



SLOVENSKO FARMACEVTSKO DRUŠTVO

SEKCIJA FARMACEVTSKIH TEHNOLOGOV

30. simpozij Sekcije farmaceutskih tehnologov

**STABILIZACIJA
METASTABILNIH OBLIK
UČINKOVIN**

**ZBORNİK PREDAVANJ
PROCEEDINGS**

13. junij 2019, PIC Lek, Ljubljana



član skupine Sandoz



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Scientific and Organizing Committee:

dr. Miha Homar
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dr. Natalija Škrbina Zajc

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VSEBINA

PROGRAM

Odon Planinšek

Relevantna vprašanja pri razvoju metastabilnih formulacij za izboljšanje raztapljanja zdravilnih učinkovin

Primož Benkič

Kako nestabilno postane stabilno – kratek pregled teorije polimorfnih prehodov v suspenzijah s primeri

Dušan Teslič

Razvoj procesov kristalizacije metastabilnih kristalnih oblik – primeri iz prakse

Darko Uršič

Vrednotenje raztapljanja metastabilnih trdnih farmacevtskih oblik

Biljana Janković

Process challenges for production of amorphous solid dispersions

Nils Rottmann

Hot melt extrusion – An introduction to the technology and to downstream processing

Špela Zupančič

Stabilizacija amorfnih oblik učinkovin z vgrajevanjem v nanodostavne sisteme – primer nanovlaken s poloksamerom

Dejan Klement

Študij in napovedovanje stabilnosti metastabilnih oblik učinkovin – analizni pristopi

Klemen Naveršnik

Fizikalno stabilno, kemijsko nestabilno

PROGRAM

30. simpozij Sekcije farmacevtskih tehnologov Stabilizacija metastabilnih oblik učinkovin

13. junij 2019, PIC Lek, Ljubljana

8.00 – 8.45 Registracija

9.00 – 9.10 Miha Homar, predsednik strokovno - organizacijskega odbora
Uvodni pozdrav

Pozdrav predstavnika Lek farmacevtske družbe d.d., Ljubljana

Dopoldanska sekcija

9.15 – 10.40

Odon Planinšek - Univerza v Ljubljani, Fakulteta za farmacijo

Relevantna vprašanja pri razvoju metastabilnih formulacij za izboljšanje raztapljanja zdravilnih učinkovin

Primož Benkič - Krka, tovarna zdravil, d.d., Novo mesto

Kako nestabilno postane stabilno – kratek pregled teorije polimorfnih prehodov v suspenzijah s primeri

10.45 – 11.30 ODMOR

11.30 – 13.00

Dušan Teslič - Lek farmacevtska družba d.d., Ljubljana

Razvoj procesov kristalizacije metastabilnih kristalnih oblik – primeri iz prakse

Darko Uršič - Krka, tovarna zdravil, d.d., Novo mesto

Vrednotenje raztapljanja metastabilnih trdnih farmacevtskih oblik

13.00 – 14.00 KOSILO

Popoldanska sekcija

14.00 – 16.05

Biljana Jankovič - Lek farmacevtska družba d.d., Ljubljana

Procesni izzivi izdelave amorfnih trdnih disperzij

Nils Rottmann - BASF

Hot melt extrusion – An introduction to the technology and to downstream processing

Špela Zupančič, Univerza v Ljubljani, Fakulteta za farmacijo

Stabilizacija amorfnih oblik učinkovin z vgrajevanjem v nanodostavne sisteme – primer nanovlaken s poloksamerom

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Klemen Naveršnik - Lek farmacevtska družba d.d., Ljubljana

Fizikalno stabilno, kemijsko nestabilno

16.10 **Sklep simpozija**

Relevantna vprašanja pri razvoju ¹metastabilnih ²formulacij za ³izboljšanje raztapljanja zdravilnih učinkovin.

Odon Planinšek



30. simpozij Tehnološke sekcije SFD, 13 Junij 2019



1

Različna stanja zdravilne učinkovine-različne lastnosti

KEMIJSKO IDENTIČNO-FIZIKALNO RAZLIČNO

Kemijske lastnosti -kemijska reaktivnost/stabilnost -fotokemijska reaktivnost	Kinetika - hitrost raztapljanja -reakcije v trdnem -stabilnost -hitrost rasti kristalov	Mehanske lastnosti -kompaktibilnost -kompresibilnost -pretočnost -natezna trdnost
Fizikalne lastnosti -prevodnost-gostota -higroskopnost -lomni količnik -barva -morfologija delcev	Površ. Lastnosti -površinska energija -specifična površina	Termodinamične lastnosti -kemijski potencial, prosta energija, topnost -entalpija in entropija -toplotna kapaciteta - tališče, sublimacija -parni tlak

OKUS

Annu. Rev. Chem. Biomol. Eng. 2011. 2:259–80 IF=7,7

2

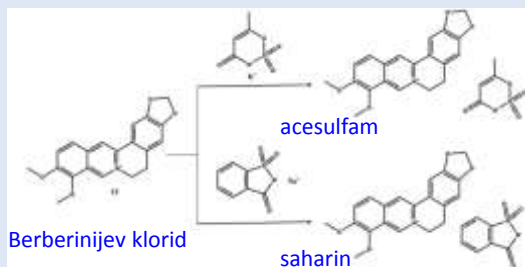
Oblikovanje zdravil usmerjenih v pacienta

Na vsakih 100 predpisanih zdravil namenjenih terapiji kroničnih stanj, odstotek pacientov, ki ne sledijo zdravljenju raste od 40% po šestih mesecih na skoraj 70% po enem letu.

Neaderenca je glavni razlog slabega izida zdravljenja in naj bi v ZDA povzročila med 100 in 300 milijardami dolarjev škode.

Stroške zdravljenja bi lahko znižali z osredotočenjem na razloge za neaderenco.

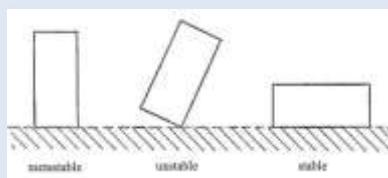
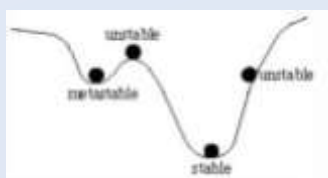
catalentaprsupplement_2016



Cryst. Growth Des. 2016, 16, 933–939, IF=4,1

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¹Metastabilno vs. stabilno



Metastabilno stanje snovi

- Oblika, ki je termodinamično nestabilna, vendar jo lahko izoliramo
- Zahteva dovedeno energijo, ki inducira pretvorbo v stabilnejše stanje

-Topilo
-Temperatura
-Mehanske obremenitve

<https://www.dictionary.com/browse/metastable>

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1 Metastabilno vs. stabilno

Manj stabilna kristalna oblika



Stabilnejša kristalna oblika

Amorfno stanje



Kristalno stanje

Hipoteza pravi, da je steklasto stanje metastabilno in ne nestabilno.

Če to velja mora vsaka mikroskopska strukturna enota stekla imeti položaj statičnega ravnotežja, pri čemer so vsi položaji naključno porazdeljeni.

MORREL H. COHEN & DAVID TURNBULL *Nature* 203, 964 (1964)

Sol



Prosta baza, kislina

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1 Metastabilno vs. Stabilno

KRISTAL

Paracetamol

Stabilna oblika:

-I (se uporablja v zdravilih)

Meta(ne)stabilne oblike:

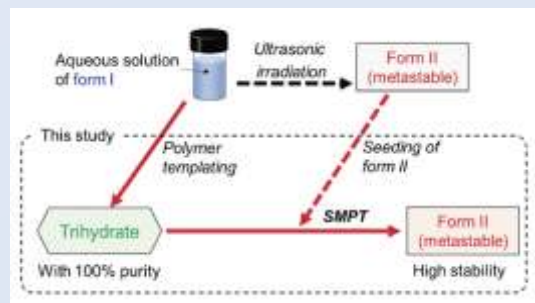
-II (boljša topnost, stisljivost)

-III (zelo nestabilna)

-monohidrat

-dihidrat

-trihidrat



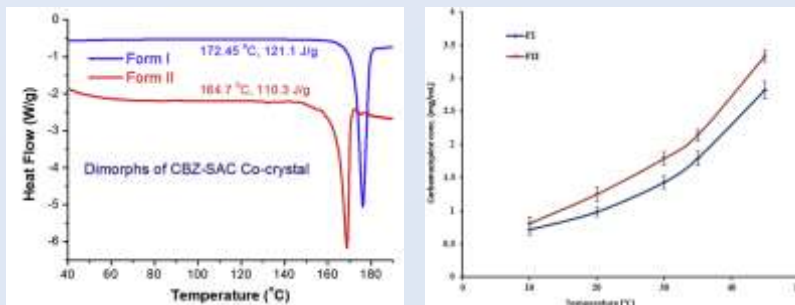
SMPT=solution-mediated phase transformation



Yoichiro Mori et al 2017 *Appl. Phys. Express* 10(1):015501, IF=2,6

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1 Metastabilno vs. Stabilno KOKKRISTAL



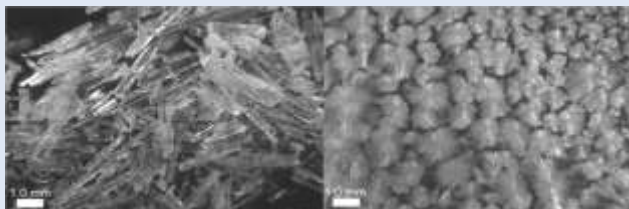
Polimorfni obliki kokristala **karbamazepina in saharina v razmerju 1:1**
 -oblika I stabilna
 -oblika II metastabilna

J Pharm Sci. 2017, 106(8):2009-2014., IF=3,1

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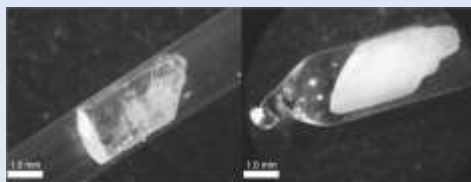
1 Metastabilno vs. Stabilno HIBRIDNI KOKKRISTAL

Benzojska kislina in natrijev benzoat 2:1



Oblika A (stabilna)

Oblika B (metastabilna)



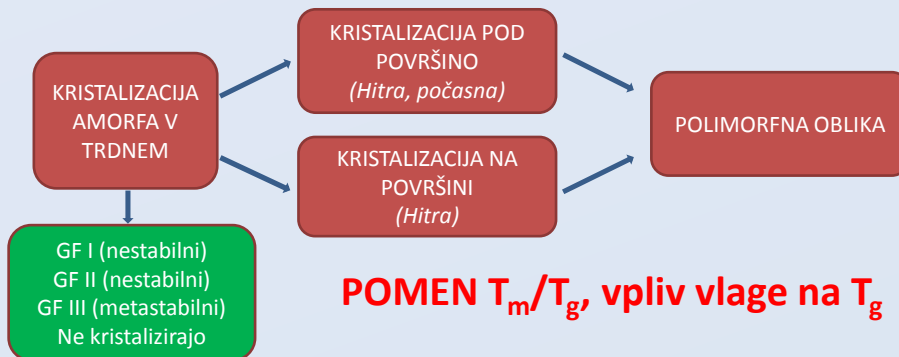
CrystEngComm, 2012, 14, 6744-6749, IF=3,9

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1 Metastabilno vs. Stabilno

AMORF

Ohlajanje taline, odparevanje topila, kondenzacija pare, mehanske poškodbe kristalov, dehidracija hidratov



AAPS Journal, Vol. 14, No. 3, September 2012, IF=1,6

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2 Formulacija oziroma disperzija

Fizikalna zmes učinkovine in pomožnih snovi



Tableta.
kapsula

KRISTALNE UČINKOVINE

Registrirano zdravilo s famotidinom vsebuje metastabilno obliko učinkovine B

SOLVATI: darunavir ethanolate, indinavir sulfate ethanolate, warfarin sodium isopropanol solvate

International Conference on Harmonization Q6A guideline (1999)

Lin, SY/ Pharm. Res. 31 (2014)7: 1619-1631 IF=3,4

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2 Formulacija oziroma disperzija

Fizikalna zmes učinkovine in pomožnih snovi



Tableta.
kapsula

AMORFNE UČINKOVINE

Compound	Class	MW (g mol ⁻¹)	T _m (°C) ^a	T _g (°C) ^b
<i>Pure amorphous drugs</i>				
Cefuroxime axetil ^d	Amorphous	510.5	n.a.	77.4
Nelfinavir mesylate	Amorphous	663.9	n.a.	114.9
Quinapril hydrochloride ^e	III	475.0	~97	90.8
Rosuvastatin calcium ^f	Amorphous	500.6	n.a.	n.a.
Zafirlukast	III	575.7	194.8	103.3

N. Wyttenbach, M. Kuentz / *Eur. J. Pharm. Biopharm.* 112 (2017) 204–208, IF=4,5

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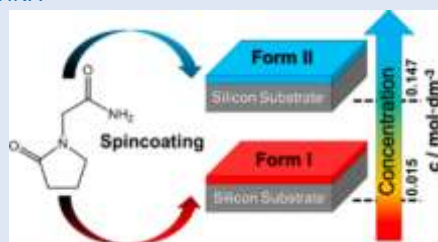
2 Formulacija oziroma disperzija

Interaktivna disperzija učinkovine in pomožne(ih) snovi



Tableta.
kapsula

KRISTALNA UČINKOVINA



Piracetam

Pri sobni temperaturi ni pretvorbe metastabilne oblike I v termodinamično stabilnejši obliki II ali III v času 9 mesečnega spremljanja

Cryst. Growth Des., 2018, 18 (7), 4123–4129, IF 4,0

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2 Formulacija oziroma disperzija

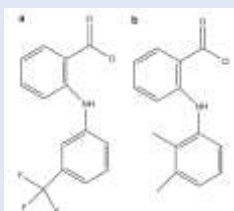
Interaktivna disperzija učinkovine in pomožne(ih) snovi



Tableta.
kapsula

KRISTALNA UČINKOVINA

Preprečitev polimorfnega prehoda flufenaminske kisline (metastabilne oblike I v stabilno obliko III) oblike v trdnem stanju z uporabo **strukturno podobne molekule**.
(ALI OBSTAJAJO STRUKTURNO RAZLIČNE MOLEKULE ZA ISTI NAMEN?)



Mešani kristal (trdna raztopina) flufenaminske kisline (a) in mefenaminske kisline (b) v razmerju **99,75:0,25**

J Pharm Sci. 2010 Sep;99(9):4013-22, IF=3,7

13

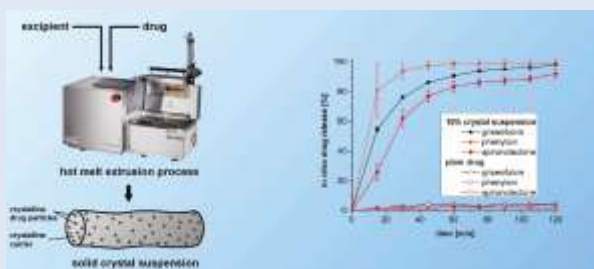
2 Formulacija oziroma disperzija

Interaktivna disperzija učinkovine in pomožne(ih) snovi



Tableta.
kapsula

KRISTALNA UČINKOVINA



GRISEOFULVIN, FENITOIN, SPIRONOLAKTON + MANITOL,
-disperzije stabilne 90 dni pri 40 °C in 75% RV zraka.

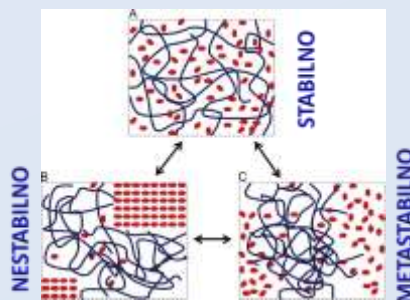
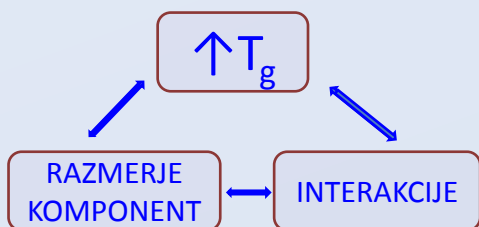
Mol. Pharmaceutics 2011, 8, 727–735, IF 5,5

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POSEBNOST -metastabilno?

2 Formulacija oziroma disperzija

AMORFNA TRDNA DISPERZIJA



Tri možna stanja trdnih v trdni disperziji sestavljeni iz učinkovine in polimera (rdeče-molekule učinkovine, modro-verige polimera).

Acta Pharmaceutica Sinica B 2014;4(1):18–25(IF 3.972)

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2 Formulacija oziroma disperzija

Interaktivna disperzija učinkovine in pomožne(ih) snovi



Tableta.
kapsula

DETEKCIJA AMORFNOSTI

-TERMIČNA ANALIZA meja zaznavnosti 1-5%
-RENTGENSKA ANALIZA meja zaznavnosti 1-5%

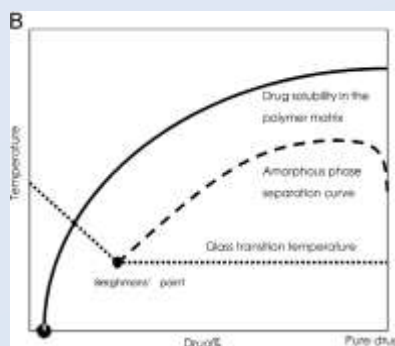
RAMANSKA MIKROSKOPIJA –fazna separacija z domenami 100 µm
DINAMIČNA MEHANSKA ANALIIZA –fazna separacija z domenami 10 nm
JEDRSKA MAGNETNA REZONANCA V TRDNEM –“--

Acta Pharmaceutica Sinica B 2014;4(1):18–25(IF 3.972)

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2 Formulacija oziroma disperzija

AMORFNA TRDNA DISPERZIJA



Acta Pharmaceutica Sinica B 2014;4(1):18–25(IF 3.972)

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2 Formulacija oziroma disperzija

KINETIČNA STABILIZACIJA AMORFNIH TRDNIH DISPERZIJI

Višja vsebnost učinkovine v trdni disperziji od topnosti v trdni fazi je omogočena s kinetično stabilizacijo amorfa

Kinetična ulovitev molekul učinkovine v polimeru zniža mobilnost molekul

Dosežemo jo med izdelavo disperzije s:

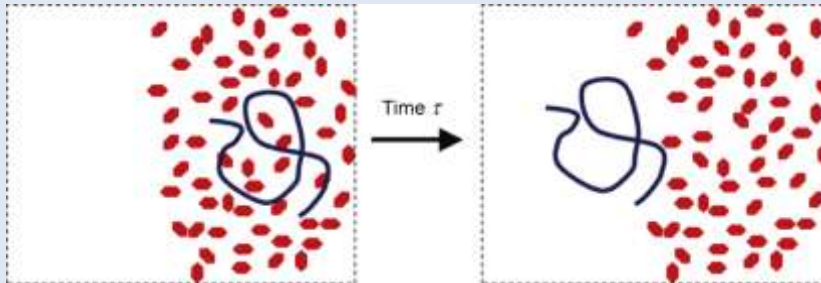
- hitrim odparevanjem topila
- hitrim ohlajanjem taline

Eur. J. Pharm. Biopharm. 135 (2019) 1–12, IF=4,5

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2 Formulacija oziroma disperzija

AMORFNA TRDNA DISPERZIJA



Vlaga zniža T_g in s tem viskoznost

$$D \cong \frac{kT}{6\pi\eta R} \sim 10^{-20} \text{ m}^2/\text{s}$$

$$t \cong \frac{R^2}{D} \sim 100 \text{ years}$$

Acta Pharmaceutica Sinica B 2014;4(1):18–25(IF 3.972)

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2 Formulacija oziroma disperzija

AMORFNA TRDNA DISPERZIJA

IZBIRA POLIMERA : TOPNOST V TALINI, INTERAKCIJE Z UČINKOVINO

-Napovedovanje in merjenje temperature steklastega prehoda:

Gordon–Taylorjeva enačba, termična analiza

-Računanje topnosti učinkovine v polimeru:

Osnova izračuna so temične lastnosti komponent+aktivnosni koeficient

Upoštevanje odbojnih in privlačnih van de Waalsovih interakcin in možnosti tvorbe vodikovih vezi, Flory-Huggins interakcijski parameter.

-Merjenje topnosti učinkovine v polimeru

Uporaba termične analize

Mol. Pharm. 11 (2014) 4189–4198, IF=4,4

Mol. Pharm. 14 (2017) 4374–4386. IF=4,6

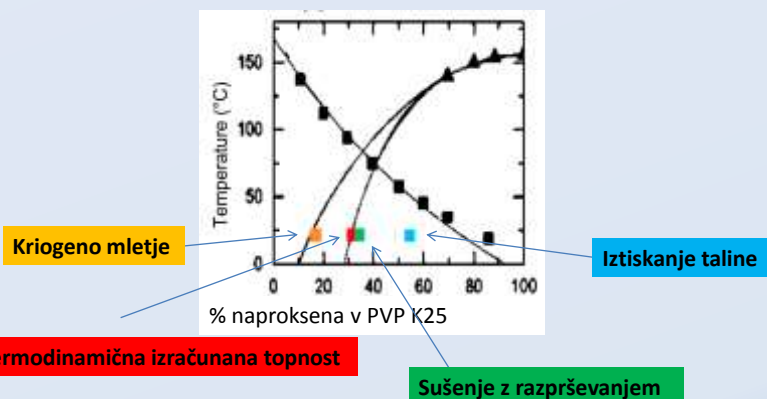
20

2 Formulacija oziroma disperzija

AMORFNA TRDNA DISPERZIJA

-Tehnika izdelave disperzij lahko poveča število interakcij med komponentama v trdni disperziji.

IZBIRA POLIMERA : TOPNOST V TALINI, INTERAKCIJE Z UČINKOVINO

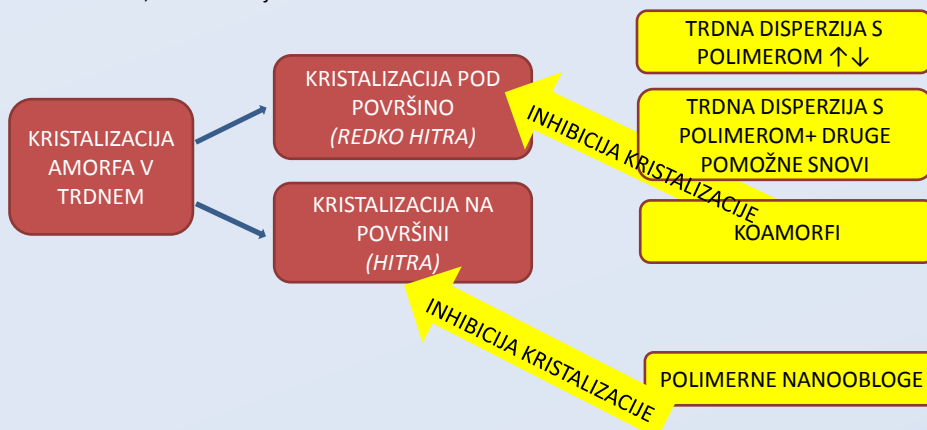


Mol. Pharm. 11 (2014) 4189–4198, IF=4,4

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2 Formulacija oziroma disperzija

Ohlajanje taline, odparevanje topila, kondenzacija pare, mehanske poškodbe kristalov, dehidracija hidratov



AAPS Journal, Vol. 14, No. 3, September 2012, IF=1,6

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2 Formulacija oziroma disperzija Industrijske metode izdelave metastabilnih disperzij

Examples of commercially available medicines using solid dispersion technologies.

Product name	Drug substance	Carrier	Preparation method	Year of approval
Cesamet™ (US); Casemes® (Austria)	Nifedipine	PVP	N.A.	1985 (FDA)
Sporanox®	Itraconazole	HPMC	Spray drying on sugar beads	1992
Prograf™	Tacrolimus	HPMC	Spray drying	1994 (FDA/MHRA)
Gris-PEG™	Griseofulvin	PEG	Melt extrusion	2000 (FDA)
Crestor®	Rosuvastatin	HPMC	Spray drying	2004 (EMA); 2002 (FDA)
Cymbalta®	Duloxetine	HPMCAS	N.A.	2004 (EMA, FDA)
Kalitra®	Lopinavir/ritonavir	PVP-VA	Melt extrusion	2005 (FDA); 2001 (EMA)
Eucrasyl® Galvusnet™	Vildagliptin/Metformin HCL	HPC	Melt extrusion (metformin)	2007 (EMA)
Intefence®	Etravirine	HPMC	Spray drying	2008 (EMA, FDA)
Modigraf®	Tacrolimus	HPMC	Spray drying	2009 (EMA)
Samsco®	Toboptan	N.A.	Granulation	2009 (EMA, FDA)
Zovis™ (US); Gervican®/Varubla® (EU)	Remifentanyl	HPMC	Spray drying	2010 (EMA, FDA)
Ormeo™	Itraconazole	HPMC	Melt extrusion	2010 (FDA)
Jansyn®/Jade™	Emtricitabine	PEG, Pulvislaner 188	Spray melt	2010 (FDA)
Novo®	Ritonavir	PVP-VA	Melt extrusion	2010 (FDA); 2009 (EMA)
Iscedin™ (US); Iscico ® (EU)	Telaprevir	HPMCAS	Spray drying	2011 (EMA, FDA)
Zelboraf®	Vemurafenib	HPMCAS	Co-precipitation	2012 (EMA); 2011 (FDA)
Kalydrex®	Isacaftor	HPMCAS / SLS	Spray drying	2012 (EMA, FDA)
Nouafill®	Itracozazole	HPMCAS	Melt extrusion	2014 (EMA); 2013 (FDA)
Viekira™ (US); Viektra® (EU)	Ombitasvir/Paritaprevir/Ibinavir	PVP-VA/TPGS	Melt extrusion	2014 (EMA, FDA)
Orkambi®	Lumacaftor/ivacaftor	HPMCAS/SLS	Spray drying	2015 (EMA, FDA)

HPMC—hydroxypropyl methylcellulose; HPC—hydroxypropylcellulose; HPMCAS—hydroxypropyl methylcellulose acetate succinate; PEG—polyethylene glycol; PVP—povidone; PVP-VA—povidone-vinyl acetate (copovidone); SLS—Sodium Lauryl sulfate; TPGS—d-alpha Tocopheryl Polyethylene Glycol 1000 Succinate. N.A.—Not available; US—United States of America; EU—European Union; EMA—European Medicines Agency; FDA—Food and Drug Administration; MHRA—Medicines and Health Products Regulatory Agency.

Adv Drug Deliv Rev. 2016 May 1;100:85-101, IF=11,6

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2 Formulacija oziroma disperzija

AMORFNE TRDNE DISPERZIJE V REGISTRIRANIH ZDRAVILIH

VISOKA VSEBNOST UČINKOVINE

Telaprevir 375 mg v 375 mg HPMCAS+ ostale pomožne snovi

UČINKOVINA Z VISOKIM TALIŠČEM

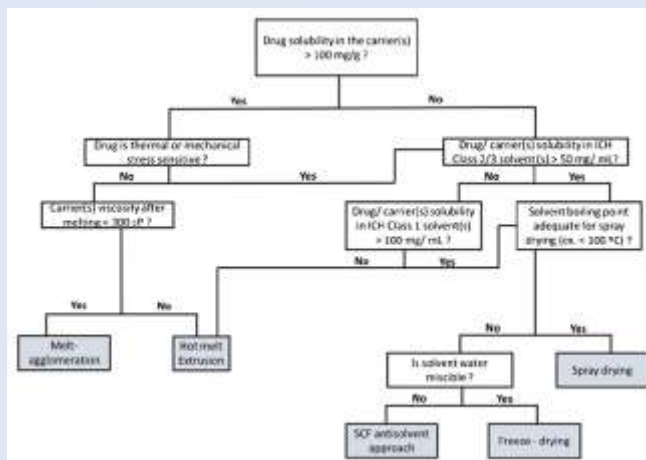
Ivakaftor, 291 °C –sušenje z razprševanjem,
Itrakonazol, 166 °C –iztiskanje taline

Acta Pharmaceutica Sinica B 2014;4(1):18–25(IF 3.972)

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2 Formulacija oziroma disperzija

Industrijske metode izdelave metastabilnih disperzij



Odločitveno drevo za izbiro metode izdelave trdne disperzije

Adv Drug Deliv Rev. 2016 May 1;100:85-101, IF=11,6

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2 Formulacija oziroma disperzija

RAZMERJE UČIKOVINA POMOŽNE SNOVI

- Vpliv tehnologije izdelave amorfnih trdnih disperzij
- Možne interakcije (vodikove vezi) prispevajo k topnosti polimera v pomožni snovi, stabilizirajo disperzijo

Comparison of highest drug loadings of NAP obtained per manufacturing technique and per polymer.

Technique	Polymer	Drug loading
Spray drying	PVP	30-35%
	PVP-VA	40-45%
	HPMC	20-25%
	HPMC-AS	20-25%
Hot melt extrusion	PVP	35-60%
	PVP-VA	45-60%
	HPMC	20-25%
	HPMC-AS	15-20%
Cryo-milling	PVP	15-20%
	PVP-VA	10-15%
	HPMC	< 5%
	HPMC-AS	10-15%

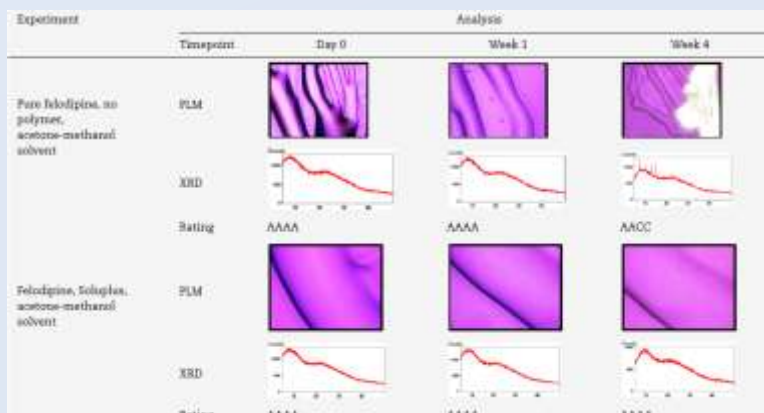
t=0

Eur. J. Pharm. Biopharm. 135 (2019) 1-12, IF=4,5

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2 Formulacija oziroma disperzija (META)STABILNOST DISPERZIJE

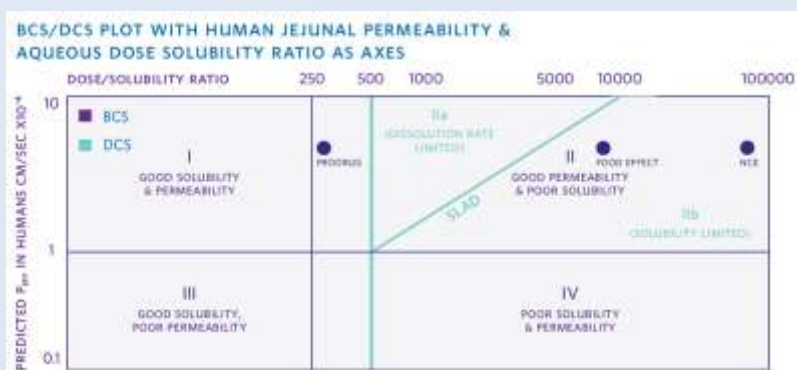
-TESTIRANJE STABILNOSTI AMORFNIH TRDNIH DISPERZIJ Z IZDELAVO TANKIH FILMOV



Chem. Eng. Res. Des. 2016: (110: 192-199), IF=1,1

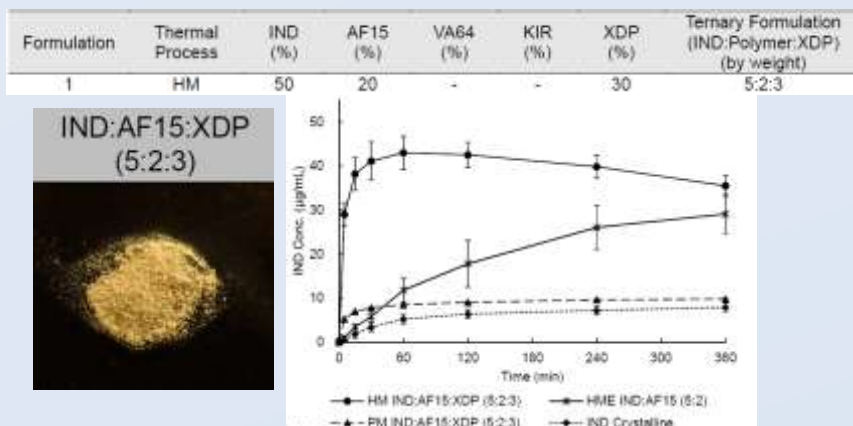
27

3 izboljšanje raztapljanja zdravilnih učinkovin



28

³izboljšanje raztapljanja zdravilnih učinkovin

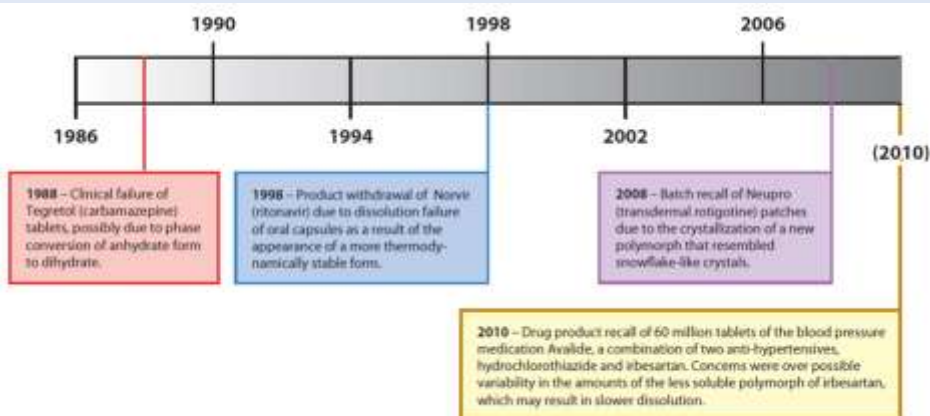


J. of Pharm.Sci., 2018 107(1), 362–371.

29

ZAKLJUČEK

Vsaka **napaka** je vselej tudi dobra šola in **gonilo napredka**.



30

Kako nestabilno postane stabilno

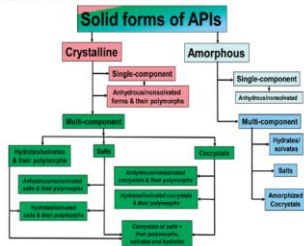
Primož Benkič
13. junij 2019



Živeti zdravo življenje.

Polimorfizem v farmaciji

Scheme 1. The Diversity of Solid Forms That Can Exist for an API Is Extensive and Has Been Exacerbated by the Evolution of Multi-Component Solid Forms of APIs Such As Stochiometric Cocryystals*



*Note that non-stoichiometric forms such as amorphous polymer dispersions and inclusion compounds are not included in the above chart.

2148

doi.org/10.1021/acs.cgd.8b00461 Cryst. Growth Des. 2012, 12, 2147–2152

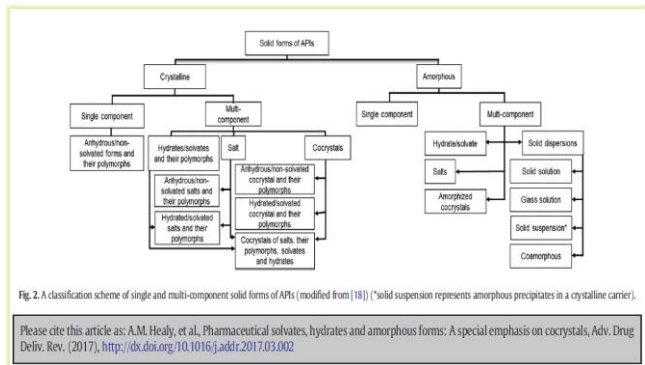
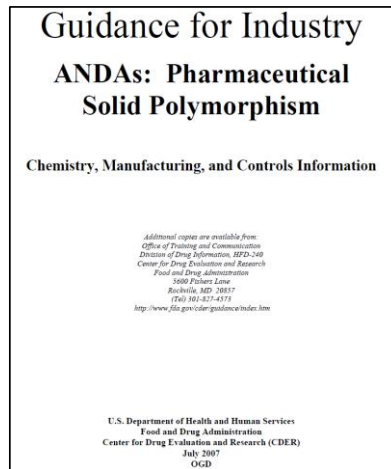
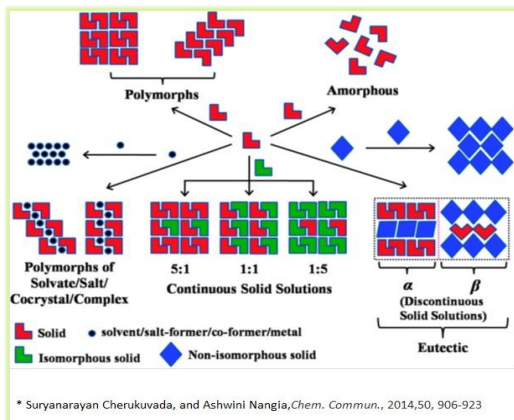


Fig. 2. A classification scheme of single and multi-component solid forms of APIs (modified from [18]) (*solid suspension represents amorphous precipitates in a crystalline carrier).

Please cite this article as: A.M. Healy, et al, Pharmaceutical solvates, hydrates and amorphous forms: A special emphasis on cocryystals, Adv. Drug Deliv. Rev. (2017), <http://dx.doi.org/10.1016/j.addr.2017.03.002>



Polimorfizem v farmaciji



www.krka.si



Polimorfizem v kristalografiji



WIKIPEDIJA
Prosta enciklopedija

Glavna stran
Doprinosila
Izbrani članki
Najkrajši članek
Zadnje spremembe
Občestvo
Portal občestva
Pod tipo
Kontaktna stran
Pomoč

Stran Pogovor

Prebrni

Uredi

Uredi kodo

Zgodovina

Iskanje po Wikipediji

Delovanje in razvoj Wikipedije omogočajo večji prispevki[skrij]

Polimorfizem (kristalografija)

Iz Wikipedije, proste enciklopedije

V kristalografiji je **polimorfizem** sposobnost trdnine, da ima več kot eno kristalno strukturo. Polimorfizem se se lahko pojavlja v vsaki kristalinični snovi, vključno s polimeri, minerali in kovinami in je soroden z alotropijo, ki se nanasa na trdne elemente. Popolna morfologija snovi ni opisana samo s polimorfizmom, ampak tudi z drugimi spremenljivkami, na primer s kristalnim habitom, lomom, barvo črte, trdoto itd.

Če ima snov samo dva polimorfa, govorimo o **dimorfizmu**.

Polimorfizem je pomemben predvsem na področju farmacije, agrokemije, pigmentov, barvil, hrane in eksplozivov.

Kadar je polimorfizem rezultat razlike v kristalnem skladu, se imenuje **polimorfizem kristalnega sklada**. Polimorfizem je lahko tudi posledica obstoja različnih konformacij iste molekule. V tem primer govorimo o **konformacijskem polimorfizmu**. **Pseudopolimorfizmu** so različni tipi kristalov posledica hidratacije ali solvatacije. Primer organskega polimorfa je glicin, ki kristalizira v monoklinskih ali heksagonalnih kristalih. Mnogo kristalnih struktur tvorijo kremen (SiO₂). Najpomembnejše so α-SiO₂, β-SiO₂, indmit, kristobalit, cezi in stišovit.

Analogen pojav za amorfne snovi se imenuje **poliamorfizem** in pomeni, da ima amorfna snov več amorfnih modifikacij.

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Termodinamski vidik

Termodinamski modeli veljajo za:

- Različne kristalne strukture z ENAKO kemijsko sestavo
- Amorfno stanje je del faznega diagrama
- Enake gradnike razporejene v različne simetrijske skupine

Tudi solvati, hidrati, kokristali, soli imajo vsak zase svoj polimorfizem, kjer je osnovna kristalografska enota sestavljena iz dveh ali več molekul

Termodinamski vidik

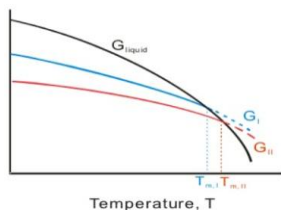
Prosta Gibbsova entalpija

$$G = H - T \cdot S$$

Prosta entalpija je energijski potencial/gonilna sila, ki poganja vse procese v vesolju in prehaja iz višjega proti nižjemu stanju.

- **Entalpija H** zajema solvatacijsko entalpijo, entalpijo kristalne rešetke/talilno entalpijo, vse interakcije med gradniki/molekulami, delo zaradi spremembe volumna, itd
- **Entropija S** predstavlja urejenost sistema. S kristalizacijo se urejenost sistema povečuje, medtem ko se z desolvatacijo nered okolice/raztopine poveča
- **Pri vsakem procesu se celokupna entropija sistema in okolice poveča. Čeprav s kristalizacijo dobimo bolj urejen sistem, se je nered v vesolju kljub temu povečal.**

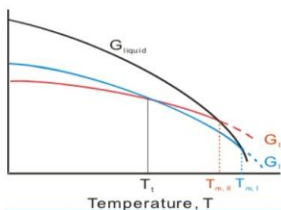
Termodinamski vidik



Monotropen

- Nižja **G** → bolj stabilen je polimorf
- Višja **G** → bolj topen je polimorf
- Višja **S** → večji nered v sistemu
- Gonilna sila kristalizacije je prehajanje iz stanja z višjo G v stanje z nižjo G:

Raztopina → amorf → oblika K → oblika T



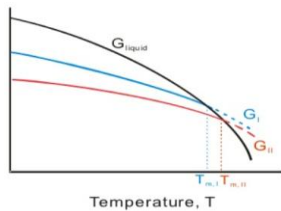
Enantiotropen

$$G = H - T \cdot S$$

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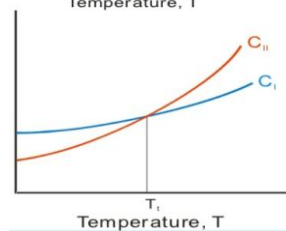
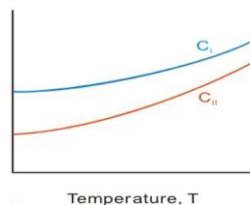
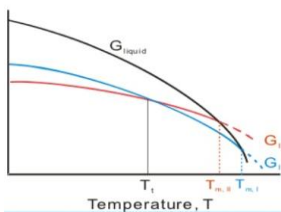
Termodinamski vidik



Monotropen

$$\ln x = -\frac{\Delta H_{tal}}{RT} \left(\frac{1}{T} - \frac{1}{T_{tal}} \right)$$

Enantiotropen



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Kinetični vidik

Oswaldovo pravilo

- Kristalne oblike postopoma prehajajo iz **najvišje** Gibbsove entalpije proti **najnižji**



RAZTOPINA

AMORFNE OBLIKE in
NEKRISTALINIČNE OBLIKE

KINETIČNE, METASTABILNE
KRISTALNE OBLIKE

STABILNE KRISTALNE OBLIKE

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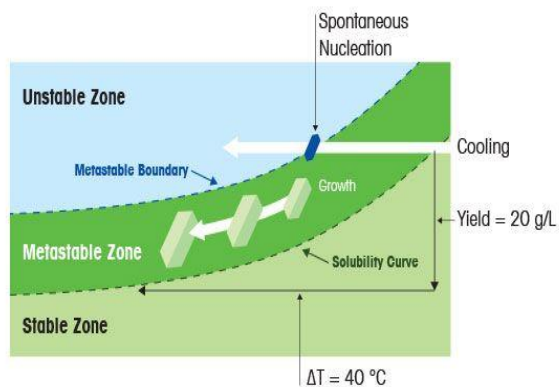


Kinetični vidik

Hitrost nukleacije

$$B = \frac{dN}{dT} = k_N (c - c^*)^n$$

PRENASIČENJE pove,
koliko koncentracija
topljenca presega
termodinamsko topnost



*https://www.mt.com/sk/sk/home/applications/L1_AutoChem_Applications/L2_Crystallization/reocrystallization.html

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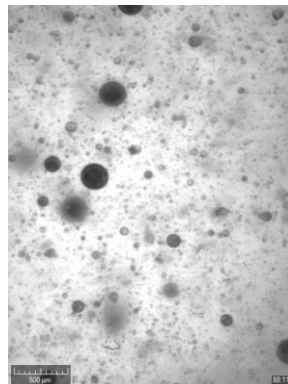


Kinetični vidik - Primarna nukleacija

Hitrost nukleacije

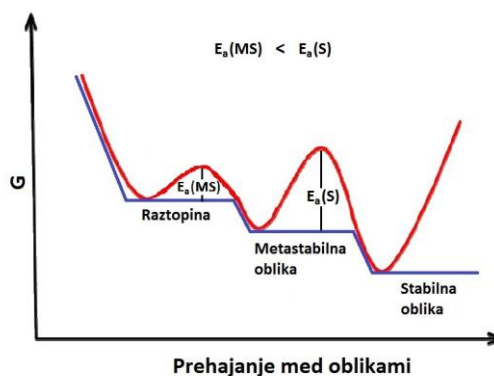
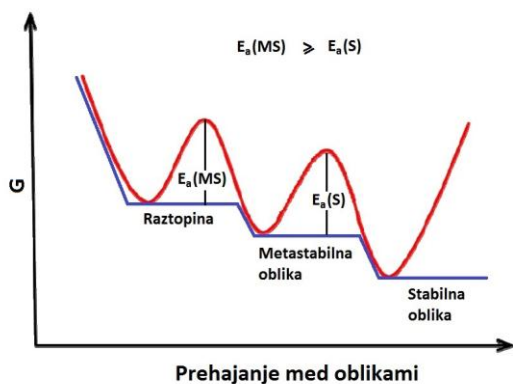
$$B = \frac{dN}{dT} = k_N (c - c^*)^n$$

PRENASIČENJE pove,
koliko koncentracija
topljenca presega
termodinamsko topnost



Kinetični vidik

Aktivacijska energija – indukcijski čas



Kinetični vidik

PRENASIČENJE

- Hitro ohlajanje
- Hitro odparevanje
- Dodatek antitopila
- Sprememba pH
- Tlak itd

NIŽANJE AKTIVACIJSKE ENERGIJE

- Odvisno od primera do primera

PROCESNI VIDIK

- Slaba ponovljivost izvedbe
- Iskanje parametrov, kjer je kinetika nastajanja metastabilne oblike največja
- **Uporaba cepiva za usmerjanje kinetike metastabilne oblike**
- **Previdnost zaradi zunanjih vplivov**

Nadzor nukleacije in kontaminacije



Disappearing Polymorphs

Acc. Chem. Res., Vol. 28, No. 4, 1995 197

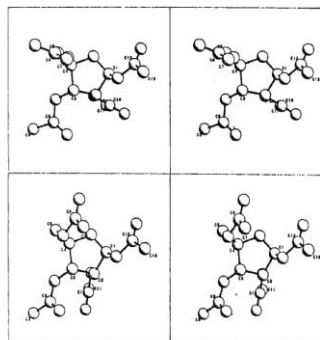
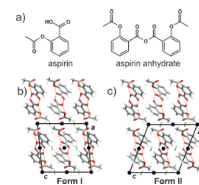
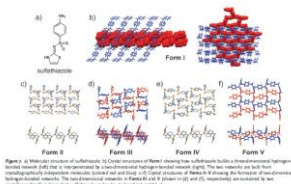
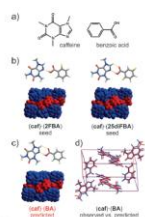
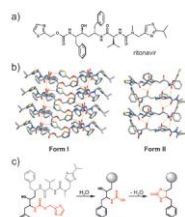
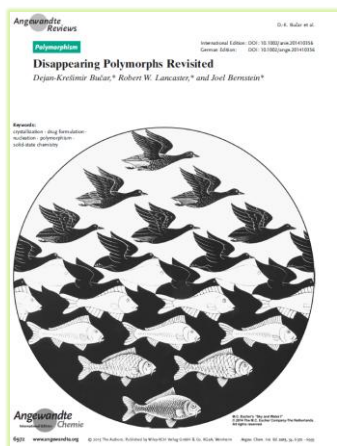


Figure 2. Stereoviews of the two forms of I. In both cases the view is on the plane of C1—O—C4 of the furanose ring; upper, monoclinic A form; lower, orthorhombic B form. For clarity, only carbon atoms are labeled.

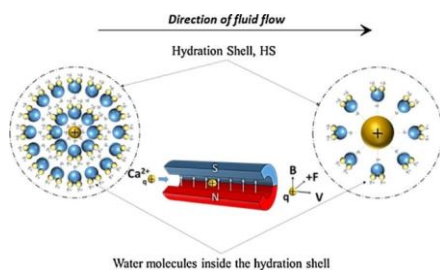
Nadzor nukleacije in kontaminacije



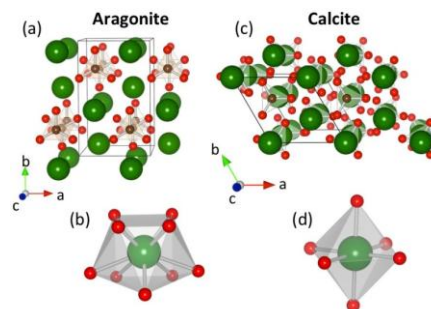
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Kalcit ali Aragonit



Po prehodu ionov skozi magnetno polje je Ca^{2+} ion manj hidratiran in lahko tvori več interakcij s karbonatnimi anioni



* <https://www.esrf.eu/home/news/spotlight/content-news/spotlight/spotlight263.html>

www.krka.si



Kalcit ali Aragonit

- Za nastanek aragonita potrebujemo več interakcij med Ca^{2+} ioni in karbonatnimi ioni
- Takih interakcij v raztopini je več, če je hidratacija Ca^{2+} ionov manjša po prehodu skozi magnetno polje
- Aktivacijska energija za nukleacijo aragonita se zniža, zato aragonit prične kristalizirati iz nižjega prenasičenja kot sicer
- Kinetika kristalizacije aragonita postane večja od kalcita, zato metastabilna oblika prevlada

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Kalcit ali Aragonit

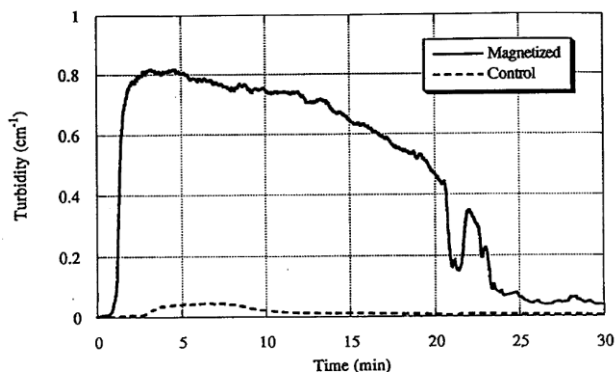


Fig. 3. Turbidity recorded as function of time. The magnetic treatment reduces the induction time, and greatly accelerates the nucleation and crystallization process.

* Y. Wang et al, Wat. Res., Vol. 31 (1997), 346-350

- Zaradi prehoda skozi magnetno polje se voda nacepi s kristali metastabilne aragonitne oblike
- Očem nevidni nanodelci aragonita usmerjajo kristalizacijo kalcijevega karbonata v aragonitno obliko

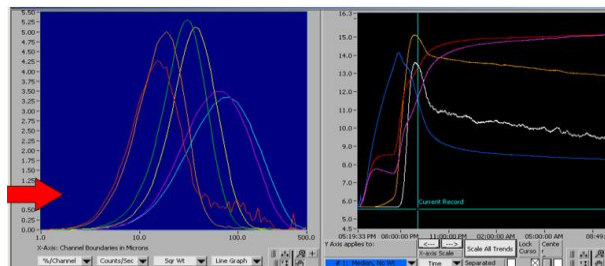
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„Nevidna“ nacepitev s termodinamsko obliko

PROCES

- Priprava solvatne oblike polimorfa učinkovine z uparevanjem topila
- Desolvatacija z maceracijo solvatne oblike v antipilu, da smo dosegli veliko prenasičenje
- Spremljanje konca maceracije s FBRM sondo, da smo jo pravočasno zaključili in preprečili prehod metastabilne oblike nastale z desolvatacijo v termodinamsko



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„Nevidna“ nacepitev s termodinamsko obliko

OPAŽANJA

Substanca ima močno tendenco do oprijemanja na površino reaktorja

Delež neuspešnih poskusov večji poleti kot pozimi

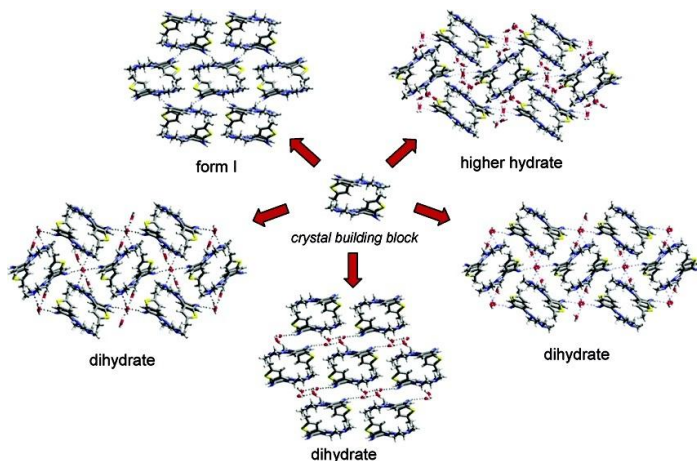
Oblog manj pozimi, ker je hladnejši zrak hladil vrat reaktorja med uparevanjem

Z nobeno analizno tehniko nismo uspeli dokazati zametkov termodinamske oblike v solvatu

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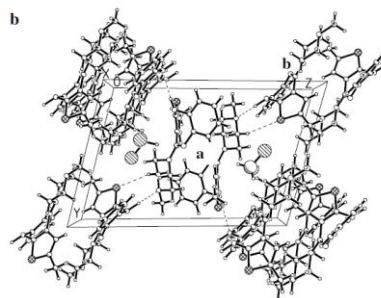


„Nevidna“ nacepitev s termodinamsko obliko



* S. M. Reutzel-Edens et al., Cryst. Growth. Des., Vol. 3(2003), 897-907

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* Irena Wawrzycyca-Gorczyca et al., Jour. Mol. Struct., Vol. 830 (2007), 188-197

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„Nevidna“ nacepitev s termodinamsko obliko

HIPOTEZA

- Molekula se tekom priprave solvata z uparevanjem zaradi oblog adsorbira na na površino sten reaktorja
- Planarno adsorbirane molekule inducirajo kristalizacijo termodinamske oblike s planarno strukturo že tekom priprave solvata, saj ima termodinamska oblika planarno strukturo
- Solvat je kontaminiran/nacepeljen s termodinamsko obliko, čeprav analize metode tega ne detektirajo
- **Metastabilna oblika ima cik-cak pakiranje, zato se je med njeno pripravo potrebno izogibati efektom, ki favorizirajo planarno strukturo**

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„Nevidna“ nacepitev s termodinamsko obliko

POTRDITEV HIPOTEZE

Reaktor	XRPD analiza	XRPD po maceraciji	Opažanja
Steklen	Solvat	Metastabilna in ~1% termodinamske oblike	Uparina rahlo oprijeta na stene reaktorja
Teflonski	Solvat	Metastabilna oblika	Uparina se ne oprijema na stene reaktorja
Kovinski	Solvat + znaten delež Termodinamske oblike	Termodinamska in ~1% metastabilne oblike	Uparina močno oprijeta na stene reaktorja

Z uparino iz teflonskega reaktorja smo lahko čas maceracije podaljšali na več dni in ni prišlo do nastanka termodinamske oblike, torej so topila in procesni parametri ustrezno izbrani, da oblika brez drugih zunanjih faktorjev termodinamska oblika ne more spontano nukleirati.

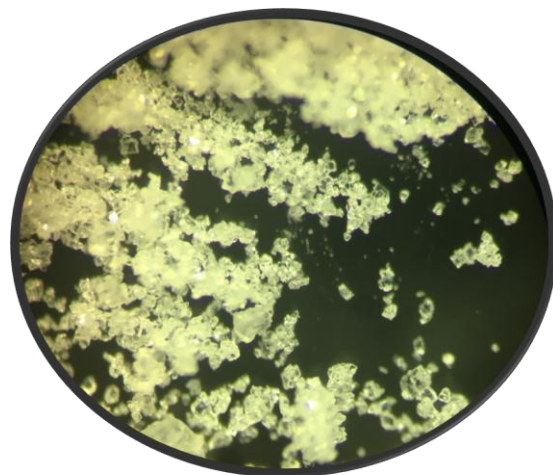
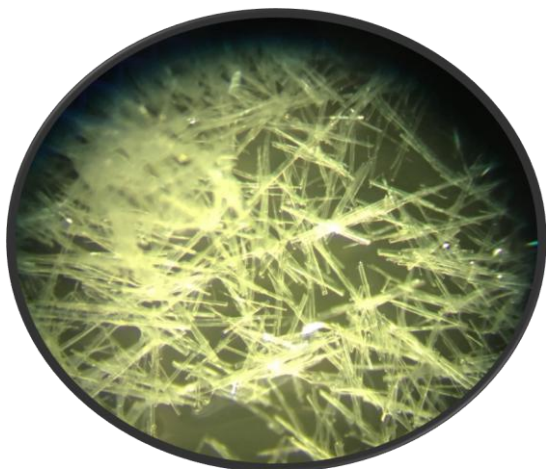
„Nevidna“ nacepitev s termodinamsko obliko

SKLEP: Zaradi interakcije planarnih molekul učinkovine s kovinsko/stekleno površino reaktorja smo med pripravo solvata injicirali kristalizacijo termodinamske oblike, čeprav je primarna nukleacija solvatne oblike iz topila preferenčen proces

NAUK: Na nukleacijo prave pojavne oblike ne vpliva samo temperatura, hitrost ohlajanja, koncentracija, sestava topil itd, ampak tudi zunanja okolica. To je lahko magnetno polje, ali pa bolj običajna stvar, kot je površina reaktorja ali prisotnost kakšnih drugih prašnih delcev v raztopini.

Čeprav včasih izgleda problem nerazložljiv, je lahko s poznavanjem strukture kristalnih oblik in njihovih fizikalno-kemijskih lastnosti rešitev na dlani.

Kvadri in iglice



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Kvadri in iglice

PROCES

- Kontrola metastabilne oblike s cepitvijo
- Zelo ozko temperaturno območje za spontano nukleacijo metastabilne oblike
- Čistost cepiva potrjena z XRPD in DSC
- Odločitev za optimizacijo procesa brez cepivo s spontano nukleacijo v metastabilno obliko



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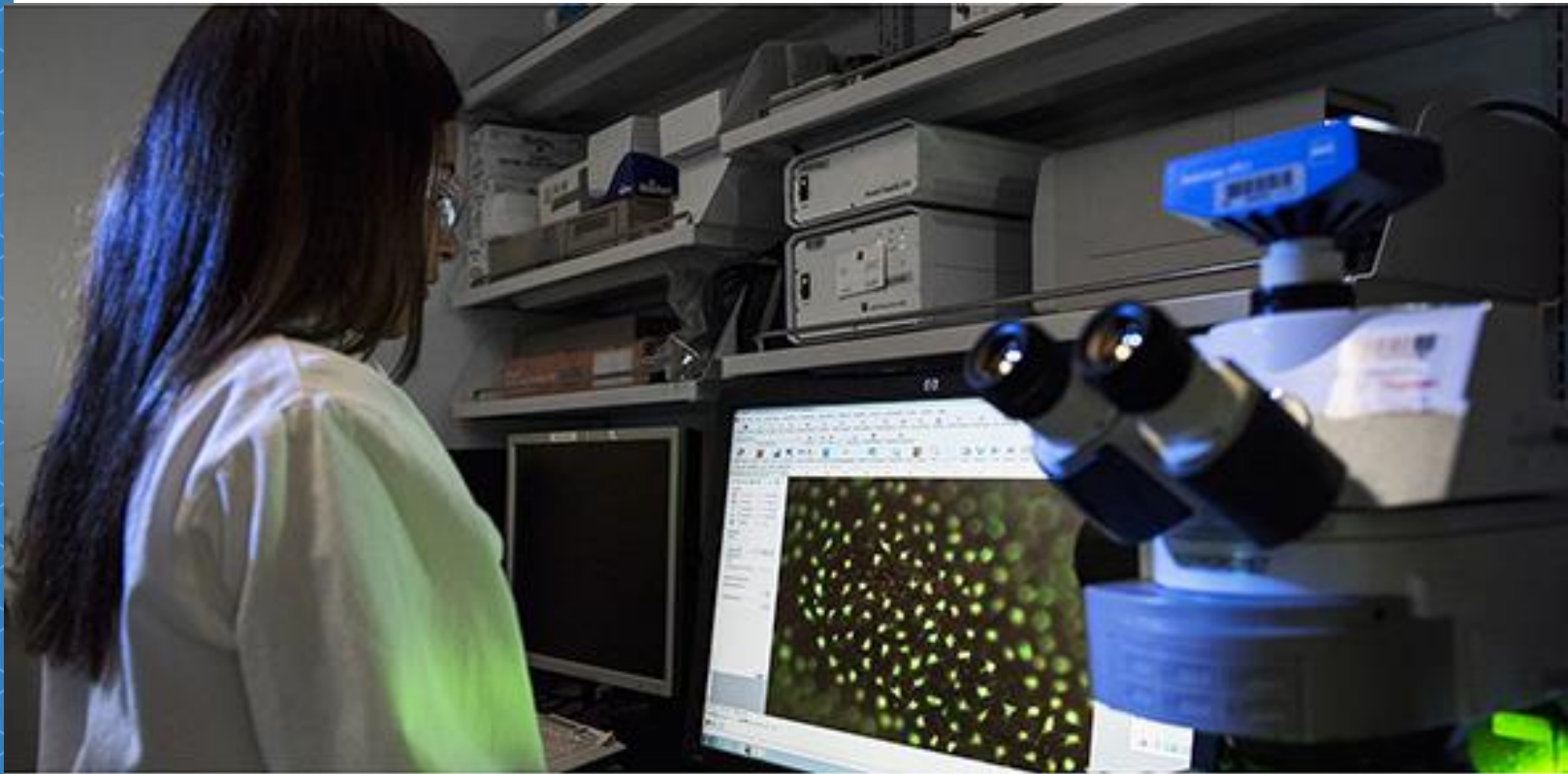
Kvadri in iglice

- Kontrola metastabilne oblike s cepitvijo
- Zelo ozko temperaturno območje za spontano nukleacijo metastabilne oblike,
- Čistost cepiva potrjena z XRPD in DSC

- Odločitev za optimizacijo procesa brez cepiva s spontano nukleacijo v metastabilno obliko,
- Vpliv okolice



Živeti zdravo življenje.



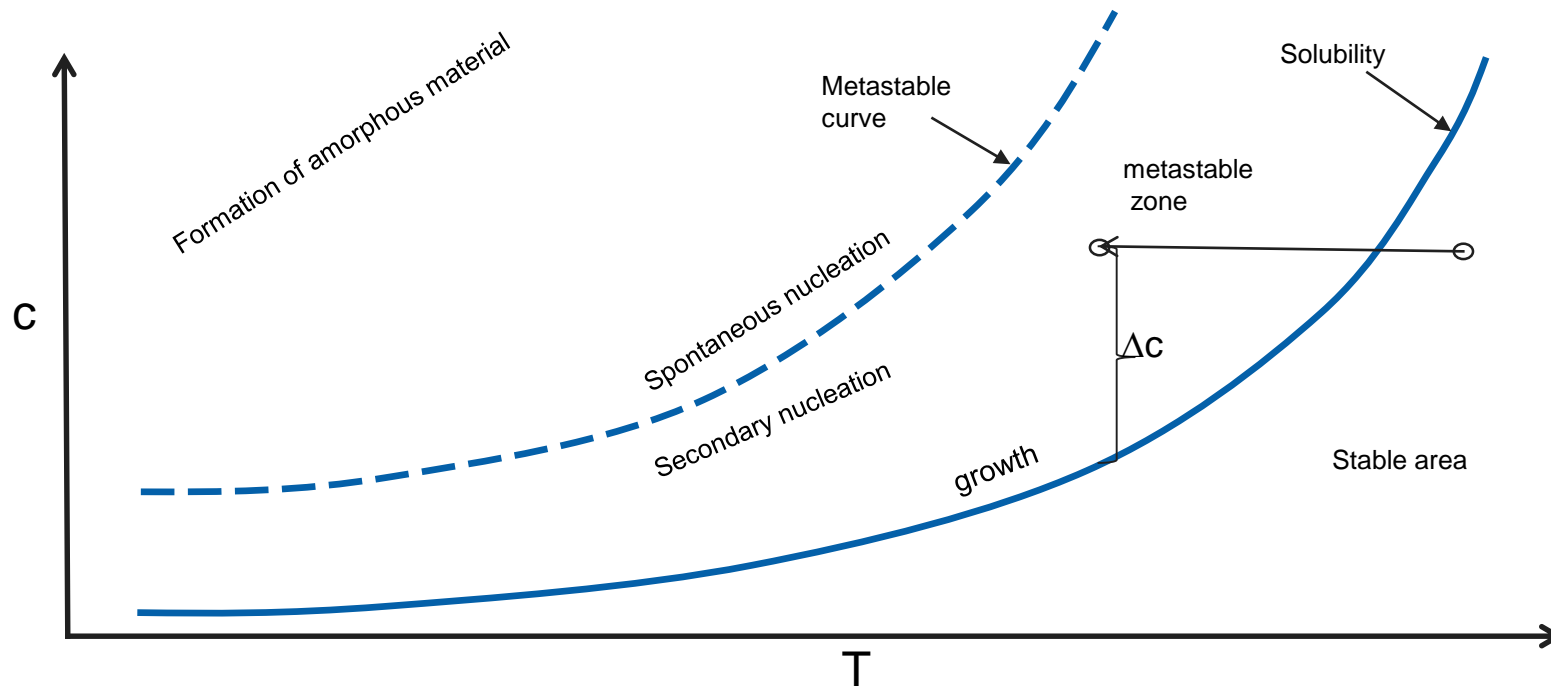
Crystallization of Metastable Compounds – Case Studies

Dušan Teslić, Head Particle Engineering & Synthesis

Ljubljana
June 13th, 2019

Crystallization from solutions - theoretical concepts

SUPERSATURATION - driving force for crystallization
 $\Delta c = c - c_{\text{equilibrium}} > 0$



NUCLEATION

GROWTH

AGGLOMERATION

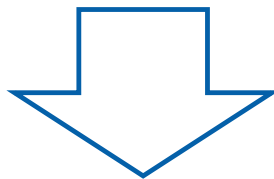
$$R_n = k_n \Delta C^n$$

$$R_g = k_g \Delta C^g$$

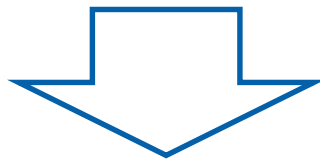
$$R_a = f(\Delta c, \text{stirring rate}, \dots)$$

Crystallization with polymorphism – theoretical concepts

- Ostwald's Step Rule
 - In general it is not the most stable but the least stable polymorph that crystallizes first

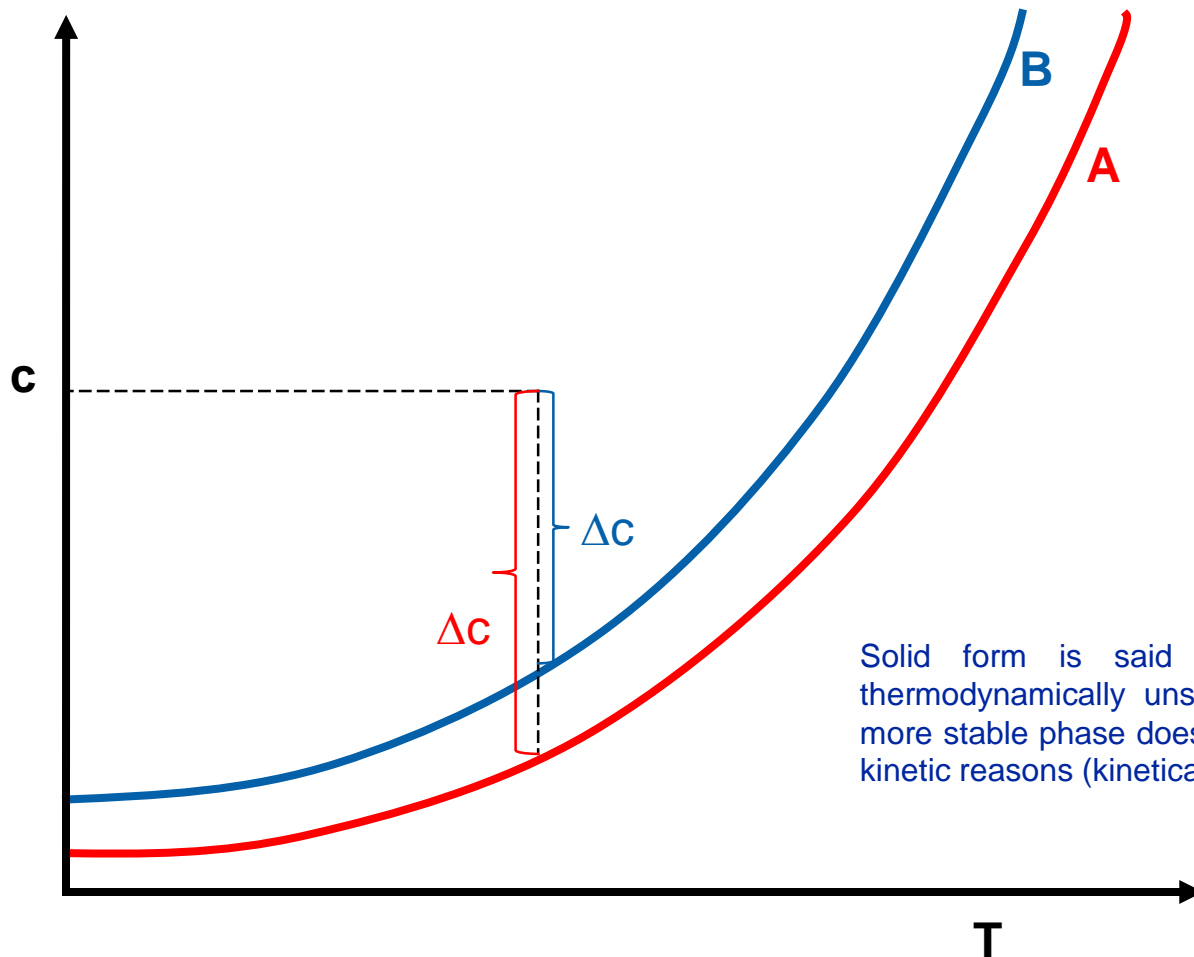


For unseeded polymorphic crystallization, the first nucleation event can be a metastable form



**It is often advisable to seed
polymorphic systems for better control**

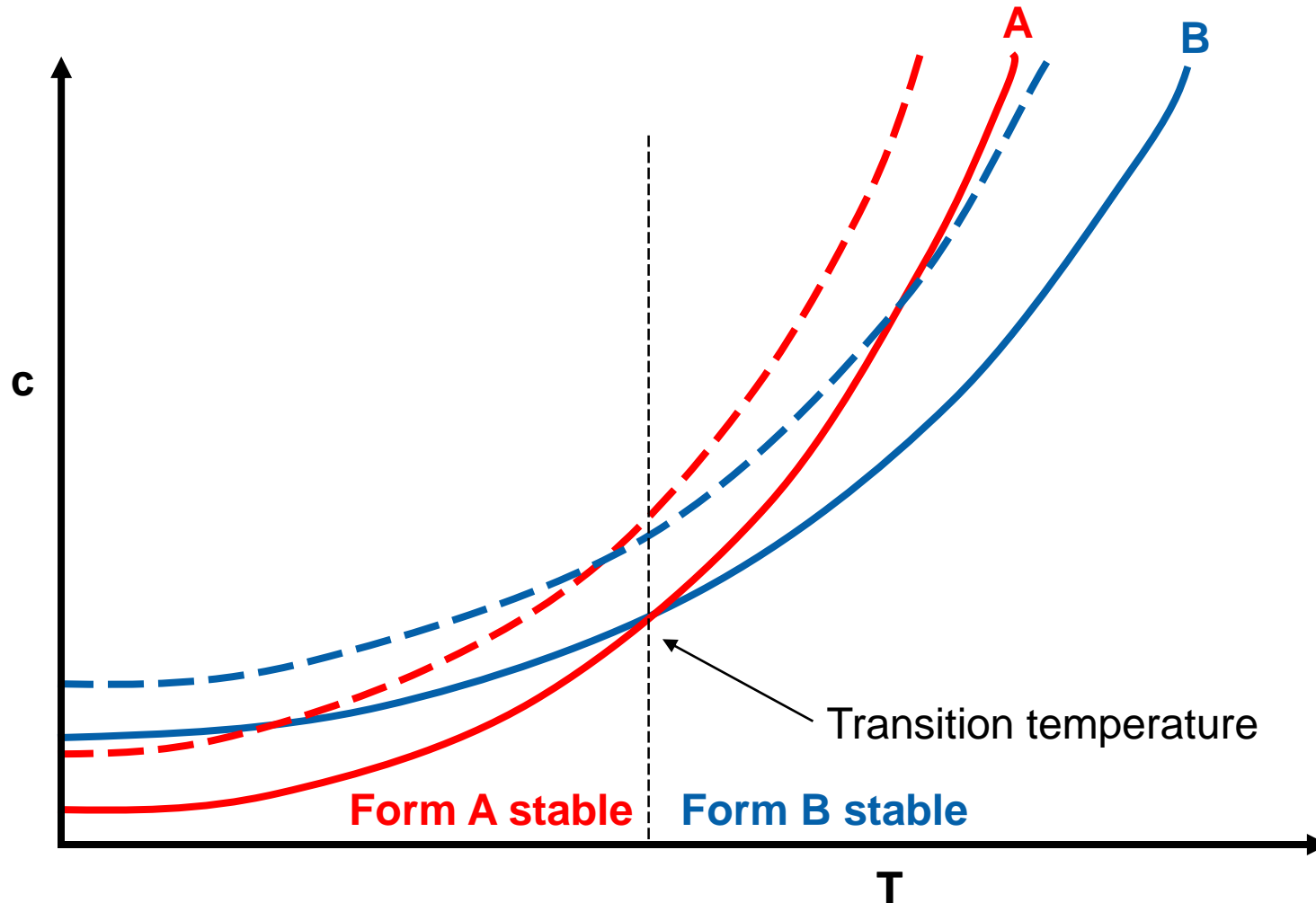
Monotropic system



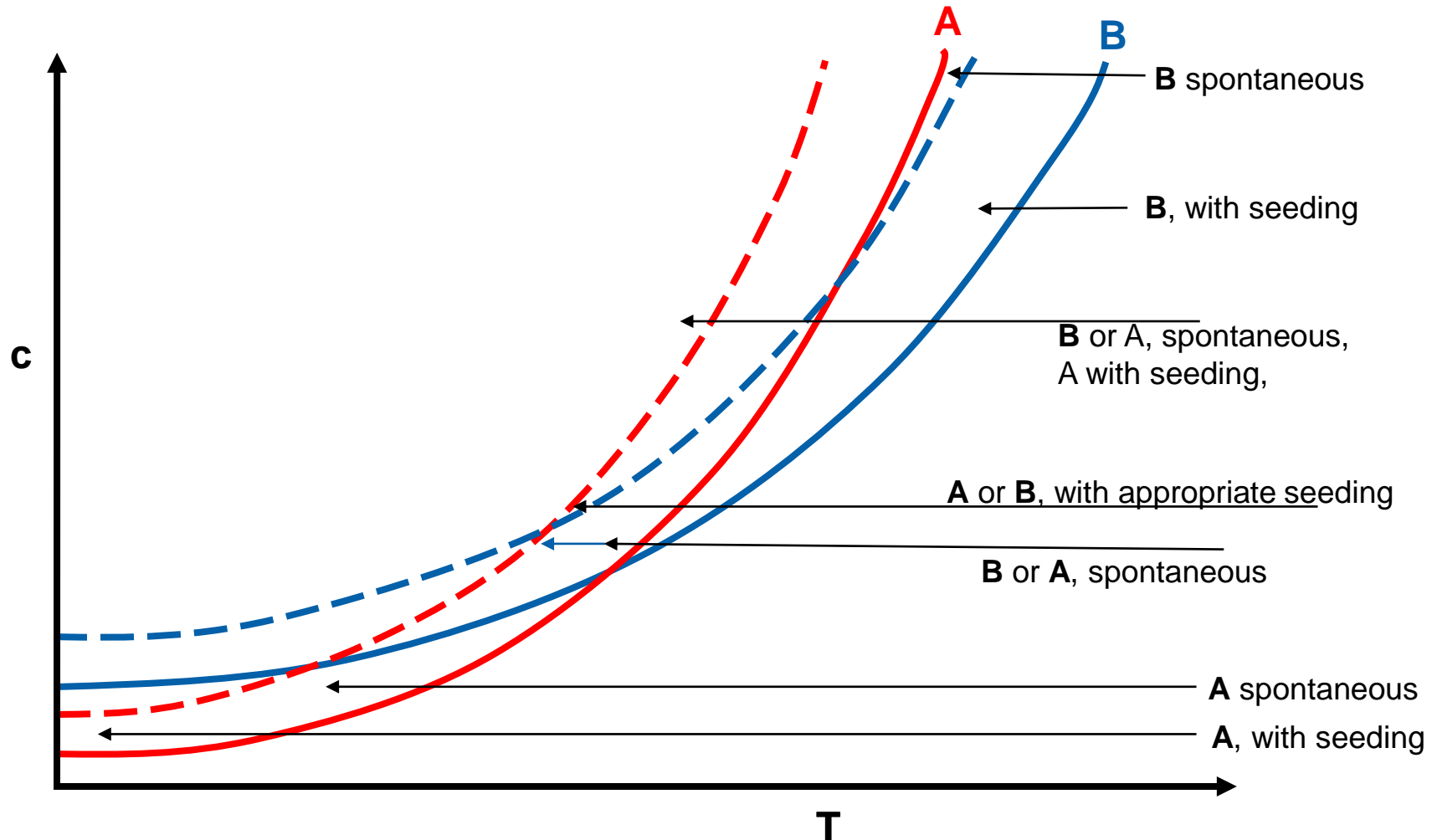
Only one stable form

Solid form is said to be metastable when it is thermodynamically unstable but the phase change to a more stable phase does not occur immediately because of kinetic reasons (kinetically stable).

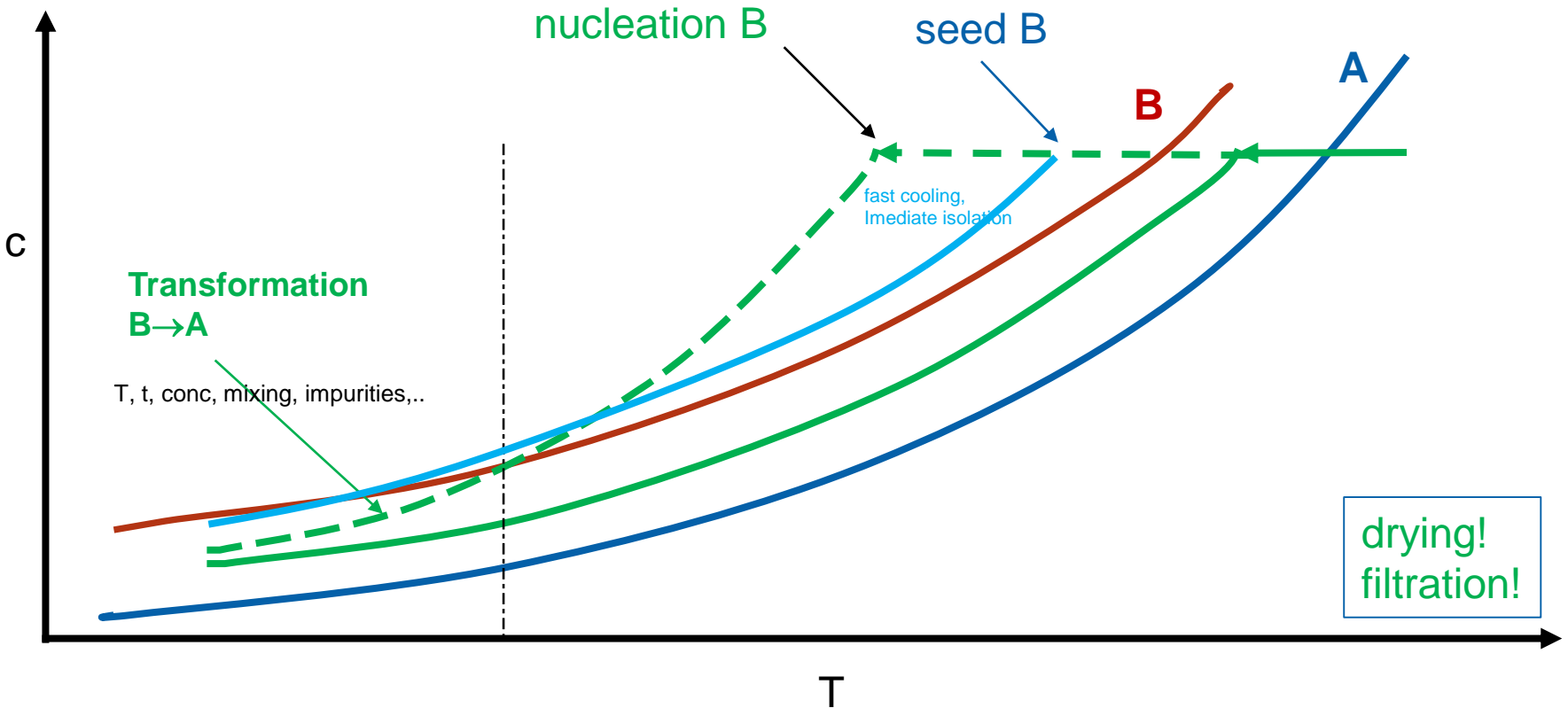
Enantiotropic system



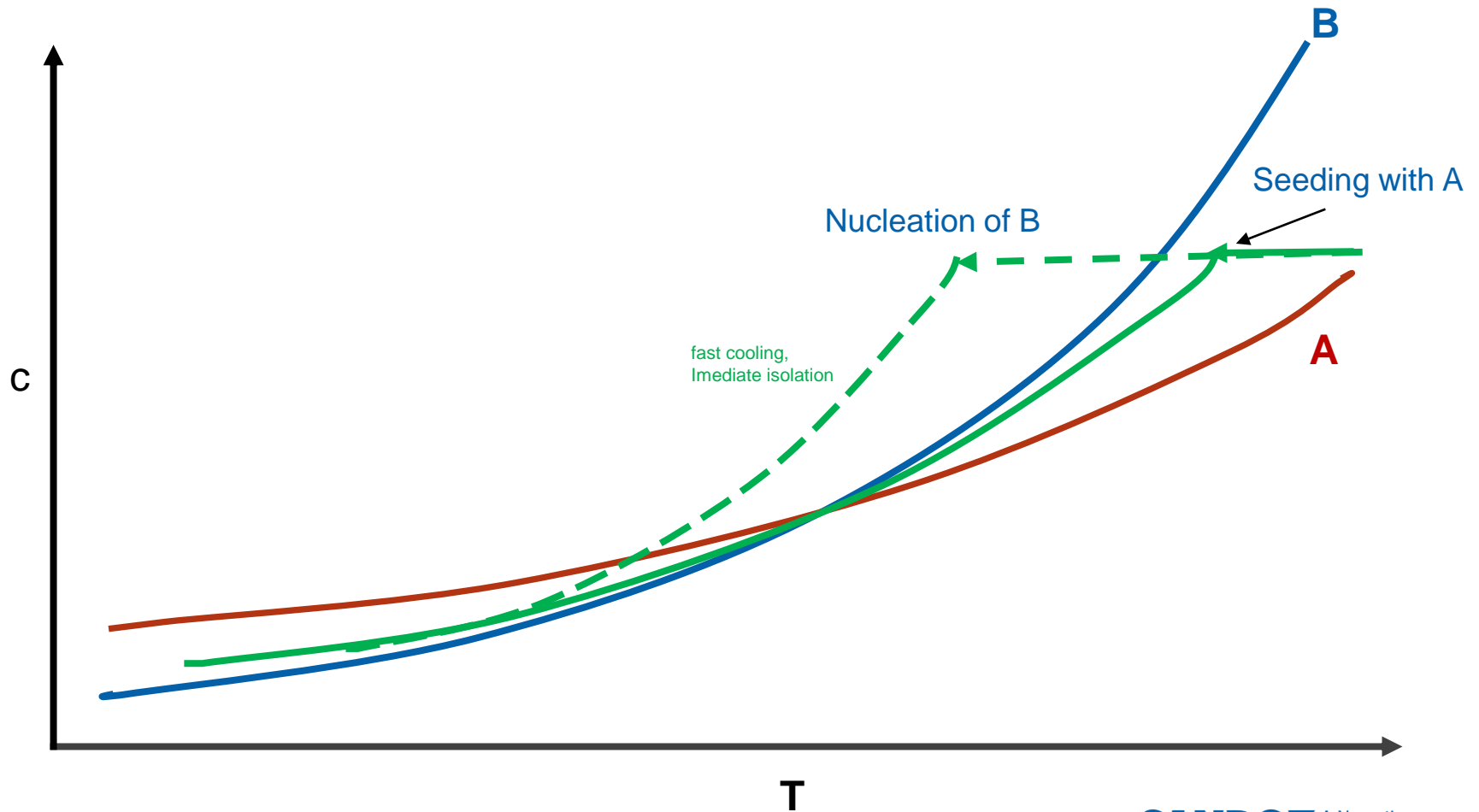
Crystallization of enantiotropic polymorphs



Monotropic system – isolation of stable form A & metastable form B



Monotropic system – isolation of (stable) form B



Case study 1 - particle engineering of BCS4 compound

API development

FDF development

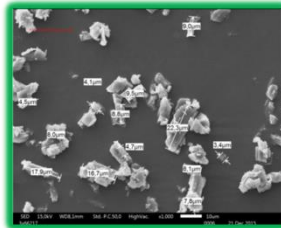
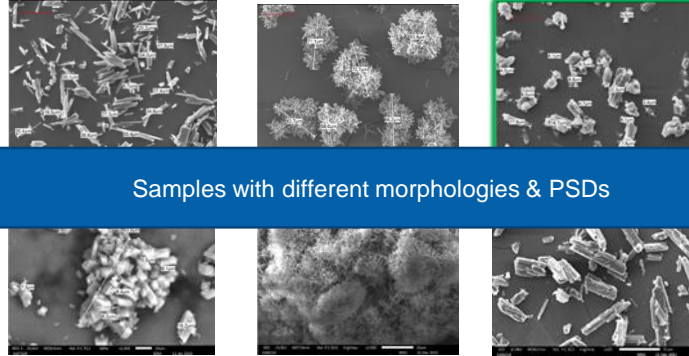
Initial solvent/crystallization techniques screening

Targets for PSD and morphology agreed with FDF

Cooling/antisolvent crystallization with seeding in two solvent system chosen

Process optimization

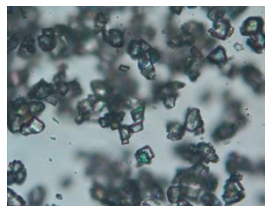
Specification limits for particles set, parameters for crystallization process defined.



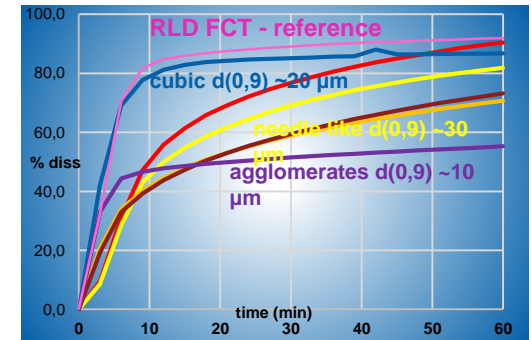
Cubic non - agglomerated particles gave best results for FDF

Samples with different PSDs, & degree of agglomeration

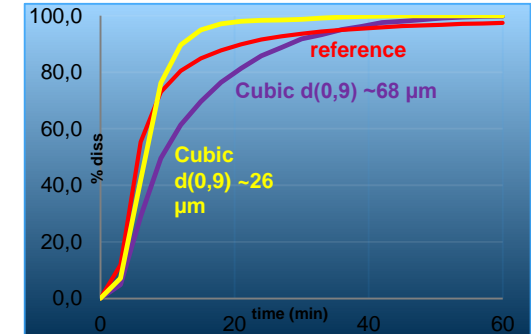
QbD approach



FDF evaluation (dissolution tests, processability,..)

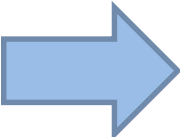


FDF evaluation (dissolution tests,...)

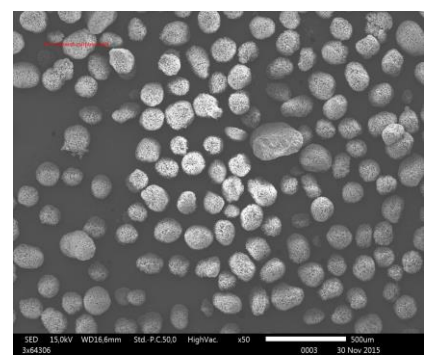
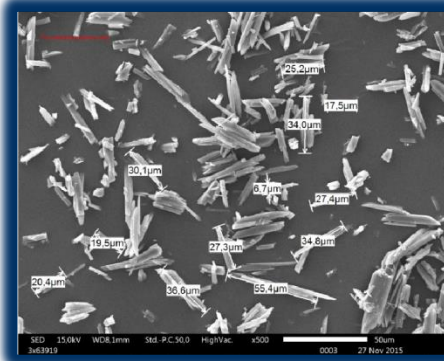
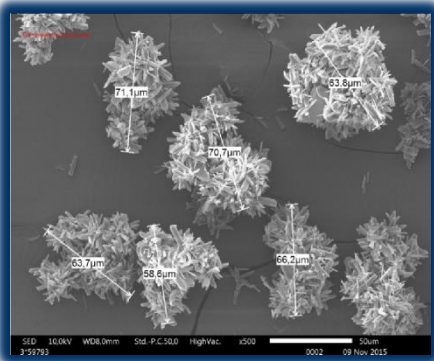
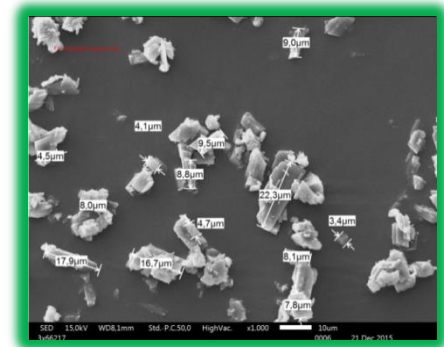
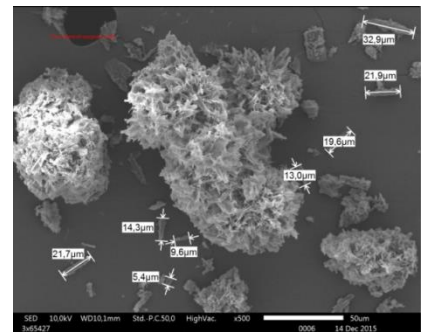
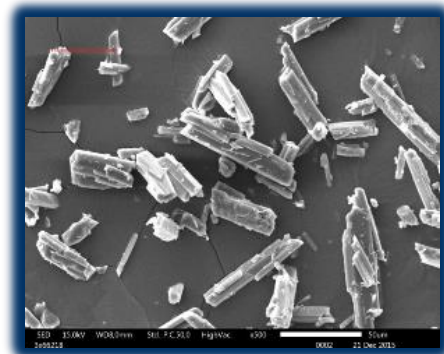
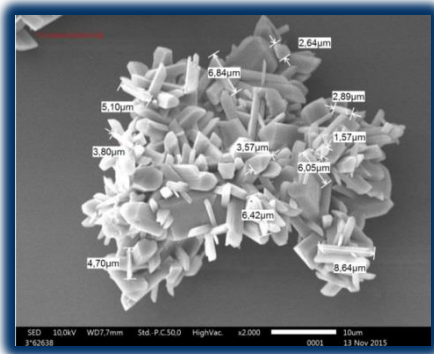


Screening crystallization experiments

- Different solvents (Class 3)
- Different crystallization techniques
- Different crystallization parameters



Different morphologies & PSDs of Form B



Initial solvent/crystallization techniques screening

Morphology, particle size & polymorphism?

Influence of:

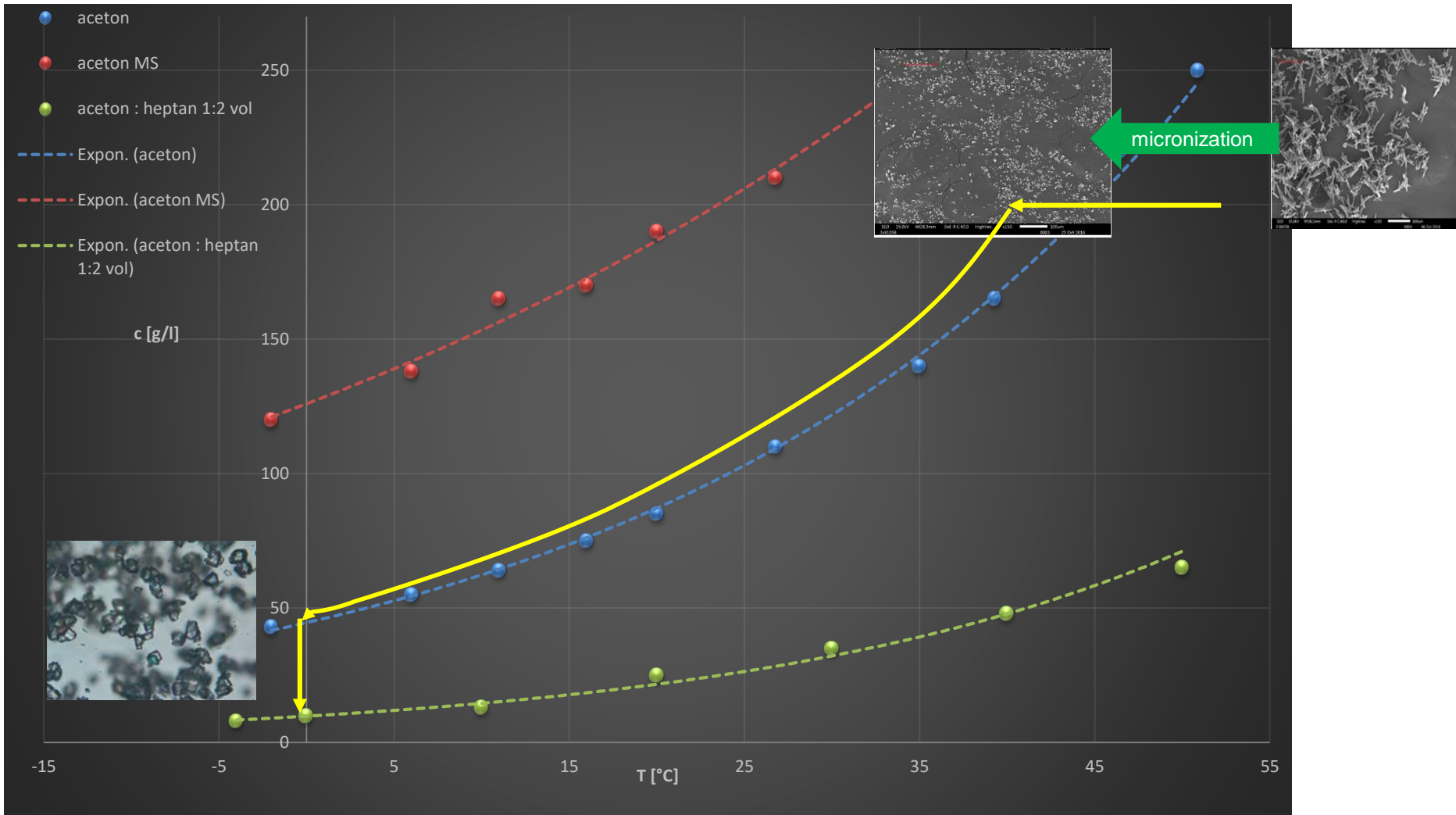
- **Solvents** → crystallization in different class 3 solvents checked (Acetone, EtOH, IPrOAc, EtOAc, MEK, n-butanol, IPrOH...)
- **Crystallization technique:**
 - Cooling crystallization
 - Fast cooling
 - Slow cooling
 - Antisolvent crystallization
- **Seeding/no seeding**

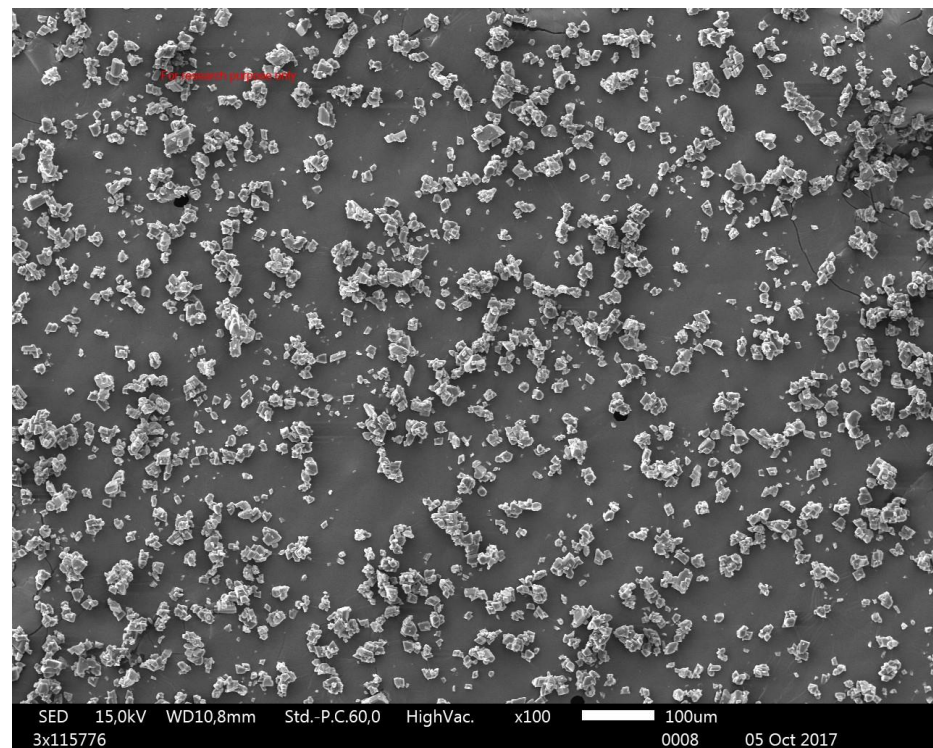
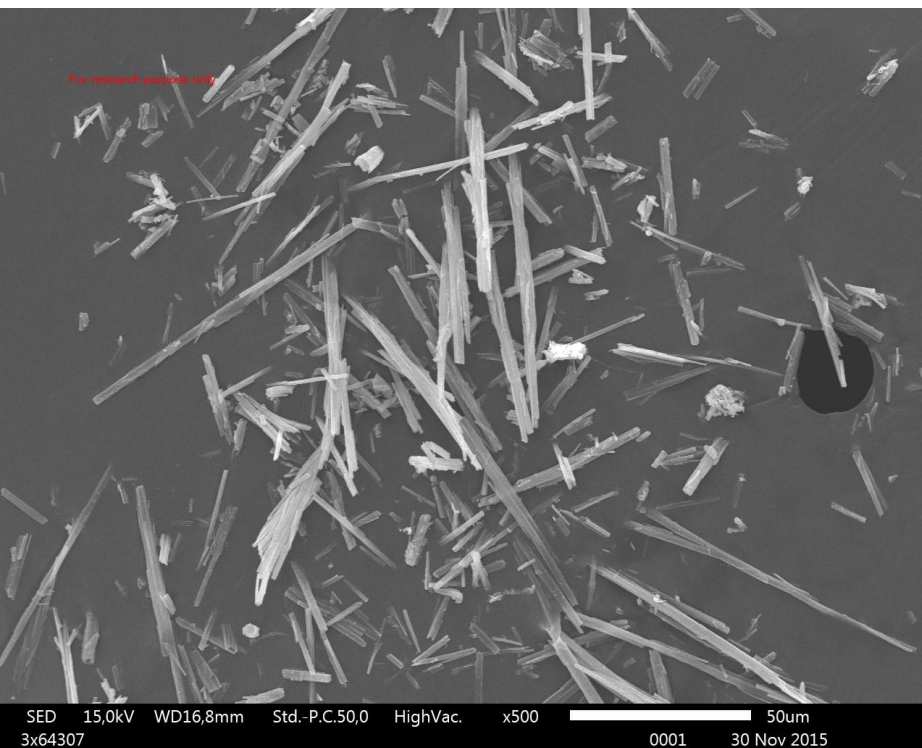
Screening
results

- **Solvents strongly influence morphology. Different morphologies for Form B possible (cubic, needles, spherulites, agglomerates, porous spherical particles,...)**
- **Seeding with Form B is necessary to assure crystallization of Form B**
 - **Desired cubic morphology was produced only in Acetone**
 - **Slow cooling seeded crystallization**
 - **Seed: Form B, d90 < 10 microns, ~10%**

Case study 1

Cooling crystallization with seeding followed by antisolvent crystallization





PILOT PLANT RESULTS:

Yield: 94-96% !

d₉₀: 30-40µm

Shape of crystals: 100%
cubic,

low degree of agglomeration

Case study 2 - crystallization of metastable (MS) hydrate

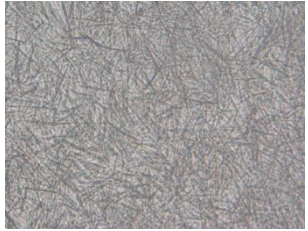


Challenges

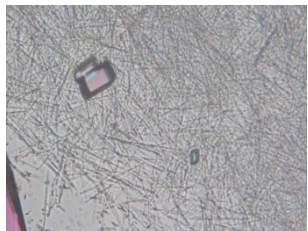
- Crystallization of metastable solvate
- Influence of impurities on polymorphism
- Instability of solvate in suspension

experiments

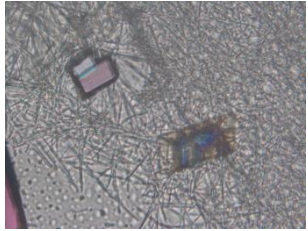
- Different crystallization techniques
- Solvent & antisolvent systems
- Additives for polymorphism
- Polymorph transformation kinetics
- Scale up effects
- Drying (sublimation, gas purging, vacuum)



hydrate



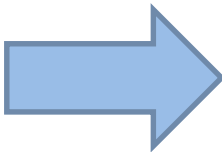
hydrate + traces



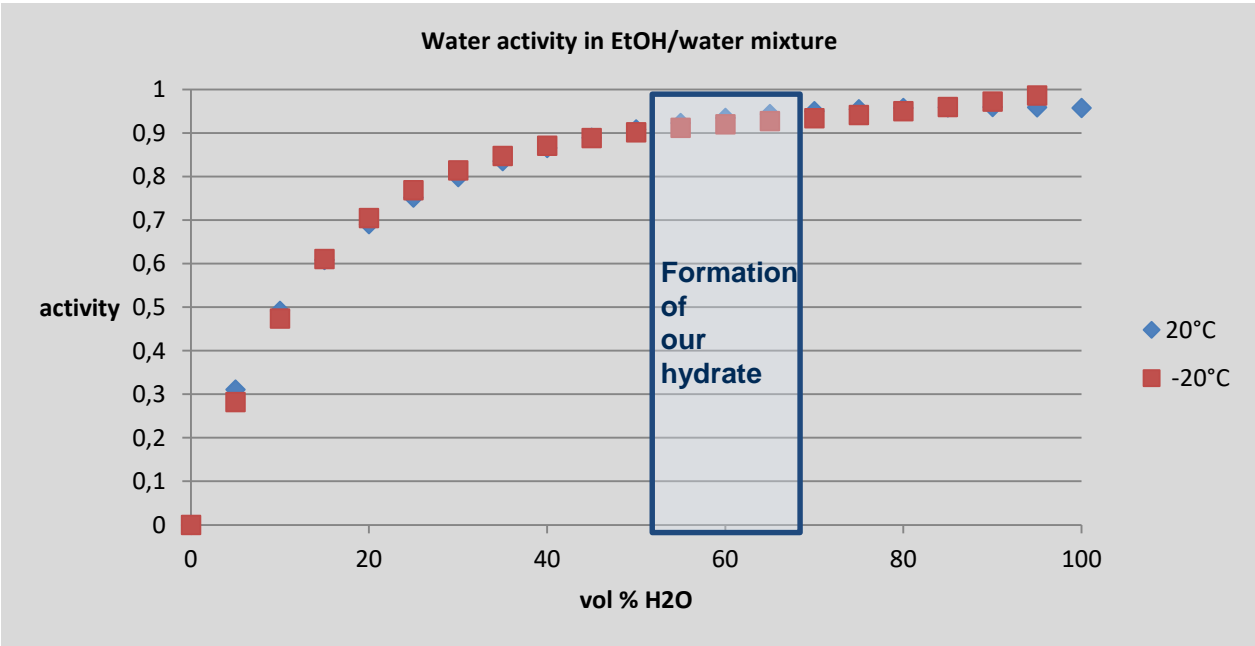
hydrate + traces

Case study 2 - Crystallization of Metastable Hydrate

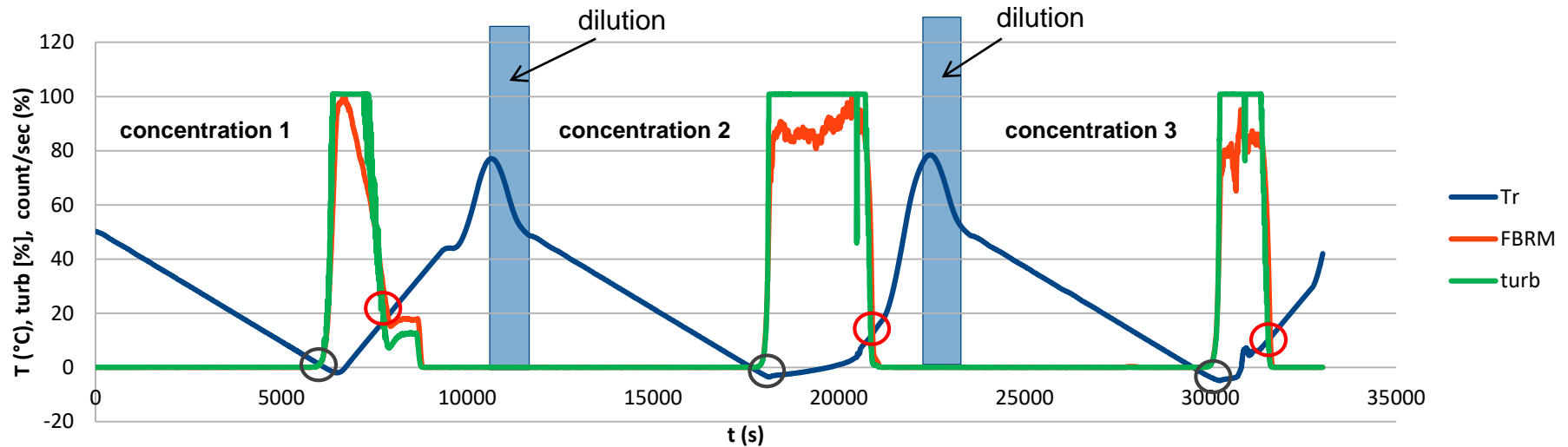
- Amount of water needed for hydrate?
- Solvents combination?
- Stability of hydrate in suspension?
- Solubility data?
- Acceptable yield?
- Possibility for scale up?
- Desired product quality?



Type of crystallization process

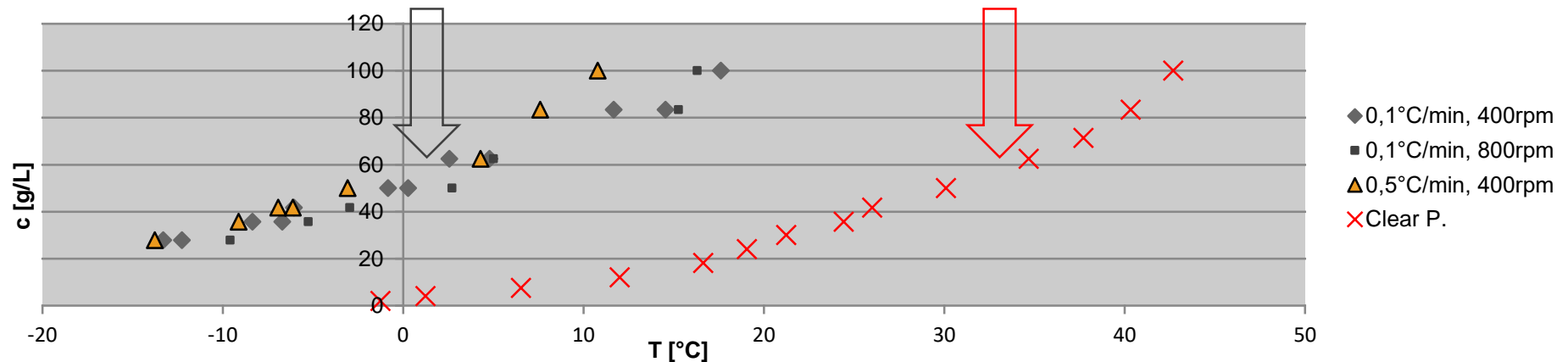


Turbidity & FBRM – solubility and metastable zone measurements



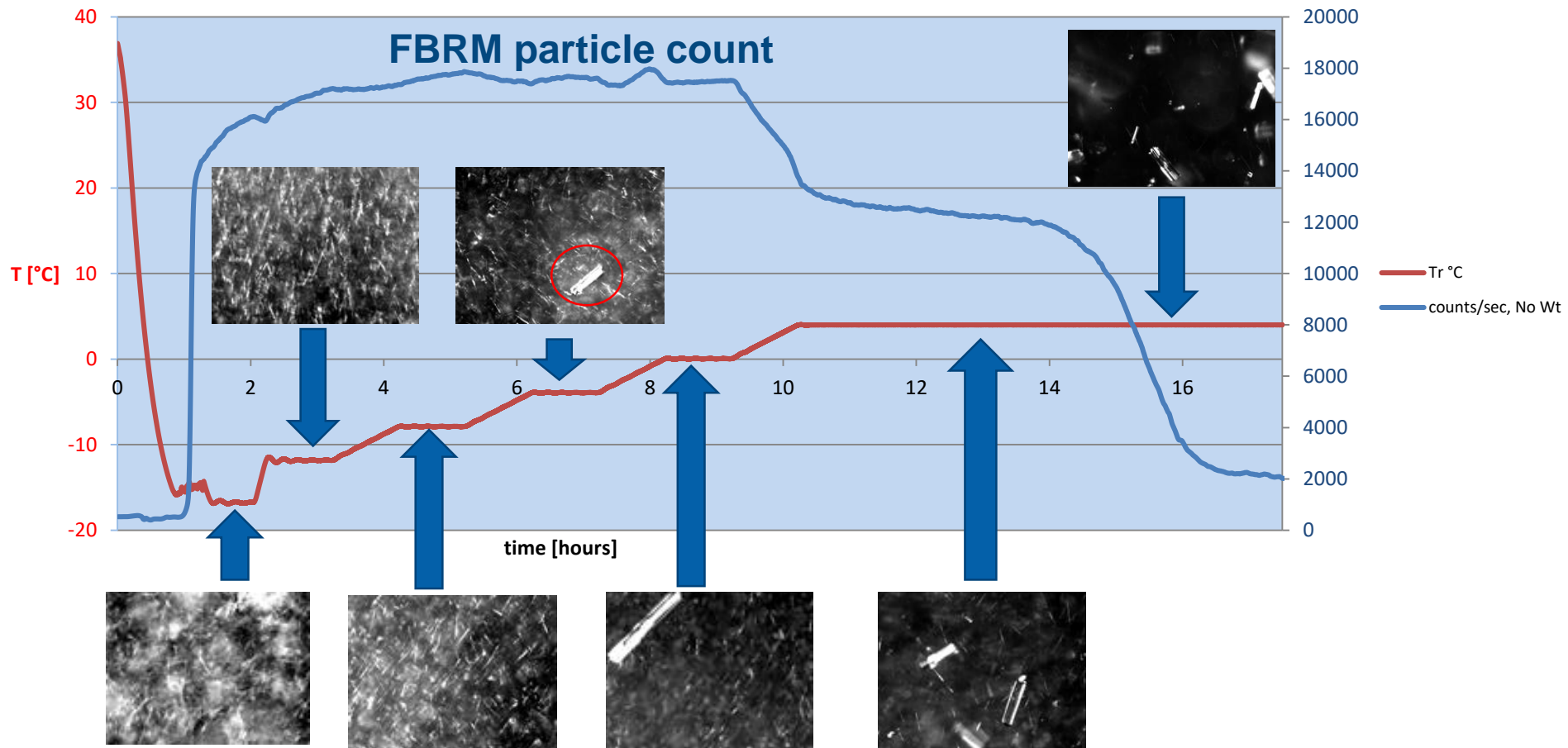
○ metastable points

○ Solubility points



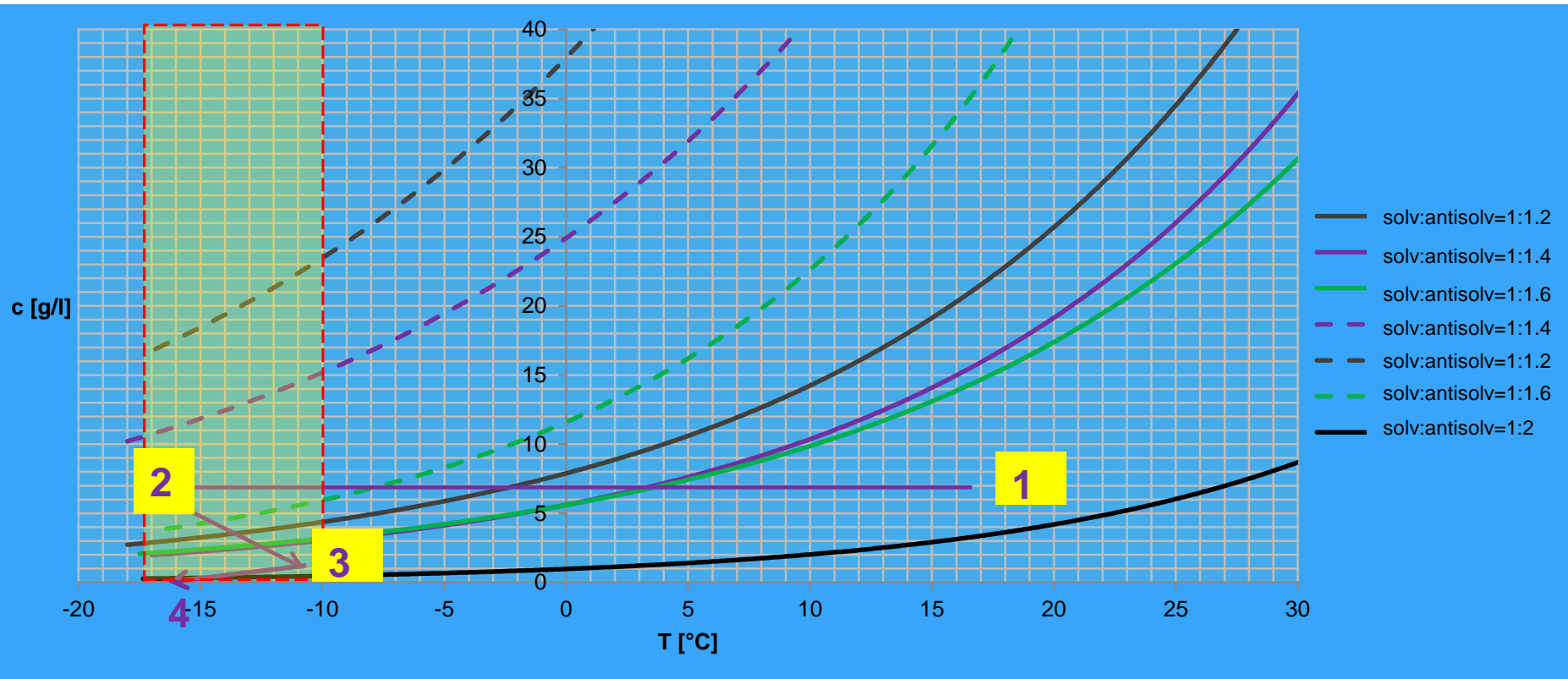
- Metastable zone - influence of cooling & stirring rate checked – **SCALE UP!!**
- Solubility & MS curves determined for different solvent:antisolvent ratios

PVM & FBRM for monitoring polymorphic transformation



Result of PVM monitoring & equilibration tests:
Solvate stable in suspension at $T < -10^{\circ}\text{C}$!

Construction of „phase diagram“



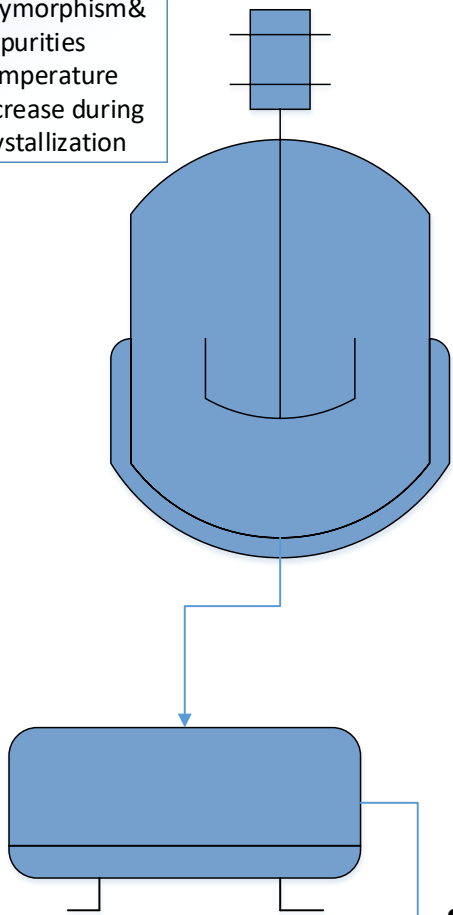
1→2 cooling to crystallization starting point - „travel“ through metastable zone

2→3 antisolvent crystallization – close to freezing point!!

3→4 cooling crystallization

Process, Equipment & Scale Up Challenges

- Solvate
- Poymorphism & Impurities
- Temperature increase during crystallization



- dissolution**
 - Temperature
 - Amount of solvent
 - Amount of crude
- cooling SCALE UP!**
 - CPP: Cooling rate/ time
 - Final temperature
 - Stirring rate
- crystallization SCALE UP!**
 - CPP: Temperature
 - antisolvent addition rate
 - Stirring rate
- filtration SCALE UP!**
 - CPP: Temperature
 - Pressure
 - Maximum Time
- drying to solvate**
 - CPP: Temperature
 - CPP: Pressure
 - Time
 - Nitrogen flow

1st time right scale up!

- packaging**
 - Nitrogen atmosphere
- sieving**
 - Screen size
 - Rotor speed
- drying/ desolvation to desired polymorph**
 - Temperature
 - Pressure
 - Drying time

Thank you

VREDNOTENJE RAZTAPLJANJA METASTABILNIH TRDNIH OBLIK

Darكو Uršič
Junij 2019



Živeti zdravo življenje.

Osnovni problem vrednotenja

- Metastabilne trdne oblike
- stabilna trdna oblika
- metastabilne raztopine
- obarjanje
- kaj smo določili?

Poenostavitev: raztapljanje soli v neugodnem pH

Raztapljanje/obaranje

- raztapljanje $\rightarrow \Delta c = k_R (C_{S,R} - c)$
- obarjanje $\rightarrow \Delta c = k_O (c - C_{S,O})$
- obarjanje ene oblike v drugo $\rightarrow C_{S,O} < C_{R,O}$

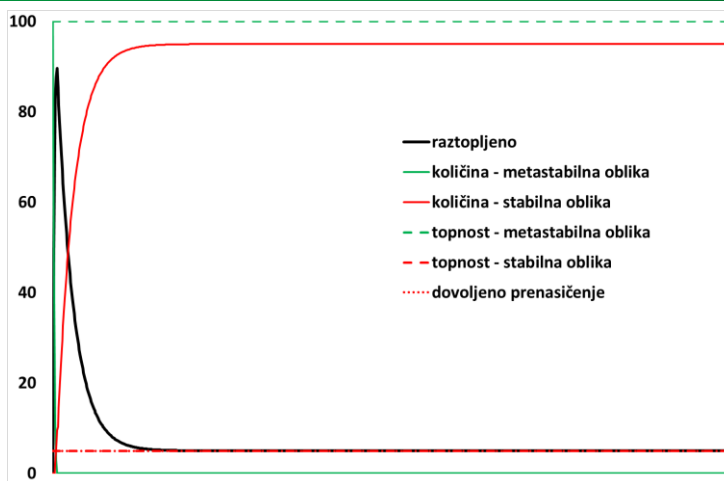
Obaranje

- razlika med raztopljeno koncentracijo in topnostjo je gonilna sila
- število ‚kristalov‘
- obarjanje tekočine? \rightarrow baze
- voda kot ‚plastifikator‘
- mesto obarjanja

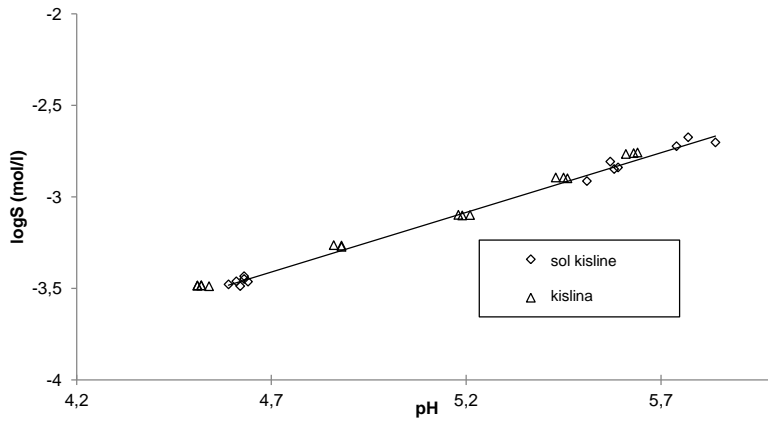
Testiranje - topnost

- želimo topnost metastabilne oblike
 - Ali prihaja / je prišlo do obarjanja?
- stresanje 24h/72h → kaj dobimo?
- vpliv presežka

Topnost – hitro obarjanje



Primer – naproksen

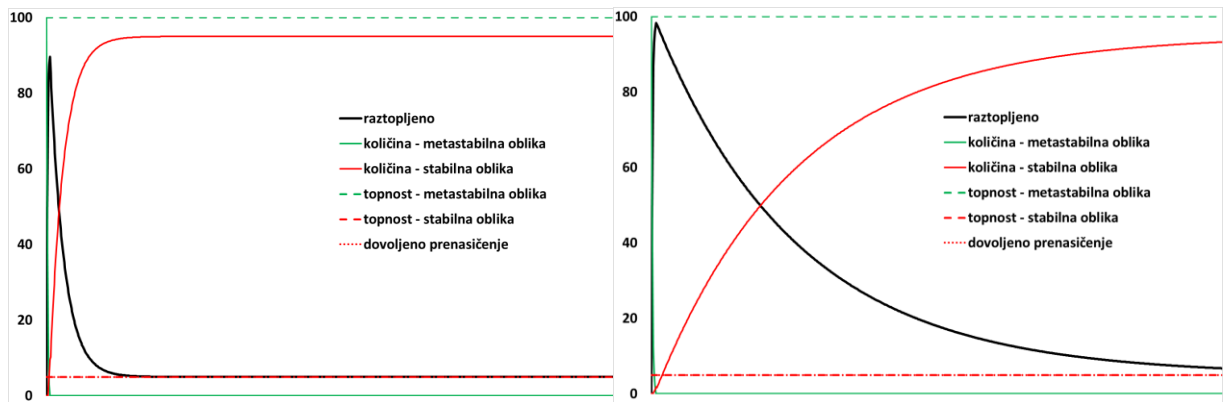


www.krka.si

diplomsko delo, Tadej Dolenc, 2013



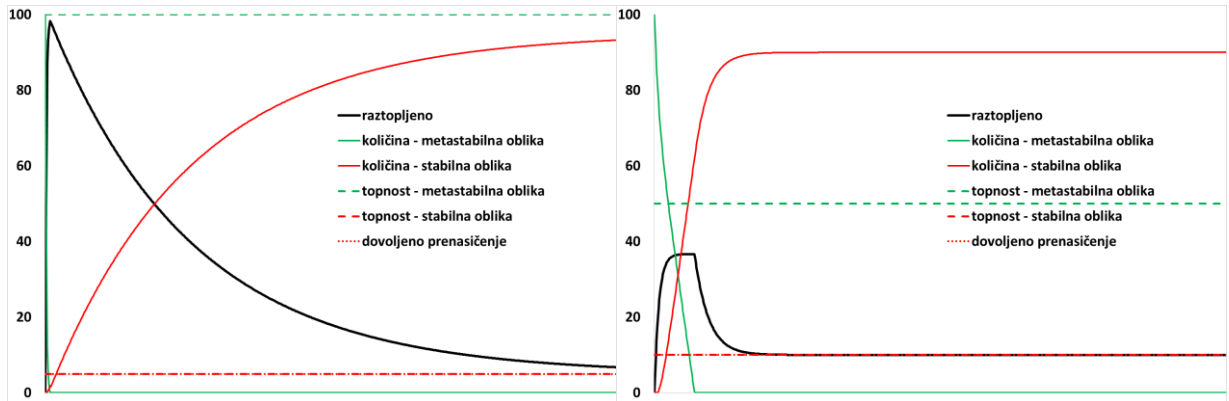
Primer – počasno obarjanje



www.krka.si



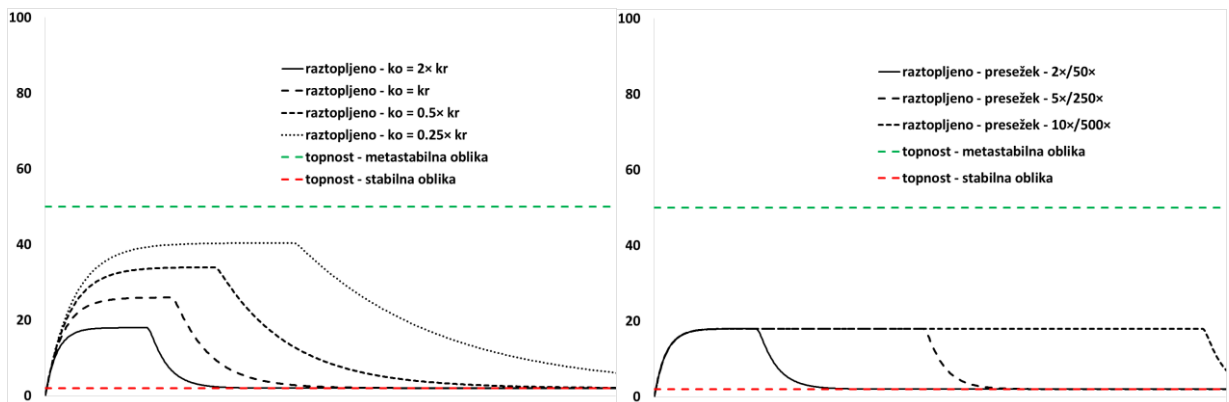
Primer – počasno obarjanje/nižja topnost



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Primer – počasno obarjanje/večji presežki



www.krka.si

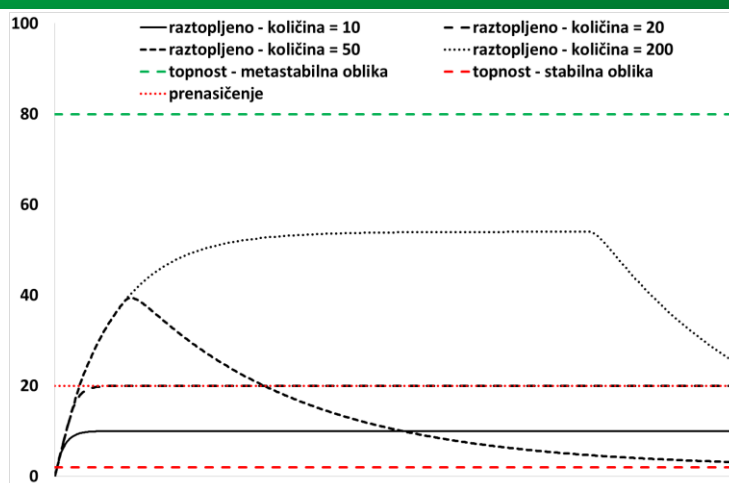


Obarjanje - supersaturacija

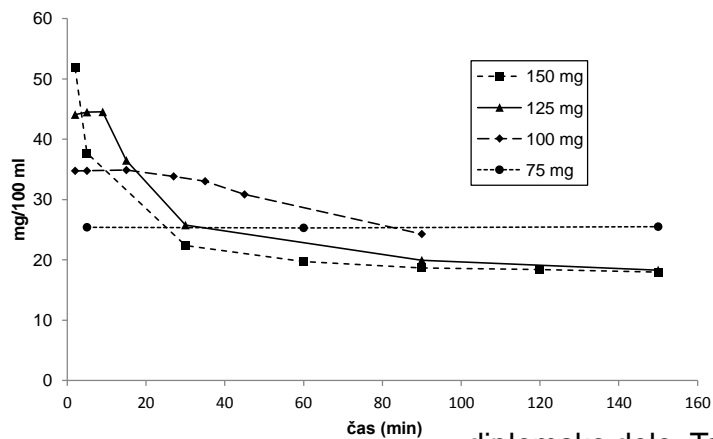
- površinska energija
→ faktor prenasičenja
- indukcijski čas

Faktor prenasičenja in indukcijski čas sta lastnosti **stabilne** oblike (C_s), sistema in koncentracije

Primer – prenasičenje



Primer – sol bazične učinkovine



www.krka.si

diplomsko delo, Tadej Dolenc, 2013



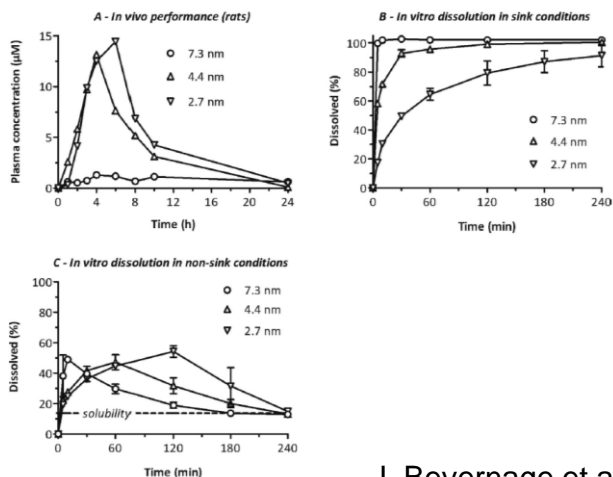
Obarjanje – dodajanje PAS

- spremembe
 - $C_{S,R}$, $C_{S,O}$
 - k_R , k_O
 - faktor prenasičenja
 - dodatna kristalizacijska jedra
 - ‚sistem v celoti‘

www.krka.si



Testiranje raztapljanja - primer



www.krka.si

J. Bevernage et al., Int J Pharm 453 (2013)



Testiranje raztapljanja

- biorelevantnost sistema raztapljanja
 - volumen
 - mediji in preskoki med njimi \rightarrow Fassif/Fessif,....
 - obremenitve \rightarrow hidrodinamika VS strižne sile
 - selektivno odstranjevanje permeabilnih učinkovin
 - ‚vlažni‘ žepki

www.krka.si



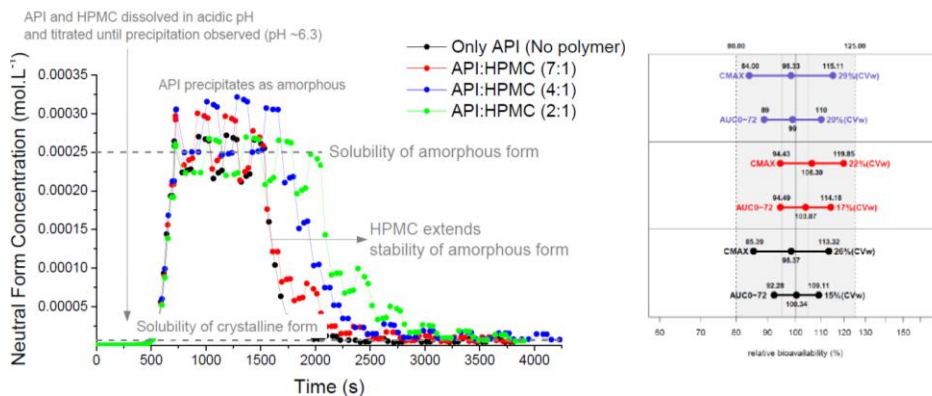
„Fitanje“ sistema raztapljanja

- napovedljivost za druge FO/učinkovine
- pomen testiranja
 - akademski svet → napredek znanosti
 - (generični) industrijski svet → napovedovanje BeQ

www.krka.si



Primer



1. Eudragit EPO

2. PVP K90

3. No polymer

J. Beranek, Zentiva, Biorelevant, 2016

www.krka.si



Zaključki

- težavnost izvedbe
- pozornost pri ,obravnavi' rezultatov
- prilagajanje sistema rezultatu
- ,napovedna moč'?

SDC Slovenia



Process challenges for production of amorphous solid dispersions

Biljana Janković, PhD
Pharmaceutical Development, SDC Slovenia
June, 2019

Manufacturing technologies for solid dispersions

Chemically identical but physically different amorphous solid dispersions (ASD) can be produced by:

1. Solvent evaporation technologies

- ✓ Spray drying; tray drying, granules-layering, freeze drying, electro-spraying

2. Heat based technologies

- ✓ Hot-melt extrusion; melt-quench cooling (Kinetisol®)

3. Mechanochemical activation:

- ✓ Cryo-milling

Manufacturing technologies for solid dispersions

- Drug loading

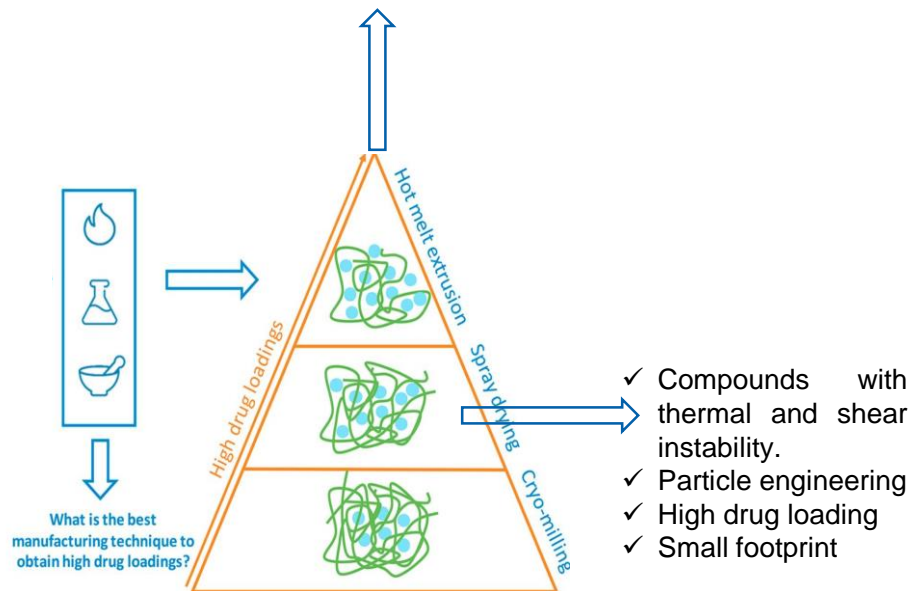
- ✓ Solubility of API in different polymers;
- ✓ Kinetic trapping;

- Selection of polymer

- Properties of drug substance

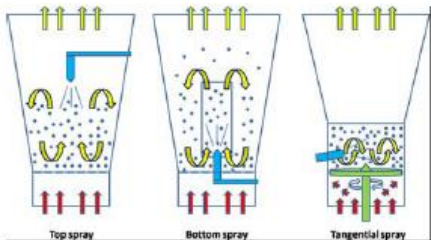
The order of the techniques for high drug loadings in ASD is as follows: hot melt extrusion > spray drying > cryo-milling.

- ✓ Solvent-free continuous process
- ✓ Small footprint

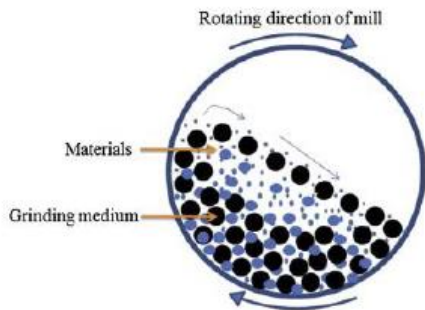


Solvent based technologies for ASD

Granules-layering



Fluid Bed Coater

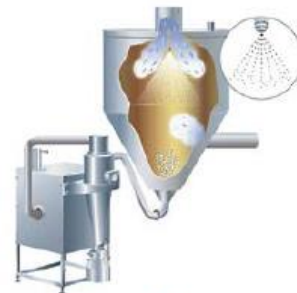


Mechanical Reduction (Ball Mill)

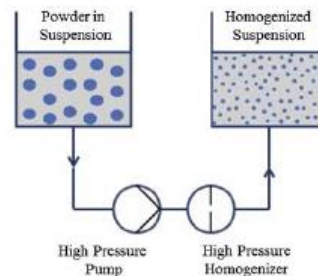
- Particle size depends from carrier;
- Milling needs to be implemented for tailoring particle properties

Disadvantages:

- Organic solvent
- Residual solvent
- Material density issues

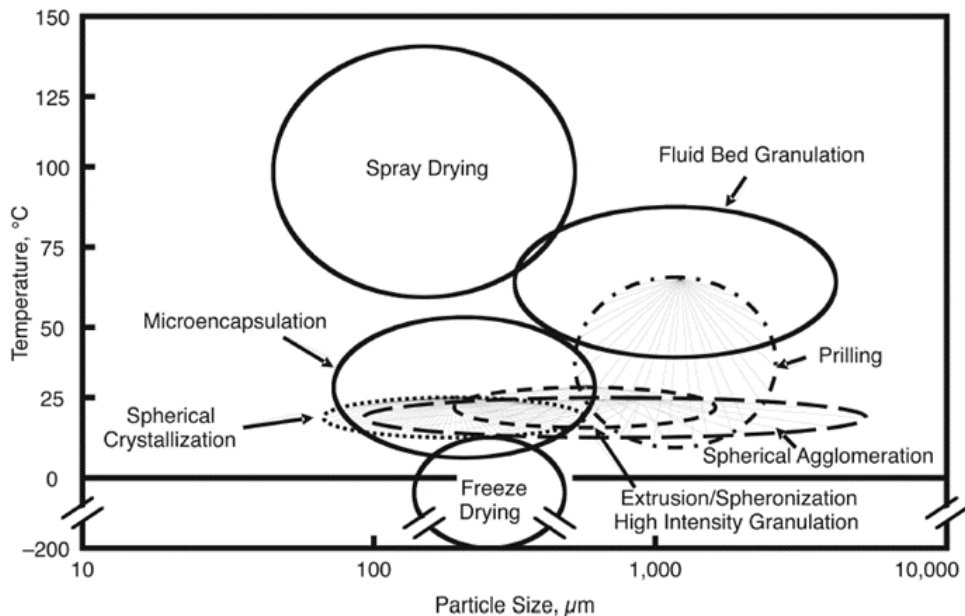


Spray Dryer



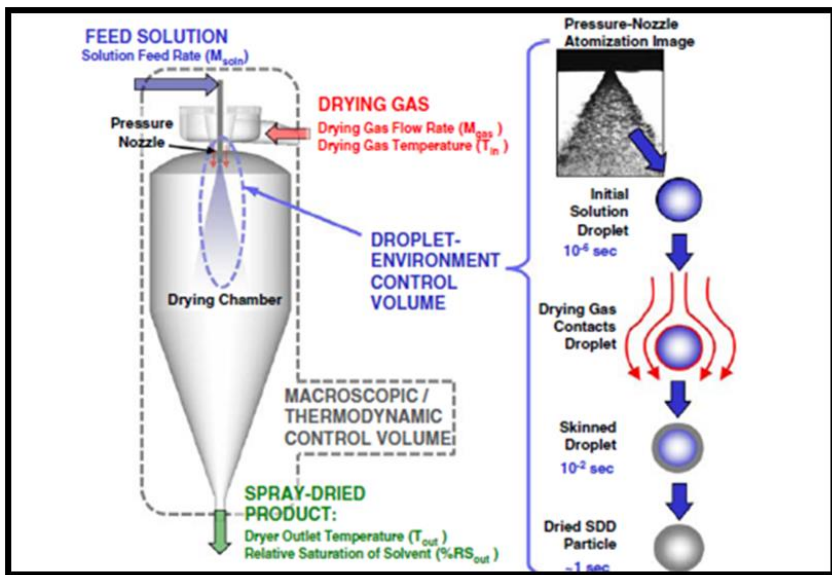
High Pressure Homogenization

Spray drying vs granule-layering



- ✓ Consistency in particle size, bulk and tapped density;
- ✓ It can be used for particle engineering of drug substances and excipients;
- ✓ Beside amorphisation, spray drying can be applied for mass-production of liposomes and encapsulation of flavors;

Spray drying technology



Critical process parameters

Type and size of nozzle

Nozzle pressure

Spray rate

Air flow

T inlet or T outlet

Relative saturation of solvent (%)

Thermodynamic design space (scale up rule)

Energy needed for evaporation of solvent = Energy lost during drying

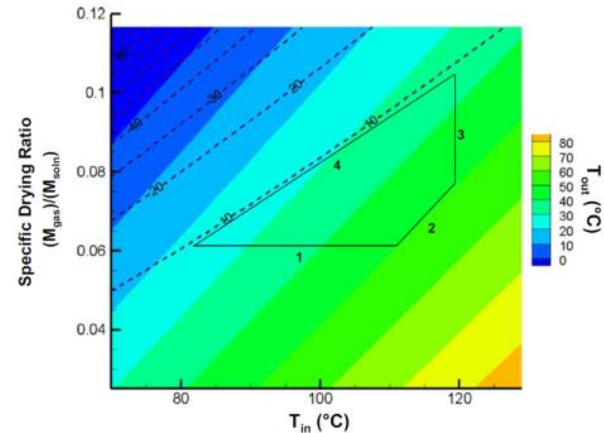


Solution spray rate

Air flow, difference between T_{inlet} and T_{outlet}



$$\text{Specific drying ratio} = \frac{\text{Solution spray rate}}{\text{Air flow}}$$



Influence of process to ASD properties

- Solvent evaporation processes: Roto-evaporation vs. spray drying

API + polymer= HPMC or PVP
or HP55

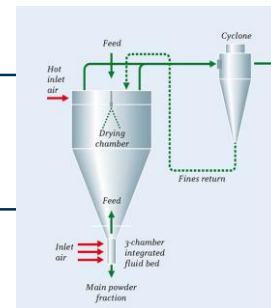
Acetone:ethanol=1:1

1. rotary evaporator at about 40 °C
2. Drying under vacuum in a tray dryer (40°C; 30 mbar; 12h)
3. Milling

API + polymer= HPMC or
PVP or HP55

Acetone:ethanol=1:1

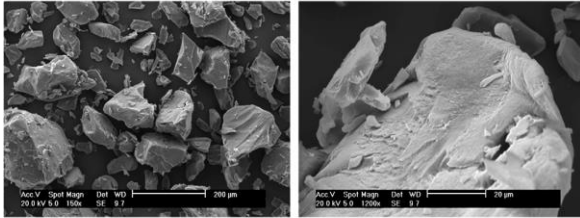
Fluidized spray drying



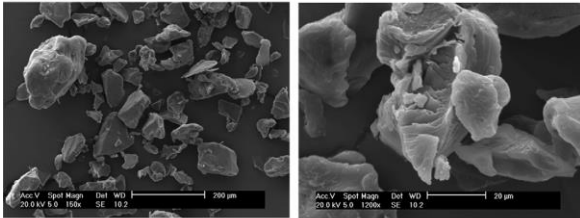
Powders were characterized by contact angle, X-ray photoelectron spectroscopy, SEM

Influence of process to ASD properties

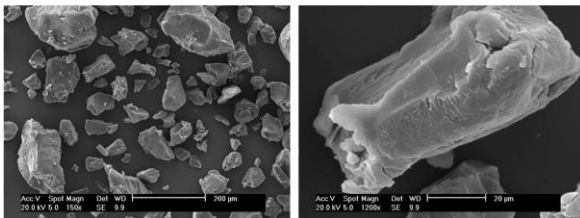
A. Formulation 3



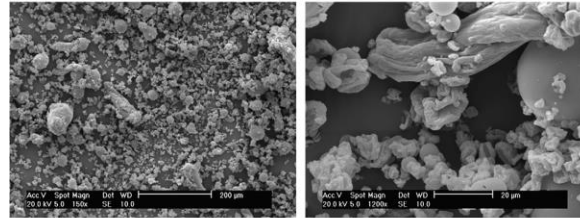
B. Formulation 5



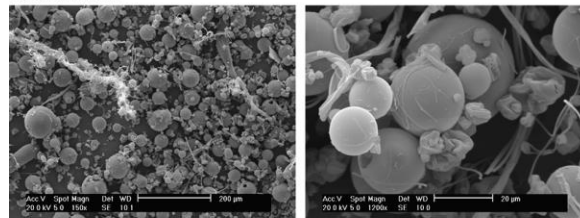
C. Formulation 12



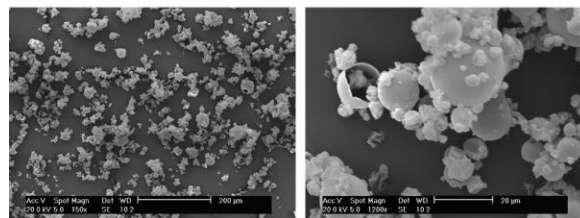
A. Formulation 1



B. Formulation 2



C. Formulation 4



Dense and compact structures with particles (some over 100 µm) having an irregular form and sharp edges.

Fine particles with smooth surfaces. Spherical particles are observed, some larger than 20 µm in size, together with a fine material.

Influence of process to ASD properties

X-ray photoelectron spectroscopy results – quantify the amount of drug on the powder surfaces

Table 2

Solid dispersions containing drug N and drug A prepared by roto-evaporation (RO), spray drying (SD) and fluidized spray drying (FSD)

Formulation	Drug	Drug conc. in bulk ^b	Carrier	Drying technology	Drug conc. at surface ^b	Surface excess of drug ^a	θ (deg)
1	N	20%	HPMC	SD	30%	1.5	39
2	N	20%	PVP	SD	47%	2.4	44
3	N	20%	HPMC	RO	16%	0.80	ND
4	A	20%	PVP	SD	25%	1.3	48
5	A	20%	HPMC	RO	9%	0.45	35
6	A	10%	HP 50	FSD	3%	0.30	ND ^c
7	A	50%	HP 50	FSD	52%	1.0	58
8	A	10%	HPMC	FSD	20%	2.0	80
9	A	50%	HPMC	FSD	54%	1.1	72
10	A	10%	HPMC swollen	FSD	9%	0.9	56
11	A	50%	HPMC swollen	FSD	65%	1.3	80
12	A	20%	HPMC/poloxamer (10%)	RO	13% drug % poloxamer	0.65	34

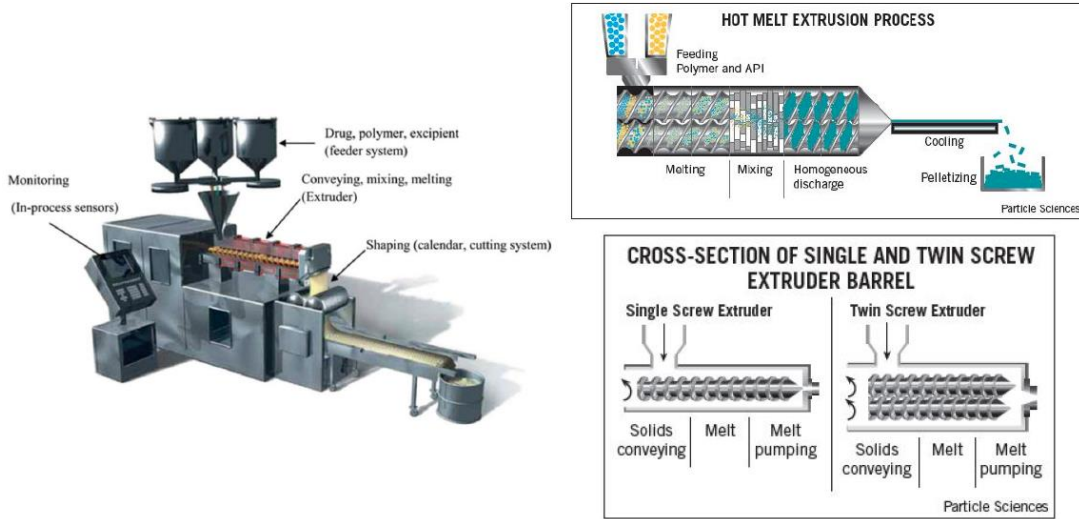
^a Calculated as surface coverage/bulk concentration.

^b Drug concentration in bulk (weight%), drug conc. at surface (atomic%).

^c Not determined due to too rapid drop adsorption.

- ✓ The spray drying methods led, in all cases, to an enrichment of the drug on the surface, although the level varies considerably with the choice of excipient.
- ✓ Roto-evaporation technique consistently produced fairly well encapsulated drug, regardless of excipient and drug used. This slow drying technique seems to promote drug encapsulation, compared to fast preparation methods (spray drying and fluidized spray drying)
- ✓ Solid dispersion powders prepared by the slow methods demonstrated improved bioavailability compared to products prepared by the fast methods.

Hot melt extrusion = mixing and melting

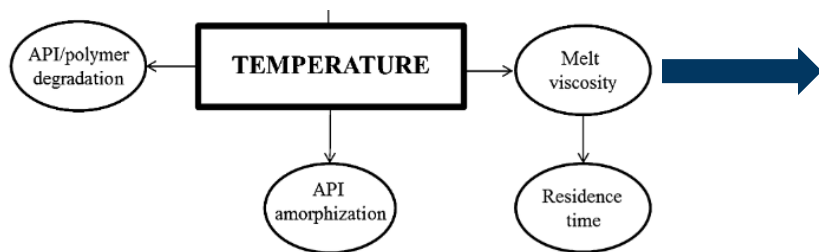


General critical process parameters for HME are:

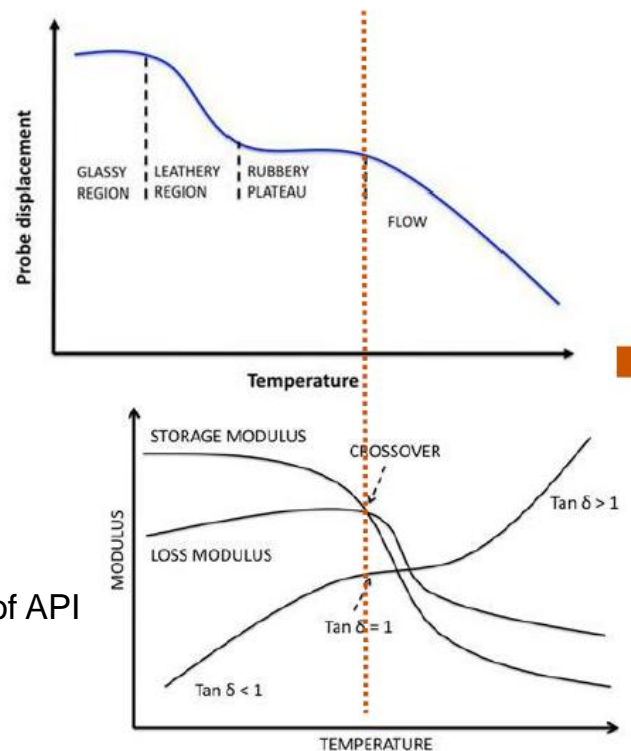
1. Screw speed = creates shear forces that will generate additional heat;
2. Screw configuration= 1 kneading zone at 2 third of the barrel length is sufficient for mixing at molecular level = important for higher drug loadings in ASD;
3. Feeding rate;
4. Barrel temperature = controls melting and softening process.

Hot melt extrusion = mixing and melting

Barrel temperature

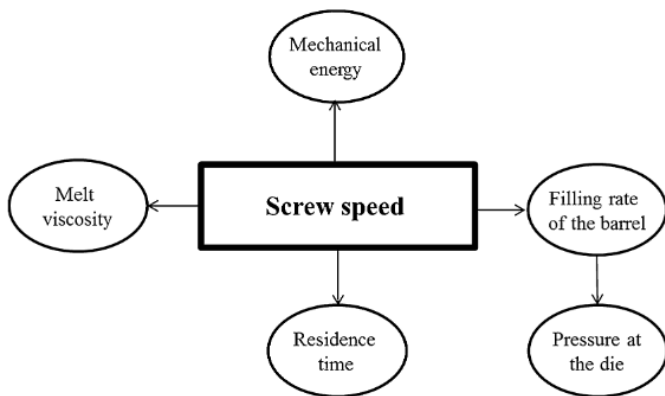


- ✓ Based on polymer/API mix (no traces of crystalline phase)
- ✓ Limits of barrel T is based on melt viscosity and degradation tendency of API
- ✓ ↑ of barrel T = ↑ drug dissolution (e.g. Itraconazole)
- ✓ ↑ of barrel T + tween screw extruder = ↑ drug dissolution



Hot melt extrusion = mixing and melting

- ✓ In scaling up = screw speed is related to increase of feeding rate (20-50% of filling for tweek screw extruder)
- ✓ When amorphization is targeted, the screw speed would need to be high in order to obtain a high shear mixing with reduced residence time.
- ✓ For scale up= specific mechanical energy and feed rate should be maintaining constant when moving from one extruder to another.



$$\text{Filling \%} = \frac{\text{FR} \times \text{RTD}}{\rho \times V_{\text{free}}} \times 100$$

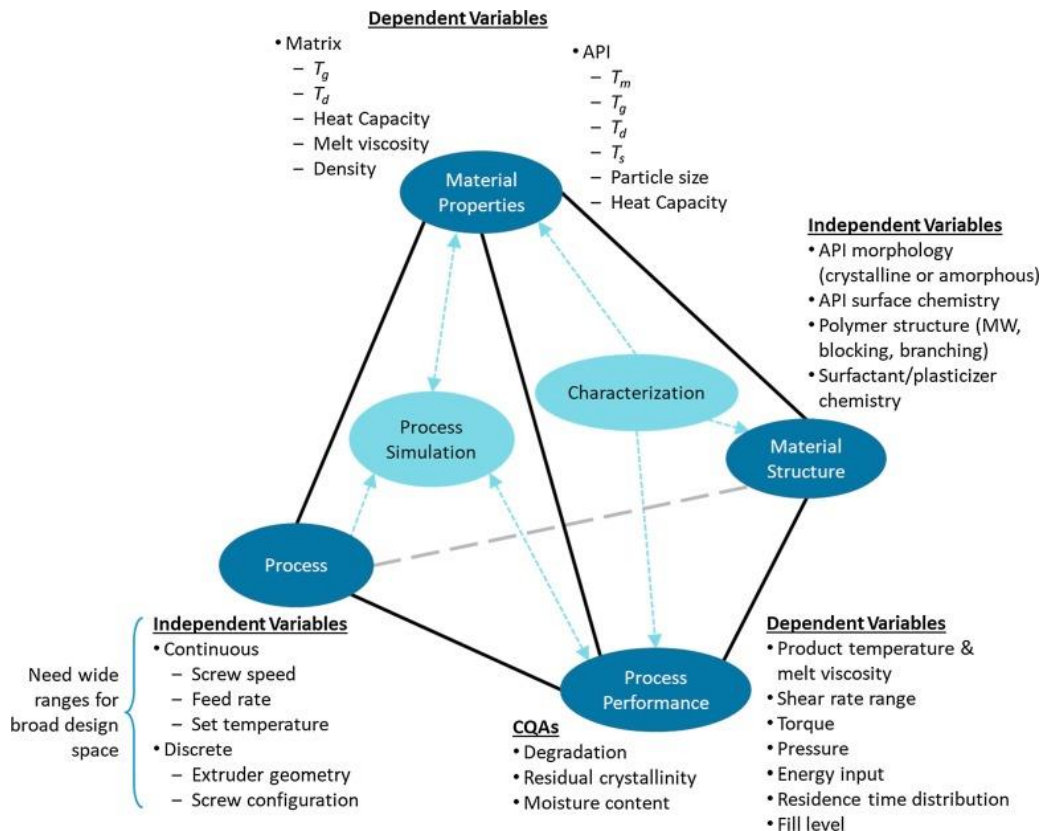
FR – feed rate (g/min)

RTD – mean residence time (min)

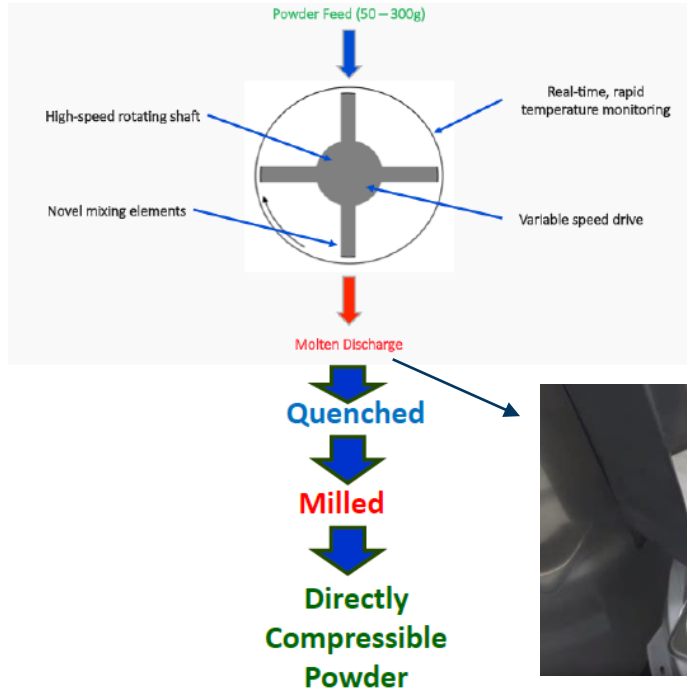
ρ - bulk viscosity of polymer/mix (g/min)

V_{free} - extruder free volume (mL)

Hot melt extrusion = complex process



Kinetisol[®] technology



Advantages:

- Best technology for high melting point/low organic solubility drugs;
- Short residence times (< 20 sec);
- Not limited by melt viscosity;
- Suitable for the most of the conventional polymers for ASD (HPMCAS, HPMC; PVP etc)

Kinetisol® technology – importance of post-processing

Vemurafenib (BSC IV)

- aqueous solubility of crystalline vemurafenib is $< 0.1 \mu\text{g/mL}$
- equilibrium solubility In FASSIF remains lower $< 2 \mu\text{g/mL}$
- log P value of 3.0, low permeability in Caco-2 cell model
- Mw 490 Da < 500 Da (Lipinski rule)
- $T_m=272 \text{ }^\circ\text{C} \rightarrow$ **HME is dismissed**
- High dose in formulation

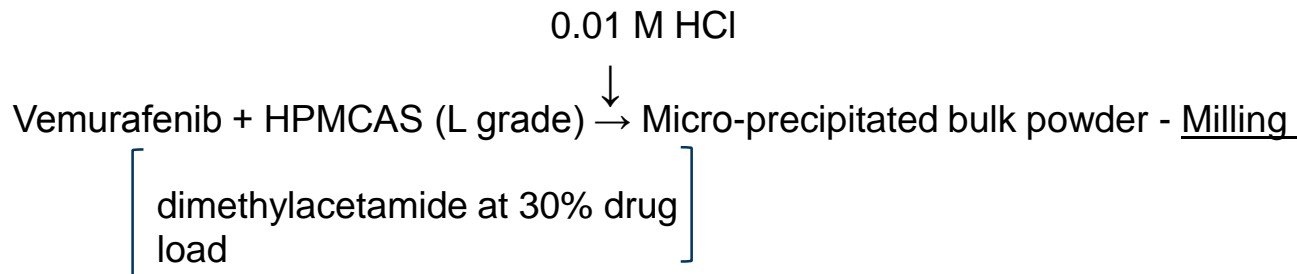
Spray drying is not the technology of choice



Organic solvent	Solvent class	Solubility (mg/mL)	Maximum drug % (w/w) in feed
Dimethylacetamide	2	> 500	53.4
Methanol	2	4.57	0.6
Acetonitrile	2	1.40	0.2
Dichloromethane	2	1.95	0.1
Isopropanol	1	3.56	0.5
Acetone	1	< 6	0.8

Kinetisol® technology – importance of post-processing

1. Zelboraf® - solvent controlled coprecipitation process



2. Alternative process - Kinetisol® - quench cooling

Vemurafenib + HPMCAS (L grade)= 1:2.5

Quenching at 180 °C, cooling and pressing into blocks - Milling

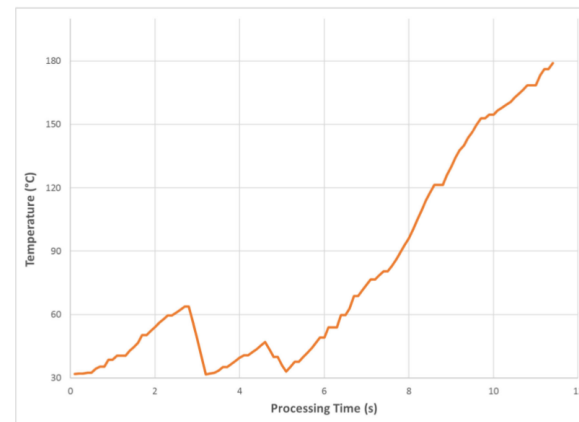
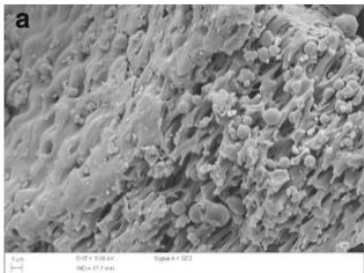


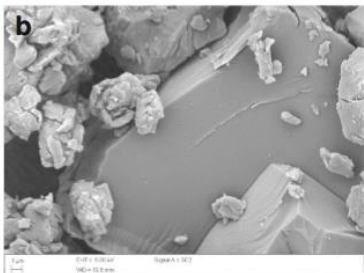
Fig. 3. KinetiSol profile for processing an amorphous solid dispersion of vemurafenib at 2400 rpm

Kinetisol[®] technology – importance of post-processing

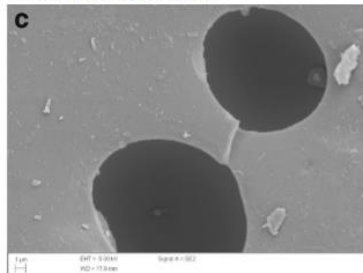
MBP material



KSD cryomilled material



KSD material, < 250 μm. Dark circles are large cavities as observed in the cross section of Figure 7.d



Unmilled cross section of quenched KSD material (upper right region, lower left region is carbon tape)

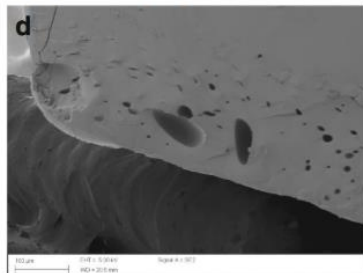


Fig. 7. Scanning electron microscopy images of MBP and KSD materials. **a** MBP material. **b** KSD cryomilled material. **c** KSD material, < 250 μm. Dark circles are large cavities as observed in the cross section of **(d)**. **d** Unmilled cross section of quenched KSD material (upper right region, lower left region is carbon tape)

Table IV. Particle Size Distribution and Specific Surface Area for MBP and KSD Amorphous Solid Dispersions of Vemurafenib

Sample	D10 (μm)	D50 (μm)	D90 (μm)	Specific surface area (m ² /g)
MBP	2.39 ± 0.13	74.14 ± 1.68	220.90 ± 5.65	6.13 ± 0.05
KSD < 250 μm	14.02 ± 0.84	132.74 ± 3.43	300.79 ± 2.62	0.20 ± 0.02
KSD Cryo	2.14 ± 0.23	12.94 ± 1.42	78.96 ± 3.43	1.21 ± 0.06

Kinetisol® technology – importance of post-processing

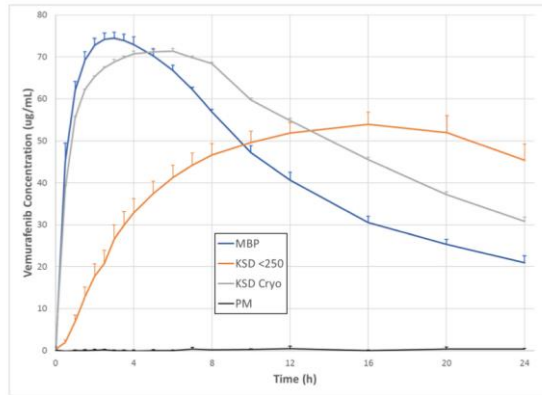
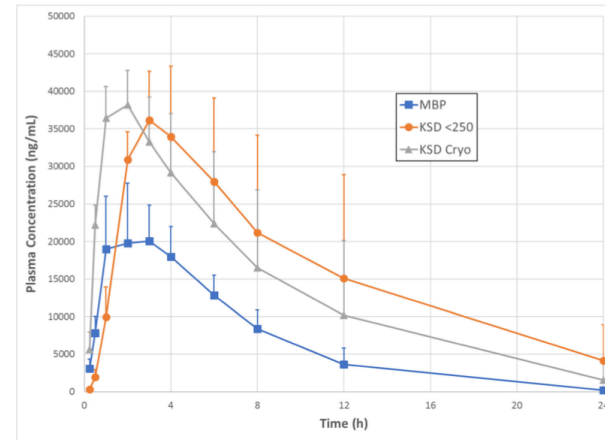
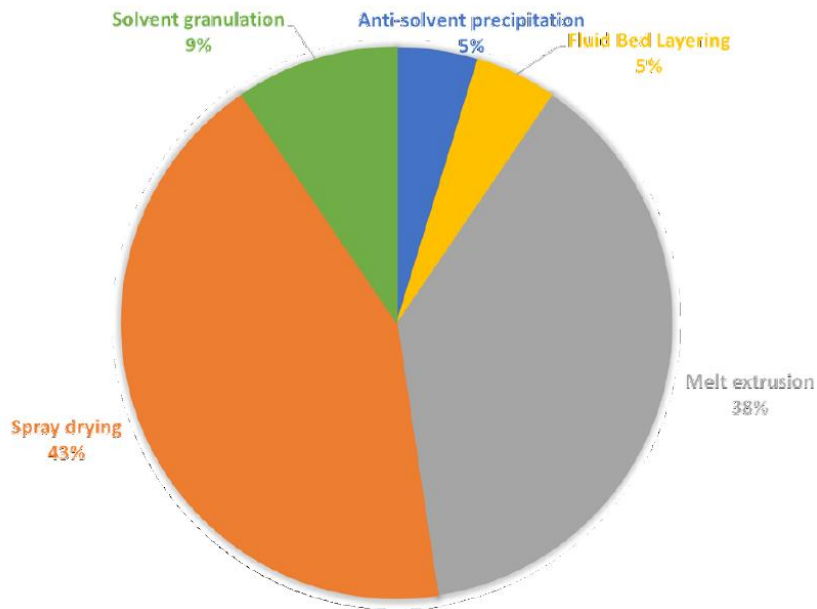


Fig. 8. In-vitro dissolution of MBP and KSD amorphous solid dispersions and physical mixture of vemurafenib in pH 6.5 FaSSIF media



- For fusion-processed materials like Kinetisol® solid dispersions, milling is a significant contributor to surface area and release rate, whereas for porous materials like MBP and spray-dried dispersions, the pores are the primary driver of release rate with reduced impact from milling.
- Substantial portion of the surface area of the MBP material is contained within the inner network of the material. During dissolution, polymer dissolved and saturated the inner channels of a porous material which created viscous media in these channels for which drug dissolution was significantly slowed.

Conclusions



- ✓ Growing interests of innovator industry for improvement of poor aqueous solubility of drug substances via amorphous solid dispersions;
- ✓ Products made by spray drying and melt extrusion
 - Currently, the most commercially viable options
 - Suitable alternatives are limited
- ✓ Deep understanding of material properties of ASD influenced by process needed!



Thank you



We create chemistry

Hot Melt Extrusion

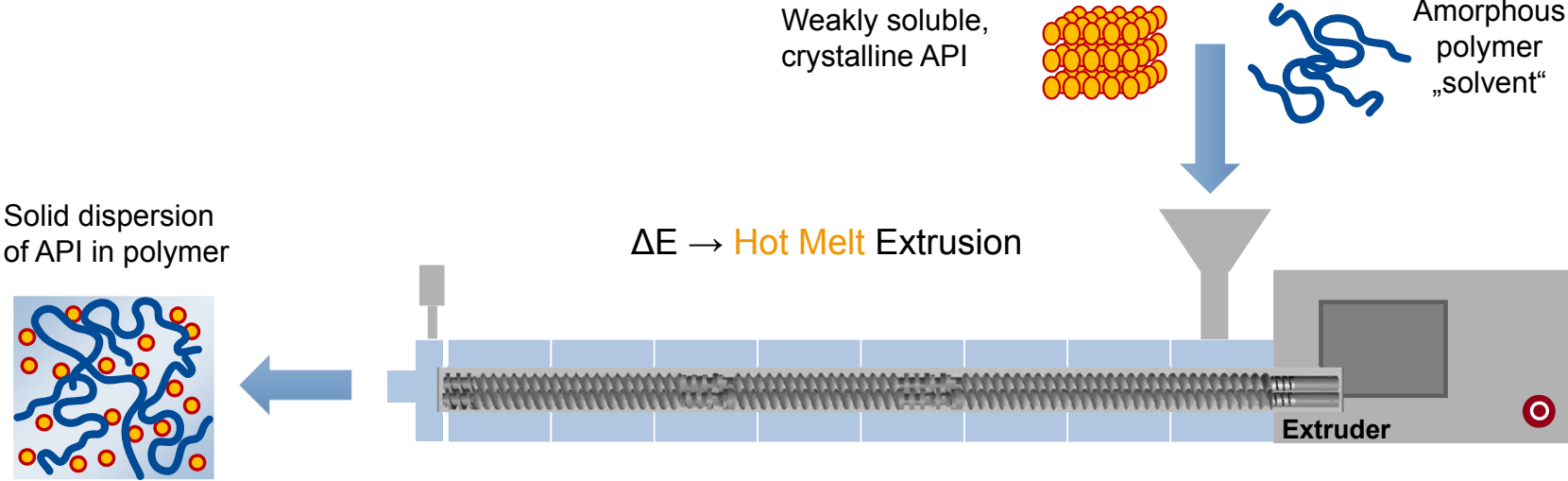
An introduction to the technology and to downstream processing

Nils Rottmann | Pharmaceutical Technological Symposium Ljubljana | 13. June 2019



Hot melt extrusion

Introduction

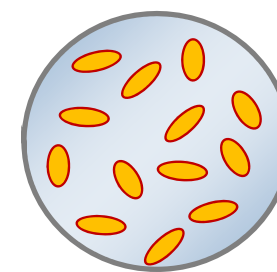
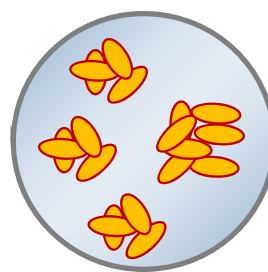
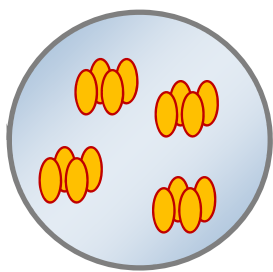


A weakly soluble crystalline API and an amorphous polymer are transferred into a solid dispersion by introducing thermal and mechanical energy

Source: N. Rottmann, European Application Lab (Pharma Solutions Europe, CIS Countries, Middle East, and Africa), BASF SE, Ludwigshafen, Germany

Amorphous matrices:

Glass suspensions vs. glass solutions



	Glass suspension		Glass solution
API	crystalline	amorphous	molecularly dispersed
Matrix (polymer)	amorphous	amorphous	amorphous
System stability	almost stable	only kinetically stabilized (oversaturation)	Ok (below saturation solubility)

Amorphous matrices:

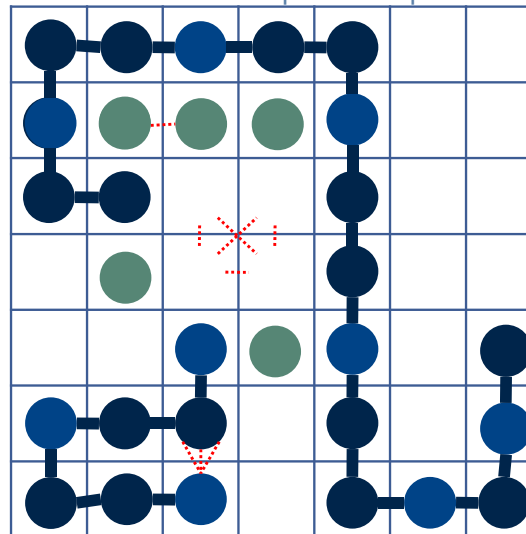
Glass suspensions vs. glass solutions

Amorphous suspension

can be molecularly dispersed but
 Interaction forces between A + B are weaker than self-association between A-A or B-B so that
 Nuclei formation and Nuclei growth are Kinetically controlled and system tend to recrystallise

VS.

Animation for amorphous suspension



Solid glass solution

Molecularly dispersed but steric adjacency is allowed if Interaction forces between A + B are stronger than self-association between A-A or B-B
 Directed H-Bonding are stronger than the weaker non-directed dispersive and polar attractions

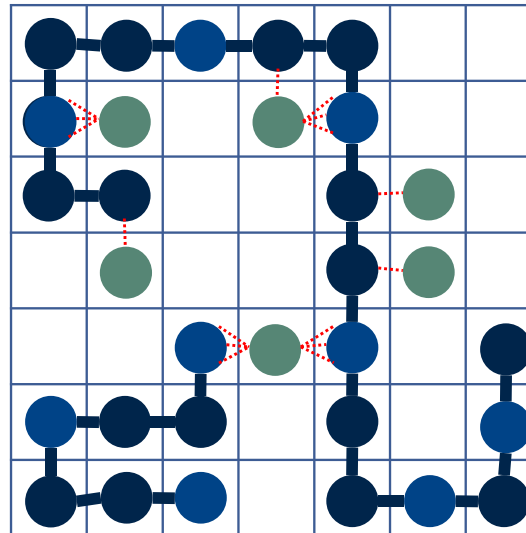
Amorphous matrices: Glass suspensions vs. glass solutions

Amorphous suspension

can be molecularly dispersed but
Interaction forces between A + B are weaker than self-association between A-A or B-B so that
Nuclei formation and Nuclei growth are Kinetically controlled and system tend to recrystallise

VS.

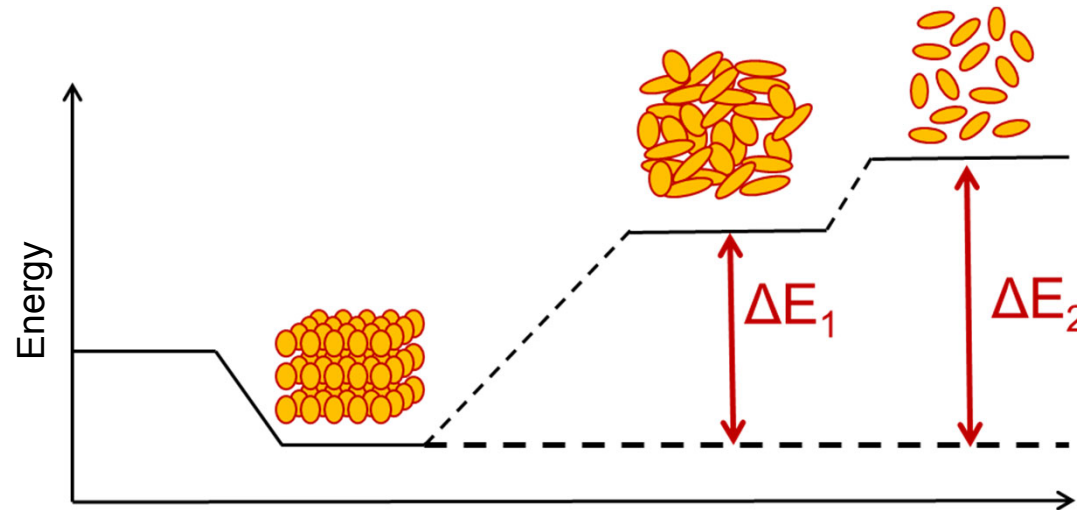
Animation for glassy solution



Solid glass solution

Molecularly dispersed but steric adjacency is allowed if Interaction forces between A + B are stronger than self-association between A-A or B-B
Directed H-Bonding are stronger than the weaker non-directed dispersive and polar attractions

Amorphous matrices: Thermodynamics & crystallinity



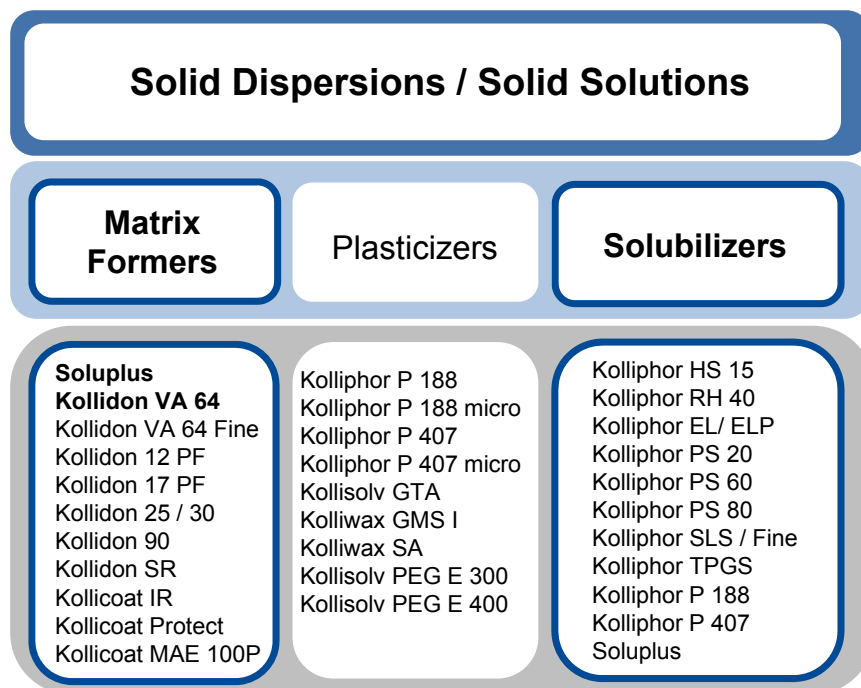
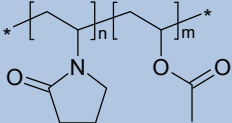
- ⇒ Crystalline structures are thermodynamically favored
- ⇒ Leaving the crystalline state requires energy (lattice energy)

Source:

A. Gryczke, Global Technical Marketing Pharma Solutions, BASF SE, Ludwigshafen, Germany

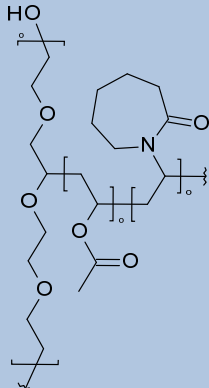
Polymers in hot melt extrusion

Polymers for hot melt extrusion: Overview

Kollidon® VA 64

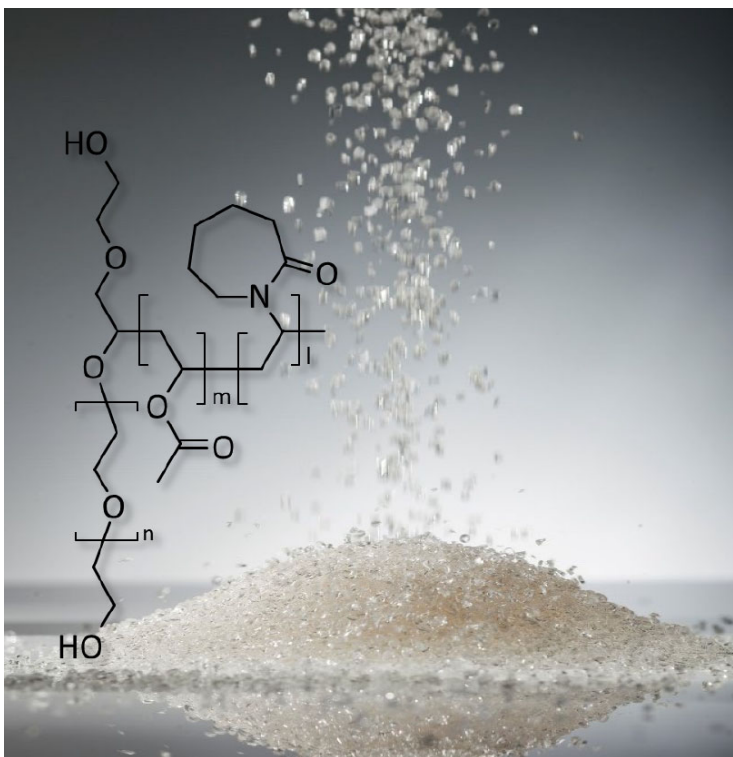
- Established matrix former especially in hot melt extrusion



Soluplus®

- Innovative matrix and solubilizer in one
- taylored for HME use
- increases solubility and bioavailability

Polymers for hot melt extrusion: Soluplus®



- “The Solid Solution“: solubilizer and matrix for solid dispersions
- PEG 6000/ vinylcaprolactam/ vinyl acetate grafted copolymer
- Tg: ~ 70 °C
- soluble in water, acetone, ethanol, dimethylformamide, ...

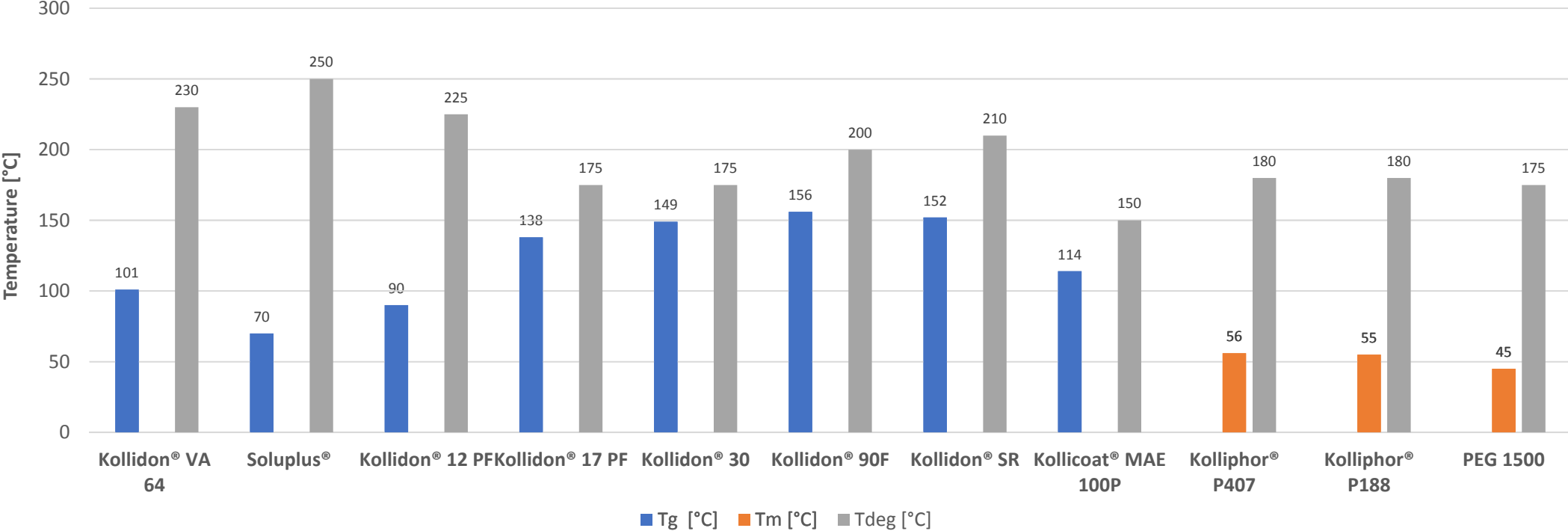
BREAKING NEWS: **Soluplus® approved in Europe!**

Approval in: UK Germany France Italy Poland Romania Slovakia Russia

- Drug products:
 - Febuxostat 80mg and 120mg film coated tablet by Zentiva
 - “Lopirita” (Lopinavir and Ritonavir) by Izvarino Pharma / Nanopharma

Polymers for hot melt extrusion:

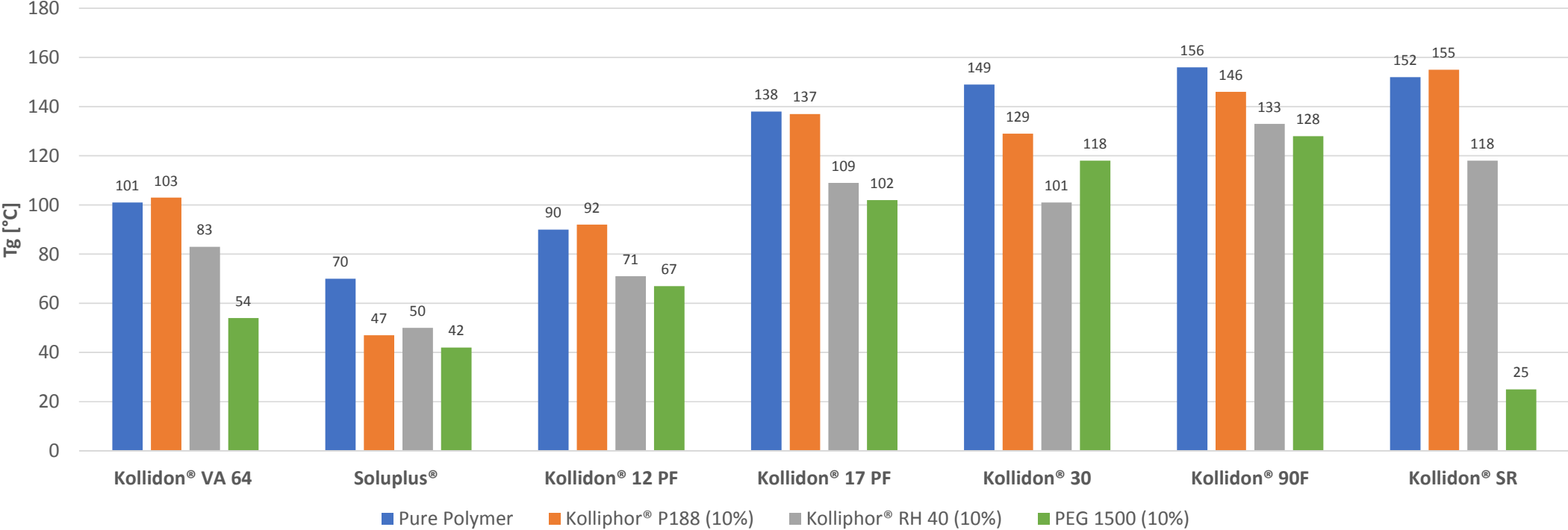
Glastransition (T_g), melting (T_m) & degradation temperatures (T_{deg})



Source: K. Kolter, A. Gryczke, M. Karl, Hot Melt Extrusion with BASF Pharma Polymers, 2nd Edition, BASF SE, Ludwigshafen, Germany

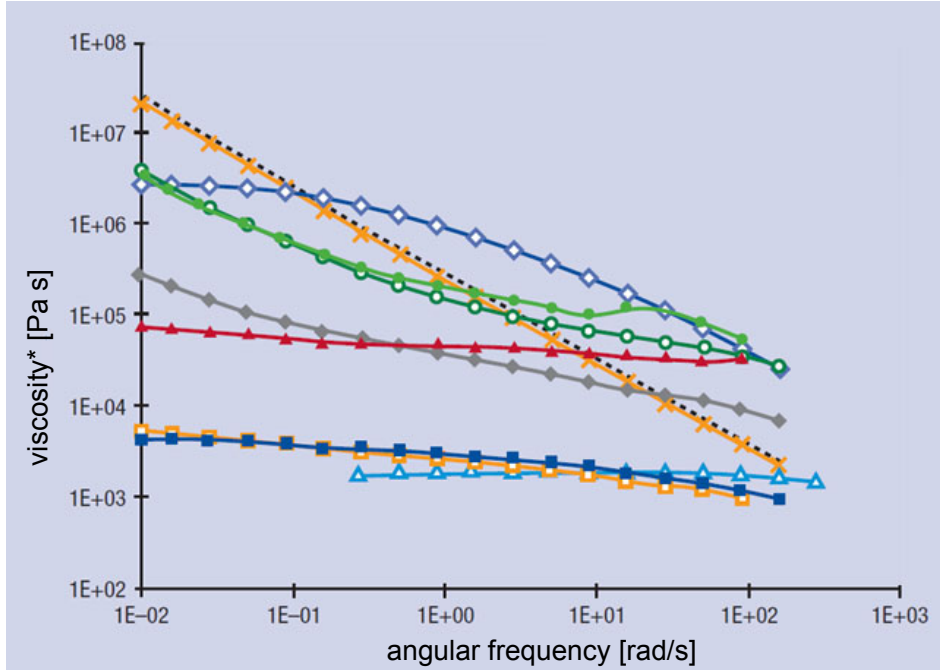
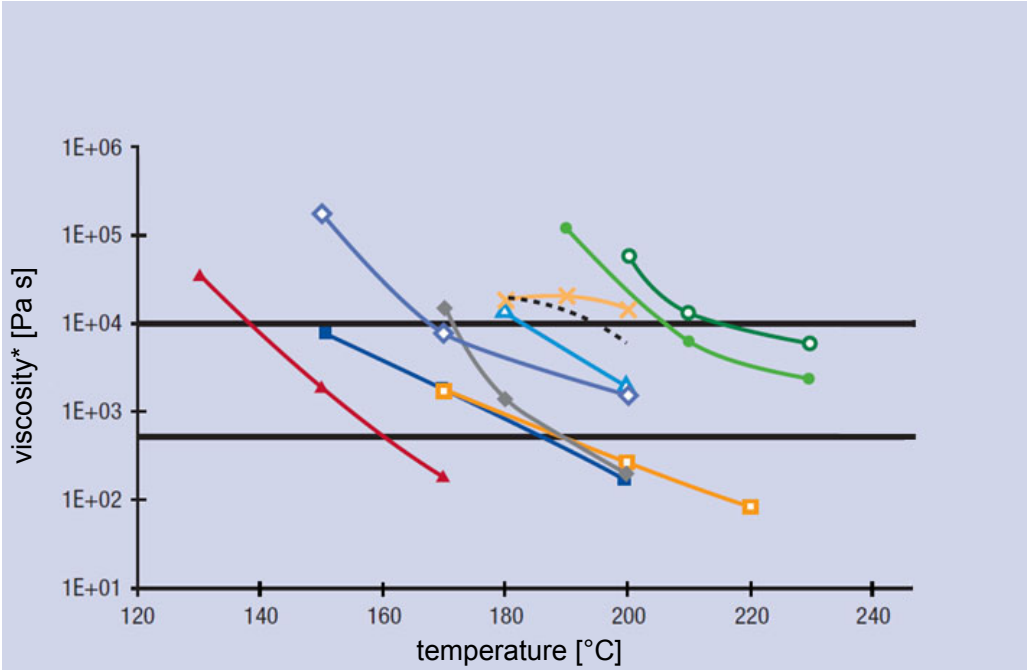


Polymers for hot melt extrusion: Effect of plasticizer on the T_g



Source: K. Kolter, A. Gryczke, M. Karl, Hot Melt Extrusion with BASF Pharma Polymers, 2nd Edition, BASF SE, Ludwigshafen, Germany

Polymers for hot melt extrusion: Melt rheology

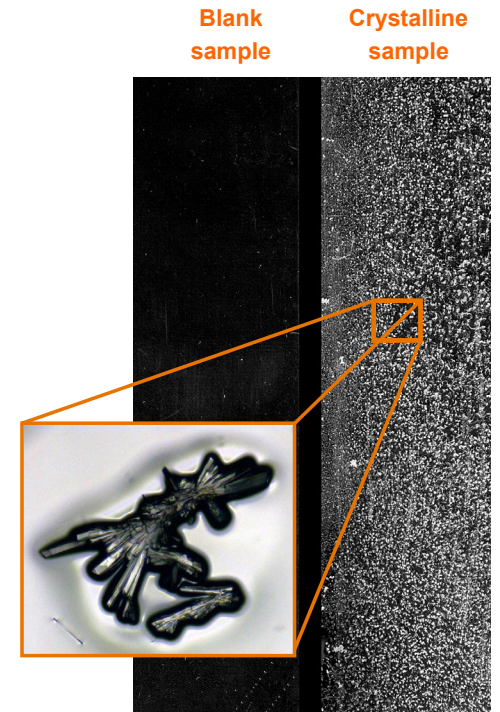
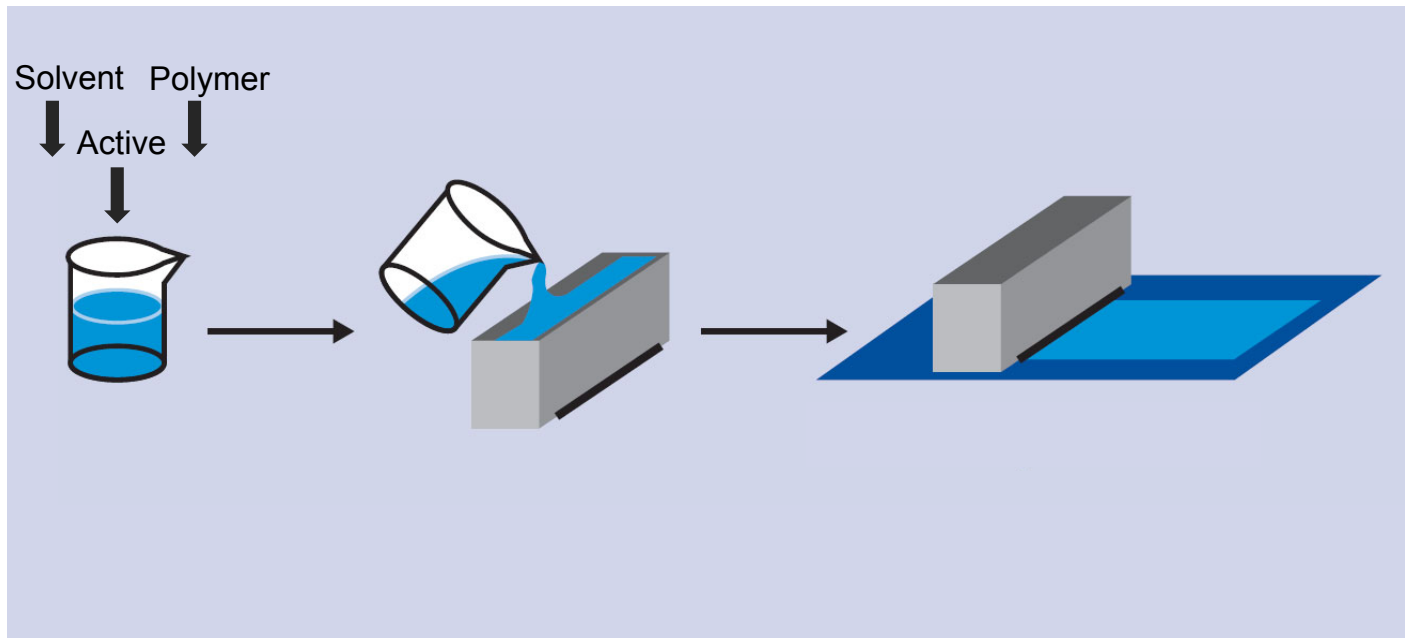


- Kollidon VA 64 (170 °C)
- ▲ Kollidon 12 PF (130 °C)
- Kollidon 30 (190 °C)
- ◆ Kollocoat SR (170 °C)
- ✕ Kollocoat IR (180 °C)
- Soluplus (170 °C)
- ▲ Kollidon 17 PF (180 °C)
- Kollidon 90 F (200 °C)
- ◆ Kollocoat MAE 100P (150 °C)
- - - Kollocoat Protect (180 °C)

Source: K. Kolter, A. Gryczke, M. Karl, Hot Melt Extrusion with BASF Pharma Polymers, 2nd Edition, BASF SE, Ludwigshafen, Germany

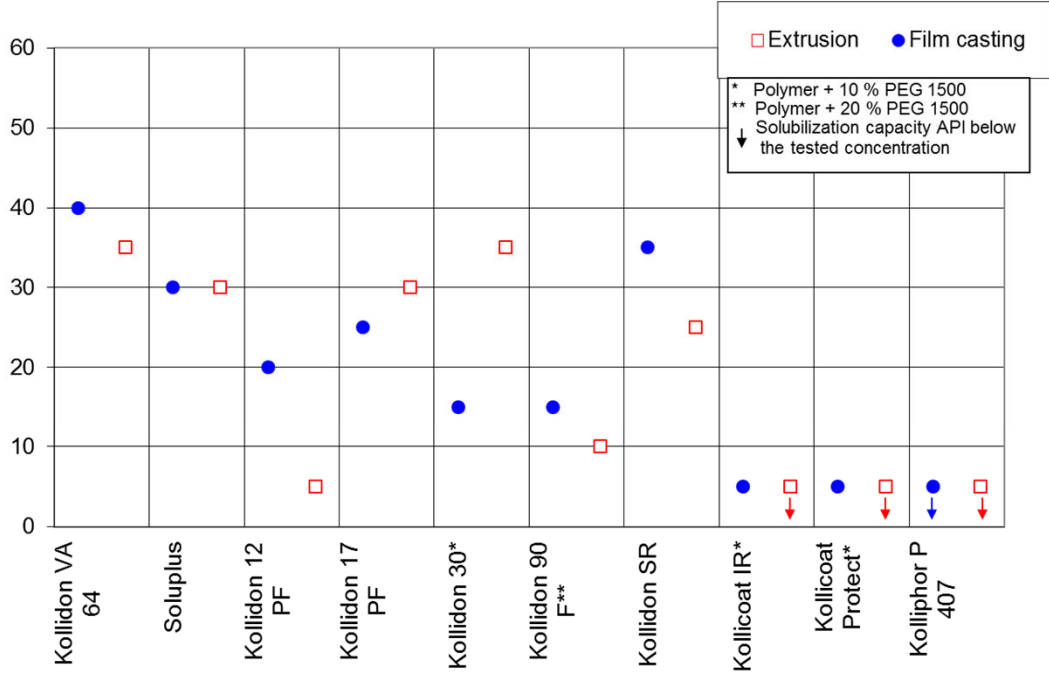


Screening of polymers for hot melt extrusion: Active/polymer combination – film casting

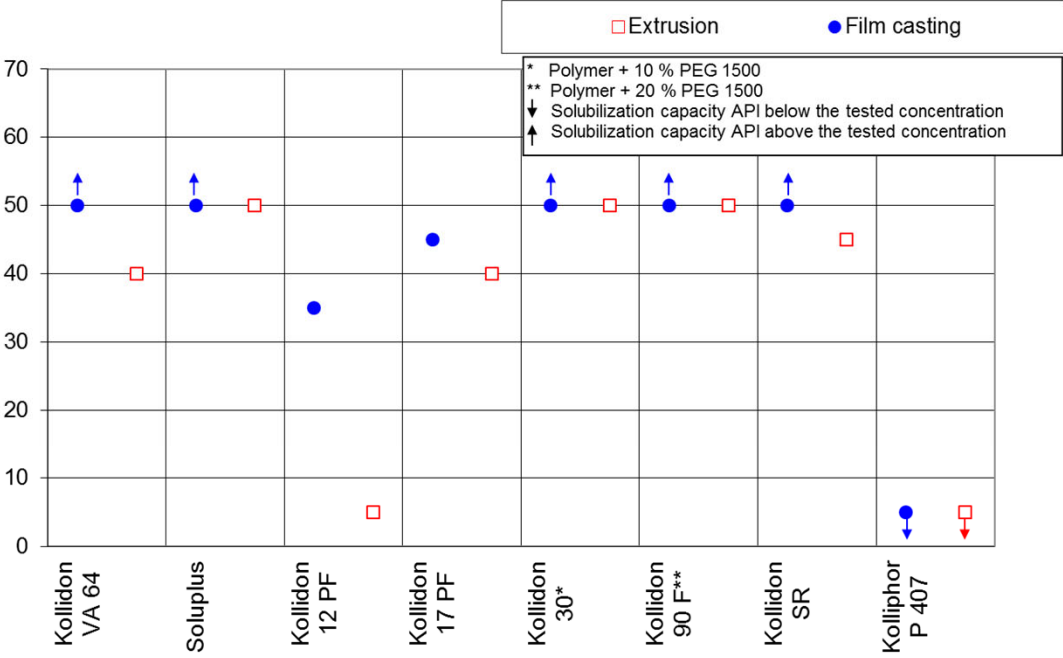


Screening of polymers for hot melt extrusion: Film casting vs. hot melt extrusion

Carbamazepine:



Itraconazole:



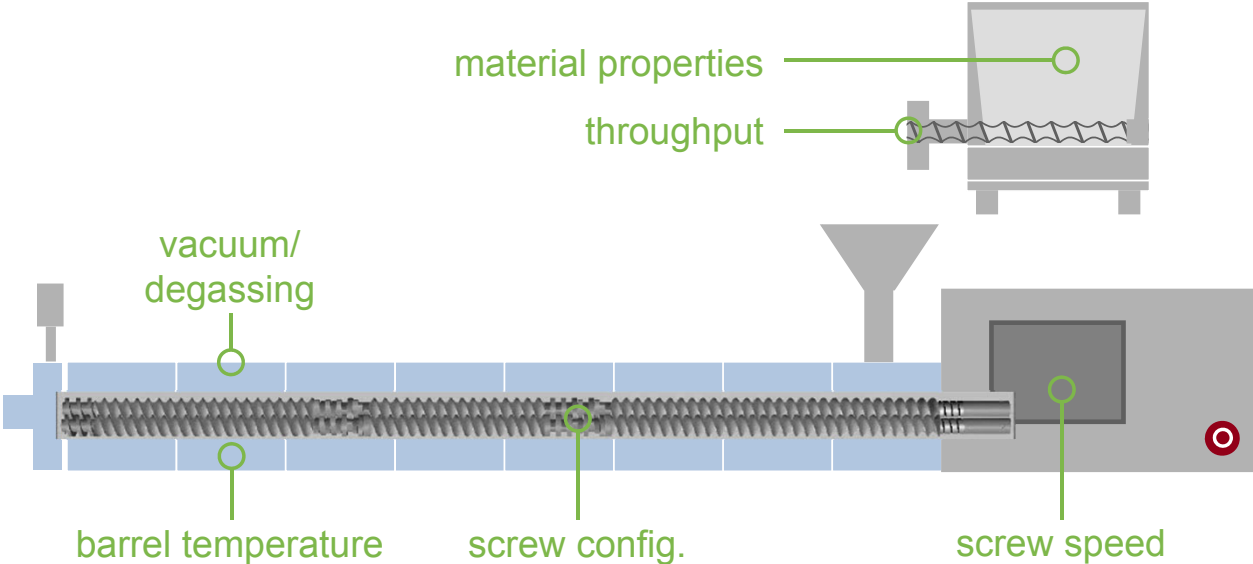
Source: M. Karl, Development Pharma Solutions, BASF SE, Ludwigshafen, Germany

Hot melt extrusion process

Process

Main process parameter

- melt temperature ○
- torque ○
- residence time distribution ○
- extrusion pressure ○



Process

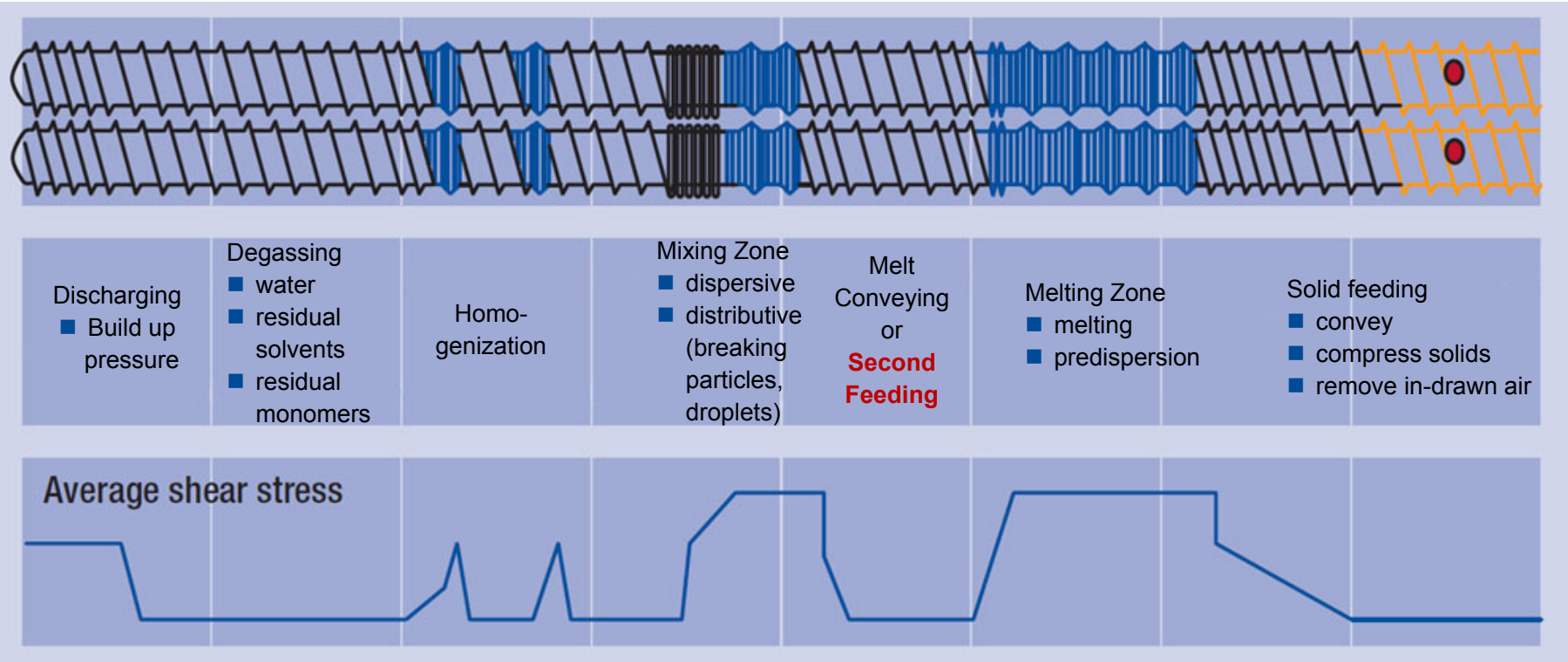
Screw elements



Source: N. Rottmann, European Application Lab (Pharma Solutions Europe, CIS Countries, Middle East, and Africa), BASF SE, Ludwigshafen, Germany

Process

Typical screw design



Source: K. Kolter, A. Gryczke, M. Karl, Hot Melt Extrusion with BASF Pharma Polymers, 2nd Edition, BASF SE, Ludwigshafen, Germany

Process

Screw design

- What is the minimum residence time to achieve proper dispersion?
- What is the maximum residence time to avoid degradation?
- Consider that residence time is meaning residence time distribution having a tail
- Which process operations need to be undertaken in the extruder? (Melting, dispersing, degassing, etc.)

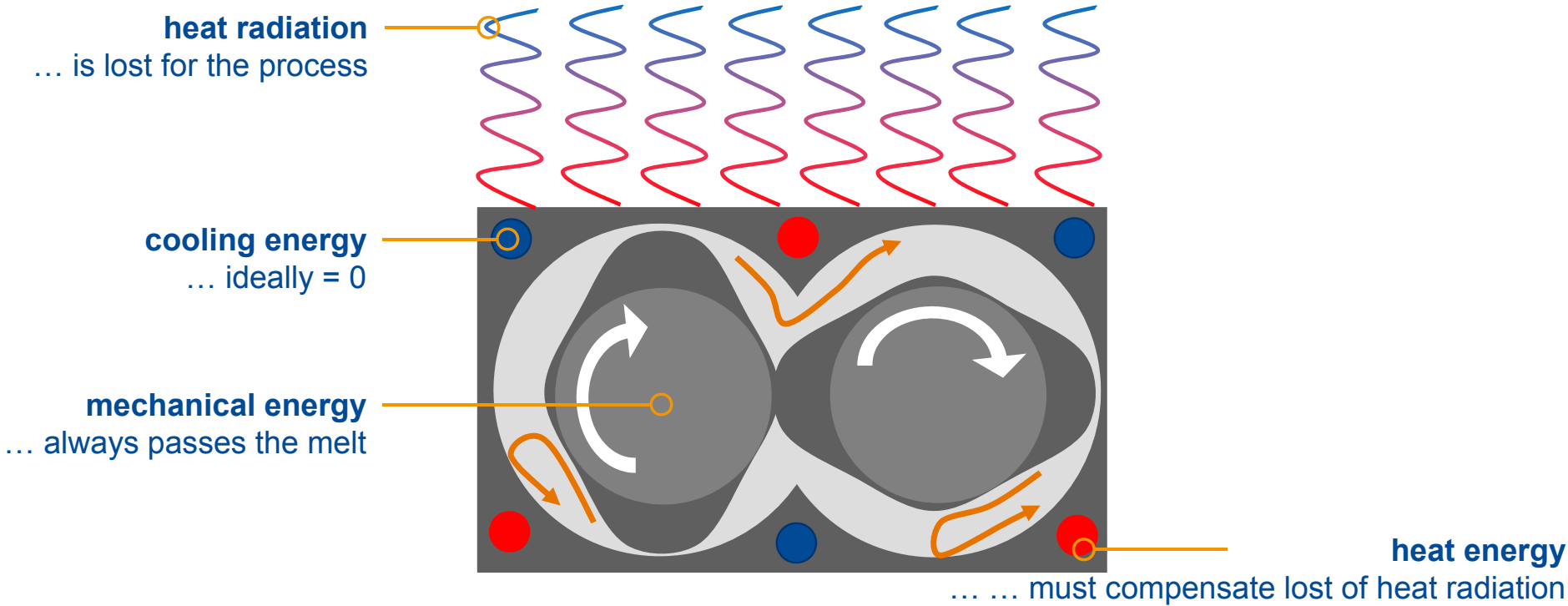
Process Temperature



- What is the maximum tolerated temperature?
- What is the minimum required temperature to disperse the drug?
- What is maximum allowed feed zone temperature?

Process

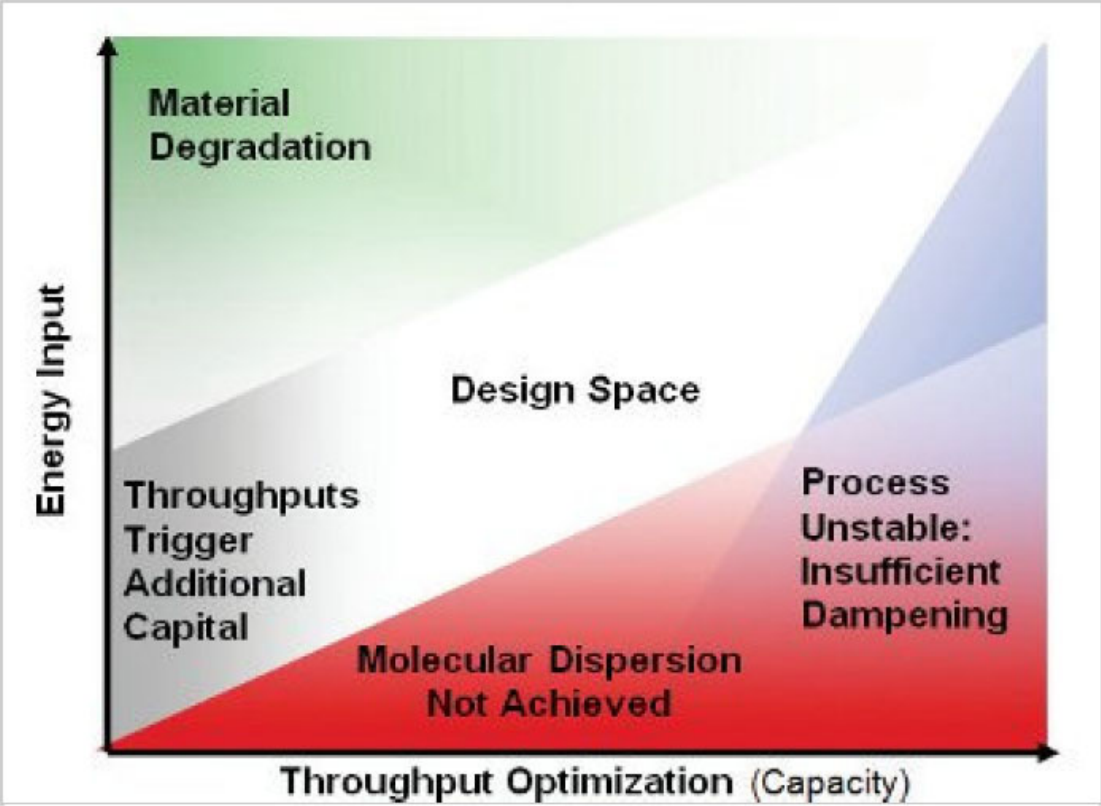
Energies in hot melt extrusion processes



Source: A. Gryczke, Global Technical Marketing Pharma Solutions, BASF SE, Ludwigshafen, Germany

Process

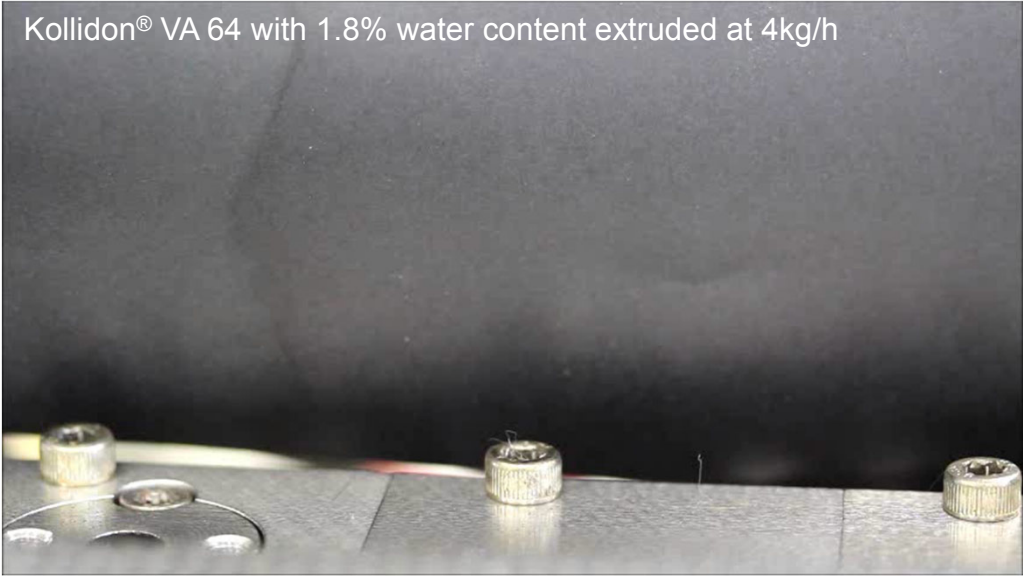
Design space for hot melt extrusion processes



Source: : Mike Lowinger, MSD, Westpoint, PA, USA

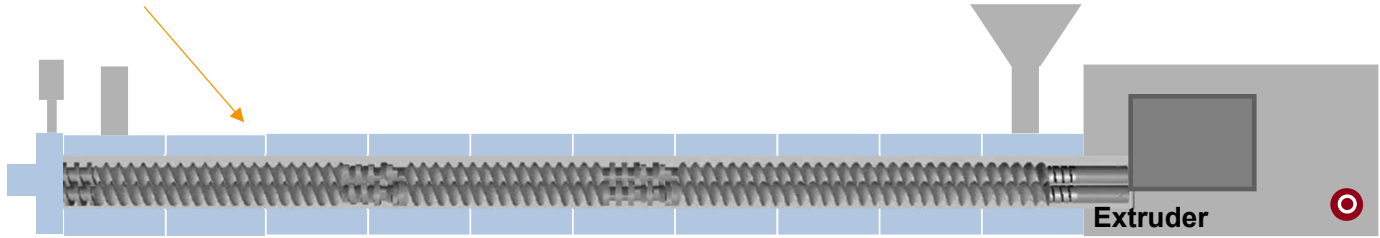
Process

Degassing – a low water content is important!



2% water = 80g/h steam@4kg/h
2% water = 800g/h steam@40kg/h

4.5% water = 180g/h steam@4kg/h
4.5% water = 1800g/h steam@40kg/h



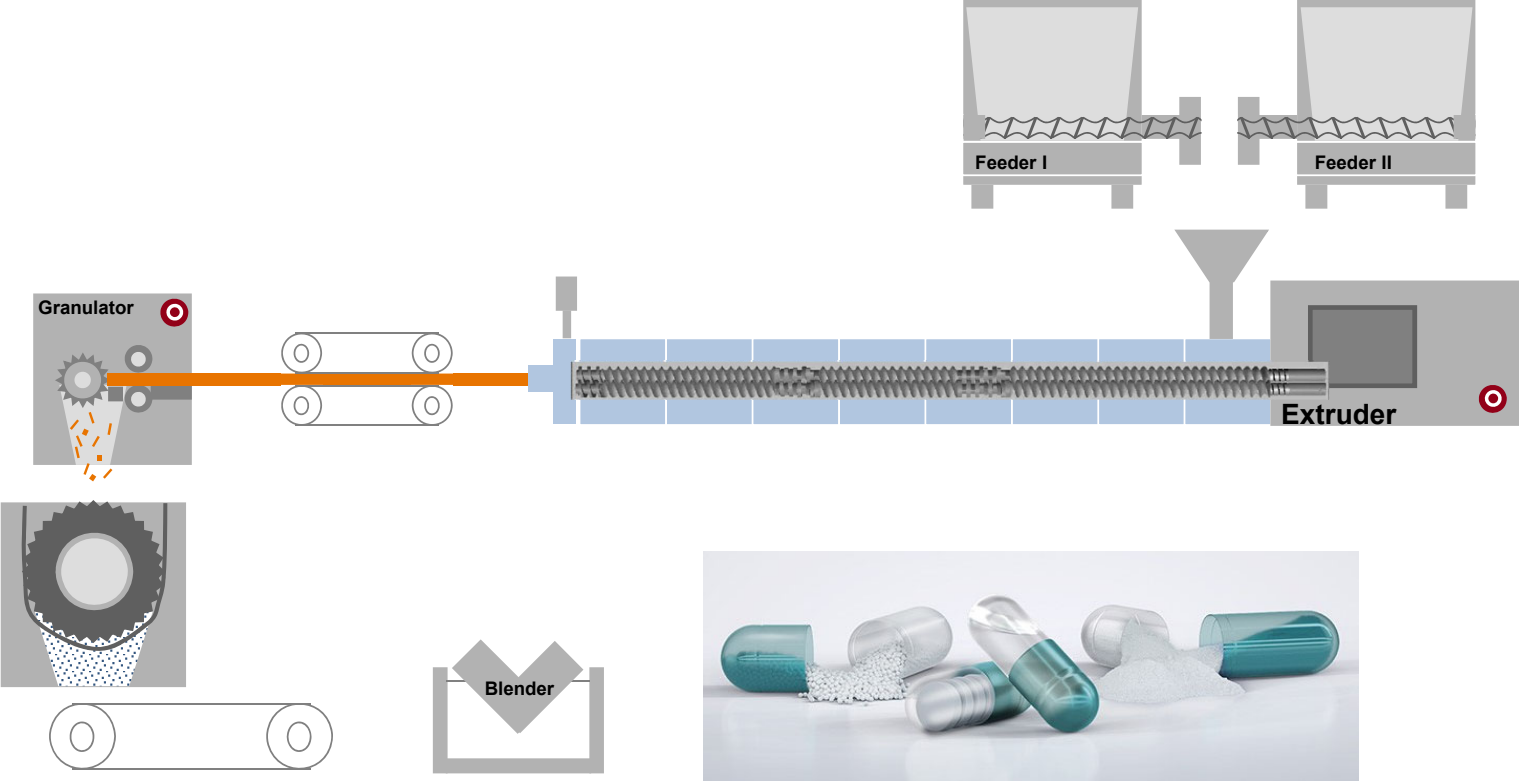
Source:

A. Gryczke, Global Technical Marketing Pharma Solutions, BASF SE, Ludwigshafen, Germany

Downstream processing

Downstream processing

Capsule filling



Source: N. Rottmann, European Application Lab (Pharma Solutions Europe, CIS Countries, Middle East, and Africa), BASF SE, Ludwigshafen, Germany

Downstream processing

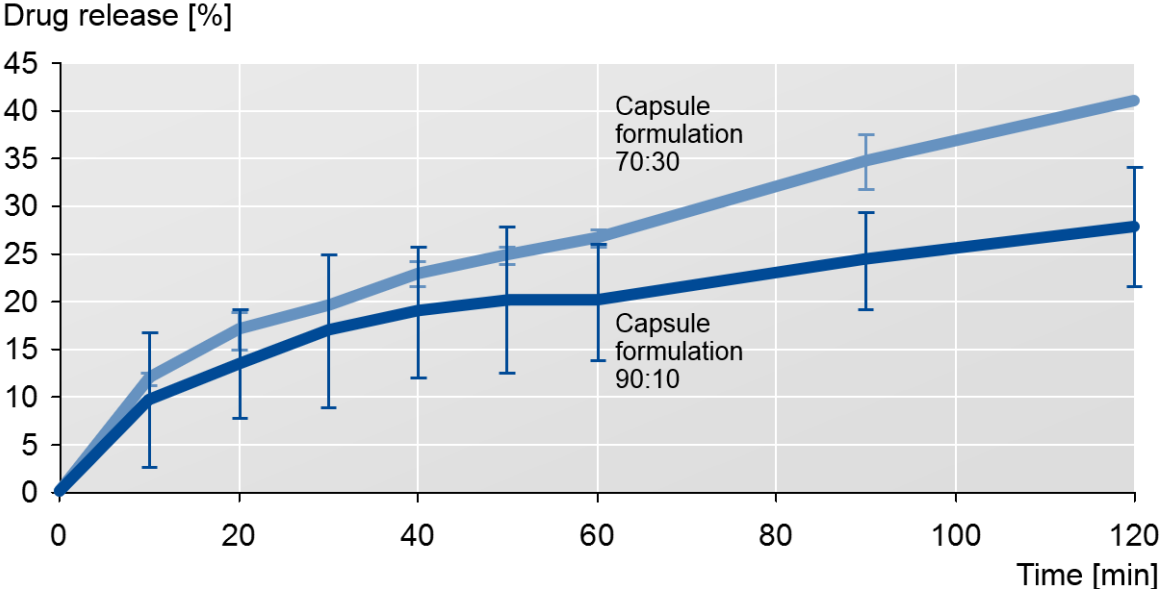
Capsule filling – case study (Carbamazepine/Soluplus®)

Capsule formulation 70:30

- Solid solution Carbamazepine 70 %
- Kollidon® CL 15 %
- Microcrystalline cellulose 15 %

Capsule formulation 90:10

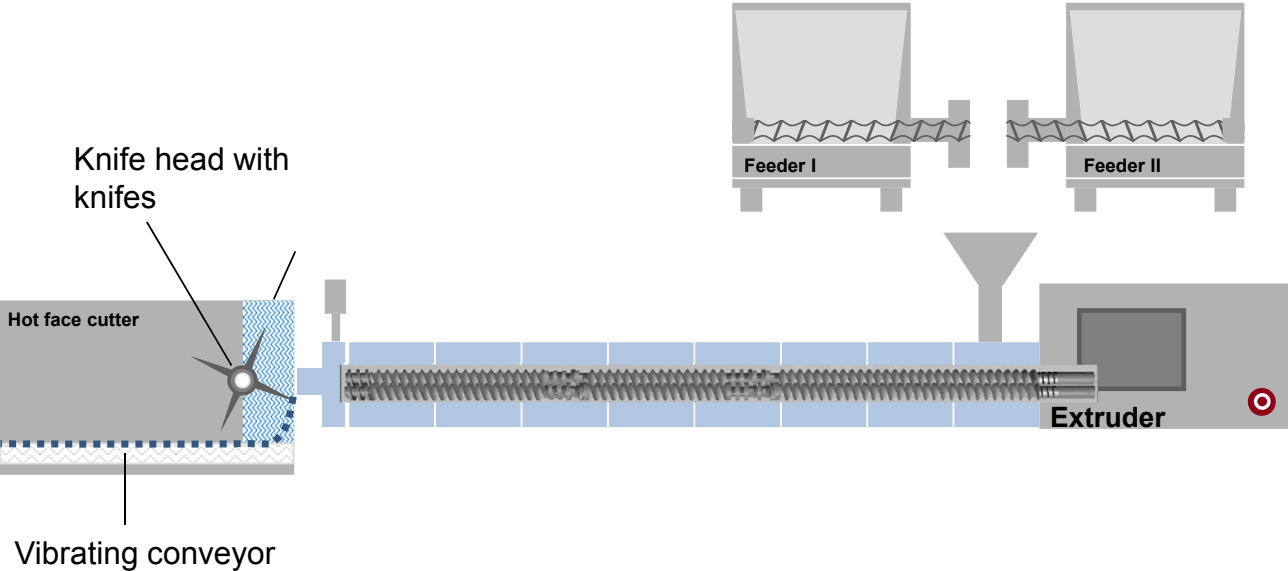
- Solid solution Carbamazepine 90 %
- Kollidon® CL 10 %



Source: N. Rottmann, European Application Lab (Pharma Solutions Europe, CIS Countries, Middle East, and Africa), BASF SE, Ludwigshafen, Germany

Downstream processing

Air cooled hot face cutting

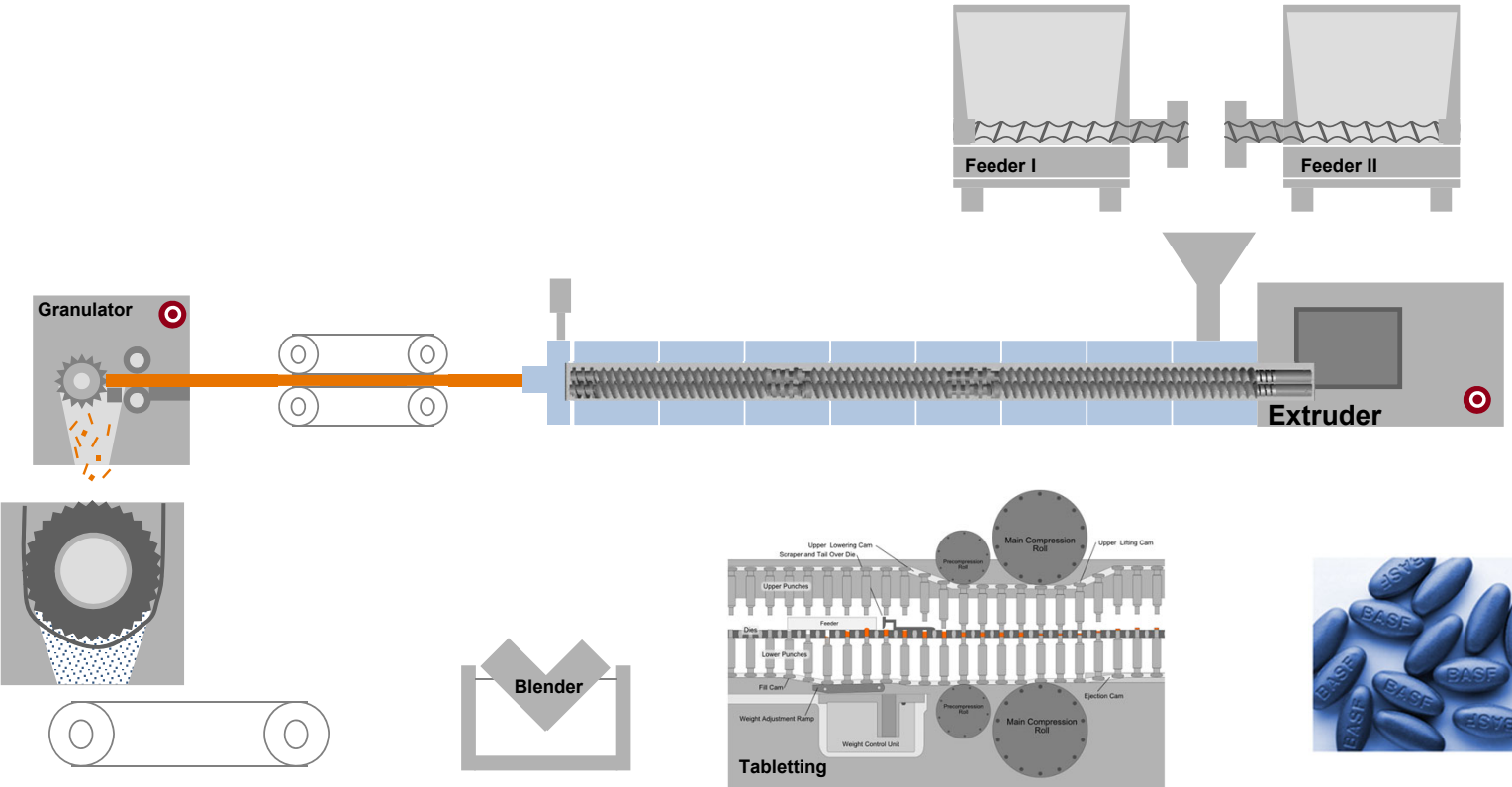


Source:

A. Gryczke, Global Technical Marketing Pharma Solutions, BASF SE, Ludwigshafen, Germany

Downstream processing

Compression



Source: N. Rottmann, European Application Lab (Pharma Solutions Europe, CIS Countries, Middle East, and Africa), BASF SE, Ludwigshafen, Germany

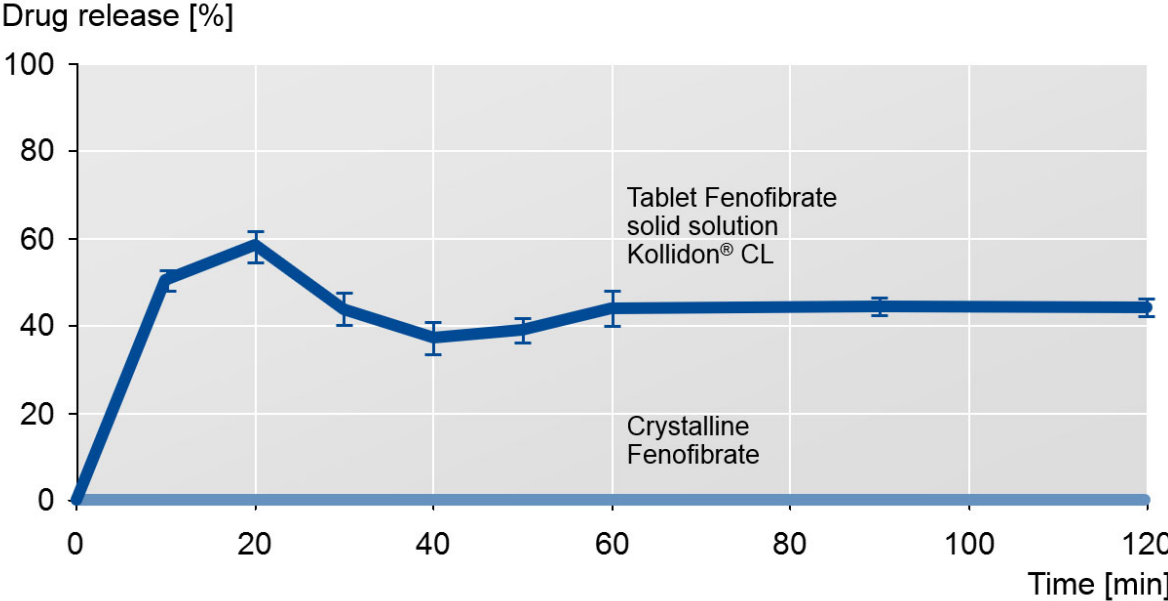
Downstream processing

Compression – case study (Fenofibrate/Soluplus®)

Capsule formulation 70:30

- Solid solution (20 % API) Soluplus®/Fenofibrate 60%
- MCC (Avicel® PH102) 29%
- Kollidon® CL 10%
- Magnesium stearate 0.5%
- Aerosil® 200 0.5%

Extrudates milled <500 µm
 12 mm tablet 550mg
 single punch press 18kN



Source: N. Rottmann, European Application Lab (Pharma Solutions Europe, CIS Countries, Middle East, and Africa), BASF SE, Ludwigshafen, Germany

Downstream processing

Compression – case study (Impact of disintegrants on solid solution formulations)

Capsule formulation 70:30

■ Solid solution (20 % API) Soluplus®/Fenofibrate	60%
■ MCC (Avicel® PH102)	29%
■ Disintegrant*	10%
■ Magnesium stearate	0.5%
■ Aerosil® 200	0.5%

Extrudates milled	<500 µm
12 mm tablet	550mg
single punch press	18kN

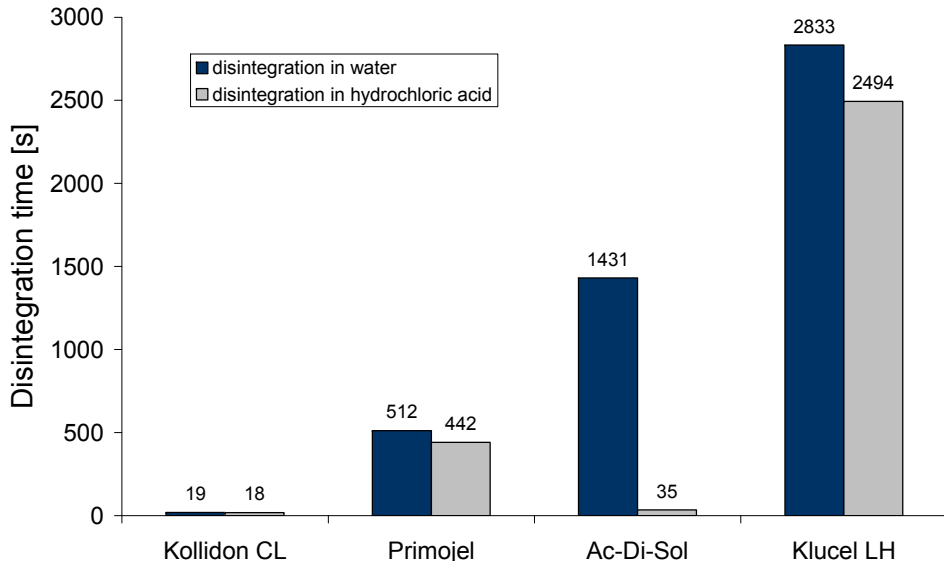
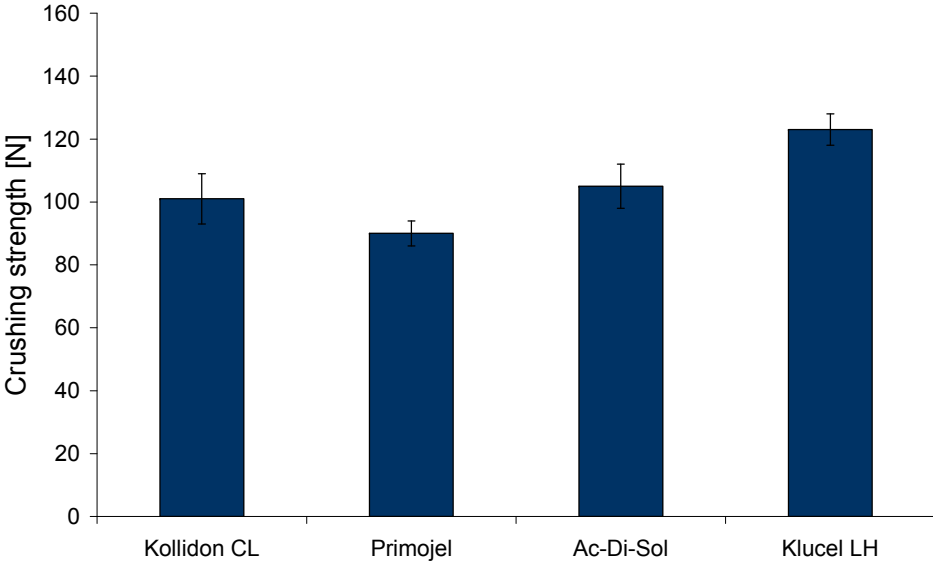
* Disintegrants:

- Kollidon® CL
- Primojel®
- Ac-Di-Sol®
- Klucel® LH 11



Downstream processing

Compression – case study (Impact of disintegrants on solid solution formulations)



Source: N. Rottmann, European Application Lab (Pharma Solutions Europe, CIS Countries, Middle East, and Africa), BASF SE, Ludwigshafen, Germany

Downstream processing

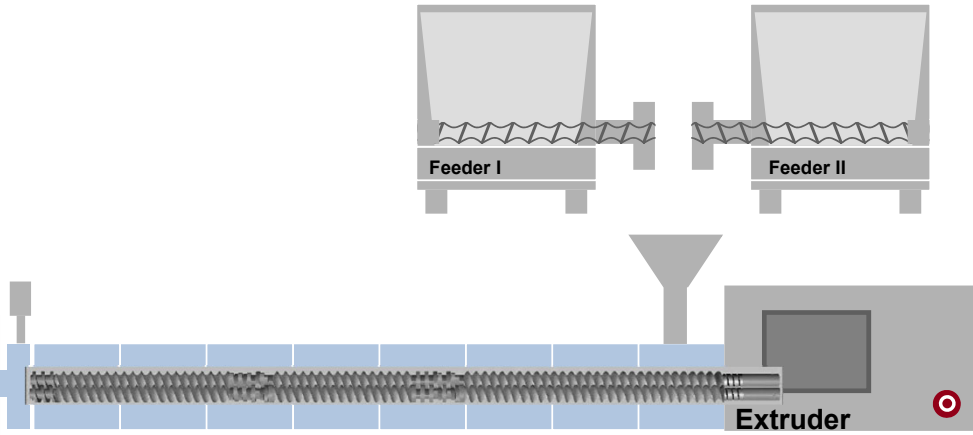
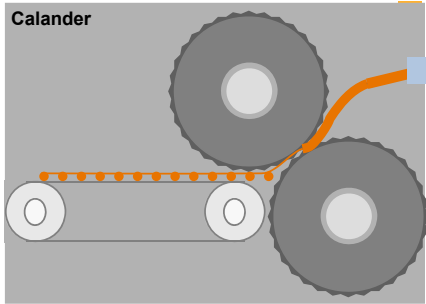
Compression – case study (recommendations)

- Extrudate should be milled or at least cut.
- In order to avoid lumping of the milled extrudate which would lead to a delayed and reduced drug release particular attention must be paid to the formulation:
 - A disintegrant (10 – 15 %) has to be used in the formulation in order to receive an appropriate drug release.
 - Additional microcrystalline cellulose or other fillers (20 – 30 %) facilitate the dissolution of extrudates.
They act as spacer or pore former during dissolution.



Downstream processing

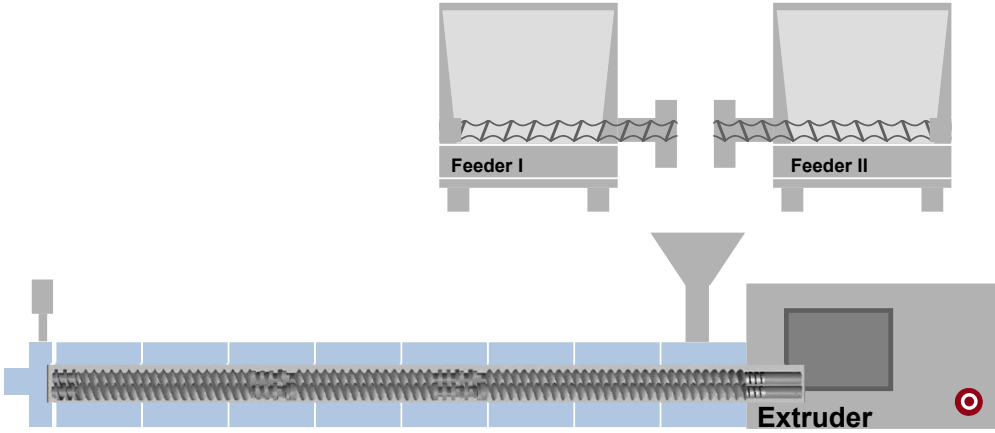
Calandring



Source: N. Rottmann, European Application Lab (Pharma Solutions Europe, CIS Countries, Middle East, and Africa), BASF SE, Ludwigshafen, Germany

Downstream processing

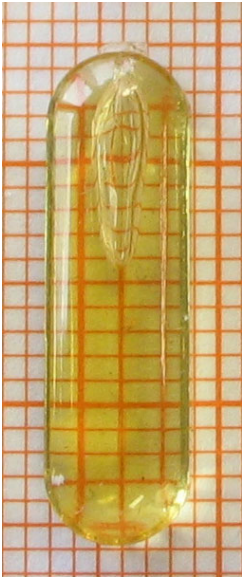
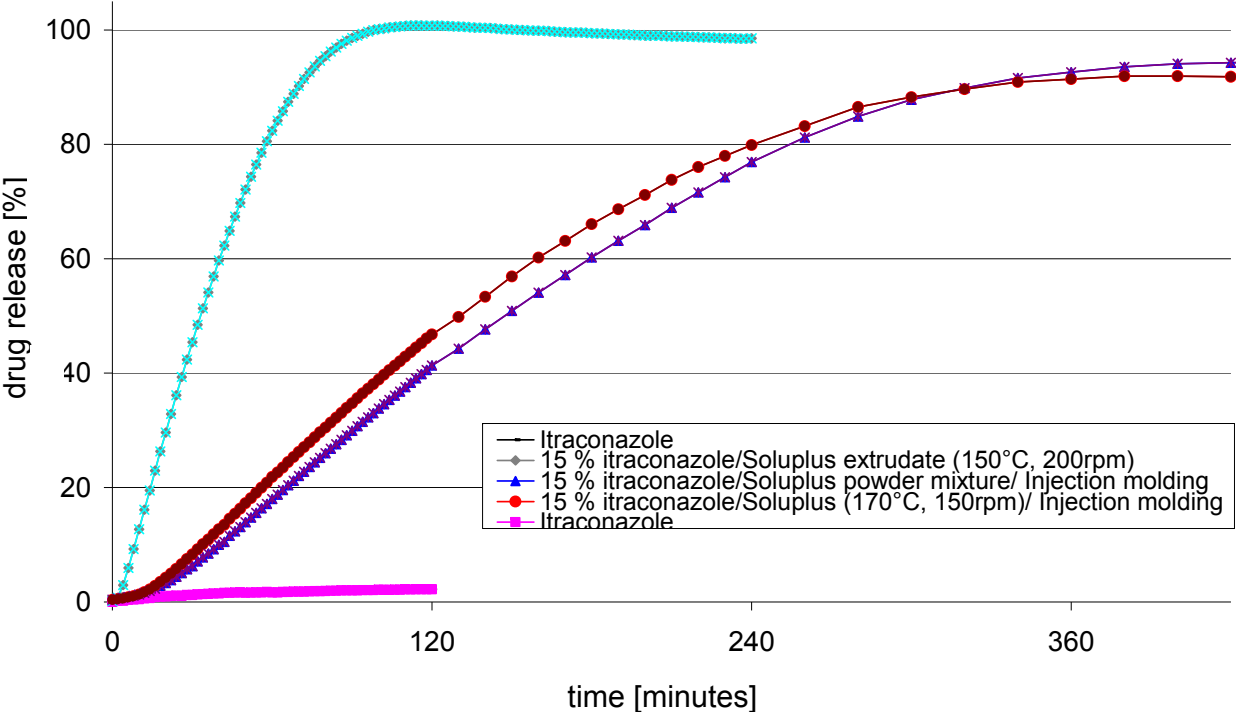
Injection moulding



Source: N. Rottmann, European Application Lab (Pharma Solutions Europe, CIS Countries, Middle East, and Africa), BASF SE, Ludwigshafen, Germany

Downstream processing

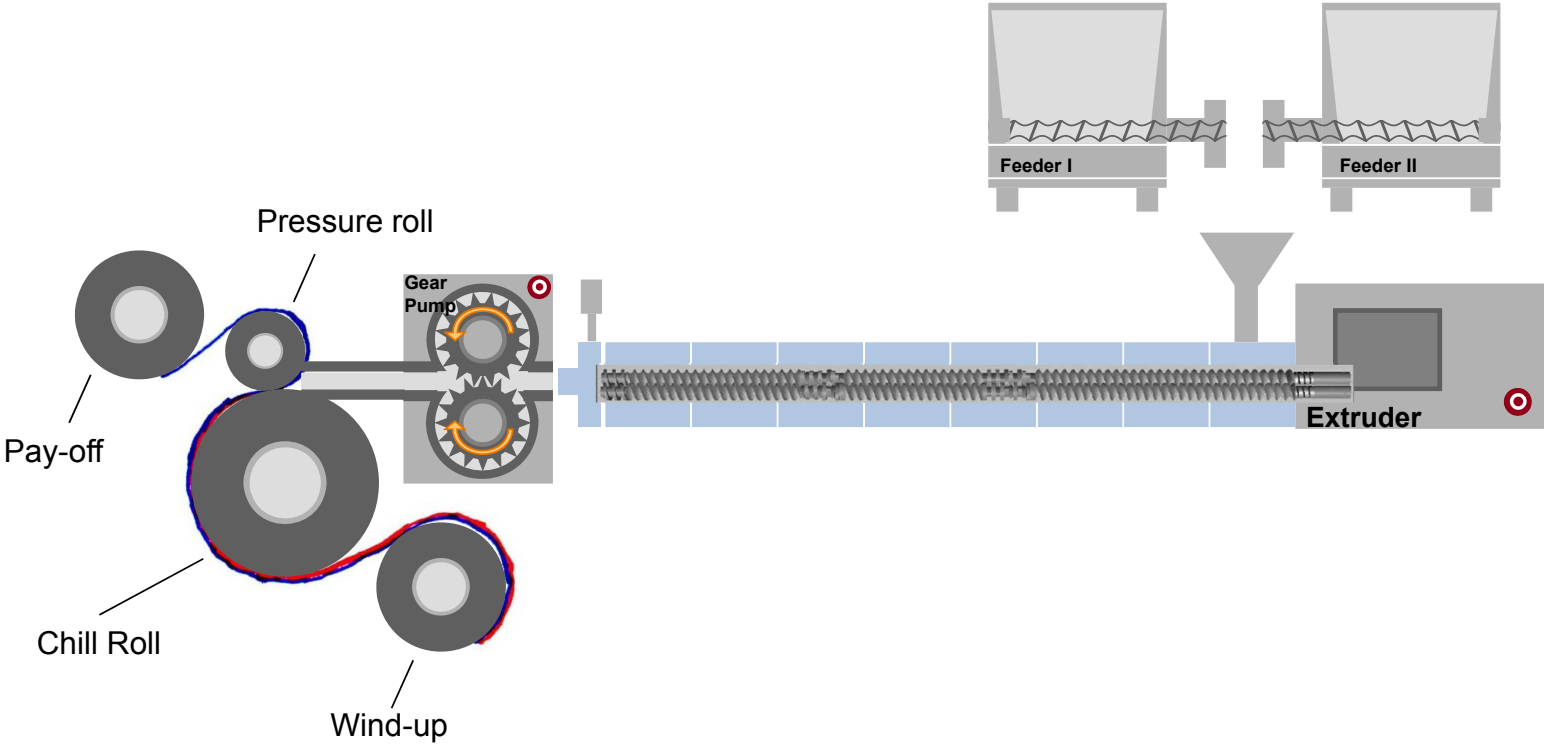
Injection moulding – case study (Itraconazole/Soluplus®)



Source: A. Gryczke, Global Technical Marketing Pharma Solutions, BASF SE, Ludwigshafen, Germany

Downstream processing

Extrusion Coating (e.g. for patch manufacturing)



Source: N. Rottmann, European Application Lab (Pharma Solutions Europe, CIS Countries, Middle East, and Africa), BASF SE, Ludwigshafen, Germany

Downstream processing

Extrusion Coating (e.g. for patch manufacturing)

Inside the extruder the compounding of ingredients happens, then melt gets extruded through a die. Via down streaming the melt gets cooled (solified) and shaped.

Strand line

- Common
- need to be milled
- Usually no calibration included

Injection Molding

- Not Common yet
- Final dosage form
- Fast
- Reasonable cost
- Unique shapes

Chill Roll

- Common
- Need to be milled
- Very well controlled cooling of extrudate
- Good to controll morphology of extrudate

Catheter/Films

- Common
- Medical Devices
- TTS
- Other patches

Downstream processing

Extrusion Coating (e.g. for patch manufacturing)

New formulas for successful drug delivery
Hot-melt extrusion for enhanced solubility and bioavailability

Andreas Gryczke, an enabler in excipients

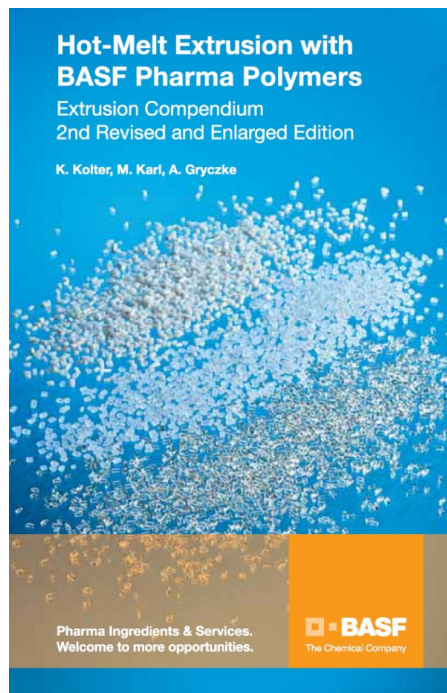


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Extrusion Compendium
2nd Revised and Enlarged Edition

K. Kolter, M. Karl, A. Gryczke



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Thomas Reintjes (Editor)



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Contact

Nils Wilhelm Rottmann

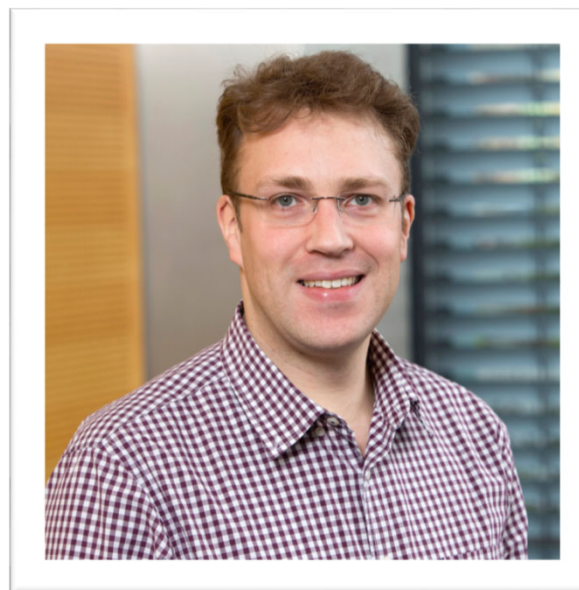
European Application Lab
Pharma Solutions & Human Nutrition

BASF SE
G-ENP/SE – Nutrition & Health (Europe, Africa, West Asia)

Phone: + 49 (0) 621 / 60 – 99 712
Mobile: + 49 (0) 173 / 319 72 57
Fax: + 49 (0) 621 / 60 – 66 99 712

Mail: nils.rottmann@basf.com

Internet: www.pharma.basf.com



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dr. Špela Zupančič

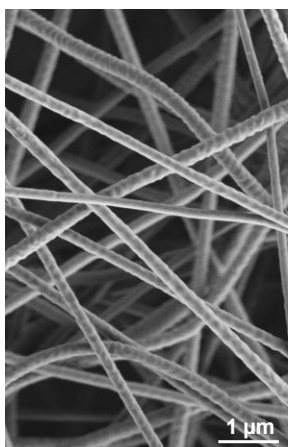
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Stabilizacija amorfnih oblik učinkovin z vgrajevanjem v nanodostavne sisteme – primer nanovlaken s poloksamerom



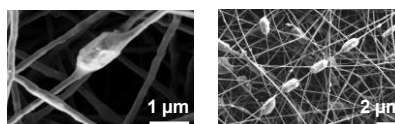
NANOVLAKNA

Vlakna s premerom od
1 nm do 1000 nm



UPORABA V FARMACIJI

- Dostavni sistem za učinkovine, proteine in celice

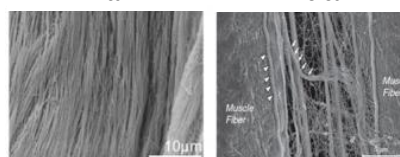


Zupančič, Š. et al. Biomacromolecules 2018, 19, 4299–4306

- Za izboljšano regeneracijo tkiv

kita

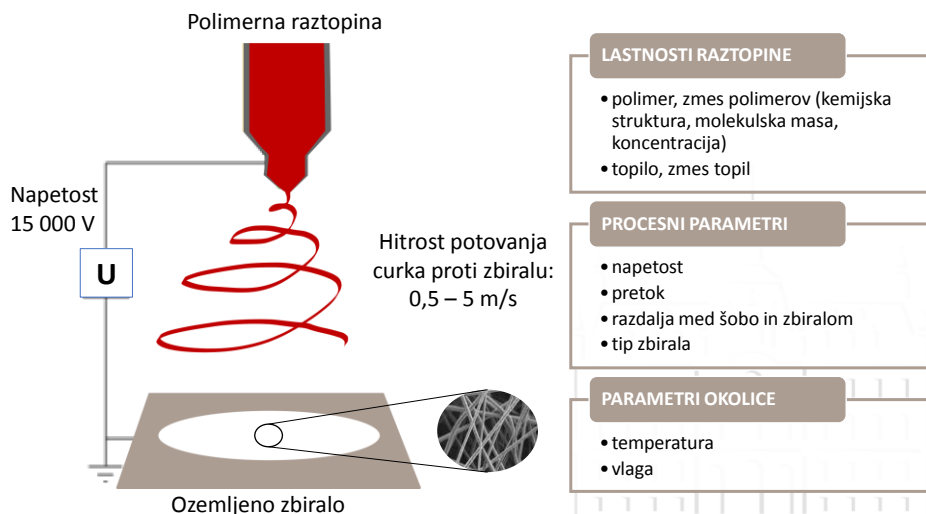
mišica



Jun, I. et al. Int J Mol Sci. 2018 19(3): 745

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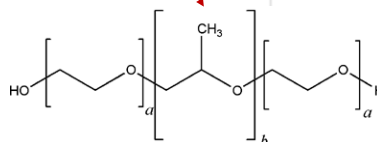
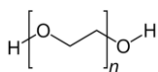
ELEKTROSTATSKO SUKANJE



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NAMEN

- Razvoj nanovlaken z **20 %** (m/m) vsebnostjo **karvedilola** (skoraj netopna ZU)
- Pomožni snovi: **polietilen oksid (PEO)** (400 kDa) : **poloksamer 407** = 1 : 1



- Namen: **povečanje topnosti in hitrosti raztapljanja karvedilola**

POLIMERNE DISPERZIJE

POLIMERNE DISPERZIJE

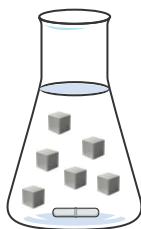
PROCESNI PARAMETRI

- napetost = 15 kV
- pretok = 1,414 mL/h
- razdalja med šobo in zbiralom = 15 cm

PARAMETRI OKOLICE

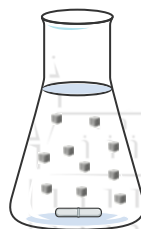
- sobna temperatura
- relativna vlaga < 30 %

karvedilol
+
polimerna raztopina
v vodi



S1 - SUSPENZIJA

karvedilol v **acetonu**
+
polimerna raztopina
v vodi



S2 - NANOSUSPENZIJA

karvedilol
+
polimerna raztopina
v **etanolu**

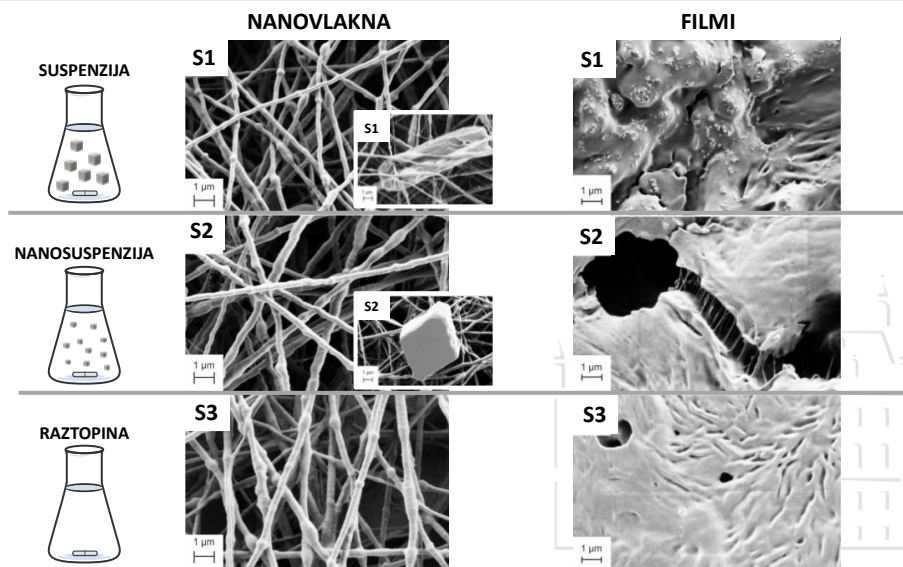


S3 - RAZTOPINA

Kajdič, S. et al. Eur J Pharm Sci. 2018; 117: 331-340.

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IZDELANA NANOVLAKNA IN FILMI

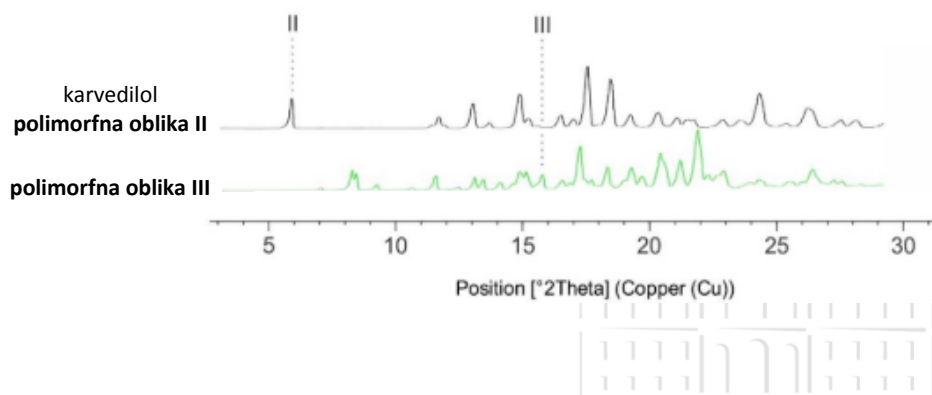


Kajdič, S. et al. Eur J Pharm Sci. 2018; 117: 331-340.

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POLIMORFNE OBLIKE KARVEDILOLA




Rentgenska praškovna difrakcija



Kajdič, S. et al. Eur J Pharm Sci. 2018; 117: 331-340.

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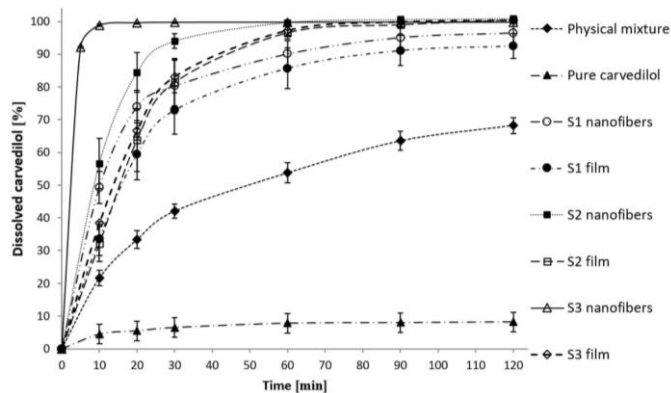
POLIMORFNE OBLIKE KARVEDILOLA V NANOVLAKNIH IN FILMIH

Medij	Dostavni sistem	Polimorfna oblika takoj po izdelavi	Polimorfna oblika po 1 letu
	voda	nanovlakna	II
	film	II	II
	voda/acetone	nanovlakna	III
	film	III	III
	etanol	nanovlakna	/
	film	II (sledi)	II

Kajdič, S. et al. Eur J Pharm Sci. 2018; 117: 331-340.

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HITROST RAZTAPLJANJA



Hitrost raztapljanja karvedilola poviša:

- Prisotnost poloksamera
- Vgradnja karvedilola v nanovlakna (sledijo filmi)
- Amorfn oblika karvedilola (sledi polimorfna oblika III in nato II)

Kajdič, S. et al. Eur J Pharm Sci. 2018; 117: 331-340.

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ZAKLJUČEK

1. Topilo v polimerni disperziji ključno vpliva na kristalizacijo karvedilola.
2. Karvedilol v nanovlaknih v 1 letu ni izkristaliziral.
3. Nanovlakna pospešijo hitrost raztapljanja v primerjavi s filmi ali fizikalno zmesjo.

Kajdič, S. et al. Eur J Pharm Sci. 2018; 117: 331-340.

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Študij in napovedovanje stabilnosti metastabilnih oblik učinkovin – analizni pristopi

dr. Dejan Klement
junij 2019

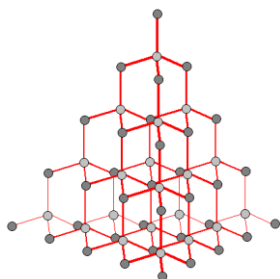


Živeti zdravo življenje.

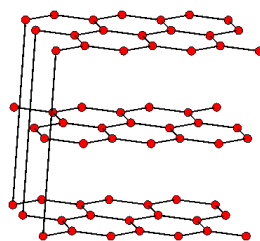
Vsebina

1. Kaj so polimorfne oblike in kaj so metastabilne polimorfne oblike?
2. Kaj nas motivira za študij in napovedovanje fizikalne stabilnosti učinkovin?
3. Kakšno je fizikalno-kemijsko ozadje študija fizikalne stabilnosti?
4. Kakšne analizne metode lahko uporabimo?
5. Prikaz pristopa z Ramansko spektroskopijo in rentgensko praškovo difrakcijo na realnem primeru iz farmacevtske industrije.

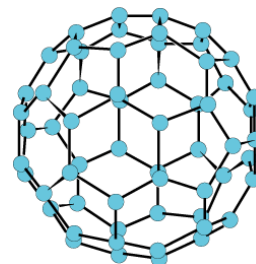
Polimorfizem



diamant



grafit



fuleren

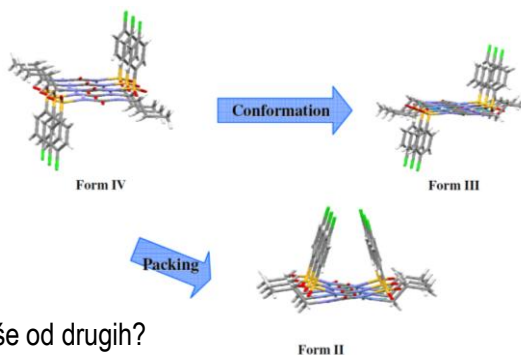
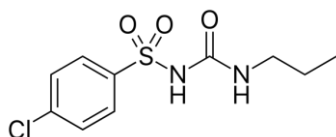
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Polimorfizem: orientacijski (pakiranje) in konformacijski

- Zmožnost obstoja določene trdne snovi v vsaj dveh kristaliničnih fazah, za katere je značilna enaka molekulska formula, vendar različna razporeditev gradnikov (atomov, ionov, molekul) v kristalu.

polimorfizem
kloropropamida



- Ali veste, zakaj so ene čokolade okusnejše od drugih?

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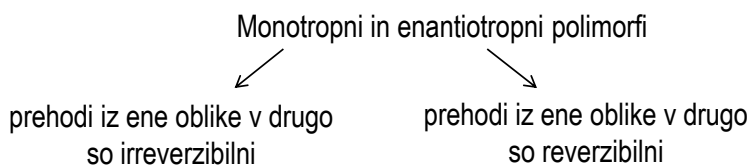
Polymorphism in Pharmaceutical Compounds, Advancements and Futuristic Trends in Material Science, 2011

Thermodynamic and kinetic investigation of agomelatine polymorph transformation, Pharmaceutical Development and Technology, 2014



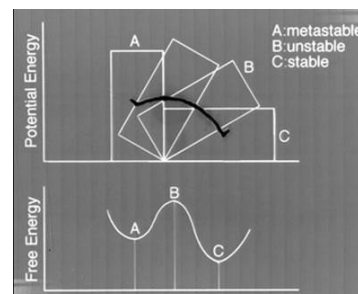
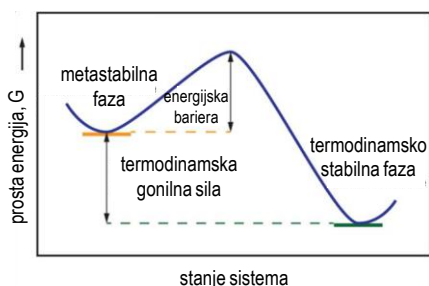
Polimorfizem v farmaciji

- Več kot polovica vseh učinkovin na trgu nastopa v vsaj dveh kristalnih oblikah.
- Različni polimorfi določene spojine izkazujejo različne fizikalne in kemijske lastnosti (topnost, tališče, gostota, trdnost, oblika kristalitev, optične in električne lastnosti, parni tlak, pretočnost, kemijska stabilnost, biorazpoložljivost ...).



Metastabilna oblika

- Gre za termodinamsko nestabilno obliko, ki se lahko pretvori v energijsko nižje ležeče in termodinamsko stabilno obliko.



- Se ne nanaša nujno na kristalinično obliko, tudi amorfna oblika je termodinamsko metastabilna.
- Zanimajo nas tiste metastabilne faze, ki izkazujejo dovolj visoko aktivacijsko bariero.

Uporaba učinkovine, ki izkazuje polimorfizem, v razvoju formulacije

- Izberemo polimorf z najnižjo energijo, ker predstavlja termodinamsko najbolj stabilno obliko.
- Uporaba metastabilne oblike je lahko kljub temu v določenih primerih upravičena:
 - dosega boljšo biorazpoložljivost (metastabilne oblike navadno izkazujejo boljšo topnost)
 - izkazuje boljšo kemijsko stabilnost
 - izkazuje boljše fizikalne lastnosti (pretočnost, filterabilnost, mehanske in morfološke lastnosti)

STABILNOSTNO TVEGANJE

Vzroki za stabilnostno tveganje:

- intrinzična nestabilnost metastabilne oblike (posledica točno določene strukture, kristaliničnosti, deleža kristalinične faze, oblike in velikosti kristalitov) – definirana z $\Delta G = G_{\text{meta. f.}} - G_{\text{stab. f.}}$
- nestabilnost kot posledica procesa izdelave formulacije in shranjevanja:
 - izpostavitve povišani T
 - izpostavitve povišani vlažnosti (vlažna granulacija)
 - izpostavitve mehanski obremenitvi (kompaktiranje, tabletiranje)
 - interakcija s pomožnimi snovmi
- Moramo vzdrževati pogoje, ki ne bodo omogočali pretvorbe MF v SF tekom izdelave formulacije kakor tudi ne shranjevanja (roka uporabnosti izdelka).

Predmet te predstavitve – študij in napovedovanje stabilnosti

- Želimo si pristopov, s katerimi bi lahko čim bolj natančno in v čim krajšem možnem času pravilno predvideli fizikalno stabilnost učinkovine.

Osredotočeni smo na stabilnostne študije v razvojni stopnji.



Prednosti, ki jih prinaša hitro napovedovanje:

- izbor polimorfne oblike za končno formulacijo
- optimizacija ključnih procesnih parametrov
- selekcija perspektivnih formulacijskih poskusov
- odločitev o pogojih hranjenja

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Arrheniusova enačba

- Opisuje temperaturno odvisnost številnih termično aktiviranih procesov v trdnem.

$$k = Ae^{-\frac{E_a}{RT}}$$



$$\ln k = \ln A - \frac{E_a}{RT}$$

k...konstanta hitrosti

A...frekvenčni faktor

E_a ...aktivacijska energija [kJ/mol]

R...plinska konstanta (0,00831 kJ/mol)

T...absolutna temperatura [K]

- Konstanta reakcijske hitrosti povezuje delež pretvorbe „ α “ s časom.
- Obstajajo različni kinetični modeli za pretvorbe v trdnem, s katerimi opisujemo eksperimentalne podatke.

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Kinetični modeli

- Eksperimentalne podatke poskušamo popisati z različnimi kinetičnimi modeli in vsakič izračunamo korelacijski koeficient R^2 .
- $R^2 > 0,9 \longrightarrow$ model dobro popisuje podatke
- Izberemo kinetični model, ki daje najboljše korelacijske koeficiente preko celotnega temperaturnega območja.

Kinetic model	Equation
Nucleation models	
Power law (P2)	$\alpha^{1/2} = kt$
Power law (P3)	$\alpha^{1/3} = kt$
Power law (P4)	$\alpha^{1/4} = kt$
Avrami-Erofe'ev (A2)	$[-\ln(1-\alpha)]^{1/2} = kt$
Avrami-Erofe'ev (A3)	$[-\ln(1-\alpha)]^{1/3} = kt$
Avrami-Erofe'ev (A4)	$[-\ln(1-\alpha)]^{1/4} = kt$
Prout-Tompkins (B1)	$\ln \alpha / (1-\alpha) = kt$
Geometrical Contraction models	
Contracting area (R1)	$\alpha = kt$
Contracting area (R2)	$1 - (1-\alpha)^{1/2} = kt$
Contracting area (R3)	$1 - (1-\alpha)^{1/3} = kt$
Diffusion models	
1-D diffusion (D1)	$\alpha^2 = kt$
2-D diffusion (D2)	$(1-\alpha)\ln(1-\alpha) + \alpha = kt$
3-D diffusion-Jander equation (D3)	$[1 - (1-\alpha)^{1/3}]^2 = kt$
Ginstling-Brounshtein (D4)	$[1 - (2\alpha/3)] - (1-\alpha)^{2/3} = kt$
Reaction-order models	
First-order (F1)	$-\ln(1-\alpha) = kt$

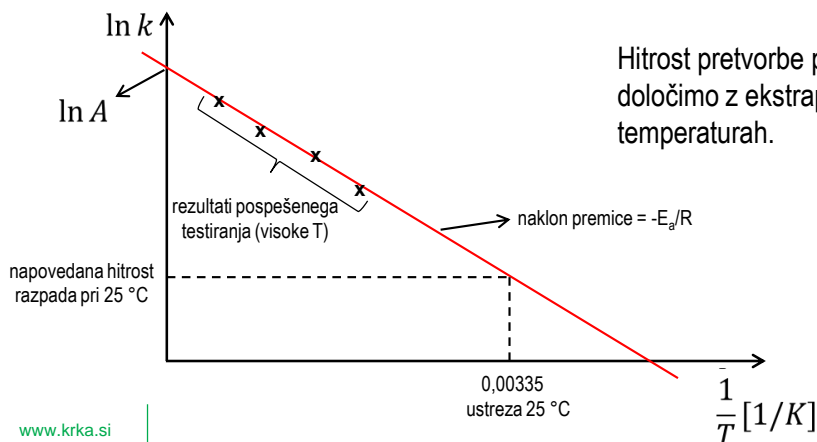
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Thermodynamic and kinetic investigation of agomelatine polymorph transformation, Pharmaceutical Development and Technology, 2014



Arrheniusova enačba

- Iz statističnih razlogov je priporočljivo izvesti pospešeno stabilnost pri 4 različnih stresnih temperaturah.



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Analizni pristopi

- Analizni pristopi morajo temeljiti na kvantitativnih „solid-state“ analiznih metodah.
- Za raziskavo kinetike faznega prehoda je dobro uporabiti več kot eno analizno metodo.



www.ni.rca.si

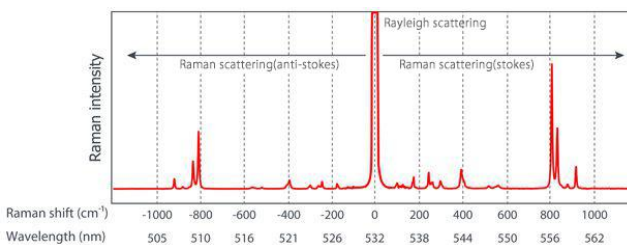
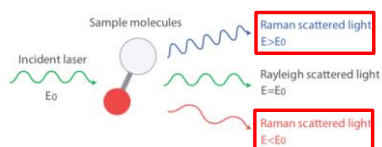


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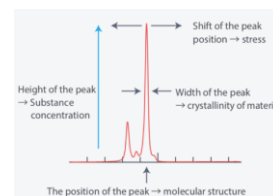
Ramanska spektroskopija: osnove tehnike

- Temelji na neelastičnem sipanju monokromatske svetlobe.

Scattering of light by molecules



- Pri Ramanski študiji pri povišanih T uporabljamo posebno komoro, ki omogoča in-situ snemanje spektrov.
- Izvedba in-situ kinetične študije je mogoča le pri dovolj visokih temperaturah.



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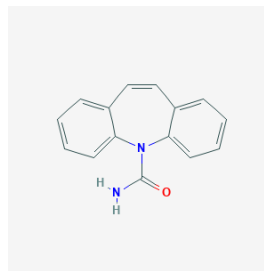
Ramanska spektroskopija: študij pretvorbe karbamazepin oblike III v obliko I

- Polimorfa izkazujeta razlike v položajih in intenzitetah vrhov.

Assignment of FT-Raman bands to molecular vibrations for carbamazepine form III and form I

Form III	Form I	Approximate description of vibrational mode	Form III	Form I	Approximate description of vibrational mode
3071w		$\nu(\text{CH})$ asymmetric, aromatic	874w	876w	$\nu(\text{C}-\text{N}-\text{C})$
	3061m	$\nu(\text{CH})$ aromatic	853vw	853vw	Amide V/ $\delta(\text{C}-\text{H})$ aromatic
3043w		$\nu(\text{CH})$ aromatic	723m	720m	$\nu(\text{C}-\text{N}-\text{C})$ 3° amide
3020w	3024m	$\nu(\text{CH})$ non-aromatic	691mw	699w	δ aromatic, in-plane C-H wag <i>cis</i>
1624s	1621s	$\nu(\text{C}=\text{C})$ non-aromatic	646vw	646vw	$\delta(\text{O}-\text{C}-\text{N})$ ring/ $\delta(\text{C}=\text{O})$
1600ms	1598s	$\delta(\text{N}-\text{H})$ amide II	620vw	620w	$\delta(\text{O}-\text{C}-\text{N})$ ring
1588m sh		$\nu(\text{C}=\text{C})$ aromatic	582w	582w	$\delta(\text{O}-\text{C}-\text{N})$
1565s	1563s	$\nu(\text{C}=\text{C})$ aromatic	559w		δ aromatic, out-of-plane
1489m	1489m	$\nu(\text{C}=\text{C})$ symmetric, aromatic/ $\nu(\text{C}-\text{N})$ amide III	546w	546w	δ aromatic, out-of-plane
1460vw	1461vw	$\delta(\text{CH})$ aromatic, in-plane	538w sh	537w	δ aromatic, out-of-plane
1439vw	1440vw	$\nu(\text{C}-\text{C})$ aromatic	486vw	481w sh	
1412w	1406w	$\nu(\text{C}=\text{C})/\delta(\text{CH})$	469vw	473vw	
1309ms	1305ms	$\delta(\text{CH})$ in-plane, non-aromatic	454w	458w	
1273vw	1271w	$\nu(\text{C}-\text{C})$	413w	413w	Lattice vibration
1250mw	1253mw	$\nu(\text{C}-\text{N})$ amide III 1° amide	390m	394mw	Lattice vibration
1221m	1218m	$\nu(\text{C}-\text{N})$ amide III	375mw	371w	Lattice vibration
1204w	1206w sh	$\nu(\text{C}-\text{C})$ ring	330w	332w	Lattice vibration
1160w	1155w	$\nu(\text{C}-\text{C})$ ring/ $\nu(\text{C}-\text{N}-\text{C})$ asymmetric	272w	263w	Lattice vibration
1130w	1133w	$\rho(\text{NH}_2)$	253mw		Lattice vibration
1110w	1110w	$\rho(\text{NH}_2)$	227vw		Lattice vibration
1042m	1040m	$\delta(\text{C}-\text{H})$ aromatic, in-plane	182ms		Lattice vibration
1025m	1025ms	$\delta(\text{C}-\text{H})$ aromatic, in-plane	170w	172s	Torsion
987w	968w	$\nu(\text{C}-\text{N})$	120w	116vs	Lattice vibration
949w	955vw	$\delta(\text{C}-\text{H})$ aromatic, out-of-plane	105s		Lattice vibration
936vw	943vw	$\delta(\text{C}-\text{H})$ aromatic, out-of-plane			
884vw sh	888vw sh	$\nu(\text{C}-\text{N}-\text{C})$ ring, symmetric			

ν : Stretch, δ : bend, ρ : rocking, s : strong, m : medium, w : weak, v : very, sh : shoulder.



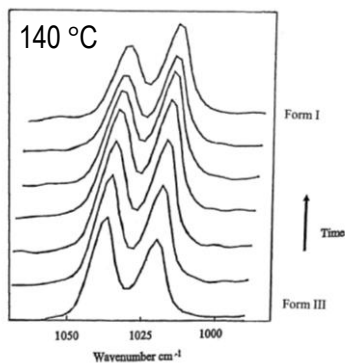
www.krka.si

Use of in situ FT-Raman spectroscopy to study the kinetics of the transformation of carbamazepine polymorphs, Journal of Pharmaceutical and Biomedical Analysis, 2004.

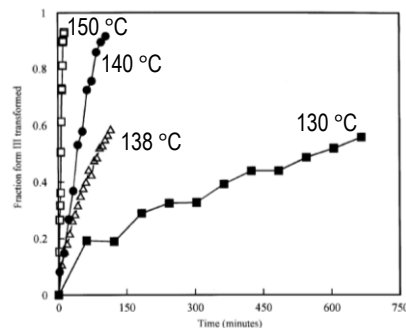


Ramanska spektroskopija: študij pretvorbe karbamazepin oblike III v obliko I

- Izbor spektralnega območja, kjer so prisotne jasne spektralne razlike med polimorfnima oblikama.
- Razlika v relativnih int. dveh upogibnih C-H nihanj pri 1040 in 1025 cm^{-1} iz ortosubstituiranega benzenovega obroča.
- Vzorci so se segrevali izotermalno pri 130, 138, 140 in 150 $^{\circ}\text{C}$.



$$\frac{I_{1040}}{I_{1025}}$$



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Ramanska spektroskopija: korelacijski koeficienti različnih kinetičnih modelov

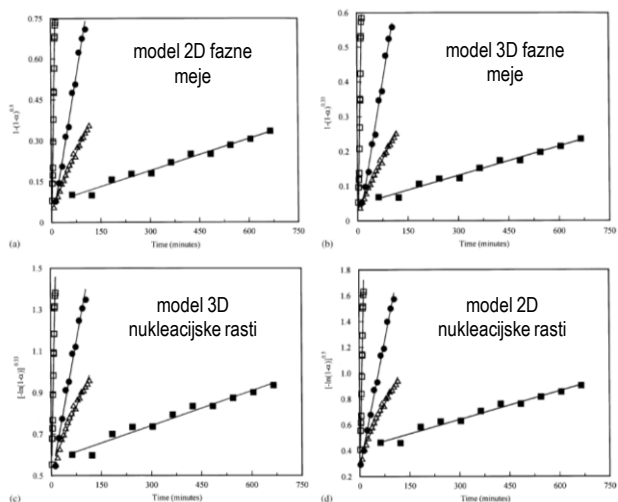
Kinetic model	Equation	Correlation coefficient (r^2)			
		150 °C	140 °C	138 °C	130 °C
Prout-Tompkins	$\ln \alpha/(1-\alpha) = kt$	0.935	0.939	0.924	0.951
Avrami-Erofeev ($n = 2$)	$[-\ln(1-\alpha)]^{1/2} = kt$	0.992	0.990	0.987	0.986
Avrami-Erofeev ($n = 3$)	$[-\ln(1-\alpha)]^{1/3} = kt$	0.992	0.990	0.978	0.982
First order	$-\ln(1-\alpha) = kt$	0.988	0.987	0.991	0.988
One dimensional phase boundary	$1-\alpha = kt$	0.991	0.989	0.986	0.990
Two dimensional phase boundary	$1-(1-\alpha)^{1/2} = kt$	0.988	0.985	0.997	0.991
Three dimensional phase boundary	$1-(1-\alpha)^{1/3} = kt$	0.985	0.981	0.996	0.990
One dimensional diffusion	$\alpha^2 = kt$	0.974	0.968	0.993	0.986
Two dimensional diffusion	$(1-\alpha)\ln(1-\alpha) + \alpha = kt$	0.966	0.959	0.992	0.985
Three dimensional diffusion	$[1-(1-\alpha)^{1/3}]^2 = kt$	0.947	0.938	0.988	0.981
Ginstling-Brounshtein	$[1 - (2\alpha/3)] - (1-\alpha)^{2/3} = kt$	0.975	0.972	0.998	0.991

- Kinetični modeli faznih mej v tem primeru najbolje popisujejo podatke čez celotno temperaturno območje.
- Reakcije v trdnem je mogoče velikokrat popisati z več kinetičnimi modeli, kar kaže na kompleksnost tovrstnih pretvorb.

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Ramanska spektroskopija: določitev aktivacijske energije



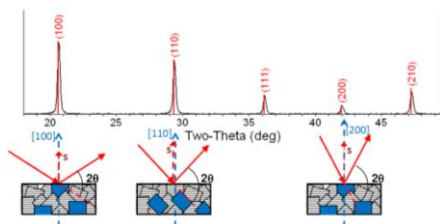
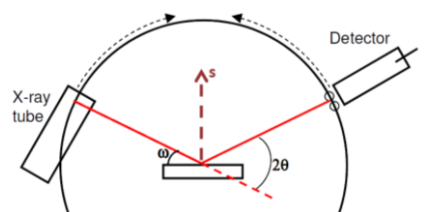
Arrheniusov graf

Kinetični model	Aktivacijska energija [kJ/mol]
Avrami-Erofeev ($n=2$)	354,8
Avrami-Erofeev ($n=3$)	344,4
Two dimensional phase boundary	359,6
Three dimensional phase boundary	368,1

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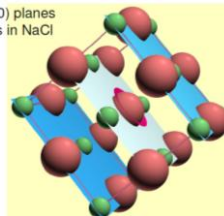


Rentgenska praškovna difrakcija (XRPD): osnove tehnike

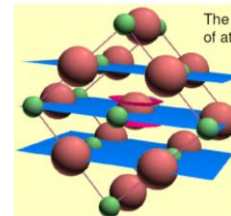


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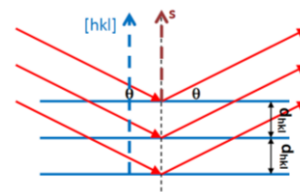
The (200) planes of atoms in NaCl



The (220) planes of atoms in NaCl



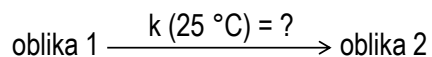
$$\text{Bragg's Law} \\ \lambda = 2d_{hkl} \sin \theta$$



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XRPD: Opis realnega primera problema napovedovanja fizikalne stabilnosti

- Učinkovina lahko nastopa v več različnih polimorfnih oblikah.
- Zanimata nas obliki 1 in 2, pri čemer je oblika 1 metastabilna faza, oblika 2 pa termodinamsko stabilna faza.
- Zanima nas, kakšno fizikalno stabilnost lahko pričakujemo za obliko 1, pri čemer se omejujemo na čisto učinkovino, in ne na učinkovino vgrajeno v formulacijo.



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Eksperiment

- Izotermalni pristop: izpostavitve vzorca čiste oblike 1 na več različnih temperatur (60, 70, 80 in 90 °C).
- Jemanje vzorcev iz pogojev na določene časovne periode in analiziranje z XRPD.



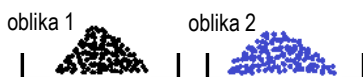
www.krka.si



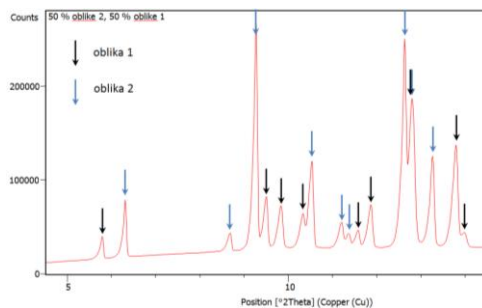
XRPD

- Pogoji za uspešno implementacijo XRPD pri napovedovanju fizikalne stabilnosti:

- potrebujemo čisti obliki 1 in 2



- v difraktogramu zmesi moramo imeti dobro ločen vsaj en rel. dobro intenziven uklon od posameznih oblik



- vzorec nam mora omogočati izničenje vpliva preferenčne orientacije (ob mletju se nam vzorec ne sme pretvarjati v drugo obliko)

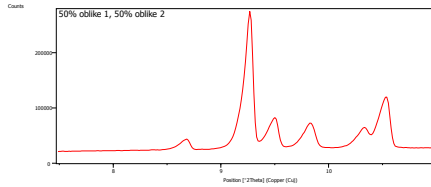


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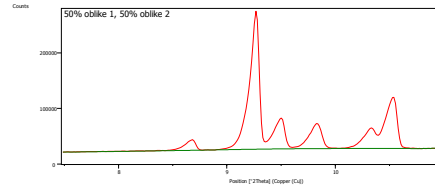


XRPD – obdelava rezultatov

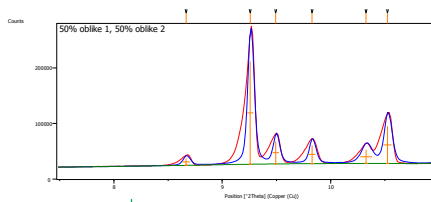
1. Izmerjen difraktogram



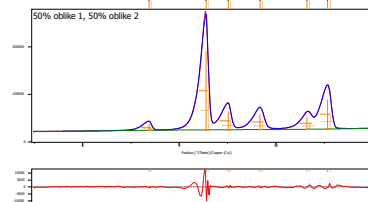
2. Določitev ozadja



3. Vstavitev uklonov



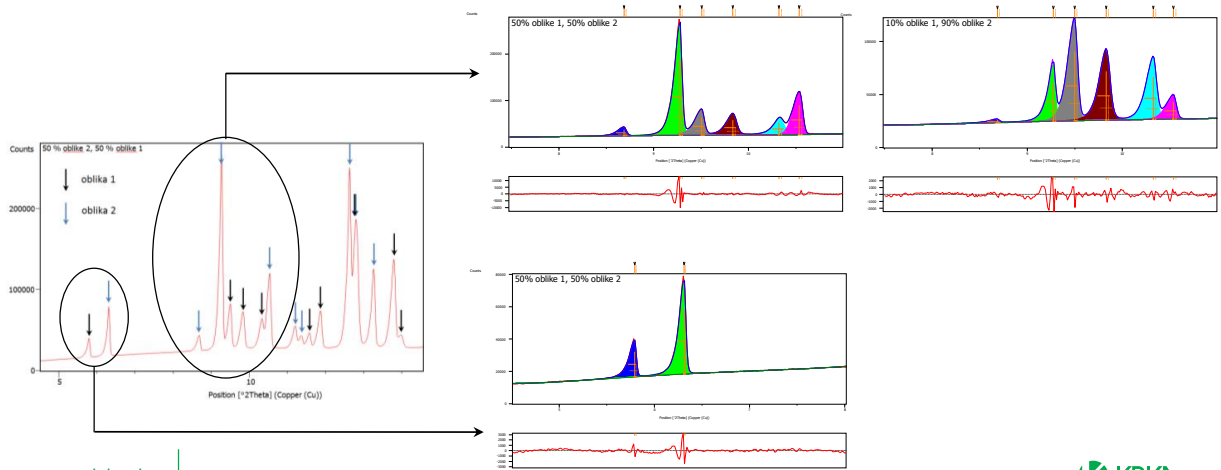
3. Prilaganje difraktograma



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XRPD – obdelava rezultatov

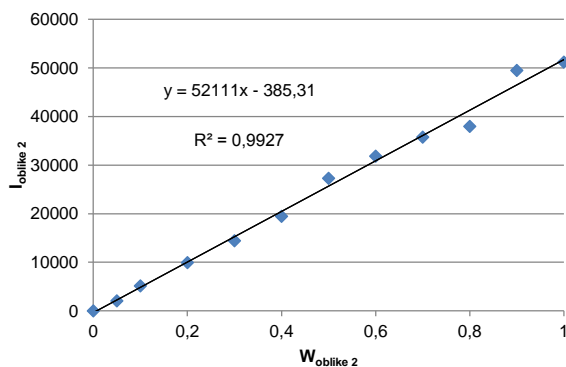


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XRPD – umeritvena premica

➤ Priprava umeritvene premice

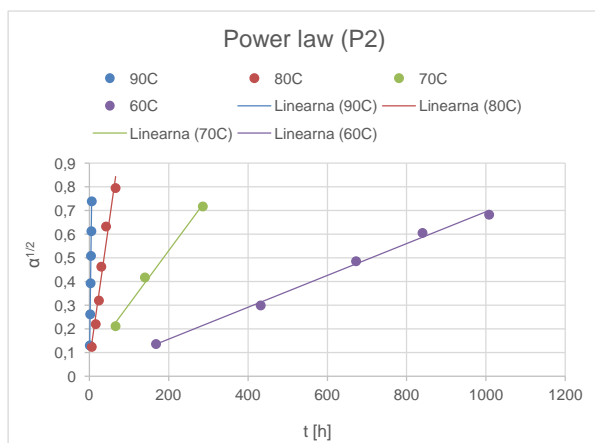


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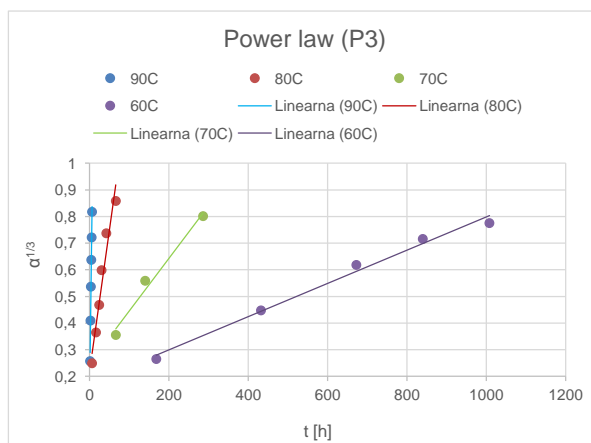
Kinetični model: nukleacijski modeli

$$\alpha = k^2 t^2 \iff \alpha^{1/2} = kt$$



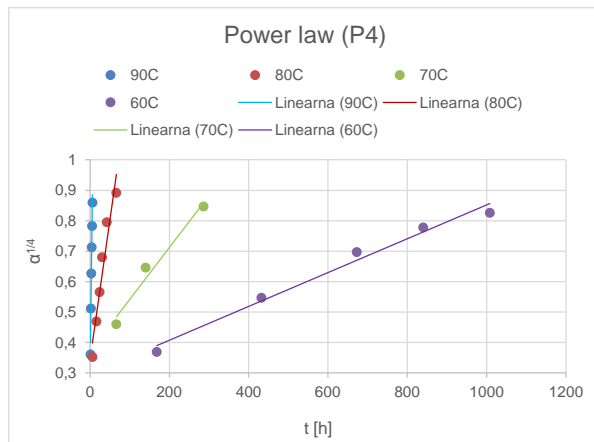
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$$\alpha = k^3 t^3 \iff \alpha^{1/3} = kt$$



Kinetični model: nukleacijski modeli

$$\alpha = k^4 t^4 \implies \alpha^{1/4} = kt$$



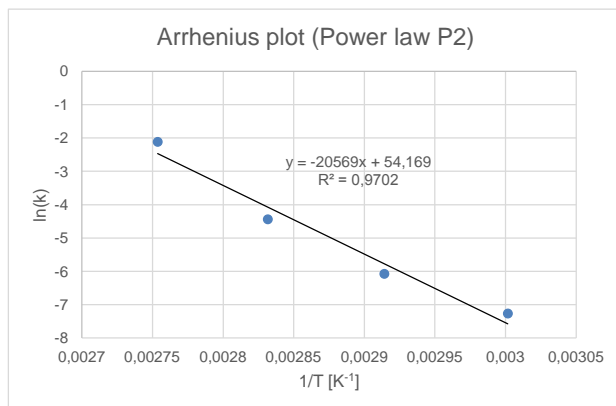
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KINETIČNI MODEL	ENAČBA	Korelacijski koeficient R ²			
		60 °C	70 °C	80 °C	90 °C
Power law (P2)	$\alpha^{1/2} = kt$	0.9952	0.9936	0.9645	0.9985
Power law (P3)	$\alpha^{1/3} = kt$	0.9891	0.9816	0.9454	0.9872
Power law (P4)	$\alpha^{1/4} = kt$	0.9826	0.9731	0.9993	0.9764

➤ Kinetični model Power law (P2) najbolje opiše eksperimentalne podatke.



Arrheniusov graf za kinetični model P2



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$$E_a = 171 \text{ kJ/mol}$$

$$\text{Razpolovni čas } t_{1/2} (25 \text{ °C}) = 220 \text{ let}$$

$$t_{0,03} (25 \text{ °C}) = 54 \text{ let}$$

$$t_{0,01} (25 \text{ °C}) = 31 \text{ let}$$

$$t_{0,01} (40 \text{ °C}) = 1 \text{ leto}$$

$$t_{0,005} (40 \text{ °C}) = 0,8 \text{ let}$$



Povzetek

- Pojasnili pojma polimorfizem in metastabilna pojavna oblika.
- Kadar pri razvoju izdelka uporabimo metastabilno obliko, obstaja tveganje fizikalne stabilnosti.
- Potrebni učinkoviti analizni pristopi napovedovanja fizikalne stabilnosti.
- Izvedemo pospešena stabilnostna testiranja (pri visokih T).
- Eksperimentalne podatke popišemo z najustreznejšim kinetičnim modelom.
- S pomočjo Arrheniusove enačbe izračunamo konstanto reakcijske hitrosti pri želeni temperaturi.



Živeti zdravo življenje.

SDC Slovenia



Fizikalno stabilno, kemijsko nestabilno

Klemen Naveršnik, Lek d.d., ESD
 Simpozij tehnološke sekcije SFD
 Ljubljana, 13. junij 2019

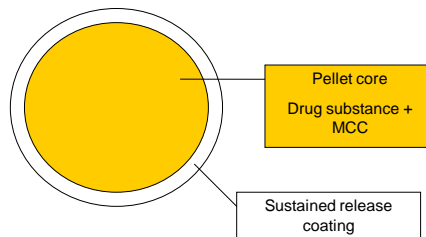


Case study 1: sustained release pellets (4mg)

Drug substance: crystalline
 (needle shaped) very stable,
 high solubility

Problem: Poor drug product
 stability (oxidative
 degradant)

Compatibility studies
 (binary mixtures):
 No incompatibility detected



Stability results

sample	Oxidative degradant (80°C, 5 days) %	XRPD
DS	ND	Crystalline
DS lyophilized	0.1	Crystalline
DS dry milled	ND	Not tested
DS + MCC Dry mixture	ND	Not tested
DS + MCC Dry mixture, milled	ND	Not tested
DS + MCC Wet kneading	0.6	Not tested
DS + MCC pellet	0.4	Crystalline

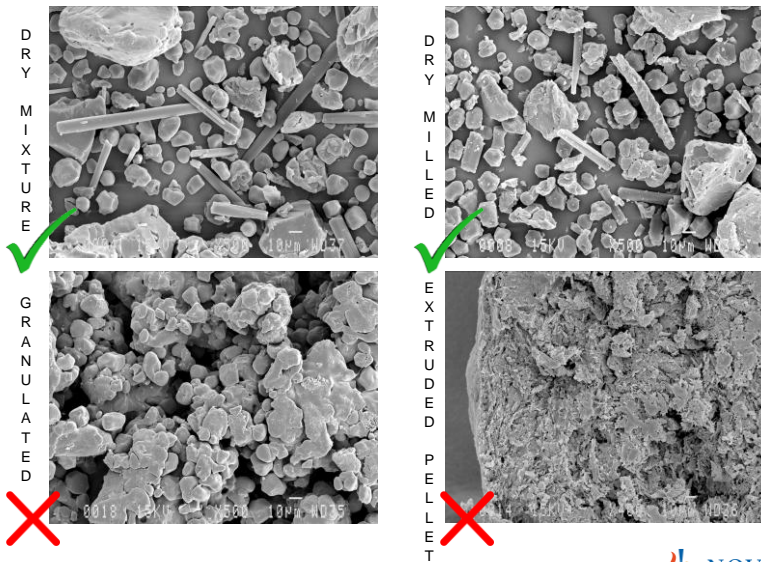
DS...drug substance
MCC...microcrystalline cellulose
ND...none detected
XRPD...X ray powder diffraction

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Drug substance + MCC: SEM



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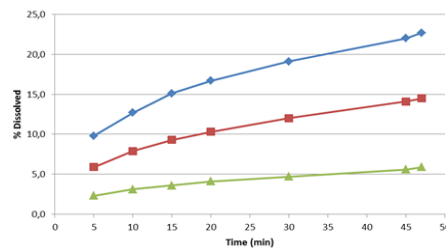
Learnings

- XRPD data was not useful (low dose, partially amorphous API was not detected).
- Compatibility study based on binary mixtures was not indicative of product stability.
- Amorphous DS was chemically stable due to rapid crystallization (physically unstable).
- Drug product inadvertently stabilized the amorphous state (MC „adsorbate“) and thus chemically destabilized the product.
- Solution: drug layering onto placebo pellet with no excipients in drug layer.

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Case study 2: Solid dispersion of DS + HPMC-AS; film coated tablets

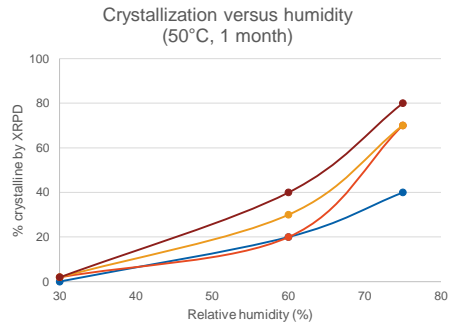


Sample	Degree of DS crystallinity by XRPD	Dissolution rate reduction (relative to sample A)
A	Amorphous	0
B	20 %	35
C	40 %	74

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Stability data

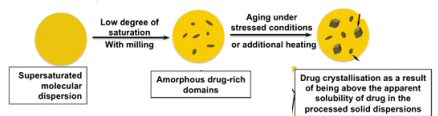


- Humidity is a key driver of instability
- High drug loading decreases stability
- High temperature significantly accelerates crystallization ($E_a > 200\text{kJ/mol}$): an increase in 10°C can accelerate crystallization onset by $> 20\text{ x}$
- If 50°C 1 month or 40°C 3 months pass \rightarrow low risk for long term stability failure (low humidity)

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Prediction of crystallization onset is difficult



Credit: <https://doi.org/10.1007/s11095-018-2408-3>

Classical stability (timed pull-points): many time-points are required to capture crystallization onset

Solution: continous stability monitoring (TAM, HT-XRPD)

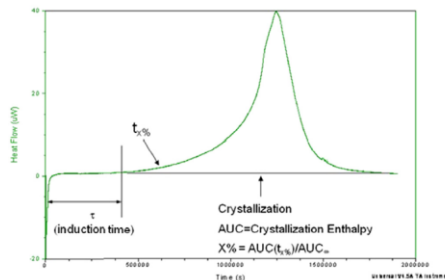


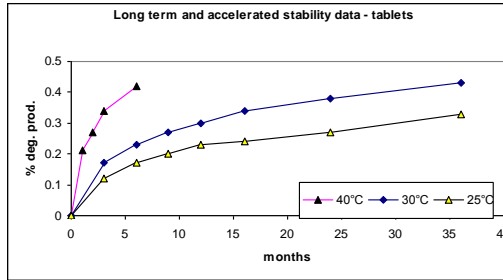
Figure 1. Representative TAM thermal trace.

Credit: <http://dx.doi.org/10.1016/j.xphs.2016.03.029>

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Case study 3: chemical stability



Pressure sensitive API, stability depends on compression force during tableting

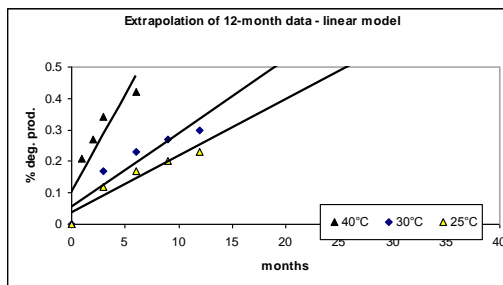
Package = cold form foil, water remains constant

Curvature in stability data plot

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Linear extrapolation

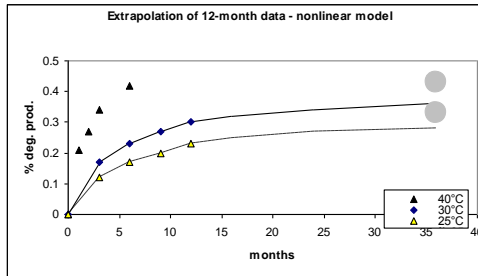


Linear extrapolation:
 $R^2=0.90$
Prediction: through the roof

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Nonlinear extrapolation



$$y = \frac{x}{ax + b}$$

a=shape parameter

(1/a = ceiling value)

b=rate parameter

(1/b = initial rate)

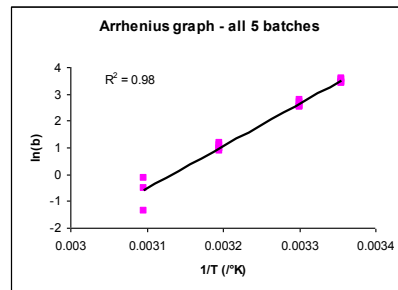
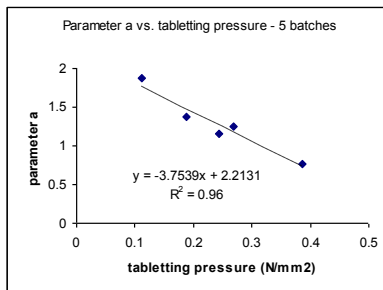
Accelerated data provided critical curve shape information. This information was not revealed in earlier forced degradation data (not enough data points)

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Metamodel

$$k = Ae^{-E_a/RT} \quad y = \frac{x}{ax + b}$$



a=shape parameter (1/a = ceiling value)

Independent of temperature, strongly dependent on tableting pressure.

Theoretical interpretation: degree of amorphization during compression

b=rate parameter (1/b = initial rate)

Temperature dependent, Arrhenius behaviour

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Prediction based on metamodel

Five batches of data altogether (four strengths)

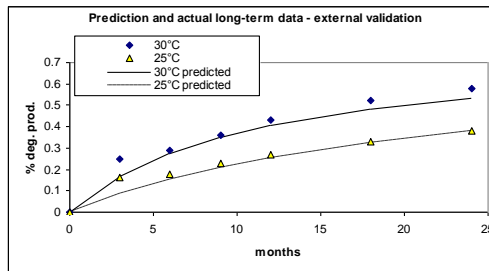
Four batches were used in model calibration, remaining batch for prediction **Inputs:**

→ metaparameters E_a and A to predict rate parameter b

→ Tableting pressure to predict shape parameter a

Outputs:

→ % degradant at any given time and temperature



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Ultimate goal

Have a stability prediction on amorphous → crystalline conversion (time of onset),

without the need for stability studies,

but instead based on measure-able properties of solid dispersion such as:

T_g , solubility parameters, humidity, DSC events, enthalpy relaxation and fragility parameters, molecular mobility etc.



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