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Thermodynamics of non-stoichiometric pharmaceutical hydrates

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Abstract

Different physical and mathematical models of non-stoichiometric hydrates derived form previous work in inorganic hydrates are reviewed. A theoretical link between the order of water molecules in the hydrate and the shape of the isotherm is outlined. The comparison of the models with sorption isotherms and structural data of well-known cases from the literature and one in-house case shows that the model can fit many experimental situations and is in good agreement with qualitative assessments of the order in the hydrates.

Keywords: Non-stoichiometric hydrates; Thermodynamics; Structure–sorption isotherm relationship

1. Introduction

Hydrate forms of drug substances are very common, and therefore they have been widely studied in the pharmaceutical literature (e.g. Morris, 1999). Hydrates are characterized by various methods, e.g. powder X-ray diffraction to determine the structure, DSC to determine bonding energy and sorption isotherm to measure hydration.

It is well-known that at least two kinds of hydrates can exist (Vippagunta et al., 2001):

- Stoichiometric hydrates are those with well-defined water content and a different crystal structure than the anhydrous drug or other hydrates. Their sorption isotherms are step-shaped isotherms with the pressure of the hydration/dehydration transition being a function of temperature.
- Non-stoichiometric hydrates are those with continuously variable composition within a certain range, without any significant corresponding change in the crystal structure, except usually some anisotropic expansion of the crystalline network to accommodate the additional water molecules. However, it is also common that a non-stoichiometric hydrate loses crystallinity when the very last water molecules desorb (Mimura et al., 2002). Their sorption isotherms can have various shapes, corresponding to types I, II, III or V sorption isotherms.

Fig. 1(a–c) shows the schematic shape of possible isotherms. P is the water partial pressure, and ε is the

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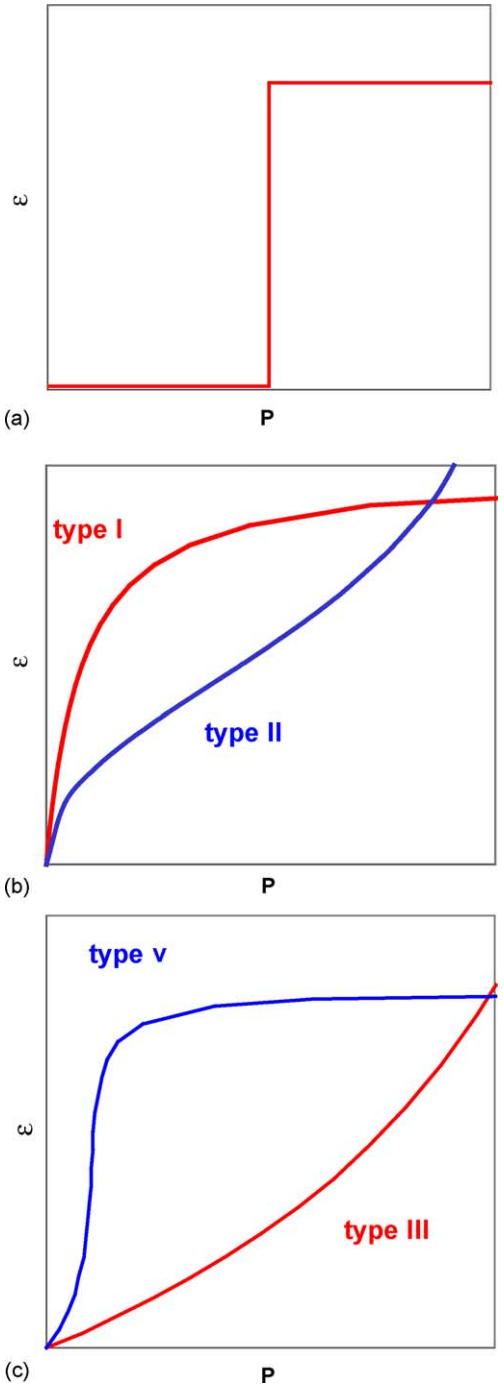

Fig. 1. Schematic shape of the sorption isotherm in a case of a stoichiometric hydrate (a) or a non-stoichiometric hydrate (b) and (c), where ε water uptake and P partial pressure of water vapor.

amount of water sorbed in mole of water per mole of anhydrous drug substance.

Pharmaceutical hydrates have been alternatively classified from a structural point of view (Morris, 1999 or Vippagunta et al., 2001) into three categories:

- Class I are the isolated site hydrates, where water molecules are located at well-defined and isolated crystallographic sites.
- Class II are channel hydrates or planar hydrates where water molecules are included in the crystal next to each other, forming either channels or planar networks.
- Class III are ion coordinated hydrates.

Class I hydrates are often stoichiometric, class II are generally non-stoichiometric. For class III, the situation is unclear, as ion associated hydrates can be either stoichiometric or non-stoichiometric. In case of cromolyn disodium (Chen et al., 1999; Stephenson and Diseroad, 2000), it was shown that in fact part of the water is well located on crystallographic sites, whereas some is disordered in channels: this hydrate is strongly non-stoichiometric. However, in the case of Fenoprofene sodium (Stephenson and Diseroad, 2000), water is located in well-defined crystallographic sites: this hydrate is strictly stoichiometric.

The thermodynamic modeling of sorption isotherms has not been studied very often despite the fact that many experimental sorption isotherms have been reported in the literature. The main contribution on this topic was given by Zografi and co-workers (Hancock and Zografi, 1993; Shambling et al., 1998; Zhang and Zografi, 2001), in particular for hydration of amorphous macromolecular substances like cellulose and starch, peptides and proteins, or polyvinylpyrolidone-sugar mixtures. They have shown that Vrantas' theory of adsorption, derived from the original Flory–Huggins model of polymer solutions, provides satisfactory models of isotherms.

Sacchetti (1998) also studied the water sorption isotherm of microcrystalline cellulose and on polyvynilpyrolidone from a thermodynamic point of view, and derived the activity coefficients and the excess free enthalpy of the system.

Surprisingly, a literature search did not reveal any example of a sorption isotherm model for non-macromolecular pharmaceutical substances.

The aim of this paper is to show that using thermodynamic concepts and models it is possible:

- to correlate stoichiometric and non-stoichiometric behavior with variance of the system according to the Gibbs' rules of phase;
- to correlate sorption isotherm shape of non-stoichiometric hydrates with a degree of order in the crystal.

The thermodynamic approach to be presented was originally developed for inorganic hydrates by Soustelle et al. (1971) and Soustelle (1994). Mineral hydrates differ from organic hydrates by the nature and intensity of water/substrate interaction, as water is mainly linked by chemisorption in mineral hydrates instead of by H-bond as in organic hydrates. However, we will show that these thermodynamic models are still relevant for organic hydrates, and we will use the theory without modification.

It should be mentioned that surface adsorption is not taken into account in this discussion. It can, however, have a contribution in the experimental sorption isotherm curves. It is, therefore, a limitation of our approach.

2. Material and methods

2.1. Preparation of RPR102341

RPR102341 was prepared by crystallization of the crude product in ethanol–water mixtures.

2.2. Water sorption/desorption studies

Sorption/desorption studies were carried out in a VTI MB-300G microbalance equipped with a Cahn Balance. Resolution of the balance is 1 μg. Experiments were carried out with about 20 mg drug substance. Equilibrium criterion was $\Delta m \leq 5$ μg for 1 h.

3. Gibbs' phase rule

For a system in equilibrium, the phase rule relates the number of components (substances), variables (temperature, pressure) and phases to the degree of freedom or variance F:

$$F = C + N - \phi \quad (1)$$

F is the degrees of freedom, i.e. the number of independent (so called intensive) variables that must be arbitrarily fixed to establish the state of the system; C the number of independent components, i.e. the number of components minus the number of stoichiometric relationships; ϕ the number of phases and N is the number of non-compositional variables; in this case, $N = 2$ (pressure and temperature).

The formation of a hydrate can be described as a quasi-reaction:

Anhydrous (or low level hydrate) + Water (vapor)

→ Hydrate (or high level hydrate)

In such a system, we have three components (compound, water and resulting hydrate), and one reaction, therefore $C = 3 - 1 = 2$; $\phi = 1$ (gas phase) + number of solid phases $= 1 + \phi_s$, where ϕ_s is the number of the solid phases in the system.

Finally:

$$F = 4 - \phi = 3 - \phi_s \quad (2)$$

Let us come back to phenomenology:

(a) For a stoichiometric hydrate having a single step isotherm, $F = 1$, since for a given temperature there is only one equilibrium pressure.
(b) For a non-stoichiometric hydrate having a continuous isotherm, $F = 2$, as there is a continuous change of solid phase composition with partial pressure vapor.

We can deduce from Eq. (2) the number of solid phases in each case (Table 1).

It turns out from Table 1 that stoichiometric or monovariant hydrates are necessarily polymorphic (also mentioned by Byrn et al., 1999), whereas non-stoichiometric hydrates are necessarily non-polymorphic.

4. Thermodynamic model of stoichiometric hydrates

Let us consider the equilibrium between two stoichiometric hydrates with n and $(n + p)$ molecules of

Table 1
Implication of Gibbs' phase rule on the number of solid phases

Case	Degree of freedom	Solid phase number
Stoichiometric hydrates	$F = 1$ mono-variant hydrate	$\phi_s = 2$; (1) anhydrous (or low level hydrate); (2) hydrate (or high level hydrate)
Non-stoichiometric hydrates	$F = 2$ di-variant hydrate	$\phi_s = 1$

water per molecule of substrate ($n = 0$ in the particular case of anhydrous).

$$\mathrm{S},(n+p)\mathrm{H_2O} \Leftrightarrow \mathrm{S},(n)\mathrm{H_2O} + p\mathrm{H_2O} \quad \text{(I)}$$

This model has also been developed elsewhere (Chen and Grant, 1998).

The application of mass action law gives:

$$\frac{P_w^p \times a(\mathrm{S}, n\mathrm{H_2O})}{a(\mathrm{S},(n+p)\mathrm{H_2O})} = e^{(-p\Delta G_I/RT)} \quad (3)$$

a(S,nH$_2$O) and a(S,($n+p$)H$_2$O) are the activities of the two solid phases, P_w is the water partial pressure at equilibrium and ΔG is the Gibbs free enthalpy of hydration per mole of water. Index I relates to equilibrium (I).

Since, by convention, activities of pure solid phases are equal to 1, the equilibrium (III) can be simplified:

$$P_w(\mathrm{eq}) = e^{(-\Delta G_I/RT)} \approx K_I^0 \times e^{(-\Delta H_I/RT)} \quad (4)$$

$$K_I^0 = e^{(-\Delta S_I/R)} \quad (5)$$

in a sufficiently small temperature range (e.g. ~50 °C) where the enthalpy and entropy of hydration, respectively, ΔH and ΔS, can be considered as constant and can easily be deduced from Van't Hoff's plot (ln(P_w) versus 1/T).

5. Thermodynamic model for non-stoichiometric hydrates

Below we discuss various physical models of non-stoichiometric hydrates developed by Soustelle et al. (1971).

We explore the system with the following characteristics:

- Hydration is of an n-hydrate to an ($n+p$)-hydrate. The anhydrous is a particular case, with $n = 0$.
- The solid phase is considered as a solid solution in equilibrium with the vapor phase. The difference between the models will be the quasi-chemical species we take into consideration.

In addition, one should notice following points:

- The three models that we will propose, describe only the water inside the solid and not the water on the surface of the solid (adsorption).
- Models A and B will describe only crystalline solids, whereas model C will describe amorphous or crystalline solids with some disorder.

5.1. Non-stoichiometric hydrates with fixed location of water molecules

There are two proposed models where water molecules are considered to be in fixed ordered locations in the crystal lattice.

5.1.1. Substitution solid solution of a ($n+p$)-hydrate in a n-hydrate: model A

We consider the case where some structural elements have n molecules of water per molecule of anhydrous solid, whereas others have ($n+p$) molecules of water per molecule of anhydrous solid. We can, therefore, consider the solid phase as a solid solution of the n-hydrate and of the ($n+p$)-hydrate (see Fig. 2).

The equilibrium is written:

$$\langle \mathrm{S},(n+p)\mathrm{H_2O}\rangle \leftrightarrow \langle \mathrm{S},n\mathrm{H_2O}\rangle + p\mathrm{H_2O} \quad \text{(II)}$$

Equilibrium (II) seems similar to equilibrium (I), but here we suppose that the two hydrates are isomorphic, or in other words are the same phase.

Where:

$\langle$S,nH$_2$O$\rangle$ and $\langle$S,($n+p$)H$_2$O$\rangle$ are the n and ($n+p$)-hydrates;
H$_2$O is the vapor water.

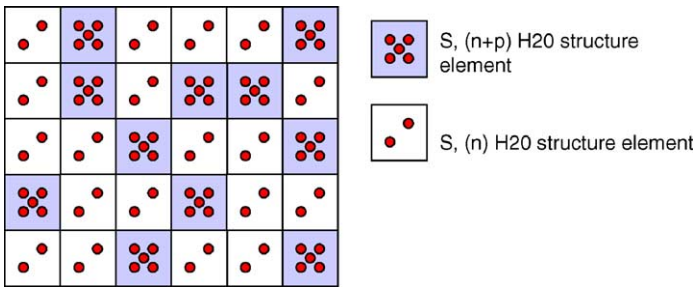

Fig. 2. Schematic representation of the solid as a solid solution of n and $(n+p)$-hydrates. In the example $n=2$, $p=3$. During addition of the three last molecules, the first two stay in place.

Equilibrium is simply given by:

$$K_{\mathrm{II}}(T) = \mathrm{e}^{-(\Delta G_{\mathrm{II}}/RT)} = \frac{\gamma_1 x_1 P_{\mathrm{w}}^{\mathrm{p}}}{\gamma_2 x_2} \tag{6}$$

x_1 and x_2 are the molar fractions of n and $(n+p)$-hydrates, respectively; γ_1 and γ_2 the activity coefficients of n and $(n+p)$-hydrates, respectively; $K_{\mathrm{II}}(T)$ the equilibrium constant at T, for equilibrium (II) and ΔG_{II} is the standard free enthalpy of hydration whose value depends on the definition of the reference state for water.

Remark that standard enthalpies, entropy, and the free energy of hydration depend on the definition of reference states. For the n and $(n+p)$-hydrates the choice is unambiguous: pure hydrates are the reference state. For water, the reference should be chosen as a hypothetic solid phase having the same structure as the hydrate.

In addition:

$$\varepsilon = nx_1 + (n+p)x_2 \tag{7}$$

ε is the moles of water per mole of anhydrous solid, actual stoichiometric ratio of the hydrate.

Thus, taking into account that $x_1 + x_2 = 1$:

$$x_1 = \frac{(n+p-\varepsilon)}{p} \tag{8}$$

$$x_2 = \frac{(\varepsilon - n)}{p} \tag{9}$$

Finally, by substitution x_1 and x_2 by their value from Eqs. (8) and (9) in Eq. (6), the value of ε can be obtained after some elementary mathematical manipulations:

$$\varepsilon - n = \frac{\frac{\gamma_1}{\gamma_2} p P_{\mathrm{w}}^{\mathrm{p}}}{K_{\mathrm{II}}(T) + \frac{\gamma_1}{\gamma_2} P_{\mathrm{w}}^{\mathrm{p}}} \tag{10}$$

5.1.1.1. Limit case: Henry's law. For $p=1$ and for and P_{w} close to 0, Eq. (10) simplifies to Henry's law

$$\varepsilon - n \approx \frac{\gamma_1}{\gamma_2 K_{\mathrm{II}}(T)} P_{\mathrm{w}} \approx \frac{1}{\gamma_2^{\infty} K_{\mathrm{II}}(T)} P_{\mathrm{w}} \tag{11}$$

Taking into account obvious $x_2 \sim 0$, $\gamma_1 \sim 1$, where γ_2^{∞} is the activity coefficient for $(n+p)$-hydrate at infinite dilution.

5.1.1.2. Limit case: Langmuir isotherm. If the activity coefficients are constant and $p=1$, the above isotherm reduces to the Langmuir adsorption isotherm (see, for instance, Adamson, 1982), which was originally developed for surface adsorption but is very common in the zeolite microporous adsorption, for instance (Simonot-Grange, 1987).

$$\varepsilon - n = p\frac{aP_{\mathrm{w}}}{1 + aP_{\mathrm{w}}} \tag{12}$$

where:

$$a = \frac{\gamma_1}{\gamma_2 K_{\mathrm{II}}(T)} \tag{13}$$

5.1.1.3. Activity coefficients models. In the case where we cannot consider the activity coefficients as constant, we propose to evaluate the activity coefficient by the Margules method often used for modeling phase transitions in multi-component solutions (Prausnitz et al., 1986). Margules' equations of second and third order are indicated in Table 2.

Table 2
Margules development

Second order ($A_{12} = A_{21}$)	Third order ($A_{12} \neq A_{21}$)
$RT \ln(\gamma_1) = A_{12}x_2^2$	$x_2^2(A_{12} + 2(A_{21} - A_{12})x_1)$
$RT \ln(\gamma_2) = A_{12}x_1^2$	$x_1^2 \times (A_{21} + 2(A_{12} - A_{21})x_2)$

A_{12} and A_{21} are the constants, which reflect the interaction between n and $(n+p)$-hydrates. The simplest symmetric solution (order 2) assumes that the constants are equal. However, this is generally not the case and the third order asymmetric model gives a better fit for real systems. Margules' model, which considers the molar volumes of the components equal, is only one of the numerous models to represent activity coefficients in solution thermodynamics. Many more sophisticated models were developed to fit for instance binary or multi-component liquid vapor equilibriums (Van Laar, Wilson, NRTL, etc., ..., see Prausnitz et al., 1986), and they are commonly used to calculate distillation unit operations in commercial chemical engineering software.

The second order Margules model is equivalent to the well-known Bragg–Williams model or to the Flory–Huggins model for polymers if one replaces molar fraction by volume fraction. Margules' theory of the activity coefficient is a regular solution model in that it only takes into account enthalpic contributions to the excess free energy.

If we limit Margules' equations to the first quadratic term, A_{12} is the net energy to mix the components 1 and 2:

$$A_{12} = N_A \left(E_{12} - \frac{1}{2}(E_{11} + E_{22}) \right) \tag{14}$$

where E_{11}, E_{12} and E_{22} are the interaction energies between 1–1, 1–2 and 2–2, respectively, at the molecular level and N_A is the Avogadro's number.

A negative value of A_{12} means that 1–2 interaction is attractive (in this case 1 and 2 will trend to mix), whereas a positive value means that the interaction is repulsive. In this latter case, on the microscopic scale 1–1 and 2–2 clusters will tend to form, and at low temperature or for an excessive value of A_{12}, as we will see below, phase separation will occur.

5.1.1.4. Isosteric heat of sorption. Substituting the activity coefficients in (10) with the help of the Margules equations (above), the equilibrium can be presented as follows:

$$P_w = K_{II}(T) \frac{(\varepsilon - n)}{(n + p - \varepsilon)} \exp\left(\frac{A_{12}}{RT} \left(1 - 2\frac{(\varepsilon - n)}{p} \right) \right) \tag{15}$$

According Van't Hoff, the isosteric (ε = cste) heat of adsorption (as derived from Van't Hoff's diagram) is given by

$$\Delta H = \Delta H_{II} - A_{12} \left(1 - 2\frac{(\varepsilon - n)}{p} \right) \tag{16}$$

where ΔH_{II} is the standard enthalpy relative to the constant K_{II}.

5.1.1.5. Shape of the isotherms. It is interesting to study the shape of the isotherms from these models (Figs. 3 and 4):

- For $A_{12}/RT = 0$ or $A_{12}/RT < 0$, the shape of the isotherm is "type I". For highly negative values of A_{12}/RT indicating a very strong water–solid interaction, isotherm slope is very steep and the isotherm is close to a step pattern: for very small values of the partial vapor pressure, the solid is already close to saturation.
- For $0 < A_{12}/RT < 2$ an inflexion point can be observed (mainly in the range of 1–2) and the sorption isotherm is the"type V".

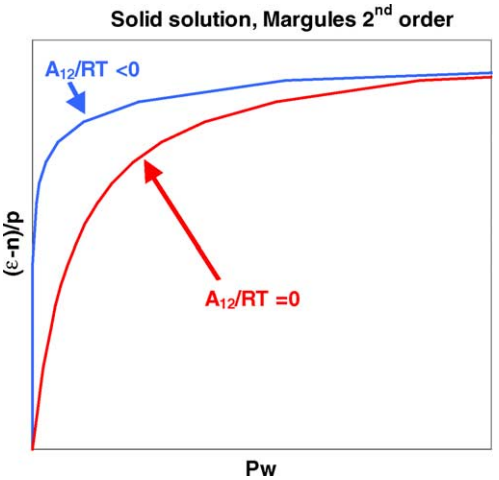

Fig. 3. Solid solution Margules second order for $A_{12}/RT \leq 0$. Type 1 isotherm: model A.

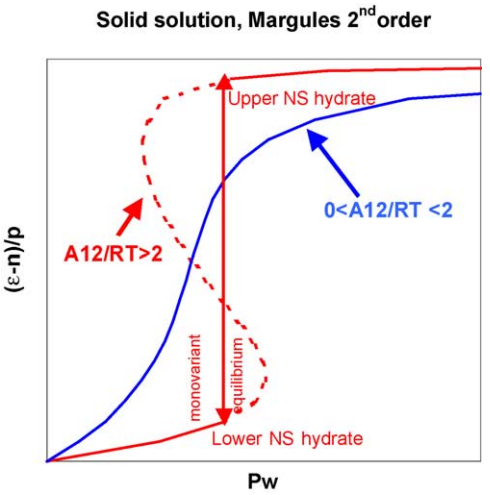

Fig. 4. Solid solution Margules second order for $0 < A_{12}/RT < 2$ (type V isotherm) and $A_{12}/RT \geq 2$ (phase separation). Model A.

- Using the Margules equation, we can see from Fig. 4 that if $A_{12}/RT > 2$, at low T, for instance, the model predicts a phase separation between a lower non-stoichiometric hydrate (whose composition is close to (n)-hydrate) and an upper non-stoichiometric hydrate (whose composition is close to ($n + p$)-hydrate). Both upper and lower hydrates have a limited non-stoichiometric range and are related by a solid/solid transition (or monovariant equilibrium), similar to true stoichiometric hydrates in what Soustelle called the "limit of di-variance" (Soustelle et al., 1971). In other words (n)-hydrate and ($n + p$)-hydrate have a limited mutual solubility, at least at low T (note: as A_{12} is approximately independent of the temperature, at $T > A_{12}/2R$ the thermal motion is sufficient to make the hydrates completely soluble in each other). This result is obviously not specific to a solid solution of hydrates: the same result is classically obtained for regular liquid or alloy solutions as well as for polymer solutions (for value of Flory parameters $\chi >$ critical value depending of polymer/polymer volume ratio, de Gennes, 1979).

5.1.2. Crystallographic vacant location: model B

In this model, we still discuss the equilibrium between (n)-hydrate and ($n + p$)-hydrate. An additional assumption we make is that the water molecules are associated into clusters of q molecules on well-defined crystallographic sites in the skeleton of the n-hydrate. In addition, we assume that a fraction of the crystallographic sites are free. Finally, we assume that water molecules can move from site to site through channels in a 1D, 2D or 3D network. The channels will allow dehydration without recrystallization as water molecules can easily migrate (see Fig. 5).

This case could correspond to non-stoichiometric channel or planar hydrates, where water is preferentially located in cavities. It is also very close to the case of zeolites, even if the nature of the bonding is clearly different and stronger in zeolites (physisorption in organic crystals instead of chemisorption in zeolites).

The equilibrium between water vapor, clusters and free sites can be written as quasi-chemical reaction:

$$\langle H_2O\rangle_q \leftrightarrow q[H_2O] + \langle \ldots\rangle_q \quad \text{(III)}$$

where $\langle H_2O\rangle_q$ is the clusters of water molecules at crystallographic positions; $\langle \ldots\rangle_q$ the free sites and $[H_2O]$ is the vapor water.The equilibrium is simply given by:

$$\frac{P_w^q a_1}{a_2} = \frac{P_w^q \gamma_1 x_1}{\gamma_2 x_2} = K_{III}(T) \quad (17)$$

a_1, x_1 and γ_1 are the activity, site fraction and activity coefficient of free crystallographic adsorption; a_2, x_2 and γ_2 are activity, site fraction and activity coefficient

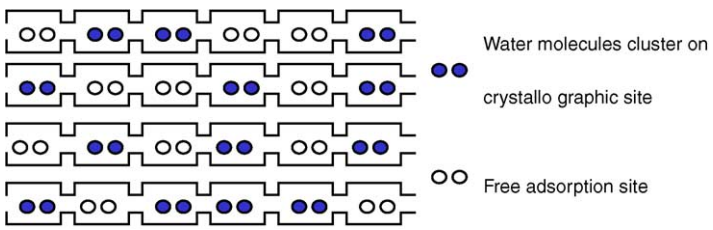

Fig. 5. Schematic representation of the model for $q = 2$: clusters of two water molecules are randomly distributed in the crystallographic sites and can move through channels.

of water clusters and $K_{III}(T)$ is the equilibrium constant at T, for equilibrium (III).

If ε is the number of moles of water per mole of anhydrous solid, we have:

$$n_2 = \frac{\varepsilon - n}{q} \text{ occupied sites} \tag{18}$$

and

$$n_1 = \frac{p}{q} - \frac{\varepsilon - n}{q} = \frac{p + n - \varepsilon}{q} \text{ free sites} \tag{19}$$

Therefore:

$$x_1 = \frac{n_1}{n_1 + n_2} + = \frac{p + n - \varepsilon}{p} \tag{20}$$

$$x_2 = \frac{n_2}{n_1 + n_2} = \frac{\varepsilon - n}{p} \tag{21}$$

Finally, the isotherm equation is obtained by substituting x_1 and x_2 by their value in Eqs. (20) and (21):

$$\varepsilon = n + \frac{\frac{\gamma_1}{\gamma_2} p P_w^q}{K_{III}(T) + \frac{\gamma_1}{\gamma_2} P_w^q} \tag{22}$$

This equation is similar to the previous isotherm of model A for $p = q$ (Eq. (10)). Therefore, the sorption isotherms have the same shape and all the above discussions about Henry and Langmuir limit cases and activity coefficients, including solid/solid separation, remains unchanged.

Basically, models A and B are very close. However, in our opinion:

- model A, which describes the non-stoichiometric hydrate as a solid solution of (n)-hydrate and ($n + p$)-hydrate, probably gives a easier understanding of phase separation;
- model B, probably gives a more intuitive representation of the site and channel hydrate.

In the experimental part, we will use Eq. (22) to fit the experimental data, as there is an additional freedom with $p \neq q$.

5.2. Non-stoichiometric hydrates with disordered water distribution: model C

In this model, we simply assume a partition equilibrium of water between the vapor phase and the solid solution. The solid can either be crystalline or amorphous. As in the previous model, we assume that molecules can be associated in clusters of q molecules, even if $q = 1$ is probably a common case. As we do not assume any position or interaction with a site, this model is describes disordered water molecules. It does not mean that there are absolutely no privileged positions, but only that the molecules can easily move from one position to another position. To understand this, imagine a system with periodic energy minima. Depending on the energy difference between the low energy and the high-energy positions ΔE, the relative concentration of molecules in the high and the low energy state will vary as $e^{-(\Delta E/kT)}$. Therefore, if the difference in energy is small compared to thermal agitation, the molecules can easily move to the upper band and the system is disordered; elsewhere the molecules are mainly trapped in sharp energy minima and the system is ordered. Note that ΔE should be equal to the activation energy for diffusion. See Fig. 6(a and b).

Solution equilibrium can be represented by:

$$q[H_2O] \leftrightarrow \ll H_2O \gg_q \tag{IV}$$

$\ll H_2O \gg q$ is the clusters of q molecules in solution in the solid.

Nota bene: high q values signify presence of a condensed water phase within micropores, for instance.

The equilibrium is described simply by:

$$\frac{P_w^q}{\gamma_2 x_2} = K_{IV}(T) \tag{23}$$

where x_2 is the molar fraction of q-clusters and $K_{IV}(T)$ is the equilibrium constant at T, for equilibrium (IV).

It is particularly interesting to consider pure water as reference state for water in the solid. Then

$$K_{IV}(T) = P_w^*(T)^q \tag{24}$$

where $P_w^*(T)$is the pressure of the water at the liquid–vapor equilibrium at T.

From (23) and (24) the expression for equilibrium simplifies to:

$$\gamma_2 x_2 = \left(\frac{P_w}{P_w^*(T)} \right)^q \tag{25}$$

$$x_2 = \frac{\varepsilon - n}{q\left(1 + \frac{\varepsilon - n}{q}\right)} \tag{26}$$

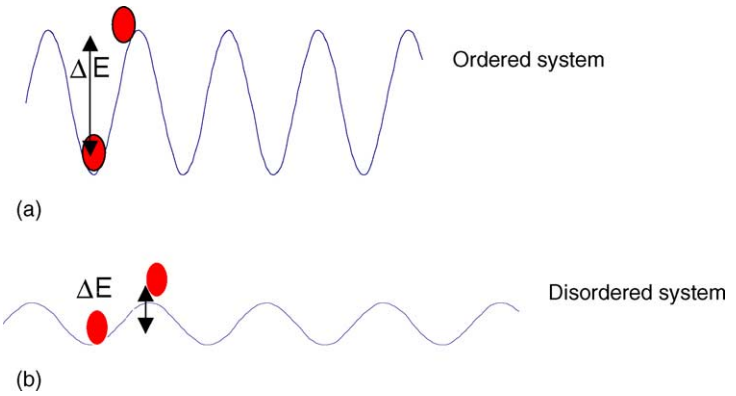

Fig. 6. Scheme of water–substrate interaction (a) strong interactions and localized water (b) weak interaction and poorly localized (or disordered) water.

$$\varepsilon = n + \frac{q\left(\dfrac{P_w}{P_w^*(T)}\right)^q}{\gamma_2 - \left(\dfrac{P_w}{P_w^*(T)}\right)^q} \tag{27}$$

The ratio $(P_w/P_w^*(T))$ is simply the relative humidity.

Using the Margules equation limited to the second order, the equilibrium is presented as:

$$\frac{P_w}{P_w^*(T)} = \frac{\varepsilon - n}{1 + \varepsilon + n} e^{(A_{12}/(RT(1+\varepsilon-n)))} \tag{28}$$

5.2.1.1. Shape of the isotherm

The shape of the isotherm is:

- Type III for constant activity coefficients. As we will see later in the examples, the sorption isotherm with $q = 1$ and constant activity coefficient is very typical for water sorption on amorphous drug substances. If the value of q is increased, which is equivalent to a liquid condensation, the shape of the isotherm changes with increasing slope, which is close to what is observed with deliquescent solids (Fig. 7a).
- Type II (with a shoulder) when using Margules' models for activity coefficients with $A_{12} < 0$. This depicts the fact that the initial molecules are very strongly attracted by the solid, and therefore should be more or less localized, whereas the subsequent molecules may be mobile (Fig. 7b).

When using a second order Margules equation to model activity coefficients, for $A_{12}/RT > 2$, a phase separation is also predicted.

5.3. Comments on the models

We have proposed two kinds of models for non-stoichiometric hydrates:

- Two very close models (A and B), which assume water location on crystallographic positions.
- A model (C) assuming disordered water distribution in the amorphous or crystalline solid.

All three models are "solid solution" models, and for all of them we have taken into consideration the deviation from "ideal solution" by modeling the activity coefficients by Margules' method with one or two terms. Use of other models for the activity coefficient is of course possible and should be investigated.

It is interesting to notice that the shape of the isotherm is dependent on the model:

- Localized water is in agreement with type I (negative second derivative) or type V isotherms.
- Non-localized water is in agreement with type III (positive second derivative) or type II. Some order should exist for the first molecules adsorbed in type II isotherms.

Therefore, a theoretical link between localization of the molecules the structure of the hydrates and the shape of the isotherm has been suggested. In next part of the article we will compare theory with available experimental data in order to establish the validity of this approach.

To do this comparison we have extracted from the literature some water sorption isotherms and

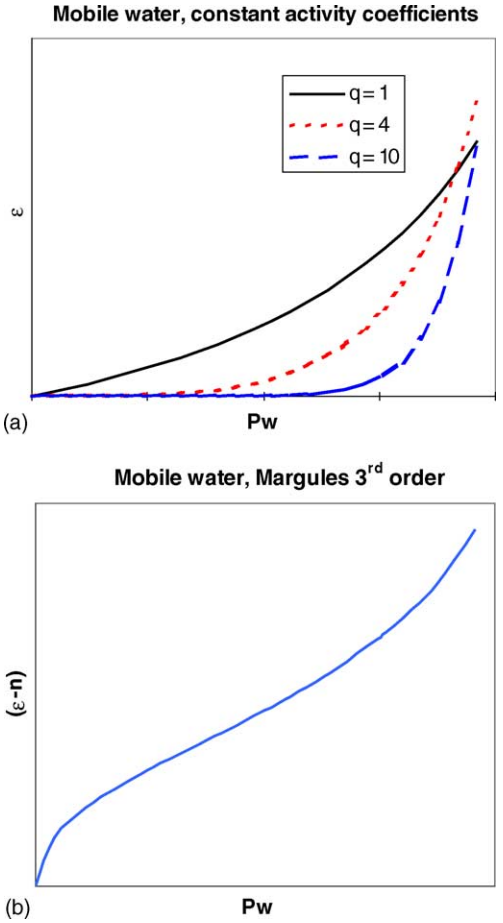

Fig. 7. Mobile water sorption isotherms (a) constant activity coefficients, various values for q, type III isotherms, (b) activity coefficients according Margules third order model.

also some structural information when it was available.

6. Model versus experiment

In this part, we will compare models' prediction with experimental sorption/desorption data and structural data (when available). The objective is to estimate to what extent the models:

(1) Provide a good mathematical fit of the sorption isotherm.
(2) Are in agreement with the structural data.

Most data to be discussed, except for that of RPR102341, were obtained from the literature. Data for sorption isotherms from the literature were extracted from the appropriate published graphics, except for the case of Celiprolol hydrochloride where the numerical data were tabulated by the authors.

It should be mentioned that measuring sorption isotherms by automatic systems is sometime not the best tool to evaluate the true equilibrium due to the time lag between the sorption and desorption curves. This is mainly the case for the stoichiometric hydrates because of the re-crystallization process. In such a case slurries are a more accurate way to determine critical transition water activity (Zhu and Grant, 1996). In the case of non-stoichiometric hydrates, however, the hydration/dehydration process is much faster, and therefore lag is generally not an issue. To compensate for this, when we had the data, we have taken the mean value between sorption and desorption. By commodity we have considered for all isotherms $T = 22\,^{\circ}\mathrm{C}$ corresponding to a saturating water vapor pressure of 19.83 Torr.

Experimental data have been fitted using the two following equations:

- Eq. (22) (model B or A if $p = q$) for vacant crystallographic sites or ordered water molecules.
- Eq. (28) (model C) for non-stoichiometric hydrates with disordered water.

For the both models, we have examined the case of constant activity coefficients and Margules' equations of the second and third order.

6.1. Type I isotherms

6.1.1. Classical type I: Cefaclor and Celiprolol

Cefaclor sorption isotherm has been reported by Stephenson et al. (1998). Fig. 8 shows that the sorption isotherm at room temperature is in a very good agreement with a very simple Langmuir model.

The actual best-fit equation is : $\varepsilon = \dfrac{0.46 P_w}{1 + 0.32 P_w}$

The authors have shown that crystal structure does not change upon dehydration except for some changes in d-spacing to accommodate the water molecules. As a crystal structure was not solved, it is not possible to confirm that the water molecules are located at the crys-

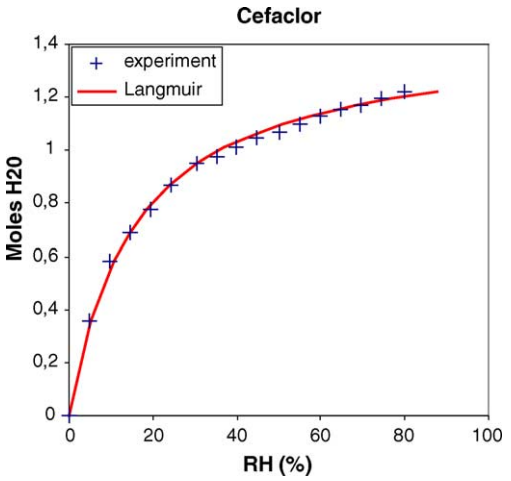

Fig. 8. Cefaclor isotherm and the best-fit (Langmuir isotherm).

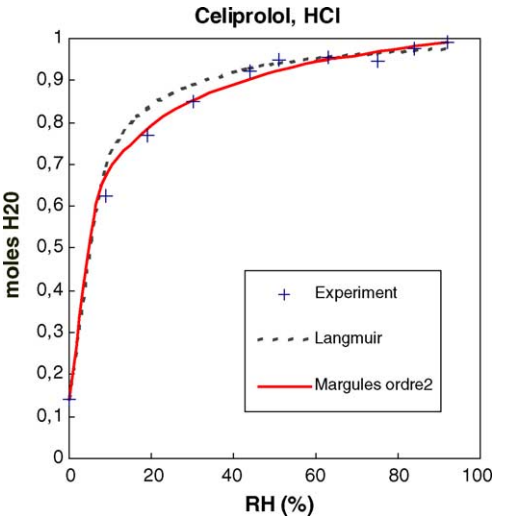

Fig. 9. Celiprolol hydrochloride, isotherm and best-fit.

tallographic sites, however, it seems to us a reasonable assumption.

In the case of Celiprolol HCl, Burger et al. (1988) have studied the hydration of form III into the H form (form III was submitted to 7 and 13 days at well-defined relative humidity conditions and the samples were analyzed by Karl Fischer analysis). They have shown that the hydration is progressive, and that for RH $\geq$ 40% the stoichiometric ratio is close to monohydrate. They have concluded from their studies that form III and form H are the same crystal lattice and that the water molecules are hosted in cavities in the crystal. This is exactly what we assume in model B.

As the experimental hydration level at RH = 0% is 0.14, we have assumed that $n = 0.14$ and we have fitted the data to a simple Langmuir equation and a second order Margules equation. Although the Langmuir model is in satisfactory agreement with the experimental data, Margules' equation with a slightly negative value of A_{12}/RT shows a better fit, indicating that the interaction of the first adsorbed molecules is somewhat stronger (see Fig. 9). The best-fit parameters are reported in Table 3.

6.1.2. *Type I isotherm plus insertion water: Spirapril monohydrate and Erythromycin A dihydrate*

Spirapril monohydrate and Erythromycin A dihydrate sorption isotherms are reported by Stephenson et al. (1998). Hydrates of both products exhibit type I isotherms (or nearly type I isotherm for Erythromycin A). Both hydrates can lose water to give a nearly isomorphic anhydrous structure, and the only effect observed is the gradual change in unit cell dimensions during hydration or dehydration.

The structure studies for Spirapril hydrochloride monohydrate and Erythromycin A dihydrate have shown the existence of, respectively, one and two crystallographic sites for water per anhydrous molecule. In addition for both products water molecules can migrate along channels from one site to another.

However, Spirapril hydrochloride monohydrate and Erythromycin A dihydrate can adsorb slightly more water than the theoretical stoichiometric ratio (respectively, approximately 1.2 molecules versus 1 and 2.5 molecules versus 2). As these additional water molecules cannot be located at crystallographic sites we have made the assumption that they are disordered at interstitial sites (model C) according to the scheme

Table 3
Parameters for best-fit of Celiprolol hydrochloride monohydrate sorption isotherm

Celiprolol HCl	Best-fit
Langmuir	$\varepsilon = 0.14 + \dfrac{0.84P_w}{1 + 0.96P_w}$
Margules	$n = 0.14$
	$p = q = 1$
	$K = 1.90$
	$A_{12}/RT = -0.9$

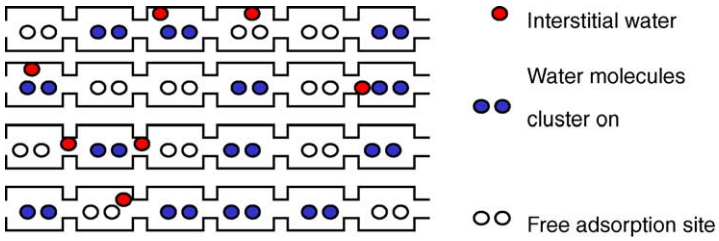

Fig. 10. Water cluster on crystallographic sites and interstitial disordered molecules.

on Fig. 10. An alternative assumption is that the disordered water molecules may also be localized on some amorphous phase around the crystals.

In this case, we can assume that the global water content can be estimated by two parallel equilibria. Assuming a simple Langmuir equilibrium for the crystallographic sites and $q = 1$:

$$\varepsilon - n = \varepsilon_{\text{cryst}} + \varepsilon_{\text{Disor}} = p\frac{aP_{\text{w}}}{1 + aP_{\text{w}}} + \frac{\dfrac{P_{\text{w}}}{P_{\text{w}}^{*}(T)}}{\gamma_2 - \dfrac{P_{\text{w}}}{P_{\text{w}}^{*}(T)}} \tag{29}$$

Figs. 11 and 12 show a very good agreement between the model and the experiment.

In order to fit the data we have used $p = 1$ and 2 for Spirapril HCl and Erythromycin A, respectively.

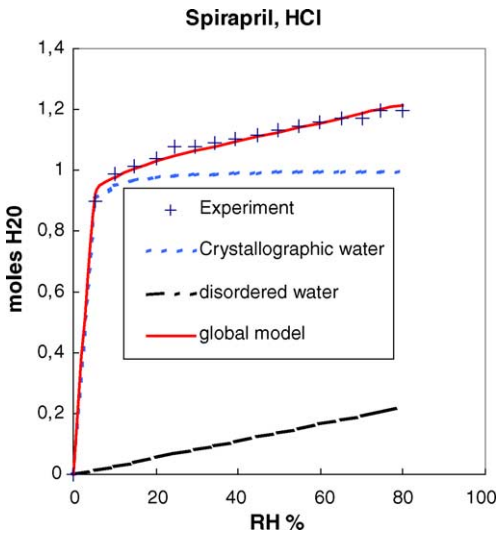

Fig. 11. Spirapril hydrocloride monohydrate isotherm and best-fit.

The value of the parameter "a" is determined at low RH by the negative curvature of the isotherm, whereas the value of "γ_2" is determined by the shape of the isotherm at higher RH. Therefore, there is no possible mathematical interaction between the parameters, and as such these results are truly physically meaningful and are not a simple mathematical representation of the isotherm without any physical significance. The best-fit parameters are reported in Table 4.

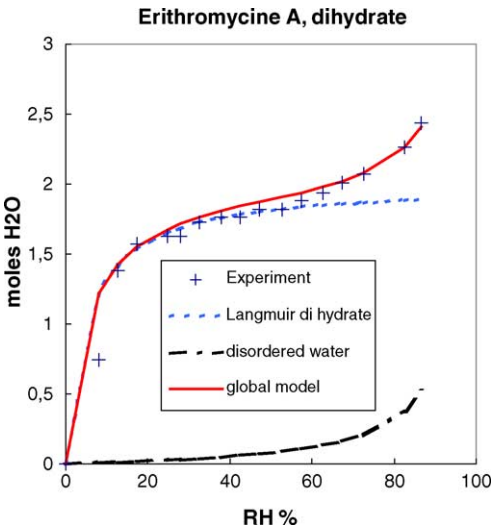

Fig. 12. Erythromycin A dihydrate isotherm and best-fit.

Table 4
Parameters for best-fit of Erythromycin A dihydrate and Spirapril hydrocloride monohydrate sorption isotherm

Molecule	Best-fit equation
Erythromycin A dihydrate	$\varepsilon = 2\dfrac{0.96P_{\text{w}}}{1 + 0.96P_{\text{w}}} + \dfrac{0.08P_{\text{w}}}{19.83 - P_{\text{w}}}$
Spirapril monohydrate	$\varepsilon = \dfrac{9.52P_{\text{w}}}{1 + 9.52P_{\text{w}}} + \dfrac{5.89P_{\text{w}}}{437 - P_{\text{w}}}$

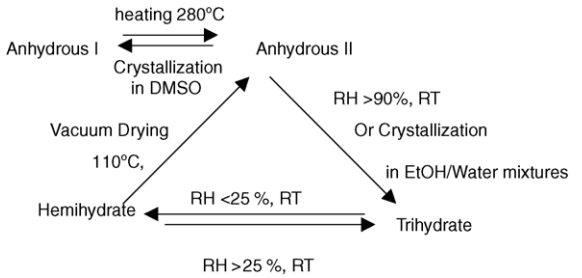

Fig. 13. Interconversion scheme of different forms of RPR102341.

6.2. Type V isotherm

6.2.1. RPR102341

RPR102341 was an antibacterial agent developed by Rhône Poulenc Rorer; polymorphism studies have shown existence of four distinct crystalline phases (Authelin, internal report 1995):

- anhydrous I;
- anhydrous II;
- hemihydrate;
- trihydrate.

Fig. 13 shows interconversion scheme of the different forms.

Anhydrous I and II are enantiotropic forms according Burger Heat of Transition rule (an endothermic transition anhydrous I → anhydrous II at about 280 °C is observed in DSC experiments). Anhydrous II is not the thermodynamically stable anhydrous form at room temperature but it is quite kinetically stable.

The trihydrate is the thermodynamically stable form at ambient relative humidity. However, the anhydrous II can take a lot of water (up to 1.2 mol/mol) reversibly if the relative humidity is maintained at a lower level than about 80%. During sorption, X-rays powder diffraction peaks move slightly towards small angles as a result of the expansion of the unit cell dimensions due to water incorporation. The sorption isotherm is of type V. It can be seen in Fig. 14 that the isotherm can be fitted by the model of non-stoichiometric adsorption at crystallographic sites, with a Margules equation limited to the first term.

The best-fit parameters are

$$n = 0,\ p = 1.28; q = 1; K = 5.38\,\text{Torr};\ \frac{A_{12}}{RT} = 1.43$$

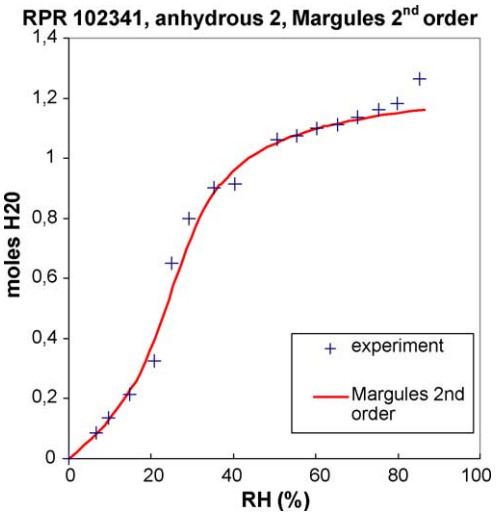

Fig. 14. RPR102341 isotherm and best-fit.

The relatively high value of A_{12}/RT shows that the system is close to solid/solid phase separation. Theoretically solid phase separation should occur at approximately −60 °C (213 K), when A_{12}/RT increases to 2, and an additional non-stoichiometric hydrate, close to 1.2 mol/mol, and with a distinct X-ray diagram should appear (as explained in Fig. 4). We have, however, no experimental evidence to confirm this theoretical prediction.

6.3. Modeling experimental data for non-stoichiometric hydrates with disordered water molecules

6.3.1. Type III isotherm: amorphous Erythromycin A

Amorphous Erythromycin A sorption isotherm was reported by Stephenson et al. (1998). As most amorphous products, amorphous Erythromycin A adsorbs a significant amount of water. Furthermore, the sorption isotherm very clearly fits well with the disordered solid solution model B with constant activity coefficients. Refining up to order three brings only a very tiny improvement of the fit as shown in Fig. 15. We can remark that the constant positive curvature of the isotherm is in agreement with the disorder of the amorphous phase. This shape of isotherm is extremely common for amorphous drug substances.

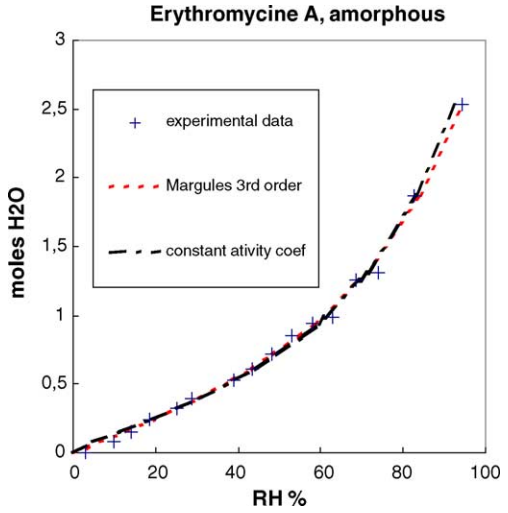

Fig. 15. Erythromycin A amorphous sorption isotherm and best-fit.

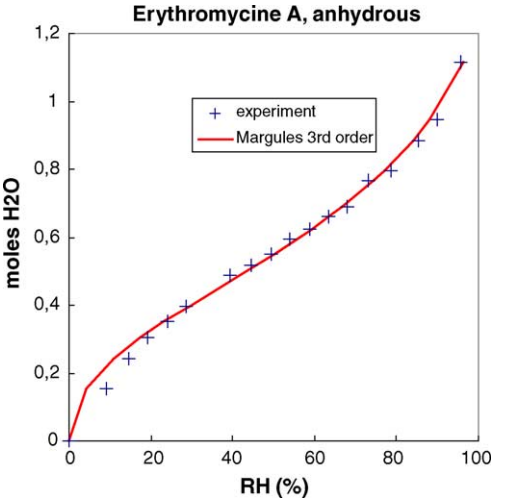

Fig. 16. Erythromycin A anhydrous sorption isotherm and best-fit.

6.3.2. *Type II isotherms: Erythromycin A anhydrate, disodium Cromoglycate, LY297802 tartrate, FK041*

There are not as many type II isotherms reported in the literature, and such sorption isotherms are normally considered as atypical. In all cases, disorder of the water molecules has been shown. We will study four of them using model C with a third order Margules equation. Best-fit parameters are reported in Table 5.

Anhydrous Erythromycin A is reported by Stephenson et al. (1998). Despite its denomination, the "anhydrate" can adsorb up to roughly 1.2 mol of water per molecule of solid without changing its crystal structure. According the authors, the water molecules are allowed to move into channels. Fig. 16 shows good agreement between model C (using third order Margules equation) and experiment, except at very low relative humidity.

Disodium Cromoglycate is a well-known and historic case of a non-stoichiometric hydrate (Cox et al., 1971; Stephenson and Diseroad, 2000; Vippagunta et al., 2001). It has been shown that disodium Cromoglycate can adsorb up to 9 mol of water per molecule of the active compound. Anisotropic expansion of the unit cell during water sorption has been shown. The crystalline structure has been solved (Hamrodakas et al., 1973; Chen et al., 1999). It has been shown that two

Table 5
Parameters for best-fit of disodium Cromoglycate, anhydrous Erythromycin A, LY297808 tartrate and FK401 sorption isotherms

Molecule	n	q	A_{12}/RT	A_{21}/RT
Disodium Cromoglycate	0	1	−751	−327
Anhydrous Erythromycin A	0	1	−3	2.4
LY297802 tartrate	0	1	−1.5	3.6
FK401	1	1	−51	−14

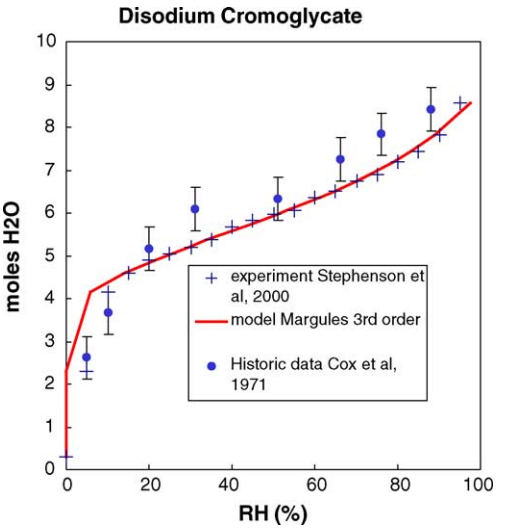

Fig. 17. Disodium Cromoglycate sorption isotherm and best-fit. We have used recent data from Stephenson and Diseroad (2000) for fit and indicated mean sorption/desorption value from the historical paper from Cox et al. (1971), error bar: ±0.5 mol/mol.

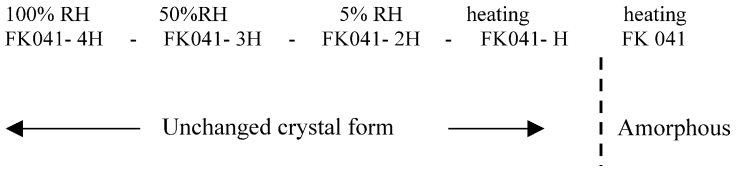

Fig. 18. Interconversion scheme of FK041 hydrates according Mimura et al. (2002).

of the water molecules are ordered, whereas the others are mainly disordered in channels.

Fig. 17 shows good agreement with experimental data except for RH $\leq$ 10%.

FK041 (Mimura et al., 2002) is an interesting case: it forms a channel "clathrate" with water, 2-propanol, ethanol or acetone. The water composition can vary continuously from a monohydrate to a tetrahydrate without any change of the diffraction pattern. However, when FK041 looses the monohydrate molecule, it tends to amorphize. The authors have summarized the system by the following scheme (Fig. 18).

Two of the three non-stoichiometric water molecules are assumed to move easily within channels in the crystal structure where they are weakly bound.

We have modeled the equilibrium considering that there is a mono-variant equilibrium between the anhydrous amorphous and the crystalline monohydrate at RH $\sim$ 0% and the non-stoichiometric water molecules in the disordered solution within the solid. Fig. 19 shows a very good agreement of the model with the experiment. The very negative values of the Margules parameter imply a very small value of the water activity coefficient for $x_2 \sim 0$, probably due to the very strong attraction of the water between the mono and dihydrate (isotherm nearly vertical at very low RH) and a distinct localization of this part of water.

The non-stoichiometric sorption isotherm of LY297802 was reported by Reutzel and Russel (1998). The authors have shown by C-13 Solid State NMR measurements that water is bound to tartaric ions by weak hydrogen bonds. They also show that molecules easily move, an easy diffusion suggest also weak energy gaps from site to site, suggesting also some disorder.

Fig. 20 shows that the model C fits quite well the isotherm.

6.4. Cellulose and other macromolecules

As already noted, many published works cover the domain of macromolecules, notably cellulose

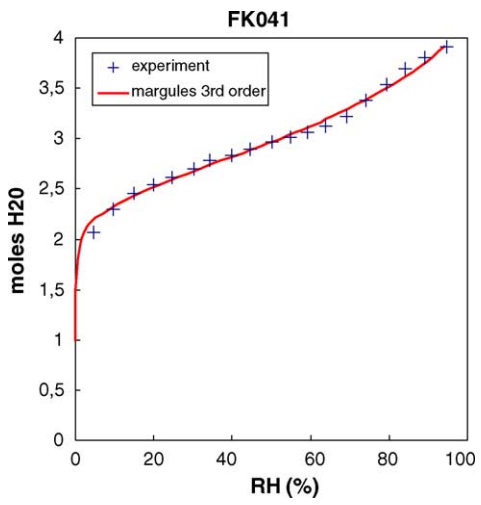

Fig. 19. FK041 sorption isotherm and best-fit.

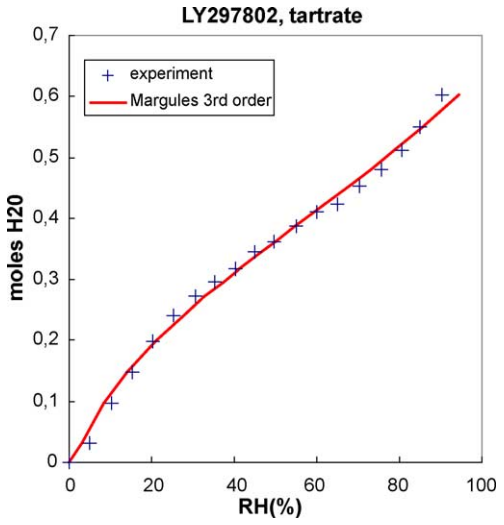

Fig. 20. LY297802 sorption isotherm and best-fit.

(Zografi and Kontny, 1986) and peptides and proteins (Shambling et al., 1998). The shape of sorption isotherms for macromolecules is very close to that of model C with non-constant activity coefficients, showing a shoulder at low relative humidity.

The theoretical approach is close to model C. However, authors have corrected it using Vrantas' theory of adsorption on macromolecules (Hancock and Zografi, 1993).

We will not, however, try to fit these data to Margules' model, as even a good fit would rather be a pure mathematical exercise without physical meaning.

7. Conclusion

Models are always a rough simplification of reality. However, the models developed by Soustelle et al. (1971) and Soustelle (1994) that we have reinvestigated here reveal, in our opinion, interesting information:

- The models based on different physical assumptions permit one to explain four of five known sorption isotherm types.
- There seems to be a strong link, already underlined by Soustelle et al. (1971) between isotherm shape and order in the hydrates:
  - Type I isotherms deduced from models A and B correspond well to site adsorption hydrates (Celiprolol HCl, Cefaclor, Spirapril HCl, Erythromycin A dihydrate).
  - Type V isotherms deduced from models A and B can represent rare situations like RPR102341.
  - Type III isotherms deduced from model C for disordered hydrates with constant activity coefficients are in good agreement with sorption isotherms of amorphous products such as amorphous Erythromycin A.
  - Type II isotherms also deduced from model C but using non-constant activity coefficients represent well intermediate-order situations where the molecules can move easily along crystals channels (disodium Cromoglycate, LY297802, FK041).

This is only the first attempt to approach correlation of structure and adsorption isotherms in pharmaceutical hydrates, in contrast to the large work already done in liquid solutions and also inorganic salts or in alloys. We hope it will bring an additional effective and easy tool to understand and interpret experimental data for small organic compounds.

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