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Solvent screening and crystal habit of metformin hydrochloride

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ABSTRACT

A multi-well setup with video-microscopy was used to study the influence of solvent on solubility, nucleation, and crystallization of an Active Pharmaceutical Ingredient (API): metformin hydrochloride (MET.HCl). Starting with 13 solvents covering a wide variety of polarity and proticity, we found 63 crystallization medium for MET.HCl solid generation: good solvents, good co-solvents and anti-solvent systems. For toxicological reasons, we limited the number of crystallization medium to 18: 3 good solvents (class 3), 3 good co-solvent systems and 12 anti-solvent systems. In order to study the influence of crystallization medium on nucleation temperature, crystal habit and polymorphism of MET.HCl, crystallization was studied by a cooling temperature method. Different crystal habits were observed by optical and scanning electron microscopies, and solid phase were characterized by X-ray powder diffraction, indicating that all the crystals correspond to the thermodynamic stable polymorphic form A of MET.HCl. Finally, the enthalpy of fusion and the melting temperature of MET.HCl were determined by DSC and confirmed the X-ray powder diffraction results.

1. Introduction

Crystallization is an important unit operation which is widely used in the chemical, food, and pharmaceutical industries. This process plays critical roles in the development, formulation and manufacturing of an Active Pharmaceutical Ingredient (API).

In crystallization from solution, temperature, supersaturation, hydrodynamic (agitation rate) and medium of crystallization (additives, pH and solvent) are important parameters. Changes in the crystallization conditions can alter the crystal properties such as particle size, shape, purity, mechanical and thermodynamic (i.e. phase) properties. Moreover, according to the way supersaturation is achieved, different crystallization processes are carried out: by cooling, evaporating solvent or adding an anti-solvent to the solution.

Here, we focus on the influence of the solvent on solubility, polymorphism, crystallinity, and crystal habit [1,2]. Crystal habit describes the external structure while the polymorphic state refers to the internal structure of a crystal [3,4]. Consequently, the selection of a solvent or a solvent mixture is necessary and the first step in the screening of crystallization conditions is usually a solvent screening. This preliminary screening step is used to determine if an API can exist in multiple solid phases, not only polymorphs but also hydrates, solvates, and amorphous phases [4]. When several phases exist for an API, it is essential to know which phase is the most stable and thus to determine relative thermodynamic stability [5]. Furthermore, it is crucial to produce the right phase for an API because the phases differ in terms of solubility and dissolution rate [6]. The use of varied solvents may also result in different crystal habits which usually determine the handling properties and other physical properties of an API powder [7]. Several research papers demonstrated the effect of solvents on API crystallization [6–9].

In this paper, we present a methodology for the rapid screening of crystallization conditions and phases of MET.HCl using a multi-well setup with video microscopy [10]. This methodology allows us to perform a rapid screening in miniaturized scales (0.1–1 mL). Previously, the multi-well setup was used to study solubility, nucleation, crystal habit and polymorphism of an API [10]. In this work, metformin hydrochloride (MET.HCl), an oral anti–hyperglycemic drug, belonging to the biguanide class, was selected. This choice was dictated by the commercial importance of this drug and the lack of extensive studies on solvent effect on MET.HCl crystallization.

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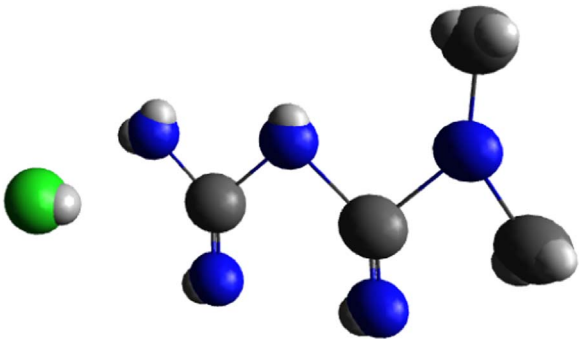

Fig. 1. Chemical structure of MET.HCl.

2. Materials and methods

2.1. Materials

Metformin hydrochloride ($C_4H_{12}ClN_5$), with the chemical structure shown in Fig. 1, was supplied by AAHP industry (Constantine, Algeria). Physical properties of MET.HCl were determined by Differential Scanning Calorimetry (DSC) SETARAM 131 Evo. Moreover, the crystals of the pure substance, as furnished from AAHP industry, were observed by optical microscopy (OM) Nikon Eclipse TE 2000-U (Fig. 4a), and under a scanning electron microscope (SEM) JEOL 6320F (Fig. 6a). All the crystals obtained by crystallization were characterized by X-ray powder diffraction X'Pert pro PANALYTICAL.

2.2. Experimental procedure

2.2.1. Physical characterization

A DSC SETARAM 131 Evo model calorimeter was used to measure the melting temperature T_m and the melting enthalpy ΔH_m. Approximately 5 mg of MET.HCl crystals was sealed in a hermetic aluminum pan of 120 μl. The sample was heated from 303 K to 573 K at a rate of 10 K/min and then cooled to 303 K by 25 K/min. The measurement was performed in triplicate.

Reversed optical microscopes Nikon Eclipses TE 2000-S, with ×4 or ×10 objectives are linked to CCD cameras for the acquisition of the images in real time. Software can record images at regular intervals.

Before the observation of MET.HCl crystals with the scanning electron microscope (SEM) JEOL 6320F, the samples were coated in vacuum with Carbon in a nitrogen atmosphere. The instrument was used at an acceleration voltage of 3 kV.

The x-ray powder diffraction X'Pert pro PANALYTICAL was used to identify crystal phases. The samples were placed in a non-rotative aluminum sample holder, then, scanned over the range of 4–50° 2Θ, with a speed of 0.056°/s and a total time of 15 min for each scan.

2.2.2. Experimental setup for crystallization studies

The device used here is home-made [10] (since marketed by ANACRISMAT). A reversed optical microscope Nikon Eclipses TE 2000-S is connected to two multi-well blocks (12*2 well), each block thermostatted independently by Peltier elements (± 0.1 °C). The mounting assembly is fixed on a motor plate (X, Y) for sequential image acquisition. In this screening, we used standard HPLC glass vials with 1 mL of solvent, the set-up and the vials used are shown in Fig. 2.

2.2.3. Method

The most common approach in solvent screening consists in using different solvents or solvent mixtures. A change of solvent affects the solvent/solute interactions therefore the interfacial energies and solubilities. The solvents are generally chosen from those authorized by the pharmacopoeia [11], but the choice can also be extended. Solvents covering a wide variety of polarity and proticity should be used [4]. In order to obtain different crystal habits, solvents reflecting a wide range of polarities were used and the screening was performed with the 13 solvents listed in Table 1.

In this study, we followed the procedure described in [10]. We used the successive additions method to measure solubility over a temperature range [20–60 °C]. As a start, we put 5 mg of MET.HCl and 1 ml of solvent in each vial then the temperature was fixed at 20 °C and images were taken regularly to follow the solute dissolution in the vials. In the case where the crystals are completely dissolved, 5 mg of solute was added repeatedly into the vials containing no crystals until the crystals do not dissolve anymore. Whereas in the case where the vials contain an excess of crystals, the solubility at 20 °C was bracketed according to the following formula [10]

$$C_{20\,°C} - 5 < S_{20\,°C} < C_{20\,°C} \quad (1)$$

We repeated the same procedure to temperatures 40 °C and 60 °C and the solubility can be implemented by the formula:

$$C_{T\,°C} - 5 < S_{T\,°C} < C_{T\,°C} \quad (2)$$

$S_{T\,°C}$ is the solubility of MET.HCl in mg/ml at a given temperature T.

$C_{T\,°C}$ is the concentration of MET.HCl given by the ratio of the solute total mass (mg) added to 1 mL of solvent at a given temperature T (°C) for which crystals do not dissolve.

$C_{T\,°C} - 5$ is the concentration at a given temperature T (°C) for

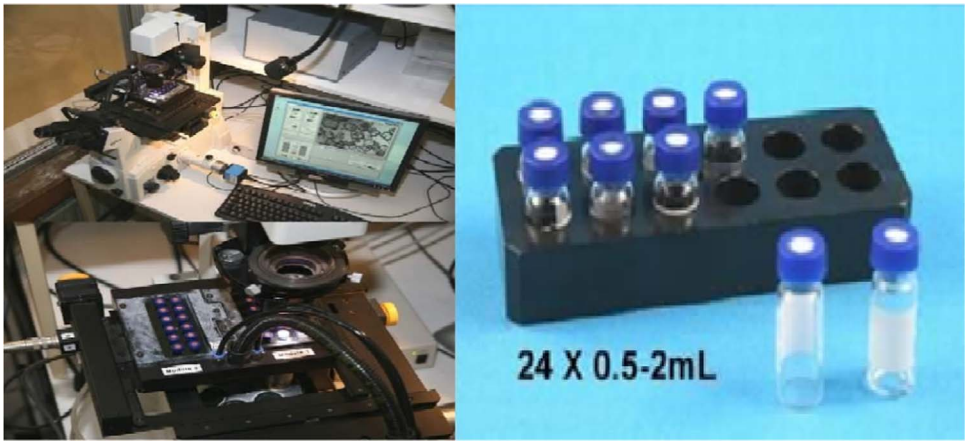

Fig. 2. Images of multi-well, Peltier blocks and corresponding 1 mL vials.