Pharmaceutical Drugs: Being careful with what we eat
Polymorphism in drugs and drug delivery

Why?

• Solubility and pharmacological or toxicological activity strongly depend on a given mass of the initial phase of the raw material

• For practical and regulatory considerations

• Amorphous pharmaceuticals are markedly more soluble than their crystalline counterparts

• Stability of the commercial phase
Paracetamol: Solubility of Polymorph I

Therapeutic Index (recommended quantities), very limited:
Normal dose: 4 g/day (close to overdose!)
Overdose: 5g/day can damage the liver.
**Dose and Elimination**

\[ C(t) = C_0 \exp(-kt) \]

**Threshold**


Modifications to increase solubility

Caffeine, citric acid and their cocrystals.
Manufacturing problems hit Abbott’s HIV drug ritonavir

Capsules of Abbott Laboratories’ protease inhibitor Norvir (ritonavir) are likely to become unavailable by the middle of August. The company has a problem with the manufacture of the anti-HIV capsules which it cannot resolve at present.

The problem relates to “undesirable” crystal formation. Abbott says that a series of recent production batches of Norvir capsules failed the approved test for dissolution, and were not released for marketing. Investigation of the reason for the failure showed the presence of a new crystalline form of ritonavir which affects the way it dissolves, and possibly its absorption. Retained samples from a number of marketed batches of capsules were examined and there was no evidence of the unwanted crystalline form.

Mr Mark Haywood (managing director, Abbott Laboratories) said that teams were working round the clock to try to resolve the issue, but at present the company had no idea why the problem was occurring.
Ritonavir: Polymorphism

NORVIR: antiretroviral drug used to treat HIV infection and AIDS

Drug's development was financed by ..........over $200,000,000 by Abbott Labs

We know that polymorphs exist, although we DON’T know when they will appear and how much damage they will cause.

Oral capsule formulation removed from the market, switch to Norvir suspension while researchers worked to solve the problem. The capsules have been replaced with refrigerated gelcaps.

NOW: 100mg heat-stable ritonavir tablet, not refrigerated

2002 5 forms identified.
BEIJING — A huge state-owned Chinese pharmaceutical company that exports to dozens of countries, including the United States, is at the center of a nationwide drug scandal after nearly 200 Chinese cancer patients were paralyzed or otherwise harmed last summer by contaminated leukemia drugs.
Pressure-Temperature phase diagrams

Key Variables: P and T

The “solution”: Provide ONLY the amorphous phase, BUT who can assure that it doesn’t crystallize?

The question:

Disclosing the polymorphism of a one-component system is to find the unambiguous statement regarding the relative stabilities of the phases involved

The tools:

The Thermodynamics of SIMPLE systems

The meaning of “SIMPLE”:

SIMPLE means nothing but “a thermodynamic system for which the equilibrium states can be described by 2 variables”
The variables: **The original variables** (those initially used by Gibbs):

Gibbs, on the basis of the 2 principles of Thermodynamics:

*First principle: the internal energy $U$ of any state of homogeneous matter at equilibrium has reached a minimum value.*

*Second principle: under these circumstances, the entropy $S$ of the system has reached a maximum value.*

By the entropic form of the first principle:

$$dU = T \cdot dS - p \cdot dV$$

Thus, energy $U$ of each state can be represented by a surface in the 3-D space $U$ ($S,V$), in which:

$$T = \left( \frac{dU}{dS} \right)_V \quad p = -\left( \frac{dU}{dV} \right)_S$$
The variables: The original variables (those initially used by Gibbs):

Within the “original formalism” of the $U(S,V)$ surfaces, all the phases of the matter can be represented in a $S$-$V$ phase diagram:

Is this phase diagram well known (even familiar) for you?
The variables: Legendre Transformation $U(S,V)$ to $G(T,p)$

The reason (not mathematical): $T$ and $P$ can be “easily” controlled (and they are “intensive” variables (while $S$ and $V$ are “extensive”))

(but DON’T FORGET: We still need 2 variables for a SIMPLE SYSTEM)

The Gibbs function for EACH state of a simple system corresponds to a monotonous surface:

$$G^i(T,p) = H^i - T \cdot S^i$$

The stability criterion:

For a given system at given $P$ and $T$, the stable phase is that with the **MINIMUM** value of the Gibbs function.
The variables: Legendre Transformation $U(S,V)$ to $G(T,p)$

$$G^i(T,p) = H^i - T \cdot S^i,$$ thus

$$dG^i = -S^i \cdot dT + V^i \cdot dp$$

$$S = -\left( \frac{dG}{dT} \right)_p \quad V = \left( \frac{dG}{dp} \right)_T$$

Plane at constant $P$

$$\Delta H^{\alpha \rightarrow \beta} = T^{\alpha \rightarrow \beta} (S^\beta - S^\alpha)$$

Plane at constant $T$

$$\Delta v^{\alpha \rightarrow \beta} = v^\beta - v^\alpha$$
Triple Points: Three $G^i (T,p)$ surfaces can cross (once) together with the $P,T$ projection of the crossing

$G^i (T,p)$ are monotonous surfaces!

Doesn’t matter what $\alpha, \beta, \gamma$ are!!! (solid, liquid, vapor,...)

Pressure is essential among the physical variables defining the state of the compound, and, together with temperature, is also a constitutive factor in the construction of phase diagrams; thus neither is alone sufficient to describe the state. Okumura et al., J. Pharm. Sci. (2006), 95, 689
Building up the TOPOLOGICAL pressure-temperature phase diagram

For a given material/substance, there are:
• **only one** liquid (L) phase and
• **only one** vapor (V) phase.

Thus, there is **ONLY ONE VAPORIZATION (L+V) CURVE** on the p-T phase diagram.

**Remember:** This curve is the projection on the p-T plane of the intersection between the G surfaces of the liquid and the vapor.
The measurements: DSC or DTA, or Adiabatic Calorimetry. What are they measuring?

Solid + Liquid Equilibrium

Endothermal process
Solid+liquid equilibrium: What do we know

2 Possibilities:

FIRST: Calculation: Clapeyron (TOPOLOGICALLY CORRECT)

\[
\left( \frac{dp}{dT} \right)_{\alpha \rightarrow \beta} = \frac{\Delta S_{\alpha \rightarrow \beta}}{\Delta v_{\alpha \rightarrow \beta}} = \frac{\Delta H_{\alpha \rightarrow \beta}}{T_{\alpha \rightarrow \beta} \Delta v_{\alpha \rightarrow \beta}}
\]

Commercial DSC

X-ray and liquid density methods
Solid+liquid equilibrium: What do we know

2nd Possibility:

It can be measured, *BUT*, pay attention, in this equilibrium *there is NOT vapor*, only *liquid and solid* phases must coexist!

*HP-DTA: How does it work? A basic picture*
Solid+liquid equilibrium: What do we know

High-Pressure Differential Thermal Analysis

We learned in the beautiful city of Bochum...

Financial resources: Sanofi Aventis and AstaZeneca
Experiments... At different P

For each P... T of transition

DIAGRAMA P-T
Final Pressure-Temperature Phase diagram (where all the phases have been located and, obviously, where for each \( p \) and \( T \), the phase or 2-phase equilibrium are known).
The polymorphism

Trivial question: how many equilibrium curves? They come from the intersection of the $G$ surfaces, and the intersection between 3 of them give the TRIPLE POINTS.

The answer (Riecke, E. Z. Phys. Chem. 1890, 6, 411): Riecke equation

For a pure compound (simple system), involving “$n$” polymorphs, the number of Triple Points (C) is given by:

$$C = \frac{(n + 2)!}{3!(n + 2 - 3)!}$$

Dimorphism ($n=2$) ....... $C = 4$
Trimorphism ($n=3$)....... $C = 10$
Tetramorphism ($n=4$)..... $C = 20$
Pentamorphism ($n=5$)... $C = 35$
...

...
Metastable phases or Metastable transitions can appear.....

But $G(T,P)$, and these plots are “projections” at constant pressure !!!!!!!!

New $G(T,p)$ surfaces, coming from high-pressure, can be there!!!!!!!!

So, $T$ is not enough and $P$ must be considered
The Dimorphism: The SIMPLEST case of a SIMPLE SYSTEM

Easy part: ONE L+V curve

$L+\nu$

Sample
The Dimorphism: The SIMPLEST case of a SIMPLE SYSTEM

Easy part: ONE $L+V$ curve
Melting temperatures for Polymorphs ($S_1$ and $S_2$)
The Dimorphism: The SIMPLEST case of a SIMPLE SYSTEM

Easy part: ONE L+V curve
Melting temperatures for Polymorphs (S1 and S2)
The Dimorphism: The SIMPLEST case of a SIMPLE SYSTEM

Easy part: ONE L+V curve
Melting temperatures for Polymorphs (S1 and S2)
Sublimation curve (S2+v)
The Dimorphism: The SIMPLEST case of a SIMPLE SYSTEM

Case 1

Easy part: ONE L+V curve
Melting temperatures for Polymorphs (S1 and S2)
Sublimation curve (S2+\nu)
Sublimation curve (S1+\nu)
Case 2

Easy part: ONE L+V curve
Melting temperatures for Polymorphs (S1 and S2)
Sublimation curve (S2+v)
Sublimation curve (S1+v)
The Dimorphism: The SIMPLEST case of a SIMPLE SYSTEM

Case 1

Case 2
Case 1 (enantiotropy)

The Dimorphism: The SIMPLEST case of a SIMPLE SYSTEM

Vapor

Liquid

Polymorph 1

Polymorph 2

endothermic
The Dimorphism: The SIMPLEST case of a SIMPLE SYSTEM

Case 2 (monotropy)
We didn’t pay attention to the slope of the equilibrium curves.....

Case 1 (enantiotropy)

Imagine $S_1$-$S_2$

S$_2$-S$_1$-L

Imagine $S_1$-$S_2$

endothermic

Polymorph 1

Polymorph 2

Vapor

Liquid

stable

métastable

super-métastable
Case 2 (monotropy)

We didn’t pay attention to the slope of the melting equilibrium curves.....

Imagine $S_2-L$

$S_2+S_1+L$

Polymorph 1

Liquide

Vapeur

$T_{fus} S_2$

$T_{fus} S_1$

$Tr$

$S_1 - S_2$

$S_1 - S_2 - v$

$S_2 - v$

$S_2 - l$

$S_1 - l$

$S_1 - l - v$

$S_2 - l - v$

stable

métastable

super-métastable
Don’t get tired: 
**Roozeboom** did 112 years before.....

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The dimorphism ...
The dimorphism ...Examples
Progesterone (steroid hormone)

"Normal" pressure measurements

DSC/DTA

X-RAY / density

J. Pharm. Sci. 2009, 98, 1657

II-I exc.

$\Delta_{I-II} H > 0$

$\Delta_{I-II} \nu < 0$
The dimorphism ... Examples

“High-Pressure DTA measurements”

**Phase I (Melting)**

- 190.5 MPa
- 177.7 MPa
- 130.2 MPa
- 111.5 MPa
- 68.9 MPa
- 38.7 MPa
- \( p = 0.1 \text{ MPa} \)

**Phase II (Melting)**

- 187.0 MPa
- 45.1 MPa
- 32.3 MPa
- \( p = 0.1 \text{ MPa} \)

*J. Pharm. Sci. (USA), 2009, 98, 1657*
The dimorphism ...Examples

**Progesterone**

P-T phase diagram

Barrio et al., J. Pharm. Sci., 2009, 98, 1657
Rimonabant: A delicate case of Dimorphism

Perrin et al., J. Pharm. Sci. 102, 2311 (2013).
Rimonabant: A delicate case of Dimorphism

Answer to industry: Phase II is the stable phase (always)
CASE 4 of ROOZEBOOM
(overall monotropy)
The polymorphism ...

A case of trimorphism: dl-camphor (10 triple points)

The polymorphism ...

**A case of trimorphism:** d-camphor

(10 triple points)

The polymorphism ...

A case of tetramorphism: \((CH_3)_3CCl\)
(20 triple points)

A case of pentamorphism:
(35 triple points)

Who wants to try!!!!!!!!!!!!!!!!!!!!!!
Crystallization of the amorphous phases...

* Classical Theory of Nucleation:

The ENERGY needed for nucleation of a critical nucleus

\[ W^*(T) \propto \frac{1}{\Delta G(T)} \]

(so, when T decreases, \( \Delta G \) increases, and \( W^* \) diminishes, thus the probability to nucleate increases)

* Mobility of molecules (viscosity)

(when T diminishes the viscosity increases, and thus the probability for growth and nucleation diminishes)
Crystallization of the amorphous phases...
Crystallization of the amorphous phases...

\[
\log(\tau) = 1000 / T \quad [K]
\]

\( T_g = 284 \text{ K} \quad 271 \text{ K} \quad 252 \text{ K} \quad 232 \text{ K} \)

\( \tau(T_g) = 100 \text{ s} \)

Ternidazole (PhD Michela)
Crystallization of the amorphous phases...

Relaxation times (mobility) as a function of P and T
Crystallization of the amorphous phases...

Identification of Isochronal Line

(identical relaxation time, so identical mobility)

One can disentangle the thermodynamics effects from the mobility effects
Crystallization of the amorphous phases...

\[
\varepsilon'_N(t) = 1 - \exp(-kt^n)
\]

- \(n\) is Avrami exponent
- \(k\) crystallization rate constant
(related with nucleation and growth)
Crystallization of the amorphous phases...
A falta de pan.... Encapsulation of Drugs

* Cyclodextrins
* Biodegradable Polymers for Microencapsulation of Drugs
A falta de pan....

* Pillared Graphene?
Final remarks:

A) Polymorphism: Completely UNPREDICTIBLE problem.

B) Amorphous Phase: Completely UNPREDICTIBLE problem
Gràcies per escoltar!!