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ORIGINAL ARTICLE

Stability and thermophysical properties of azithromycin dihydrate

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Thermogravimetric analysis

Abstract The aim of this paper was to describe the temperature effect on the stability and the thermophysical properties of azithromycin (AZ). First, the density, the heat capacity and the solubility of original (commercial) AZ were determined. Second, the original samples were heated at 50 °C and 80 °C and their PLM, DSC, TGA and XRD data were compared to those of the original AZ. According to our results, the original AZ was a dihydrate which converted to anhydrate when heated up to 80 °C. The dehydration induced a change of crystal habit while the crystalline lattice remained unchanged.

1. Introduction

Azithromycin (AZ) is a macrolide antibiotic derived from erythromycin. This product has a high bacteriostatic action in front of a wide spectrum of pathogenic bacteria and is used mainly for the treatment of respiratory and dermatological infections. The solid state of azithromycin depends on the solvent used in the crystallisation process (Montejo-Bernardo et al., 2006). When the antibiotic is crystallized in a water acetone mixture, the product obtained (azithromycin) is the dihydrate (Djokic et al., 1988). If the antibiotic is crystallized in a water alcohol mixture the azithromycin form obtained is the monohydrate (Montejo-Bernardo et al., 2006).

The commercial product is formed of dihydrated crystals ($C_{38}H_{72}N_2O_{12}\cdot 2H_2O$). The drying of hydrates is always a difficult step in the industrial process. Indeed, the hydrates can undergo a dehydration which can affect the properties of the pharmaceutical ingredient, such as its stability, dissolution rate and bioavailability. Several mechanisms of dehydration have been reported in the literature (Garnier et al., 2002). They

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depend on the hydrate crystalline structure and on the dehydration conditions. Harsh dehydration conditions are likely to lead to an amorphous compound, whatever the hydrate type. In some cases, this amorphous compound can transform into a new crystalline form by nucleation and growth. This phase transition can occur simultaneously with the dehydration process. It is also facilitated if the water produced by dehydration is still in liquid state around the particles and favours a solvent mediated phase transition. Obviously, the anhydrate obtained in both cases, i.e. in amorphous state or crystallized in a new polymorphic form will have completely different properties from those of the initial hydrate. On the contrary, gentle dehydration of non stoichiometric hydrates can lead to the formation of isomorphic desolvates (Stephenson et al., 1998). The lattice of these hydrates has the particularity to form tunnels inside of which the water molecules are located. This is often the case with the active principal ingredients because of the big difference of size between the pharmaceutical molecules and the water molecules. The water is then removed without altering the crystal lattice substantially from that of the original solvate form (pseudopolymorphism) (Stephenson et al., 1998). It is rather a continuous transition, although different steps can be observed when the water molecules are involved in different types of bonds in the structure. The isomorphic desolvate is generally unstable (Yu et al., 1998). The lattice of the anhydrous material can undergo a relaxation (i.e. a non-isotropic reduction of the unit cell) in order to improve its stability (Stephenson and Diseroad, 2000). The isomorphic desolvate is also highly hygroscopic since it will always tend to reabsorb water molecules to recover its stability (Liggins et al., 1997). However the dehydration/rehydration loop is not always reversible. The particle size and the chemical stability can be affected. Marcelo et al. (2005) realised an accelerated transformation of three azithromycin pseudo-polymorphs and suggested that the monohydrate and dihydrate crystalline forms of azithromycin are stable whereas the anhydrous form evolves to dihydrate.

In this paper the thermophysical properties of azithromycin and its stability at different temperatures were investigated with the aim to predict its drying behaviour during manufacturing.

2. Materials and methods

2.1. Samples preparation

Three types of samples were used in this study. The first type (AZC) was the commercial (supposed to be dihydrate) azithromycin (maximal total impurities content of 1.43%) provided by the ERCROS Company (Spain). The second (AZ50) was the commercial product heated during 48 h in a batch oven at 50 °C. The third (AZ80) was the commercial product heated during 48 h in a batch oven at 80 °C. In order to prevent the rehydration, the samples were stored and transported from oven to apparatus in hermetically sealed recipients.

2.2. Polarized light microscopy (PLM)

AZC, AZ50 and AZ80 samples were viewed by polarized light microscopy (Leica DML) for a magnification = 100×.

2.3. Apparent density

The density of a powder depends on its compaction degree. The apparent density is defined as the average of the aerated and tapped densities. The aerated density was obtained by simply filling a cylinder of 100 ml with the powder. For the tapped density, the cylinder filled with the powder was tapped 10 times on a flat wood plate and the final volume occupied by the powder was measured. Analyses were repeated 10 times.

2.4. Specific heat capacity

Heat capacity measurements were carried out on a DSC apparatus (2920, TA instruments Inc., New Castle). A typical calibration run in modulated mode was performed with 20 mg of sapphire. Ten milligrams AZ samples were placed in sealed aluminium pans. The scan for commercial and heated samples (AZC, AZ50 and AZ80) was run 6 times between 0 °C and 100 °C at a heating rate of 5 °C/min under nitrogen purge (40 ml/min).The modulation amplitude and period were respectively set to ±1 °C and 60 s.

2.5. Solubility

The solubility of AZC in four solvent mixtures with different acetone–water volume fractions (0–100, 25–75, 50–50 and 75–25) was measured as a function of temperature. For each solubility point, around 20 ml of solvent was kept at a given temperature in a 250 ml jacketed vessel equipped with a thermostat and a magnetic mixer. The vessel was also equipped with a condenser to recover the evaporated solvent. When the temperature was stable, AZC powder was added step by step as far as dissolution was observed. The added mass was recorded. Each step could take several hours for the dissolution to be completed. The last step was identified when few particles remained in suspension. The suspension was then maintained under agitation for one day in order to be sure that the particles would no longer dissolve and to detect an eventual phase transition.

2.6. Rehydration curves

Rehydration experiments were carried out in the ambient air (20 °C at 50% of relative humidity). Immediately after being removed from the oven the dehydrated samples (AZ50 and AZ80) were placed in a desiccator until they reached the room temperature. Then they were exposed to the ambient air and their weight was measured at regular time intervals. The relative sample mass M/M_0 (where M and M_0 are the sample's weight at time t and zero, respectively) was plotted as function of time.

2.7. Differential scanning calorimetry – thermogravimetric analysis

The heat flow versus temperature curves were recorded using the DSC apparatus (see Section 2.4). The temperature axis and cell constant of DSC were calibrated with indium. A heating rate of 2 °C/min was employed over a temperature range of 0–250 °C after a 5 min stabilization period under nitrogen