Title: Exploring the Relationship of Drug BCS Classification, Food-Effect, and Gastric pH-Mediated Drug Interactions

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BACKGROUND:

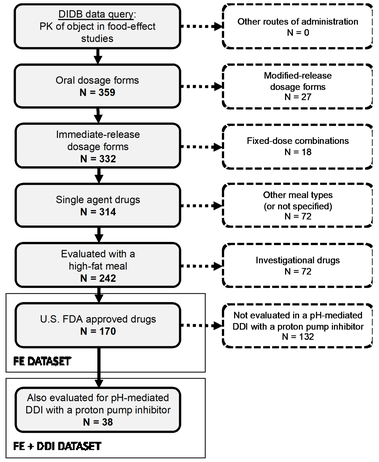
Food-effect (FE) and **gastric pH-mediated drug-drug interactions** (DDIs) are absorption-related. Here, we evaluated if the Biopharmaceutical Classification System (BCS) may be correlated with FE or pH-mediated DDI observed.

METHODS:

Trends in FE data were investigated for **170 drugs** with clinical FE studies from the literature and new drug applications (2013-2019) (UW Drug Interaction Database & Drugs@FDA search).

FE studies were defined as:

- No effect (AUC ratio [AUCR] Fed/Fasting, 0.80-1.25),
- Positive (AUCR ≥1.25), or
- Negative (AUCR ≤0.8)



A **subset of 38 drugs** was also evaluated to determine whether FE results can inform the need for a gastric pH-mediated DDI study.

RESULTS:

- Overall, drugs with significantly positive FE (AUCR ≥2.0; N=14) were BCS Class 2 or 4, while drugs with significantly negative FE (AUCR ≤0.5; N=2) were BCS Class 1 or 3 (Table 1 & Figure 2).
- **Lack of FE** was aligned with the **lack of a pH-mediated DDI** for all seven BCS Class 1 or 3 drugs (azacitidine, baricitinib, cobimetinib, eliglustat, isavuconazonium (isavuconazole), osimertinib, and ponatinib) but not for BCS Class 2 or 4 drugs in this dataset (Figure 1).
- For the 12 BCS Class 2 or 4 weak base drugs (WBDs) with a **positive FE**, only 6 had a pH-mediated DDI (AUCR ≤0.8) (Figure 1).
- Among the 13 BCS Class 2 or 4 WBDs with **no FE**, 6 had a pH-mediated DDI (AUCR ≤0.8): acalabrutinib, dacomitinib, entrectinib, palbociclib, riociguat, and velpatasvir (Figure 1).

The lack of a **food-effect aligned with** the lack of a **pH-mediated DDI** for BCS Class 1 or 3 drugs, but not for BCS Class 2 or 4 drugs.

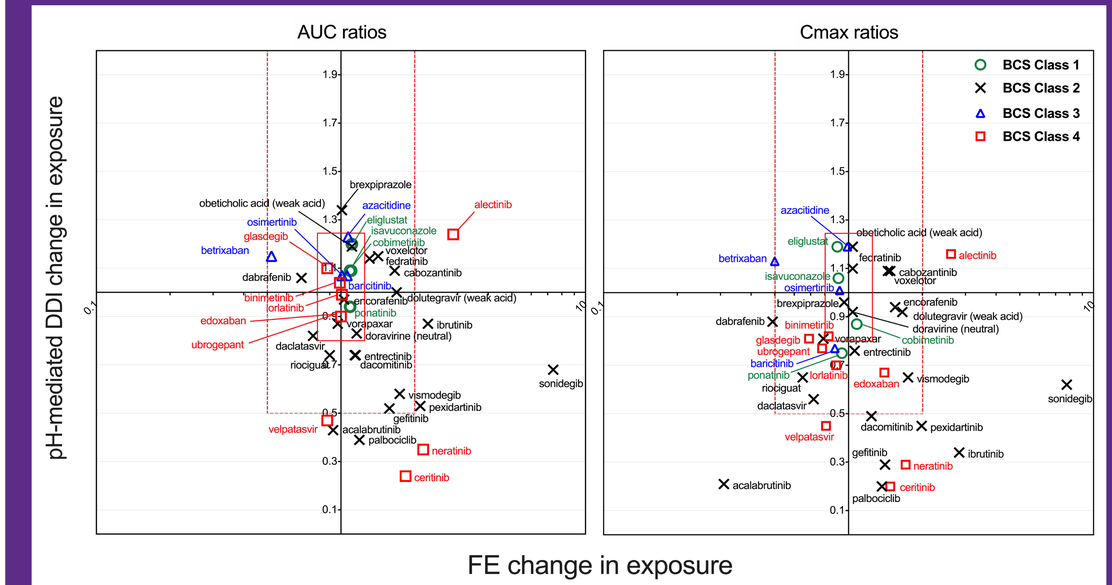


Figure 1. Change in drug exposure (AUC and C_{max} ratios) of weak base drugs during evaluation of FE and gastric pH-mediated DDI, by BCS class; — AUC and C_{max} ratios within 0.8–1.25; --- AUC and C_{max} ratios within 0.5–2.0 (drugs are weak bases, unless otherwise specified).

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Table 1. Overall summary of FE dataset by BCS class based on AUCR; *N* (%)

	N drugs	No FE (AUCR 0.8-1.25)	Positive FE (AUCR ≥1.25)	Negative FE (AUCR ≤0.8)
BCS Class 1	25	24 (96)	0 (0)	1 (4)
BCS Class 2	69	39 (57)	26 (38)	4 (6)
BCS Class 3	26	16 (62)	3 (12)	7 (27)
BCS Class 4	26	19 (73)	6 (23)	1 (4)
BCS Class not specified*	24	12 (50)	8 (33)	4 (17)

**Including BCS Class 1/3 (N=6), BCS Class 2/4 (N=17), and BCS Class 3/4 (N=1).*

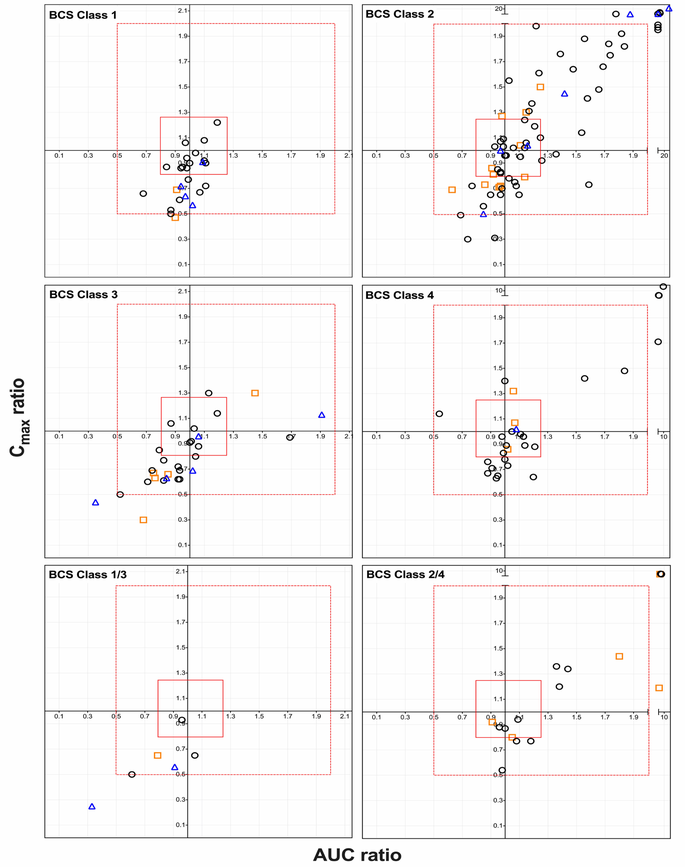

Figure 2. AUC and C_{max} ratios for all drugs with FE studies, by BCS class: △ amphoteric or neutral; ○ weak base; □ weak acid; — AUC and C_{max} ratios within 0.8–1.25; --- AUC and C_{max} ratios within 0.5–2.0.

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