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DRcaps® Capsules Achieve Delayed Release Properties for Nutritional Ingredients in Human Clinical Study

A gamma-scintigraphy study confirms delayed release properties of DRcaps capsules in human subjects



INTRODUCTION

More consumers are addressing their digestive health as a cornerstone of optimizing the nutritional benefits of their diets and overall health, including immune support, cardiovascular health, joint health, and more. As a result, they are driving healthy growth in probiotics and nutritional enzymes, especially those in convenient supplement delivery forms.

Probiotics and enzymes are sensitive to acid and run the risk of being rendered less effective while crossing the low pH of the stomach on their way to the intestinal tract.

Global sales of probiotic supplements were \$3.3 billion in 2013 and are poised to nearly double to \$5.5 billion by 2018, with North America, Europe and Asia Pacific leading the growth.^{1,3}

Sales in digestive enzymes have been accelerating at a slower pace, but are expected to gain speed as a growing number of consumers embrace systemic enzymes to address other health issues, including inflammation, skin care, wound healing, joint health, and cardiovascular health. In the United States, the world's number 1 supplement market, sales of enzyme products and digestive formulas through both conventional and natural channels combined continue to grow.²

But the industry has concerns about delivery methods that can help support maximum effectiveness of probiotics and nutritional enzymes. Both work best in the intestines. However, both probiotics and enzymes are also sensitive to acid and run the risk of being rendered less effective while crossing the low pH of the stomach on their way to the intestinal tract. Additionally, probiotics – as living bacteria – can easily be prematurely activated by variations of temperature, oxygen, and humidity before they are consumed, whether delivered in yogurts, vials, capsules, or tablets.

Supplement manufacturers have turned to a range of dosage delivery solutions for the purpose of enhancing protection of moisture and acid-sensitive ingredients. Some environments, especially the low pH of the stomach, can destroy some acid-sensitive strains. Additionally ingredients



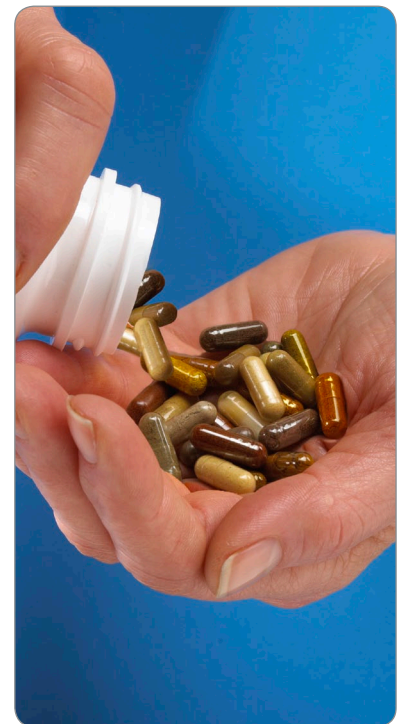
that are very hygroscopic and need protection in the packaging from early activation due to environmental moisture or water content of the capsule or coating create specific challenges. Occasionally taste masking is required. Many ingredients target release to the upper gastrointestinal tract where the ingredient action is optimized, thus a delayed or targeted release delivery is important. Unfortunately, many of these attempted solutions might solve one issue but not others. They offer variable shelf life for the ingredients but limited proof of delivery to the intestines while increasing manufacturing time and costs.

Enteric coatings are often applied to tablets to provide protection and delay release. Conventional film coatings for acid-resistance involve costly manufacturing processes that are complex and may lead to waste, delays and yield loss. Coating techniques require use of chemicals and solvents that do not fit many consumers' preference for 'healthy and natural' products. Coatings have variable moisture levels, variable bulk density and variable compressibility. The incremental costs, multi-step preparation and potential yield issues can be operationally challenging.

Vegetarian capsules with a three-fold lower moisture content than gelatin, have provided an excellent alternative.

Encapsulation is one of the standard technologies for oral dosage delivery forms. However, for some ingredients gelatin capsules may not provide sufficient protection against moisture (leading to early activation or ingredient degradation) or may become brittle (leading to capsule breakage). In addition, some consumers prefer supplements that do not contain any animal ingredients such as gelatin. Therefore, vegetarian capsules made of plant derived cellulose such as Vcaps® and Vcaps® Plus capsules with a three-fold lower moisture content than gelatin, have provided an excellent alternative.

Made of plant-based hydroxypropyl methylcellulose (HPMC), both Vcaps® and Vcaps® Plus capsules have low water content of 3% to 9% at ambient conditions, with an average of less than 6%, and maintain their mechanical stability under stressed condition of temperature and low relative humidity. Ideally suited for moisture sensitive and hygroscopic ingredients, both capsules were designed for immediate release applications such as the majority of vitamins, minerals and supplements.



Introducing DRcaps Capsules

A third HPMC option, DRcaps® capsule, was developed to effectively address all of the various challenges and shortcomings of delivering acid-sensitive ingredients. The revolutionary dosage form offers unique polymer properties formulated within the capsule itself to slow the capsule opening after swallowing without adding coating ingredients that increase manufacturing time and costs. With moisture content of 4% to 6% in 50% relative humidity, low moisture DRcaps capsules inherently enhance stability for moisture-sensitive probiotics. The innovative polymer properties also mask the taste and odor of ingredients; therefore, by protecting against early disintegration, DRcaps capsules actually reduce the potential for unpleasant odors, aftertaste and reflux from supplements. In particular, the unique polymer properties were designed to resist acid in order to protect nutritional ingredients from full release and disintegration in the stomach and allow for complete dissolution in the intestine.

DRcaps Capsule Advantages

- Acid resistance protects nutritional ingredients without the need for film coatings.
- Plant-based, vegetarian capsule designed to release when you need it.
- Enhanced stability for moisture sensitive and hygroscopic ingredients.
- Taste and odor masking of herbal or mineral ingredients which can increase digestive comfort.

With moisture content of 4% to 6% in 50% relative humidity, low moisture DRcaps capsules inherently enhance stability for moisture-sensitive probiotics.

Human Clinical Study

To clinically assess the efficacy of DRcaps capsules for resistance to stomach acids for delayed delivery properties of ingredients, Capsugel commissioned the independent laboratory, Bio-Images Research, in Glasgow, Scotland, to conduct a gamma scintigraphic *in vivo* study. The human clinical study was designed to evaluate the disintegration behavior of unbanded DRcaps capsules in human subjects. Completed in spring 2013, the study documents through images and data the success of unbanded DRcaps capsules' resistance to stomach acids for delivery of ingredients.

Study Protocol and Execution

The study was designed to investigate the *in vivo* behavior of DRcaps capsules using qualitative and quantitative scintigraphic methods to assess the gastrointestinal transit of the capsules and release of capsules based on the scintigraphic images obtained. Gamma scintigraphy is an established technique in which a radio label is swallowed and the disposition in the gut is photographed externally over time.

In this study, DRcaps capsules were filled with 290 mg of cold lactose monohydrate and approximately 10 mg of lactose monohydrate radiolabeled with 99mTc-DTPA. The capsules were closed and stored in individual, labeled plastic bijous in lead pots.

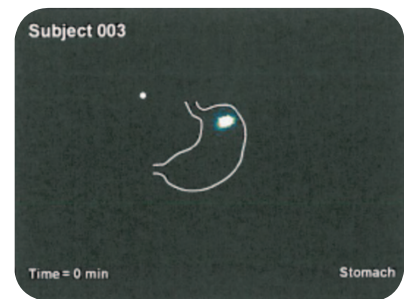
After meeting eligibility requirements, eight subjects were enrolled. Each subject consumed a light breakfast comprising one slice of crisp bread, five grams of jam, and 200 mL apple juice. Approximately 30 minutes later, each subject swallowed whole one DRcaps capsule filled with the radio label with 150 mL of room temperature water.

Scintigraphic images were taken following the dosing until complete capsule radiolabel release, i.e. capsule disintegration, was confirmed. Anterior and posterior abdominal images of 25-second duration each were acquired after dosing and then every five minutes up to four hours after dosing, then every 10 minutes to a maximum of 10 hours after dosing.

Trained personnel analyzed the images with Weblink software relating to the position of the capsule in the gastrointestinal tract and onset and complete radiolabel release from the capsule.

Three scenarios of capsule disintegration were noted: begun and completed in the stomach, started in the stomach and finished in the small intestine, and commenced and completed in the small intestine.

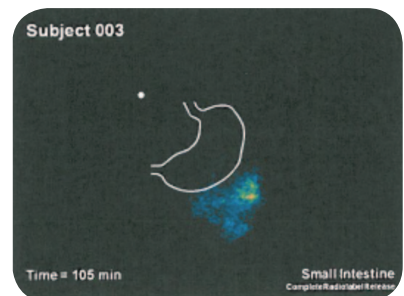
DRcaps capsule administered



Intact DRcaps capsule reaches the stomach



DRcaps capsule starts to release the contents



DRcaps capsule has left the stomach and releases its contents in the intestine

Study Results and Conclusion

- DRcaps unbanded capsules displayed delayed release properties.
- Disintegration started approximately 45 minutes later than a typical immediate release capsule of about 5 minutes.
- For the majority of subjects, complete release took place in the intestine.
- Complete release occurred 20 minutes after the onset of release.
- DRcaps unbanded capsules significantly reduced opportunity for nutritional ingredient degradation compared with standard immediate release capsules.

The results of this *in vivo* human clinical trial presents empirical evidence of successful acid-resistance and delayed release properties of DRcaps capsules. The innovative DRcaps capsule targets release after a certain time period, protecting ingredients from full disintegration in the stomach.

Data and images showed radiolabeled release began at a mean time of 52 minutes when the capsules were about to leave the stomach and a full 45 minutes later than a typical immediate release capsules. While the lactose ingredients in the capsules were inert and didn't require moisture protection from premature activation like probiotics, the delayed release properties can be applied to any ingredient. This gives confidence that DRcaps capsules are an excellent choice for delivery of acid-sensitive ingredients, in particular probiotic and enzyme ingredients that work best in the intestines, where complete release of ingredients was observed in the majority of subjects.

The fact that the polymer exhibits delayed release properties without the use of costly coatings is a major bonus, allowing for economical and quick product launches and vegetarian product with great appeal to this fast-growing lifestyle market.

Radiolabel release parameters and gastric emptying times (DRcaps capsule A)

Subject Number	Onset of release (min)	Site of onset	Completion of release (min)	Site of completion	Time from onset to complete (min)	Gastric emptying time (min)
001	52.5	S	67.5	S	15.0	N/A
002	57.5	S	97.5	S	40.0	N/A
003	47.5	S	102.5	SI	55.0	97.5
004	37.5	SI	42.5	SI	5.0	37.5
005	32.5	SI	42.5	SI	10.0	32.5
006	47.5	S	57.5	SI	10.0	55.0
007	87.5	SI	97.5	SI	10.0	87.5
008	52.5	S	67.5	SI	15.0	55.0
Mean	51.9		71.9		20.0	60.8
St Dev	16.6		24.6		17.7	26.3

S – stomach; SI – small intestine; N/A – not applicable

References

1. NBJ/Engredea Monograph, *Probiotics Forecast 2013-2014: An in-depth look at the latest news, innovations and market trends.*
2. "New Frontiers in Nutritional Enzymes," by Lisa Olivo, *Nutraceuticals World*, October 1, 2012, www.nutraceuticalsworld.com/issue/2012-10/view-features/new-frontiers-in-nutritional-enzymes/.
3. *Euromonitor International database 2014, Fixed Exchange Rates.*

