M6013

In vitro Evaluation of the Performance of a Locally-acting Gastrointestinal Drug, Sucralfate

Manar Al-Ghabeish[1], Xin Feng[1], Adil Mohammad[1], Robert Lionberger[2], Patrick Faustino[1], Muhammad Ashraf[1]

Division of Product and Quality Research, Office of Testing and Research, office of Pharmaceutical Quality(OPQ), [2]Office of Generics(OGD), CDER,FDA, MD20993

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PURPOSE

To date, the lack of efficient bioequivalence pathways for locally-acting gastrointestinal (GI) drug products has limited the availability of generic drugs in this category. For example, sucralfate is an insoluble aluminum salt of sucrose octasulfate. It is marketed for the treatment of duodenal ulcer. The poor absorption of sucralfate in the GI tract makes traditional bioequivalence approach based on pharmacokinetics not applicable and, thus, it presents a challenge to establish bioequivalence for the drug products.

In vitro tests were developed to characterize the performance of sucralfate suspension and investigate the effects of formulation attributes and process parameters on the product performance. *In vitro* performance tests were divided into two groups: (1) Evaluation of the changes that occur in sucralfate under acidic conditions including aluminum release and electrostatic interactions that lead to aggregation or paste formation. The aluminum release was quantified by Inductively Coupled Plasma-Mass Spectrometry, while the sucralfate aggregation was characterized by analyzing rheological properties (apparent viscosity) and sedimentation rate and volume. (2) Assessment of the protein binding of sucralfate under acidic conditions. Because ulcer region has a higher protein content than intact mucosa, protein binding could be used as a measure of ulcer-specific binding.

METHODS

Focused Beam Reflectance Measurement (FBRM): Sucralfate sample of 1 g API, or 10 mL of suspension was added (total volume was 70 mL) and stirred. The FBRM used to collect particle count before and during acid titration at 37 °C.

Rheology and sedimentation rate: Rheological behaviors for sucralfate suspension (with or without acid treatment) were evaluated using stress-controlled hybrid rheometer equipped with a peltier concentric cylinder. After rheological analysis, the sample was resuspended and placed in a graduated cylinder. The volume of the sediment was recorded over time **.**

Aluminum (Al) release: USP dissolution apparatus 2 was used to analyze the Al release from sucralfate suspension. 10 mL of sucralfate suspension was added to each of the six vessels (900mL, pH 1, 37 °C) and 1.0 mL of sample was filtered and withdrawn at the specified time points. Also, 1mL of suspension diluted in 50 mL of water was treated with different volume of 1N HCl and left for over and hour to measure the Al release at different pH values.. Al was quantified by Inductively Coupled Plasma-Mass Spectrometry (ICP-MS)

Assessment of the protein binding of sucralfate: Bovine serum albumin (BSA) was used as model protein. The protein binding of sucralfate was determined by adding sucralfate suspension (1 mL) into BSA solutions of known concentrations and analyzing free BSA concentration as a function of time using dissolution apparatus 2 with mini paddle. The effects of BSA concentration, pH of medium, incubation and paddle rotation speed were investigated

RESULTS

Particle size count and acidic titration

During titration of sucralfate API, suspended particles started to aggregate and eventually formed one mass. This was accompanied by a sudden decrease in the count of fine particles (≤50 µm). The aggregation was occasionally associated with a temporary increase in the count of the large particles (>300 µm).
In case of suspension, aggregation and/or paste was not observed.

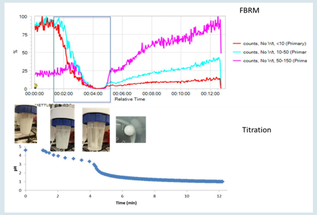

Figure 1: Particle count (FBRM) and images results of sucralfate API acid titration (1N HCl) at 37 °C.

Rheology of suspension and sedimentation rate

The suspension showed a non-Newtonian (rate index <1) and shear thinning behavior.(Figure 2)

The addition of acid resulted in an increase in the apparent viscosity due to the ionic interaction of charged molecules with the release of Al cations of sucralfate. (Figure 3)

The increase in the viscosity may explain the decrease in sedimentation rate and increase in sediment volume observed.(Figure 4)

On the other hand, the addition of the same volume of 12N HCl resulted in particle aggregation and further acceleration of sedimentation and reduction in the sediment volume. (Figure 4)

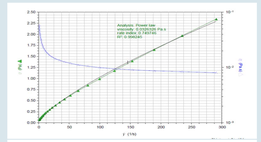

Fig 2:The stress and viscosity of sucralfate suspension as function of shear rate

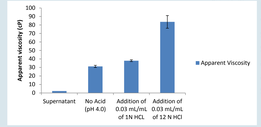

Fig 3: The viscosity of sucralfate suspension with and without the addition of strong acid

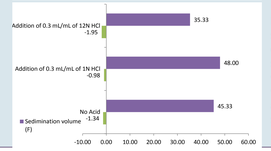

Fig 4: The sedimentation of sucralfate suspension with and without the addition of strong acid

Aluminum content by ICP-MS

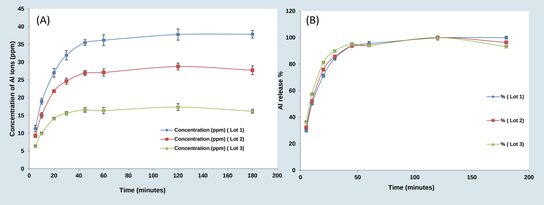

Figure 5: Al release in ppm (A) and in % (B) from sucralfate suspension during dissolution at pH 1.0

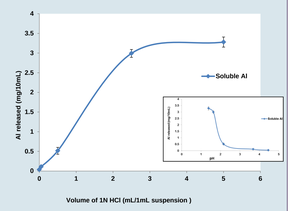

Figure 6: Al release for 1.0 mL (diluted to 50 mL) sucralfate suspension as a function of) volume of HCl added.

The release of Al reaches equilibrium after 1 hour.
The three lots show different Al release extent due to difference amount present in the volume of suspension used.
The amount of Al released from the suspension after 1 hour using was pH (acid) dependent and reached maximum at pH lower than 2.

Protein binding

Suconly in acidic medium (pH 1-2), while very limited binding was observed in medium with pH higher than 2.5.
The 150 rpm paddle speed provided enough agitation to keep sucralfate particles suspended. Compared to 100 rpm (high variation)
All soluble BSA was found to be bound to sucralfate (1mL) at concentration below 2 mg/mL.
ralfate exhibited high protein binding rate

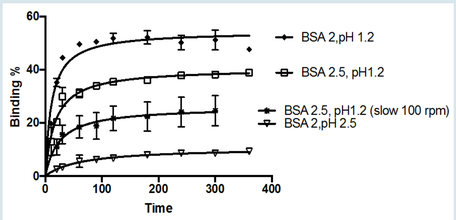

Figure 7: BSA binding % to 1 mL sucralfate suspension at different BSA conc. and pH values

CONCLUSION

In an effort to develop *in vitro* tests to evaluate the performance of sucralfate suspension, the most promising *in vitro* tests found are: analysis of apparent viscosity, sedimentation rate and volume, Al release and protein binding in the presence of acid.

DISCLAIMER

This scientific publication reflects the views of the authors and should not be construed to represent FDA's views or policies

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