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An observational study of the effect of vibration on the caking of suspensions in oily vehicles

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ABSTRACT

An oily suspension of penethamate (PNT) that was physically stable on storage, caked solidly during road/air transport. This paper reports on the caking behaviour of PNT oily suspension formulations exposed to vibrations in a lab-based test designed to simulate road/air transport. The lab-test was used to study the effects of container type (glass v PET) and formulation (oil, surfactant type and concentration) on the physical stability of suspension under vibration. Redispersibility of the sediment was lower at longer vibrations times and at higher intensity of vibration. Caking on vibration was strongly influenced by the type of container (caking in glass but not in PET) possibly due to tribo-charging of particles. Caking on vibration was dependent on the formulation: type and concentration of surfactant; type of oil. The physical stability of oily suspensions, and the effect of vibration are two areas which have been largely neglected in the pharmaceutical literature. This paper discusses some potential mechanisms for the observations but studies using fully characterised materials are required. Finally we conclude that static testing of physical stability of oily suspensions is not sufficient and that a vibrational stress test is required.

1. Introduction

This paper is about a caking problem in an oily suspension of the penicillin prodrug, PNT. Caking in aqueous pharmaceutical suspensions was studied over 50y ago (Haines and Martin, 1961a,b,c). These studies on aqueous suspensions of bismuth subnitrate and sulfamerazine demonstrated that reduction in the zeta potential of the suspended particles, by addition of monobasic phosphate in the case of bismuth subnitrate and aluminium ion for sulfamerazine, actually reduced caking, a somewhat surprising result since electrostatic repulsion was known to prevent coagulation of colloids. Thus the concept of controlled flocculation was coined. Standard pharmaceutical science teaching texts have presented this theory for many years as a means of controlling caking in aqueous suspensions (Florence and Attwood, 2011; Sinko, 2011). Subsequently, the role of polymers and surfactants in flocculation of aqueous suspensions was investigated and this too is now covered in the teaching texts. Whether the DLVO theory is applicable to charged particles in non-aqueous media is debatable (Morrison, 1993). In a rare paper on an oily pharmaceutical suspension, the results in part seem contrary to those for aqueous suspensions. Cefazolin sodium particles in ethyl oleate, had a Zeta potential (ζ) of −27 mV. Surprisingly, this suspension is said to have flocculated whereas a suspension in peanut oil with $\zeta = -2.6$ mV did not flocculate. However, as for aqueous suspensions, the flocculated system in ethyl oleate was easily redispersed and the unflocculated suspension in peanut oil caked (Su et al., 1984).

Non-aqueous colloidal dispersions have been of interest to oil industries and in electronic imaging processes for many years. Within the pharmaceutical sciences, interest has been limited, an exception being the formulation of suspensions in chlorofluorocarbons (CFC) and hydrofluoroalkanes (HFA) for pressurized metered dose inhalers (pMDI). For non-aqueous suspensions, such as those used in pMDIs, some have assumed that electrostatic effects are negligible (Parsons et al., 1992); these authors showed that aggregation of particles and adhesion to container walls correlated with the surface energy and polarity of the particles. However, in a detailed and extensive review, Morrison discusses charging of particles and stabilisation of charges in non-aqueous media (Morrison, 1993).

As in aqueous dispersions, charging in non-aqueous dispersions may be due to adsorption of ions or ionisation of functional groups

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on the particle surface. Such processes might be due to impurities or trace water in the system. The influence of trace water is complex because it influences both the formation of structures which stabilize charge in non-aqueous vehicles, the dissociation of ionic molecules, and reactions on particle surfaces. In the presence of trace amounts of surfactants, water can contribute to inverse micelle formation. The way water is distributed is system dependent. In addition to ion transfer, Lewis acid-base reactions between the solid and vehicle are postulated (Labib and Williams, 1984).

When a solid is suspended in a non-aqueous liquid, the surface of the solid can become charged by an electron donor-acceptor reaction. This was studied by measuring the electrophoretic mobilities of solid material in a series of liquids with different electron donicities. The donicity of the solid was then defined as the donicity of the liquid in which the solid had zero electrophoretic mobility (Labib and Williams, 1984). But this donicity series is based on average charging of the surface and this is questionable given the recent revelation that there exists a random mosaic of positive and negative charges on the nanoscale, following contact between two surfaces (Baytekin et al., 2011).

Once the dispersed phase of a suspension has sedimented, there is opportunity for particles in the sediment to rub together, particularly if the suspension is exposed to vibration. When dielectric materials (non-conductors/insulators which polarize in an electric field) are brought into contact and then separated, they are charged; hence materials have been ranked in the triboelectric series. However, it has been shown that tribo-charging of surfaces occurs even when two surfaces of the same material are brought into contact and then separated. Using Kelvin Force Microscopy (KFM) it was shown that the charge on each surface is a random mosaic of positive and negative nano-regions (Baytekin et al., 2011). Some of the charging appears due to transfer of material from one surface to another suggesting there is heterolysis of bonds leading to the transfer of charged components from one surface to the other; hence, the nano-mechanical properties of the material are likely to be important.

The effect of vibration on sedimentation in non-Newtonian fluids which exhibit a yield shear stress is of importance in the food industry. Whether or not a particle sediments depends on whether the vibrational forces are sufficient to exceed the yield stress (Paul Singh et al., 1991).

Although compaction of powders has been extensively studied in the pharmaceutical sciences, particularly in tabletting, the behaviour of suspension sediments on exposure to vibration, has not been addressed. Sediments are dense suspensions of particles which are completely or partially surrounded by the suspending medium. These so-called granular dispersions, show peculiar flow properties (jamming, localization, ageing) which are not well understood (Kiesgen de Richter et al., 2015). These authors studied the behaviour of ideal systems comprising uniform glass spheres or zirconium in an aqueous medium exposed to sinusoidal vibrations of varying amplitudes and frequencies. They found that compaction occurs by a two-stage process: the first stage begins at the bottom of the packing and the compaction front travels upward through the suspension; the second stage is a homogeneous slow stochastic process which depends on the vibration and the average free volume per particle. Eventually particles become jammed when the free volume is insufficient for the particles to rearrange. Pharmaceutical suspension sediments are far more complex being: irregular-shaped particles, typically with a mean diameter $<50\,\mu m$ and with a distribution of particle sizes. The vehicle may be non-Newtonian and the exposure to vibration highly variable. The friction coefficient between particles and cohesion between particles may vary, particularly if tribo-charging takes place in the vibrating sediment.

This is an observational paper describing the behaviour of some oily suspensions of the prodrug PNT, particularly their caking behaviours under vibration, and how this behaviour was influenced by the container and composition of the oily vehicle. It aims to highlight an important but under-researched area of pharmaceutical formulation science.

2. Materials

PNT (batch no. PE-0808001, purity 98.5%, particle size: D_{90}–25 μm) was kindly donated by Bioquim, SA, Barcelona, Spain. Sunflower oil (Ph Eur grade) was purchased from Sigma-Aldrich (USA), Ethyl oleate (Ph Eur grade) was purchased from Sigma-Aldrich (UK), Miglyol® 812N (medium chain triglyceride) (Ph. Eur grade) and Miglyol 840 (propyleneglycol dicaprylocaproate)(Ph. Eur grade) were obtained from Cremer Oleo GmbH & Co., Germany. Tween 80 (Ph Eur grade) was purchased from Sigma–Aldrich, MO, USA. Span 80 was purchased from Sigma-Aldrich (NZ), Peg-12-oleate was kindly supplied by Bayer (NZ). Lipoid S-100 (Soy phosphatidylcholine) was purchased from Lipoid GmbH (Germany). Polyvinylpyrrolidone (PVP K30) was purchased from Sigma-Aldrich (NZ). All other chemicals and solvents were of analytical grade (BDH Chemicals Ltd., England, or Ajax Finechem, New Zealand).

Moisture contents of the oils were determined by volumetric Karl Fisher titration (Jain et al., 2015); viscosities of the oils were taken from the literature. The solubilities of PNT in Miglyol® 812N (MIG812), ethyl oleate (EO) and sunflower oil (SO) were determined at 30 °C by shaking oil with excess PNT for 24 h and the mass dissolved quantified by a validated stability-indicating HPLC assay (Jain et al., 2009) (Table 1).

3. Methods

3.1. Preparation of suspensions in EO

Two 35%w/w PNT suspension formulations in EO were prepared without (Formulation A) and with 0.15% Tween 80 (Formulation B). The formulations were prepared by dispersing PNT in EO or in a mixture of EO and Tween 80 using an Ultra-Turrax T25 mixer (Staufen, Germany) at 9500 rpm for 1 min. Suspensions were assessed for particle size of PNT, rheology and sedimentation behaviour.

3.2. Particle size measurements

Each formulation uniformly mixed by shaking then an aliquot (0.05 mL) was taken and mixed with EO (15 mL) and the particle size measured by laser diffraction analysis (LA 960 Laser Particle Size Analyser, Horiba, Irvine, CA).

3.3. Rheological measurements of formulations

The viscosities of Formulations A and B were measured using a HAAKE Rheostress 1 rotary viscometer fitted with concentric outer (Z10 DIN 53019) and inner (Z10 DIN 530) cylinders in a temperature controlled water-jacket (20 °C). The suspension was thermally equilibrated for 2 min. prior to testing at shear rates of $1\,s^{-1}$, $10\,s^{-1}$ and $100\,s^{-1}$, each for 300 s. The viscosity was calculated using HAAKE Rheowin 3.61 software.

3.4. Assessment of sedimentation

The sedimentation volumes of Formulation A and B were determined in duplicate by storing 10 mL of each formulation in a stoppered undisturbed measuring cylinder at 20 °C. The separation