastest and slowest gastric half-emptying times, 5 or 30 min, in this set of experiments. Comparing the results of the GIS dissolution tests between 5 and 30 min gastric half-emptying time, $t_{max}$ was delayed from 12.5 to 15 min in the gastric chamber, and from 25 to 30 min in the duodenal chamber. After achieving $t_{max}$ in both chambers, the amounts of dissolved drug were steadily decreased as the contents were transferred to the next chamber. In contrast, the amount of the dissolved drug in the jejunal chamber steadily increased because of transfer from the duodenal chamber.

With five different gastric half-emptying times, the sum of the dissolved drug in the duodenal and jejunal chambers was calculated as shown in Figure 4e. The gastric half-emptying time influenced the drug amount in the duodenal and jejunal chambers. However, the gastric half-emptying time did not influence the dissolution rate of metoprolol tablets, which were completely dissolved within 20 min (Fig. 4f).

Figure 5 shows that the predicted oral absorption of metoprolol by GastroPlus™ using the dissolution profiles from the GIS along with human clinical data. Shifts of plasma concentration–time curves were observed because of slow gastric half-emptying time. Plasma concentration–time profile

Figure 4. The dissolved drug concentration–time profiles of metoprolol in the gastric, duodenal, and jejunal chambers with the fastest and slowest gastric half-emptying time: 5 (a) and 30 min (b). Dissolved drug–time profiles of metoprolol in the gastric, duodenal, and jejunal chambers with 5 (c) and 30 min (D). The sum of dissolved drug–time profiles of metoprolol in the duodenal and jejunal chambers (e). The sum of dissolved drug–time profiles of metoprolol in the gastric, duodenal, and jejunal chambers (f). Each data point represents mean ± SD ($n = 3$).
concentration curves to clinical data. These results are consistent with those observed for propranolol (Table 2).

**DISCUSSION**

The gastric-emptying time and the transit time in the GI tract are important factors to predict in vivo dissolution because the gastric-emptying time can affect fluid volume in stomach and the transit time can affect drug dissolution and drug absorption in the small intestine. However, most in vitro dissolution apparatuses do not consider gastric-emptying time and intestinal transit or residence time. The incorporation of these factors into an in vitro dissolution apparatus can lead to better predictions of in vivo dissolution. Therefore, it is necessary to develop a dissolution apparatus, the GIS, to simulate gastric emptying to predict better in vivo dissolution. In the human fasted state, it has been reported that liquids gastric half-emptying time was 4.2, 12, and 15.8 min. In this set of dissolution studies, five different gastric emptying half-times (5, 10, 15, 20, and 30 min) were tested with the GIS, and pharmacokinetics parameters were obtained by GastroPlus\textsuperscript{TM} based on the dissolution results with the GIS. Those pharmacokinetics parameters were compared with human clinical data.

As propranolol and metoprolol are highly soluble over the physiological pH range and also highly permeable in the entire small intestine, it is likely that gastric-emptying rate itself is the rate-limiting step to appearance of drug in the bloodstream. As shown in Figures 2f (propranolol) and 4f (metoprolol), total dissolution rate in the entire GIS system was not influenced by gastric emptying or transit rate because both drugs are of high solubility. However, the appearance of dissolved drug in the duodenal and jejunal chambers was delayed for both drugs with an increase in gastric-emptying half-time, which can be attributed simply to the slower gastric emptying.

Although direct comparison of experimental and predicted results requires direct measurement of drug concentrations in solution in the intestinal fluid, a qualitative comparison can be made based on average plasma levels in the literature. The comparison of pharmacokinetics parameters and plasma concentration curves between human clinical data and in silico data can suggest the suitable transit time for the GIS to predict in vivo dissolution. In silico software revealed that the time of maximum plasma concentration ($T_{\text{max}}$) and maximum plasma concentration ($C_{\text{max}}$) were influenced by the gastric half-emptying time. By comparing these pharmacokinetics parameters with human clinical data, the gastric half-emptying time between 5 and 10 min for the GIS studies provided a good match to human in vivo systemic availability (and presumably the luminal fluid dissolution) in the fasted state (Figs. 3 and 5; Table 2). This relatively rapid estimate of gastric emptying time using the GastroPlus\textsuperscript{TM} simulation for these rapidly disintegrating and dissolving IR dosage forms is consistent with one study that indicated a more rapid emptying of liquids from the stomach. However, it is shorter than other measurements indicating a gastric half-emptying time of about 15 min.

In this study, dissolution tests with the GIS were performed for propranolol and metoprolol. Propranolol and metoprolol exhibited different times for complete dissolution (propranolol: 7.5 min; metoprolol: 20 min) (Figs. 2f and 4f). With a gastric half-emptying time of 5 min, this difference clearly influenced drug concentration in each chamber, but this difference did not influence drug concentration in the duodenal and jejunal chamber with a gastric half-emptying time of 30 min (Figs. 2 and 4). Comparing the concentration profiles ($C_{\text{max}}$ concentration/dose ratio) between propranolol and metoprolol with the gastric half-emptying time at 5 min, metoprolol exhibited 126% and 57% higher $C_{\text{max}}$ in the gastric and duodenal chambers than propranolol. However, metoprolol exhibited 28% lower $C_{\text{max}}$ in the jejunal chamber than propranolol. Furthermore, comparing $t_{\text{max}}$ between propranolol and metoprolol with the gastric emptying time at 5 min, a $t_{\text{max}}$ difference was observed in each chamber, propranolol (2.5 min) versus metoprolol (12.5 min) in the gastric chamber, and propranolol (12.5 min) versus metoprolol (25 min) in the duodenal chamber. As these results show, the GIS can evaluate disintegration time and dissolution rate in each chamber depending on test drugs. However, the short gastric-emptying time suggested requiring further direct measurement in the luminal intestinal fluid.

The GIS can not only assess $C_{\text{max}}$ and $t_{\text{max}}$, but can also evaluate the in vivo dissolution profile. For example, Carino et al.\textsuperscript{11} performed the ASD, of which the GIS is an adaption with a jejunal compartment, to estimate bioavailability of carbamazepine (BCS class II drug) that has three different crystal forms. Dissolution profiles of different carbamazepine crystal forms in the duodenal chamber were compared with oral bioavailability of those crystal forms in dogs. The results showed an excellent correlation between the ASD dissolution results and dog bioavailability. For BCS class II weak basic drugs, the precipitation rate and supersaturation in the GI tract will significantly affect oral bioavailability. The GIS allows these phenomena in the duodenal and jejunal chambers to be observed and measured, in a less complex environment than the luminal intestinal fluid, and can provide valuable information with which to predict in vivo dissolution. Thus, the GIS appears to be a very useful tool for the development of oral drug formulations.

**CONCLUSION**

The dissolution results with the GIS system provide a convenient means of quantitating drug concentration in the chambers representing the stomach, duodenum, and jejunum that directly impact in vivo drug absorption. This in vitro GI com-
partment concentration is the information needed for the prediction of oral drug absorption. The gastric half-emptying time in the fasted state was determined in these studies as a part of the GIS development. This is a significant factor for a multi-compartment dissolution apparatus in the prediction of in vivo dissolution. In this study, the gastric half-emptying time for the GIS was observed to be between 5 and 10 min, and although it is in general agreement with previous reports of the gastric emptying of liquids, it is shorter than other reported values. This requires direct verification by measuring luminal fluid concentrations in the future.

REFERENCES