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SOLUBILITY AND TRANSFORMATION OF THE SOLID FORMS OF AMLODIPINE BESILATE TO ITS FREE BASE

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Salt formation is an effective way to modify the important physicochemical properties of drug substances, such as solubility, dissolution rate, chemical stability, melting point, and processibility. Nowadays nearly 50% of the drug substances used for therapeutic purposes are in salt forms. However, formulating a drug product utilizing salt form often leads to increased tendency for formation of hydrates and polymorphs, and thus results in undesired variability in final drug product's properties during processing and storage. Also, when a given salt comes in contact with an aqueous medium, the relative concentration of the ionized and the neutral state of the dissolved drug molecules depends on the pH, and the free base or acid may precipitate out and lead to an undesired phase transformation. In order to achieve effective control of the chemical and physical stability of salt active pharmaceutical ingredients (API) during processing, a comprehensive understanding of the mechanism of the solid state transition between the solid forms of a salt and its free base or acid is required.

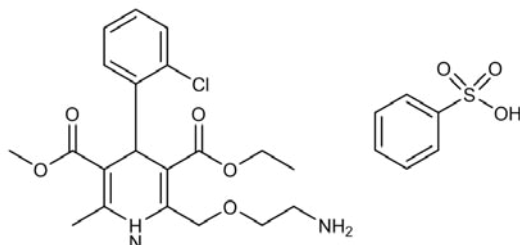


Figure 1. Chemical structure of amlodipine besilate (AMB)

In the present work, the solubility of the different solid forms of amlodipine besilate (AMB) and its free base (AM), and the transformation between the solid phases are studied. AMB is used in the treatment of hypertension and coronary artery diseases. AMB has a molecular weight of 567.1 g/mol, pK_a 9.1, $\log P$ (*n*-octanol/water) 2.96 [1, 2]. It has been reported that AMB is capable of forming a monohydrate (MH) and a dihydrate (DH) [3, 4]. The chemical structure of AMB is shown in Figure 1 and the Raman spectra of the different solid forms of AMB and its free base are shown in Figure 2.

Solubility of the solid forms of AMB and the free base

The solubility of the solid forms of AMB and its free base in water were measured at room temperature (~ 22°C). The AMB DH was the thermodynamically stable form in pure water at room temperature. During the solubility measurement of AMB MH and anhydrate (AH), solid samples were taken and analyzed with Raman spectroscopy to monitor the solid phase transformation. It was observed that AMB AH transformed to DH within three hours, whereas AMB MH remained unchanged for more than 6 hours. The pH was kept at 11.5 by adding NaOH solution when the solubility of the free base was measured. The solubility results are shown in Table 1.

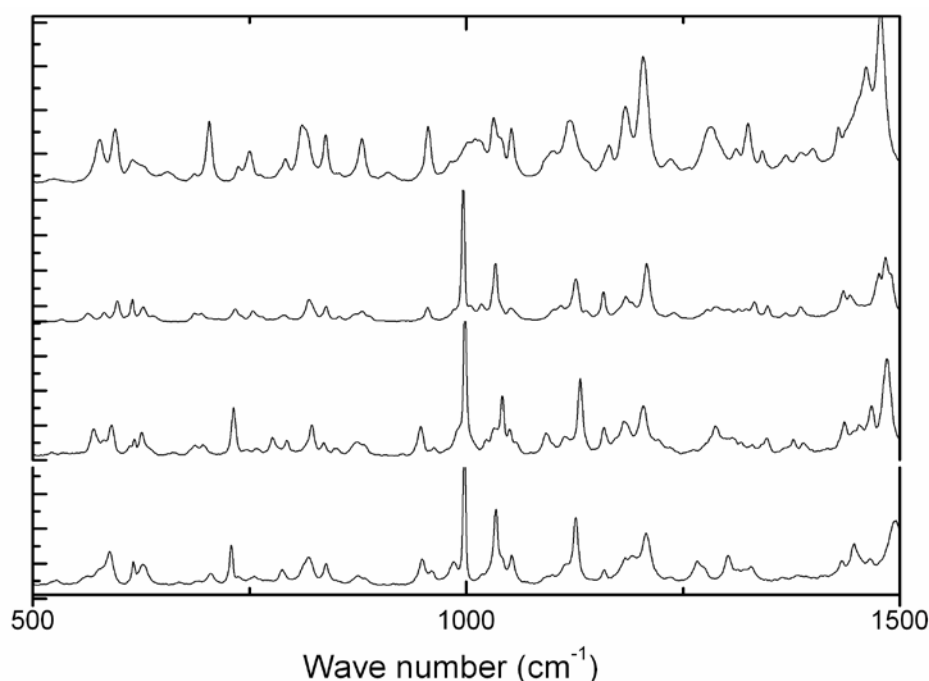


Figure 2. Raman spectra of the solid forms of AMB, from up to down: AM free base, AMB dihydrate, AMB monohydrate, AMB anhydrate.

Table 1 Aqueous solubility of the solid forms of AMB and its free base at room temperature (average of 6 measurements)

Solid forms	AMB AH	AMB MH	AMB DH	AM free base
Solubility (mg/ml)	2.179 ± 0.068	1.785 ± 0.008	1.305 ± 0.033	0.051 ± 0.002

When the salt dissolves in water, the following dissociation equilibrium between the ionized and the non-ionized species is attained (B denotes the besilate ion and AM denotes the free base of AMB):

(1)

The dissociation constant can be written as:
$$K_a = \frac{[H^+][AM]}{[AMH^+]} \quad (2)$$

Since the K_a (pK_a) of the system is known, the relative concentration of AM and AMH^+ at different pH can be calculated. The pH-solubility of AMB can be obtained from the

measured solubility of the AMB solid forms and its free base shown in Table 1 with the following equations:

$$\text{At } \text{pH} > \text{pH}_{\text{max}}, S_{\text{Total}} = \left(1 + \frac{[\text{H}^+]}{K_a}\right) S_0 \quad (3)$$

$$\text{At } \text{pH} < \text{pH}_{\text{max}}, S_{\text{Total}} = \left(1 + \frac{K_a}{[\text{H}^+]}\right) \sqrt{K_{SP}} \quad (4)$$

$$\text{Where } \text{pH}_{\text{max}} = \text{p}K_a + \log\left(\frac{S_0}{\sqrt{K_{SP}}}\right) \quad (5)$$

Where K_{SP} is the solubility product of the salt and S_0 is the intrinsic solubility of the free base. The pH-solubility profiles of AMB are shown in Figure 3.

Precipitation of the free base from saturated solutions of AMB DH, MH and AH

Saturated aqueous solutions of AMB AH, MH and DH were prepared by suspending the corresponding solids in water for sufficient time and then the suspension was filtrated. 200 ml of saturated AMB solution was mixed with a magnetic stirrer. NaOH solution (0.3M) was added with a 100 μl pipette and the pH of the solution was monitored with a pH meter. Liquid samples were taken with syringe filters and the concentration of (AM + AMH⁺) was measured with a UV spectrometer. The measured concentrations are shown in Figure 3 versus the pH of the solution. As shown in Figure 3, the pH increased from 6.5 to 8.2 when the first 100 μl of NaOH solution was added to the system. At this pH, the dissociation equation (1) was shifted to the right hand side and the concentration of the non-ionized AM was increased significantly. The concentration of AM was calculated from the measured total concentration of (AM + AMH⁺), and the supersaturation with respect to the free base AM was plotted in Figure 4. The solution remained clear and no nucleation of the free base occurred until 400 μl of NaOH was added, which led to the pH of the solution further increased to about 9.1. Further addition of NaOH caused the turbid of the solution, which indicated the onset of nucleation of the free base. The crystallization of the free base consumed AM in solution phase and caused further shifting of the dissociation equation (1) to the right hand side, which leads to the decreasing of the pH.

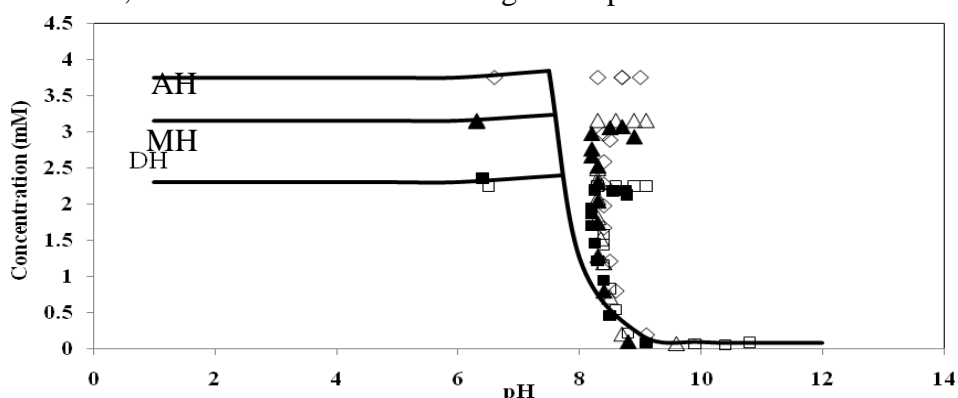


Figure 3. Solubility profiles of AMB anhydrate, monohydrate and dihydrate (–); Concentration profiles of the AMB during precipitation of the free base from saturated solutions of AMB DH, MH and AH with (solid symbols) or without (open symbols) the presence of the AMB solid

Effect of the AMB MH and DH seed crystals on the precipitation of the free base

The effects of the AMB MH and DH seed crystals on the precipitation of the free base were studied by performing the precipitation experiments in saturated solutions of AMB MH and DH with the presence of 100 mg of the corresponding crystals. The results are shown in Figure 3 and 4 with the solid symbols. It can be observed that the maximum pH attained in the solution was reduced by the presence of the crystals. As shown in Figure 4, with feeding of NaOH to the system, the supersaturation with respect to the free base AM increased to a maximum and then started to decrease. The maximum of the supersaturation S implied that at this moment, the consuming rate of AM by crystallization exceeded the generating rate of AM through the dissociation shown by equation (1). It is obvious that the presence of the seed crystals of AMB MH and DH reduced the maximum value of supersaturation, which suggested that the crystal surfaces facilitated the nucleation of the free base.

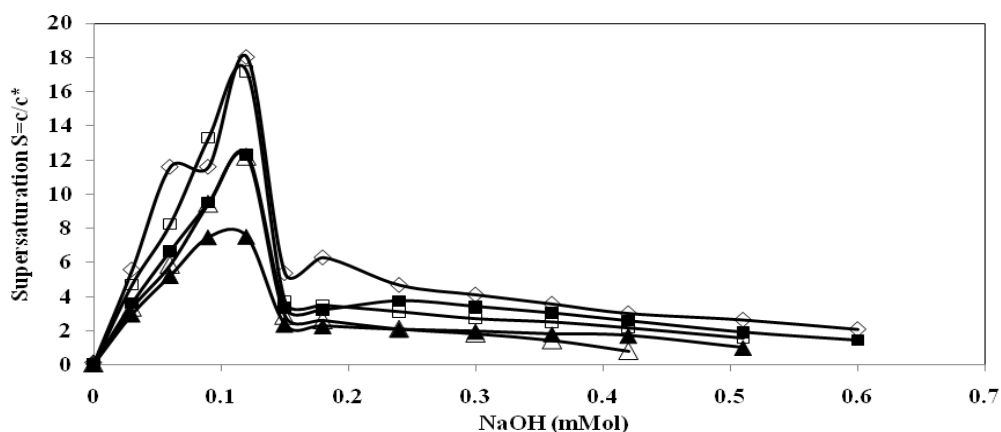


Figure 4. Supersaturation profiles of the free base AM during precipitation from saturated solutions of AMB DH (Δ), MH(\square) and AH(\diamond) with (solid symbols) or without (open symbols) the presence of the AMB solid

The results of the present study demonstrated that the precipitation of the free base AM from saturated solution of AMB solid forms was driven out by the shifting of the dissociation equation (1), which is caused by the pH change of the solution. It has been observed that the presence of the surfaces of AMB MH and DH crystals facilitated the nucleation of the free base. The results of the phase transformation of the AMB solid forms to the free base during processing will be presented in the full manuscript due to the limited length of this abstract.

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