Poster Number

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Development of *In Vitro* Protein Binding Method for Bioequivalence Evaluation for Sucralfate Suspension

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PURPOSE

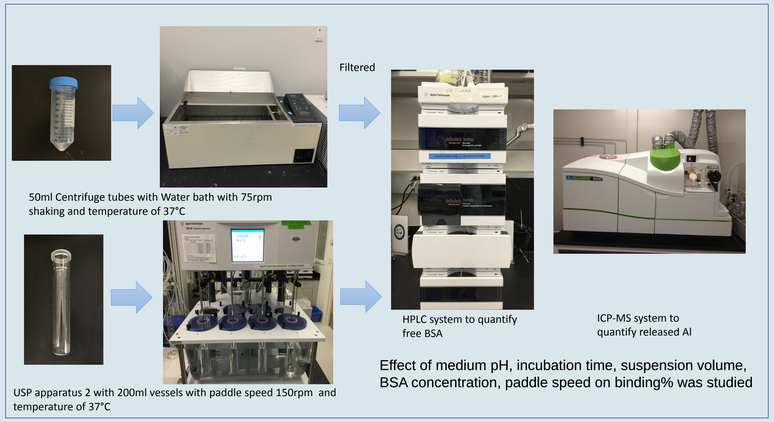
Sucralfate is an aluminum salt of sucrose octasulfate. It is a locally acting drug indicated for the short term treatment of active duodenal ulcer. Sucralfate is not absorbed systemically and thus pharmacokinetic evaluation approaches will not offer meaningful information to evaluate the bioequivalence between drug products. When reacts with acid, sucralfate releases aluminum (Al) and forms negatively charged aggregates. Thus Al release enables sucralfate to bind the positively charged proteins overexpressed in the ulcer area which is one of the mechanisms of action previously confirmed by *in vitro* and *in vivo* studies. The purpose of this study was to develop standardized, discriminatory *in vitro* evaluation methods based on the mechanism of action of sucralfate which are expected to be useful for comparing performance of sucralfate drug products.

OBJECTIVE

To develop an *in vitro* method for the evaluation of the performance of sucralfate based on protein binding and Al release.

METHODS

Two experimental set-ups were used: centrifuge tubes with water bath shaker and dissolution apparatus 2 with mini paddle/mini vessels.



Effect of medium pH, incubation time, suspension volume, BSA concentration, paddle speed on binding% was studied

Figure 1. Centrifuge tubes and dissolution vessels were used as protein binding "reactor"; the free protein was quantified by HPLC and the Al released was quantified by ICP-MS.

RESULTS

Protein Binding with Centrifuge Tube Method

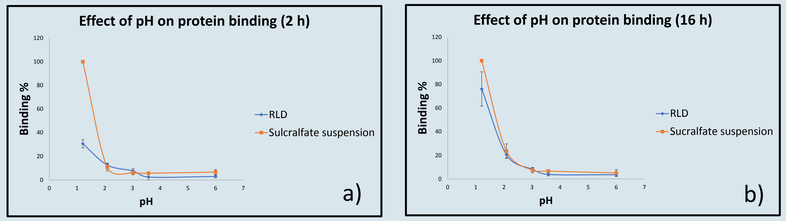
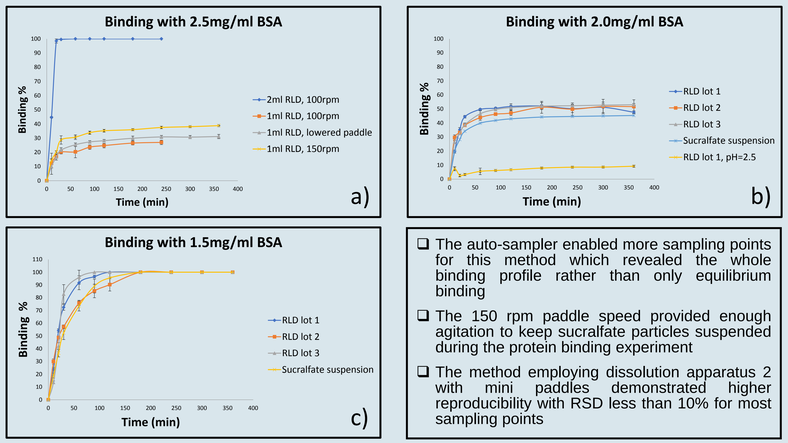


Figure 2. BSA binding results from centrifuge tube method: a) 0.5 ml sucralfate binding with 2.5 mg/ml BSA with different pH and 2 hours incubation time; b) 0.5 ml sucralfate binding with 2.5 mg/ml BSA with different pH and 16 hours incubation time.

- ❑ The centrifuge tube method involved a lot of manual operations and only limited incubation time points can be tested
- ❑ The protein binding process was time dependent. In acidic medium (pH=1.2), % binding significantly increased when incubation time increased from 2 to 16 hours
- ❑ Sucralfate suspension exhibited high protein % binding only in acidic medium (pH 1-2), while very limited % binding was observed in medium with pH higher than 2.5

Protein Binding with USP Apparatus 2 Method



- ❑ The auto-sampler enabled more sampling points for this method which revealed the whole binding profile rather than only equilibrium binding
- ❑ The 150 rpm paddle speed provided enough agitation to keep sucralfate particles suspended during the protein binding experiment
- ❑ The method employing dissolution apparatus 2 with mini paddles demonstrated higher reproducibility with RSD less than 10% for most sampling points

Figure 3. BSA binding results from USP Apparatus 2 method a) effect of suspension volume and instrument setting; b) binding kinetic profiles of RLD and sucralfate suspension with 200 ml, 2.0 mg/ml BSA; c) binding kinetic profiles of RLD and sucralfate suspension with 200 ml, 1.5 mg/ml BSA; pH=1.2

Al Release with USP Apparatus 2 Method

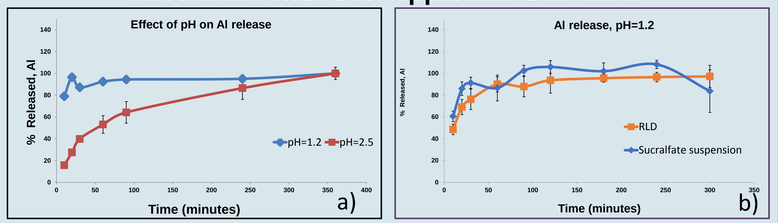


Figure 4. Al release profiles: a) effect of pH on Al release; b) Al release of RLD and Sucralfate suspension.

- ❑ Even a slightly increase of pH can significantly delay the release of Al
- ❑ In pH=1.2 medium, the Al release rate was fast and within 1 hour all Al was released; however in the pH=2.5 medium, the release rate was significantly decreased

CONCLUSIONS

- ❑ Experimental factors that were found to impact the BSA protein binding of sucralfate were sucralfate dose, BSA concentration, time of incubation and pH of the medium.
- ❑ The experimental set up using dissolution apparatus was found to be a robust *in vitro* method for the performance evaluation of sucralfate suspension when using standardized instrumentation. With this set up, protein binding and Al release of sucralfate suspension can be evaluated at the same time.
- ❑ Protein binding is more directly related to the mechanism of action of sucralfate and might be a better *in vitro* parameter to evaluate performance of sucralfate suspension.

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