Capturing The Significance of X-Ray Crystallography in Pharmaceutical Field:

The Application to Characterize New Salt, Co-Crystal and Co-Amorphous

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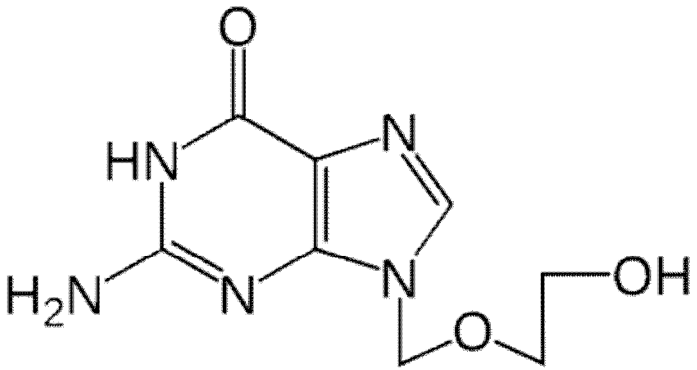
Acyclovir



- Guanosine analogue antiviral drugs.
- The treatment of herpes simplex virus infections.

Outline

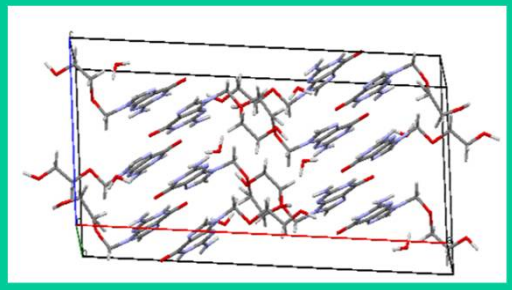
- Screening and Characterization
  - Screenig methods and used additives
  - Selected cocrystals (PXRD、TG/DTA、DSC）
- Application for oral dosage form
  - Intrinsic dissolution of selected cocrystal
  - Crystal structure of selected cocrystal
  - Mechanism for solubility enhansment
- Application for transdermal dosage form
  - Transdermal adsorption propertiy of selected complex
  - Solubility of amorphous comples
  - Improvement of transdermal properties

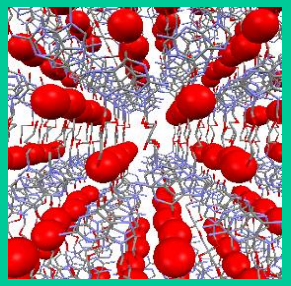
2/3 Hydrate

Commercially available

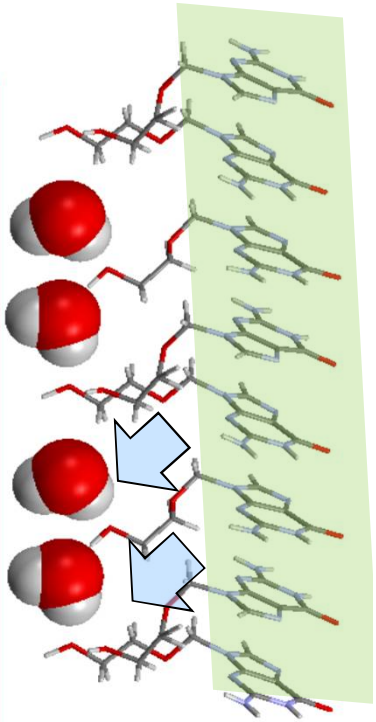
P2$_1$/n
a 25.459(1) Å
b 11.282(1) Å
c 10.768(1) Å
β 95.16(1) °
Volume
3080.342 Å^3
Z 12
R-factor 5.3 %

Recrystalized from ethanol solution





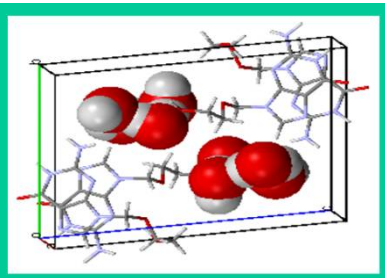
Column structure
Stacking purine moiety



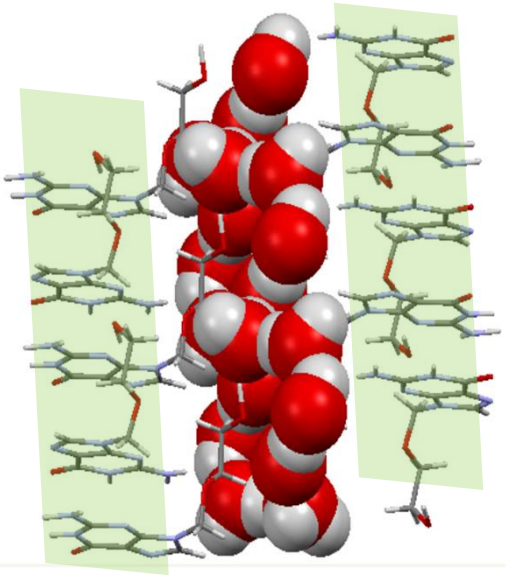
Dihydrate

From ammonium solution

P-1
a 6.8386(7) Å
b 11.3679(14) Å
c 14.942(2) Å
α 82.845(4) °
β 82.419(3) °
γ 89.326(3) °
Volume
1142.5(2) Å^3
Z 4
R-factor 7.71 %

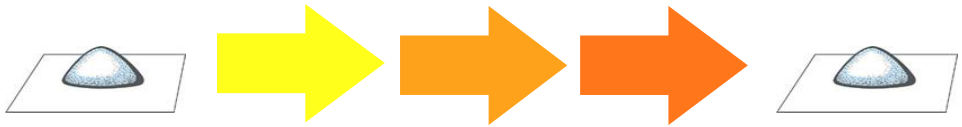


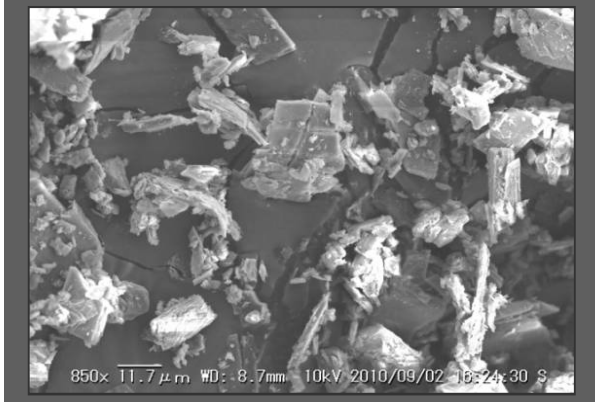
Channel structure
Stacking purine moiety



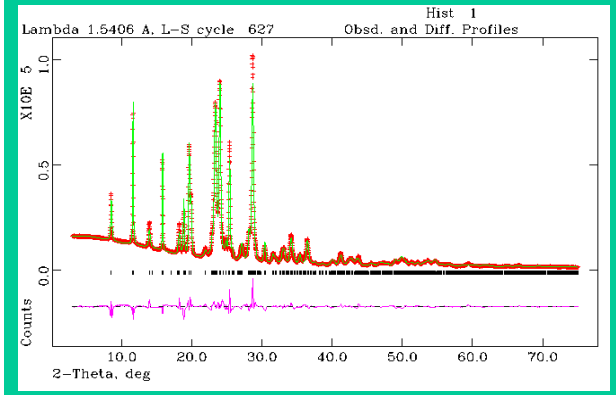
Anhydrate2

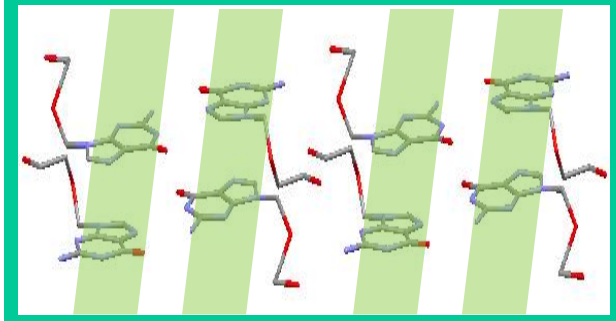
Dehydration of hydrates





$P2_1/c$
a 10.9399(6) Å
b 11.1837(6) Å
c 8.1164(4) Å
β 108.6277(34) °
Volume
941.009 Å^3
Z 4

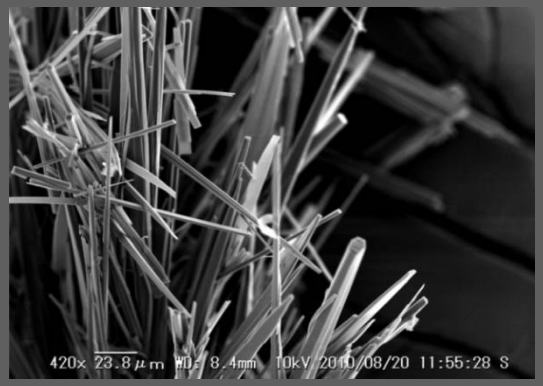


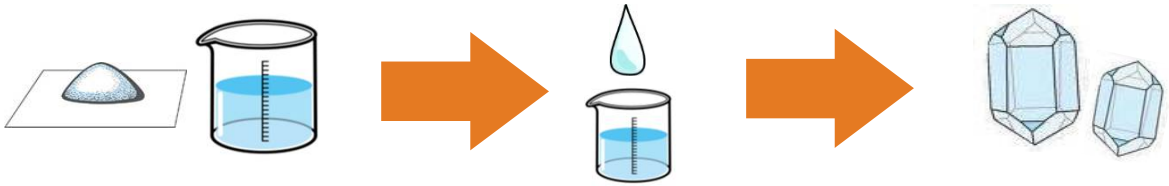


Stacking purine moiety

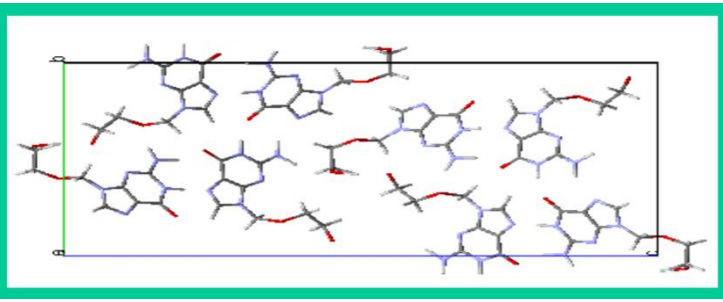
Anhydrate2

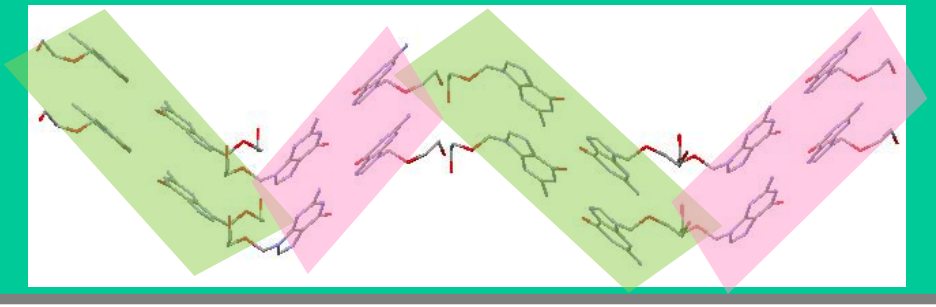
Crystallization by Vapor-Diffusion. Procedure. (DMF+Acetonitrile)





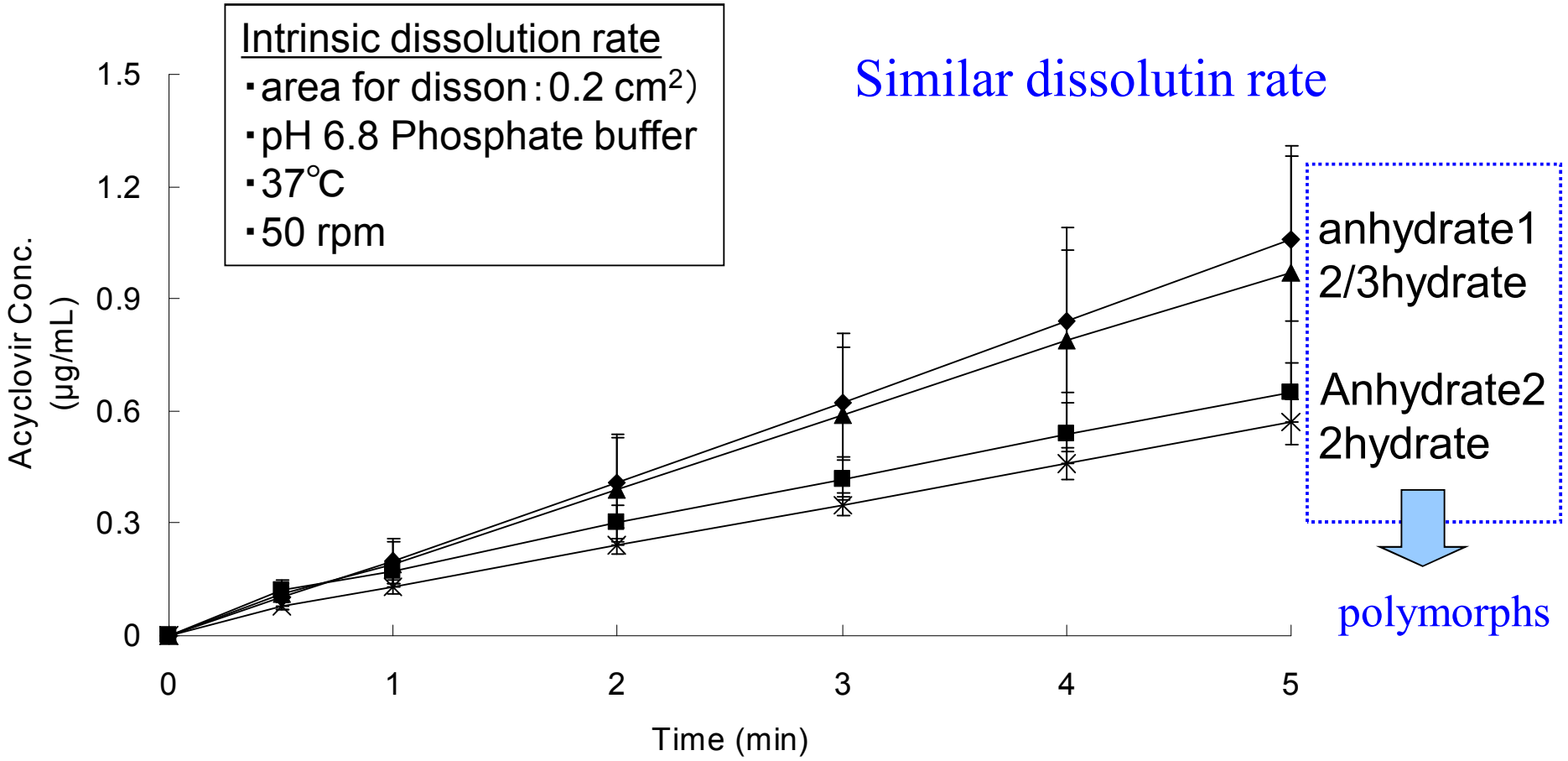
P $2_12_12_1$
a 4.5387(10) Å
b 15.0308(3) Å
c 28.3320(6) Å
Volume
1932.82 Å^3
Z 8
R-factor 9.88 %





Different stacking mode

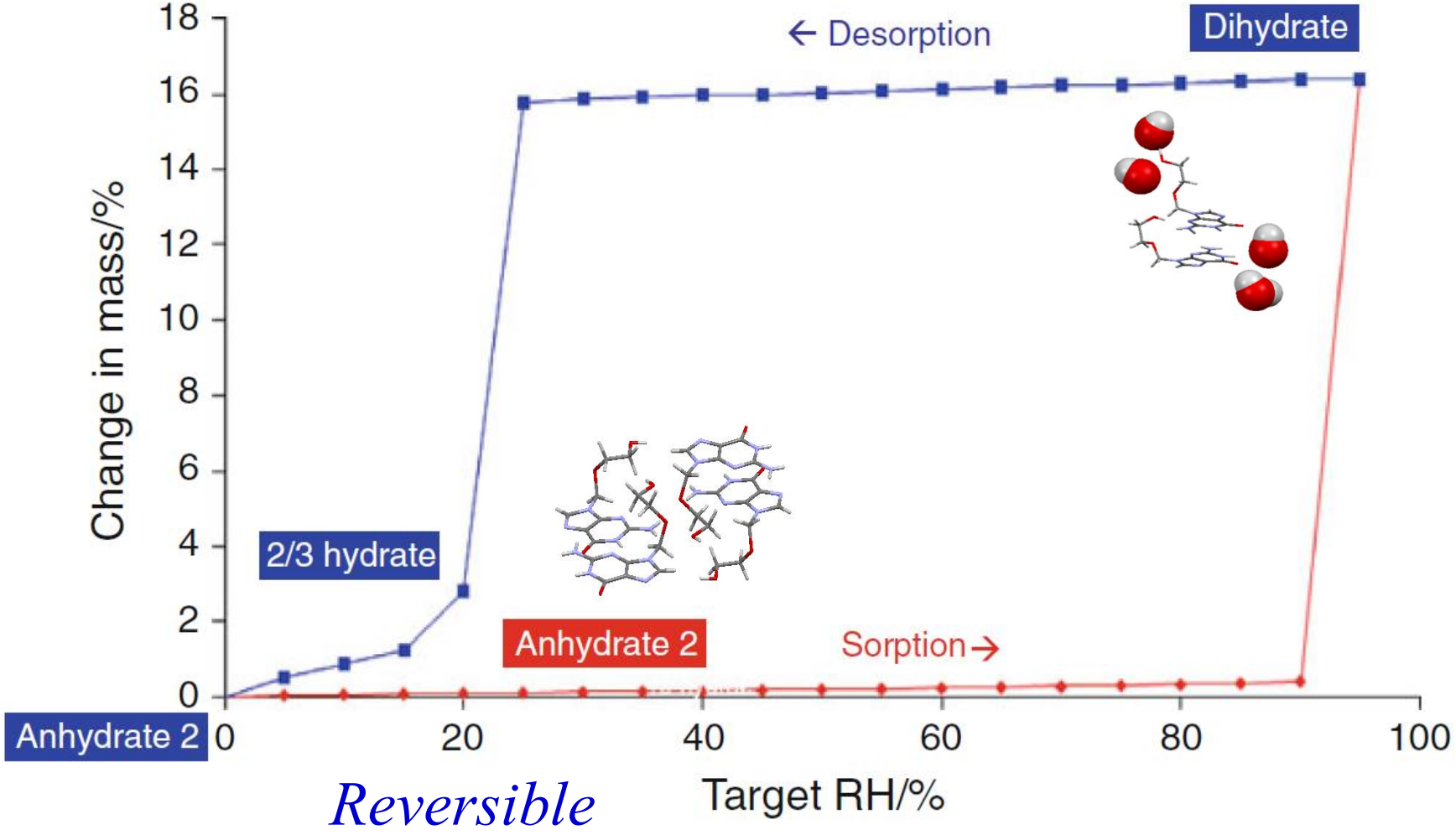
Dissolution properties for acyclovir polymorphs



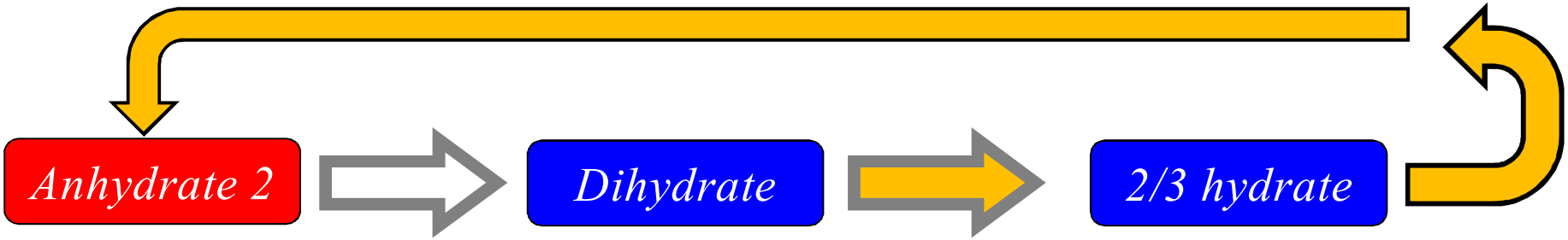
Transformation of anhydrate to hydrate was quick.
Anhydrates were useless

Hydration mechanisum？

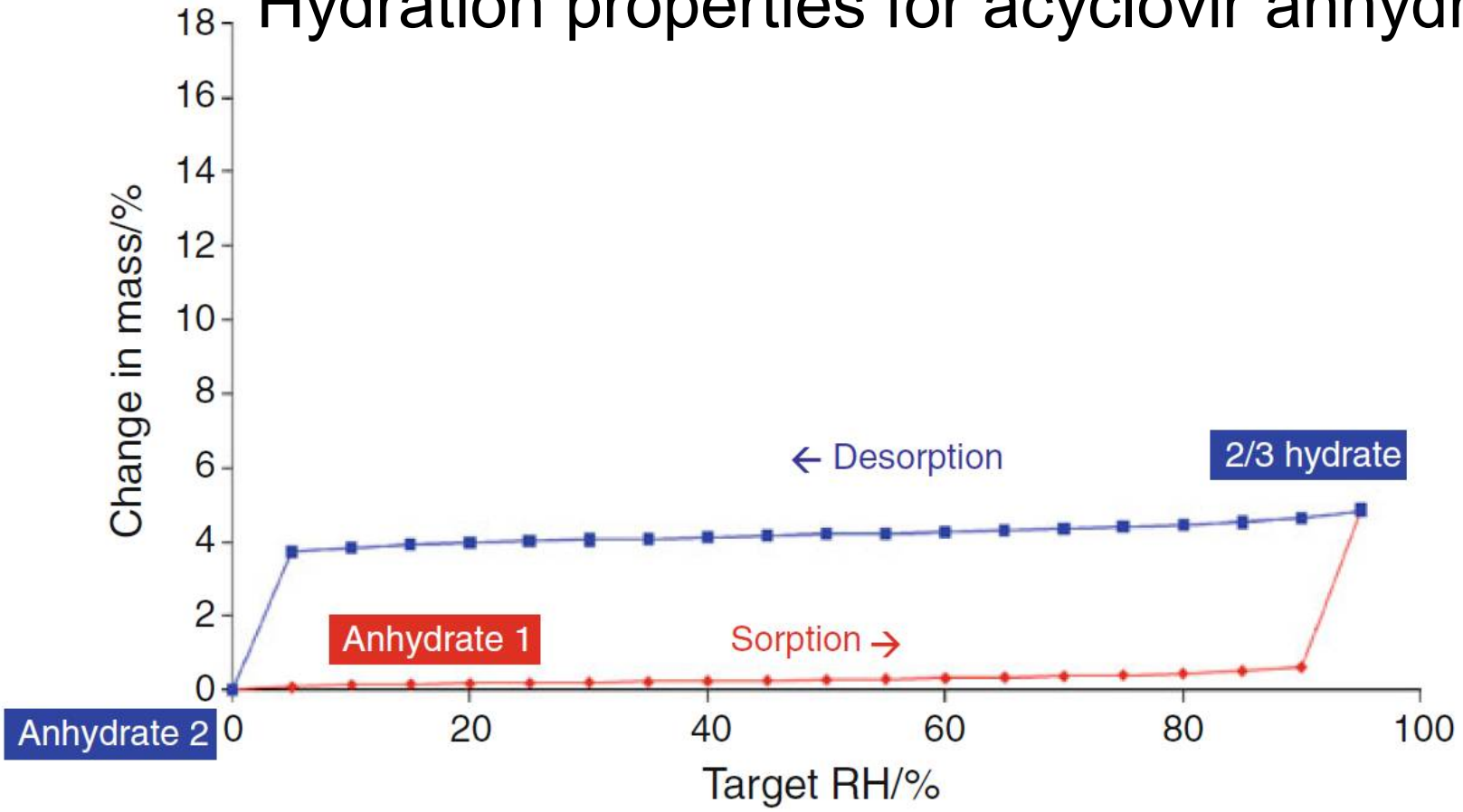
Hydration properties for acyclovir anhydrate2

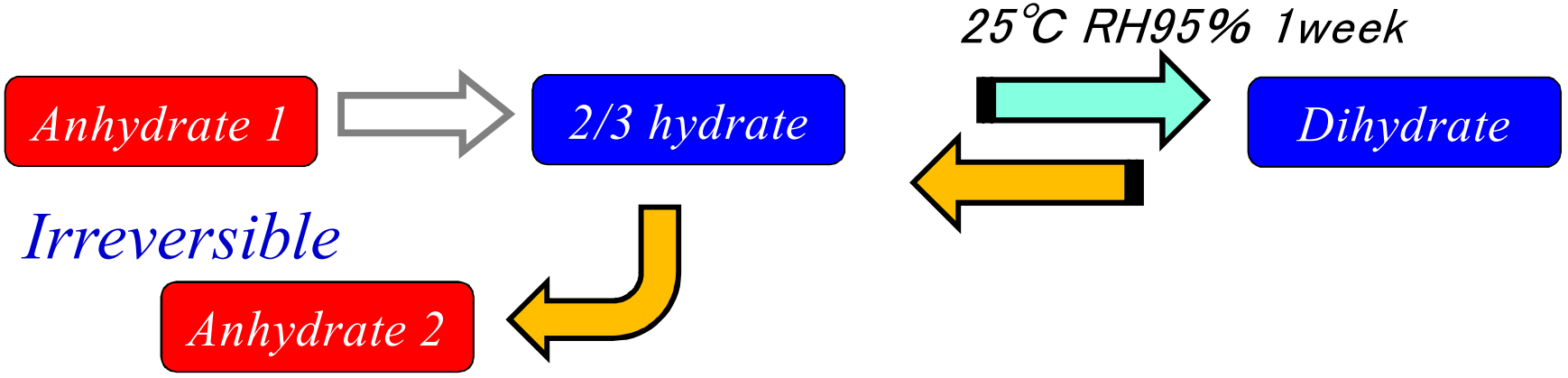


Reversible

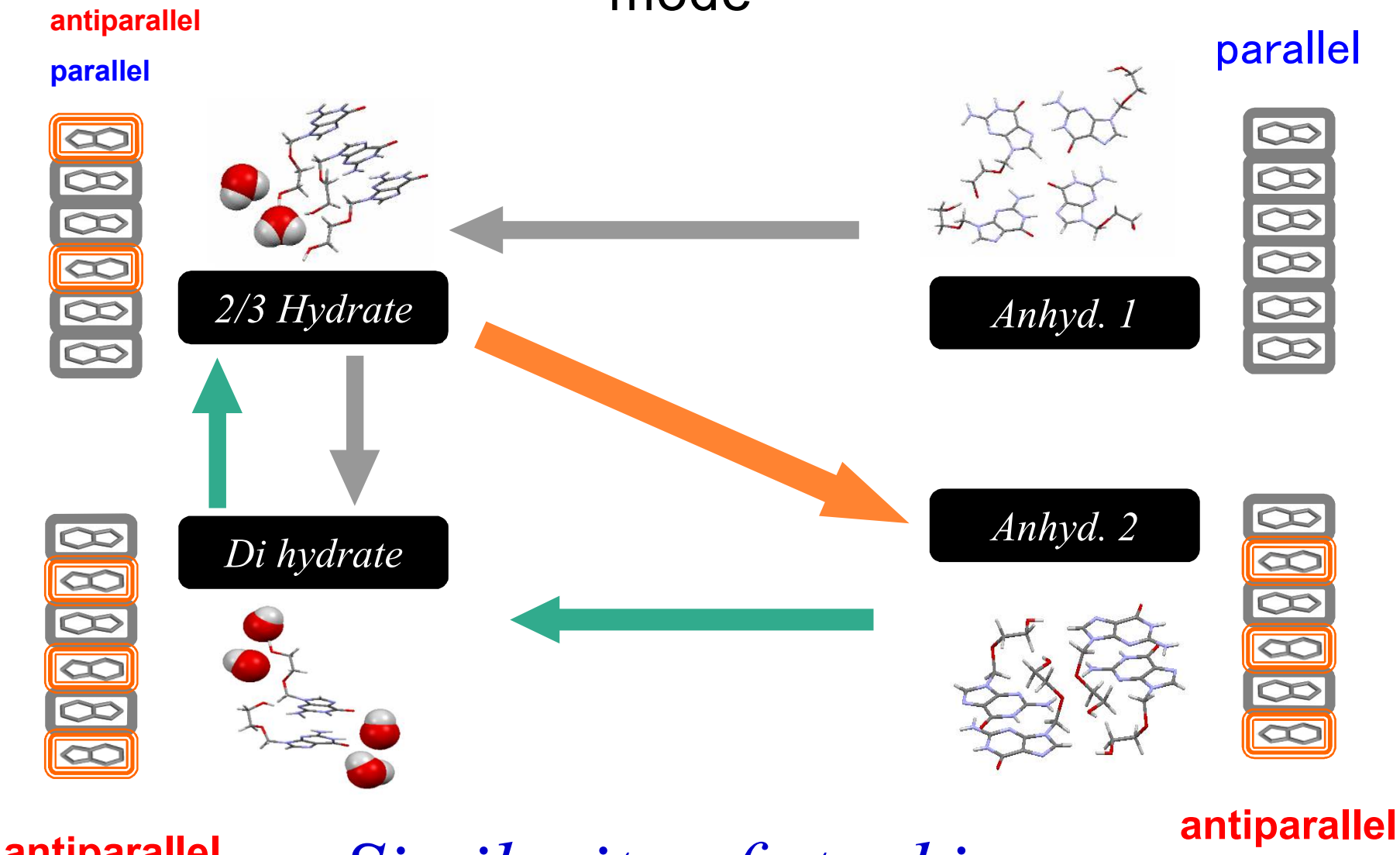


Hydration properties for acyclovir anhydrate1





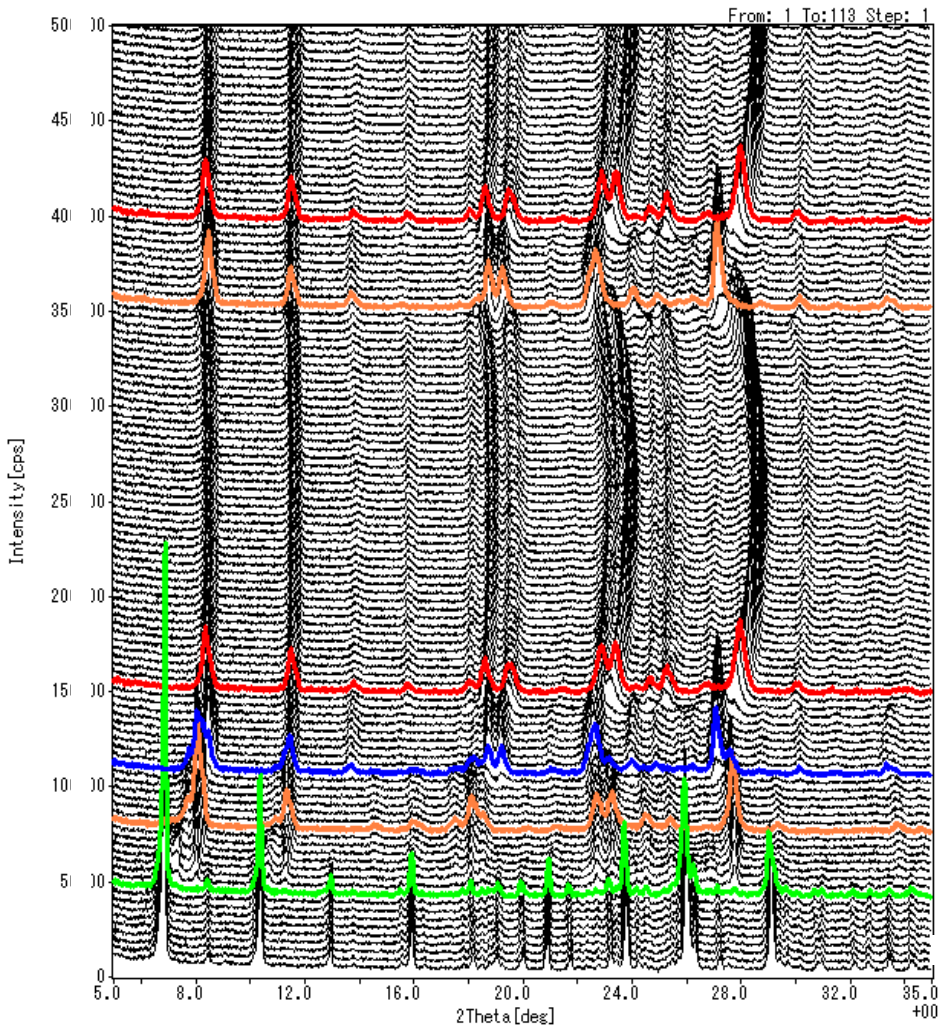
Comparison between transition behavior and stacking mode

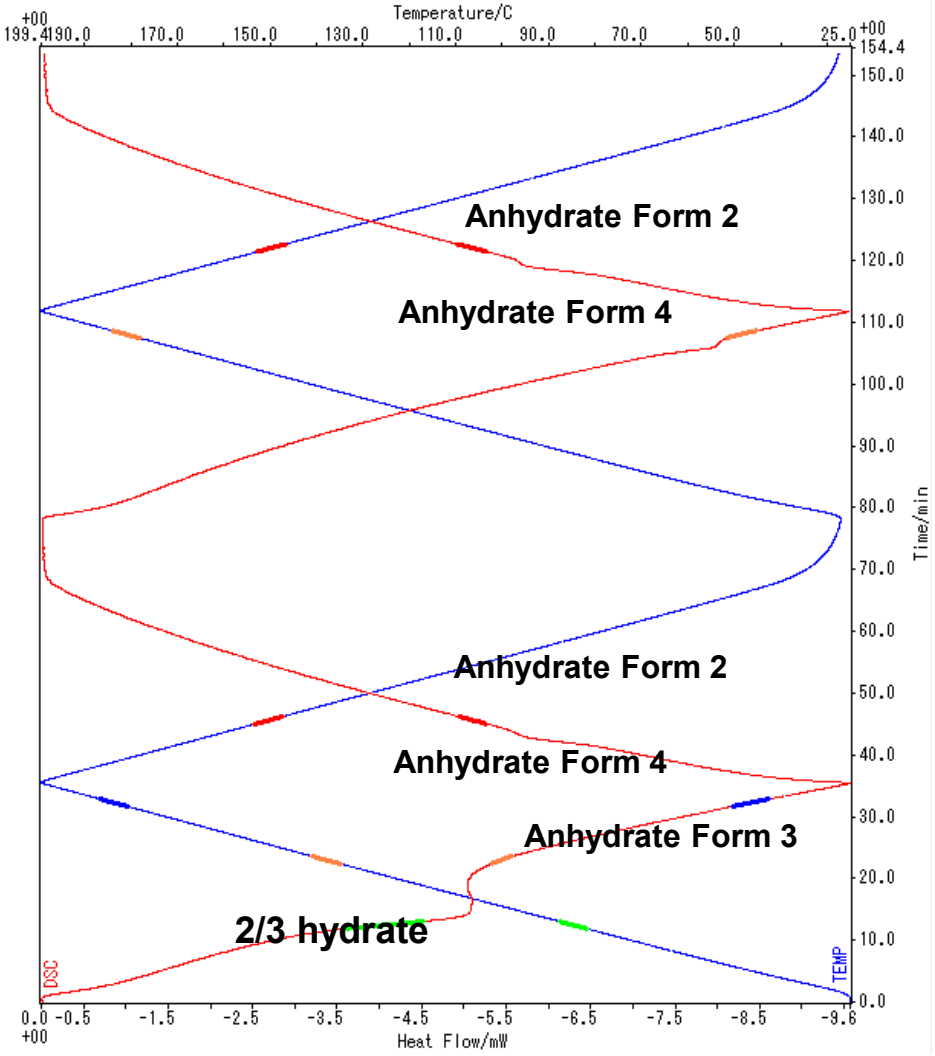


Similarity of stacking

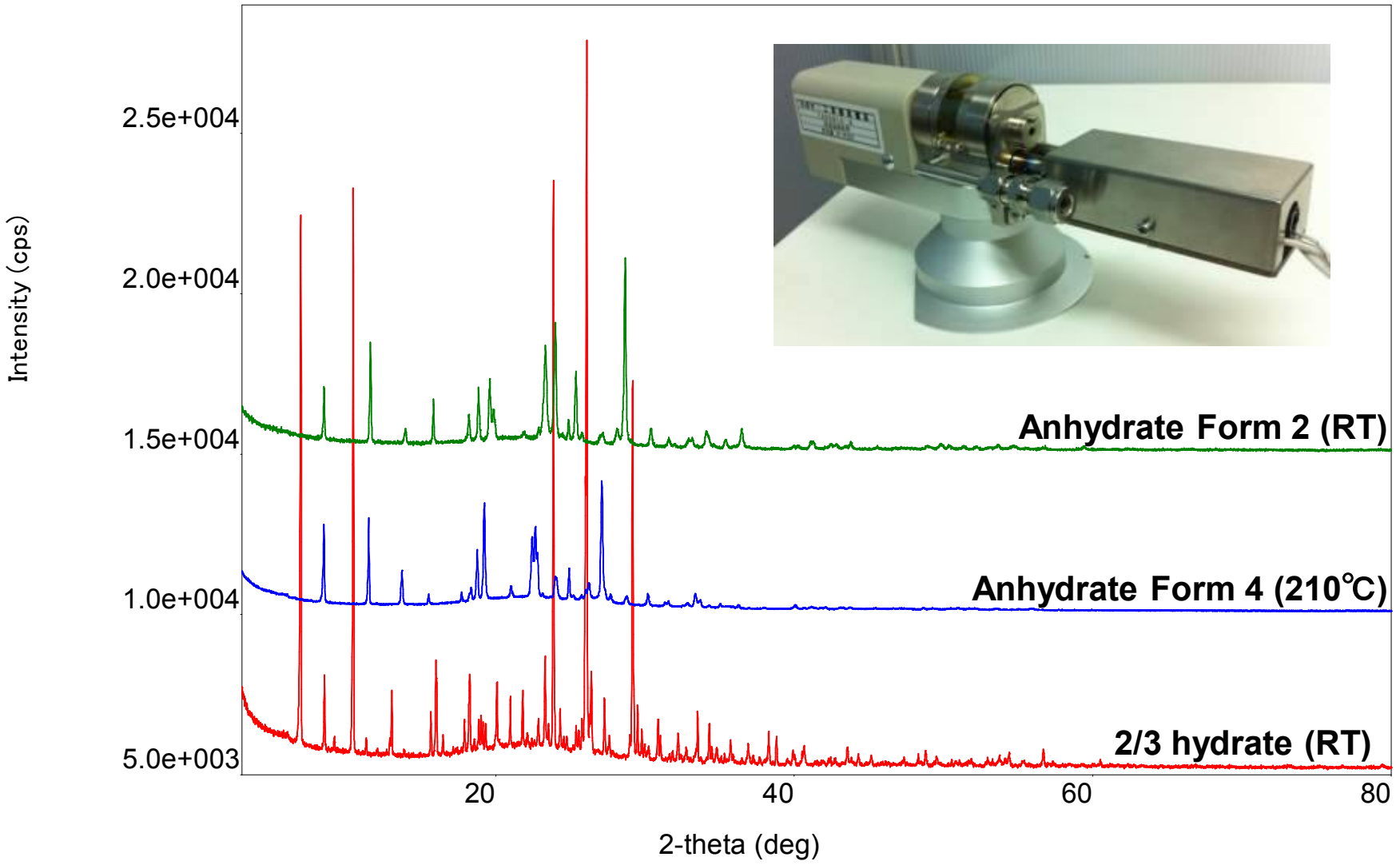
The phase transition mechanism is complicated.

X-ray DSC

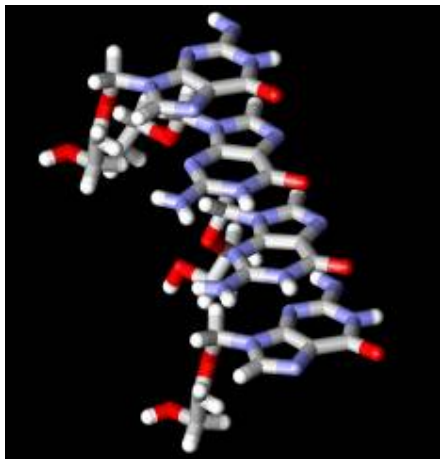




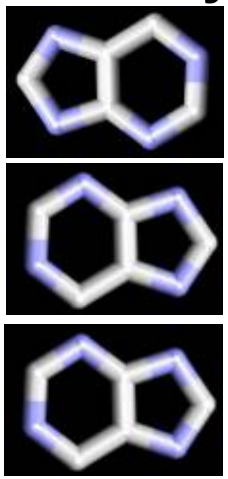
XRPD patterns of acyclovir using HT capillary sample holder



Comparison from the view of stacking structure

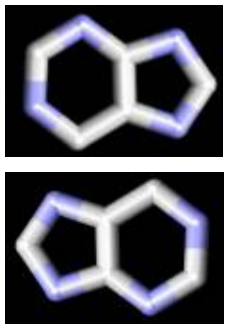


2/3 hydrate

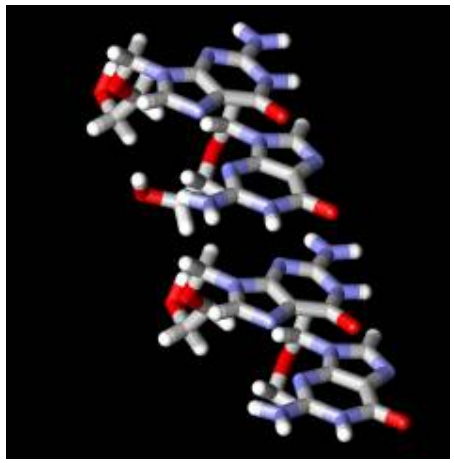


antiparallel

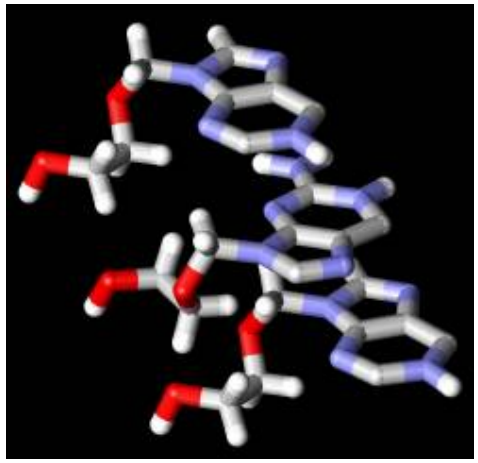
parallel



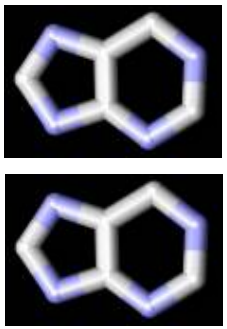
antiparallel



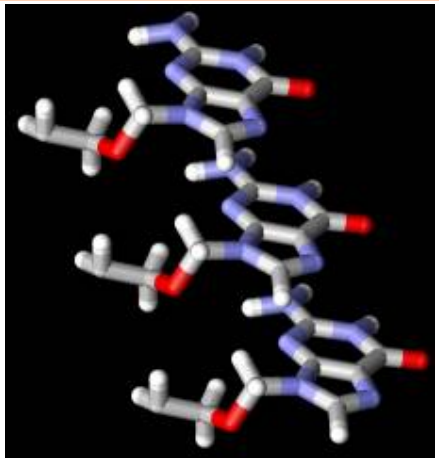
Anhydrate Form 4



Anhydrate Form 2

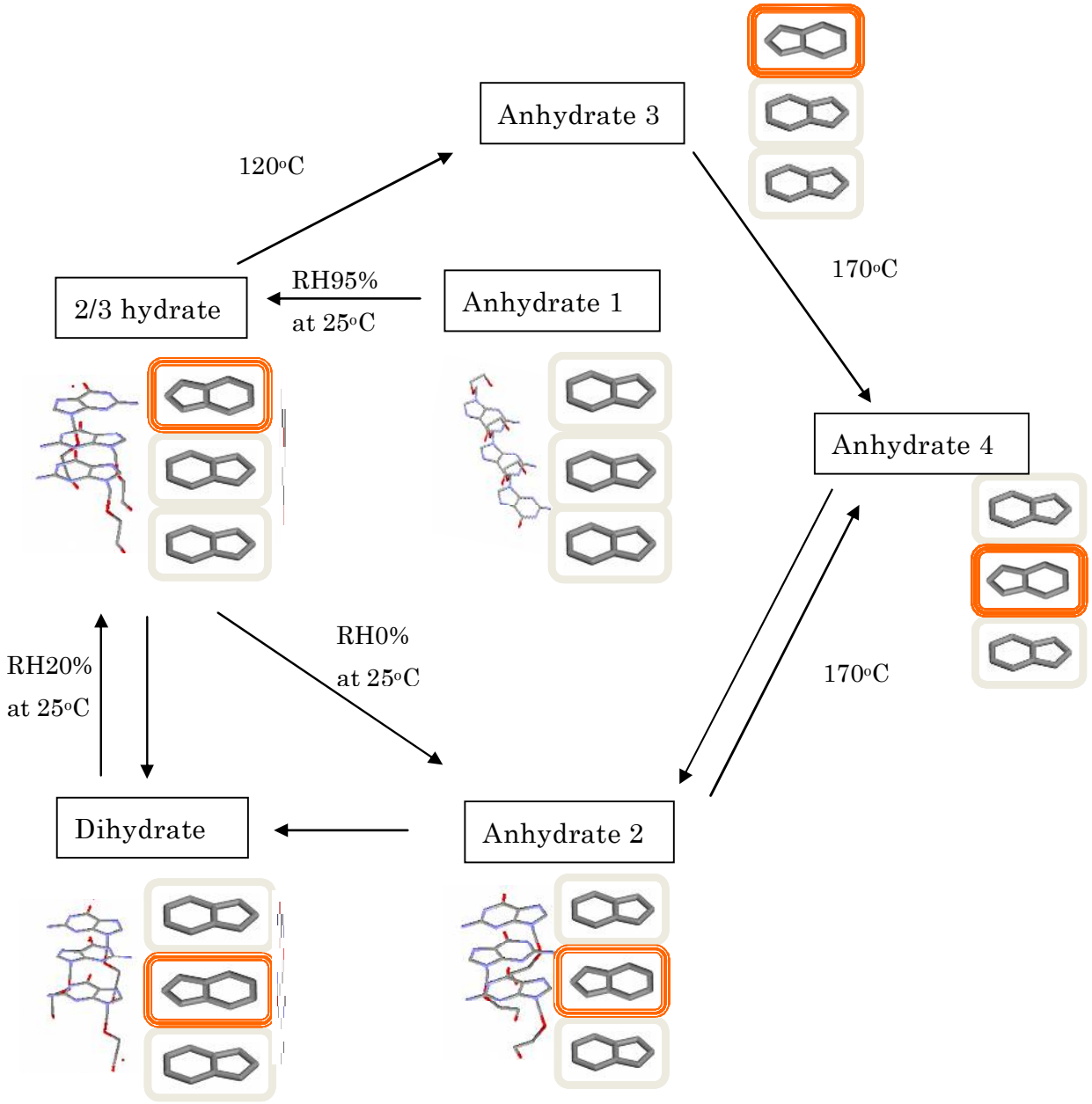


parallel



Anhydrate Form 1

Phase Transition of Acyclovir polymorphs



Conclusion

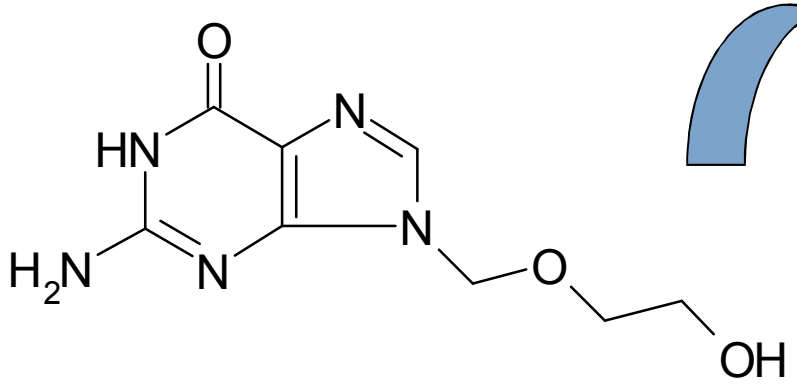
- There are two packing manners for purine moiety. Anhydrate 1, anhydrate 2, 2/3 hydrate and ACV dihydrate were packed in parallel, antiparallel, mixture of parallel—anti-parallel and parallel manners, respectively.

- Based on the packing manner of ACV, it can be seen why the phase transformation occurs with readily or with difficulty.

Outline

- Characterization
  - Screenig methods and used additives
  - Selected cocrystals (PXRD、TG/DTA、DSC）
- Application for oral dosage form
  - Intrinsic dissolution of selected cocrystal
  - Crystal structure of selected cocrystal
  - Mechanism for solubility enhansment
- Application for transdermal dosage form
  - Transdermal adsorption propertiy of selected complex
  - Solubility of amorphous comples
  - Improvement of transdermal properties

dissolution properties



Sprangly soluble in water

Dissolution rate and solubility for water

Activity related to the solubility in base

Oral dosage form

Bioavailability : low

D. Patel, *et al*. *Drug. Dev. Ind. Pharm.* 33:1318 (2007).

Transdermal

Transdermal Absorption : low

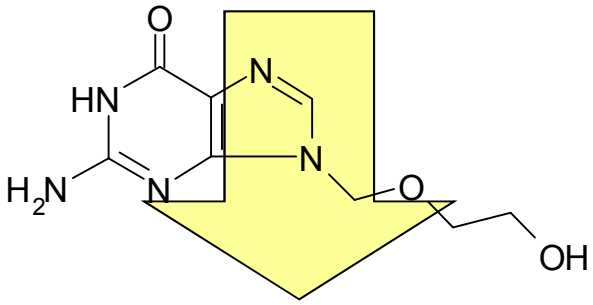
D. J. Freeman, *et al*. *Antimicrob. Agents Chemother.* 29:730 (1986).

Improvement of solubility

Improvement of the physicoshemical properties

methods

- polymorphs
- Salt formation
- Package
- gringing
- Solvate
- Cocrystal
- Solid dispersion
- amorphous



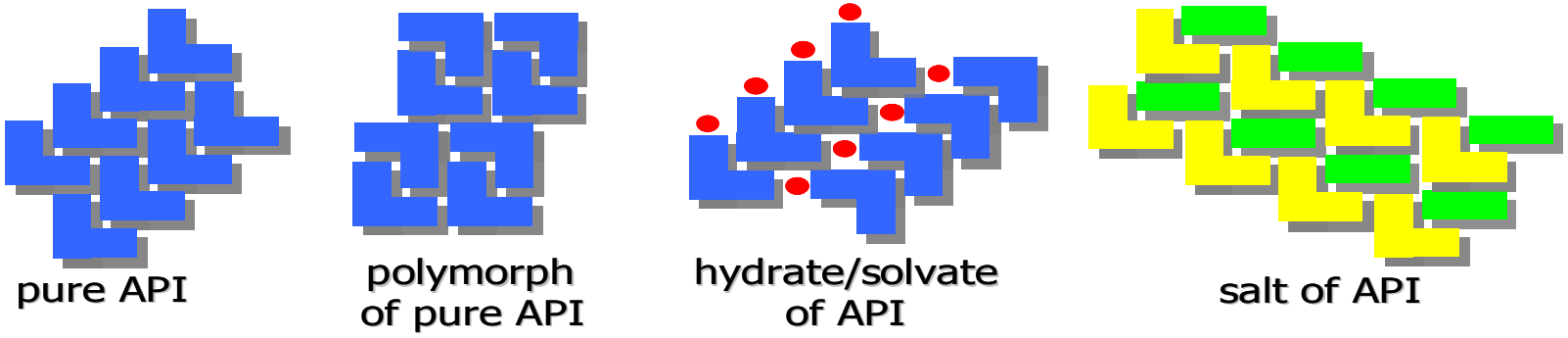
Applicaton for oral dosage form

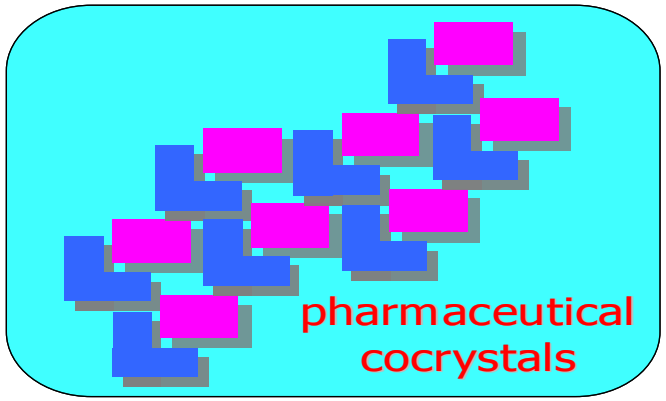
Cocrystal→Improvement of dissolution properties

Application for transdermal dosage form

Amorphization→Increase the solubility in base→ Increase the absorption

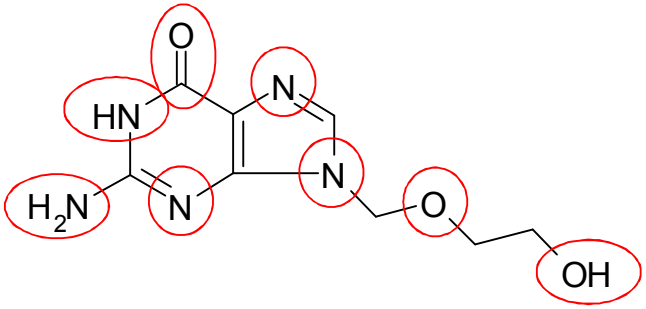
Cocrystal・・・





: Multicomponent crystal
: Hydrogen bonding, Neutral

Multicomponent crystal
Hydrogen bonding, Neutral



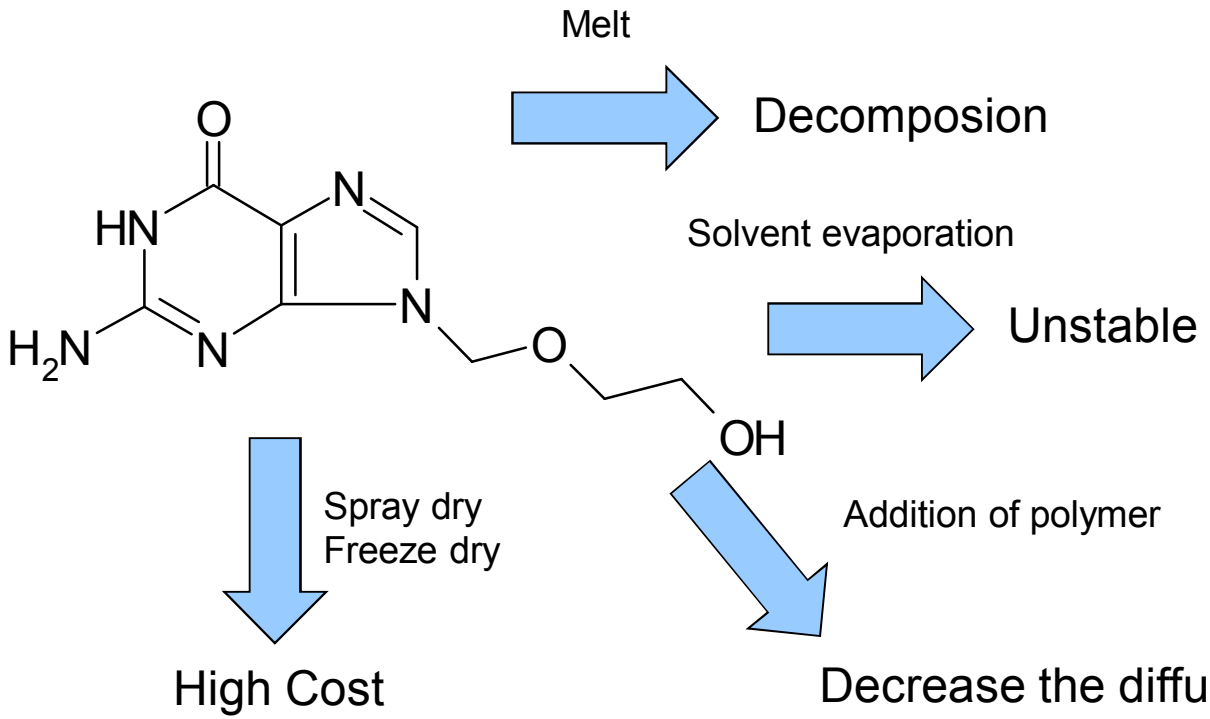
○ :Hydrogen bond donor or acceptor sites

ACV has many functional groups,
Capable to make hydrogen bonding

Cocrystal formation

Generally recognized as safe compound

Amorphization of Acyclovir



Comventional methods isn't suitable for the amorphization

Preparation of Amorphous complex with additives

Outline

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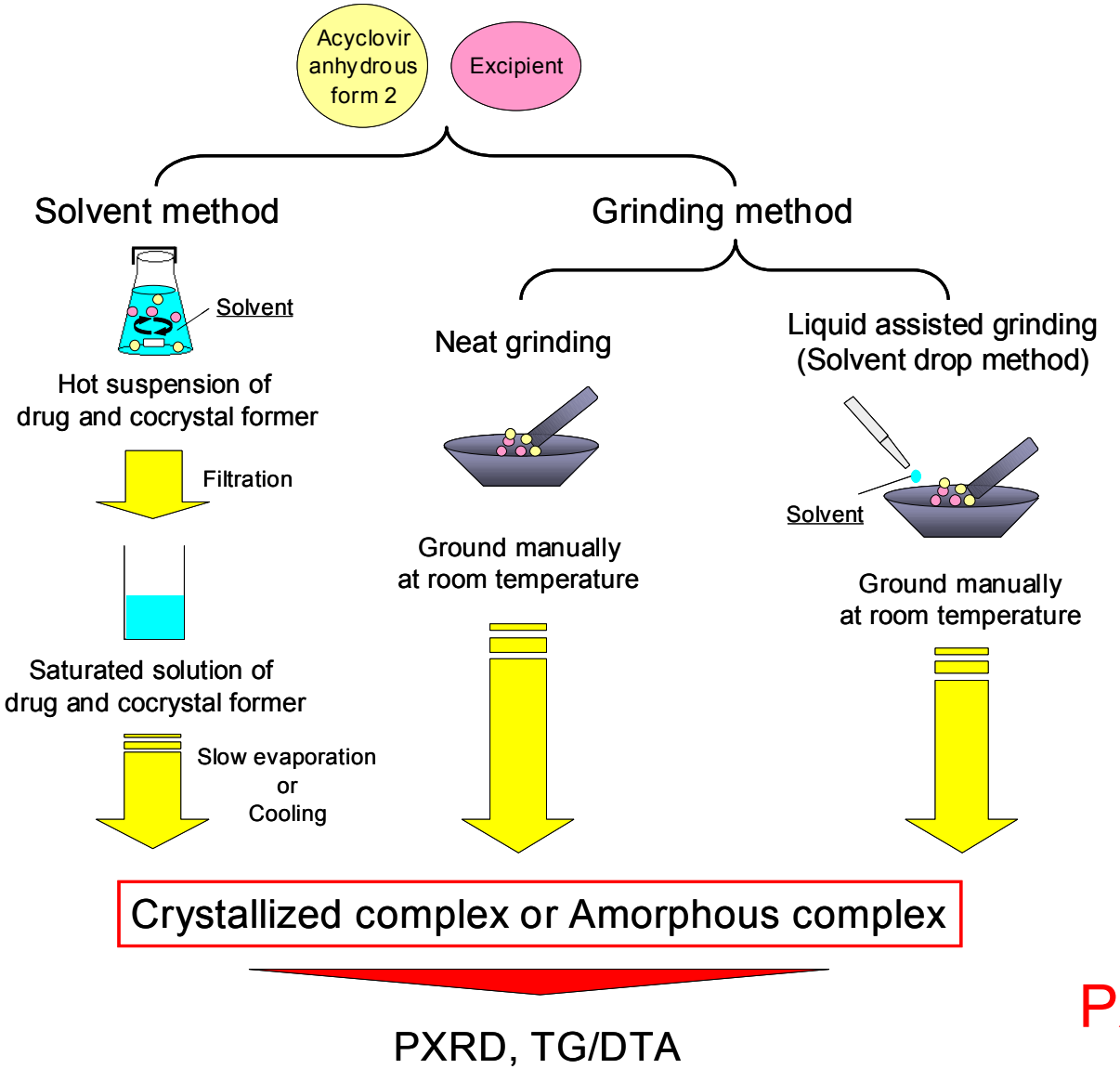
  - Mechanism for solubility enhansment
- Application for transdermal dosage form
  - Transdermal adsorption propertiy of selected complex
  - Solubility of amorphous comples
  - Improvement of transdermal properties

Screening methods



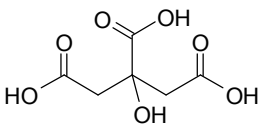
Screening by
Solvent, Grinding

Liquid assisted grindig

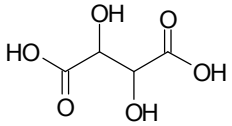
14additives
9 solvent

Evaluated by
PXRD, Themal Analysis

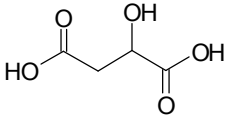
Generally recognized as safe compounds used



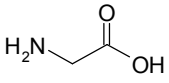
Citric acid



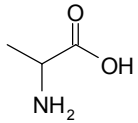
Tartaric acid



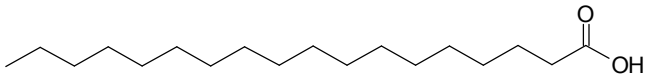
Malic acid



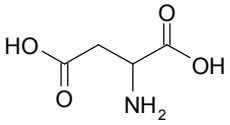
Glycine



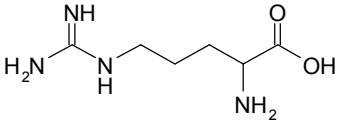
Alanine



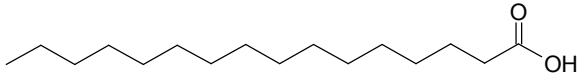
Stearic acid



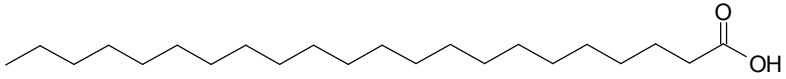
Aspartic acid



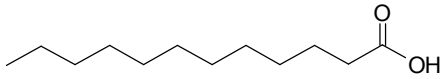
Arginine



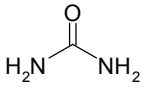
Palmitic acid



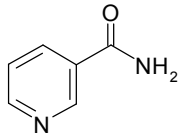
Docosanoic acid



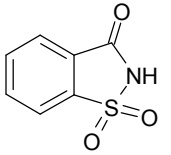
Lauric acid



Urea



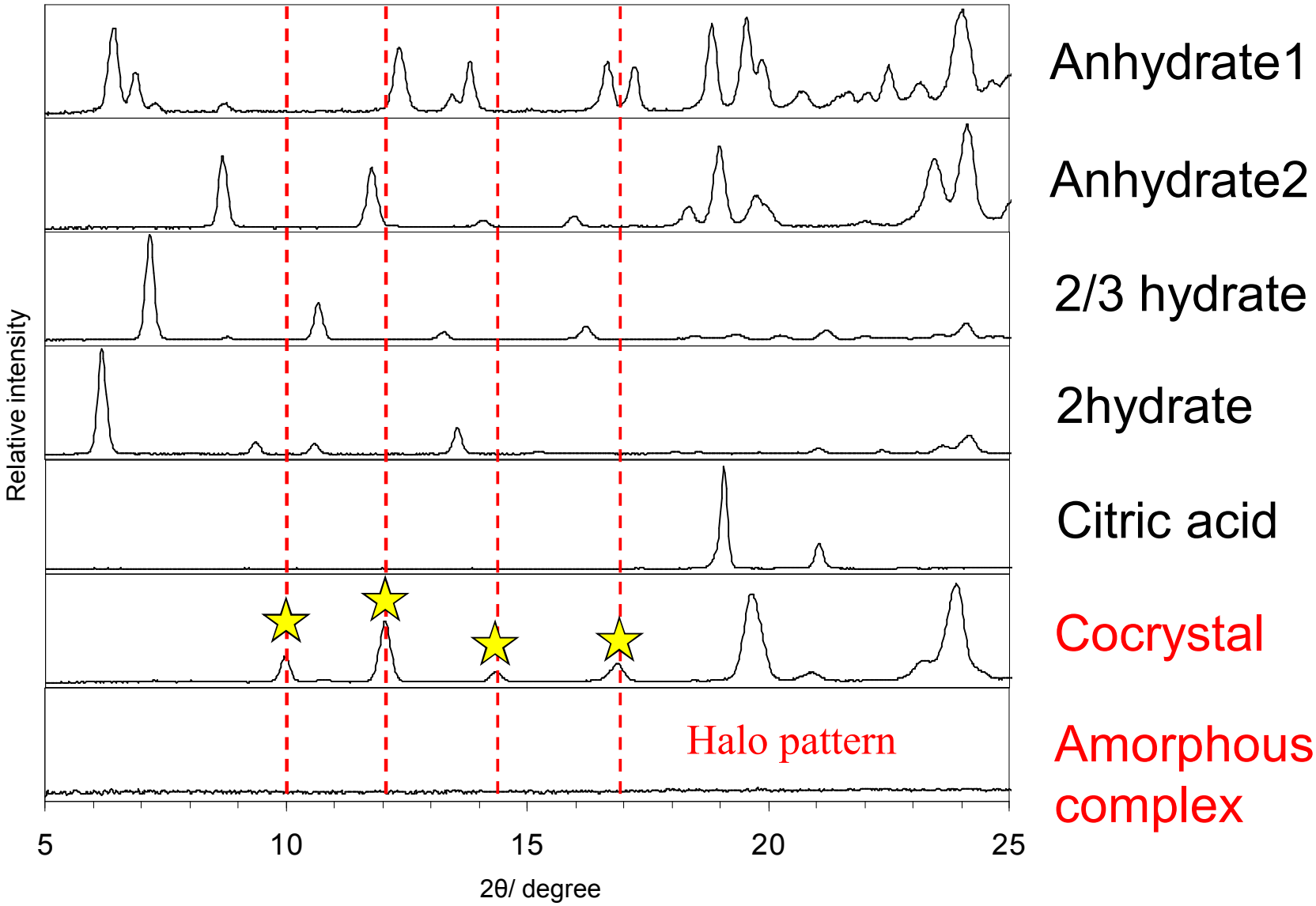
Nicotinamide



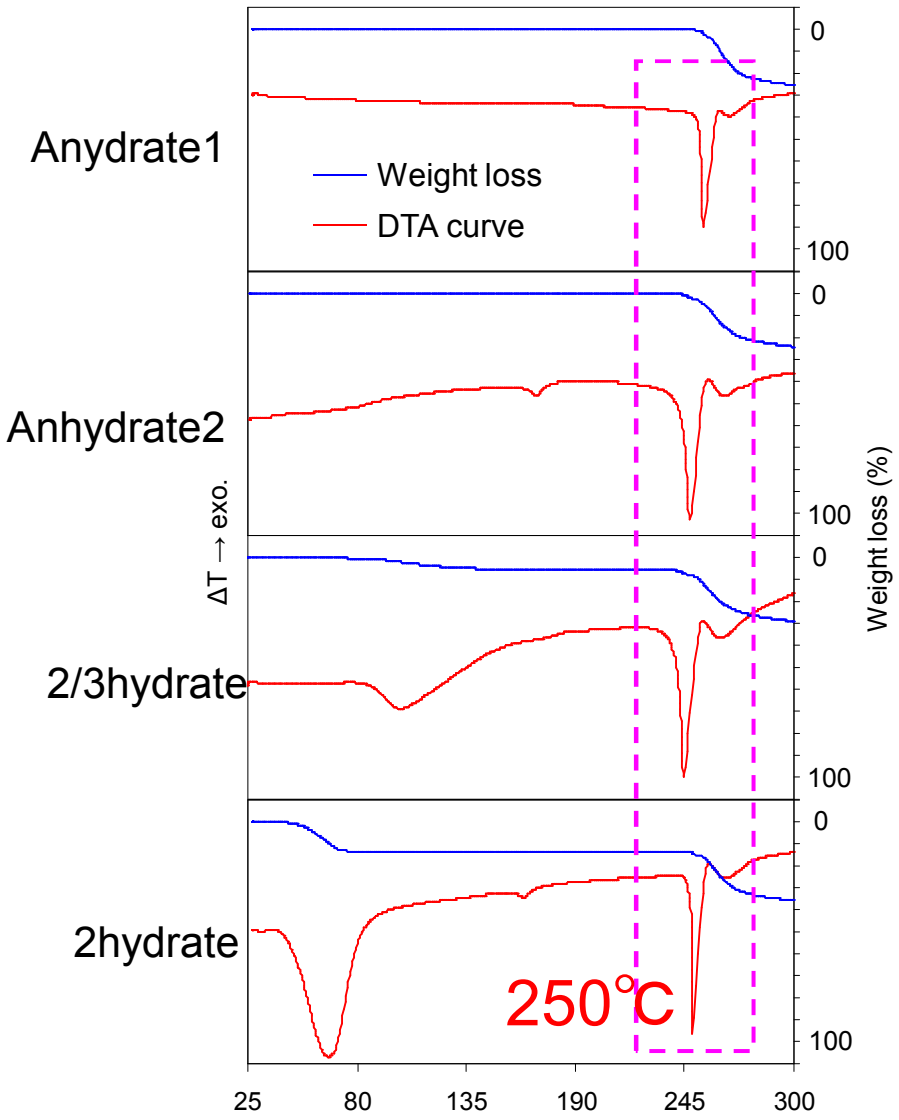
Saccharin

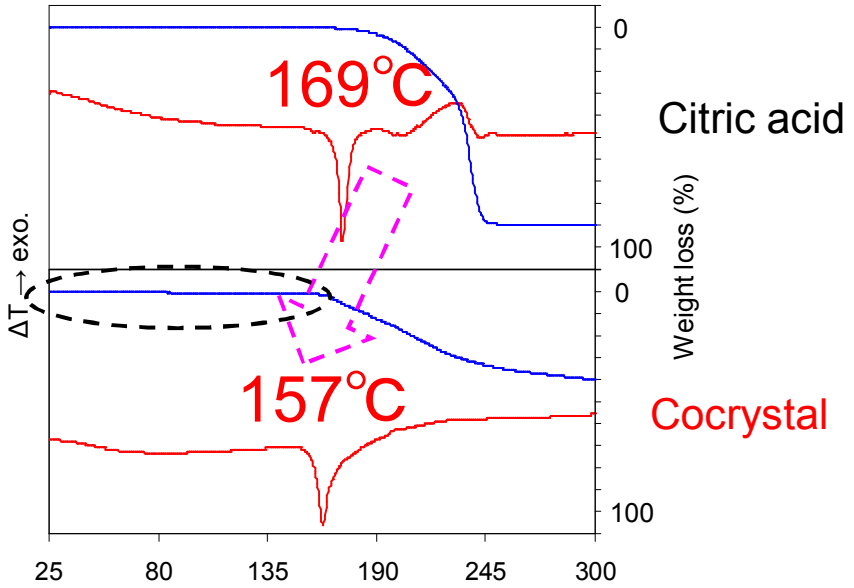
Existence of the records as Oral or Trandermal application

PXRD patterns of samples



TG/DTA curve of samples

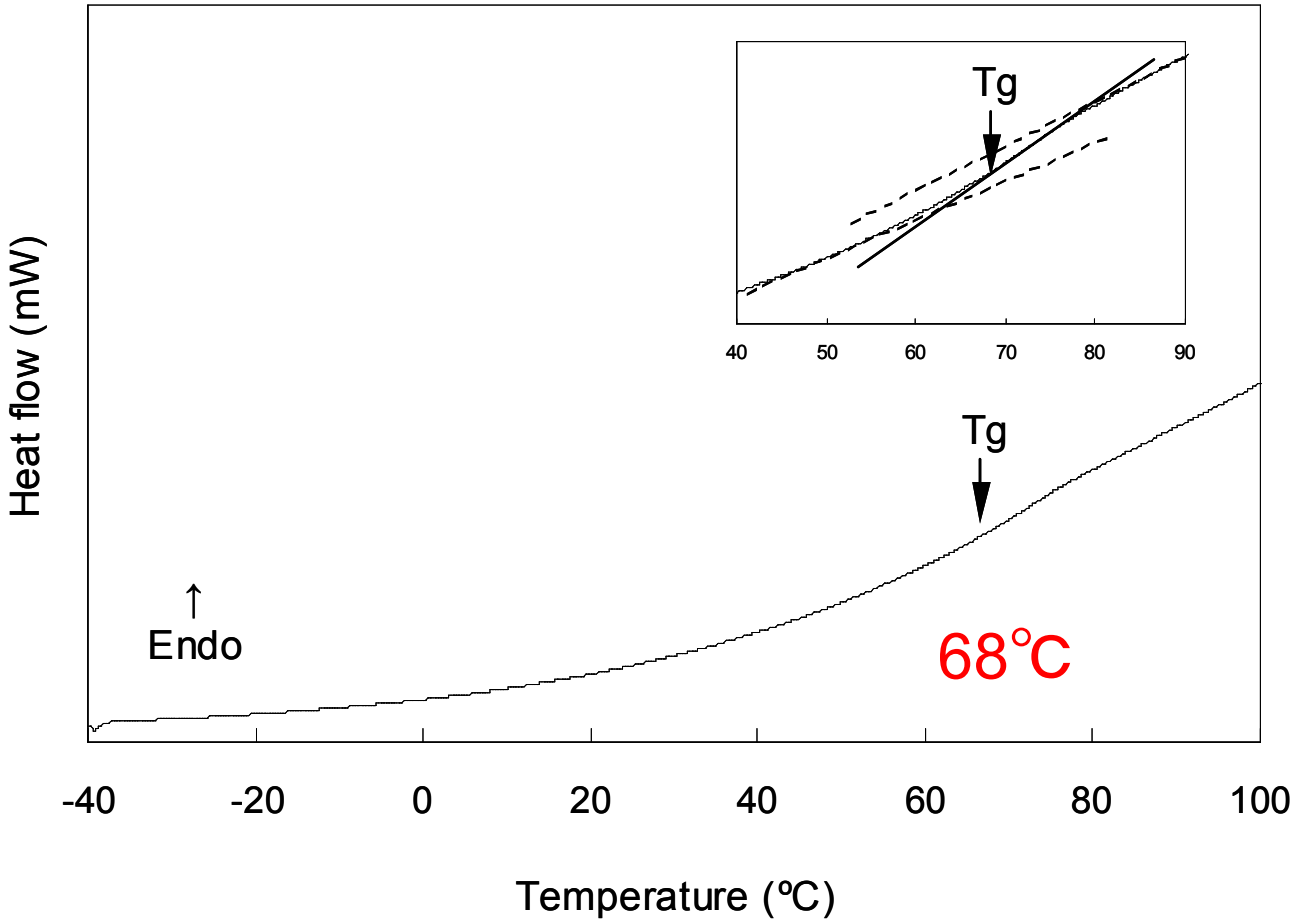




Clear difference in curves

No possibility of the formation of solvate

DSCcurves of amorphous complex



Glass transition temperature Tg was higher than the room temperature.
Confirmation of the physical stability of amorphous complex

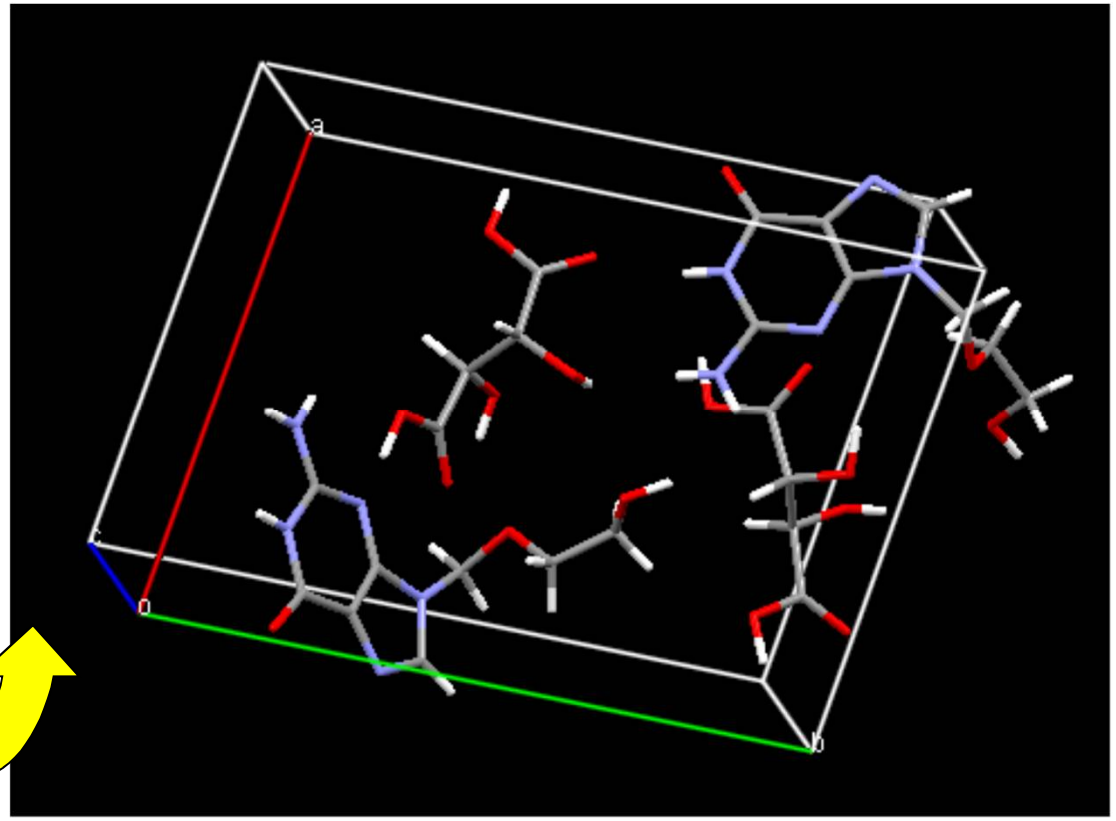
Outline

- Characterization
  - Screenig methods and used additives
  - Selected cocrystals (PXRD、TG/DTA、DSC）
- Application for oral dosage form
  - Intrinsic dissolution of selected cocrystal
  - Crystal structure of selected cocrystal
  - Mechanism for solubility enhansment
- Application for transdermal dosage form
  - Transdermal adsorption propertiy of selected complex
  - Solubility of amorphous comples
  - Improvement of transdermal properties

Crystal structure of Acyclovir - Citric acid Cocrystal

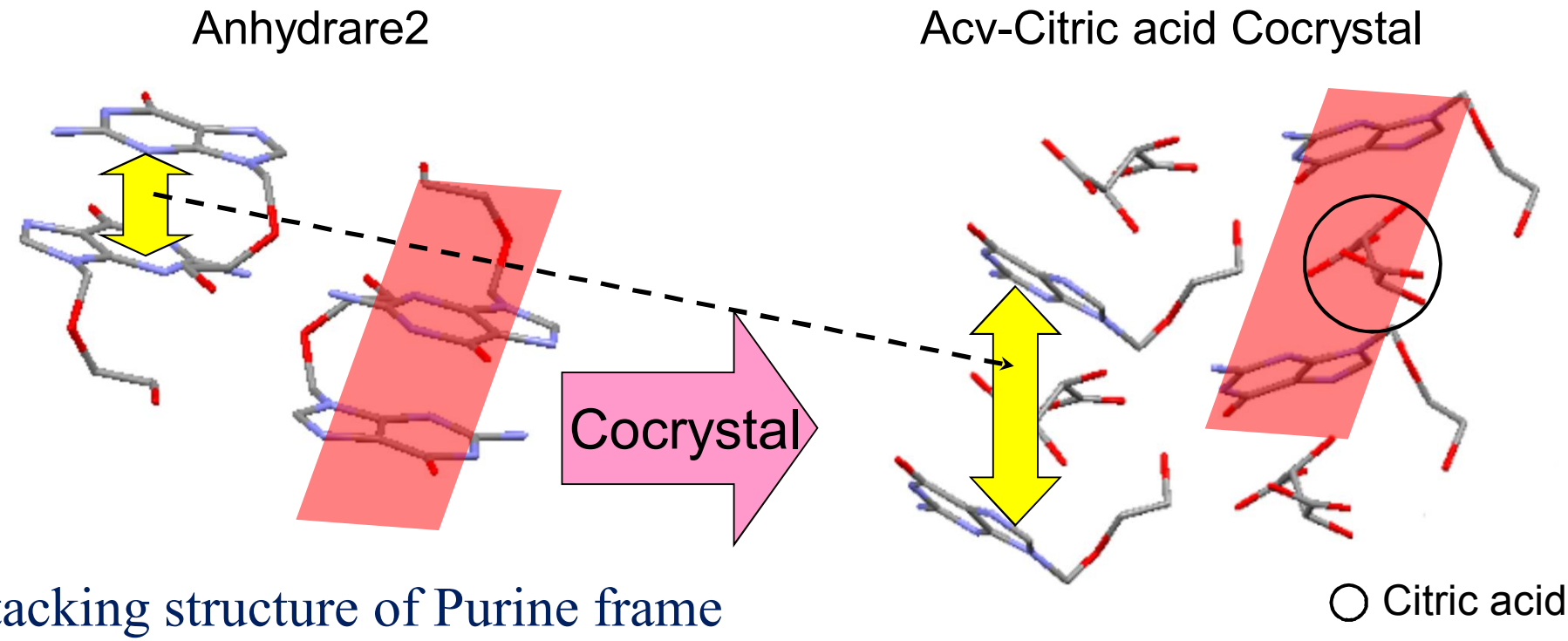
Single crystals weren't obtained

Crystal structure analysis using powder diffraction data obtained by synchrotron radiation



Stoichiometry of Acyclovir : Citric acid was 1:1

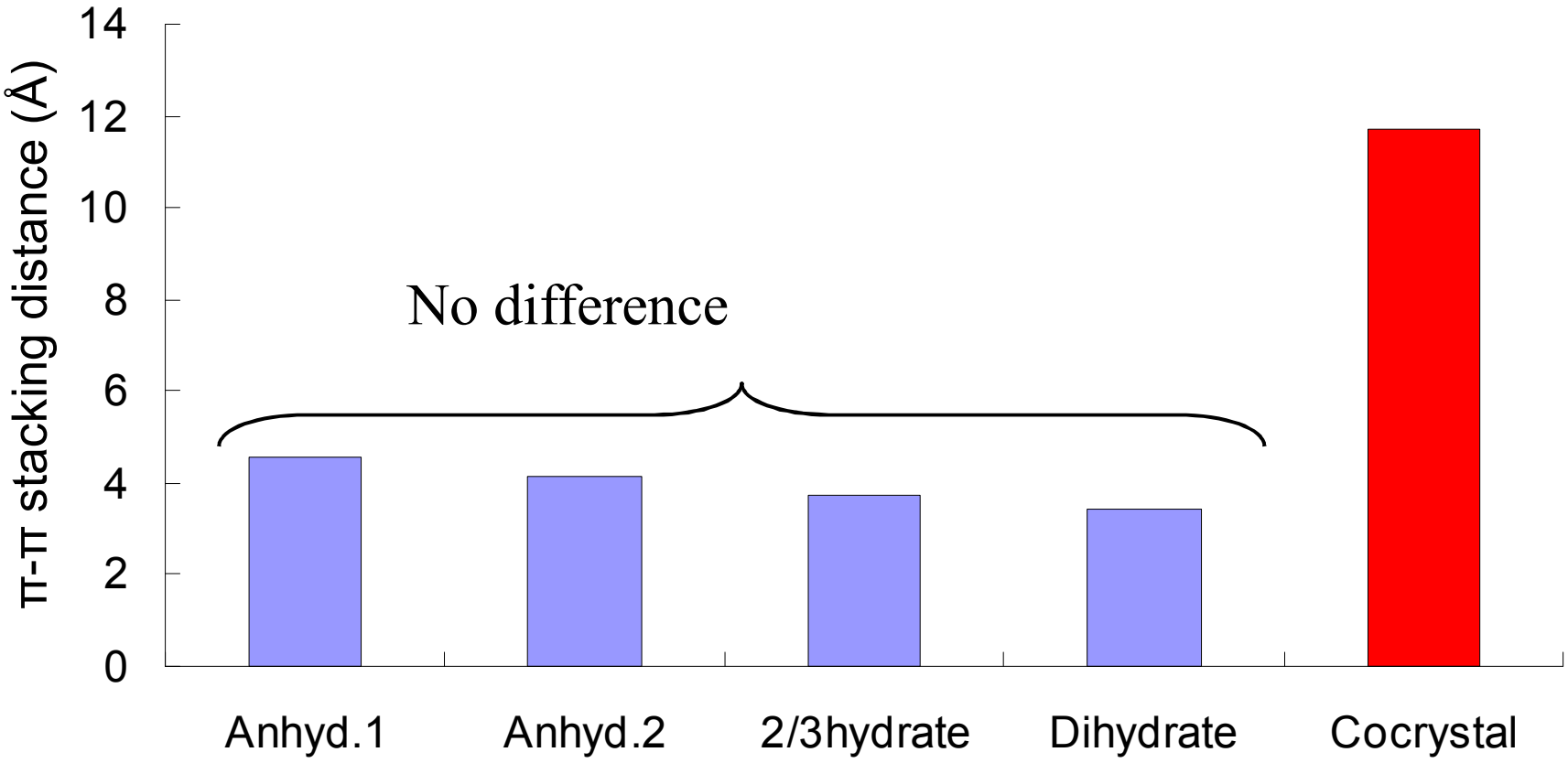
Comparison of stacking structure of Acyclovir and its cocrystal



Un-stabilize the stacking structure by intercalation of citric acid

Enhancement of the solubility

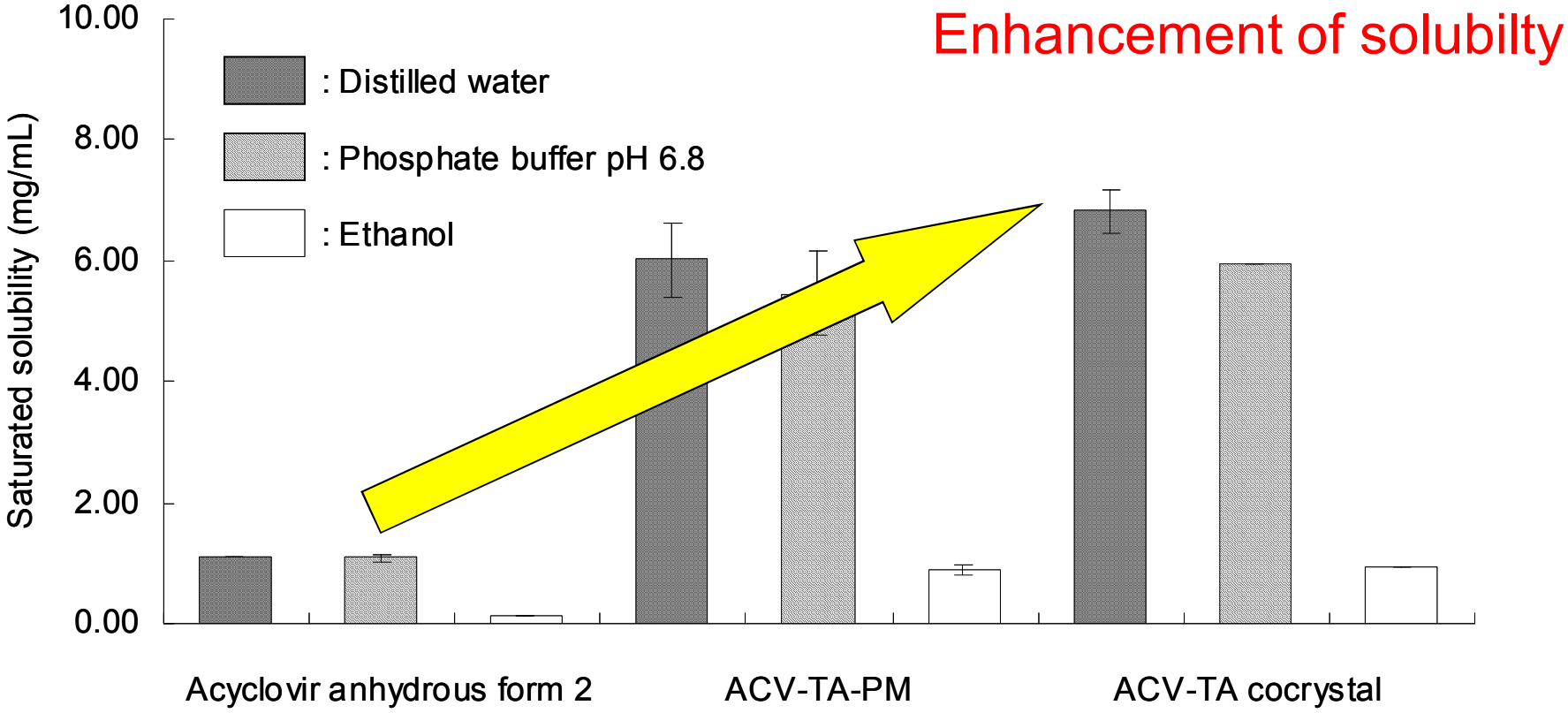
Distance in the purine frame in the crystals



Change in the crystal strucuture by cocrystal

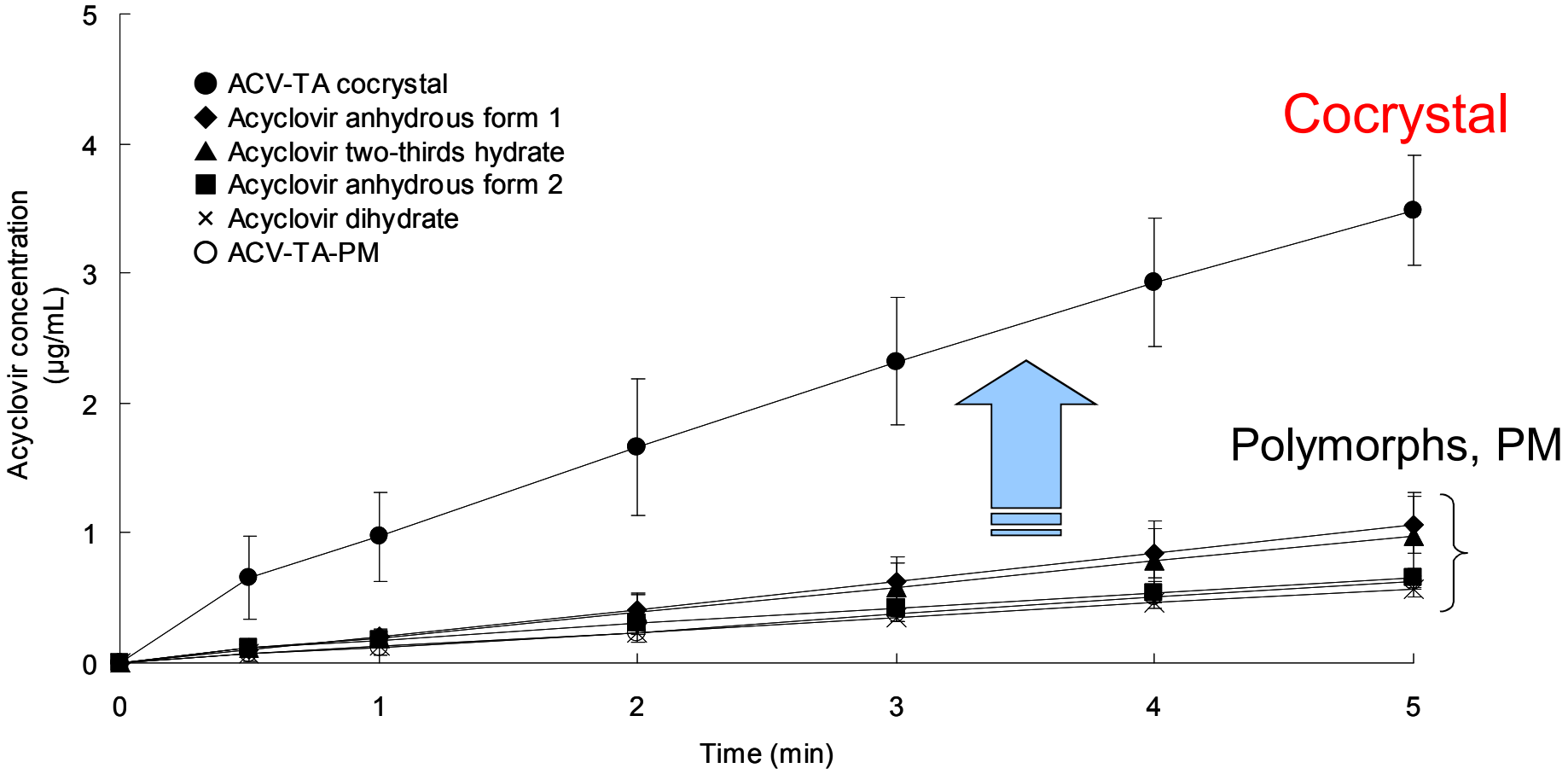
Improvement of dissolution property

Saturated Solubility of Cocrystal in various solvents



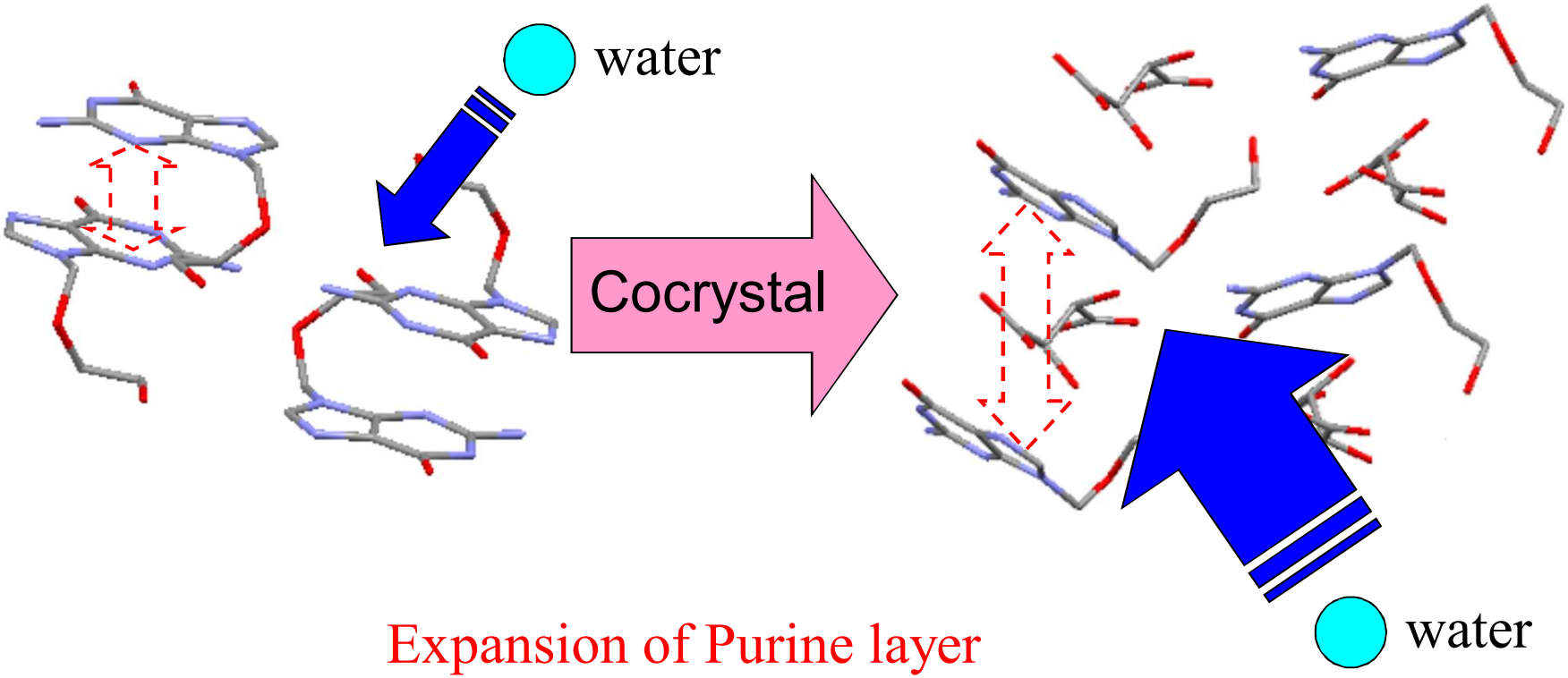
Physical mixture showed the similar solubility compare to the Cocrystal
ACV and Citric acid was interacted, even in the solution.

Initial dissolusion profiles for ACV samples



Remarkable enhancement of solubility was observed.

Mechanism for improvement of dissolution property of ACV by Cocrystal formation



Expansion of Purine layer

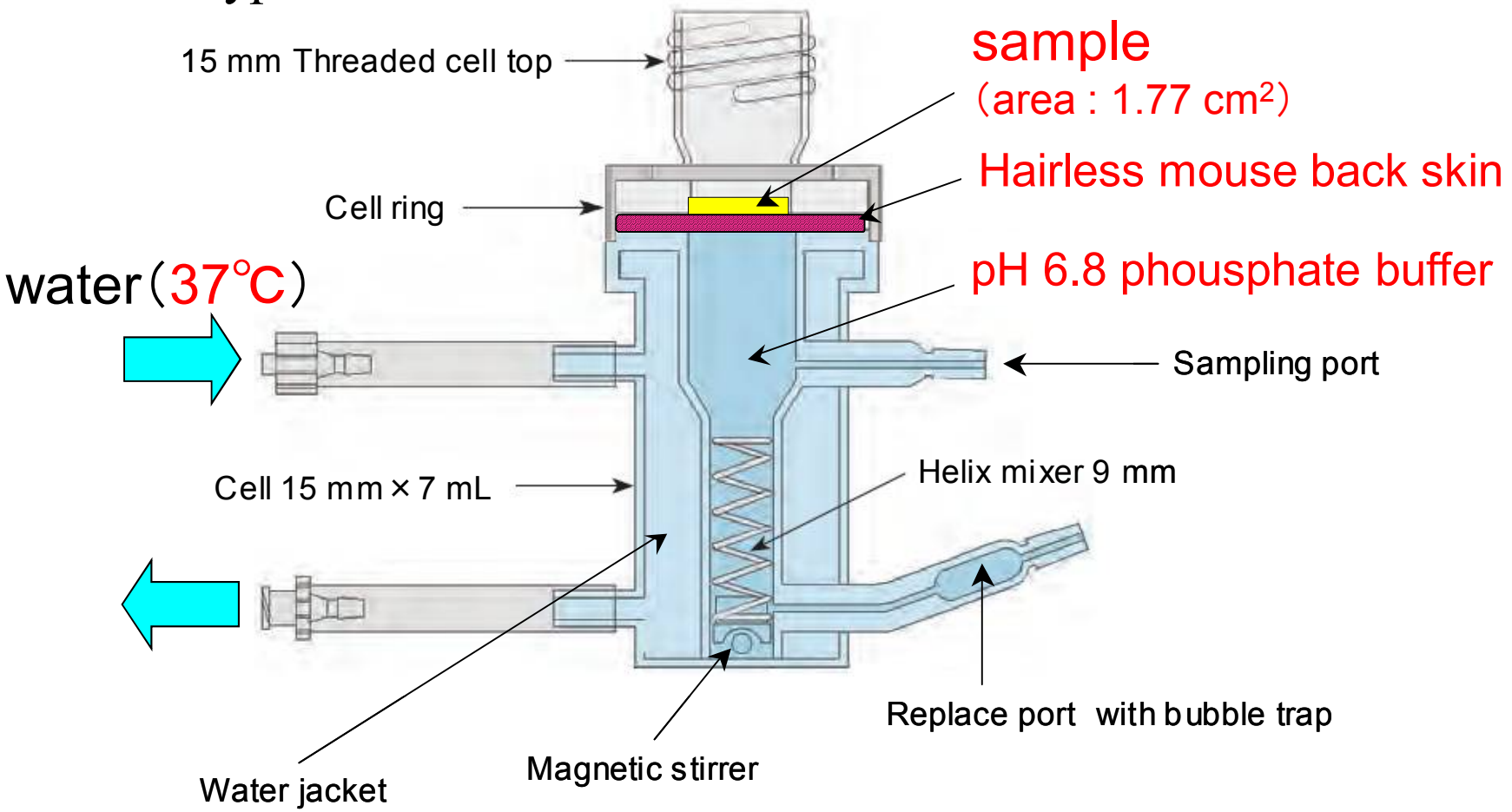
Decrease in the lattice energy

Outline

- Characterization
  - Screenig methods and used additives
  - Selected cocrystals (PXRD、TG/DTA、DSC）
- Application for oral dosage form
  - Intrinsic dissolution of selected cocrystal
  - Crystal structure of selected cocrystal
  - Mechanism for solubility enhansment
- Application for transdermal dosage form
  - Transdermal adsorption propertiy of selected complex
  - Solubility of amorphous comples
  - Improvement of transdermal properties

In vitro Transdermal test for ACV ointment

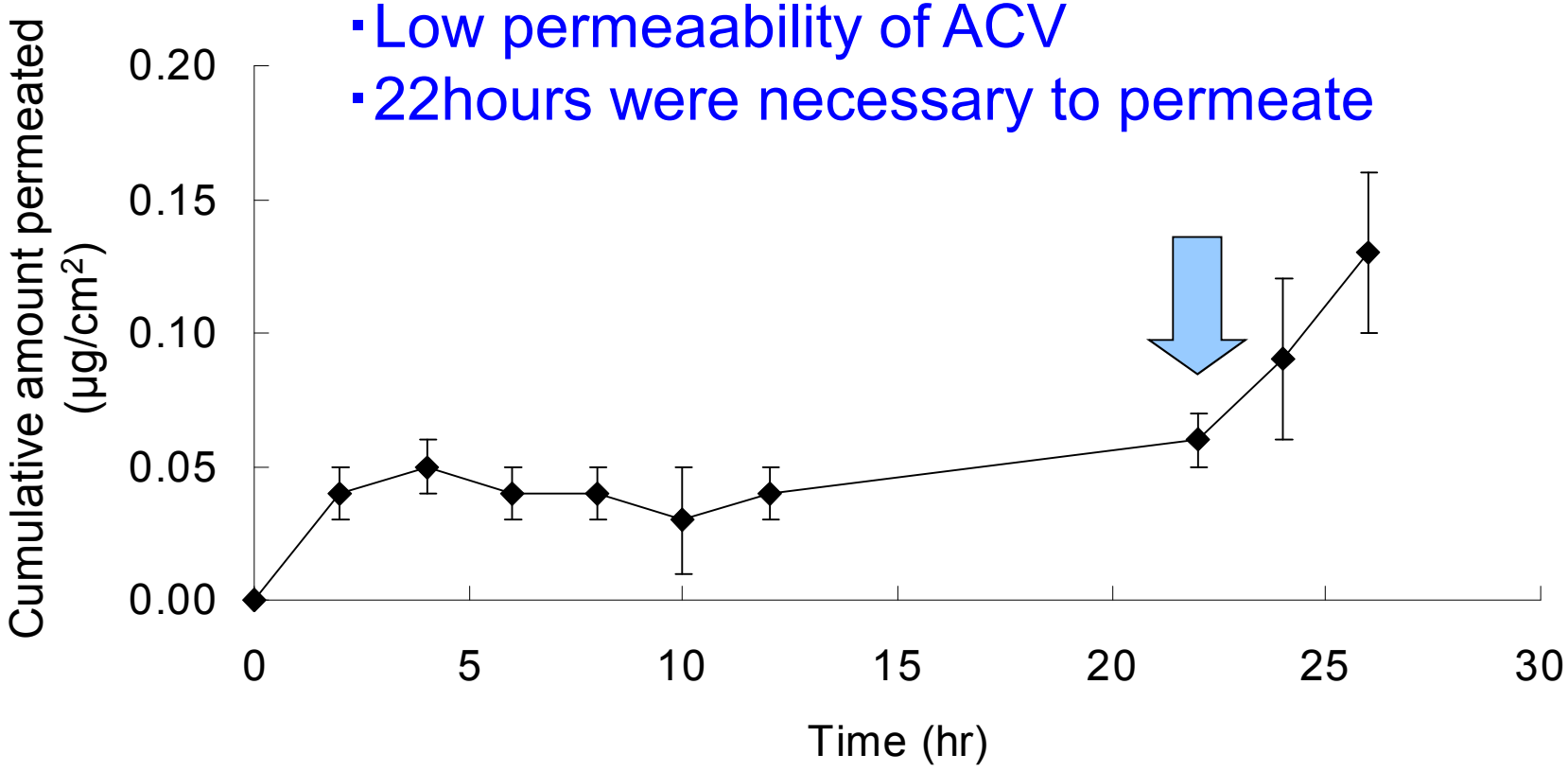
＜Franz type diffusion cell＞



Ointment base : Macrogol

Permeability of ACV

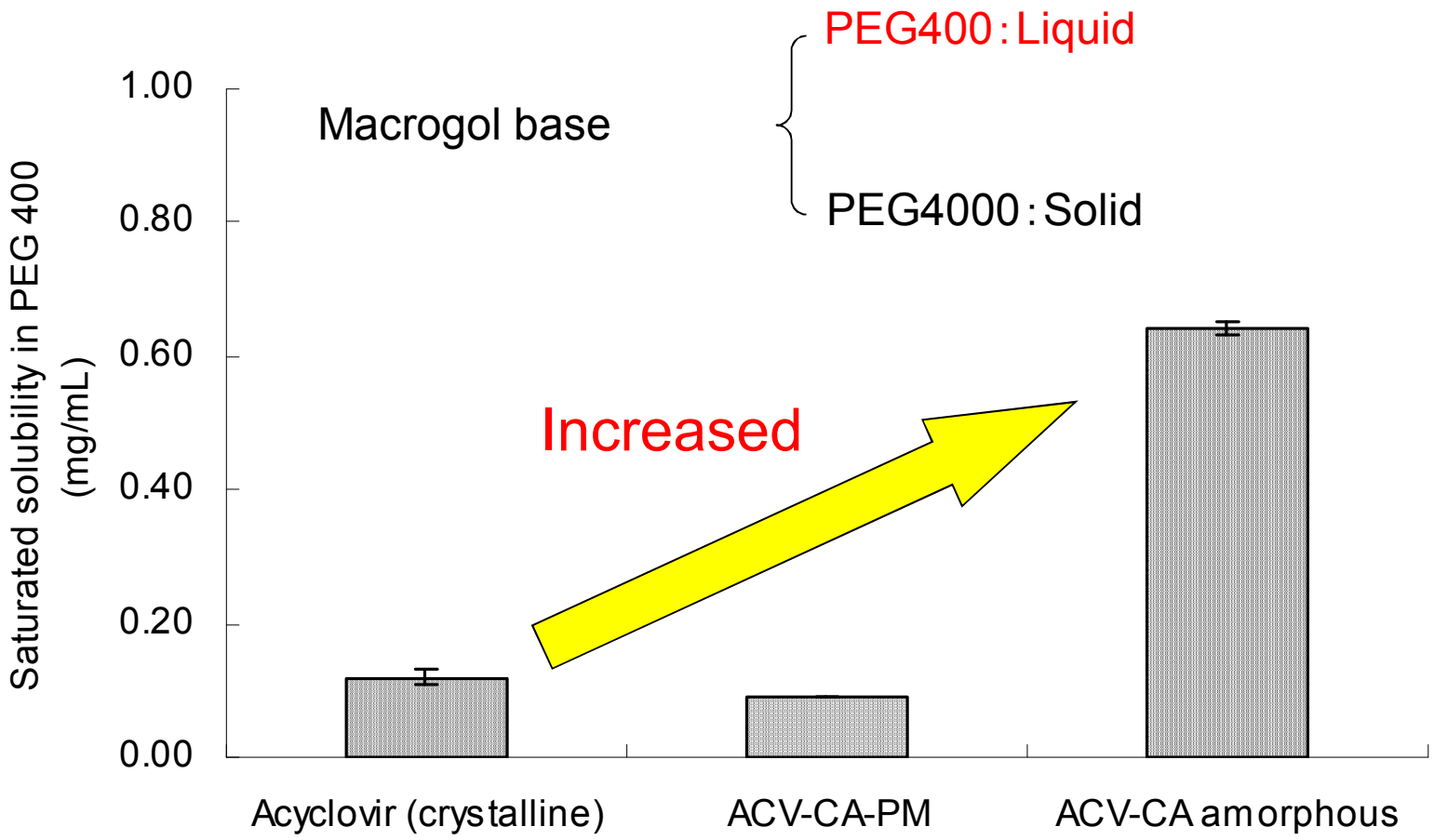
- Low permeaability of ACV
- 22hours were necessary to permeate



Application of amorphous complex？

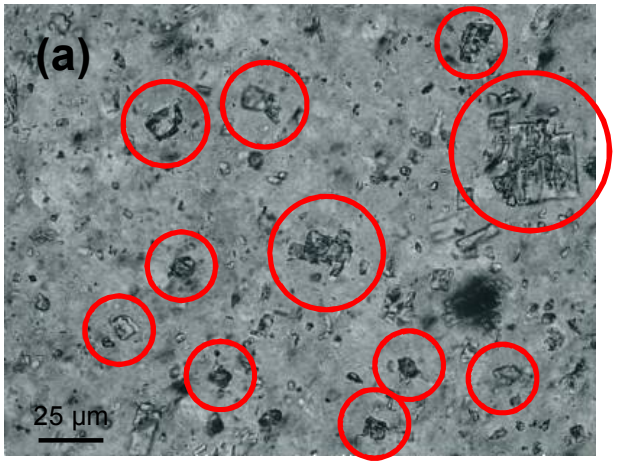
Solubility of ACV in PEG400

Saturated solubility of ACV in Mcrogol base



Microscopic picuture of samples

ACV

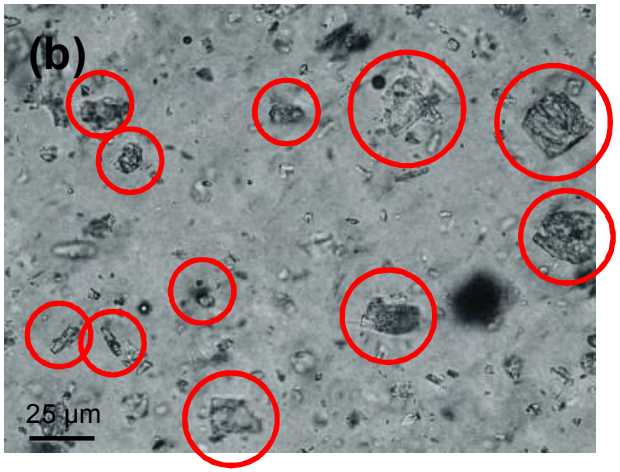


Low solubility

↓

Crystallization

ACV - Tartalic acid
Physical Mix.

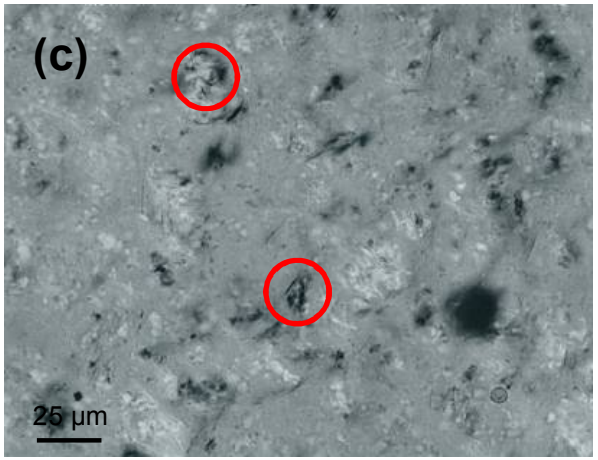


Low solubility

↓

Crystallization

ACV - Tartalic acid
amorphous



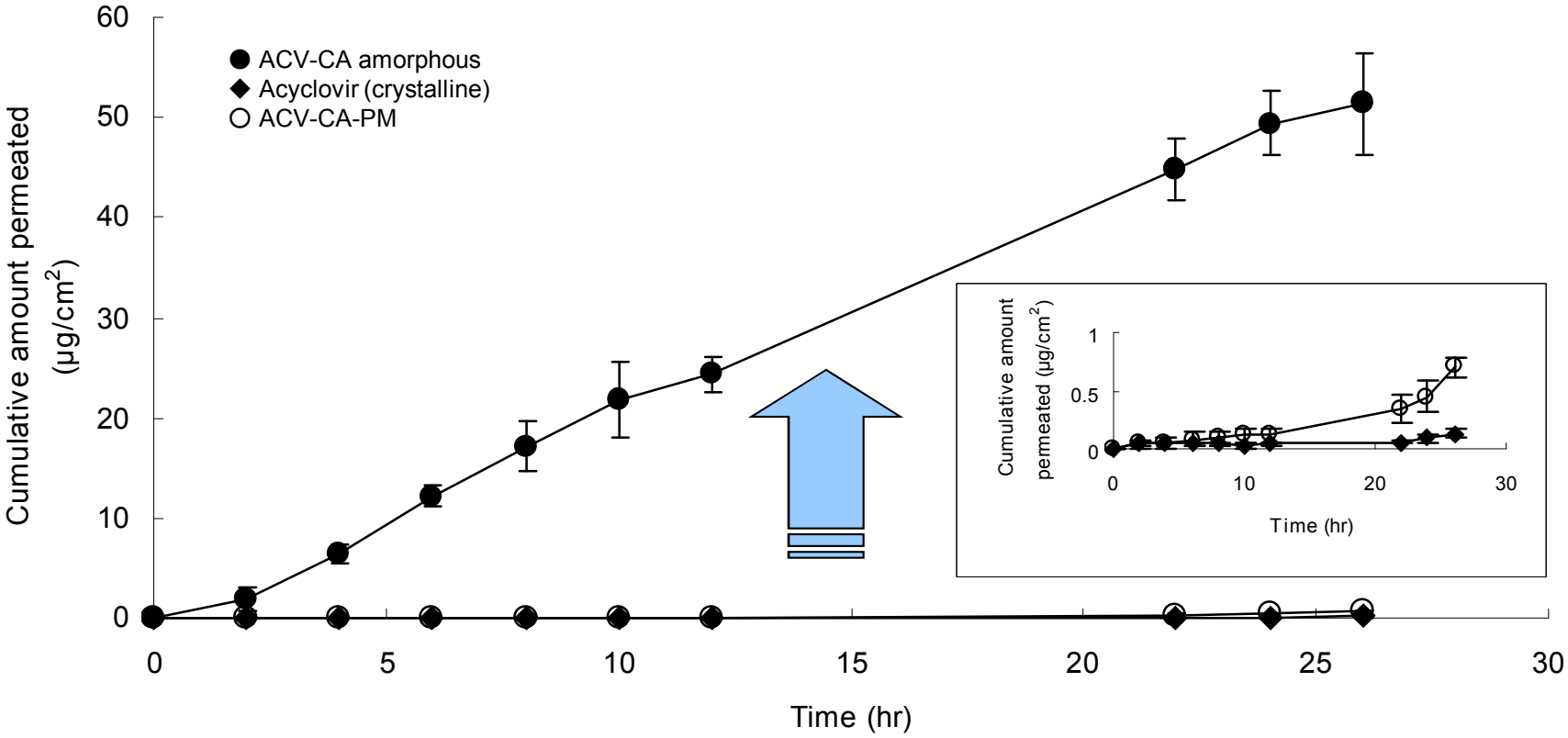
Solubility : High

↓

Almost dissolved

Amorphous ACV complex was dissolved in super saturated states.

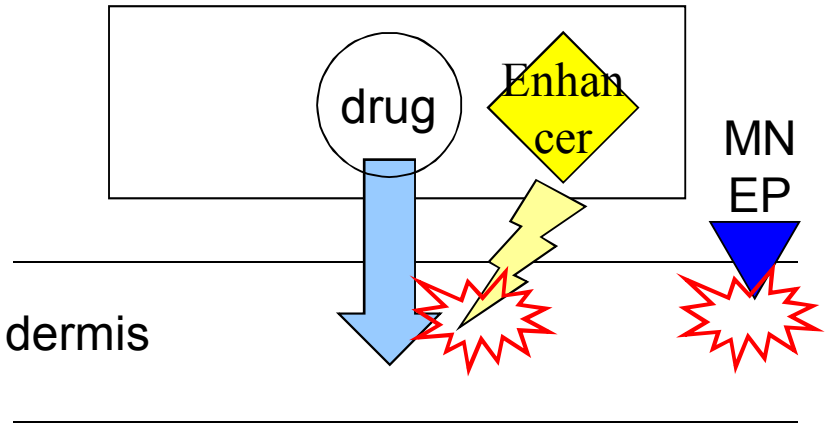
Permeability of ACV samples



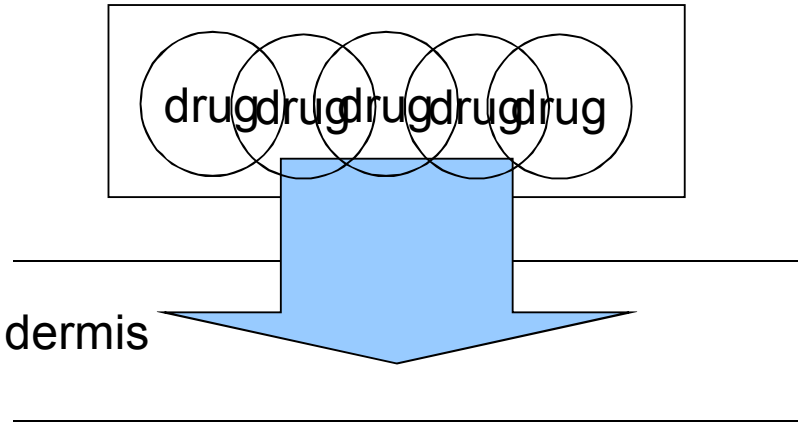
Improvement of permeability of ACV was achieved

Advantage of amorphization for transdermal application

Comventional



amorphization



Chemical, physical enhacement methods might affects the barrier function of skin

Increase the concentration gradient may not affect the barrier function

Safer method for transdermal application