Innovation in Functional Excipients for Oral Drug Delivery

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BASF Pharma Solutions, NA

CRS 2022 Annual Meeting & Expo

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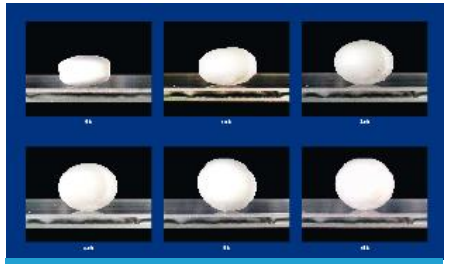
Outline

- Innovation in Pharmaceutical Excipients
- Innovation: BASF Excipient Launches
  - New Excipients
  - Novel Excipients
- Selected Examples/ Case Studies
- Summary & Conclusions

Dedicated to innovation: BASF Excipient launches



Kollicoat® SR 30 D

Strong and reliable sustained release coating

Kollidon® SR

A versatile sustained release matrix excipient

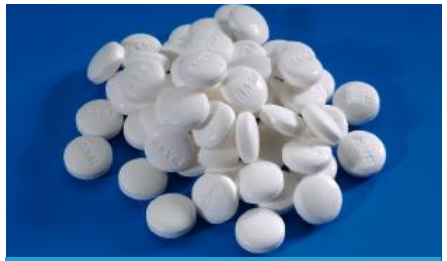
Kollicoat® IR

The coating superstar

1998	1999	2000	2001	2002	2003	2004
Kollicoat® MAE 30 DP		Kollidon® SR			Kolliphor® P 188 micro	
Ludipress® LCE	Kollicoat® MAE 100 P	Kollicoat® SR 30 D		Kollicoat® IR	Kolliphor® P 407 micro	Kollicoat® Protect

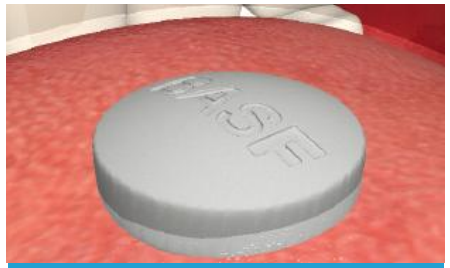
Coatings | Tablet excipients | Active formulations | Solubilizer

Dedicated to innovation: BASF launches



Ibuprofen DC 85®

Cost-effective tablet manufacturing and outstanding tablet performance



Ludiflash®

Extremely fast disintegrating and creamy mouth feel

Soluplus®

The solid solution

Kollicoat® Smartseal 30 D

Active protection

2005: Kollidon® VA 64 Fine

2006: Ibuprofen DC 85; Kollidon® CL-F / CL-SF

2007: Ludiflash®; Kollidon® 30 LP; Ibuprofen Sodium

2008

2009: Soluplus®

2010: PeroXeal™; Kollicoat® Smartseal 30 D

2017: Kolliphor® P 188 Bio; Kollicoat® MAE 100-55

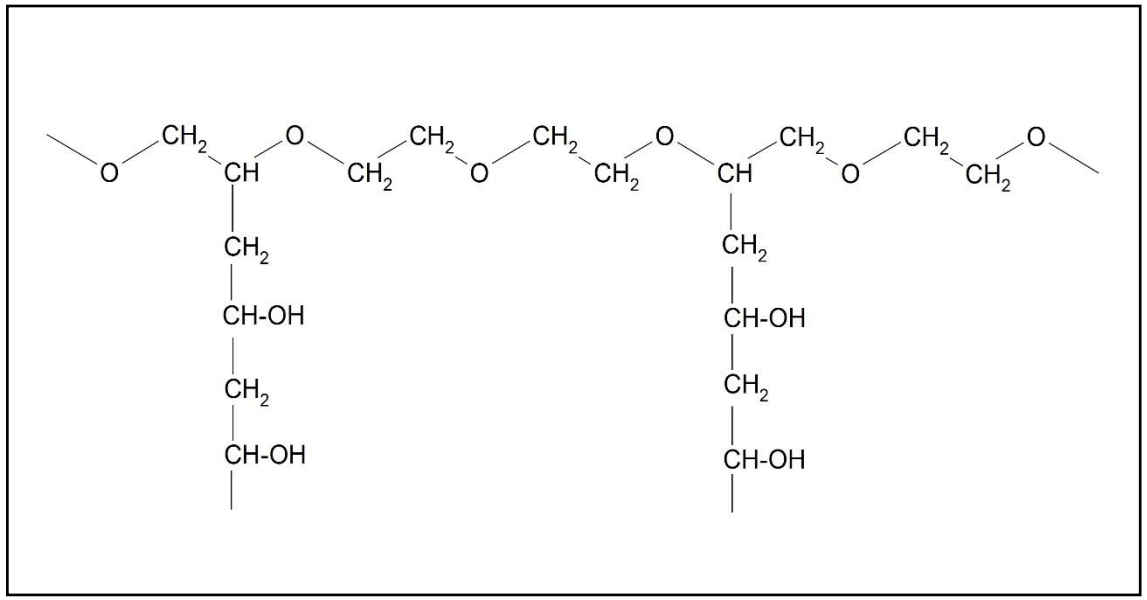
2018: Kollicoat® Smartseal 100 P

2021: Kollitab™ DC 87L

Coatings | Tablet excipients | Active formulations | Solubilizer | Biologics

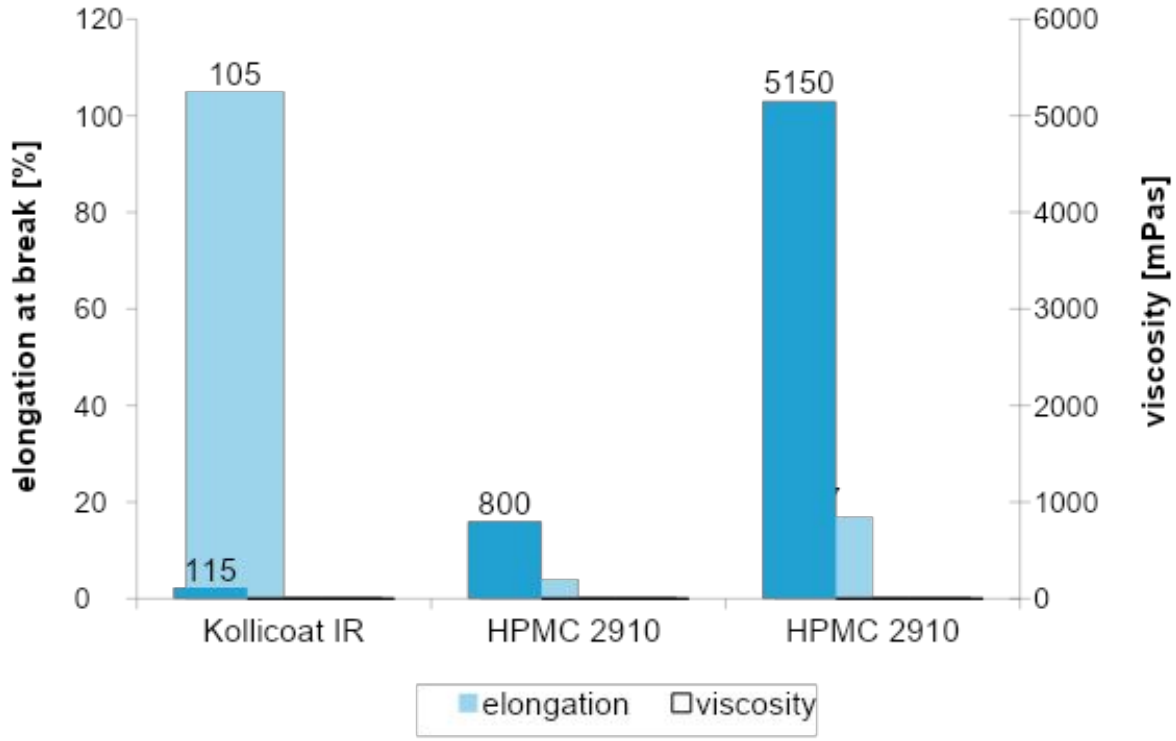
BASF We create chemistry

Innovation in instant release coating: Kollicoat® IR



Polyvinyl alcohol - polyethylene glycol graft copolymer

PVA-units: 75 %
PEG-units: 25 %
Solubility in water: > 50 %
45,000 Dalton



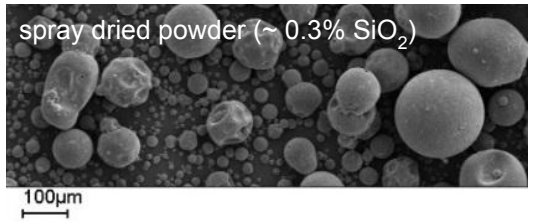
Kollicoat® IR is available as….

Single Polymer

Kollicoat® IR

by BASF

for individual innovative coating needs and more



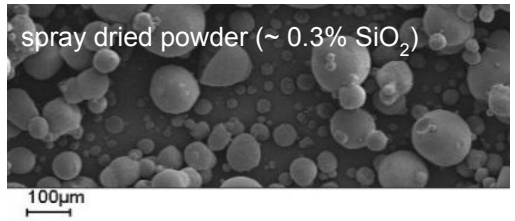
Polymer Mixture

Kollicoat® Protect

by BASF

(60% Kollicoat® IR / 40% PVA)

for the formulation of protective IR coatings



Pigmented and fully formulated system

OPADRY® QX

by Colorcon

(consists of Kollicoat® IR)

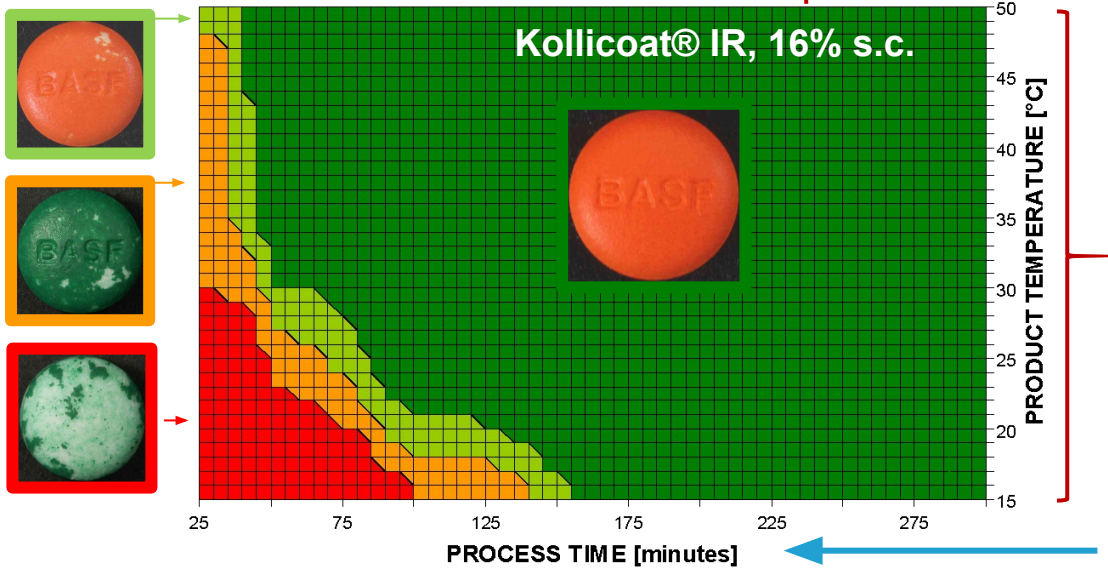
CPhI Pharma Awards 2017

Fast reliable coating options for IR / taste masking, seal coating, moisture barrier and granulation applications.

BASF We create chemistry

Cost efficient and reliable coating: Kollicoat® IR for easy and economic film coating

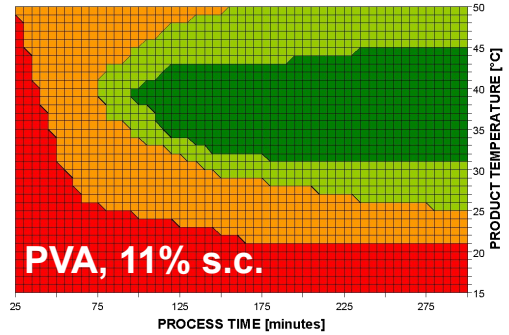
Coating with 50 mPas polymer solution; no plasticizer; s.c.= solid content

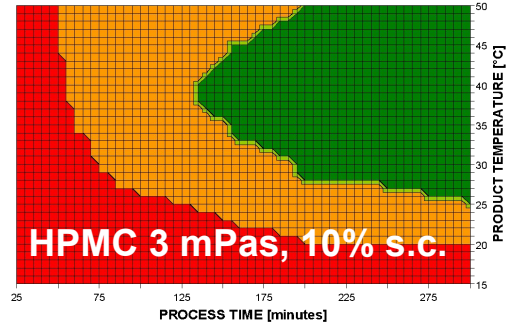


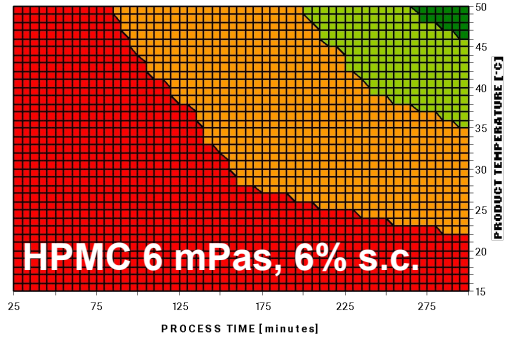
Highest solid content

No temperature limitations

Fastest processes







Kollicoat® IR gives fastest and most stable film coating processes

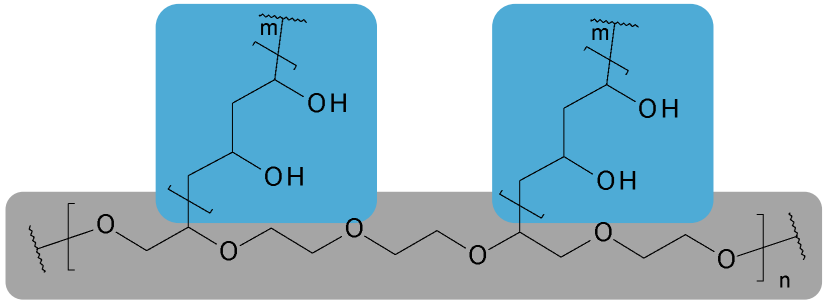
- saves time & energy
- reduces batch failures
- eases upscales / equipment changes / site transfers

BASF
We create chemistry

Wet binders
Kollicoat® IR - The New Binder

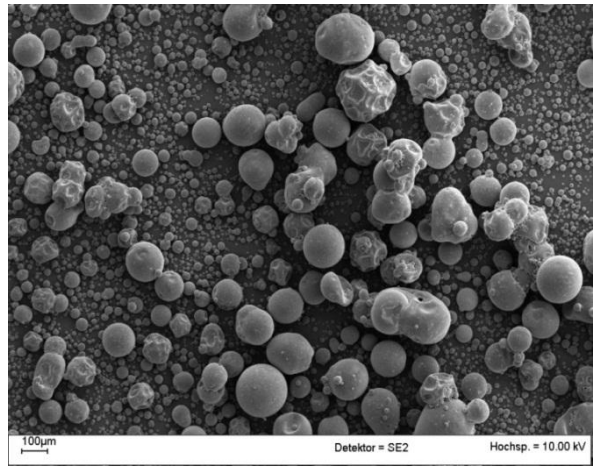
Kollicoat® IR:

Polyvinyl alcohol (PVA) grafted onto PEG 6000



Monographs:

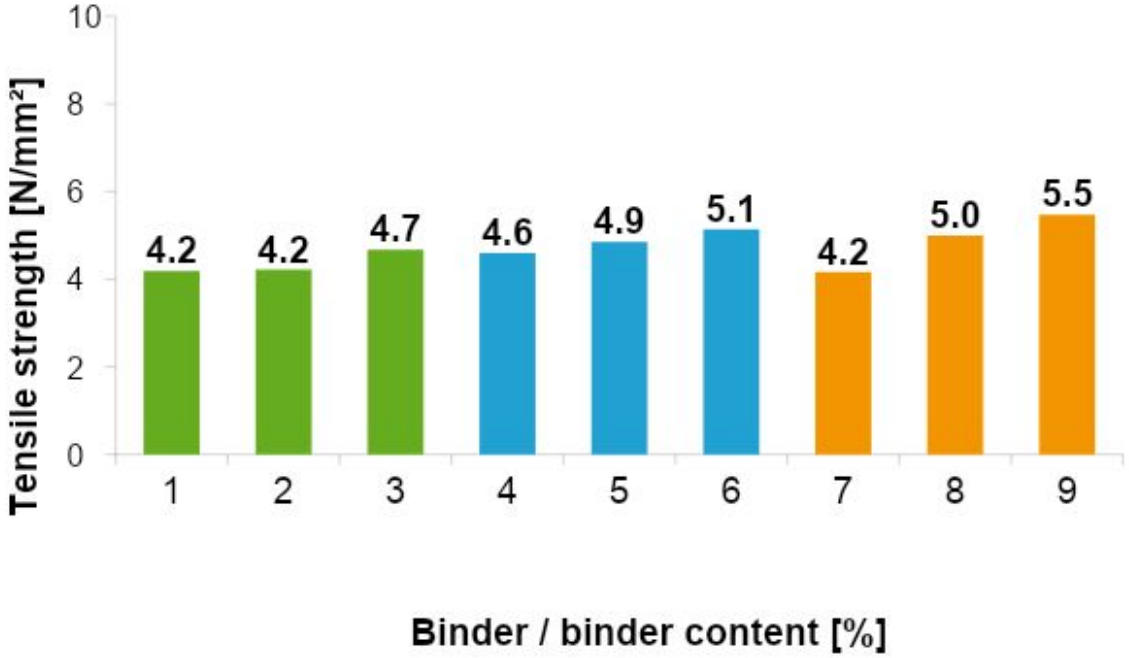
- Ph. Eur.:
  'Macrogol Poly(Vinyl alcohol) Grafted Copolymer'
- USP/NF: 'Ethylene Glycol and Vinyl Alcohol Copolymer'
- JPE: 'Polyvinyl alcohol - polyethylene glycol graft copolymer'

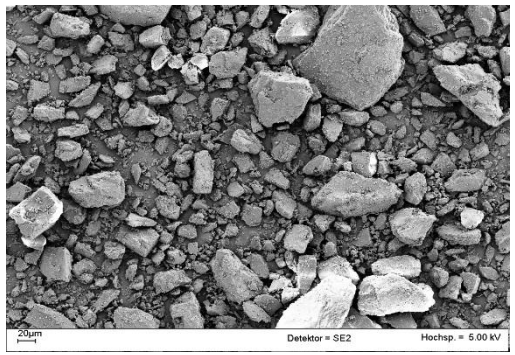


Kollicoat® IR is a new and peroxide-free wet binder for special requirements

Wet binders
Tablet tensile strength (HSG)

Tensile strength of lactose tablets from HSG granules (15 kN compr. force)





Tableting of lactose granules:

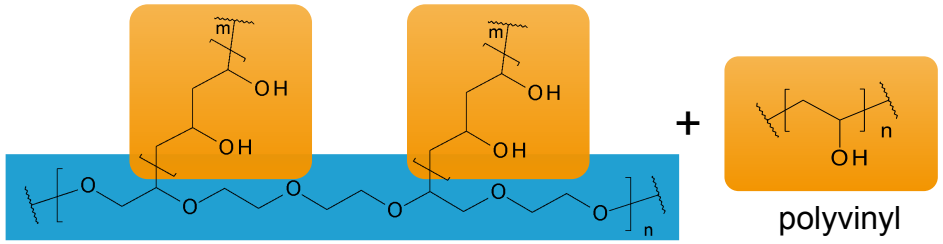
- Equipment: Korsch XP-1
- Speed: 10 tablets/min
- Tablet height: 2.6 mm
- Tablet weight: 185 mg
- Compression force: 15 kN

Tablets obtained from Kollicoat® IR HSG lactose granules reveal tensile strengths similar to those of Kollidon® 90 F – however, Kollicoat® IR has a much lower solution viscosity

Instant release coatings with moisture and oxygen protection Kollicoat® protect

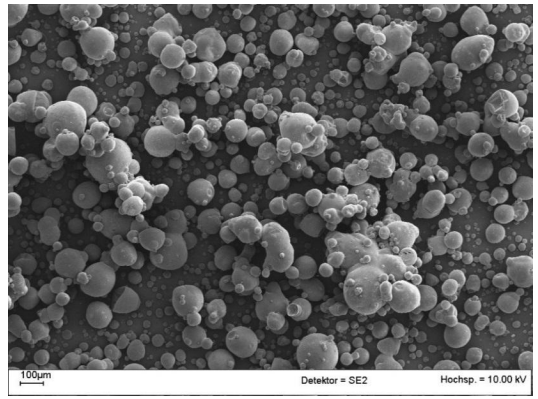
Kollicoat® Protect

- Innovative polymer composition for protective IR film coatings (oxygen and moisture protection)
- Composition:
  - 55-65% Kollicoat® IR
  - 35-45% Polyvinyl alcohol (PVA)
  - 0.3% Colloidal silica



Kollicoat® IR

polyvinyl alcohol



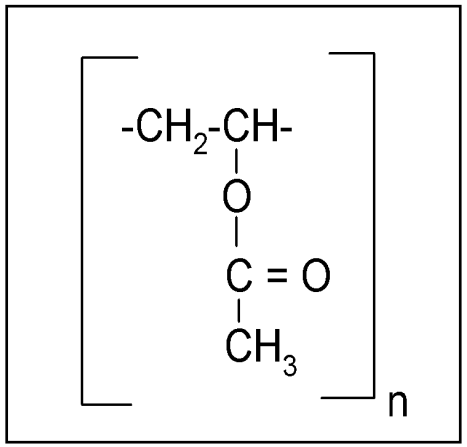
Kollicoat® Protect gives an oxygen and moisture protective IR coating when formulated with pigments

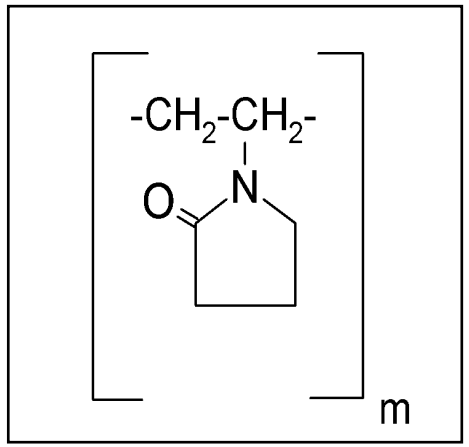
- Very high pigment loadings possible
- Protective action by pigment load

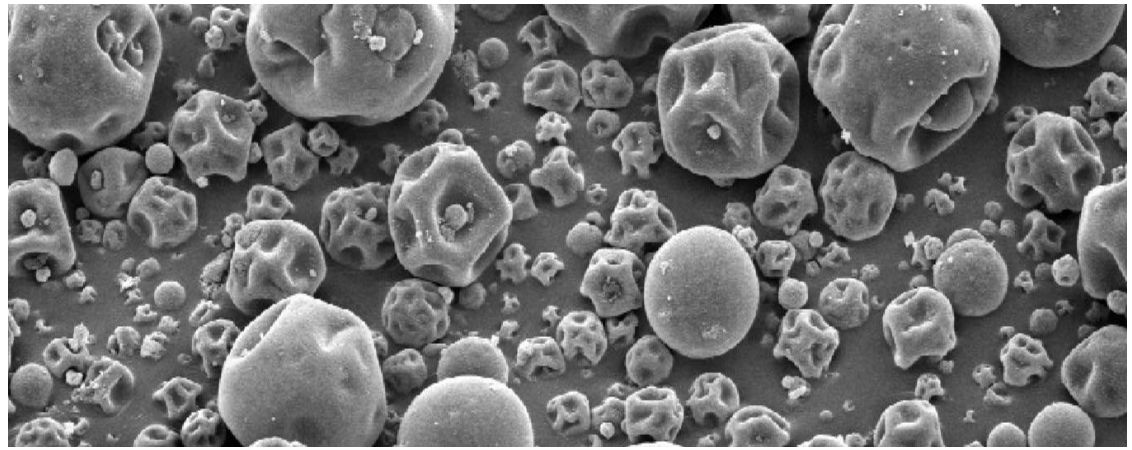
Sustained release matrices
Kollidon® SR

- Outstanding compressibility
- Excellent flowability
- Suitable for wet granulation, melt granulation and HME
- Typically resulting in a first order release

Kollidon SR is a spray formulated mixture of 80 % polyvinyl acetate and appr. 20 % polyvinylpyrrolidone



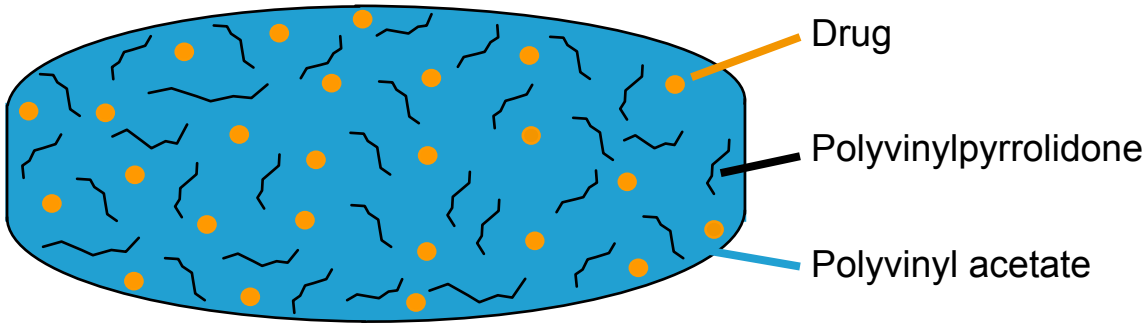




Kollidon SR is in particular suitable for the manufacture of different sustained release matrices like tablets, pellets, granules, extrudates.

Sustained release matrices
Kollidon® SR theory of dissolution

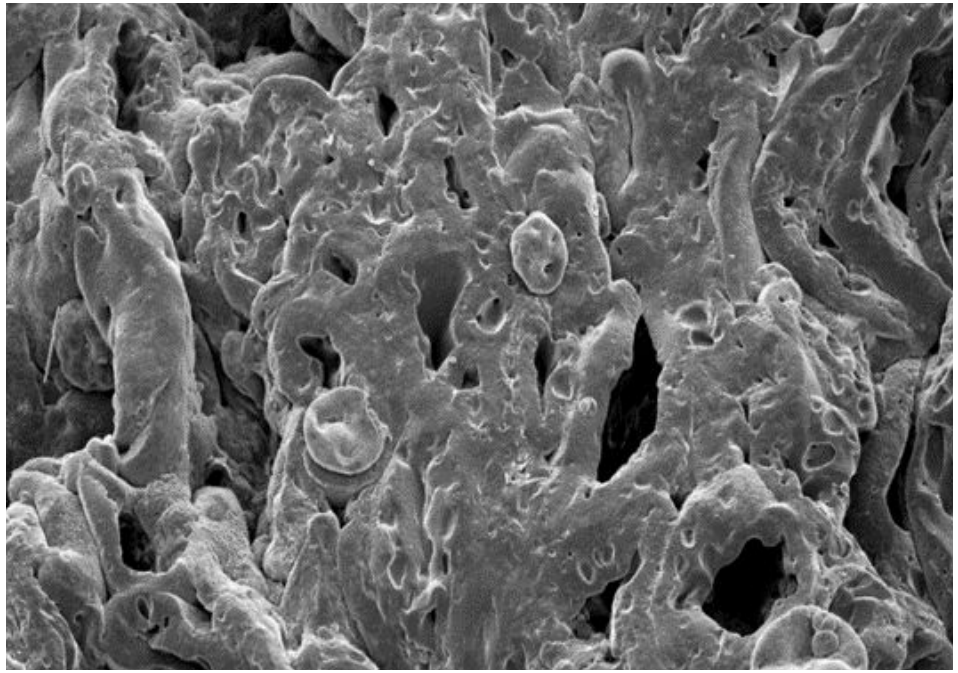
Tablet



Function of PVP: creating pores for diffusion
improvement of compressibility

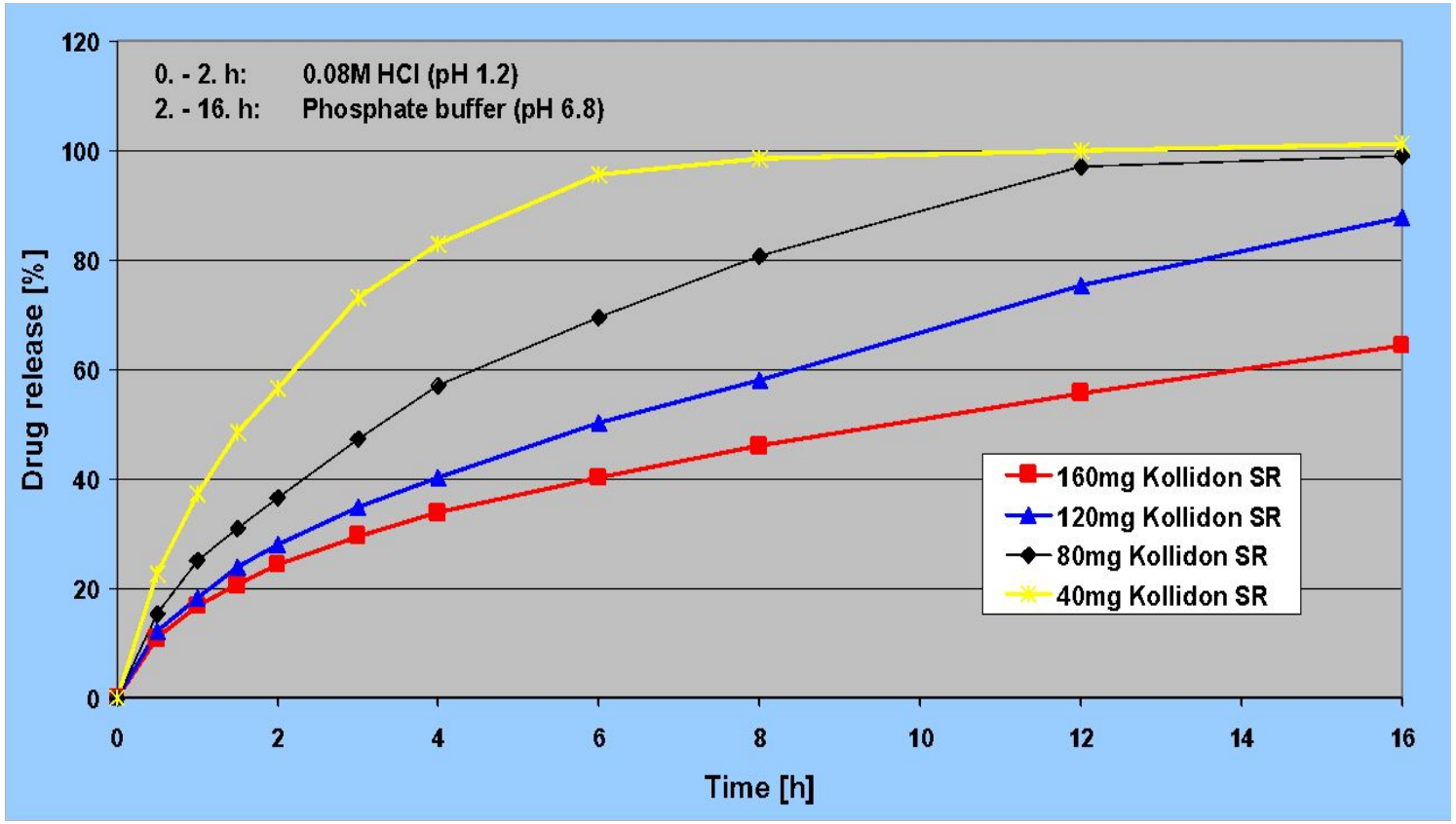
Function of PVAc: inert, swellable matrix polymer

Fracture of a released tablet



Sustained release matrices
Kollidon® SR in caffeine sustained release tablets

Drug release of caffeine tablets as a function of the amount of Kollidon® SR



Kollidon SR usually results in 1st order release profiles

Abuse-deterrent sustained release matrices Kollidon® SR

- Outstanding compressibility results in extremely high mechanical strength (hardness): > 300 N
- Mechanical strength can be even enhanced by tempering at higher temperatures
- Kollidon SR consists of polymers soluble in water (PVP) and organic solvents (polyvinyl acetate)
- Various manufacturing methods can be employed:
  - Direct compression
  - Wet granulation
  - Melt granulation
  - Hot melt extrusion/injection molding

→ **Difficult to break and grind**

→ **Difficult to extract and purify the active**

Kollidon SR offers opportunities for abuse-deterrent formulations

Formulation safety: Prevention of alcohol-induced dose dumping (ADD)

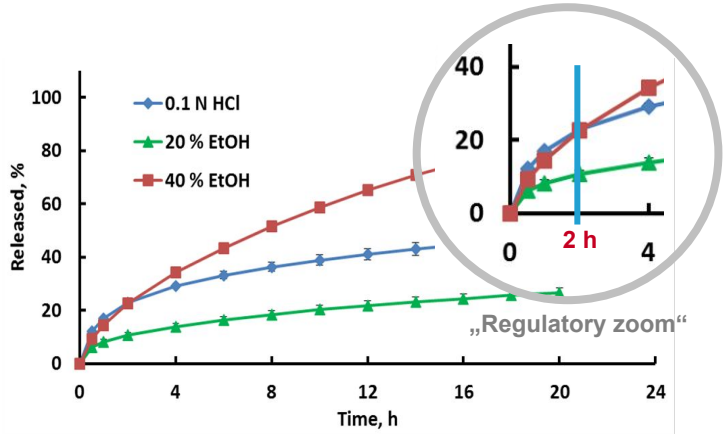
- ADD = Dose dumping as a result of alcohol consumption in relation to drug administration
- Some oral MR dosage forms contain APIs and excipients with higher solubility in ethanolic solutions
- ADD is particularly severe for APIs with narrow therapeutic index

Modified Release Dosage Forms with Kollidon® SR*

Kollidon® SR: 80% PVAc, 20% Kollidon® 30; for MR matrix tablets by direct compression;

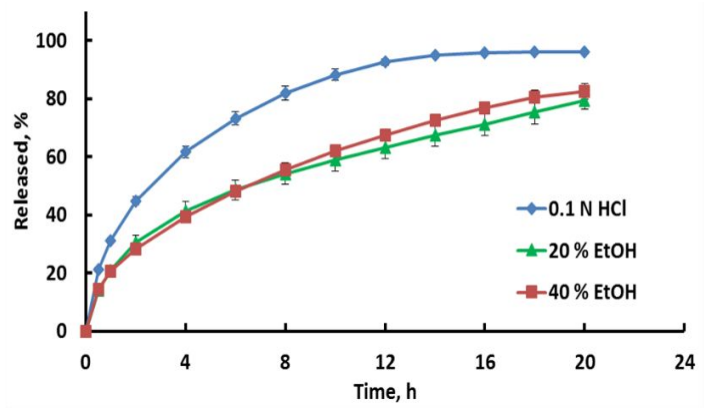
Formulation: 25% Tramadol HCl, 75% matrix

- pure Kollidon® SR matrix



⇒ sufficient from a regulatory perspective (FDA: 2 hours; EMA: 20% EtOH)

- 1:1 mixture with Kollidon® 90 F



⇒ Full protection at all test conditions at all times

BASF We create chemistry

Kollidon SR for gastric retention
Sustained release floating system

Technology: direct compression of highly porous drug – Kollidon SR formulations at low compression forces + possibly coating

Influence of compression force on apparent density and floating behaviour of Dilitiazem tablets

Compression force [kN]	Apparent density [g/cm³]	Floating behaviour
2.36	0.81	immediately
2.94	0.91	immediately
3.76	0.97	immediately
4.11	0.99	after 45 min/immediately
4.79	1.03	after 90 min
6.61	1.09	24 to 48 hours

Table3

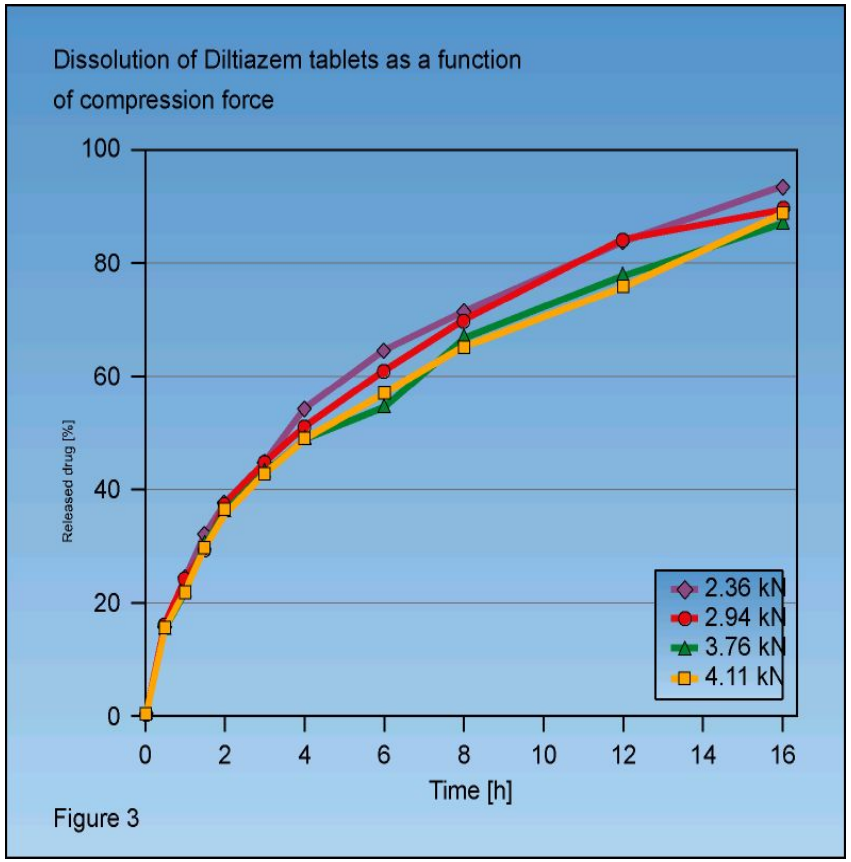
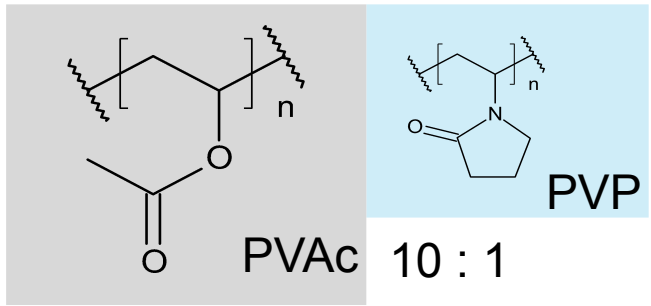


Figure 3

Sustained release
Kollicoat® sustained release (SR) 30 D

Kollicoat® SR 30 D is an 30% aqueous polymer dispersion

- ~ 70% water
- ~ 27.0% polyvinyl acetate (PVAc)
- ~ 2.7% Kollidon® 30 (PVP)
- ~ 0.3% sodium lauryl sulfate (SLS)



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

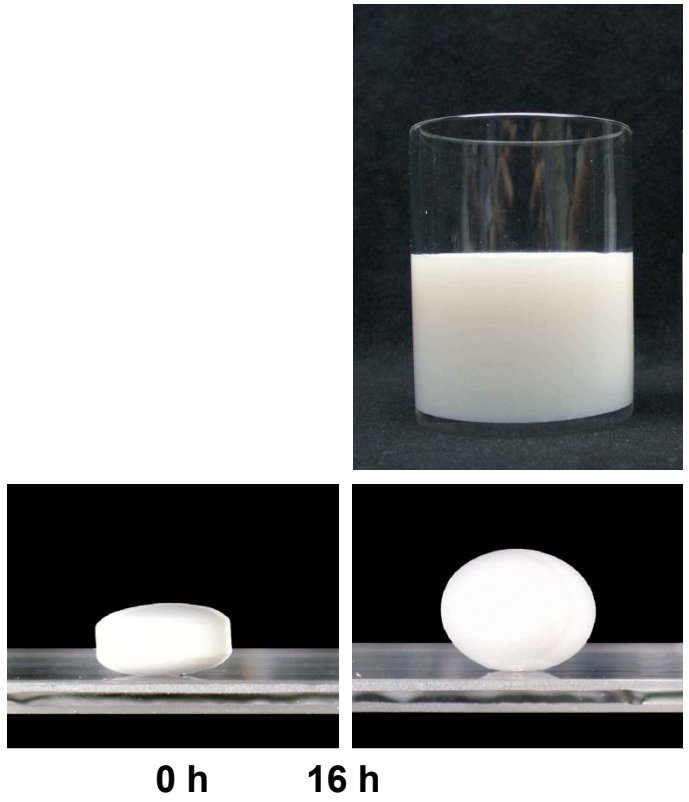
Monographs:

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

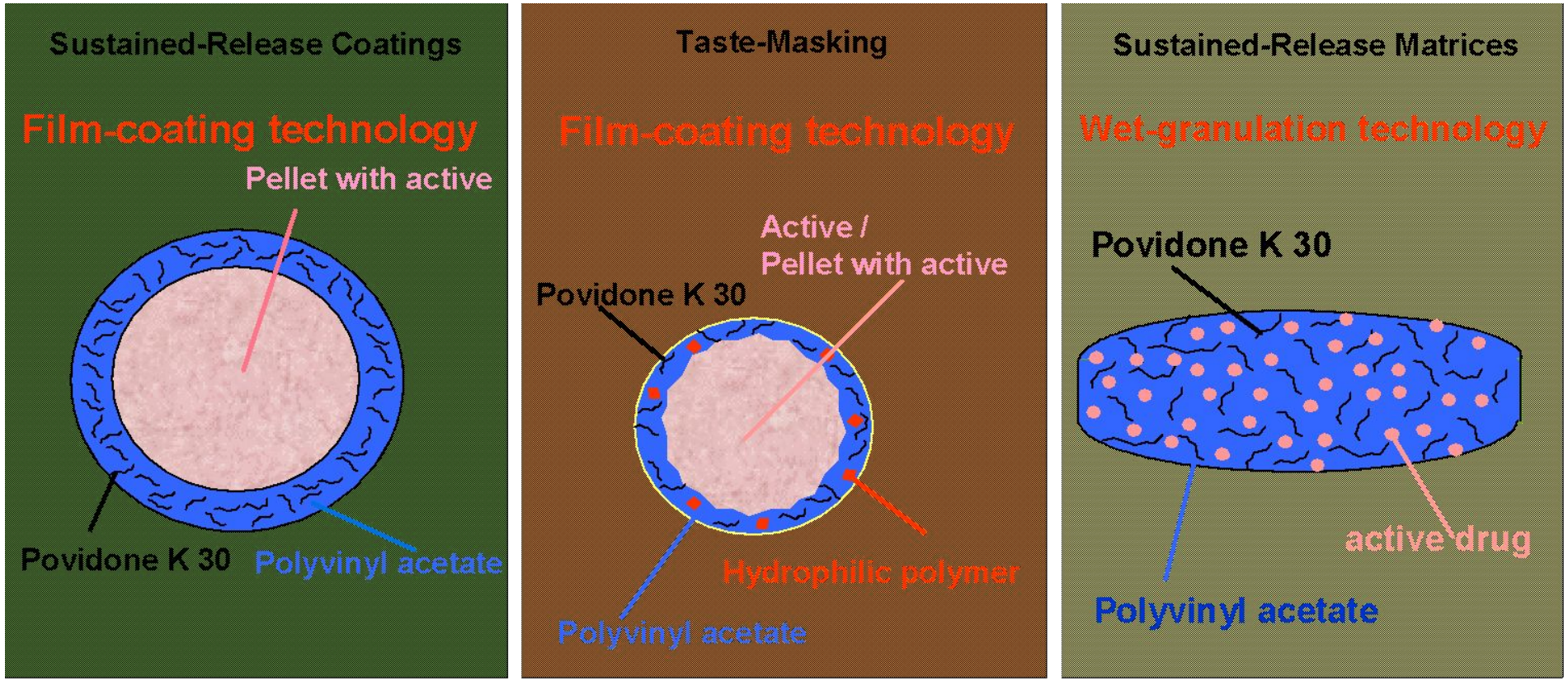
Kollicoat® SR 30 D is a polymer dispersion for sustained release applications

Sustained release
Kollicoat® SR 30 D

- Polyvinyl acetate (PVAc) – a versatile and highly flexible polymer
  - MFFT: 18°C
  - pH value of dispersion : ~4.5
  - High plasticity
  - Lipophilic diffusion barrier
  - Slightly swellable in aqueous media (insoluble)
  - Excellent film forming properties
  - Strong, stable sustained release
  - pH-independent release



Kollicoat® SR 30 D - applications

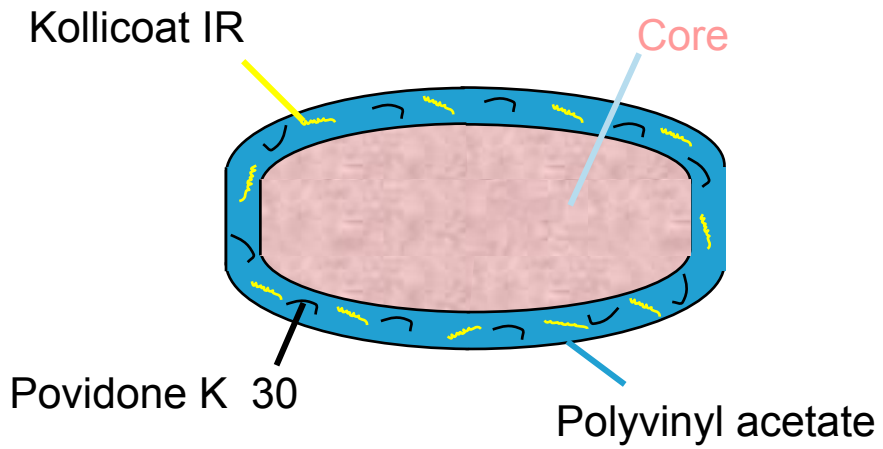


Sustained release
Kollicoat® SR 30 D single unit drug delivery systems

Structure of diffusion controlled drug delivery system (DDS):

Tablet core coated with:

- Kollicoat® SR 30 D and Kollicoat® IR (ratios: 1:1 to 8:2)
- Coating level: 10 – 20 mg/cm²

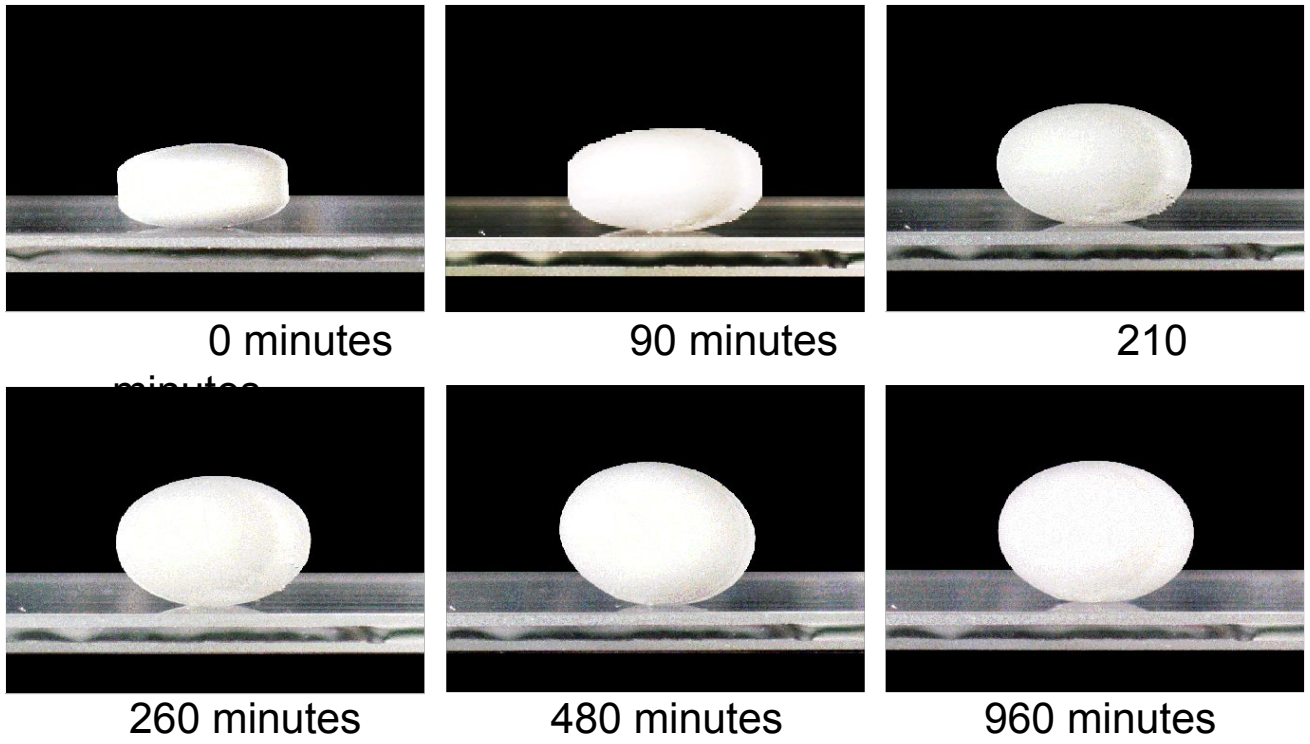


Tablet core (350 mg): 163.2 mg propranol HCl, 136.8 mg Ludipress®, 25 mg Kollidon® VA 64, 20 mg Kollidon® CL, 3 mg Aerosil 200, 2 mg Mg stearate
Coating plasticizer: 10% triacetin based on Kollicoat® SR 30 D solids

In the DDS drug release is controlled by osmotic diffusion through the coating pores

Sustained release
Kollicoat® SR 30 D single unit drug delivery systems

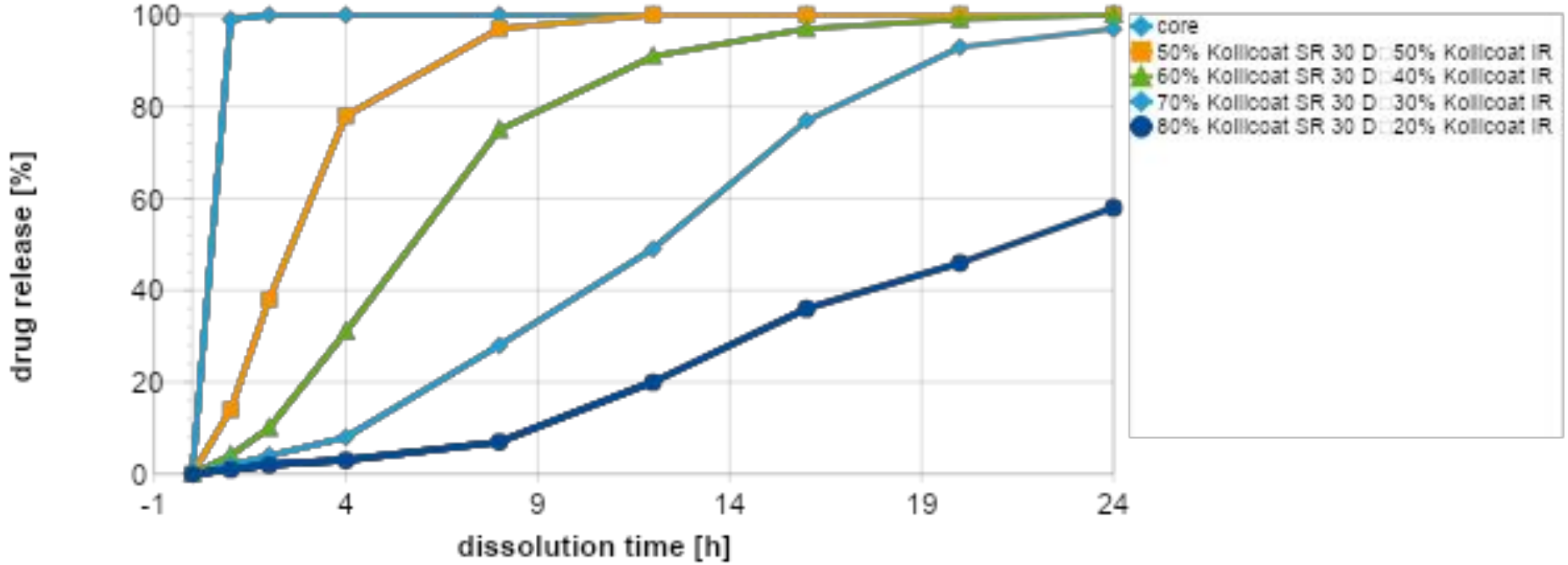
Swelling behavior of the DDS in dissolution medium



The pores in Kollicoat® SR 30 D films allow core swelling while the coating stays intact

Sustained release
Kollicoat® SR 30 D single unit drug delivery systems

DDS drug dissolution rate as function of coating composition



The amount of Kollicoat® IR in the SR coating allows to fine-tune the release profile

Sustained release
Kollicoat® SR 30 D for pH-independent release

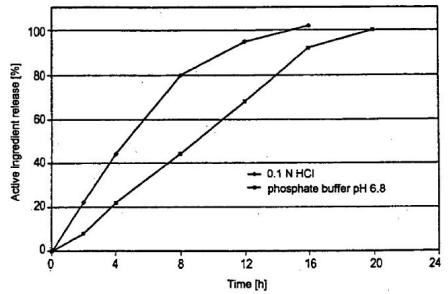
Principally, Kollicoat SR 30 D releases drugs pH-independently if the active is pH-independently soluble

Active	Active
Higher solubility in gastric and intestinal fluid	Kollicoat SR 30 D
Higher solubility in gastric fluid	Kollicoat SR 30 D + enteric coating (1st layer Kollicoat MAE 30 DP; 2nd layer Kollicoat SR 30 D
Higher solubility in intestinal fluid	Kollicoat SR 30 D + reverse enteric coating (Kollicoat Smartseal + Kollicoat SR 30 D

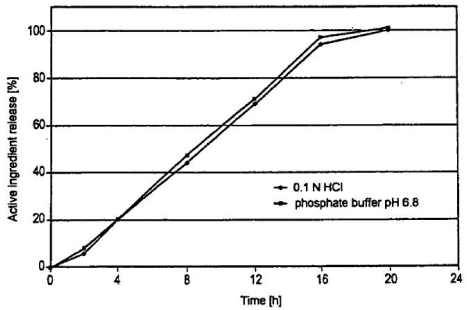
Example

pH-dependently soluble active verapamil-HCL
Solubility: 7.1% in 0.1 HCl; 0.2% in PB 6.8

Kollicoat SR 30 D



Kollicoat SR 30 D + Kollicoat MAE 30 DP



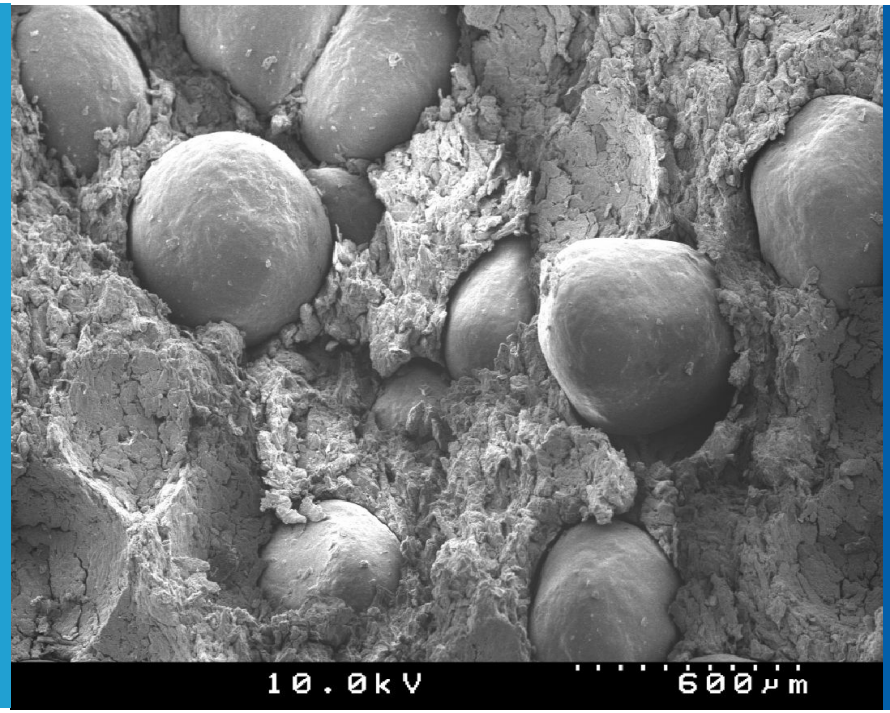
Kollicoat SR 30 D offers solutions also for pH-dependently soluble actives

Sustained release
Kollicoat® SR 30 D for MUPS (multiple unit particulate system)

What counts for this application: Flexibility and robustness of the coating polymer

CHALLENGE

No cracking upon compression



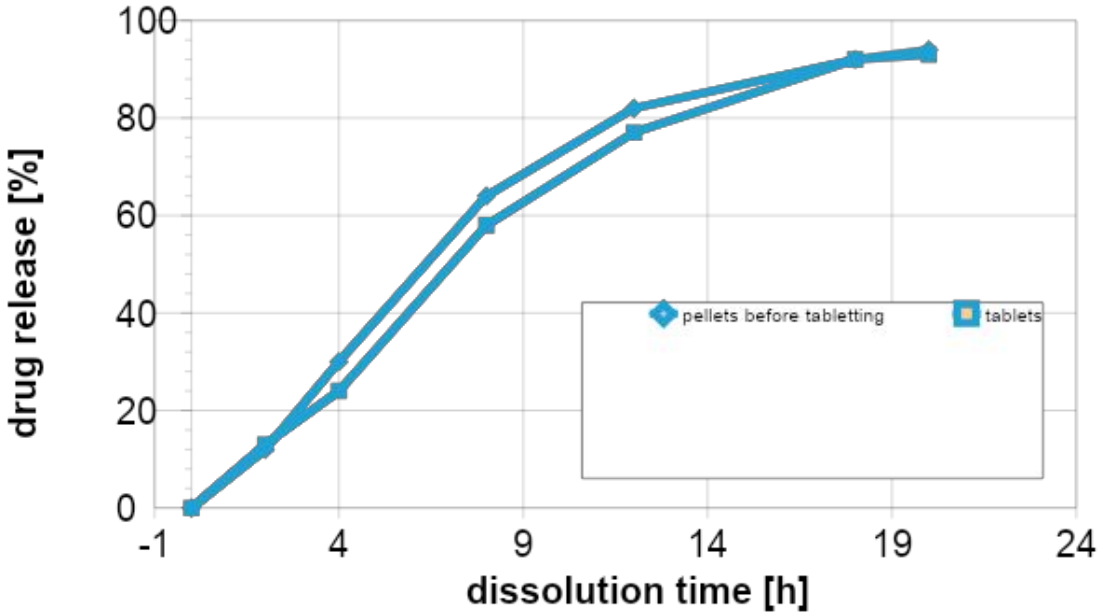
SOLUTION

Optimal design of pellet core, coating and tablet

SEM of a broken tablet

Sustained release
Kollicoat® SR 30 D in MUPS tablets

Impact of tableting on pellets in a MUPS tablet



Source: Bodmeier: APV/APGI Paris, 2000

Pellets coating level:
2 mg/cm^2

Film:
32 mg Kollicoat SR 30 D (solid)
3 mg TEC (= 9% of polymer)
160 mg propranolol HCl

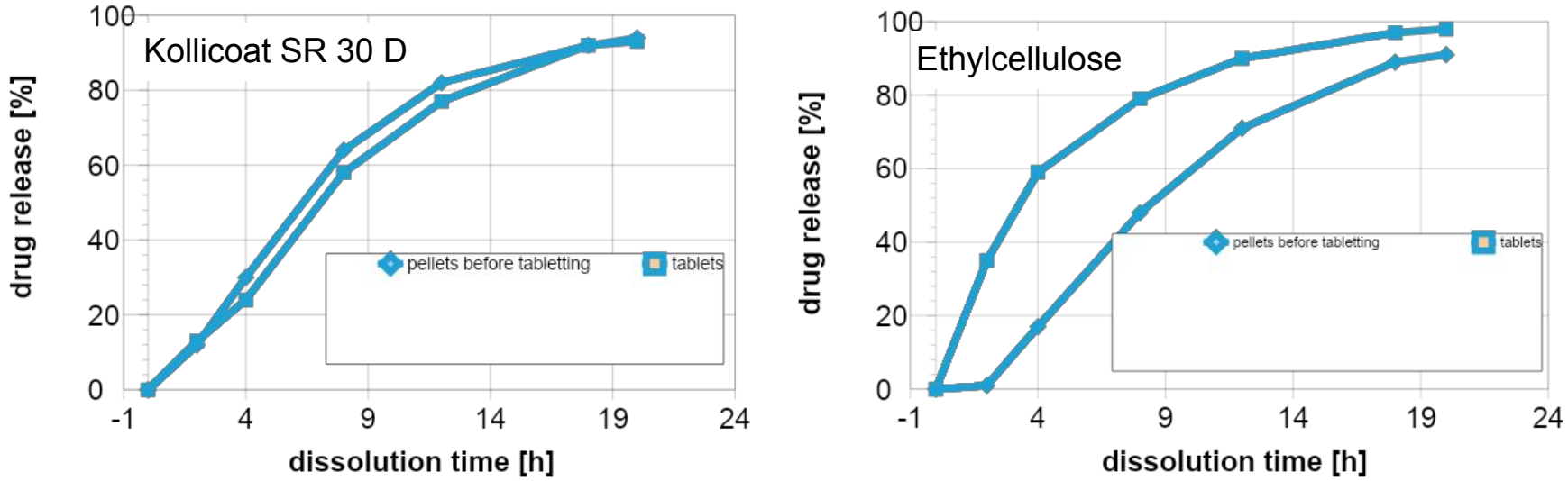
Tablet:
50% pellets
50% MCC
400 mg tablets

MUPS= Multiple Unit Pellet System

The release profile of pellets coated with Kollicoat® SR 30 D is not impacted by compression into MUPS tablets.

Sustained release
Kollicoat® SR 30 D in MUPS tablets

Impact of tableting on pellet dissolution in a MUPS tablet



Source: Bodmeier: APV/APGI Paris, 2000

In contrast to the stable Kollicoat® SR 30 D pellets,
ethyl cellulose based pellets suffer during the compression into MUPS tablets.

Sustained release and gastric retention
Kollicoat® SR 30 D for floating pellets

Floating verapamil pellets

Extruded pellets

20% verapamil-HCl

20% sodium hydrogencarbonate

Coating thickness: 55µm

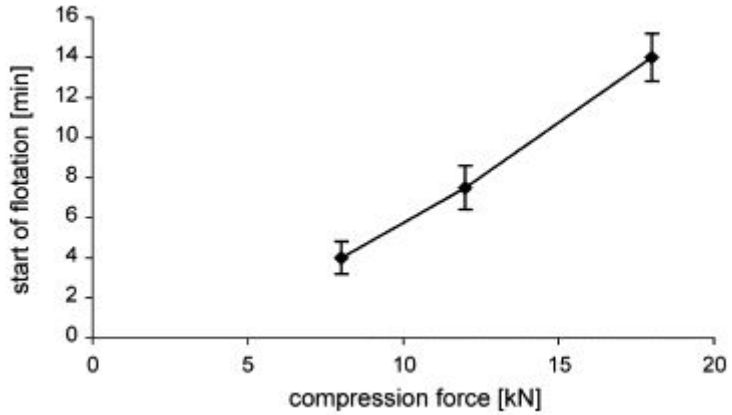
Formulation VI: MCC, mannitol, crospovidone

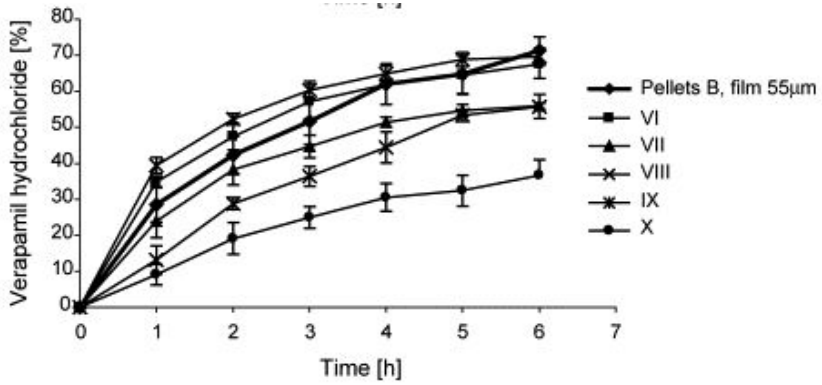
→ release like pellets

Formulation X: sorbitol, crospovidone

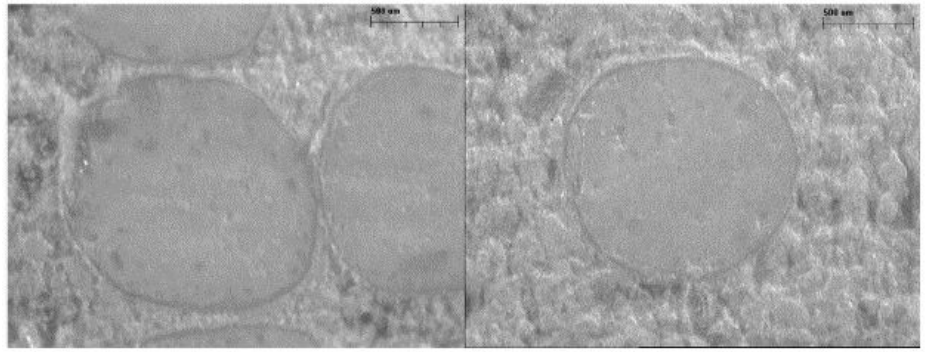
→ slower release due to insufficient disintegration

Formulation VI





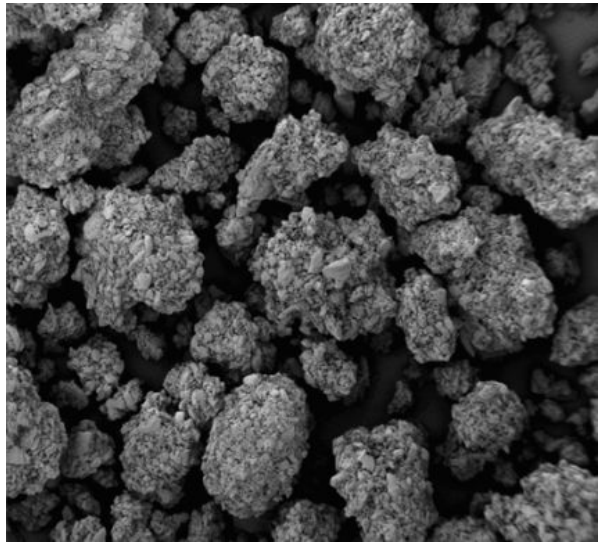
Formulation VI

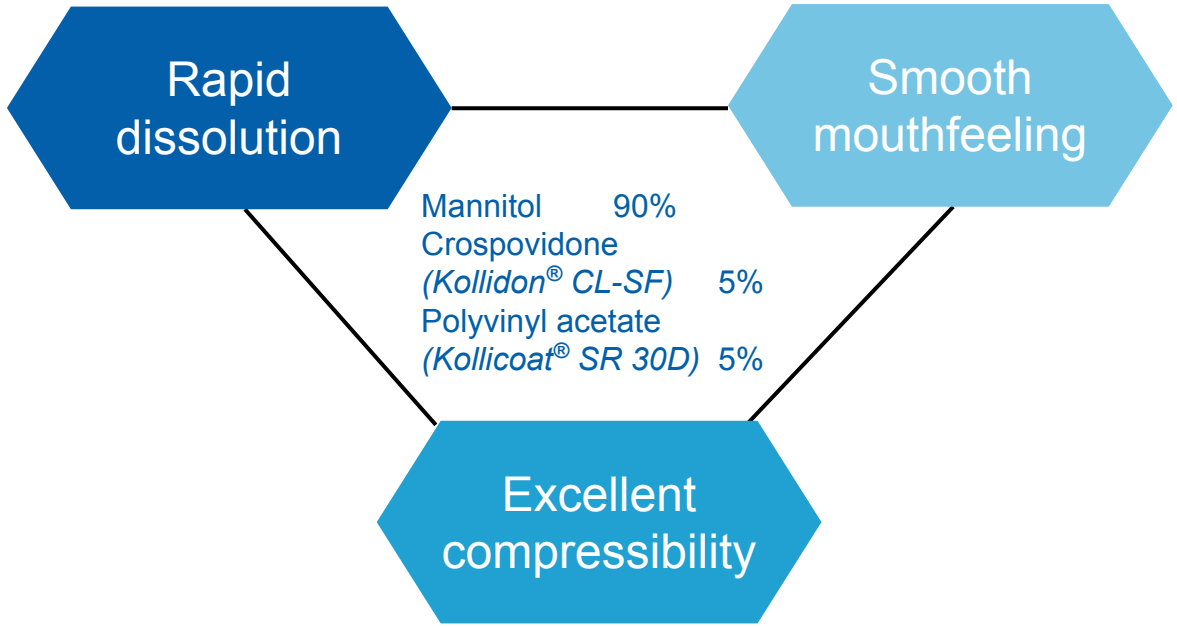


W. Sawicki, R. Lunio, Compressibility of floating pellets with verapamil hydrochloride coated with dispersion Kollicoat SR 30 D, Eur. J. Pharm. Biopharm. 60 (2005), 153-158

Innovation in ODTs (oral dispersibles)
Ludiflash®

Property triangle





Ludiflash® – the easiest and most reliable way of developing and manufacturing of ODT

ODT minitablets: 1 mg Hydrochlorothiazide based on Ludiflash®

Composition

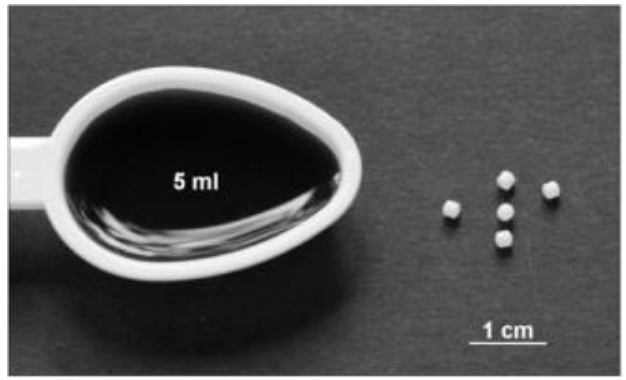
Hydrochlorothiazide 15.4% (w/w)
Ludiflash 81.1% (w/w)
Sodium stearyl fumarate 3.5% (w/w)

Geometry and manufacturing process

Geometry: biconvex mini-tablets of 2 mm diameter
Tablet mass: approximately 6.5 mg
Tooling: Euro-B 19-tip mini-tableting tool (Ritter, Stapelfeld, Germany).
Compression forces: 5.5 kN and 8 kN
Rotation speed: 10 rpm
Instrumented rotary tablet press (Pressima, MX-EU-B/D, IMA Kilian, Cologne, Germany)

Tablet characteristics

Compression force (kN)	5.5	8.0
Crushing strength (kN)	5.7 ± 0.5	8.1 ± 1.4
Friability (%)	< 1	< 1
Simulated wetting test	3.0 ± 0.2	4.9 ± 0.4



Ludiflash® showed best results regarding hardness and simulated wetting time
The promising results indicate that orally disintegrating minitablets may serve as a novel platform technology for paediatrics in future.

I. Stoltenberg and J.Breitkreutz, Eur. J. Pharm. Biopharm. 78 (3) 462-469 (2011)

Coated ODT tablets
Ludiflash tablets with coating of Kollicoat IR and Kollidon CL-M

The first coated ODT

Tablet

Loratadine 10.0 mg tablet based on Ludiflash

Coating

Combination of an extremely quick dissolving polymer (Kollicoat IR) and a finely divided crospovidone (Kollidon CL-M)

Benefits:

Nice outlook and application of color to ODT

No impact on disintegration time

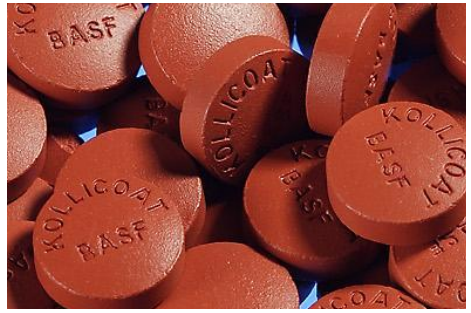
Opportunity to have 2 subsequent taste sensations:

one coming from the coating and the second coming from the core, e.g. sweet and sour

Coating example

Kollicoat IR	44%
Kollidon CL-M	15%
Talc	20%
TiO2	13.5%
Red iron oxide	6.5%
Grapefruit aroma	1.0%

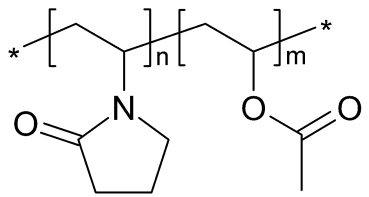
Disintegration in <30s



Ludiflash® coated ODT tablets combine quick disintegration, nice appearance and surprising sensations

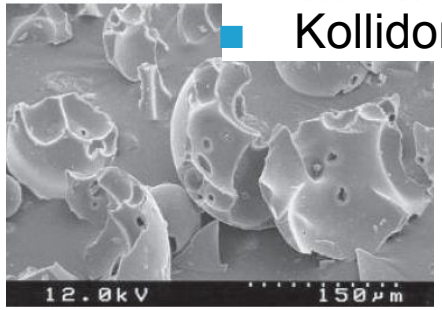
Dry binders
Kollidon® VA 64 and VA 64 Fine

"Copovidone" Ph. Eur., USP
"Copolyvidone" JPE
(vinylpyrrolidone - vinyl acetate copolymer)



n : m = 6 : 4

PSD	Kollidon® VA 64	Kollidon® VA 64 Fine
> 250 µm [%]	≤ 2	0
< 50 µm [%]	~15 ± 8	> 90



Kollidon® VA 64

Spray dried powder consisting of hollow-spheres and debris

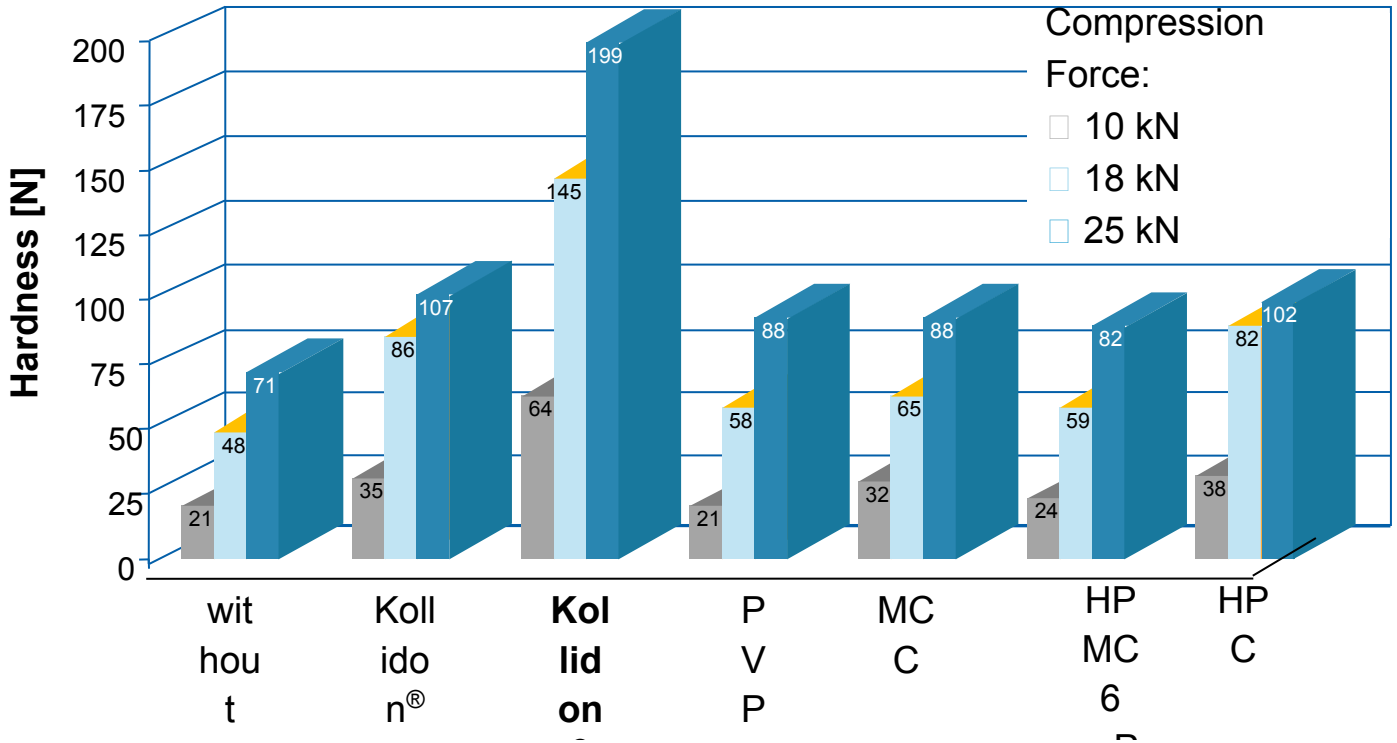
Kollidon® VA 64 fine

Sprayed to achieve small hollow spheres with thin walls

Kollidon® VA 64 Fine has a very hollow structure to optimize dry binding efficacy

Dry binders
Benchmarking tablet hardness

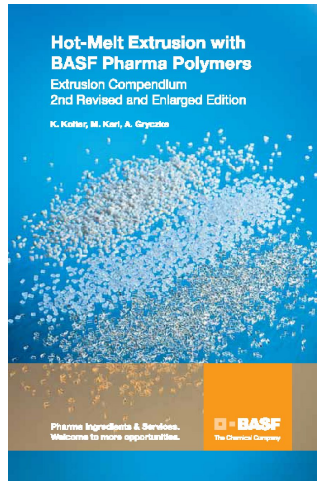
Hardness of lactose tablets with different dry binders:



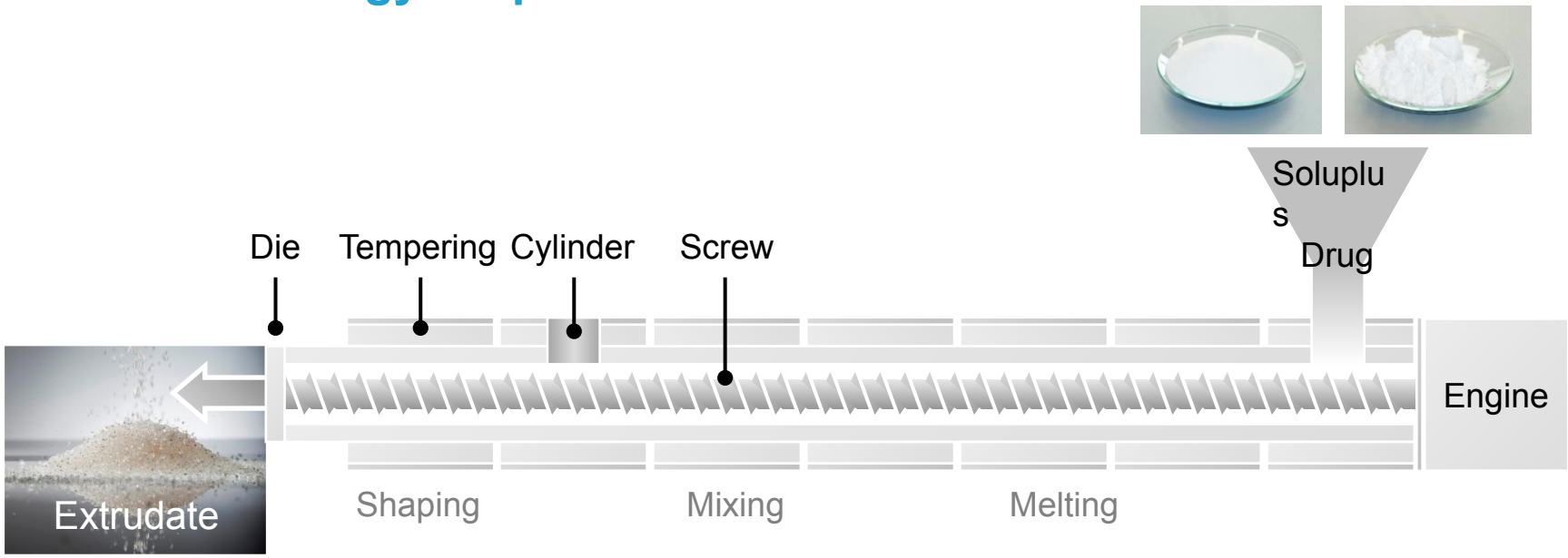
Composition	[mg]
Dry binder	50 .00
Vitamin C	200.00
Ludipress®	231.25
Kollidon® CL	15.00
Aerosil	1.25
Mg stearate	2.50
Tablet weight	500.00

Kollidon® VA 64 Fine gives the hardest tablets

BASF technologies: Hot-Melt Extrusion



BASF developed this technology for pharma

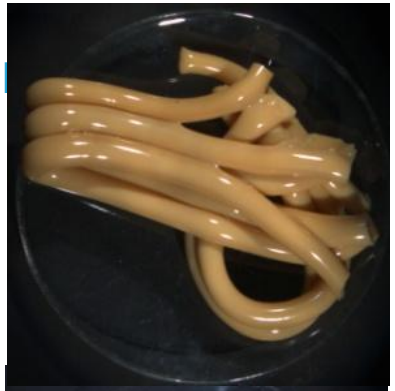


Temperature: above T_g of polymer *(60 – 200 °C)*
Residence time: variable *(0.5 – 5 min)*

BASF exceipients for Hot Melt Extrusion

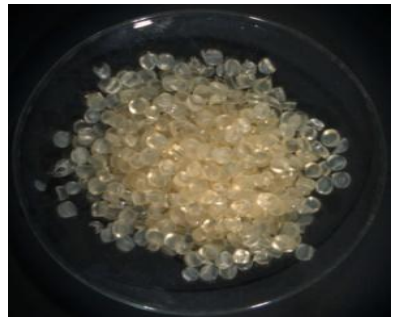
Kollidon VA 64

160°C



180°C

Kollicoat IR



160°C

Kollidon 12 PF

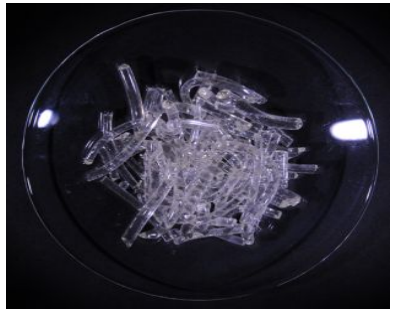
100°C

145°C

Kollicoat Protect

160°C

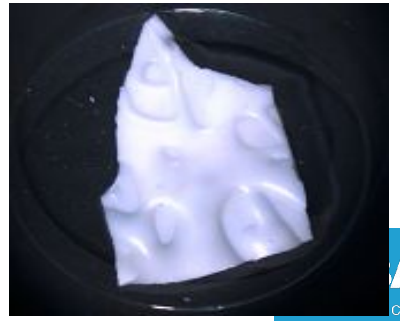
Kollidon 17 PF



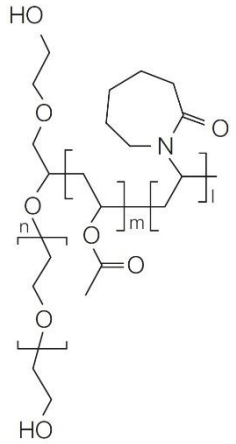
175°C

Appearance of the extrudates

Poloxamer P 407



Two in one: Soluplus®

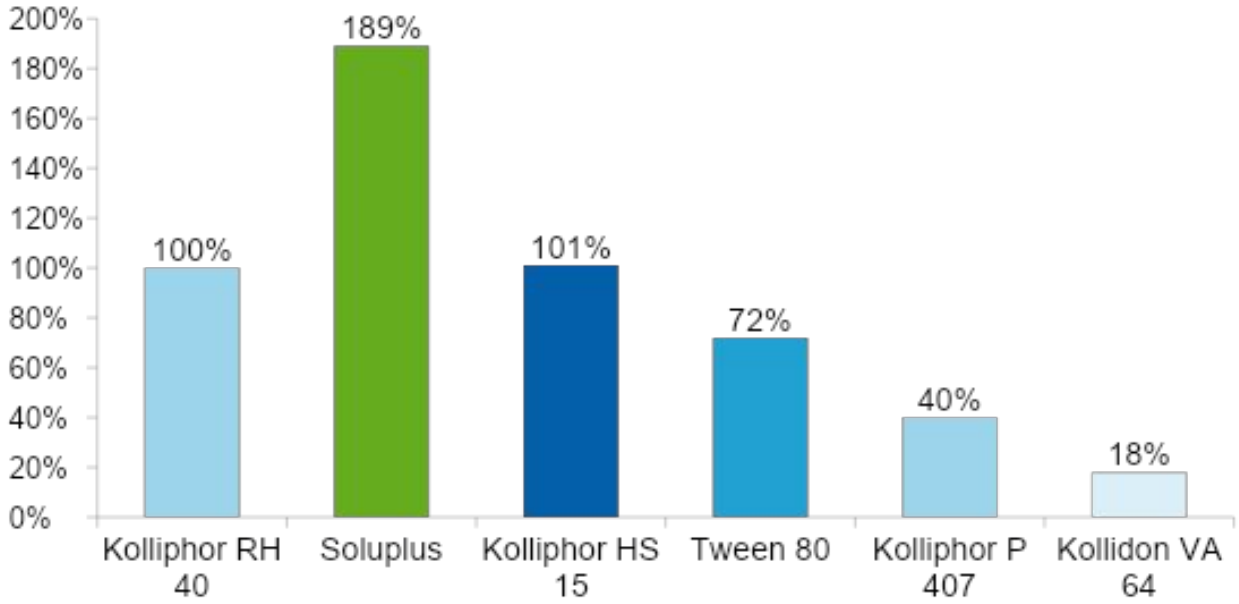


Honored with Silver Award

CPhI worldwide

Award 2010

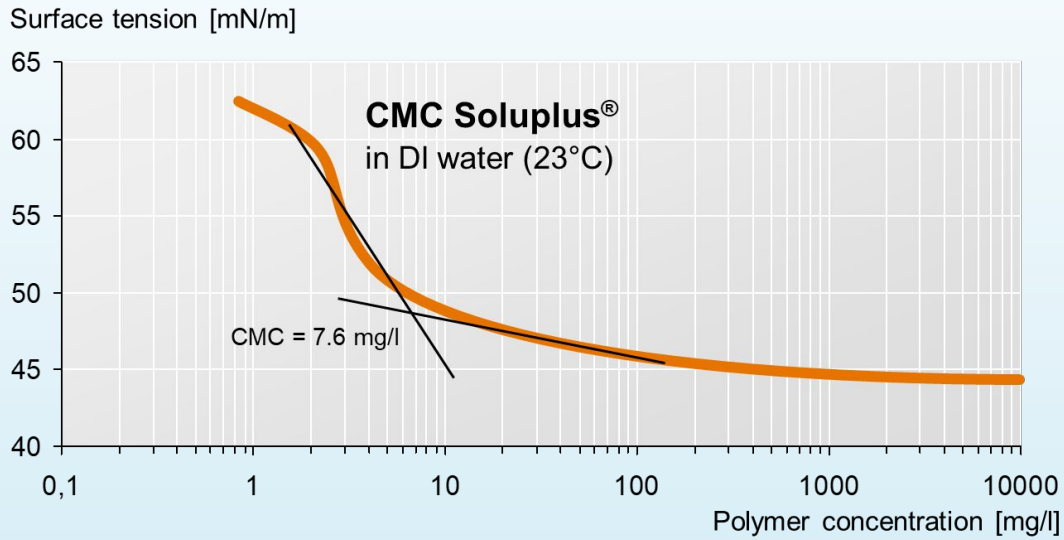
- PEG 6000 / vinylcaprolactam / vinyl acetate (13/57/30)
- Critical micelle concentration *(CMC)*
  7.6 mg/L
- Glass transition temperature
  ~ 70°C
- Molecular weight
  ~ 118 000 g/mol
- Solubilization capacity
  (average based on 9 APIs)



BASF We create chemistry

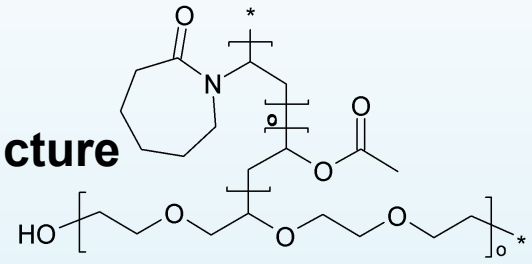
Solubilization of drug by Soluplus

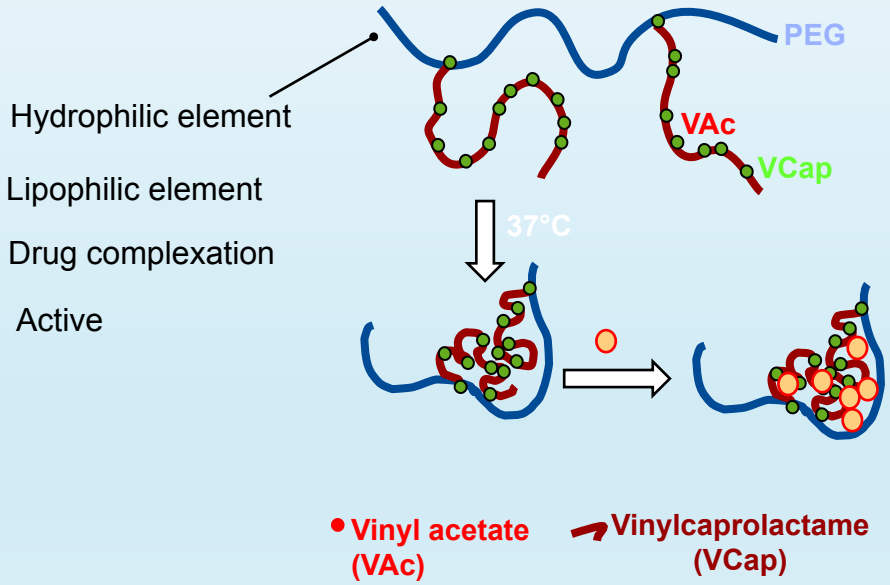
Soluplus® has a much lower CMC hence considered as a potent solubilizer



- Approximate HLB ≈ 14
  - Based on moieties weighted average
- Micelle Size
  - 70 to 100 nm in pH 7 buffer
  - Independent of conc. and temp

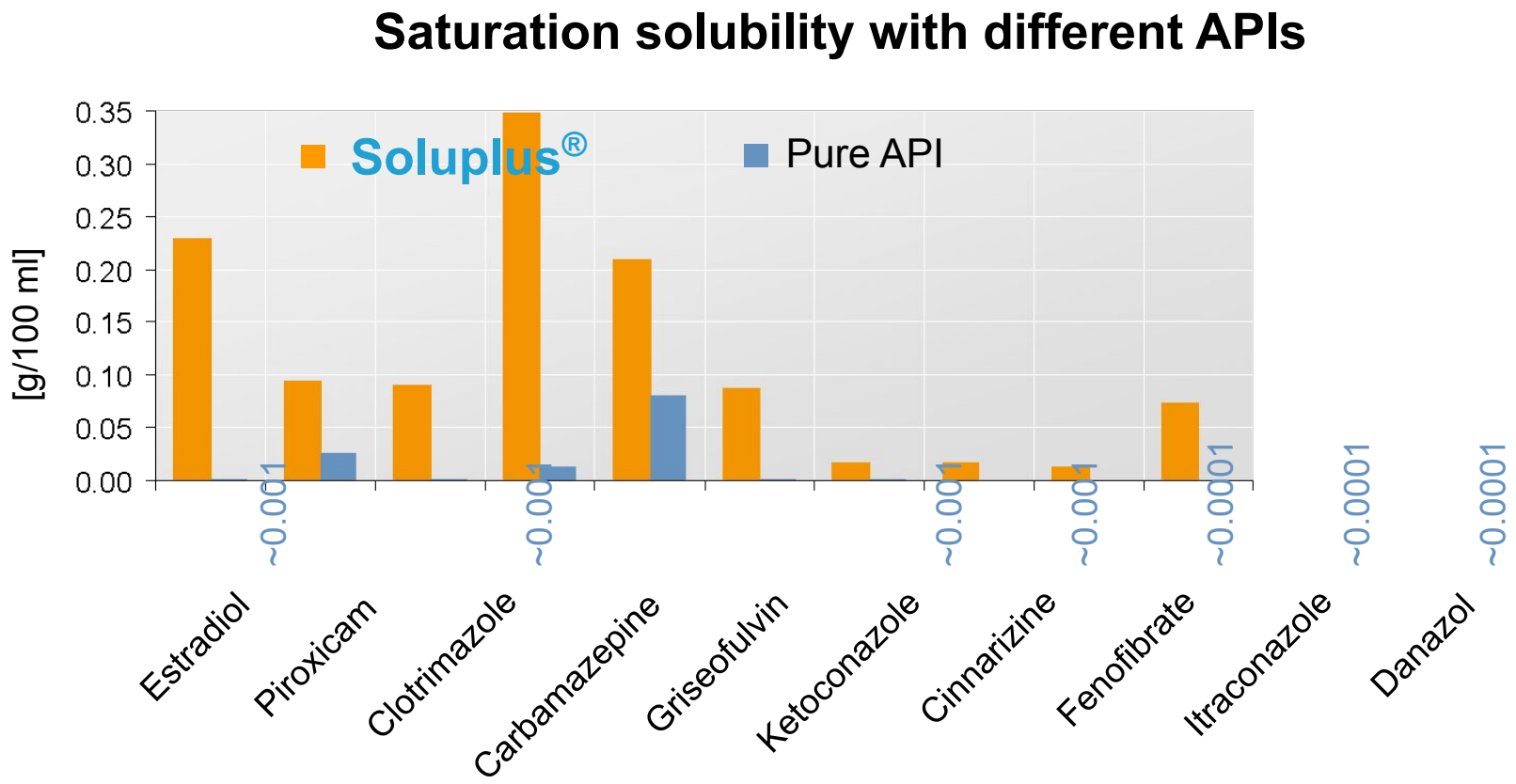
Soluplus®
Amphiphilic structure





Doherty and York, 1987 JPS, 1987, 76, 731-737; Raghavan et al,IJP, 2001, 212, 213-225

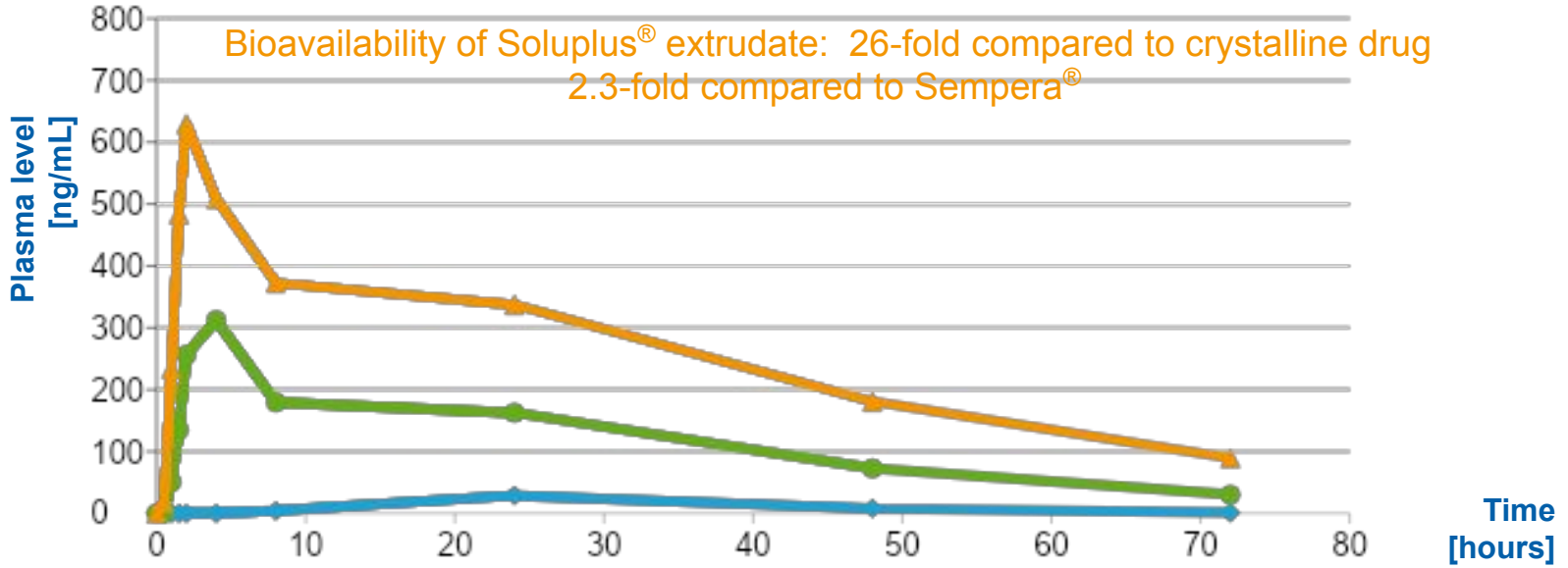
Soluplus® as Solubilizer: Soluplus® gives manifold increase in solubility for APIs of various chemical structures



phosphate buffer pH 7.0; 10% solubilizer solution, saturation solubility detected after 72h stirring

Bioavailability studies with Soluplus® formulations

Itraconazole



Bioavailability = area under the curve (AUC)

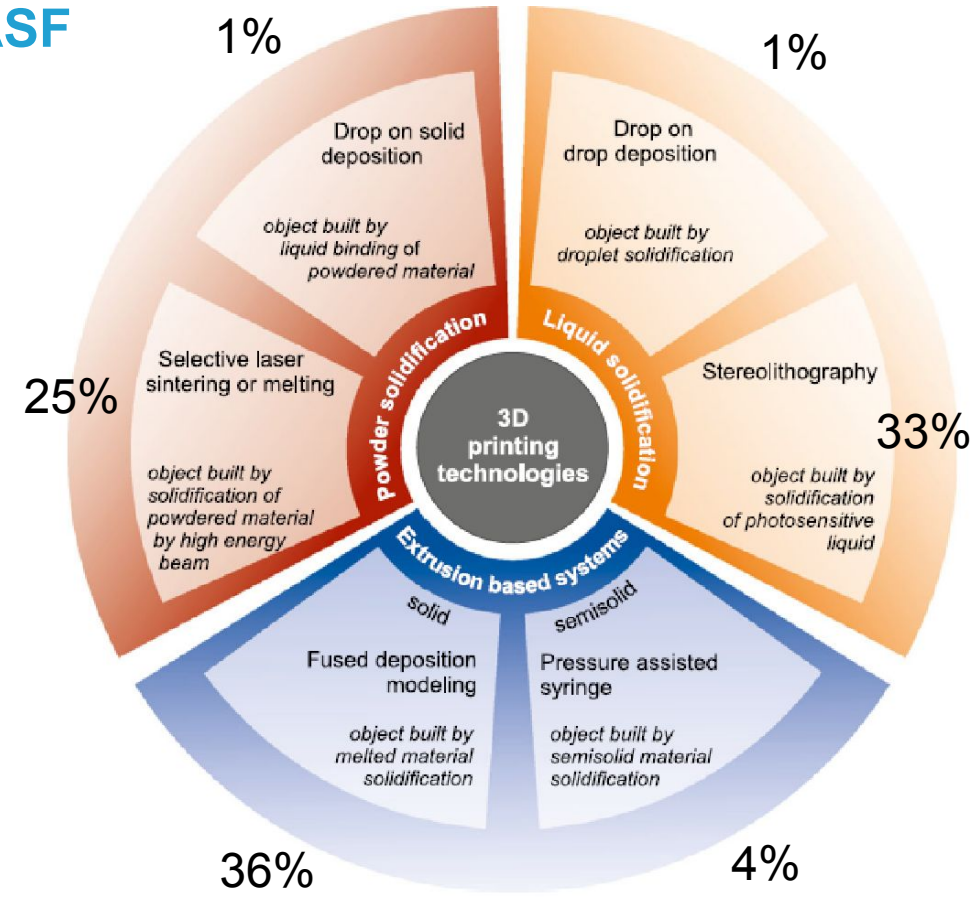
- Itraconazole – Soluplus® extrudate
- Sempera®
- Itraconazole crystalline

The Soluplus® formulation outperforms the registered drug Sempera® by a factor of 2.3

3D printing technologies

- **Fused Deposition Modeling (FDM)** - a thermal extrusion method
- **Stereolithography (SLA)** - a method that uses high energy UV light to photo-polymerize a liquid resin to create solid parts
- **Selective Laser Sintering (SLS)** - a powder bed method that uses a laser or heat to sinter powder particles together to create a solid object.
- **Semi-Solid Extrusion (SSE) -** a method that is based on cold extrusion of semi-solid materials (gels or pastes) that solidify to create a solid object

Equipment at BASF



Jamroz et al., Pharm. Res., 2018, 35, 176

Trenfield et al., Trends in Pharmacol. Sci., 2018

Fused deposition modeling: Kollicoat® IR – extruded filaments

For immediate release purposes

Priority 1	Die temperature [°C]	Torque [Nm]	Appearance	Tackiness	Flexibility	Winding on 8 cm spool
Kollicoat® IR with 10 to 17.5 % Kollisolv® PEG 400	170	≤ 80		No	1-2	Yes (Strings ~2.2 mm)

Priority 2	Die temperature [°C]	Torque [Nm]	Appearance	Tackiness	Flexibility	Winding on 8 cm spool
Kollicoat® IR with ≤ 5 % Kolliphor® RH 40	170	≤ 77		Slight stickiness	3-4	Yes (Strings ~2.5 mm)

Fused deposition modeling : Soluplus ® - extruded filaments

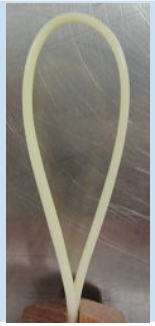
For immediate release and solubilization purposes

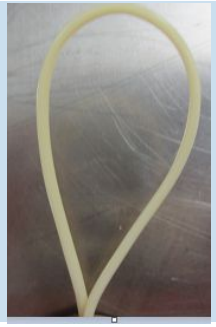
Priority #1	Die temperature [° C]	Torque [Nm]	Appearance	Tackiness	Flexibility	Winding on 8 cm spool
Soluplus® with 5-10 % Kollisolv® PEG 400	150	≤ 53		No	1	Yes (Strings ~1.5 mm)

Priority 2	Die temperature [° C]	Torque [Nm]	Appearance	Tackiness	Flexibility	Winding on 8 cm spool
Soluplus® with 10 to 15 % Pluriol® E 1500 or Kolliphor® P 188	150	≤ 24		No	1-5	Yes (Strings ~1.5 mm)

Fused deposition modeling : Kollidon® SR – extruded filaments

For sustained release purposes

Priority 1	Die temperature [° C]	Torque [Nm]	Appearance	Tackiness	Flexibility	Winding on 8 cm spool
Kollidon® SR with 5 to 10 % Kollisolv® PEG 400	160	≤ 60		No	1-6	Yes (Strings ~1.8 mm)

Priority 2	Die temperature [° C]	Torque [Nm]	Appearance	Tackiness	Flexibility	Winding on 8 cm spool
Kollidon® SR with ≤ 7.5 % Kolliphor® P 188	160	≤ 61		Slight stickiness	1	Yes (Strings ~1.9 mm)

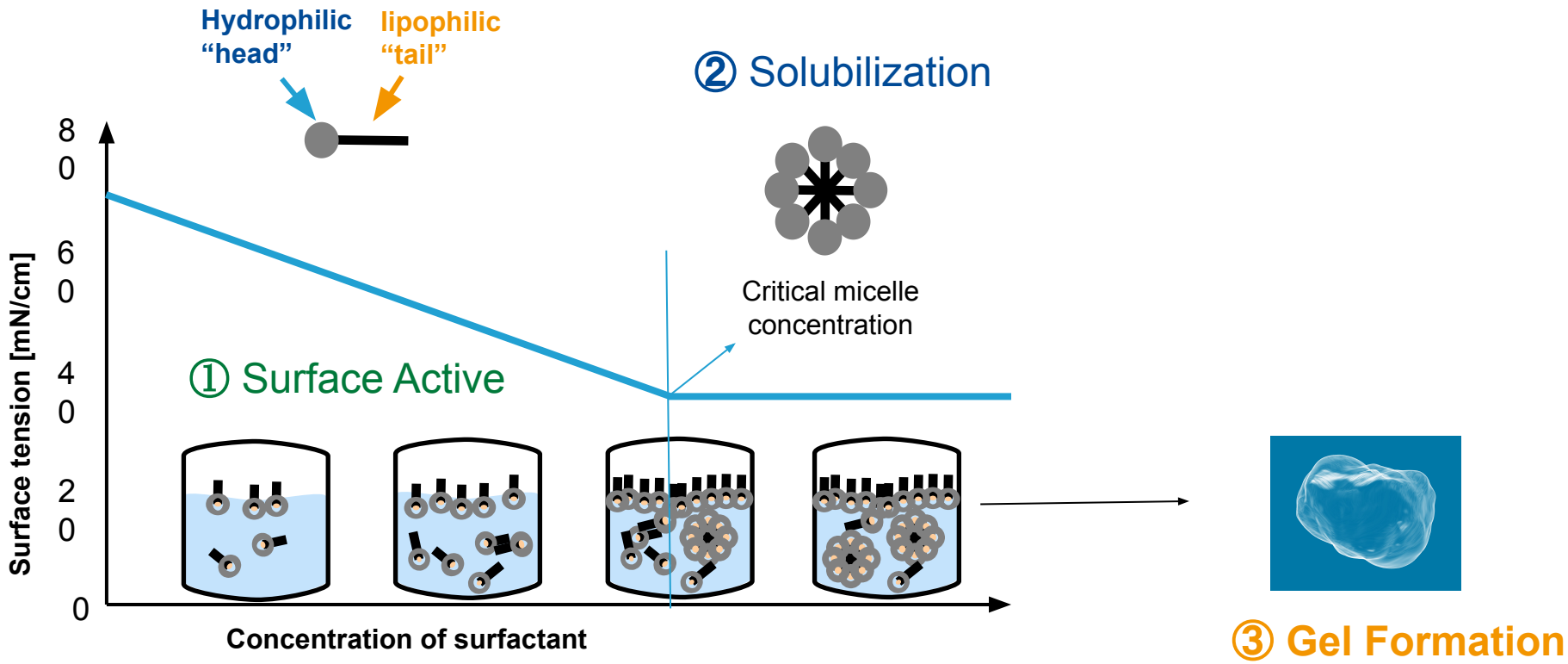
Physicochemical properties make the difference: Kolliphor P 188 micro and P 407 micro

Unique fine poloxamer grades

- Lubricant (water-soluble, enhancing dissolution)
- Pore-former
- Meltable binder

- Kollisolv® P124 Geismar
- Kolliphor® P188 Geismar
- Kolliphor® P188 Bio
- Kolliphor® P188 micro Geismar
- Kolliphor® P338 Geismar
- Kolliphor® P407 Geismar
- Kolliphor® P407 micro Geismar

Behavior of poloxamer's in water



Poloxamer's are multi-functional depending on the usage levels.

Summary & Conclusions

Because todays formulation problems cannot be solved with yesterday's excipients, there is a need to develop innovative excipient solutions

- BASF is at the forefront of innovation with new and novel excipients addressing the unmet needs of the Pharmaceutical Industry.
- FDA’s Novel excipient pilot program is expected to give impetus to innovation, both for new and novel excipients.
- BASF has a deep and profound understanding of various suitable excipients and formulations

Allow our expert team to provide you with Innovative solutions to address your unmet formulation needs & faster commercialization of your products

We create chemistry