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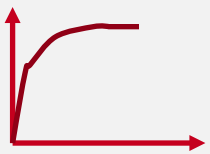
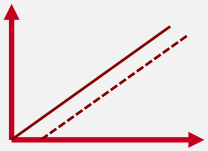
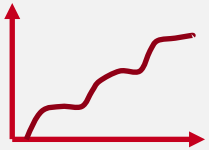
Faster coating processes with advanced enteric coating formulations

BASF Pharma Solutions

Controlled Release Systems

- All drug release rates are *controlled*
- However, there exists different classifications depending on this control

	Modified Release		
			
Immediate	Sustained = Extended	Enteric = Delayed	Pulsatile
The active ingredient is quickly released in the media (saliva, stomach, etc.)	The active ingredient is dosed at a predefined rate, over an extended period of time	The active ingredient is released after the stomach, in the small intestine or colon.	Release of the active ingredient is programmed in short bursts over a period of time.

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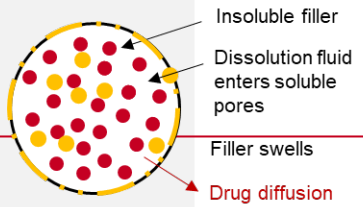
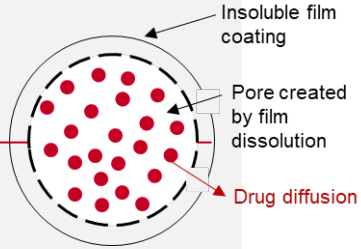
Sustained Release formulations are divided into Matrix and Reservoir systems

	Matrix (monolithic)	Reservoir
What is?	API mixed with insoluble excipients	Coated insoluble or soluble cores
Mode of action	• Swelling • Diffusion • Erosion	• Dissolution • Diffusion
Processing	• Wet granulation • 3D Printing • Direct compression	• Coating
Typical excipients	• HPMC • HPMC-acetate succinate • High Mw povidone • High Mw PEO • Co-processed excipients	• Polyvinyl acetate dispersions • Ethyl cellulose • Biodegradable polymers





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Agenda

- BASF enteric release polymers
- MAE case study
- Virtual Pharma Assistants

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The most important considerations when preparing coating suspensions…

Solvent	MFFT min. film forming temperature	Solids Content
• Safety • Mixtures • Temperature	• Related to Tg • Modified with plasticizers • Stability	• Process efficiency • Viscosity

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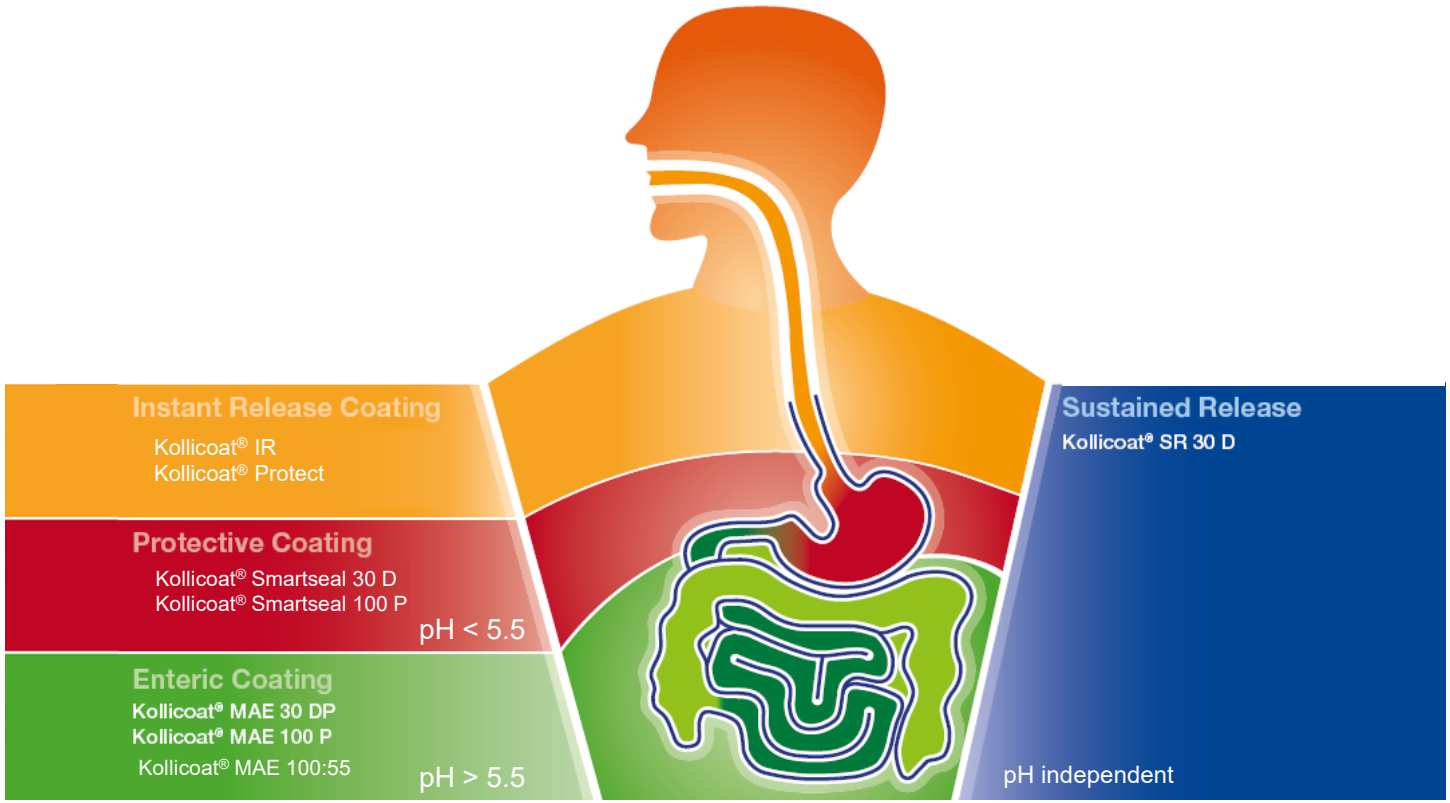
BASF has a portfolio of coatings for your needs



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Enteric or gastroresistant coatings

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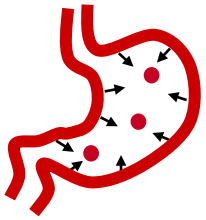
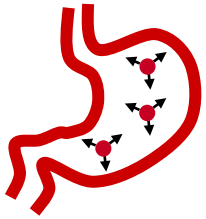
When do we use enteric coatings?



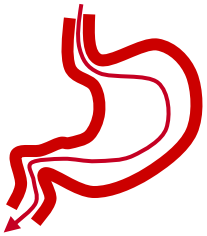
Protection of gastro-sensitive active ingredients

→ Proton-Pump Inhibitors, Enzymes, Peptides, Antibiotics



Protection of gastric mucosa from aggressive actives

→ COX-1-Inhibitors, Iron Compounds, Acetylsalicylic acid, Diclofenac-Sodium



Gastrointestinal targeting

→ Budesonide, Clarithromycin, Doxazosin, Pancreatic Enzymes

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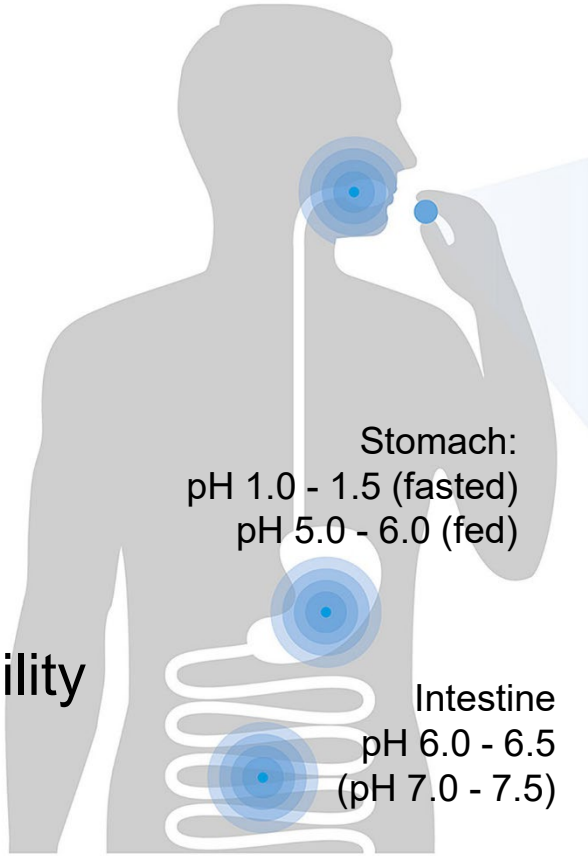
Gastroresistant Polymer Coatings

- Should not dissolve at gastric pH (1 - 4)
- Can be combined with pore formers to tune opening pH
  - Subcoats can be used to limit API interactions or accelerate the coating process
- Required quantity depends on polymer solubility and core surface area.



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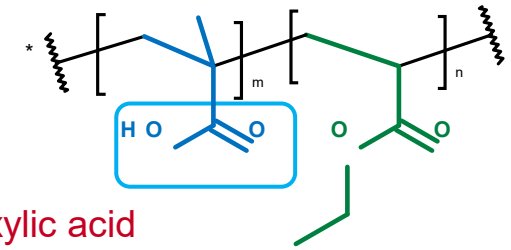
Methacrylic Acid Ethylacrylate (1:1) copolymer (MAE polymer)

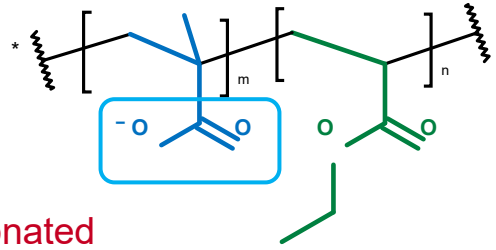
Methacrylic Acid **Ethylacrylate**



Carboxylic acid functional group

pH < 5.5

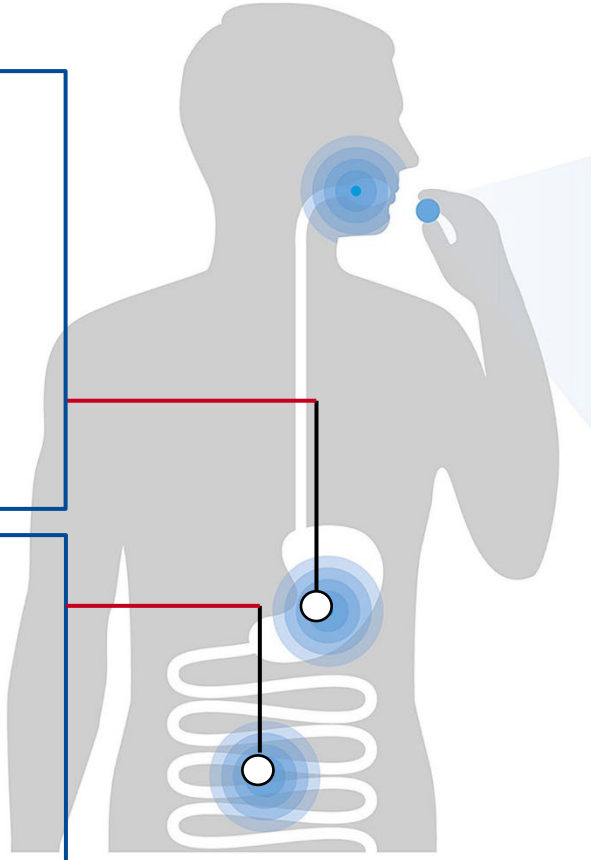
Insoluble
in the gastric acids
⇒ Protection



Deprotonated carboxylic acid

pH > 5.5

Readily soluble
in the intestine
⇒ Instant Release



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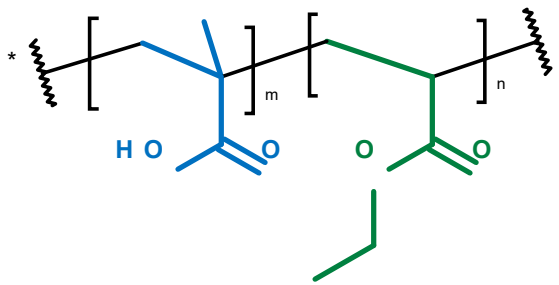
MAE application guide: Plasticizer
The crucial ingredient for MAE



Methacrylic acid ethyl acrylate 1:1 copolymer:

- low MFFT: 22 – 27 °C
- high Tg: 113 – 117 °C

MFFT = minimum film forming temperature, Tg = glass transition temperature

- Low MFFT
  ⇒ the polymer is very hydrophilic and dispersion water acts as plasticizer in the coating process
- High Tg
  ⇒ After drying, plasticizing water is gone and Kollicoat® MAE films are brittle.

Kollicoat® MAE grades always need a plasticizer to maintain flexibility in the dry state!

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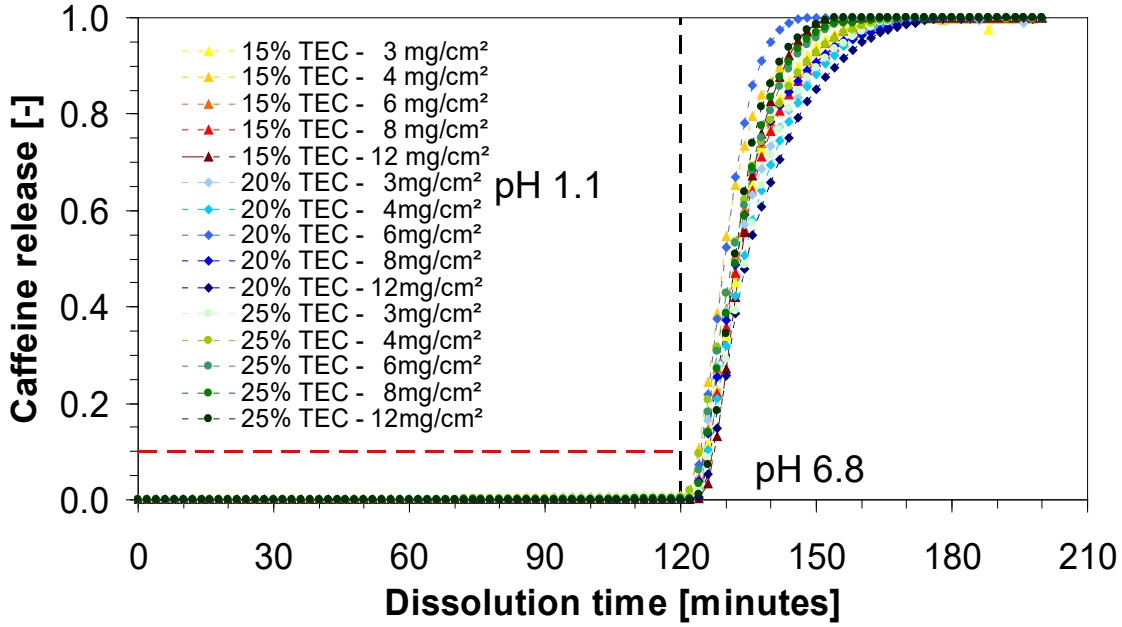
MAE application guide: Plasticizer
How much is required?

10 % triethyl citrate (TEC)
⇒ insufficient; crackings

15 - 25 % triethyl citrate (TEC)
⇒ good functionality



15 -25% plasticiser are recommended to ensure flexible films.
Suitable are eg. triacetin, triethyl citrate, acetyltriethyl citrate, and PEG 400

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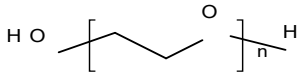
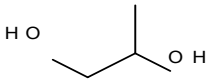
MAE application guide: Plasticizer

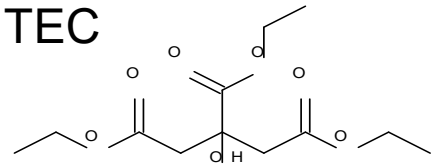
Plasticizer Nature



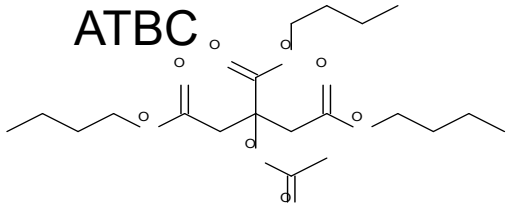
PEGs



PG



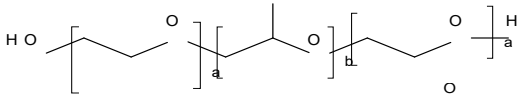
TEC



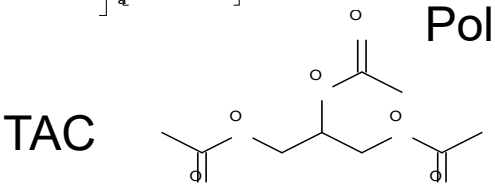
ATBC

hydrophilicity

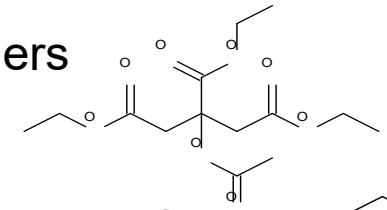
lipophilicity



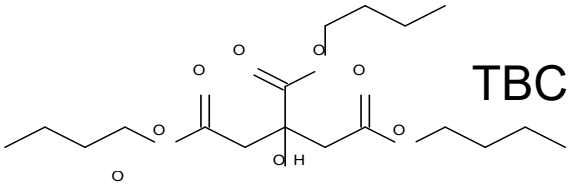
Poloxamers



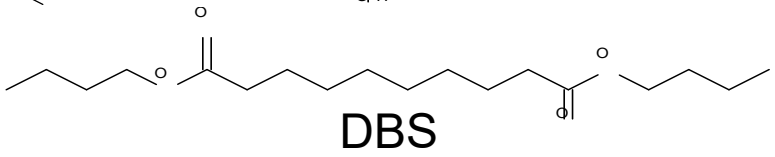
TAC



ATEC



TBC



DBS

PEG = polyethylene glycol, PG = propylene glycol, TEC = triethyl citrate, ATBC = acetyl tributyl citrate, TAC = triacetin, ATEC = acetyl triethyl citrate, TBC = tributyl citrate, DBS = dibutyl sebacate

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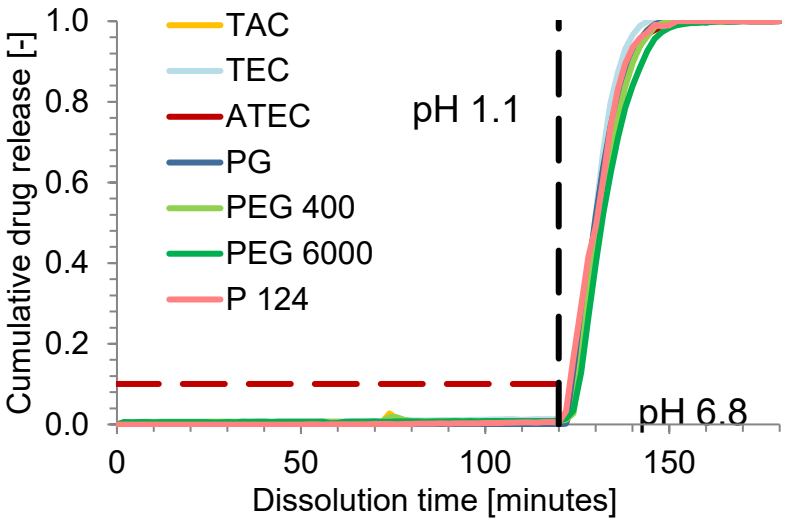
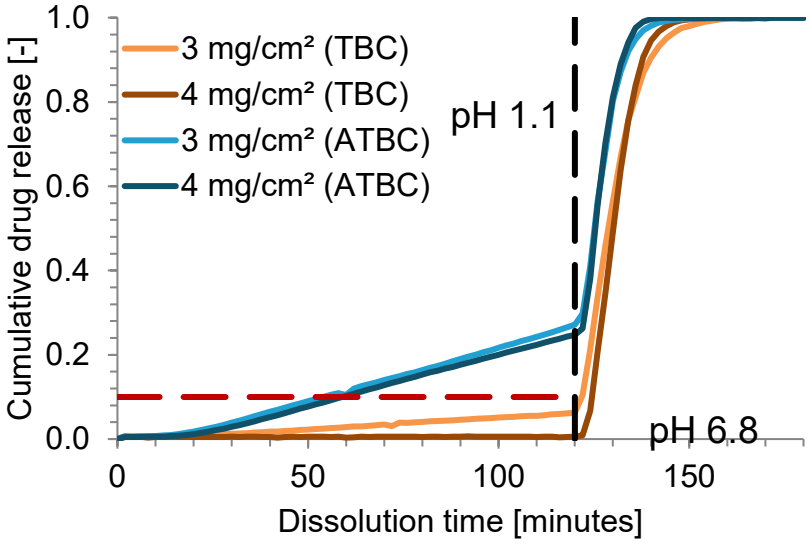
MAE application guide: Plasticizer
Importance of Chemistry

Dissolution of caffeine tablets
(15% hydrophilic plasticiser, 3 mg /cm^2)



Dissolution of caffeine tablets
(15% lipophilic plasticiser)



The type of plasticizer matters. Hydrophobic plasticizers are more difficult to introduce into the hydrophilic polymer and may give weaker functionality. Thus, higher coating levels might be necessary.

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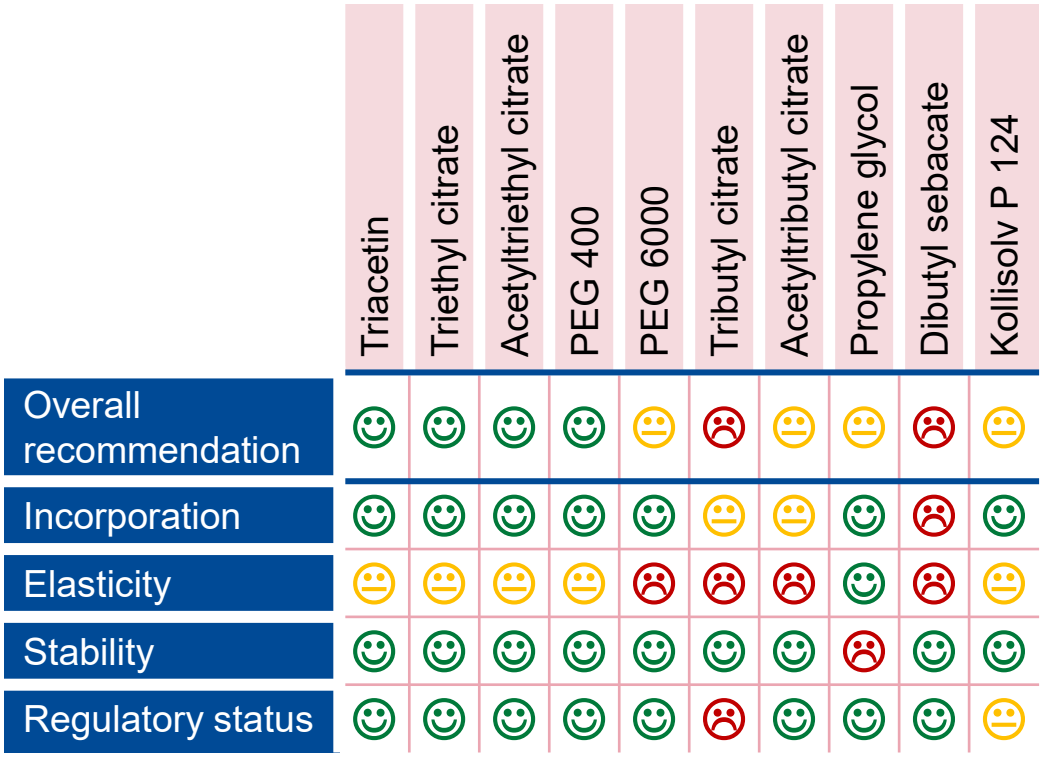
MAE application guide: Summary Plasticizer

Comparing various plasticisers regarding their effect on methacrylic acid/ethyl acrylate copolymer;
Th. Agnese, Th. Cech, M. Haberecht;
9th Central European Symposium on Pharmaceutical Technology;
September 20 – 22, 2012; Dubrovnik, Croatia

- A plasticizer is always needed to provide flexibility in the dry state
- 15% - 25% plasticizer recommended
- The plasticizer nature affects
  - MFFT
  - Tg
  - (Dissolution profile)



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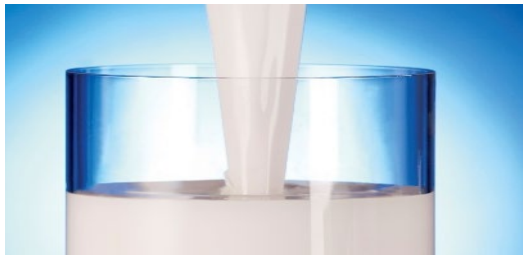
Methacrylic Acid Ethylacrylate (1:1) copolymer: Kollicoat® MAE is available as…

Polymer Dispersion

Kollicoat® MAE 30 DP

- for aqueous coating
- Ready-to-coat

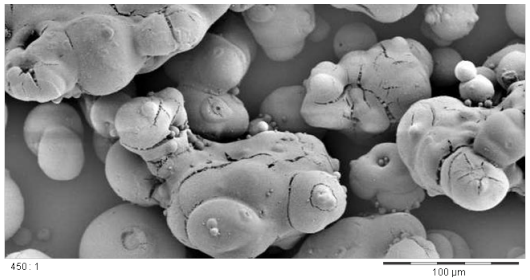


Equivalent to Eudragit L 30 D-55

Polymer Powder

Kollicoat® MAE 100-55

- for aqueous & organic coating
- Redispersion into water requires neutralization step (NaOH handling)

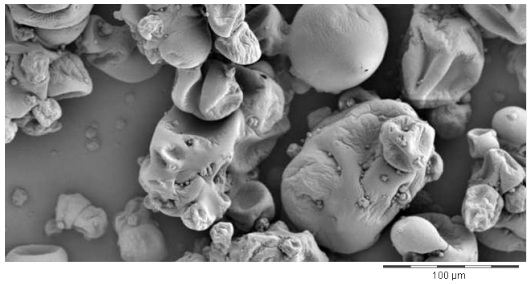


Equivalent to Eudragit L 100-55

Pre-neutralized Powder

Kollicoat® MAE 100 P

- for aqueous coating
- Ready for redispersion ⇒ handling advantage over 100-55 powder



Unique BASF polymer

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Enteric Coating
Kollicoat® MAE Summary

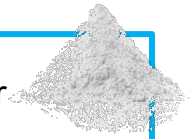
Polymer Dispersion

Kollicoat® MAE 30 DP

Polymer Powder

Kollicoat® MAE 100-55

Pre-neutralized Powder



Kollicoat® MAE 100 P

Application guide:

- Plasticizers:
  always needed, 15 – 25% recommendend
- Acid sensitive APIs:
  may degrade even though no release can be detected; use a subcoat

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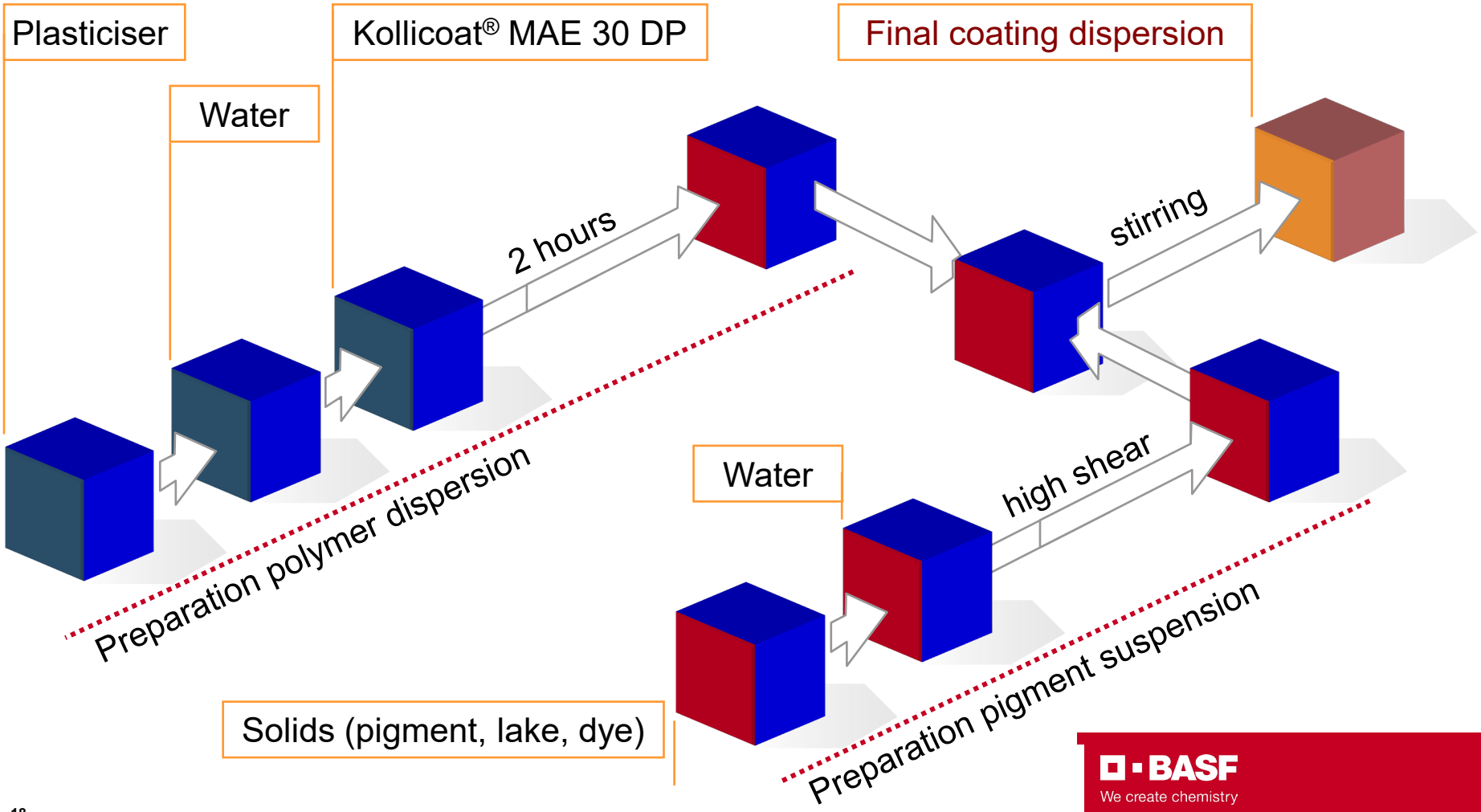
Preparation procedure for coating dispersions (MAE 30D)



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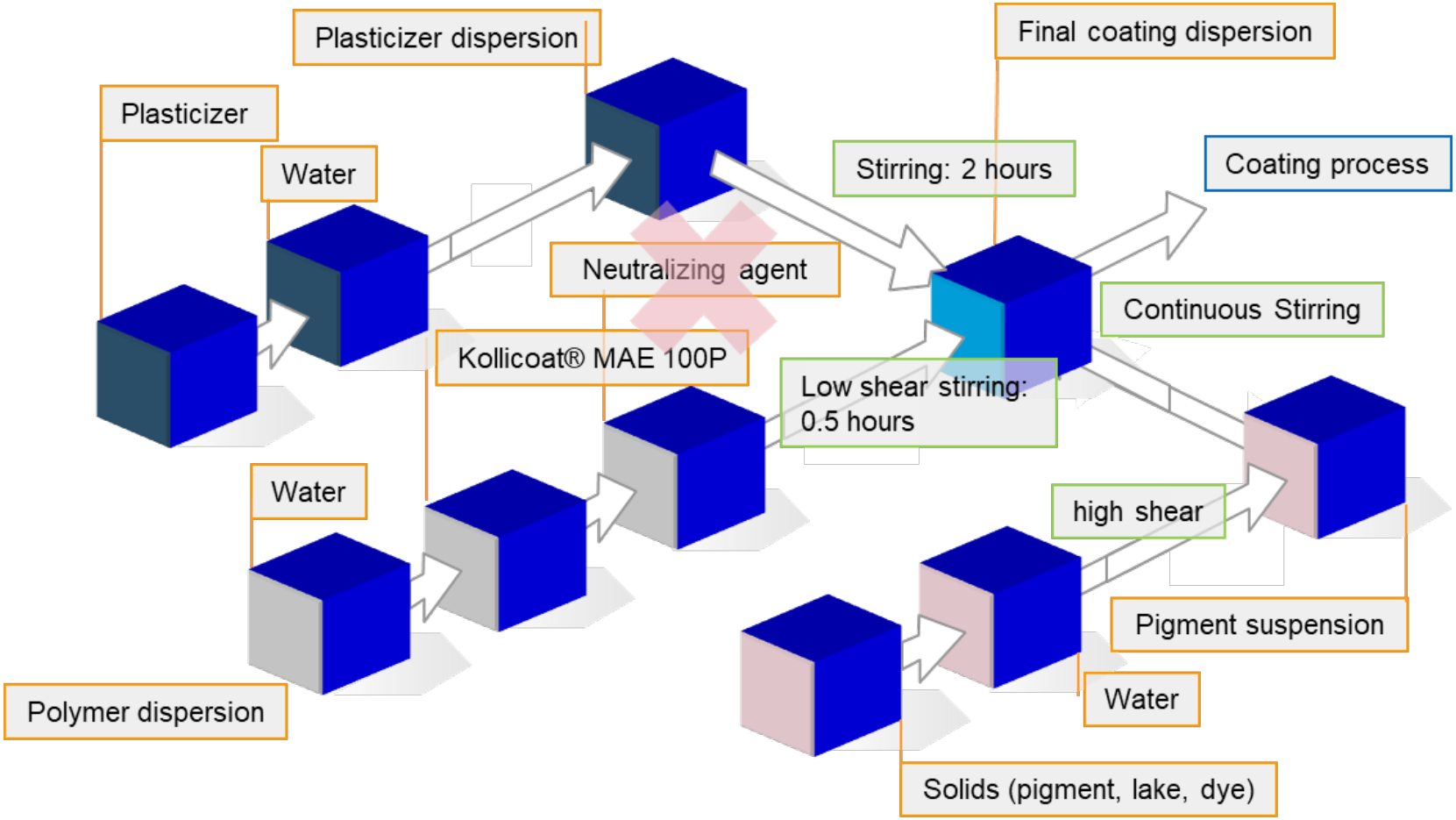
Preparation procedure for powder grades (MAE 100:55 and MAE 100P)



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MAE application guide: acid sensitive APIs
Pantoprazol mini tablets

Pantoprazole minitablets (Ø=2.0 mm)

Pantoprazole is acid sensitive. Therefore, a subcoat is needed to separate it from the acidic MAE layer.

Top-coat
Kollicoat® MAE 30 DP 90.9%
Triethyl citrate (TEC) 9.1%

Sub-coat
Kollicoat® IR + TiO_2 99.5%
FD&C Blue No. 1 0.5%

Minitablet (Ø=2.0 mm)
Pantoprazole Na hydrate 11.90%
Ludipress® LCE 75.80%
Kollidon® VA 64 Fine 4.90%
Kollidon® CL 4.90%
Mg-stearate 2.5%

**Remember: MAE 30D is acidic and dispersions are NOT neutralized. That is why a subcoat is needed, to prevent interaction with core tablet.*

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General recommendations

- Apply a subcoat
  - Minimize interaction between core and enteric polymer
  - Ensures reproducible drug release
  - Recommended (especially!) for MCC cores
  - Kollicoat® IR 20-25% w/w
- Kollicoat® MAE at 20% w/w in top coat

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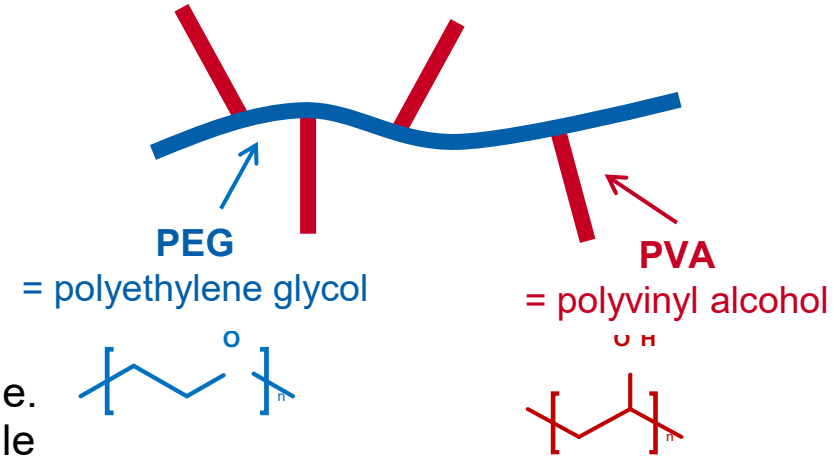
Subcoat - Kollicoat® IR



- Composition:
  PVA side chains grafted onto PEG 6000 backbone.
  ⇒ combination of PVA and PEG into **one** molecule

- **Does NOT** require a plasticizer

- Pharmacopoeial Compliance:
  USP/NF, Ph.Eur., and JP

- Applications:
  - unique high-performance polymer for film coating and wet binder (peroxide free)

~ 25 % PEG &
~ 75% PVA units
Mw: ~ 45 000

CAS-Nr: 96734-39-3

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Traditional (enteric) vs. Modern (w/sub-coat) coating approach

Disadvantages:
- Polymer destabilization
- Pores due to pigments
- Sedimentation of insoluble components

⬇ Solids content

⬆ Process Time

Traditional

"Self – Made" Formula
- Polymer (Kollicoat® MAE)
- Plasticizer (triethyl citrate, TEC)
- Opacifier (talc)
- Pigment (titanium dioxide)
- Colorant (iron oxide)
- Additives (surfactant)

Solids content: up to 20%
Preparation time: 1.5 hrs

Coating Process*
Coating level: up to 14 mg/cm²
Coating time: **up to 9 hrs**

Total Time: 10.5 hrs

Modern approach

Immediate release (IR) sub-coat
- Kollicoat® IR
- Pigments

Solids content: up to 30%
Preparation time: 0.5 hrs

Enteric release (ER) top-coat
- Polymer (Kollicoat® MAE)
- Plasticizer (triethyl citrate, TEC)

Solids content: up to 34.5%
Preparation time: 0.25 hrs

Coating Process*
Coating level (IR): up to 3 mg/cm²
Coating time: **1.25 hrs**
Coating level (ER): up to 5 mg/cm²
Coating time: **2.0 hrs**

Total Time: 4.0 hrs

**For a 500 kg lot*

Advantages
- Max solids content
- Less API-coating interaction (prazoles)
- Less core impact on functionality

⬆ Solids content

⬇ Process Time

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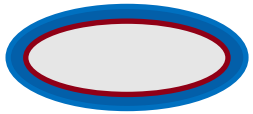
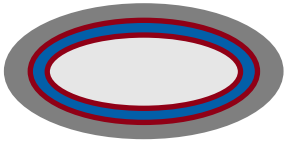
Kollicoat® IR serves all your instant release coating needs and more



Instant release coating – moisture and oxygen protection

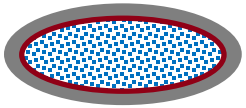
Even fast melting tablets are coated with Kollicoat® IR based formulations, still allowing for very fast dissolution



Sub-coating

Safe and easy application, providing high process reliability while maintaining the formulation simple

→ no further excipients are required



Wet binder

Strong wet binder for all types of fillers, peroxide free character

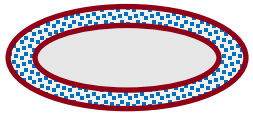
→ providing high degree of formulation safety

Drug layering

Due to its excellent binding capacity, elasticity and peroxide free character, Kollicoat® IR is ideal for drug layering

→ high drug load

→ no interaction with API



Pore former

Reliable component in sustained release film-coating formulations

→ high elasticity prevents cracks and supports product safety

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Kollicoat IR – Applications

Effective and cost-efficient coating process!

Parameter	Kollicoat IR		Hypromellose (HPMC)	
Batch size	8.5 kg	165 kg	8.5 kg	165 kg
Max core temperature	50 °C	50 °C	38°C	46°C
Solid concentration	20 %	20 %	12 %	12 %
Amount of spray suspension applied	1.49 kg	28.9 kg	2.48 kg	48.1 kg
Spray rate	37.2 g/min	410 g/min	27.5 g/min	290 g/min
Minimum time for the coating process	**40 min**	**70 min**	**90 min**	**165 min**

Equipment: XL Lab 01, Premium 200 (both Manesty); Coating: ca. 3.5 % solids

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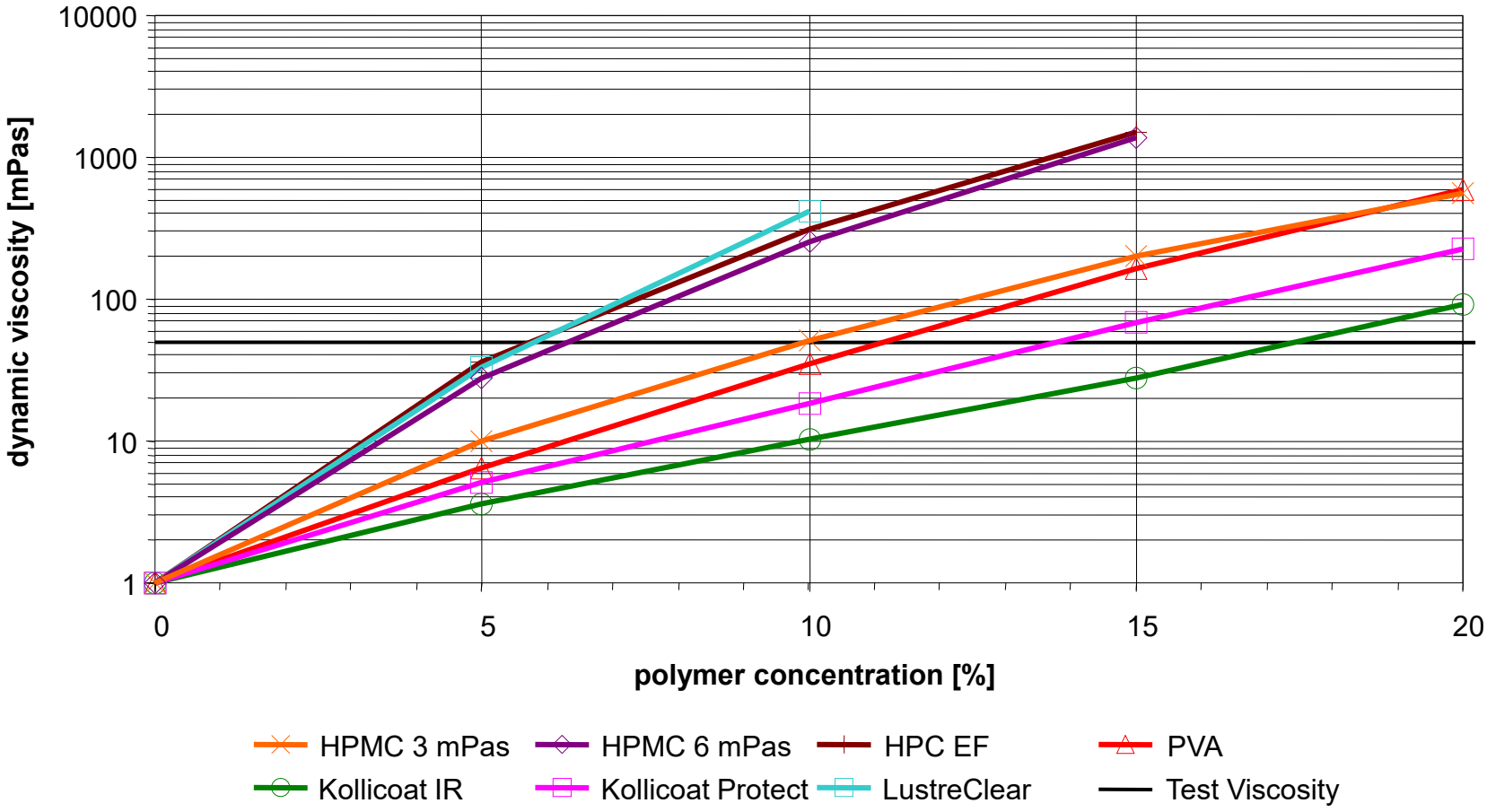
Properties of the Polymer Solution

Viscosity as Function of Solid Content



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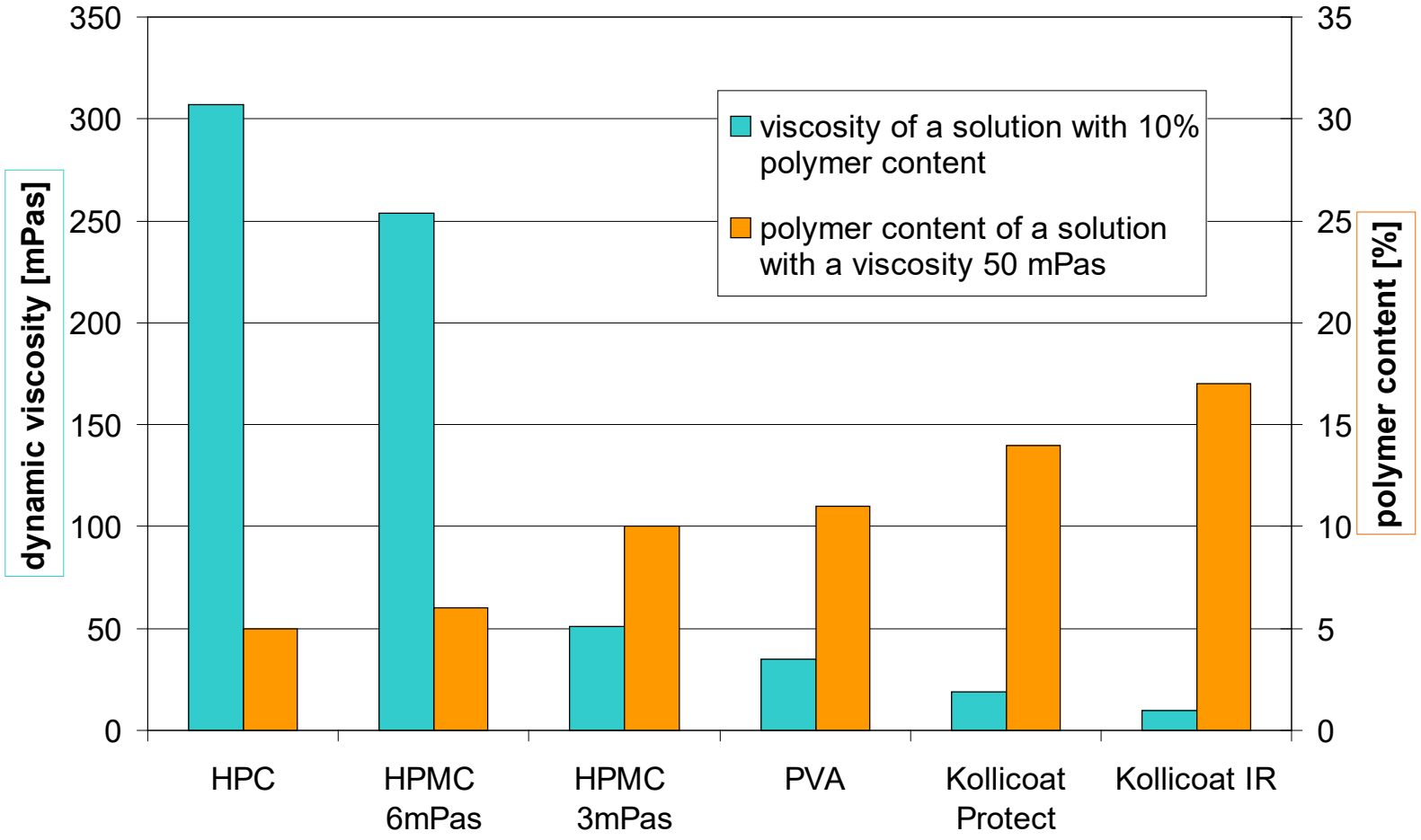
Properties of the Polymer Solution

Viscosity as Function of Solid Content



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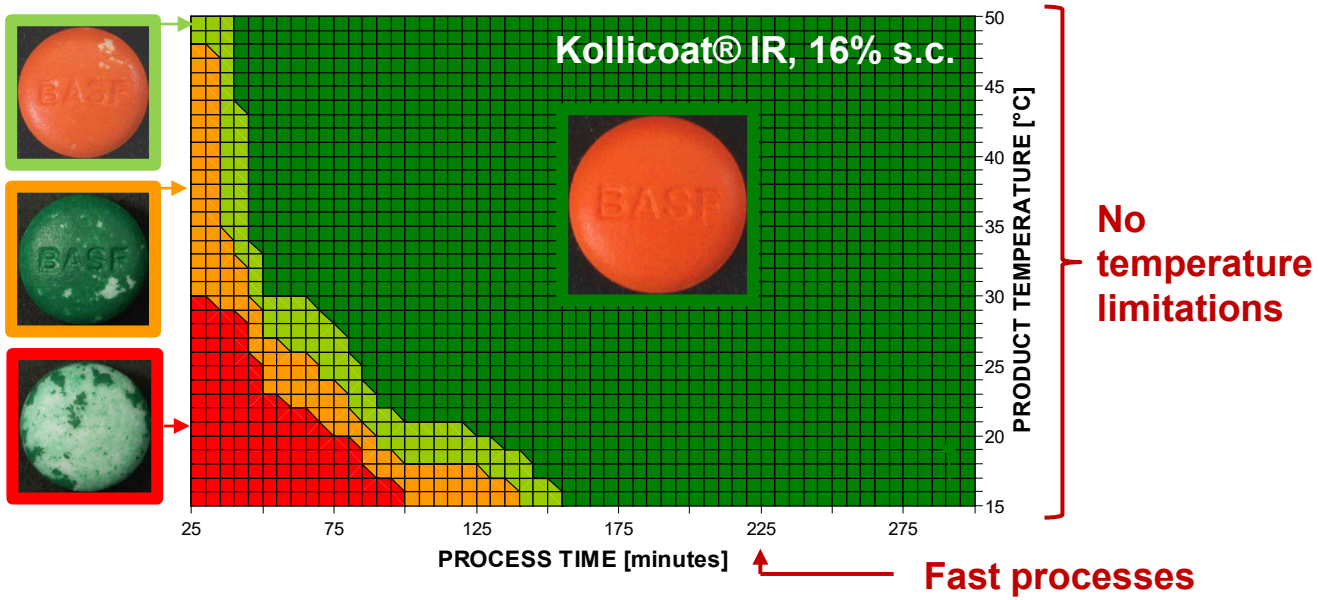
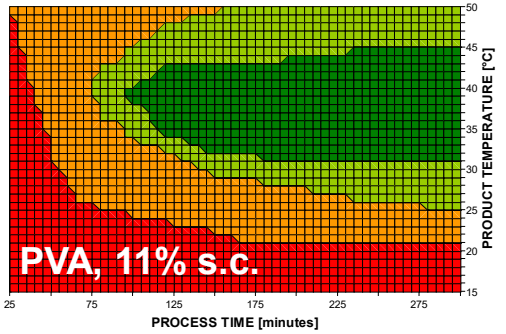
Kollicoat® IR enables easy and economic film coating

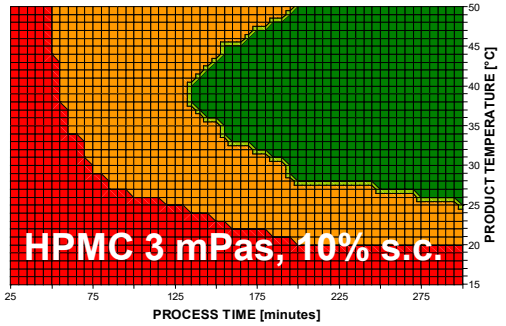
Coating with 50 mPas polymer solutions; s.c.= solid content

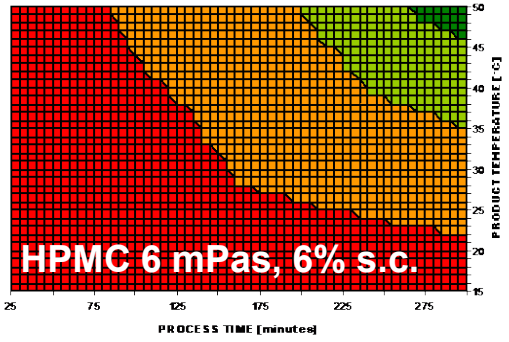


No temperature limitations

Fast processes







Kollicoat® IR gives faster and more stable film coating processes than other film coating polymers. This

- saves time
- saves energy
- reduces batch failures

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Summary

- Consider the **3 pillars** when preparing coating suspensions
  - Solvents
  - MFFT
  - Solids Content
- Nature of the polymer will dictate the **plasticizer used** and potential API interactions
- Applying a subcoating can accelerate enteric coating processes

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We have virtual assistants!

Register at:

virtualpharmaassistants.basf.com

For samples:

pharma-solutions@basf.com

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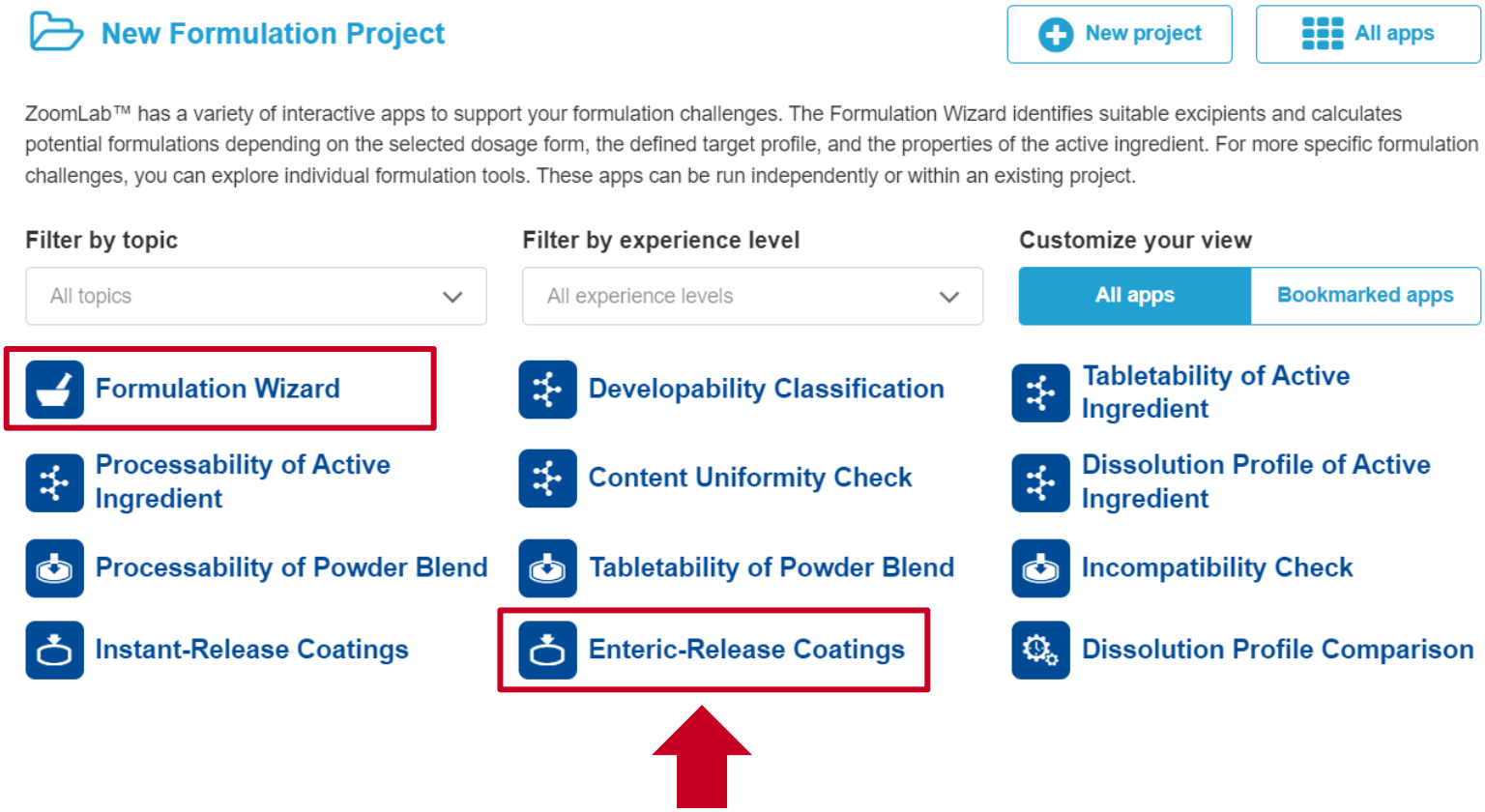
Leveraging our virtual assistant to predict your next enteric coating formulation - Zoomlab



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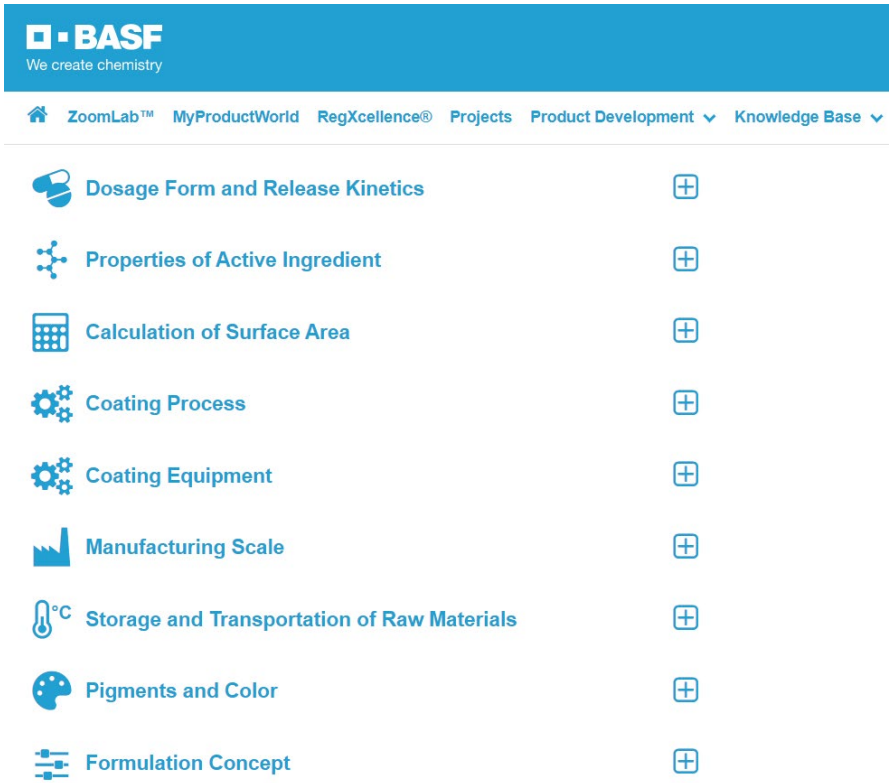
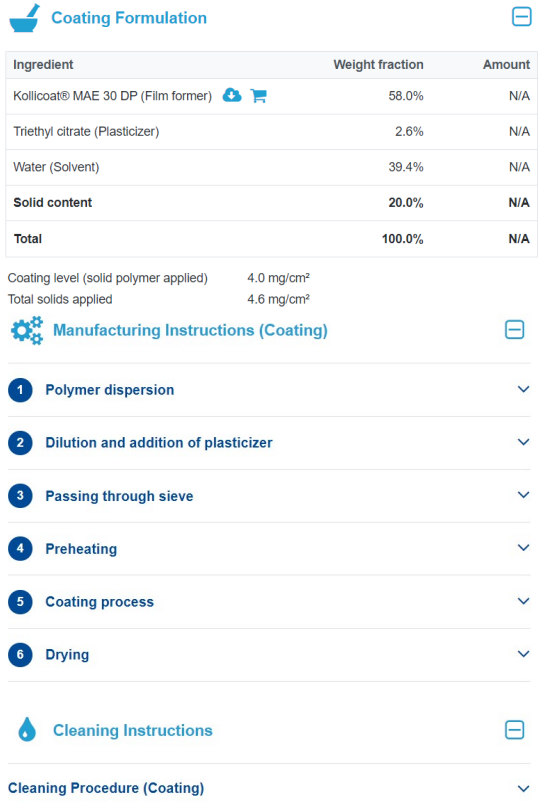
Instantly receive information on *how* to prepare, apply and clean the suspension tanks.





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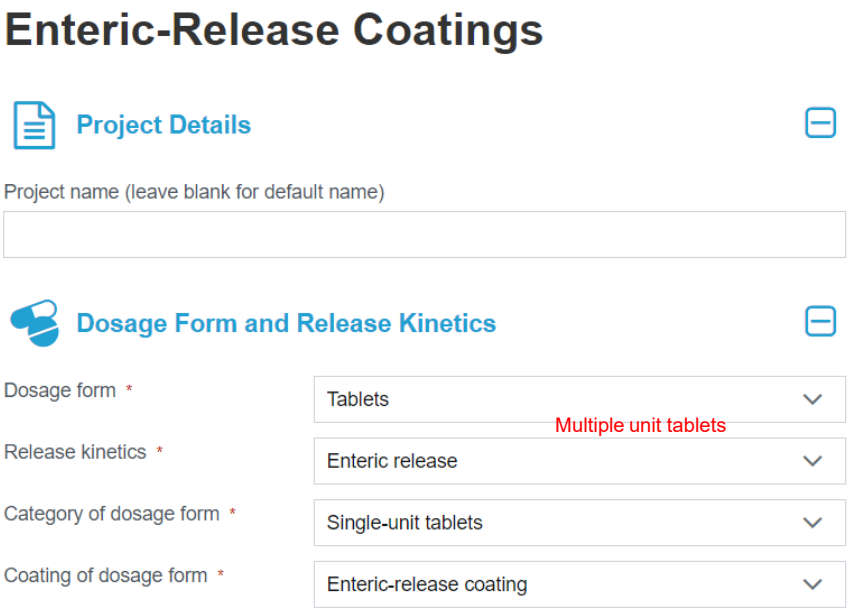
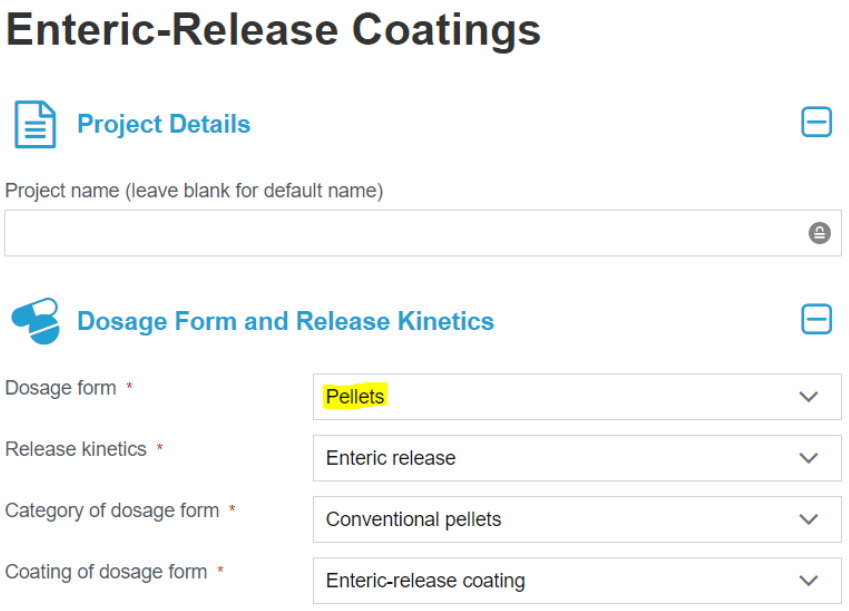
You can choose tablets or pellets. The system will automatically calculate the recommended coating weight gain based on superficial area.





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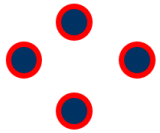
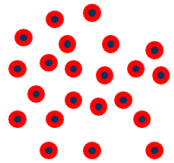
Pellets have a larger superficial area compared to tablets, as such you will need *more* polymer to coat the product.

Calculation of Surface Area



- (●) Round tablets, convex
- ( ) Capsule-shaped tablets / Oblong tablets
- ( ) Individual shape (e.g., oval tablets etc.)

Tablet diameter (mm)	
Tablet thickness (mm)	
Belly band (mm)	
Surface area per tablet (mm²)	
Tablet weight (mg)	
Batch size (kg)	1.00
Total surface area (m²)	



Coating Formulation

Ingredient	Weight fraction	Amount
Kollicoat® MAE 30 DP (Film former)	58.0%	0.086 kg
Triethyl citrate (Plasticizer)	2.6%	0.004 kg
Water (Solvent)	39.4%	0.058 kg
Solid content	**20.0%**	**0.030 kg**
Total	**100.0%**	**0.148 kg**

Coating level (solid polymer applied) 4.0 mg/cm²
Total solids applied 4.6 mg/cm²

SA (m^2) = 0.64

Coating Formulation

Ingredient	Weight fraction	Amount
Kollicoat® MAE 30 DP (Film former)	58.0%	0.274 kg
Triethyl citrate (Plasticizer)	2.6%	0.012 kg
Water (Solvent)	39.4%	0.186 kg
Solid content	**20.0%**	**0.095 kg**
Total	**100.0%**	**0.473 kg**

Coating level (solid polymer applied) 4.0 mg/cm²
Total solids applied 4.6 mg/cm²

SA (m^2) = 2.06

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For APIs sensitive to hydrolysis the system recommends coating formulations w/ alcohol

Proceso de recubrimiento – Sensibilidad a la hidrólisis

Properties of Active Ingredient

Active ingredient (leave blank for new active ingredient)

- Select active ingredient - | Load data

Structural features and functional groups of the active ingredient

- [ ] Acidic groups (e.g., carboxylic acid, β-dicarbonyl group, sulfonamide or phenol)
- [ ] Acidic groups in ionized form (e.g., sodium or potassium salt of carboxylic acid)
- [ ] Basic groups (e.g., amine, imine, guanidine or nitrogen containing heterocycle)
- [ ] Basic groups in ionized form (e.g., hydrochloride, sulfate or acetate)
- [ ] Primary or secondary aliphatic amino groups
- [ ] Quaternary ammonium groups

Potential stability problems of the active ingredient

Sensitivity to heat	Not sensitive to heat
Sensitivity to hydrolysis	Sensitive to hydrolysis
Sensitivity to light	Not sensitive to light
Sensitivity to oxidation	Not sensitive to oxidation

Subcoating Formulation

Ingredient	Weight fraction	Amount
Kollidon® VA 64 (Film former)	9.5%	N/A
Triethyl citrate (Plasticizer)	0.5%	N/A
Isopropyl alcohol (Solvent)	90.0%	N/A
Solid content	**10.0%**	**N/A**
Total	**100.0%**	**N/A**

Coating Formulation

Ingredient	Weight fraction	Amount
Kollicoat® MAE 30 DP (Film former)	58.0%	N/A
Triethyl citrate (Plasticizer)	2.6%	N/A
Water (Solvent)	39.4%	N/A
Solid content	**20.0%**	**N/A**
Total	**100.0%**	**N/A**

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Internal

For APIs sensitive to hydrolysis the system recommends coating formulations w/ alcohol

Properties of Active Ingredient

Active ingredient (leave blank for new active ingredient)

- Select active ingredient - | Load data

Structural features and functional groups of the active ingredient

- [ ] Acidic groups (e.g., carboxylic acid, β-dicarbonyl group, sulfonamide or phenol)
- [ ] Acidic groups in ionized form (e.g., sodium or potassium salt of carboxylic acid)
- [ ] Basic groups (e.g., amine, imine, guanidine or nitrogen containing heterocycle)
- [ ] Basic groups in ionized form (e.g., hydrochloride, sulfate or acetate)
- [ ] Primary or secondary aliphatic amino groups
- [ ] Quaternary ammonium groups

Potential stability problems of the active ingredient

Sensitivity to heat	Not sensitive to heat
Sensitivity to hydrolysis	Sensitive to hydrolysis
Sensitivity to light	Not sensitive to light
Sensitivity to oxidation	Not sensitive to oxidation

Coating Process

- ( ) Aqueous coating only (organic coating excluded)
- ( ) Aqueous coating preferred (organic coating not excluded)
- (•) Organic coating preferred (aqueous coating not excluded)
- ( ) Organic coating only (aqueous coating excluded)

Coating Formulation

Ingredient	Weight fraction	Amount
Kollicoat® MAE 100-55 (Film former)	8.7%	N/A
Triethyl citrate (Plasticizer)	1.3%	N/A
Isopropyl alcohol (Solvent)	90.0%	N/A
Solid content	**10.0%**	**N/A**
Total	**100.0%**	**N/A**

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Zoomlab supports your lab, pilot and production scale trials.

Manufacturing Scale

- (●) Laboratory scale
- ( ) Pilot / production scale

Coating Formulation

Ingredient	Weight fraction	Amount
Kollicoat® MAE 30 DP (Film former)	58.0%	N/A
Triethyl citrate (Plasticizer)	2.6%	N/A
Water (Solvent)	39.4%	N/A
Solid content	**20.0%**	**N/A**
Total	**100.0%**	**N/A**

Coating level (solid polymer applied) 4.0 mg/cm²
Total solids applied 4.6 mg/cm²

Manufacturing Scale

- ( ) Laboratory scale
- (●) Pilot / production scale

Coating Formulation

Ingredient	Weight fraction	Amount
Kollicoat® MAE 30 DP (Film former)	87.0%	N/A
Triethyl citrate (Plasticizer)	3.9%	N/A
Water (Solvent)	9.1%	N/A
Solid content	**30.0%**	**N/A**
Total	**100.0%**	**N/A**

Coating level (solid polymer applied) 4.0 mg/cm²
Total solids applied 4.6 mg/cm²

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Enteric polymers are acidic, requiring bases for partial neutralization before dispersing in water. Basic APIs require a subcoating to limit interactions.

Properties of Active Ingredient

Active ingredient (leave blank for new active ingredient)

- Select active ingredient - | Load data

Structural features and functional groups of the active ingredient

- [ ] Acidic groups (e.g., carboxylic acid, β-dicarbonyl group, sulfonamide or phenol)
- [ ] Acidic groups in ionized form (e.g., sodium or potassium salt of carboxylic acid)
- [ ] Basic groups (e.g., amine, imine, guanidine or nitrogen containing heterocycle)
- [ ] Basic groups in ionized form (e.g., hydrochloride, sulfate or acetate)
- [ ] Primary or secondary aliphatic amino groups
- [ ] Quaternary ammonium groups

Potential stability problems of the active ingredient

Sensitivity to heat	Not sensitive to heat
Sensitivity to hydrolysis	Not sensitive to hydrolysis
Sensitivity to light	Not sensitive to light
Sensitivity to oxidation	Not sensitive to oxidation

Subcoating Formulation

Ingredient	Weight fraction	Amount
Kollicoat® IR (Film former)	15.0%	N/A
Water (Solvent)	85.0%	N/A
Solid content	**15.0%**	**N/A**
Total	**100.0%**	**N/A**

Coating Formulation

Ingredient	Weight fraction	Amount
Kollicoat® MAE 30 DP (Film former)	58.0%	N/A
Triethyl citrate (Plasticizer)	2.6%	N/A
Water (Solvent)	39.4%	N/A
Solid content	**20.0%**	**N/A**
Total	**100.0%**	**N/A**

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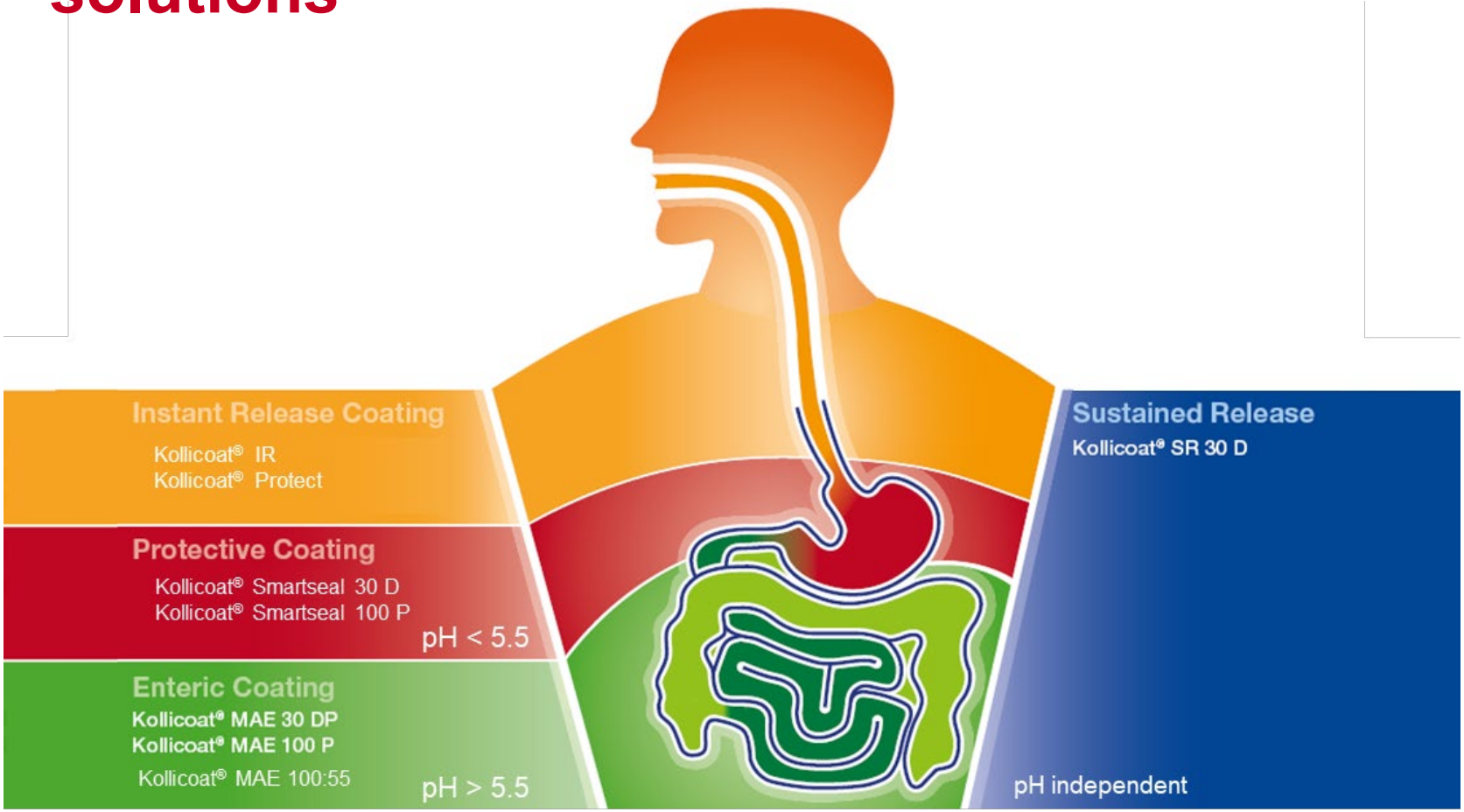
BASF has an extesive portfolio for your coating solutions



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