Dissolution Enhancement by Modifying the Physical Form of the Active Pharmaceutical Ingredient

Raj Suryanarayanan (Sury), Ph.D.
University of Minnesota
Minneapolis, MN 55455
surya001@umn.edu

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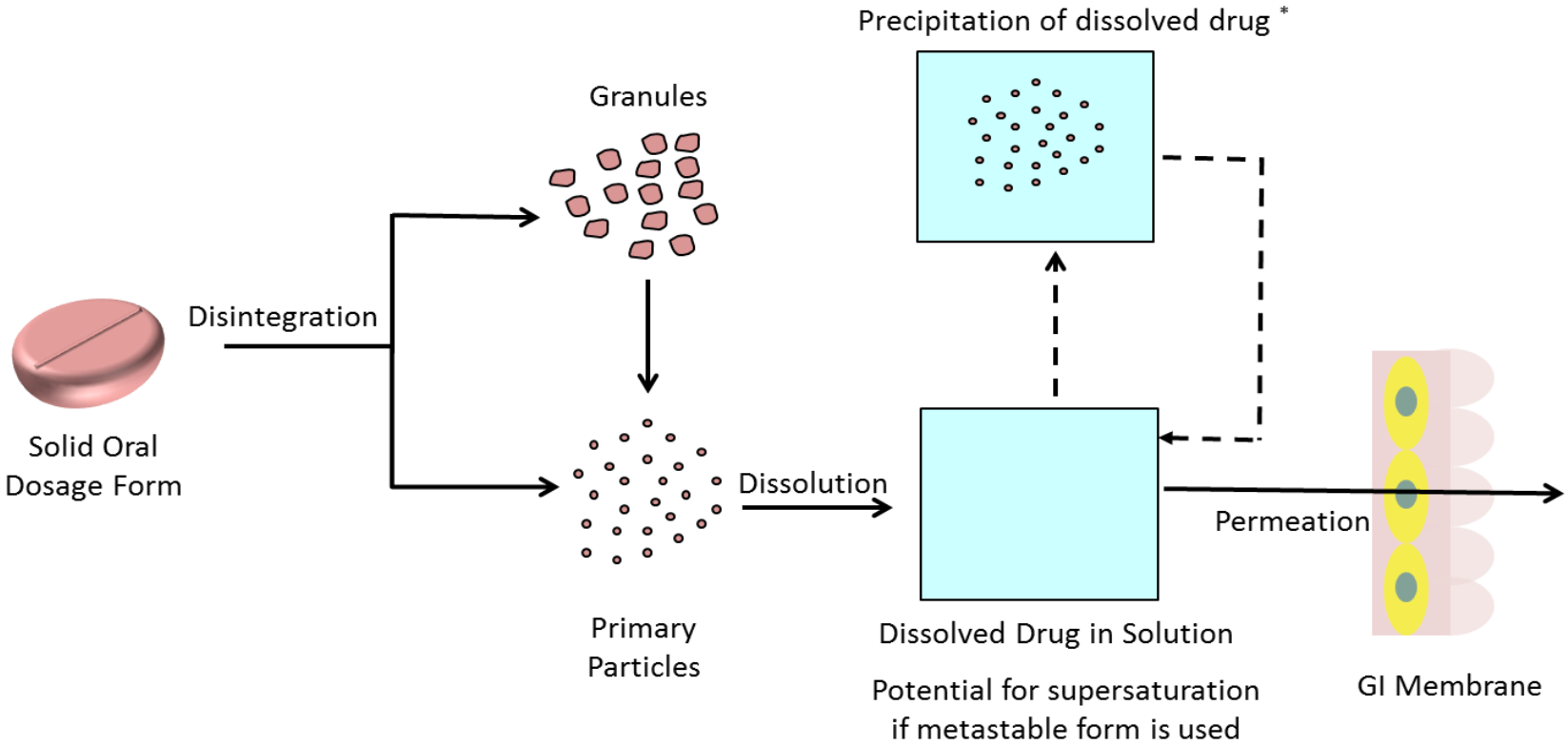
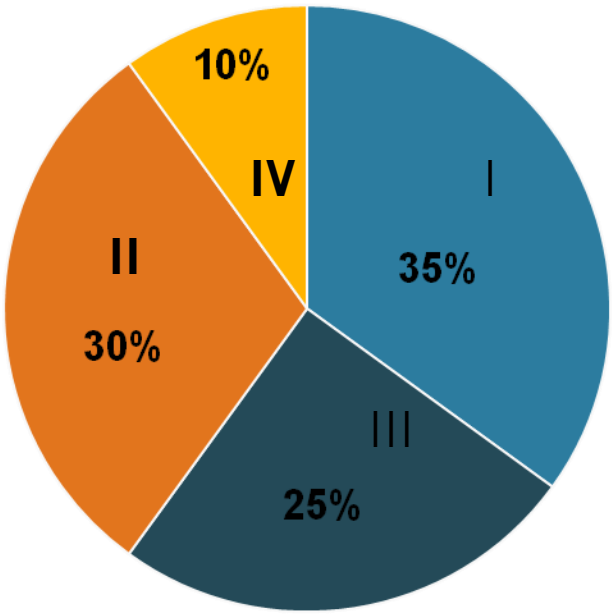
Problem statement


Precipitation of dissolved drug *
Granules
Disintegration
Solid Oral
Dosage Form
Dissolution
Permeation
Primary
Particles
Dissolved Drug in Solution
Potential for supersaturation
if metastable form is used
GI Membrane

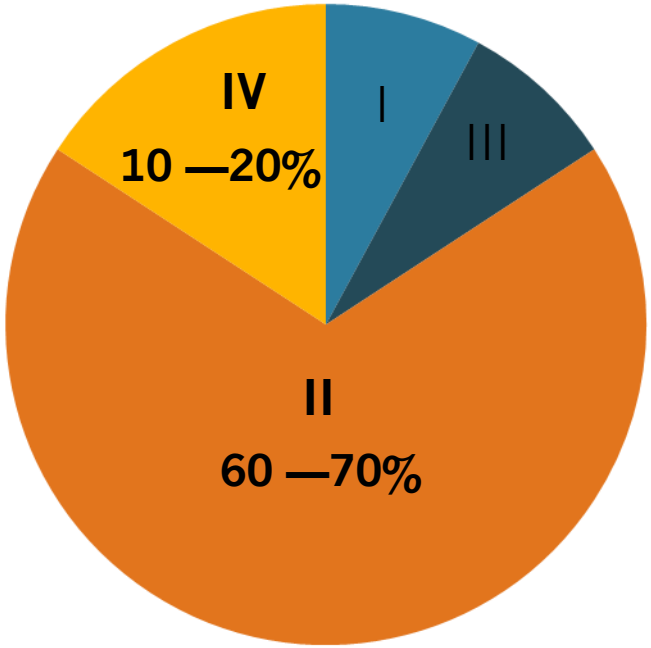
Biopharmaceutics Classification System (BCS)

Class I High solubility High permeability	Class II Low solubility High permeability
Class III High solubility Low permeability	Class IV Low solubility Low permeability

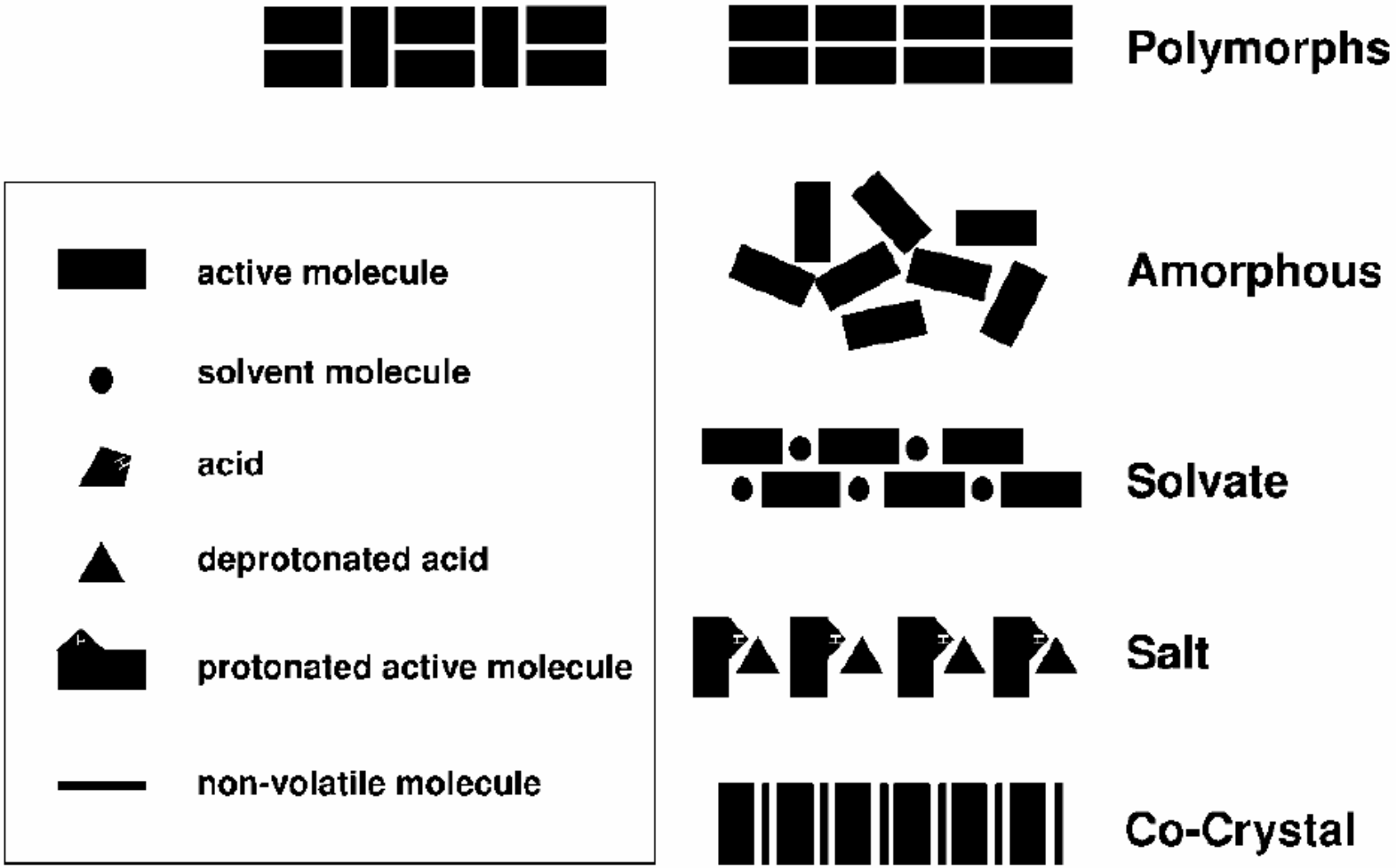
% Drugs on Market



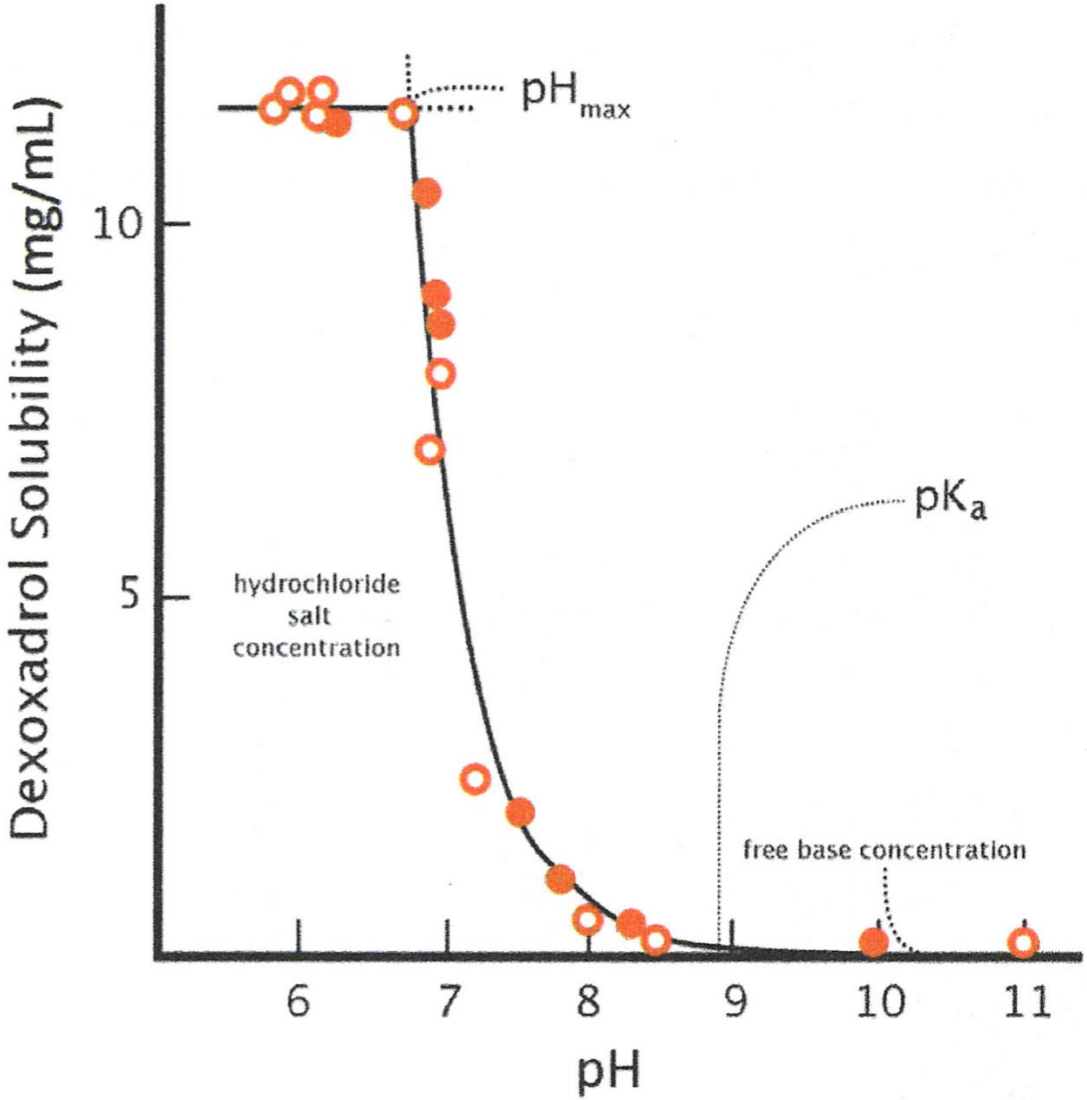
% Drugs in R&D Pipeline



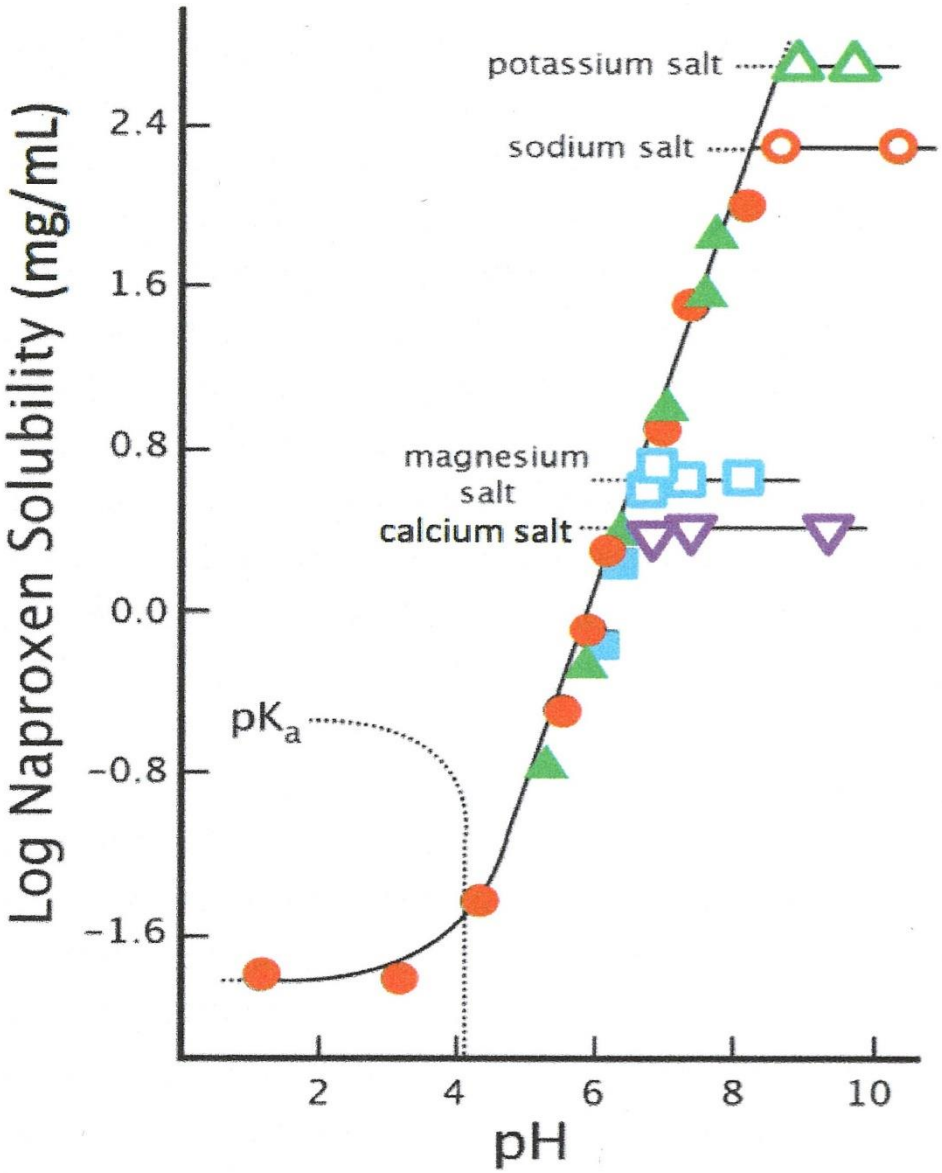
Babu & Nangia, Crystal Growth & Design, 2011



Hilfiker, 2007



Flynn and Roberts, Physical and Biophysical Foundations of Pharmacy Practice, 2015



Flynn and Roberts, Physical and Biophysical Foundations of Pharmacy Practice, 2015

Salt formation

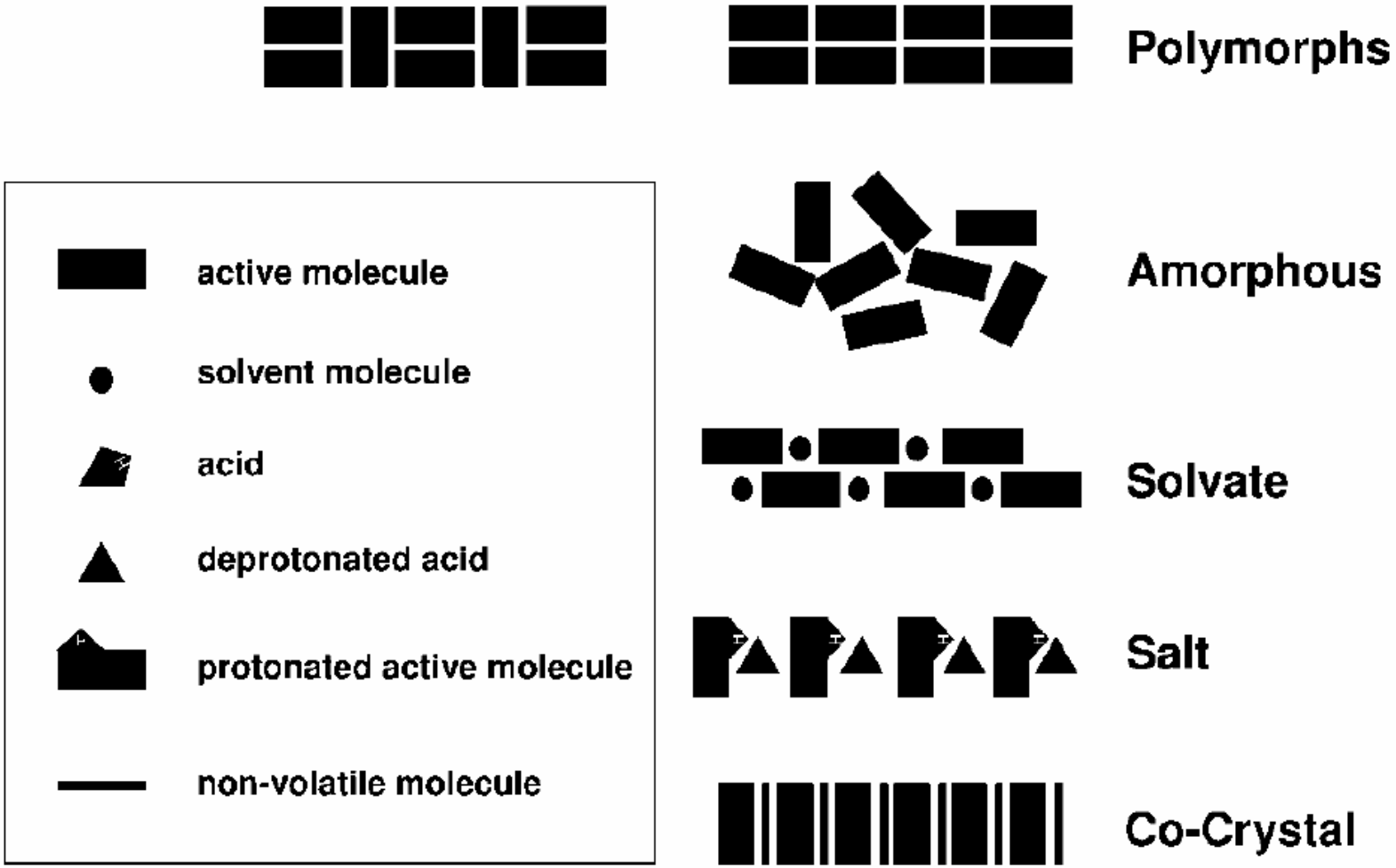
Effective for ionizable compounds

Works only over a limited pH range

Solubility mediated by the counterion

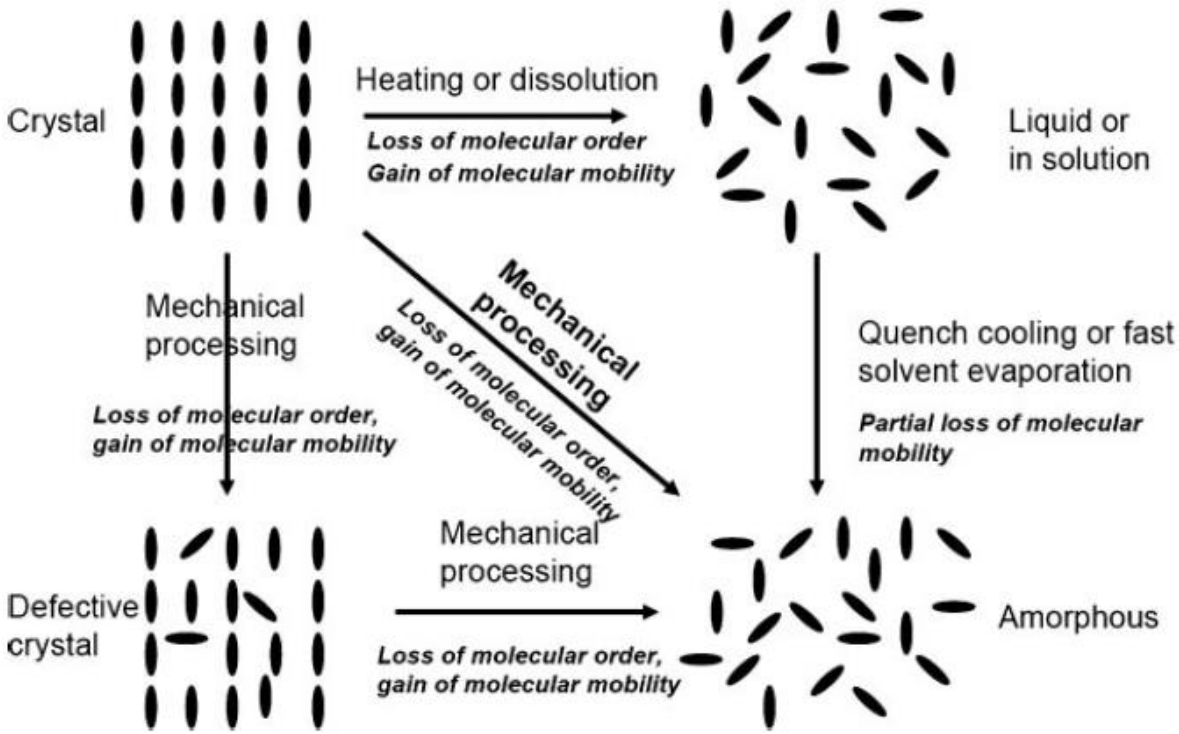
Is there a ‘universal’ approach

Will work for nonionizing compounds



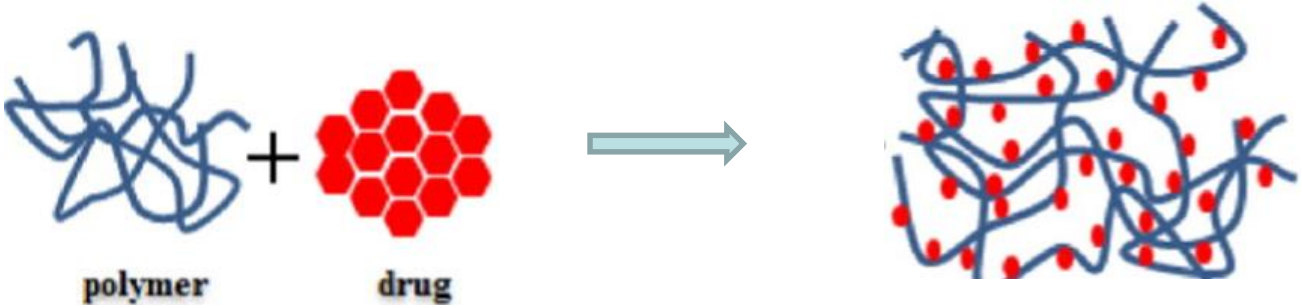
Hilfiker, 2007

Crystal to Amorphous Transformation



Feng et al, J Pharm Sci 97 (2009) 3207

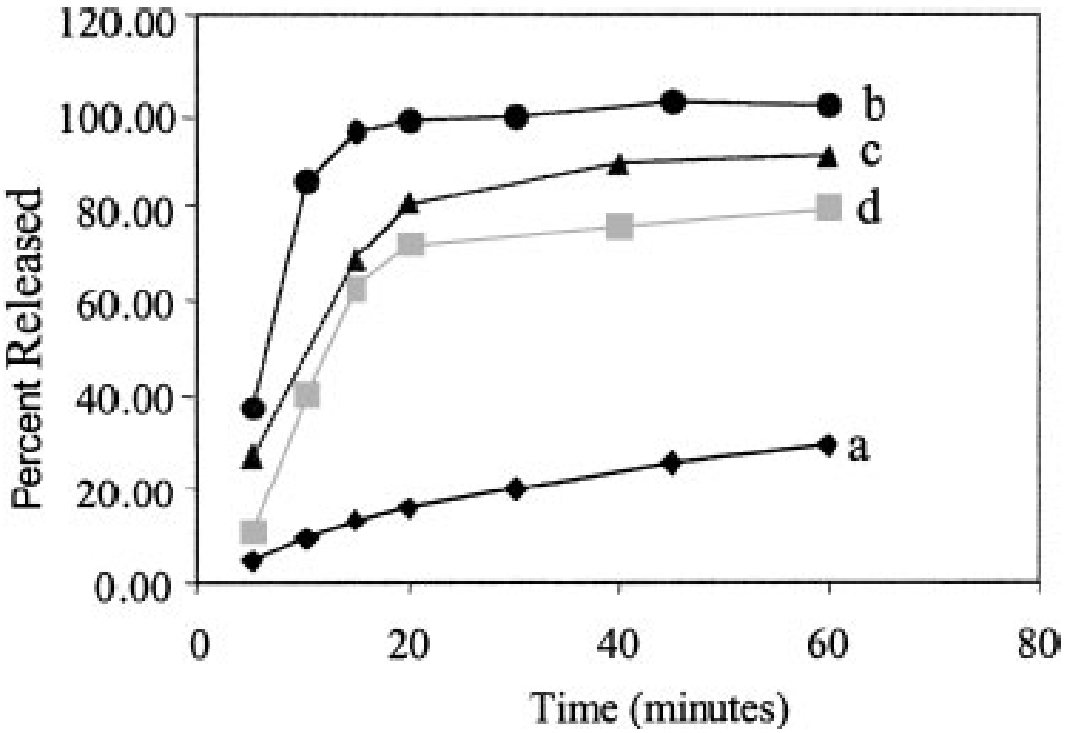
Amorphous Solid Dispersion



Advantages

- Higher stability
- Higher solubility?
- Higher bioavailability

Wang et. al. (2017)

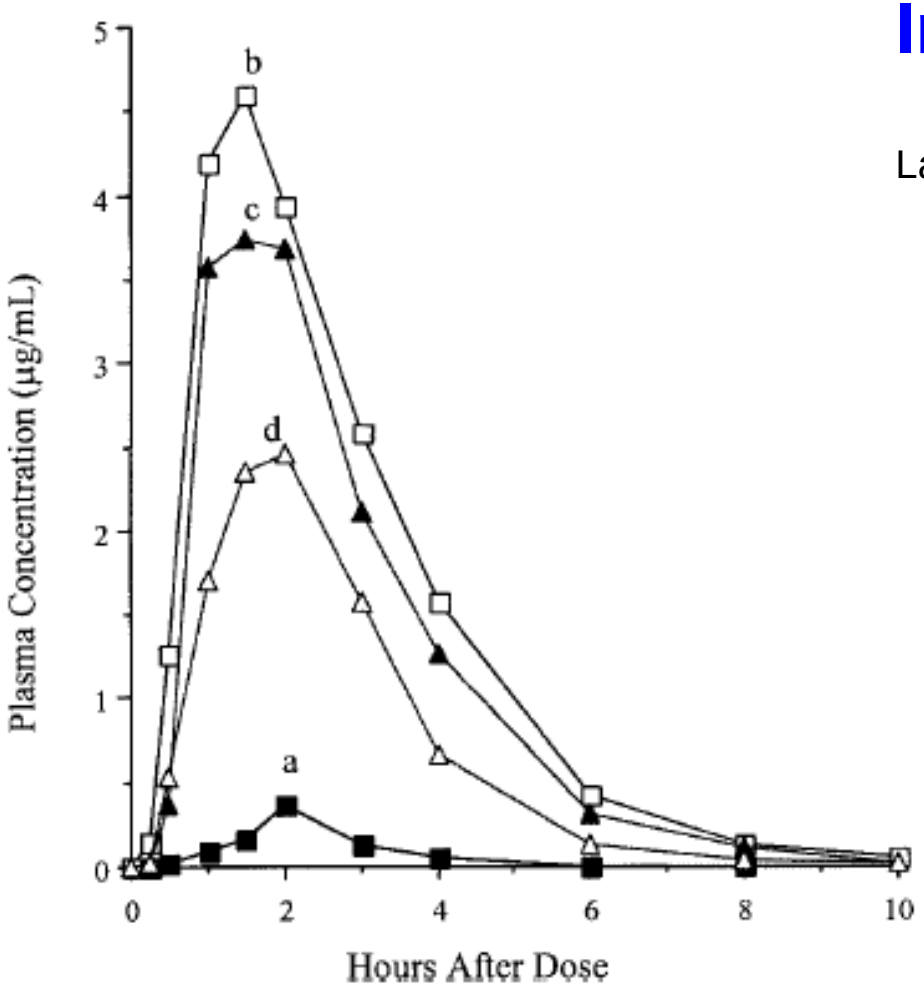


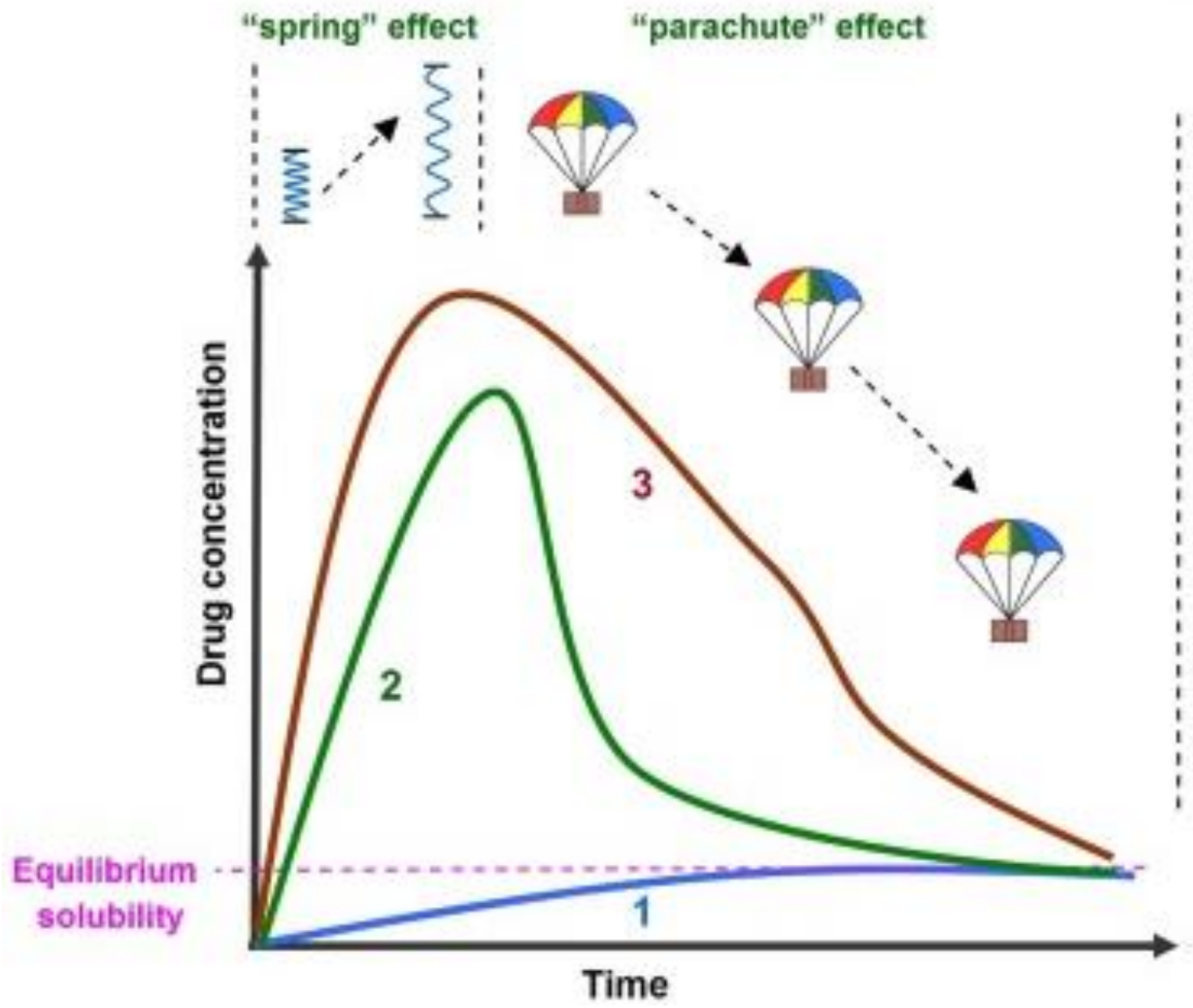
a. Physical mixture of crystalline ritonavir + polyethylene glycol (PEG) – 10:90 (w/w)
b. Amorphous solid dispersion – 10% PEG
c. Amorphous solid dispersion – 20% PEG
d. Amorphous solid dispersion – 30% PEG

Law et. al., J. Pharm. Sci., 2004

In Vivo

Law et. al., J. Pharm. Sci., 2004




"spring" effect
"parachute" effect
Drug concentration
3
2
1
Equilibrium solubility
Time

GOALS

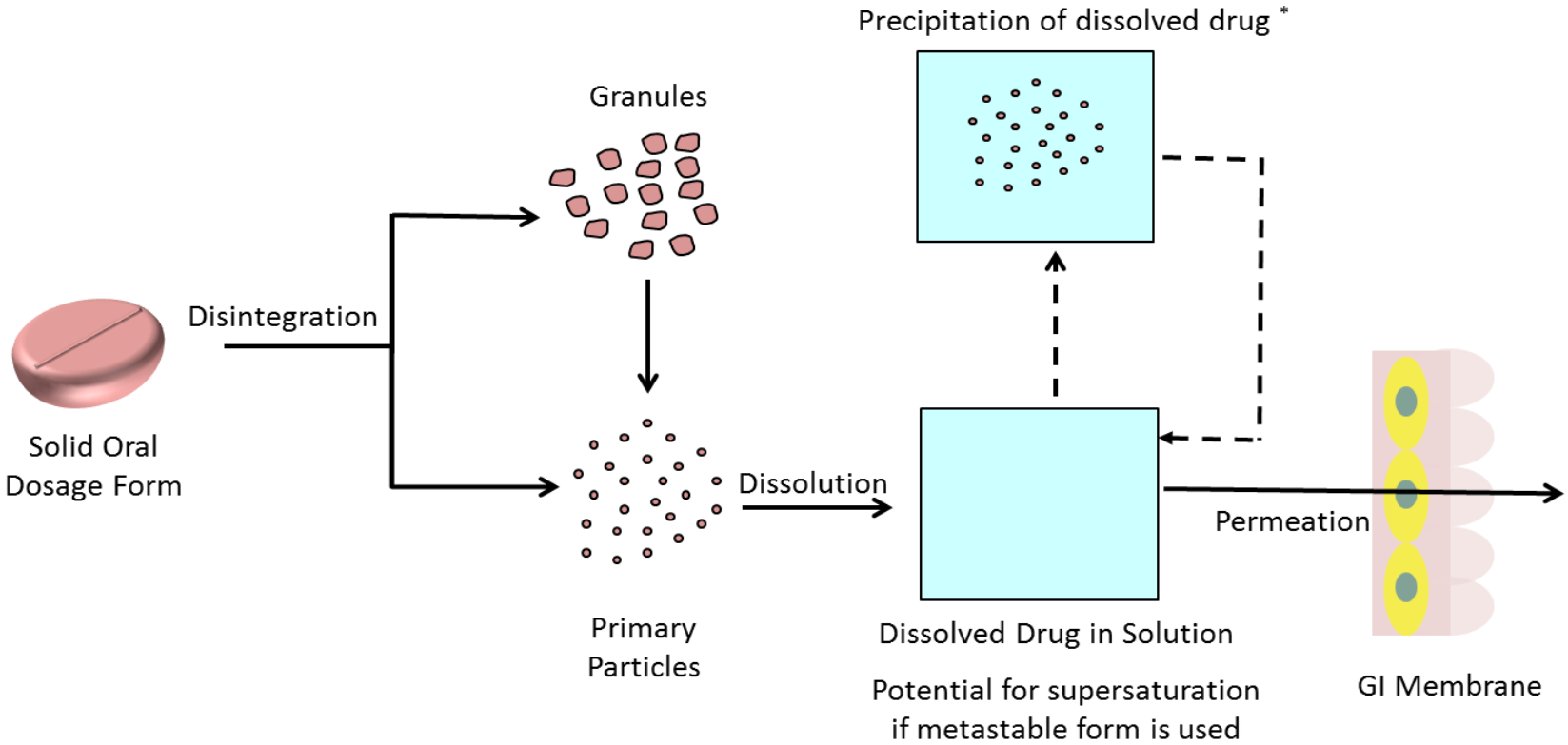
Solubility (dissolution rate) enhancement

Maintain supersaturation

Prevent drug crystallization

Ability to tailor the degree of supersaturation

Ultimate goal: tailor the release to the desired rate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Granules
Disintegration
Solid Oral
Dosage Form
Dissolution
Permeation
Primary
Particles
Dissolved Drug in Solution
Potential for supersaturation
if metastable form is used
GI Membrane

Sustaining supersaturation in solution

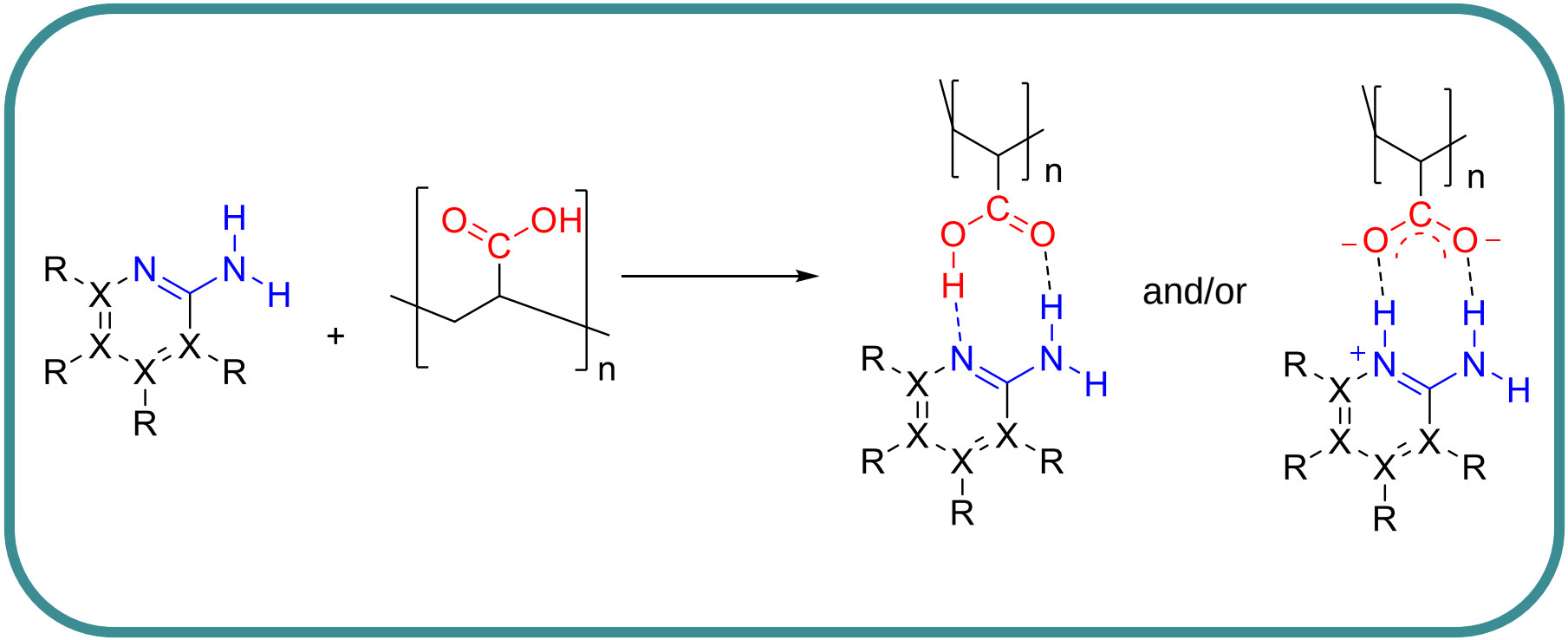
Drug-polymer interaction

Additional acidic excipient (for basic drugs)

Crosslinking of polymer

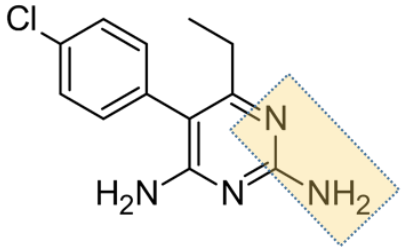
Hypothesis

The drug–polymer interactions between amino aromatic nitrogen and carboxylate/carboxylic acid would retain the drug in an amorphous state and effectively resist crystallization (i.e. physically stable).

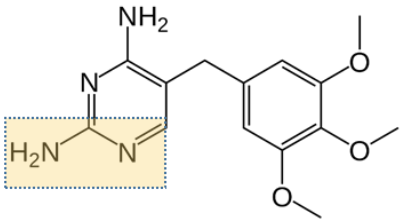


Duggirala et al. *Chemical Communications*, 55 (2019) 5551

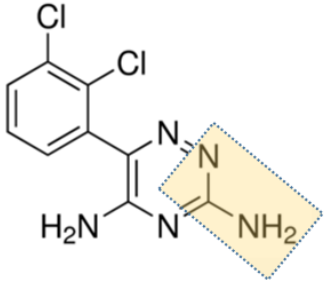
Model Drugs and Polymer



Pyrimethamine
pK_a of base = 7.3

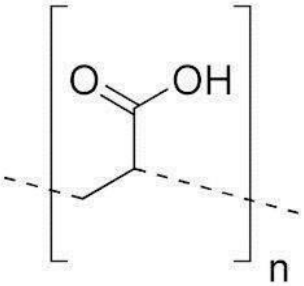


Trimethoprim
pK_a of base = 6.6



Lamotrigine
pK_a of base = 5.7

Crystallization propensity



Polyacrylic acid

pK_a of carboxylic acid: 4.2

<u>"Solid dispersions – Rotary evaporator; 65% w/w drug loading"</u>

Glass transition temperatures (Tg) of ASDs

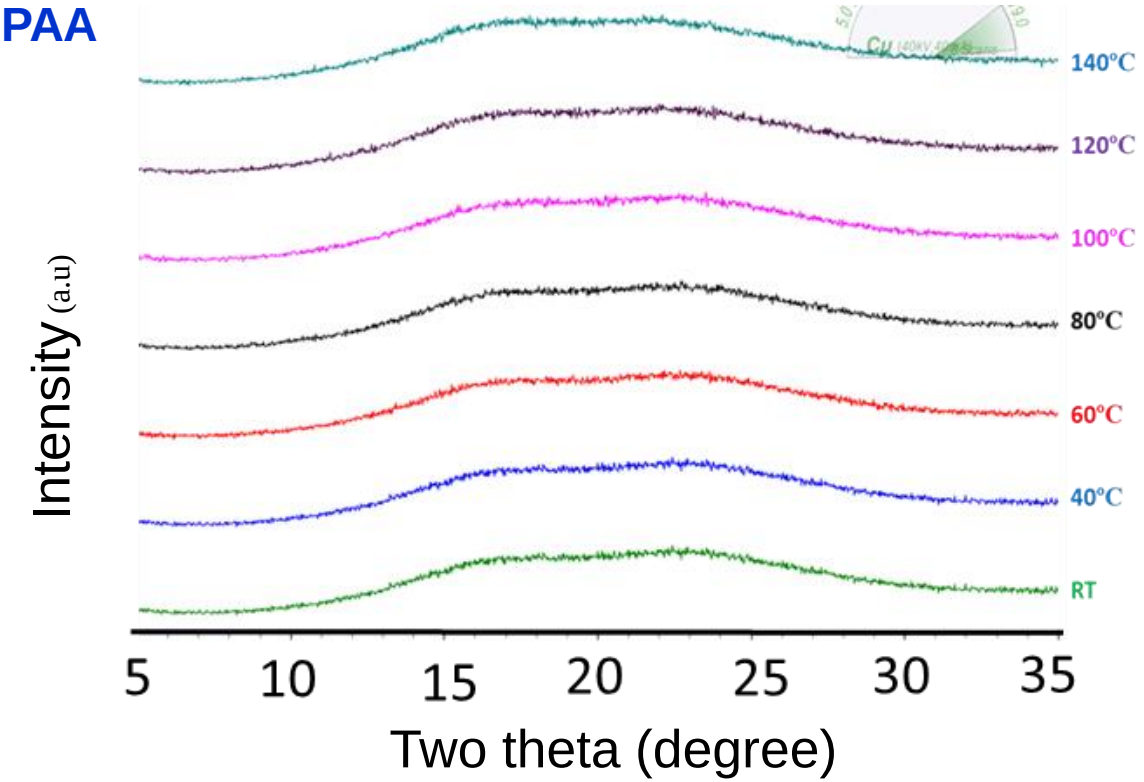
S. No.	T_g of neat phase (°C)	Predicted T_g of ASDs from the Fox equation (°C)	T_g of ASDs (°C)
1	PAA (106)	NA	NA
2	PYR (ND)	PYRPAA (76)	PYRPAA (108)
3	TRI (59)	TRIPAA (69)	TRIPAA (109)
4	LAM (90)	LAMPAA (95)	LAMPAA (118)

Duggirala NK, et al. *Chemical Communications*. 2019;55(39):5551-4.

Physical Stability Studies of ASDs

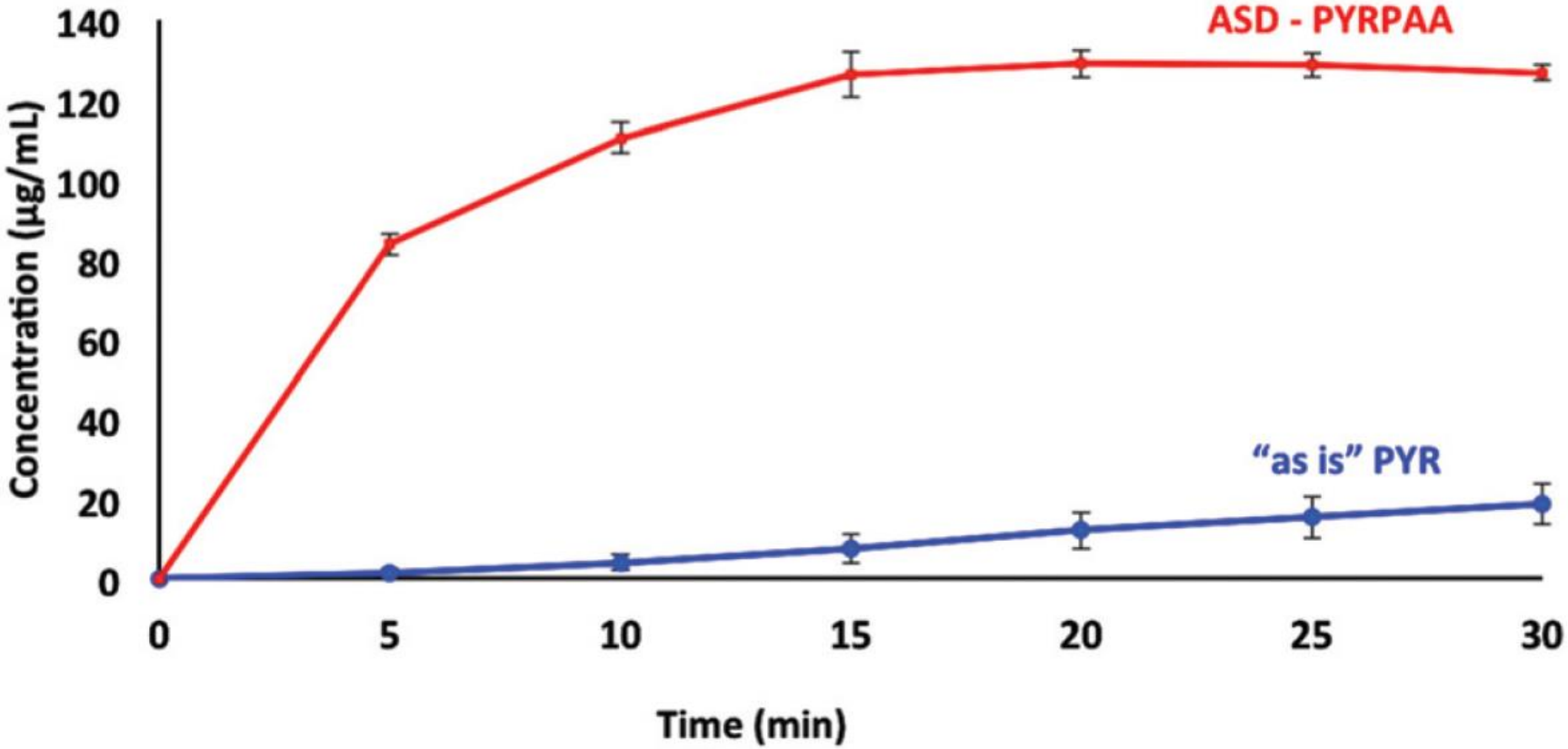
ASD's are physically stable
- Temperature (140 ˚C)
- Slurry for 24 hours
- 40 ˚ C/75% RH - 5 months

PYRPAA



Duggirala NK, et al. *Chemical Communications*. 2019;55(39):5551-4.

Dissolution



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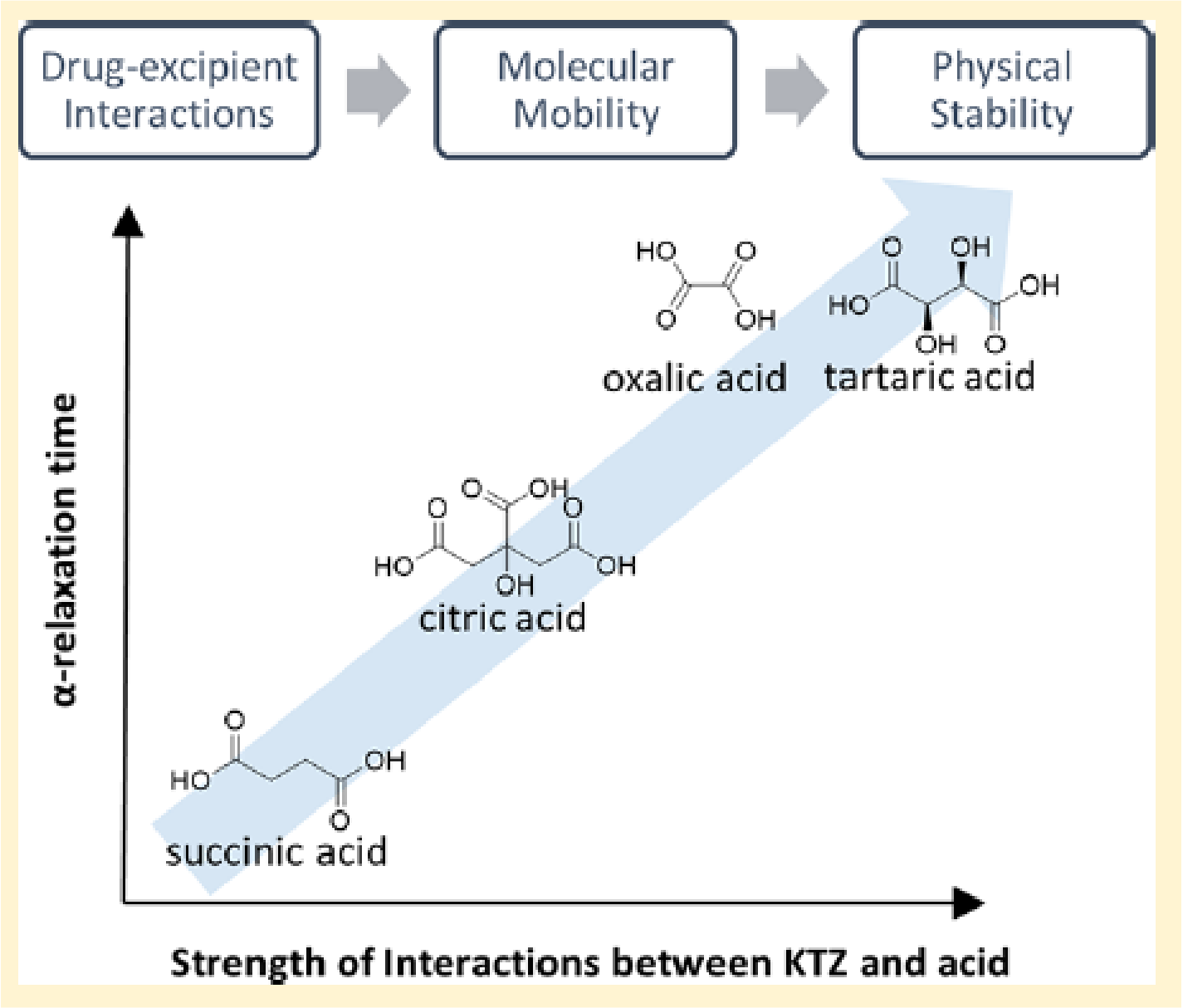
Combining salt formation and amorphization strategies

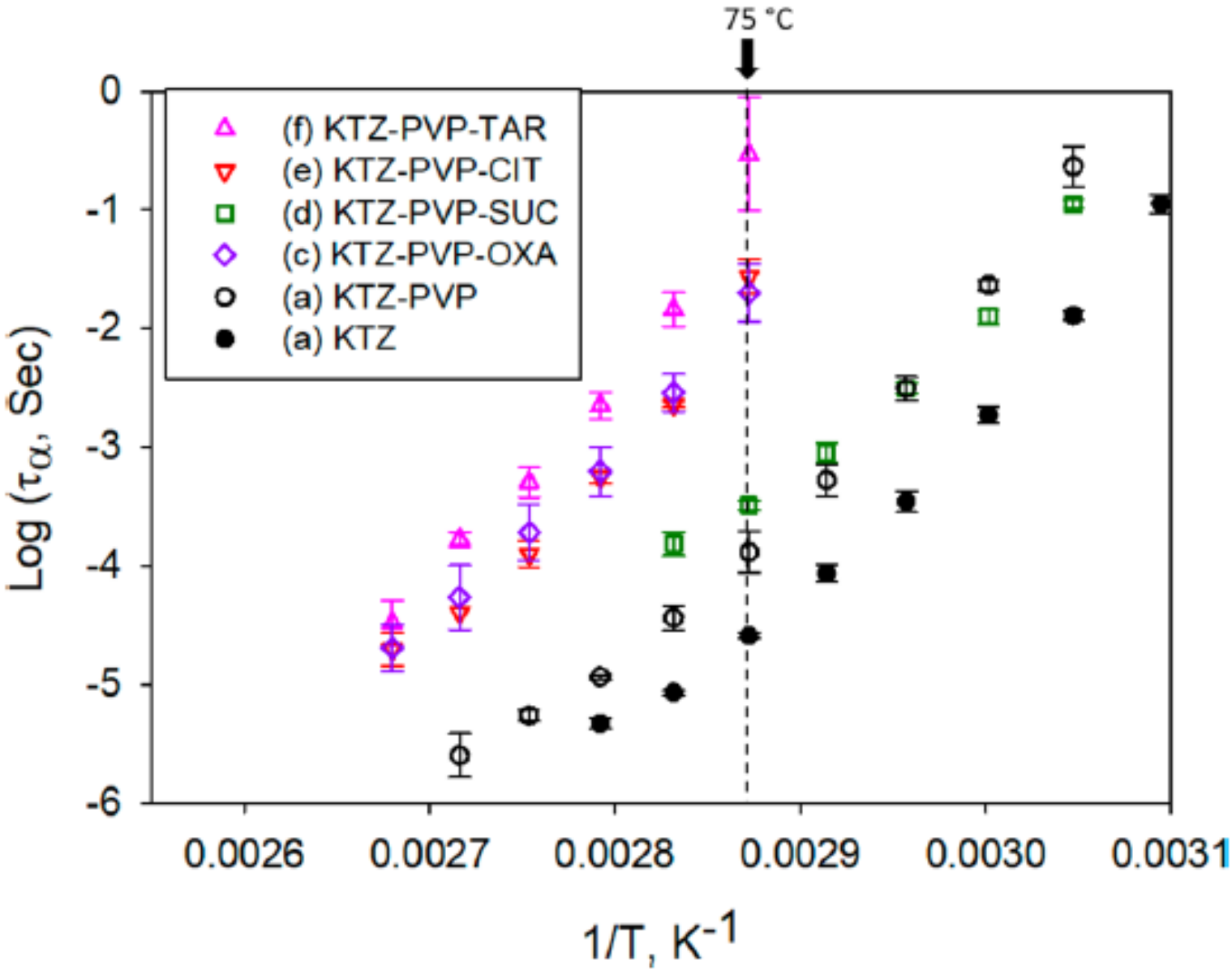
Ketoconazole – weakly basic drug

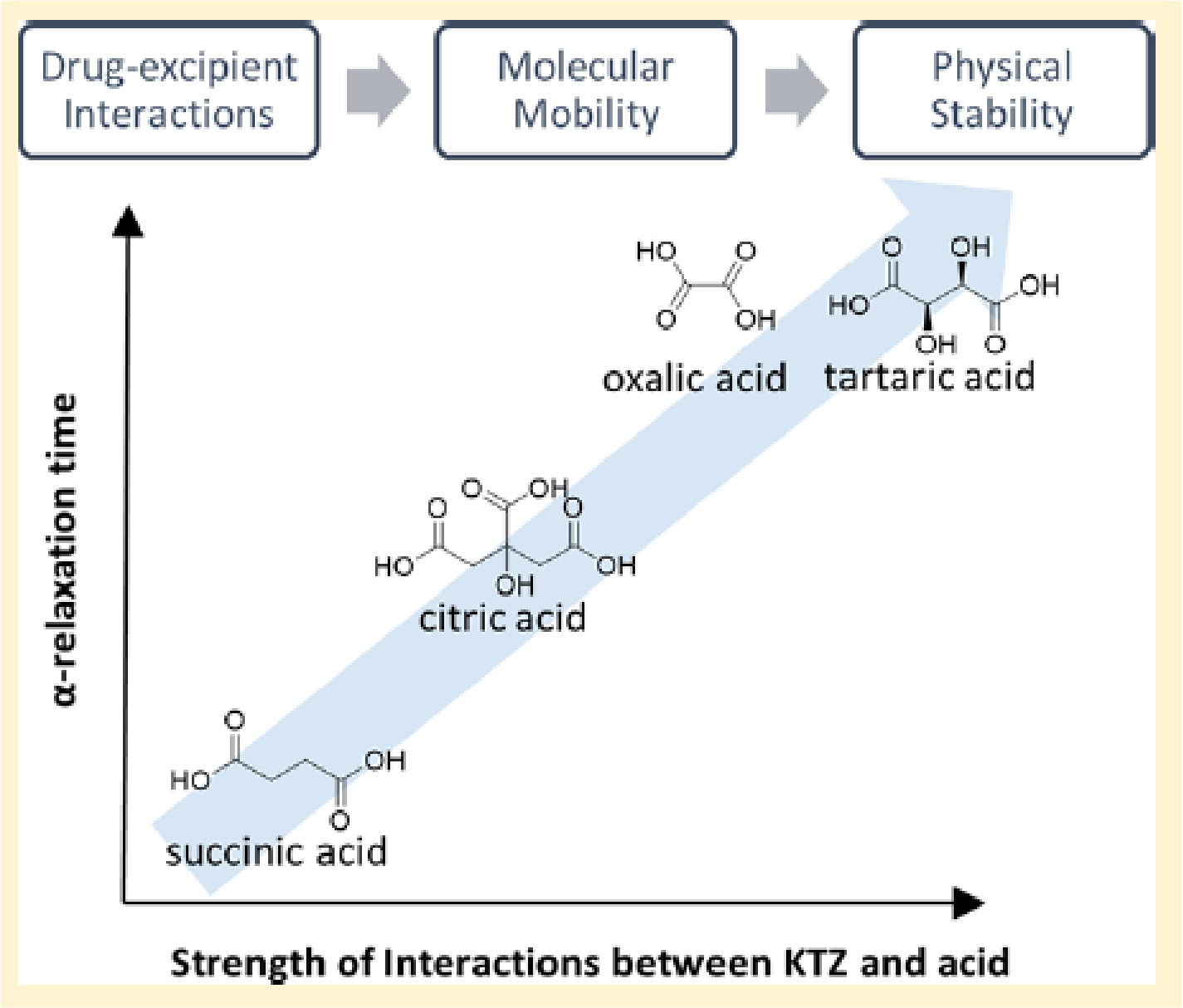
Drug:acid coamorphous system

ionic or hydrogen bonding interaction

Effect on molecular mobility, stability and dissolution behavior


Drug-excipient Interactions
Molecular Mobility
Physical Stability
α-relaxation time
oxalic acid
tartaric acid
citric acid
succinic acid
Strength of Interactions between KTZ and acid


75 °C
(f) KTZ-PVP-TAR
(e) KTZ-PVP-CIT
(d) KTZ-PVP-SUC
(c) KTZ-PVP-OXA
(a) KTZ-PVP
(a) KTZ
Log (τα, Sec)
0
-1
-2
-3
-4
-5
-6
0.0026
0.0027
0.0028
0.0029
0.0030
0.0031
1/T, K-1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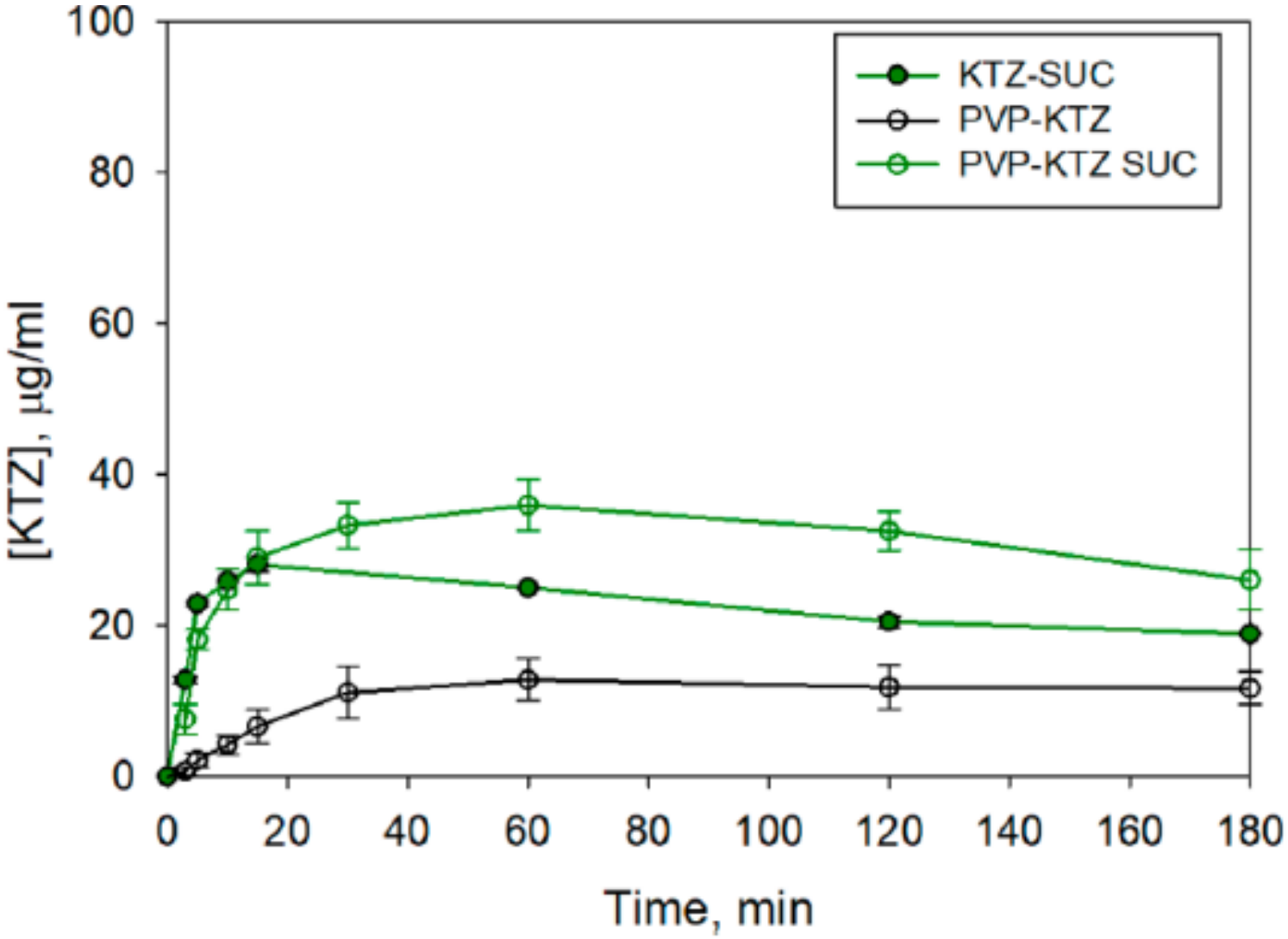
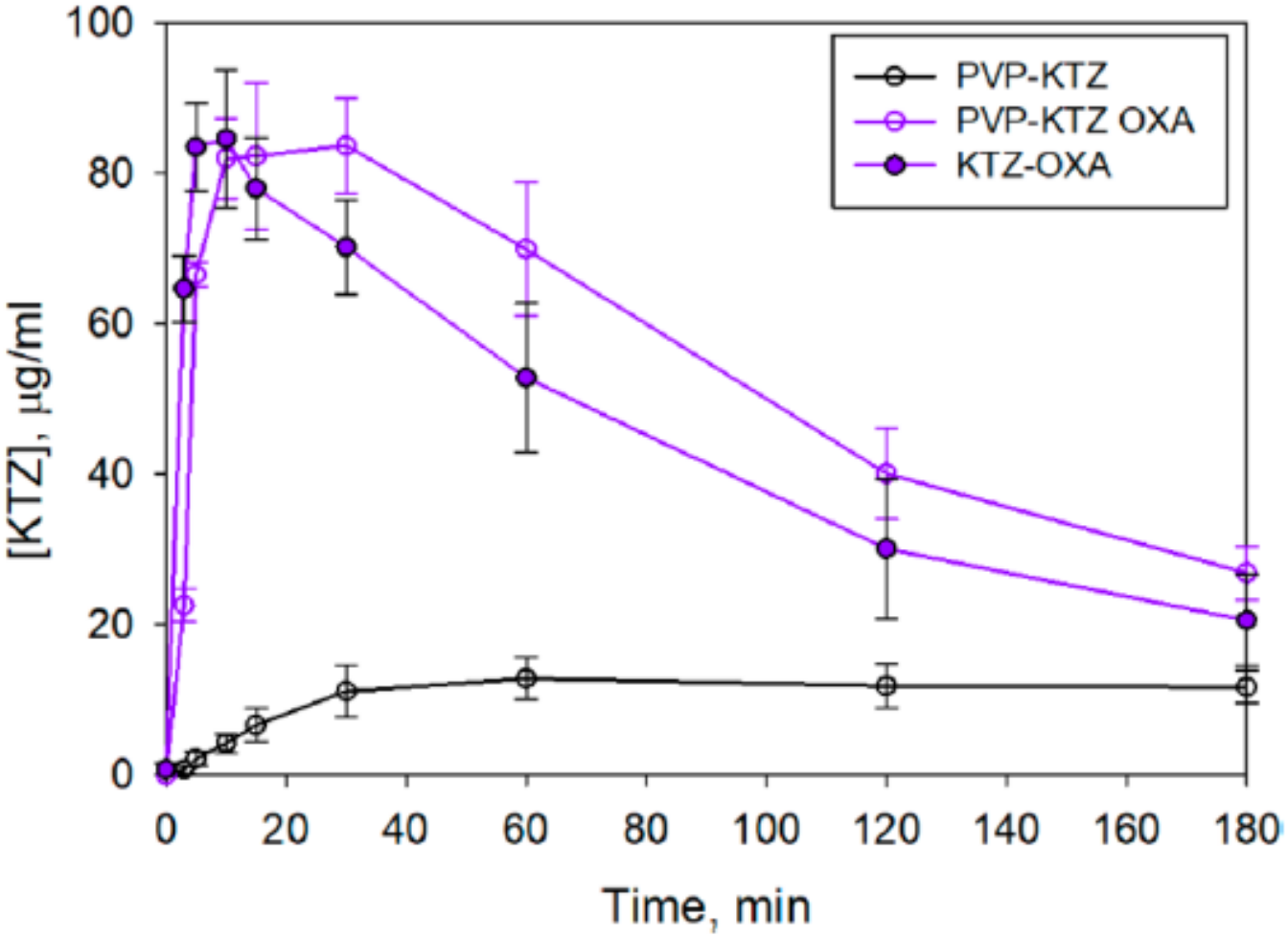
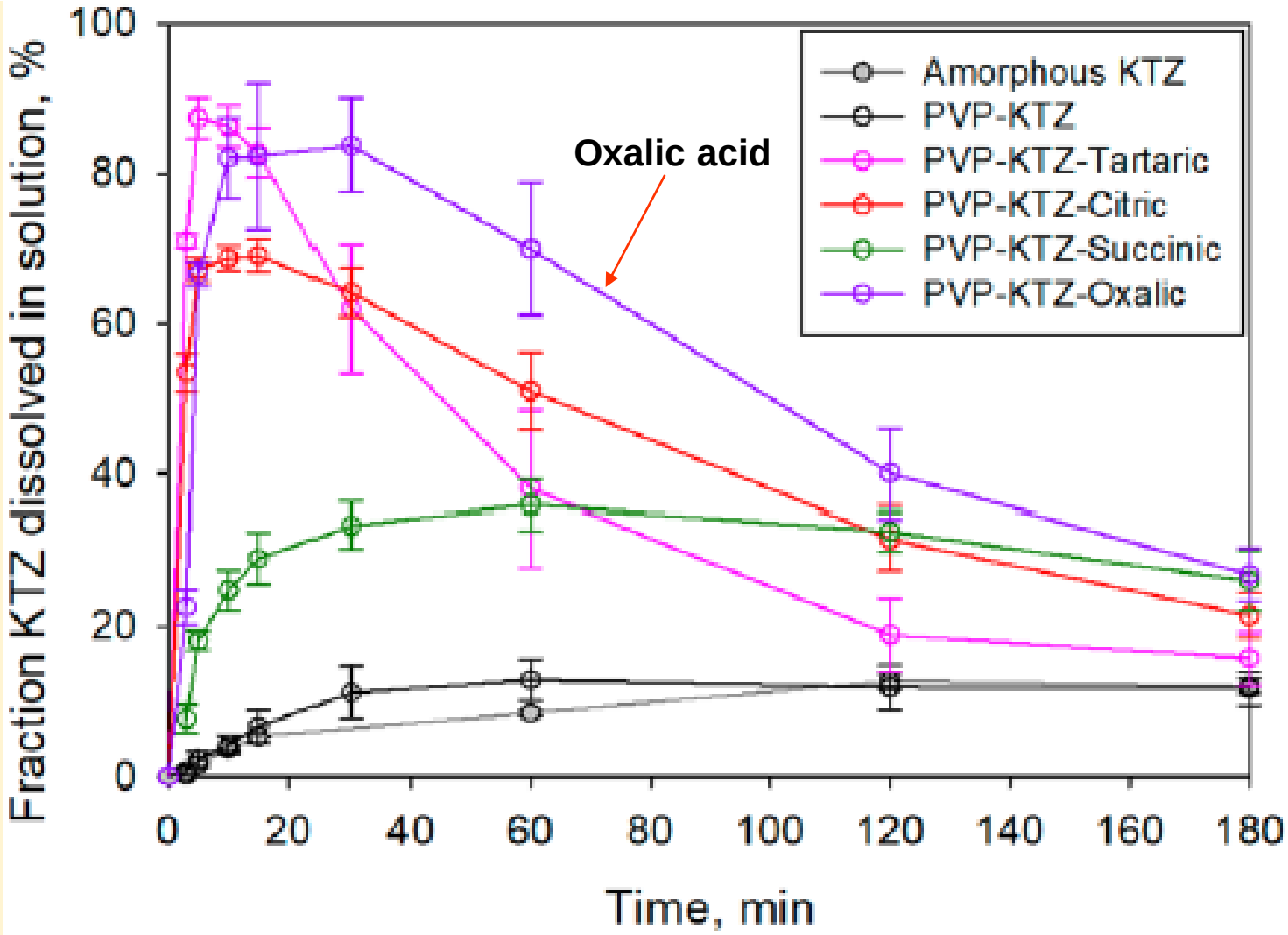
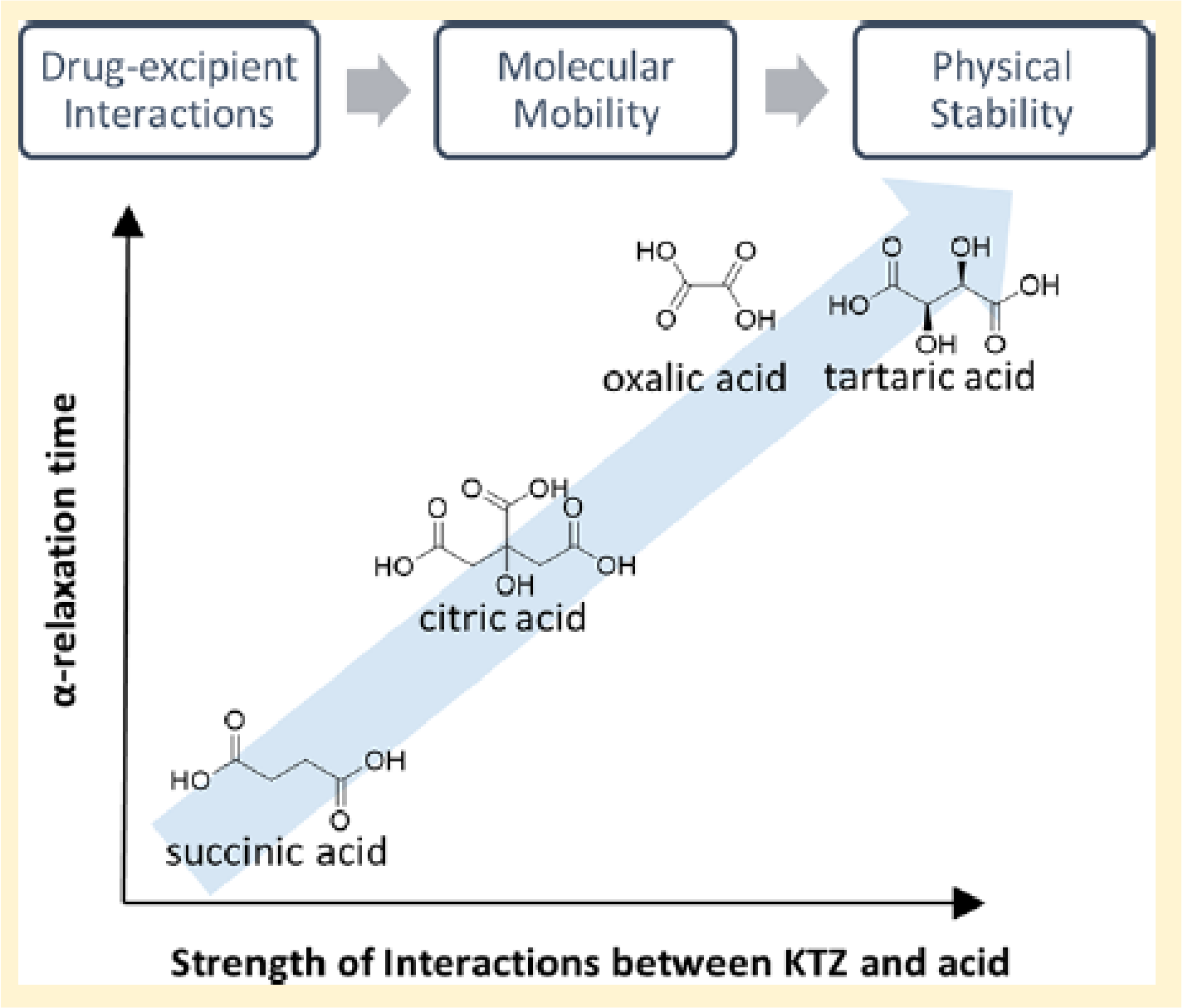

KTZ-SUC
PVP-KTZ
PVP-KTZ SUC
[KTZ], µg/ml
Time, min
0
20
40
60
80
100
120
140
160
180


PVP-KTZ
PVP-KTZ OXA
KTZ-OXA
[KTZ], µg/ml
Time, min
0
20
40
60
80
100
120
140
160
180


Fraction KTZ dissolved in solution, %
100
80
60
40
20
0
0
20
40
60
80
100
120
140
160
180
Time, min
Oxalic acid
Amorphous KTZ
PVP-KTZ
PVP-KTZ-Tartaric
PVP-KTZ-Citric
PVP-KTZ-Succinic
PVP-KTZ-Oxalic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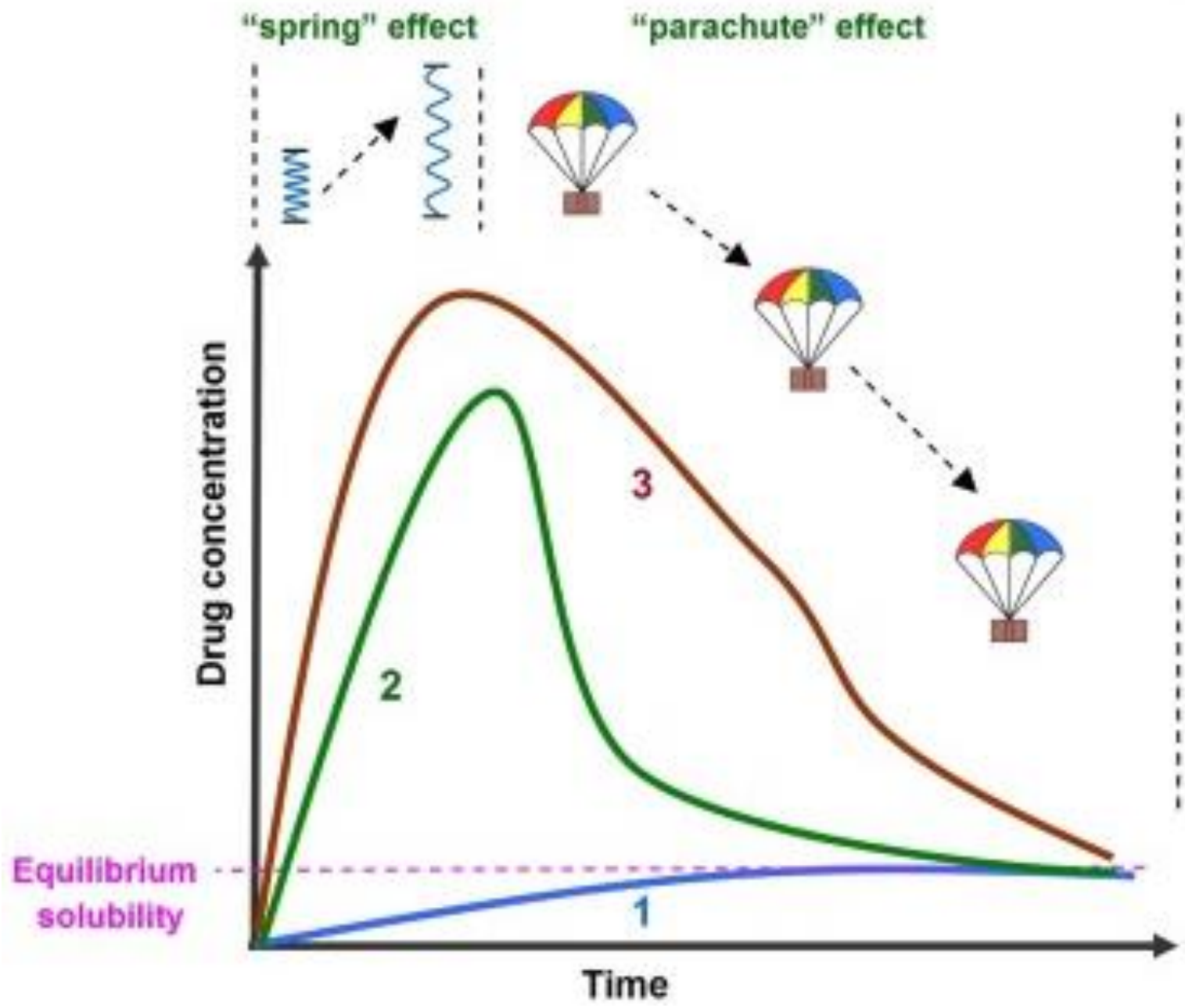
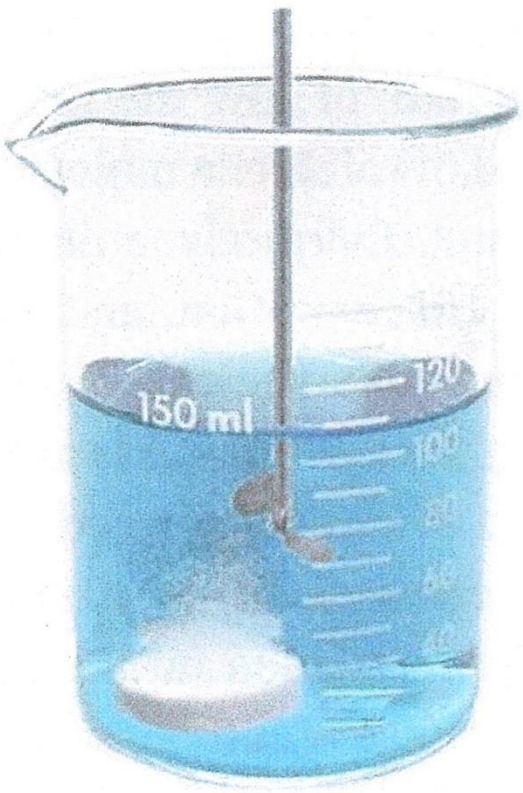
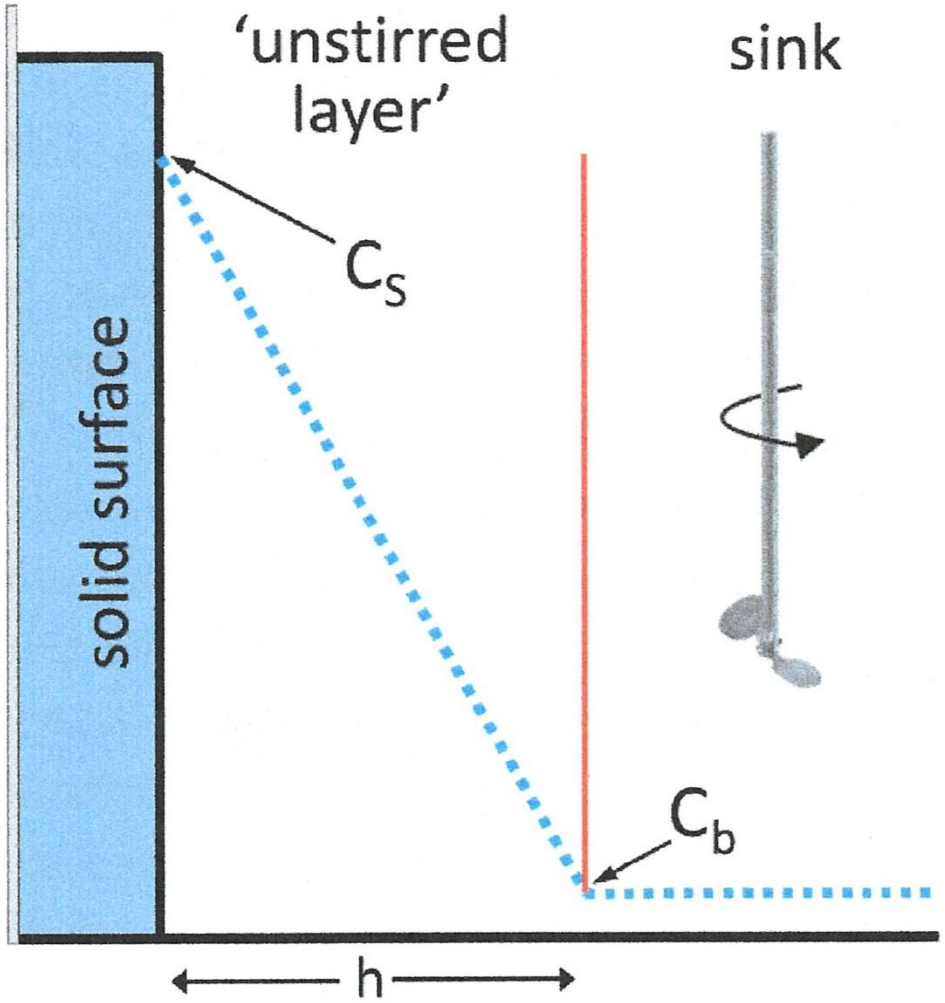

"spring" effect
"parachute" effect
Drug concentration
3
2
1
Equilibrium solubility
Time

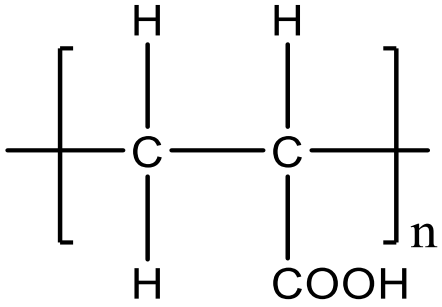




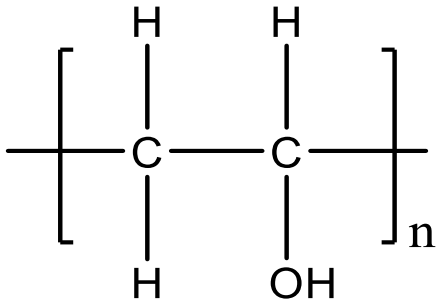
Flynn and Roberts, Physical and Biophysical Foundations of Pharmacy Practice, 2015

Crosslinking: An avenue to develop stable amorphous solid dispersion with (i) high drug loading and (ii) tailored dissolution profile

Model system



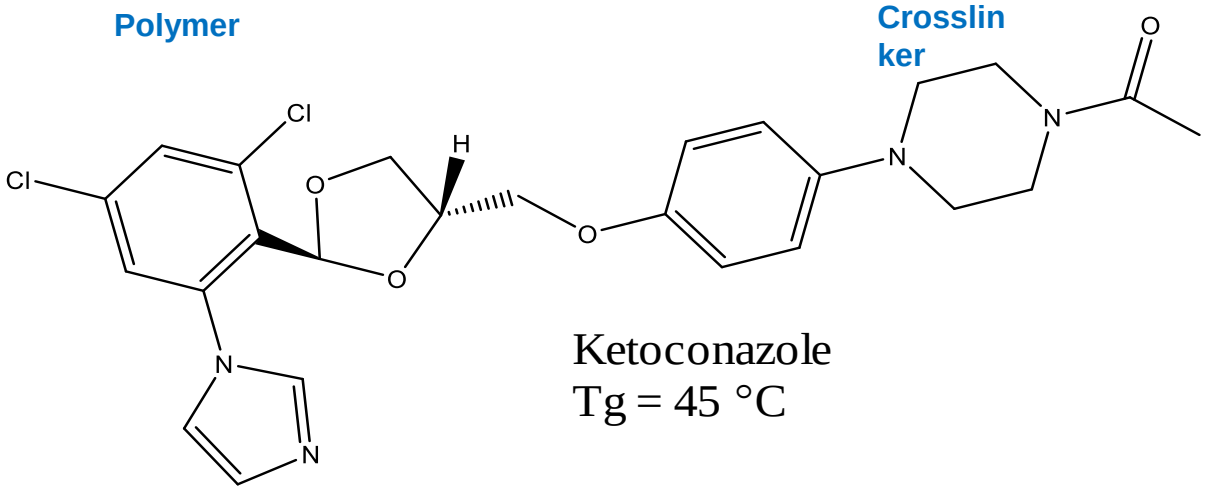
Poly (acrylic acid)
T_g = 106 °C



Poly (vinyl alcohol)
Tg = 85 °C

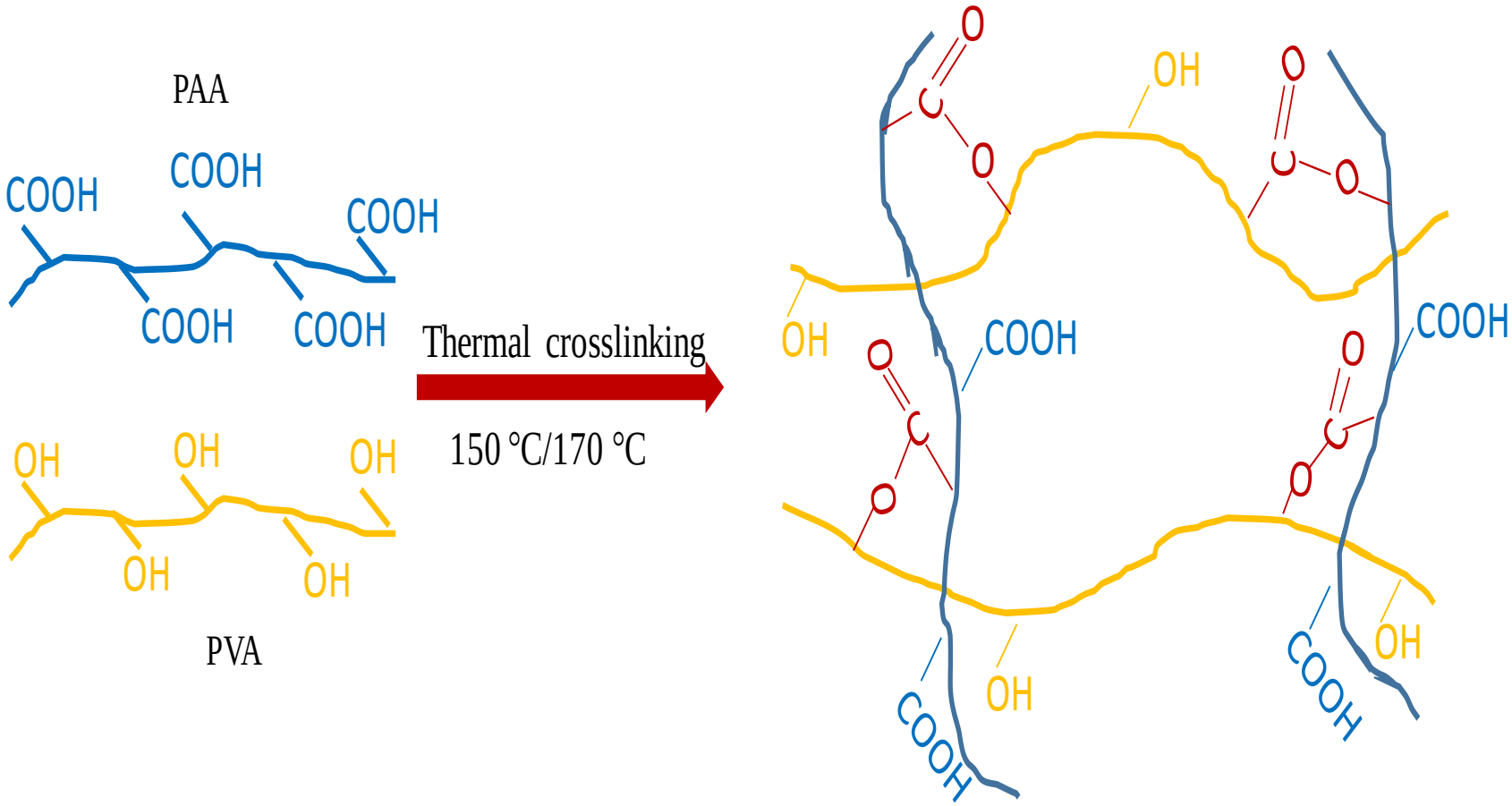
Polymer

Crosslin ker



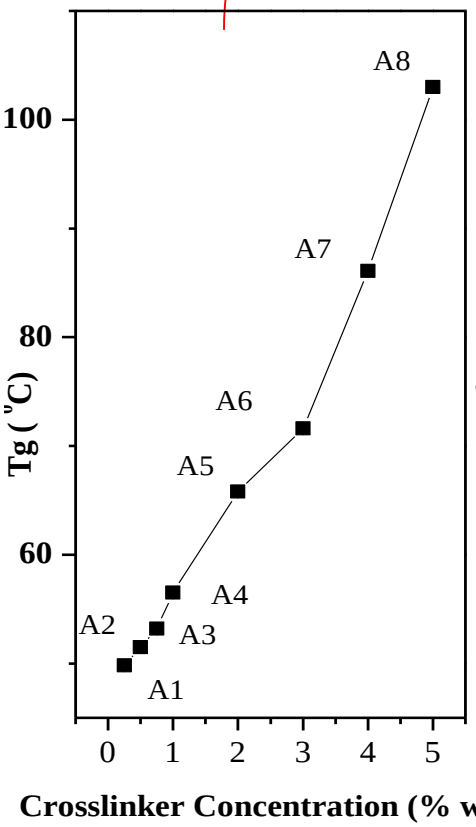
Ketoconazole
Tg = 45 °C

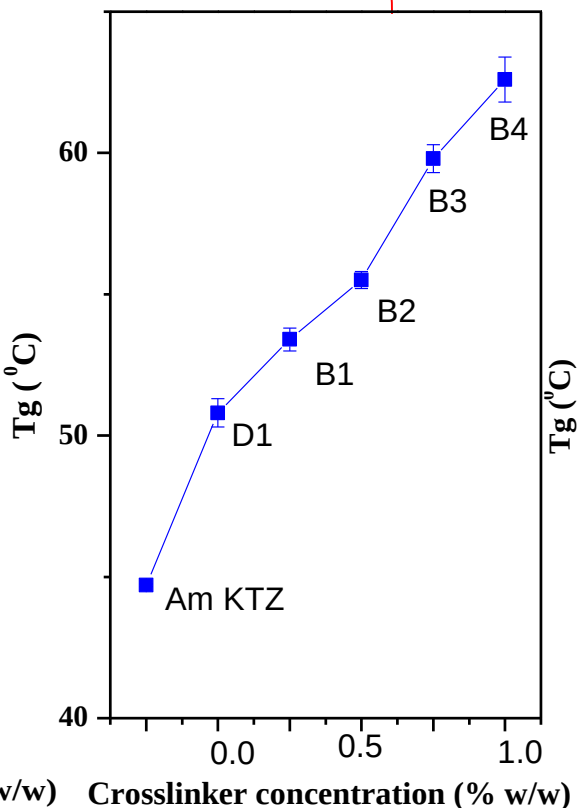
Crosslinking reaction



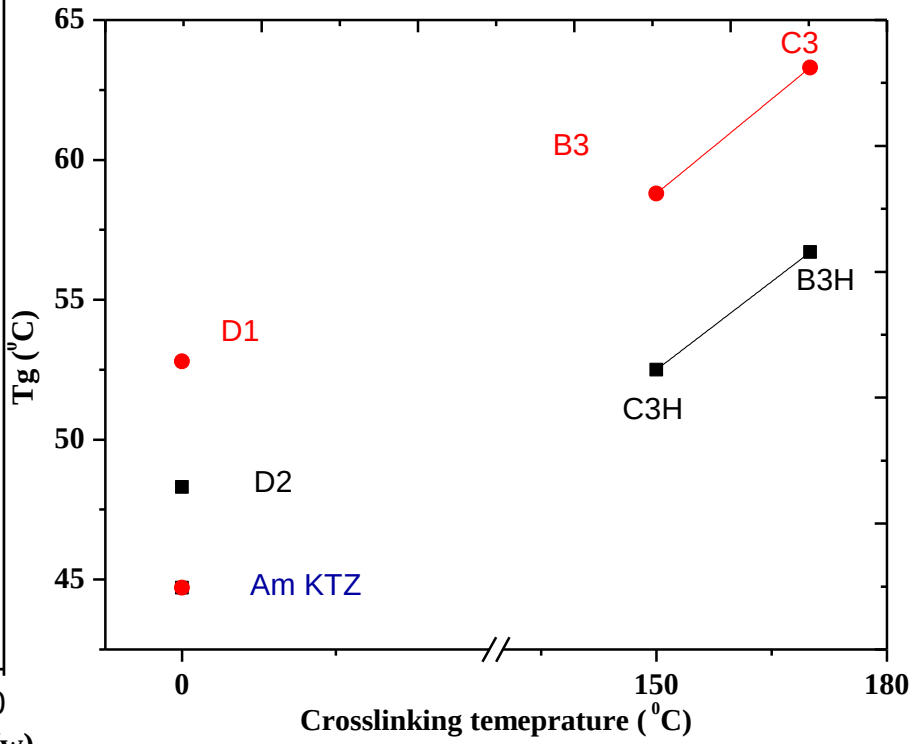
Effect of crosslinking density on thermal properties

Crosslinker concentration





Crosslinking temperature

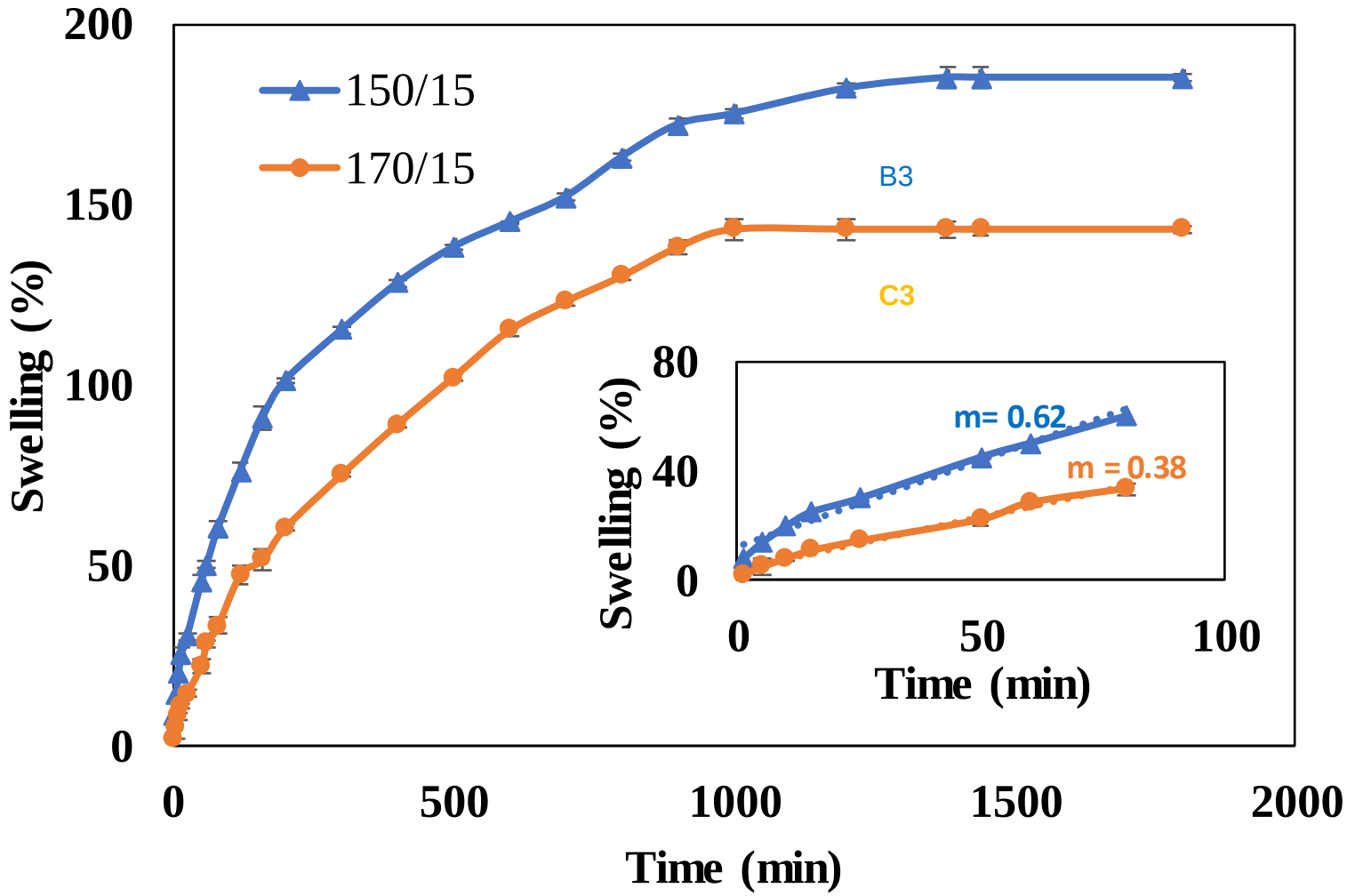


135 °C / 120 min

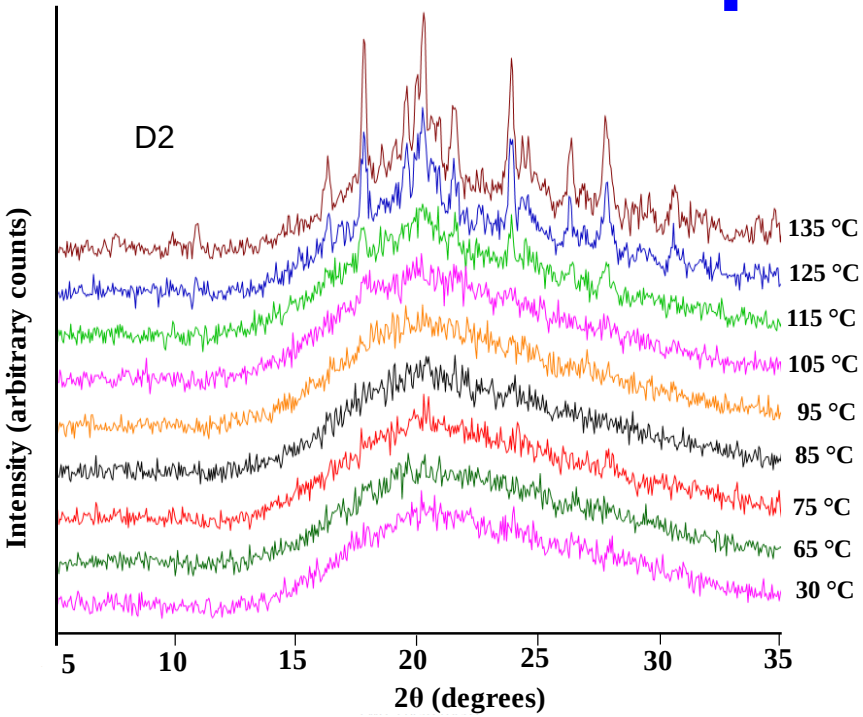
150 °C / 15 min

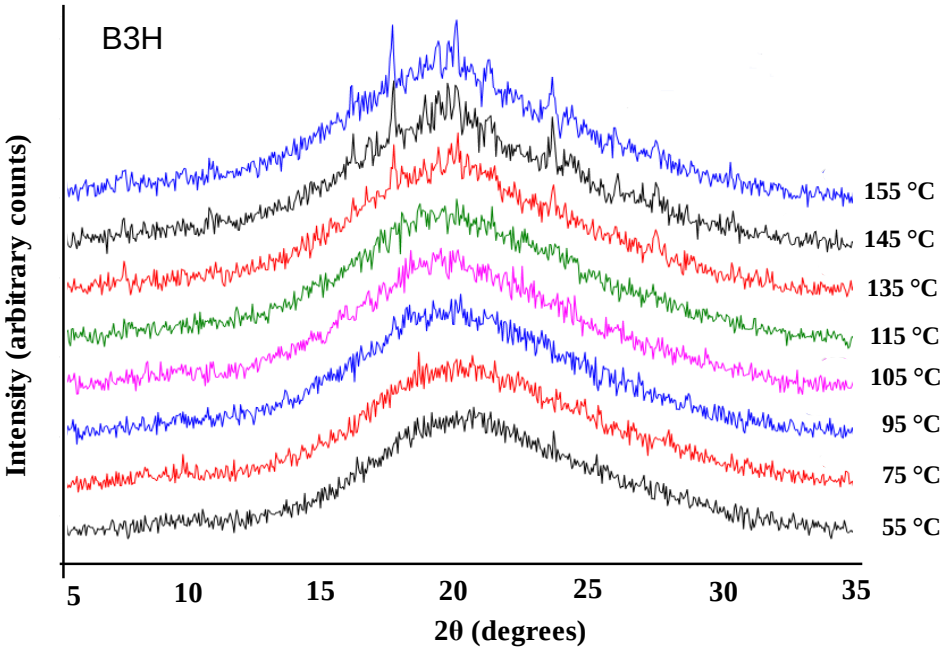
Volumetric swelling studies

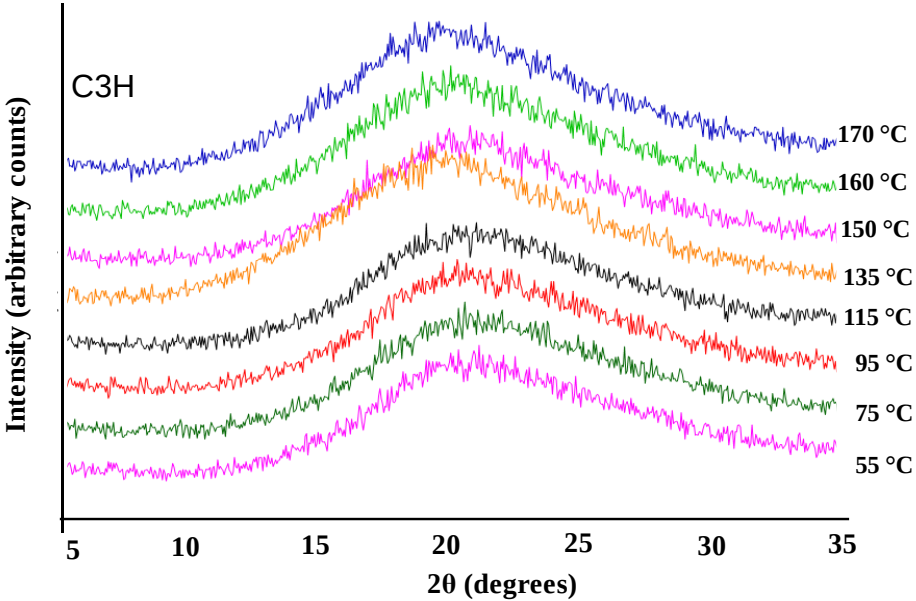
Effect of crosslinking temperature



Variable temperature XRD patterns

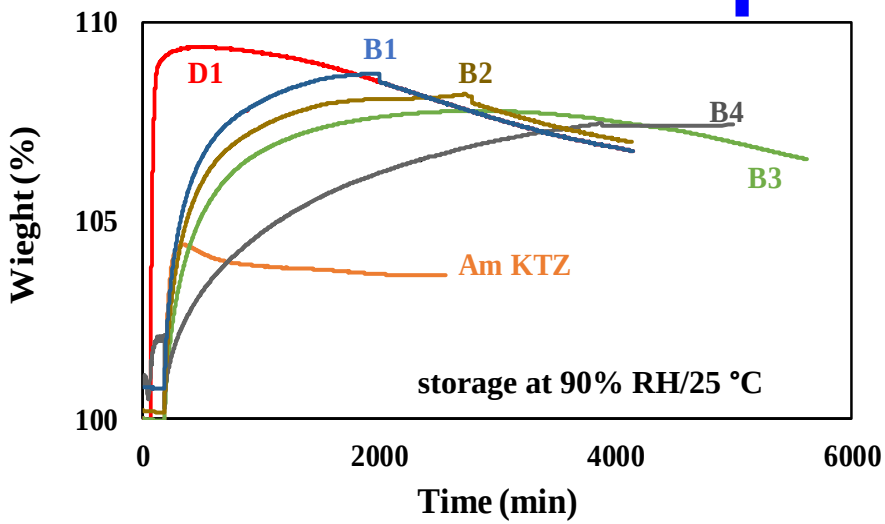




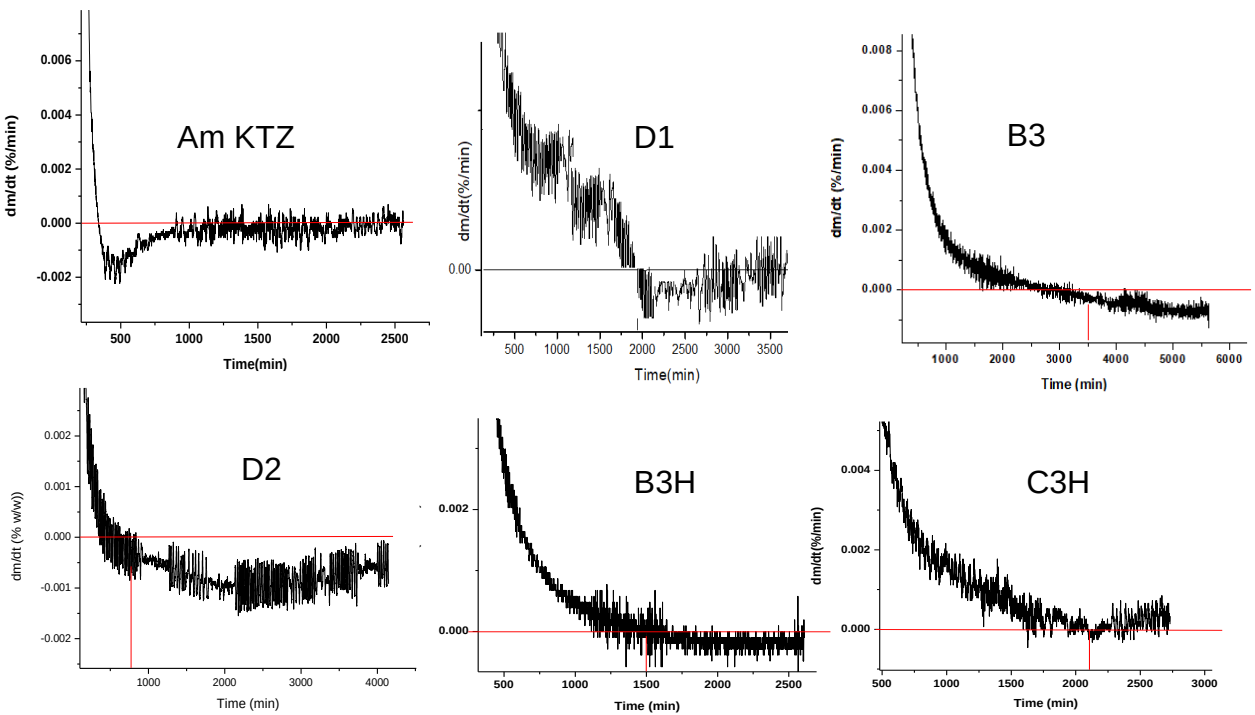


- Thermal crosslinking of the polymer retarded KTZ crystallization and enhanced the physical stability of the system.
- In addition, the crosslinking temperature provides an avenue to modulate the physical stability at high drug loading

Water sorption and physical stability profiles



- With the increase in the crosslinker concentration, there was a progressive decrease in the total amount of sorbed water (up to 2000 minutes)
- These are consistent with the results of the swelling study.

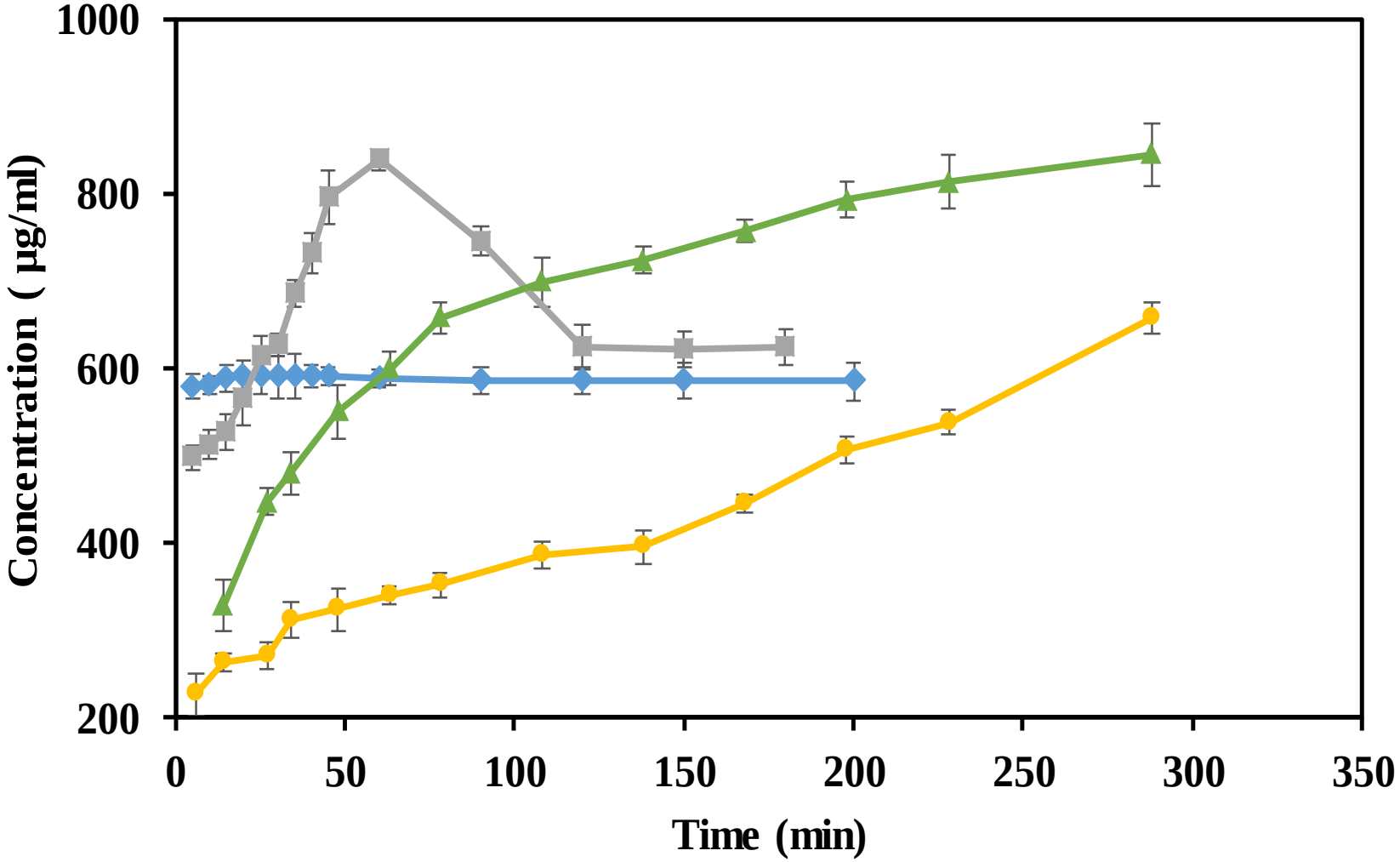


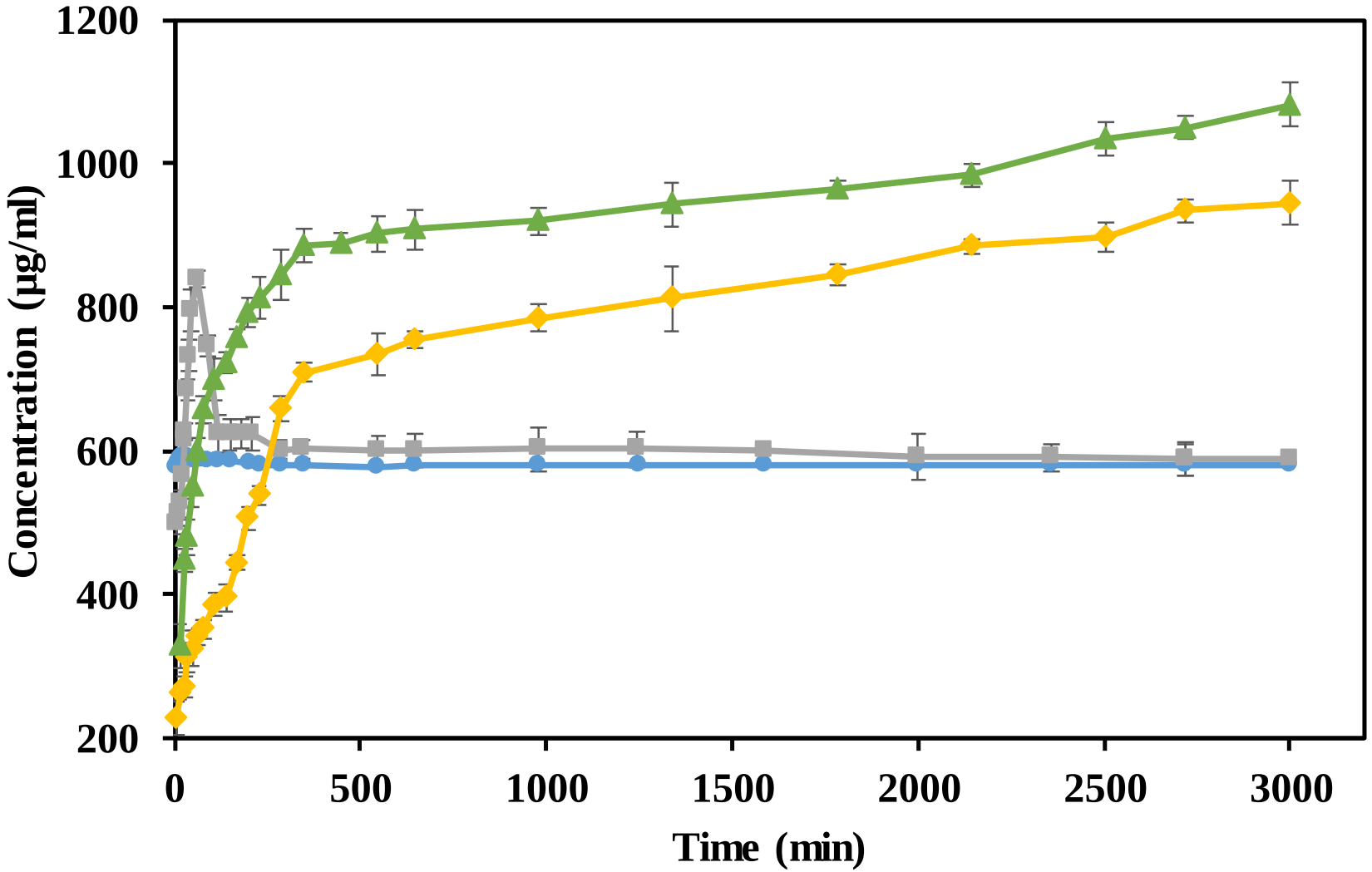
- Weight loss following water sorption is a consequence of crystallization
- The onset time for crystallization increased as a function of crosslinker concentration and crosslinking temperature as is evident from the derivative plots

Long term and accelerated physical stability of the ASDs

Stability	Storage condition	KTZ retained amorphous for:	
		B3H[a]	C3H[b]
Long Term Stability	8±3 °C/20±4 %RH	>24 months[c]	>24 months[c]
	23±3 °C/32±5 % RH	>18 months[c]	>18 months[c]
Accelerated Stability	40 ± 2 °C/75±5 % RH	20 days	31 days
	60 ± 2 °C/75±5 % RH	4 days	7 days
	80 ± 2 °C/75±5 % RH	7 hours	17 hours
	80 ± 2 °C	2 days	4 days

- The sample crosslinked at 170 °C / 15 min (C3H) resisted crystallization for longer time period than the sample crosslinked at 150 °C / 15 min (B3H).
- This is because of the high crosslinking density of the system, C3H. This robust stability can be predominantly attributed to the ability of the crosslinked matrix to retard KTZ crystallization.


1000
800
600
400
200
Concentration (µg/ml)
0
50
100
150
200
250
300
350
Time (min)


1200
1000
800
600
400
200
Concentration (µg/ml)
0
500
1000
1500
2000
2500
3000
Time (min)

Take home messages

- Solubility (and dissolution rate) enhancement can be achieved by drug amorphization

- Maintaining the supersaturated state in solution can be a challenge
  - May not be able to practically realize the solubility enhancement

Take home messages … contd

- Polymeric dispersions provide an avenue to maintain supersaturation
  - Drug-polymer interaction
  - Modulating the microenvironmental pH
  - Modifying the polymer matrix (degree of crosslinking)

THANK YOU