# Fasted-State Motility-Dependent Gastric Emptying and Plasma Level Variation: Bioequivalence Implications for BCS Class I Drugs

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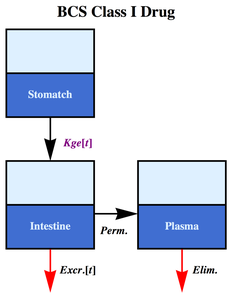
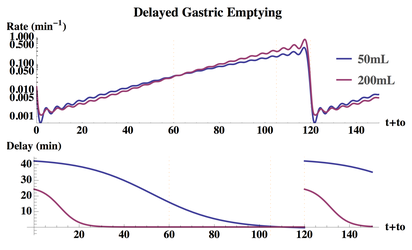
## Purpose

Fasted-state cyclical contractions associated with gastrointestinal motility transport content from the stomach into the small bowel in a pulsatile manner, influencing the concentration presented at the absorption site. In the case of high solubility/ permeability (BCS Class I) drugs, this physiological factor presents a source of inter- and intra-subject variability affecting plasma levels, thus having bioequivalence (BE) implications.




### Continuous periodic function

$$\rho_2\left(\sum_{k=1}^{25}\frac{(-1)^k\sin(-\phi\pi k(t-\tau))}{k}+\rho_1\right)^{\rho 3}+s$$

Estimating a slat wave with sum of sines (25)
$\rho 1$ = Length/amplitude of phase I
$\rho 2$ = Length/amplitude of phase II relative to phase I
$\rho 3$ = Length/amplitude of phase III
$s$ = $K_{ge}$ range
$\tau$ = phase shift
$\phi$ = half the fundamental frequency (approx. once every 120 min)

### Piecewise continuous lag time function

$$a-\frac{b}{c+d\left(exp\left[-e(t_0 \bmod\left[2/\phi\right])+f\right]\right)}$$

Sigmoidal decay model
$a$ = initial lag (max Phase I lag), equivalent ot maximum asymptote
$b$,$c$ = minimum asymptote and shape
$d$ = decay rate
$e$ = adjusts location of maximum decay (relative to max/min asymptote)
$f$ = Amplitudinal difference between min/max lag times

**Gastric Emptying $T_{50}$**

| Vol. | Phase I (min) | Phase II (min) | Phase III (min) | Avg. |
|---|---|---|---|---|
| 50mL | 47.3 ± 12.2 | 12.16 ± 6.191 | 3.58 ± 0.1924 | 30.09 ± 21.34 |
| 200mL | 37.77 ± 15.33 | 6.751 ± 3.481 | 2.18 ± 0.1483 | 22.97 ± 20.35 |

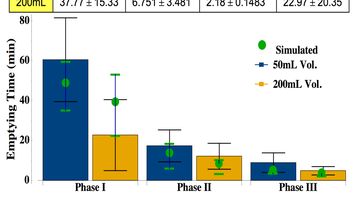



Figure 1: Above table shows the simulated ranges of phase-dependent emptying half-lives for 50mL and 200mL volumes. Chart below shows emptying half-times $t_{1/2}$ (green dots) compared to measured [1] times in different phases and volumes.

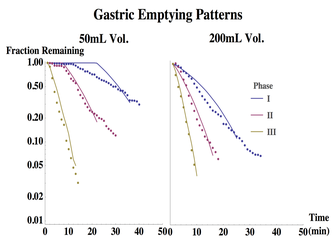



Figure 1: Gastric emptying patterns for 50mL and 200mL volumes based on measured subject data [1].

## Methods

A physiologically-based model was constructed to account for cyclical gastric emptying rates. The time-dependence was represented by a periodic, piecewise-continuous function that increased from phase I through III. Assuming fasted state and linear metabolism, simulated emptying rates corresponded to *in vivo* studies [3]. The range of volumetric emptying was also evaluated against results from *in vivo* studies [2]. The variations in $C_{max}$ and $T_{max}$ were calculated relative to the randomly-chosen dosing times. The population reference was calculated using 10000 simulations. Samples of 6, 12, or 24 virtual subjects were randomly chosen and evaluated as pilot or BE trials.

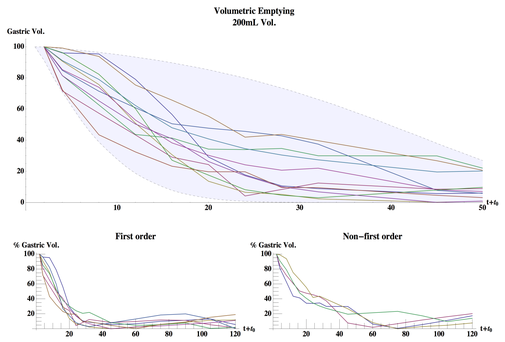



Figure 2: Above, the predicted gastric emptying results for a 35-minute range (shaded region) with superimposed volumetric emptying data from subjects measured by MRI [2]. Below, emptying patterns show both first-order (left, ~75%) and non-first order (right, ~25%) emptying patterns which correspond to the distribution of simulated emptying patterns.

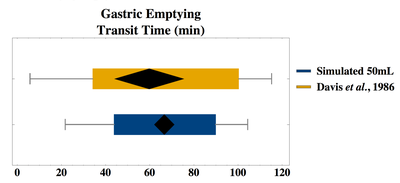



Figure 3: Accordance of measured [3] versus simulated gastric emptying transit time ranges. The black diamonds represent the confidence intervals of the means which overlap, and the difference in the means is statistically insignificant (Mann-Whitney $p$ = 0.46)

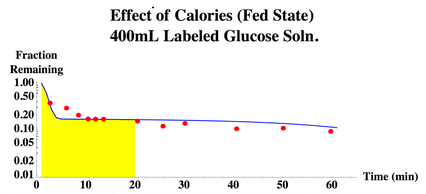



Figure 4: Emptying of 400mL labeled glucose solution for a subject with pyloroplasty (red dots) [4]. The yellow shaded region represents deviation from the predicted (blue line) emptying pattern due presumably to the glucose-induced fed state, after which the fasted-state prediction agrees with the measurements.

## Results

Approximately a quarter of the subjects in the volumetric emptying study displayed non-first order emptying and 20% of the simulations showed similar kinetics. For BE studies, approximately 14-58% of the FDA-required mean $C_{max}$ 90% confidence intervals of the samples exceeded the reference simulation 80-125 range for a 7-min. half-life drug in a small 50mL volume; for a 200mL volume, 32-60% failed. For long 4-hr. elimination half-lives in 50mL and 200mL volumes, the sample confidence intervals constituted 8-17% and 9-20% of the 80-125 population ranges, respectively.

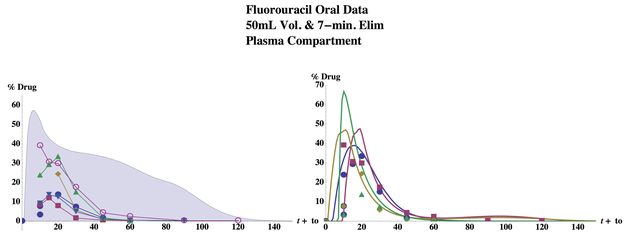



Figure 5: Plasma level variations of oral fluorouracil (dose- and weight-adjusted) [5]. Left, the shaded regions represent the envelope of plasma level predictions without knowing the dosing time $t_0$. Right, plasma level predictions can be reproduced as a function of dosing time $t_0$.

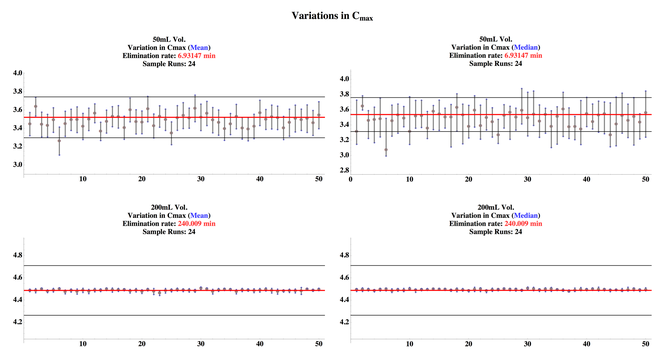



Figure 6: Top, Plasma level variations result in the test median (left) or mean (right) 90% confidence intervals falling outside the reference 80-125 range for short a short half-life drug in a 50mL volume. Bottom, the plasma level variation is much less pronounced with increased gastric volume and elimination half-life.

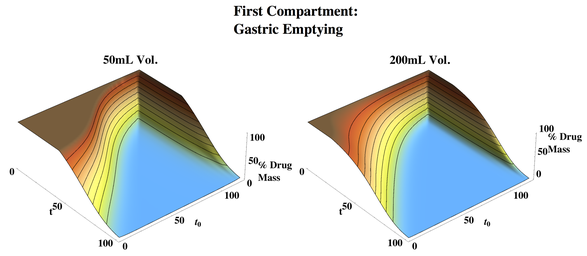



Figure 7: Dosing-time $t_0$ dependence on gastric emptying for 50mL (left) and 200mL (right) volumes. The smaller volume shows significantly longer delay that is only seen in the initial phase of the larger volume.

## Conclusions

We fit a Fourier series approximation to gastric emptying results and independently validated the function. Significant variation in $C_{max}$ is predicted due to gastric emptying alone for BCS Class I drugs. Considerably more variation in plasma levels is predicted with a 50mL volume of fluid. The volume-dependence of gastric emptying and the resultant $C_{max}$ variation suggest further investigations regarding patient compliance are needed.

**50mL Vol. Percent Failed BE Studies (median $C_{max}$ 90% CI)**

| Half−life (min) | 6 samples | 12 samples | 24 samples |
|---|---|---|---|
| 7 | 100. | 100. | 70. |
| 14 | 100. | 76. | 24. |
| 30 | 66. | 18. | 0. |
| 60 | 22. | 0. | 0. |
| 240 | 0. | 0. | 0. |

**50mL Vol. Percent Failed BE Studies (mean $C_{max}$ 90% CI)**

| Half−life (min) | 6 samples | 12 samples | 24 samples |
|---|---|---|---|
| 7 | 60. | 48. | 10. |
| 14 | 52. | 16. | 0. |
| 30 | 10. | 0. | 0. |
| 60 | 2. | 0. | 0. |
| 240 | 0. | 0. | 0. |

**200mL Vol. Percent Failed BE Studies (median $C_{max}$ 90% CI)**

| Half−life (min) | 6 samples | 12 samples | 24 samples |
|---|---|---|---|
| 7 | 100. | 100. | 100. |
| 14 | 98. | 98. | 60. |
| 30 | 66. | 14. | 0. |
| 60 | 16. | 0. | 0. |
| 240 | 2. | 0. | 0. |

**200mL Vol. Percent Failed BE Studies (mean $C_{max}$ 90% CI)**

| Half−life (min) | 6 samples | 12 samples | 24 samples |
|---|---|---|---|
| 7 | 60. | 56. | 28. |
| 14 | 54. | 24. | 2. |
| 30 | 12. | 0. | 0. |
| 60 | 0. | 0. | 0. |
| 240 | 2. | 0. | 0. |

**50mL Vol. Percent of BE 80−125 Interval (median $C_{max}$90% CI)**

| Half−life (min) | 6 samples | 12 samples | 24 samples |
|---|---|---|---|
| 7 | 216.071 | 146.938 | 89.5305 |
| 14 | 145.095 | 93.7344 | 61.843 |
| 30 | 89.2475 | 59.3729 | 36.7597 |
| 60 | 58.1959 | 34.0272 | 23.7504 |
| 240 | 25.5668 | 17.5743 | 7.89091 |

**50mL Vol. Percent of BE 80−125 Interval (mean $C_{max}$90% CI)**

| Half−life (min) | 6 samples | 12 samples | 24 samples |
|---|---|---|---|
| 7 | 139.514 | 84.4214 | 56.251 |
| 14 | 89.1478 | 55.6091 | 40.444 |
| 30 | 55.8721 | 36.8311 | 25.3804 |
| 60 | 35.9503 | 23.2347 | 16.3633 |
| 240 | 16.2382 | 11.6667 | 7.51746 |

**200mL Vol. Percent of BE 80−125 Interval (median $C_{max}$90% CI)**

| Half−life (min) | 6 samples | 12 samples | 24 samples |
|---|---|---|---|
| 7 | 224.242 | 180.532 | 137.419 |
| 14 | 159.231 | 113.038 | 82.1787 |
| 30 | 91.9919 | 66.7816 | 44.436 |
| 60 | 53.512 | 33.4287 | 22.6752 |
| 240 | 22.2328 | 8.84269 | 4.71071 |

**200mL Vol. Percent of BE 80−125 Interval (mean $C_{max}$90% CI)**

| Half−life (min) | 6 samples | 12 samples | 24 samples |
|---|---|---|---|
| 7 | 148.431 | 98.2169 | 68.7774 |
| 14 | 104.313 | 63.5664 | 45.2496 |
| 30 | 58.9055 | 38.7715 | 25.4509 |
| 60 | 33.359 | 20.9054 | 13.8327 |
| 240 | 13.6453 | 10.1514 | 6.44006 |

Table 1: Summary statistics: failed BE trials using 50mL and 200mL volumes; percent of 80-125 range covered by mean/median 90% confidence interval, the resultant variation in $C_{max}$ due to gastric emptying.

## References

1. Oberle *et al.*, Gastroenterology, 99(5): 1275-1282 (1990)
2. Marciani *et al.*, Molecular Pharmaceutics, Submitted Feb 2014.
3. Davis *et al.*, Gut 27:886-892 (1986).
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## Acknowledgements

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