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A Stochastic Fluid Packet Emptying and Transit Model:
A Physiological Approach to Gastrointestinal Transit of Fluid

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PURPOSE

Fasted-state gastrointestinal (GI) fluid transit occurs not as a first-order, deterministic process, (typically averaged) and viewed continuous approximation, but rather as a discrete process involving fluid packets interrupted by varied time periods of no emptying. The emptying of these fluid packets is known to occur in pulses which vary in both size and timing. The influence this pulse emptying has on the concentration of drug presented to the intestinal absorbing surface is significant. This physiological factor presents a source of inter- and intra-subject variability that can significantly affect plasma levels e.g. C_{max} and thus have significant bioequivalence (BE) implications on the observed intra and inter subject variability of test products, for immediate release as well as controlled release dosage forms.

We develop in this report a novel, stochastic process describing cyclical fasted-state gastrointestinal motility variation and use it to describe how gastric content is propelled in discretized fluid pockets into the small intestine based on the known motility phase dependant gastric emptying. The time of dosing is random relative to the periodic fasted state migrating motor complex (MMC) cycle using a Fourier series approximation and a non-homogenous (MMC dependant) Poisson process is used to capture the inter-pulse timings. Two random processes control fluid transit: the volume of the random fluid packet emptied into the small intestine , and the time the fluid packet pulses out of the stomach. The Poisson process describing the pulse of fluid packets is memory-less and determined by the intensity parameter, $\lambda(t)$, which evolves with the MMC.

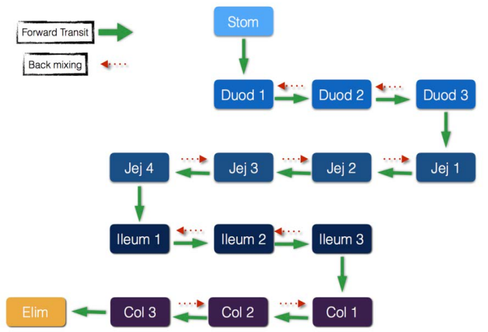

Figure 1: Schematic Diagram

METHOD

The volume of each packet is also a random variable, based on previous experimental results conducted via MRI. The mean packet volume in the stomach compartment is 8 mL. The packet volume formation is dependent on the current volume in the stomach and normally distributed about the mean packet. The relationship between stomach volume and packet volume is illustrated in Fig. 2.

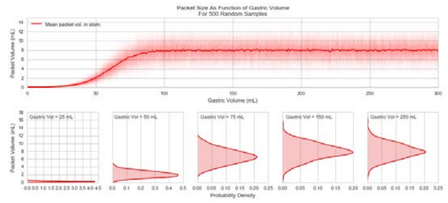

Figure 2: Volume of packet formed as a random variable. The packet volume depends on the current volume in the stomach, thus tending to zero as the stomach is emptied. Top: the red line shows the stomach profile while the blue is that of the small bowel. Bottom: probability distribution of packet size for 25, 50, 75, 150, and 250 mL volumes in the stomach.

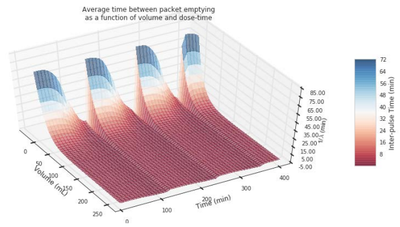

Figure 2: Average time between fluid packet emptying as a function of time and gastric fluid volume. With very large volumes, the distentive effect dominates, essentially leading to continuous emptying, while as the volume is reduced, emptying is again dependent on the cyclical MMC.

The MMC cycle is approximately 120 minutes. Fig. 3 illustrates the effect of the mean time between packet emptying (defined as the inverse of the mean rate, $\lambda(t)^{-1}$), evolves with respect to both time and volume of fluid in the stomach compartment. Larger fluid volumes induce distention and so empty more rapidly, thus shorter waiting times between emptying of packets. However, as the volumes decrease, the MMC cycle begins to dominate and so the phase-dependence is really evidenced. Dosing time t0 is defined as the time of administration relative to the MMC cycle, i.e. $\lambda(t + t0)$.

RESULTS

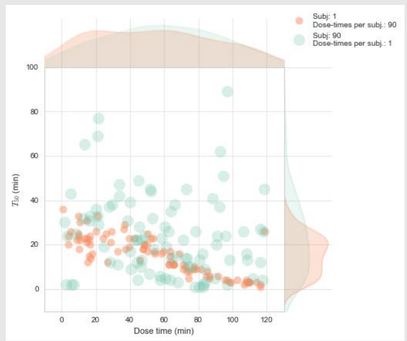

Figure 3: The distributions of gastric emptying half-times in minutes due to solely dose time (intra-subject, shown in orange, n = 90) as well as based on physiological variations (inter-subject, shown in light green, n = 90).

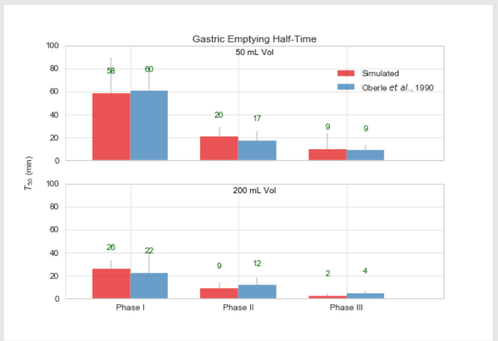

Figure 4: Simulated (red) and experimental (blue)6 duo denal appearance half-times for 50 mL (top panel) and 200 mL (bottom panel) volumes.

RESULTS (cont'd)

Simulating repeatedly over MMC phase by varying dose time, from 0 to 120 minutes, the range of gastric emptying half-times agreed with experimental values. The distribution of inter-subject gastric emptying half-times (T_{50}) has a fatter tail with a mean T_{50} = 23.95 minutes versus 15.71 minutes for intra-subject variation which does span a large subset of the inter-subject distribution.

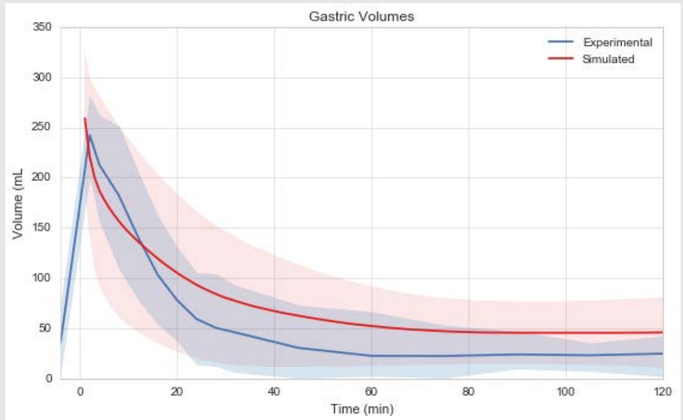

Figure 5: Simulated gastric profiles for 24 virtual subjects with random dose time t0 (red lines, mean prediction as thick red line) superimposed over volumetric emptying data from 12 subjects measured by MRI3.

CONCLUSION

The implications of GI motility as a physiological process must be evaluated in detail, especially with regard to absorption kinetics and BE implications. This study indicates that pulsed fluid packet kinetics model can be developed using a stochastic process that accounts for not only mean transit times but also comparable distributions about the means. This in turn will allow the development of more physiologically accurate simulation methods. The advantages of this approach include a utilization of a stochastic process rather than first-order ODE which is an oversimplification arising from averaged transit rates; accounting for experimentally-measured free fluid volumes throughout GI tract; and incorporation motility and reflect volumetric effects and transit times, all of which in turn allow for accurate predictions of concentrations along the GI tract.

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