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# Polymorphism and kinetic behavior of binary mixtures of triglycerides

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ABSTRACT

The work is aimed at investigating the polymorphism and the phase transition kinetics of binary lipid mixtures with potential application in controlled drug delivery. The lipid systems, constituted of glyceryl tristearate (GTS) added with different amounts (1.0–7.5% w/w) of a medium-chain liquid triglyceride ($C_{10}$–$C_{12}$ acyl derivative – MCT), were studied by differential scanning calorimetry, by X-ray diffraction and hot-stage microscopy. The liquid lipid, although present in small amount, modified the thermal profile and the diffraction pattern of the systems, indicating that it promoted the formation of the GTS stable polymorph, β, during the re-solidification of the melted mixture. This promotion effect of MCT was concentration-dependent and evident for systems containing MCT > 2.5%. Also the kinetics of transformation of GTS polymorphs was affected by the percentage of the liquid component. The α → β-transition was a biphasic process which for GTS–MCT mixture (99:1) superimposed that of pure GTS, while followed a different trend for systems containing percentages of MCT higher than 2.5.



## 1. Introduction

Many liquid, semi-solid and solid lipids are involved in the formulation of drug dosage forms because of their versatile properties. Nowadays, many natural, semisynthetic and synthetic products are employed as matrices for drug formulation or as coating materials, and they can be of a single chemical structure or mixtures of definite and tunable composition. Among the lipids for pharmaceutical applications, triacyl glycerides (TAGs) represent the most employed classes. TAGs allow formulating active pharmaceutical ingredients, often possessing very poor solubility and/or permeability, thus enhancing their bioavailability; they make possible taste masking or protection of sensitive drugs from environmental or biological accidents; they can control modulate the delivery of drugs from modified release dosage forms. Moreover, most of them are GRAS listed (FDA, 2014) biodegradable and nontoxic (Traul et al., 2000). TAGs as lipid excipients offer undoubted advantages from the technological point of view as they can be processed by several methods, such as melt extrusion (Liu et al., 2001), melt granulation (Evrard et al., 1999; Zhang and Schwartz, 2003), spray cooling (Cavallari et al., 2005), spray drying (Chauhan et al., 2005), supercritical fluid techniques (Salmaso et al., 2009), which generally employ mild process conditions. Most of these techniques involve the melting of lipids; the crystallization of metastable polymorphic forms during re-solidification step represents an issue that should be addressed. TAGs in general exhibit three polymorphic forms (α, β′ and β) which have been identified by different techniques, such as X-ray diffraction (Lavigne et al., 1993; Norton et al., 1985), differential scanning calorimetry (DSC) (Hagemann and Rothfus, 1983; Bouzidi and Narine, 2012), Raman spectroscopy (Simpson and Hagemann, 1982), calorimetry (Norton et al., 1985; Charbonnet and Singleton, 1947) and microscopy (Okada, 1964). Many factors influence how a TAG crystallizes from the melt, including composition, tempering regime, presence of other lipids or additives and mechanical treatment (shear, stirring, etc.). A systematic examination of the properties of TAG-containing materials, with particular emphasis on polymorphism, crystallization and microstructure of individual, binary and ternary systems has been conducted (Boodhoo et al., 2008, 2009a,b; Bouzidi et al., 2010). The knowledge of the structure and properties of lipids used in pharmaceutical application is of extreme importance for their influence on the performance of the dosage form. In particular, the conversion from metastable to stable form of a lipid excipient, that may occur during the product shelf life, would alter the formulation and compromise its physical integrity, modify the distribution of the

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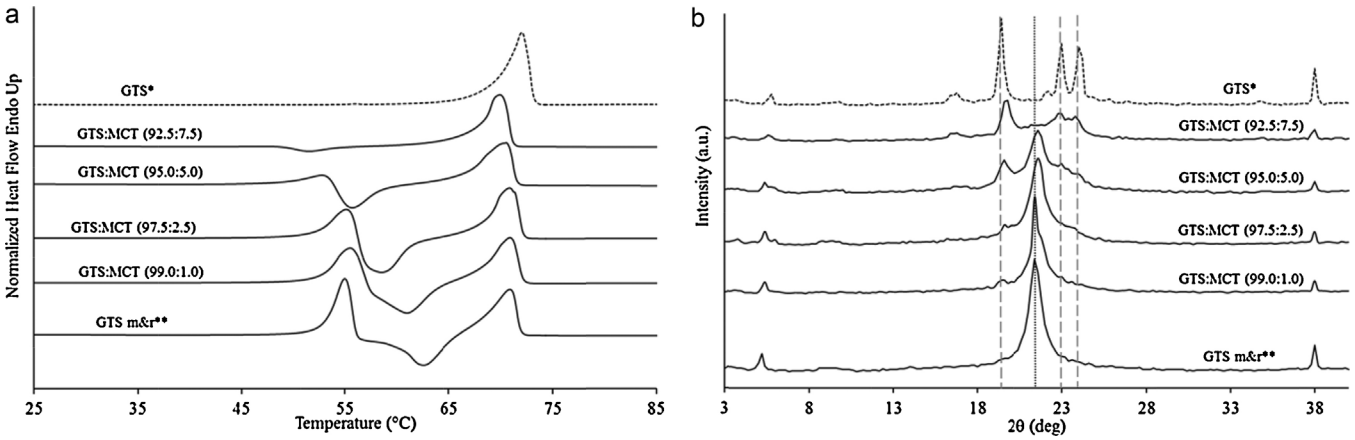


**Fig. 1.** DSC profiles (a) and XRPD spectra (b) of GTS and GTS–MCT freshly re-solidified systems (*GTS as received; **GTS melted and re-solidified).

drug in the dosage form and change the solid state properties of the active substance; these changes are often referred as aging in the literature (Sutananta et al., 1994). Therefore, the behavior of the dosage form and the release and bioavailability of the carried drug could be unexpected and unpredictable.

Mixtures of lipids containing a significant proportion of a liquid lipid are often employed as carriers of drugs, and these liquid components are medium-chain or unsaturated fatty acid glycerides. These substances are included in the mass of the lipid carrier in order to enhance the solubility of lipophilic drugs and to prevent the drug segregation or leakage during the shelf-life of the product; when present in high percentage they can form liquid domain in the mass of the formulation (Xia et al., 2014). The importance of these liquid lipids lies in their interactions with the drug, but also with the other components of a formulation: it was demonstrated that medium-chain glycerides, when associated with long-chained lipids, significantly affect the crystalline structure and stability of the system, and their effect is concentration-dependent (Windbergs et al., 2009).

The present work is aimed at investigating the phase transition behavior of binary TAGs mixtures constituted of glyceryl tristearate (GTS) as solid component, and caprylic/capric triglyceride (MCT) as liquid lipid. In particular, systems containing low amounts of MCT were studied with the aim of elucidating the role played by the medium-chain triglycerides on the GTS crystal phase formation as well as on its polymorphic conversion during and after the mixture production.

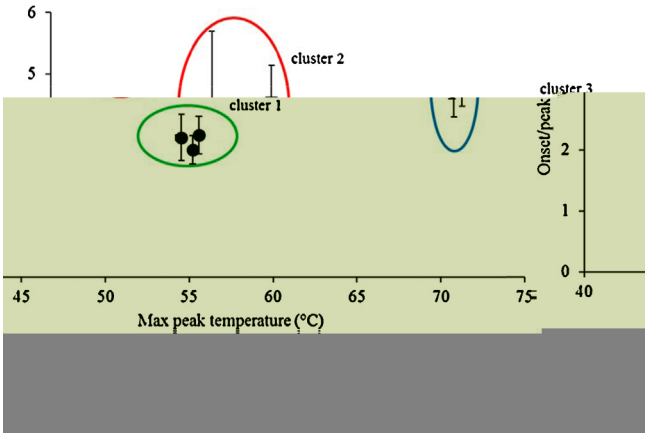


**Fig. 2.** Difference between onset and maximum peak temperatures as a function of peak temperature. Circle = α-form of pure GTS and GTS–MCT mixtures with MCT ≤ 2.5%; square = α-form of GTS–MCT mixtures with MCT > 2.5%; triangle = β-form of pure GTS and GTS–MCT mixtures.

## 2. Experimental methods

### 2.1. Materials

Glyceryl tristearate (Dynasan 118 Mikrofein – 97.7%) was a CREMER product (CREMER OLEO GmbH, Witten, D), caprylic/capric triglyceride (Labrafac™ Lipophile WL1349) was a gift from Gattefossé (Milano, I). The materials were used as received, without any further treatment.

### 2.2. Preparation of mixtures

The mixtures constituted of GTS and MCT (liquid content from 0.0 to 7.5% w/w) were prepared by melting the solid lipid in a water bath (85.0 °C) and incorporating the liquid triglyceride under stirring. The melt was then solidified by immersion in an ice bath (0.0 °C).

### 2.3. Differential scanning calorimetry

DSC analyses were performed with a Pyris 1 (PerkinElmer, USA). The samples were prepared introducing an aliquot of the melted mixture equivalent to 5 mg of GTS in an aluminum pan that was then rapidly cooled in an ice bath (0.0 °C) and sealed. Thermal scans were recorded at a heating rate of 5 °C min$^{-1}$ under dry nitrogen purge (20 mL min$^{-1}$). Two sets of analysis were carried out: the scanning range was from 25 to 85 °C in the first and from −55.0 to 25.0 °C in the second one. The sample was maintained at

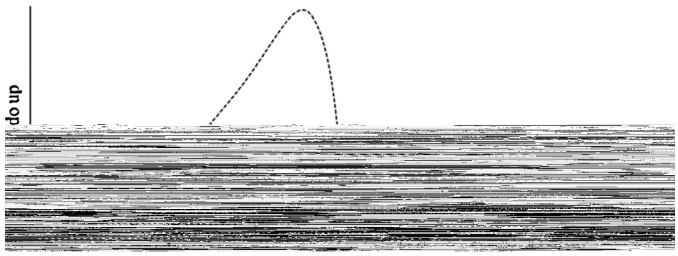


**Fig. 3.** DSC of freshly re-solidified systems in the temperature range from −55.0 to 25.0 °C: the profiles from −20.0 to 20.0 °C are shown.