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Significance of lipid matrix aging on in vitro release and in vivo bioavailability

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Abstract

A polyglycolised glyceride carrier, Gelucire 50/13, was incorporated with paracetamol as a model drug, filled into hard gelatin capsules and stored at three different temperatures for various lengths of time. The resultant solidified matrix within the capsule was subjected to thermal analysis using differential scanning calorimetry (DSC) to ascertain its supramolecular structure. Polymorphic transformations towards more stable gelucire forms were observed upon aging the matrices, with samples stored at a temperature near the melting range of the lower temperature gelucire melting fraction showing the most profound changes. The increase in the rate of drug release from aged samples could be correlated to the alterations to the supramolecular structure of the gelucire. Accelerated drug release from aged samples could also be seen from in vivo studies using healthy human volunteers, although the extent of absorption was not affected. Therefore, even though the sustainability of release may be compromised by aging the gelucire matrices, the bioavailability of the incorporated drug is unlikely to be affected.
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Keywords: Lipid matrices; Gelucire®; Aging; In vivo; Sustained release; DSC

1. Introduction

Lipid based materials are fast becoming the carriers of choice for oral delivery of new chemical entities (NCE) and well-established active agents (Mueller et al., 1994; Constantinides, 1995; Chambin et al., 2004). NCEs that had been developed are mostly hydrophobic, thus presenting associated problems such as low and erratic bioavailability. Solubilisation into lipid carriers followed by intraluminal processing circumvent these inherent limitations (Humberstone and Charman, 1997). However, more hydrophilic drugs which are already in existence can also be reformulated into certain lipid based carriers for modification of their release profiles (Saraiya and Bolton, 1990; Esquisabel et al., 1996; Hamdani et al., 2002). These carriers include the gelucires, which are a family of polyglycolised glyceride bases, consisting of polyethylene glycol (PEG) esters of various fatty acids, tri-, di-, and monoglycerides of the fatty acids, with some of the corresponding free fatty acids and PEGs present in small quantities.

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Each type of gelucire is characterized by two numbers, the first being the nominal melting point and the second being the hydrophile–lipophile balance (HLB) number. In general, the higher melting bases with a bigger proportion of lipophilic components in them are used as coating and matrix agents for sustained release formulations, whilst those with more hydrophilic components within are suitable as bioavailability enhancers. The amphiphilicity of the base conferred by the long hydrocarbon chain and the alcohol moieties means that both hydrophilic and hydrophobic drugs can potentially be incorporated into these carriers.

However, lipid based carriers are known to be affected by stability issues, particularly those associated with the changes to the matrix structure upon aging. These changes have been attributed to polymorphic transformations within the lipid component and also to the progressive increase in the crystallinity of the matrix components (Sutananta et al., 1994; Hamdani et al., 2002), which in turn could result in a modification of the in vitro and in vivo releases of the incorporated drugs. In a system such as gelucire whereby the characterization of the glycerides is made even more complex by esterification with PEG, the poor understanding of the phase changes has made it very difficult to predict its release behaviour. Variations in the results of drug release studies upon aging is a function of the components within the particular gelucire, conditions of storage and incorporated drugs (Remuñán et al., 1992; Sutananta et al., 1995; San Vicente et al., 2000). Even though these investigations were vital in establishing the role of aging in altering drug release in vitro, studies that examine the relevance of these findings in vivo are scarce. Dennis et al. (1990) found that aged formulations of ketoprofen dispersed in G50/13:G50/02 base mixture gave an increased rate of drug release in vitro but this observation was discovered to be insignificant in vivo.

In our current study, Gelucire 50/13 (G50/13), which has a sufficiently high melting point to form sustained release matrices and a balance of components that allows both hydrophobic and hydrophilic drugs to be incorporated within was chosen as the model gelucire. G50/13 has the capacity to alter its dimensions through its gelling and swelling abilities up to the extent necessary for sustaining its controlled-release properties (Kopcha et al., 1991; Prapaitakul et al., 1991; Esquisabel et al., 1996). Most dosage forms, including lipid containing ones, are usually stored for a certain length of time before being used. The storage conditions that these forms are subjected to on leaving the manufacturing plant are not always easily controlled and it would be unduly optimistic to predict an absence of temperature fluctuations within their environs. As these factors have the potential of altering the performance of the dosage form, it is essential to attempt to elucidate any mechanism of change within the solid-state structure, especially in relation to its consequent behaviour in vivo. Therefore, our current study aimed to address the above issue by investigating the release behaviour of a relatively hydrophilic drug from a lipid matrix before and after storage at different temperatures, which represent the aging process. The association of structural modifications to the matrix after aging, as indicated by thermal analysis, to changes in drug release was investigated. More importantly, the significance of such modifications as shown in in vitro systems, to drug release in healthy human volunteers was determined.

2. Materials and methods

2.1. Materials

Gelucire 50/13 was purchased from Gattefossé (Saint-Priest, France). The model drug used was paracetamol (Wenzhou Pharmaceutical, China) and the hard gelatin capsules used were of size 0. The paracetamol was sieved to give particles of $\leq$300 μm in size. All other chemicals and reagents used were either of analytical reagent (AR) grade or of high performance liquid chromatography (HPLC) grade.

2.2. Preparation of liquid filled hard gelatin capsules

10% w/w of the drug was weighed accurately, added to the molten gelucire at 75 °C and mixed using a magnetic hot plate stirrer for 10 min to ensure homogeneity and removal of thermal history. The drug did not completely dissolve in the molten carrier and remained as a dispersion. This was also observed by Khan and Craig (2003) at the same drug loading. The mixture was then filled into hard gelatin capsules size 0 using preheated pasteur pipettes and left to set under ambient

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