Comparison of Enteric Polymer Coated to Commercially Available Acid Resistant Capsules for Delayed Release Delivery

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ABSTRACT SUMMARY
We compared the dissolution of two different enteric capsule dosage forms. One enteric capsule was coated using a traditional pan coating process and a methacrylate based coating system, the comparator formulation used the same powder blend, filled into a readily available acid resistant capsule. Commercially available acid resistant capsules and enteric coated HPMC capsules both protected the API (active pharmaceutical ingredient) from acid degradation, and inhibited release of the drug under acidic conditions. However, on neutralization of the pH during dissolution, substantially different dissolution profiles were observed. The commercially available acid resistant capsule released most of the drug on neutralization, while the traditionally coated capsule exhibited a much longer dissolution profile. While the commercially available acid resistant capsules perform to the claimed specifications, the observed differences in performance when comparisons are made to enteric coated capsules indicate differences in in vivo performance are likely.

INTRODUCTION
Reduction in the development time of pharmaceutical dosage forms is often paramount to the success, of a drug development program. Controlled release or delayed release products are not immune this intense competition. Industry excipient suppliers are working to provide dosage form manufacturers tools that will facilitate and speed up the development process. For controlled/delayed release products, capsule manufacturers have developed capsules that are acid resistant, potentially reducing the time required for development. Delayed release (enteric coated) capsule dosage forms are developed for multiple reasons. These reasons are varied and range from drug/acid incompatibility to masking undesirable side effects from dissolution in the stomach (ie. fish oil). Many examples of delayed release enterically coated enzyme formulations have been studied, with significant differences in product performance identified between purportedly equivalent products (1).

For capsules, development of an enteric coated delayed release dosage form for clinical use can add a considerable time to product development timelines, throughout the development lifecycle of a product. Not only does the addition of an enteric coating process add development time, many problems can occur during the development, further exacerbating delays (2). On top of this QbD considerations become more complicated, adding additional complexity to the overall development program.

The commercial availability of acid resistant capsules is an attractive alternative to the enteric coating development process.

The purpose of our investigation was to determine the differences between commercially available acid resistant capsules and capsules coated with enteric polymer.

EXPERIMENTAL METHODS
Capsule Manufacture: Capsules were prepared using a common blend of drug, by filling a predetermined weight (based on the target dose) into HPMC capsules. Capsules were either HPMC or acid resistant HPMC/HPMCP (ARCaps CapsCanada®).

A portion of the HPMC (non-acid resistant) capsules were coated with an enteric polymer, selected such that dissolution would occur at pH 5.5. Methacrylic Acid Copolymer, NF, Type C (Eudragit L, Evonik) with composition: Eudragit (62.5 w/w%), Triethyl Citrate (6.25 w/w%), NF Talc, USP (31.5 w/w%) with a thickness of 10.6 mg/cm² and applied with Vector LDCS pan coater.
**Dissolution Testing:** Capsule dissolution was conducted using USP type bath with a 2 stage dissolution method. Dissolution media for stage 1: 750mL 0.1N HCl with samples maintained for 2 hours. Stage 2 dissolution media: 250mL 0.2M Tribasic sodium phosphate 0.25% SDS added to stage 1 media to raise pH to 6.8. Samples remained in stage 2 for 4 hours. Samples analyzed for Drug content after 30min, 1hr, 2hr, 3hr and 4hr time intervals. Dissolution baths were maintained at 37°C outfitted with paddles at 100 RPM. 5mL aliquots were taken a prescribed time intervals for analysis.

**Degradation Products Analysis:** Manufactured capsules were analyzed using a validated HPLC method. Capsules were assayed after being exposed to 2 hours of acidic media. Samples collected were analyzed using Shimadzu LC-2010HT High Performance Liquid Chromatograph (HPLC) system equipped with ACE 5 C18 150x4.6mm column and UV detector.

**RESULTS AND DISCUSSION**

*Stage 1 Dissolution (Acid Stage):* Both the enteric coated and acid resistant capsules were observed to remain intact for the two hours of exposure to the acid stage. The uncoated HPMC capsule was observed to dissolve. Analysis of the dissolution media demonstrated that slightly more drug was released from the acid resistant capsule when compared to the enteric coated capsule. See Table 1 below.

<table>
<thead>
<tr>
<th>Sample</th>
<th>% Recovery from the acid stage of dissolution</th>
<th>QC Limit</th>
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<tbody>
<tr>
<td>HPMC Acid Resistant</td>
<td>0.08%</td>
<td>NMT 10%</td>
</tr>
<tr>
<td>4 HPMC Enteric Coated</td>
<td>&lt;0.01%</td>
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Although more drug was released from the acid resistant capsule, both products were well within the prescribed QC limit of not more than 10%

*Stage 2 Dissolution (Neutral pH):* Dissolution profiles comparing HPMC, Acid Resistant HPMC and Enteric Coated HPMC capsules are provided in figure 1.

Multiple process related factors are most likely responsible for the observed faster dissolution of the commercially available acid resistant capsules in relation to the enteric polymer coated capsules. Coating thickness, polymer matrix composition, and inhibition of capsule shell hydration are most likely responsible for the differences.

![Stage 2 Dissolution Profile](image)

Figure 1. Stage 2 4 hours dissolution profile. (■) Uncoated, (▲) HPMC coated (traditional pan-coated HPMC capsules), and (●) HPMC enteric(Commercially available acid resistant capsules).

**Degradation Products:** Results from Analysis of Drug degradation after exposure to acidic media indicate both the acid resistant and enteric coating processes adequately protect the drug from acid degradation, as no degradation products were observed in any tested sample.

**CONCLUSION**

Acid resistant enteric capsules, and Capsules coated with enteric polymer both adequately protected the evaluated drug from acid degradation.

Switching between a pre-manufactured acid resistant capsule during the development program to a dose manufactured by enterically coating capsules may impact the clinical results. Different dissolution profiles suggest possible differences in clinical pK results.

**REFERENCES**