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Different amorphous solid-state forms of roxithromycin: A thermodynamic and morphological study

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ABSTRACT

The striking impact that different preparation methods have on the characteristics of amorphous solid-state forms has attracted considerable attention during the last two decades. The pursuit of more extensive knowledge regarding polyamorphism therefore continues. The aim of this study was firstly, to investigate the influence of different preparation techniques to obtain amorphous solid-state forms for the same active pharmaceutical ingredient, namely roxithromycin. The preparation techniques also report on a method utilizing hot air, which although it is based on a melt intermediary step, is considered a novel preparation method. Secondly, to conduct an in-depth investigation into any physico-chemical differences between the resulting amorphous forms and thirdly, to bring our findings into context with that of previous work done, whilst simultaneously discussing a well-defined interpretation for the term polyamorphism and propose a discernment between true polyamorphism and pseudo-polyamorphism/atypical-polyamorphism. The preparation techniques included melt, solution, and a combination of solution-mechanical disruption as intermediary steps. The resulting amorphous forms were investigated using differential scanning calorimetry, X-ray powder diffraction, hot-stage microscopy, scanning electron microscopy, and vapor sorption. Clear and significant thermodynamic differences were determined between the four amorphous forms. It was also deduced from this study that different preparation techniques have a mentionable impact on the morphological properties of the resulting amorphous roxithromycin powders. Thermodynamic properties as well as the physical characteristics of the amorphous forms greatly governed other physico-chemical properties i.e. solubility and dissolution.

1. Introduction

Several different preparation techniques have been identified and used in obtaining amorphous forms of drugs in current literature. Typical methods to prepare amorphous forms of a drug are based on three intermediary steps, namely melt, solution, or solid (Savolainen et al., 2007; Patterson et al., 2005). The best known method is that of quench cooling of the melt which is based on molten drug as intermediary step (Savolainen et al., 2007; Patterson et al., 2005). During the process of quench cooling of the melt, the cooling step is so rapid that the drug molecules are not able to rearrange into a crystalline lattice therefore becoming "frozen" in a disorganized state (Savolainen et al., 2007; Patterson et al., 2005). Precipitation, spray-drying and freeze-drying are considered solution-based methods, with rapid removal of the solvent thereby inhibiting the rearrangement of the drug molecules into an ordered state (Savolainen et al., 2007; Patterson et al., 2005). Milling is based on a solid-state transition as intermediary step with mechanical activation causing a direct, but time and degree of added energy dependent, disruption of the crystalline lattice (Savolainen et al., 2007; Patterson et al., 2005). Lastly, an amorphous form may be achieved through a combination of solution, mechanical activation and the melt of a drug. An example of the aforementioned would include hot melt extrusion (Savolainen et al., 2007; Patterson et al., 2005).

It follows that one cannot ignore the fact that there are indeed differences in the physico-chemical behaviour of amorphous solids formed through different preparation techniques. Graeser et al., 2008 conducted a study on possible differences in physico-chemical properties and stability between amorphous forms of simvastatin prepared by cryo-milling and quench-cooling of the melt, and found that cryo-milled amorphous samples have different properties in comparison with the quench-cooled amorphous state (Graeser et al., 2008). Their thermodynamic

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parameters suggested that the cryo-milled amorphous form was less disordered compared to the quench-cooled form (Graeser et al., 2008). Furthermore, the cryo-milled samples had a lower stability and decreased recrystallization enthalpy (Graeser et al., 2008). Another study conducted by Sheth et al., 2004 proved that a process of cryogrinding of piroxicam forms I (P_I) and II (P_{II}) resulted in two different amorphous forms, namely P_{AI} from form I and P_{AII} from form II. These two amorphous forms differed in terms of their recrystallization behaviour. During a study of the local structures of the amorphous phases of piroxicam the authors concluded that amorphous piroxicam forms, P_{AI} and P_{AII}, had the same local amorphous NN order but differed in their residual longer – range order – possibly explaining differences in their respective recrystallization processes (Sheth et al., 2004).

Savolainen et al., 2007 investigated the molecular level differences in the amorphous state of indomethacin prepared from both α- and γ-polymorphs using different preparative techniques- including milling, quench cooling of a melt, slow cooling of a melt and spray drying (Savolainen et al., 2007). Differences in the amorphous samples could be found on a molecular level between the milled samples and the quench cooling and also between the slow cooling of a melt and spray drying (Savolainen et al., 2007). The recrystallization temperature varied between the milled, slow cooled and quenched cooled samples (Savolainen et al., 2007). The recrystallization showed an onset at higher temperatures for the amorphous forms obtained from a melt intermediary step, compared to the milled and spray dried samples (Savolainen et al., 2007). In addition, an increase in hydrogen-bonding properties was noted with the melted samples as opposed to the milled samples (Savolainen et al., 2007). Patterson et al., 2005 investigated the influence of thermal and mechanical preparative techniques on the amorphous state of four poorly soluble compounds, and concluded that the proneness for amorphous conversion of the compounds in question, through thermal and mechanical techniques, were compound specific (Patterson et al., 2005). Furthermore the amorphous test samples that were investigated were all prone to recrystallization, irrespective of whether the quench cooled or ball milled method was applied. (Patterson et al., 2005).

From literature overviews it is evident that differences between amorphous forms of the same drug do exist. However, most authors are either hesitant to apply the term polyamorphism to the varying amorphous forms of the same drug, or they speculate that the different amorphous forms of the given drug could be described as polyamorphism. This can be ascribed to the current definition of polyamorphism which signifies the possible existence of two distinct amorphous states of the same material separated by a clear phase transition. It must be noted that this definition has limited application to organic compounds. Reports on polyamorphic forms which have been identified through clear phase transitions between amorphous phases were all on inorganic compounds (Hancock et al., 2002).

Up to this point in time no well-defined phrase or term has been established to describe the different energetic states of pharmaceutical amorphous forms of the same drug. The most appropriate term is probably that of pseudo-polyamorphism, as proposed by Shalaev and Zografi (2002). It is clear that numerous challenges still exist to fully understand the amorphous solid-state forms of pharmaceutical molecules. The lack of a clear and well-described definition to group different amorphous forms of the same drug is still evasive, and after more than three decades still challenges the pharmaceutical scientist.

Preceeding studies on the investigation of possible polyamorphism emphasized and investigated differences in short range molecular order and varying molecular energetics. However, none investigated the impact that physical characteristics, i.e particle morphology could have on other physico-chemical properties of a given drug.

Previous studies on amorphous roxithromycin proved that it is possible to prepare amorphous forms of this drug by means of various methods (Aucamp et al., 2012; Biradar et al., 2006). All these methods were employed in an effort to improve the aqueous solubility of this macrolide antibiotic. However, up to this point in time, no comparative study was done to investigate physical, chemical and stability differences of roxithromycin amorphous forms prepared through different methods. Considering this it was decided that amorphous roxithromycin should be investigated further in an effort to provide more insight on the term “polyamorphism”.

2. Material and methods

2.1. Materials

Crystalline roxithromycin anhydrate (Form III) was purchased from DB Fine Chemicals Pty. Ltd. (Johannesburg, South Africa). Ultrapure water with a resistivity of 18.2 $M\Omega\,cm^{-1}$ was used throughout this study and all other reagents used were either of chromatography or analytical grade.

2.2. Methods

2.2.1. Preparation of roxithromycin amorphous solid-state forms

The chloroform desolvated amorphous form of roxithromycin (R-CD) was prepared through a slow evaporative method followed by a desolvation process (Aucamp et al., 2012). Approximately 15 g of roxithromycin was added to 200 mL of chloroform while stirring continuously and heating the solution to approximately 60 °C. The beaker containing the resulting solution was covered with Parafilm®. After slow evaporation of the chloroform, a dense mass was obtained. The desolvated amorphous roxithromycin was subsequently obtained by desolvation of the solvated solid-state form in a laboratory oven (Binder, Germany) for 24 h at 60 ± 2 °C.

The second amorphous form of roxithromycin was prepared through a quench cooling method (R-QC). Approximately 200 mg of crystalline roxithromycin was evenly distributed on the surface of a Petridish. The sample was placed in a laboratory oven (Binder, Germany) at 120 ± 5 °C until a complete melt was obtained. The resulting melt was subsequently quench cooled on a cool surface (Aucamp et al., 2013).

A third amorphous form was prepared through slow cooling of molten roxithromycin (R-SC). Approximately 200 mg of crystalline roxithromycin was evenly distributed in a Petridish. The sample was heated to 120 ± 5 °C in a vacuum oven with an applied vacuum of 1.3 kPa. After a molten product was obtained the temperature was lowered to 25 ± 5 °C. The sample was left to cool down slowly.

The last amorphous form was prepared through the application of hot air (R-HA). This is a novel method allowing the sample to be heated and melted in a gentler manner. This method has the advantage of accurate temperature control with no temperature overshooting. Approximately 60 mg of crystalline roxithromycin was placed on a 0.25 mm thick stainless steel sheet. Hot air (130 ± 5 °C) was directed towards the back of the stainless steel sheet. After a molten product was obtained the hot air was directed from heating underneath, towards directly on the melt to ensure complete melting of the product without any seed crystals remaining.

2.2.2. Differential scanning calorimetry (DSC)

A Shimadzu (Kyoto, Japan) DSC-60 instrument was used to record the DSC thermograms. Samples (3–5 mg) were accurately weighed and sealed in aluminum crimp cells with pierced lids. The samples were heated from 25 to 250 °C with a heating rate of 10 °C/