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

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Purpose
It has been shown that 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 a system combining absorption chamber with USP 1 and 2 dissolution apparatus can be used to study drug-drug interactions (DDI) of the final dosage forms.

Methods
Over the counter phenazopyridine hydrochloride 97.5 mg dose tablets (AZO Urinary Pain Relief® Maximum Strength, i-Health, Inc., AZO or Brand) and the phenazopyridine hydrochloride tablets (the same dose, Pain Relief Maximum Strength, CVS Health, Generic) were used in the study as model drug products. A MacroFLUX\(^{TM}\) device (Pion Inc.) consisted of 6 cylindrical absorption chambers with 15 mL working volume and a filter supported artificial lipophilic membrane (Double-Sink\(^{TM}\) PAMPA model, Pion) 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). 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\(_{\text{blank}}\)) that simulated unmodified or modified gastric fluid respectively. After 30 min 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).

Results
AZO formulation dissolved fast in SGF\(_{1.6}\) reaching 90% dissolved at 30 min when it was converted to FaSSIF. Dissolved amount stayed at 100% in the FaSSIF. Generic formulation was dissolving slower reaching ~ 62% dissolved after 30 min of dissolution in SGF\(_{1.6}\). Compound continued dissolving slowly after conversion to FaSSIF going from ~70% to ~85% dissolved between 40 min and 240 min of experiment. Dissolution of both Brand and Generic forms was slower in SGF\(_{4.0}\) with dissolved amounts of ~50% and ~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. The flux of phenazopyridine 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\(_{\text{blank}}\) ->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 ~30% in first 30 min with slow dissolution in FaSSIF reaching 90% dissolved after 250 min. The Generic form was practically insoluble in FaSSIF\(_{\text{blank}}\) with ~65% dissolved at 250 min 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 phenazopyridine in the receiver compartment after 240 min 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\(_{\text{blank}}\)->FaSSIF). Corresponding values for the Generic formulation were 1.74±0.19 mg, 1.74±0.02 mg and 0.88±0.08 mg.

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., pH 1.6 – pH 4.0). 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).

References