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ACCEPTED MANUSCRIPT

Optimization of experimental conditions for the monitoring of nucleation and growth of racemic Diprophylline from the supercooled melt

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ABSTRACT

Since more and more pharmaceutical substances are developed as amorphous forms, it is nowadays of major relevance to get insights into the nucleation and growth mechanisms from supercooled melts (SCM). A step-by-step approach of recrystallization from a SCM is presented here, designed to elucidate the impact of various experimental parameters. Using the bronchodilator agent Diprophylline (DPL) as a model compound, it is shown that optimal conditions for informative observations of the crystallization behaviour from supercooled racemic DPL require to place samples between two cover slides with a maximum sample thickness of 20 µm, and to monitor recrystallization during an annealing step of 30 min at 70 °C, *i.e*. about 33 °C above the temperature of glass transition. In these optimized conditions, it could be established that DPL crystallization proceeds in two steps: spontaneous nucleation and growth of large and well-faceted particles of a new crystal form (primary crystals: PC) and subsequent crystallization of a previously known form (RII) that develops from specific surfaces of PC. The formation of PC particles therefore constitutes the key-step of the crystallization events and is shown to be favoured by at least 2.33 wt% of the major chemical impurity, Theophylline.

Keywords: A1. Crystal morphology; A1. Impurities; A1. Nucleation; A2. Growth from melt; A1. Optical microscopy; B1. Organic compounds

1. Introduction

The crystallization of organic compounds from an amorphous state is still poorly predictable and insufficiently understood [1-3]. This topic is of great relevance during the pharmaceutical development of potential new drugs and solid dispersions, in relation to the dissolution advantage [4-6] and therefore higher bioavaiability provided by amorphous forms [7,8]. However the current knowledge in this area mainly relies on case-by-case observations and lacks a widely accepted methodology [9-11]. Crystallization events are obviously expected in the temperature range of the supercooled melt, *i.e*. between the glass transition and melting [12] but have also been reported in the glassy state, being then called devitrification [13-16]. Beyond the well-established impact of temperature [17] (since the driving force for crystallization is proportional to T_m-T), many other interdependent parameters were shown to be involved in the so-called 'tendency-to-crystallize', including the amorphization method [18-22], the presence of additives and excipients [23,24], the molecular mobility [25-28], the density [29], the primary and secondary relaxation phenomena [30-32], the fragility [33], the interface energy [34], surface effects [35-36], relative humidity [37], *etc*. This non-exhaustive list highlights the importance of reaching a better knowledge about the physico-chemical properties of amorphous materials but it should be kept in mind that nucleation and growth mechanisms also play a decisive role in the

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