

CAPSUGEL®

Challenges in Developing Stable and Efficient Probiotic Formulations

Morgan Laloux

morgan.laloux@capsugel.com

+32 491 73 20 53



Summary

Challenges in Formulating Probiotics

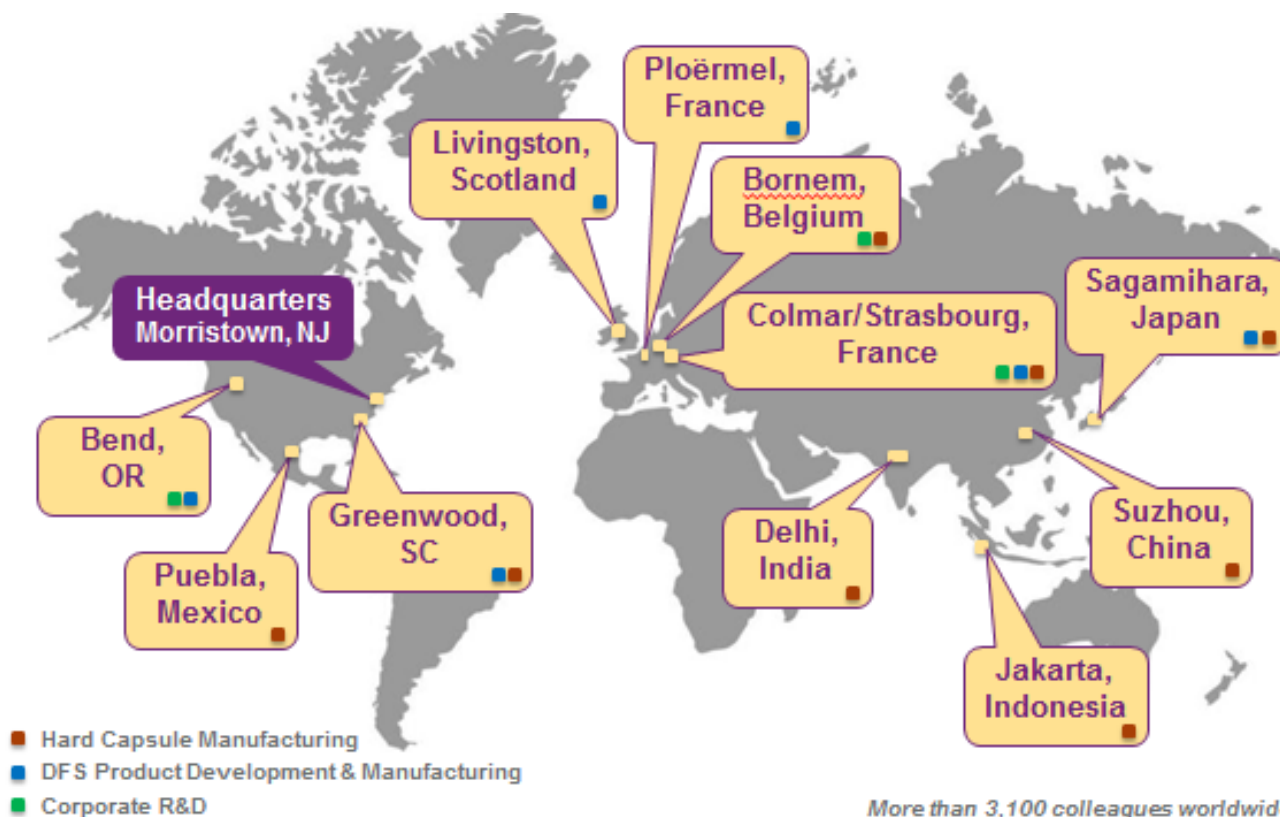
Formulating Probiotics in Capsules

- 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



1 hard gelatin and vegetarian capsule manufacturer
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



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

Challenges	Capsugel Solution
Maximum Shelf Life	Adapt water content of capsule to offer best conditions ensuring long shelf life.
Strain survival and efficiency	Specific capsule was developed to ensure passage of probiotics through stomach.
Specific needs of children and consumers with swallowing difficulties	Easy-to-open capsule for sprinkle usage on food without capsule swallowing.
Combination products	DUOCAP™: “2-in-1” capsules that allow effective delivery of combination products.



Increase Shelf Life: Low Moisture Capsules

Specialty Polymers: HPMC 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

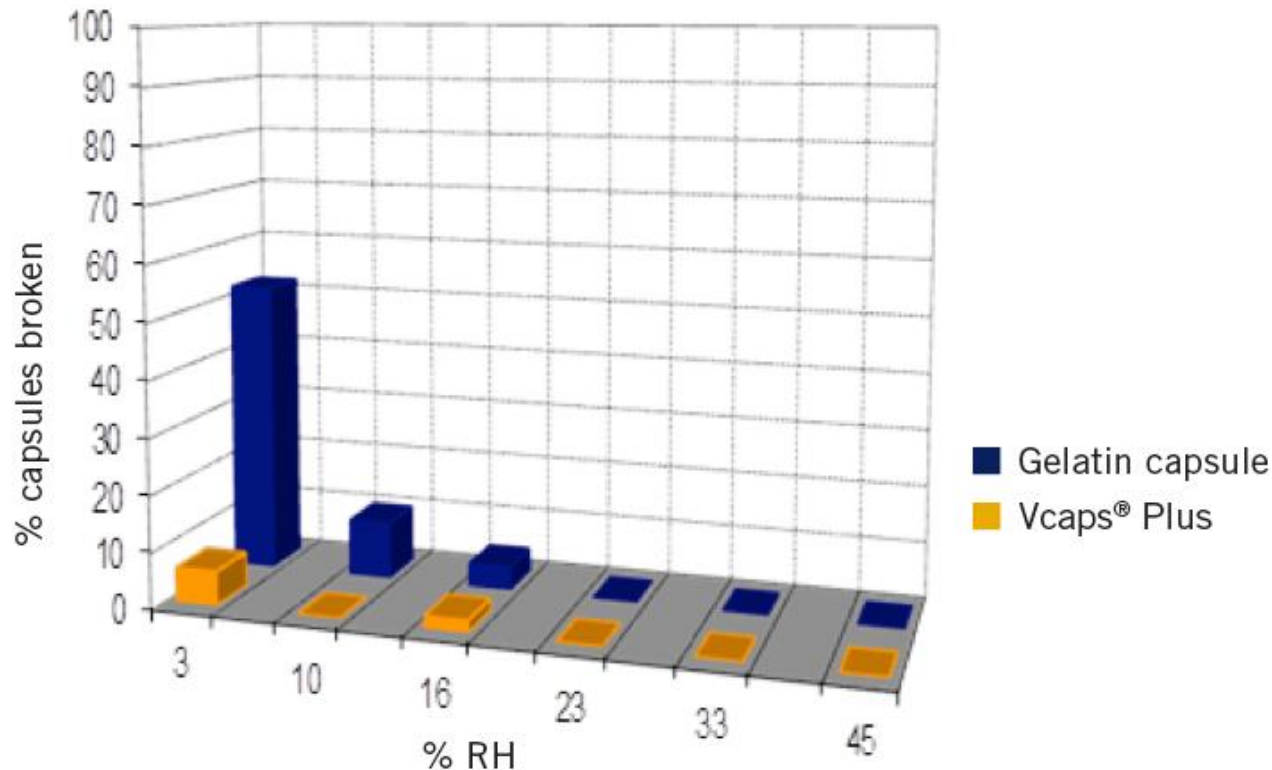
Composed of HPMC
and Gellan Gum
High resistance to
dissolution at pH 1.2



Mechanical Properties: HPMC Capsules

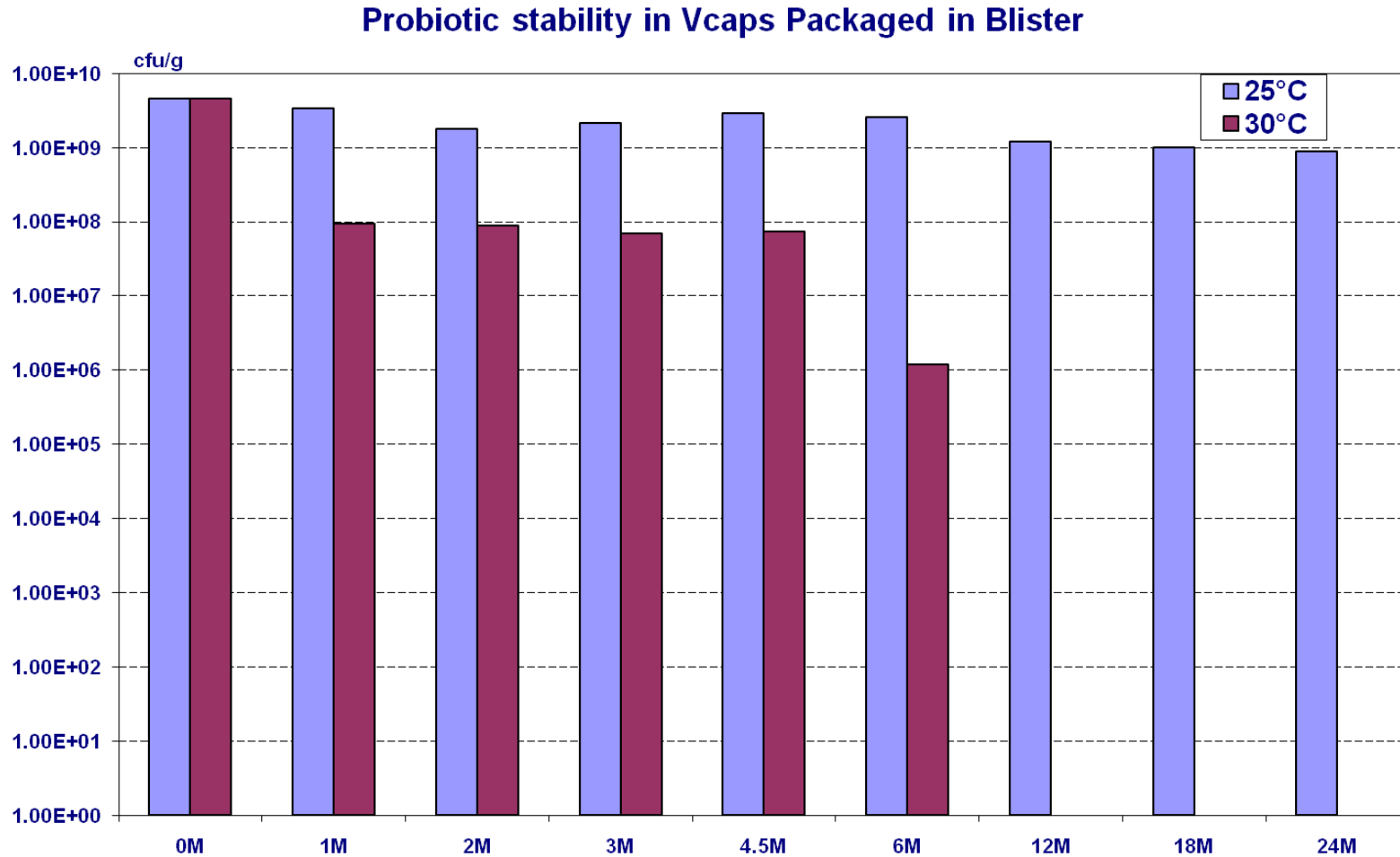
Gelatin capsules exhibit reduced mechanical resistance when water content decreases.

Standard HPMC have an increased mechanical stability at all humidities.



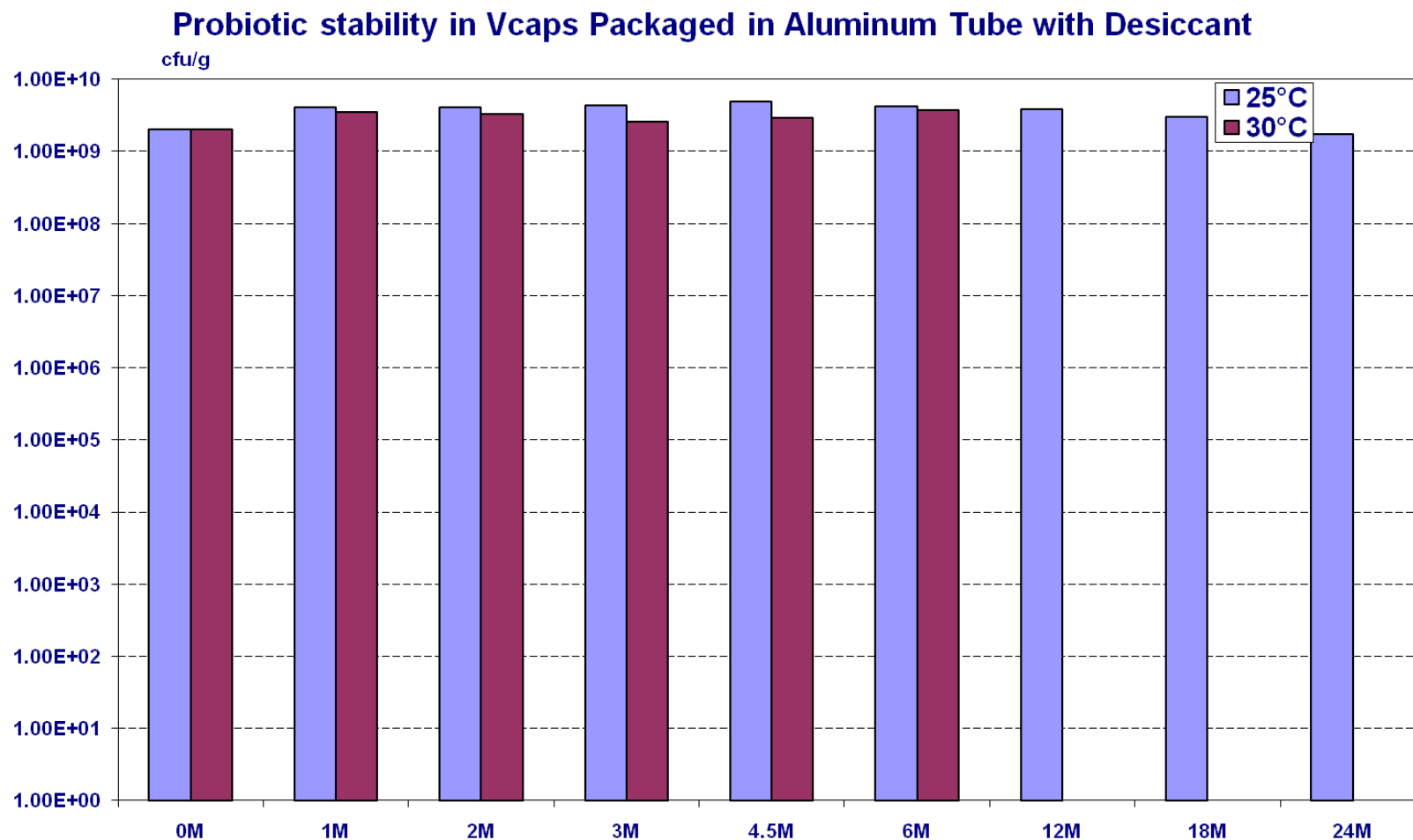
For probiotic application Capsugel's propose **low moisture HPMC** capsule enabling increased shelf life of finished product.

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



In-Vitro Tests

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

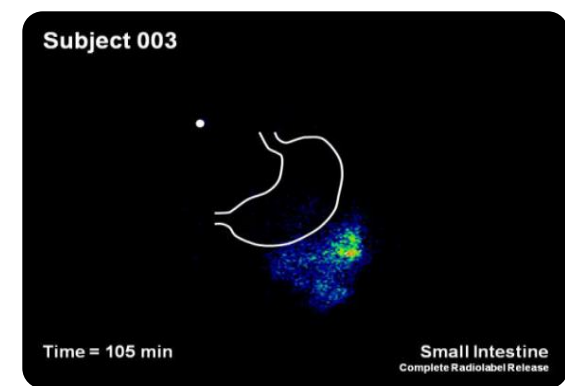
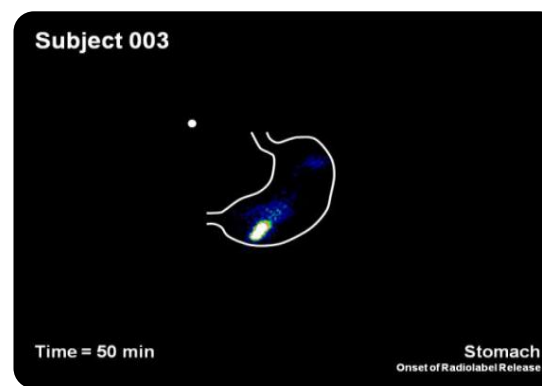
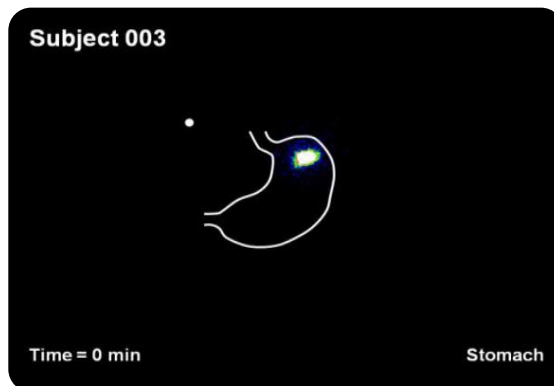
^c Capsugel, 10 Rue Timken, 68027 Colmar Cedex, France

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

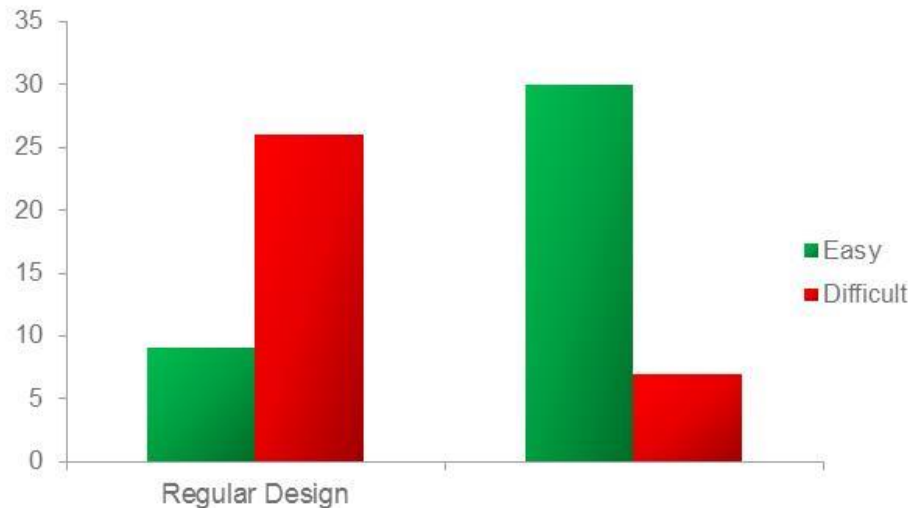
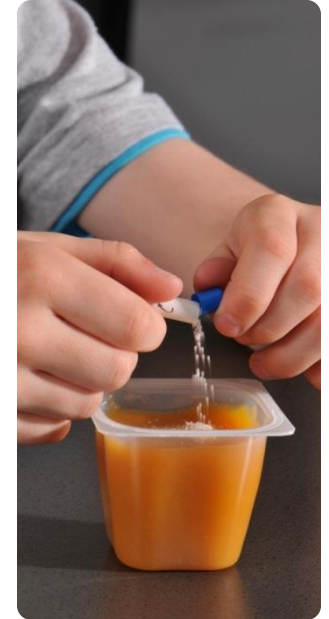
Swallowing issues

- 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
DUOCAP™ 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

Storage conditions	T0	T 1M	T 2M	T 3M	T 6M	T 9M	T 12M	T 18M	T 24M	T 36M
4-8°C	X	X	X	X	X	X	X	X	X	X
25°C/60% RH		X	X	X	X	X	X	X	X	X

Packaging:

- PP bottle (no desiccant)

Tests performed:

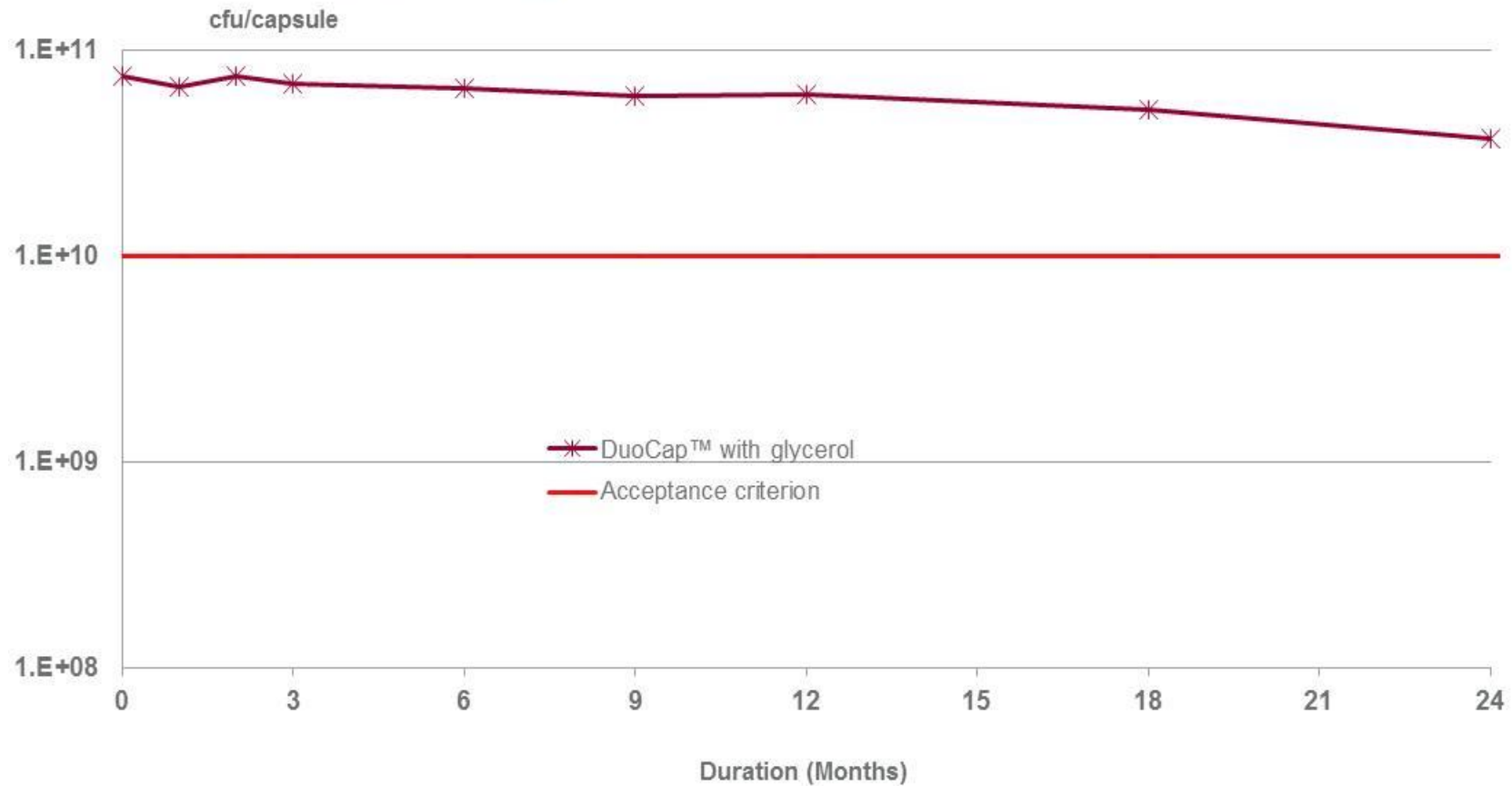
- Total count viability performed by Capsugel QC department in Colmar

Latest results:

- **Stability confirmed after 24 months at 25C/60% RH for DUOCAP™ with glycerol in outer capsule**

Stability Results





Stability of Probiotic in Glycerol DuoCaps filled in PP bottle stored for 24M at 25°C/60%RH



Stability Study confirmed stability of probiotic in DUOCAP™

Conclusion

Capsugel's Probiotic Portfolio

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



CAPSUGEL®