Challenges in Developing Stable and Efficient Probiotic Formulations

Morgan Laloux
morgan.laloux@capsugel.com
+32 491 73 20 53
Summary

Challenges in Formulating Probiotics

Formulating Probiotics in Capsules

• Increase Shelf Life: Low moisture capsules
• Protection from Stomach acidity: DRcaps™
• Probiotics for Consumers with Swallowing Difficulties: Coni-Snap® Sprinkle Capsules
• Combination Products: DUOCAP™

Conclusion
Capsugel at a Glance

World’s Leading Provider of dosage form solutions for Health & Nutrition, OTC, Generics, Specialty & Branded Pharmaceuticals

Innovative, High-Quality, Products, Services, global scalability

Innovative drug-delivery technologies, specialized manufacturing, and a collaborative approach to address clients’ most pressing product development challenges

# 1 hard gelatin and vegetarian capsule manufacturer

More than 3,100 colleagues worldwide
Challenges in Formulating Probiotics
Parameters Influencing Probiotics Stability

Probiotics have to pass two main hurdles:
• Stability over shelf life
• Efficient delivery in appropriate site in the GI tract

Parameters influencing Stability:
• Humidity
• Temperature
• Pressure/ temperature build up during tableting
• Coating stressful conditions
• Acid stomach conditions

We will focus our presentation on solutions developed by Capsugel to efficiently formulate lyophilized probiotics
Formulating Probiotics In Capsules
## Major Challenges in Formulating Probiotics in Capsules

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<tr>
<th>Challenges</th>
<th>Capsugel Solution</th>
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<td>Maximum Shelf Life</td>
<td>Adapt water content of capsule to offer best conditions ensuring long shelf life.</td>
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<td>Strain survival and efficiency</td>
<td>Specific capsule was developed to ensure passage of probiotics through stomach.</td>
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<tr>
<td>Specific needs of children and consumers with swallowing difficulties</td>
<td>Easy-to-open capsule for sprinkle usage on food without capsule swallowing.</td>
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<td>Combination products</td>
<td>DUOCAP™: “2-in-1” capsules that allow effective delivery of combination products.</td>
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Increase Shelf Life:
Low Moisture Capsules
Capsugel has developed HPMC capsule line with different film compositions.

- **Vcaps® Plus Capsules**
  Composed of Pure HPMC and water with no additives
  Rapid dissolution at all pH

- **Vcaps® Capsules**
  Composed of HPMC and a gelling agent
  Delayed dissolution at pH 1.2

- **DRcaps™ Capsules**
  Composed of HPMC and Gellan Gum
  High resistance to dissolution at pH 1.2
Mechanical Properties: HPMC Capsules

Gelatin capsules exhibit reduced mechanical resistance when water content decreases.

Standard HPMC have an increased mechanical stability at all humidities.

For probiotic application, Capsugel’s propose low moisture HPMC capsule enabling increased shelf life of finished product.
Stability in Vcaps® Low Moisture Packed in Alu / Alu Blister

High stability observed with Low Moisture HPMC up to 24 months minimum
Stability in Vcaps® Low Moisture Packed in Aluminum Tube with Desiccant

High stability observed with Low Moisture HPMC up to 24 months minimum
Protection from Stomach Acidity:
DRcaps™ capsules
Composition of DRcaps™

Composition:
- HPMC (Hypromellose) is produced from pine tree cellulose
- Gelling agent
- Water

Properties:
- Capsule is resistant to dissolution in acidic media
Capsugel evaluated the resistance of DRcaps™ capsules to acidic media by different methods:

- In-Vitro Dissolution
- In-Vitro Disintegration
- In Vitro GIT Model, SHIME (Prodigest - Simulator of the Human Intestinal Microbial Ecosystem)

A novel hypromellose capsule, with acid resistance properties, permits the targeted delivery of acid-sensitive products to the intestine

Massimo Marzorati a, Sam Possemiers a,b, An Verhelst b, Dominique Cadé c, Nicolas Madit c, Tom Van de Wiele a,*

a Laboratory of Microbial Ecology and Technology (LabMET), Ghent University, Coupure Links 653, 9000 Gent, Belgium
b ProDigest, Technologiepark 3, 9052 Gent, Belgium
c Capsugel, 10 Rue Timken, 68027 Colmar Cedex, France
DRcaps™ capsules: Acid Resistance – In Vivo

DRcaps™ capsule Human Clinical Study (N= 8 subjects)

Key Study Findings:

• DRcaps™ capsules displayed delayed release properties
• Disintegration started approximately 52 minutes after ingestion
• For the majority of subjects, complete release took place in the intestine
• Complete release occurred 20 minutes after the onset of release
Probiotics for Consumers with Swallowing Difficulties: Coni-Snap® Sprinkle Capsules
Rationale for Developing Coni-Snap® Sprinkle Capsule

Swallowing issues
• Affects 35% of the general population and 18%-22% of all persons in long-term care facilities
• 45% of institutionalized elderly and 36% of adolescent report swallowing issues

Coni-Snap® Sprinkle
Evaluation of product performance by 37 participants in 2 panels
• Parents of young children
• Elderly individuals (over 80) and not impaired

81% of Participants found new design easy to open
Combination Products
DUOCAPE™ capsules
DUOCAP™ Probiotic capsule

**DUOCAP™ technology creates an internal barrier to prevent water migration in probiotic internal capsule:**

- Perfect for moisture sensitive compounds: Glycerol in external capsule prevents water absorption in internal capsule
- Designed to improve stability and facilitate delayed release
- Internal capsule can be DRcaps™: delivers probiotic in intestine
- Could allow second ingredient to expand health claims (e.g. Vitamin D)
Proof of Concept

Inner capsule Vcaps® Plus size 3
Filled with 100% Probiotic

Filled in outside Vcaps® Plus size 00
Containing glycerol

Storage conditions:
- 4-8°C and 25°C/60% RH

<table>
<thead>
<tr>
<th>Storage conditions</th>
<th>T0</th>
<th>T 1M</th>
<th>T 2M</th>
<th>T 3M</th>
<th>T 6M</th>
<th>T 9M</th>
<th>T 12M</th>
<th>T 18M</th>
<th>T 24M</th>
<th>T 36M</th>
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<tbody>
<tr>
<td>4-8°C</td>
<td>X</td>
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<tr>
<td>25°C/60% RH</td>
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Packaging:
- PP bottle (no desiccant)

Tests performed:
- Total count viability performed by Capsugel QC department in Colmar

Latest results:
- Stability confirmed after 24 months at 25°C/60% RH for DUOCAP™ with glycerol in outer capsule
Stability Study confirmed stability of probiotic in DUOCAP™
Conclusion
# Capsugel’s Probiotic Portfolio

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<th>Solutions</th>
<th>Applications</th>
<th>Polymer</th>
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<tr>
<td>Vcaps' Plus</td>
<td>Increased shelf life can be obtained with low moisture HPMC capsule</td>
<td>HPMC Low Moisture</td>
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<tr>
<td>DRcaps</td>
<td>Survival and efficiency: probiotics are protected and delivered to intestine</td>
<td>HPMC</td>
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<tr>
<td>Coni-Snap</td>
<td>Alternative to Sticks and Sachets, Solves swallowability issues</td>
<td>Gelatin and HPMC</td>
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<tr>
<td>DUOCAP™</td>
<td>Synergy enhancement, efficacy in protecting probiotics in presence of other actives</td>
<td>HPMC</td>
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