A Literature Review on the Performance of Tiny Tract for In Vitro Modeling (tiny-TIM) to Predict Food-Drug and pH-Dependent Drug-Drug Interaction Risks

Yuhua Chang[1,2], Gang Zhao[1,2], Duyen Nguyen[2], Qi Zhang[2], Hye Lim Lim[2]

[1.] Oak Ridge Institute for Science and Education, Oak Ridge, TN 37830, USA

[2.] Division of Therapeutic Performance II, Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. FDA, Silver Spring, MD 02993, USA

Introduction

- Drug substances can be formulated as amorphous solid dispersions (ASDs) to enhance their solubility and dissolution. However, ASDs are inherently metastable or unstable systems and as such susceptible to crystallization.
- Drug products containing ASDs are classified as high-risk products with regard to bioinequivalence because in vivo performance differences due to formulation and/or manufacturing variation may not be detected with a single in vivo bioequivalence study under fasting or fed conditions.
- Tiny-TIM model may provide insights into the bioavailability of various oral dosage forms, considering both fed and fasting conditions.
- The objective of this project was to conduct a literature review of tiny-TIM model and its current predictive performance on the effect of food and elevated pH on the bio-accessibility of active pharmaceutical ingredients (APIs) and ASD products.
- This work may support the utilization of tiny-TIM model for regulatory decisions.

Methods

- Keywords used for literature search: TIM, tiny-TIM, simulation.
- Information collected from literature: APIs, dosage form, formulation, food / pH effect on drug absorption from published clinical data, and food / pH effect predicted by tiny-TIM modelling.

Results

- Tiny-TIM is an intricate and dynamic model designed to replicate the conditions in the stomach and small intestine of the adult human.

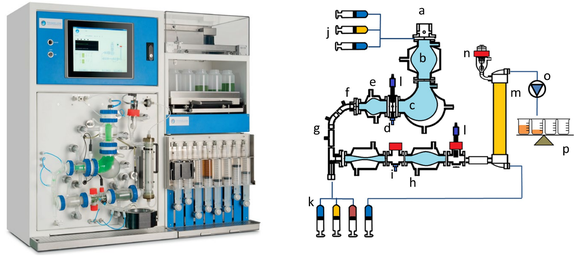

Figure 1. Graphical representation of the tiny-TIM model including an advanced gastric compartment (agc). a: meal inlet, b: corpus, c: proximal antrum, d: gastric port, e: distal antrum, f: pyloric valve, g: peristaltic valve, h: small intestinal compartment, i: small intestinal port, j: gastric secretions, k: intestinal secretions, l: pH electrodes, m: filtration system, n: level sensor, o: sample pump, p: sample bottles. Reprinted from Verwei et al., Int J Pharm. 2016 Feb 10;498(1-2):178-86.

A total of 24 drug products were collected from the literature (references available upon request) for TIM modeling prediction (with itraconazole evaluated for both food and pH effect):

- 12 drug products were collected for prediction of food effect (Table 1).
- 13 drug products were collected for prediction of pH effect (Table 2).

The TIM prediction was arbitrarily grouped into three categories to better understand the prediction performance of TIM Modeling:

- High predictability: TIM prediction is deviated < 20% of that of the in vivo data.
- Moderate predictability: TIM prediction is deviated ≥ 20 and < 100% of that of the in vivo data.
- Low predictability: TIM prediction is deviated ≥ 100% of that of the in vivo data.

Table 1. Prediction of food effect using TIM systems (tiny-TIM and TIM-1*) (* indicates data from TIM-1)

APIs	Dosage form	Meal Type	Bio-accessibility Ratio (fed/fasted) from tiny-TIM or TIM-1*	Ratio of AUC (fed/fasted) from clinical studies	Prediction % (TIM/in vivo)*100	Predictability
Danirixin	Tablets	High fat meal	0.6*	0.6	100%	High
Diclofenac	Tablets IR	Ensure Plus	1.0*	1.0	100%	High
Ciprofloxacin	Tablets ER	High fat meal	1.0	1.0	100%	High
Acetaminophen	Tablets IR	Standard meal	1.0*	0.9	111%	High
Acetaminophen	Powder	Infant formula	1.0	1.0	100%	High
Fosamprenavir	Tablets IR	Scandi-shake Mix	1.0*	1.0	100%	High
Ibuprofen	Capsules	High fat meal	1.0	0.9	111%	High
Celecoxib	Capsules	High fat meal	2.0*	1.6	125%	Moderate
Undisclosed drug	Tablets (10 mg)	High fat meal	2.9	2.2	132%	Moderate
Itraconazole	Capsules	High fat meal	3.9	1.6	244%	Low
Nifedipine	Tablets MR	High fat meal	3.6	1.7	218%	Low
Posaconazole	Suspension	High fat meal	12.1	4	303%	Low

Table 2. Prediction of elevated pH effect from acid reducing agents (ARAs) using tiny-TIM system

APIs	Dosage Form	Ratio of bio-accessibility (ARA/Non-ARA) from tiny-TIM	Ratio of AUC (ARA/Non-ARA) from clinical studies	Prediction % (TIM/in vivo)*100	Predictability
GDC-A	Tablets	1	1	100%	High
GDC-E	Tablets	1	1	100%	High
GDC-F	Capsules	1	1	100%	High
Alectinib	Capsules	1	1	100%	High
Dasatinib	Powder	0.4	0.4	100%	High
Dipyridamole	Powder	0.6	0.63	95%	High
Itraconazole	Capsules	0.6	0.55	109%	High
GDC-C	Tablets	0.8	0.75	107%	High
GDC-B	Tablets	0.2	0.33	61%	Moderate
Erlotinib	Powder	0.7	0.5	140%	Moderate
GDC-D	Tablets	0.7	0.46	152%	Moderate
Atazanavir	Capsules	0.7	0.06 - 0.41	171 – 1166%	Low
Ketoconazole	Powder	0.4	0.08	500%	Low

Table 3. A summary of TIM prediction of food effects from Table 1

Food Effect	High Pre	Moderate Pre	Low Pre
Negative	1	0	0
No	6	0	0
Positive	0	2	3

Table 4. A summary of TIM prediction of pH (ARAs) effects from Table 2

pH (ARAs) Effect	High Pre	Moderate Pre	Low Pre
Negative	4	3	2
No	4	0	0

*__Pre__ as in Tables 3 and 4 is abbreviated for Predictability.

Results (continued)

- When food has no effect on drug absorption (n = 6) or had negative effect on drug absorption (n = 1) , the TIM prediction deviated < 20% of that of in vivo data. For the five drug products with positive food effect, the TIM prediction deviated from 25% to 203% of that of in vivo data (Tables 1 and 3).
- When elevated pH has no effect on drug absorption (n = 4), the TIM prediction deviated < 20% of that of in vivo data. When elevated pH has negative effect on drug absorption, the TIM modeling prediction has variable performance: deviated < 20% (n = 4), deviated ≥ 20% but < 100% (n = 2), or deviated ≥ 100% (n = 3) from that of in vivo data (Tables 2 and 4).
- Among 24 drug products collected, only one formulated in ASD was evaluated in tiny-TIM modeling (Itraconazole capsule).
  - The food effect is overestimated by 144% compared to clinical studies (Table 1).
  - The pH effect predicted by tiny-TIM is comparable to that from clinical studies (Table 2).

Conclusion

- Tiny-TIM system may reliably predict the effect of food and elevated pH on drug absorption in some cases.
- The tiny-TIM prediction may not always be accurate:
  - It may over-estimate the food effect.
  - It may under-estimate the pH effect.
- This work highlights that additional improvement and validation are needed, in order to apply the tiny-TIM system to investigate the effect of food intake and gastric pH modification on the bio-accessibility of drug products for regulatory decision making including those for generic drugs.

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