Solubility and transformation of the solid forms of amlodipene besilate to its free base

Qu, Haiyan; Savolainen, Marja Riikka; Christensen, Lars Porskjær; Rantanen, Jukka Tapio

Publication date:
2011

Document Version
Publisher's PDF, also known as Version of record

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

Haiyan Qu[1], Marja Savolainen[2], Lars P. Christensen[1], Jukka Rantanen[2]

[1] Institute of Chemical Engineering, Biotechnology and Environmental Technology, Faculty of Engineering, University of Southern Denmark, Niels Bohrs Allé 1, DK-5230, Odense M, Denmark; tel. +4565507494, email: haq@kbm.sdu.dk

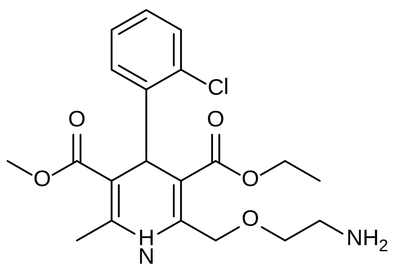
[2]Department of Pharmaceutics and Analytical Chemistry, Faculty of Pharmaceutical Sciences, University of Copenhagen, Universitetsparken 2, 2100 Copenhagen, Denmark.

Introduction

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. 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.

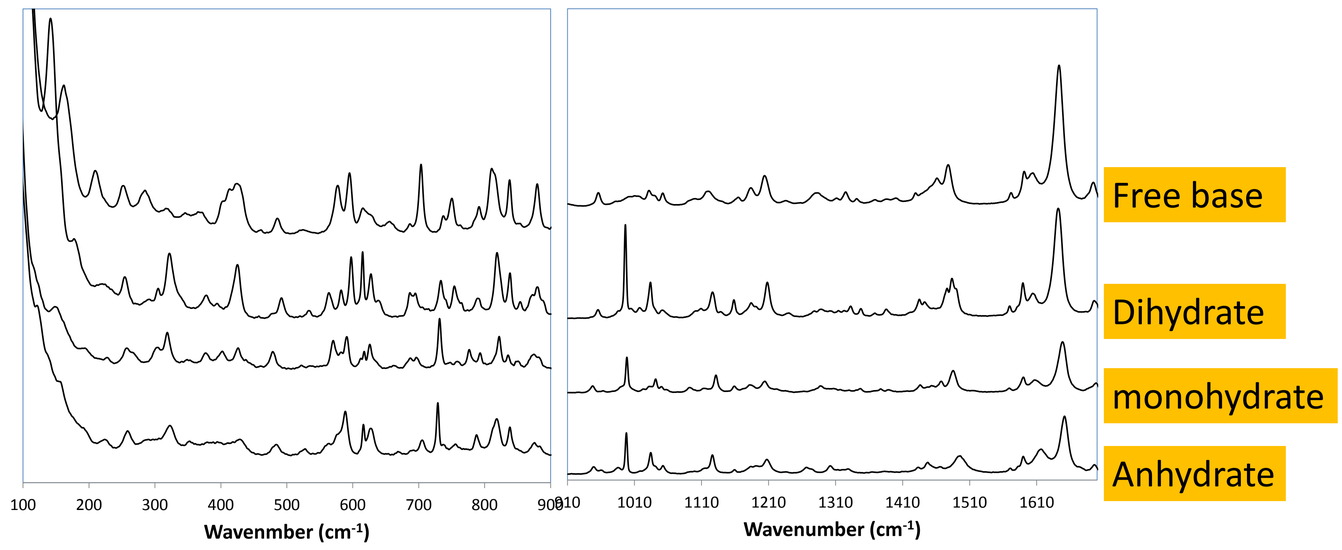
The objective of the present work is to explore the underlying mechanism of the transformation of the anhydrate, monohydrate and dihydrate of a salt to its free base. The nucleation of the free base from saturated salt solutions with and without the presence of the different solid forms of the salt was investigated. Subsequently, the obtained results on free base nucleation was applied to the interpretation of the transformation of different solid forms of the salt to the free base when the salt was mixed with excipients and water.

Materials and methods



The model compound, amlodipine besilate (AMB) is used in the treatment of hypertension and coronary artery diseases

AMB has a pK_a of 9.1. AMB is capable of forming a monohydrate (MH) and a dihydrate (DH). Raman spectra of the different solid forms of AMB and its free base are shown at the right .



Results: pH-solubility profile and nucleation of the free base

The following dissociation equilibrium between the ionized and the non-ionized species is attained in AMB solution:

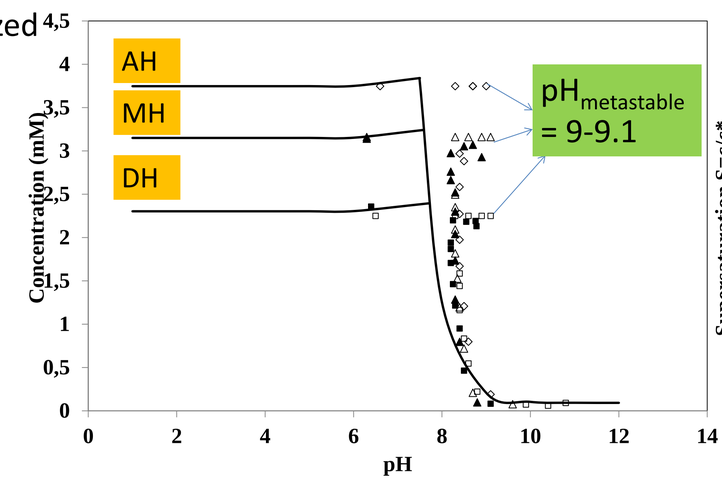
$$AMH^+ + B^- \rightleftharpoons AM + B^- + H^+ \qquad K_a = \frac{[H^+][AM]}{[AMH^+]}$$

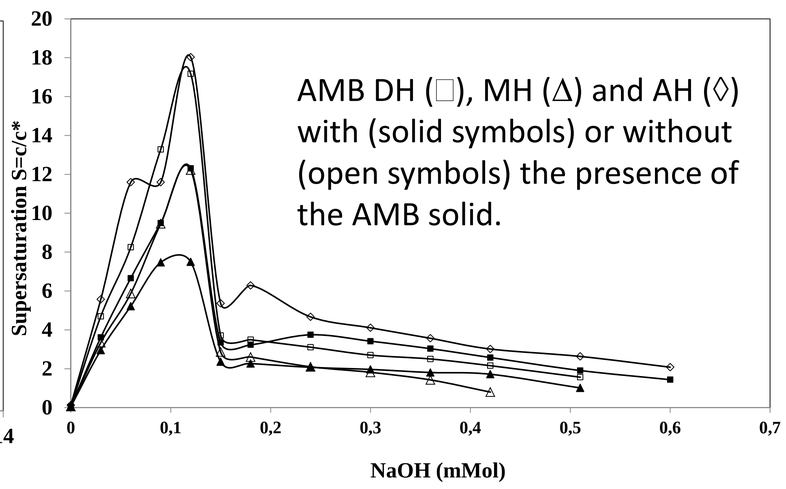
B denotes the besilate ion and AM denotes the free base of AMB.

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

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

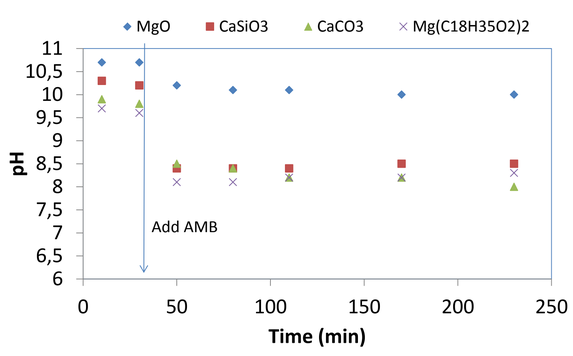
$$pH_{max} = pK_a + \log\left(\frac{S_0}{\sqrt{K_{SP}}}\right)$$





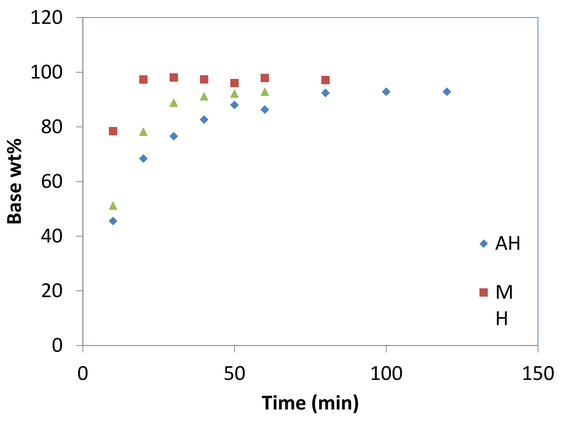
Solubility and Concentration (left) and supersaturation (right) profiles of the AMB during precipitation of the free base from saturated solutions of AMB. Nucleation happens when the supersaturation reaches a certain level, where the pH approaches 9-9.1. This pH resemble to the metastable zone limit in solution crystallization, and thus is defined as $pH_{metastable}$ in the present work.

Results: Transformation of AMB solid forms to the free base in excipients suspensions with different pH values



AMB solid forms transformed to the free base within 2 hours in MgO suspension, in which the pH after adding AMB is above the $pH_{metastable}$.

10-15% AMB transformed to the free base within 24 hours in $CaSiO_3$ suspension; whereas no transformation happened in the suspension of $CaCO_3$ and $Mg(C_{18}H_{35}O_2)_2$ in which the pH after adding AMB is below the $pH_{metastable}$.



In MgO suspension, regardless of the highest solubility of AMB AH, AMB MH showed the highest transformation rate. This might be attributed to the different effects of the surfaces of the different solid forms of AMB.

Summary and conclusions

The results of the present study demonstrated that the precipitation of the free base AM from saturated solution of AMB was driven out by the shifting of the dissociation equation , which is caused by the pH change of the solution. Nucleation of the free base happened when the pH of the solution reached a certain value $pH_{metastable}$, which corresponds to the certain level of supersaturaion that is related to the Gibbs free energy barrier for nucleation. The transformation behaviour of AMB in excipients suspensions confirmed that $pH_{metastable}$ can be used to predict the stability of AMB salt at different micro-enviromental pH. This observation also reflected the crucial role of nucleation in salt-to-free base transformation.

Acknowledgements: Danish Council for Independent Research (Technology and Production Sciences)

E-mail: haq@kbm.sdu.dk