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Structural and thermal characterization of glyceryl behenate by X-ray diffraction coupled to differential calorimetry and infrared spectroscopy

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Abstract

Physical and thermal properties of glyceryl behenate (Compritol® 888 ATO) used as sustained-release matrix in pharmaceutical applications are studied by coupled time-resolved synchrotron X-ray diffraction and Differential Scanning Calorimetry combined with Infrared Spectroscopy. With these techniques, all polymorphs formed in glyceryl behenate, analyzed as received and after various thermal treatments from quenching to slow crystallization, are characterized. By using different well-controlled mixtures of mono-, di- and tribehenate, we identify each lamellar phase observed in the glyceryl behenate. Finally the influence of the crystallization rate on the formation of preferential conformations was also analyzed in order to bring insights into the polymorphism of glyceryl behenate. By changing the crystallization rate of the sample, it was shown that one can favor the formation of preferential polymorphs in the sample. In particular the crystallization at 10 °C/min seems to be well adapted for producing a single lamellar phase with a period of 60.9 Å while a crystallization rate of 0.4 °C/min produces three different lamellar phases.

Keywords: Excipient; Solid dosage forms; Lipids; Glyceryl behenate; Compritol® 888 ATO; X-ray diffraction; Differential scanning calorimetry

1. Introduction

Glycerides are a family of molecules used in the field of pharmaceutics as excipient mainly for solid dosage forms. Among them, Compritol® 888 ATO (glyceryl behenate, an atomized mixture of mono-, di- and tribehenate of glycerol) was first introduced on the pharmaceutical market as a solid-phase lubricant for tablet formulations (Jannin et al., 2003; N'Diaye et al., 2003). That excipient consists of a mixture of mono-, di- and tribehenate of glycerol (18%, 52% and 28% in weight, respectively) and presents a drop point ranging from 69 °C to 74 °C and a hydrophilic–lipophilic balance value of 2 (HLB is used as a measure of the polarity of the surface-active molecule). More recently, this mixture of glycerides has been designed to provide sustained release of drugs. Such release would not be obtained from more defined compound like pure di- or triglyceride. Hence, over the past decade, glyceryl behenate has been used for controlled-release applications by direct compression and more recently by: hot-melt coating (Barthélémy et al., 1999; Faham et al., 2000a,b), melt granulation or pelletization (Hamdani et al., 2002; Zhang and Schwartz, 2003) or the formation of solid–lipid nanoparticles (Freitas and Muller, 1999). This glyceride mixture is known to exhibit a complex polymorphism depending on many parameters such as crystallization rate or temperature of storage (Hamdani et al., 2003). As drug release depends on the stability of the crystalline structures formed, it is of prime importance to characterize any possible structural evolution of the excipient. Therefore, a description of the various structures formed as a function of time and temperature variations, is necessary both for the pharmaceutical science as it is linked to drug and excipient polymorphism and for a more general understanding of the thermal and structural behaviors of the glyceride mixtures (Small, 1986; Gunstone and Padley, 1997) which is also widely used in food and cosmetics. It is worth to remember that glycerides are naturally abundant molecules used for energy storage as well as building molecules in living systems. The mono-, di-, triglyceride mixture naturally results of lipase action and is of biological importance. Therefore, the

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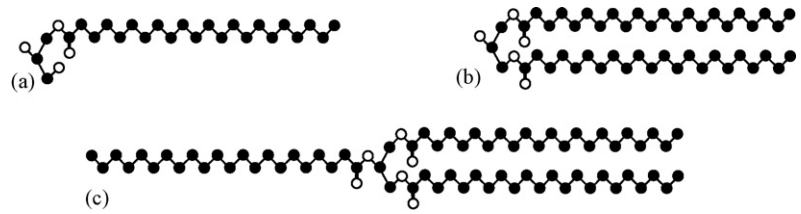

Fig. 1. Monobehenate (a), dibehenate (b) and tribehenate (c) of glycerol, the carbon and oxygen atoms are represented by black and white dots, respectively. For clarity the hydrogen atoms are not represented.

solid mixtures obtained with the long chain fatty acid are especially interesting candidates for controlled release of drugs. The amount of monoglycerides which are lyotropic molecules should be adjusted in these Generally Recognized As Safe (GRAS) mixtures to obtain the release expected.

Crystallization of glycerides has been the subject of an extensive literature exploiting the description of a variety of experimental tools (Pascher et al., 1981, 1992; Pascher, 1996; Goto et al., 1995; Di and Small, 1993). Such abundance of sources is related with the wide range of glycerides made from saturated or unsaturated acids, short or long chain acids, even or odd carbon numbered, mixed acid chains or mono acid chains, etc.

Lipid polymorphism is due to the numerous lateral packing possible of fatty acid chains specifically designated as sub α, α, β′ and β (Jackson and Lutton, 1950; Larsson, 1966; Chapman, 1962), each of them corresponding to a particular lateral organization of the hydrocarbon chains. In short: the most stable phase is the β variety for pure monoacid saturated triglyceride (TAGs), and the β′ phase for a mixture of fatty acids with long chains (De Jong and Van Soest, 1978), whereas the most stable phase for 1,2-diacyl-glycerol is β′ while the β variety is observed for 1,3-diacyl-glycerol (Kodali et al., 1990). A longitudinal stacking of the molecules in layers results of lateral packing. The stacking of lipid layers ranges from 1 to 6 chain layers with bilayers or trilayers, noted 2L or 3L, respectively, being the most frequently observed stacking. The crystalline phase is noted 2Lα for alpha bilayers lateral packing and 3Lβ for beta trilayers lateral packing. As a consequence of the diversity of possible structures formed, glycerides mixtures may exhibit a complex polymorphic behavior and the different structures developed by samples as a function of temperature or time are still unknown.

In this study, the structure and the polymorphic evolutions of glycerides mixtures, widely employed in controlled release formulations have been characterized by use of coupled X-Ray Diffraction and Differential Scanning Calorimetry. X-ray diffraction allows the study of the structure corresponding to both short reticular distances between hydrocarbon chains (lateral packing is observed in WAXS region) and long spacing (longitudinal stacking is observed in SAXS domain). Using temperature and enthalpy of transition measurements, DSC highlights energetic phenomena occurring during the heating or the cooling of the sample. By coupling these two techniques, we can link structural changes to phase transitions (Brubach et al., 2004). In addition, Infrared Spectroscopy has been used to determine chain positioning and conformation of glycerides at the molecular level.

The aim of this study is to evidence all possible polymorphs of Compritol® 888 ATO existing at room temperature for various rates of crystallization using simultaneous recordings of DSC coupled with SAXS and WAXS as a function of temperature from the same sample. The formation of these polymorphic forms will then be related to specific composition of Compritol® 888 ATO.

2. Materials and methods

Compritol® 888 was supplied by Gattefossé S.A.S, Saint Priest, (France) as an atomized (ATO) powder. Compritol® 888 ATO is synthesized by esterification of glycerol with behenic acid (C_{22} fatty acid) and therefore consists of a mix of monobehenate (Fig. 1a), dibehenate (Fig. 1b) and tribehenate (Fig. 1c) of glycerol, the diester fraction being predominant. Samples of monobehenate, dibehenate and tribehenate were also provided by Gattefossé S.A.S, Saint Priest, France (see Table 1).

X-ray diffraction measurements were performed at the D22 beam line of the synchrotron storage ring LURE-DCI, University of Paris Sud, Orsay, France. The D22 beam line allows high quality recording with low noise. Moreover SAXS, WAXS and DSC measurement data are collected simultaneously for sake of phase accuracy. The position sensitive linear detectors of SAXS and WAXS were calibrated, respectively, with silver behenate and tristearin (SSS) (Keller et al., 1998). All figures are presented

Table 1
Composition in monobehenate, dibehenate and tribehenate of each sample

	Monobehenate (%)	Dibehenate (%)	Tribehenate (%)
Compritol® 888 ATO	18	52	28
Dibehenate rich (Dibrich)	10	79	11
Tribehenate rich (Tribrich)	12.6	47.1	39.9
Monobehenate rich (Monobrich)	88	11	0.3
Tribehenate	0	0	100