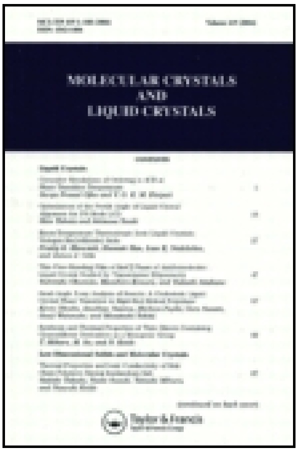

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INFLUENCE OF WATER ADSORBED ON AVICEL PH 101® ON THE THERMAL DECOMPOSITION OF*p*-AMINOSALICYLIC ACID

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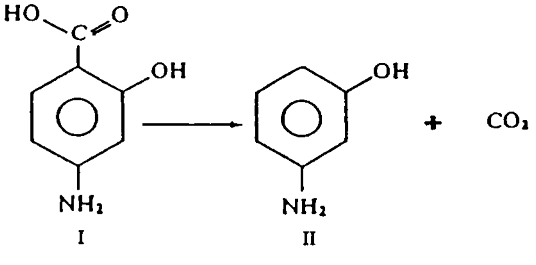
Abstract The importance played by the water adsorbed on Avicel PH 101® and, especially by its "unbound" fraction,on the stability of PAS/Avicel PH 101® mixture is revealed in this work. Beyond the monolayer, any additional water uptake by the system induces an increase of the decarboxylation rate of *p*-aminosalicylic acid and a decrease of the apparent process activation energy, which tends towards the value obtained for aqueous solution.

INTRODUCTION

A solid pharmaceutical preparation normally contains several additives (excipients) which may play an important role on the stability, the dissolution rate, and the bioavailibility of the active ingredients. Many studies[1-5] reported the destabilisation of drugs by additives. In addition to the solid/solid interactions, it is a well-known fact that the water adsorbed on the surface of the excipient/drug mixtures affects the stability of the drug.[6-8] It has been established that, according to both the physico-chemical state and the amount of water adsorbed as well as to the nature of the excipient, only part of the water influences degradation kinetics.[9-11]

The purpose of this work is to quantitatively assess the influence of water on the decomposition of a 5% dilution *p*-aminosalicylic acid (PAS) in microcrystalline cellulose (Avicel PH 101®) by relating the reaction kinetic parameters to the thermodynamic and dielectric properties of the water/Avicel PH 101® system.

p-Aminosalicylic acid (I) decomposes according to a decarboxylation process, yielding carbon dioxide and *m*-aminophenol (II) (MAP).[12]



EXPERIMENTAL

Compounds:

p-Aminosalicylic acid (Aldrich-Chemie; West-Germany) and microcrystalline cellulose (Avicel PH 101®; FMC Corp., USA) were used as received.

Sample Preparation and Storage Conditions:

Individual 200 mg samples were prepared by mixing 10 mg (5%) *p*-aminosalicylic acid with 190 mg (95%) Avicel PH 101®. The samples were equilibrated for two days in a 40 °C thermostated bath at different relative humidities, P/P_0 , (Table I). The amounts of water adsorbed by the mixture were assumed to be equal to those adsorbed by Avicel PH 101® alone exposed to the same experimental conditions. The samples with thus defined water contents, Q_{H2O}, were then sealed and stored in automatically controlled ovens set at the 50, 60, 70 and 80 °C kinetic temperatures.

TABLE I Relative humidity equilibrium conditions, P/P_0, at 40 °C and corresponding water contents, Q_{H2O}, of the samples.

P/P_0 (%)	Q_{H2O}(mol H_2O/mol PAS)[a]
0.0	0.0
8.0	3.45
23.1	5.93
35.8	7.95
51.2	9.76
76.2	12.92
95.0	15.23

[a] amount of water adsorbed on 190 mg Avicel PH 101® at 40 °C divided by the number of moles of PAS (6.53 10^{-5} moles)

Quantitative Analysis:

Simultaneous quantitative analysis of PAS and MAP was performed by high performance liquid chromatography (HPLC) using a column (25 cm x 0.4 cm) containing 10 μm Nucleosil® RP-18 packing. To maintain column efficiency, a precolumn (5 cm x 0.4 cm), with identical filling, served as a filter. Once separated, PAS and MAP concentrations were monitored by a UV detector set at 254 nm, linked to an electronic integrating recorder. The composition of the mobile phase was a water-methanol mixture (45:55) with 0.5 mmol/L of Na_2HPO_4; the flow rate was 2 mL/min at a pressure 150 atm. Methylparaben (methyl *p*-hydroxybenzoate) at a concentration of 3.28 mmol/L was used as internal standard.

RESULTS AND DISCUSSION

Kinetics:

Solid state degradation kinetics of 5:95 (w/w) PAS/Avicel PH 101® mixtures were carried out at four temperatures and at seven different water contents. Figure 1 shows an example of a plot of the remaining percentage of PAS versus time.

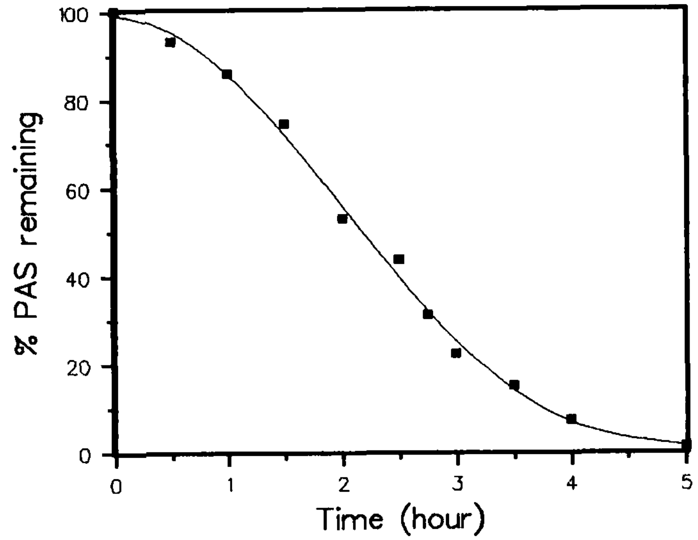


FIGURE 1. Percent *p*-aminosalicylic acid remaining-time curve at 80 °C and at 9.76 mol H_2O/mol PAS.

In the absence of any postulated kinetic model, the evolution of the percentage of the undecomposed PAS, α, versus time, t, was treated according to a 5th order maximum polynomial function, the a_i coefficients of which were estimated by the SPSS program using the stepwise regression method.

$$\alpha(t) = \sum_{i=0}^{5} a_i t^i$$

That decarboxylation proceeds according to the same mechanism whatever the experimental conditions, was verified by plotting (on the same figure) the $\alpha(t)$ values as a function of the reduced time, t/t_{50}, for each of the 28 decomposition kinetic curves (Figure 2). (t_α (t_{50}) is defined as the time period required for the drug to decompose to α% (50%) remaining of the content initially present in the sample).

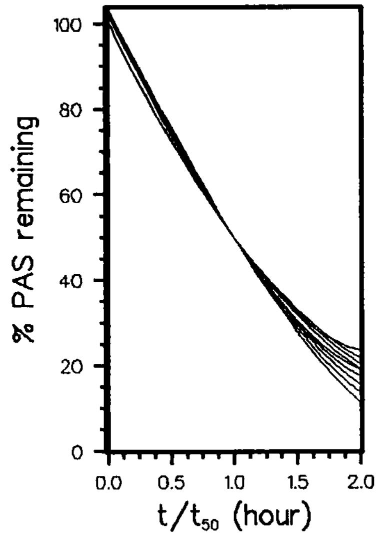


FIGURE 2. Percentage of undecomposed PAS, α, as a function of the reduced time (t/t_{50}), for different PAS decomposition kinetics.

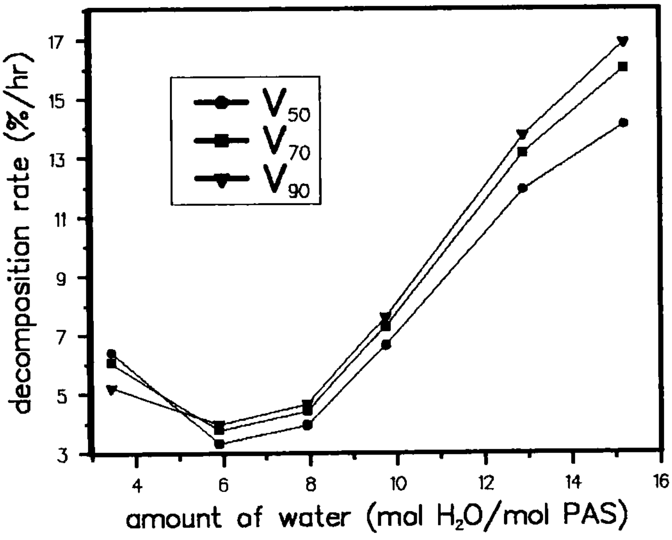


FIGURE 3. Instantaneous decomposition rate, V_α, of PAS at three stages of decomposition and at 70 °C versus the water amount, Q_{H2O}.

The evolutions of the instantaneous reaction rates at different stages of decomposition versus the water content, Q_{H2O}, of the samples are given on Figure 3. The instantaneous rates, V_α, are obtained by setting $t = t_\alpha$ in the derivative of equation 1 with respect to time. From the results analysis, it stands out that, for any given amount of water, the rates are identical along the decomposition course and that the decomposition rates are quite constant up to a 6.03 mol H_2O/mol PAS water content. This value corresponds to the amount of water adsorbed on Avicel PH 101, as a monolayer divided by the number of moles of PAS in the sample. Beyond this value, the rate increases continuously with the increasing free water content.

The last statement can also be observed on Figure 4 which shows, at different temperatures, the influence of the water content on the instantaneous decomposition rate of PAS, V_{90}, calculated at $t = t_{90}$.

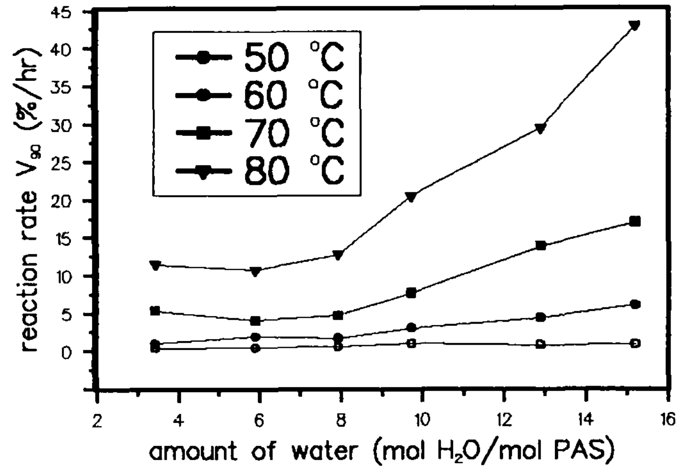


FIGURE 4. Influence of the amount of water, Q_{H2O}, on the instantaneous decomposition rate, V_{90}, at 50, 60, 70 and 80 °C.

The correlation described between the degradation rate of PAS and the water content of the system at a fixed stage of decarboxylation can still be observed on Figure 5. This figure reports the instantaneous rate of decomposition versus the dielectric constant, ϵ, of the water adsorbed on Avicel PH 101®. Beyond the monolayer, the rate of decarboxylation increases with the increasing value of the dielectric constant. The rapid increase of the dielectric constant, ϵ, with the water content indicates that any additional amount of water beyond the monolayer corresponds to a more and more weakly bound water which is called free water.

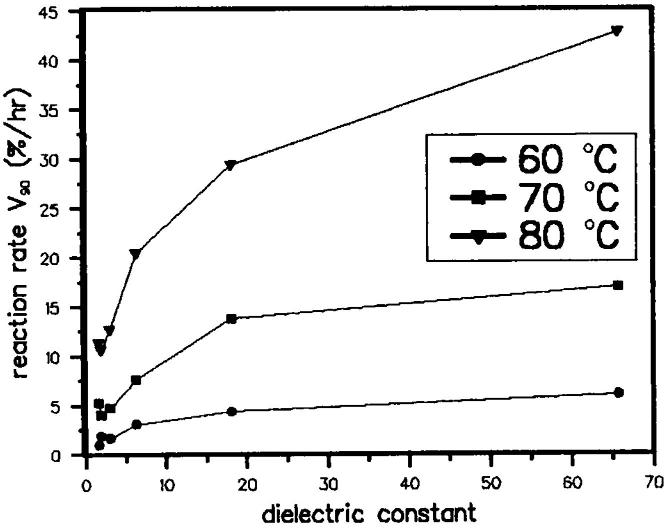


FIGURE 5. Instantaneous decomposition rate, V_{90}, versus the dielectric constant, ϵ, of the water adsorbed on Avicel PH 101® at 60, 70 and 80 °C.

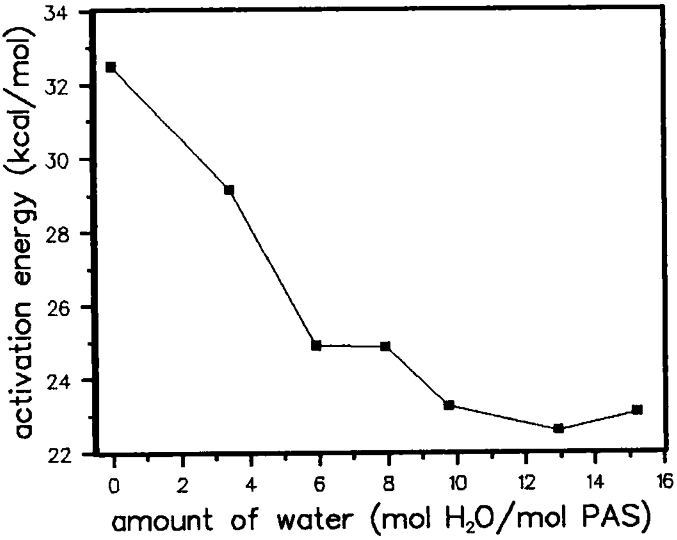


FIGURE 6. Apparent decarboxylation activation energy (kcal/mol) versus the water content, Q_{H2O}, of the system.

Finally, regardless of the details of the mechanism involved, an apparent activation energy has been calculated at different water contents from the linear regression of the instantaneous rates, $d\alpha(t)/dt$, versus the reciprocal absolute temperature. Figure 6 shows the influence of the number of moles of H_2O per mole of PAS on the apparent decarboxylation activation energy at 10% of decomposition (α = 90). The apparent activation energy decreases with the increasing amount of water present in the sample and tends towards the limit value of the activation energy for aqueous solution, i.e., 19.6-21.7 kcal/mol.[13-15]

CONCLUSION

The results of this study demonstrate that both the presence of water in the Avicel PH 101®/PAS mixture as well as the temperature influence the stability of PAS. The PAS decarboxylation is accelerated with the increasing water content as well as with temperature increase.. The influence of water becomes clearly apparent for water amounts greater than that adsorbed on Avicel PH 101® as a monolayer, i.e., with the increase of more loosely bound water. The availability of water for the reaction is not the same whether it is in direct contact with the excipient (bound water) or adsorbed on other water molecules (free water).

The apparent activation energy of the decarboxylation process decreases with the increasing number of moles of H_2O per mole of PAS, in agreement with Ruelle's quantum-chemical studies[16-18] on the decarboxylation mechanism which show that the addition of successively one and two water molecules to the decarboxylating species decreases the activation barrier; the decarboxylation reaction proceeds by proton transfer through water molecules. As a result, the solid-state decomposition of *p*-aminosalicylic acid mixed with Avicel PH 101® under high temperature and high humidity conditions is assumed to occur in solution in a layer of loosely bound sorbed water.

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