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Engineering novel topical foams using hydrofluroalkane emulsions stabilised with pluronic surfactants

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ABSTRACT

Aesthetics are very important for topical products and as a consequence elegant vehicles such as sprays and foams are often preferred by patients. Pressurised systems are ideal to dose foams, however, as so little is known about the influence of formulation characteristics on foam properties, the rational design of these systems difficult. This study aimed to assess the capability of pluronic surfactants to stabilise topical pressurised hydrofluoroalkane (HFA) emulsions and attempted to define the formulation characteristics that had an impact upon foam properties. *In situ* phase diagrams and conductivity measurements were used to characterise the HFA emulsions. Cryo-scanning electron microscopy images, collapse time (C_t) and wetting time (W_t) were used to assess the foams post dosing, i.e. after removal of the HFA. The results indicated that foam stability was a direct function of HFA emulsion type; HFA-in-water (HIW) emulsions generated stable foams, they had 30–100 μm bubble diameter with *c.a.* 40 bubbles in a 0.45 mm × 0.40 mm area; water-in-HFA (WIH) emulsions created quick-breaking foams they contained 20–200 μm sized bubbles and had 20 bubbles in an area of 0.45 mm × 0.40 mm. Therefore, the rational design of pressurised topical foams can be achieved if the formulation is analysed *in situ*.

1. Introduction

Efficient drug delivery into the skin is difficult as the *Stratum corneum* (SC), the outmost layer, forms a formidable barrier to the penetration of therapeutic agents. This problem is compounded by the inefficient release of drugs from the majority of commercial ointment and cream formulations (Surber and Smith, 2005). For example, the topical application of levothyroxine cream has previously been reported to deliver only 0.8% of the applied drug into the skin (Padula et al., 2008). The inadequacy of topical products has driven research into the development of novel vehicles such as sprays and foams. The manipulation of the administration vehicle is a simple, low cost and efficient method to improve drug delivery to the skin (Ricciatti-Sibbald and Sibbald, 1989). Diclofenac, heparin, fluticasone propionate, lidocaine and several sex hormones have all previously been incorporated within topical sprays (Morgan et al., 1998; Hegarty et al., 2002; Kaygusuz and Susaman, 2003; Brunner et al., 2005; Gorski et al., 2005), whereas clobetasol propionate, betamethasone valerate, minoxidil, and pyrethrins have all been incorporated in foams (Amerio et al., 2003; Tanojo et al., 2004; Reid and Kimball, 2005; Rundegren et al., 2005).

Foams have many distinct advantages over other topical dosage forms including ease of application, lower density and the ability to alter skin moisturisation (Purdon et al., 2003). As a result of their benefits, patient compliance is often improved with foams compared to more conventional dosage forms (McCarty and Feldman, 2004). In addition, the potential of contaminating the unused portion of the medication is minimised as the foam is often dosed from a sealed airtight container. Furthermore, foams have been reported to enhance topical drug delivery efficiency. For example, Franz et al. (2000) showed that a clobetasol propionate foam produced a significantly greater percutaneous drug absorption compared to a solution; the total drug adsorption after 12 h was 2.6% for the foam and 1.2% using the solution. However, despite their advantages the development of topical foams for commercial use remains unattractive as their development is often time consuming and thus costly. The behaviour of drug-loaded foams is often unpredictable and rational development is impossible as there are very little published data that links formulation characteristics with the foam properties.

Pressurised foam systems usually contain a highly volatile liquid propellant to enable ejection of the dose. In addition, the foam can also contain either aqueous or non-aqueous co-solvents

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to enhance excipient compatibility. Non-aqueous systems usually incorporate non-polar solvents such as ethanol, acetone, hexadecyl alcohol, glycol ethers and polyglycols (Ricciatti-Sibbald and Sibbald, 1989), but due to the skin irritancy problems arising from these solvents, aqueous foams are preferred (Trumbore et al., 2007). However, many topical therapeutic agents, for example steroids and antibiotics demonstrate poor solubility in aqueous vehicles and therefore innovative formulation strategies are required to facilitate the development of homogeneous products containing these pharmaceutical actives.

Most of the commercially available foams use hydrocarbon propellants, which are explosive, flammable and causes great inconvenience during production, consumption and disposal. In addition, as a result of their hazardous nature no *in situ* analysis of these systems can be performed and therefore it is difficult to assess the interactions between the propellants and other excipients in the formulations. Hydrofluoroalkane (HFA) propellants are attractive alternatives to hydrocarbons as they are non-explosive and non-flammable compressed gases which are usually liquefied under pressure for storage. HFAs have been approved for pharmaceutical use, but as most drugs and surfactants display low solubility in HFA, without the help of an organic co-solvent such as ethanol, no previous studies have generated aqueous based HFA foams (Vervaet and Byron, 1999; Dickinson et al., 2000; McDonald and Martin, 2000; Butz et al., 2002; Gupta et al., 2003).

Blondino and Byron (1998) showed that some hydrophilic surfactants demonstrate appreciable solubility in HFA and more recently, Ridder et al. (2005) demonstrated that several pluronic surfactants, exhibited good solubility in HFA propellants. The generation of aqueous HFA foams may be possible if HFA soluble surfactants are used to emulsify the water in the HFA (Zhao et al., 2008). However, it is very difficult using current scientific knowledge to predict what properties the HFA emulsions should exhibit in order to generate elegant foams. Therefore, the aims of this study were to determine the feasibility of using pluronic surfactants to generate HFA aqueous foam formulations and to investigate the effect of the formulation characteristics on the physical stability of the foams after dose application.

2. Materials and methods

2.1. Materials

The HFA propellants tetrafluoroethane (HFA 134a) and heptafluoropropane (HFA 227) were kindly donated by Solvay Fluor GmbH (Frankfurt, Germany). Pluronic 10R5, 17R2, 17R4, 25R4, 31R1, L61, L81, L101, L121, L31, L35, L43, L44NF, L62D, and L92 were provided by BASF (New Jersey, USA). Poloxamer 188 (pluronic F68) and poloxamer 407 (pluronic F127) were acquired from BASF (Ludwigshafen, Germany). Methocel E4M (hydroxypropyl methylcellulose) was obtained from Colorcon Ltd. (Dartford, UK). Sodium chloride was provided by Sigma–Aldrich Ltd. (Gillingham, UK). HPLC (high performance liquid chromatography) grade water was sourced from Fisher (Leicestershire, UK).

2.2. Methods

2.2.1. Pluronic hydrofluoroalkane solubility

The determination of surfactant solubility in the liquefied HFAs was conducted visually at ambient temperature ($23 \pm 2\,^{\circ}C$) using a commonly described method (Blondino and Byron, 1998). A known amount of surfactant together with a small magnetic flea was placed in a 10 ml plastic coated glass canister (Schott UK Ltd., Stafford, UK) which was sealed with a CV20 continuous valve (Gift from Rexam Beauty & Pharma, Suresnes, France). As liquefied propellants with vapour pressure of 5.72 bar (HFA 134a) and 3.90 bar (HFA 227) at 20 °C, respectively, HFAs were added gradually by weight using a pressurised filler (Pamasol Willi Mäder AG, CH-8808 Pfäffikon SZ, Switzerland) until the surfactant dissolution was visibly apparent.

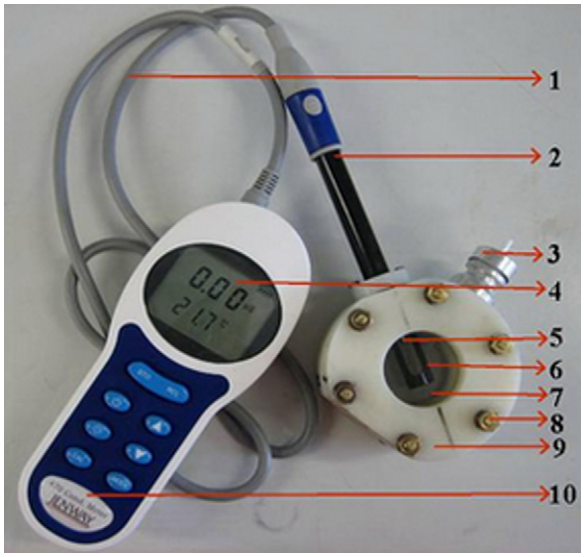

Fig. 1. The in-house designed conductivity cell for the analysis of HFA emulsions (1: connection cable, 2: conductivity probe, 3: continuous valve, 4: display screen, 5: temperature probe, 6: test plate, 7: glass window, 8: sealing screw, 9: plastic cell bulk body, 10: conductivity meter).

2.2.2. Hydrofluoroalkane emulsion preparation

HPLC grade water and 0.1% (w/v) methocel E4M was added to a 10 ml canister. The appropriate surfactant, pluronic F127, L62D or L31, selected based on their solubility in HFA, was added. The canister was sealed with a 100 μl metered spray valve (Valois UK Ltd., Bletchley, UK) and HFA was filled into the canister. To ensure the homogeneity, the whole mixture was stirred over twelve hours at 1000 rpm using a motorless electronic magnetic stirrer plate (Variomag® Telesystem HP15, Florida Scientific Services, Inc., Daytona Beach, USA). The HFA mixtures containing pluronic F127 were prepared in order to represent HFA-in-water (HIW) emulsions, i.e. water was the continuous phase. The mixtures containing pluronic L62D or L31 were formulated as water-in-HFA (WIH) emulsions, i.e. HFA was the continuous phase. To confirm the type of the HFA emulsion system the conductivity was assessed using a pressurised cell that was designed in-house (Fig. 1) containing a conductivity probe (Jenway epoxy bodied, K = 1) connected to a conductivity meter (Jenway 470 conductivity meter IP65) (VWR, Leicestershire, UK). The meter was calibrated with standard solutions (84 and 12,880 μS, Jenway) (VWR, Leicestershire, UK) and the conductivity of 0.1% (w/v) methocel containing 1% (w/v) sodium chloride and HFA 134a/227 was tested by simply filling the solvent into the pressure cell. Selected foam systems (Table 1) were prepared directly in the sealed pressure cell with a continuous valve using the previously described method (Blondino and Byron, 1998). The conductivity of the solvent or the emulsion in the pressure cell was determined in triplicate.

2.2.3. Hydrofluoroalkane emulsion stability

The emulsion stability was evaluated by recording the time that it took for phase separation (creaming/sendimentation) to occur at ambient temperature. A stable emulsion was defined as the one for which the phase separation time exceeded 60 min, otherwise the