

An Investigation into the Interaction between Taste Masking Fatty Acid Microspheres and Alkaline Buffer using Thermal and Spectroscopic Analysis

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ABSTRACT: Fatty acid-based microspheres may be used for the controlled delivery and taste masking of therapeutic agents, although the mechanisms involved in the release process are poorly understood. In this investigation, microspheres composed of high purity stearic and palmitic acid were prepared using a spray-chilling protocol. In addition, samples of binary fatty acid systems, fatty acid salts and acid-soaps were prepared to allow comparison with the microspheres. The interaction with alkaline buffer, into which release is known to be rapid, was studied using DSC and powder XRD with a view to examining the physicochemical changes undergone by the microspheres as a result of exposure to this medium. New species were identified for the postimmersion microsphere systems; similarities between the thermal and spectroscopic properties of these materials and the acid-soap references indicated the formation of acid-soaps during the exposure to the medium. The data indicate that simple exposure to buffer may result in the formation of acid soaps. This in turn has implications for understanding not only the release of drugs from the microspheres but also the biological fate of fatty acids on ingestion. © 2006 Wiley-Liss, Inc. and the American Pharmacists Association *J Pharm Sci* 95:1022–1028, 2006

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INTRODUCTION

Stearic acid and its corresponding salts have been used in pharmaceutical manufacturing for many years, particularly as the magnesium salt in tablet and capsule formulations. A more recent development has been the use of stearic acid as monoliths or in micro-/nano-encapsulated formulations^{1–6} whereby the fatty acid is used to confer controlled drug release properties. An example of a commercial product based on this technology is stearic acid coated cefuroxime axetil (SACA), marketed as a paediatric oral suspension of

cefuroxime axetil.^{7,8} Cefuroxime axetil has a strong bitter taste causing low patient compliance, particularly in children and infants who form a significant proportion of the target patient group. In this formulation, stearic acid is spray chilled with the drug to form coated microspheres, resulting in a taste-masking effect while also allowing release of the drug in the lower gastrointestinal tract.

Previous studies on the drug release behaviour from fatty acid microspheres have indicated that the release is faster in an alkaline as opposed to acidic or neutral dissolution medium.¹ It was also noted that after exposure to the alkaline buffer (pH 8.0 sorensens modified phosphate buffer) a further peak was seen on the DSC trace of the stearic acid microspheres; the authors suggested the possibility of soap or acid-soap formation, the latter being

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more likely due to the absence of characteristic melting peaks for the soaps. Acid-soaps are a group of molecular complexes formed between fatty acids and their corresponding soaps and are believed to be formed as a result of partial as opposed to complete conversion to the salt form. They were first observed in 1832 in partially hydrolysed soap solutions.⁹ Subsequently, systematic phase studies of anhydrous acid-soaps with fixed stoichiometries of 1:1, 1:2 or 2:1 fatty acid to soap were carried out by McBain et al.^{10,11} In particular, powder X-ray diffraction studies of crystalline 1:1 acid-soaps exhibited long spacings distinct from those of the crystalline fatty acids and soaps.^{12,13} Since then, extensive studies on the crystal structure of acid-soaps have subsequently been performed using XRD, NMR and FT-IT.^{14–18} Low- and wide-angle X-ray diffraction studies of 1:1 acid-soaps in water showed the existence of crystalline and liquid crystalline aggregates, including inverted hexagonal and bilayer structures.¹⁸ Interestingly, this led to the suggestion that acid-soaps could be one of the possible physical states of free fatty acids during transport and metabolism in the human body.^{18,19} Several preparation methods for acid-soaps have been reported, amongst which the most widely used are solvent evaporation and alkaline titration.^{14,20} A less widely investigated approach is the melt crystallisation of acid and soap mixtures. Here we investigate the validity of this method by comparison to published thermal and spectroscopic data. However, other than the suggestion by Robson et al.^{1–3} there have been no published reports whereby simple exposure to alkali at comparatively low temperatures may result in acid-soap formation. The present study is therefore intended to establish whether indeed such a transformation may be taking place for the microspheres under study, with implications for understanding the associated drug release mechanisms.

A further potentially relevant issue is the purity of the fatty acid. Commercial grade stearic acid is typically composed of circa 50% stearic acid (C₁₈), 40% palmitic acid (C₁₆), and 3%–5% of other medium and short chain saturated fatty acids (C₁₄ and C₁₂). This has led to several inconsistencies in the published literature in terms of fatty acid behaviour and underpins our decision to use pure grade materials in this study. However, we have also included studies on mixed systems in order to simulate commercial grade material. The aim of the present study is to study the nature of the interaction between the fatty acids and the alkaline

buffer using high purity stearic and palmitic acids by immersing the microspheres in buffer for controlled periods of time followed by washing and drying. In this manner it is intended that the mechanism responsible for the changes to the microspheres may be identified using standards (fatty acid mixes, sodium salts of the fatty acids, acid-soaps) prepared using the same raw materials.

MATERIALS AND METHODS

Materials

High purity (99%+) stearic (SA) and palmitic acid (PA), sodium stearate (SS) and sodium palmitate (SP) (99% pure) were purchased from Sigma Aldrich Co Ltd (Gillingham, UK). The pH 8.0 Sorensens modified phosphate buffer (SMPB) was prepared by using Na₂HPO₄·12H₂O, NaH₂PO₄·2H₂O and NaCl purchased from BDH (Poole, UK) at HPLC grade. The stearic-palmitic acid mixes were formed by melt-cooling the physical mixtures of stearic acid and palmitic acid at 50:50 w/w% and 30:70 w/w% compositions.

Fatty Acid Microspheres

The fatty acid microspheres were prepared using a spray chilling technique. The raw materials were mixed and melted in a water bath at 80°C then transferred to the mixing vessel of the spray chilling apparatus. The molten material was atomised under a 6 bar pressure through the pressure nozzle located on the bottom of the mixing vessel. Approximately 150 mg of fatty acid microspheres were weighed and dispersed in 900 mL pH 8.0 SMPB buffer at 37°C ± 0.5°C. Samples were stirred at 100 rpm using a USP paddle dissolution apparatus. After specified time periods of mixing, the microspheres were separated from the buffer solution using a Birlshy filter. The isolated microspheres were washed with deionised water at least three times and then left at 40°C vacuum oven to dry to constant weight. The treated microspheres were stored in a desiccator at room temperature before being further analysed. The microspheres are indicated by an M following the composition (e.g. SAM and PAM for pure stearic and palmitic acid microspheres, 50:50 SA:PAM for 50:50 microspheres etc.).

Fatty Acid-Soaps

Stearic acid, palmitic acid and their sodium soaps were used as raw material to prepare the

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