Poster# W1130-10-64

Refining Predictions of Food Effects on Drug Absorption: Models Predicting Gastric Emptying and Bile Concentrations Based on Fat Content and Caloric Intake

James Mathew Mullin
Simulations Plus, Inc., Lancaster, CA.

CONTACT INFORMATION: jim.mullin@simulations-plus.com

aaps PharmSci 360

PURPOSE

In the realm of pharmaceutical R&D, the quest for enhanced predictive accuracy and efficiency for Fed State PBPK models has never been more pressing. this work seeks to revolutionize the current state-of-the-art by accounting for the influence of meal calories and fat content on critical physiological processes—gastric emptying and intestinal bile concentrations. The implications of this research offer the promise of refined clinical data predictions, especially pertinent to BCS class II molecules. By deciphering how drug formulations interact with meals of varying composition, such as a low calorie/fat versus high calorie/fat FDA breakfast, we aim to unravel valuable insights that can inform drug labeling, reduce food effect studies, and expedite formulation development. We will review the high-level results of this new model on prediction of a multitude of compounds in the fed state.

OBJECTIVES

We aim to review the key parameters updated in Gastroplus™ to modulate fed-state gastric emptying and bile salt concentration based on meal composition of calories and fat. Then evaluate the effectiveness of these new model parameters in predicting fed-state pharmacokinetics.

METHODS

Data was gathered from 15 literature studies of gastric emptying rate with a wide variety of meal types and caloric intake as shown in Figure 1. This data was analyzed to determine the shape of the gastric emptying profile, either zero or first-order, and to analyze the gastric emptying half-time. The resulting correlations were used to predict zero-order gastric emptying based on calories and were added to Gastroplus v9.7 software (Simulations Plus, Inc.). In the actual implementation, the calories are defined as a percentage of total daily calories so they can be used in pediatrics. Additionally, based on biliary excretion data in literature and bile concentrations in feces, a dynamic bile salt concentration model was developed to predict steady-state bile concentration based on fat content. The steady-state bile concentrations were then incorporated as defaults in GastroPlus™ 9.7 and later and tested against 8 literature and internal consulting study PBPK models.

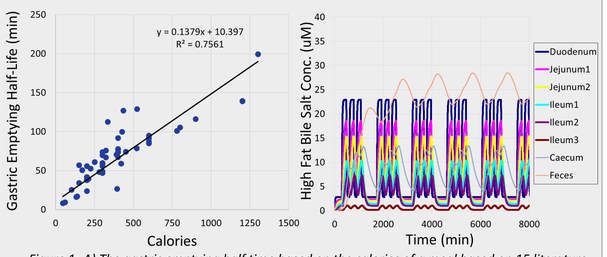

Figure 1: A) The gastric emptying half time based on the calories of a meal based on 15 literature studies of various meal types. B) Dynamic bile salt model to determine steady state concentrations of bile in the intestine based on literature biliary excretion and concentration data.

RESULTS

Of initial importance was validating the functional form of gastric emptying utilized in the new and improved fed-state models. Therefore, we analyzed 15 literature papers, as shown in Figure 2, and found that 60% of gastric emptying papers indicated zero-order emptying in the fed-state while only 20% definitively showed exponential gastric emptying profiles. The other 20% of papers did not show the full emptying profile but rather overall results.

The choice of zero-order emptying, the caloric content of a meals impact on gastric emptying, and the meal fat% effect on bile salt concentration was evaluated by analyzing PBPK results of 8 compounds with literature data or internal consulting studies dosed with various low, moderate, or high fat meal types. Models were built with GastroPlus™ version 9.7 utilizing a mixture of ADMET Predictor™ *in silico* predictions and measured *in vitro* properties for biopharmaceutical inputs and PBPK models utilized the Lukacova method for tissue partition coefficients. Axitinib is an excellent example of the utility of the fed-state models because it is a high permeability compound and has a low dose and high enough FaSSIF solubility that the pharmacokinetics are sensitive to the assumption of gastric emptying. Therefore, we predicted the pharmacokinetics of a literature study with the original model, as well as the new model where gastric emptying is based on calories and fat%[1]. The high fat high calorie meal was utilized in conjunction with study protocols and either an exponential or zero-order profile shape was predicted to validate the choice of emptying profile. Figure 3 shows that the best combination of Cmax and Tmax prediction is exhibited by the new fed state high fat meal with zero order emptying with a Tmax error of 6.7% vs. 36% for the original fed-state model as shown in Figure 2. The second example is for an internal study of a low solubility BCS Class II kinase inhibitor. For micronized drug dosed with FDA breakfast meal of 850 calories and 50% fat we can see the optimal Cmax prediction is with the zero-order gastric emptying vs. the exponential profile (25.3% and 4.7% absolute error) given the same emptying time constant for each model as shown in Figure 4. A full overview of all validation cases is shown in Figure 5.

Reference	Meal Type	Profile Shape
Hunt (1954)	Sucrose + Pectin	Zero-order
Velchik (1989)	Egg Sandwich	Zero-order
Kwaitek (2009)	Ensure	Zero-order
Moore (1984)	Salad + Dressing	Zero-order
Doran (1998)	Hamburger + Tomato Sauce	Zero-order
Speigel (2000)	Soup + Egg Sandwich	Zero-order
Kunz (1999)	Pancakes, Potatoes, Eggs	Zero-order
Goetze (2007)	Emulsified oil, glucose, or albumin	Zero-order
MARCIANI (2001)	Emulsified Oils	Zero-order
Hunt (1985)	Polycose	Profile not available
Braden (1995)	Liquid or Oat flakes and Milk	Profile not available
Cunningham (1991)	Mashed Potatoes, Butter, Beans	Profile not available
Calbert (1997)	Glucose + Protein Isolate	Exponential
McHugh (1979)	Glucose	Exponential
GHOOS (1993)	Egg Sandwich	Exponential

Figure 2: Summary of gastric emptying profiles and associated meal types from various gastric emptying literature papers.

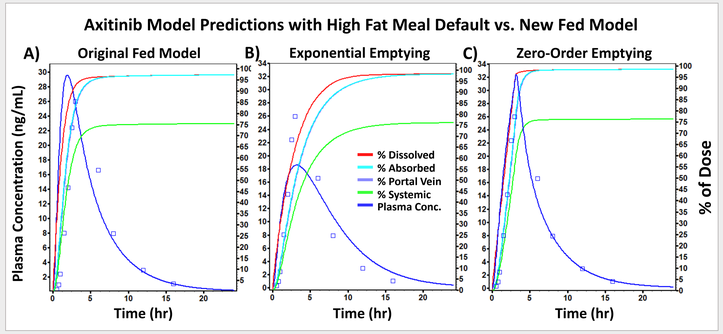

Figure 3: A) Model prediction of Axitinib based on default GastroPlus™fed state model, B) Model prediction of fed-state pharmacokinetics of Axitinib with exponential emptying rate based on new calorie and % fat model, and C) model prediction with zero-order emptying (same emptying time calorie assumption as prediction B). Blue, red, cyan, light blue, and green curves correspond to plasma concentration, % dissolved, % absorbed, % portal vein, and % systemic circulation.

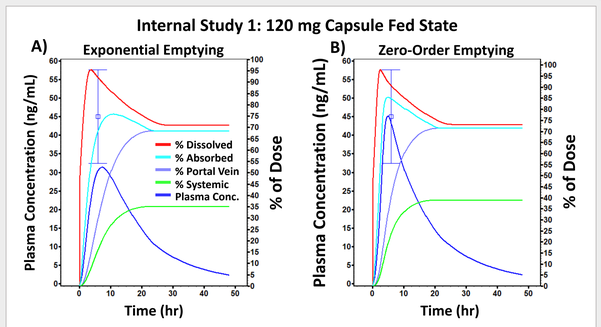

Figure 4: A) Model prediction of fed-state pharmacokinetics of internal study 1 with exponential emptying rate based on new calorie and % fat model vs. B) model prediction with zero-order emptying (same emptying time as prediction A). Blue, red, cyan, light blue, and green curves correspond to plasma concentration, % dissolved, % absorbed, % portal vein, and % systemic circulation.

		GP 9.7 New Model Settings		Original Model
	Meal Type	Exponential	Zero-order	
Dolutegravir	High Fat / High Calorie			
	Mod. Fat / Mod. Calorie			
	Low Fat / Low Calorie			
Lapatinib	Low Fat / Low Calorie			
	High Fat / High Calorie			
Ixazomib	High Fat / High Calorie			
Axitinib	Normal Meal			
	High Fat / High Calorie			
Dasatinib	Low Fat / Low Calorie			
	High Fat / High Calorie			
Internal Study 1	FDA High Fat Breakfast			
Internal Study 2	High Fat / FDA Breakfast			
Internal Study 3	High Fat / FDA Breakfast	ND		

Figure 5: Heat map of validation study results for new GastroPlus™fed-state model based on meal calories and fat%. Heat map shows the predictive accuracy of the new zero-order emptying model is superior against original model or fat% and calorie model with exponential emptying for 8 compounds dosed with different meal types. (red less accurate, green highest accuracy)

CONCLUSIONS

New fed-state models have been added to Gastroplus™ that allow scientists the ability to account for a specific meal type to better predict the extended Tmax and increased Cmax in high-fat meal studies with BCS Class II molecules. The physiologic parameters are based on literature data for gastric emptying and biliary excretion and are applied to both adult and paediatric models. The model has been evaluated against 8 compounds that were dosed with various meal types and the accuracy of the model was compared against the original Gastroplus™ fed-state model as shown in Figure 5. In 69% of the case studies analyzed the new Gastroplus fed meal model is more accurate. We continue to monitor the literature to explore additional meal variables like protein and carbohydrate content so we can expand the usefulness of the model. Furthermore, the interaction of drug with food is another key missing link for accurate fed-state predictions. We hope to deliver models which account for increased solubility of drug in meal contents as information becomes available.

REFERENCE

1. Pithavala, *Cancer chemotherapy and pharmacology,* 70 (2012): 103-112

SimulationsPlus