Application of Dissolution Profile Comparison for Gastric pH-Dependent Drug-Drug Interaction Prediction

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INTRODUCTION

Absorption of orally administered weak base drugs (WBDs) with pH-dependent solubility may be reduced when co-administered with acid-reducing agents (ARAs), leading to clinically significant drug-drug interactions (DDIs). Given the possibility of compromising drug efficacy because of pH-dependent DDI, it is important that pharmaceutical companies and regulatory agencies evaluate whether a WBD has a potential for pH-dependent DDIs and mitigate the DDI risk as appropriate.

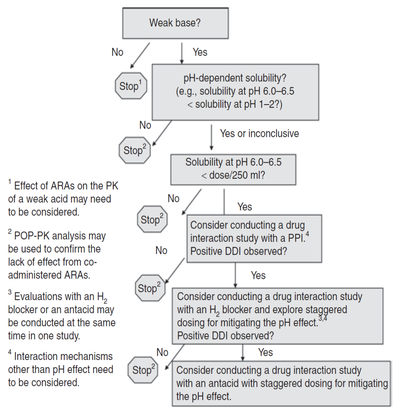

Figure 1. Proposed preliminary conceptual framework for clinical DDI evaluation with ARAs (e.g., proton pump inhibitors (PPIs), H2 blockers or antacids) for WBDs under fasting conditions. (Zhang L, et al, Clin Pharmacol Ther, 2014).

A preliminary conceptual framework for predicting gastric pH-dependent DDI potential for WBDs based on their solubility and clinical dose was proposed in our previous publication (**Figure 1**) [1]. This framework does not include gastric pH-dependent DDI potential evaluation using in vitro dissolution data, which could be important for DDI predictions of drug products with formulation modifications to mitigate such DDI potential (e.g., use of acidulants, surfactants, or solid dispersion to enhance drug solubility in high pH).

OBJECTIVES

To assess how dissolution profile comparisons under different pH conditions may be incorporated to predict gastric pH-dependent DDIs.

METHODS

- Drug product information (Drug substance physicochemical properties and formulation details) and pH-dependent DDI trial designs and results for new molecular entities (NMEs) approved by the U.S. FDA during 2003-2018 that included dedicated clinical DDI studies with ARAs.
- 28 NMEs with available dissolution profiles generated in pH 1.2-2.0, 4.5, and 6.8 media were collected from new drug application (NDA) submissions and Drugs@FDA [2]. These media were selected to mimic gastric conditions under fasted (pH 1.2~2.0), or fed states (pH 4.5), or when ARAs are co-administered (pH 6.8).
- "Predicted" positive: Similarity factor (f_2) was used to compare dissolution profiles for possible pH-dependent DDI prediction (i.e., dissolution profiles at pH 1.2~2.0 vs. pH 6.8 and at pH 4.5 vs. pH 6.8 were compared to predict DDIs at fasting and fed conditions). We defined f_2<50 indicating non-similar dissolution profiles as **"predicted positive"** DDI (**Figure 2**).

$$f_2 = 50 \times \log\left\{\left[1 + (1/n)\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} \times 100\right\}$$

Fasted condition: pH 1.2 (2.0) vs pH 6.8
Fed condition: pH 4.5 vs pH 6.8
⇨ $f_2 \geq 50$ Negative DDI
$f_2 < 50$ Positive DDI

Figure 2. Proposed calculation of "predicted" DDI interaction using similarity factor (f_2) to compare dissolution profiles at different pH media.

- "Observed" positive: This is defined as when a clinical DDI study shows a decrease in drug's peak plasma concentration (C_{max}) or area under the plasma concentration-time curve (AUC) ≥25% when co-administered with ARAs.
- Prediction accuracy (PA) = ((TP + TN)/total N) ×100%.

RESULTS

62 NME drugs that were approved from 2003 to 2018 have dedicated clinical DDI studies with ARAs. After excluding drugs with confounding factors for pH dependent DDI (e.g., with enzyme- or transporter-mediated DDI), 28 drugs with presented dissolution profiles at pH 1.2-2.0, 4.5 and 6.8 were recorded, including 2 neutral compounds, 2 weak acids and 24 weak bases. Refer to Table 1 for 13 representative NMEs.

Table 1. Background information of NMEs with dissolution comparisons and DDI predictions (13 representative NMEs)

Drug Name	Approval Year	DDI study with ARA condition (Fed or Fasted)	Dosage Form	Highest Strength	Special Excipient	Base, Acid or Neutral?	f_2 (pH1.2~2.0 vs pH 6.8)	f_2 (pH 4.5 vs pH 6.8)	Predicted DDI	Observed DDI	Prediction Outcome[c]	Diseases Indication
IRESSA (gefitinib)	2003	Fasted	IR Tablet	250 mg	Sodium lauryl sulfate	Base	16.01		Yes	Yes	TP	Beast and lung cancer
REYATAZ (atazanavir sulfate)	2003	Fasted/ Fed (light meal)	IR Capsule	300 mg	No	Base	1.25	~46	Yes/Yes	Yes/Yes	TP/TP	HIV, antiviral
PREZISTA[d] (darunavir ethanolate)	2006	Fed (standard meal)	IR Tablet	400 mg[a]	No	Base	16.69	95.59	No	No	TN	HIV, antiviral
ISENTRESS (Raltegravir)	2007	Fasted	IR	600 mg	No	Acid	12.65		Yes	Yes	TP	HIV, antiviral
NUCYNTA (tapentadol hydrochloride)	2008	Fasted	IR Tablet	100 mg	No	Neutral[b]	52.23		No	No	TN	analgesic
ONGLYZA (saxagliptin hydrochloride)	2009	Fasted	IR Tablet	5 mg	No	Base	72.72		No	No	TN	Type II diabetes
MULTAQ[d] (dronedarone hydrochloride)	2009	Fed	IR Tablet	400 mg	No	Base	51.7	13.2	Yes	No	FP	Rhythm problems
PRADAXA (dabigatran etexilate mesylate)	2010	Fasted /Fed (light meal)	IR Capsule	150 mg	Tartaric acid	Base	3.5	37.14	Yes/Yes	Yes/Yes	TP/TP	Blood thinner
EDURANT[d] (rilpivirine hydrochloride)	2011	Fasted/ Fed (standard meal)	IR Tablet	25 mg	No	Base	4.31	6.71	Yes/Yes	Yes/Yes	TP/TP	HIV, antiviral
XALKORI (crizotinib)	2011	Fasted	IR Capsule	250 mg	No	Base	6.67		Yes	No	FP	Lung cancer
XARELTO (rivaroxaban)	2011	Fasted	IR Tablet	10 mg[a]	sodium lauril sulfate	Neutral	51.7 (6.5)		No	No	TN	Blood thinner
INLYTA (axitinib)	2012	Fasted	IR Tablet	5 mg	No	Base	2.45		Yes	Yes	TP	Kidney cancer
BOSULIF (bosutinib monohydrate)	2012	Fasted	IR Tablet	500 mg	No	Base	11.33		Yes	Yes	TP	Leukemia

Note: [a]The dose used here is the highest dose for dissolution tests, but not the highest strength for FDA approval and commercialization; [b]The drug substance is ionizable with pKa over 9.0. However, at physiological pH (1-8), the drug is considered un-ionizable, with no pH-dependent solubility. [c]TP, true positive (predicted positive and observed positive); TN, true negative (predicted negative and observed negative); FP: false positive (predicted positive and observed negative). [d] Taken with food as indicated in the label

Table 2. Prediction summary of pH dependent DDIs for all NMEs and WBDs (from 2003-2018) using dissolution profile comparison

Database	TP (%)	TN (%)	FP (%)	FN (%)	Prediction Accuracy
NMEs (n = 28)	16 (57%)	9 (32%)	3 (11%)	0	25/28 (89%)
WBDs[a] (n = 24)	15 (63%)	6 (25%)	3 (12%)	0	21/24 (88%)

Note: Data source: Drugs @ FDA. Notes: FP, false positive; TP, true positive; TN, true negative; FN: false negative. Prediction accuracy = ((TP + TN)/total N) ×100%. [a] excluding 2 weak acid, and 2 neutral drugs

Figure 3. Representative dissolution profiles of NMEs at different pHs

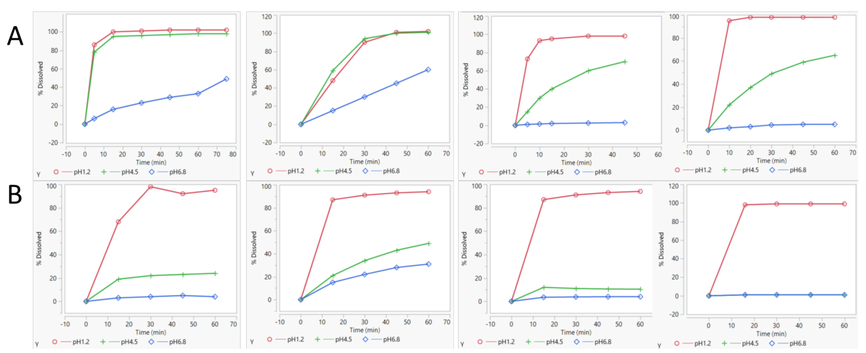

Figure 3. Dissolution profiles of drugs in pH 1.2-2.0, 4.5 and 6.8 media were compared and presented. Representative pH-dissolution plots of drugs that belong to (A), true-positive (TP) drugs that showed pH-dependent DDI with ARAs even in the presence of food; (B), true-positive (TP) drugs for which food significantly mitigated the pH-dependent DDI with ARAs.

Table 3. Representative clinical DDI studies with ARAs (2003-2018)

Drug Name	Labeling Recommendation	Dosing Timing	Study Design	ΔCmax with ARA	ΔAUC with ARA	ARA	Food Condition
IRESSA (gefitinib)	Histamine H_2-receptor antagonists may potentially reduce efficacy	Concomitant	Single-dose drug (250 mg) + multiple dose ranitidine (450 mg)	70%↓	44%↓	H_2 blocker: ranitidine	Fasted
REYATAZ (atazanavir sulfate)	Coadministration with famotidine substantially decreases plasma concentrations of the drug, which may result in loss of therapeutic effect and development of resistant	Concomitant	Multiple-dose drug (400 mg) + multiple-dose famotidine (40 mg b.i.d.)	47%↓	41%↓	H_2 blocker: famotidine	Fed
	Coadministration with omeprazole (40 mg once daily) substantially decreases plasma concentrations of the drug, which may result in loss of therapeutic effect and development of resistant	Concomitant	Multiple-dose drug (400 mg)+ multiple-dose omeprazole (40 mg q.d.)	96%↓	94%↓	PPI: omeprazole	Fasted
CYMBALTA (duloxetine hydrochloride)	Drugs that raise the gastrointestinal pH may lead to an earlier release of duloxetine. However, co-administration of Cymbalta with aluminum- and magnesium-containing antacids or Cymbalta with famotidine, had no significant effect on the rate or extent of duloxetine absorption after administration of a 40 mg oral dose. It is unknown whether the concomitant administration of proton pump inhibitors affects duloxetine absorption	Staggered: drug administered 1, 2 or 4h before or after dosing of ARAs	Single-dose 40 mg + famotidine 40 mg; Mylanta 20 ml given after dosing of duloxetine	No significant effect		H_2 blocker: famotidine; Antacid: Mylanta	Fasted
PREZISTA (darunavir ethanolate)	No change in darunavir PK, and no dose adjustment needed	Concomitant	Ranitidine (150 mg, BID) with Darunavir/ritonavir (400/100 mg, BID)	4%↓	5%↓	H2 blocker: ranitidine	Fed
		Concomitant	Omeprazole (20 mg) daily with Darunavir/ ritonavir (400/100mg, BID)	2%↑	4%↑	PPI: omeprazole	Fed
ISENTRESS (Raltegravir)		Concomitant	Single dose of 400 mg drug with omeprazole	↑300-400%	↑300-400%	PPI: omeprazole	Fasted
NUCYNTA (tapentadol hydrochloride)	No change in tapentadol PK, and no dose adjustment needed	Staggered: drug administered 2h after dosing of omeprazole	Single-dose drug (80 mg) + multiple-dose omeprazole	No significant effect		PPI: omeprazole	Fasted
ONGLYZA (saxagliptin hydrochloride)	No clinically meaning full change in saxagliptin exposure	Staggered: drug administered 3h after famotidine	Single-dose drug+single-dose famotidine (40 mg)	14%↑	3%↑	H_2 blocker: famotidine	Fasted
		Concomitant	Sing-dose drug +multiple-dose omeprazole (40 mg q.d.)	2%↓	↑13%	H_2 blocker: famotidine	Fasted
MULTAQ (Dronedarone hydrochloride)	No clinically meaningful change in dronedarone exposure and no dose adjustment needed	Concomitant	Multiple doses of 400 mg BID drug for 14 days+multiple dose 40 mg OD pantoprazole at 7-14 days	↑13%	↑7%	PPI: pantoprazole	Fed
PRADAXA (dabigatran etexilate mesylate)	No clinically meaningful change in drug exposure	Staggered (drug administered 10 h after H2 blocker)	Single-dose drug+ multiple-dose ranitidine (150mg q.d)	Not change	2%↑	H2 blocker: ranitidine	Fasted
	Dose need to be adjusted when dosed together with 40 mg PPI pantoprazole	Concomitant	Singe-dose drug + pantoprazole (40 mg) BID	40%↓	29%↓	PPI: pantoprazole	Fasted
EDURANT (rilpivirine hydrochloride)	Administered H2-receptor antagonists at least 12 before or at least 4h after the drug	Staggered: famotidine administered 2, 12h before or 4h after drug	Single-dose drug (150 mg)+single-dose famotidine (40 mg)	2h before: ↓85%	2h before ↓76%	H_2 blocker: famotidine	Fed
	should not be co-administered with PPIs	Concomitant	Multiple dose drug (150 mg) with multiple dose omeprazole (20 mg)	↓40%	↓40%	PPI: omeprazole	Fed

CONCLUSIONS

- Comparison of dissolution profiles generated at pH 1.2~2.0, 4.5, and 6.8 may be particularly useful to predict gastric pH-dependent DDI potential for immediate-release (IR) WBD drug products with formulation modifications to mitigate such DDI (e.g., use of acidulants, surfactants or solid dispersion to enhance drug solubility) or predict pH-dependent DDI under fed condition for those products that have to be taken with food.
- With similar prediction accuracy as using solubility and clinical dose, dissolution profile comparison may provide additional considerations to help evaluate the need for conducting a dedicated clinical DDI study with ARAs, contributing to a more efficient drug development program. With more cases and data available, additional evaluations will be conducted to further evaluate and refine the conditions for this approach.

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REFERENCES

[1] Zhang L, et al. Clinical Pharmacology & Therapeutics, 96(2):266-277, 2014.

[2] DRUGS@FDA: https://www.accessdata.fda.gov/scripts/cder/daf/