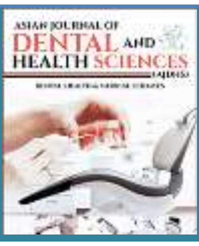

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Effect of pH on Pharmaceutical Ingredients / Drugs / Chemicals

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Abstract

The word excipient is derived from the Latin excipere meaning to except, which is simply explained as other than. Pharmaceutical excipients are basically everything other than the active pharmaceutical ingredient. Ideally, excipients should be inert, however, recent reports of adverse reactions have suggested otherwise. Pharmaceutical excipients are substances other than the active pharmaceutical ingredient (API) that have been appropriately evaluated for safety and are intentionally included in a drug delivery system. Solubility, which defines the liquid /solid equilibrium, is a key parameter to control a crystallization process. As the API is a weak acid (pKa = 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 [1,2]. For this, one of the initial data needed is the solubility of the product in the mother solution. 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 [3,4].

Definition of partition coefficient (p*K*a)

When a weak acid dissociates in solution according the scheme below (1), we can express the acid 1onization constant (*K*a) using equation (2). The negative logarithmic form of the acid 1onization constant (3) is more commonly used. Rearrangement of equation (3) affords the Henderson-Hasselbalch equation (4). In a similar manner we can employ these equations for theconjugate acid forms of basic functional groups (5).

$$HA + H2O \rightleftharpoons A + H3O^{+} \quad (1)$$

$$Ka= A \ \ H3O+ \ \ HA \quad (2)$$

$$pKa = \log 10Ka \quad (3)$$

$$pH=pKa+\log A \ \ AH \quad (4)$$

$$BH^{+} + H2O \rightleftharpoons B + H3O^{+} \quad (5)$$

Material and Methods

Chemicals

Sodium hydroxide

Molecular weight- 39.997g/mol

Chemical formula- NaOH

Sodium chloride

Molecular weight- 58.44g/mol

Chemical formula – NaCl

Hydrochloric acid

Molecular weight- 36.458 g/mol

Chemical formula –HCl

Ammonium chloride

Molecular weight- 53.491g/mol

Chemical formula -NH_4Cl

Apparatus

- PH meter
- Measuring Cylinder-5ml
- Volumetric flask- 100ml
- Pipette-5ml
- Beaker- 100ml
- Glass rod

Experimental

Sodium Hydroxide

Table 1: API solubility as a function of Sodium Hydroxide concentration, at 20°C

NaOH concentration (mol/L)	Solubility (mol/L)	pH
0.00	0.0478	3.60
0.78	0.39997	3.57
0.95	0.395973	3.53
0.99	0.3799	3.50
1.21	0.4839	3.48
1.84	0.73597	3.44
2.65	1.05992	3.42
3.55	1.41989	3.40

Sodium Chloride

Table 2: API solubility as a function of sodium chloride concentration, at 20°C

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

Hydrochloric Acid

Table 3: API solubility as a function of Hydrochloric Acid concentration, at 20°C

HCL concentration(mol/L)	Solubility (mol/L)	pH
0.00	0.2943	5.60
0.78	0.2843	5.57
0.89	0.3244	5.53
0.99	0.36093	5.50
1.38	0.5031	5.48
1.96	0.71451	5.44
2.75	1.00259	5.42
3.43	1.2578	5.40

Ammonium Chloride

Table 4: API solubility as a function of Ammonium Chloride concentration, at 20°C

NH4CL concentration(mol/L)	Solubility(mol/L)	pH
0.00	0.0497	4.60
0.79	0.0.225	4.57
0.89	0.4760	4.53
0.99	0.5295	4.50
1.38	0.73817	4.48
1.96	1.08442	4.44
2.75	1.47100	4.42
3.43	1.8347	4.40

Results

NaOH is strong base, so this will produce 0.1 mol/L of OH ion solution. This will produce a pH of 13. To summarize, NaCl decrease the solubility and reduce the activity of hydrogen ion, the net effect is a small reduction in PH (by about 0.01). The PH of the hydrochloric acid is 2 according to the given data which indicates that it is acidic in nature. The PH value of the solution will decrease (basically less than7) as the solution will become slightly acidic (PH value 4.5 to 6).

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.

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