A Canine Biorelevant Dissolution Method for Predicting in vivo Performance of Sustained Release Solid Oral Dosage Forms

Paul L. Walsh, Sunny Bhardwaj, Mengwei Hu, Rebecca Nofsinger, James Mann, Abdenour Djemai, Annette Bak

Merck Research Labs, K15-A318, 2000 Galloping Hill Road, Kenilworth, NJ 07033

paul.walsh@merck.com

ABSTRACT SUMMARY

The development of an in vitro biorelevant dissolution method for the prediction of the PK performance of sustained release solid oral dosage forms in beagle dogs is described. Increased agitation to mimic the dog gastric and intestinal motility and emptying forces as well as the inclusion of the recently described canine fasted state simulated intestinal fluid (FaSSIF) gave significantly improved correlation to deconvoluted PK data obtained for erodible matrix controlled release tablets.

INTRODUCTION

Biorelevant dissolution can be a fast and easy method for predicting the in vivo performance of solid oral dosage forms, including evaluating and rank-ordering the relative ability of sustained release dosage forms to control the release of API. Preclinical species can also be a useful tool for evaluating the proof of concept for a sustained release oral dosage form prior to evaluating such formulations in human trials. Beagle dogs are an attractive option for such preclinical studies due to their usefulness in pharmacodynamics studies as well as the ease of access in the early development space. There are some disadvantages to this animal model, however, including the differences in the gastrointestinal anatomy and physiology of canines as compared to humans, including the variable pH of gastric fluids as well as the amount of bile salts and the osmolality of the intestinal fluid. These differences point to the need for a canine-relevant dissolution method which can be used for oral matrix controlled release dosage forms. The work presented herein discusses the development of such an in vitro two-stage dissolution method which better mimics the gastrointestinal tract of the beagle dog while maintaining the simplicity of standard dissolution methods.

EXPERIMENTAL METHODS

Erodible matrix controlled release dosage forms were prepared using Colorcon® excipients, including anhydrous lactose, microcrystalline cellulose, and METHOCEL™ K100LV and K4M. 200 mg tablets (5/16” diameter concave) were prepared with an active loading of 5% (10 mg), and METHOCEL™ K100LV loading between 20 and 40%, with ~1% magnesium stearate for lubrication. The tablets were pressed on a Carver Press at 2500 lbs pressure, and tested for content uniformity and hardness. Tablets were dosed to fasted beagle dogs and the plasma concentration of API was quantified over the course of 24 hours.

Two-stage biorelevant dissolution was performed on the tablets encased in a sinker in a Distek 2100B USP II bath at 37°C with an Evolution 4300 autosampler. The initial volume of SGF was added and allowed to equilibrate for 30 minutes prior to beginning the experiment. The second stage was made by adding an equivalent volume of 2X concentrated FaSSIF and adjusting the pH accordingly. Collected samples were analyzed by HPLC to quantify the amount of API released at increments over the course of 24
hours. Table 1 summarizes the differences between the dissolution methods used for the human relevant and canine relevant dissolution methods. Human-relevant FaSSIF was prepared using SIF powder as described by biorelevant.com, while canine relevant FaSSIF was prepared as recently described by Dressman et al.4-5

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Human Dissolution</th>
<th>Canine Dissolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vessel Volume</td>
<td>1 L</td>
<td>100 mL</td>
</tr>
<tr>
<td>Fluids and Volumes</td>
<td>250 mL SGF (pH 2), 500 mL FaSSIF (pH 6.5)</td>
<td>25 mL SGF (pH 4), 50 mL canine FaSSIF (pH 7.5)</td>
</tr>
<tr>
<td>Timing for Stages</td>
<td>30 min SGF, 23.5 hrs FaSSIF</td>
<td>1 hr SGF, 23 hrs FaSSIF</td>
</tr>
<tr>
<td>Paddle Speed</td>
<td>50 RPM</td>
<td>200 RPM</td>
</tr>
</tbody>
</table>

Table 1. Summary of the dissolution parameters used for two-stage human-relevant and canine-relevant dissolution.

RESULTS AND DISCUSSION

Visual observations of the tablets during the dissolution experiments immediately pointed towards the differences in the dissolution methods. After 24 hours, residual tablet was leftover in the human-relevant dissolution while the tablet had completely disintegrated in the canine-relevant method. This is reflected in the total amount of API detected in the dissolution fluid between the two methods. Pharmacokinetic data collected from beagle dogs dosed with the sustained release tablets was deconvoluted to determine the fraction absorbed over the time course for easy comparison to the dissolution results. Figure 1 shows a summary of the results from the two different biorelevant dissolution methods and the comparison to the deconvoluted PK data.

The differences between the two methods have an obvious effect on the total amount of API released over time. The higher paddle speed increases the hydrodynamic forces inflicted upon the dosage form, mimicking the higher gastric forces. Furthermore, it is well known that erodible matrix formulations are susceptible to differences in ionic strength of the dissolution media.4 Canine relevant FaSSIF, as recently described by Dressman et al, not only has a higher bile salt content, which allows for improved solubilization of poorly soluble API, but also has a lower osmolality, which increases the rate at which erodible matrix sustained release tablets disintegrate. These two factors have the largest effect on the overall rate of release of the API, and are critical in increasing the IVIV relationship between the observed dissolution rate and the absorption profile based on deconvoluted plasma PK after oral administration.

![Absorption Profile](image_url)

**Figure 1.** Summary of human and canine biorelevant two-stage dissolution data and deconvoluted PK data for an erodible matrix formulation.

CONCLUSION

A biorelevant dissolution method has been developed to better predict the in vivo performance of erodible matrix sustained release oral dosage forms in a commonly used preclinical species, the beagle dog. Changing parameters such as the paddle speed, fluid volume, and fluid composition allowed for better IVIV relationship between the in vitro dissolution results and the deconvoluted PK data obtained for an example formulation.

REFERENCES