Laminar Dispersive and Distributive Mixing with Dissolution and Applications to Hot Melt Extrusion (HME)

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Oral drug delivery products

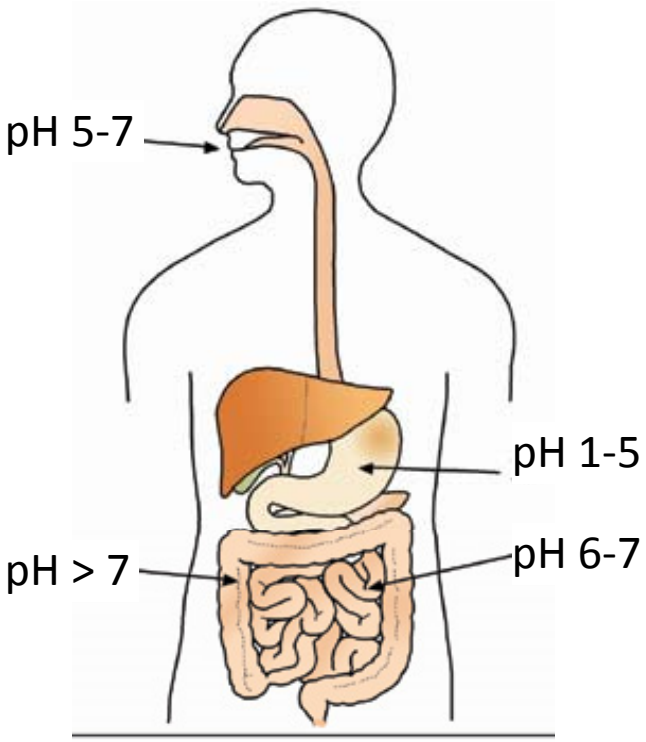


Figure adapted from: Rocca J. et al. (2004). Drug Delivery Technology **4**

For the API to be **Bio-available** it must **necessarily dissolve in the GI tract** (stomach or Small Intestines)

API Solubility and Permeability

High Ionic and H-bonding capability

⇓

High Solubility in the GI Tract

High Lipophilicity (Hydrophobicity)

⇓

High permeability to get to the blood stream

Bio-availability (high API concentration in blood stream)

⇓

Bio-availability = (Solubility) X (Permeability)

Oral Drug Delivery Products (tablets, capsules..)

ACTIVE PHARMACEUTICAL INGREDIENT (API) = Ibuprophen

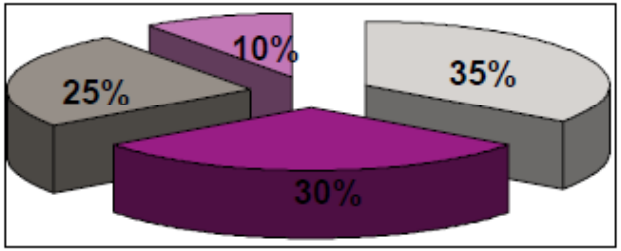
(water soluble)

INACTIVE (EXCIPIENT) INGREDIENTS (binders/additives)

What if the API were Very Poorly Water soluble?..

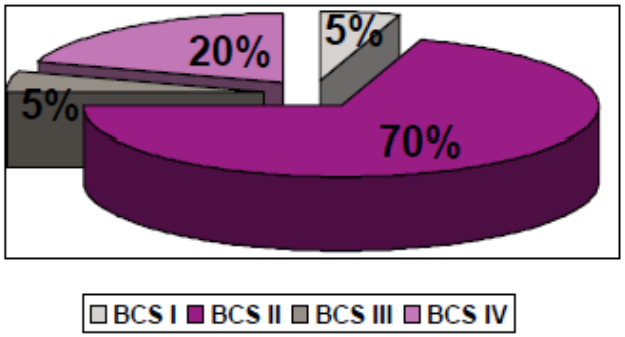
Need for Solubility Enhancement

Marketed drugs



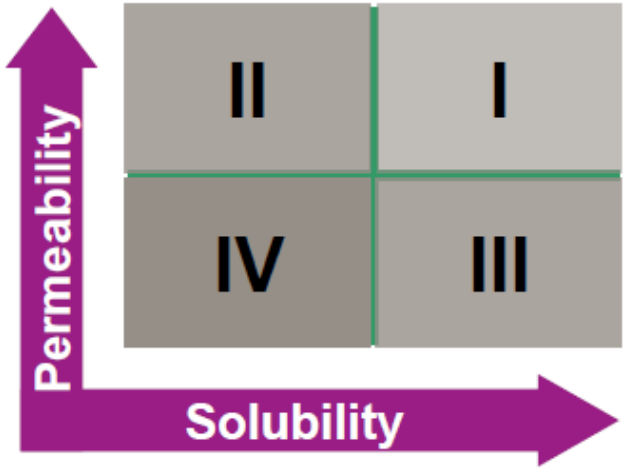
Number of poorly soluble drugs is increasing!

New Chemical Entities



From: Benet L. Wu C.-Y. et al 2006, Bulletin Technique Gattefosse 99:9-16

Biopharmaceutical Classification System



Class I:	High solubility and high Permeability
Class II:	**Low solubility and high Permeability**
Class III:	High solubility and low Permeability
Class IV:	Low solubility and low Permeability

Pharmaceutical
Hot Melt Extrusion (HME) Holds the Potential of Dramatically Increasing API Solubility

Polymer API

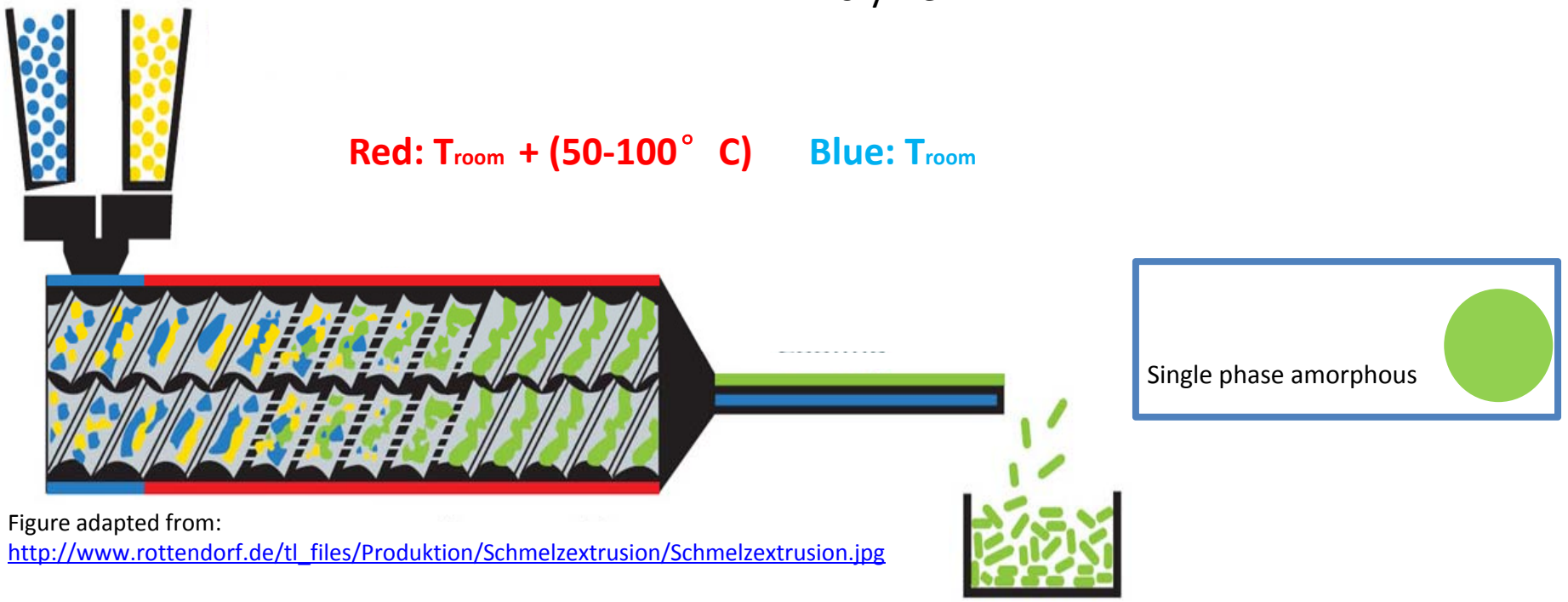
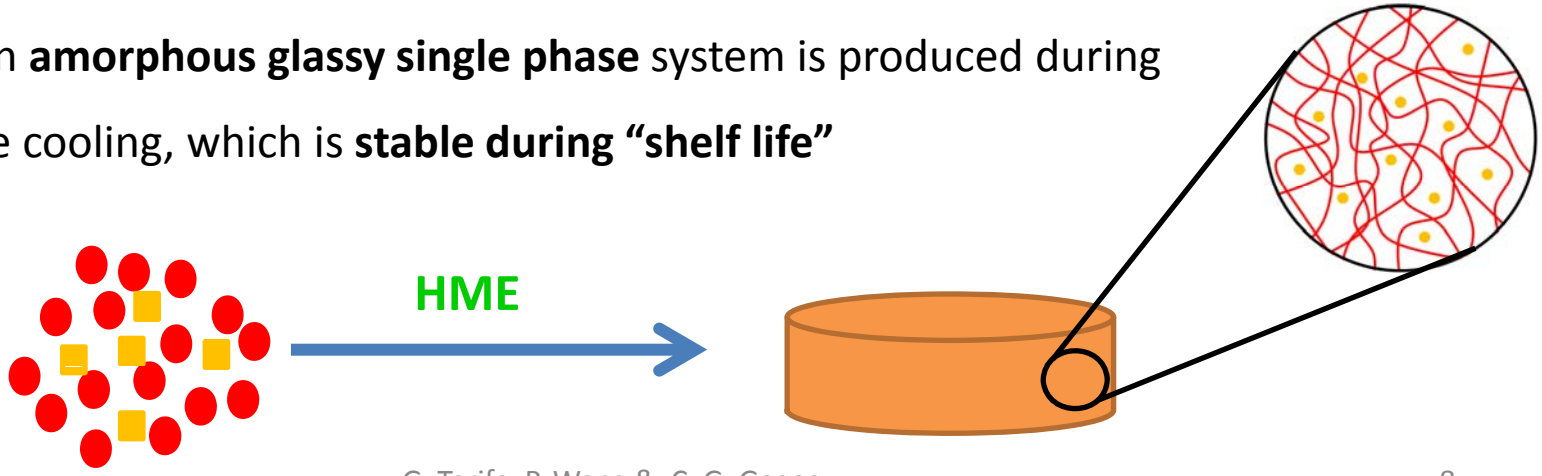


Figure adapted from:
http://www.rottendorf.de/tl_files/Produktion/Schmelzextrusion/Schmelzextrusion.jpg

Why Does HME Result in a Dramatic Increase in API Solubility?

- **A poorly soluble API and hydrophilic Polymer Excipient** are extruded, much like in an extrusion **compounding** process
- **Process Conditions**: $T_{m,API} > T_{process} > T_g + (50\sim100°C)$ and $t_{res} = 60 – 200s$
- The API, **with enhanced solubility at the elevated $T_{process}$** dissolves in the molten polymer **forming a homogenous solution**
- Ideally, an **amorphous glassy single phase** system is produced during extrudate cooling, which is **stable during "shelf life"**

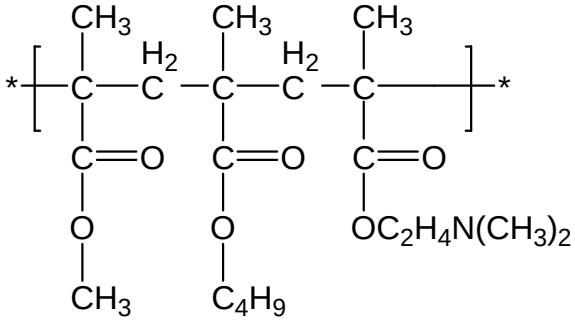


Example: H M Batch Mixing

$T_{m,\ API} > T_{process} > T_g + (50\sim100°C)$

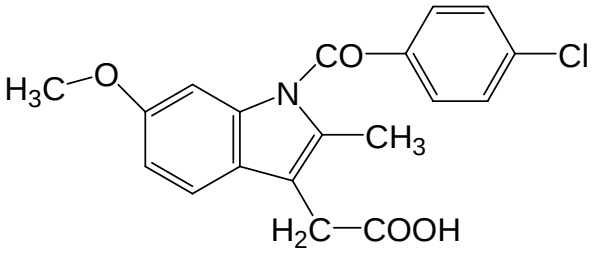
Eudragit™ E PO : Indomethacin
(70 : 30)

Run #	Process Temperature (°C)	rpm	Sampling Time
1	100	20	55, 100, 145 285 420
2	100	100	
3	110	20	
4	110	100	
5	140	20	



Eudragit ™ E PO (E PO)

T_g= 48 °C



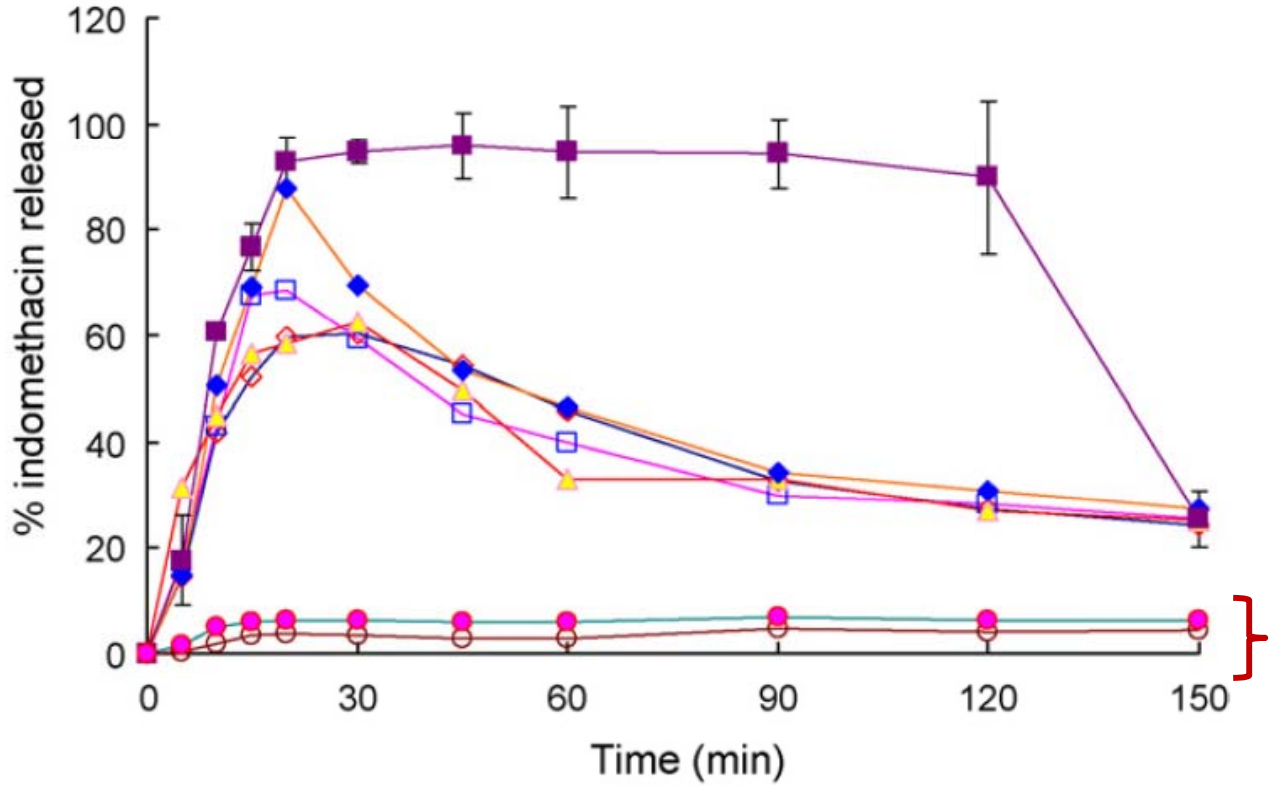
Indomethacin (INM)

T_m= 162 °C

Batch Mixer

Dramatic Increase of API solubility

H M Batch-mixed INM and Eudragit™ EPO.



Crystalline API (INM)
(pure & physical mixture)

Fig. 9. Dissolution profiles in pH 1.2 buffer solution of runs at: (○) 100% INM; (●) physical mixture; (◊) 100 °C 20 rpm; (△) 110 °C 20 rpm; (□) 100 °C 100 rpm; (♦) 110 °C 100 rpm; (■) 140 °C 20 rpm.

From H. Liu et al. Int. J. of Pharm., **383** 161 (2010).

Polymer Excipients Used in Oral Drug Delivery

	Soluble in all pH	pH-dependent Soluble Polymers	Swellable
Low T_g **Shelf life Stability?**	• Polyethylene Glycol • Polaxamer • Soluplus	• Polymethacrylates - Eudragit E - Eudragit L & S • Polyvinyl Acetate Phthalate	• Polymethacrylates - Eudragit N - Eudragit RL & RS
High T_g **API Degradation During HME?**	• Povidone • Copovidone • Hydroxypropyl cellulose • Hypromellose	• Hypromellose Phthalate. • Hypromellose Succiyl Acetate • Cellulose Acetate Phthalate	• Ethycellulose • Cellulose acetate

Pharmaceutical HMR Process Objectives

API dissolved in hydrophilic polymer

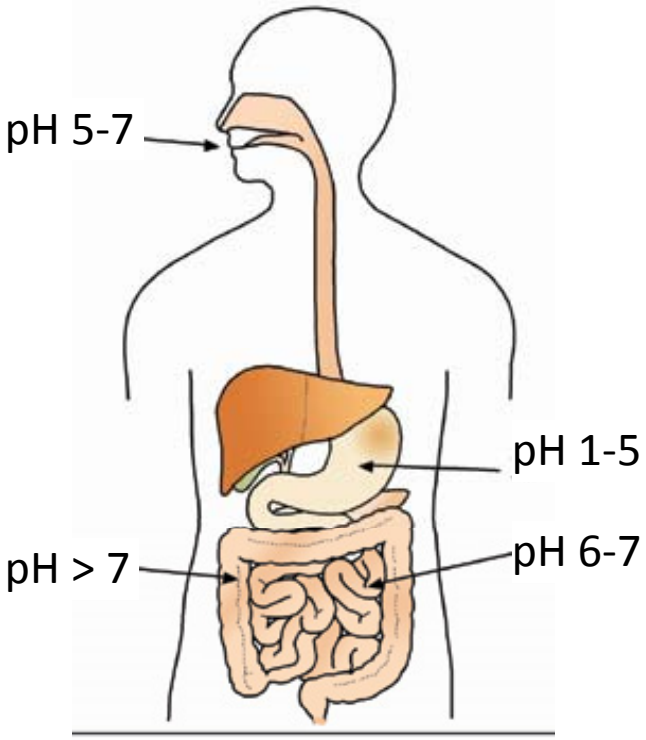
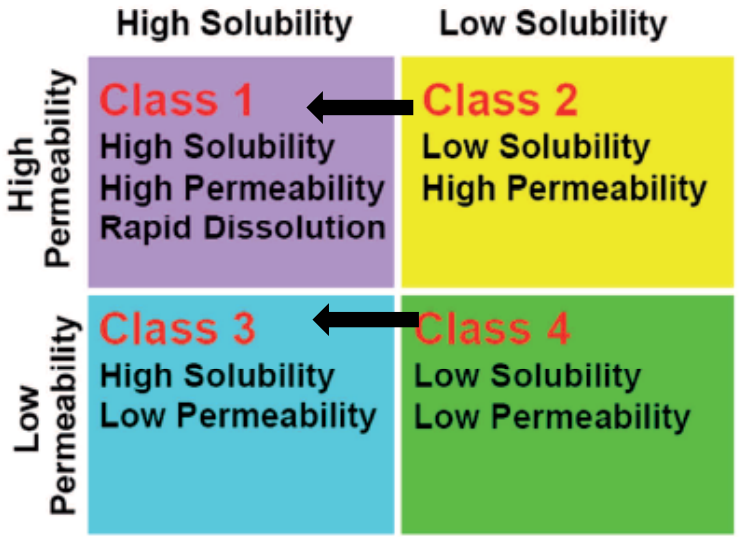
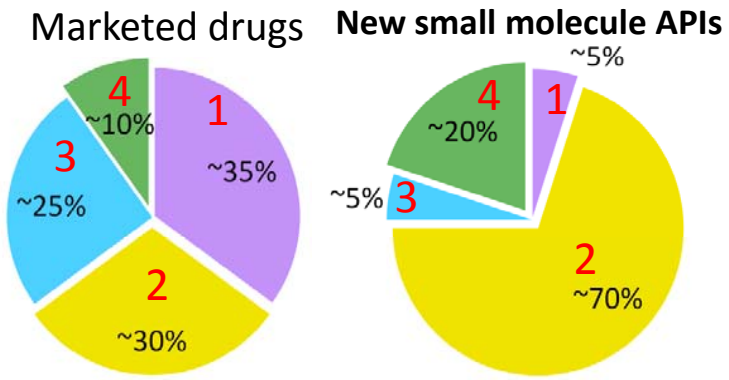


Figure adapted from: Rocca J. et al. (2004). Drug Delivery Technology **4**

Biopharmaceutical classification system **(BCS)** for APIs:



Result / objective of HME



Figures adapted from: Benet, L. Z. et al. (2006). Bulletin Technique Gattefassé **99**: 9-16.

Drug delivery systems produced HME

Name	Polymer	Application	Indication
Dapivirine-Maraviroc	EVA	Implant	Anti-Viral (HIV)
Lacrisert®	HPMC	Implant	Dry eye syndrome
Nuvaring	EVA	Implant	Contraceptive
Zoladex	PLGA	Implant	Prostate cancer
Implanon	EVA	Implant	Contraceptive
Ozurdex®	PLGA	Implant	Macular Edema
Kaletra	PVP-VA	Tablet	Anti-Viral (HIV)
Norvir®	PVP-VA	Tablet	Anti-Viral (HIV)
Eucreas®	HPMC	Tablet	Diabetes
~~Zithromax®~~	~~HPMC~~	~~Tablet~~	~~Antibiotic~~
Gris-PEG®	PEG	Tablet	anti-fungal
Rezulin®	Povidone (PVP)	Tablet	Diabetes
PalladoneTM	EC + Eudragit® RS	Tablet	Pain
Cesamet®	Nabilone	Tablet	
~~Posaconazole~~			~~Anti-fungal~~
Anacetrapib			Cardiovascular disease

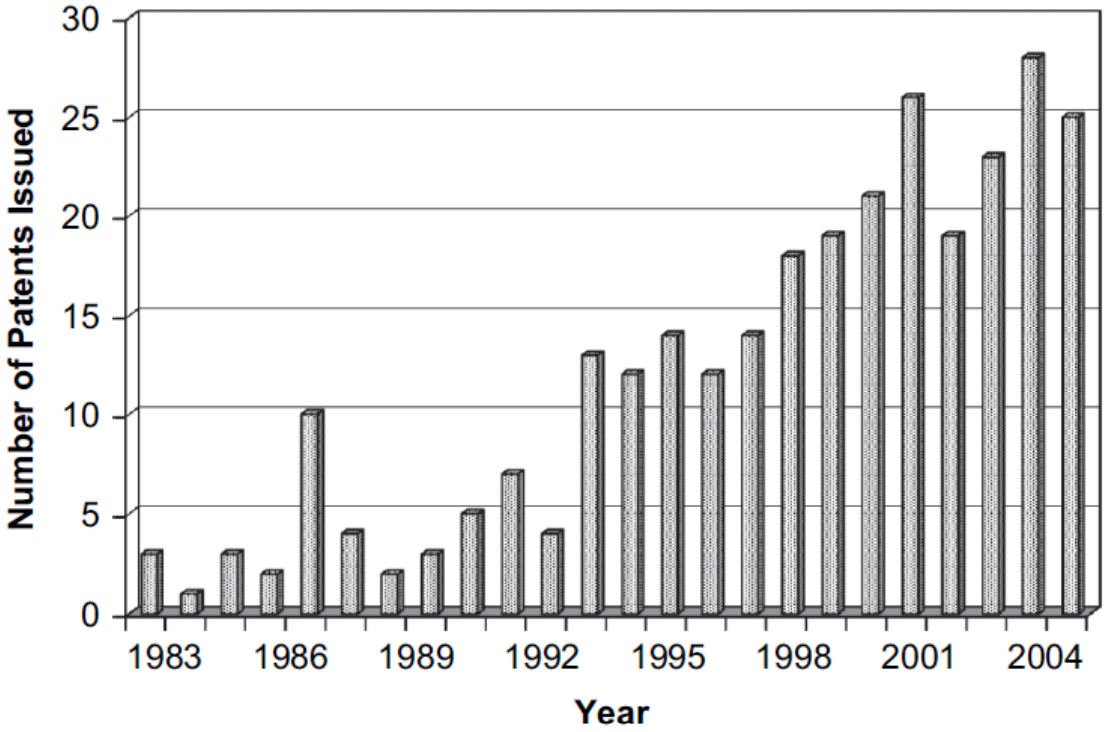
Withdraw from the market

Marketed

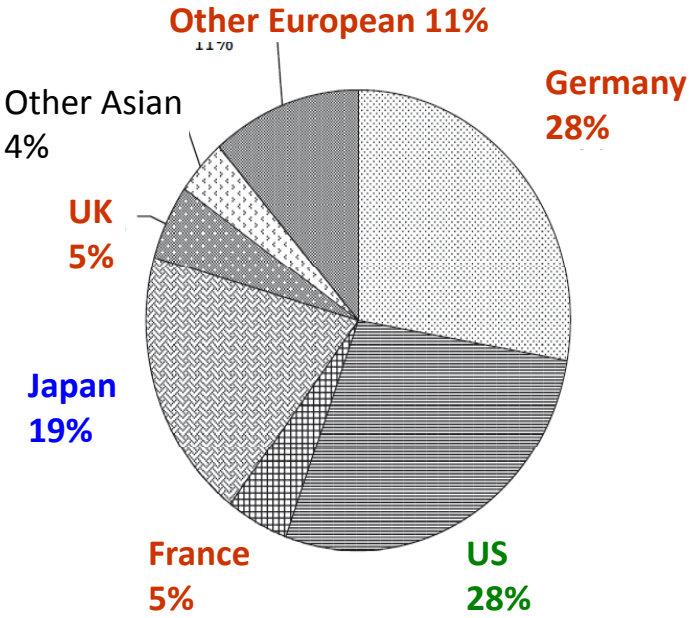
Under development

HME patents from 1983 to 2006

Number of HME patents issued for pharmaceutical applications



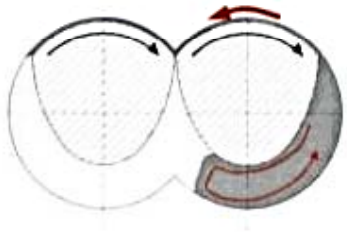
World distribution of issued HME patents



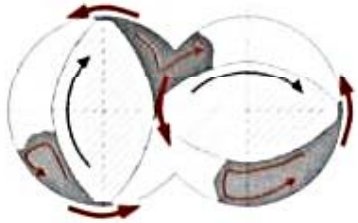
Figures adapted from: Crowley, M.M. et. al. (2007). Drug Dev. Ind. Pharm. **33**, 909-926.

The Leistritz Pharma Nano 16 at NJIT/PPI

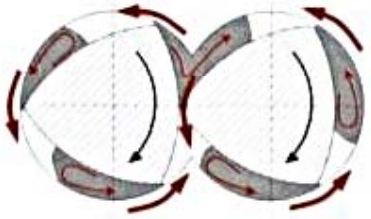
Figure taken from: http://www.alec-usa.com/tsrpt0210.htm



Single-flighted: 1 partial



Double-flighted: 3 partial

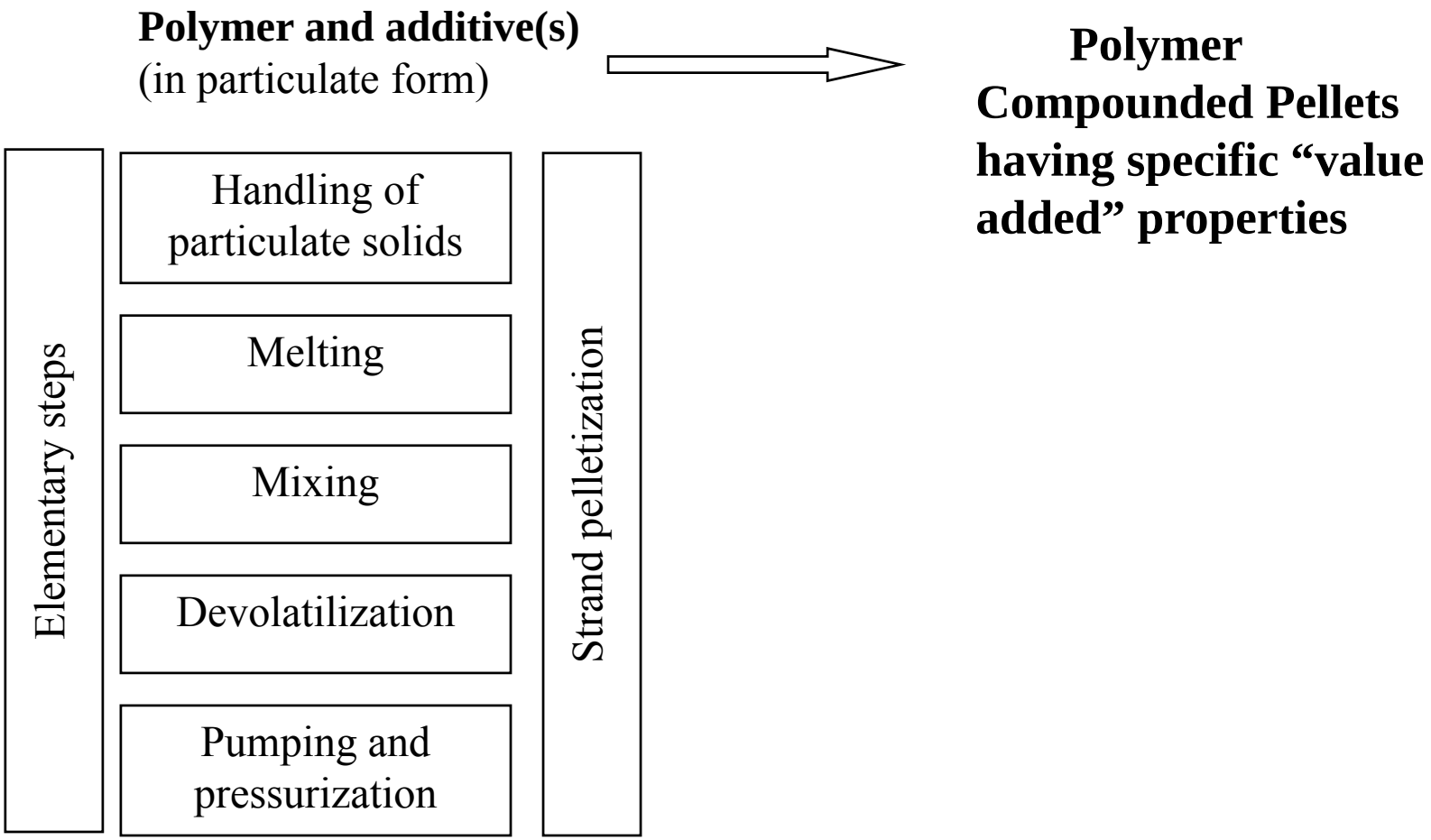


Triple-flighted: 5 partial

Figures adapted from K. Kohlgrüber (2008)

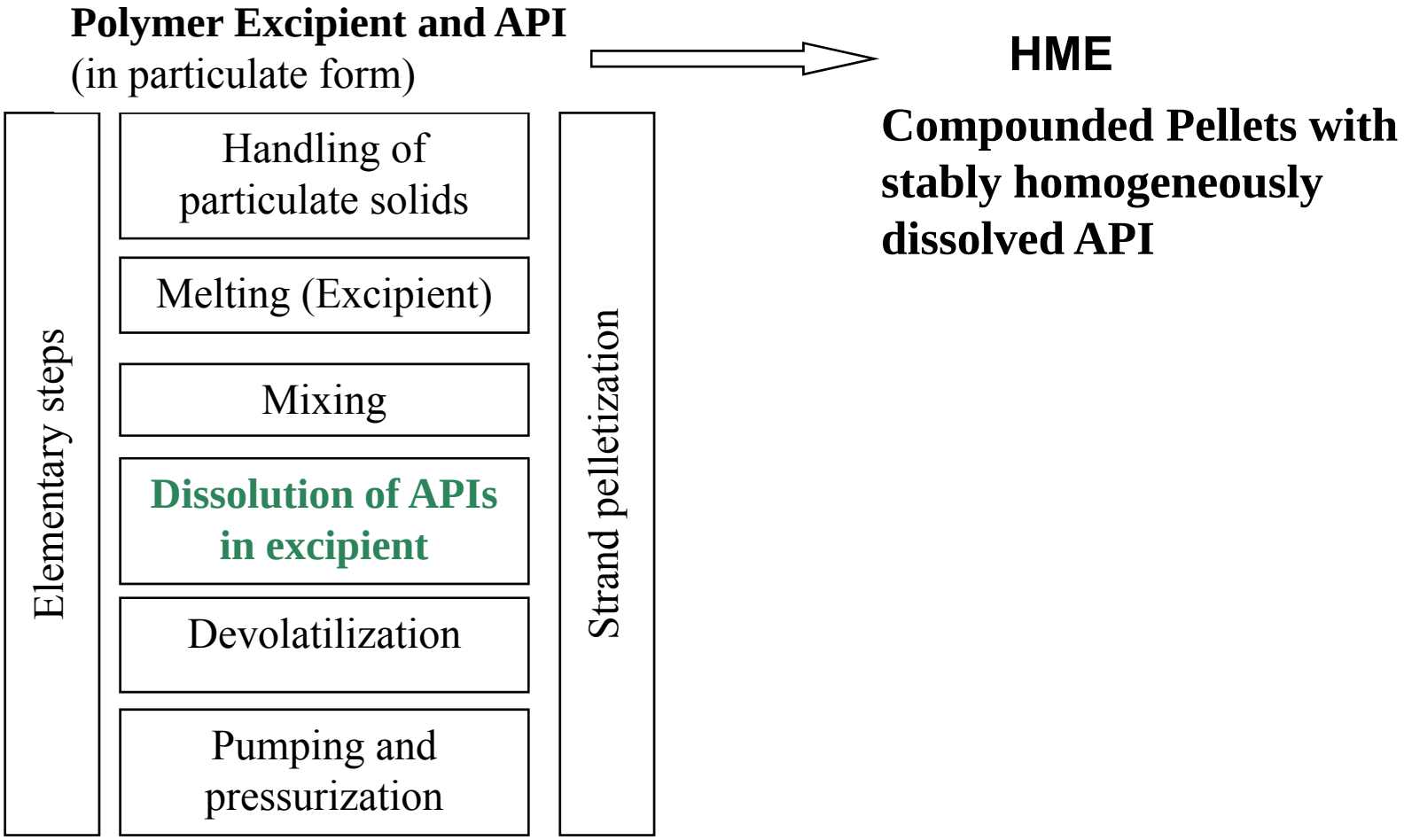
- **Co-rotating , Self-wiping TSE.**
- **Very small "Tri-lobal" free volume.**
- **Micro-plunger allows to work with small batches of 20-100g.**

Elementary Steps of Polymer Compounding



Tadmor and Gogos, *Principles of Polymer Processing, 2nd Ed (2006)*

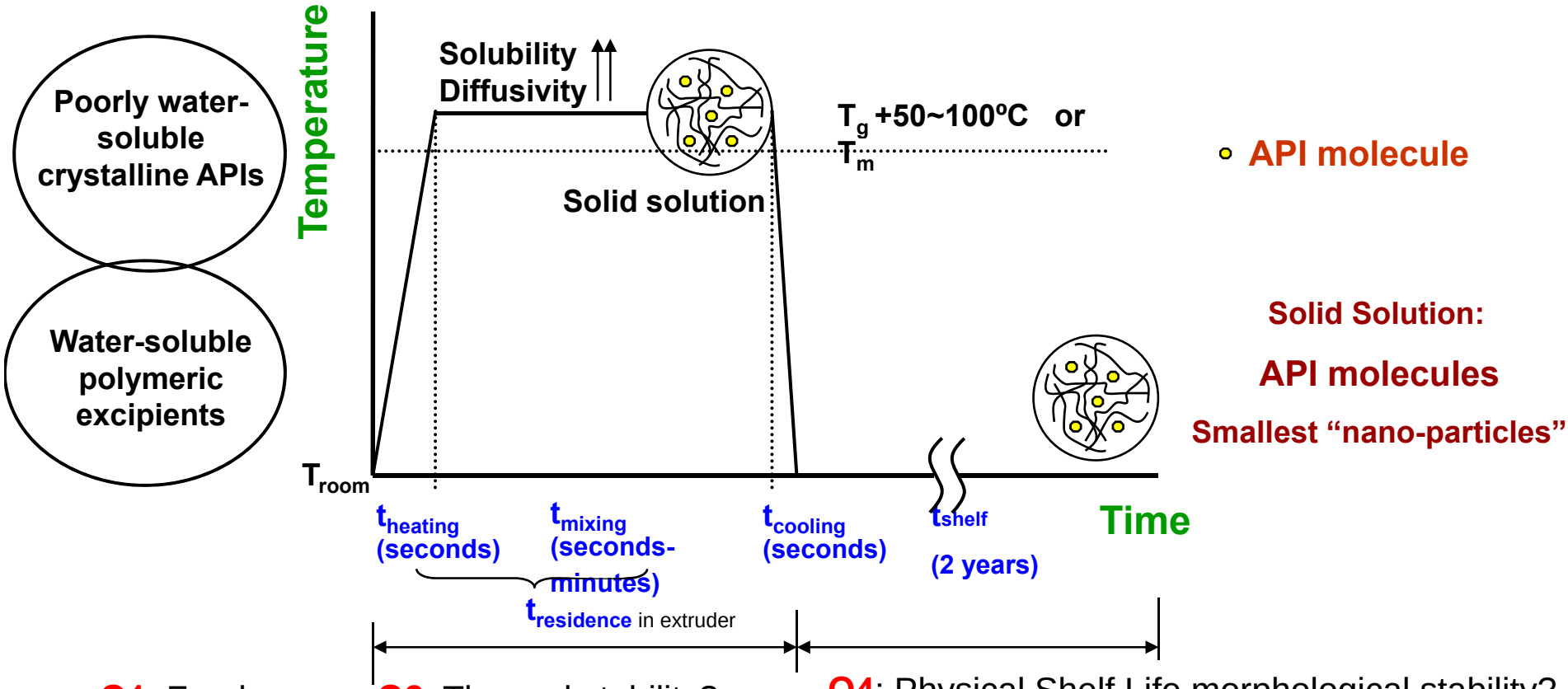
Elementary Steps of Pharmaceutical Hot Melt Extrusion Processes



Gogos and Liu, 2011

The HME Process

Thermo-mechanical History and Fundamental Process Issues



Q1: Feed homogeneity?

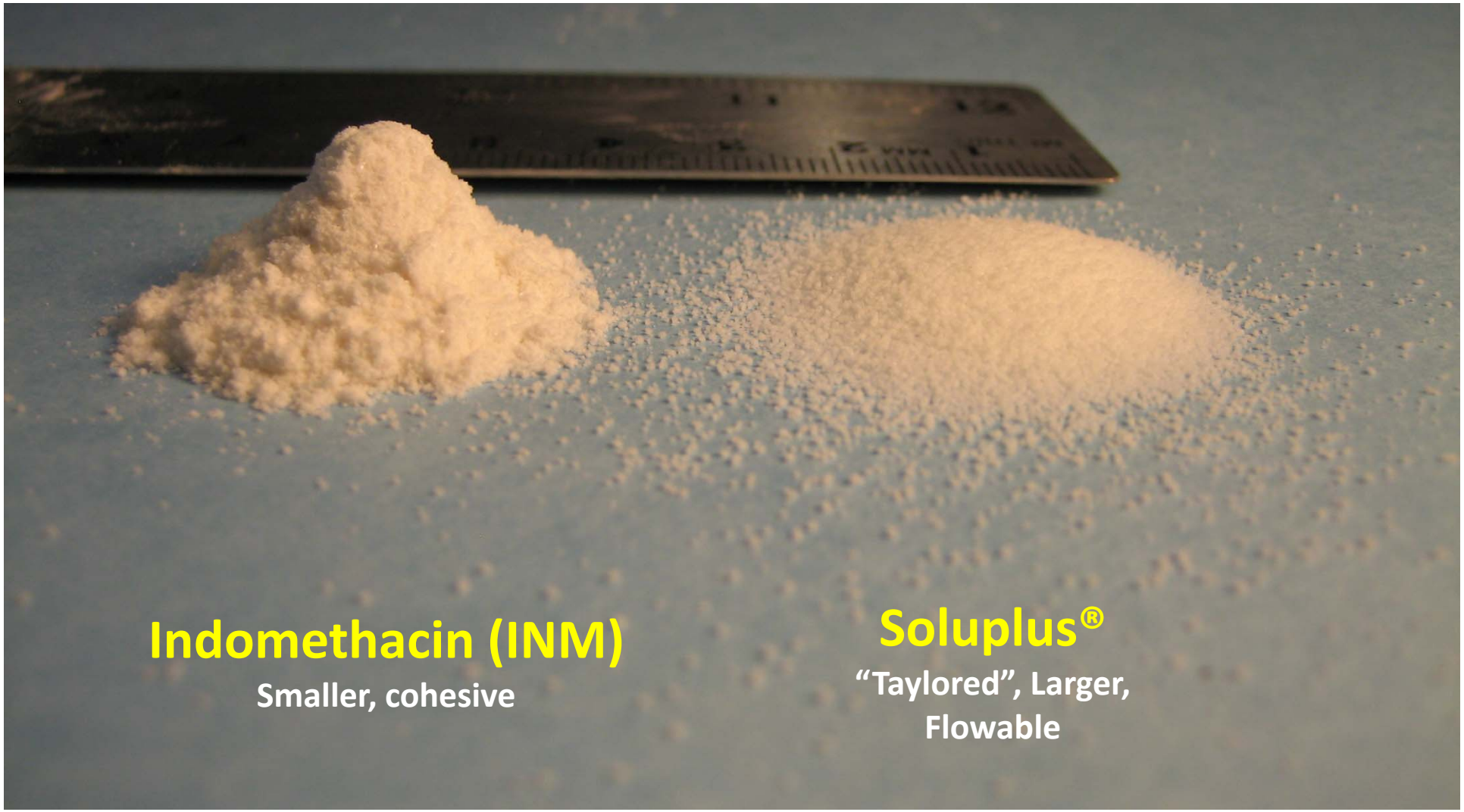
Q2: Thermal stability?

Q3: Attainment of solid dispersions?

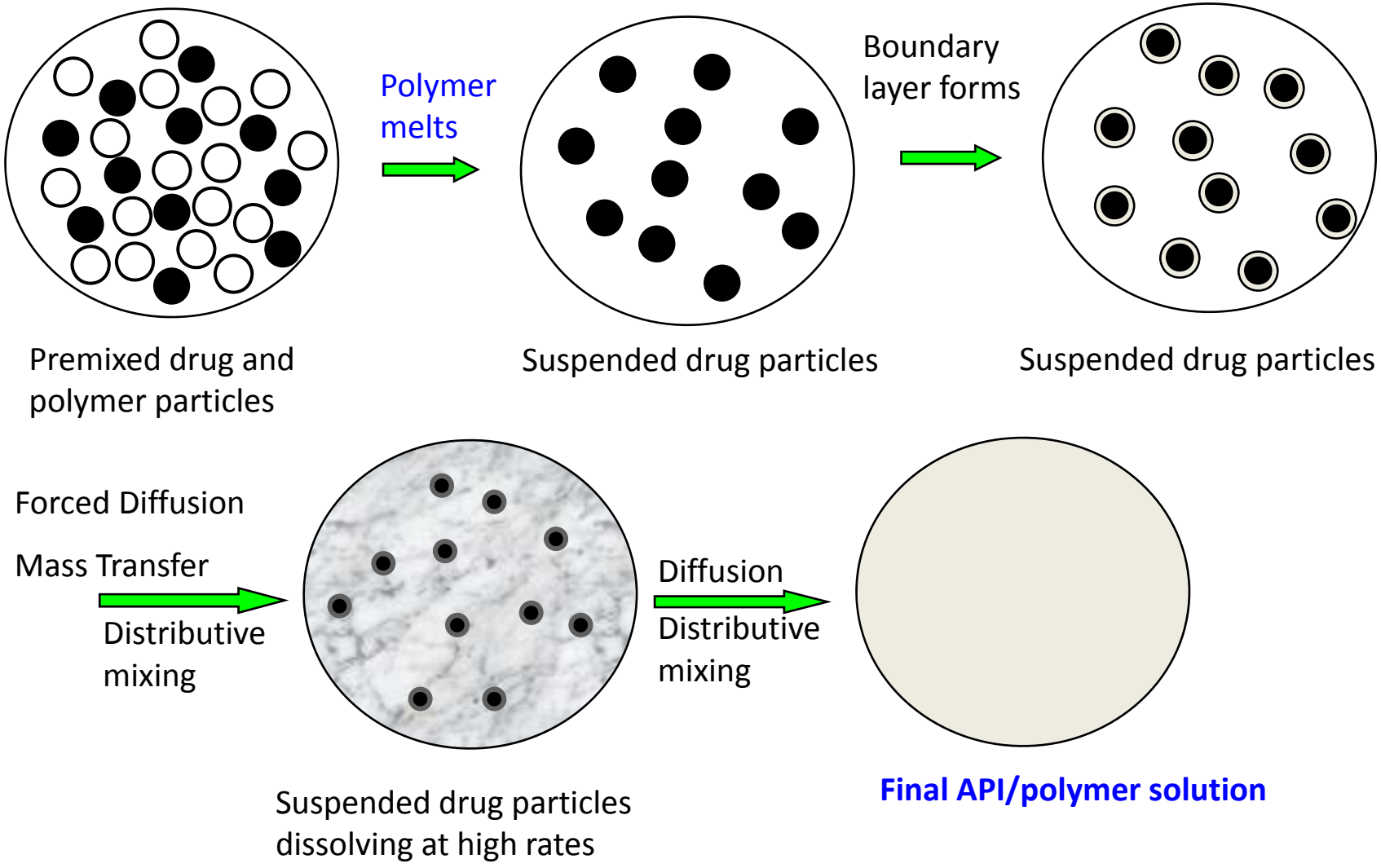
Q4: Physical Shelf Life morphological stability?

Gogos and Liu 2011

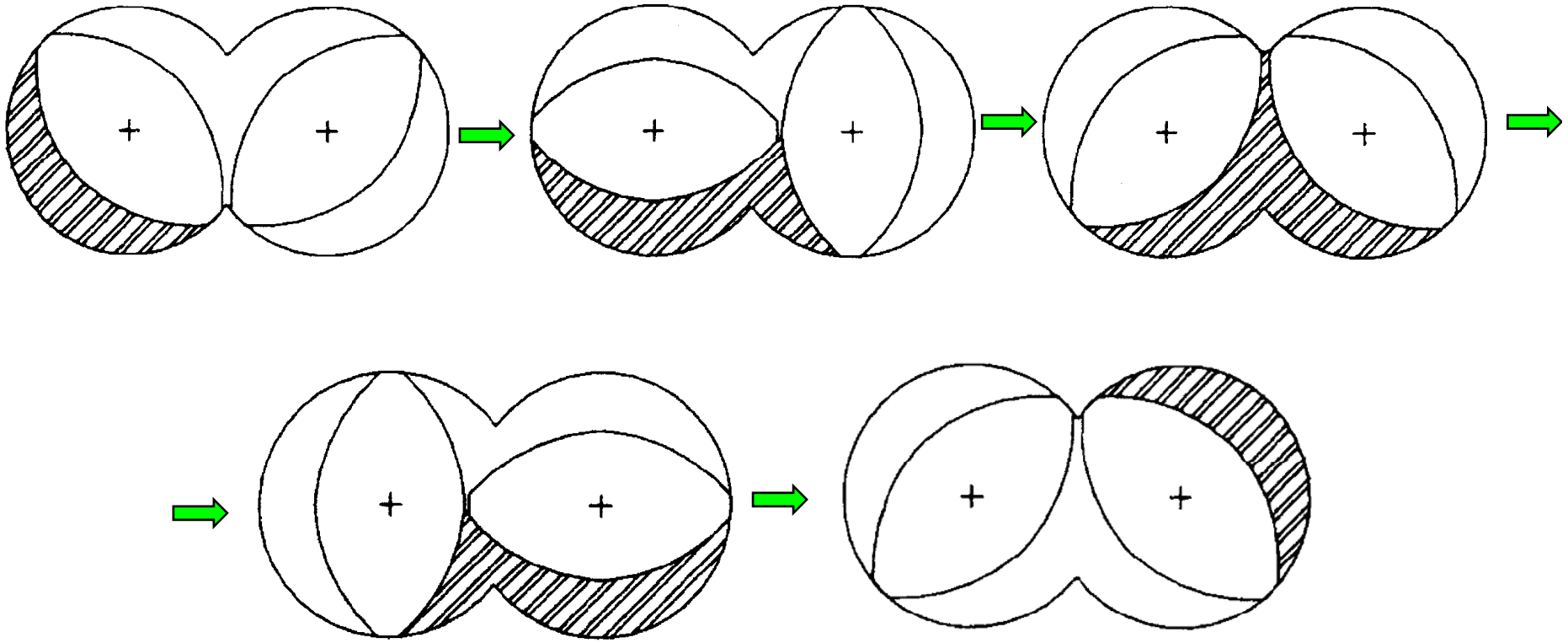
Particulates Handling: Dissimilar Flowabilities of APIs and Polymer Excipients



$T_{processing} > T_g + (50\sim100\ ^oC)$; $T_{process} < T_{m,\ API}$



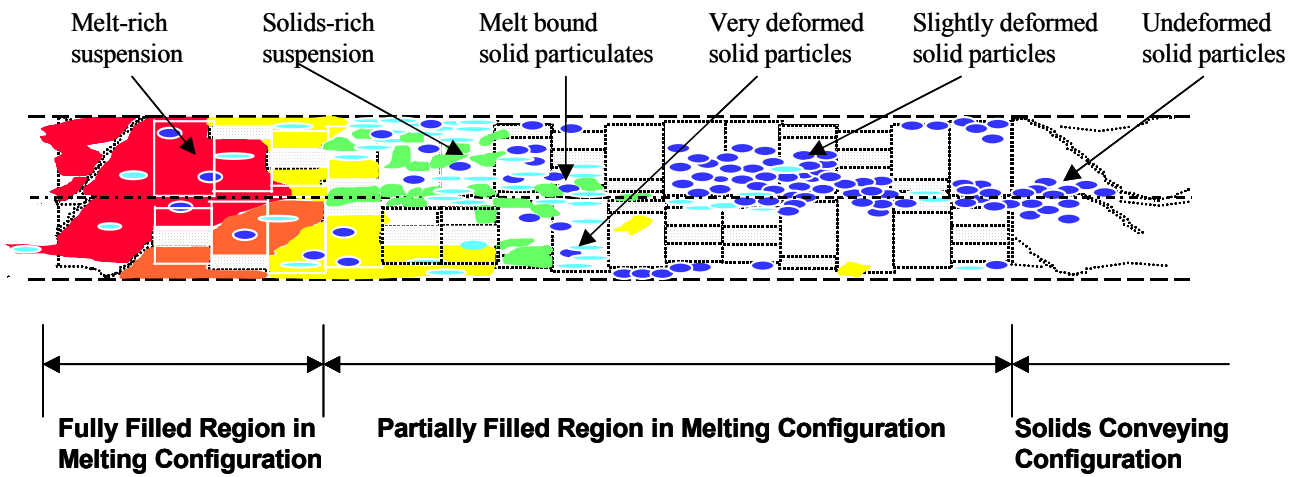
Repeated Expansion/Contraction Deformations
in FULL [F/R] Kneading Elements



Result in Rapid and Space-wise Uniform Melting and Mixing

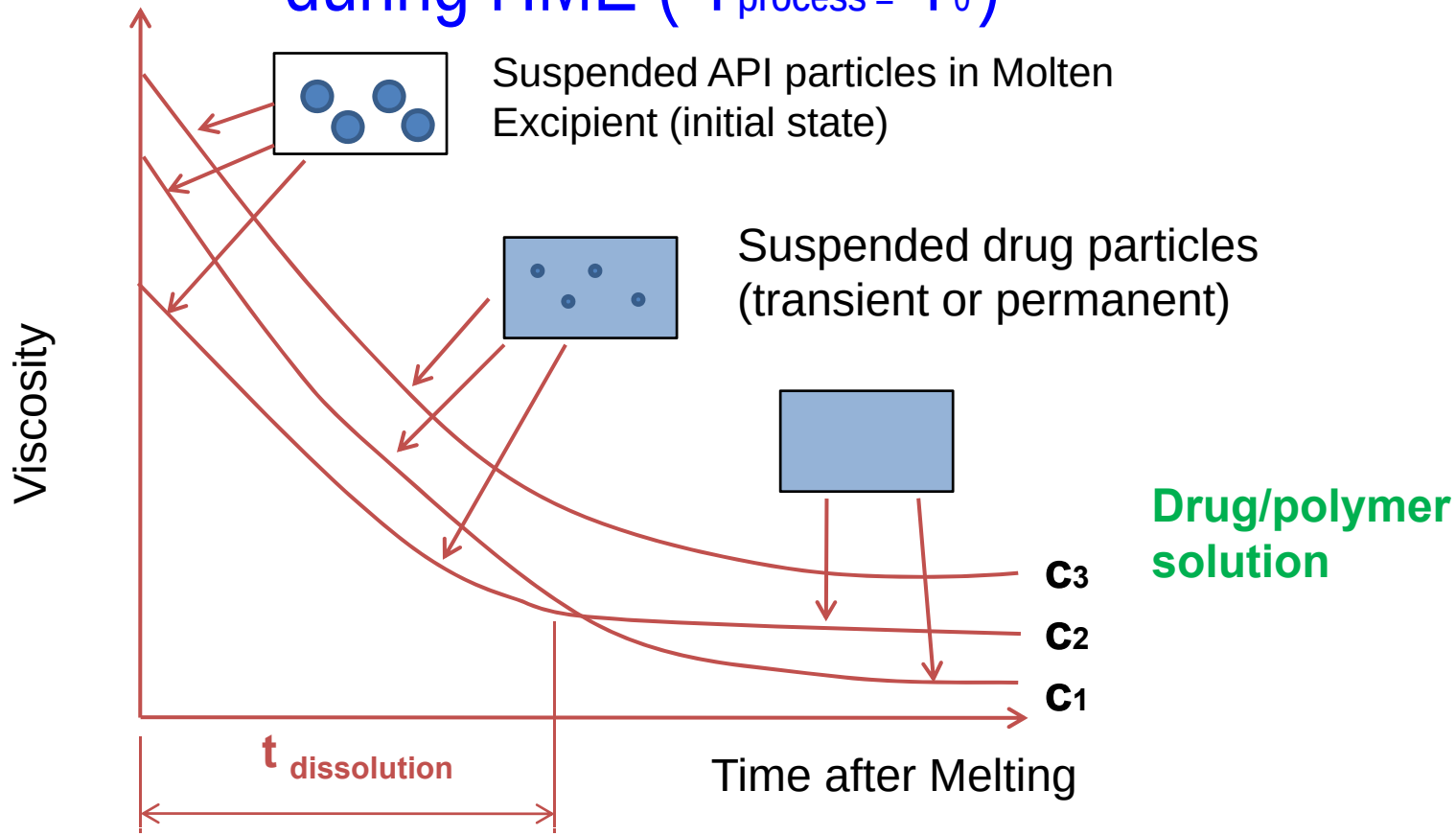
Tadmor and Gogos *Principles of Polymer Processing 2nd Ed* (2006)

Melting Mechanism in Co-rotating Twin Screw Extruders

				"States" of the Stream Schematic Representation Co-TSE Screw Configuration
VED	PED VED (DMM)	PED	Conduction	Melting Mechanisms (Pellets)
VED	PED VED (DMM)	PED	Conduction	Melting Mechanisms (Powder)

Tadmor and Gogos, *Principles of Polymer Processing, 2nd Ed (2006)*

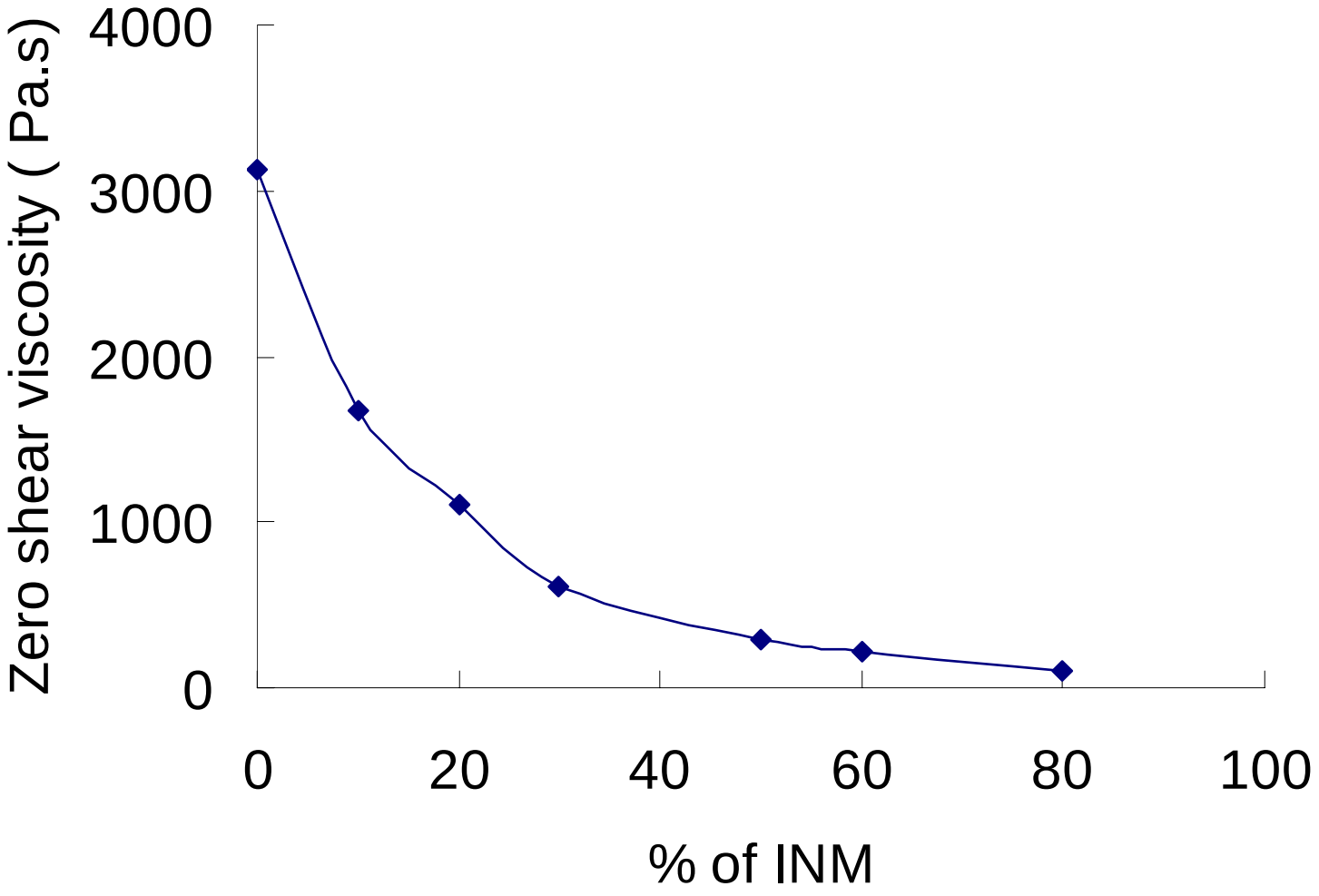
Evolution of API Particulates Suspension and Dissolution during HME ($T_{process} = T_0$)



$c_1 < c_2 < c_3$

$c_1 <$ solubility @ $T_0 < c_3$

Zero shear viscosity vs. INM% in Eudragit™ EPO at 145°C (Strong Intermolecular Forces)



- **Amorphous solid solutions** → ↑ API Apparent solubility → Higher free energy; No lattice energy

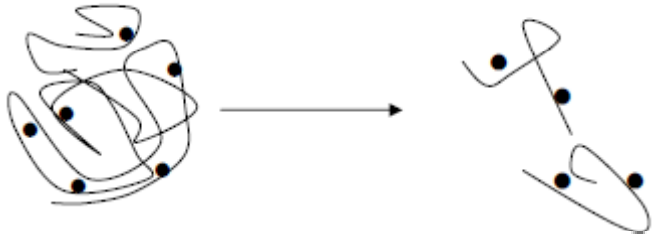


Figure adapted from: 2009 Evonik HME workshop

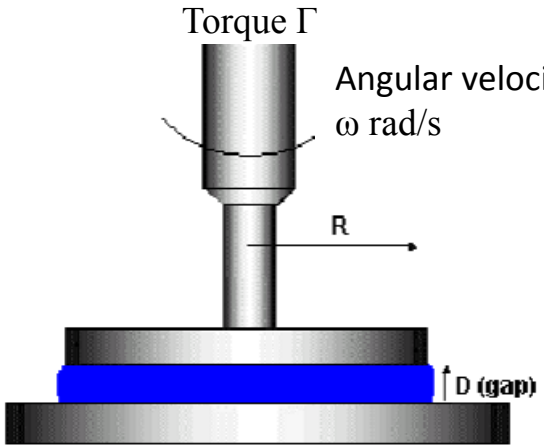
- **Stability of the amorphous state** → Reduce mobility $T_g >> T_{storage}$; Polymer-API Specific interactions

↑ Strength

Type of bond	Bond energy [kJ/mol]
Ionic bonds	600-1500
Hydrogen bonds	35- 51
Dipole-Dipole	up to 10

HME Processing Temperature Solubility Determination Using RMS Rheometry

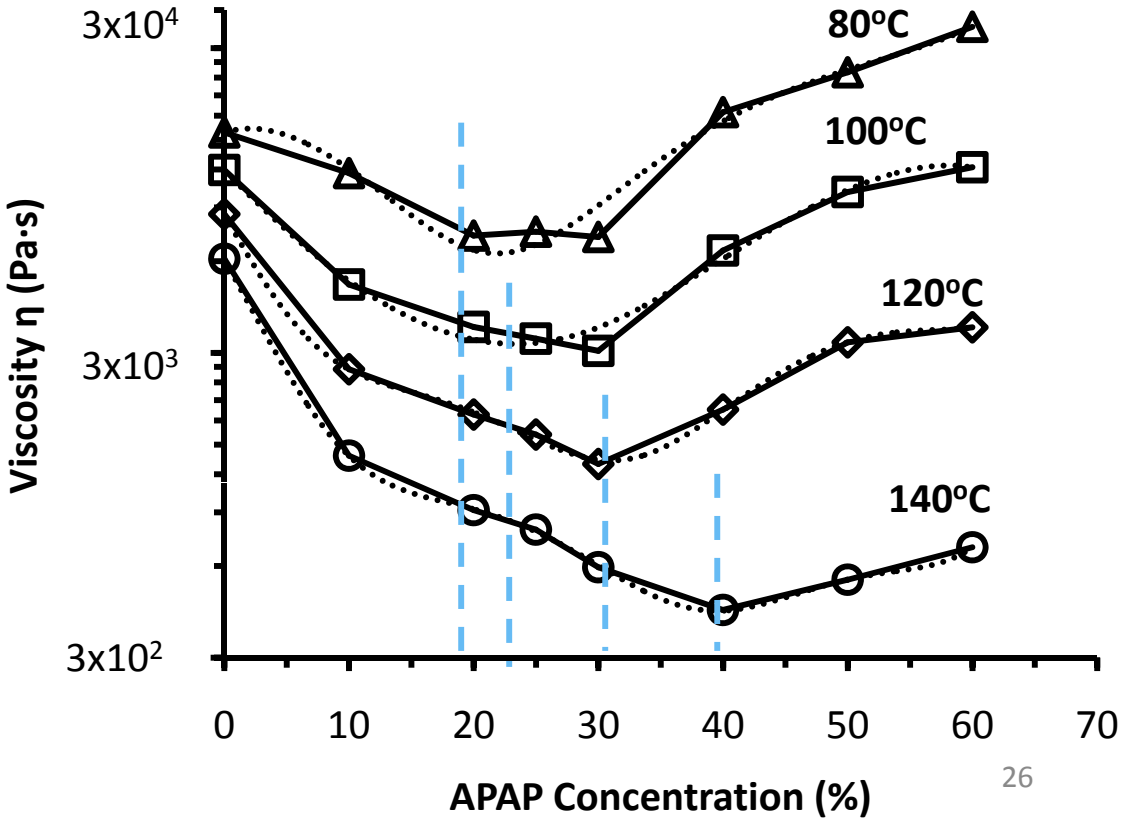
$$\eta = \tau / \dot{\gamma}$$



$$\dot{\gamma} = \frac{R}{D}\omega \qquad \tau = \frac{2}{\pi R^3}\Gamma$$

Shear rate Shear stress

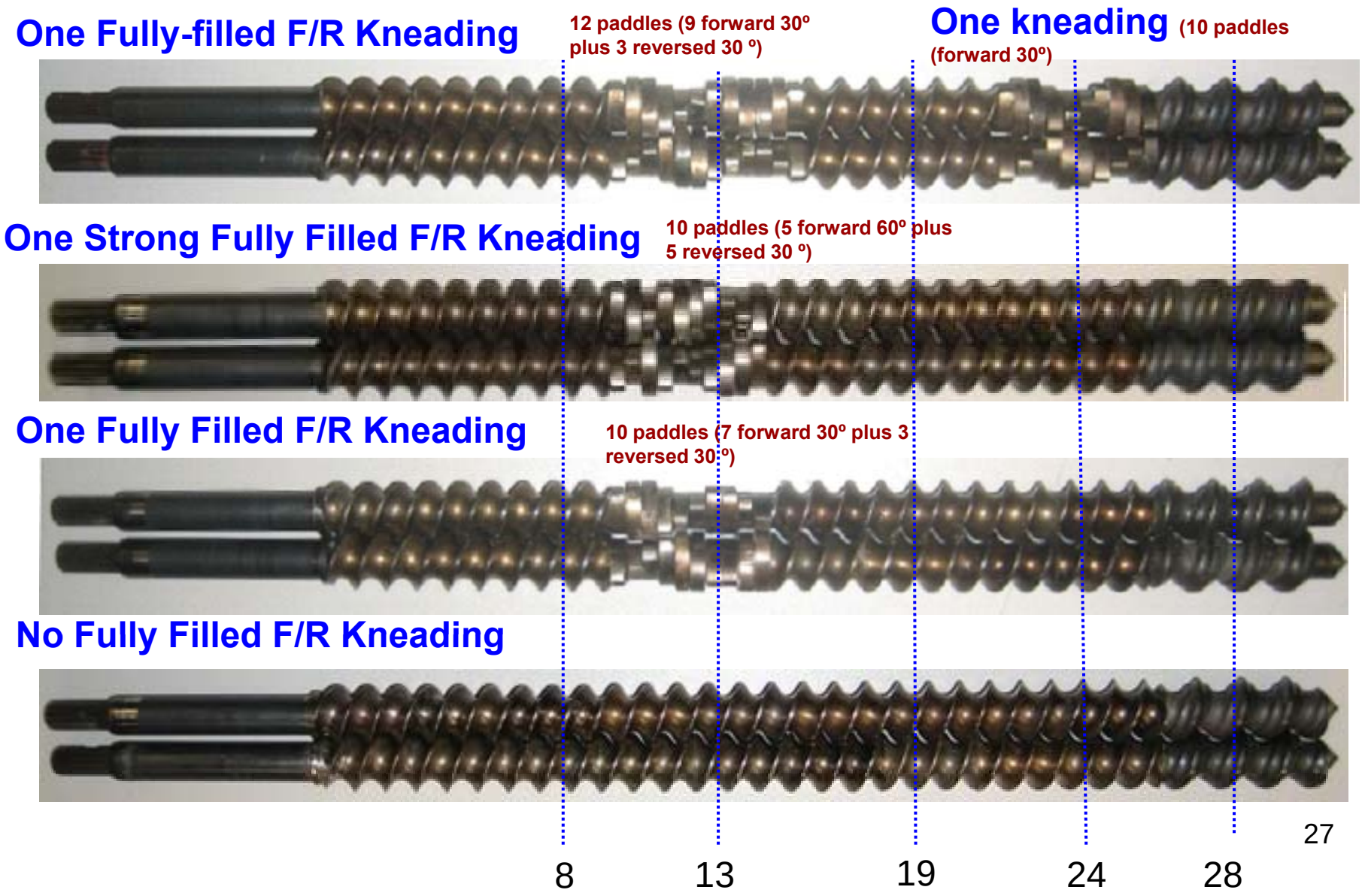
- η decreases indicating drug dissolution induced plasticization
- η increases due to the formation of API particle /molten polymer "suspension" formation



T_m (APAP) 170 °C
T_m (PEO) 62 °C

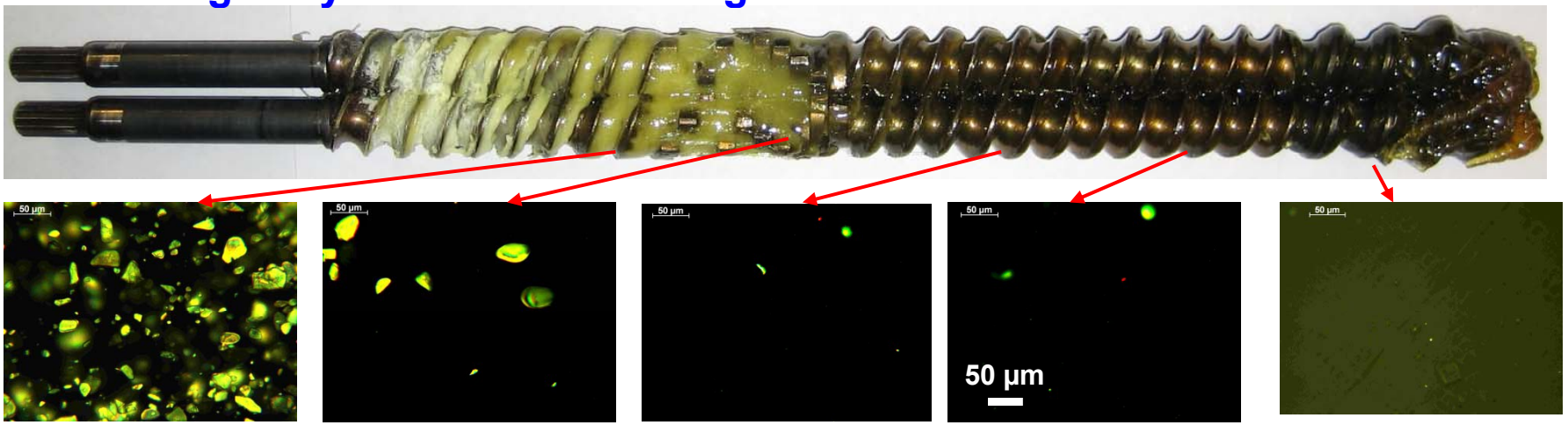
M. Yang et al 2010

B. TSE: Effects of Screw Configuration on the Dissolution of Indomethacin in Eudragit® E PO (E PO:INM=70:30)

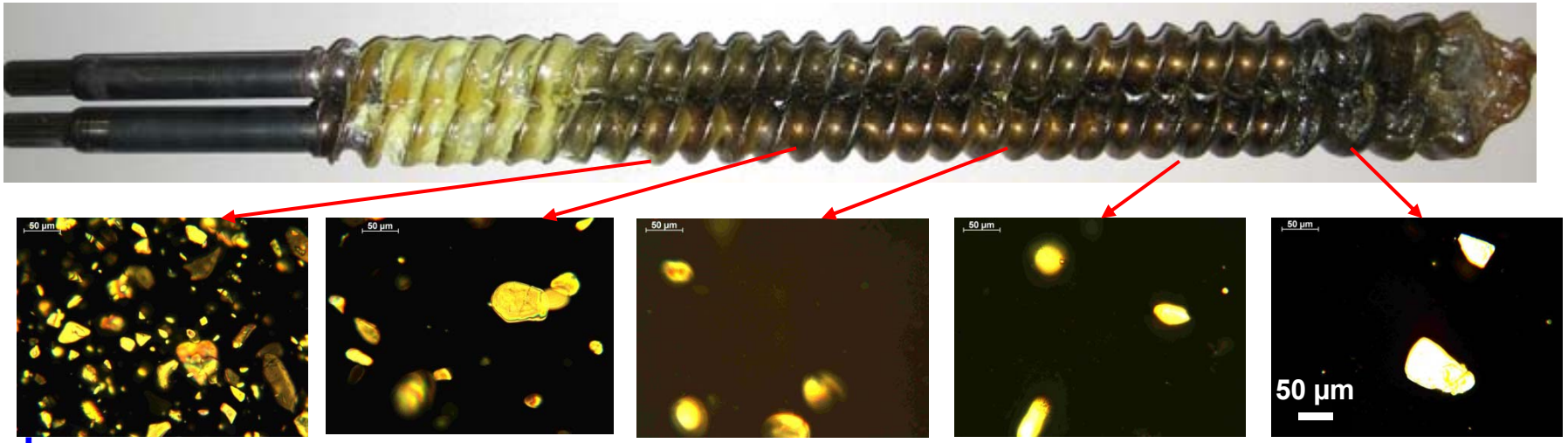


Morphology Evolution (140 ºC 50rpm 0.2kg/hr)

One Strong Fully Filled F/R Kneading



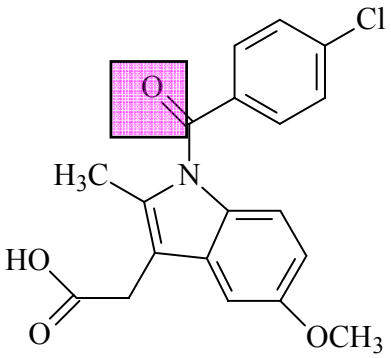
No Fully Filled F/R Kneading



Lobe no.	8	13	19	24	28

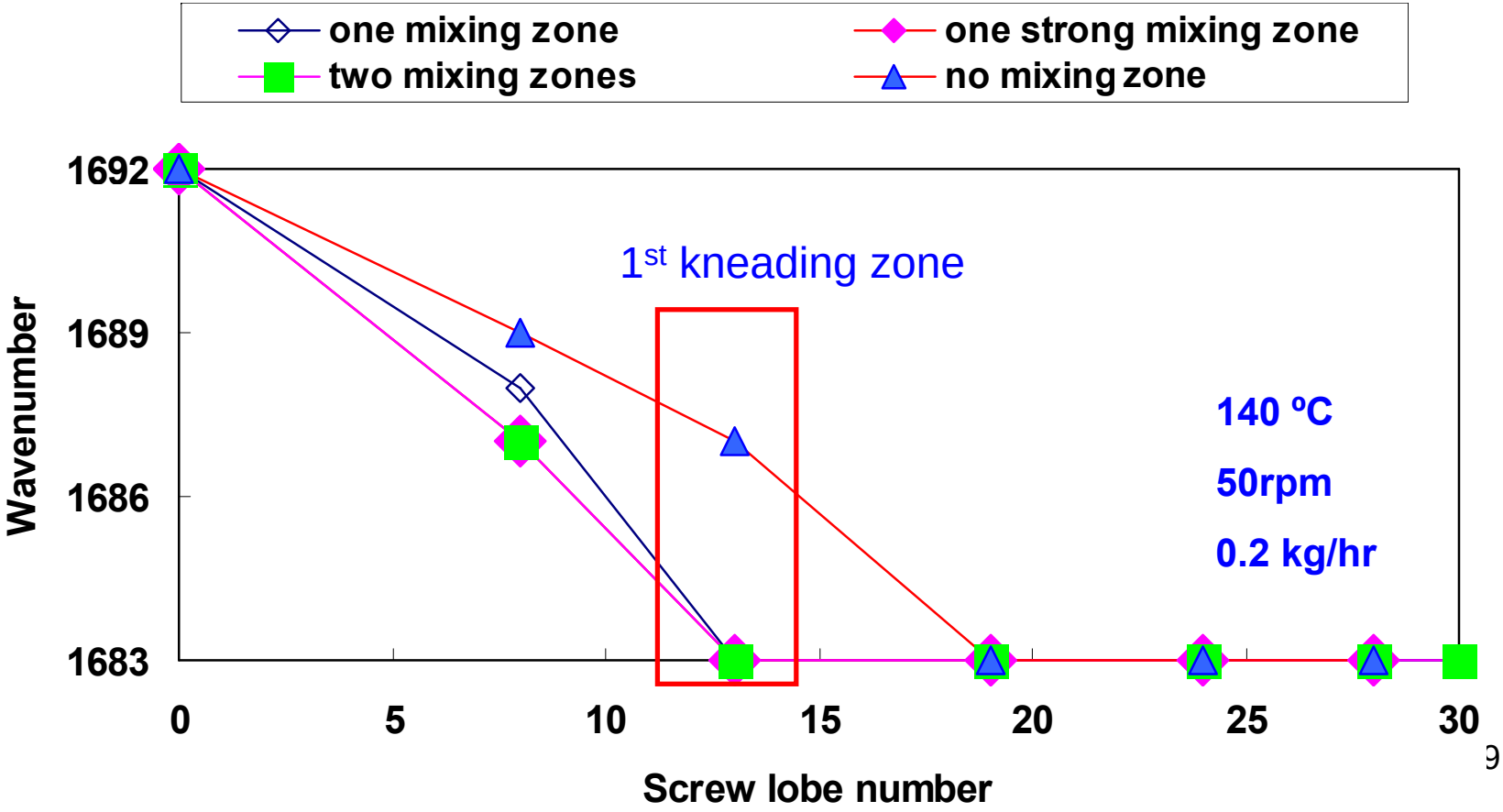
Liu et al., Advances in Polymer Technology. 2011: doi: 10.1002/adv.20256.

Shift of the INM Benzoyl C=O Stretch Peak along the screw axial position

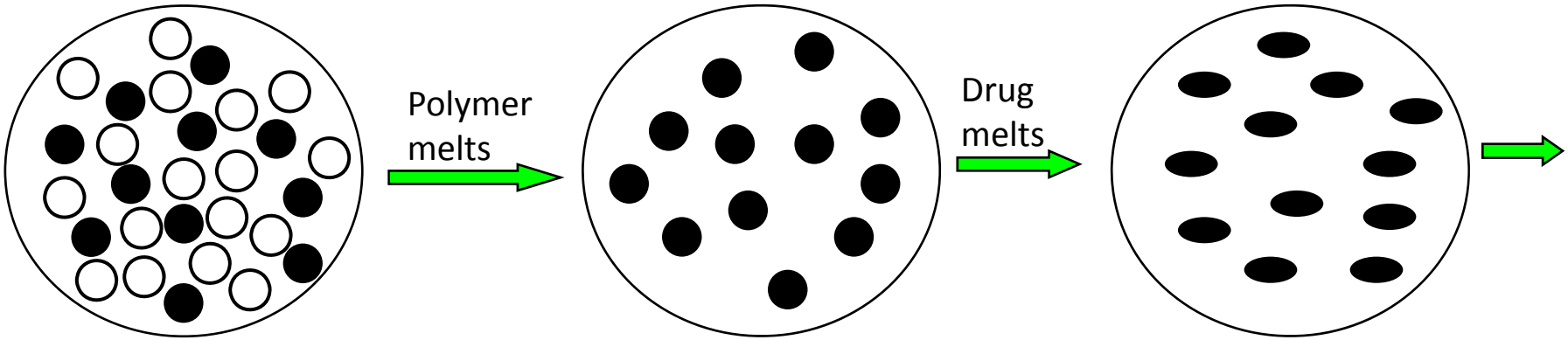


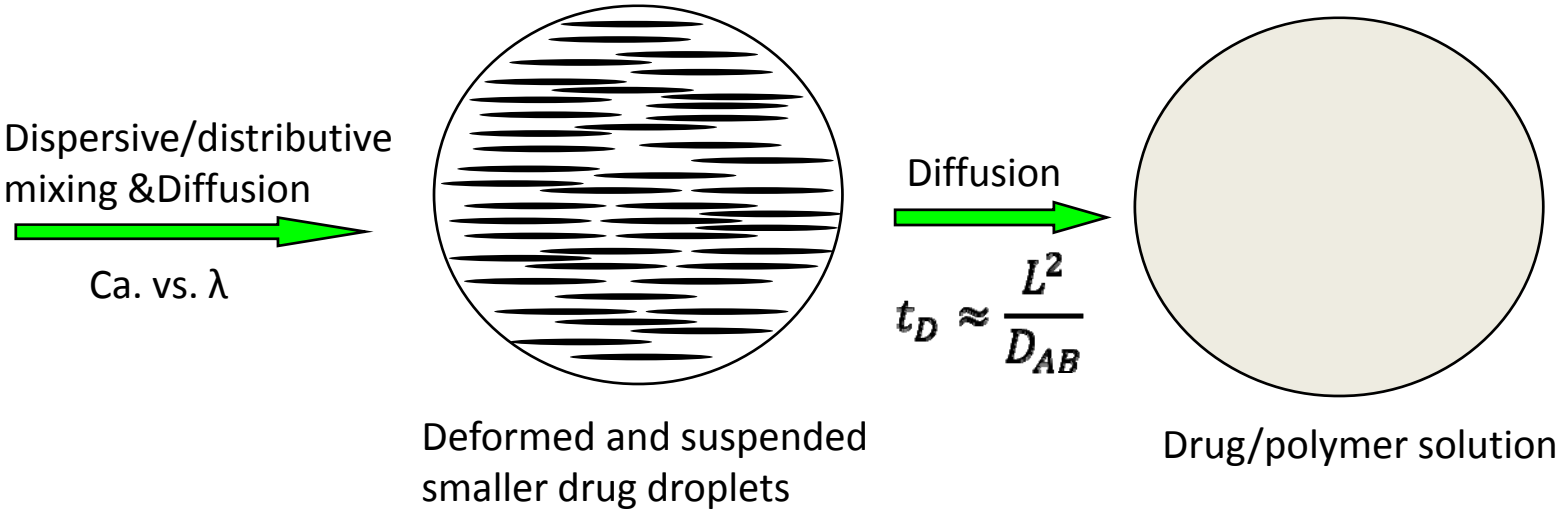
Benzoyl *v* C=O

1692 cm^{-1} for γ- INM
1683 cm^{-1} for amorphous INM
(*Taylor and Zografi, 1997*)



$T_{processing} > MT_{polymer} / T_g + 50\sim100\ ^{o}C$ and $T_{processing} > MT_{drug}$





Foam extrusion in drug delivery

1. Physical Blowing Agents as fugitive plasticizers:

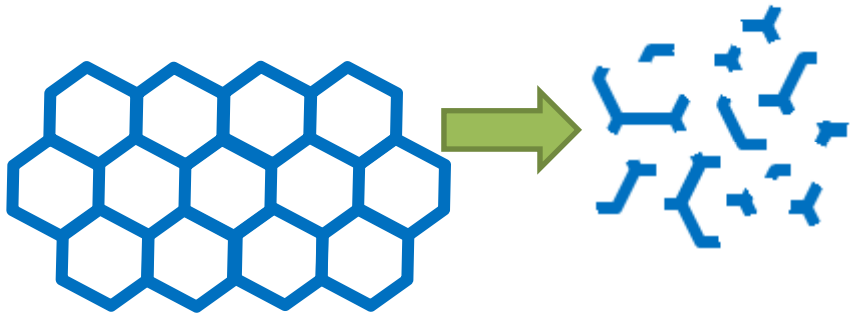
Processing temperature can be decreased without adding “dead weight” to the formulation and without affecting the long term stability and performance of the product.

2. Floating oral dosages:

Some APIs must be absorbed in the stomach due to therapeutic reasons or API’s instability at higher pHs.

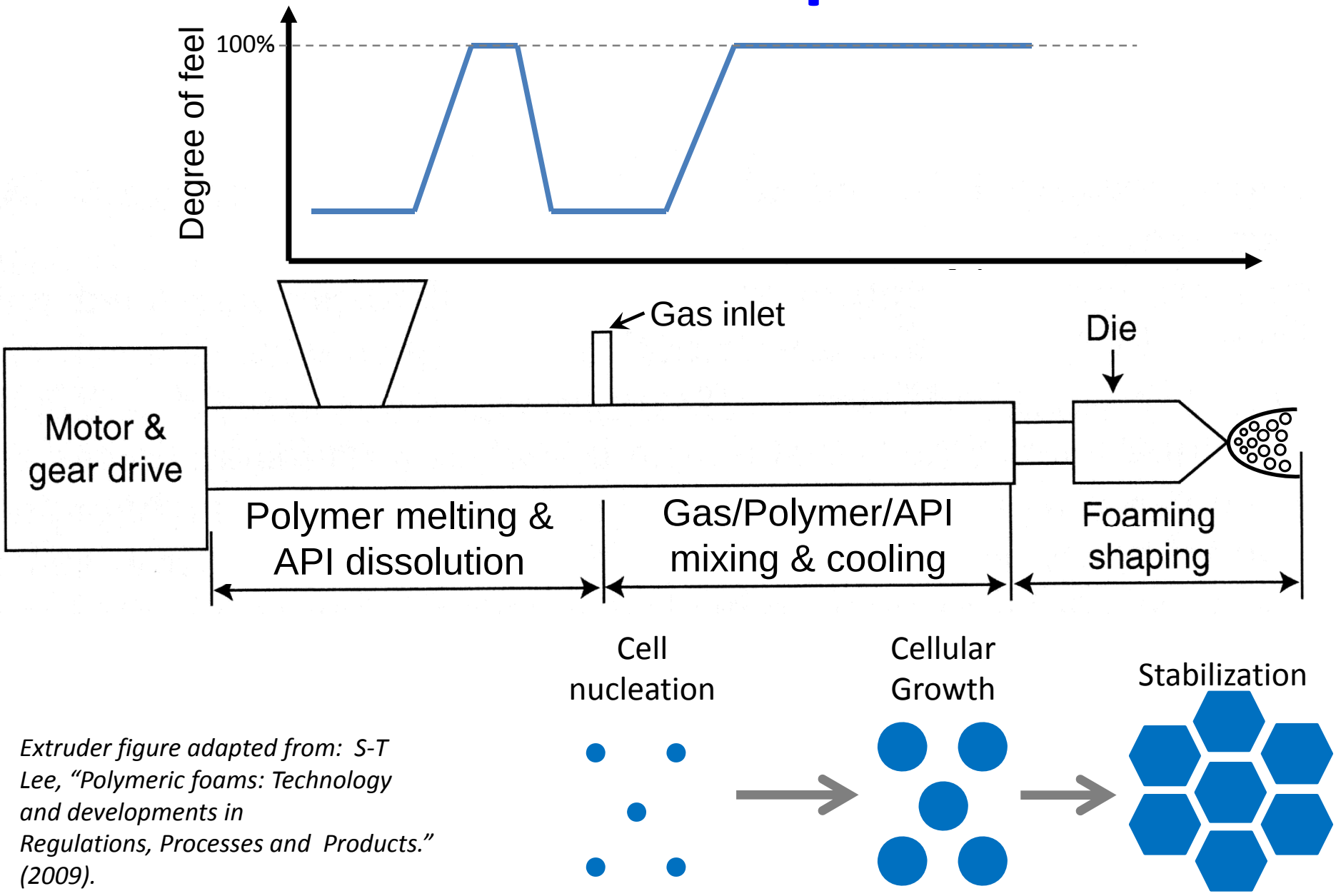
3. Foams to improve milling efficiency of HME products

By milling foamed structures it is possible to obtain smaller particles with narrow particle size distribution and higher surface are.



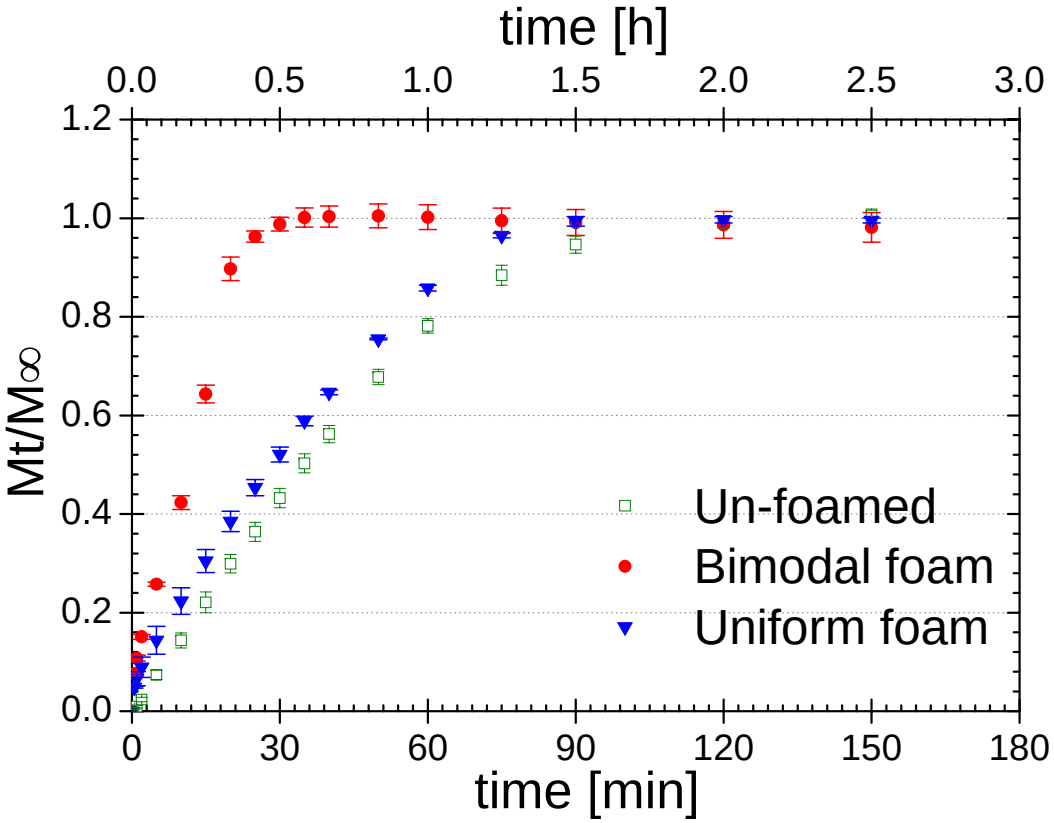
4. Increasing dissolution/release rate

Foam extrusion process

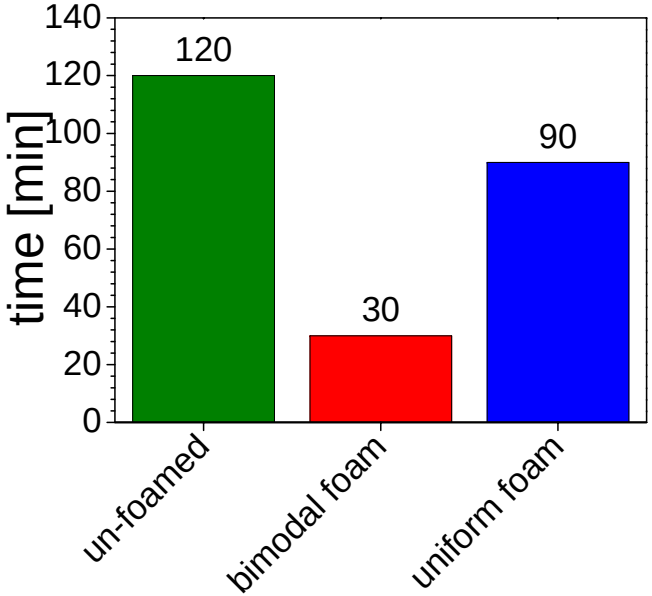


Extruder figure adapted from: S-T Lee, "Polymeric foams: Technology and developments in Regulations, Processes and Products." (2009).

INM's release Foam vs. Un-Foamed

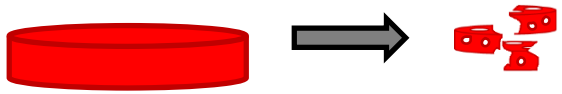


TIME FOR COMPLETE INM'S RELEASE

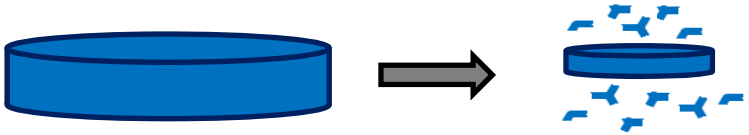


Un-foamed disk

Bimodal foamed disk



Uniform foamed disk

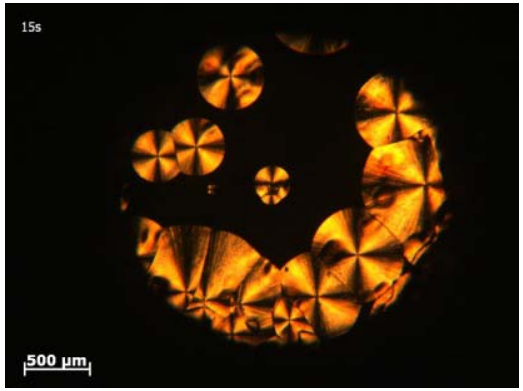
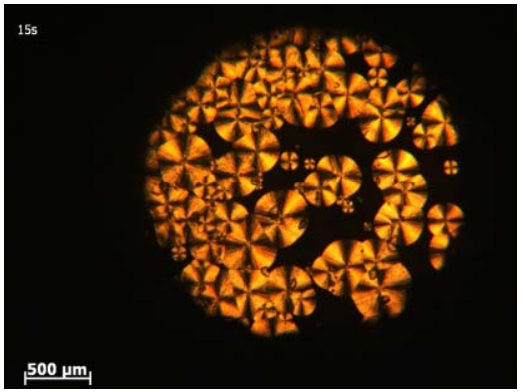
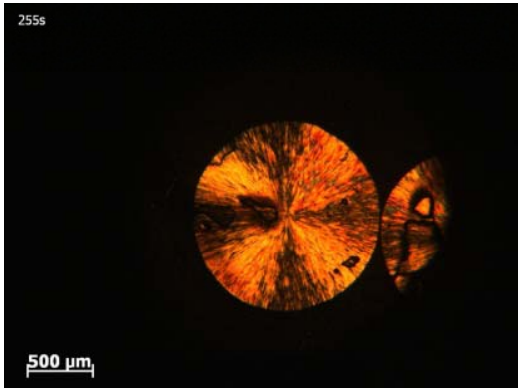
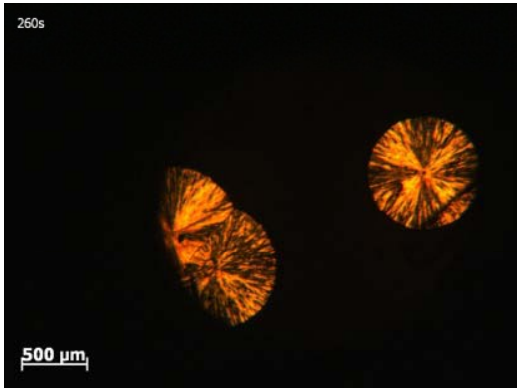
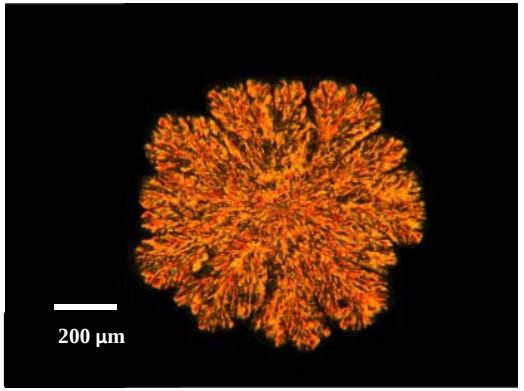


Higher surface area & shorter diffusional lengths accelerate solvent absorption.

Random collapse and breakdown of cellular structure is key for an overall increase in release rate. This behavior is favored by non-uniform cellular structures

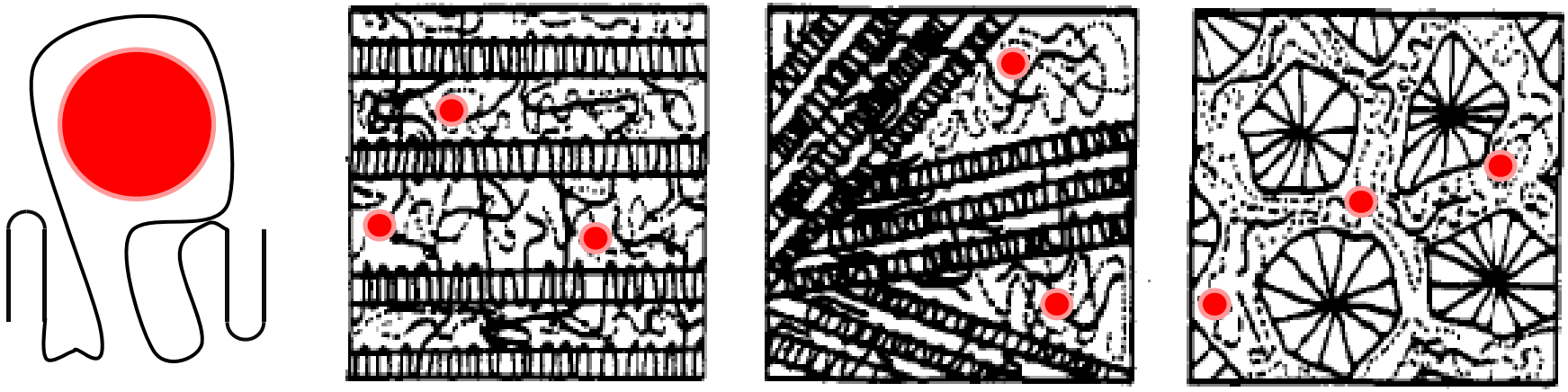
Determination of ambient temperature solubility for shelf life stability

- spherulitic morphology and growth rate, number of spherulitic nuclei

	PEO	1%APAP-PEO	10%APAP-PEO
30 °C			
50 °C			

- @30 °C, # of spherulitic nuclei of 10%APAP-PEO>>PEO
- @50 °C, Maltese cross patterns and spherulite structure of 10%APAP-PEO was destroyed

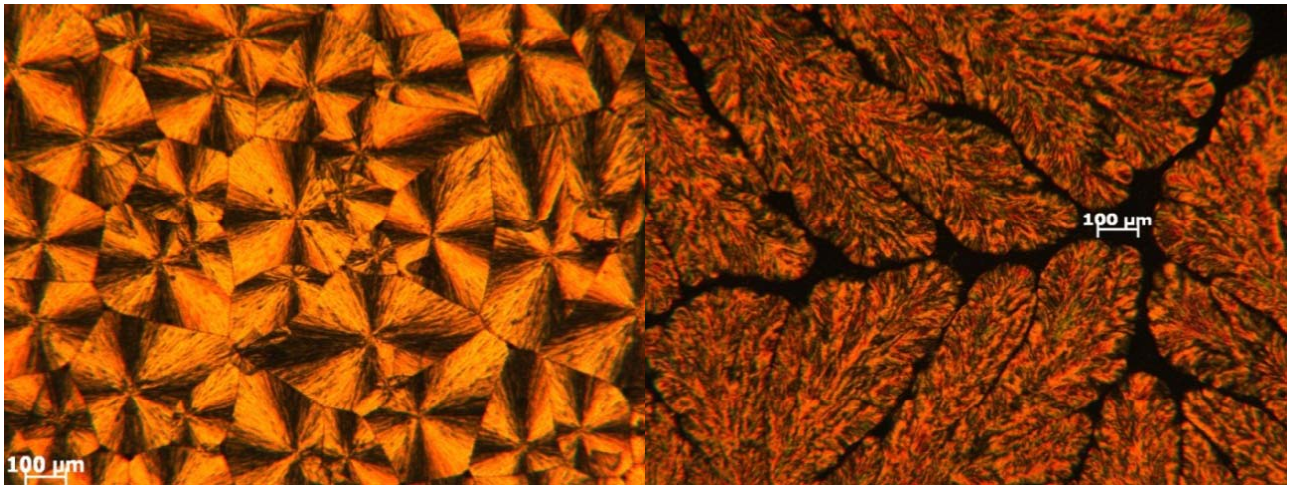
Possible modes of segregation in a binary blend that is miscible in the amorphous state and contains one crystallizing component



a. Intralamellar b. Interlamellar c. Interfibrillar d. Interspherulitic

APAP might locate between PEO spherulites (interspherulitic)@50 °C

10%APAP-PEO @30 °C



10%APAP-PEO @50 °C

- Crevecoeur G, Groeninckx G. Binary blends of poly(ether ether ketone) and poly(ether imide): miscibility, crystallization behavior and semicrystalline morphology. Macromolecules. 1991; 24 (5): 1190-5.

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