INTRODUCTION

Due to its ease of administration, a large percentage of pharmaceutical drug products are administered orally. Oral drug product performance already starts in the stomach. Gastric parameters impact the behavior of pharmaceutical formulations consumed with water (fasted conditions) or a solid / liquid meal (fed conditions). To more accurately study the disintegration of drug products and subsequently the release and solubility of the active ingredient, the advanced gastric compartment (AGC) was developed as part of the dynamic in vitro gastrointestinal model TIM (Minekus et al., 1995). To ensure physiological relevance of simulated parameters, we here describe the TIM-AGC in terms of gastric motility, pressure forces, gastric secretions and gastric emptying.

METHODS

Following the design and development of the TIM-AGC, experiments for technical validation were performed. The validation experiments were designed and performed based on literature with relevant data on the human stomach. The gastric motility patterns and pressure values were measured with the Smartpill® technology. For this, the Smartpill® recorded pressure values over time after introduction into the TIM-AGC. Dynamic secretions of digestive enzymes (lipase, pepsin, (swallowed) salivary amylase) and HCl were set with regard to flow rates and post-prandial concentrations. Luminal enzyme activity measurements and digestion experiments were performed to confirm the settings. Mixing of the water and meals in the body and antrum parts was monitored as well as emptying of the liquids and solids over time in the experiments with relevant liquid and solid meals in combination with water.

RESULTS

Design and construction

Alike the human stomach, the TIM-AGC consists of a body part (Figure 1A) that gradually contracts to simulate gastric tone and consequent reduction of gastric volume during emptying. The antrum part features a flexible bottom (Figure 1B) that can be moved in conjunction with antral contractions (Figure 1C).

Figure 1. TIM-AGC, A. body, B. antrum, C. contracting antrum, D. pyloric valve

Close-up of the TIM-AGC

Gastric motility and pressure forces

The three phases of gastric mixing, namely propulsion, emptying and mixing and repulsion are enabled through computer-controlled and synchronized movements of the contractile proximal and terminal antrum and the pylorus. This results in motility patterns and pressure forces. Similar patterns were observed in TIM-AGC as compared with published data of the human stomach. Figure 2 shows the comparison of pressure profiles over time and Figure 3 shows an example of the Migrating Motor Complex (MMC or also called the housekeeper wave) as observed in vivo and in the TIM-AGC.

Figure 2. Pressure profiles obtained from the Smartpill® in the human stomach (left) and in TIM-AGC (right).

Figure 3. Pressure peak obtained from the Smartpill® during MMC in the human stomach (left) and in TIM-AGC (right).

Secretions

First, measurements of luminal enzyme concentrations during ingestion of a meal were in line with in vivo observed concentrations. Figure 4 exemplarily shows the comparison of pepsin concentrations in vivo (Kalantzi et al., 2006) and in the TIM-AGC. Second, measured digestion correlated well with that measured in humans. The realistic digestibility of macronutrients of a high fat meal was 64.6%, 94.8% and 90.7% for fats, proteins and carbohydrates, respectively.

Figure 4. Theoretical (green line) and measured (red markers) pepsin concentration during gastric passage of a formula milk (Nutrilon®), compared to the gastric pepsin concentration in vivo (blue line) with Ensure plus® as a meal matrix.

Gastric emptying

In the human stomach the ingested meal disintegrates and phase separation occurs. Solids follow a linear emptying manner, while the liquid phase would empty with an exponential pattern. This clear difference as shown in vivo by Moore et al. (1981), was reproduced in the TIM-AGC (Figure 5). This indicates realistic mixing, seving characteristics and gastric emptying of the in vitro model.

Figure 5. Solid emptying in TIM-AGC (line, round markers) compared to in vivo (dotted-dashed line), and liquid emptying in TIM-AGC (line, square markers) compared to in vivo (dashed line). The dotted line presents the gastric emptying of the total meal.

CONCLUSION

The presented data indicate that the TIM-AGC realistically simulates the processes in the human stomach, such as motility patterns and pressure values, gastric secretions and the emptying of realistic meals over time. As a result, the AGC, as part of the TIM system, is an useful tool to study the gastric behavior of different drug formulations within the preclinical drug development process.

REFERENCES


TNO Triskelion, Zeist, The Netherlands