Development of an IVIVC Apparatus 3 Dissolution Method for a Highly Soluble API in an Extended Release Soft Gelatin Capsule

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PURPOSE

The purpose of this study was to develop an IVIVC Apparatus 3 dissolution method for a highly soluble API in an extended release soft gelatin capsule.

INTRODUCTION

In-vitro in-vivo correlation (IVIVC) is defined in the USP as “the establishment of a rational relationship between a biological property, or a parameter devised from drug plasma concentrations produced by a dosage form, and a physicochemical property or characteristic of the same dosage form.” If the active pharmaceutical ingredient (API) from a drug product in a QC dissolution method shows a very different profile when compared to clinical data, a common practice is to develop a new in-vitro dissolution method that would mimic the drug product response in-vivo.

This poster presents the data supporting the development of an In-vitro in-vivo correlation (IVIVR) Apparatus 3 dissolution method for a highly soluble API in an extended release soft gelatin capsule.

EXPERIMENTAL METHODS

The dissolution testing is currently performed using a 2-Stage approach, using an USP Apparatus 3 with an agitation rate of 30 dips per minute (dpm). The first stage medium consists of 250 mL of Fasted-state Simulated Gastric Fluid (FaSSGF). The second stage medium consists of 250 mL of Fasted-state Simulated Intestinal Fluid (FaSSIF).

Samples were collected at 1, 2, 4, 8, and 12 hours. Quantitation was by HPLC using a Waters NovaPak C8, 3.9 x 150 mm, 4 µm with isocratic elution using 85:15 5mM Sodium 1-Hexanesulfonate:Methanol, operating at a flow rate of 1.5 mL/min with UV detection. An external standard is used for quantitation. Also, volume evaporation from each dissolution vessel is included when calculating results.

RESULTS

The initial “QC” dissolution method was an Apparatus 3 using 250 mL of USP simulated gastric fluid without enzymes as the medium at 15 dpm. The results from the method showed controlled release over the course of 12 hours. Figure 1 displays the dissolution profiles of the 2 target samples. The capsules were used in a bioequivalence clinical study. Once in-vivo, the results show an immediate release of API, while the RLD was controlled release. Figure 2 displays the mean plasma data from the clinical study.

Figure 1: Dissolution profiles for the target formulations using USP simulated gastric fluid without enzymes

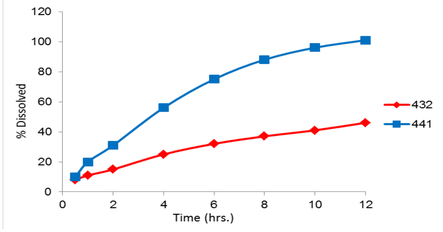
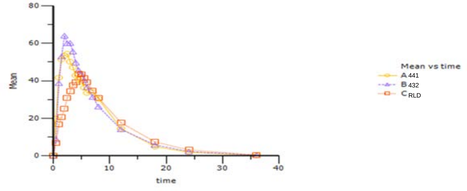
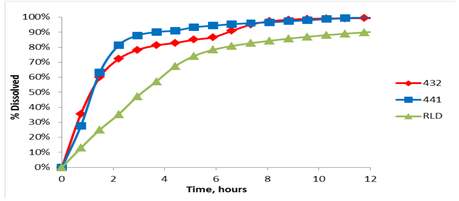


Figure 2: Mean plasma data from Pilot Study 1



The clinical data was deconvoluted to create a target dissolution profile. This target profile was used to develop an IVIVR dissolution method. Figure 3 displays the de-convoluted “target dissolution” profiles.

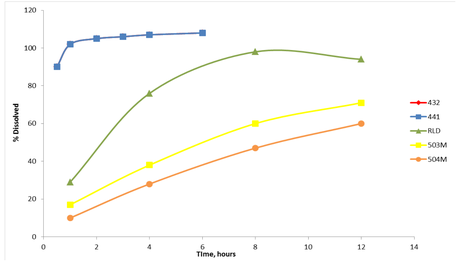
Figure 3: De-Convoluted target “dissolution profiles” from clinical data



Because the fill of the capsule is hydrophobic, it was believed it would be necessary to add a surfactant to the dissolution media to break up the fill and allow the API to dissolve almost immediately into the media. Cetyltrimethylammonium bromide (CTAB) at 2% was added to the USP Simulated Gastric Fluid without enzymes. Due to the "vertical agitation" of the Apparatus 3, simethicone was added as an anti-foaming agent.

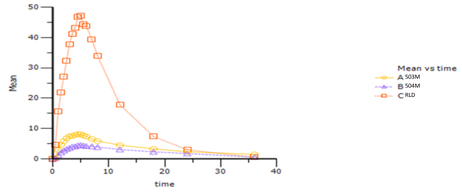
The IVIVR method was able to discriminate between the RLD and the clinical dosages, Lots 432 and 441, by generating results that could predict immediate release of the API, as was observed in-vivo. This method was used to screen re-formulated prototypes of the dosage. Figure 4 displays the dissolution profile using the IVIVR dissolution method.

Figure 4: Dissolution profiles using the initial IVIVR method developed



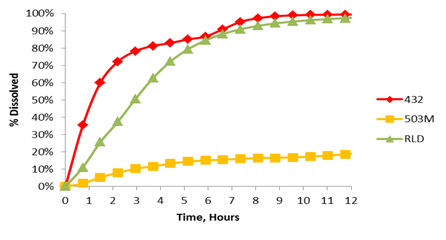
The two new drug product formulations were evaluated in the clinic. The results of the new study showed "extended release", however, the release of drug was significantly lower than the RLD. The average plasma concentration can be seen in Figure 5.

Figure 5. Mean plasma data from Pilot Study 2



After deconvoluting the second set of clinical data, a new target IVIVR dissolution profile was generated. The goal was to develop a new IVIVR method that would predict, in-vitro, the behavior observed with both sets of formulations. Figure 6 displays the de-convoluted the new “target dissolution” profiles.

Figure 6: De-Convoluted target “dissolution profiles” from both sets of clinical data

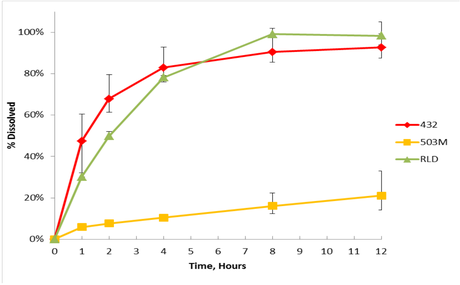


It was determined that the new IVIVR dissolution method should mimic the gastrointestinal system as much as possible. This involved moving from a single stage dissolution to a 2-stage dissolution. Also, the medium was changed to two Biorelevant™ media: Fasted-state Simulated Gastric Fluid in the first stage and Fasted-state Simulated Intestinal Fluid in the second stage.

The initial IVIVR method required a surfactant to break up the hydrophobic fill and allow the API to dissolve in the media. When moving to the bio-relevant media, the hypothesis was that without a high amount of surfactant, the hydrophobic fill would not allow for the immediate release of the initial formulation (Lot: 432) and maintain a very slow release in the second formulation (Lot: 503M)

As seen in Figure 7, the concerns were unfounded. The bio-relevant media gave both an immediate release of the API early for the initial formulation, while maintaining a very slow, extended release profile for the second formulation.

Figure 7: Final Dissolution Data from the current IVIVR method on first and second generation formulations



CONCLUSION

Dissolution testing is often used as a tool to determine how a drug product will release when in a physiological-like environment. The practice of developing an in-vitro dissolution method that can mimic what happens to a drug product in-vivo is a common practice often described as an IVIVR dissolution method. Initially, the use of the cationic surfactant CTAB and an anti-foaming agent in the dissolution media was developed to overcome the reduced dissolution caused by the highly hydrophobic semi-solid fill and closely mimic release seen in clinical data. After more data was available, the use of bio-relevant dissolution media was determined to represent the best fit for IVIVR dissolution method for this drug product. This method will be used to screen future formulations.