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 test1 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 1 and 2 dissolution apparatus can be used to study similar drug-drug interactions (DDI) of the final dosage forms.

METHOD

AZO formulation dissolved fast in SGF, 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. 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, 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 (Figure 5).

RESULTS

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 to FaSSIF. A conversion FaSSIFblank → 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 FaSSIFblank 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 (Figure 5).

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