Delayed Binding of Bile Salts by Matrix Bound Cationic Adsorbents Dispersed in Alginate Rafts

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402

Introduction

Gastroesophageal reflux disease (GERD) is a pathological condition that arises from the retrograde flow of stomach contents into the esophagus. The prevalence of GERD is significant, affecting approximately 20% of the population in Western countries (2). Furthermore, patients with GERD have marked increases in their likelihood of developing Barrett's esophagus which in turn increases the chance of developing esophageal cancers. While lifestyle modification is the most successful means by which to treat GERD, patients frequently need more immediate relief from their symptoms. Symptom management is often brought in the form of proton pump inhibitors (PPIs), H2 blockers, antacids, and/or surgical intervention. *(1,2)*.

Herein we present a formulation which delays the release of a Cationic Adsorbent via an Alginate Gel Raft designed to remain in the proton pump inhibited stomach of a patient. Additionally, a novel QC dissolution method utilizing fiber optic probes using UV analysis provides a fast throughput eliminating the need for complex HPLC separation analysis.

Methods

Reagents: DI H_2O, sodium glycocholate monohydrate (GCA) Sigma Aldrich, sodium acetate trihydrate J.T. Baker, glacial acetic acid VWR. sodium alginate Protanal CR 8223

Dissolution media Blank: 12.5mM acetate buffer pH 4.5 500mL/vessel.

Dissolution media: 12.5mM acetate buffer pH 4.5, 3.5g/L GCA Solution 500mL/vessel.

Dissolution Apparatus: Vankel Dissolution Bath (VK7000)- Dissolution bath with mini paddles apparatus 2, vessel temperature 37°C, RPM 250, run time up to 30hrs.

PION Rainbow®: *In situ* fiber optic (FO) probes with dedicated PDA (200-720 nm) for each channel with 5 mm stainless steel probes. Data collected in 2nd derivative mode λnm range (275-350)

API: Proprietary cationic adsorbent.

Sieve: U.S. standard screen size #20 stainless steel (0.841mm sieve opening)

HPLC: Shimadzu 2010A.

Three different formulations containing proprietary cationic adsorbent were prepared using varied compositions of alginate to produce distinct raft strengths along with matching placebo blends. A pH 4.5 buffer containing sodium glycocholate was used to test sequestration of bile acids of the formulations in a PPI modified stomach. The dissolution apparatus consisted of USP apparatus 2 mini paddles and a standard 1000mL USP dissolution vessel. The PION™ Rainbow Fiber Optic dissolution monitoring system probes were inserted into the USP dissolution vessel and monitored GCA sequestration in 2nd derivative mode. Accuracy was confirmed independently with HPLC to prove viability.

The API is insoluble and therefore the experiment required the monitoring of the sequestration of GCA in order to evaluate the performance of each formulation. To ensure visibility of the completion of the experiment excess GCA (3500ug/mL) was included and the endpoint was designed to achieve minimum concentration GCA of 500 µg/mL. A standard curve from 0.04 – 5.0 mg/mL was prepared in dissolution media, results for each channel are presented in **Figure 1**.

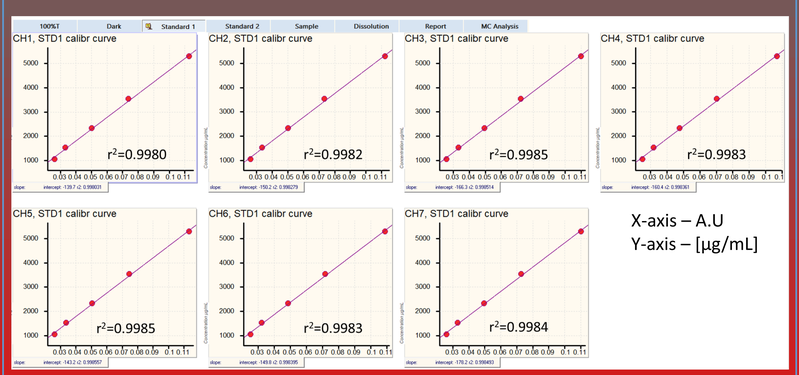

Figure 1. GCA standard curve in 12.5mM acetate buffer 5mm probe tips.

Methods Continued

All 7 channels of the Pion Rainbow system were blanked in dissolution media blank prior to placement into vessels containing dissolution media. The 7th channel was used to monitor placebo blends and facilitated a live blank during the dissolution experiment for alginate containing formulations, **Figure 2**.

To prepare samples, the compounded tablets were crushed, passed through a 20-mesh sieve screen, and then added to a dissolution vessel containing 500mL dissolution media. The formulations formed a cationic gel raft atop the dissolution media, **Figure 3**.

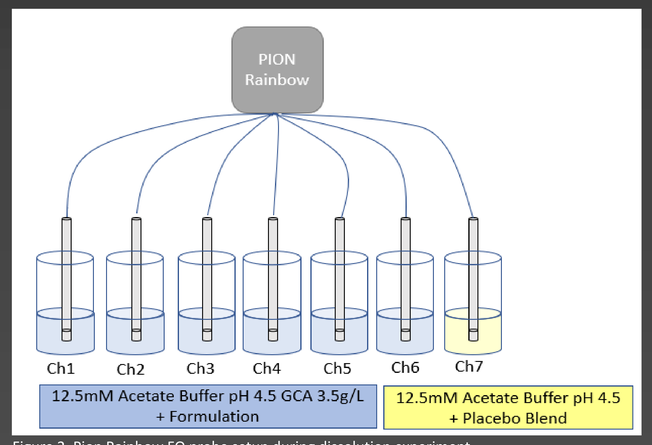

Figure 2. Pion Rainbow FO probe setup during dissolution experiment

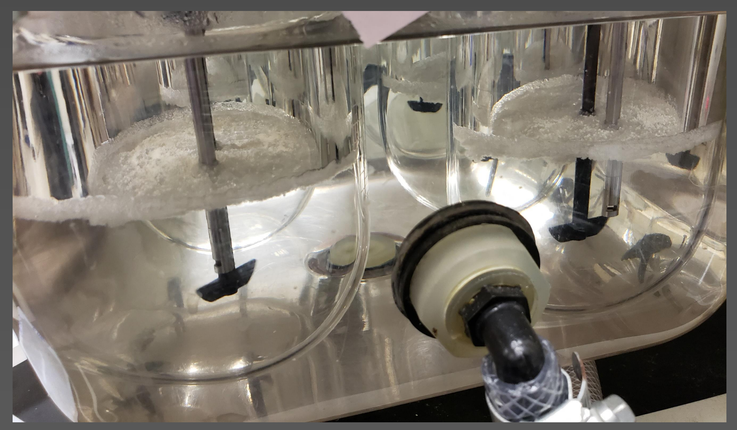

Figure 3. Ionic gel raft formation atop dissolution media with mini apparatus 2 and FO probes.

Results

The Pion Rainbow allowed for the discrimination of three distinct formulations and the neat API on dissolution, **Figure 4**. The goal was to validate tunability for delayed uptake of GCA by the API. Pion Rainbow proved feasibility by comparing 3 formulations with varied raft gel strengths (low, medium, high) compared to neat API. Each of the first initial best guess formulations for feasibility were shown to delay the release of the API from the raft which in turn delayed the uptake of the bile acid GCA within the dissolution vessel.

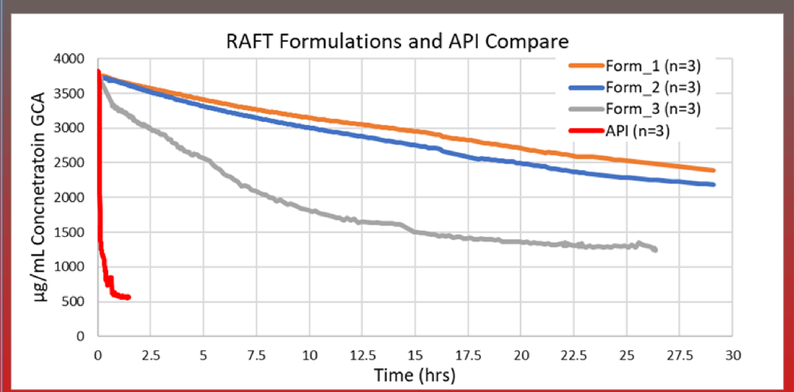

Figure 4. Pion FO probe alginate raft + API formulations and neat API GCA uptake (n=3) .

Results Continued

A standalone run was performed with aliquots sampled for HPLC analysis at 13, 21, 41, and 65 minutes. These results showed agreement between the Pion Rainbow fiber optic probe and HPLC measurements with %delta (HPLC-PION FO Probe) 5.7, 8.1, -0.6, and -0.5 respectively,

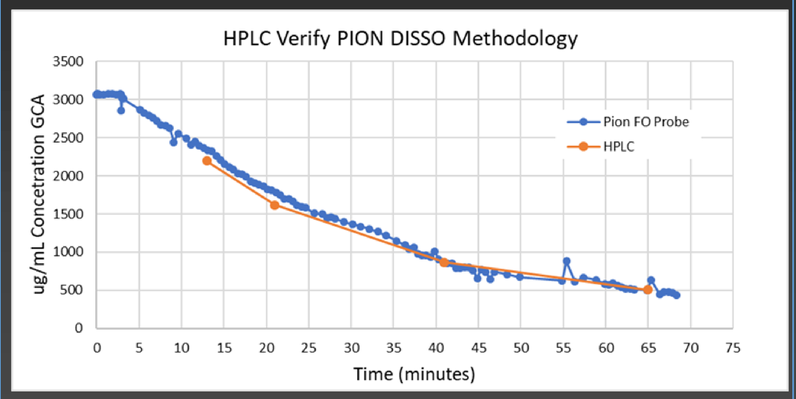

Figure 5. Pion FO probe and HPLC parity.

Based on the feasibility results, a formulation 3-factor DOE with a center point was conducted with dissolution results provided in **Figure 6**.

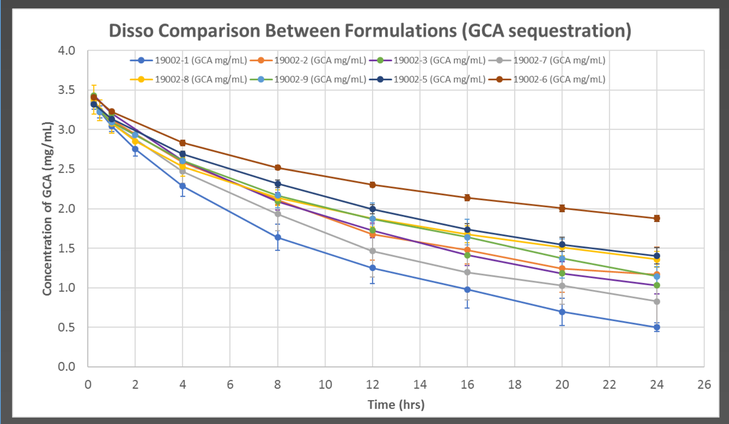

Figure 6. Formulation DOE results.

Conclusion

Pion Fiber Optic Dissolution Monitoring System shows viability for use with high throughput analysis and is therefore useful in proof of concept and/or design of experiments early on in formulation development before use of traditional HPLC methods. PION Rainbow 2nd derivative and Zero Intercept Methods (ZIM) allow for mathematical separation of UV|VIS spectra where overlap may occur eliminating the need for physical separations (HPLC).

Caution to reader: Not all matrices can be mathematically separated, a skilled scientist must review.

Learning Objectives

- Explain the benefits for fiber optic probe for DOE screening
- Provide alternate methods to develop discriminating dissolution methods
- Demonstrate dosage form API release control

Presenter Biography

Brent Hilker has a PhD in Polymer Chemistry from the University of South Florida and has worked in pharmaceuticals for 6 years and semiconductors for 4 years. Additionally, he is a 6-year veteran of the USMC.

References

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(2) Antunes C., Curtis SA. Gastroesophageal Reflux Disease. Bookshelf ID: NBK441938, © 2020, StatPearls Publishing LLC