DISSO INDIA-MUMBAI 2023
INTERNATIONAL SYMPOSIUM

BASF
We create chemistry

# Role of Excipients in Modulation of Drug Dissolution Profile

**Sandip B. Tiwari, *Ph. D.***

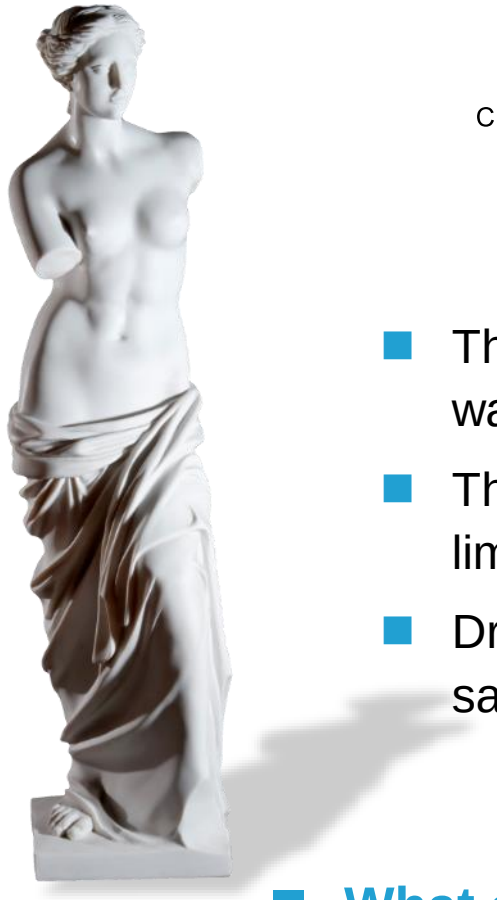
BASF Pharma Solutions, NA

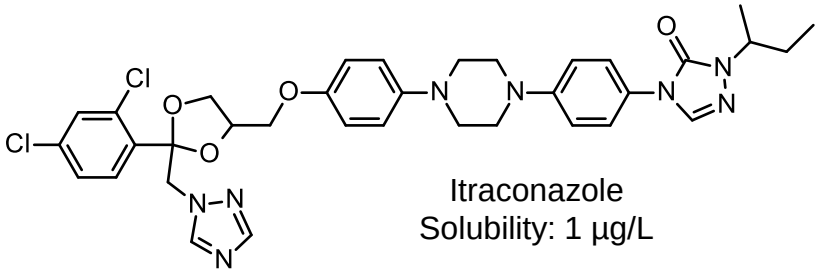
June 26 & 27, 2023

# Outline

1. Introduction to solubility and bioavailability challenges
2. Supersaturation and drug delivery systems (softgels)
   2.1 Experimental design & results
3. Amorphous solid dispersions (tablets)
   3.1 Experimental design & results
4. Conclusions

# Poor solubility of drugs is one of the key challenges in formulation development



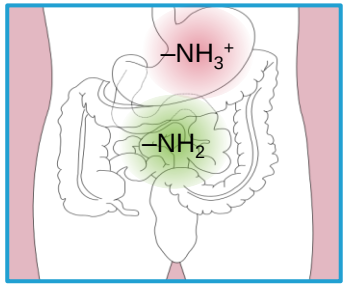



Itraconazole
Solubility: 1 µg/L

- The Venus de Milo (Marble) is 10-times more soluble in water than many other actives
- The intraluminal concentration of a drug is not necessarily limited by its solubility in gastrointestinal fluids
- Drugs may be in solution at a concentration above their saturation solubility ➔ state of supersaturation


- **What cannot be dissolved cannot be absorbed and cannot cure!**

# Supersaturating drug delivery systems can enhance oral bioavailability




## Supersaturation induced by gastrointestinal pH gradient

The intake of weakly basic drug molecules – even in the crystalline form – may result in supersaturation in the small intestine

## Administration of drugs in solution

Drugs formulated using a mixture of co-solvents, surfactants, complexing agents, and/or oils; dilution or dispersion in the GI tract generates a metastable supersaturated state

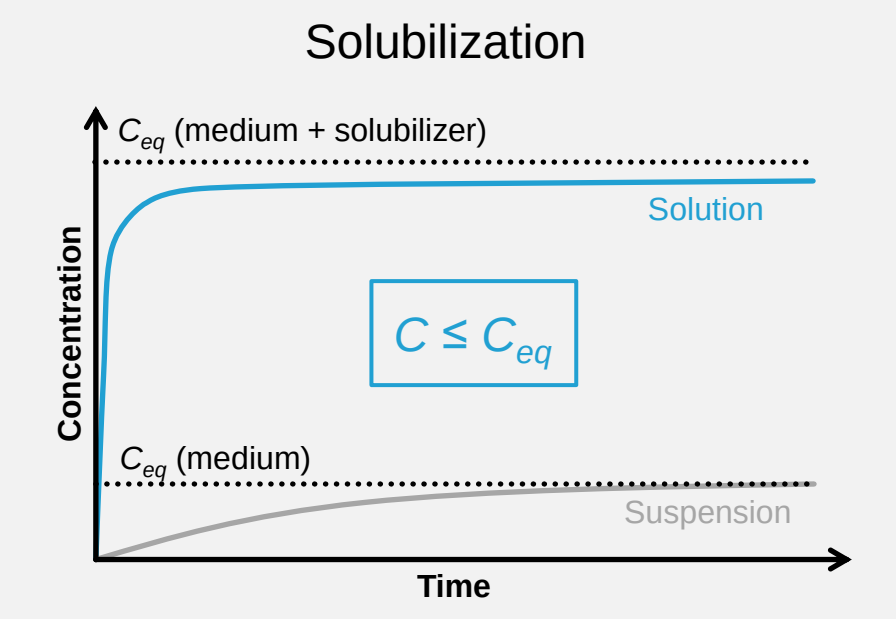
## High-energy and/or rapidly dissolving solid forms

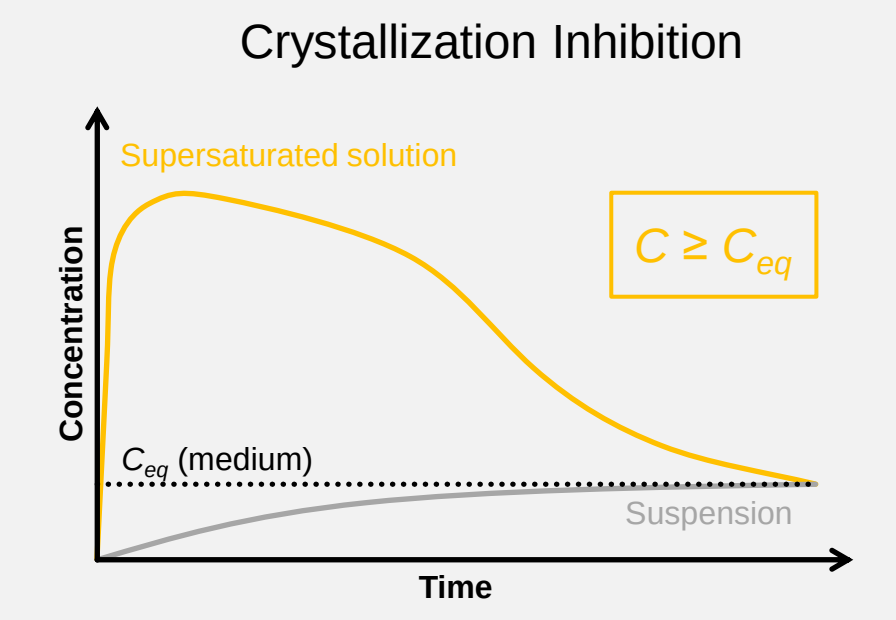
Amorphous solid dispersions, nanoparticles, co-ground mixtures, carriers based on mesoporous silica, co-crystals and crystalline salt forms, water-soluble prodrugs…

BASF
We create chemistry

# Excipients enabling supersaturation state

- Excipients like surfactants may inhibit precipitation by increasing the maximum achievable saturation concentration of the drug ($C \leq C_{eq}$, thermodynamic approach)
- Surfactants may also delay precipitation from supersaturated solutions by inhibiting crystallization ($C \geq C_{eq}$, kinetic approach)

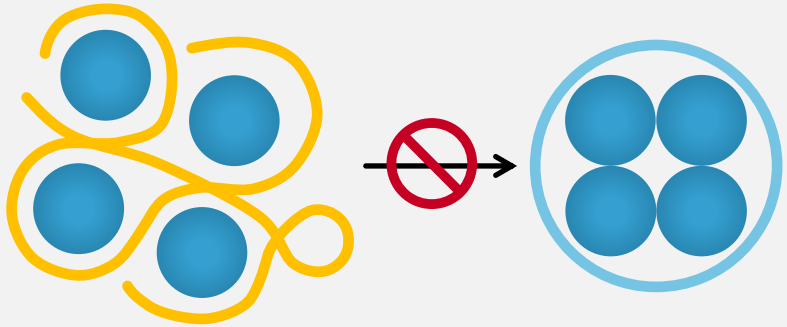



*The intraluminal concentration of a drug is not necessarily limited by its solubility in GI fluids but rather the time it can be maintained in supersaturation during the absorption window*

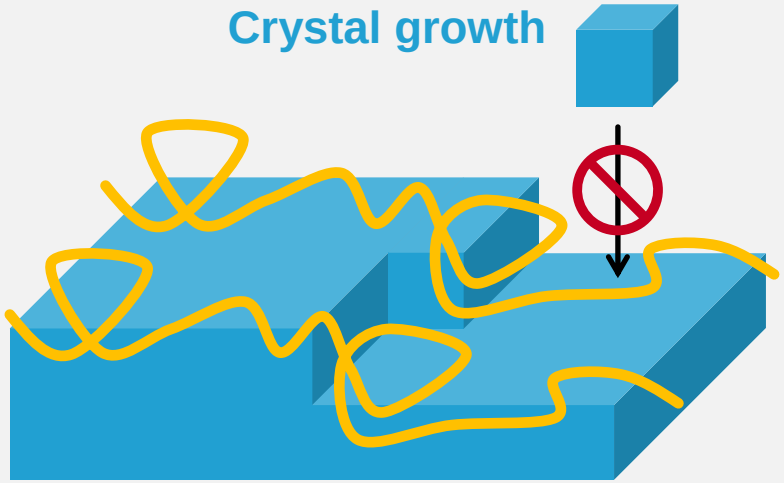
# Excipients enabling supersaturation state: mechanism of action

## Nucleation



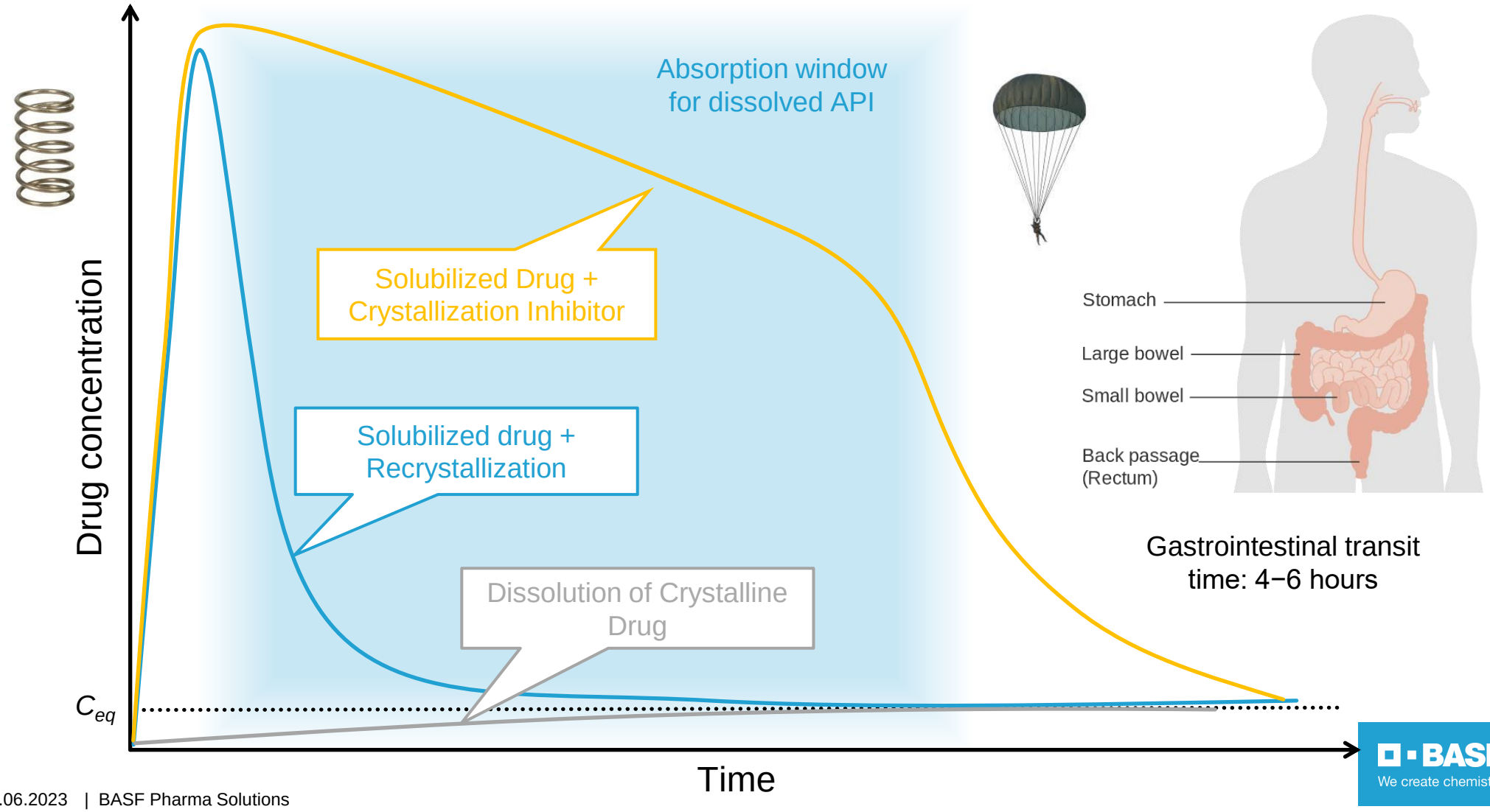
- Specific (e.g., hydrogen bonds) and non-specific (e.g., hydrophobic) interactions between drug molecules and the polymer increase the activation energy required for nucleation
- Polymers hinder the reorganization of a cluster of drug molecules into an ordered structure (rate-limiting step of the two-step nucleation model)

## Crystal growth



- Change of the adsorption layer at the crystal–solution interface
  - Diffusion of drug molecules to the crystal nuclei is hindered
- Polymers adsorb onto the crystal surface
  - Incorporation of drug molecules into the crystal lattice is hindered
  - Growth rate decreases
- Polymers alter the surface energy of the crystal face / change the level of solvation

# “Spring and parachute” approach –lever to enhance bioavailability

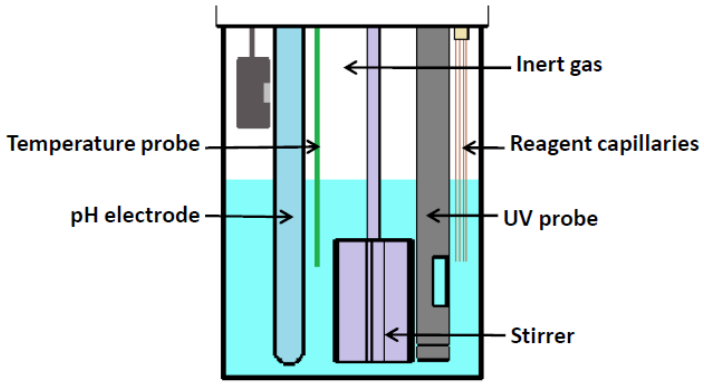


# Outline

1. Introduction to solubility and bioavailability challenges
2. Supersaturation and drug delivery systems (softgels)
   - 2.1 Experimental design & results
3. Amorphous solid dispersions (tablets)
   - 3.1 Experimental design & results
4. Conclusions

# Enabling “parachute effect” in soft gelatin capsules
# Use of Pion inForm for high throughput dissolution measurement

Pion inForm




inForm Measurement Cell

Experimental set-up

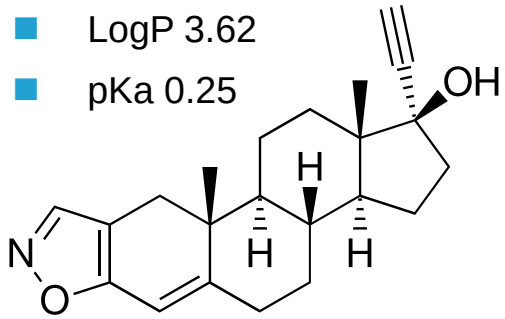
- Formulations
  - Kollisolv® PEG 400
    - Saturated with API
  - 5% of surfactant or polymeric additive is solubilized
  - 500 µL formulations
    - Representative Softgel volume
  - Dissolution media -50 mL Buffer System
    - pH 2 HCl Buffer
    - pH 6.8 Phosphate Buffer

BASF
We create chemistry

# Selection of API‘s: poorly soluble drugs with different behavior in GI conditions

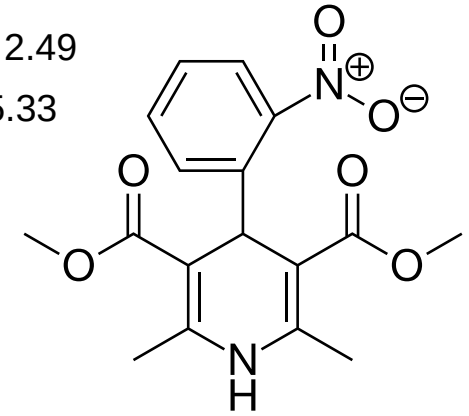
## Danazol

- Model poorly water soluble drug
- Synthetic Stearoid
- MW 337.46
- LogP 3.62
- pKa 0.25



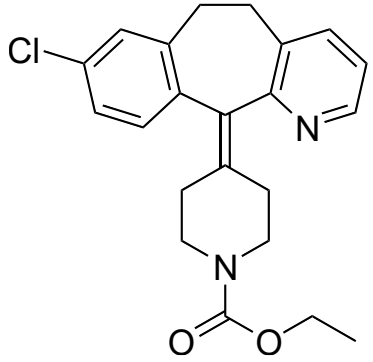

## Nifedipine

- Model poorly water soluble drug
- Calcium channel blocker
- MW 346.33
- LogP 2.49
- pKa 5.33

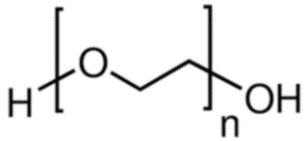



## Loratadine

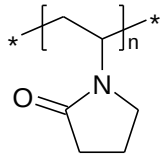
- Common OTC Drug (Claritin)
- Antihistamine
- MW 382.88
- LogP 4.55
- pKa 4.33



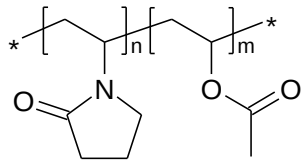

## Kollisolv® (PEG 400)



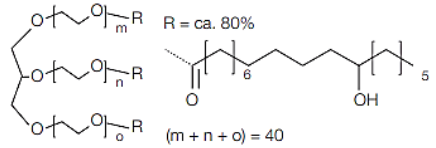

## Kollidon® (Povidone)




## Kollidon® VA 64 (Copovidone)

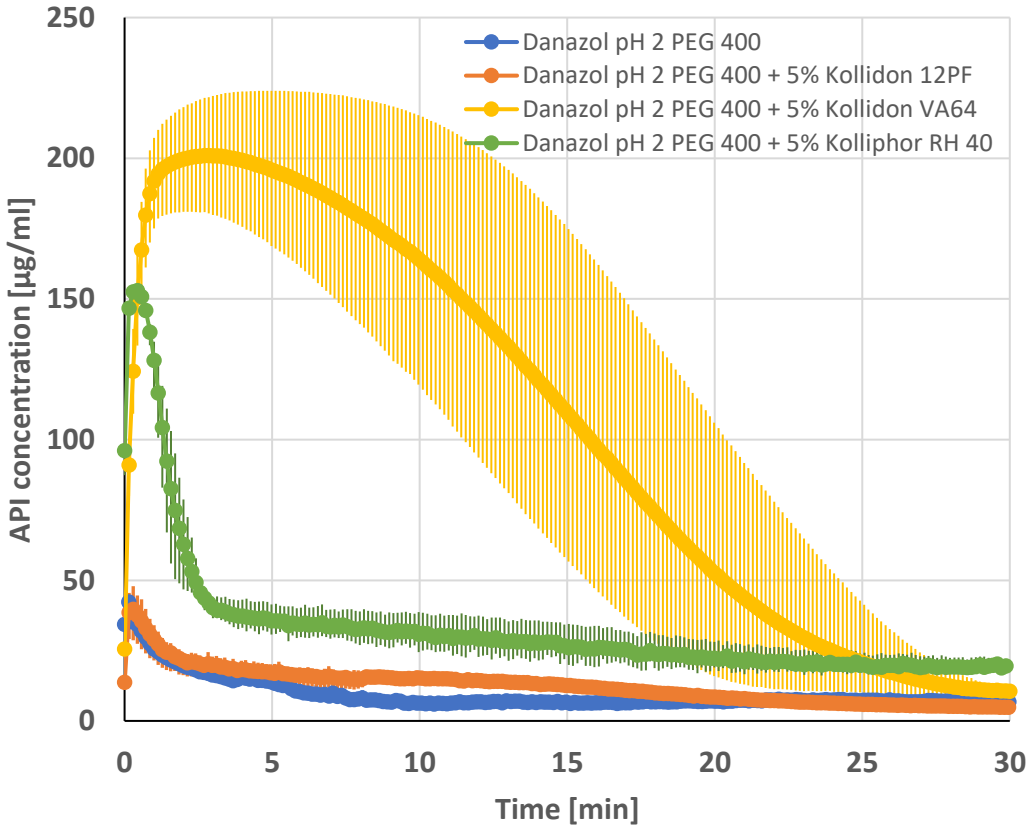



## Kolliphor® (RH 40)

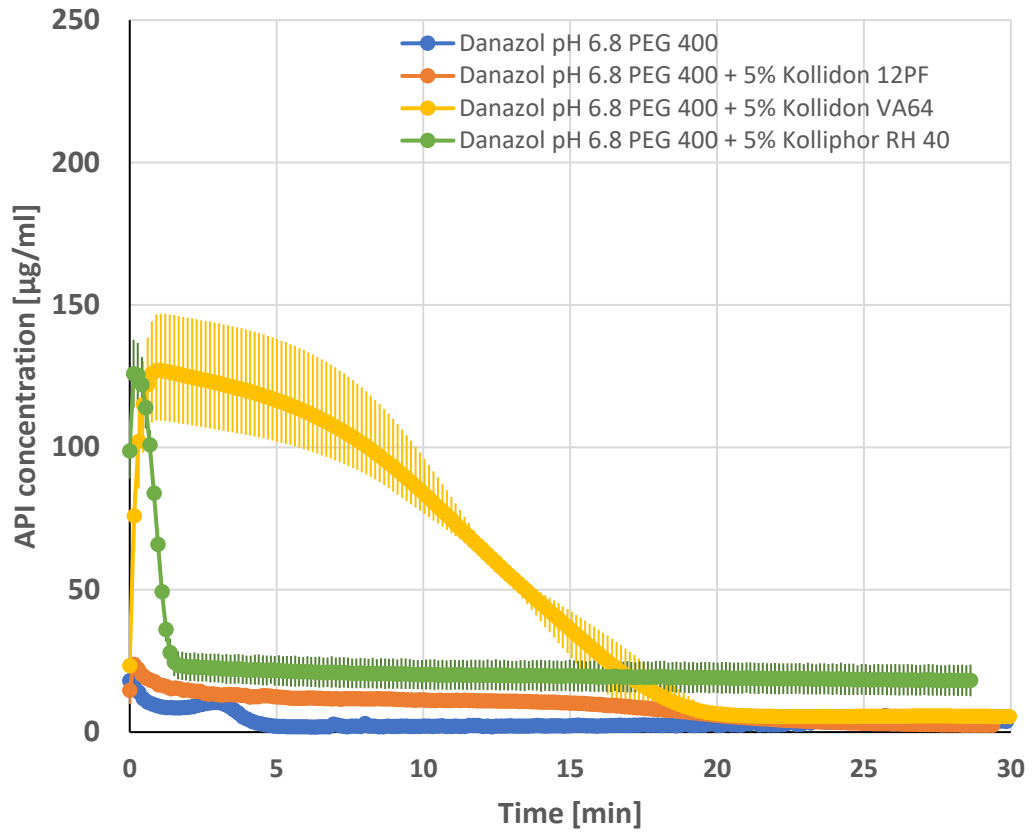


# Danazol formulation: enabling “parachute effect”

## Danazol – 500 µL in 50 mL pH 2 HCl Buffer



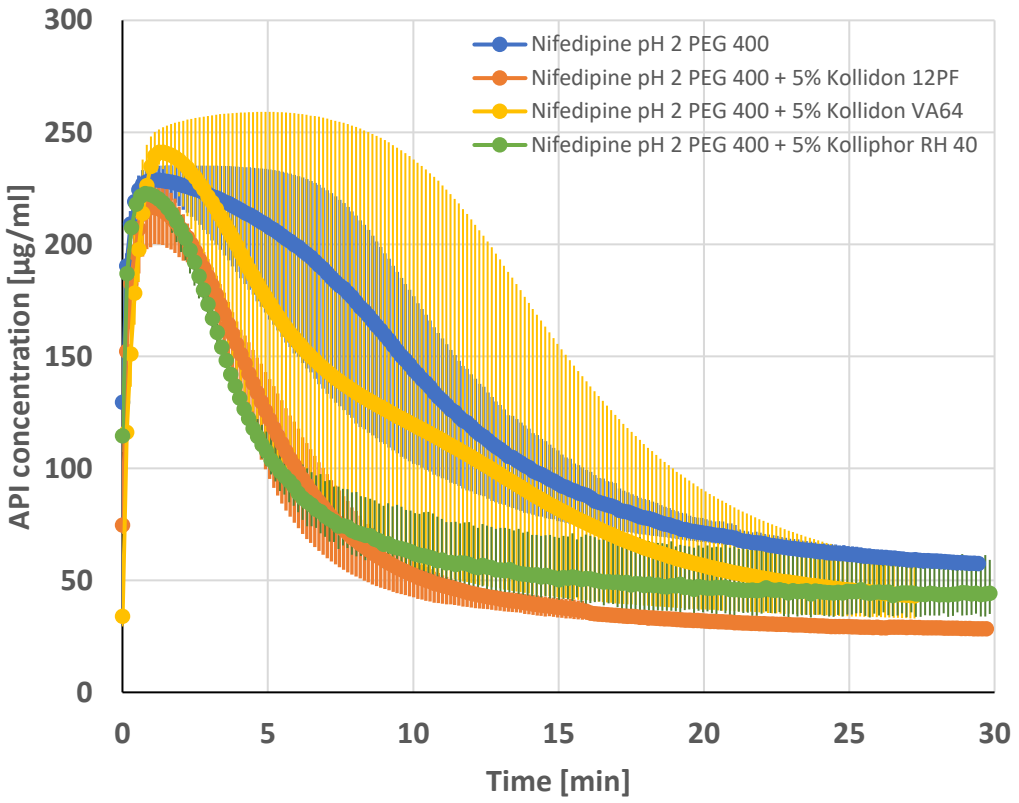

## Danazol – 500 µL in 50 mL pH 6.8 Phospate Buffer




- **Under GI conditions, a suprisingly strong inhibition is shown for formulations using Kollidon® VA 64**

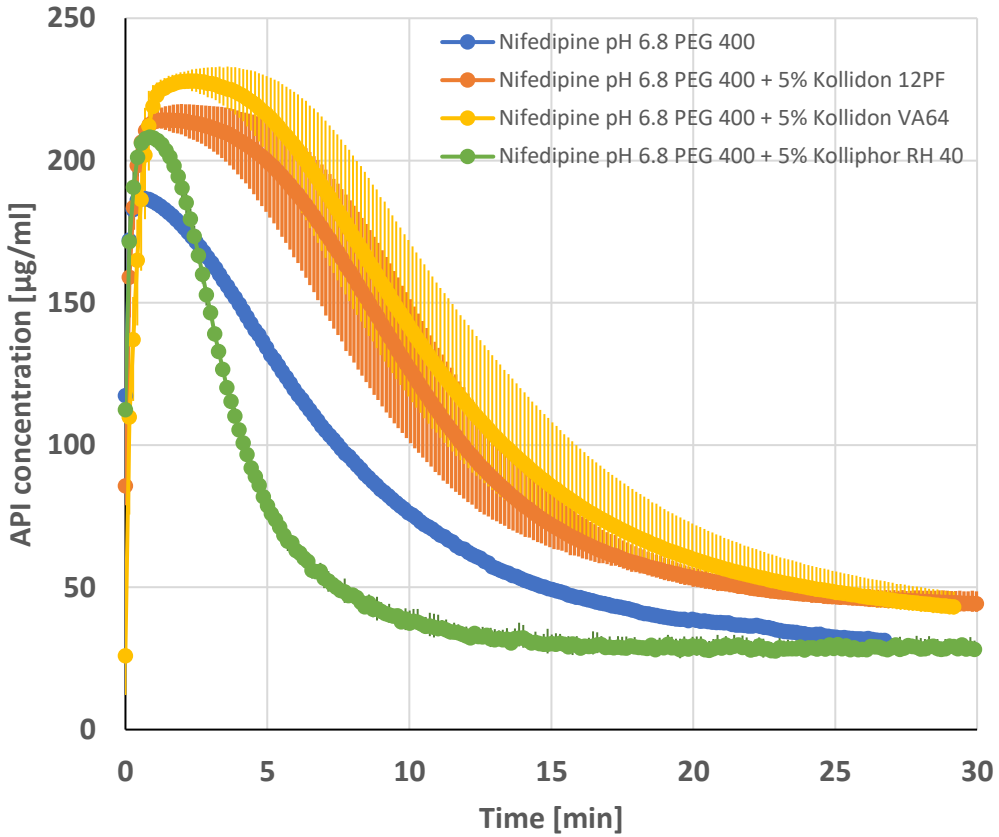
# Nifedipine formulation: “parachute effect” depended on GI conditions

## Nifedipine – 500 µL in 50 mL pH 2 HCl Buffer




- Inhibition of Nifedipine under stomach conditions were not significantly more effective than the PEG matrix alone

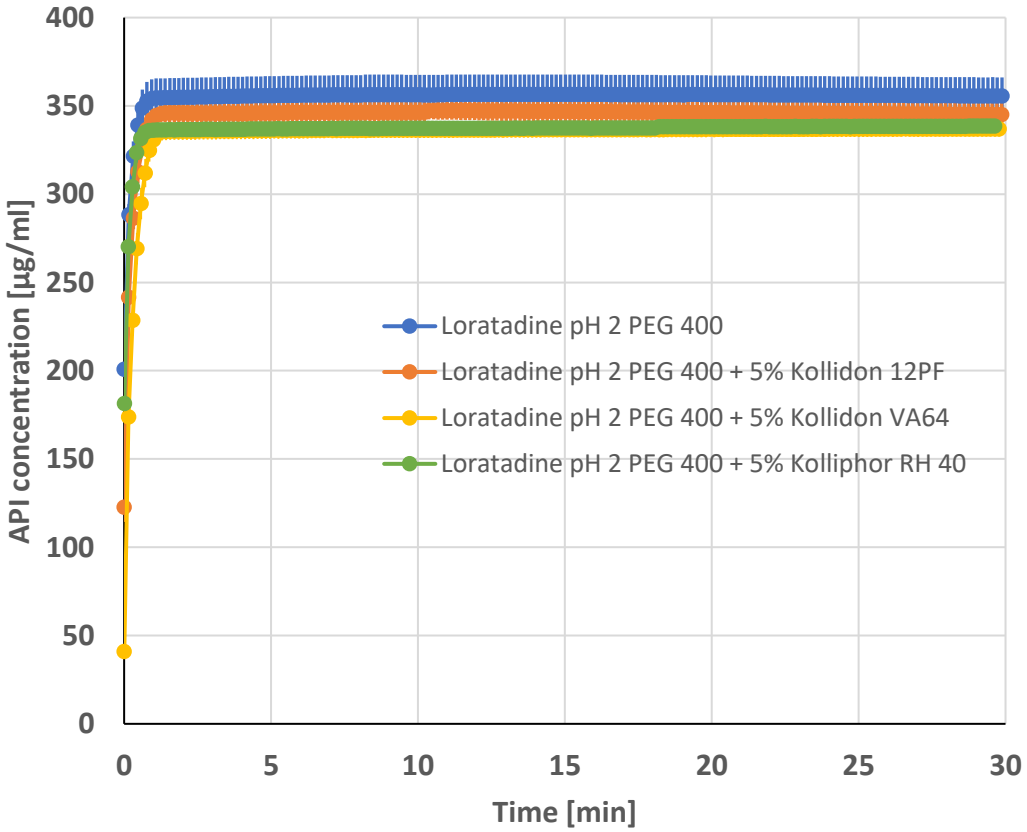
## Nifedipine – 500 µL in 50 mL pH 6.8 Phospate Buffer




- Povidone and Copovidone exhibited strong inhibition under intestinal conditions

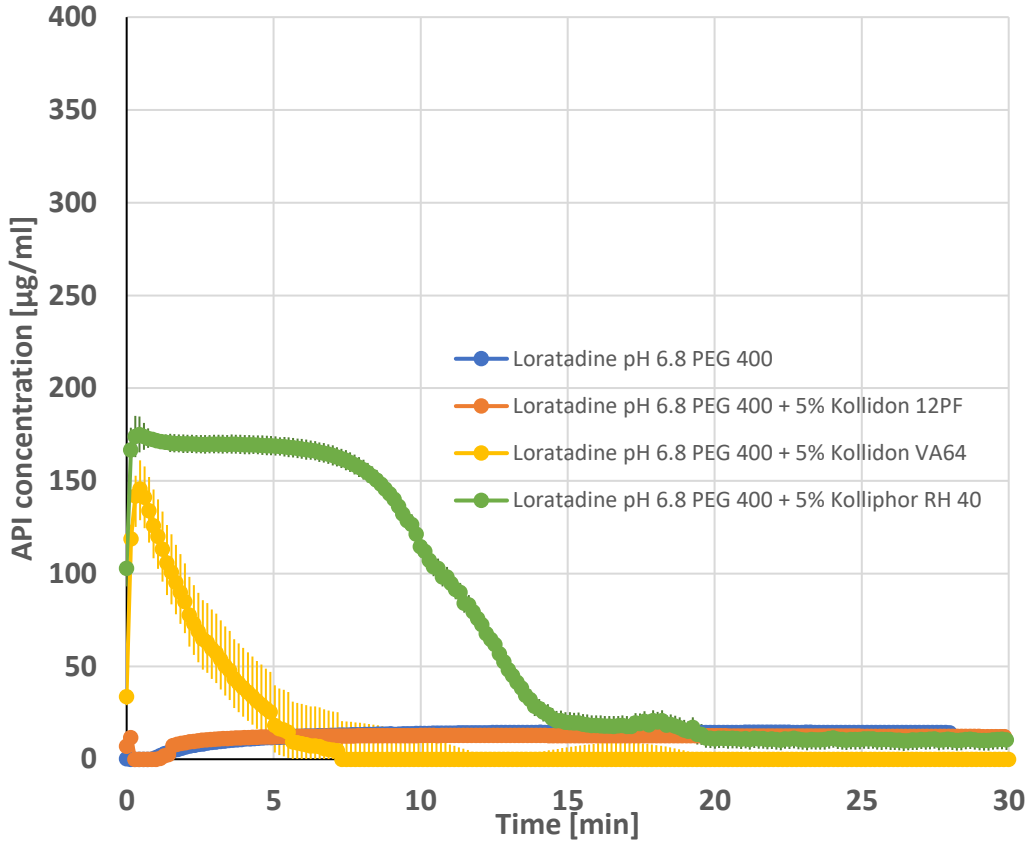
# Loratadine formulation: “parachute effect” in intestinal conditions

## Loratadine – 500 µL in 50 mL pH 2 HCl Buffer




- Loratadine is known to be soluble under acidic conditions of the stomach and no inhibition was required

## Loratadine – 500 µL in 50 mL pH 6.8 Phospate Buffer

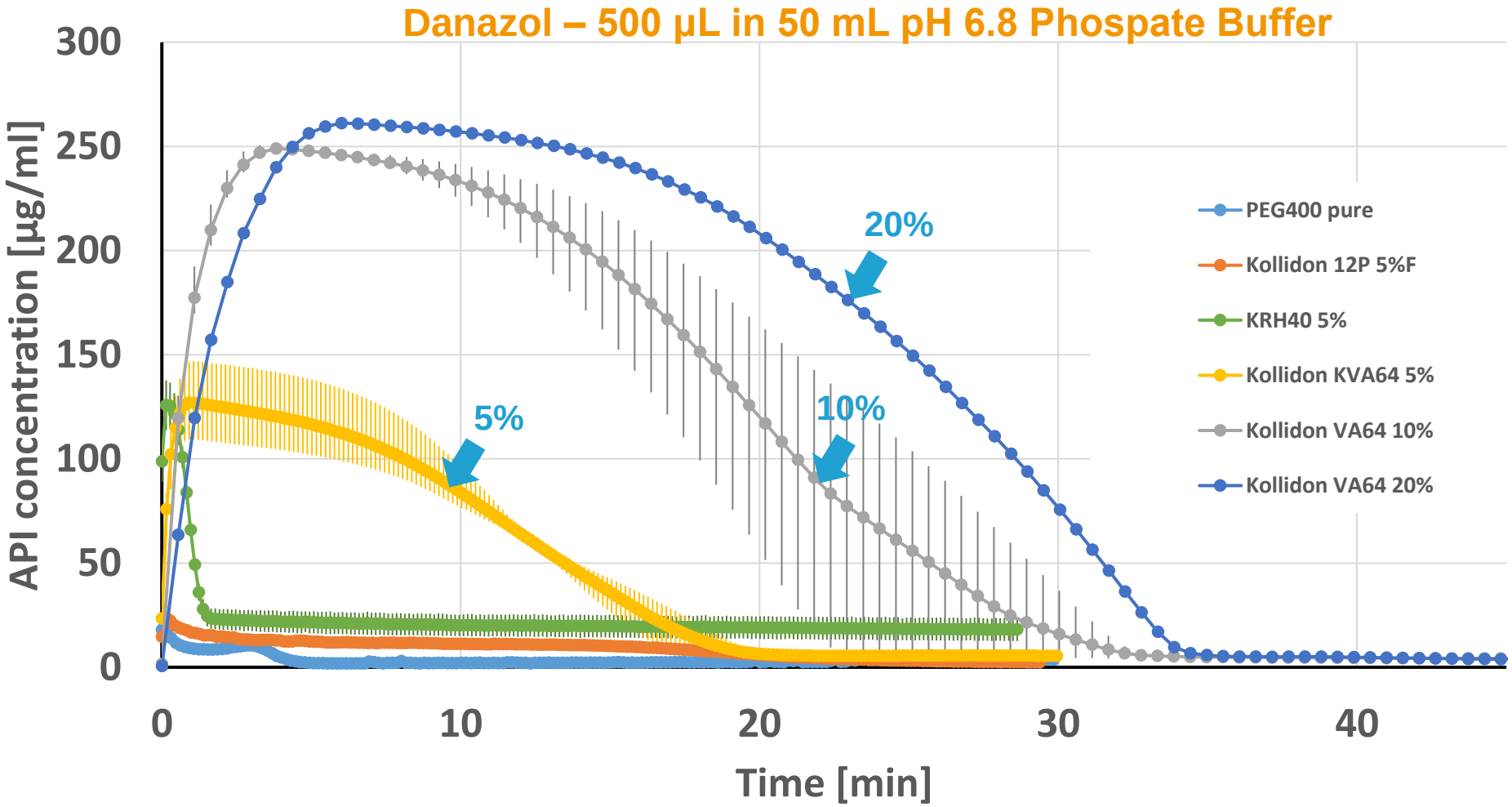



- Potent solubilizer Kolliphor® RH 40 was shown to be most effective under intestinal conditions



BASF
We create chemistry

# Danazol formulation: maximizing “parachute effect”

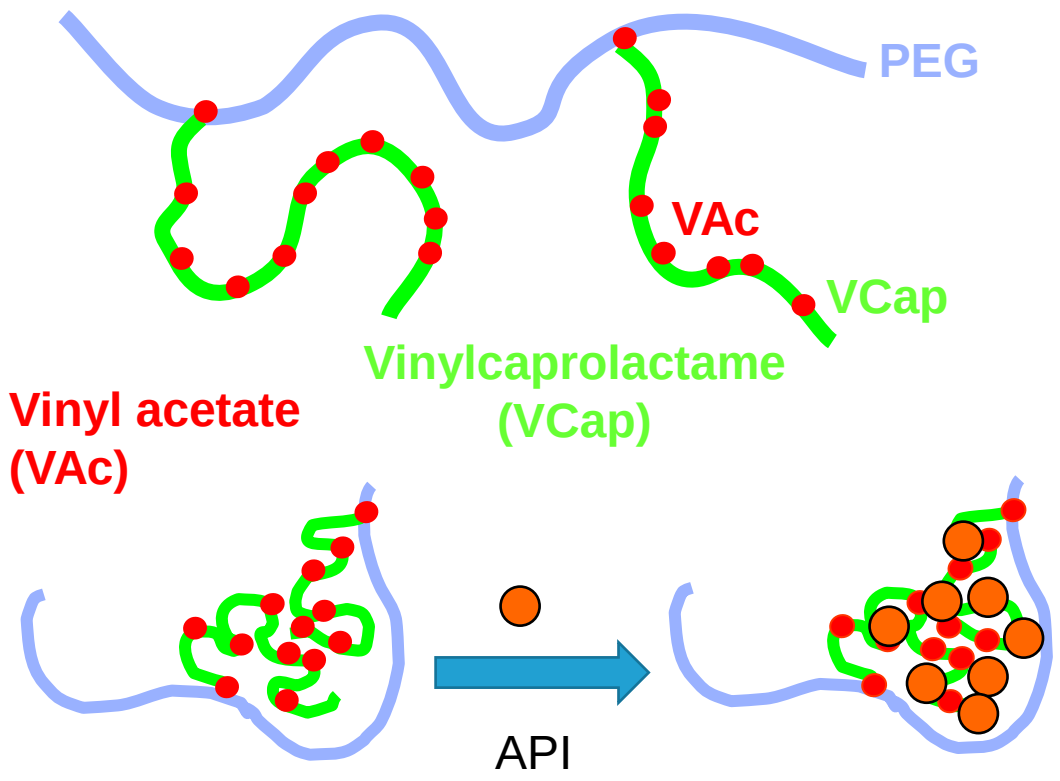


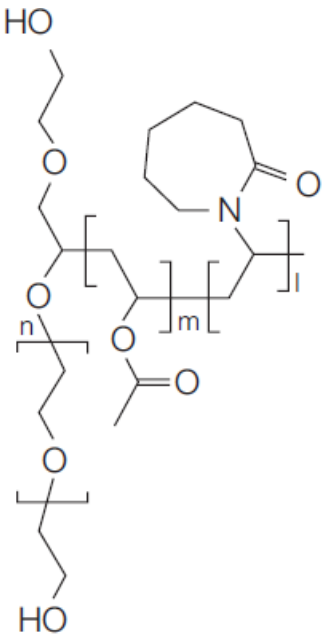

- Higher concentrations significantly extending the window further (Intestine pH 6.8, Danazol model)

# Novel excipient: Soluplus® as crystallization inhibitor

## Intermolecular Interactions between API and Polymer

- Polyvinyl caprolactam-polyvinyl acetate-polethylene glycol graft coplymer
- Longer polymeric chain length
- Crystallization Inhibitor through quasi-complexation
- H-Bonding
- VdW interactions

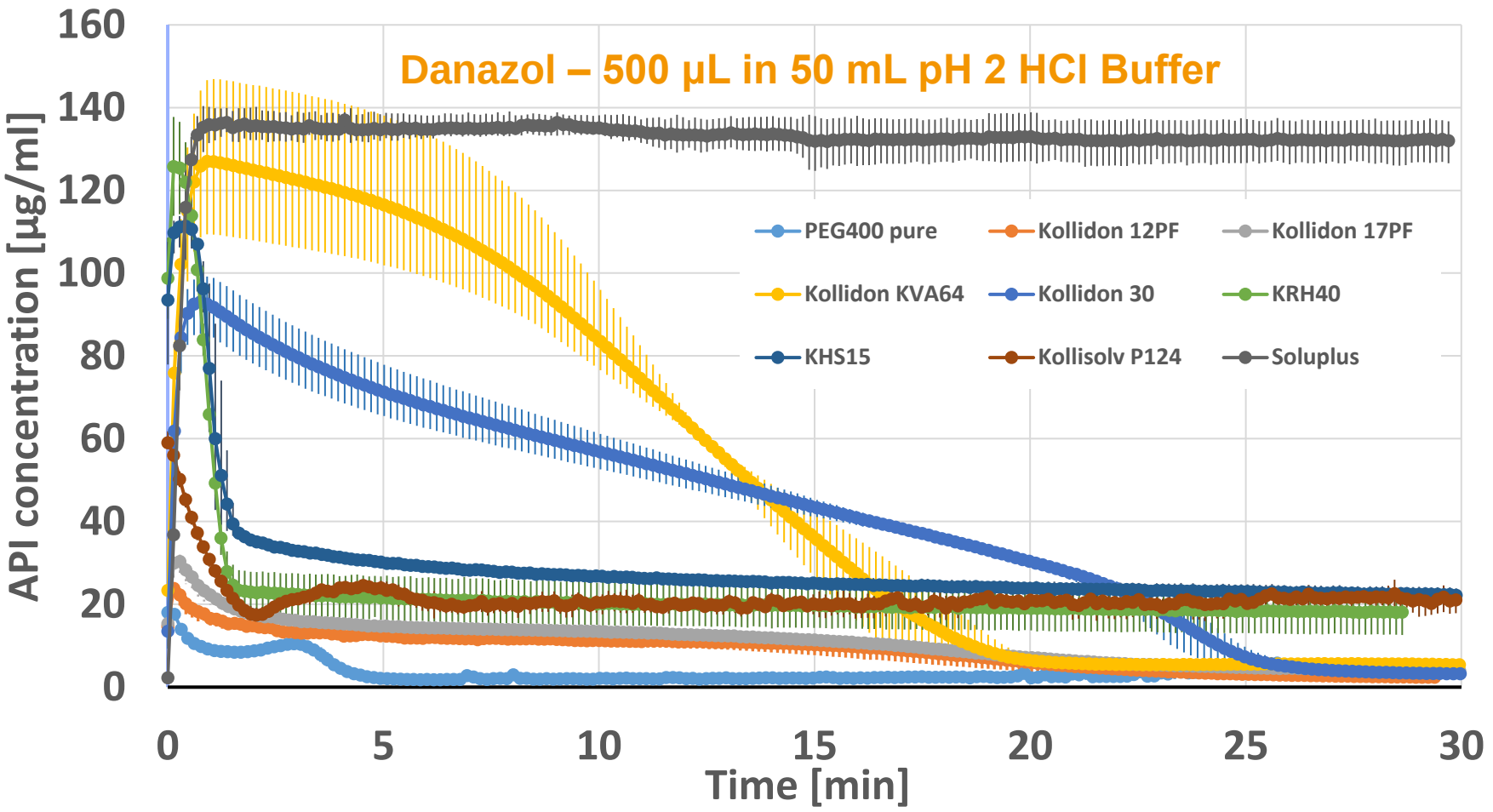


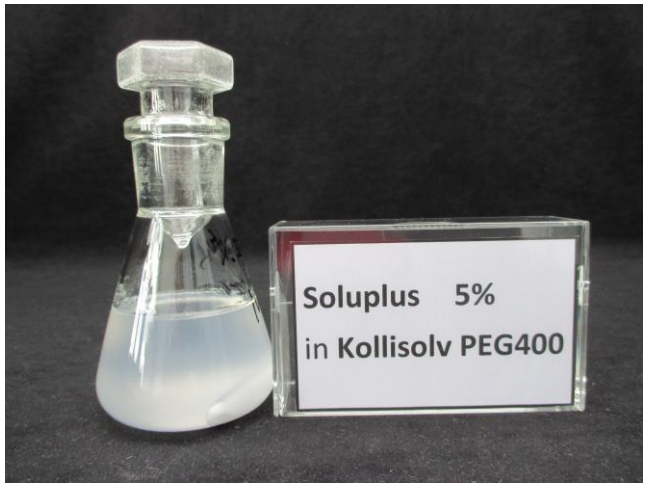




- **Soluplus carries all the pre-requisites for maintaining supersaturation by crystallization inhibition**

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

# Danazol formulation: “parachute effect” to “flying mode”



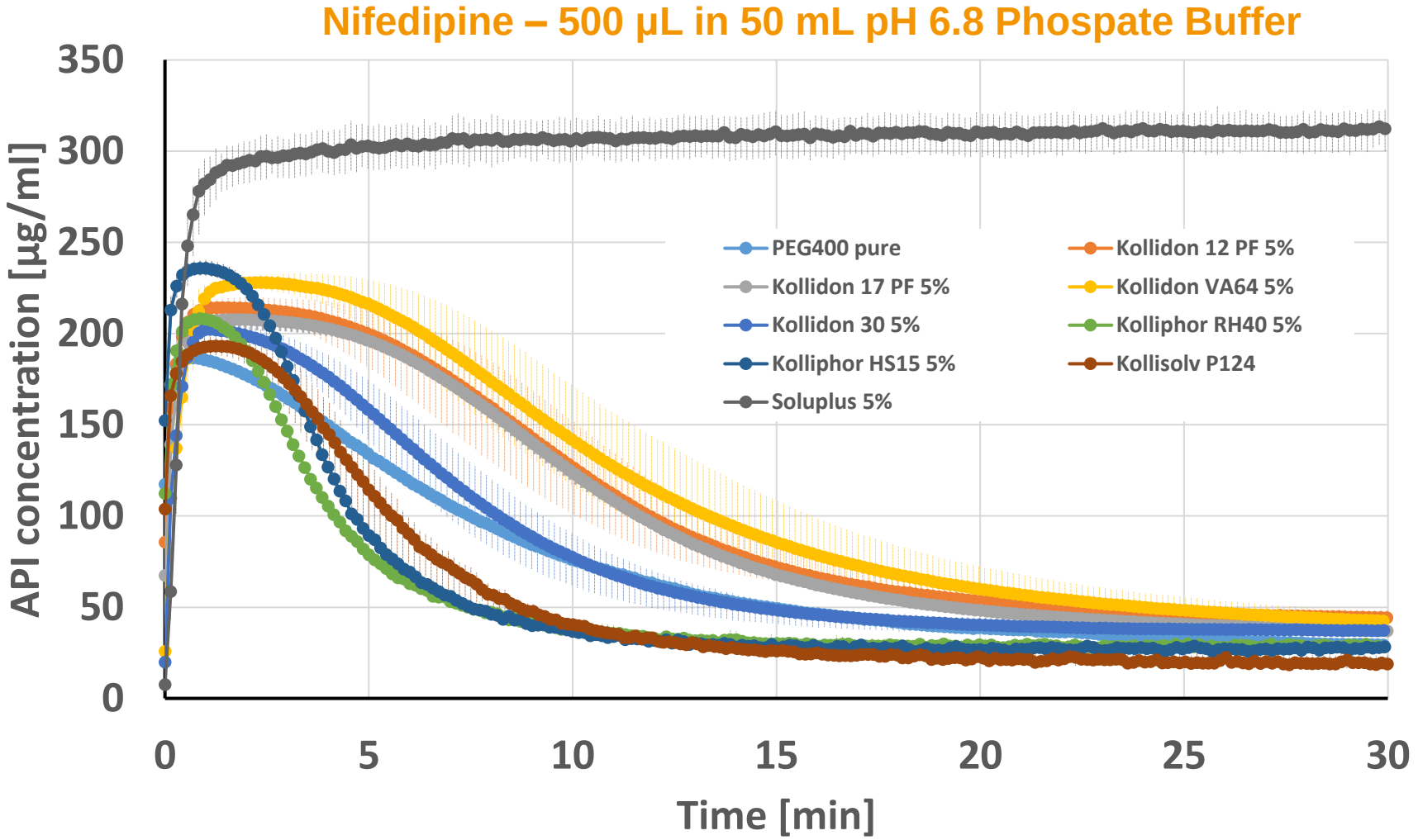

Soluplus Solution in PEG 400

- Soluplus® exhibited no-crystallization effect under acidic condition



BASF
We create chemistry

# Nifedipine formulation: “parachute effect” to “flying mode”




**Similar findings were shown for Nifedipine – but the question remains is it due to strong adsorption or complexation?**

# Conclusions: Supersaturation and drug delivery systems (softgels)

- Pion inForm could be used for high throughput screening of excipients to identify optimal formulation
- Polymeric excipients (Kollidon® 12, Kollidon® VA 64, Kollisolv® PEG 400, Soluplus® and Kolliphor® RH 40) could be better for preventing nucleation and crystal growth by
  - **Stronger** polymer- API interactions
  - **Surface active** properties
- Excipients like surfactants exert thermodynamic and kinetic effects enabling solubilization and larger absorption window.
- FDA's Novel excipient pilot program is expected to give impetus to innovation, both for new and novel excipients such as Soluplus®.

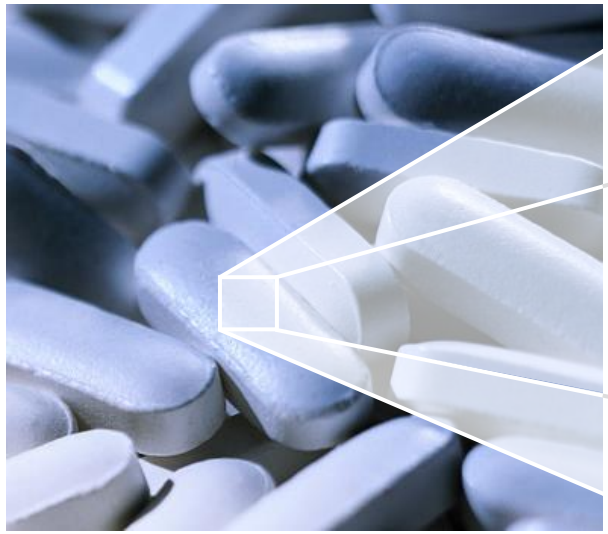
# Outline

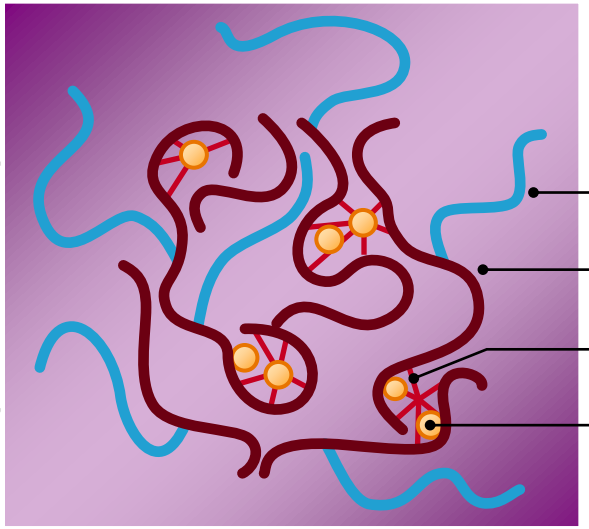
1. Introduction to solubility and bioavailability challenges
2. Supersaturation and drug delivery systems (softgels)
   2.1 Experimental design & results
3. Amorphous solid dispersions (tablets)
   3.1 Experimental design & results
4. Conclusions

# Amorphous Solid Dispersions

## The Solid Solution – Why make ASDs?

**Principle of action**: The API is solubilized in the polymer **like sugar into coffee**






ASDs are a **simple** and elegant **solid solution** of **poorly water soluble** drug **dissolved within** a **polymer** matrix

# ASD-based tablets give ample opportunity for synergistic formulation strategies

**Other (up to 10%)**

*i.e.* ***Salts*** *(NaCl, $Na_2HPO_4$, $Na_2SO_4$, KCl, $CaCl_2$)*

**Filler**

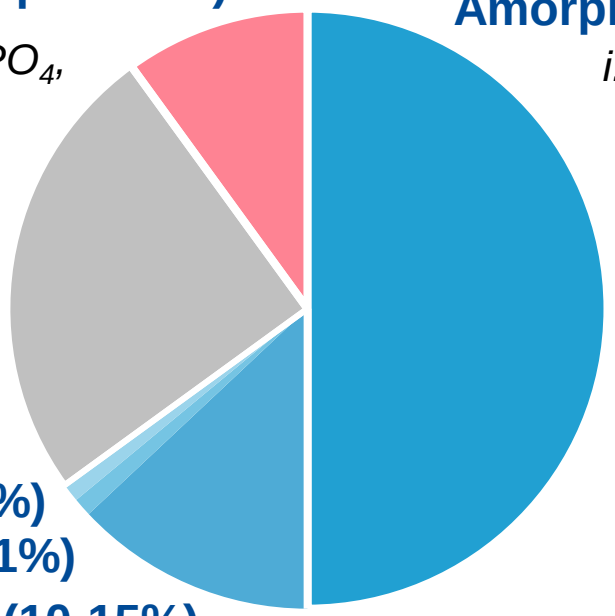
*i.e.* ***MCC,*** *lactose-based excipients*

**Glidant (0.5 - 1%)**

**Lubricant (0.5 - 1%)**

**Disintegrant (10-15%)**

*i.e. crospovidone, croscarmellose*



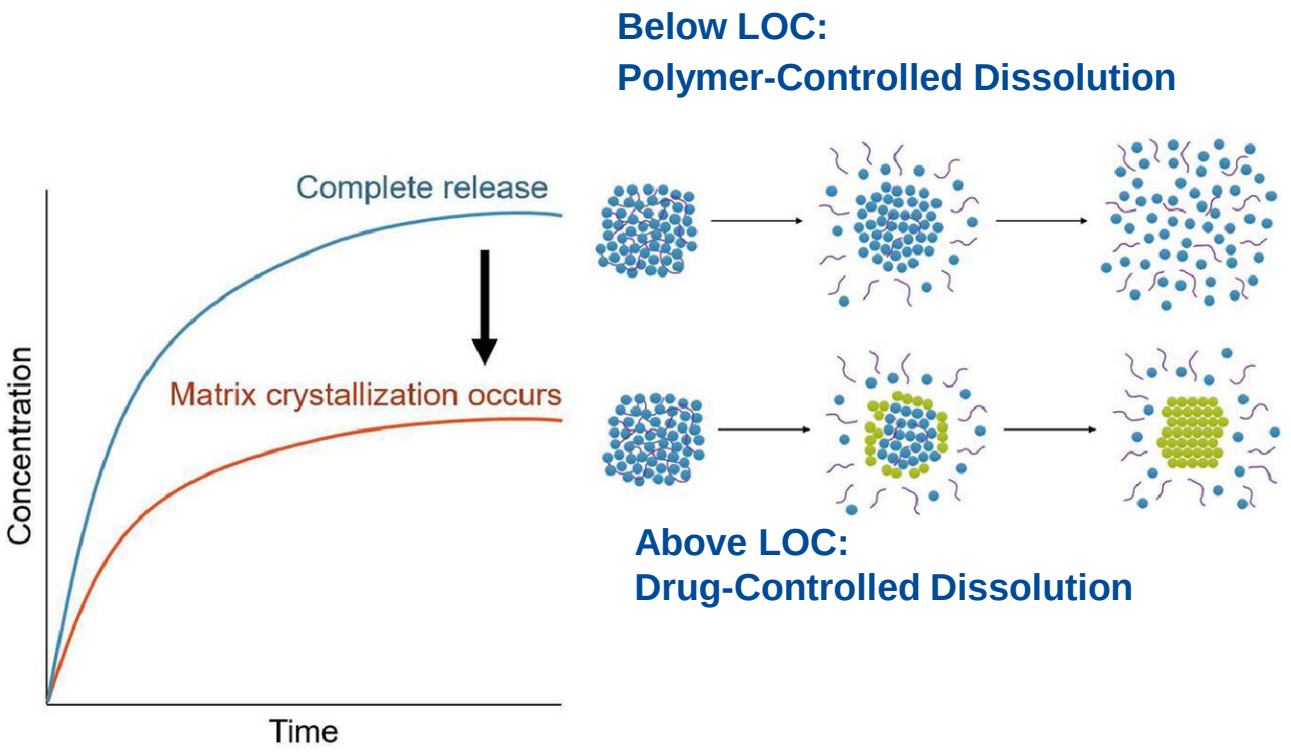
**Amorphous Solid Dispersion (30 to 70%)**

*i.e. loaded at 30% API in Kollidon® VA 64 matrix*

- Ideal matrix candidates for ASD formulation should first be identified through prescreening work.
- Then, **leading levers for independent improvements of ASD-based tablet dissolution behavior** include:
  - **Processing and tableting conditions**
  - **Choice of filler and disintegrant**
  - Other **additives and components in tablet**
- Each component can be optimized for tailored drug release behavior, as shared in case following case studies

# Recent literature has brough the topic of the Limit of Congruency (LOC) as a dissolution-dominating attribute of amorphous solid dispersions.

- **Limit of Congruency** (LOC) for an ASD is a **specific drug load that transistions** between simultaneous drug+matrix phase dissolution to a release where drug-rich surface forms and limits dissolution
- LOC is **drug and matrix specific.** LOC is determined by a sharp decline in dissolution of API from the ASD (typically around 15-40 wt%)
- Congruent release occurs when dissolution is faster than matrix phase separation
- Generation of a drug-rich porous microstructure at the dissolving interface of leads to incongruently releasing ASDs
- **LOC can be increased** through use of surfactants, solubilizers, second excipients, additives within the ASD




| Dana E. Moseson, Tze Ning Hiew, Yongchao Su, Lynne S. Taylor Formulation and Processing Strategies which Underpin Susceptibility to Matrix Crystallization in Amorphous Solid Dispersions,*Journal of Pharmaceutical Sciences*, 112, *1*, **2023**, 108-122.
| Anura S. Indulkar, Xiaochun Lou, Geoff G. Z. Zhang, and Lynne S. Taylor Insights into the Dissolution Mechanism of Ritonavir–Copovidone Amorphous Solid Dispersions: Importance of Congruent Release for Enhanced Performance *Mol. Pharmaceutics* **2019**, 16, 3, 1327–1339

# Limit of Congruency (LOC) has a strong influence on ASD behavior in dissolution, and thus also at tablet-scale

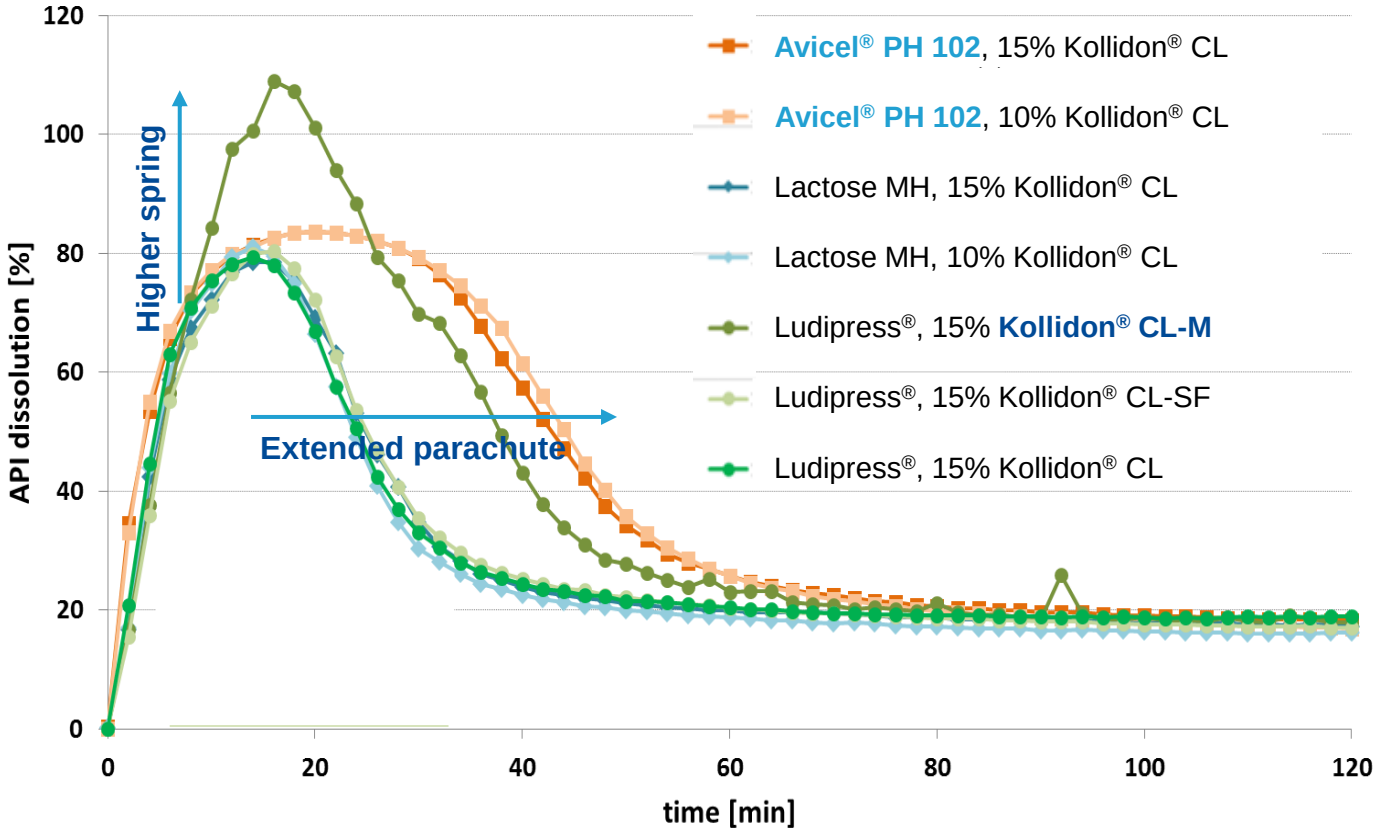
- LOC for **copovidone-based binary ASDs** is typically **15-30% API** load
- LOC **can be increased** through inclusion of **surfactants, salts, second matrix excipients**, and other additives **within the ASD**

## Case Study:

- **Nifedipine and Kollidon® VA 64** ASD-based tablets were prepared
- ASDs were prepared at **20% API load (below LOC)** and **50% API load (above LOC)**
- Different **fillers and disintegrants were evaluated for their impact** under each conditions

# Below LOC, filler and disintegrant selection influence the spring and parachute behaviors of ASD-based tablets

**20% Nifedipine in ASD with Kollidon® VA 64**
**500 mg tablet, 40 mg Nifedipine**
**For 20% API in ASD: 40% ASD; 1% Aerosil 200; 0.5% MgSt; (filler + disintegrant) = 59.5%**




**Tablet Hardness 50 – 75 N**
**USP Apparatus 2, Paddle method, 100 rpm, 37 °C, HCl 0.08 M, 700 mL**

- The **MCC as filler increased API release** (Avicel® vs Lactose and Ludipress®) by **extending parachute effect**.
- **Micronized particle size of crospovidone Kollidon® CL-M** disintegrant achieved **higher spring drug release** over larger disintegrant particles.

## Particle Size Distribution:

| | Kollidon® CL | Kollidon® CL-F | Kollidon® CL-SF | Kollidon® CL-M |
|---|---|---|---|---|
| **< 15 µm** | | | | **≥ 90%** |
| **> 50 µm** | max 80% | max 60% | max 30% | |
| **> 100 µm** | max 60% | max 20% | max 10% | |



BASF
We create chemistry

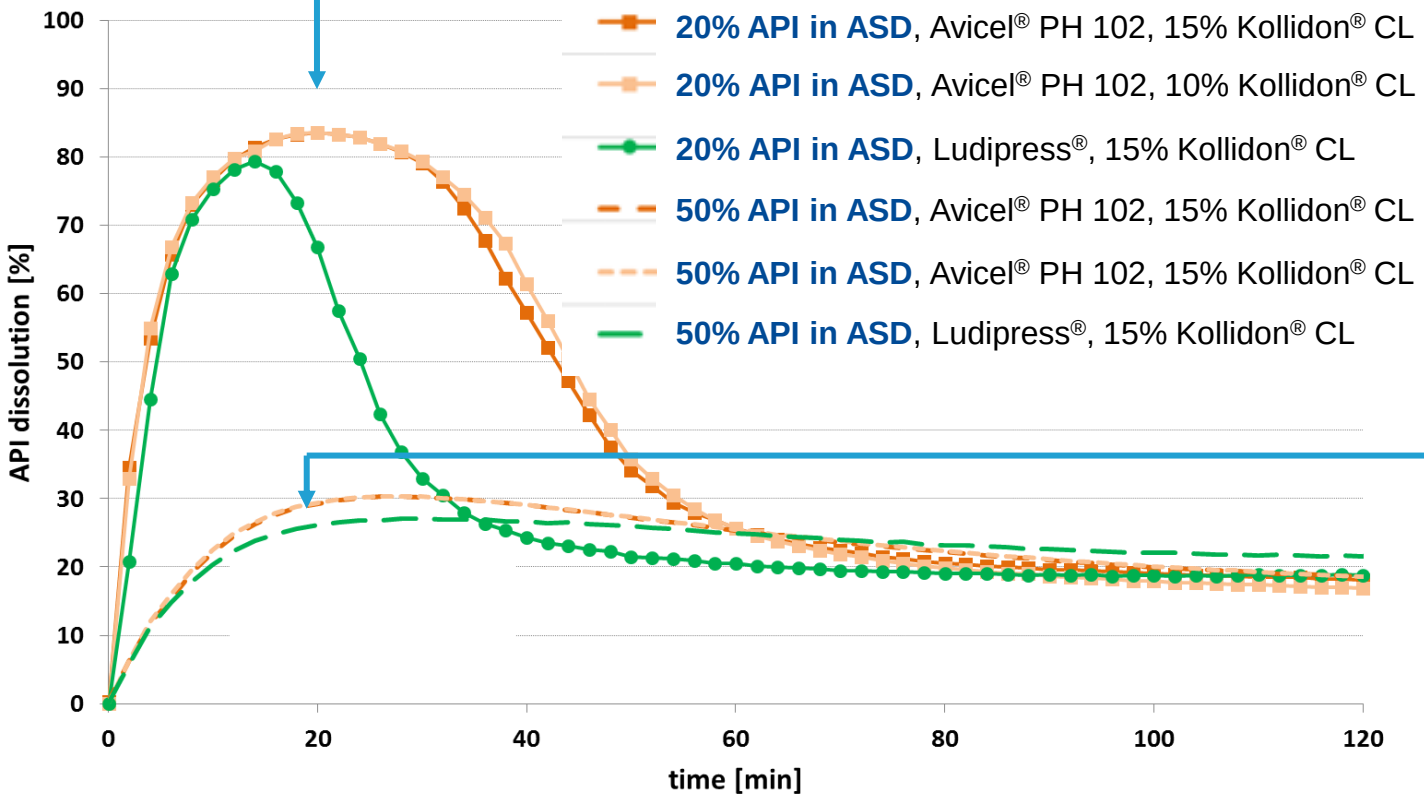
# The enhanced spring behavior is not based on a more rapid disintegration, but rather a solution/suspension-based stabilization behavior.

| | press force [kN] | hardness [N] | disintegration time [min] | friability [%] |
|---|---|---|---|---|
| **Avicel® PH 102**, 15% Kollidon® CL | 5 | 61 | < 0,5 | 1,24 |
| **Avicel® PH 102**, 10% Kollidon® CL | 5 | 75 | < 0,5 | 0,64 |
| Lactose MH, 15% Kollidon® CL | 13 | 61 | 1 – 2 | 1,05 |
| Lactose MH, 10% Kollidon® CL | 12 | 52 | 1 – 2 | 1,59 |
| Ludipress®, 15% **Kollidon® CL-M** | 7 | 61 | 5 – 10 | 1,45 |
| Ludipress®, 15% Kollidon® CL-SF | 8 | 62 | 1 – 2 | 1,19 |
| Ludipress®, 15% Kollidon® CL | 12 | 69 | 0,5 – 1 | 0,98 |

- **Micronized particle size of crospovidone Kollidon® CL-M is also used as** as a stabilizer in oral suspensions.

# Above the LOC, filler selection and wt% of disintegrant lose impact once API loading in the ASD exceeds the LOC threshold

**20% or 50% Nifedipine in ASD with Kollidon® VA 64**
**500 mg tablet, 40 mg Nifedipine**
**For 50% API in ASD: 16% ASD; 1% Aerosil 200; 0.5% MgSt; (filler + disintegrant) = 82.5%**




**Below the ASD Limit of Congruency (matrix-dominated dissolution): 20% API load in ASD**

- The **selection of filler may increase release** (Avicel® vs Ludipress®)

**Above the ASD Limit of Congruency (API-dominated dissolution): 50% API load in ASD**

- The **selection of filler** (Avicel® vs Ludipress®) **did not increase release** of Nifedipine
- **Increasing disintegrant** 10% to 15 wt% **also did not increase** drug dissolution behavior

**Tablet Hardness 50 – 75 N**
**USP Apparatus 2, Paddle method, 100 rpm, 37 °C, HCl 0.08 M, 700 mL**



BASF
We create chemistry

# Conclusions: Amorphous Solid Dispersions (ASD) Based Tablets

- **Formulating from an ASD that is below LOC** will provide the best canvas for optimizing tablet dissolution behavior
- **Micronized crospovidone** can provide a high-surface area, and thereby enable **spring effect to the dissolution of ASD-based tablets**
- **MCC** forms **better ASD-based tablets** than lactose-based excipients, and can also **extend the parachute effect during the dissolution of ASD tablets**
- The **presence of salts is helpful for disintegration**, though **too-high loading will compromise tablet properties**
- BASF has a deep and profound understanding of various suitable excipients and formulations of ASD tablets

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

BASF
We create chemistry

# Thank you!


BASF Pharma Solutions

Go to **https://virtualpharmaassistants.basf.com/s/**
to sign up for **ZoomLab™** and
**Your Virtual Pharma Assistants**

Please provide any feedback or
questions to:

**sandip.tiwari@basf.com**


We create chemistry