

Targeted delivery in food supplements: why it matters and how to apply it

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Controlled Release Society

Tech Forum Presentation, July 21st, 2019



Natures offers a broad variety of health ingredients...

Health ingredients

- Herbal extracts
- Vitamins
- Minerals
- BCAAs
- Olive oils
- Probiotics



The EUDRAGUARD[®] toolkit of nutraceutical coatings

60 years of targeted delivery leadership applied to boost effectiveness and brand preference

Bioavailability



Some ingredients are best absorbed at specific sites in the GI tract via defined release profiles

Delivery to the right location:

- Stomach
- Small intestine
- Large intestine

Delivery at the right time:

- Instant
- Delayed
- Sustained

Stability



Some health ingredients face stability challenges

Acidic environment:

- Health ingredients may be harmed by gastric juice requiring gastric resistance

Neutral environment:

- Health ingredients may be harmed by neutral pH requiring gastro retention

Protection



Specific health ingredients need a protection layer

Protection

- Improve storage stability with light, moisture or oxygen protection
- Protect ingredient from other ingredients

Taste or odor

- Improve user experience by taste or odor masking
- Easier to swallow, reflux avoidance

Gentle processing



Specific health ingredients require a gentle processing

Heat sensitive ingredients:

- Protection via low process temperatures

Short spraying time:

- Preserve effectiveness by reduced stress on ingredients

EUDRAGUARD® portfolio of nutraceutical coatings

EUDRAGUARD® protect
Tastes good, stores well



Taste and odor masking

Moisture protection

Light and oxidation protection

Instant release in stomach

EUDRAGUARD® control
Controlled delivery



Gastric resistance

Sustained release

Delayed release

EUDRATEC® GRS
Your floating solution



Gastro retention

Sustained release in stomach

Technology designed for use with EUDRAGUARD® control

EUDRAGUARD® biotic
Right to the colon



Targeted colonic delivery

Delayed release

EUDRAGUARD® natural
Natural taste & odor masking



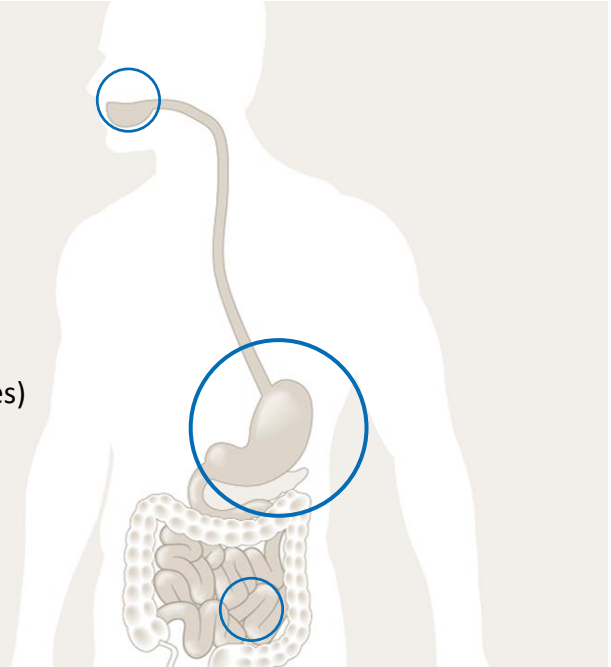
Taste and odor masking

Modulated release

Benefits across all EUDRAGUARD® products

For the reliable release of health ingredients at the right time and place plus improved consumer acceptability

- Pigments, flavors and fragrances may be added to the formulation
- Smooth, even finish for visual appeal and swallowability
- Low weight gain of polymer needed*
- Quick and easy suspension preparation
- Short spraying times
- Low spraying temperature
- Works on oral solid dosage forms (tablets, hard and soft- gels, multi-particulates)
- No batch-to batch variation of the polymer, reproducible results for coating
- May be used on conventional coating equipment
- Regulatory approval in E.U., U.S. and other countries
- Made in Europe
- Non-animal derived



* only synthetic polymers - not available with EUDRAGUARD® natural

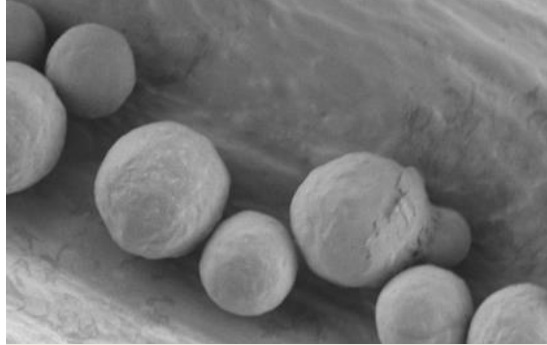
EUDRAGUARD® – optimized properties for nutraceutical dosage forms

The solution for challenging core concepts:



Soft/hard capsules

- Sufficient flexibility
- Good adhesion



Particles

- Sufficient flexibility for challenging dosage forms
- Low viscous spaying systems for less agglomeration/ tackiness



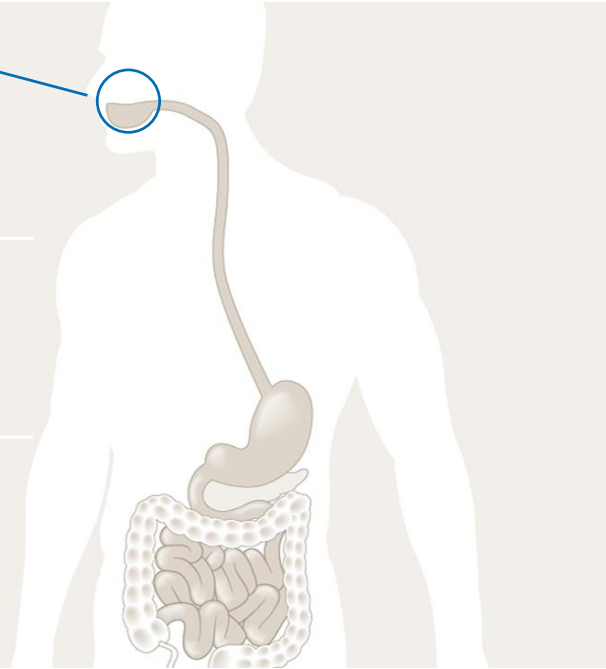
Tablets

- Low viscous spraying suspensions preventing filling or bridging of engravings
- Good adhesion to challenging core components

EUDRAGUARD® protect

Immediate release:

Functionality	<ul style="list-style-type: none">• Taste and odor masking• Moisture protection• Protection from light and oxidation
Possible Applications	<ul style="list-style-type: none">• Vitamins• Minerals• Cosmeceuticals<ul style="list-style-type: none">• Herbal extracts• BCAA
Key Benefits	<ul style="list-style-type: none">• Enhanced storage stability• Pleasant consumption (taste and odor masking)• No release in the mouth - instant release in stomach• Available in a ReadyMix version• Formulation can be either aqueous or solvent based



EUDRAGUARD® protect & EUDRAGUARD® protect ReadyMix

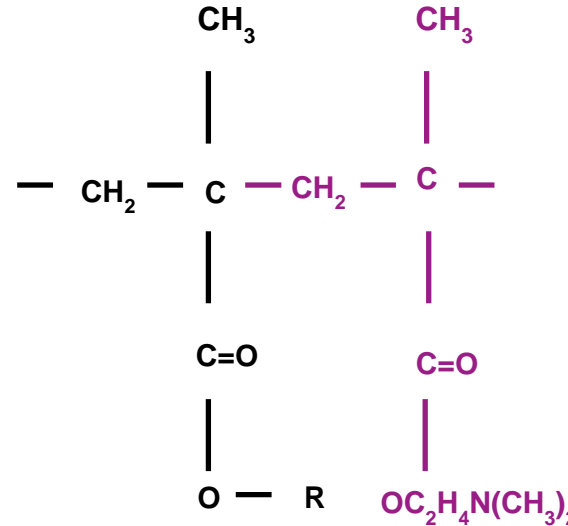
EUDRAGUARD® protect

- reliable taste and odor masking
- light, moisture & oxygen protection
- smooth and even finish
- enhanced storage stability

EUDRAGUARD® protect ReadyMix

- One-step solution for tablets, particles, soft and hard shell capsules
- quick and easy to apply at low temperatures
- wide variety of colors

E-number: E 1205



- Basic Butylated Amino Methacrylate Copolymer
- Tg ~ 50°C
- Cationic polymer

Preparation example: EUDRAGUARD® protect



EUDRAGUARD®
protect

Other
ingredients
(such as stearic
acid, tartaric
acid, and talc)

Titanium
dioxide*
*No mandatory excipients

Pigments*
*No mandatory excipients

Water

stir for
45 min

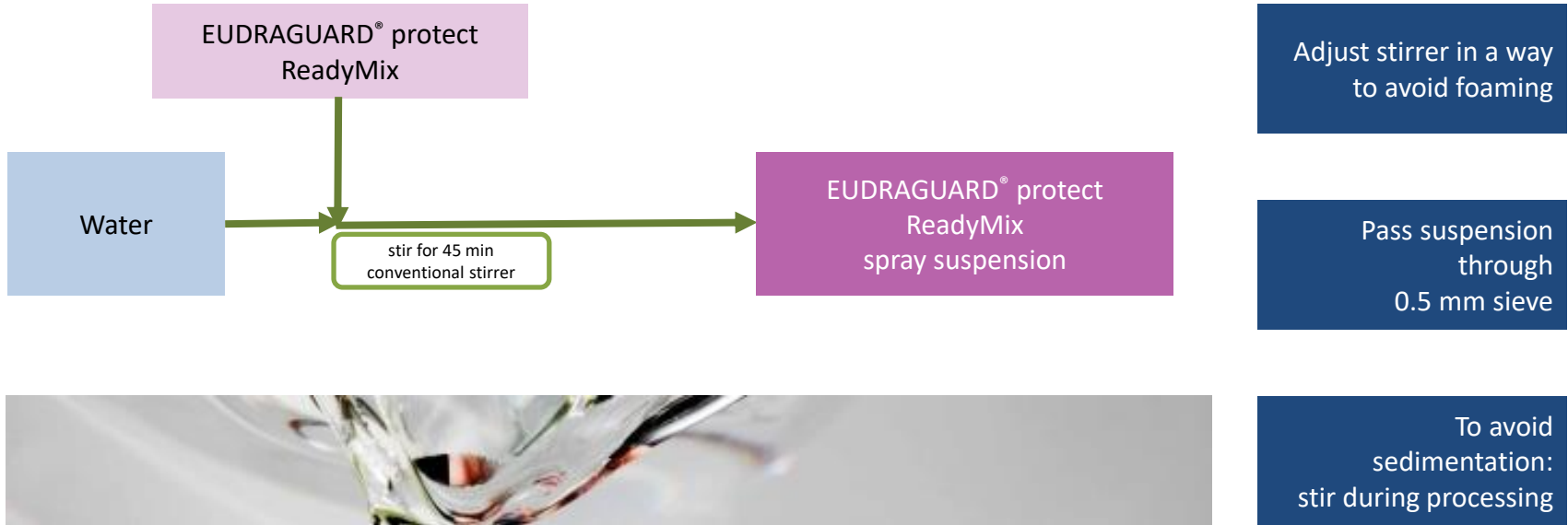
EUDRAGUARD®
protect
spray suspension

To avoid
sedimentation:
stir during processing

Adjust stirrer in a way
to avoid foaming

Pass suspension
through 0.5 mm sieve

Preparation example: EUDRAGUARD® protect ReadyMix



Actives that need environmental protection

- Herbal extracts
 - Garlic
 - Valerian root extract
- Unsaturated fat
- Vitamins
- Dried-cultured powders
 - Probiotics

Environmental factors such as temperature, humidity, oxygen and light may vary the quality of a drug substance or drug product with time.



Vitamins – a group of chemically diverse compounds

Vitamin	Temperature	Oxygen	Humidity	Light
A	XX	XX	X	XX
D3	X	XX	X	X
E	X	O	XX	X
K3	X	X	X	X
Thiamin (B1)	X	X	X	X
Riboflavin (B2)	O	O	X	X
Pyridoxine (B6)	XX	O	X	X
B12	X	X	X	O
Calcium pantothenate	X	O	X	O
Nicotinic acid	O	O	O	O
Biotin	O	O	X	X
Folic acid	XX	O	X	XX
C	O	XX	XX	O

O: stable
X: sensitive
XX: very sensitive

Light protection

- Photodegradation
 - Artificial or natural light induces degradation of actives resulting in loss of function or generation of impurities
 - Light instability is a result of absorption of short wavelength light between 300 – 500 nm
- Several options to avoid photodegradation
 - Long wavelength light (> 500 nm) in production areas
 - Colored film coatings
 - Packaging in suitable blisters/bottles (brown-colored glass)



Moisture sensitivity

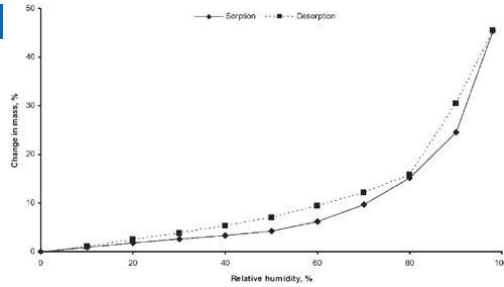
- Chemical reactions
 - Hydrolysis of the main ingredient (chemical degradation in contact with water)
 - Enhanced reaction between incompatible ingredients
- Physical changes
 - Reduction of mechanical stability
 - Discoloration, color changes
- Microbial growth



Dynamic vapor sorption measurements (DVS)

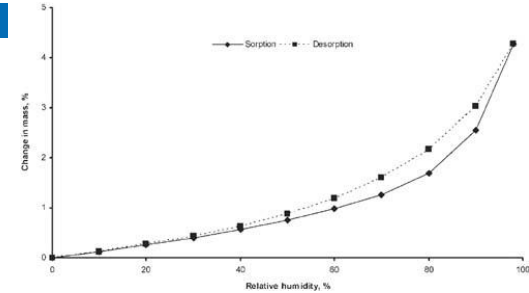
HPMC

50



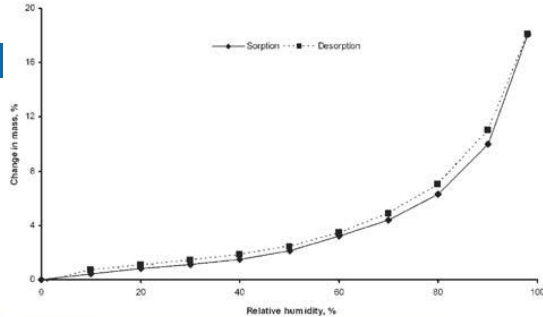
EUDRAGUARD[®] protect

5



PVA

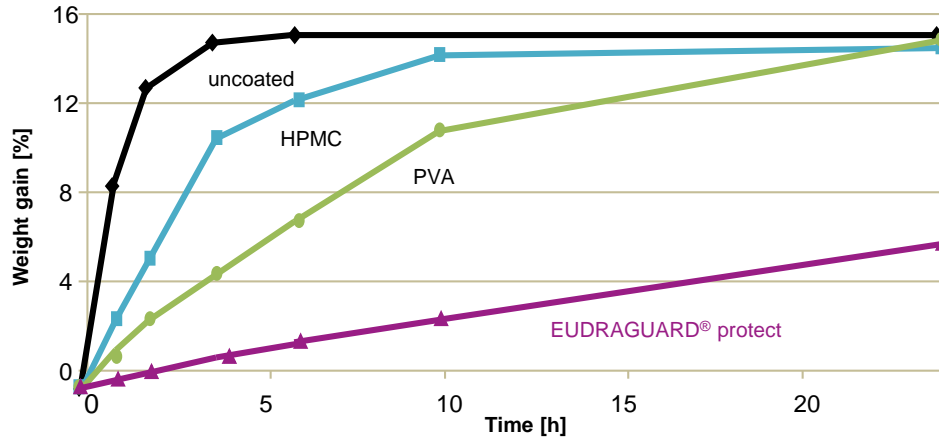
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Mind the scale!
DVS experiments show low water uptake profile of EUDRAGUARD[®] protect at up to 98 % r.h.

Moisture protection with different polymers

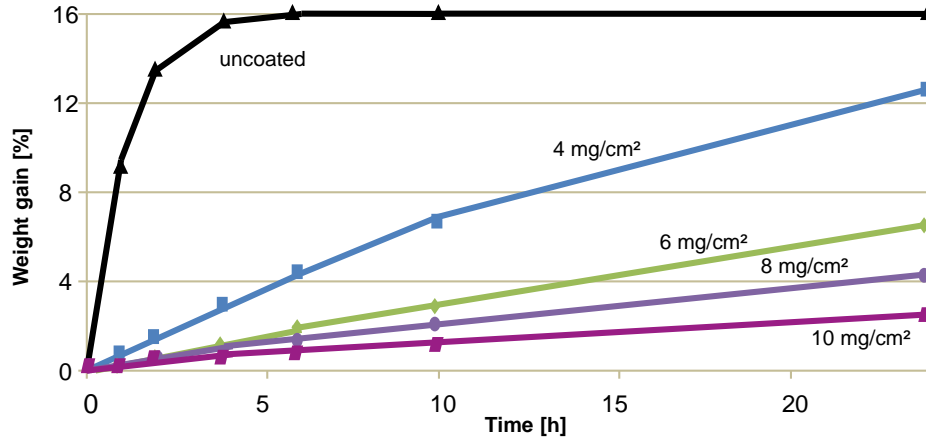
Silica tablets. Polymer applied: 6 mg/cm² –
Testing conditions:
40°C/ 75% r.h., open storage



Tablets coated with EUDRAGUARD® protect show the lowest weight gain under accelerated conditions.

Moisture protection with EUDRAGUARD[®] protect

Silica tablets – Testing
conditions: 40°C/ 75%
r.h., open storage

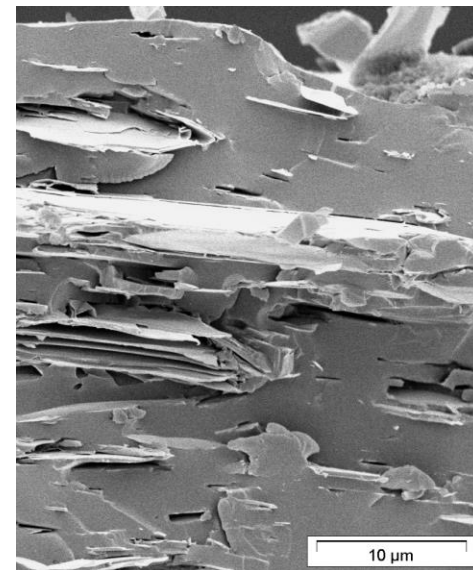


With higher polymer application level using EUDRAGUARD[®] protect the impact on moisture protection is pronounced.

Coating thicknesses for EUDRAGUARD® polymers

Type	Coating weight gain [mg/cm ²] EUDRAGUARD® protect (aqueous formulation)
Mechanical protection	1
Taste masking	1 – 2
Moisture protection	4 – 10

Depending on the substrate size and shape, coating thicknesses have to be adapted in order to achieve the protective functionality!



Cross-section of pellet coated with EUDRAGUARD® protect

Keep in mind

- **Main target is to ensure stability over shelf life and thus efficacy, and to avoid side effects caused by degradation products.**
- **Keep moisture out**
 - Use ingredients with low moisture uptake.
 - Optimize and validate your production processes.
 - Choose suitable packaging material.
- **Moisture protective coatings**
 - Protect the formulation for a certain time
 - Quality by design is key, including polymer selection, film composition and process parameters.

A combination of a functional coating with suitable packaging provides good moisture protection to the point of the patient taking the product.¹⁴



Actives that have a very characteristic smell and/or odor

- Herbal extracts
 - Garlic
 - Valerian root extract
 - and many more
- Amino acids
 - BCAAs

Smell and odor of a nutraceutical product have a huge impact on the compliance.

Especially if you'll have to take it in large doses and over a longer time.



BCAAs

Facts

- BCAA = Branched chain amino acids
- consist of 3 amino acids: Leucine, Valine & Isoleucine
- essential amino acids (cannot be synthesized by the body itself)
- beneficial for muscle growth

Unpleasant features

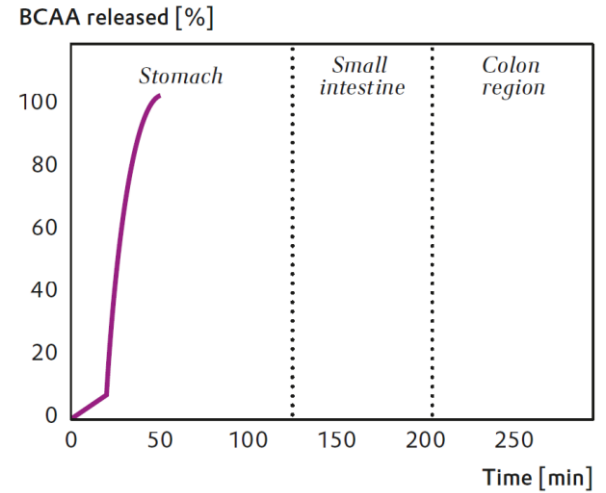
- strong & unpleasant odor



Coating with EUDRAGUARD® protect to overcome unpleasant smell and therefore to increase consumers compliance.

Dissolution profile of EUDRAGUARD® protect coated BCAAs

- no odor after EUDRAGUARD® protect coating
- Dissolution study: no slow down in release of BCAA after the coating
- BCAA are immediately released in the stomach (\triangleq pH 1.2)

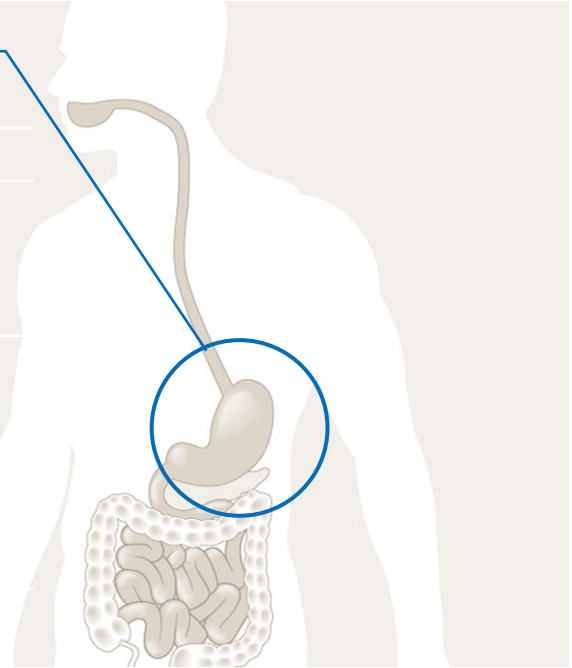


Release profile of BCAA coated with EUDRAGUARD® protect

EUDRAGUARD® control and EUDRATEC® GRS

Controlled release :

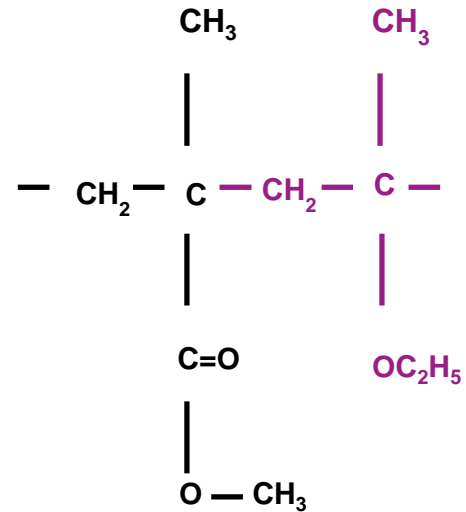
	EUDRAGUARD® control	EUDRATEC® GRS
Functionality	<ul style="list-style-type: none"> • Gastric resistance 	<ul style="list-style-type: none"> • Sustained release
Possible Applications	<ul style="list-style-type: none"> • Fish oil • garlic oil 	<ul style="list-style-type: none"> • Vitamin C • Caffeine
Key Benefits	<ul style="list-style-type: none"> • Enteric release • Acidic protection of sensitive ingredients • Avoid irritation of the mucosa • Targeted release at specific pH • Flexible polymer - especially important for soft shell capsules • Easy-to-use formulation 	<ul style="list-style-type: none"> • Gastro retention • Anthocyanins • Niacin • Polyphenols • Green teas • Creation of a floating capsule • Prolonged release for up to 4 hours • Polymer will not dissolve but gel



EUDRAGUARD® control

EUDRAGUARD® control

- aqueous-based coating system
- quick and easy to apply at low processing temperatures using standard equipment
- smooth and even finish for visual appeal and enhanced swallowability of tablets
- can be formulated into robust and versatile systems for superior performance in all solid oral dosage forms, including capsules, tablets and granules.



E-number: E 1206

Formulating with EUDRAGUARD® control

- **Recommended maximum amount for post-gastric release:**

- 20% w/w dry polymer based on the final dosage form

- **Recommended anti-tacking agents:**

- Talc
- PEG 6000
- HPC

- **Other additives can include:**

- Pore formers (e.g. alginate salts)
- Plasticizers (e.g. glycerine)

Uncoated soft gel capsules



Coated soft gel capsules

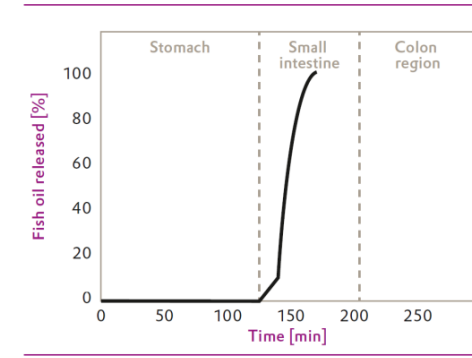


Use of glidant results in a satin finish.

Omega 3 fish-oil capsules

Challenges of fish oil capsules

- Fish oil capsules are well-known and established in the nutraceutical market.
- However, they can cause common **side effects** like the **irritation of the gastric mucosa** and **fishy burps**.
- The application of an **enteric coating** is a valuable key to overcome those unpleasant side effects.
- EUDRAGUARD® control can be used in a formulation with alginate as enteric coating to **prevent the release of ingredients in the stomach**.
- Due to its **pH depended release** in the small intestine **no reflux** can take place.
- A full enteric **functionality can be proven** in dissolution and disintegration.



Release profile of fish oil coated with EUDRAGUARD® control

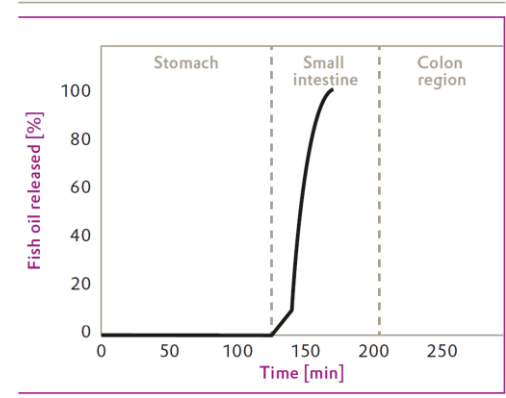
Case Study: enteric coating of softgel capsules

- Size 20 oblong softgel capsules filled with fish oil
- Batch size 6.0 kg
- Coating level: 6 mg/cm²
- Equipment: O'Hara 15"

Excipient

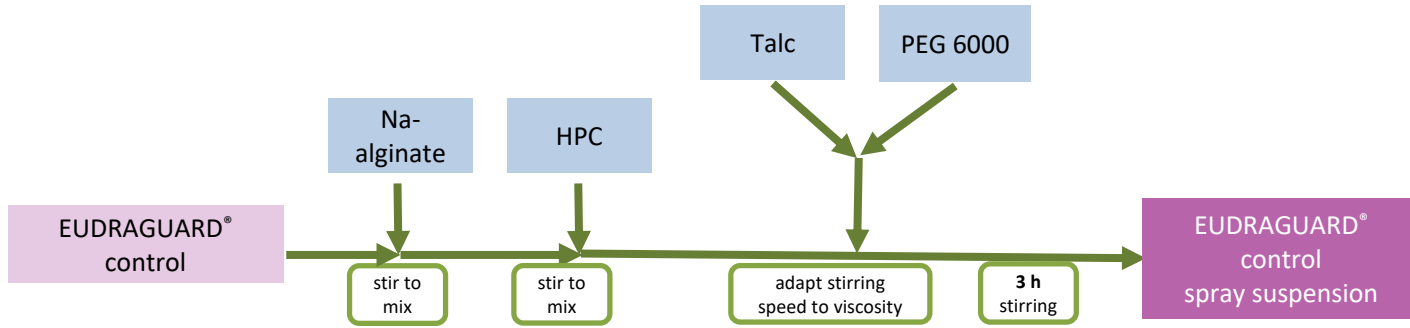
Calculated on dry polymer [%]

Excipient	Percentage	Calculated on dry polymer [%]
EUDRAGUARD® control 30% aq. dispersion	6.5 %	-
Sodium alginate	3.5 %	-
Talc	->	25.0
PEG 6000	->	5.0
HPC	->	9.75
Water, purified	q.s.	-
Solid content	10%	-



Release profile of fish oil coated with EUDRAGUARD® control

Preparation example: EUDRAGUARD® control



Up to 24 h stirring for further viscosity decrease

To avoid sedimentation:
stir the whole coating process



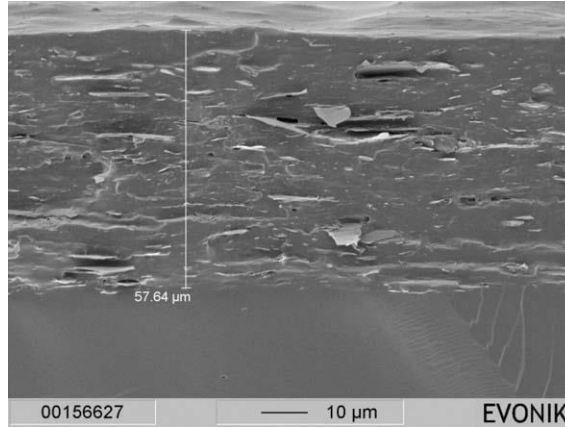
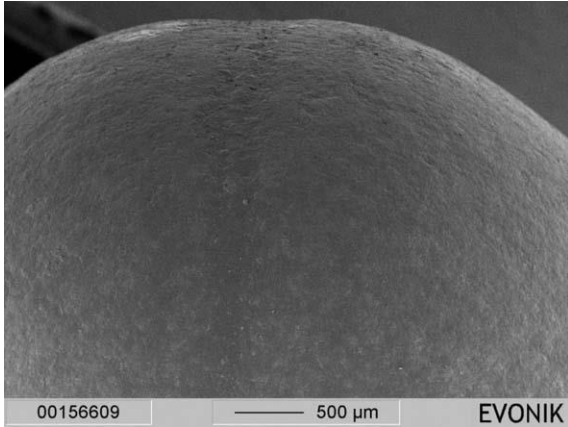
Spray process conditions – pan coating

Process

Spraying

Nozzle diameter [mm]	1.0
Spray gun type	Schlick 970 / 7-1 S 75
Pan speed [rpm]	17
Internal tube diameter [mm]	4.0
Delivery system (pump)	Watson Marlow 520
Flat pattern pressure [bar]	1.5
Atomizing air pressure [bar]	1.5
Inlet air volume [m ³ /h]	150
Inlet air temperature [°C]	43.9 - 44.5
Exhaust air temperature [°C]	27.0 - 30.1
Product temperature [°C]	28.8 - 29.9
Spray rate [g/(min*kg product)]	3.0
Process time [min]	180

SEM evaluation

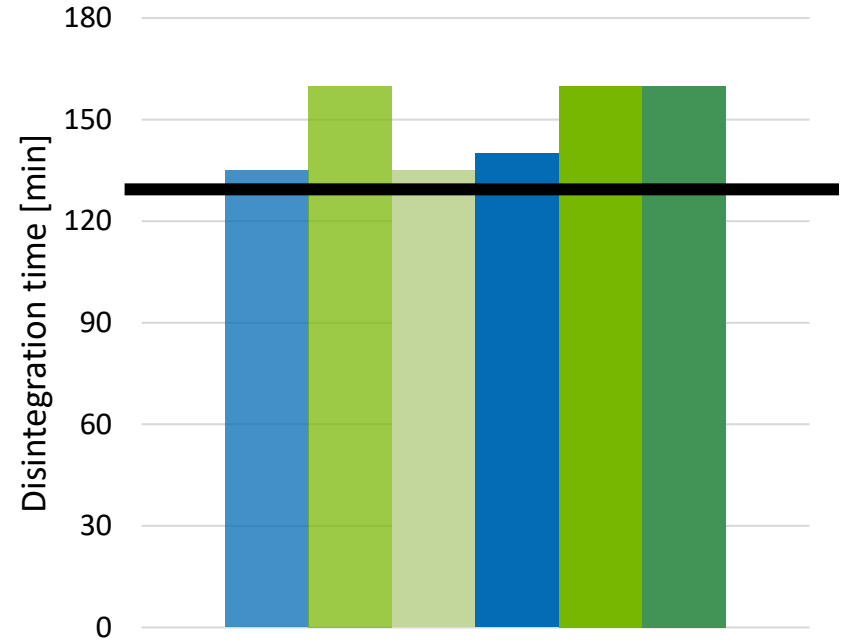


- Smooth and even coating
- Seams were visible, but well-coated
- Attractive satin appearance
- Good film adhesion

Disintegration test

Disintegration test

- n=6
 - 2h in 0.1 N HCl followed by 1h in phosphate buffer pH 6.8
- All capsules were resistant to acid for 2 h
- Capsules disintegrated within 30 minutes after switch to buffer pH 6.8



High performance coating solution for fish oil soft gelatin capsules

Fish oil capsules coated with EUDRAGUARD® control

- **Cost efficient** coating solution with proven functionality
- **Low weight gain** of polymer needed
- **Quick and easy** suspension preparation and **short spraying times** for optimized production cost
- Proven for **continuous** manufacturing
- Smooth, even finish for **visual appeal and swallowability**
- Highly flexible coating for **superior mechanical stability**
- **Low process temperatures** for sensitive soft gels
- **No batch-to batch variation** of the polymer, **reproducible** results for coating
- May be used on **conventional coating equipment**
- **Talc-free** version available
- **Non-animal** derived



EUDRAGUARD[®] biotic

Delayed release:

Functionality

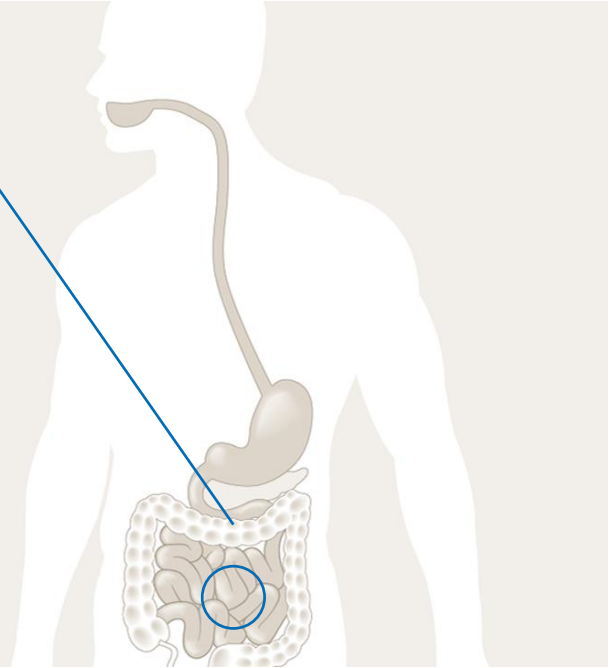
- Colonic delivery

Possible Applications

- Prebiotics
- Probiotics

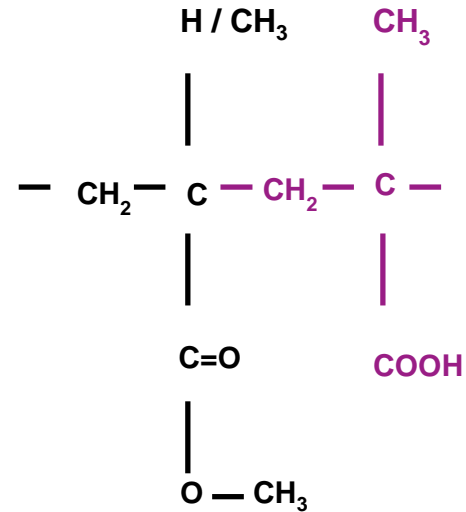
Key Benefits

- Unique market solution for targeted colonic delivery
- Targeted release above pH 7
- Easy-to-use formulation



EUDRAGUARD® biotic

- Highly flexible polymer system which makes it applicable for a great variety of dosage forms incl. soft and hard gel capsules as well as tablets
- quick and easy to apply
- requires gentle processing temperatures to ensure good product stability
- pH triggered polymer system, therefore sharp release behavior
- Smooth and even finish for visual appeal and enhanced swallowability of tablets
- Unique market solution for targeted colonic delivery



E-number: E 1207

Case Study – Probiotics

Probiotics formulation design

- Probiotics are normally **oral administrated**
- Live bacteria shall **improve gut health** and support the prevention of certain diseases
- Sufficiently high dose of **live and metabolically active microorganism** in the target region is crucial
- For many bacterial strains the target is the **colon**
- “Probiotics are supposed to work in the colon and not the small intestines or stomach, so motility issues can result in problems with probiotic bacteria reaching the proper place.”¹⁾
- Number of active probiotics is often highly affected by manufacturing processes e.g. drying
- Could be further reduced during the gastro intestinal pathway due to gastric juice, enzymes and bile salts
- **Gentle process conditions during formulation and targeted release to the colonic regions are therefore mandatory prerequisites for an appropriate health effect.**

Source: 1) https://www.nutraingredients.com/Article/2018/08/10/Use-of-probiotics-linked-to-brain-sluggishness-and-stomach-bloating-Study?utm_source=newsletter_product&utm_medium=email&utm_campaign=13-Aug-2018&c=41BGQDBwUChiNiyheqHbWK0BkcUAfb1I&p2

SAMANA® - example for a probiotic filled into hard capsule

Target

- **Probiotics formulated into a capsule for colon delivery similar to SAMANA®**
- **SAMANA® is a capsule filled with lactobacillus* and vitamin B2**

Solution

- **Evonik conducted coating trials and analytics** in application labs
- Sub-coat was applied to achieve gap sealing of the hard capsule.
- Functional coating with EUDRAGUARD® biotic applied on the capsules at about **7% weight gain** at gentle process temperatures (**max 35°C**)
- **Proven release of viable bacteria** in the colon achieved
- **Smooth and even coated capsules** with attractive appearance

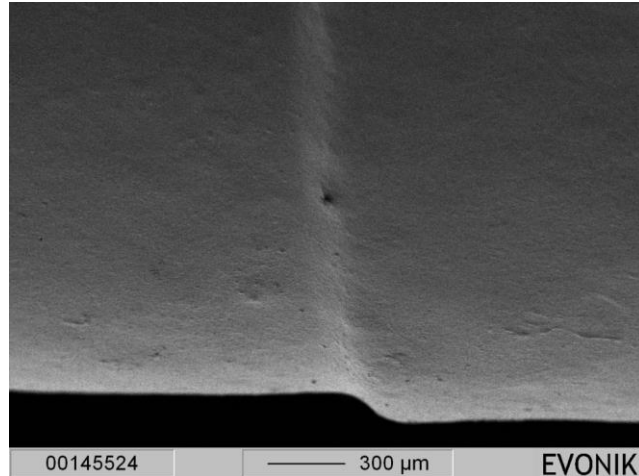


* Bacteria: Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus rhamnosus, Lactobacillus reuteri, Bifidobacterium bifidum, Streptococcus thermophilus

Smooth and even coated capsules with attractive appearance

Example of a coating with EUDRAGUARD® biotic

- Sub-coat was applied to achieve **gap sealing** of the hard capsule.
- **Smooth and even coated capsules** with attractive appearance

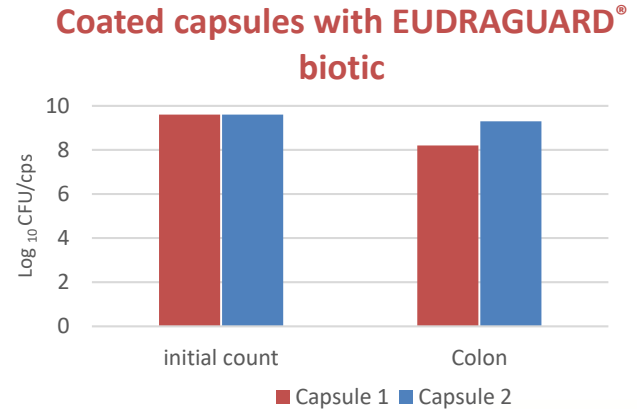
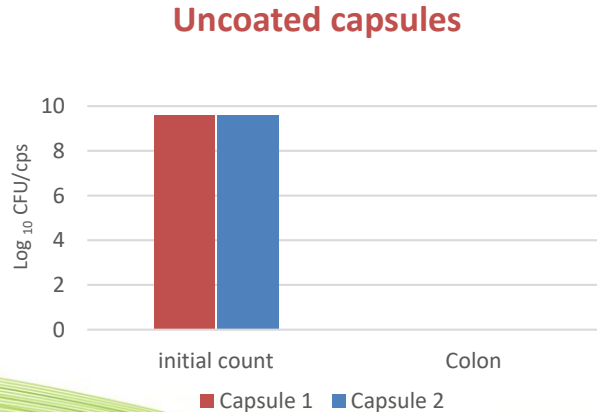


Coated capsule

(sub-coat & EUDRAGUARD® biotic coating)

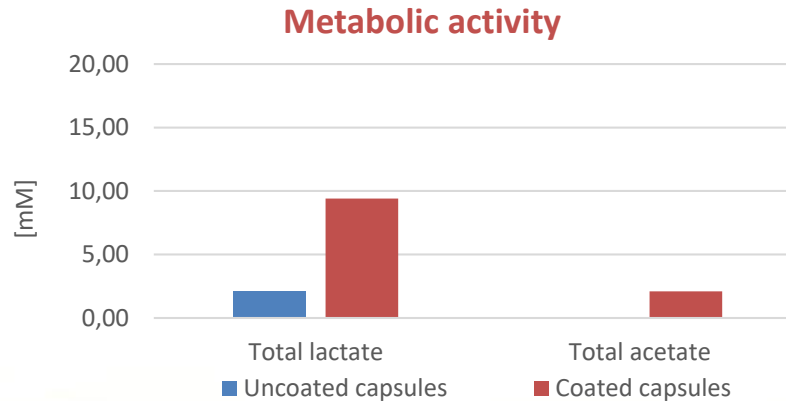
Example of proven release in colon of viable bacteria via simulated colon test

- Initial count: 9.6 log₁₀ CFU/capsule
- Species: *L. Plantarum*, *B. Bifidum*
- Capsuled have been tested for 1 h in Simulated Gastric Fluid at pH 1.2, followed by 1 h Simulated Intestine Fluid at pH 6.8, followed by a release in Simulated Colon Fluid at pH 7.4 within 1h
- Where the uncoated capsules does not show any living bacteria arriving in the colon, the capsules coated with EUDRAGUARD® biotic show nearly the same CFU as initial



Example of quantification of metabolic activity

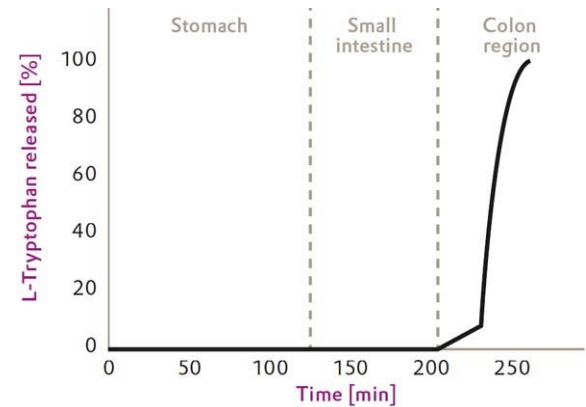
- After 24 h of colonic incubation the metabolic activity of the bacteria was measured
- The production of **lactate** was produced through the **L. plantarum**
- The production of **acetate** was produced through the **B. bifidum**
- The **increase of the metabolic activity is directly correlated to the higher number of viable cells** found in the last stage of the GI tract



EUDRAGUARD® biotic ensures release in the colon

- Health ingredient coated with EUDRAGUARD® biotic will be released directly in the colonic area.
- The pH depended release ensures a safe transport of the health ingredient to the right place.
- Therefore the health ingredient arrives intact in the colon.
- Furthermore the health ingredient arrives where it is needed at most, and not been used up by the body at any other part.

Release profile of L-Tryptophan coated with EUDRAGUARD® biotic



Recommended weight gain: 8-11% total solids based on core weight.

EUDRAGUARD® natural

Immediate or modulated release :

Functionality

- Taste and odor masking
- Modulated release

Possible Applications

- Herbal extracts
- Olive oil
- Vitamins
- Minerals

Key Benefits

- Natural system (maize starch-based coating)
- Applicable for functional food & beverages as well as for dietary supplement
- Two-component system available



Case study: bitter tasting health ingredient

Reasons for a coating:

- Health ingredient with a extremely bitter taste and a huge particle size distribution (PSD)
- Low to none-existing consumer compliance

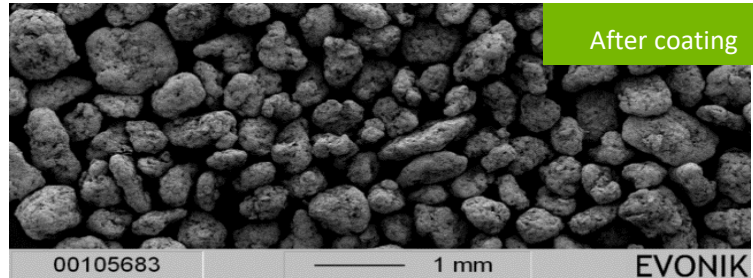
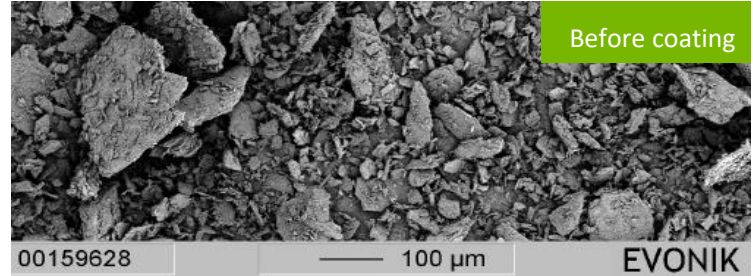


Best choice: all-natural coating with EUDRAGUARD® natural to guarantee a reliable taste masking and to optimize additionally the PSD.

Coating process and SEM investigation

Taste masking

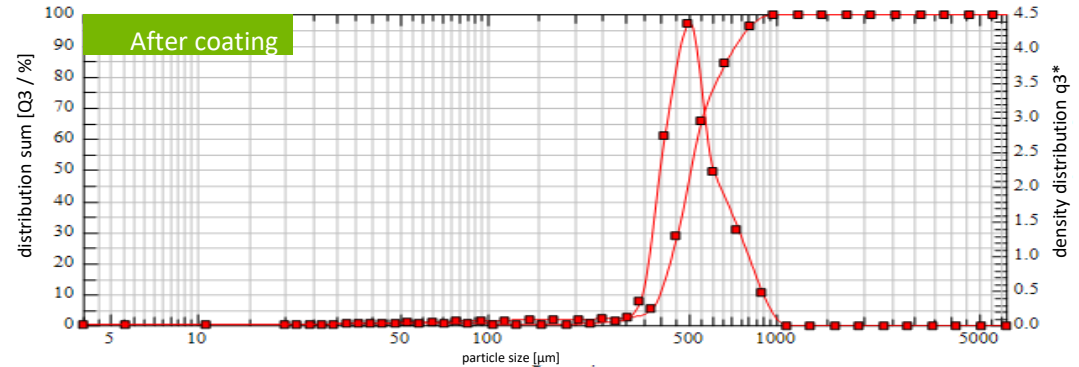
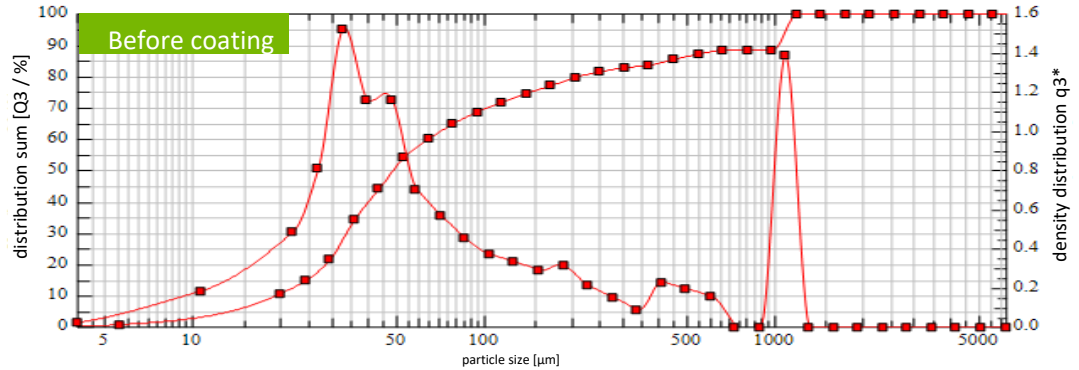
- 160 gr particles
- standard EUDRAGUARD® natural formulation
- 8.8% solid content
- standard process parameters



Particle size distribution

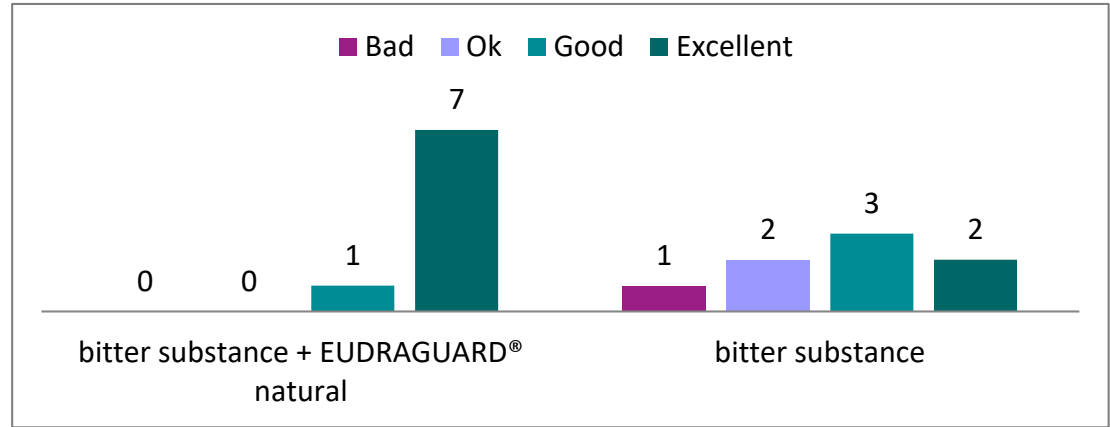
- broad PSD for mixture of different uncoated ingredients

- EUDRAGUARD® natural coating significantly improves the PSD
- reduction of fine particles
- smaller particles can be obtained by alternative technologies (e.g. spray drying)



Tasting panel analysis

- coated granules were dispersed in water before ingestion
- evaluation within human taste panel
- heterogeneous sensation of uncoated granules refer to genetic variability in human taste
- **successful bitterness reduction with EUDRAGUARD® natural coating**



The use of an electronic tongue can help to evaluate taste-masking results within the development stage and therefore facilitate those tests.

Nutritional coatings - regulatory overview

Country*	EUDRAGUARD® protect	EUDRAGUARD® control	EUDRAGUARD® biotic	EUDRAGUARD® natural
EU	Approved or no approval required	Approved or no approval required	Approved or no approval required	Approved or no approval required
US	Approved or no approval required	Approved or no approval required	Planned or ongoing activities	Approved or no approval required
Brazil	Planned or ongoing activities	Approved or no approval required	Planned or ongoing activities	Approved or no approval required
Mexico	Approved or no approval required	Approved or no approval required	Approved or no approval required	Approved or no approval required
China	Approved or no approval required	Approved or no approval required	Approved or no approval required	Approved or no approval required
Japan	Planned or ongoing activities	Planned or ongoing activities	Planned or ongoing activities	Approved or no approval required
India	Approved or no approval required	Approved or no approval required	Approved or no approval required	Approved or no approval required

Approved or no approval required

Planned or ongoing activities

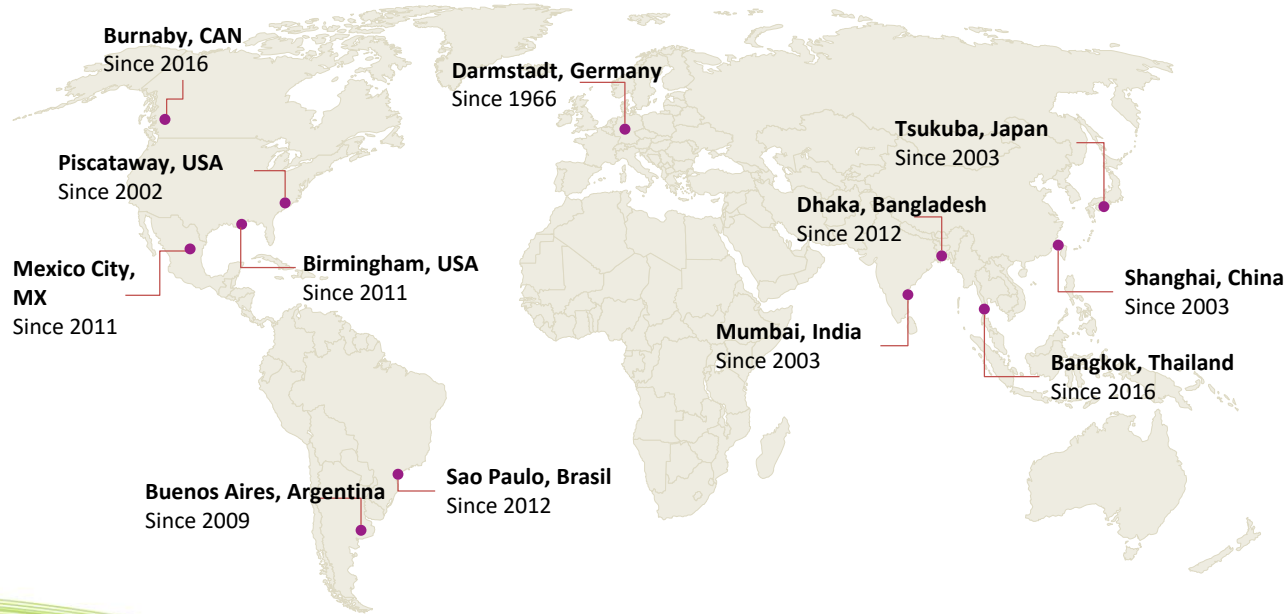
* Other countries on request

Nutritional coatings - regulatory overview

Delivery Form	Max. amount per unit*
<p><u>Monosolids</u> Unit: one piece Examples:</p> <ul style="list-style-type: none"> ▪ Tablets, including multiparticulates compressed into tablets ▪ Capsules (soft gel and hard shell) including multiparticulates filled into capsule ▪ Oral strips ▪ Multiparticulates further processed into effervescent tablets, lozenges, pastilles 	
<p><u>Multiparticulates filled directly into sachet</u> Unit: one sachet or other single piece Examples:</p> <ul style="list-style-type: none"> ▪ Powder ▪ Granules (e.g. effervescent, fast melt) ▪ Pellets 	<p><u>For units up to approx. 1000 mg:</u> EUDRAGUARD control: 20 % EUDRAGUARD protect: 10 % EUDRAGUARD biotic: 10 %</p> <p><u>For units significantly above 1000 mg:</u> EUDRAGUARD control: 200 mg EUDRAGUARD protect: 100 mg EUDRAGUARD biotic: 100 mg</p>
<p><u>Multiparticulates further processed into</u> Unit: one serving size Examples:</p> <ul style="list-style-type: none"> ▪ Gummies (serving size e.g. one small sachet) ▪ Cereal bars (serving size one piece) ▪ Chewing gums (serving size e.g. one piece) 	

Formulation Development Laboratories

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Conclusions

- Targeted delivery is a major factor to ensure efficacy of food supplement products.
- It is a valuable way to provide additional value and to build market success on.
- A simple and cost-effective way to generate targeted delivery and to provide other relevant features are functional film coatings.
- Evonik's versatile EUDRAGUARD® polymer platform enables all kinds of gastro-intestinal targeting and controlled release as well as taste masking and moisture protection.



Summary

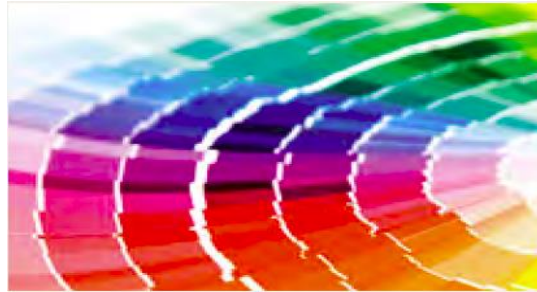
Low temperatures



Low process temperatures – 25-35°C

- ideal for soft gel capsules
- heat sensitive health ingredients

Color matching



Customized coatings due to color-matching with ReadyMix types

- related to PANTONE or RAL guide
- batch-to-batch color matching

All substrates

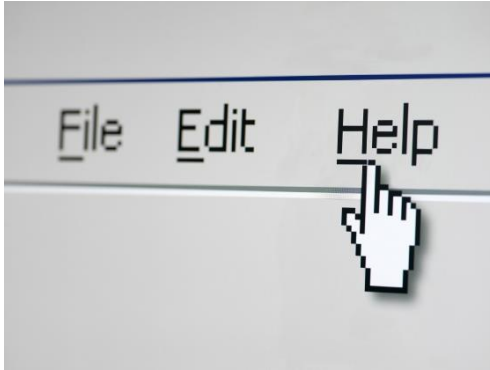


Coating of all substrates

- tablets: round, oblong, special shaped, with engravings
- hard and soft shell capsules
- pellets, granules, crystals, particles

Questions?

Support



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