In Vitro Assessments that Support In Vitro Binding Studies in Demonstrating Bioequivalence of Locally Acting Gastrointestinal Drugs

SBIA 2022: Advancing Generic Drug Development: Translating Science to Approval

Day 2, Session 5: In Vitro Binding Study for Locally Acting GI Drug Products

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Learning Objectives

You will learn to:

- ❑ Describe the rationale behind the in vitro assessments that support the binding studies for locally acting gastrointestinal (GI) drugs
- ❑ Identify examples of in vitro assessment for locally acting GI drugs recommended in product-specific guidances (PSGs)
- ❑ Describe key case study: sucralfate

Locally Acting GI Drugs

- They are not intended to be absorbed into the bloodstream
- The bioavailability of GI drugs is assessed by measurements that reflect the rate and extent to which the therapeutic ingredient is available in the GI tract
- Bioequivalence (BE) determination is based on product specific factors and the drugs' mechanism of action

In Vitro Binding Study

- Several locally acting GI drugs bind to phosphate or bile acid in the GI tract to exert their therapeutic efficacy

Examples: lanthanum carbonate and cholestyramine

- In vitro BE binding studies are a practical BE approach to assess the performance of the drug product at the site of action
- The binding study involves equilibrium and kinetic studies

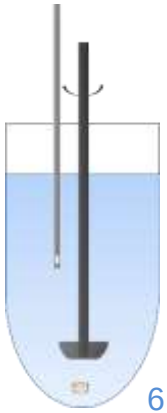
In Vitro BE Assessments

- Due to the complexity of locally acting GI drugs, other assessments may be needed to demonstrate BE:
  - ➢Active pharmaceutical ingredient (API) sameness
  - ➢Additional In vitro BE studies

  E.g., Dissolution, enzyme activity, viscosity

Example of In Vitro BE Assessments: Dissolution

- Commonly recommended in PSGs
- Different from and in addition to the quality control dissolution testing
- Measures rate and extent of the active binding moiety or related moiety released from the dosage form using biorelevant conditions



Dissolution Rationale: Case-By-Case

Ferric citrate tablet:

- In addition to demonstrating API sameness, dissolution may be used in lieu of binding studies when the test product formulation is Q1* and Q2* the same as reference
- Rationale: Formulation and manufacturing process may impact the release of the drug

*Q1 is qualitative sameness and Q2 is quantitative sameness

Dissolution Rationale: Case-By-Case

Lanthanum carbonate chewable tablet:

- Dissolution determines the release of the active binding moiety (Li) in two extreme conditions representative of chewing (whole and crushed tablet)
- Provides supportive evidence for the binding study of fully disintegrated tablet

Sucralfate tablet and suspension:

- Release of aluminum (Al) in acidic media is related to the activation of the drug (binding is not the only mechanism of action)

Dissolution Conditions to Support BE Determination

- Dissolution test conditions are found in the PSG
- Selection of appropriate pH should consider the pH ranges where drug dissolution occurs in the GI tract
- Selection of appropriate types of buffers should not confound analysis of analyte. E.g., a phosphate buffer should not be selected for phosphate binders
- For Q1/Q2 formulation, dissolution should be able to discriminate the effect of formulation and manufacturing process variability

Challenge Question #1

Which of the following is TRUE regarding in vitro assessments for BE determination of locally acting GI drugs (binders):

A. In vitro binding is the only in vitro BE assessment for binders

B. They are part of drug product quality control specifications

C. They are neither based on the drugs' mechanism of action nor product specific

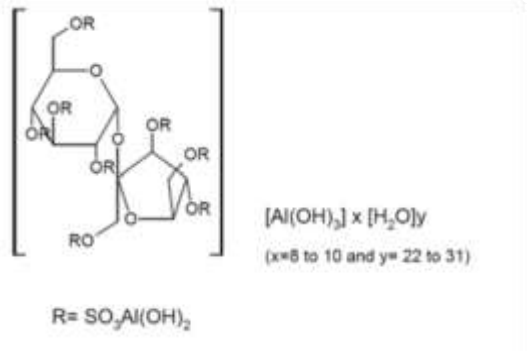
D. They may include dissolution or release of active binding moiety

In vitro assessments of

Sucralfate products

Sucralfate

- Al salt of sucrose octasulphate
- Minimally absorbed from the GI tract
- An antiulcer locally acting agent
- Administered orally (tablet or suspension)1 g four times per day up to 8 weeks
- Should be administered on an empty stomach (critical for mechanism)



Structure of Sucralfate

Drugs@FDA, NDA 018333 and NDA 019183, Labeling-Package insert
Sucralfate | C12H54Al9O55S8 - PubChem (nih.gov)

Approved Sucralfate Products

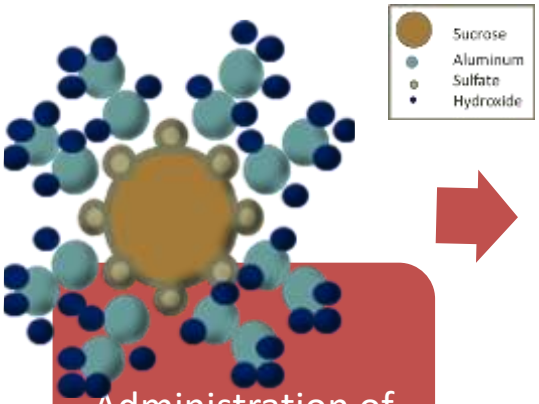
Product	Strength	Proprietary name	NDA	Approval date	Generic	PSG date recommended
Sucralfate oral tablet	1 gm	Carafate	018333	10/30/1981	A070848* A074415 A215576	09/2019
Sucralfate oral suspension	1 gm/ 10 mL	Carafate	019183	12/16/1993	A209356* A211884	10/2017

*First generic approved for tablet was 1996 and the suspension was approved in 2019

Previous BE Recommendations for Sucralfate Products

- Previous recommendations of the PSG included in vivo BE study with comparative clinical endpoints using patients with active duodenal ulcer disease
- A BE study with comparative clinical endpoints is difficult to conduct
  - Resulted in need for development of an alternative in vitro method for BE evaluation of sucralfate products

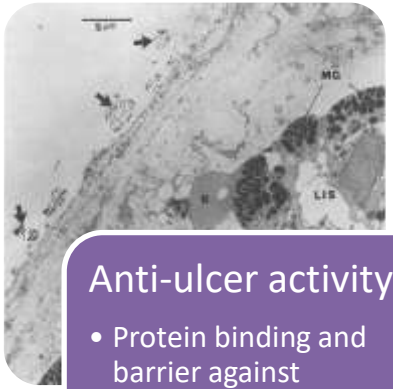
Mechanism of Action of Sucralfate



Administration of sucralfate in an empty stomach

Activation in acidic media (pH 1.2)

- Release of Al and formation of PAC*
- Formation of negatively charged sucralfate
- Formation of aggregate



Anti-ulcer activity

- Protein binding and barrier against hydrogen ions
- Inhibition of pepsin
- Bile acid binding
- Acid neutralizing (Weak)

*PAC: Poly aluminum chloride

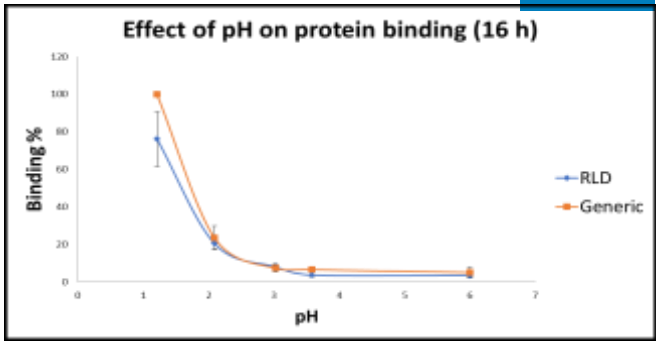
Drugs@FDA, NDA 018333 and NDA 019183, Labeling-Package insert

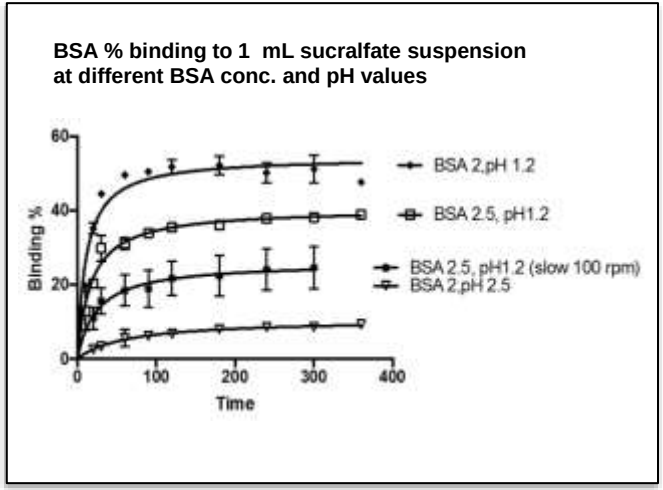
Sucralfate: From basic science to the bedside. 1995. Edited by D. Hollander and G. Tanger

BE Recommendations for Sucralfate Products

Based on the mechanism of action of sucralfate the BE recommendations include:

- Bioassays that are related to binding such as protein binding, bile acid binding, and pepsin activity
- Other in vitro assessments are included such as acid neutralizing capacity





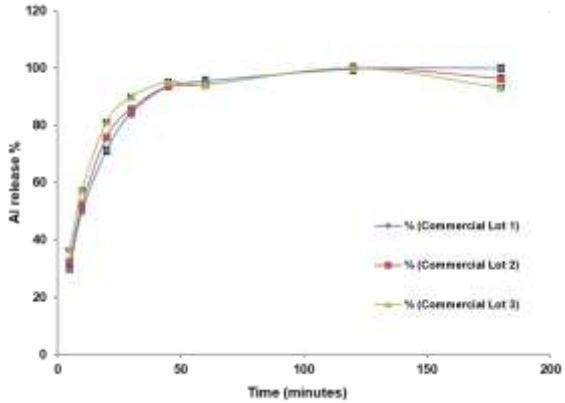
Al-Ghabeish, et al.. In Vitro Evaluation of the Performance of a Locally Acting Gastrointestinal Drug, Sucralfate.(Poster).AAPS Annual Meeting, San Diego, CA, Nov 11-15, 2017

Feng, X., et al. *Development of In Vitro Protein Binding Method for Bioequivalence Evaluation for Sucralfate Suspension*. .(Poster).AAPS Annual Meeting, San Diego, CA, Nov 11-15, 2017.

BSA: Bovine serum albumin
RLD: Reference listed drug

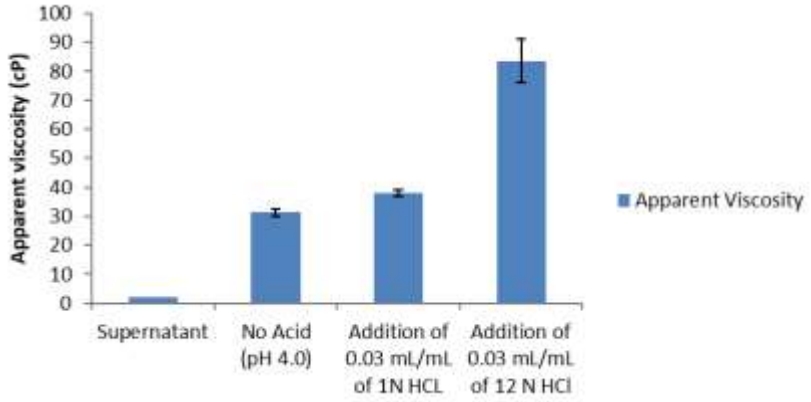
Additional In Vitro Assessments for Sucralfate

Al release at pH 1.2 (suspension and tablet)



The release of Al reaches equilibrium after 1 hour

Apparent viscosity with addition of acid (Suspension)



Addition of acid resulted in an increase in the apparent viscosity of the suspension

Al-Ghabeish, et al.. In Vitro Evaluation of the Performance of a Locally Acting Gastrointestinal Drug, Sucralfate.(Poster).AAPS Annual Meeting, San Diego, CA, Nov 11-15, 2017

Challenge Question #2

Which of the following is NOT included for BE determination of sucralfate products?

A. In vitro protein binding study

B. Pharmacokinetic study

C. Pepsin activity

D. Aluminum release (dissolution)

Summary

- In vitro BE binding is a practical BE approach to assess the performance of locally acting GI drugs at the site of action
- Due to the complexity of locally acting GI drugs, other in vitro assessments may be needed to demonstrate BE
- Dissolution is a commonly recommended in vitro assessment that can measure the rate and extent of the active binding moiety at the site of action
- Demonstrating BE for sucralfate products, locally acting GI drug, can be done using several in vitro assessments

Questions?

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Closing Thought

The more effort to understand complex drugs such as locally acting GI drugs the closer industry gets to develop more generics of complex drugs


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