APPLICATION / TECHNICAL NOTE

# Using Integrated Absorption Chamber with USP II Dissolution Apparatus to Predict Risk of Drug-Drug Interaction from pH-Modifying Agents

## Purpose

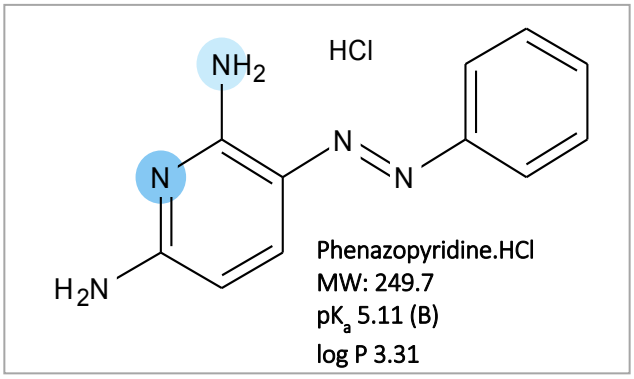
It has been shown that a miniaturized two-stage *in vitro* dissolution test[1] can be used to understand why some low-soluble weak basic drugs show reduced or highly variable absorption when co-administered with pH-modifying agents. The goal of this study was to demonstrate that an absorption chamber combined with USP I and II dissolution apparatus can be used to study similar drug-drug interactions (DDI) of the final dosage forms.

## Method

Over the counter phenazopyridine hydrochloride (PHZ) 97.5 mg dose tablets (AZO Urinary Pain Relief® Maximum Strength, i-Health, Inc., AZO or Brand) and the same dose of generic tablets (Pain Relief Maximum Strength, CVS Health, or Generic) were used in the study as model drug products (Figure 1). A MacroFLUX™ device (Pion Inc.) consisted of 6 cylindrical absorption chambers with 13 mL working volume and a filter supported artificial lipophilic membrane (Double-Sink™ PAMPA model[2], Pion Inc.) with area 3.88 $cm^2$ attached to the bottom of the chambers. These compartments were inserted into modified vessel covers of the dissolution bath (Erweka Model DT 126 light). Concentration monitoring in both dissolution and absorption chambers was enabled through fiber optic UV probes connected to the Rainbow instrument (Pion Inc.). Stirring in the absorption chamber was done using overhead stirrer bundled with measuring mini UV probe while the standard paddle of USP II apparatus provided stirring (100 rpm) in the dissolution vessels. The dissolution experiments started by dropping formulations in 850 mL of either pH 1.6 buffer ($SGF_{1.6}$) or pH 4.0/6.5 buffers ($SGF_{4.0}$/$FaSSIF_{blank}$) that simulated unmodified or modified gastric fluid respectively. After 30 minutes, the media in dissolution vessels were converted to 1062.5 mL of FaSSIF by adding media-converting concentrates. Absorption compartments in all cases contained Absorption Sink Buffer (ASB, pH 7.4, Pion Inc.).

A schematic of the experimental setup is depicted in Figure 2.

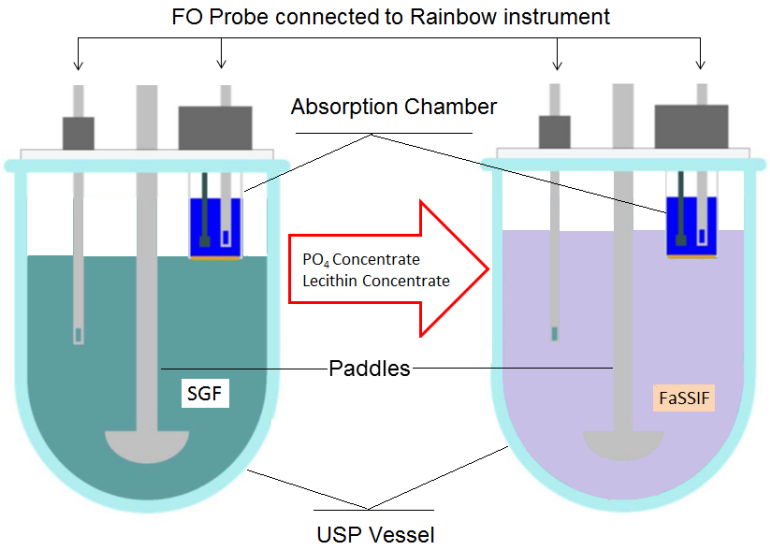
**Figure 1.** Phenazopyridine: structure, physicochemical properties and pictures of drug products studied.





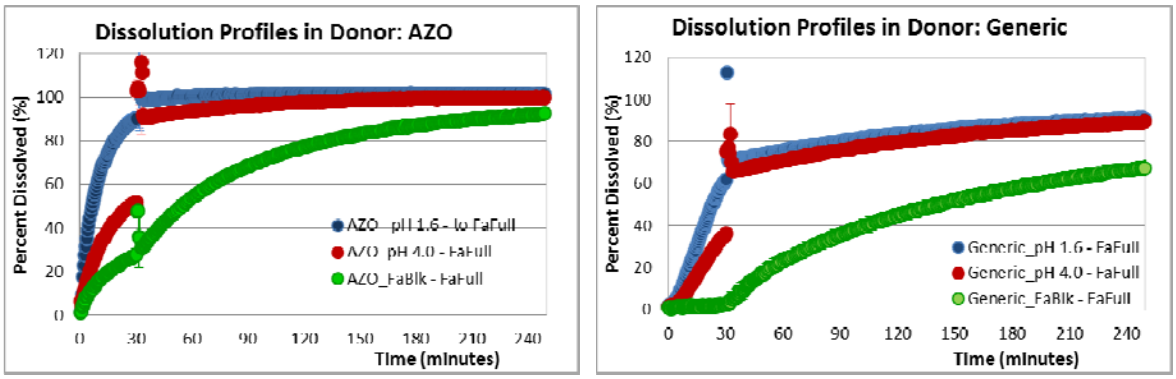
## Results

**Figure 2.** Schematic of MacroFLUX setup in media-conversion experiment.



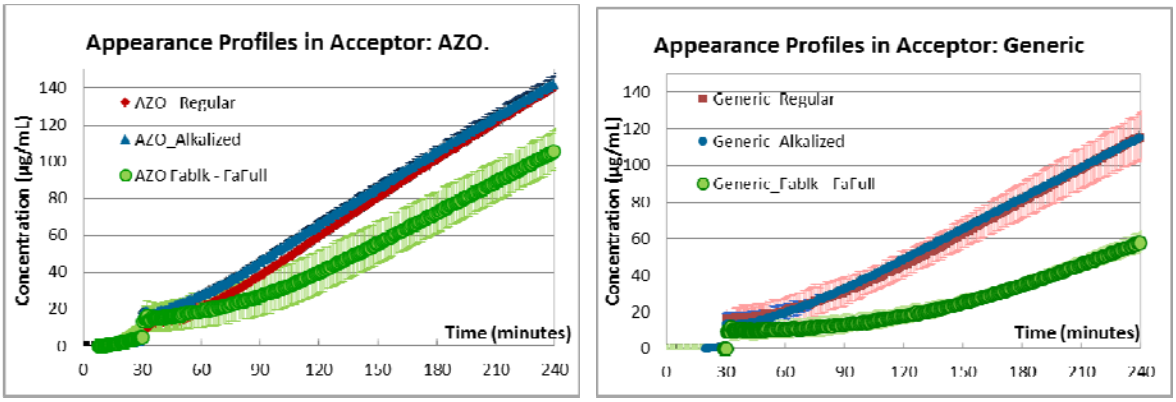

AZO formulation dissolved fast in $SGF_{1.6}$ reaching 90% dissolved at 30 minutes when it was converted to FaSSIF. Dissolved amount stayed at 100% in the FaSSIF. Generic formulation was dissolving slower reaching approximately 62% dissolved after 30 minutes of dissolution in $SGF_{1.6}$. Compound continued dissolving slowly after conversion to FaSSIF going from approximately 70% to approximately 85% dissolved between 40 minutes and 240 minutes of experiment. Dissolution of both Brand and Generic forms was slower in $SGF_{4.0}$ with dissolved amounts of approximately 50% and approximately 35% respectively. After switching to FaSSIF media, the dissolution curves for both formulations were close to their corresponding profiles from $SGF_{1.6}$ ->FaSSIF conversion assays (Figure 3).

**Figure 3.** Concentration – time profiles of PHZ in the donor chambers of MacroFLUX system obtained for AZO (left) and Generic (right) during media-conversion experiments.



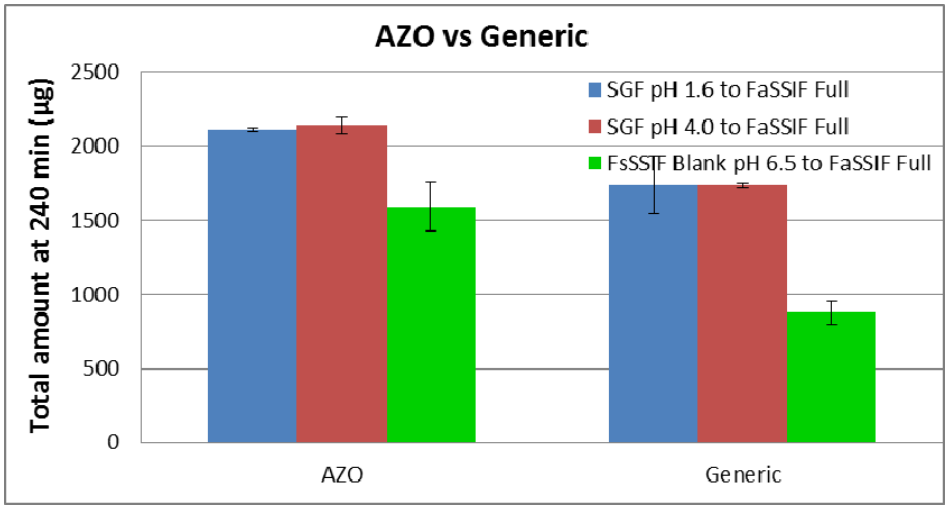

The flux can be calculated from the slope of the concentration – time profile measured in the receiver chambers (Figure 4).

**Figure 4.** Average concentration – time profiles of PHZ in the receiver chambers of MacroFLUX system obtained for AZO (left) and Generic (right) during media-conversion experiments. Vertical bars indicate standard deviations from the three measurements.




Flux of PHZ from AZO formulation was higher than the one from Generic formulation for both unmodified and modified SGF -> FaSSIF conversions. However, there was no significant difference in flux depending whether conversion was from $SGF_{1.6}$ or $SGF_{4.0}$. A conversion $FaSSIF_{blank}$ ->FaSSIF was considered as a model for extreme gastric pH modification when pH of stomach and small intestine are the same. In this case, AZO formulation dissolved only to approximately 30% in first 30 minutes with slow dissolution in FaSSIF reaching 90% dissolved after 250 minutes. The Generic form was practically insoluble in $FaSSIF_{blank}$ with approximately 65% dissolved at 250 minutes in FaSSIF. The steady state fluxes for AZO and Generic formulations were 1.2 and 1.6 times lower than in the case of $SGF_{1.6}$->FaSSIF conversion correspondingly. The total amounts of PHZ in the receiver compartment after 240 minutes from AZO formulation were 2.11 ± 0.01 mg ($SGF_{1.6}$->FaSSIF), 2.14 ± 0.05 mg ($SGF_{4.5}$->FaSSIF), and 1.59 ± 0.16 mg ($FaSSIF_{blank}$->FaSSIF). Corresponding values for the Generic formulation were 1.74 ± 0.19 mg, 1.74 ± 0.02 mg, and 0.88 ± 0.08 mg (Figure 5).

**Figure 5.** Total amount of PHZ in the receiver compartment for the Brand and Generic formulations, depending on initial pH conditions of SGF media.



## Conclusion

This study demonstrated that device combining absorption chamber with the standard USP I or USP II dissolution apparatus (MacroFLUX) can be used for assessing the risk factors associated with DDI caused by pH-modifying agents. The *in vitro* results indicated that risk of decrease in bioavailability is low for both forms when effect of pH-modifying agents is moderate (e.g., 1.6 to 4.0 increase in gastric pH condition). Generic formulation may have a higher risk of DDI when pH of the gastric compartment is increased drastically to pH similar with intestinal pH conditions (pH 6.5).

## Contributing Authors

O.Tsinman, Pion Inc.; K.Tsinman, Pion Inc.; R. Lingamaneni, Pion Inc.; J. Li, Genentech, South San Francisco, CA; D. Kou, Genentech, South San Francisco, CA; M. Ragains, Genentech, South San Francisco, CA; and L. Wigman, Genentech, South San Francisco, CA.

## References

1. Mathias et al. Assessing the Risk of pH-Dependent Absorption for New Molecular Entities: A Novel in Vitro Dissolution Test, Physicochemical Analysis, and Risk Assessment Strategy. Mol. Pharmaceutics. 2013, 10 (11), 4063–4073.

2. Avdeef A, Nielsen PE, Tsinman O. PAMPA - A drug absorption in vitro model: 11. Matching the in vivo unstirred water layer thickness by individual-well stirring in microtitre plates. Eur J Pharm Sci. 2004;22(5):365-74.