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# **Influence of pH, Temperature and Impurities on the Solubility of an Active Pharmaceutical Ingredient (API)**

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# Influence of pH, Temperature and Impurities on the Solubility of an Active Pharmaceutical Ingredient (API)

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## Abstract

Solubility, which defines the liquid /solid equilibrium, is a key parameter to control a crystallization process. This work is focused on the effects of pH, temperature and impurities on the aqueous solubility of an Active Pharmaceutical Ingredient (API).

As the API is a weak acid ( $pK_a = 3.7$ ), its solubility increases with the pH. On the basis of the experimental curve of solubility, a model was defined to fit the evolution of the solubility as a function of pH. In the case of this compound, studies revealed a weak influence of the temperature in comparison with the pH. So, the solubility of the compound is slightly impacted by the temperature.

Some experiments were carried out in order to compare the solubility of the API, at the same pH and temperature, for different concentrations of impurities found in the process. The results revealed a solubility increase in presence of acetic acid and a high solubility decrease in presence of sodium chloride. By carrying out experiments on common ions salts, the anion chloride  $Cl^-$  has been identified as the cause of the solubility decrease.

**KEYWORDS:** solubility, API, impurity, pH

## **Introduction**

In pharmaceutical industries, the control of Active Pharmaceutical Ingredient (API) crystal properties is necessary because these properties will define the pharmaceutical form of the medicine elaborated with the crystals. As the generation step of these crystals, the crystallization process has to be controlled. For this, one of the initial data needed is the solubility of the product in the mother solution.

In this study, the API crystals are obtained by an acid-base precipitation. The pH is then the main parameter of the precipitation because it has a direct impact on the API solubility. The knowledge of the evolution of the solubility as a function of pH is then needed in order to control the precipitation. Moreover, in the considered process, at the end of precipitation, the remaining solution in which crystals are suspended contains impurities such as sodium chloride and acetic acid. These impurities have an influence on the solubility of the API. As filtration and washing steps are necessary to purify crystals, the knowledge of the solubility is also paramount to determine the loss of product by dissolution during these steps.

The goal of this study is then to determine the impact of pH, temperature and concentrations of impurity on the solubility of an API.

## **Material and methods**

### ***Materials***

In all experiments, bidistilled water was used. The API solid crystals (99.9% HPLC purity) were provided by Pierre Fabre laboratories in order to have the same quality and purity during all the experiments. The pH value in the initial solutions was fixed by adding a weighed mass of hydrochloric acid (37% w/w) or sodium hydroxide (30% w/w) aqueous solutions (AnalR Normapur) to a known quantity of bidistilled water. The influence of impurities found in the processing chain of the API, on the solubility of the API, was studied. Acetic acid (Sigma Aldrich 100% purity) and different salts were used: sodium chloride (Sigma Aldrich 99% purity) and its common ions salts (Sigma Aldrich 99% purity): sodium fluoride NaF, sodium perchlorate NaClO<sub>4</sub>, lithium chloride LiCl and ammonium chloride NH<sub>4</sub>Cl. All chemicals were used without any further purification.

## ***Solubility Measurements***

Aqueous solubilities of the solid API were determined, as a function of temperature, by the analytical shake-flask method, using constant-temperature jacketed glass cells, at seven different temperatures ranging from 278K to 333K. To prepare saturated solutions, solute and distilled water were placed into the cell and stirred in a plate stirrer. Temperature was maintained with a constant-temperature (0.10 K) circulating water bath. The way of preparing the saturated solutions was slightly modified compared to the classical method because no method of the saturated solution analysis was available for this API. Here, solubility was determined by adding weighed quantities of API solid crystals to a known volume of solvent, until crystals can not be solubilised anymore. Small amounts of solid (about 20 mg) were added each time and no addition was carried out before the solution was clear. When solubility was attained, solutions were kept under stirring during 24h. The pH of saturated solutions was then measured, using a pHmeter pHM210 from Radiometer Analytical with a pH3001 electrode, and the mass of solid added was determined in order to get the solubility. The time required to reach equilibrium was determined by repetitively measuring the solubilities until constant data were obtained. The effects of impurities have been determined by adding a known amount of acetic acid and different salts to the initial solution.

The experiments were repeated three times in order to assure reproducible results. Determination solubility uncertainty  $\Delta S$  has been calculated as below :

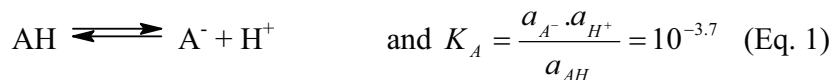
$$\frac{\Delta S}{S} = \frac{\Delta m}{m} + \frac{\Delta V}{V} + \frac{m'}{m_{total}}$$

Where  $\Delta m$  is the scale uncertainty,  $\Delta V$  is the uncertainty of the measured volume and  $m'$  is the amount of solid added. The last term is the major one, so  $\Delta S$  is lower than 5%.

## **Results**

### ***Influence of pH on the solubility***

The API studied is a weak acid ( $pK_a = 3.7$ ) and will be noted AH for its organic form and  $A^-$  for its conjugate base form. In water, the two forms are always present because of the dissociation of the species. The chemical acid constant  $K_a$  provides equilibrium of species, according to Eq. 1 :



Thus the solubility  $S$  of the API corresponds to the sum of the concentrations of the organic form and the conjugate base form (Eq. 2) :

$$S = [\text{AH}] + [\text{A}^-] \quad (\text{Eq. 2})$$

The organic form is less soluble in water than the conjugate ionic base form. As the proportion of each form is determined by the pH, the solubility of the API depends on pH. Solubility results, in mol per litre at 20°C, and the corresponding pH value of each saturated solution are reported in Table 1. As it can be observed, the solubility increases with pH. When pH is lower than  $\text{pK}_a$  (3.7), the main form is the organic one. In this zone, the solubility is almost constant and pH has no influence. When pH is higher than  $\text{pK}_a$ , the main form is the conjugate base ionic form, thus more soluble in water. In this zone, pH has a great influence on the solubility. Same solubility behaviours of weak acids according to pH have already been observed by Streng (1984, 1999).

The solubility of the organic form is then the minimum of the API solubility. It will be noted  $S_0$  and considered as a constant. Its experimental value is equal to 0,045 mol/L. Combining Eq. 1 and Eq. 2 (Myerson, 2002), the solubility  $S$  can be expressed as :

$$S = S_0 \cdot \left( 1 + \frac{K_A}{a_{\text{H}^+}} \right) = S_0 \cdot (1 + K_A \cdot 10^{\text{pH}}) \quad (\text{Eq. 3})$$

Using Eq. 3, a model can then be built in order to know the solubility of the API according to pH. At first approximation, the solution is considered as ideal and the activity of each species is considered as equal to their concentration. Results of this model are also reported in table 1. A good agreement with experimental values until  $\text{pH} = 5$ . The solubility calculated by the model is then higher than experimental ones for higher pH values.

pH at equilibrium	Solubility (mol/L)		
	Experimental	Model	Difference
1.22	0,045	0.045	0.000
2.60	0.0477	0.049	-0.001
3.25	0.0737	0.061	0.013

3.72	0.0995	0.092	0.007
4.01	0.1329	0.137	-0.004
4.24	0.1757	0.201	-0.025
4.55	0.3479	0.364	-0.016
4.93	0.6427	0.809	-0.167
5.26	1.0578	1.679	-0.621
5.39	1.4412	2.249	-0.808
5.64	2.5302	3.964	-1.434
5.79	3.5876	5.581	-1.994

Table 1: Experimental and calculated Solubilities, in mol/L, of the API in pure water as a function of pH at T= 20°C

Considering equation 3, by representing the logarithm of the solubility as a function of pH, two straight line segments can be plotted, as it can be seen in the figure 1, in relation with the two zones previously defined :

- For  $\text{pH} \ll \text{pK}_a$ ,  $\log(S) \approx \log(S_0)$
- For  $\text{pH} \gg \text{pK}_a$ ,  $\log(S) \approx \text{pH} - \text{pK}_a + \log(S_0)$

The intersection of the two lines is an experimental method to determine the  $\text{pK}_a$  value (Avdeef, 2007). However, the  $\text{pK}_a$  value found by this method (3.55) is slightly lower than the real one.

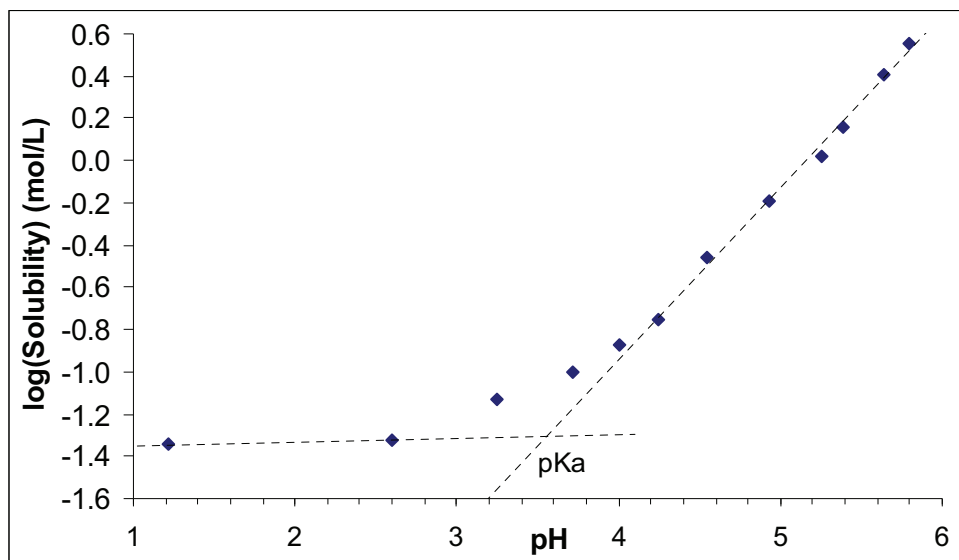


Figure 1 : Logarithm of the API solubility as a function of pH, at 20°C

### *Influence of temperature on the solubility*

Temperature is a current parameter used to control crystallization. This is due to the influence of temperature on the solubility of a compound. To determine the impact of temperature, experiments were carried out at a constant pH. However, as pH depends on temperature, at equilibrium and due to the dissociation of the API, pH values varied between 2.3 to 2.7. But as explained before, in this zone of pH, solubility is slightly dependent of pH. It is why in this part, we will consider that pH is constant.

Solubility results, in mol per litre, as a function of temperature and the corresponding pH of each saturated solution are reported in Table 2.

Temperature (°C)	Solubility (mol/L)	pH
5	0.0384	2.75
10	0.0444	2.77
20	0.0477	2.61
30	0.0517	2.46
40	0.0663	2.35
50	0.0749	2.32
60	0.0890	2.25

Table 2: Experimental API Solubilities in Pure Water as a function of temperature

The solubility increases with temperature. These results were in good agreement with most of the available literature data for organic weak acid (Mota,2002). However, solubilities do not increase significantly with temperature, in contrast to what would be expected compared to others organic products (Granberg, 2000).

Apart from empirical correlations, different thermodynamic approaches can be found for modelling the solid solubility of organic compounds in aqueous systems.

Considering a pure solid phase with no solid-solid phase transitions, assuming the difference in the heat capacities between the liquid and solid phases of the solute ( $\Delta C_p$ ) to be constant in the temperature range  $[T, T_m]$ , and neglecting the effect of pressure, the solubility of a solute  $s$  can be calculated from the following generalized expression that relates the reference-state fugacities:

$$\ln \left[ \frac{f_s^{liq}(T, P)}{f_s^{sol}(T, P)} \right] = \frac{\Delta H_{dis}}{R} \left( \frac{1}{T} - \frac{1}{T_m} \right) - \frac{\Delta C_p}{R} \left[ \frac{T_m}{T} - \ln \left( \frac{T_m}{T} \right) - 1 \right] \quad (\text{Eq. 4})$$



where  $\Delta H_{dis}$  is the enthalpy of dissolution,  $T$  is the absolute temperature,  $T_m$  is the melting temperature,  $\Delta C_p$  is the difference of the liquid and solid molar heat capacities, and  $R$  is the ideal gas constant. Using an activity coefficient model, the following expression for the solubility molar fraction ( $x_s$ ) is obtained:

$$x_s = \frac{1}{\gamma_s} \exp \left\{ -\frac{\Delta H_{dis}}{R} \left( \frac{1}{T} - \frac{1}{T_m} \right) + \frac{\Delta C_p}{R} \left[ \frac{T_m}{T} - \ln \left( \frac{T_m}{T} \right) - 1 \right] \right\} \quad (\text{Eq. 5})$$

where  $\gamma_s$  is the solute activity coefficient. In this study, the solution is considered as ideal, so the activity coefficient  $\gamma_s$  is equal to 1. The second approximation is that  $\Delta C_p$  is negligible. The equation 5 can then be simplified as:

$$x_s = \exp \left[ -\frac{\Delta H_{dis}}{R} \left( \frac{1}{T} - \frac{1}{T_m} \right) \right] \quad (\text{Eq. 6})$$

By plotting the natural logarithm of the solubility molar fraction as a function of the inverse of the temperature, as can be seen in figure 2, the slope of the linear regression line gives the enthalpy of dissolution of the API ( $\Delta H_{dis} = 11.28$  kJ/mol).

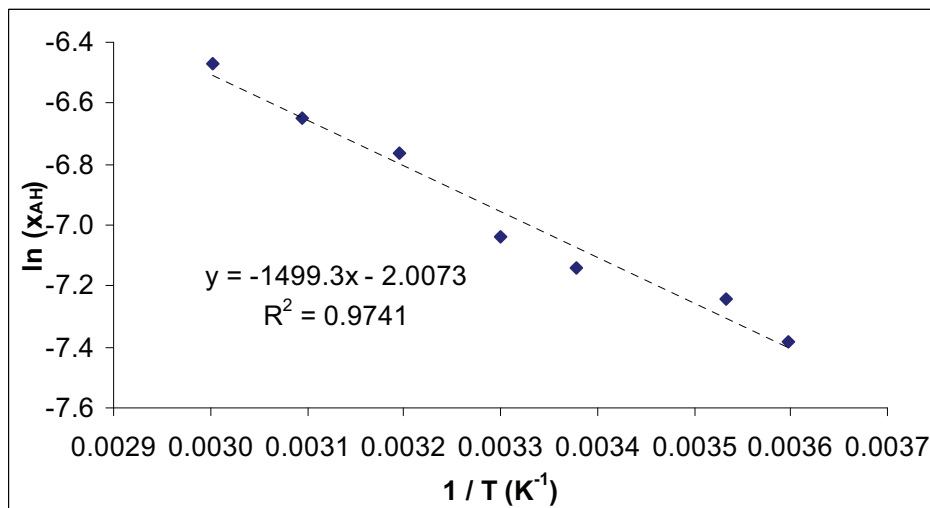


Figure 2 : Natural logarithm of the API solubility molar fraction as a function of temperature, in pure water

The enthalpy of dissolution at given temperature can also be found by using the enthalpy of melting  $\Delta H^f$ . Nordstrom (Nordstrom, 2008) has developed the model below:

$$\Delta H_{solution} = \Delta H^f(T_m) \cdot \left[ 1 + \sigma \cdot \ln\left(\frac{T}{T_m}\right) \right] \cdot \frac{T}{T_m} - R \cdot T \cdot \ln(x_{AH}) \quad (\text{Eq. 7})$$

Where  $T_m$  is the melting point of the compound and  $\sigma$  is a constant determined by the author.

Using equation 7 for various temperatures, the enthalpy of solution calculated is about 17.5 kJ/mol. So, this value is close to the one calculated with the equation 6. The difference is due to the approximations of the models.

To be sure that the temperature has a slight influence on the solubility, further experiments were carried out at different temperatures at various pH values. Results are reported in figure 3.

The higher the temperature is, the higher the solubility is. However, curves are very similar and these results confirm that the pH has more influence on the solubility than the temperature. These data are particularly interesting if the crystallization process has to be controlled. Indeed, at the end of the precipitation step, crystals are separated from the slurry by filtration and washing is generally needed to withdraw impurities. If the solubility does not change very much with temperature, washing with water at low temperature is not necessary to decrease highly API losses by dissolution.

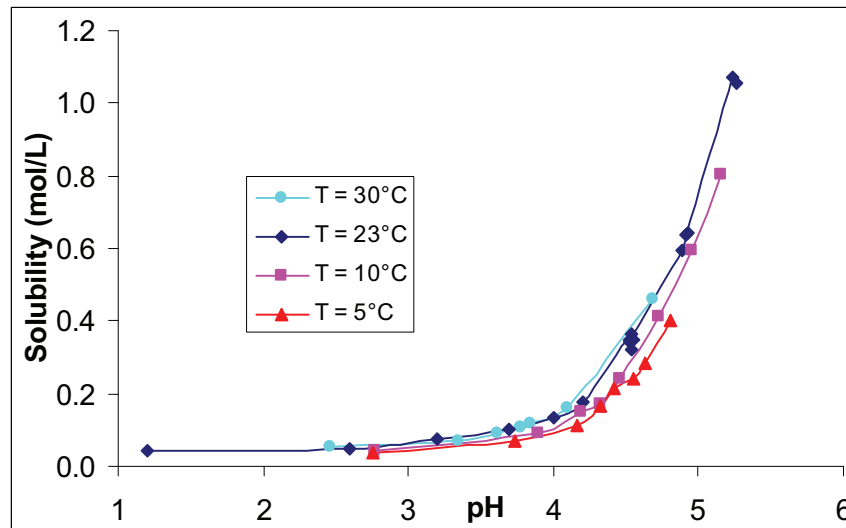


Figure 3 : API solubility as a function of pH, at several temperatures

### *Influence of the presence of impurities on the solubility*

#### Acetic acid

Experiments were carried out for different concentrations of acetic acid at 20°C and for pH varying between 2.0 and 2.4. Results reported in figure 4 show that acetic acid increases slightly API solubility. This behaviour cannot be foreseen but can be explained by a chemical affinity between acetic acid and the API, as these two compounds are weak acids and have the same chemical function.

However the increase of solubility is very low and the variations are of the same order as the uncertainty of measurements (5%) as can be seen in figure 4. The increase trend is then not very significant in comparison with the impact of the pH or the temperature.

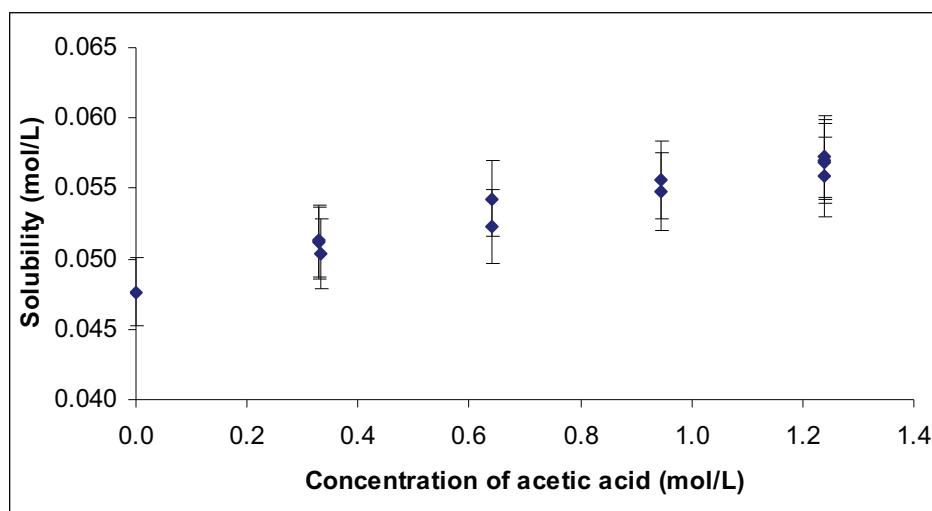


Figure 4 : API solubility as a function of acetic acid concentration, at 20°C

#### Sodium chloride (NaCl) and other salts

Sodium chloride is a by-product of the precipitation of the API. As it is very soluble in water (360 g/L), it is not present as solid but as dissociated ions. These ions interact with the solvent and have thus an influence on the solubility.

Solubility determinations were carried out for different concentrations of sodium chloride, but at the same pH of 2.50. Results are reported in table 3. API

solubility is heavily decreased by the presence of sodium chloride. For example, at a sodium chloride concentration of 3 mol/L, the API solubility is divided by 3 compared to the solubility without sodium chloride. Same phenomena were observed by Carta (Carta, 1996) on amino acids. Experiments were also carried out for the same sodium chloride concentration (2 mol/L), but for different values of pH at equilibrium. Results are reported in figure 5.

NaCl concentration (mol/L)	Solubility (mol/L)	pH
0.00	0.0477	2.60
0.68	0.0359	2.57
0.86	0.0326	2.53
0.98	0.0321	2.50
1.37	0.0273	2.48
1.95	0.0212	2.44
2.74	0.0153	2.42
3.42	0.0133	2.40

Table 3 : API solubility as a function of sodium chloride concentration, at 20°C

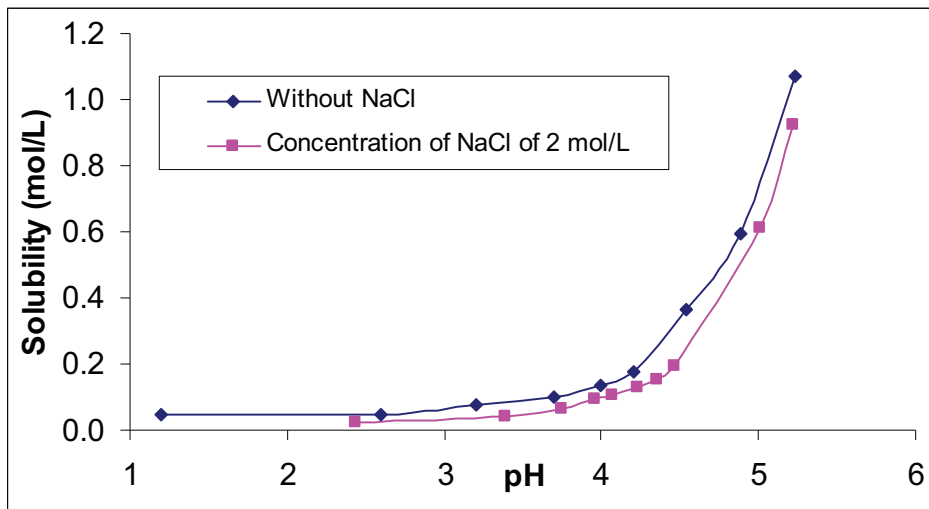


Figure 5 : API solubility as a function of pH, at 20°C, without or with sodium chloride (2 mol/L)

Sodium chloride has thus a great influence on the API solubility. However the role of sodium chloride has not been identified. Dissociated ions could interact with more molecules of water which are thus less available for API molecules. Consequently, API molecules interact with less molecules of solvent and are less solubilised. In order to check this assumption, additional experiments were carried out with other salts.

The chosen salts are monovalent ones and have a common ion with sodium chloride. They were also chosen with the Hofmeister series on which anions and cations are classified according to their hydration power. A highly hydrated ion attracts around it lots of water molecules that are better organized. These molecules are then less available for solubilising the API. They are generally called salting-out ions or water-structure makers ions (Leontidis, 2002). It is the kosmotropic effect. On the other hand, in presence of some ions, water molecules are more disorganized than they would be in pure water. This is the chaotropic effect and it enables water molecules to be more available to solubilise the API. The Hofmeister series usually present an inversion at about  $\text{Cl}^-$  (for anions) and  $\text{Na}^+$  (for cations) (Lopez-Leon, 2003).

So, for sodium  $\text{Na}^+$  or chloride  $\text{Cl}^-$  ions, one counter ion was chosen to be more hydrated and another to be less hydrated:

Kosmotropic anion				Chaotropic anion
$\text{F}^-$	>	$\text{Cl}^-$	>	$\text{ClO}_4^-$
$\text{Li}^+$	>	$\text{Na}^+$	>	$\text{NH}_4^+$
Kosmotropic cation				Chaotropic cation

Experiments were then carried out with sodium fluoride  $\text{NaF}$ , sodium perchlorate  $\text{NaClO}_4$ , lithium chloride  $\text{LiCl}$  and ammonium chloride  $\text{NH}_4\text{Cl}$ . In order to compare the results, pH at saturated solution was measured and same concentration of salt was used. A salt concentration of 0.86 mol/L was chosen in order to be lower than the solubility of the salts. This concentration is high, but the final concentration of sodium chloride at the end of the precipitation process is 2 mol/L. API solubility measurements are reported in tables 4 and 5.

The change of cation, conserving the anion chloride, seems to have no influence on the solubility. Indeed, solubility values are very close.

On the other hand, the change of anion, keeping the sodium cation, is much more significant. The solubility in presence of  $\text{NaClO}_4$  is higher than in presence of  $\text{NaCl}$ . With  $\text{NaF}$ , the solubility seems to be higher too, but the pH at

equilibrium has extremely increased (6.17 instead of 2.4), due to the dissolution of NaF in water. At this pH and if no sodium fluoride was present, the API solubility should be about 3 mol/L. However, with sodium fluoride, the solubility is 0.051 mol/L. As a kosmotropic anion, the ion fluoride has highly decreased the solubility of the API.

So, the role of the anion on the solubility decrease has been enlightened.

Salt	No salt	NaF	NaCl	NaClO <sub>4</sub>
Solubility (mol/L)	0.0477	0.051	0.033	0.041
pH	2.61	6.17	2.39	2.63

Table 4 : Anion effect on the API solubility

Salt	No salt	LiCl	NaCl	NH <sub>4</sub> Cl
Solubility (mol/L)	0.0477	0.034	0.033	0.037
pH	2.61	2.48	2.39	2.55

Table 5 : Cation effect on the API solubility

## Conclusion

This study focused on the main parameters influencing the solubility of an API. As it is a weak acid, it has been proven that the pH is the most important parameter and a model has been built to follow its evolution. The temperature revealed to be a less significant parameter but permitted to determine the enthalpy of dissolution of the API. Finally, impacts of the process impurities have been characterized. Considering the effects of hydration of ions, the presence of a kosmotropic anion explained the API solubility decrease observed. All these data permit to establish the evolution of the solubility along the process of precipitation and to control it.

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