A Laser Imaging and Neutron Reflection Investigation Into the Monolayer Behaviour of Fatty Acids Used for Taste Masking Microspheres

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ABSTRACT: Fatty acid microspheres have been used for taste masking purposes whereby the drug is preferentially released in the lower gastrointestinal tract, although the mechanisms involved are poorly understood. In this study, we use a combination of surface pressure measurements, Brewster angle microscopy (BAM) and neutron reflectivity measurements to study the phase miscibility and escaping tendency from mixed stearic and palmitic acid films with a view to relating this to drug dissolution behaviour. It was noted that mixed systems showed considerably greater film interaction and instability than those composed of the pure lipid, especially in alkaline media. BAM studies were able to identify a range of phase separated structures for both the pure and mixed systems. Neutron reflectivity studies indicated a marked selective dissolution of palmitic acid into the subphase as a function of time and allowed quantification of the rate of dissolution of this species. It is concluded that the fatty acids are interacting within the monolayer and in addition the palmitic acid is escaping the mixed monolayers and dissolving into the alkali subphase. These findings have strong relevance for understanding the mechanism of drug release from the associated microspheres. © 2007 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 97:1864–1877, 2008

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INTRODUCTION

Medium- and long-chain saturated fatty acids have been widely used in pharmaceutical and food manufacturing for a range of applications. In particular, the possibility of utilising fatty acids to adjust the dissolution rate of drugs from dosage forms has led to considerable interest within the pharmaceutical controlled release field. More specifically, stearic and palmitic acid have been used as matrix carriers in microsphere preparations for taste-masking paediatric oral formulations.[1] After oral administration, the drug remains entrapped until the microspheres reach the neutral/weakly alkaline environment of the lower gastrointestinal tract,[2] indicating that the interactions between the fatty acid matrix and alkaline environment buffer triggers the drug release from the microspheres. While this may be a simple function of ionisation, studies to date have strongly indicated that more complex mechanisms are involved. For example, differential scanning calorimetry (DSC) studies have

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indicated that a new species is formed on exposing the microspheres to alkaline buffer and that there is an empirical correlation between the formation of this species and the release of the drug.[1,3] Evidence has been presented for the species generated on exposure to alkali being acid-soaps,[4] these being a family of molecular complexes formed between fatty acids and their corresponding metal salts.[5–8] However, the link between the formation of these structures and the drug release, or indeed the initial composition of the spheres, remains poorly understood.

In this investigation, the processes associated with the interaction between the mixed fatty acid monolayers and the alkali buffer have been studied using a range of complementary monolayer techniques in order to provide information on the molecular mechanisms of drug release. Clearly, such mixed saturated fatty acid monolayers have been extensively studied in the past;[9–11] however, our focus here is to investigate three novel issues. Firstly, we investigate the interaction of the fatty acid species with a particular view to studying the possibility of acid soap formation. Secondly, we investigate the preferential dissolution of the individual species into the subphase, an issue that may well prove key to understanding their behaviour in dosage forms. Finally, we study the use of three techniques in conjunction, two of which (Brewster angle microscopy and neutron reflection studies) are still at emergent stage within the monolayer field. Brewster angle microscopy (BAM) is a recently developed technique which probes the two-dimensional organization of thin films including the size and shape of domains and heterogeneity in the films.[12,13] Under normal conditions the thickness of a monolayer is approximately 0.5% of the wavelength of visible light and is hence effectively invisible. However if plane polarized light strikes an ultra-thin film at the Brewster angle, there is zero reflection from the water surface and all reflected information is related to the film at the air/water interface. The principle advantage of BAM compared to electron microscopy and fluorescence microscopy is that it allows direct observation of the sample films without any additional preparation procedures. In addition, by combining BAM with surface pressure measurements one may be able to visualise morphology and phase transition behaviour of the monolayer in relation to the compression state of the film.

Neutron reflectivity measurements consist of using isotopic substitution of the film forming materials to produce marked differences in scattering length density and refractive index of the reflected neutron beam.[14,15] The neutron refractive index of an element can be calculated by Eq. (1):

$$n = l - \lambda^2 A + i\lambda C(l) \tag{1}$$

where $A = Nb/2\pi$, $C = Ns_a/4\pi$, N is the atomic number density, b the bound coherent scattering length, s_a the adsorption cross-section, and l is the neutron wavelength. These differences can provide information regarding the structure and composition of films, particularly in terms of the molecular dimensions. Neutron reflection is based on the classic specular reflection approach which analyzes the beam energy change as a function of incident angle. The specular reflection of a neutron beam is a measure of the neutron reflected intensity as a function of the momentum transfer, $R(Q)$, perpendicular to the reflecting surface. The magnitude of the momentum transfer (Q) is calculated from the glancing angle of incidence, θ, given by

$$Q = \frac{4\pi \sin\theta}{\lambda} \tag{2}$$

where λ is the wavelength of the incidence neutron beam. The interfacial composition is characterised by the changes in the scattering length density, $\rho(z)$, which is related to $R(Q)$ by Fourier transformation. $\rho(z)$ is perpendicular to the interfacial plane and depends on the chemical composition of the material which can be calculated via:

$$\rho = \sum n_i b_i \tag{3}$$

where n_i is the number density of element i, and b_i is its scattering length which is -3.741 and 6.675 Å^{-1} for ^{1}H and ^{2}D, respectively. In order to measure the neutron reflectivity as a function of the momentum transfer perpendicular to the reflecting surface the measurements have to be made over a wide range of momentum transfers. This can be achieved either by using a monochromatic beam and scanning a large range of incident angles, or by using the broad band neutron time of flight (TOF) method to determine the reflectivity as a function of λ at a fixed angle (θ). The most common applications of neutron reflectance to date have included the adsorption of surfactant molecules at gas–liquid or solid–liquid interfaces, the adsorption of mixed surfactants and polymer–surfactant systems and the interfacial properties of biological materials.[16,17] Neutron reflection measurements have also been used to study the