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Sulfalene: A Case Study on the Polymorphism of APIs

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Abstract: Nowadays, most of the active pharmaceutical ingredients (APIs) are produced in the solid form as pills or capsules. It has been recognized that most of the APIs in the market can present more than one crystal structure— polymorphs – a fact that has strong consequences in the physical properties (e.g. solubility, fusion point, color) of these materials, so that each polymorph is currently regarded as a unique substance. The isolation and purification of APIs is normally achieved by recrystallization from solution, a process that is currently poorly understood. Consequently, during the production stages new polymorphs are obtained, playing with the safe use of medicines as demonstrated by the well-known cases of Ritonovir and Avalide.¹ Thus, the investigation of the crystallization process from solution is currently an important field of research for the pharmaceutical industry.

It is believed that one of the key steps in the formation of a crystalline material is the nucleation process. However, the sequence of events leading to the formation of a solid form is currently unknown. Thus, in order to control the crystal phase that precipitates from solution, a deep understanding of the nucleation process is required, a topic of research that only now becomes possible with the emergence of new advanced experimental (e.g. spectroscopic and X-ray synchrotron methods) and theoretical approaches. Still, before using these methods, it is necessary to collect information relating the crystallization conditions (e.g. temperature, solvents, concentrations) and their impact in the final recrystallized solid phase.

With the goal of investigating the nucleation process of organic APIs from solution, a systematic study of sulfalene (SL, **Figure 1a**) crystallization conditions is described in this work. This compound belongs to the sulfonamide family, which was discovered in 1935, and is currently marketed for the treatment of infections of the urinary tract. Up to now, only one crystal structure has been reported for this compound, but considering the behavior of other compounds of the sulfonamide family (e.g. six polymorphs have already been identified for sulfapyridine),² it is expected that SL may also be prone to polymorphism. With this in mind, the investigation of the crystallization process of this molecule from methanol, ethanol and acetonitrile, and the subsequent characterization of the solid materials by powder X-ray diffraction and differential scanning calorimetry (DSC), is reported. The results obtained up to now, suggest the existence of at least two different crystalline phases of SL.

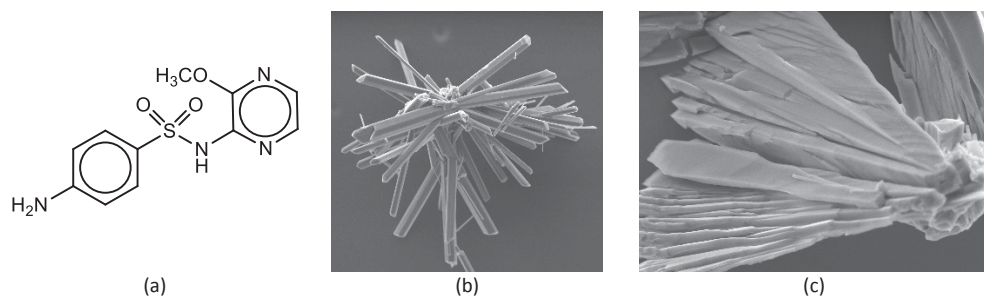


Figure 1: (a) Molecular structure of sulfalene and crystal morphologies obtained from the recrystallization from solution with (b) methanol and (c) acetonitrile by scanning electron microscopy.

Keywords: APIs, Polymorphism, Crystallization from solution, sulfonamides.

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