Introduction to Film Coating Process and an Overview of the BASF Kollicoat® Portfolio

BASF Pharma Solutions

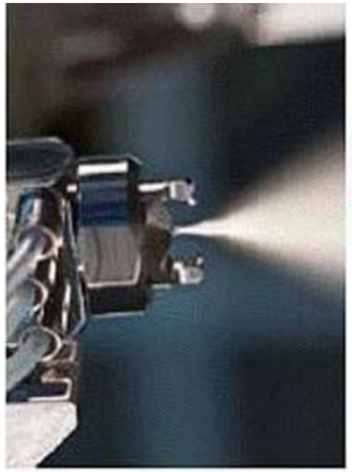
MarComm-2024-00546

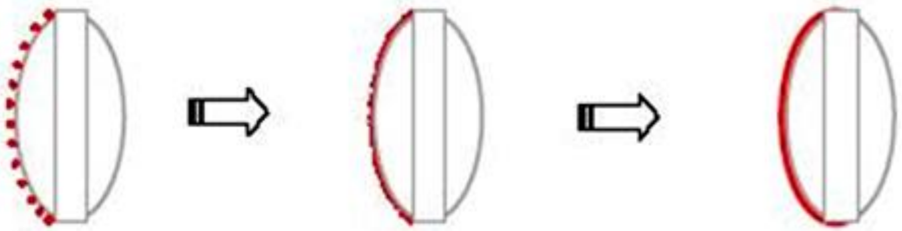
Agenda

- Introduction to film coating
- Items to be considered in the coating process
  - Polymers
  - Plasticizers
  - Anti-tacking agents
  - Coloring agents
  - Process and Equipment
- BASF Coating Polymers
  - Immediate release
  - Taste masking
  - Enteric release
  - Sustained release
- Summary: BASF Portfolio

Introduction to film coating

A **film coating** is a thin polymer-based coat typically sprayed onto a solid pharmaceutical dosage form, such as a tablet, capsule, pellet, or granule.



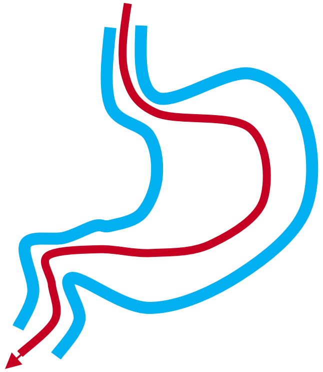


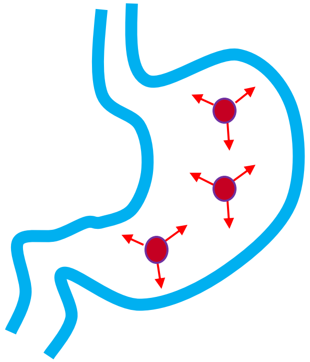
E. Bennie, Active Division, I.M.A. S.p.A., Bologna, Italy

https://pharmacentral.com/learning-hub/technical-guides/pharmaceutical-tablet-film-coating-agents/

Introduction: Reasons for coating

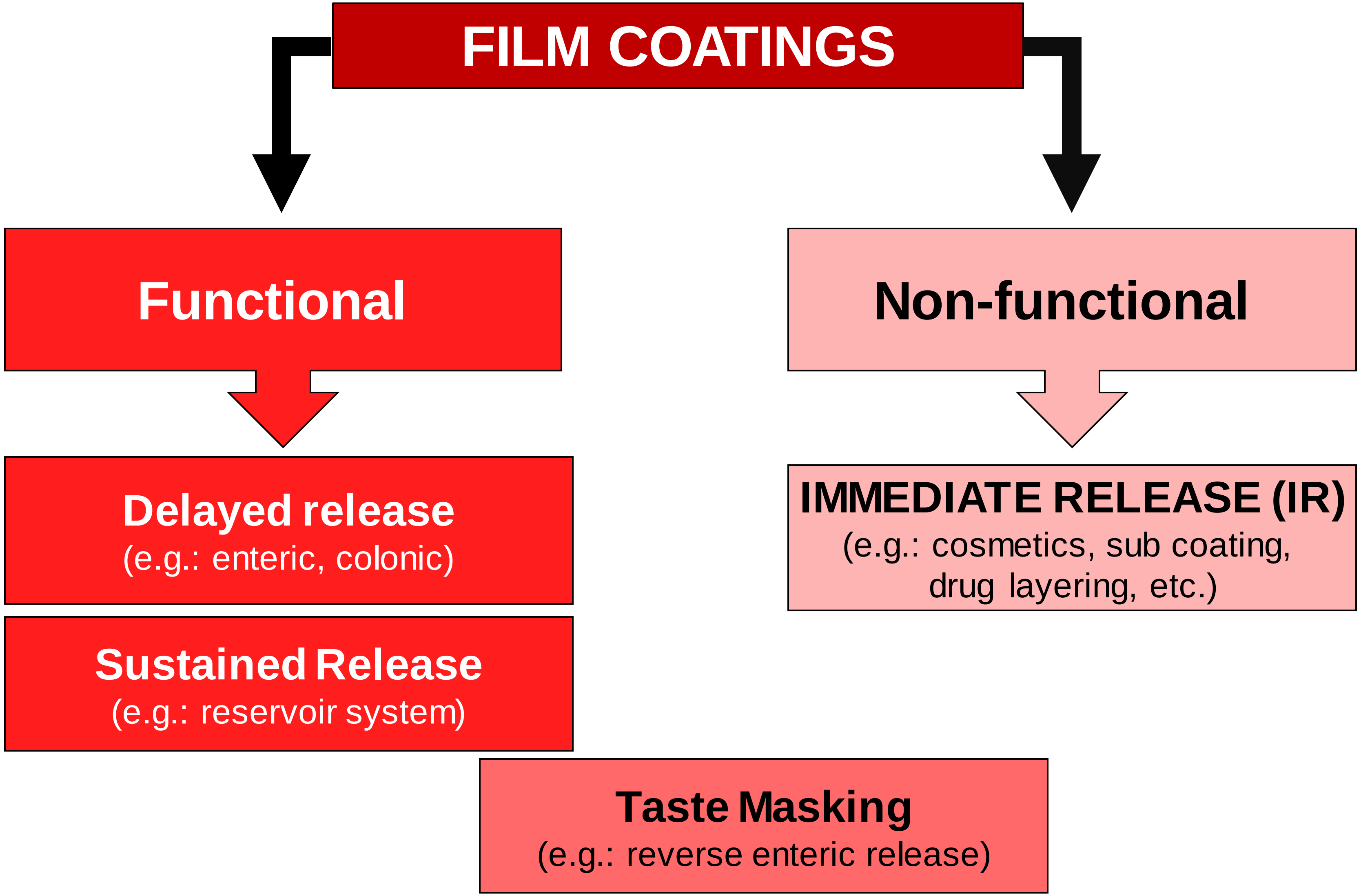
- **Patient compliance:**
  - Tablet swallow
  - Provide a desired release pattern (sustained / enteric release)
  - Taste masking, etc.
- **API Protection:**
  - Moisture
  - Light
  - Oxygen
  - Acid degradation
- Improvement of the **tablet's mechanical resistance**
- **Facilitate packaging**
- **Marketing / aesthetic**
- **Safety reason,** product identification by coloring





Introduction to film coating: Functional vs non-functional

- Functional coating: coating with a pharmaceutical function (change the drug release).
- Functional coating needs to be carefully processed because it can impact the patient's treatment.
- Non-functional coating: relevant for cosmetics and Mkt aspects. It can also provide light, O_2, and humidity protection.
- Taste masking films can be considered a functional film coating. However, they are usually immediate-release films (dissolve in the stomach).



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Coating process and formulation considerations

Polymer

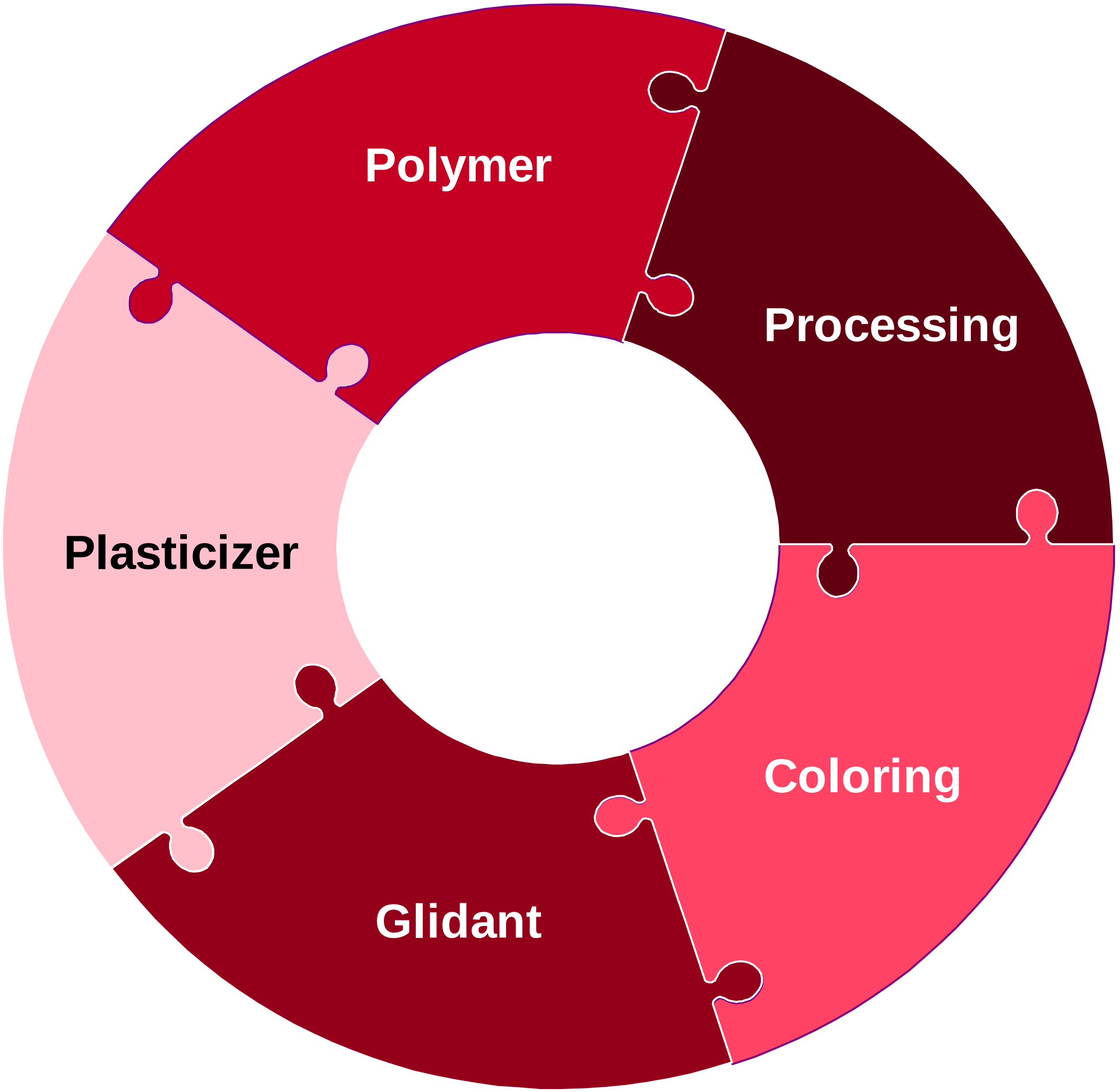
- Characteristics
- Functionality
- Formulation
- Solvent
- Process requirements

Plasticizer

- Type of plasticizer
- Quantity
- Incorporation

Glidant

- Type of glidant
- Quantity
- Effect



Processing

- Equipment
- Process settings
- Film coating functionality

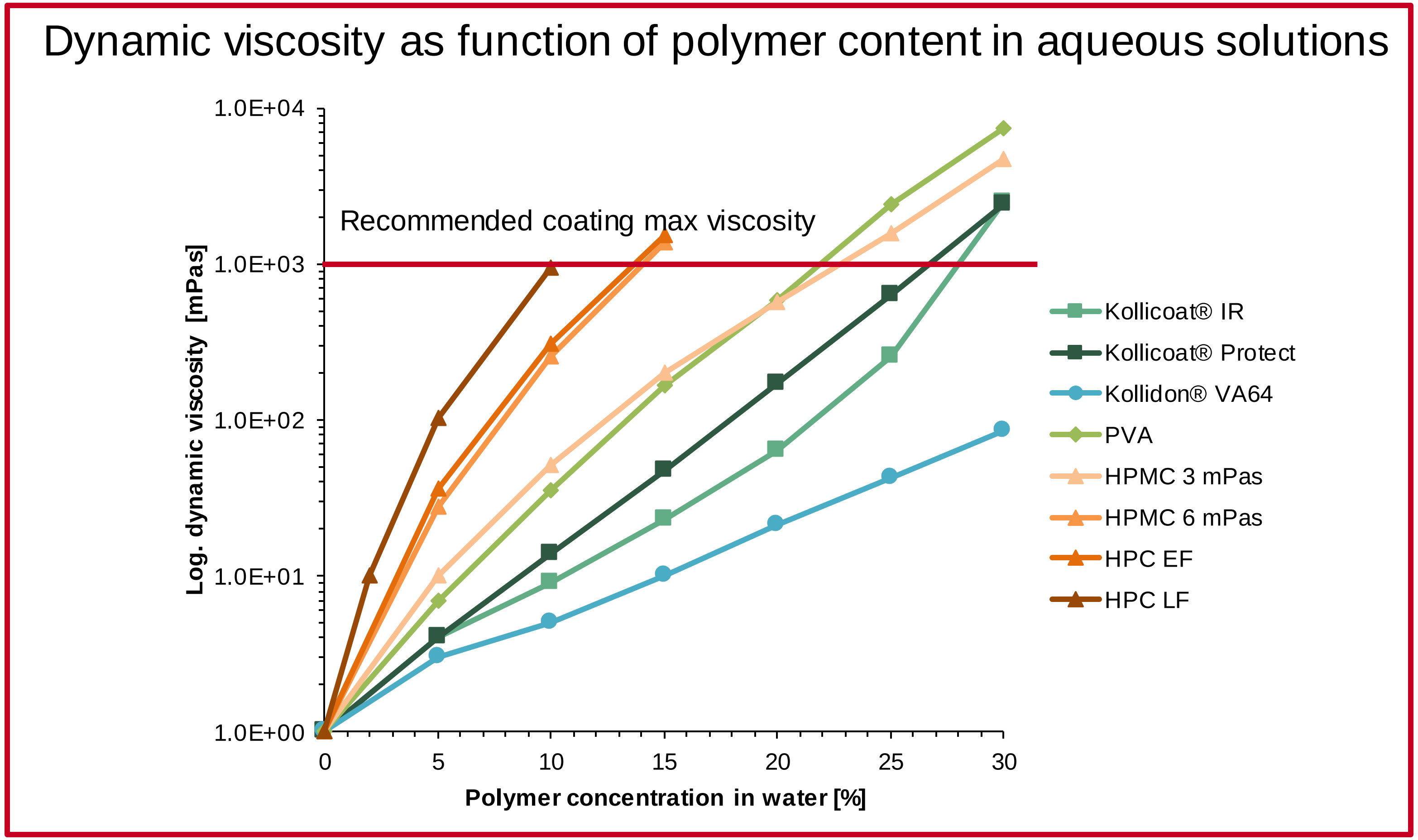
Coloring

- Type of colorant
- Quantity
- Interactions
- Light protection

Formulation focus: Non-functional polymers

- The main component of the coating system → responsible for forming the film
- Main examples of **immediate-release polymers**:
  - **HPMC** (Type 2910) – high viscous, brittle, and low flexible polymer
  - **PVA** – low viscous and responsible for moisture and oxygen protection, very tacky
  - **Copovidone** (Kollidon® VA 64) – low viscous and it can improve film adhesiveness at 10 to 20%
  - **HPC**: high viscous polymer – offers a sort of moisture and O_2 protection
  - **PVA-PEG copolymer** (Kollicoat® IR) – very low viscosity, high elasticity and easy-processing
  - **PVA-PEG + PVA** (Kollicoat® Protect) – low viscosity, excellent moisture and oxygen barrier

Non-functional polymers: Viscosity



Measurement dynamic viscosity

Equipment	ThermoFisher HAAKE RotoVisco 1
Set up measuring	Double gap concentric cylinder geometry
Tool	DG43Ti, PP60Ti
Tempering	HAAKE DC30-K10 TCL/Z

Determination of dynamic viscosity

Temperature	25.0°C ±0.2 K
Relaxing time	60 minutes
Shear rate	100 up to 3000 s^{-1}
Testing time	180 s

Dynamic viscosity was calculated as mean value of the shear rate ramp.

- Kollicoat® IR and Protect have a very low viscosity, relevant to increase solid content in suspension and reduce coating process time.

Formulation focus: Functional polymers

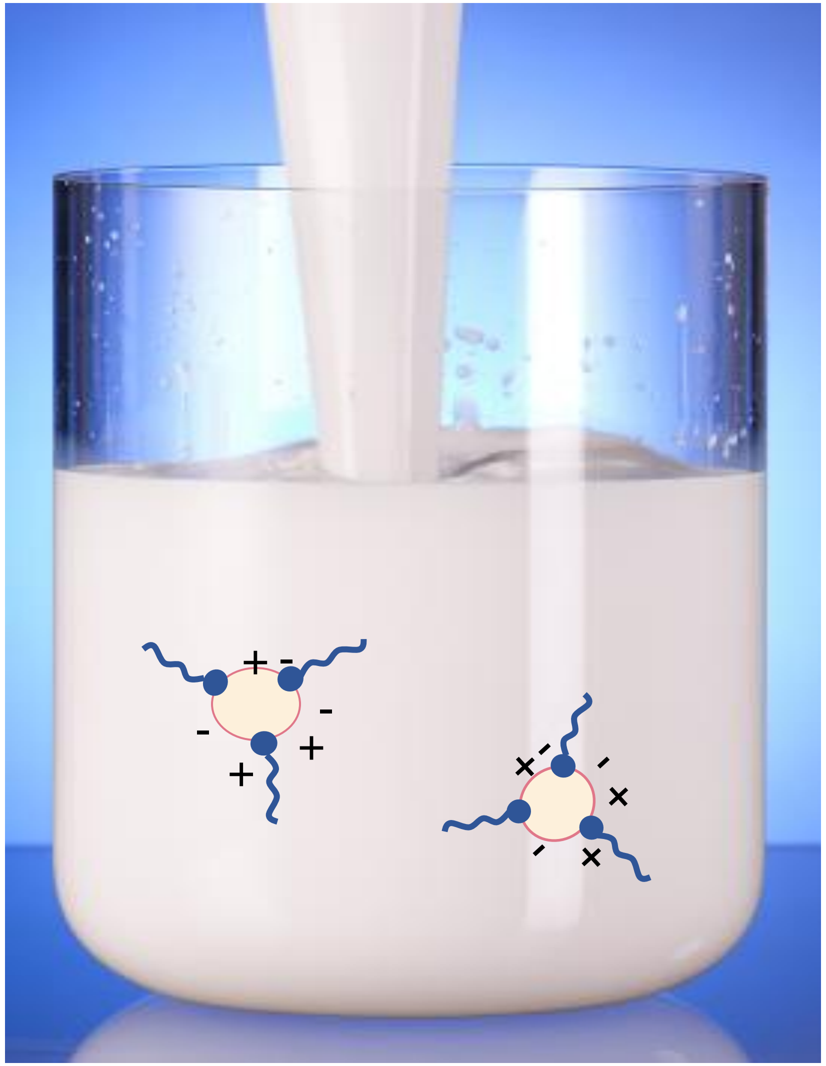
- Functional polymers have a **pharmaceutical function** and are responsible for modulating or defining drug release. They are typically available in **powders or dispersions**.

- Main examples of **delayed-release polymers** (gastric resistant):
  - **Methacrylate's - Kollicoat® MAE**
  - **HPMC Acetyl Succinate**
  - **HPMC Phthalate**
  - **Polyvinyl acetate phthalate**
  - **Cellulose acetate phthalate**
  - **Sodium alginate**

- Main examples of **sustained-release polymers** (reservoir system):
  - **Kollicoat® SR 30 D**
  - **Ethyl cellulose**

- Main example of **reverse enteric polymers** (taste masking):
  - **Kollicoat® Smartseal**

Functional polymers: Understanding dispersions



- Polymer solubilized in a solvent = solution
- Polymer suspended in a solvent = suspensions
- **Polymer disperse in a solvent = dispersions**

- In a dispersion, the polymer particles are stabilized in an aqueous environment by ionic or nonionic emulsifiers. **Emulsifiers are responsible for maintaining the polymers dispersed**;

- However, a **dispersion is a meta-stable system** (zeta potential / isoelectronic point of a dispersion). If this meta system is **destabilized, occurs polymer coagulation;**

- So, dispersions **CAN NOT** be:
  - **Frozen**
  - Treated with **high mechanical stress**
  - Freely **mixed with other materials**, as organic solvents.

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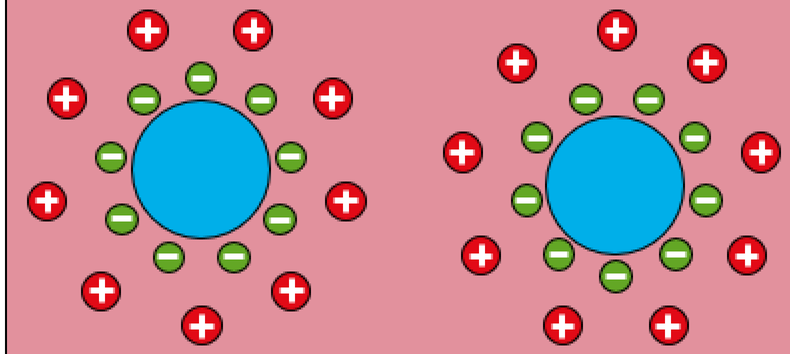
Understanding dispersions: Stabilization

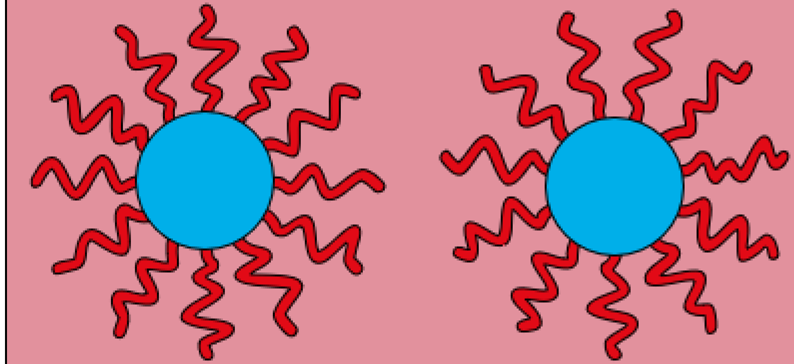
Electrostatic stabilization



Sensitive towards:

Electrolytes
pH change

Steric stabilization

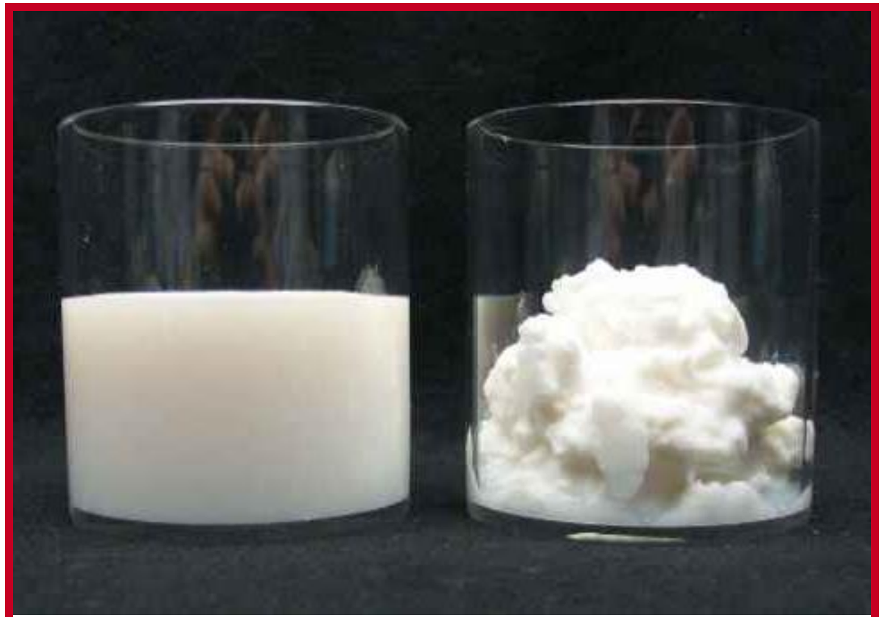


Sensitive towards:

Mechanical stress
Thermal stress
Solvent

Polymer particles in a dispersion are **stabilized by ionic or nonionic emulsifiers** via **electrostatic** and/or **steric stabilization**.

Understanding Dispersions: Causes and examples of coagulations



Mixing different materials can disrupt electrostatic or steric stabilization.

→ Coagulation of Kollicoat® MAE 30 DP when mixed with Kollicoat® SR 30 D. **Better avoid adding many materials in a dispersion.**

Ions presents in many materials can change the electrostatic stability of a dispersion causing polymer coagulation.

→ Coagulation of Kollicoat® MAE 30DP by addition of aluminium lake dyes. **Better avoid adding colourants to a dispersion.**

Abruptly changes can disrupt the dispersion metastable system and cause coagulation.

→ Coagulation of Kollicoat® MAE 30 DP by adding highly concentrated propylene glycol. **Dilute plasticizer before adding to the dispersion.**

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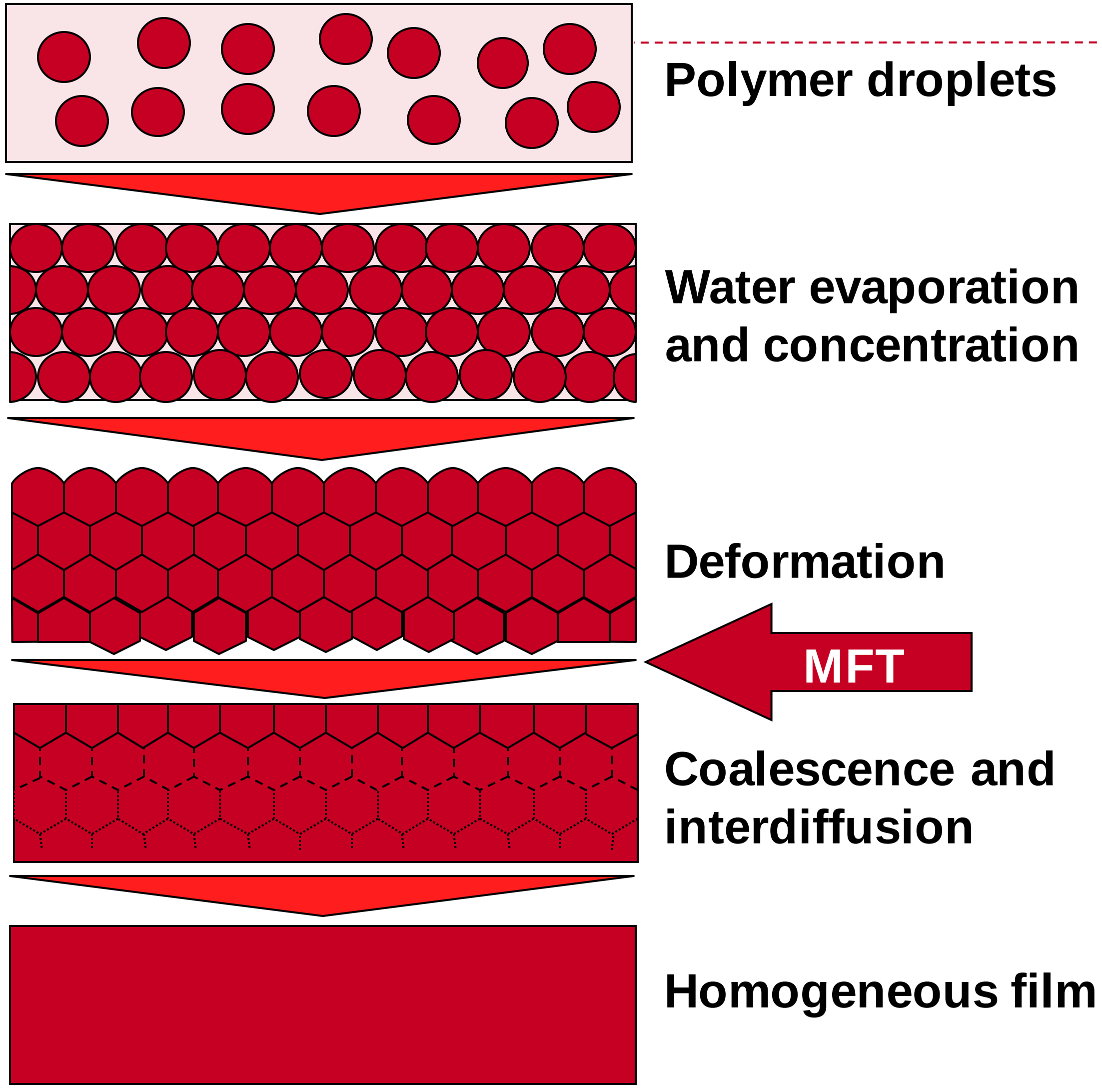
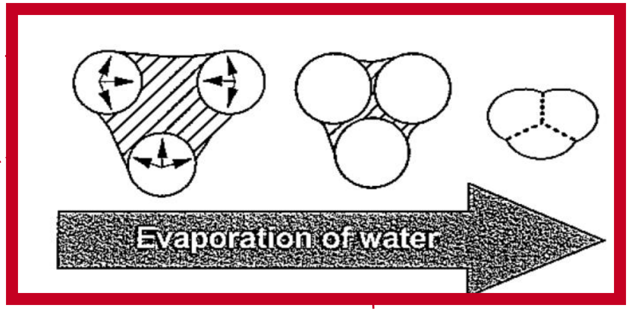
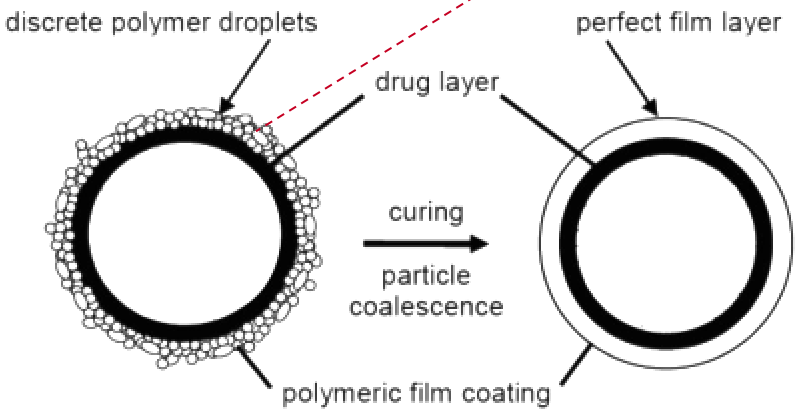
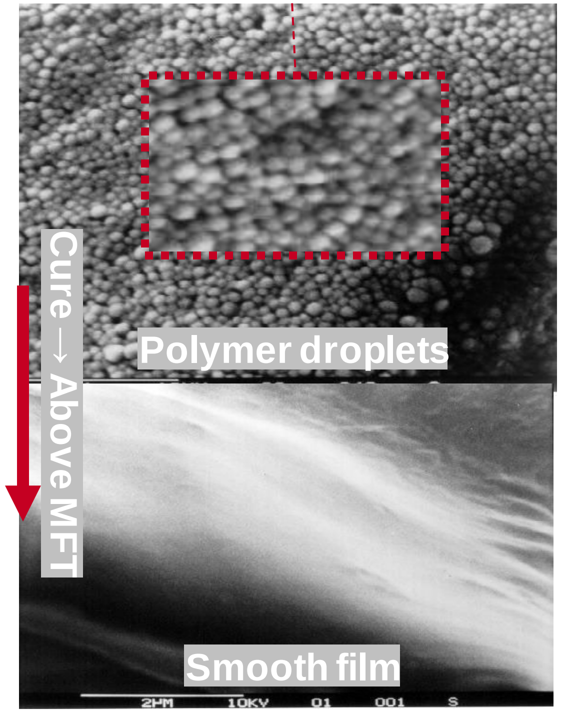
Film formation from dispersion polymer particles







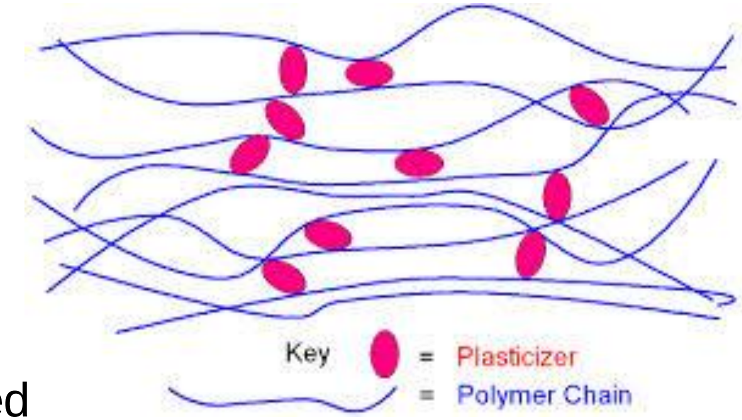
Schematic presentation of the film forming mechanism from aqueous polymer dispersions (Muschert, 2008).



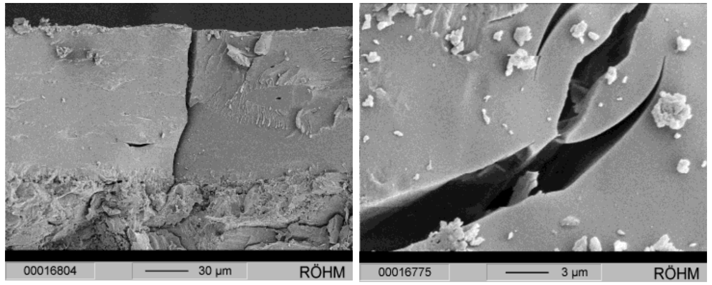
A curing step might be required for dispersions to eliminate the excess of water and form a total coalescent film.

Formulation focus: Plasticizer

- **Plasticizer** is used to **improve film elasticity and flexibility** of high brittle polymers by **increasing polymer chains mobility.**
- Higher mobility **reduces the polymer glass transition** (Tg) and the required **minimum film forming temperature** (MFFT).
- **Plasticizers:**
- Improve film formation at lower temperature
- Increase elasticity, avoiding cracking and lost of film functionality
- Plasticizers can act as pore former, increasing the drug release
- In excess it can increase polymer tackiness (extremely low Tg and MFFT)



https://www.gcsescience.com/o59.htm



Lack of plasticizer can lead to a polymer crack

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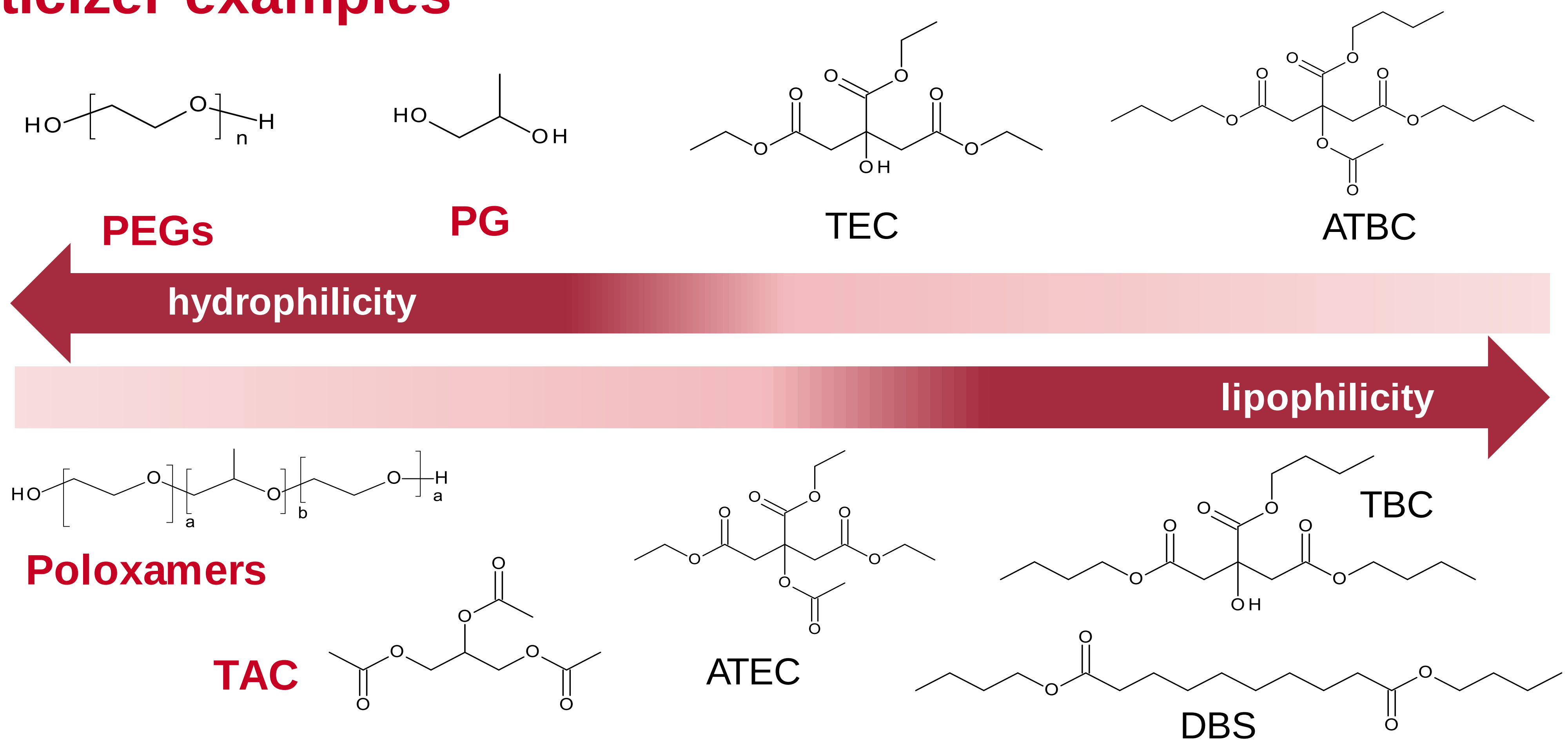
Plasticizer examples



BASF's portfolio:

Kollisolv® PEG
Kollisolv® PG
Kollisolv® GTA
Kolliphor® P124

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

Formulation: Antitacking Agent

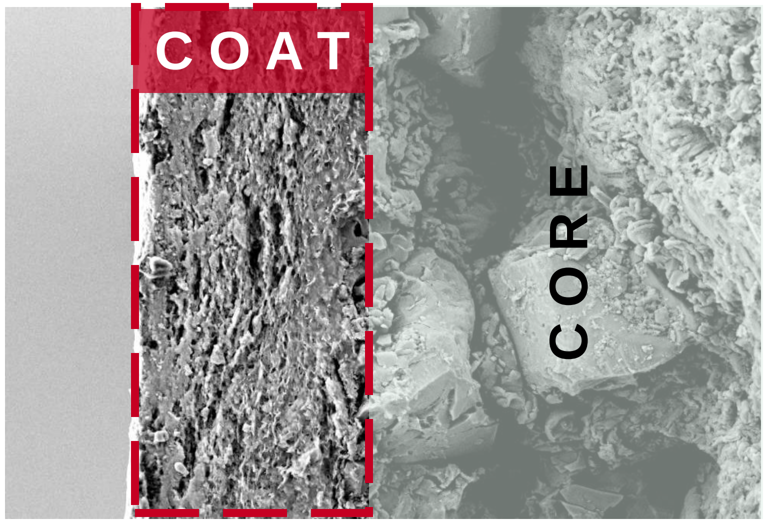
- Anti-tacking agents are used to reduce polymer tackiness and facilitate the coating process.

- Talc is the most used anti-tacking.
  - Considerations:
    - Precipitates in the tubes
    - Increase film porosity of functional coating → require ↑ weight gain
    - Hydrophobic – can delay drug release / improve moisture protection

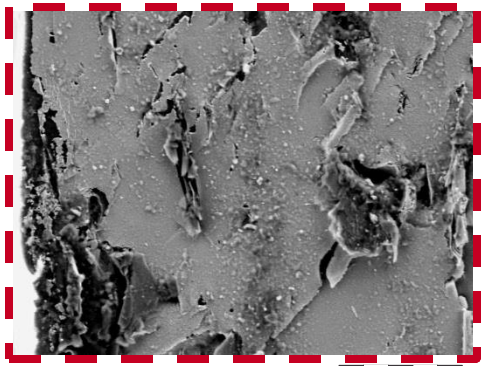
- Glycerol mono stearate **[Kolliwax® GMS II]** + Polysorbate 80 **[Kolliphor® PS 80]** (8:2) is an interesting alternative to talc:
  - No precipitates in the tubes
  - Require less amounts compared to talc

Kollicoat® MAE 30 DP film with

Kolliwax® GMS II + Kolliphor® PS 80



Talc



Formulation focus: Coloring Agents

- Pigments are responsible for coloring tablets / pellets / granules, etc.
- Colorants can be used to protect light-sensitive drugs.
- Examples:
  - TiO_2 – most used opacifier
  - Iron oxides – red, yellow, black, etc.
  - Aluminum lakes (insoluble pigments) – blue, red, yellow, etc.
- Pigments can be incompatible with some ingredients of the film coating (polymer, dispersion, plasticizer).
- Remember: adding a pigment to a functional film, you are reducing the polymer amount = ↑ weight gain = longer process
- Consider adding the pigments in a sub-coating layer.

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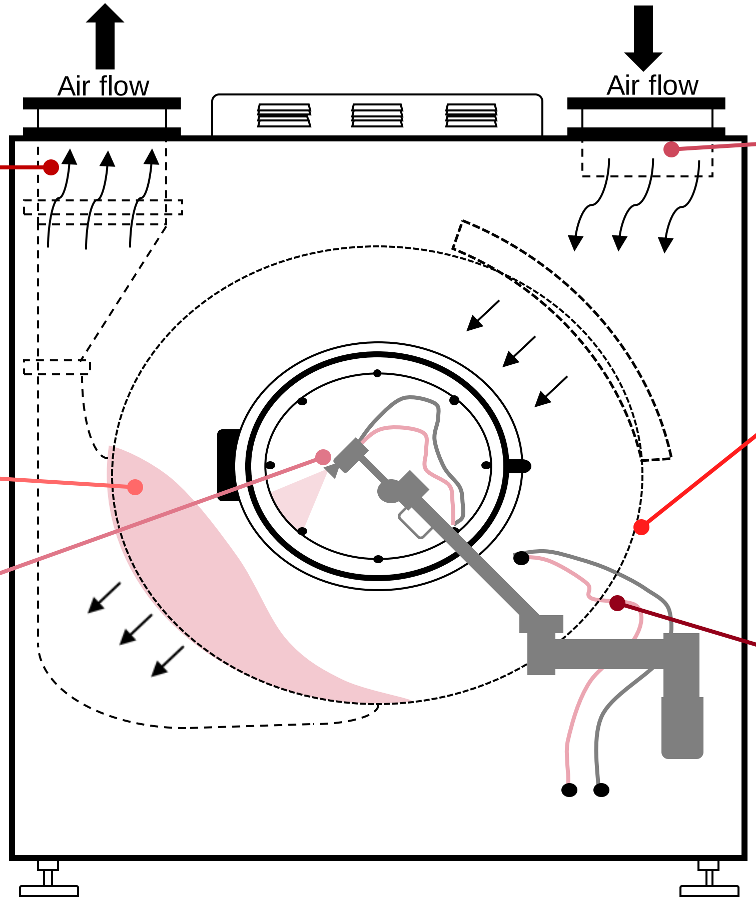
Process focus: Coater machine – tablets and hard gelatine capsules



Exhaust air
- temperature, humidity, negative pressure

Cores
- size, shape, mechanical resistance, adhesion

Spray Gun / Nozzle
- spray rate, number, atomization, angle, type, gun-to-bed distance

Inlet air
- airflow, temperature, humidity

Pan
- size, speed, load, depth, baffles, type

Formulation
- viscosity, polymer(s), solid content, stability

The film coating process is very complex
as many different parameters influence the final coating result.

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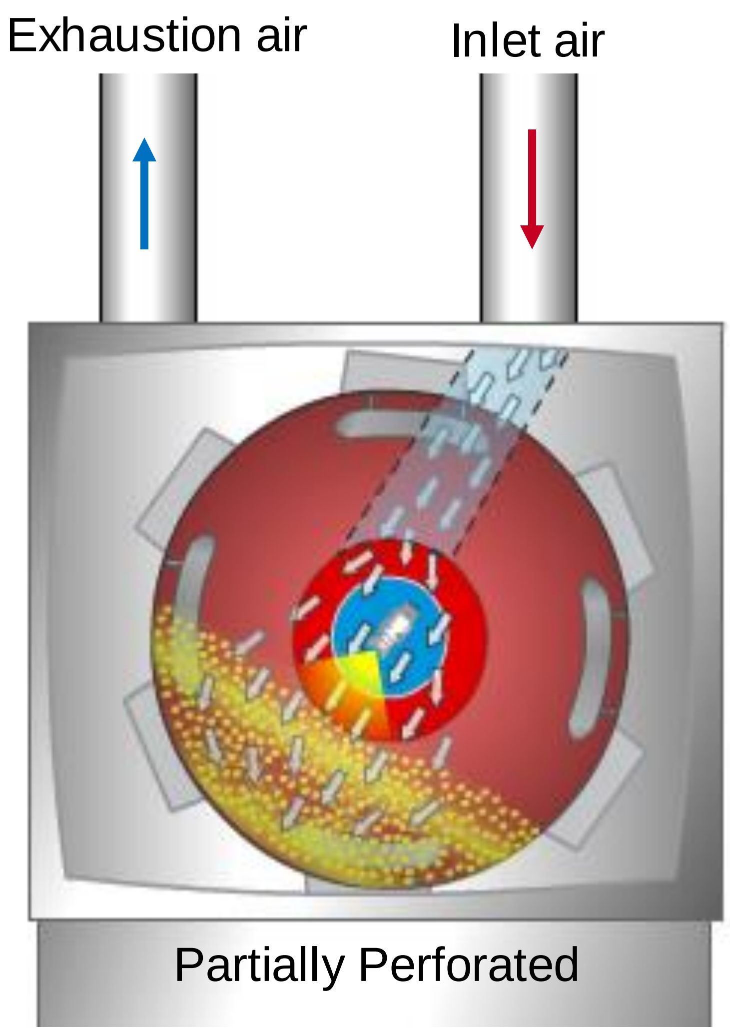
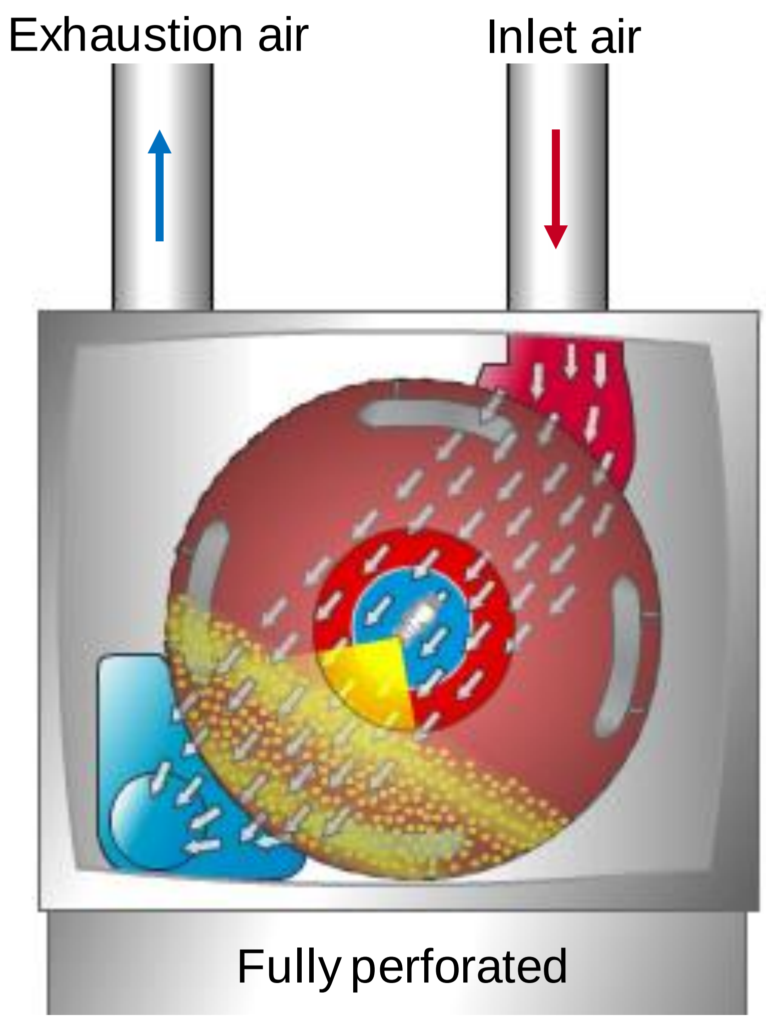
Process focus: Equipment - Pan coater

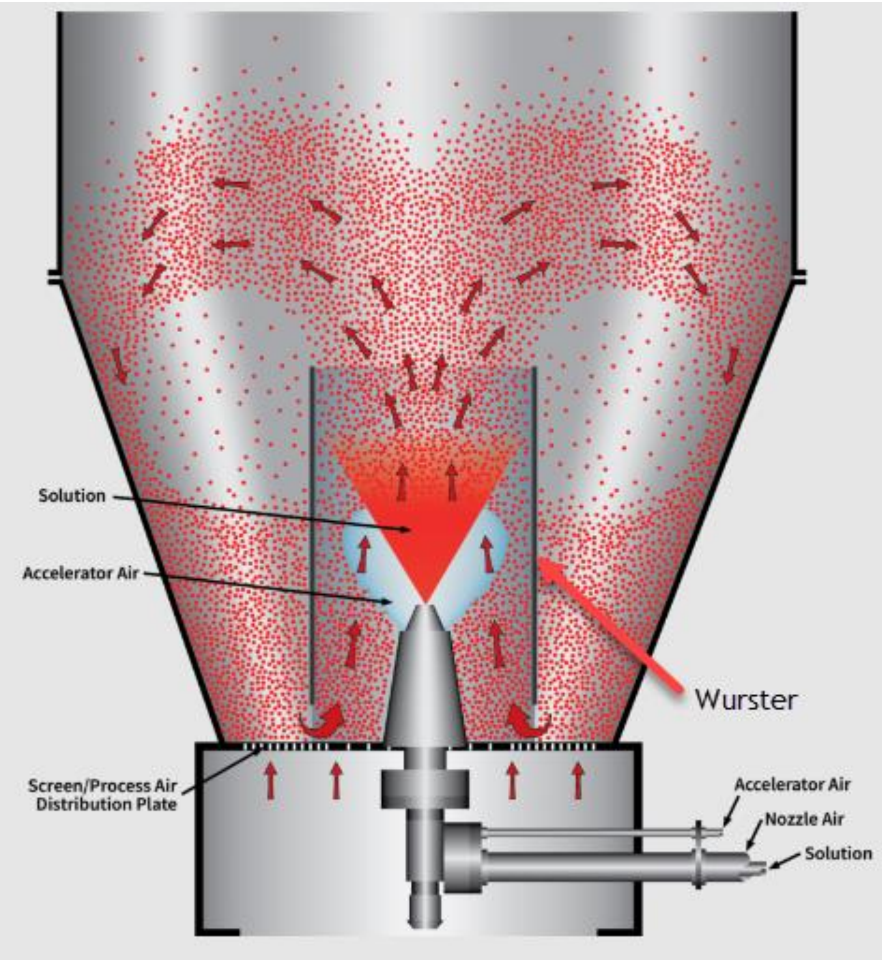


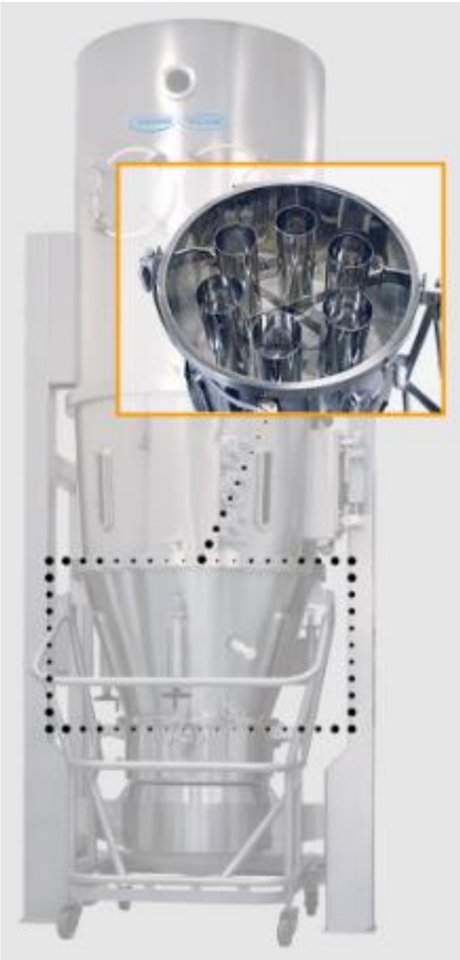


Adapted from: Chapter 34 - Development, Optimization, and Scale-Up of Process Parameters: Pan Coating. S Porter, G. Sackett and L. Liu

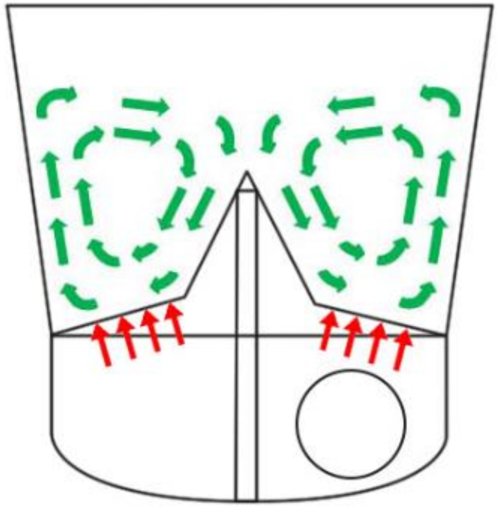
Process focus: Equipment - fluid bed Wurster and tangential

https://www.freund-vector.com/technology/fluid-bed-wurster-bottom-spray/





Freund-Vector's patented Wurster Accelerator System
VFC-M FLO-Coater®



Bohle Uni Cone BUC® Fluid Bed System – Tangential Spray

https://lbbohle.com/machines-processes/granulation-pharma/fluidized-bed-system-bfs/

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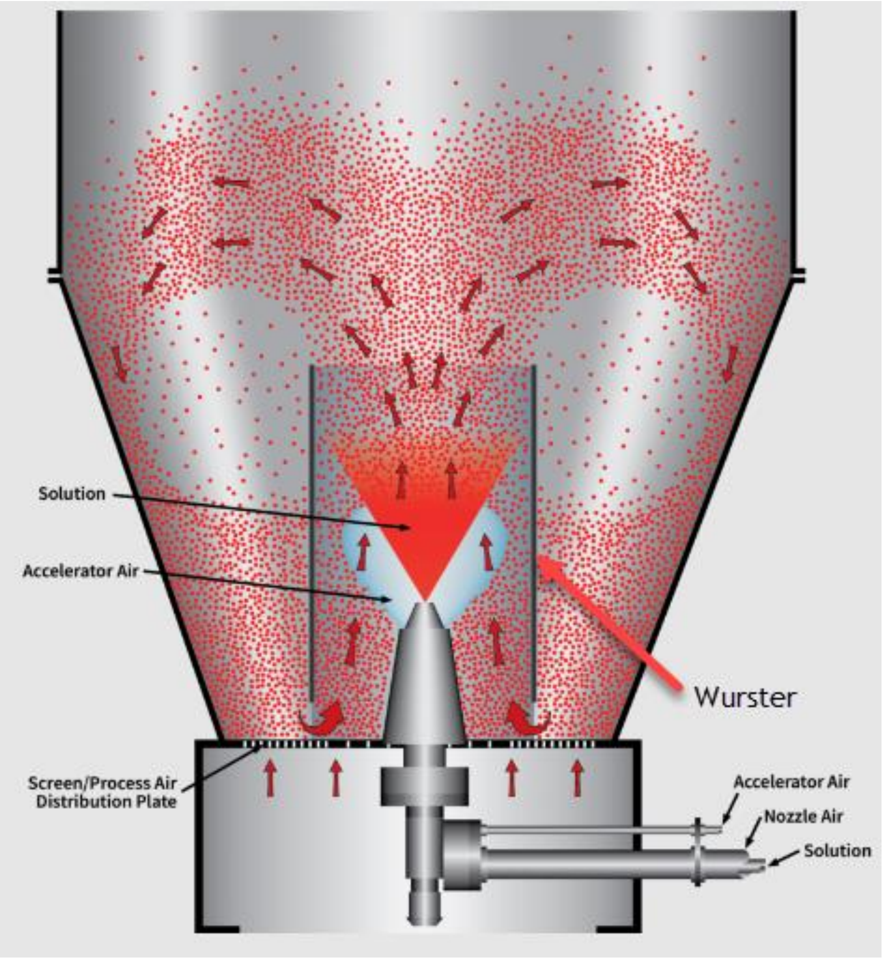
Process focus: Fluid bed – particles, granules, pellets, and minitablets

https://www.freund-vector.com/technology/fluid-bed-wurster-bottom-spray/



Spray Gun / Nozzle
- spray rate, spray gun, number, atomization

Formulation
- viscosity, polymer(s), solid content, stability

Inlet air
- airflow, temperature, humidity, negative pressure

Exhaust air and Filters
- temperature and humidity, filter pressure

Wurster or Tangential
- Height, pellet load, Wurster height

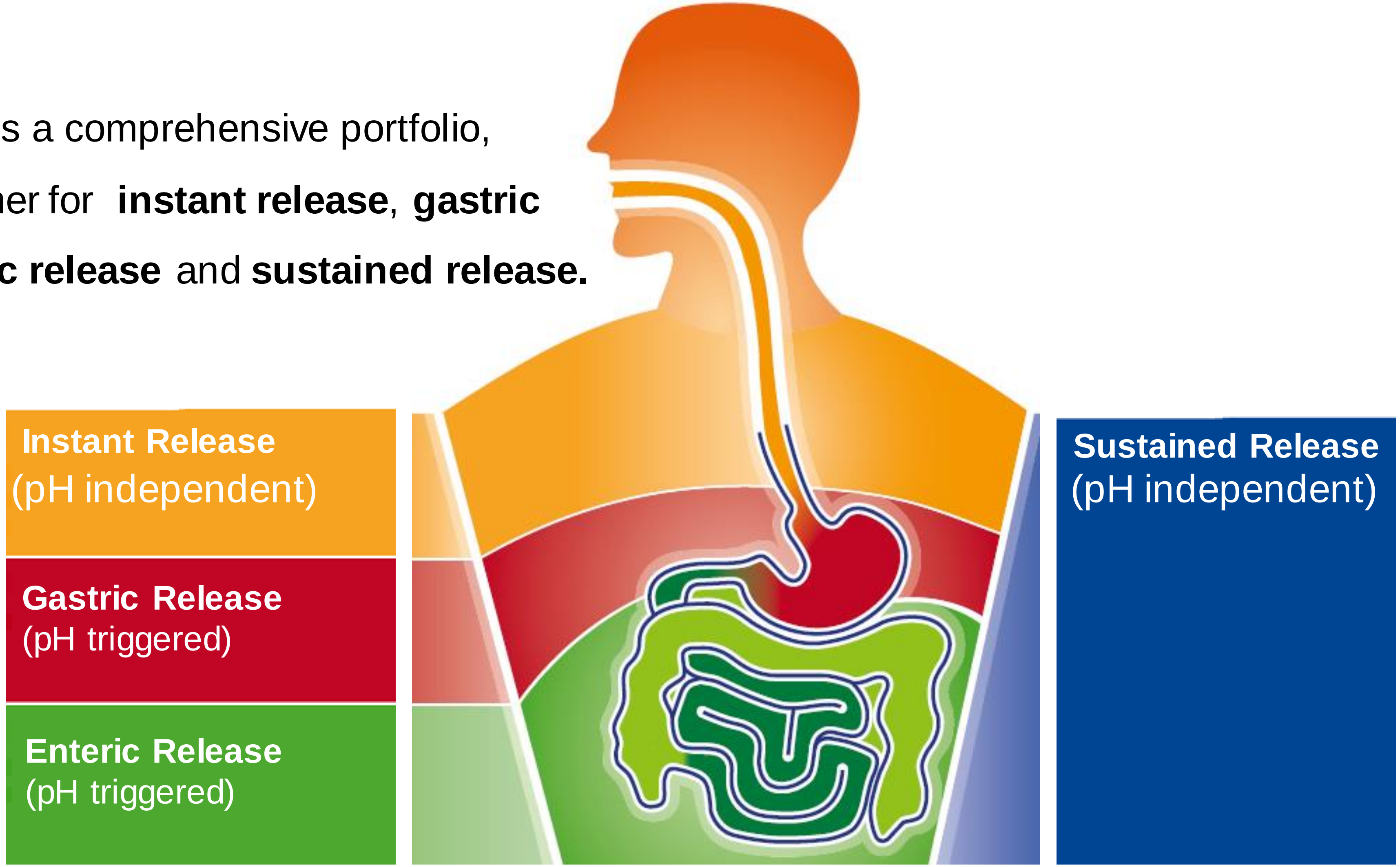
Container
- size, load, depth, Wurster height

Cores (spheres / granules)
- size, shape, mechanical resistance, adhesion

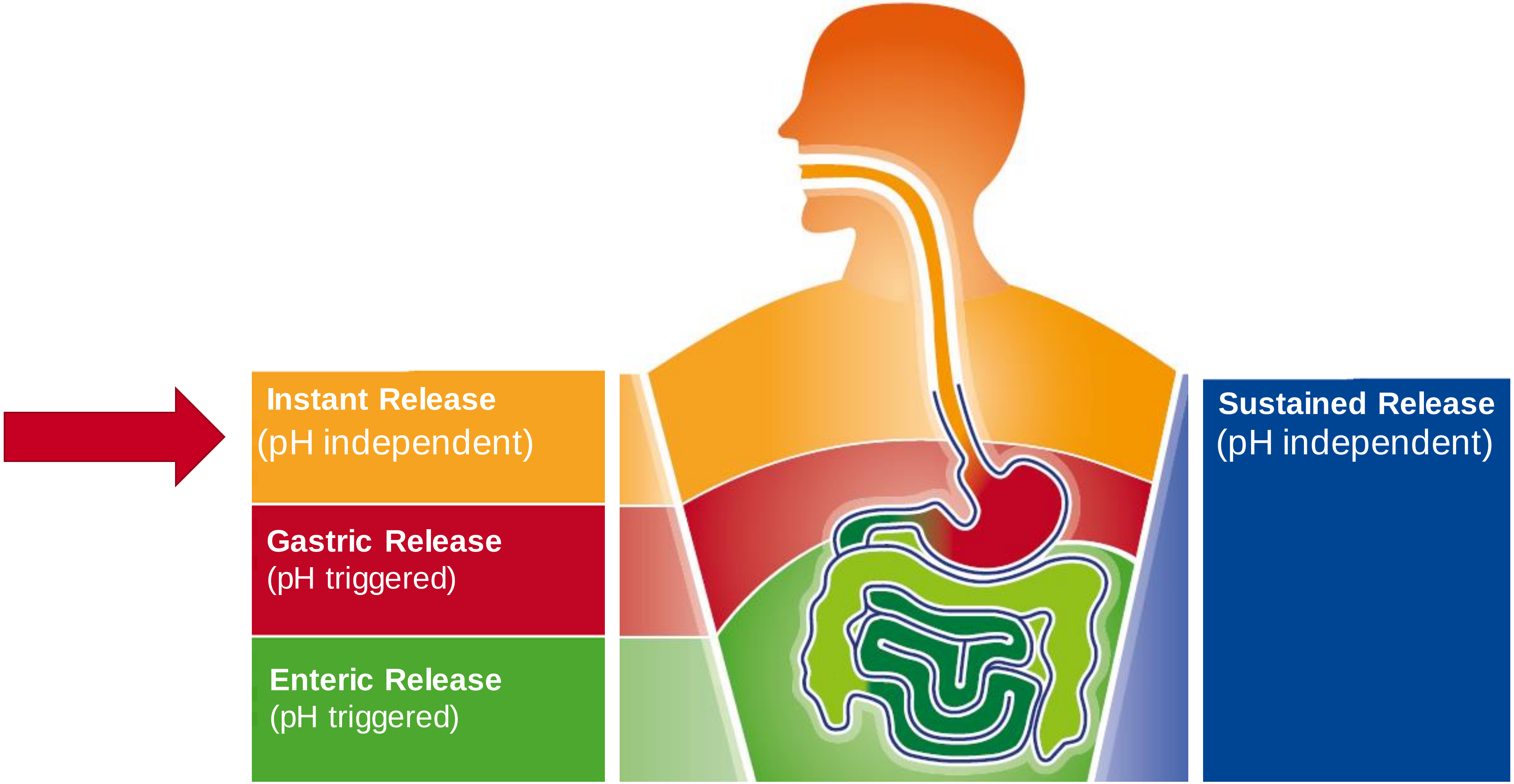
https://lbbohle.com/machines-processes/granulation-pharma/fluidized-bed-system-bfs/

Introduction to BASF Coating Polymers – Kollicoat® line

Kollicoat® line is a comprehensive portfolio, including polymer for **instant release**, **gastric release**, **enteric release** and **sustained release.**



BASF Coating Polymers - Instant Release



Formulation focus: The Evolution of Immediate-Release Film Coatings

- Kollicoat® IR is the latest polymer development in instant-release film-coating (non-functional).
- It represents the benchmark with regard to process safety, reliability, and efficiency.

Sugar coating

HPMC
Hydroxypropylmethyl cellulose

- high viscosity
- complex formulations
- long processes
- brittle coats

PVA
Polyvinyl alcohol

- low viscosity
- complex formulations
- faster processes
- reduced brittleness but tackiness

Kollicoat® IR
PVA-PEG

- lowest viscosity
- simple formulations
- fastest and most stable processes
- no brittleness

BASF instant release coating polymers

- BASF Instant Release Coatings Portfolio

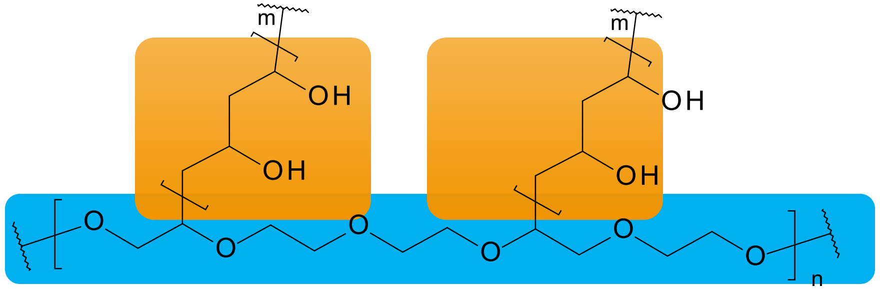
  - **Kollicoat® IR**

    The innovative polymer for instant release coatings. It is the only polymer that can be coated purely without ANY additives.

  - **Kollicoat® Protect**

    Kollicoat® IR (60%) + PVA (40%), innovative polymer for moisture and oxygen protection.

Kollicoat® IR:
polyvinyl alcohol (PVA) grafted onto PEG 6000



- The **polyvinyl alcohol** moiety provides good film-forming properties
- The **polyethylene glycol** part acts as internal plasticizer

- Ph. Eur. 'Macrogol Poly(Vinyl alcohol) Grafted Copolymer'
- USP/NF 'Ethylene Glycol and Vinyl Alcohol Copolymer'
- JPE Polyvinyl alcohol – polyethylene glycol graft copolymer

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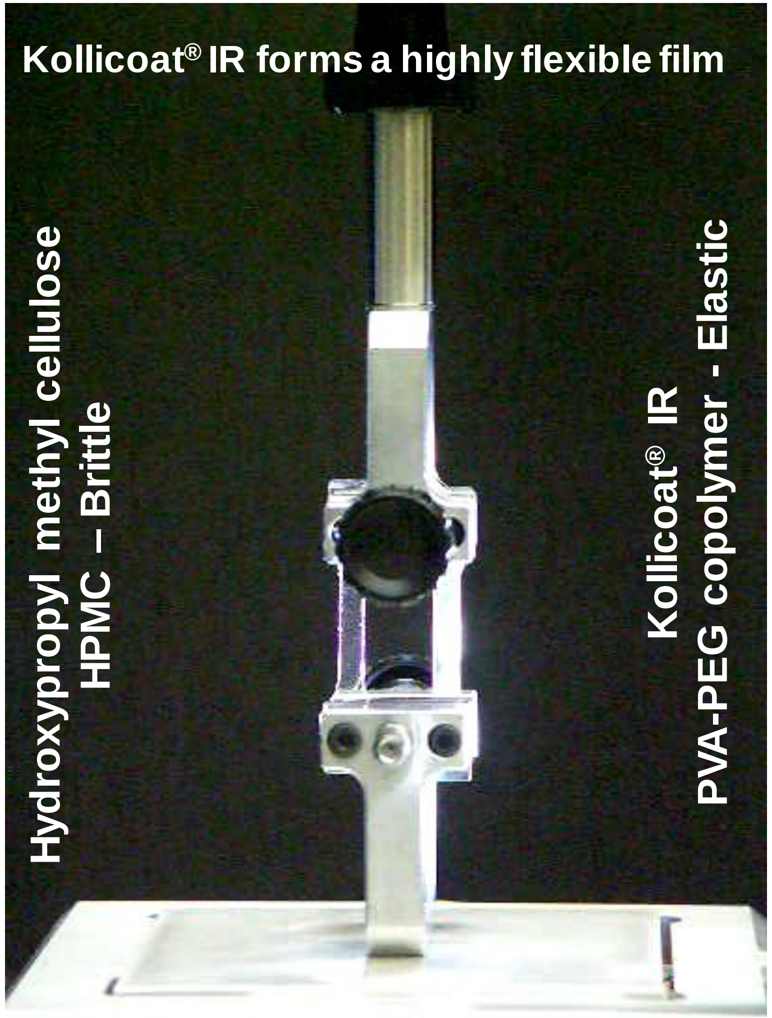
Kollicoat® IR does not need a plasticizer → simpler formulation:

- less components reduce formulation complexity
- film formation is always excellent
- elasticity is maintained upon storage
- excellent binding properties – less picking/ sticking problems
- low viscosity for faster coating processes
- high capacity to load particles (up to 75% pigments or drug load)
- less interaction with APIs, relevant to drug layering



Texture analyzer device for determination of elongation at break

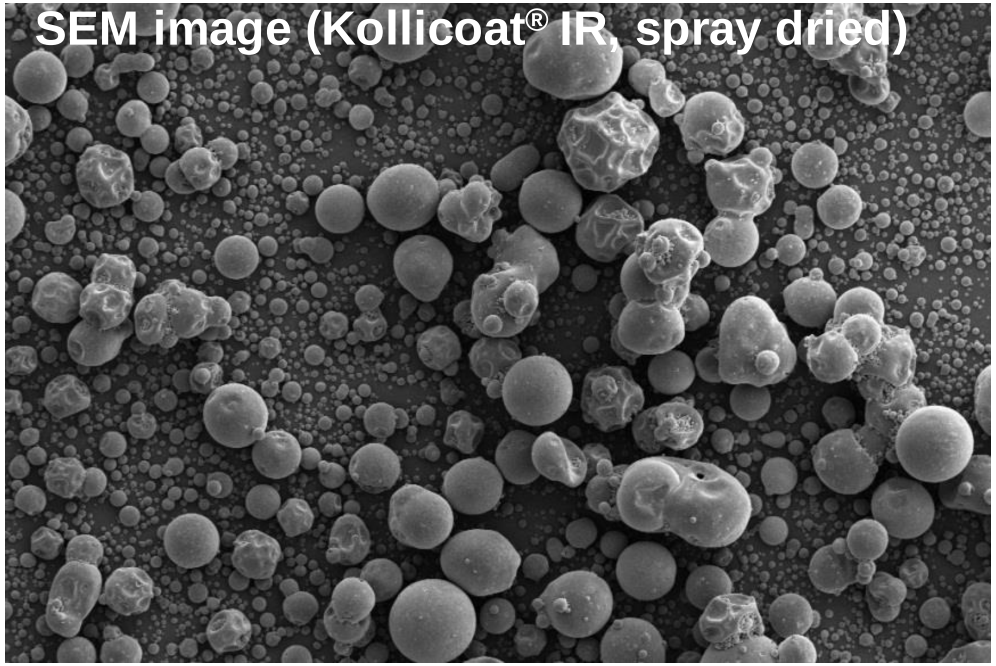
BASF instant release coating polymers: Application guide

Kollicoat® IR: graft co-polymer, combination of PVA and PEG 6000

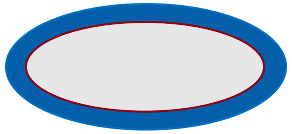
- Recommended process conditions:
  - **25% solid content**
  - **Solvent water and up to 45% EtOH**
  - **Bed temperature: 30 - 40 °C**
  - **High pigment or API load (drug layering)**

Kollicoat® Protect: Kollicoat® IR + PVA

- Recommended Process conditions:
  - **20% solid content**
  - **Solvent: water**
  - **Bed temperature: ~ 45 °C**
  - **High pigment load (up to 75%)**

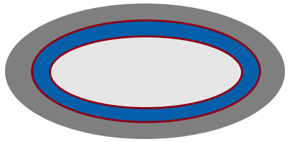


Kollicoat® IR serves all your instant release coating needs and more



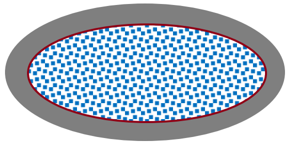
Instant release coating

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



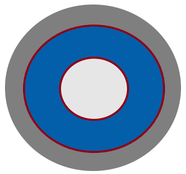
Sub-coating

Safe and easy application, providing high process reliability while maintaining the formulation simple:
→ no further excipients are required



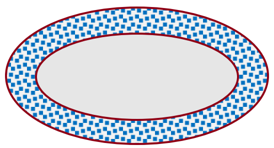
Wet binder

Strong wet binder for all types of fillers, peroxide free character and high solubility to reduce impact on drug release
→ 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
→ low/no interaction with API
→ fastest coating process
→ straightforward process



Pore former

Reliable component in sustained release film coating formulations → high elasticity prevents cracks and supports product safety

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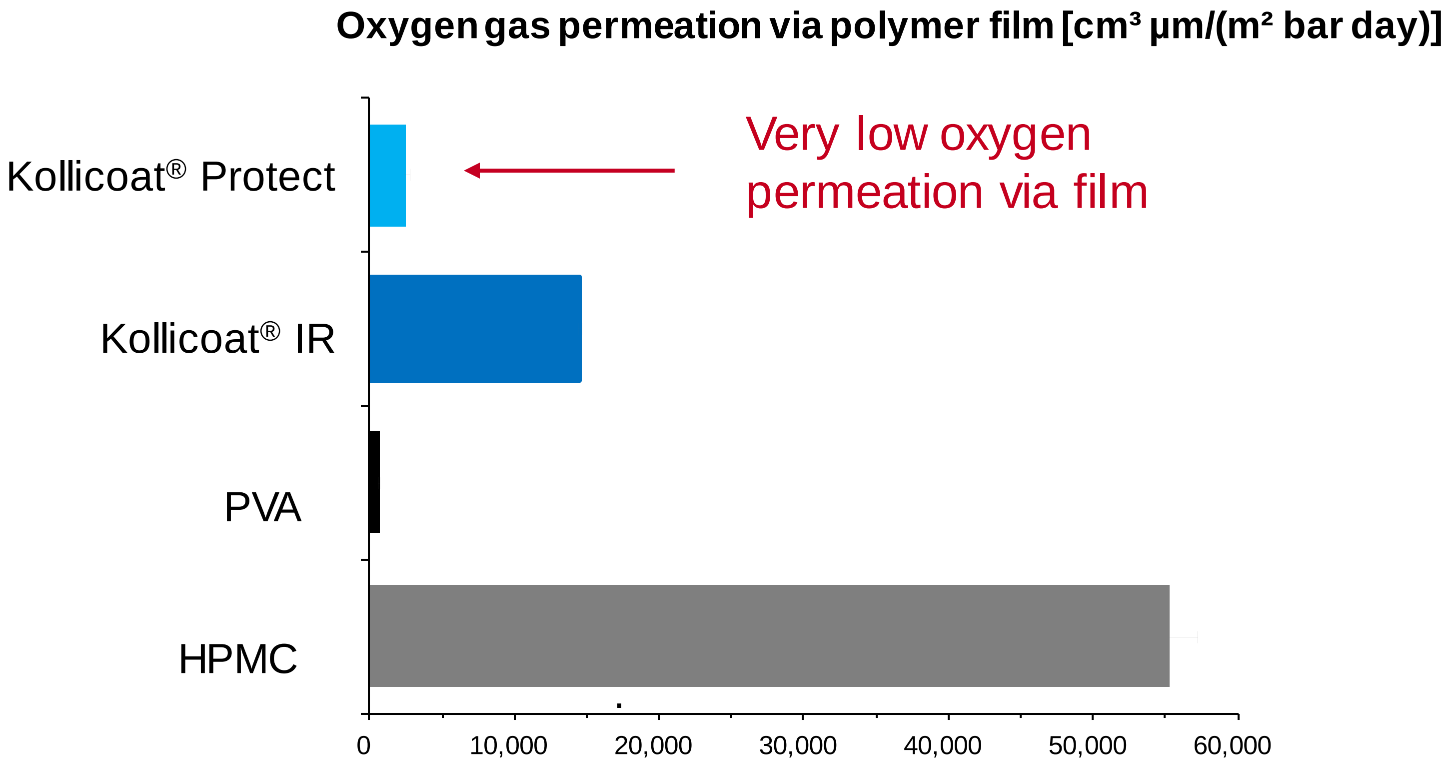
Kollicoat® IR and Kollicoat® Protect offer peroxide free oxidation protection

Kollicoat® IR and Protect help in two ways to protect your API from oxidation:

- Kollicoat® IR is intrinsically free of peroxides
- Kollicoat® Protect in addition has excellent oxygen barrier properties

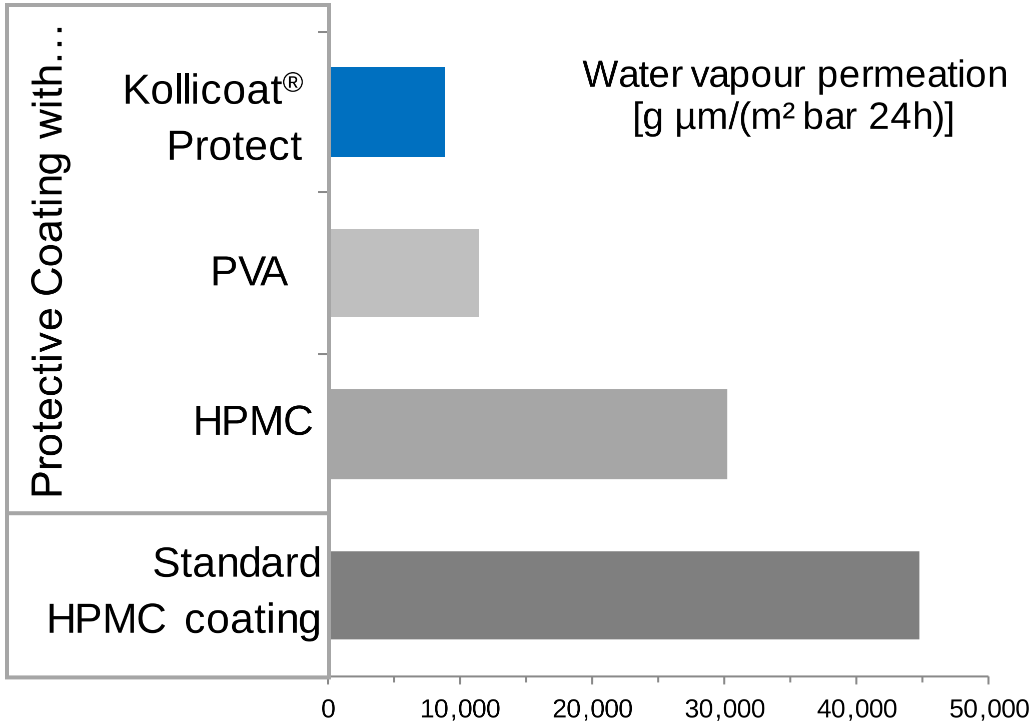


Samples: 50 µm polymer films;
Method: Diffusion Cell acc. to DIN 53380-3: 23°C / 85% r. h. → 23°C / 0% r. h.

Kollicoat® Protect can protect your API from humidity

Kollicoat® Protect can hold extraordinarily high amounts of pigments: up to 75% relative to the polymer!

Thereby, it forms a highly effective moisture barrier.

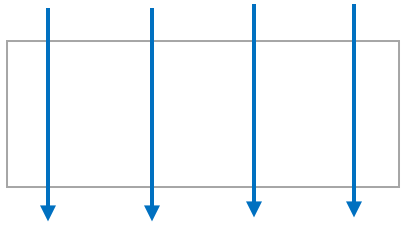


Additional components of protective coatings:

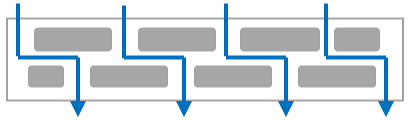
- Kollicoat® Protect based: talc, titanium dioxide, iron oxide red
- PVA based: lecithin, talc, titanium dioxide, xanthan gum
- HPMC based: MCC, stearic acid, titanium dioxide, Al-lake

Moisture diffusion theory:

- fast / direct diffusion in pure film



- prolonged diffusion via barrier in pigmented film



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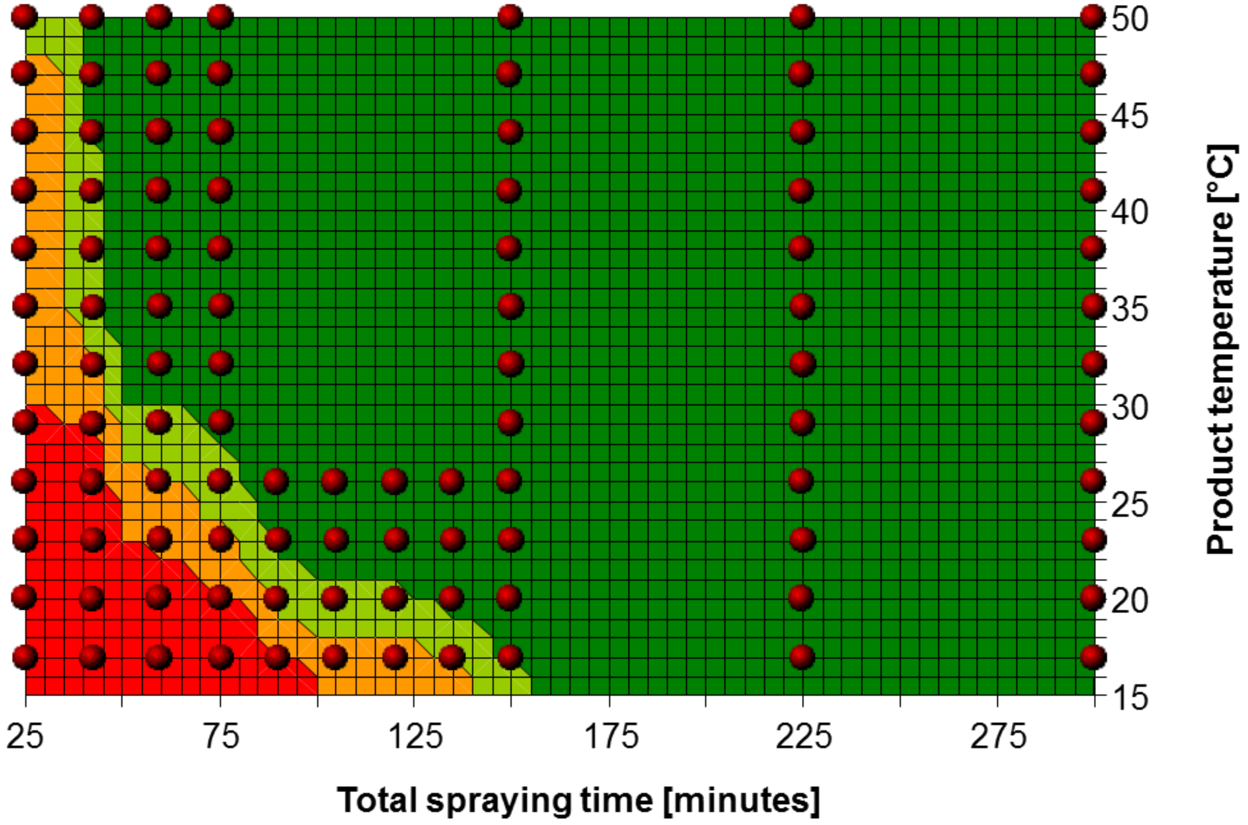
Parameters for the film-coating process: Process Chart Explanation



This visualisation is just a simplified version of the original DoE plan. In reality it takes about:

- ➢ **300 – 450 points**
- ➢ **5 – 15 batches**

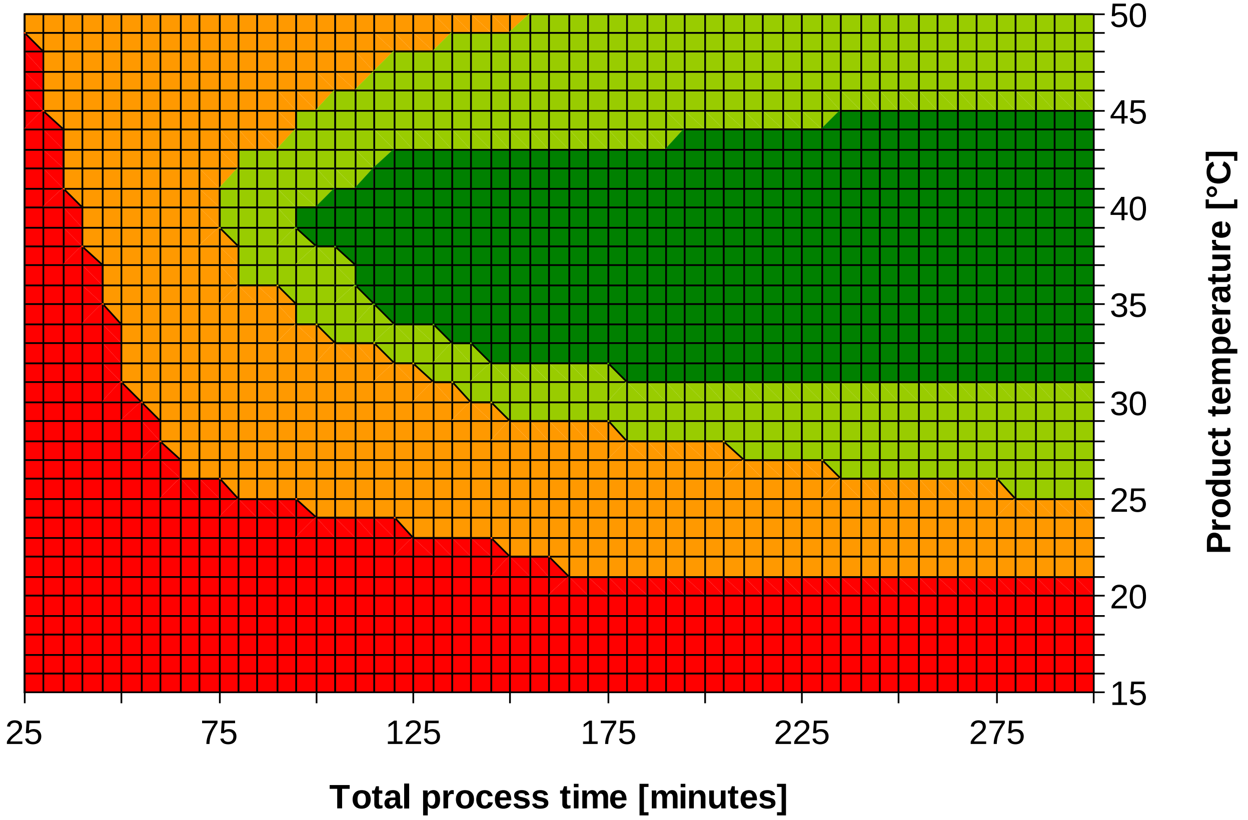
to create such kind of a Process-Parameter-Chart.

Source: ***Benchmarking of instant release film coating polymers***
Th. Cech, 2007, University of Applied Science, Bingen am Rhein, Germany

Desired chart region

Film coating impossible, sticking of the cores	Optima film coating process, surface acceptable
Film coating principally possible, surface not acceptable	Optima film coating process, best results in surface quality

Parameters for the film-coating process: HPMC 3 mPas



- Formed **film is very brittle**
- **Restrictive upper and lower** limit of the product **temperature**
- Process **time acceptable**
- Clearly **separated** quality zones

Film coating impossible, sticking of the cores

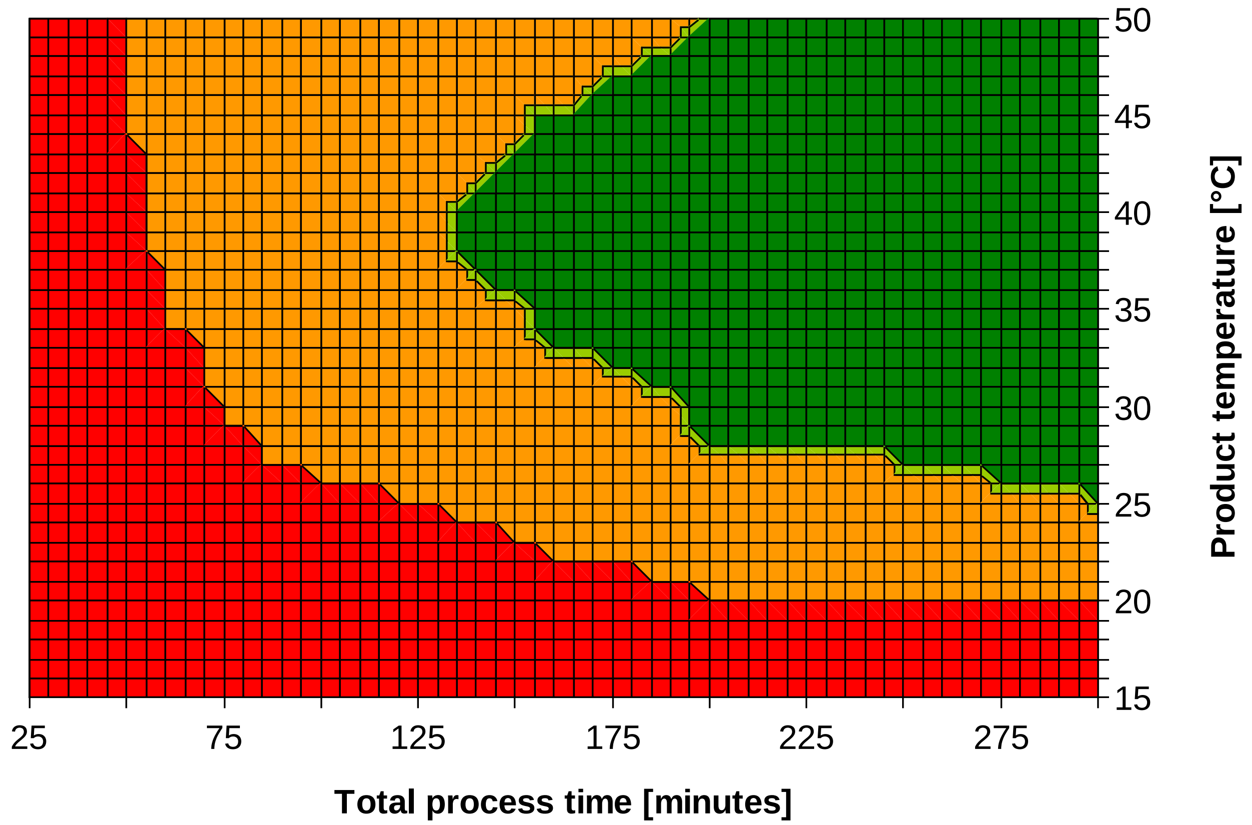
Optima film coating process, surface acceptable

Film coating principally possible, surface not acceptable

Optima film coating process, best results in surface quality

Source: ***Comparison of the coating properties of Kollicoat IR and other film forming polymers…***
Th. Cech, K. Kolter; ExcipientFest 2007, June 19/20, 2007; Cork; Ireland

Parameters for the film-coating process: HPMC 6 mPas



- **Not as brittle as HPMC 3 mPas**
- **Only lower restrictive** limit of product **temperature**
- **Extended process** time (viscosity)
- **No clearly separated** quality zones

Film coating impossible, sticking of the cores

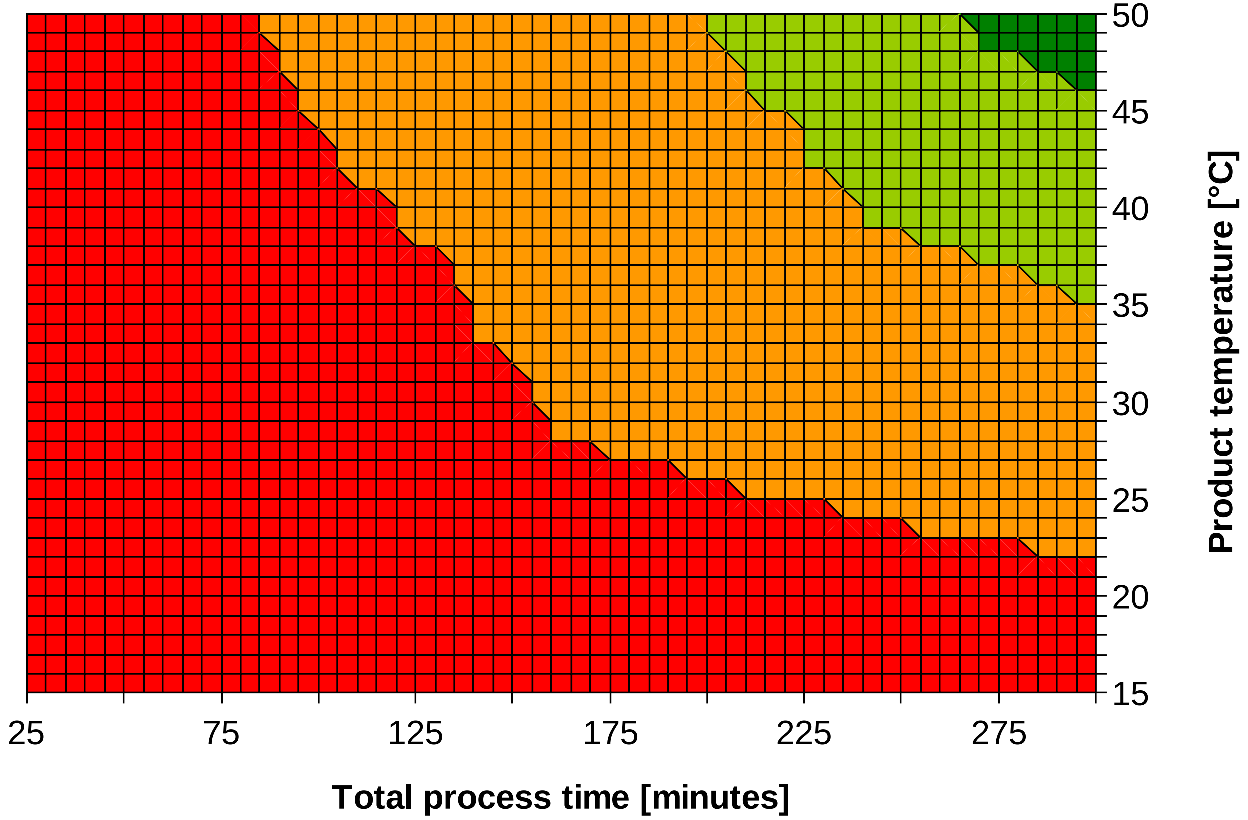
Optima film coating process, surface acceptable

Film coating principally possible, surface not acceptable

Optima film coating process, best results in surface quality

Source: ***Comparison of the coating properties of Kollicoat IR and other film forming polymers…***
Th. Cech, K. Kolter; ExcipientFest 2007, June 19/20, 2007; Cork; Ireland

Parameters for the film-coating process: PVA



- Formed **film is very flexible**
- Coating only in very **small range of (higher) temperature** possible
- Clearly **separated quality zones**

Film coating impossible, sticking of the cores	Optima film coating process, surface acceptable
Film coating principally possible, surface not acceptable	Optima film coating process, best results in surface quality

Source: ***Comparison of the coating properties of Kollicoat IR and other film forming polymers…*** *Th. Cech, K. Kolter; ExcipientFest 2007, June 19/20, 2007; Cork; Ireland*

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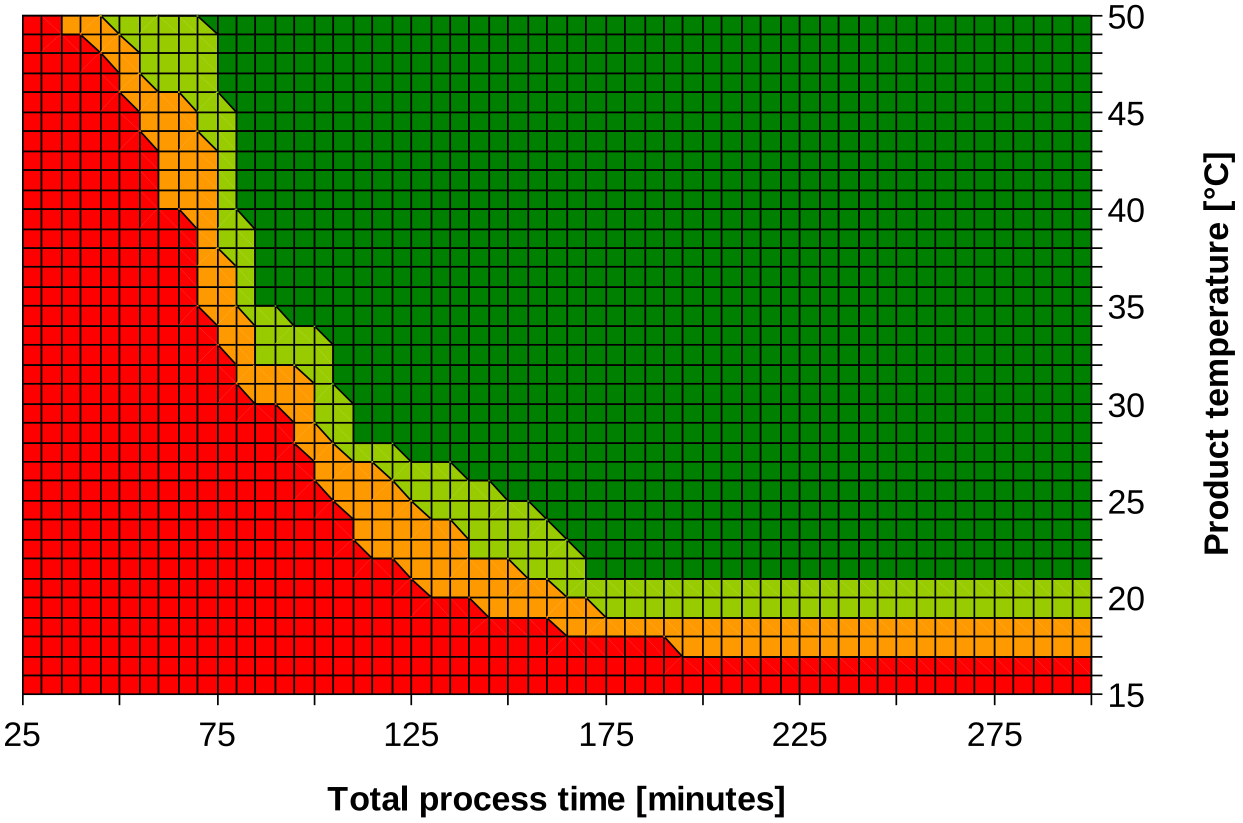
Parameters for the film-coating process: Kollicoat® Protect



- Formed **film is very flexible**
- **Wide range of usable temperature**
- **Very short process time**
- **Clearly separated quality zones**

Film coating impossible, sticking of the cores	Optima film coating process, surface acceptable
Film coating principally possible, surface not acceptable	Optima film coating process, best results in surface quality

Source: ***Comparison of the coating properties of Kollicoat IR and other film forming polymers…***
Th. Cech, K. Kolter; ExcipientFest 2007, June 19/20, 2007; Cork; Ireland

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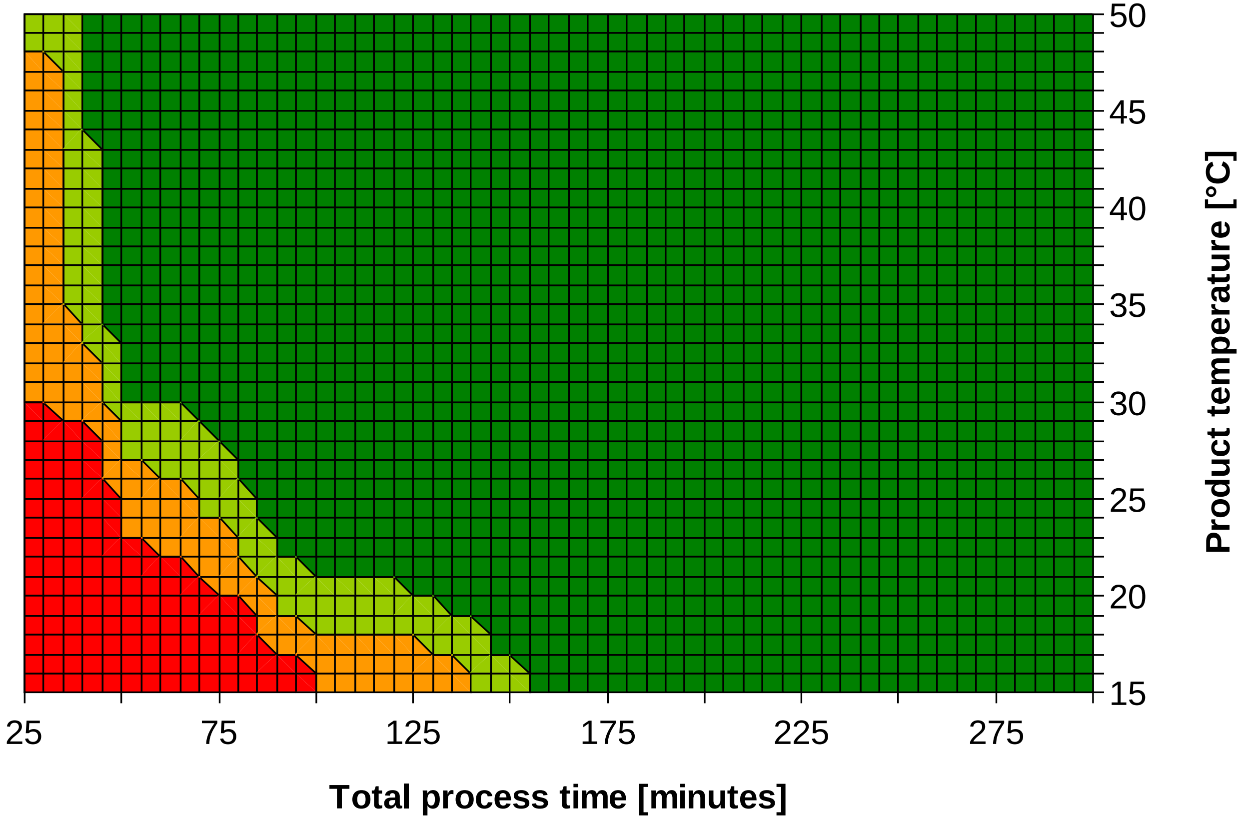
Parameters for the film-coating process: Kollicoat® IR

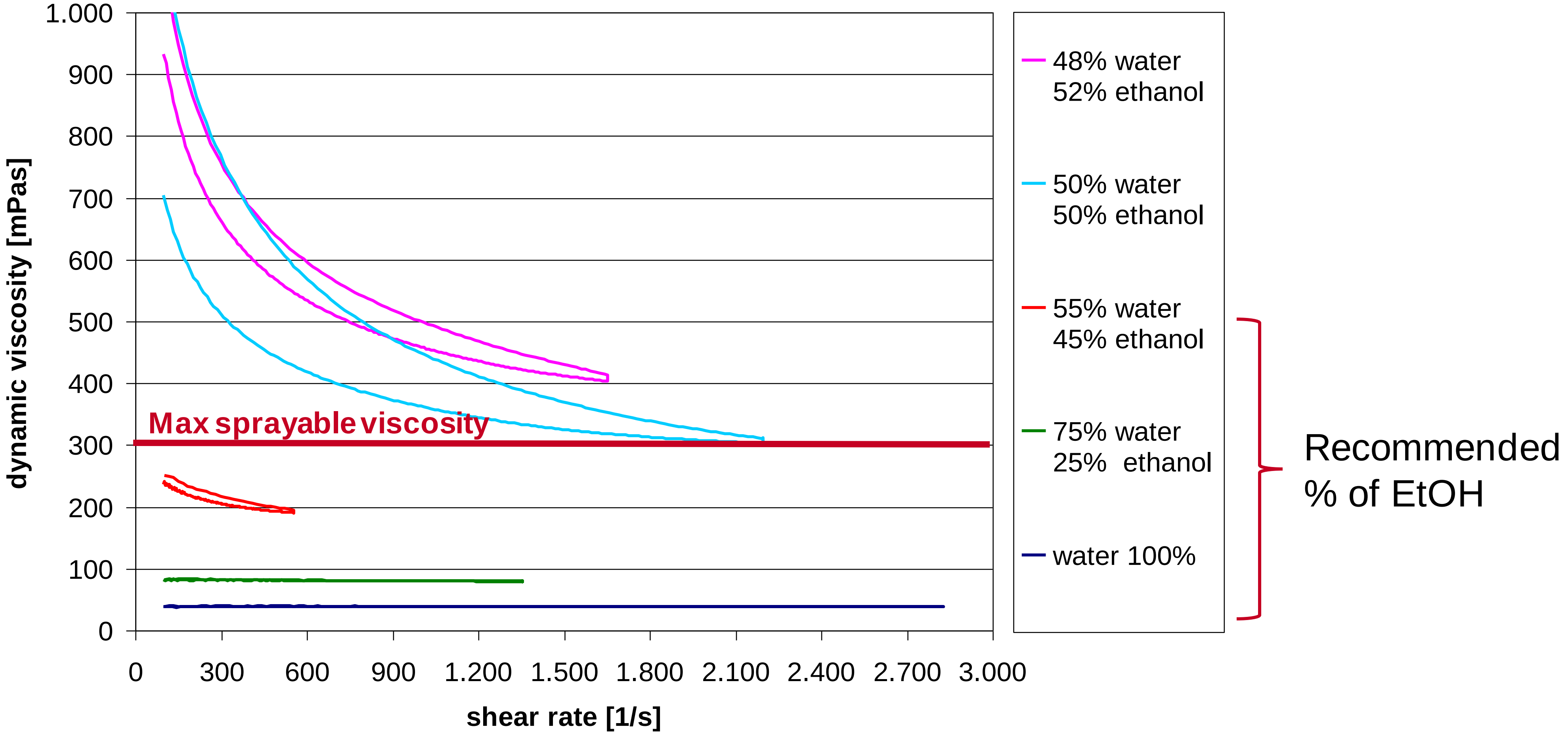


- Formed **film is very flexible**
- **Extremely wide range of usable temperature**
- **Very short process time**
- **Clearly separated quality zones**

- Film coating impossible, sticking of the cores
- Optima film coating process, surface acceptable
- Film coating principally possible, surface not acceptable
- Optima film coating process, best results in surface quality

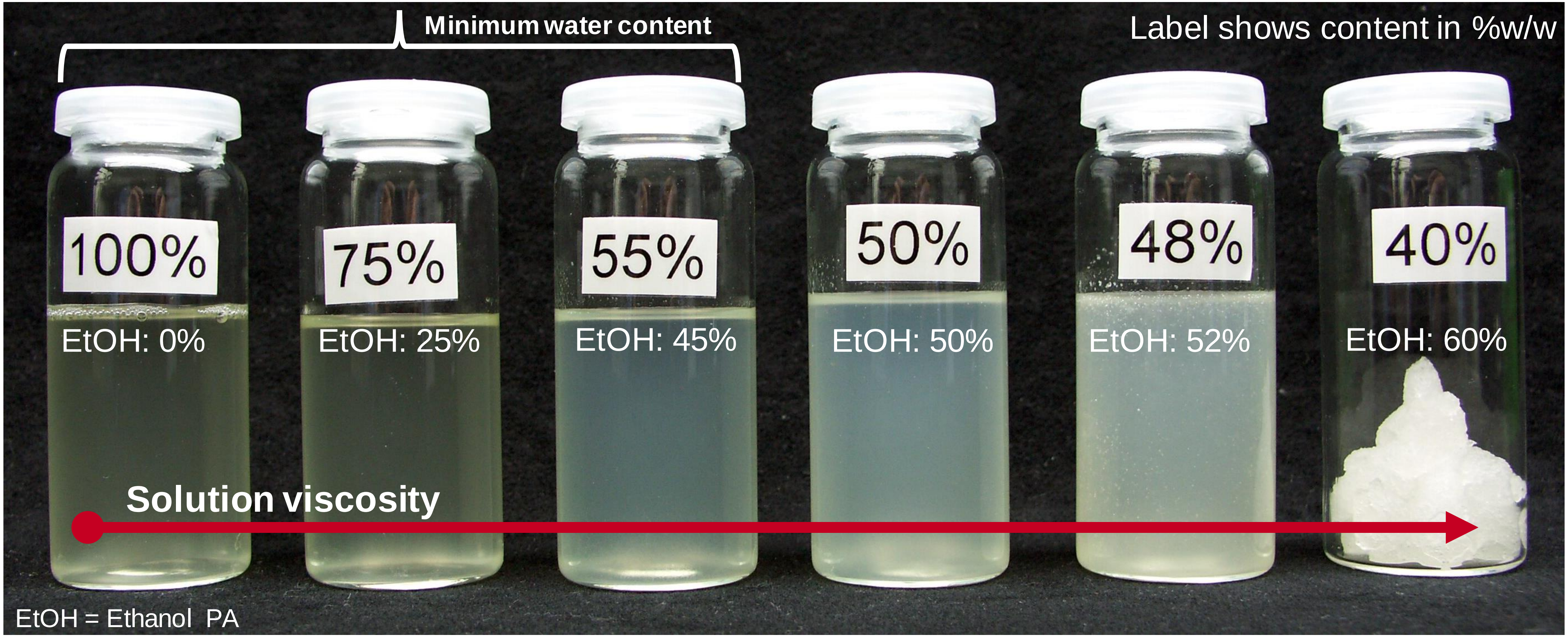
Source: ***Comparison of the coating properties of Kollicoat IR and other film forming polymers…***
Th. Cech, K. Kolter; ExcipientFest 2007, June 19/20, 2007; Cork; Ireland

Viscosity of Kollicoat® IR in ethanol – suitable for drug layering



- Some **APIs require** a certain amount of **organic solvent** to solubilize. **Drug layering formulations** using Kollicoat® IR as the film former **admit up to 45% w/w of EtOH**.

Kollicoat® IR solubility in ethanol



- Increasing EtOH % reduces Kollicoat® IR solubility in the solvents and increase the solution viscosity

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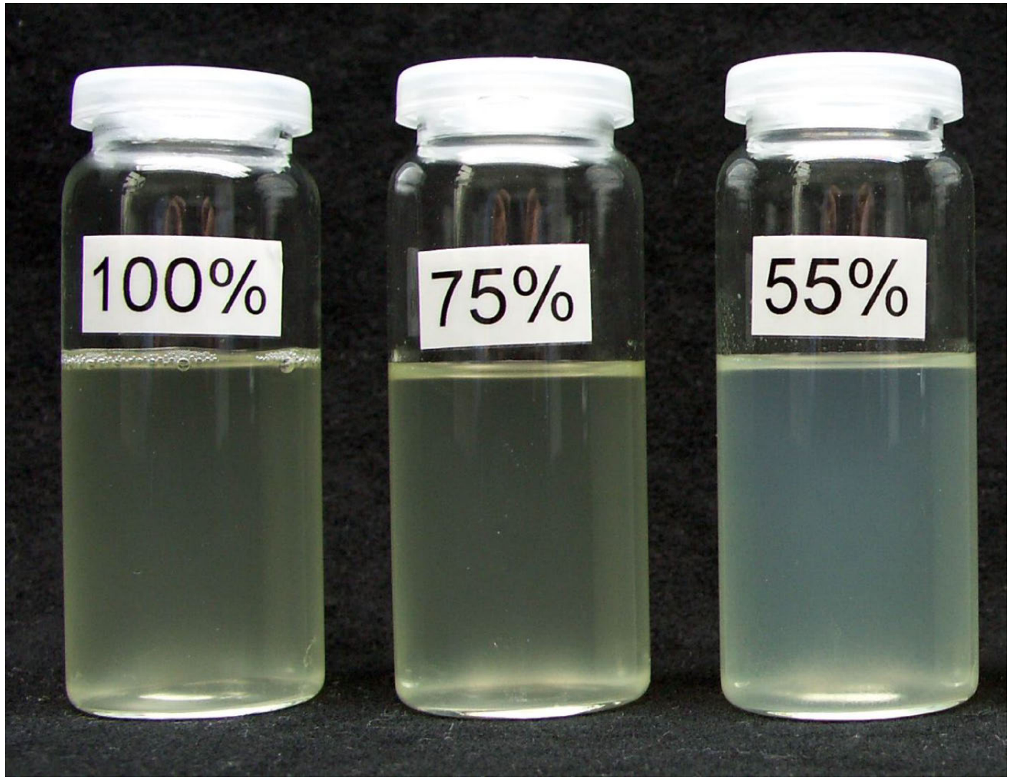
Solubility of Kollicoat® IR in different medias

- Kollicoat® IR pH-Value (solution 20% solids): 5 to 8

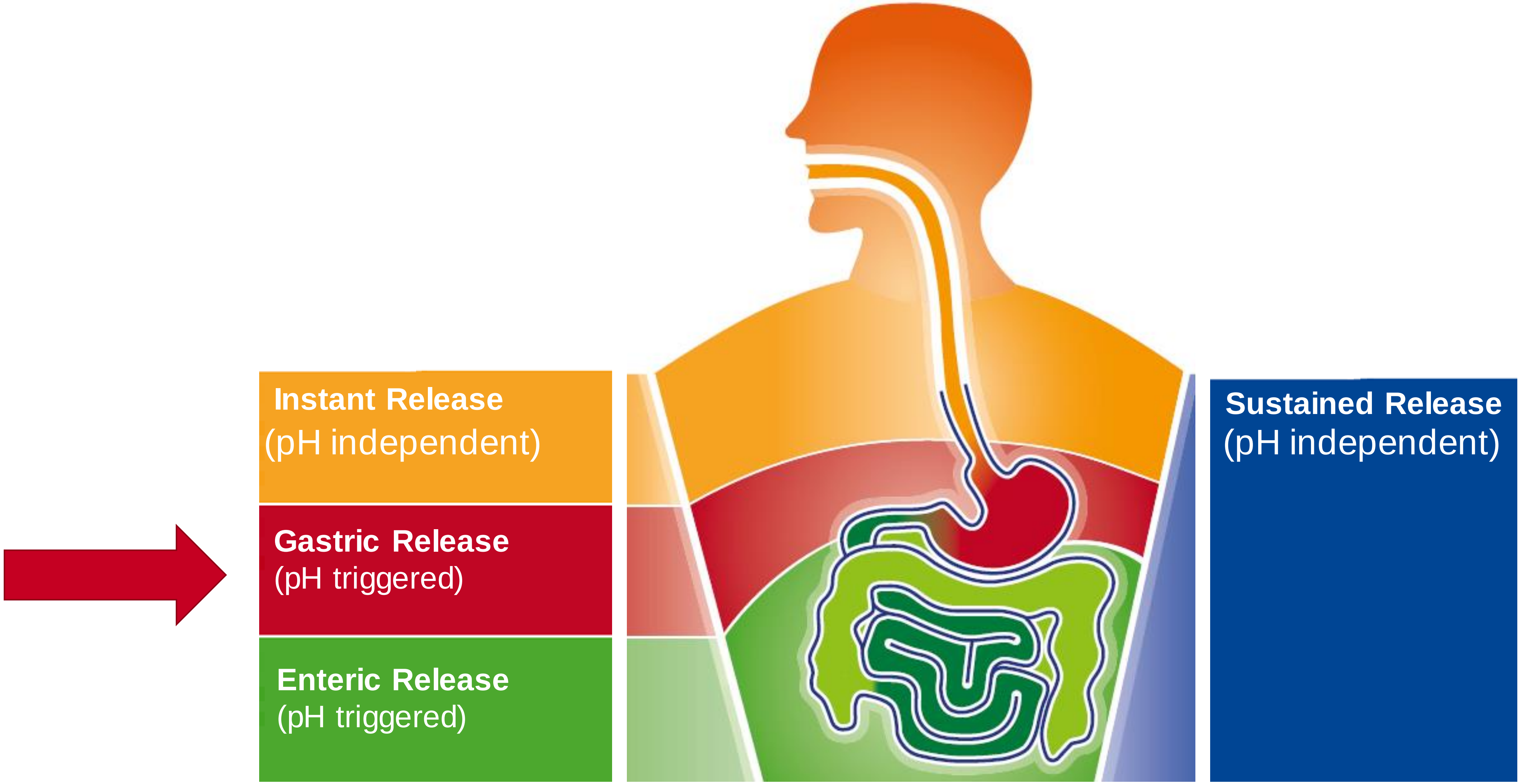
Water	up to 30 %
0,08 N-HCl	up to 30 %
Phosphate buffer 6.8	up to 30 %
Water/ethanol 1:1	up to 20 %
Oganic solvents	insoluble

Kollicoat® IR is pH-independent



- **Kollicoat® IR is highly soluble in a broad range of pH**: acid, neutron, basic and **soluble in water/EtOH 1:1** (up to 20% w/w).

BASF Coating Polymers – Taste Masking (Gastric Release)



Introduction to taste-masking

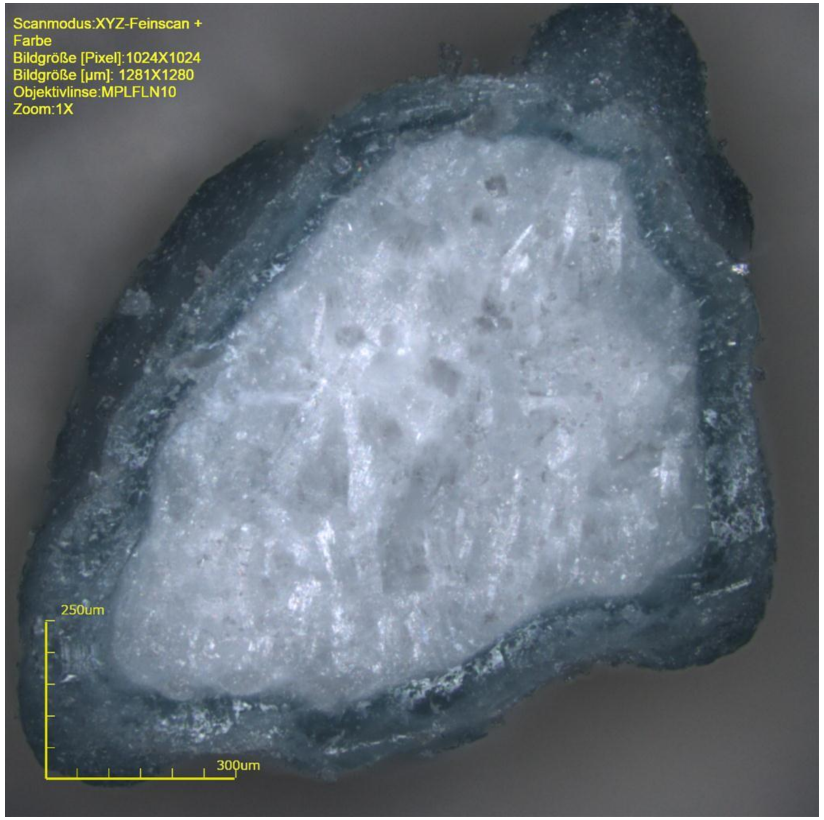
- Taste-masking is an efficient strategy to improve the unpleasant taste of APIs.

- Many alternatives are available in the pharmaceutical industry to enhance drug taste:

  - Sweeteners
  - Flavors and Aromas
  - Drug complexation: cyclodextrin / resins
  - Signal interruption
  - Encapsulation (emulsion)
  - Film-coating

Introduction to taste-masking film-coating

- A **film-coating** is a thin polymer-based coat that is typically sprayed on to a solid pharmaceutical dosage form, such as a tablet, capsule, pellet or granule.
- Taste-masking film-coating technology is an approach used to surround the drug particles (powder, granules, pellets or mini-tablets) with a polymer or lipids (encapsulation).
- The main objective is to reduce the contact of the drug and the taste buds by releasing the drug only after it has passed through the mouth.



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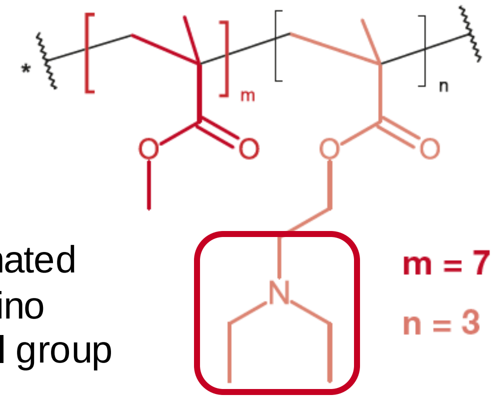
Kollicoat® Smartseal: Your first option for taste-masking film-coating

Copolymer of methyl- methacrylate & diethylaminoethyl methacrylate

MMA : DEAEMA (7:3) copolymer



Deprotonated basic amino functional group

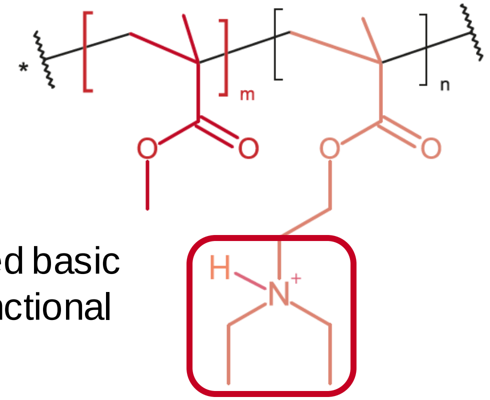
m = 7

n = 3

pH > 5.5

Insoluble in saliva

⇒ No release

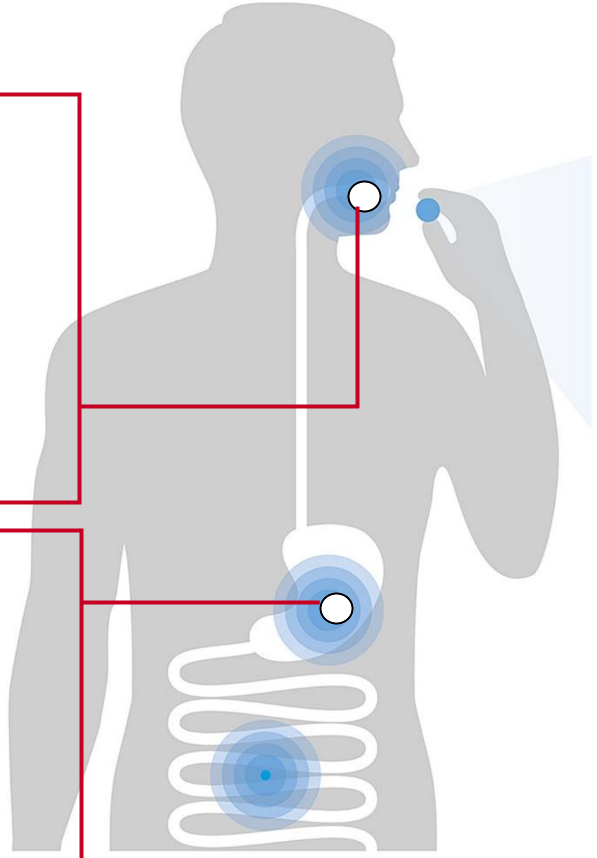


Protonated basic amino functional group

pH < 5.5

Readily soluble in the stomach

⇒ Instant Release



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Kollicoat® Smartseal is available as:

Polymer Dispersion

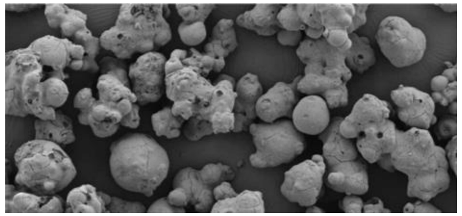
Kollicoat® Smartseal 30 DP

- Aqueous dispersion allowing for easy, reliable, and efficient processing.
- For aqueous coating only.
- A curing step is necessary

Polymer Powder

Kollicoat® Smartseal 100 P

- For aqueous & organic coating.
- Redispersion into water requires a partial neutralization step (succinic acid).
- Suitable for melting coating and HME



Smell analysis: Pure polymer and coated caffeine granules

K. Smartseal 30D

After
1 week…

Main competitor – organic coated granules

After
1 week..

K. Smartseal 100 P - organic coated granules

After
1 week…

Indian competitor polymer

Granule smell burned nose!

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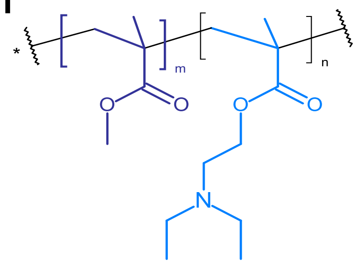
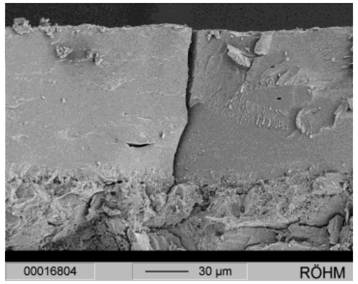
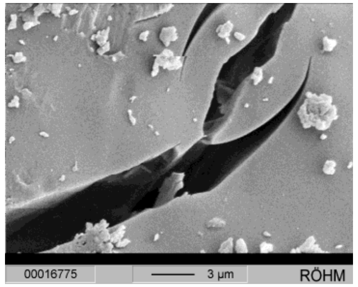
Kollicoat® Smartseal Formulation: Plasticizer

Kollicoat® Smartseal: **MMA : DEAEMA** (7:3) copolymer



- **Tg: ~ 63 °C**
- **MFFT**: **~ 57 °C**
- Water doesn‘t act as a plasticizer: **Tg ≈ MFFT**





Lack of plasticizer can lead to a polymer crack

- **Plasticizers** are used to **improve film elasticity and flexibility** of high brittle polymers by **increasing polymer chains mobility.**
- Higher mobility **reduces the polymer glass transition** (Tg) and the required **minimum film forming temperature** (MFFT).
- Kollicoat® Smartseal require a plasticizer to reduce MFFT in aqueous films.
- A **hydrophobic plasticizer** is preferred due to the lipophilicity of the polymer

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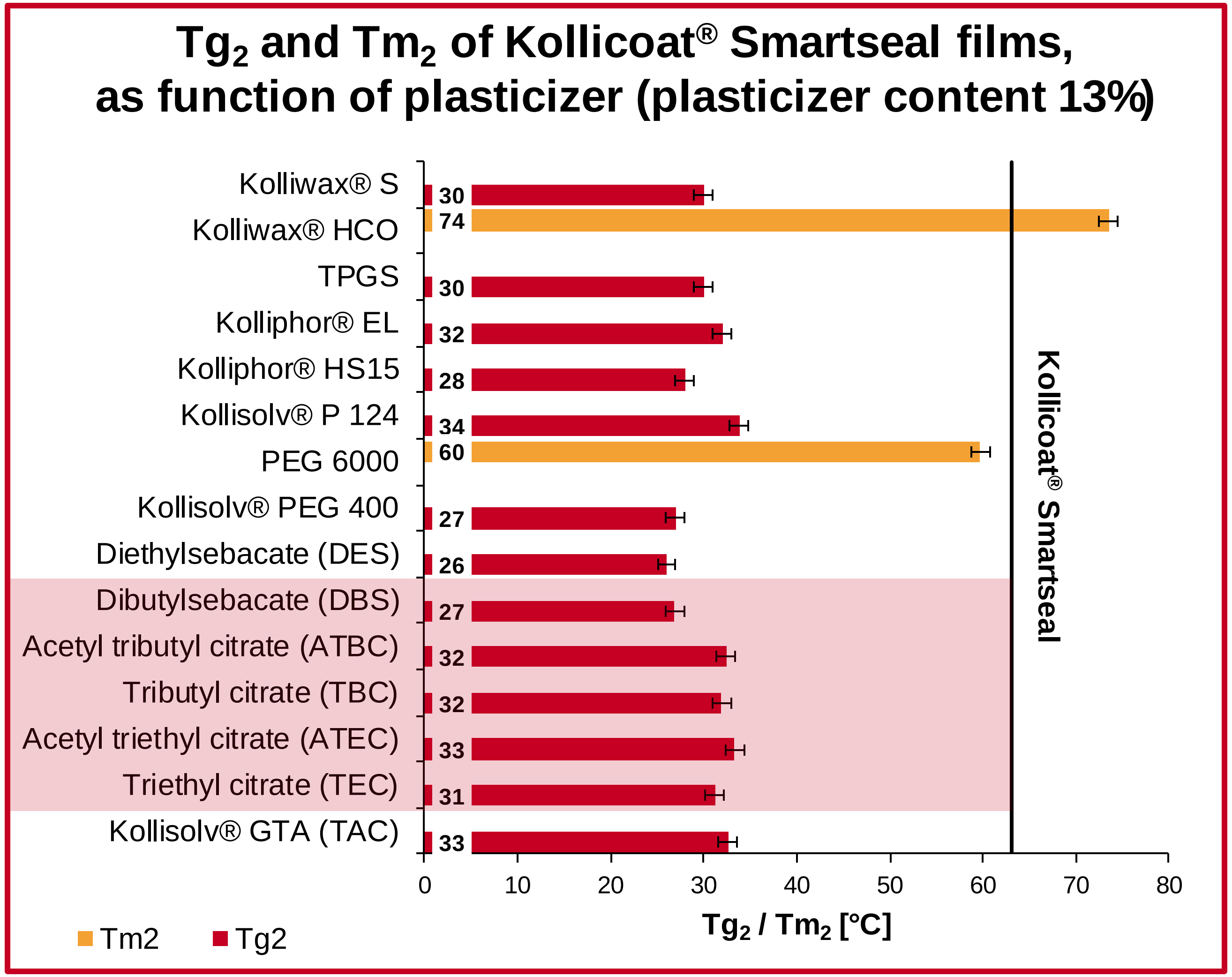
Kollicoat® Smartseal formulation: Plasticizer



Film formulation

Kollicoat® Smartseal 30 D	88.5%
Plasticizer (13%)	11.5%

Preparation isolated films

Method	sprayed onto a Teflon roll
Spray rate	7.0 g/min
Tube diameter	1 mm
Nozzle bore	0.8 mm
Nozzle speed	2.5
Distance nozzle from roll	5.5 cm
Roll speed	1.8
Spraying pressure	1.0 bar
Heater temperature	~110°C
Film surface temperature	32 – 34°C
Layer thickness	75 – 100 µm

T_g measuring

Equipment	DSC Q2000 V24.4 Build 116
Sample	8 – 9 mg
Preparation	prev. fast cooling from 150°C
Heating	20 K/min
Value	n=1

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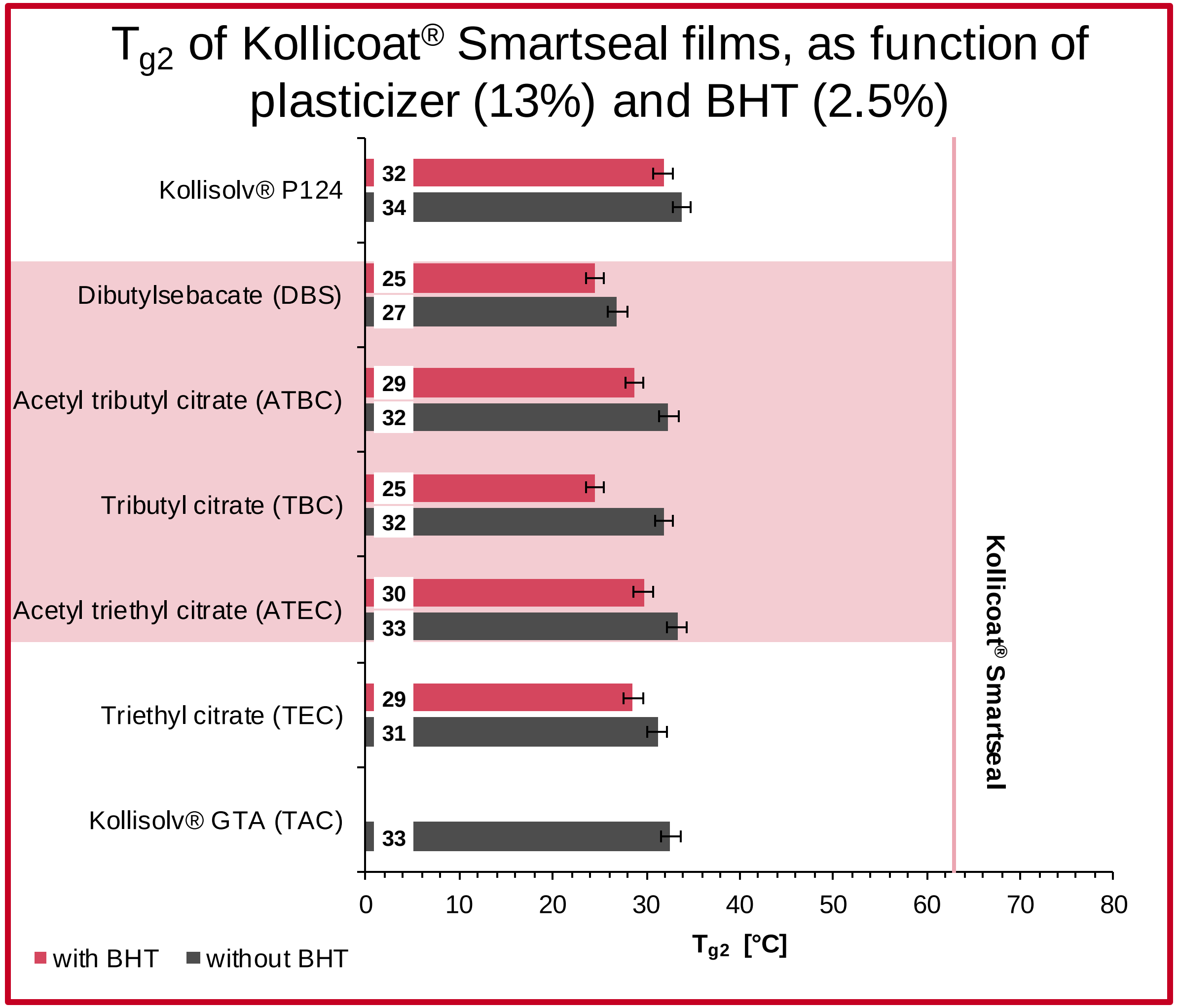
Kollicoat® Smartseal formulation: Plasticizer + BHT



Film formulation (without BHT)

Kollicoat® Smartseal 30 D	88.5%
Plasticizer	11.5%

Film formulation (with BHT)

Kollicoat® Smartseal 30 D	86.6%
Plasticizer	11.2%
Butylated hydroxytoluene (BHT)	2.2%

Preparation isolated films

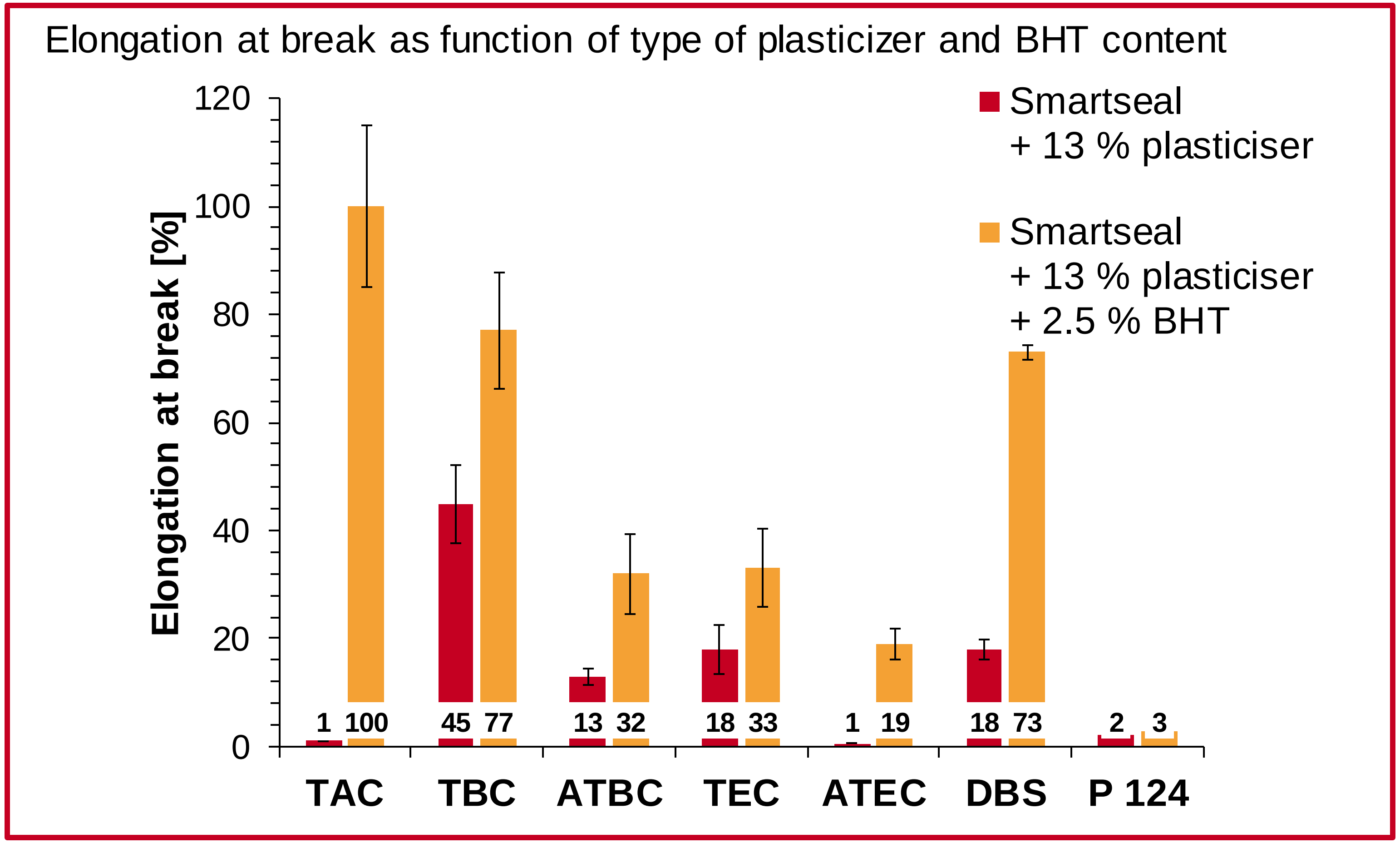
Method	sprayed onto a Teflon roll
Spray rate	7.0 g/min
Tube diameter	1 mm
Nozzle bore	0.8 mm
Nozzle speed	2.5
Distance nozzle from roll	5.5 cm
Roll speed	1.8
Spraying pressure	1.0 bar
Heater temperature	~110°C
Film surface temperature	32-34°C
Layer thickness	75-100 µm

T_g measuring

Equipment	DSC Q2000 V24.4 Build 116
Sample	8-9 mg
Preparation	prev. fast cooling from 150°C
Heating	20 K/min
Value	n=1

- BHT acts as a plasticizer

Kollicoat® Smartseal Formulation: Plasticizer + BHT



BHT has a distinctive influence on the elasticity and plasticity of the Kollicoat® Smartseal film. High values can be achieved when BHT is added.

Film formulation (without BHT)

Kollicoat® Smartseal 30 D	88.5%
Plasticizer	11.5%

Film formulation (with BHT)

Kollicoat® Smartseal 30 D	86.6%
Plasticizer	11.2%
Butylated hydroxytoluene (BHT)	2.2%

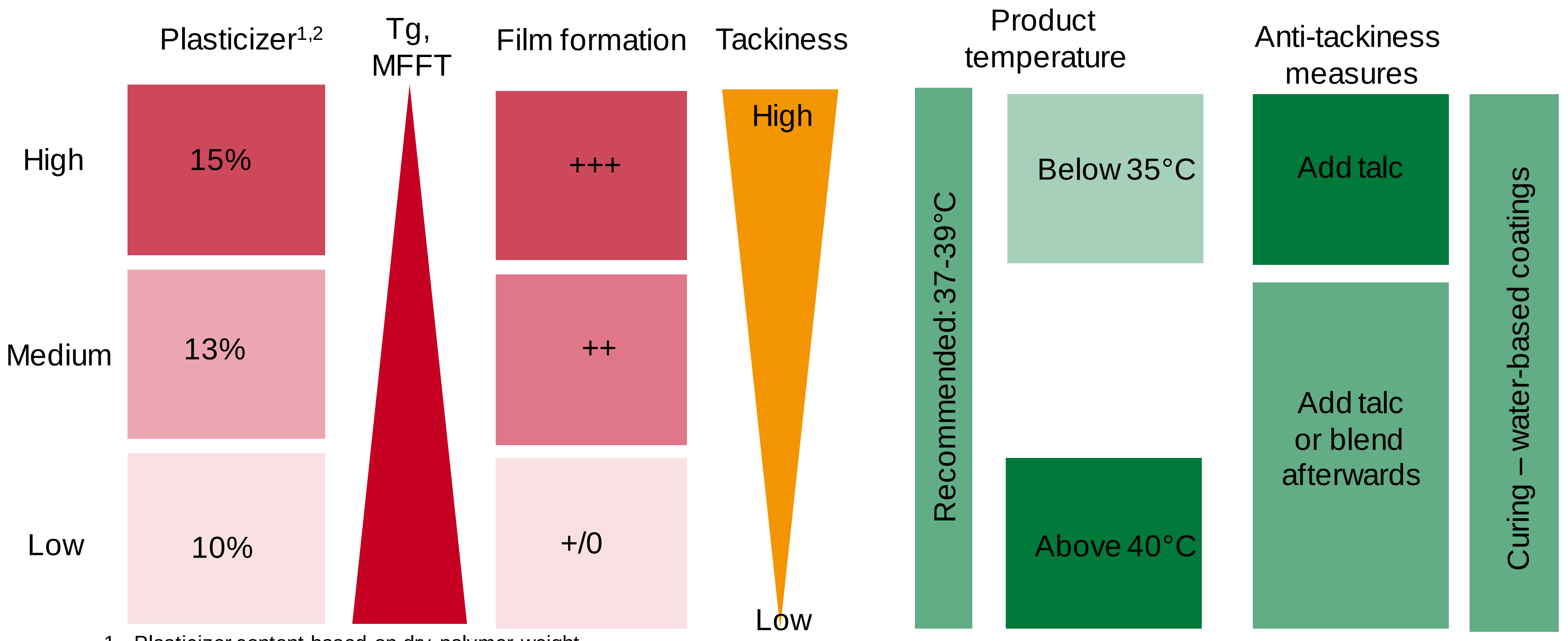
Preparation isolated films

Method	sprayed onto a Teflon roll
Spray rate	7.0 g/min
Tube diameter	1 mm
Nozzle bore	0.8 mm
Nozzle speed	2.5
Distance nozzle from roll	5.5 cm
Roll speed	1.8
Spraying pressure	1.0 bar
Heater temperature	~110°C
Film surface temperature	32-34°C
Layer thickness	75-100 µm
Curing conditions	4 h / 70°C

Elongation at Break

Texture analyser	TA XT2i
Climatic conditions	23°C/56% r.h.
Value	mean (n=6), ±SD

Kollicoat® Smartseal formulation: Plasticizer



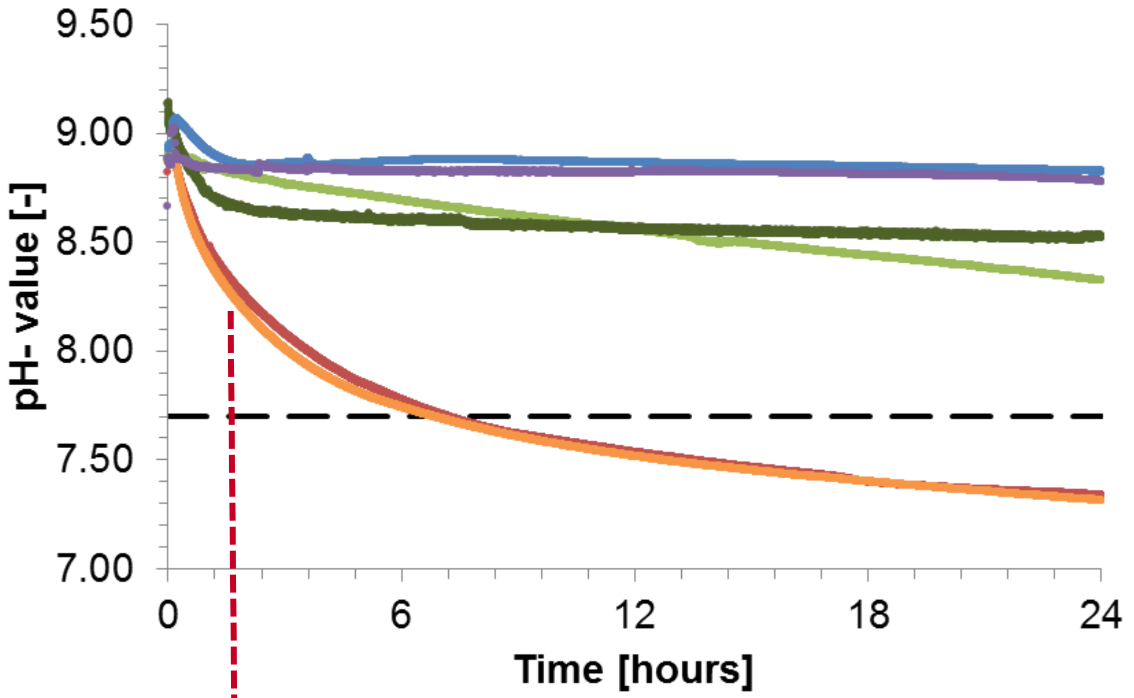
1 - Plasticizer content based on dry polymer weight

2 - The plasticizing effect of BHT needs also to be considered.

■ Process conditions (product temperature and curing step) and coating formulation (anti-tacking agent) must be adjusted to the plasticizer content.

Kollicoat® Smartseal formulation: Plasticizer

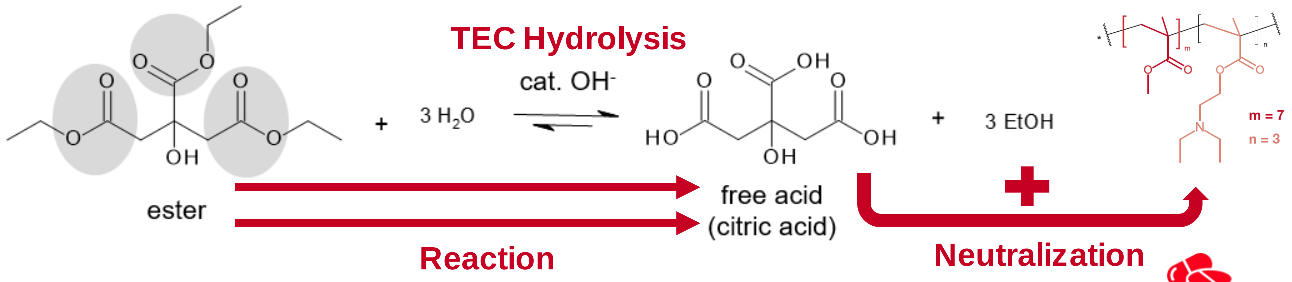
- Dispersion stability is dependent on the plasticizer type (13% plasticizer)



- TEC (triethyl citrate)
- TAC (triacetin)
- ATEC (acetyltriethyl citrate)
- **ATBC (acetyltributyl citrate)**
- **DBS (dibutyl sebacate)**
- P 124 (poloxamer 124)

Recommended Plasticizers

pH 7.8
= Isoelectric point of the dispersion
⇒ Zeta potential = zero
⇒ Dispersion no longer stable



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Kollicoat® Smartseal formulation: Plasticizer

Several plasticizers can be used in combination with Kollicoat® Smartseal. See the most recommended ones:

Recommended plasticizers:

Tributyl citrate (TBC)

Acetyltriethyl citrate (ATEC)

Acetyltributyl citrate (ATBC)

Dibutyl sebacate (DBS)

TPGS

Optimal concentration:

10 – 15% w/w
(calculated on the dry polymer)

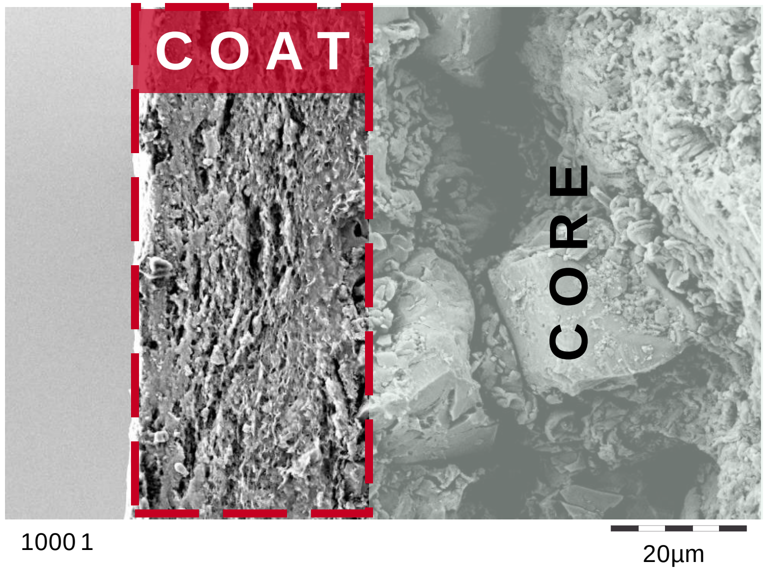
Kollicoat® Smartseal formulation: anti-tacking

- Anti-tacking agents are used to reduce Kollicoat® Smartseal tackiness during storage or when a higher amount of plasticizer is required in the formulation (also consider BHT impact on its plasticizing effect).

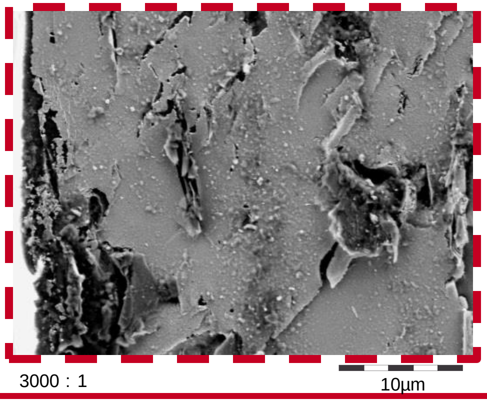
- Talc is the most used anti-tacking.
- Considerations:
  - It can precipitate in the tubes
  - Increase film-coating porosity → requires ↑ weight gain

- Glycerol mono stearate [**Kolliwax® GMS II**] + Polysorbate 80 [**Kolliphor® PS 80**] (8:2) is an interesting alternative to talc:
  - Doesn’t precipitate in the tubes
  - Require less amounts compared to talc
  - Consideration: They need to be heated (70° C) and emulsified using a high shear mixer.

Kolliwax® GMS II + Kolliphor® PS 80



Talc



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Kollicoat® Smartseal formulation: Anti-tacking agents

An anti-tacking agent is recommended to reduce particles, pellets, and tablets sticking, especially **after the coating process.**

Preference Order	Procedure	Advantage
1	Add talc to formulation and/or blend afterwards	Easiest application + excellent results
2	Magnesium stearate dry blending	Easiest application
3	Kollicoat® IR + talc (after coating)	Excellent results

- It is recommended the use of **2 – 8% w/w talc in the total formulation**. The less the better for a better taste-masking functionality at lower coating level.
- It is advised to add an anti-tacking agent in the film formulation when coating small particles or pellets and blend them with talc afterwards (add talc to the fluid bed after the coating process and start fluidization).

Kollicoat® Smartseal formulation: Anti-tacking agent

0% Talc
1% Microtalc (after)

4% Talc

6% Talc

8% Talc

- Drug release at pH 6.8 +

After 5.5 months at 30°C and 40°C / 75% RH, coated tablets blended with 1% Microtalc and those with 8% talc in the film formulation did not stick together.

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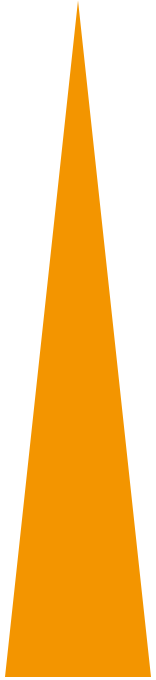
Kollicoat® Smartseal formulation: Anti-tacking agent

Talc content (% w/w)

	In Coating Suspension	Based on Dry film	Tackiness	Resistance at pH 6.8	Measures	
High	8%	40%		0	coating level 3-4 mg/cm²	Curing
Medium	4 - 6%	20 - 30%		+	coating level 2-3 mg/cm²	
Low	0 - 2%	0 -10%		++	coating level 2 mg/cm²	

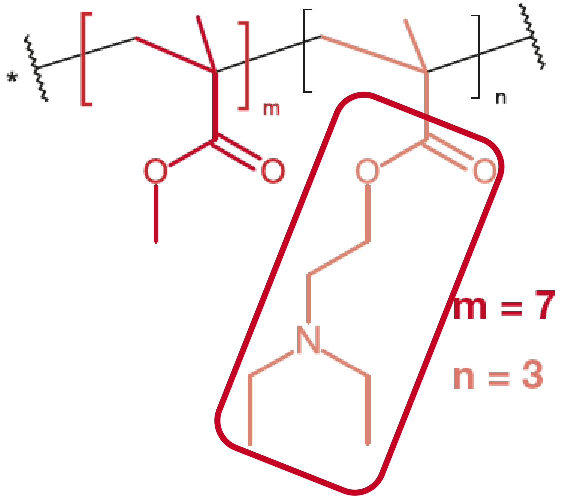


- High talc concentrations in the film coating reduce the resistance at pH 6.8.
- Curing is recommended after aqueous coating to ensure complete film forming.

Kollicoat® Smartseal formulation: Antioxidant

Antioxidant	Amount
Butylated hydroxytoluene (BHT)	1 - 2.5% related to polymer
N-acetylcysteine	1 - 2.5% related to polymer
Sodium carbonate*	1 - 2.5% related to polymer

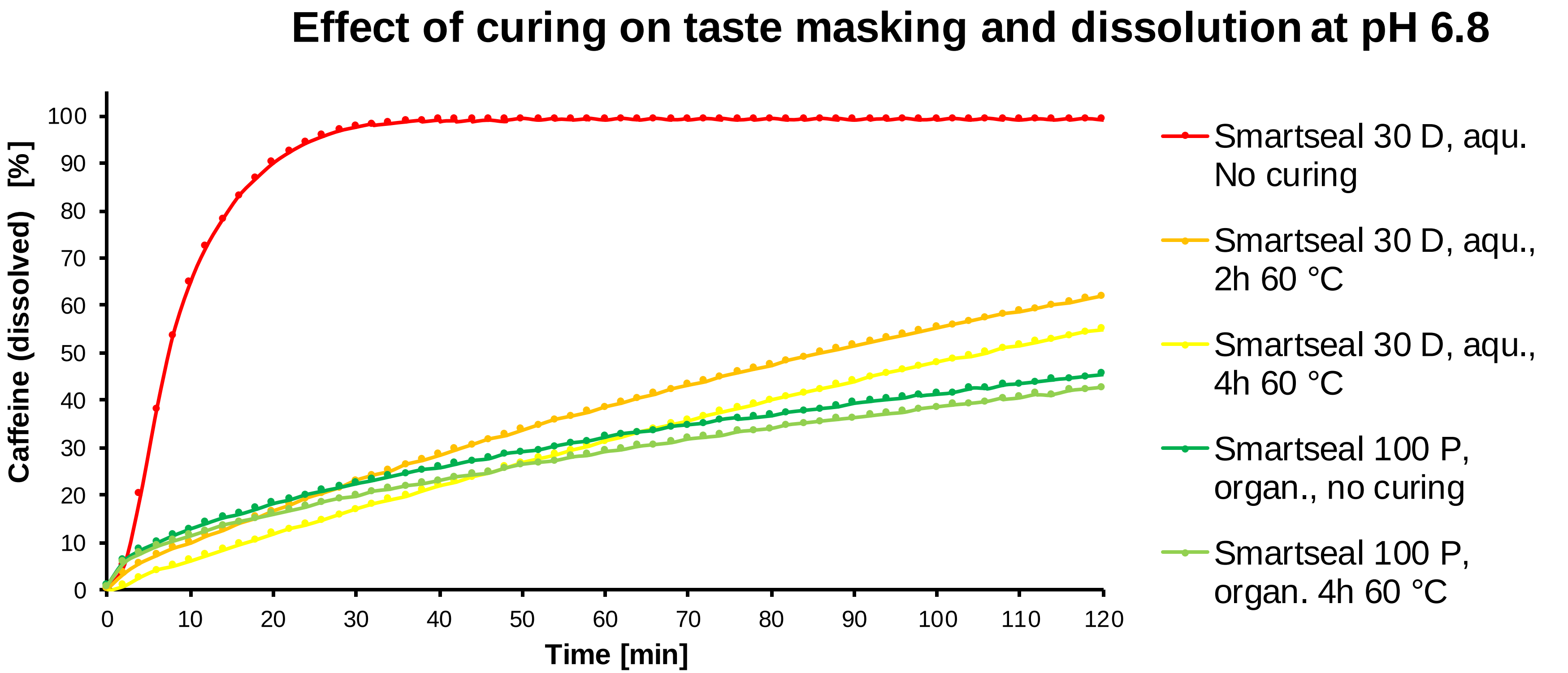
*In aqueous coating, hydrophilic antioxidants can be used alternatively.



Basic amino ester moiety group

- An antioxidant might be required to stabilize the amino ester moiety of the polymer.
- Without it, yellowing and differences on the dissolution may appear under stress conditions.
- BHT is the recommended antioxidant. Its plasticizing effect should be considered.
- **2 in 1:** TPGS acts as a plasticizer and antioxidant.
- It can be used as plasticizer at 13% (based on dry polymer) and get the benefit of its antioxidant functionality

Kollicoat® Smartseal: Evaluation of curing effects



Caffeine granules
15% weight gain

Kollicoat Smartseal 30 D aqueous:
No curing step and Curing

Kollicoat Smartseal 100 P organic:
No curing step and Curing

- Kollicoat® Smartseal 30 D needs curing to close. However, no practical difference in 2 vs 4 hrs. curing.
- Curing has no influence on performance of organic coated Kollicoat® Smartseal 100 P
- Organic Kollicoat® Smartseal 100 P w/o curing is initially comparable to release from Kollicoat® Smartseal 30 D cured

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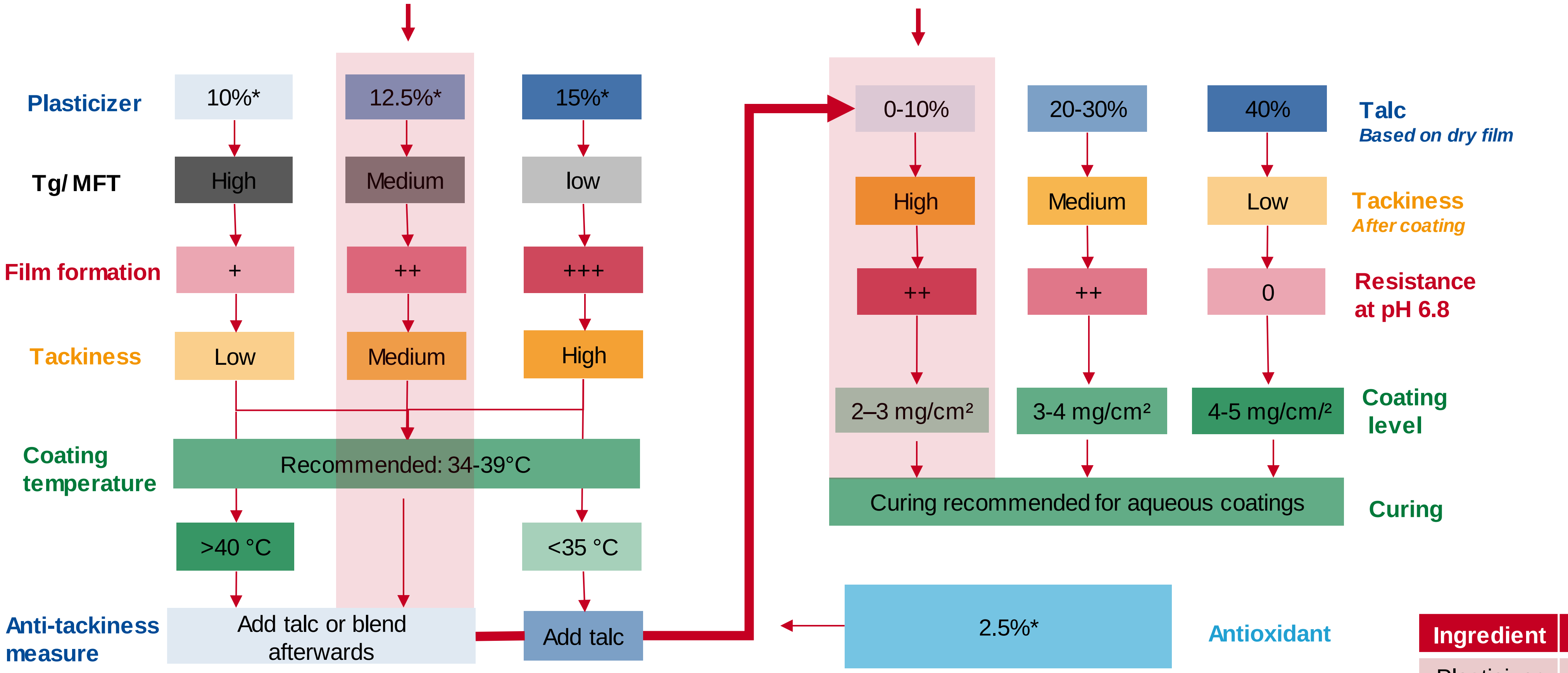
Decision tree for formulation development



*related to dry polymer

Ingredient	Recommendation
Plasticizer	DBS or ATBS
Antioxidant	BHT
Anti-tacking	Talc or GMS II + PS 80

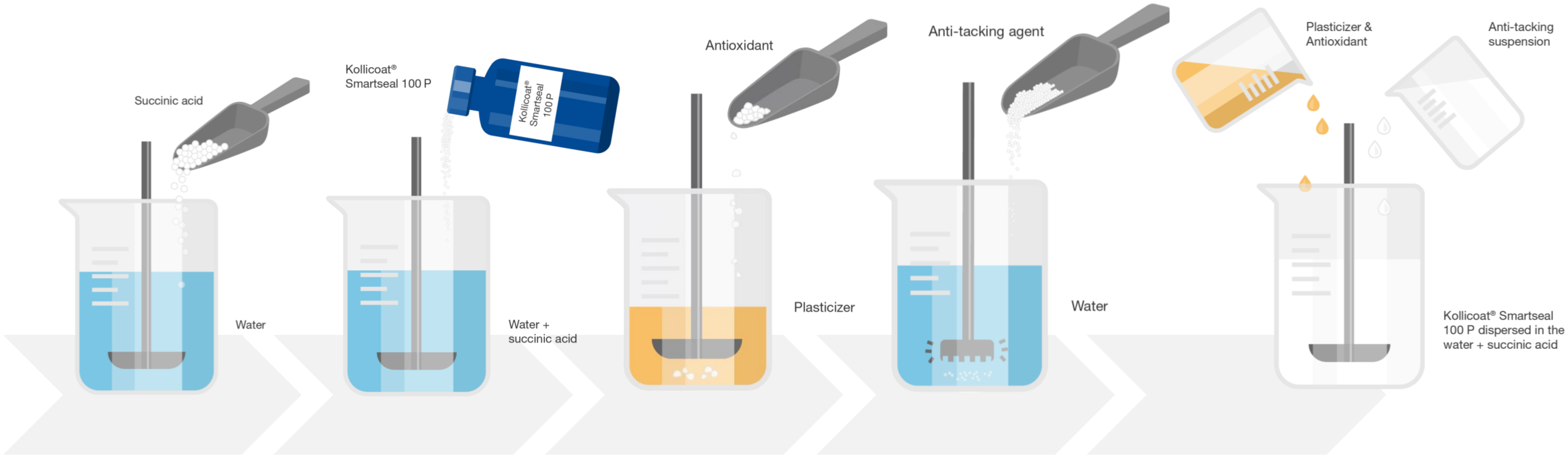
Application guide Kollicoat® Smartseal:

Ingredient	Concentration	Recommended
Plasticizer	10-15 %*	ATBS, DBS, or TPGS
Antioxidant, if required	2.5%*	BHT
Anti-tacking	0 – 40% based on total film mass	Talc or GMS II + PS 80
Colorants	0 – 10% based on total film mass	Avoid the use of colorants
Solvent: Water – K. Smartseal 30 DP Water – K. Smartseal 100P Acetone – K. Smartseal 100P	 q.s. 20 % solid content q.s. 20 % solid content q.s. 10 % solid content	 Water only Pre-neutralize with 2.5%* of succinic acid Also possible acetone + isopropanol (1:1)

*related to dry polymer weight

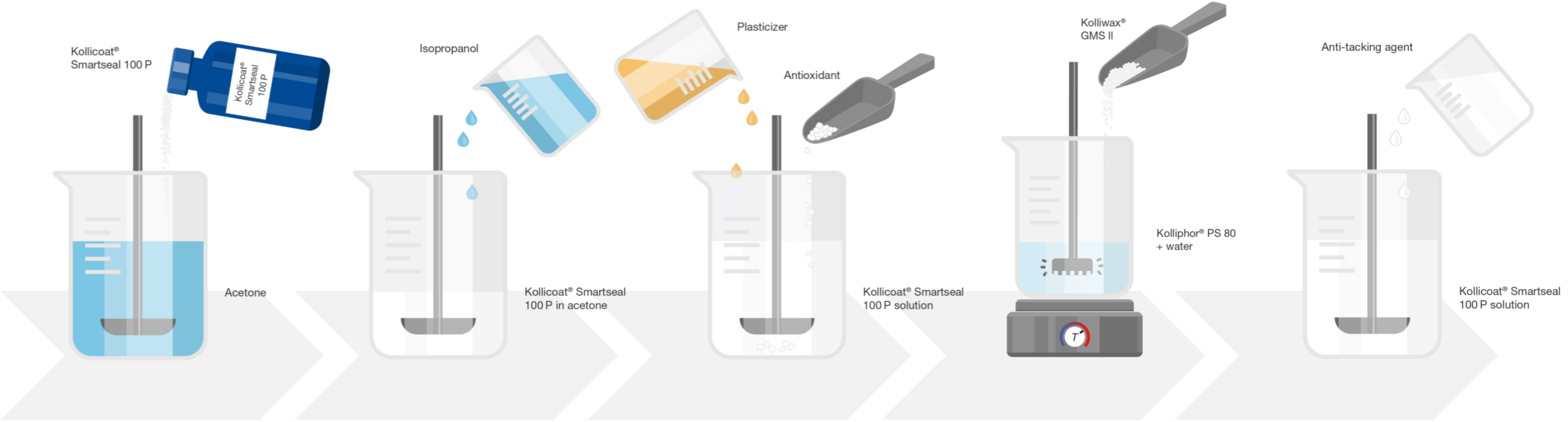
Application guide Kollicoat® Smartseal 30 D:

Application guide Kollicoat® Smartseal 100 P: Aqueous coating



Antioxidant, if required

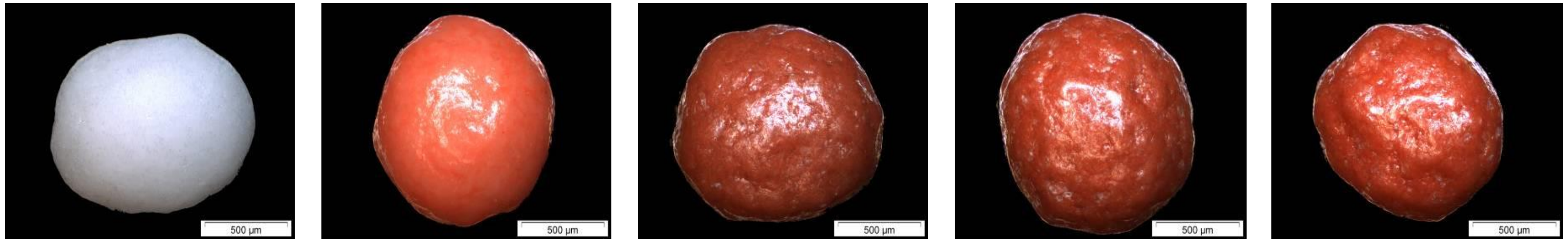
Application guide Kollicoat® Smartseal 100 P: Organic coating



Antioxidant, if required

Kollicoat® Smartseal: Summary

- The first protective polymer dispersion / new excipient
- Efficient taste-masking
- Easy-processing
- Highly suitable for coating of particles, pellets and (mini)-tablets
- Great option for taste-masking of ODT‘s formulations
- Safe to be used in oral dosage forms (vide Safety Summary)



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BASF Coating Polymers - Enteric Release

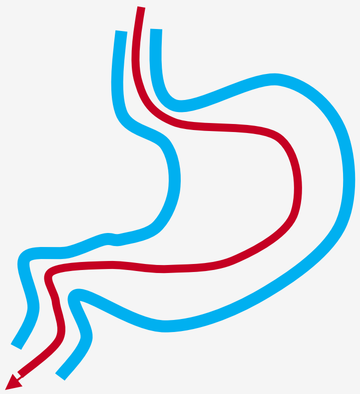
Instant Release
(pH independent)

Gastric Release
(pH triggered)

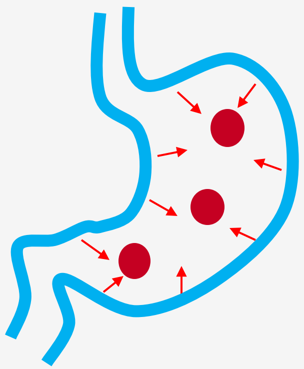
Enteric Release
(pH triggered)

Sustained Release
(pH independent)

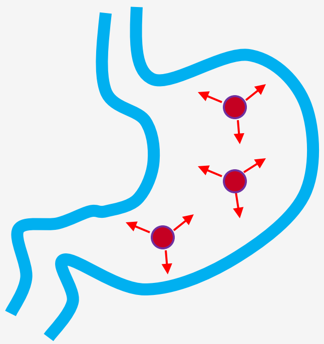
Desired functionality of an enteric coating



Gastro-
intestinal targeting



Protection of
gastro-sensitive
APIs



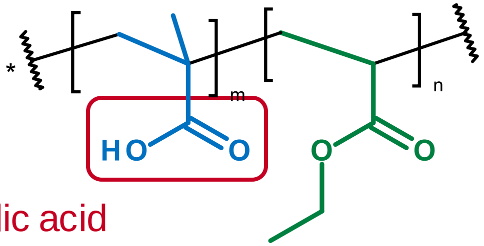
Protection of
gastric mucosa
from APIs

- Enteric Coatings must prevent any contact between the API and gastric juice

Enteric Coating: Kollicoat® MAE: Working principle

MAE: Methacrylic Acid Ethyl acrylate (1:1) copolymer

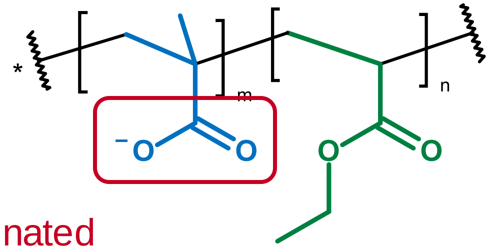
Methacrylic Acid **Ethyl acrylate**



Carboxylic acid
functional group

pH < 5.5

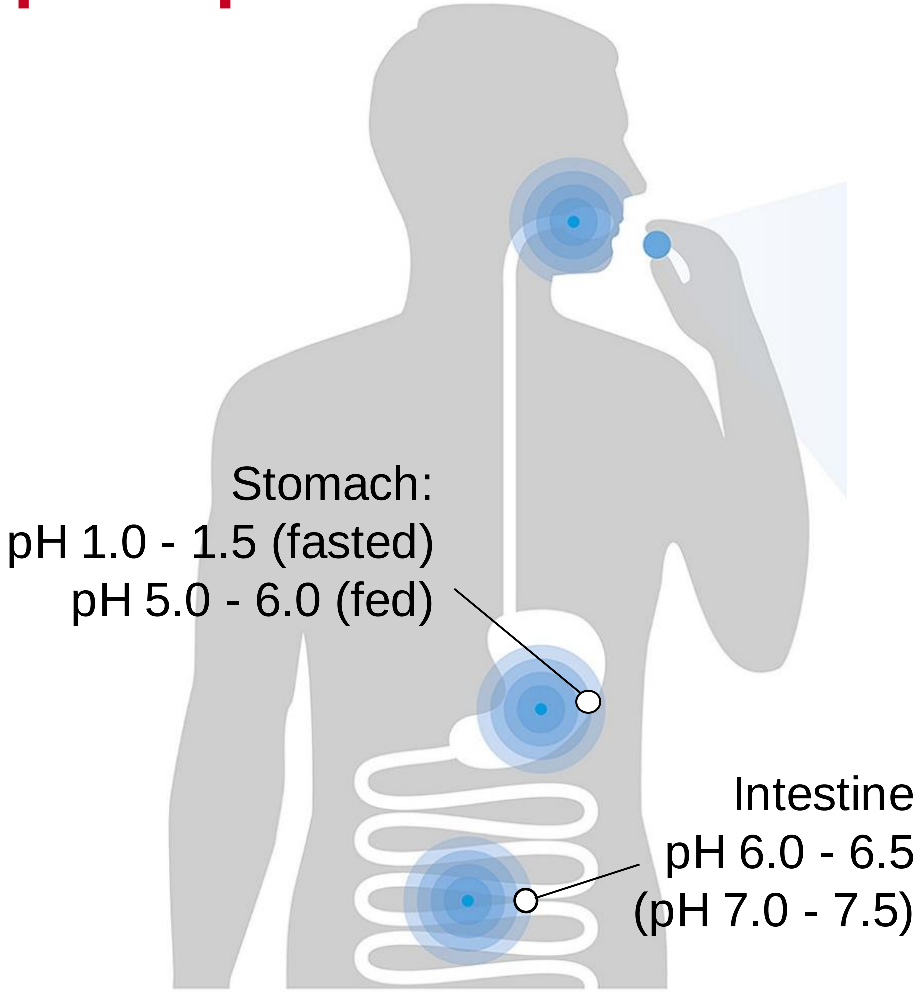
Insoluble
in the gastric juice
⇒ Protection



Deprotonated
carboxylic acid

pH > 5.5

Readily soluble
in the intestine
⇒ Instant Release



- Kollicoat® MAE has an opening pH of 5.5

Kollicoat® MAE is available as:

Polymer Dispersion

Kollicoat® MAE 30 DP

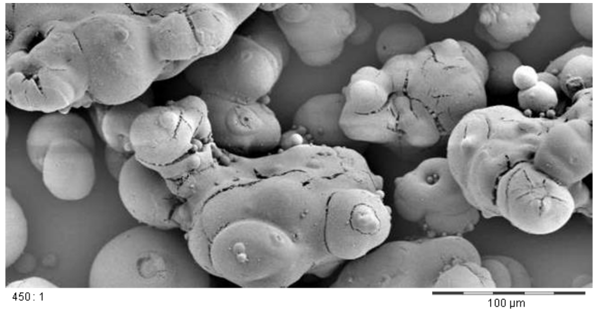
- For aqueous coating only
- Ready-to-coat (requires plasticizer)

Polymer Powder

Kollicoat® MAE 100-55

Kollicoat® MAE 100-55 Fine

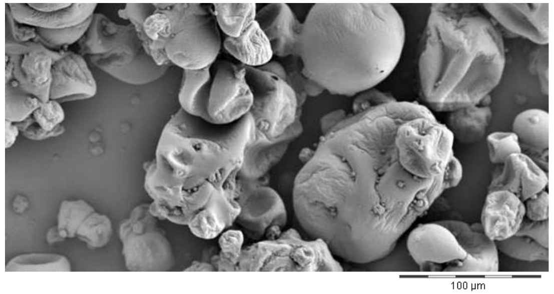
- For aqueous & organic coating
- Redispersion into water requires neutralization step (NaOH handling)



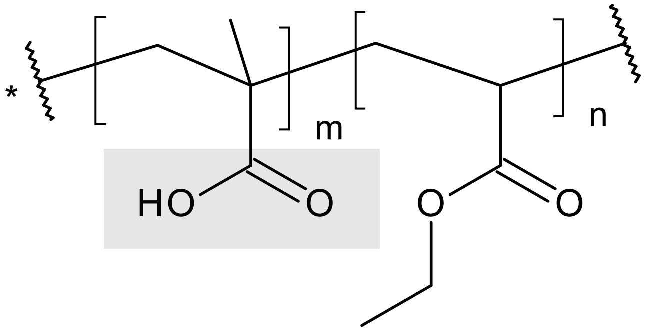
Pre-neutralized Powder

Kollicoat® MAE 100 P

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



Production of Kollicoat® MAE grades



Methacrylic Acid **Ethyl acrylate**

Polymerization

0.7% polysorbate 80
2.3% SLS

Kollicoat® MAE 30 DP

Ph. Eur.: Methacrylic Acid – Ethyl Acrylate copolymer (1:1) dispersion 30 per cent

USP/NF: Methacrylic Acid Copolymer Dispersion

NaOH
(6% to acid)

Spray agglomeration

Kollicoat® MAE 100 P

Ph. Eur.: Methacrylic Acid – Ethyl Acrylate copolymer (1:1), Type B

USP-NF: Partially-Neutralized Methacrylic Acid and Ethyl Acrylate copolymer

Kollicoat® MAE 100-55
Kollicoat® MAE 100-55 Fine

Ph.Eur.: Methacrylic Acid - Ethyl Acrylate Copolymer (1:1) Type A

USP/NF: Methacrylic Acid and Ethyl Acrylate Copolymer NF

- Kollicoat® MAE is available as aqueous polymer dispersion (Kollicoat® MAE 30 DP) or as three different powdery grades (Kollicoat® MAE 100-55, 100-55 Fine and 100 P)

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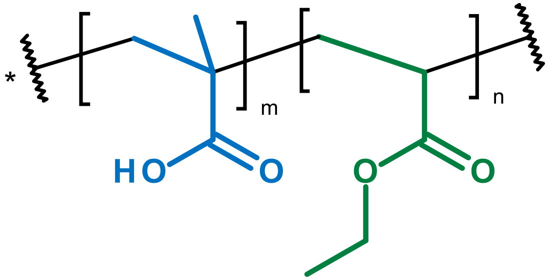
Kollicoat® MAE application guide



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

Look out!

- **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.

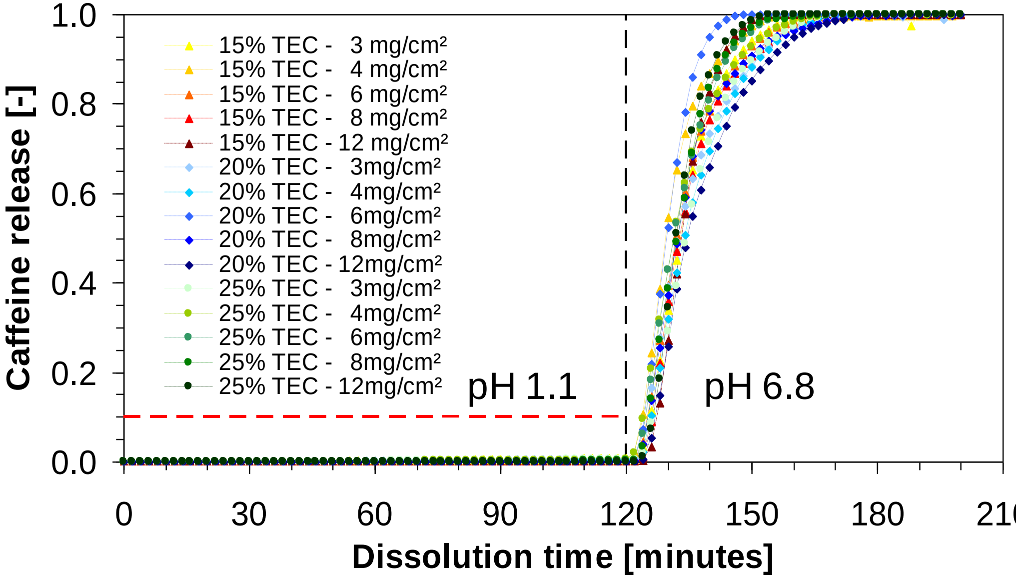
- Kollicoat® MAE grades always need a plasticizer to maintain flexibility in the dry state!

Kollicoat® MAE application guide: Plasticizer

10 % triethyl citrate (TEC)
insufficient plasticizer ⇒ **brittle film** leading to cracking

15 - 25 % related to polymer weight
Recommended ⇒ **triethyl citrate (TEC)**
MUPS requires more plasticizer (↑ film flexibility) ⇒ **20-25%***

* Including more plasticizer to the formulation might require the addition of an anti-tacking agent



Required functionality in the range of 15 to 25% of TEC

- **15 -25% plasticizer are recommended** to ensure flexible films.

Triacetin (Kollisolv® GTA), triethyl citrate, acetyl triethyl citrate, PG (Kollisolv® PG) and PEG (Kollisolv® PEG)

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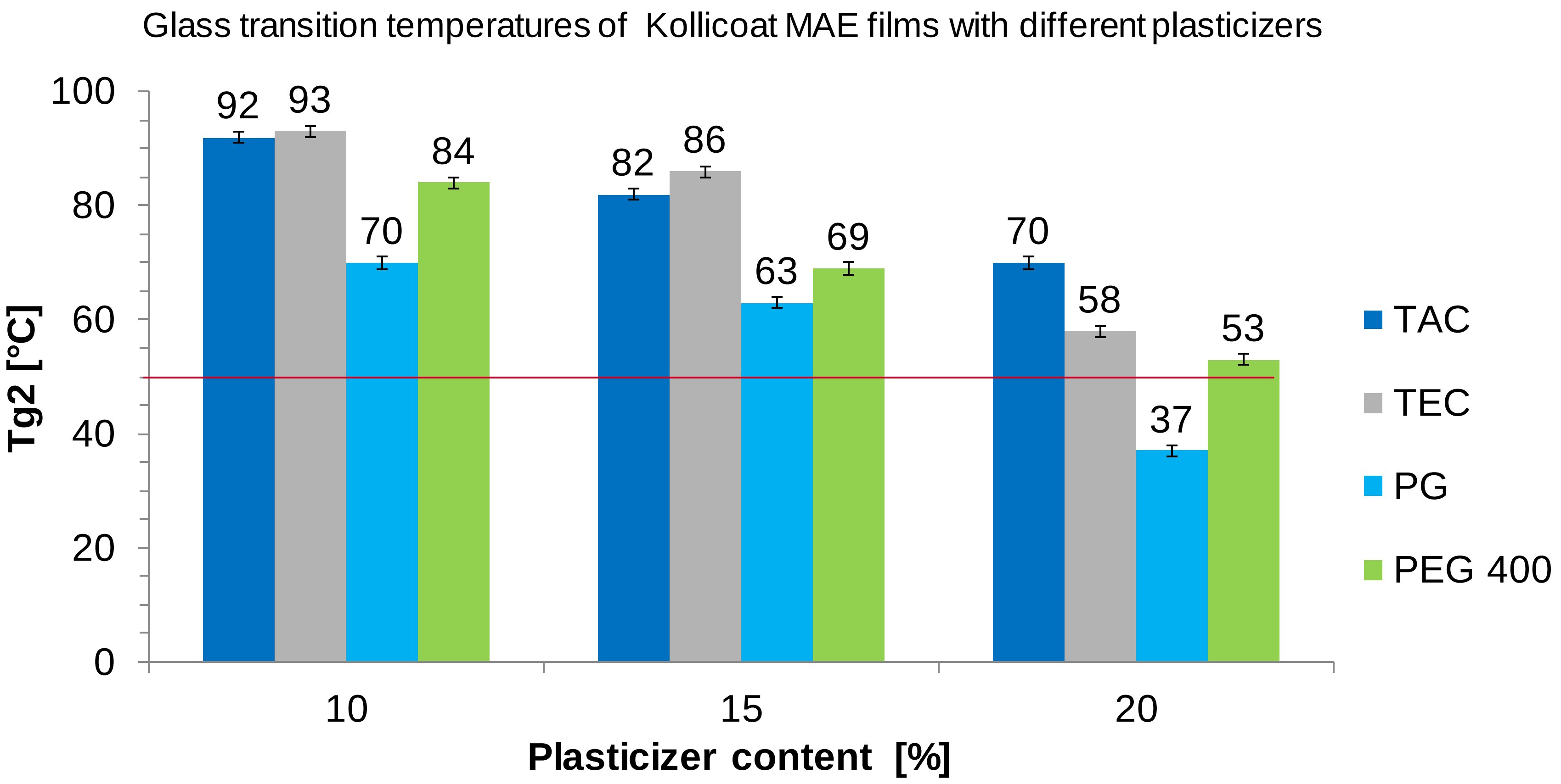
Application Guide: Plasticizer



Tg Kollicoat® MAE:
- MAE 30 D*: 119 ± 2 °C
- MAE 100 P: 114 °C

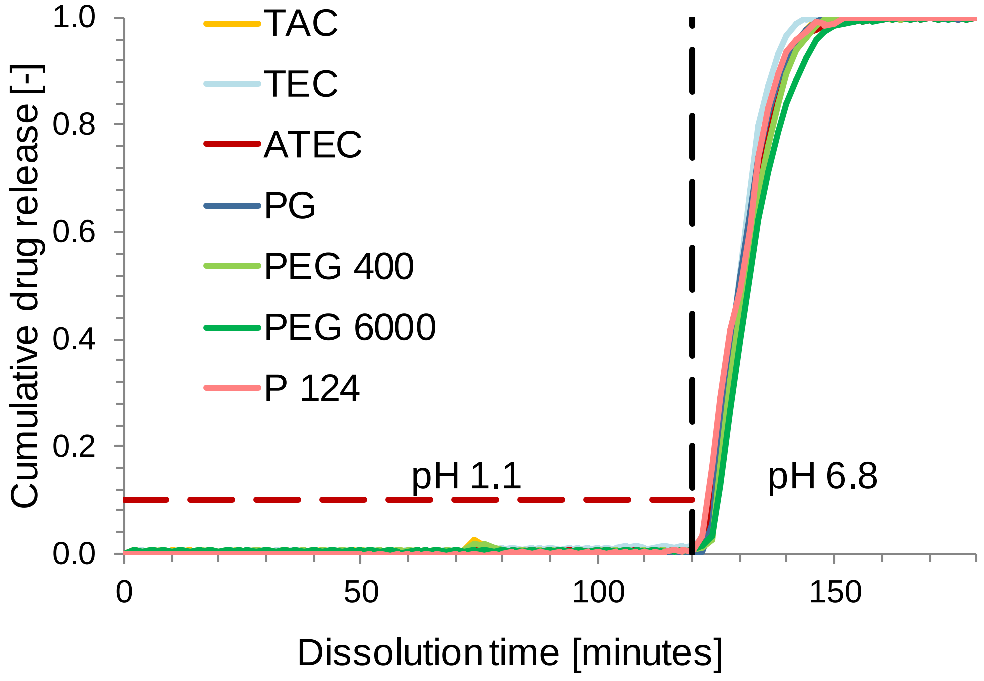
* dry film

T_g measuring
75 – 100 µm isolated polymer films
DSC Q2000 V24.4 Build 116
Sample 8 – 9 mg
fast cooling from 150°C
Heating: 20 K/min

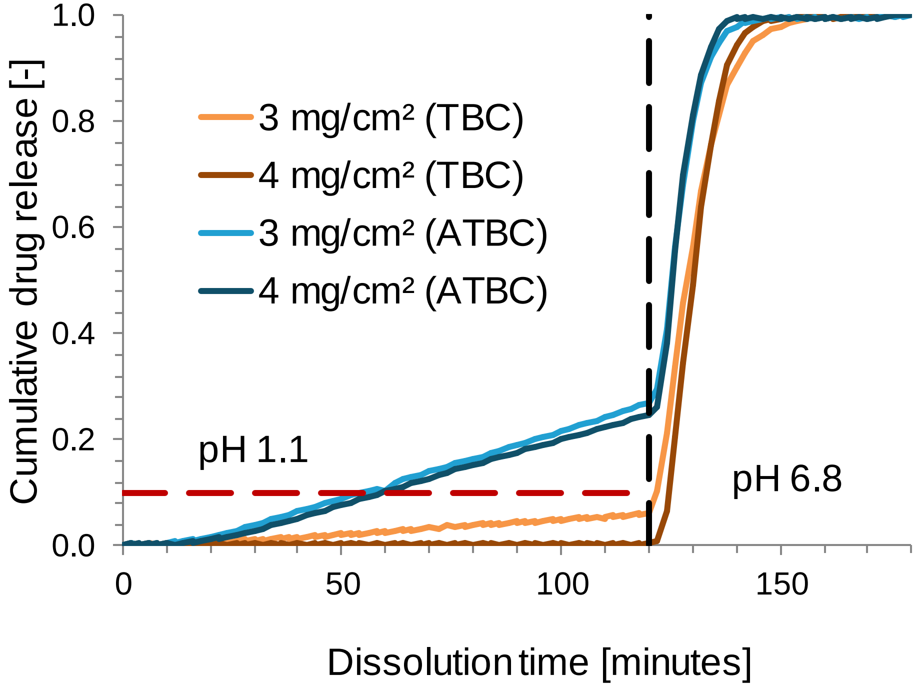
- The higher the amount of plasticizer the lower the Tg.
- To reduce tackiness, a Tg above 50 °C is recommend.

Kollicoat® MAE application guide: Plasticizer

Dissolution of caffeine tablets (15% hydrophilic plasticiser, 3 mg /cm²)



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.

Application and functionality of different grades of Kollicoat® MAE

- The aim of this study was to compare three Kollicoat® MAE grades regarding their individual functionality.
- Polymers tested: Kollicoat® MAE 30 DP, Kollicoat® MAE 100-55, Kollicoat® MAE 100P

Plasticizer content (fixed plasticizer)	Plasticizer (15% fixed content*)	Anti-tacking agent	Grade of pre-neutralisation**
• Triethyl citrate (TEC) • Concentration: 10, 15, 20%*	• Polyethylene glycol 400 (PEG 400) • Triethyl citrate (TEC) • Acetyl triethyl citrate (ATEC)	• Talc • Glycerol mono-stearate II + Polysorbate 80 (GMS II + PS 80) • Stearic acid + Polysorbate 80 (SA + PS 80)	Tested only for the Kollicoat® MAE100-55 • 4 mol% • 6 mol% • 8 mol%

**based on polymer*

***pre-neutralization agent: NaOH*

Materials and methods: Tablets formulation

Excipient	Content
Caffeine, gran. 0.2 – 0.5	15.5%
Ludipress® LCE	74.0%
Kollidon® VA 64 Fine	5.0%
Kollidon® CL-F	5.0%
Mg-stearate	0.5%

Tablet characterisation	Average (n=20)
Mass	350.0 mg
Height	5.37 mm
Diameter	9.07 mm
Crushing strength	128 N

Sieving

Equipment	Glatt GS 100
Impeller	6
Impeller speed	7000 rpm

Blending

Equipment	RRM 100
Type	tumble blender
Blender speed	17 rpm
Pre-blending	10 min
Final blending	7 min

Tabletting

Equipment	Korsch XL 100
Type	rotary press
Punches	8
Punch shape	round, concave no embossing
Punch diameter	9.0 mm
Filling curve	8 – 14 mm
Impeller speed feeder	12 rpm
Tableting speed	40 rpm
Main comp. force	8 kN

Tablet characterisation

Hardness tester	Sotax HT 100
Software	q-doc 4.00

Characteristics determined (n=20):
mass, height, diameter, crushing strength

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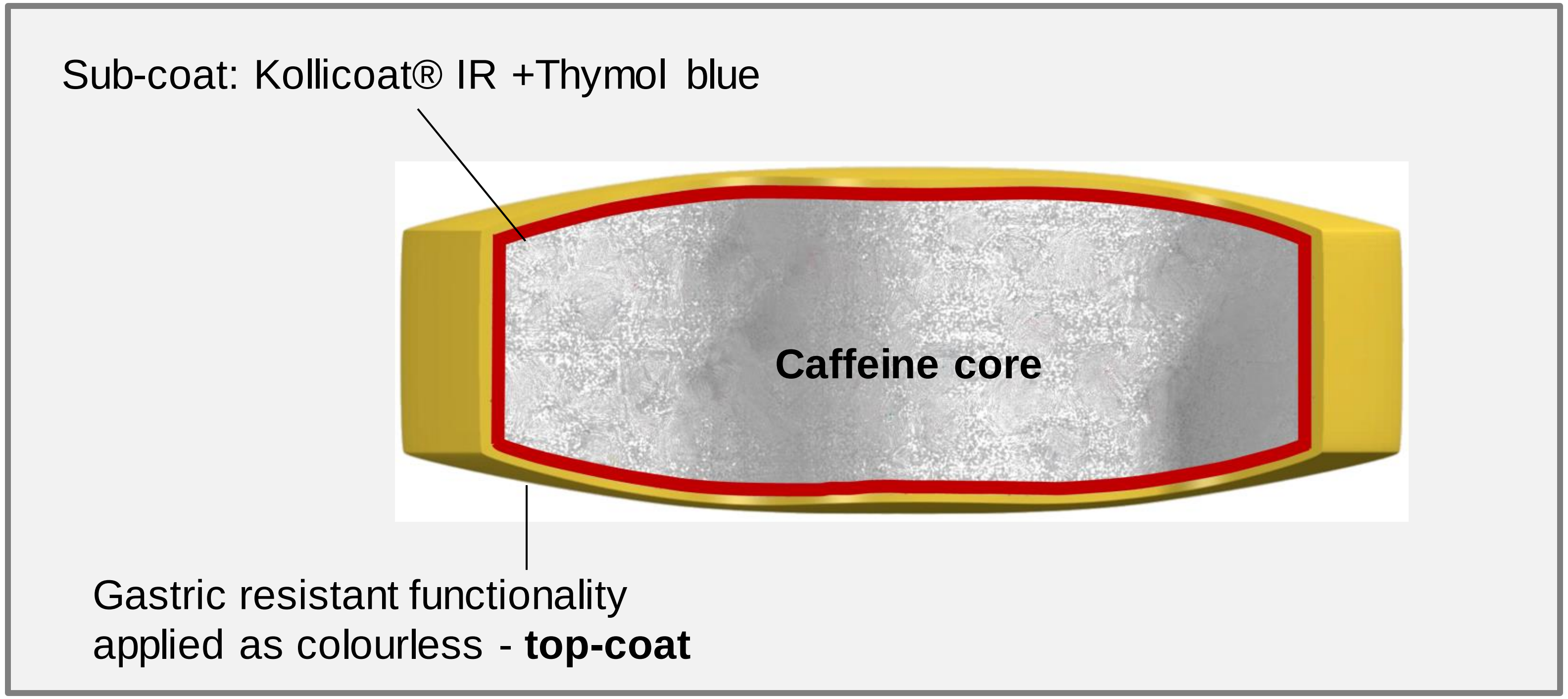
Materials and methods: Film coating



Sub-coat:

- Kollicoat® IR
- Thymol blue

Top-coat (gastric resistant):

- Kollicoat® MAE
- Plasticizer
- Anti-tacking agent (optional)

Materials and methods: Film coating

Substrate

Tablets	Ø=9.0 mm

Coating formulation (sub-coat)

Kollicoat® IR	97.7%
Thymol blue	2.3%
Solid matter content	15.4%

Coater configuration

Equipment	Manesty XL Lab 01
Type	side vented pan coater
Nozzle	OptiCoat
Nozzle orifice	1.2 mm
Drum	Ø=610 mm
Drum speed	6 rpm
Batch size	30.0 kg

Coating parameter

Inlet air quantity	350 m³/h
Inlet air temperature	50°C
Spray rate	30 g/min
Atomisation air pressure	1.2 bar
Pattern air pressure	1.2 bar
Exhaust air temperature	35°C

Substrate

Tablets	Ø=9.0 mm → sub-coated

Coating formulation (top-coat)

Kollicoat® MAE	30 DP, 100-55, 100 P
Plasticizer	PEG 400, TEC, ATEC
Plasticizer content	10, 15, 20%
Incorporation time	2 h
Anti tacking agent:	none, talc, GMS/PS80, SA/PS80
Pre-neutralizing agent	4mol%, 6mol% or 8mol%
Solid matter content	20.0%

Coater configuration

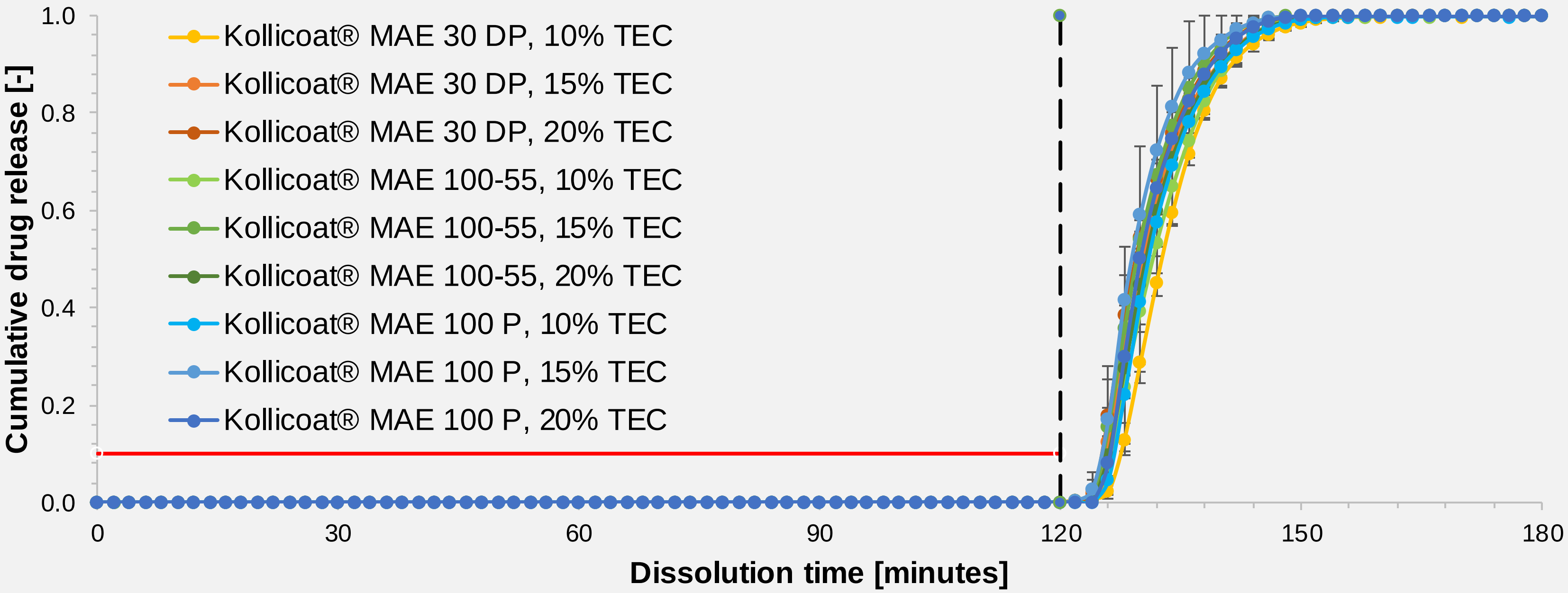
Equipment	Manesty XL Lab 01
Type	side vented pan coater
Nozzle	OptiCoat
Nozzle orifice	0.8 mm
Drum	Ø=406 mm
Drum speed	12 rpm
Batch size	2.0 kg

Coating parameter

Inlet air quantity	350 m³/h
Inlet air temperature	50°C
Product temperature	35°C
Spray rate	13 g/min
Atomisation air pressure	1.0 bar
Pattern air pressure	1.0 bar

Results and discussion – Effect of plasticizer (TEC) content

Dissolution profiles at pH 1.1, all Kollicoat® MAE grades
Plasticizers: triethyl citrate (TEC); content: 10, 15, 20%; coating level: 6 mg/cm²



All Kollicoat® MAE grades performed the same for the 3 levels of plasticizer
No drug release was observed for 2 hours at pH 1.1. After changing to pH 6.8, the API is instantly released.
No impact of plasticizer content could be seen.

Core formulation	
Caffeine, gran. 0.2 – 0.5	15.5%
Ludipress® LCE	74.0%
Kollidon® CL-F	5.0%
Kollidon® VA 64 fine	5.0%
Mg-stearate	0.5%
Coating formulation	
Kollicoat® MAE	
Plasticizer	TEC
Plasticizer content	10, 15, 20%
Coating parameters	
Coater	Manesty XL Lab 01
Type	side vented pan coater
Drum size	Ø=406 mm
Drum speed	13 rpm
Nozzle	OptiCoat
Nozzle orifice	0.8 mm
Batch size	2.0 kg
Inlet air temperature	50°C
Product temperature	35°C
Inlet air quantity	350 m³/h
Spray rate	13.0 g/min
Dissolution test	
Equipment	ERWEKA USP Dissolution Apparatus 2 - Paddle
Paddle speed	50 rpm
Temperature	37°C ±0.5 K
Medium	
pH 1.1	0.08 mol/L HCl
pH 6.8	phosphate buffer
Value	mean (n=3), ±SD

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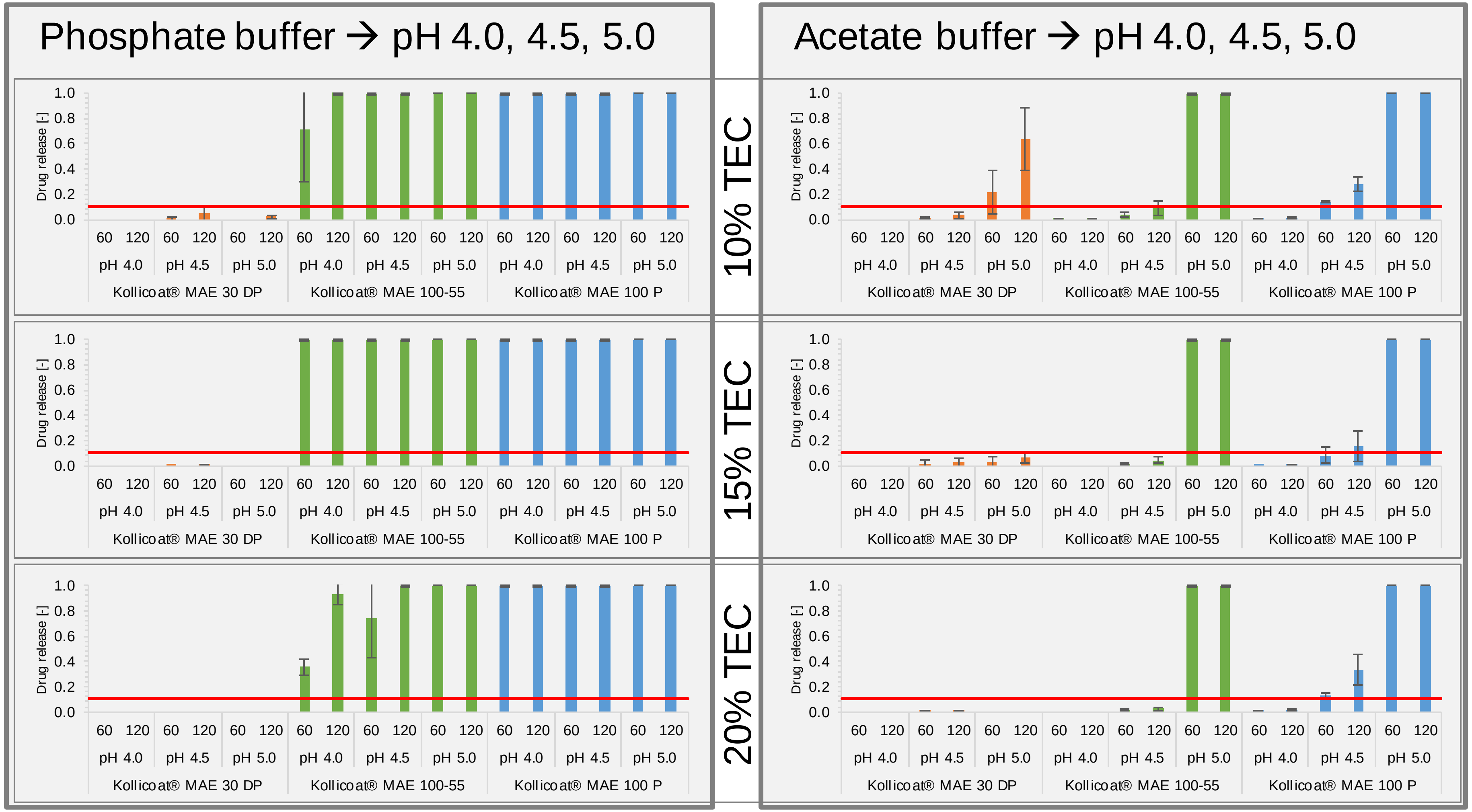
Results and discussion – Effect of plasticizer (TEC) content

Plasticizer (TEC) content: 10, 15, 20%. Dissolution test: intermediate pH-values, coating level: 6 mg/cm²



- Kollicoat® MAE grades performed distinctively at intermediate pH-values and buffer systems:
- Kollicoat® MAE 30 DP was less susceptible to fail.
- Partly pre-neutralisation of the polymer reduced film functionality.
- TEC amount had low influence in the drug release (film functionality) at intermediate pH-values, except for the K. MAE 30 DP

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Summary: Effect of plasticizer (TEC) content

- Independent of the plasticizer concentration, all three Kollicoat® MAE grades provided excellent gastric resistant functionality at pH 1.1 (fasted state) and immediate drug liberation at pH 6.8.

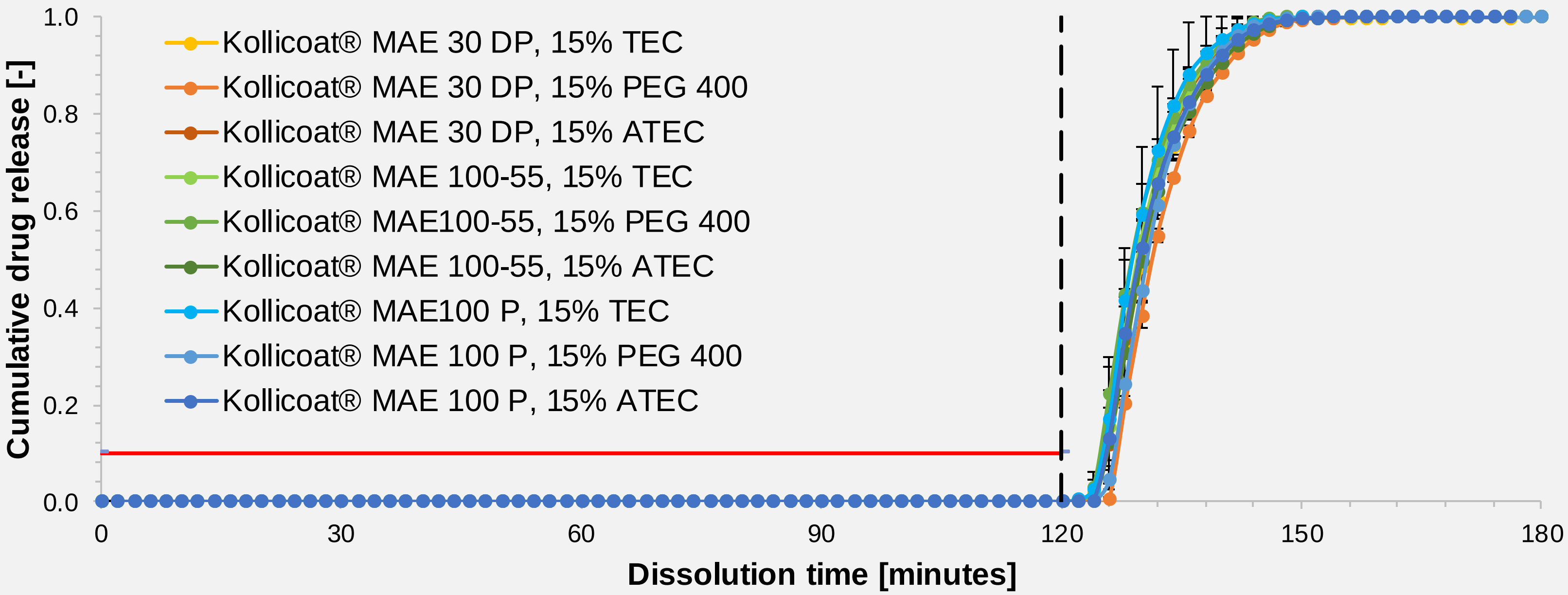
- The performance at intermediated pH-values (fed state) depended on:
    - The buffer system employed for the test (phosphate or acetate buffer).
    - The potential partly pre-neutralisation of the functional polymer groups.

- Since, the two powdery Kollicoat® MAE grades require partly pre-neutralisation for redispersion, their performance at intermediate pH-values was deficient.

- The plasticizer content affected the performance of Kollicoat® MAE 30 DP at intermediate pH-values; performance seems to improve with increasing plasticizer contents.

Results and discussion – Effect of type of plasticizer

Dissolution profiles at pH 1.1, all Kollicoat® MAE grades
Plasticizers: TEC, PEG 400, ATEC; content: 15%; coating level: 6 mg/cm²



Independent of the plasticizer used, all Kollicoat® MAE grades performed the same in artificial gastric juice (fasted state).
No drug release was observed for 2 hours.
After changing to pH 6.8, the API is instantly liberated.

Core formulation	
Caffeine, gran. 0.2 – 0.5	15.5%
Ludipress® LCE	74.0%
Kollidon® CL-F	5.0%
Kollidon® VA 64 fine	5.0%
Mg-stearate	0.5%
Coating formulation	
Kollicoat® MAE	
Plasticizer	TEC, PEG 400, ATEC
Plasticizer content	15%
Coating parameters	
Coater	Manesty XL Lab 01
Type	side vented pan coater
Drum size	Ø=406 mm
Drum speed	13 rpm
Nozzle	OptiCoat
Nozzle orifice	0.8 mm
Batch size	2.0 kg
Inlet air temperature	50°C
Product temperature	35°C
Inlet air quantity	350 m³/h
Spray rate	13.0 g/min
Dissolution test	
Equipment	ERWEKA
	USP Dissolution Apparatus 2 - Paddle
Paddle speed	50 rpm
Temperature	37°C ±0.5 K
Medium	
pH 1.1	0.08 mol/L HCl
pH 6.8	phosphate buffer
Value	mean (n=3), ±SD

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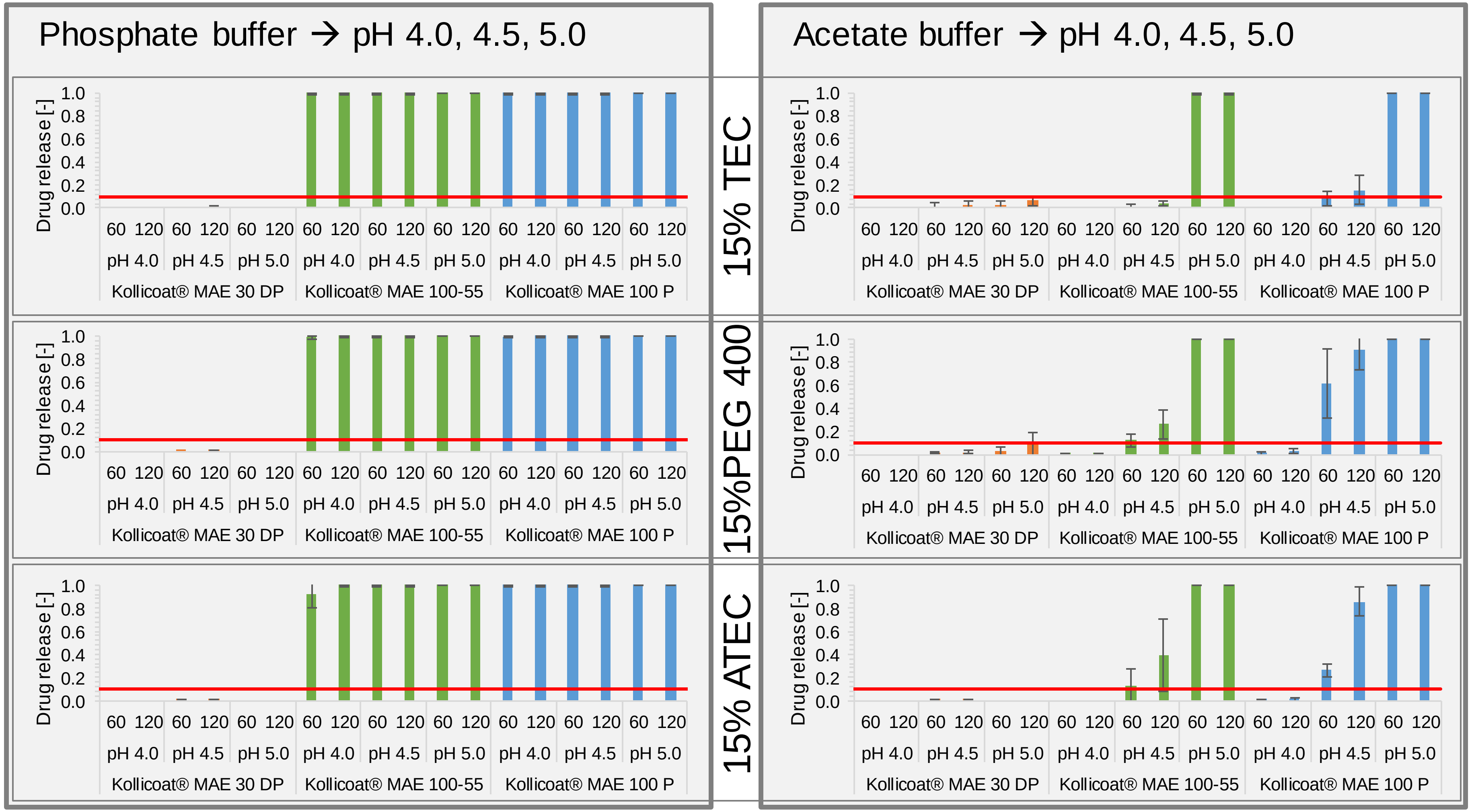
Results and discussion – Effect of type of plasticizer

Plasticizer selection, content: 15%; Dissolution test: intermediate pH-values, coating level: 6 mg/cm²



- Kollicoat® MAE grades performed distinctively at intermediate pH-values and buffer systems:
- Kollicoat® MAE 30 DP was less susceptible to fail.
- Partly pre-neutralisation of the polymer reduced film functionality;
- TEC led to a slightly better functionality for the Kollicoat® MAE powder grade.

Summary: Effect of type of plasticizer

- Independent of the plasticizer used, all three Kollicoat® MAE grades provided excellent gastric resistant functionality at pH 1.1 (fasted state) and immediate drug liberation at pH 6.8.

- The performance at intermediated pH-values (fed state) depended on:

    - The buffer system employed for the test (phosphate or acetate buffer).

    - The potential partly pre-neutralisation of the functional polymer groups.

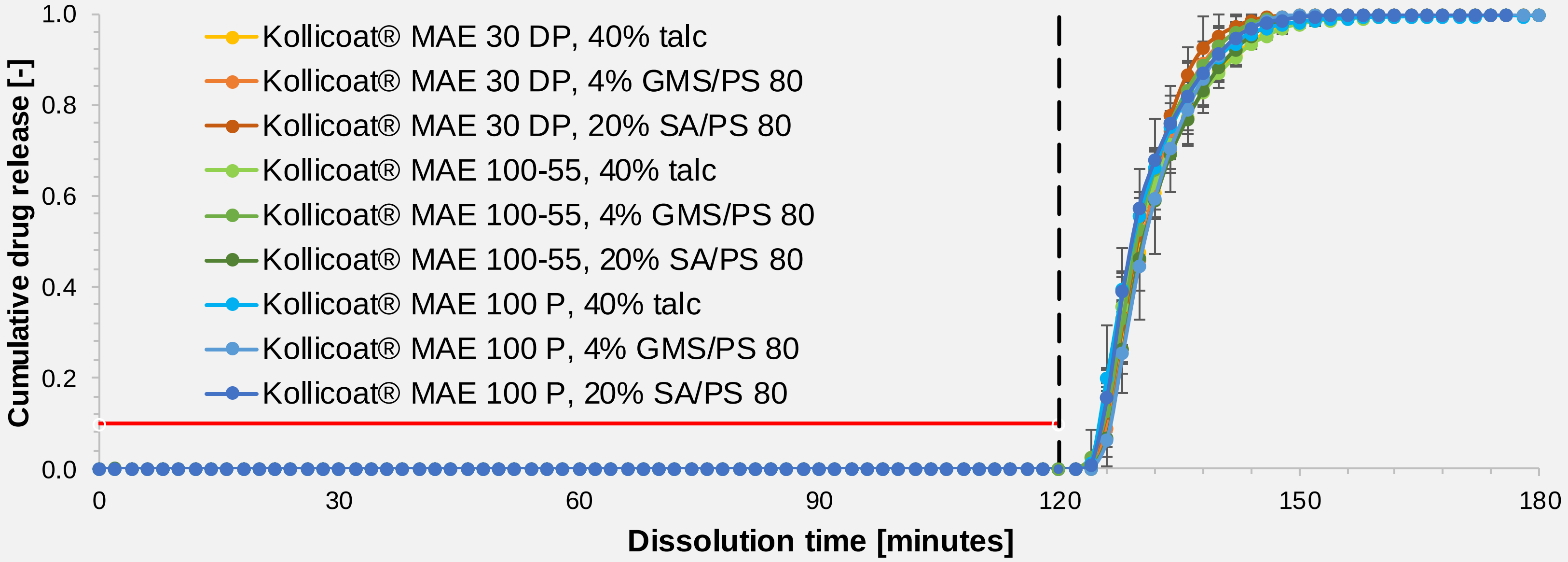
- Since, the two powdery Kollicoat® MAE grades require partly pre-neutralisation for redispersion, their performance at intermediate pH-values was poorer.

- Independent of the plasticizer, performance of Kollicoat® MAE 30 DP was excellent at all intermediate pH-values.

- In regard to the redispersed powdery grades, the plasticizer TEC provided a slightly better functionality.

Results and discussion – Effect of anti-tacking agent

Dissolution profiles at pH 1.1, all Kollicoat® MAE grades; Anti-tacking agents, plasticizer: TEC; content: 15%, coating level: 6 mg/cm²



Independent of the anti-tacking agent used, all Kollicoat® MAE grades performed the same in artificial gastric juice (fasted state).
No drug release was observed for 2 hours.
After changing to pH 6.8, the API is instantly liberated.

Core formulation	
Caffeine, gran. 0.2 – 0.5	15.5%
Ludipress® LCE	74.0%
Kollidon® CL-F	5.0%
Kollidon® VA 64 fine	5.0%
Mg-stearate	0.5%
Coating formulation	
Kollicoat® MAE	
Plasticizer	TEC
Plasticizer content	15%
Anti-tacking agent	
Coating parameters	
Coater	Manesty XL Lab 01
Type	side vented pan coater
Drum size	Ø=406 mm
Drum speed	13 rpm
Nozzle	OptiCoat (0.8 mm)
Batch size	2.0 kg
Inlet air temperature	50°C
Product temperature	35°C
Inlet air quantity	350 m³/h
Spray rate	13.0 g/min
Dissolution test	
Equipment	ERWEKA
USP Dissolution	Apparatus 2 - Paddle
Paddle speed	50 rpm
Temperature	37°C ±0.5 K
Medium	
pH 1.1	0.08 mol/L HCl
pH 6.8	phosphate buffer
Value	mean (n=3), ±SD

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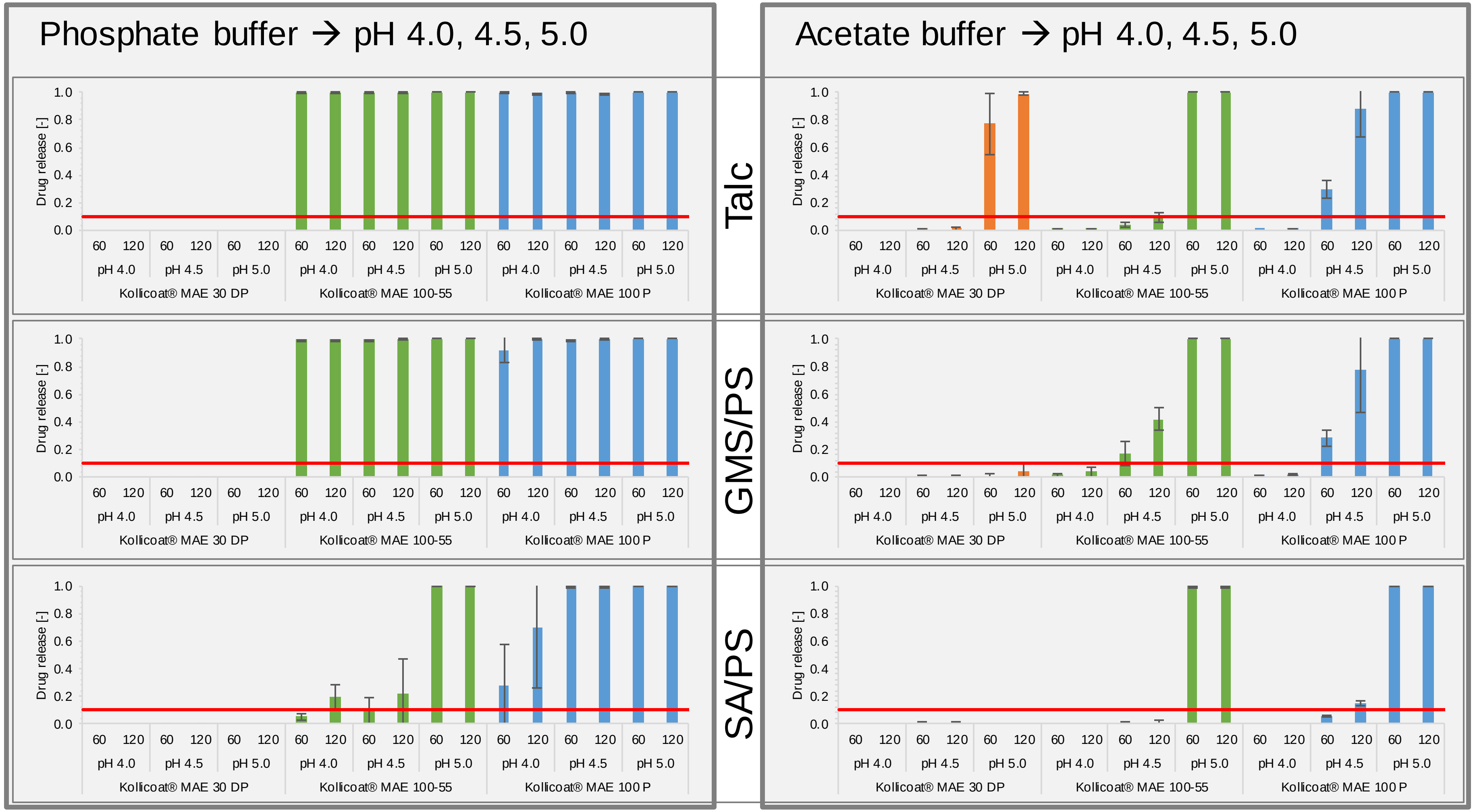
Results and discussion – Effect of anti-tacking agent



- Kollicoat® MAE grades performed distinctively at intermediate pH-values and buffer systems:
- Kollicoat® MAE 30 DP was less susceptible to fail, except for acetate buffer pH 5.0
- Partly pre-neutralisation of the polymer reduced film functionality;
- The film functionality was mostly impacted by the talc, followed by GMS/PS, and SA/PS.

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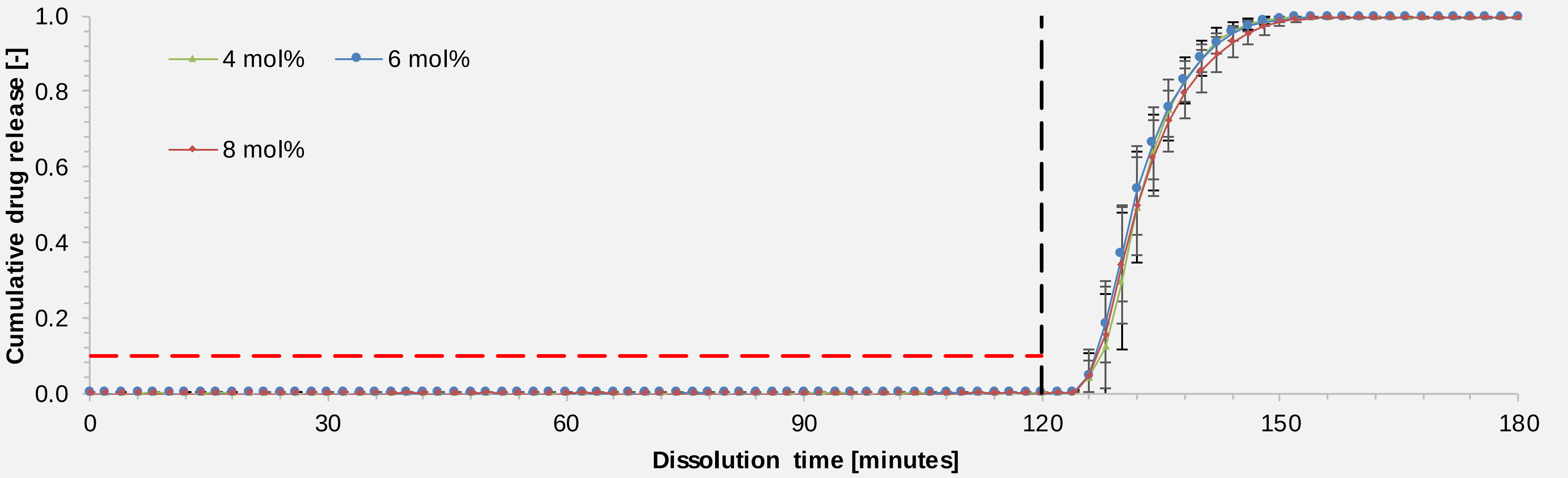
Summary: Effect of anti-tacking agents

- Independent of the anti-tacking agent added, all three Kollicoat® MAE grades provided excellent gastric resistant functionality at pH 1.1 (fasted state) and immediate drug liberation at pH 6.8.
- The performance at intermediated pH-values (fed state) depended on:
  - The buffer system employed for the test (phosphate or acetate buffer).
  - The potential partly pre-neutralisation of the functional polymer groups.
- Since, the two powdery Kollicoat® MAE grades require partly pre-neutralisation for redispersion, their performance at intermediate pH-values was poorer.
- The highly concentrated talc (40%) disturbed the coat to the largest extend resulting generally in the poorest performance.
- At the level of 15% plasticizer content, an anti-tacking agent is not required for the tablet coating process. This can reduce the film disturbance caused by extra components in the film formation. If decided to add an anti-tacking better reduce the amount and find alternatives to talc.

Results and discussion – Grade of pre-neutralization

Dissolution profiles at pH 1.1, Kollicoat® MAE 100-55; Varying pre-neutralization, plasticizer: TEC; content: 15%, coating level: 6 mg/cm²



Independent of the grade of pre-neutralisation, the 3 Kollicoat® MAE 100-55 formulations performed the same in artificial gastric juice (fasted state).
No drug release was observed for 2 hours.
After changing to pH 6.8, the API is instantly liberated.

Core formulation	
Caffeine, gran. 0.2 – 0.5	15.5%
Ludipress® LCE	74.0%
Kollidon® CL-F	5.0%
Kollidon® VA 64 fine	5.0%
Mg-stearate	0.5%
Coating formulation	
Kollicoat® MAE 100-55	
Plasticizer	TEC
Plasticizer content	15%
Pre-neutralizing agent	4, 6 or 8 mol%
Coating parameters	
Coater	Manesty XL Lab 01
Type	side vented pan coater
Drum size	Ø=406 mm
Drum speed	13 rpm
Nozzle	OptiCoat (0.8 mm)
Batch size	2.0 kg
Inlet air temperature	50°C
Product temperature	35°C
Inlet air quantity	350 m³/h
Spray rate	13.0 g/min
Dissolution test	
Equipment	ERWEKA
	USP Dissolution Apparatus 2 - Paddle
Paddle speed	50 rpm
Temperature	37°C ±0.5 K
Medium	
pH 1.1	0.08 mol/L HCl
pH 6.8	phosphate buffer
Value	mean (n=3), ±SD

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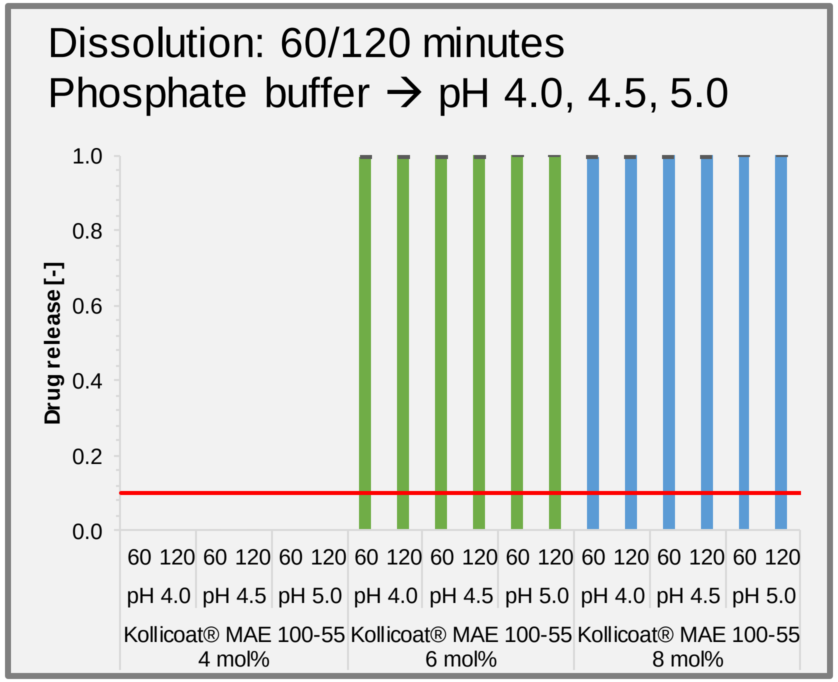
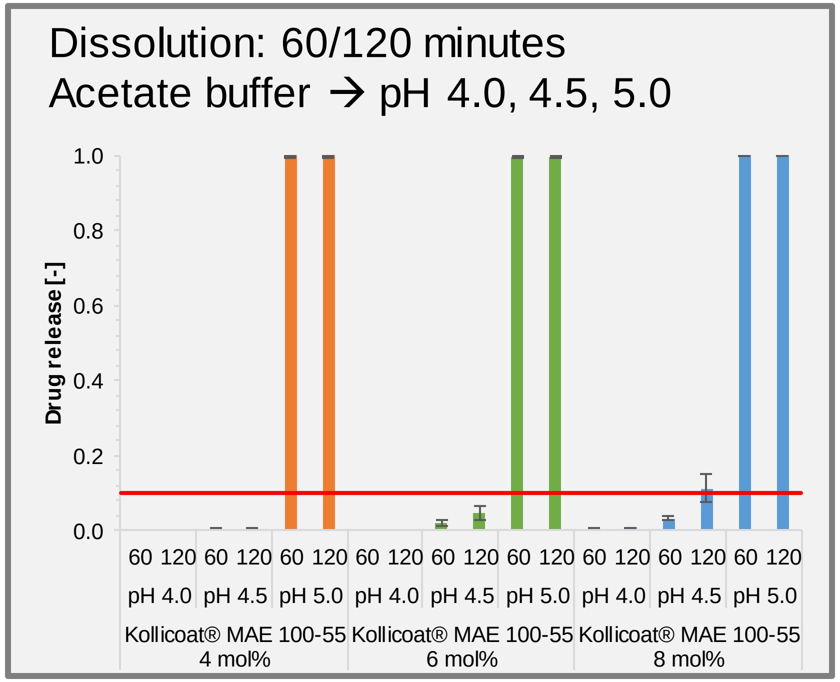
Results and discussion – Grade of pre-neutralization

Dissolution test: intermediate pH-values, coating level: 6 mg/cm²





- The grade of pre-neutralisation affects the functionality of the polymer.
- In phosphate buffer, the formulation pre-neutralised with 4 mol% provided the expected functionality at all intermediate pH-values tested.
- The higher the pre-neutralization %mol, the lower is the gastric resistance at intermediate pH-values.

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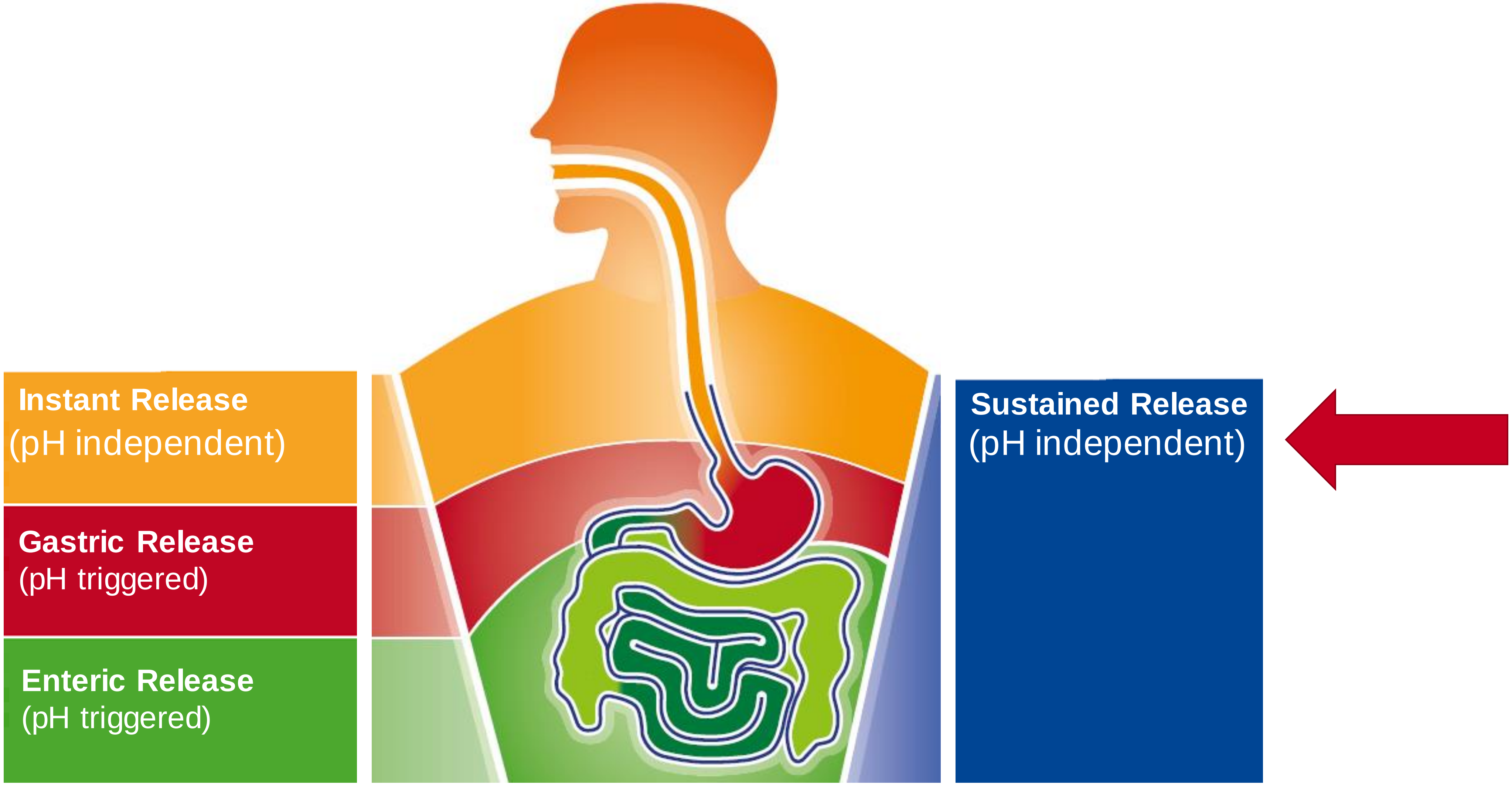
Summary: Grade of pre-neutralisation

- All three pre-neutralization levels provided gastric resistant functionality at pH 1.1 (fasted state) and immediate drug liberation at pH 6.8.
- The performance at intermediated pH-values (fed state) depended on:
    - The buffer system employed for the test (phosphate or acetate buffer).
    - The level of partly pre-neutralisation of the functional polymer groups.
- Since, the powdery Kollicoat® MAE grade 100-55 require partly pre-neutralisation for redispersion, pre-neutralisation is required.
- The lowest possible grade of pre-neutralisation required for the redispersion of Kollicoat® MAE 100-55 should be used.
- Kollicoat® MAE 100-55 should be pre-neutralised with 4 mol%.

Summary and conclusion

- All three Kollicoat® MAE grades provided excellent gastric resistant functionality at pH 1.1 (fasted state) and immediate drug liberation at pH 6.8.
- The performance at intermediated pH-values (fed state) depended on:
  - The buffer system employed for the test (phosphate or acetate buffer).
  - The potential partly pre-neutralisation of the functional polymer groups.
- Plasticizer: Triethyl citrate (TEC), recommended concentration ≥15%
- Anti-tacking agent: better not to use or use the lowest amount as possible
- Recommended anti-tacking: stearic acid + polysorbate 80 or GMS II + polysorbate 80
- Recommended pre-neutralization amount: 4% mol
- Since, the two powdery Kollicoat® MAE grades require partly pre-neutralization for redispersion, their performance at intermediate pH-values was lower compared to the Kollicoat® MAE 30 DP.

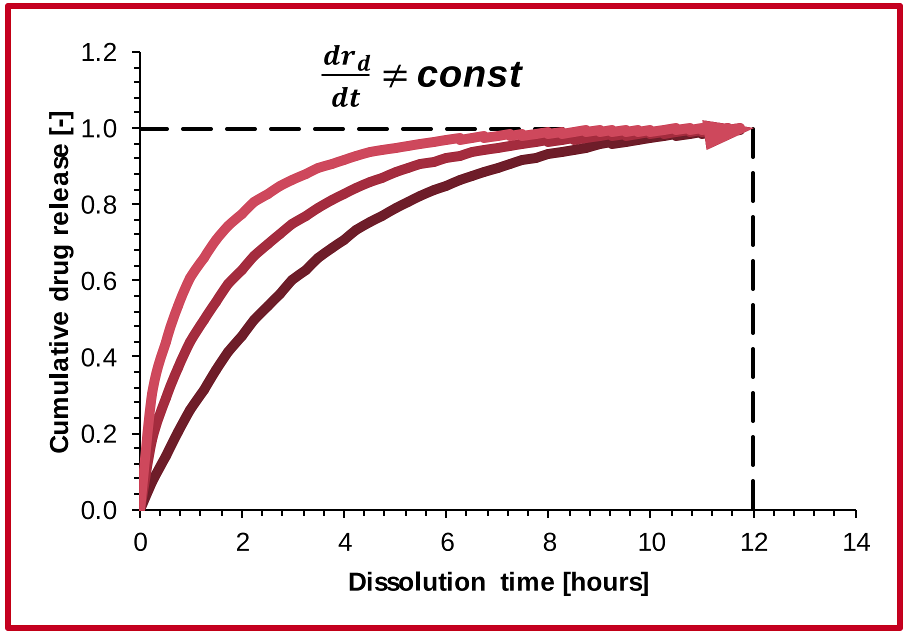
BASF Coating Polymers - Sustained Release



Sustained release dosage forms

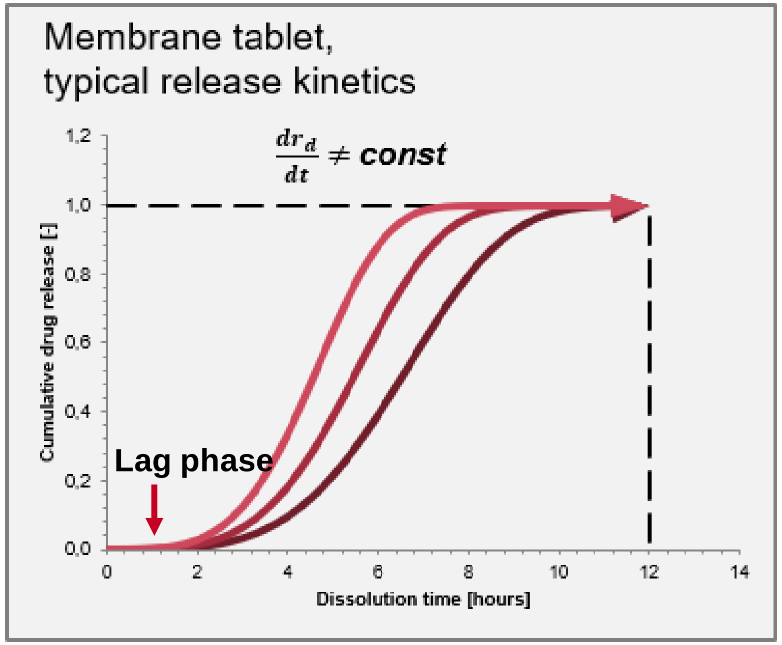
<u>Sustained release dosage forms</u>

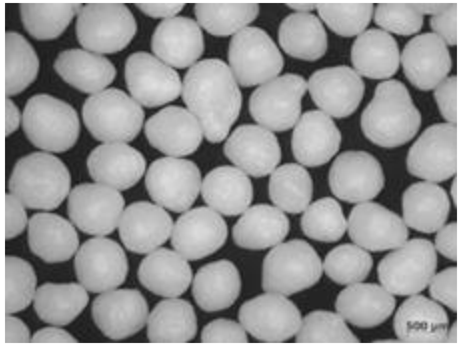
are intended for releasing the active pharmaceutical ingredient (API) with a pre-defined release rate, in order to maintain a constant API concentration for a specific period of time with the human body.



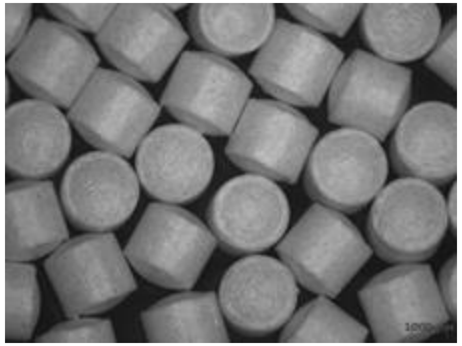
Modified release: Reservoir system

- A reservoir system (core) containing the drug is covered by an insoluble polymeric membrane.
- The core can be a **tablet**, **mini tablet**, a **granule** or a **pellet**.
- The **drug is released by diffusion** through the coating membrane

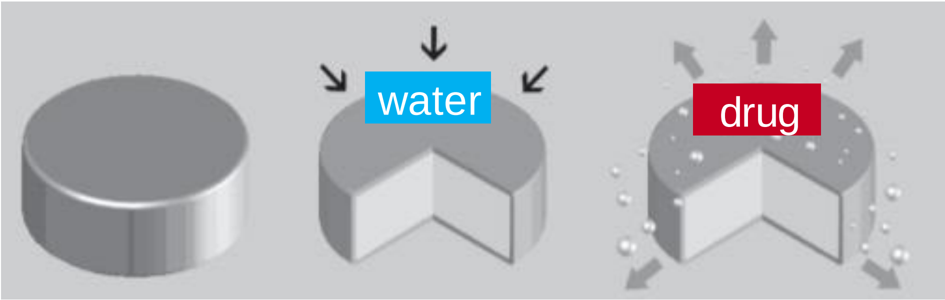




Pellet



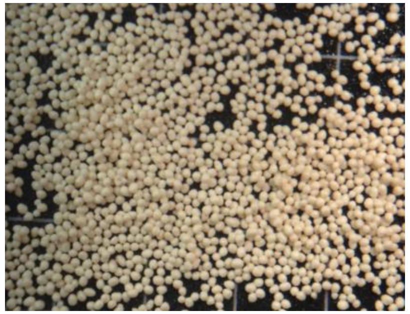
Mini tablet

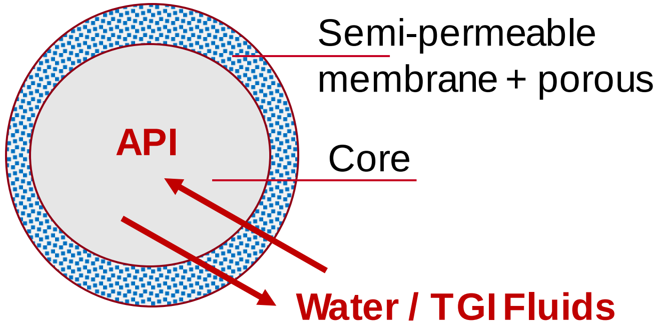


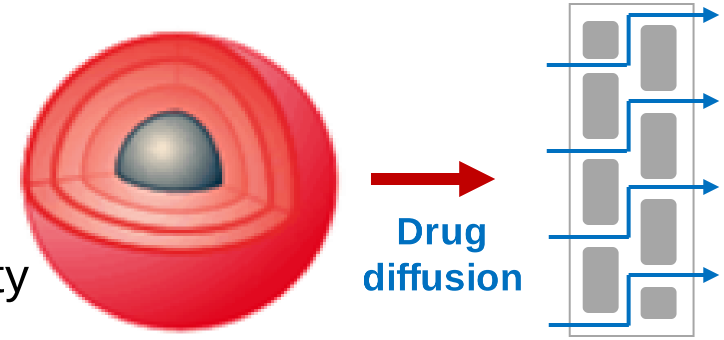
Brazilian Journal of Pharmaceutical Sciences vol. 43, n. 4, out./dez., 2007 (modified)

Reservoir system: Factors that impact drug release

- **Drug:**
  - solubility and concentration
- **Core**
  - monolithic or multiarticulate: size / osmolarity / porosity
  - surface area
  - excipients: osmotic (sugars)/ non-osmotic (MCC)/ impact on the release
- **Membrane**
  - thickness (weight gain)
  - film coating formulation: polymer, plasticizer, additives, etc.
  - porous (type and amount)
  - strength and flexibility: need to resist core expansion (swelling) and compression (granules and pellets to avoid cracking and lack of functionality
  - evaluate, when necessary, dose dumping with alcohol – media w/ 5, 20 and 40% *v/v* EtOH for at least 2h.





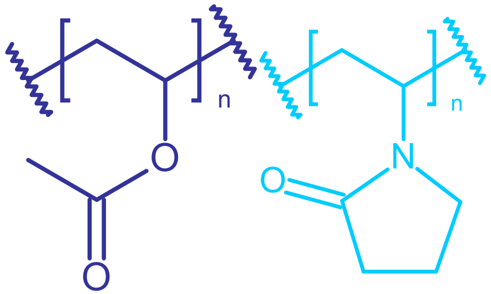


Introducing Kollicoat® SR 30 D

Polymer Dispersion

Kollicoat® SR 30 D

- Polyvinyl acetate dispersion with PVP as pore former
- for aqueous coating
- 30% solid content



PVAc : PVP
10 : 1

Composition of the solid phase:
~ 90 % polyvinyl acetate (PVAc),
~ 9 % Kollidon® 30 (PVP), ~ 1 % SLS

Main properties

- insoluble in aqueous media
- Low MFFT: 18°C
- high plasticity
- excellent film former
- pH-independent release

Monographs:

- Ph. Eur.: “Poly(Vinyl Acetate) Dispersion 30 Per Cent”
- USP/NF: “Polyvinyl Acetate Dispersion”

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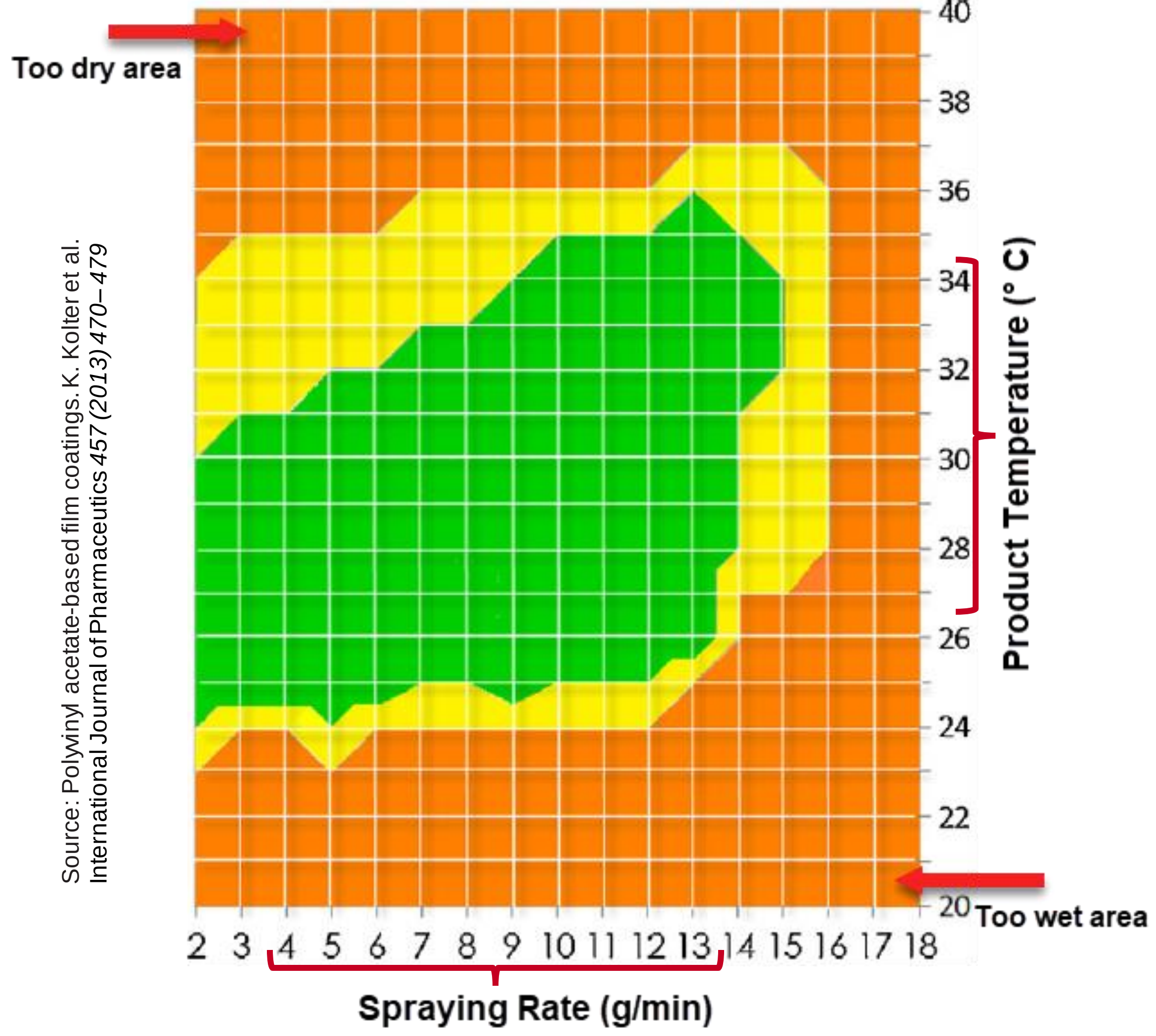
Processability chart for coating with Kollicoat® SR 30 D

Processability chart for pellet coating with Kollicoat® SR 30 D in the fluidized bed coater Glatt GPCG-1



Source: Polyvinyl acetate-based film coatings. K. Kolter et al. International Journal of Pharmaceutics *457 (2013) 470–479*

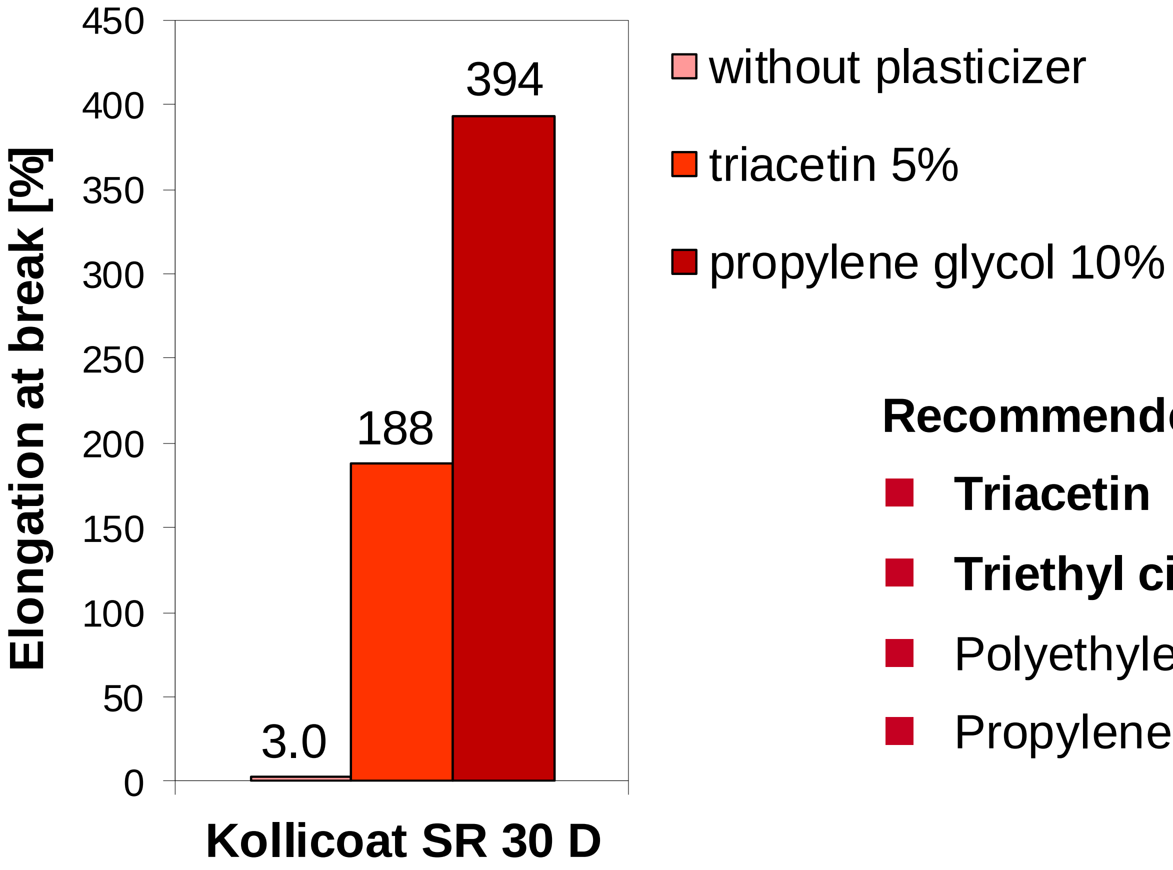
Dispersion	Aqueous dispersion, g	Water, g	TEC, g	Talc, g
Kollicoat® SR 30 D	48	48	1.4	7.2

- Green area: perfect process;
- Yellow area: acceptable process → sticking tendency could be compensated by increased air flow;
- Orange area: process is impossible:
  - too wet → sticking of pellets, or
  - too dry → electrostatic agglomerating of pellets, poor flow, film spray drying

Process considerations:

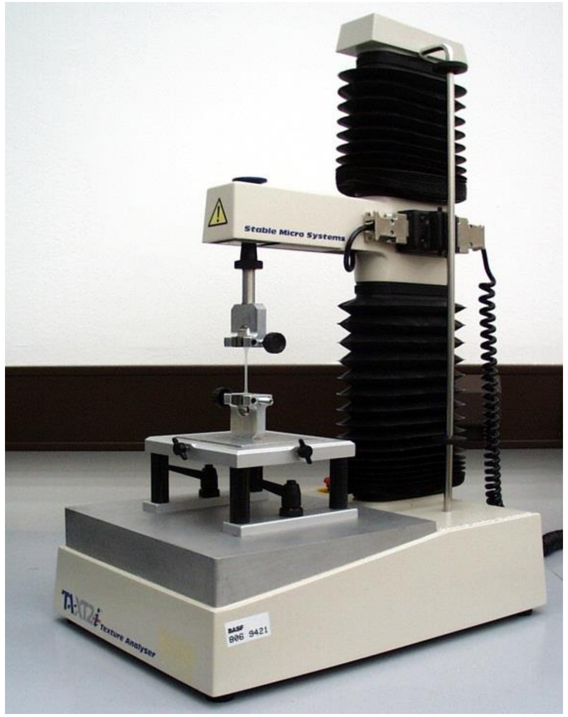
- Low temperature (below 34°C)
- Plasticizer level of 10% and above: bed temp. should be around 30°C.
- Talc reduces stickiness (20 – 40% of total solids)

Elongation at break of Kollicoat® SR 30 D films



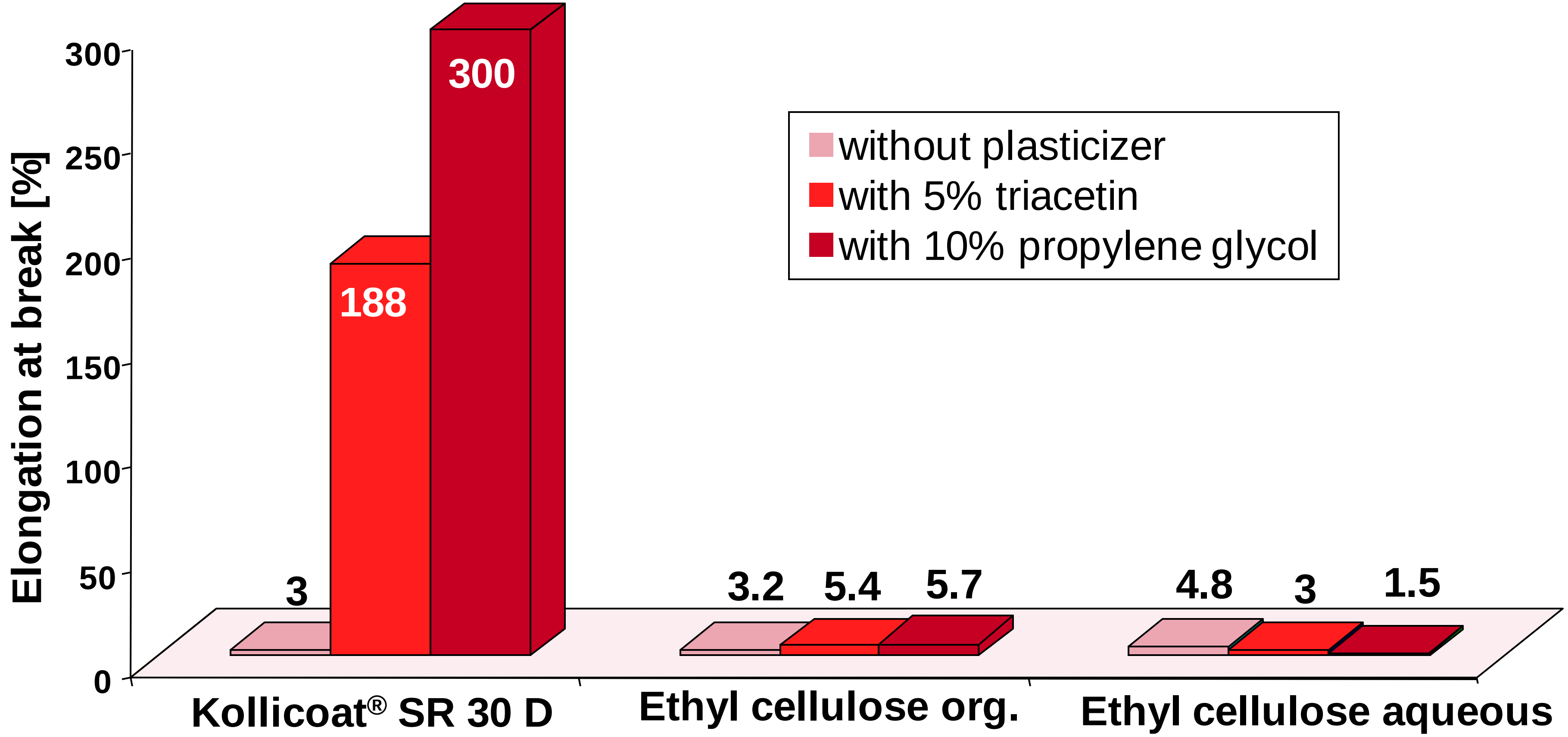
Recommended plasticizers:

- **Triacetin**
- **Triethyl citrate**
- Polyethylene glycols 400
- Propylene glycol



- Kollicoat® SR 30 D films need **5 to 10% plasticizer** (based on dry polymer) to keep film plasticity in **tablets**
- **Pellets** require **10 to 15% of plasticizer** to improve film flexibility during pellet compression (**MUPS**)

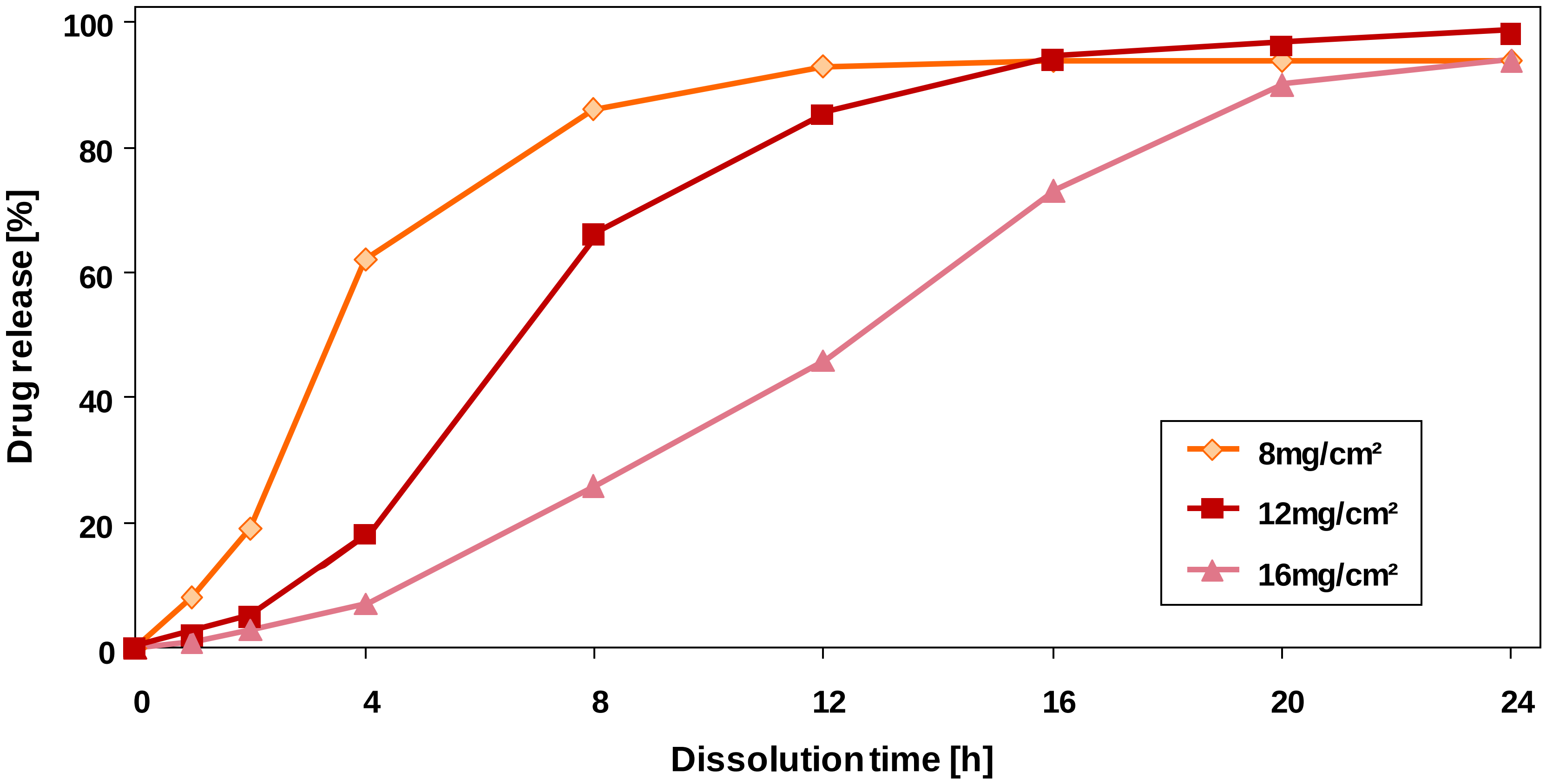
Elasticity of the film coating with different plasticizers



- Kollicoat® SR 30 D with a small amount of plasticizer exhibits high flexibility

Dissolution rate as a function of coating level

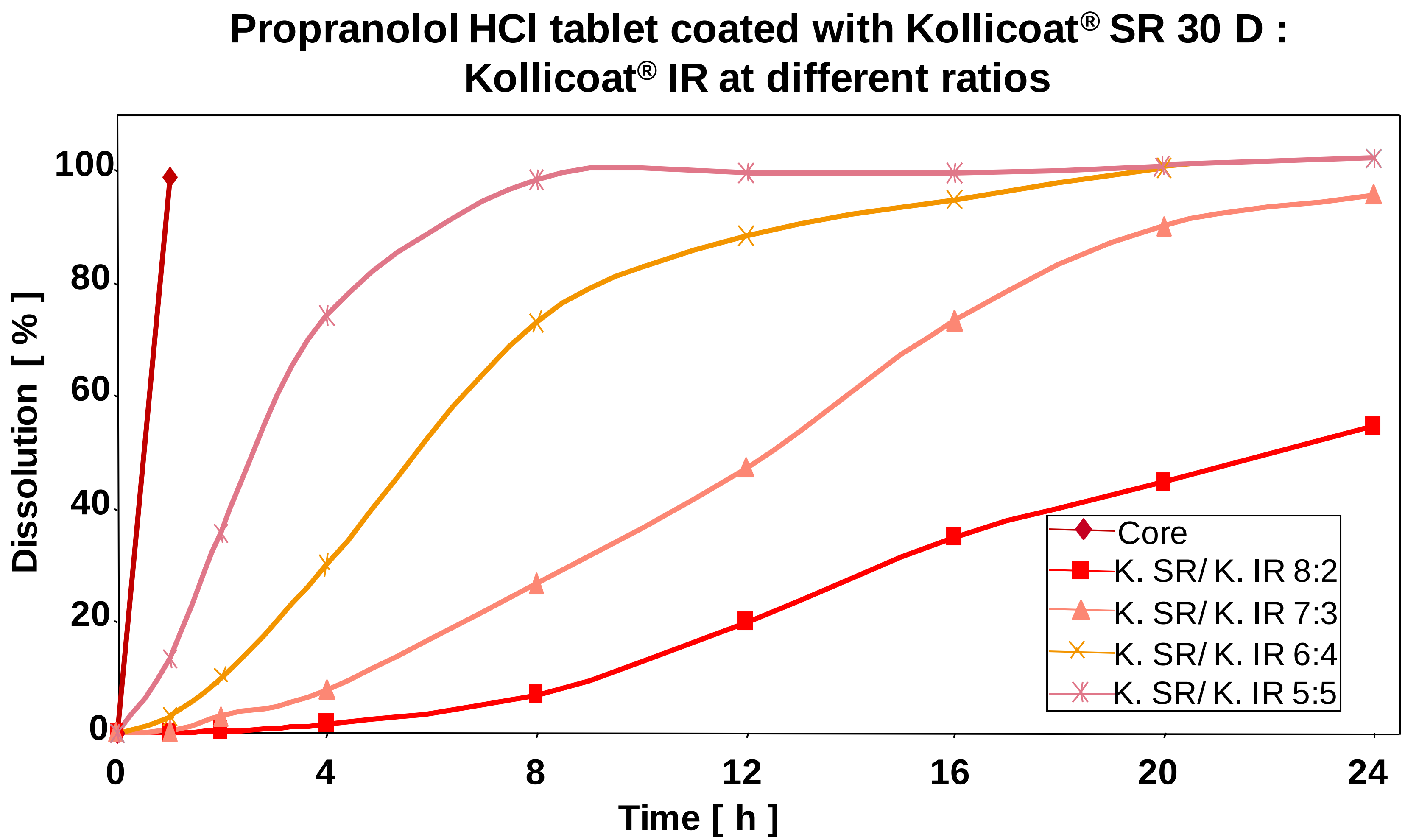
Propranolol HCl tablet coated with Kollicoat® SR 30 D : Kollicoat® IR (7:3)



- Drug release is dependent of coating level (weight gain) / coated surface (mg/cm^2)
- The higher is the coating level, the slower is the drug release

Propanolol HCl tablets
Pellets coating level: 16 mg/cm^2
Film: Kollicoat ® SR 30 D + Kollicoat ® IR
Medium: 0.08 N HCl (0-2h), PBS pH 6.8 (2-24 h), paddle 50 rpm

Dissolution rate as a function of pore former



- Drug dissolution can be adjusted by the proportion of the semi-permeable film (Kollicoat SR® 30 D) and the pore former (soluble film – Kollicoat® IR).
- The higher is the soluble pore former, the faster is the drug release

Propanolol HCl tablets
Pellets coating level: 16 mg/cm^2
Film: Kollicoat® SR 30 D + Kollicoat® IR
Medium: 0.08 N HCl (0-2h), PBS pH 6.8 (2-24 h), paddle 50 rpm

Source: Polyvinyl acetate-based film coatings. K. Kolter et al. International Journal of Pharmaceutics *457 (2013) 470– 479*

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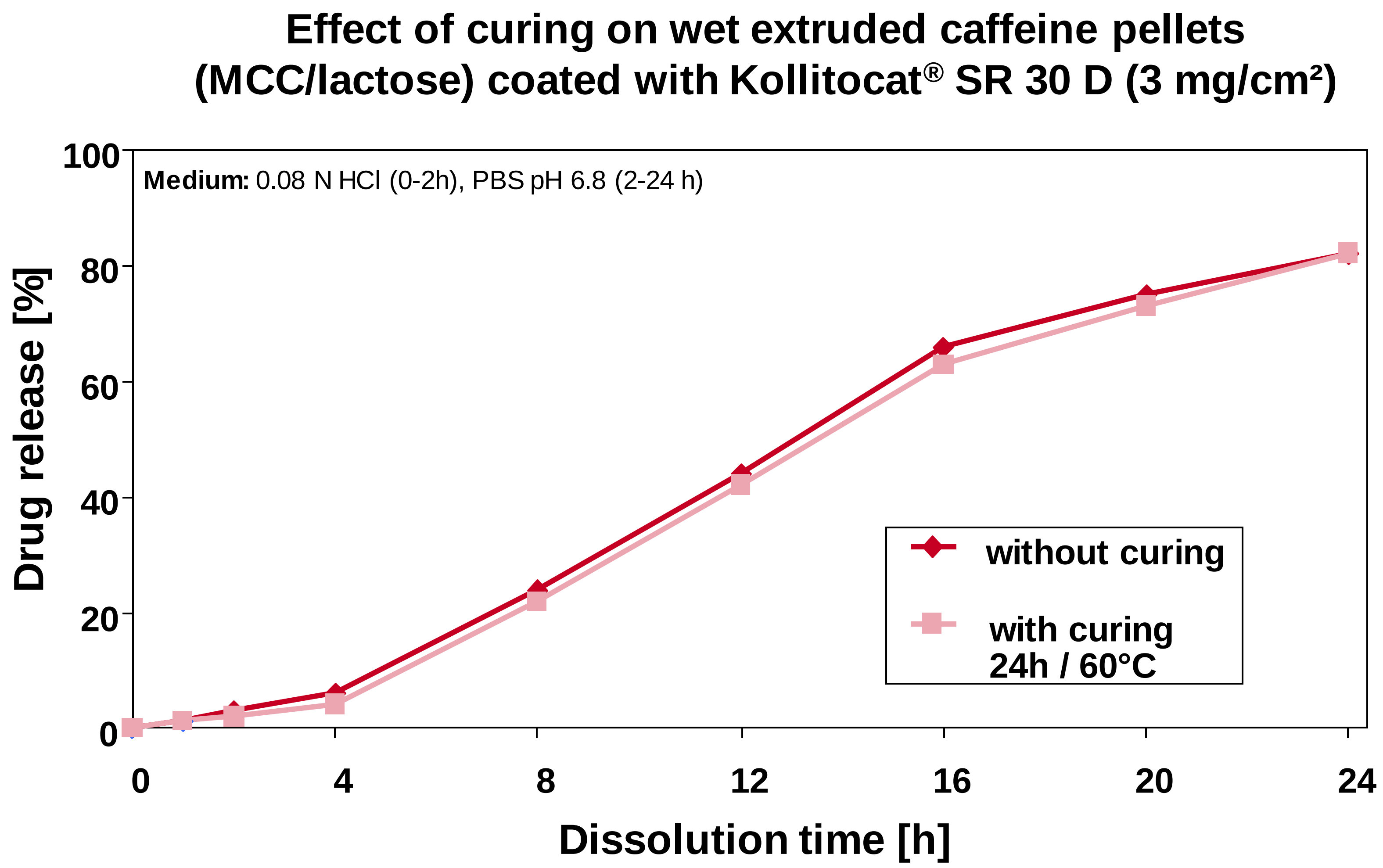
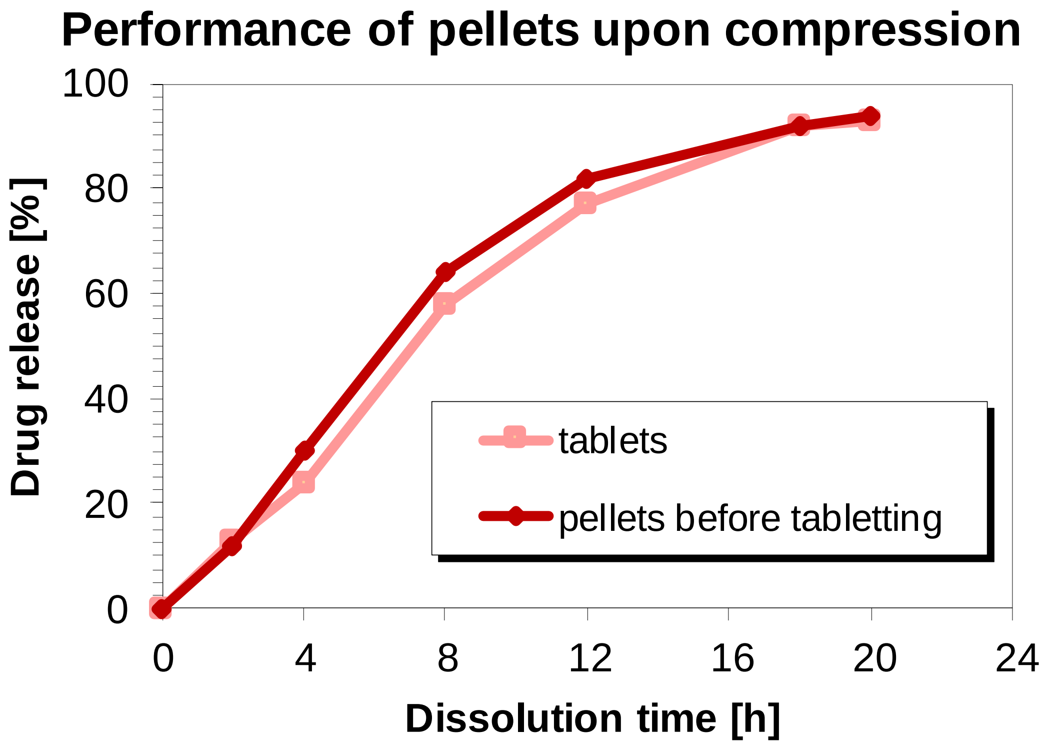
Dissolution rate as a function of the curing step

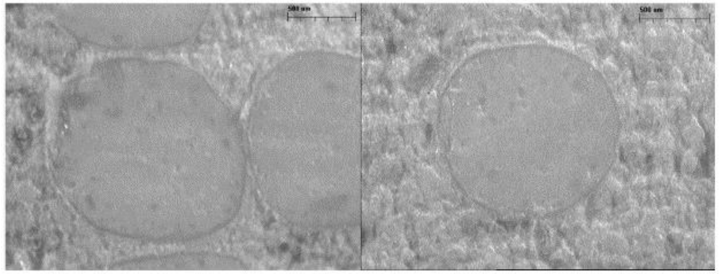


- Kollicoat® SR 30 D is not very sensitive towards curing.
- Due to the low MFT of Kollicoat® SR 30 D (dispersion), the film formed has almost complete coalescence during the coating process, reducing the need for a curing step.

Source: Polyvinyl acetate-based film coatings. K. Kolter et al. International Journal of Pharmaceutics *457 (2013) 470–479*

Kollicoat® SR 30 D is highly suitable for MUPS





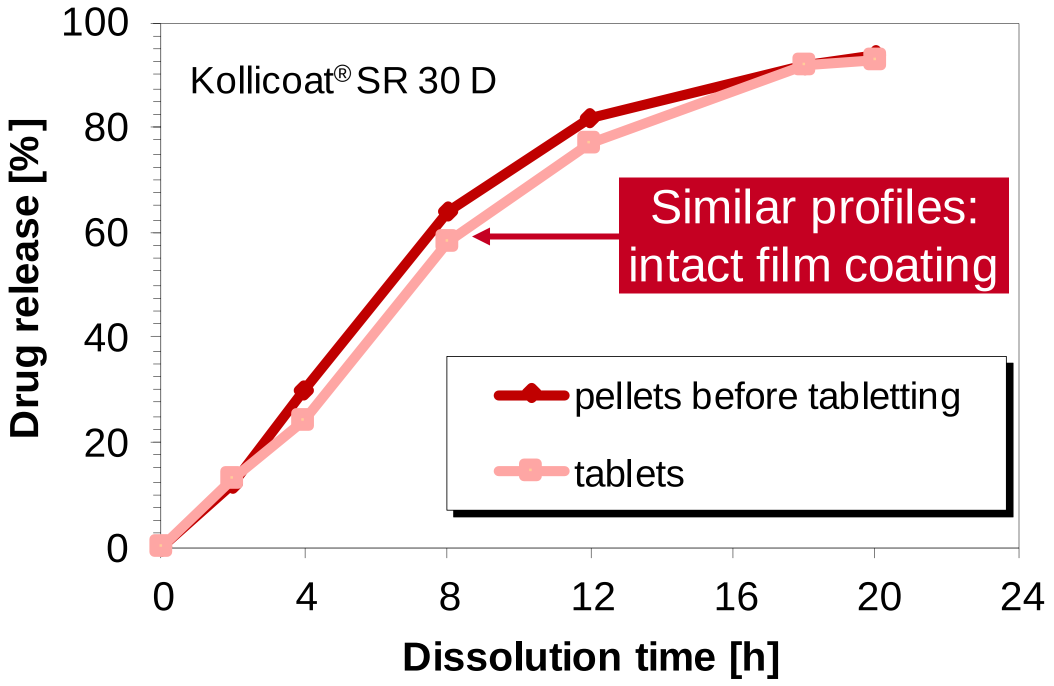
SEM of a broken MUPS (Multiple Unit Pellet System)

Propanolol HCl MUPS
Pellets coating level: 20 % w/w
Film: Kollicoat SR 30 D + 10% TEC
Tablet: 50% pellets, 50% MCC 200, compression force: 15 kN

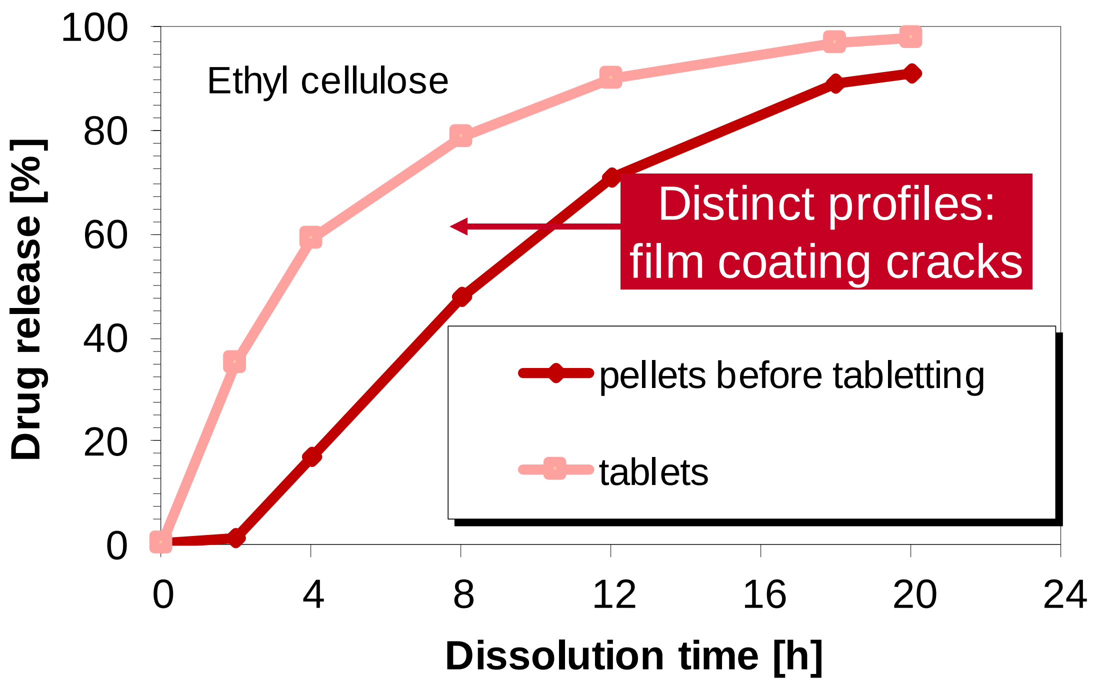
- Kollicoat® SR 30 D coatings are very stable towards compression into MUPS: **the release profile is not impacted**.
- **Plasticizer level of 10 to 15%** is recommended.

Adapted from A. Dashevsky et al. Compression of pellets coated with various aqueous polymer dispersions. International Journal of Pharmaceutics 279 (2004) 19–26

Impact of the polymer during the tableting process of MUPS



Propranolol HCl pellets coated with Kollicoat® SR 30 D + 10% w/w triethyl citrate (20% w. gain), released from tablets compressed with MCC 200 at 15 kN.



Propranolol HCl pellets coated with ethyl cellulose dispersion 30% + 25% w/w triethyl citrate (20% w. gain), released from tablets compressed with MCC 200 at 15 kN.

- In contrast to the pellets coated with Kollicoat® SR 30 D, the ethyl cellulose film-coating breaks during the compression of pellets into MUPS, releasing the drug faster.

Adapted from A. Dashevsky et al. Compression of pellets coated with various aqueous polymer dispersions. International Journal of Pharmaceutics 279 (2004) 19–26

Kollicoat® SR 30 D
Reservoir system – film flexibility

- Lactose + MCC tablets coated with Kollicoat SR 30 D and submerged in water for 24 hs.
- See tablets before and after submersion in water:
  - Before: Small and compacted tablet
  - After: Expanded tablet. Water permeated and solubilized the lactose which diffused through the film coating. MCC remained in the core due its low solubility in water.
- Observe the high film coating elasticity and flexibility, highly important to maintain an intact membrane when tablet swells and for pellets when crushed into tablets.

Summary: BASF Portfolio

	Instant Release	Gastric Release (Immediate release)	Enteric Release	Sustained Release
	Cosmetic Moisture protection	Taste masking	Gastric-resistant coating	Reservoir System
Typical features	• neutral • water soluble • powder (aqueous) • pH-value neutral	• cationic • pH dependent solubility (<5.5) • aqueous disp. and powder (organic solvent* or aqueous) • pH-value 7.5 – 10.0	• anionic • pH dependent solubility (>5.5) • aqueous disp. and powder (organic solvent* or aqueous) • pH-value 2.1 – 3.0	• neutral • insoluble • aqueous disp. (aqueous) • pH-value 3.0 – 5.5
Portfolio	Kollicoat® IR, Protect	Kollicoat® Smartseal 30 D, Smartseal 100 P	Kollicoat® MAE 30 DP, MAE 100-55, MAE 100-55 Fine, MAE 100 P	Kollicoat® SR 30 D

*organic solvent suitable for the powder grade

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