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In Vivo Predictability of Flux Measurements for Assessment of Bioavailability Reduction due to Drug–Drug Interactions with Acid Reducing Agents

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PURPOSE

The challenge of developing poorly soluble drugs continues to grow as more and more new chemical entities (NCEs) are poorly soluble. Formulation strategies often rely on maintaining a supersaturated state for poorly soluble drugs. A large portion of modern patients are medicated to reduce stomach acidity, and Drug–Drug Interactions (DDI) with Acid Reducing Agents (ARAs) can dramatically increase pharmacokinetic variability and decrease bioavailability—especially for weak bases. This study evaluated pH-shift flux measurements as in vivo predictive tool for DDI assessment.

METHOD(S)

Three research drug products were received from Genentech and used as model formulations:

Compound A: BCS Class IIa Salt
Formulated Tablet, 200 mg of API;
pK_a 4.3 (monoprotic acid)
logP 6.18
Solubility:
- 0.1 µg/mL at pH 1.0
- 3.18 mg/mL in FaSSIF

Compound B: BCS Class IIb
Formulated Tablet, 20 mg of API
pK_a 1.53, 4.3 (di-protic base)
logP 2.1
Solubility:
- 0.75 mg/mL at pH 1.0
- < 1 µg/mL in FaSSIF

Compound C: BCS Class IIb
Formulated Tablet, 50 mg of API
pK_a 1.1, 3.3, 5.0 (tri-protic base)
logP 3.3
Solubility:
- > 100 mg/mL at pH 1.0
- ~1 µg/mL in FaSSIF

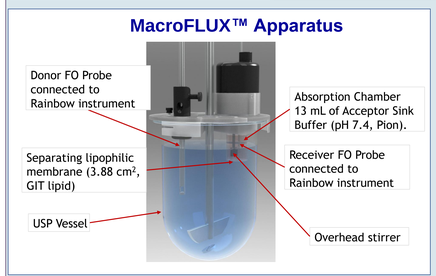

Figure 1. A MacroFLUX™ device (Pion Inc.) consisted of absorption chambers inserted into modified vessel covers of the USP apparatus II dissolution bath. *In situ* concentration monitoring in both dissolution and absorption chambers was enabled through fiber optic UV probes connected to the Rainbow instrument (Pion Inc.).

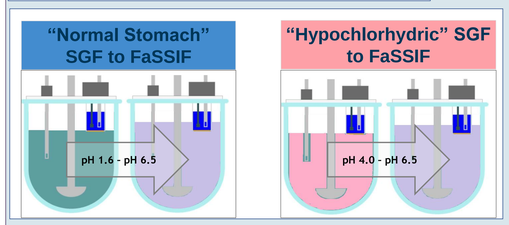

Figure 2. Schematic of the experimental setup to study DDI of ARAs.

- **800 mL SGF to 1000 mL FaSSIF after 30 min in the same vessel**
- **Continuous monitoring dissolution and flux for 6 hours**
- **Full size formulated products in USP apparatus II**

RESULTS

Compound A (BCS Class IIa) No DDI Expected in Clinic Studies

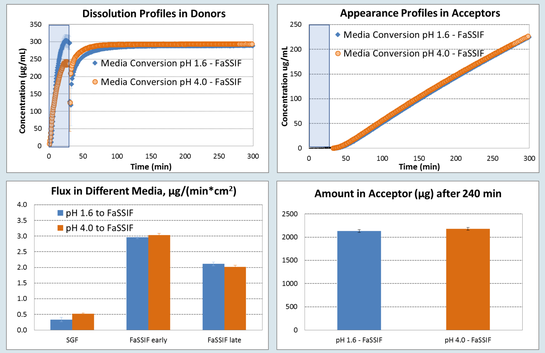

Figure 3. Dissolution profile (top left); appearance profile (top right); flux values (bottom left) were calculated by fitting concentration-time profile in the receiver with straight line ((15 – 30 min for SGF, 40 – 100 min for FaSSIF early and 300 – 360 min for FaSSIF late) and multiplying by a ratio of receiver volume to the area of the membrane; accumulated amount of Compound A in the receiver chamber (bottom right).

Compound B (GDC-0941[1], BCS Class IIb) Strong DDI Expected in Clinic Studies

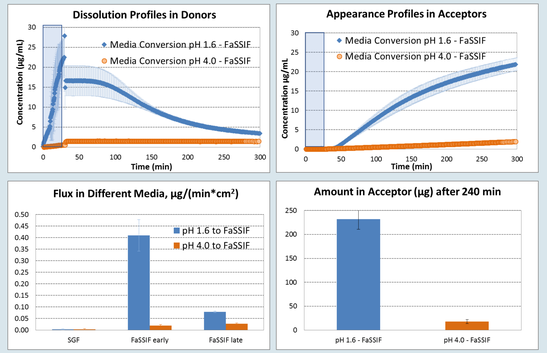

Figure 4. Same as Figure 3, but for Compound B

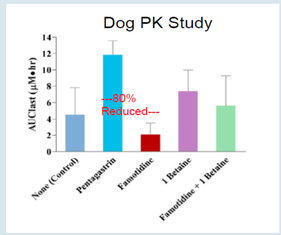

Figure 6. AUC in dog PK study for GDC-0941 reported in Ref. 1

Compound C (BCS Class IIb) Product Formulated to Minimize DDI from ARA

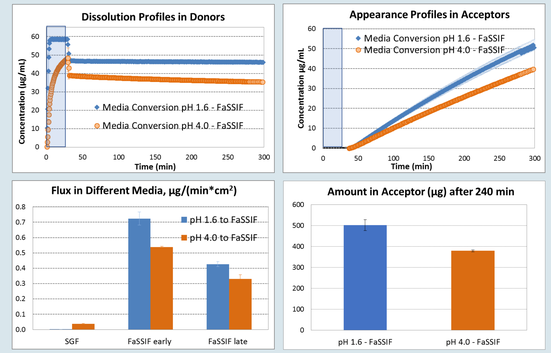

Figure 5. Same as Figure 3, but for Compound C

Clinical rBA

Pretreatment		A/B	
A	B	Cmax ratio	AUC_{0-24} ratio
ARA	No	0.52	0.74
rabeprazole			

Table 1. C_{max} and AUC reduction due to ARA in dog studies.

- **No difference in flux or absorbed amount *in vitro***
- **No DDI of ARA in human studies**

- **>90% reduction in flux and absorbed amount *in vitro***
- **~80% reduction in AUC due to DDI of ARA in dog PK studies**

- **~25% reduction in flux and absorbed amount *in vitro***
- **Correlated with dog PK results**

CONCLUSION(S)

- MacroFLUX™ can be used for assessing the risk factors associated with DDI caused by ARAs.
- In vitro data correlated well with PK data (animal and human) and correctly rank-ordered formulations designed to minimize DDI in hypochlorhydric patients.
- Membrane is stable to pH change, formulations and biorelevant media.
- Use of FO eliminated need for the sampling.

REFERENCES

1. Pang J, Dalziel G, Dean B, Ware JA, Salphati L. Pharmacokinetics and absorption of the anticancer agents dasatinib and GDC-0941 under various gastric conditions in dogs - Reversing the effect of elevated gastric pH with betaine HCl. Mol Pharm. 2013;10(11):4024–31.

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